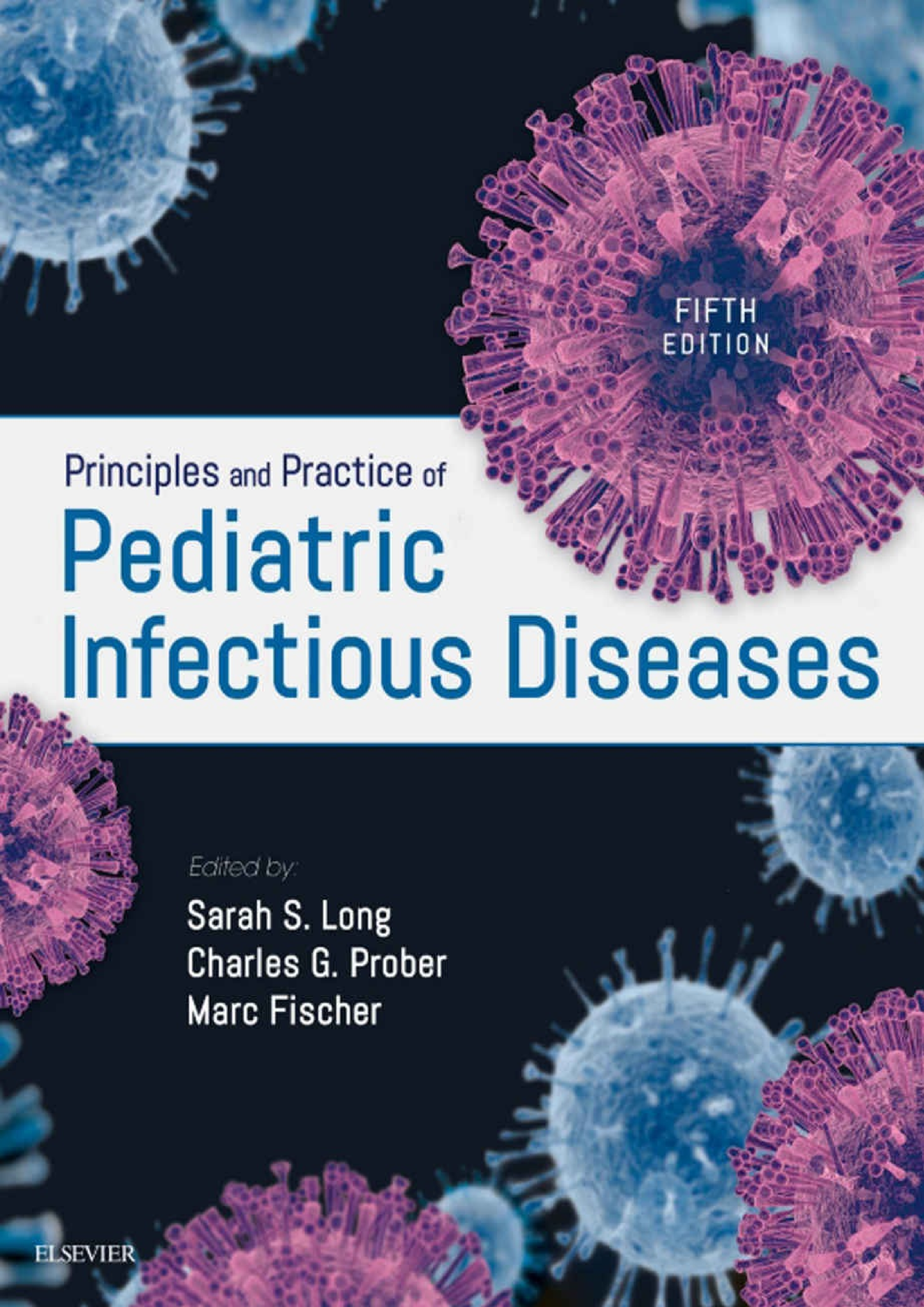

FIFTH EDITION

Principles and Practice of
Pediatric Infectious Diseases

Edited by:

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Principles and Practice of Pediatric Infectious Diseases

FIFTH EDITION

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Chapter 217: Togaviridae: Alphaviruses
Chapter 218: Flaviviruses
Chapter 220: Hepatitis C Virus
Chapter 239: Caliciviruses
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Preface

The field of infectious diseases is ever changing with emerging pathogens, globalization of people and microbes, escalating antimicrobial resistance, increasing cohorts of children living with immunocompromising conditions, novel diagnostic methods, expanding therapeutic options, and continuous development of vaccines and strategies for implementation. As the conditions on the ground become increasingly complex, so do the roles of infectious diseases experts. On a micro-level, these experts are entrusted to plan the approach to an individual patient with a potentially previously undescribed infection, while on a macro-level they are challenged to expand the field's knowledge, educate others, and steward the public's health.

Our goal is to provide a comprehensive, reliable, up-to-date reference focused on evidence-based, practical information that is required to care for neonates, infants, children, and adolescents with any infectious disease. Our aim is to guide the clinician to understand the problem, diagnose the etiology, and manage the patient to optimize outcome. This scope also includes epidemiology, control, and prevention of infectious diseases that will aid policy development, as well as management of individual patients. Features permeating the fifth edition of this book include web-based resources, important contact information, notation of key references, and electronic links to primary literature for easy access to expanded, current information as well as for obtaining restricted therapeutic agents or accessing experts for management of rare diseases. We have also added new tables, figures, image-illustrated cases, scan- and slide-ready graphics and algorithms, and Key Points boxes consisting of concise summaries.

We have engaged subject-specific experts as authors and have edited all chapters to reflect a prescribed, predictable, and focused format that will reward the reader with answers to the question, What should I do next? With a substantial number of authors from the Centers for Disease Control and Prevention, the American Academy of Pediatrics' Committee on Infectious Diseases and the Section on Infectious Diseases, the Pediatric Infectious Diseases Society, and infection prevention advisory groups, we have attempted to present consistent recommendations and to build a compendium of best practices. Examples of new content are highlighted here, within the context of the four major sections of the book.

Part I. Understanding, Controlling, and Preventing Infectious Diseases: a primer in biostatistics; expanded use of immunoglobulin products; latest vaccines and schedules for routine immunizations and for special hosts, and adverse event–reporting systems; listings of resources in electronic, telephone, and paper media; up-to-date recommendations for infection prevention for hospitals and offices; special considerations for children who are in out-of-home care, are exposed to pets and exotic animals, are traveling, or are immigrating.

Part II. Clinical Syndromes and Cardinal Features of Infectious Diseases: Approach to Diagnosis and Initial Management: new content on conditions that mimic infectious diseases (such as hemophagocytic lymphohistiocytosis and macrophage activation syndrome); developmental stages of innate and adaptive immunity; recognition and management of infections and risks due to congenital and acquired immunocompromising conditions; new chapters on infections related to biologic modifier therapy and to receipt of corticosteroids; expanded content on central nervous system infectious and parainfectious conditions; new morbidities and evidence-based approaches to preventing healthcare-associated infections.

Part III. Etiologic Agents of Infectious Diseases: significant new entries related to molecular diagnostic approach, antimicrobial resistance, and therapies for bacterial infections, especially infections due to staphylococci, pneumococci, gonococci, mycobacteria, and gram-negative bacilli; recently discovered or relevant viruses (including Ebola and Zika), new antiviral therapies, new vaccines, and some under development; evidence and guidance where evidence is incomplete for use and monitoring of agents to treat fungal infections; comprehensive and latest guidance for management of protozoal infections, including toxoplasmosis, malaria, and other pathogens of immigrants.

Part IV. Laboratory Diagnosis and Therapy of Infectious Diseases: through the burgeoning world of molecular diagnostics, the *best tests* for laboratory identification of infectious agents; *differentiating features* of commonly used laboratory tests to measure the inflammatory response and predict the cause; *new insights* into principles of use of anti-infective therapies; *expanded primer* on the pharmacodynamic basis of optimal use of antimicrobial agents; mechanisms and *best laboratory techniques* to detect newly emerging antimicrobial resistance; *new antimicrobial agents* for treating bacterial, fungal, viral, and parasitic infections.

The primary audience for our textbook is the subspecialist in infectious diseases who provides care for or advises on policy regarding infants, children, and adolescents. We hope that our book also serves as a daily "consultant" for pediatricians and family physicians and a valuable resource for surgeons, clinical microbiologists, experts in infection control, health policy makers, and other health professionals who care for and about children.

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Dedication

With our spouses (Bob, Laura, and Lisa)

our offspring (Stephen, Suzanne, and Caroline; Meghan and Andrew; Sydney and Madison)

and other loved ones

whose patience and endurance are our bedrock,

We share the achievement of this book.

To our mentors and colleagues, who share

knowledge and stimulate learning,

We give credit for the book's value.

To those who practice medicine as an art based on science,

and for the children whom they will serve,

We offer the book's lessons.

To Larry K. Pickering,

for his advancement of the field of pediatric infectious diseases, *his outstanding leadership of the*

Advisory Committee on Immunization Practices of the Centers
for Disease Control and Prevention,

and for his vital role as an associate editor of Principles and Practice of Pediatric Infectious Diseases

from its inaugural edition through its fourth,

We dedicate this book.

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Clinical Approach to the Infected Neonate

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Sarcocystis Species

Monica M. Farley MD, Professor of Medicine, Director, Division of Infectious Diseases, Emory University School of Medicine, Atlanta, Georgia

Listeria monocytogenes

Anat R. Feingold MD, MPH, Associate Professor of Pediatrics, Cooper Medical School of Rowan University; Chief, Division of Infectious Diseases, Children's Regional Hospital-Cooper, Camden, New Jersey

Anaerobic Cocci; *Anaerobic Gram-Positive*

Nonsporulating Bacilli (Including Actinomyces)

Kristina N. Feja MD, MPH, Clinical Associate Professor of Pediatrics, Rutgers Robert Wood Johnson Medical School; Chief, Division of Pediatric Infectious Diseases, Saint Peter's University Hospital, New Brunswick, New Jersey

Babesia Species (Babesiosis)

Adam Finn MA, BM, BCh, PhD, Professor of Paediatrics, University of Bristol; Honorary Consultant Paediatrician, Bristol Royal Hospital for Children, Bristol, United Kingdom

Neisseria meningitidis

Marc Fischer MD, MPH, Medical Epidemiologist, Arboviral Diseases Branch, Centers for Disease Control and Prevention, Fort Collins, Colorado

Coltivirus (Colorado Tick Fever); *Flaviviruses*; *Bunyaviruses*

Patricia M. Flynn MD, Professor of Pediatrics and Preventive Medicine; University of Tennessee Health Science Center, Member, Department of Infectious Diseases, St. Jude Children's Research Hospital, Memphis, Tennessee

Cryptosporidium Species; *Cystoisospora (Isospora) and Cyclospora Species*; *Microsporidia*

LeAnne M. Fox MD, MPH, DTM&H, Medical Officer, Division of Parasitic Diseases and Malaria, Center for Global Health, Centers for Disease Control and Prevention, Atlanta, Georgia

Blood and Tissue Nematodes: Filarial Worms; *Intestinal Trematodes*

Michael M. Frank MD, Professor of Pediatrics and Immunology, Duke University School of Medicine; Attending Physician, Duke University Medical Center, Durham, North Carolina

Complement in Control of Infectious Agents

Douglas R. Fredrick MD, Clinical Professor of Ophthalmology and Pediatrics, Stanford University School of Medicine; Vice Chair of Education, Department of Ophthalmology, Stanford University Medical Center, Stanford, California

> *Conjunctivitis in the Neonatal Period (Ophthalmia Neonatorum)*; *Conjunctivitis Beyond the Neonatal Period*; *Infective Keratitis*; *Infective Uveitis, Retinitis, and Chorioretinitis*; *Endophthalmitis*

Robert W. Frenck Jr., MD, Professor of Pediatrics, University of Texas Health Science Center; Section of Infectious Diseases, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

> *Giardia intestinalis (Giardiasis)*

Sheila Fallon Friedlander MD, Professor of Clinical Dermatology and Pediatrics, University of California San Diego; Director of Pediatric Dermatology Training Program, Rady Children's Hospital San Diego, San Diego, California

> *Subcutaneous Tissue Infections and Abscesses*; *Dermatophytes and Other Superficial Fungi*

Hayley A. Gans MD, Associate Professor of Pediatrics, Stanford University Medical Center, Stanford, California

> *Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome*

Gregory M. Gauthier MD, MS, Associate Professor (CHS) of Medicine, Division of Infectious Diseases, School of Medicine and Public Health, University of Wisconsin Madison, Madison, Wisconsin

> *Blastomyces dermatitidis (Blastomycosis)*

Jeffrey S. Gerber MD, PhD, Assistant Professor of Pediatrics, University of Pennsylvania School of Medicine; Division of Infectious Diseases, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

Clinical Syndromes of Device-Associated Infections

Francis Gigliotti MD, Professor and Chief of Infectious Diseases, Vice Chair of Pediatrics for Academic Affairs, University of Rochester School of Medicine and Dentistry, Rochester, New York

Pneumocystis jirovecii

Mark A. Gilger MD, Professor and Vice Chair of Pediatrics, Baylor College of Medicine; Pediatrician-in-Chief, Sister Angela Clare Moran, CCVI Endowed Chair in Pediatrics, The Children's Hospital of San Antonio, Texas, San Antonio, Texas

Helicobacter pylori; Other Gastric and Enterohepatic Helicobacter Species

Carol A. Glaser DVM, MD
Attending Physician, Pediatric Infectious Diseases, Kaiser Permanente, Oakland;
Section of Pediatric Infectious Diseases, University of California San Francisco, San Francisco, California

Encephalitis; Parainfectious and Postinfectious Neurologic Syndromes

Amanda F. Goddard MD, Assistant Professor of Pediatrics, Tufts University School of Medicine; Division of Pediatric Infectious Disease, Floating Hospital for Children at Tufts Medical Center, Boston, Massachusetts

Passive Immunization

Benjamin D. Gold MD, Attending Physician, Children's Center for Digestive Healthcare, Pediatric Gastroenterology, Hepatology, and Nutrition, Children's Healthcare of Atlanta; Guest Research Scientist, Helicobacter Laboratory, Centers for Disease Control and Prevention, Atlanta, Georgia

Helicobacter pylori

Jane M. Gould MD, Associate Professor of Pediatrics, Drexel

University College of Medicine; Hospital Epidemiologist, Attending Physician, Section of Infectious Diseases, St. Christopher's Hospital for Children, Philadelphia, Pennsylvania

Infection Following Burns; Healthcare-Associated Infections; Topical Antimicrobial Agents

Michael Green MD, MPH, Professor of Pediatrics, Surgery, and Clinical and Translational Research, University of Pittsburgh School of Medicine; Attending Physician, Division of Infectious Diseases, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pennsylvania

Infections in Solid Organ Transplant Recipients

David Greenberg MD, Professor of Pediatrics, Faculty of Health Sciences, Gen-Gurion University of the Negev; Chief, Pediatric Infectious Disease Unit, Soroka University Medical Center, Beer-Sheva, Israel

Moraxella Species

Tanya Greywal MD, Department of Dermatology, University of California San Diego; Rady Children's Hospital San Diego, San Diego, California

Dermatophytes and Other Superficial Fungi

Daniel Griffin MD, PhD
Clinical Instructor of Medicine, Division of Infectious Diseases; Associate Research Scientist, Department of Biochemistry and Molecular BioPhysics, Columbia University College of Physicians and Surgeons, New York, New York;
Director, Parasites Without Borders, Inc., Port Washington, New York;
Physician, Infectious Disease and Travel Medicine ProHealth Care, Plainview, New York

Tissue Nematodes

Patricia M. Griffin MD, Chief, Enteric Diseases Epidemiology Branch, Division of Foodborne, Waterborne, and Environmental

Diseases, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Other Vibrio Species

Alexei A. Grom MD, Professor of Pediatrics, University of Cincinnati College of Medicine; Division of Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

Fever and the Inflammatory Response

Kathleen Gutierrez MD, FAAP, Associate Clinical Professor (Emerita), Pediatrics—Infectious Disease, Stanford University School of Medicine, Stanford, California

Osteomyelitis; *Infectious and Inflammatory Arthritis*; *Diskitis*

Julie Gutman MD, MSc, Medical Officer, Malaria Branch, Centers for Disease Control and Prevention, Atlanta, Georgia

Plasmodium Species (Malaria)

Judith A. Guzman-Cottrill DO, Professor of Pediatrics, Division of Infectious Diseases, Oregon Health & Science University, Portland, Oregon

Pediatric Healthcare Epidemiology; *The Systemic Inflammatory Response Syndrome (SIRS), Sepsis, and Septic Shock*

Aron J. Hall DVM, MSPH, Epidemiologist, Division of Viral Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Enteric Diseases Transmitted Through Food, Water, and Zoonotic Exposures; *Caliciviruses*

Jin-Young Han MD, PhD, Associate Professor of Pediatrics, University of Arkansas for Medical Sciences; Section of Infectious Diseases, Arkansas Children's Hospital, Little Rock, Arkansas

Aseptic and Viral Meningitis; *Bartonella Species (Cat-Scratch Disease)*

Marvin B. Harper MD, Associate Professor of Pediatrics, Harvard Medical School; Chief Medical Information Officer, Attending Physician in Emergency Medicine and Infectious Diseases, Boston Children's Hospital, Boston, Massachusetts

Pneumonia in the Immunocompromised Host; *Infection Following Bites*

Julie R. Harris PhD, MPH, Epidemiologist, Field Epidemiology Training Program, Centers for Disease Control and Prevention, Atlanta, Georgia

Intestinal Nematodes

Christopher J. Harrison MD, Professor of Pediatrics, University of Missouri-Kansas City School of Medicine; Attending Physician and Director of Infectious Diseases Laboratory, Children's Mercy Hospital Kansas City, Kansas City, Missouri

Chronic Meningitis; *Recurrent Meningitis*; *Focal Suppurative Infections of the Nervous System*

David B. Haslam MD, Associate Professor of Pediatrics, University of Cincinnati College of Medicine; Cincinnati Children's Hospital Medial Center, Cincinnati, Ohio

Classification of Streptococci; *Enterococcus Species*; *Viridans Streptococci, Abiotrophia and Granulicatella Species, and Streptococcus bovis Group*; *Goups C and G Streptococci*; *Other Gram-Positive, Catalase-Negative Cocci: Leuconostoc and Pediococcus Species and Other Genera*

Sarah J. Hawkes MBBS, DTM&H, PhD, Professor of Global Health, Institute for Global Health, University College London, London, United Kingdom

Treponema pallidum (Syphilis)

J. Owen Hendley MD †, Professor of Pediatrics, University of Virginia School of Medicine, Charlottesville, Virginia

Rhinoviruses

Marion C.W. Henry MD, MPH, Commander, Medical Corps, US Navy; Division Head, Pediatric Surgery, Naval Medical Center—San Diego, San Diego, California

Appendicitis

Joseph A. Hilinski MD, Associate Professor of Pediatrics, Emory University School of Medicine, Division of Infectious Diseases, Emory Children's Center, Atlanta, Georgia

Myocarditis; *Pericarditis*

Susan L. Hills MBBS, MTH, Medical Epidemiologist, Arboviral Diseases Branch, Centers for Disease Control and Prevention, Fort Collins, Colorado

Flaviviruses

Scott D. Holmberg MD, MPH, Chief, Epidemiology and Surveillance Branch, Division of Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, Georgia

Hepatitis C Virus

Deborah Holtzman PhD, Associate Director for Science, Division of Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, Georgia

Hepatitis C Virus

David K. Hong MD, Medical Director, Karius, Inc., Menlo Park, California

Osteomyelitis; *Infectious and Inflammatory Arthritis*; *Diskitis*

Peter J. Hotez MD, PhD, Dean, National School of Tropical Medicine; Professor of Pediatrics and Molecular Virology and Microbiology, Baylor College of Medicine; Texas Children's Hospital Endowed Chair of Tropical Pediatrics; Head, Section of Pediatric Tropical Medicine; Director, Sabin Vaccine Institute, Texas Children's Hospital Center for Vaccine Development; Professor of Biology, Baylor University; Baker Institute Fellow in Disease and Poverty, Rice University, Houston, Texas

Classification of Parasites; *Intestinal Nematodes*

Katherine K. Hsu MD, MPH, Associate Professor of Pediatrics, Boston University Medical Center; Medical Director, Division of STD Prevention & HIV/AIDS Surveillance, Massachusetts Department of Public Health, Boston, Massachusetts

Neisseria gonorrhoeae; *Other Neisseria Species*

David A. Hunstad MD, Associate Professor of Pediatrics and Molecular Microbiology, Washington University School of Medicine & Health Sciences; Attending Physician and Chief, Pediatric Infectious Diseases, St. Louis Children's Hospital, St. Louis, Missouri

Infectious Complications in Special Hosts

Loris Y. Hwang MD, MS, Associate Professor of Pediatrics, Director of Adolescent Reproductive Health in Clinical Care and Research, David Geffen School of Medicine at The University of California Los Angeles; Attending Physician, Division of Adolescent and Young Adult Medicine, University of California Los Angeles, Mattel Children's Hospital UCLA, Los Angeles, California

Human Papillomaviruses

Mary Anne Jackson MD, Professor of Pediatrics, University of Missouri-Kansas City School of Medicine; Director, Division of Infectious Diseases, Children's Mercy Hospital Kansas City; Kansas City, Missouri

Lymphatic System and Generalized Lymphadenopathy;

Mediastinal and Hilar Lymphadenopathy

Richard F. Jacobs MD, Professor of Pediatrics, Robert H. Fiser, Jr., M.D. Endowed Chair in Pediatrics, University of Arkansas for Medical Sciences, Little Rock, Arkansas

Bartonella Species (Cat-Scratch Disease)

Ravi Jhaveri MD, Associate Professor of Pediatrics, University of North Carolina School of Medicine; Division of Infectious Diseases, University of North Carolina Medical Center, Chapel Hill, North Carolina

Fever Without Localizing Signs

Kateřina Jirků-Pomajbíková DVM, PhD, Institute of Parasitology, Biology Center of the Czech Academy of Sciences, České Budějovice, Czech Republic

Balantioides coli (Formerly Balantidium coli)

Jeffrey L. Jones MD, MPH, Medical Epidemiologist, Division of Parasitic Diseases and Malaria, Center for Global Health, Centers for Disease Control and Prevention, Atlanta, Georgia

Clonorchis, Opisthorchis, Fasciola, and Paragonimus Species

Mahima Karki, Research Assistant, Department of Pediatric Surgery, Boston Children's Hospital, Boston, Massachusetts

Peritonitis

M. Gary Karlowicz MD, Professor of Pediatrics, Eastern Virginia Medical School; Attending Physician, Division of Neonatal-Perinatal Medicine, Children's Hospital of The King's Daughters, Norfolk, Virginia

Healthcare-Associated Infections in the Neonate

Ben Z. Katz MD, Professor of Pediatrics, Northwestern University Feinberg School of Medicine; Attending Physician, Division of Infectious Diseases, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois

Epstein-Barr Virus (Mononucleosis and Lymphoproliferative Disorders)

Ishminder Kaur MD, Clinical Assistant Professor of Pediatrics, Drexel University College of Medicine, Section of Infectious Diseases, St. Christopher's Hospital for Children, Philadelphia, Pennsylvania

Mucocutaneous Symptom Complexes; *Abdominal Symptom Complexes*; *Topical Antimicrobial Agents*

Gilbert J. Kersh PhD, Research Biologist, Division of Vector-Borne Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Coxiella burnetii (Q Fever)

Jay S. Keystone MD, MSc (CTM), Professor of Medicine, University of Toronto, Tropical Disease Unit, Toronto General Hospital, Toronto, Ontario, Canada

Protection of Travelers

Muhammad Ali Khan MD, MPH, Assistant Professor of Pediatrics, George Washington University School of Medicine & Health Sciences; Director of Endoscopy, Pediatric Gastroenterology and Hepatology, Children's National Health System, Washington, District of Columbia

Chronic Hepatitis

David W. Kimberlin MD, Professor of Pediatrics, University of Alabama at Birmingham School of Medicine; Sergio Stagno Endowed Chair in Pediatric Infectious Diseases, Children's Hospital of Alabama, Birmingham, Alabama

Introduction to Herpesviridae; *Herpes Simplex Virus*; *Antiviral Agents*

Martin B. Kleiman MD, Ryan White Professor Emeritus of Pediatrics, Indiana University School of Medicine, Ryan White Center for Pediatric Infectious Disease and Global Health, Riley Hospital for Children, Indianapolis, Indiana

Histoplasma capsulatum (Histoplasmosis)

Bruce S. Klein MD, Professor of Pediatrics and Medicine, Medical Microbiology, and Immunology, Division of Infectious Diseases, School of Medicine and Public Health, University of Wisconsin Madison, Madison, Wisconsin

Blastomyces dermatitidis (Blastomycosis)

Karl Klontz MD, MPH, Medical Epidemiologist, Center for Food Safety and Applied Nutrition, United States Food and Drug Administration, College Park, Maryland

Clostridium difficile

Barbara Knust DVM, MPH, Epidemiologist, Viral Special Pathogens Branch, Centers for Disease Control and Prevention, Atlanta, Georgia

Bunyaviruses

Andrew Y. Koh MD, Assistant Professor of Pediatrics and Microbiology, Director of Pediatric Hematopoietic Stem Cell Transplantation, University of Texas Southwestern Medical Center, Dallas, Texas

Fever and Granulocytopenia; *Infections in Children With Cancer*

E. Kent Korgenski MS, MT(ASCP), Outcomes Data Analyst/Consultant, Intermountain Healthcare, Pediatric Clinical Program, University of Utah Department of Pediatrics, Salt Lake City, Utah

Laboratory Diagnosis of Infection Due to Bacteria, Fungi, Parasites, and Rickettsiae

Paul Krogstad MD, Professor of Pediatrics and Molecular and Medical Pharmacology, David Geffen School of Medicine at The University of California Los Angeles, Los Angeles, California

Diagnosis and Clinical Manifestations of HIV Infection

Preeta Krishnan Kutty MD, MPH, Medical Epidemiologist, National Center for Immunizations and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Chlamydia (Chlamydophila) psittaci (Psittacosis)

Christine T. Lauren MD, Assistant Professor of Dermatology and Pediatrics, Columbia University Medical Center, New York, New York

Papules, Nodules, and Ulcers

Hillary S. Lawrence MD, Assistant Professor of Dermatology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma

Superficial Bacterial Skin Infections and Cellulitis

Amy Leber PhD, Clinical Associate Professor of Pathology and Pediatrics, The Ohio State University College of Medicine; Director of Clinical Microbiology and Immunoserology, Department of Laboratory Medicine, Nationwide Children's Hospital, Columbus, Ohio

Klebsiella and Raoultella Species; *Enterobacter, Cronobacter, and Pantoea Species*; *Acinetobacter Species*; *Less Commonly Encountered Nonenteric Gram-Negative Bacilli*; *Eikenella, Pasteurella, and Chromobacterium Species*

Grace M. Lee MD, MPH, Associate Professor of Population Medicine & Pediatrics, Harvard Medical School; Director, Center for Healthcare Research in Pediatrics, Harvard Pilgrim Health Care Institute & Harvard Medical School; Associate Medical Director of Infection Control, Boston Children's Hospital, Boston,

Massachusetts

Pneumonia in the Immunocompromised Host

Eugene Leibovitz MD, Professor of Pediatrics, Faculty of Health Sciences, Ben-Gurion University of the Negev; Chief, Pediatric Emergency Medicine Department, Attending Physician, Pediatric Infectious Disease Unit, Soroka University Medical Center, Beer-Sheva, Israel

Moraxella Species

Eyal Leshem MD, Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Viral Gastroenteritis

Stéphanie Levasseur MD, FRCPC, Assistant Professor of Pediatrics, Columbia University Medical Center; Division of Cardiology, Morgan Stanley Children's Hospital of New York-Presbyterian, New York, New York

Endocarditis and Other Intravascular Infections

David B. Lewis MD, Professor of Pediatrics, Chief, Division of Allergy, Immunology, and Rheumatology, Department of Pediatrics, Stanford University School of Medicine, Stanford, California

Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome; *Infectious Complications of Cell-Mediated Immunity Other Than AIDS: Primary Immunodeficiencies*

Robyn A. Livingston MD, Associate Professor, University of Missouri-Kansas City School of Medicine; Medical Director, Infection Prevention and Control, Attending Physician, Pediatric Infectious Diseases, Children's Mercy Hospital Kansas City, Kansas City, Missouri

Recurrent Meningitis

Eloisa Llata MD, MPH, Medical Epidemiologist, Division of Sexually Transmitted Disease Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia

Pelvic Inflammatory Disease

Sarah S. Long MD, Professor of Pediatrics, Drexel University College of Medicine; Chief, Section of Infectious Diseases, St. Christopher's Hospital for Children, Philadelphia, Pennsylvania

Mucocutaneous Symptom Complexes; *Prolonged, Recurrent, and Periodic Fever Syndromes*; *Respiratory Tract Symptom Complexes*; *Bordetella pertussis (Pertussis) and Other Bordetella Species*; *Anaerobic Bacteria: Classification, Normal Flora, and Clinical Concepts*; *Clostridium botulinum (Botulism)*; *Laboratory Manifestations of Infectious Diseases*; *Principles of Anti-Infective Therapy*

Ben A. Lopman PhD, MPH, Epidemiologist, Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Viral Gastroenteritis

Yalda C. Lucero MD, PhD, Assistant Professor of Pediatrics, Faculty of Medicine, Hospital Luis Calvo Mackenna, University of Chile, Santiago, Chile

Aeromonas Species

Jorge Luján-Zilbermann MD, MS, Clinical Associate Professor of Pediatrics, University of South Florida College of Medicine; Medical Director, Hill-Top Research, Inc., St. Petersburg, Florida

Infections in Hematopoietic Stem Cell Transplant Recipients

Katherine Luzuriaga MD, Professor of Program in Molecular

Medicine, Pediatrics, and Medicine, Vice Provost, UMass Center for Clinical and Translational Science and Global Health, University of Massachusetts Medical School, Worcester, Massachusetts

Introduction to Retroviridae; *Human T-Cell Lymphotropic Viruses*; *Human Immunodeficiency Virus*

Noni E. MacDonald MD, MSc, FRCPC, Professor of Pediatric Infectious Diseases, Department of Pediatrics, Dalhousie University; Co-Director MicroResearch, IWK Health Center, Halifax, Nova Scotia, Canada

Epididymitis, Orchitis, and Prostatitis

Yvonne A. Maldonado MD, Senior Associate Dean for Faculty Development and Diversity, Professor of Pediatrics and Health Research and Policy, Stanford University School of Medicine; Chief, Division of Pediatric Infectious Diseases, Berger-Raynolds Distinguished Fellow and Attending Physician, Lucile Packard Children's Hospital at Stanford, Stanford, California

Rubella Virus; *Mumps Virus*; *Rubeola Virus: Measles and Subacute Sclerosing Panencephalitis*; *Polioviruses*

John Manaloor MD, Assistant Professor of Clinical Pediatrics, Indiana University School of Medicine; Ryan White Center for Pediatric Infectious Disease, Riley Hospital for Children at Indiana University Health, Indianapolis, Indiana

Agents of Eumycotic Mycetoma: Pseudallescheria boydii (Anamorph Scedosporium apiospermum)

Chitra S. Mani MBBS, DCH, FAAP, Professor of Pediatrics, Medical College of Georgia; Attending Physician, Division of Infectious Diseases, Children's Medical Center, Augusta, Georgia

Acute Pneumonia and Its Complications

Kalpana Manthiram MD, MSCI, Adjunct Assistant Professor, Division of Pediatric Infectious Diseases, Vanderbilt University School of Medicine, Nashville, Tennessee; Clinical Fellow, National

Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland

Prolonged, Recurrent, and Periodic Fever Syndromes

Gary S. Marshall MD, Professor of Pediatrics, University of Louisville School of Medicine; Chief, Division of Infectious Diseases, Kosair Children's Hospital, Louisville, Kentucky

Chronic Fatigue Syndrome

Stacey W. Martin MSc, Epidemiologist, Division of Bacterial Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Principles of Epidemiology and Public Health

Almea Matanock MD, Preventive Medicine Resident, Population Health Workforce Branch, Division of Scientific Education and Professional Development, Centers for Disease Control and Prevention, Atlanta, Georgia

Vibrio cholerae (Cholera)

Catalina Matiz MD, Assistant Professor of Dermatology, University of California San Diego School of Medicine; Department of Dermatology, Rady Children's Hospital San Diego, San Diego, California

Subcutaneous Tissue Infections and Abscesses

Alison C. Mawle PhD, Senior Scientist, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Active Immunization

Tony Mazzulli MD, Professor of Laboratory Medicine and Pathobiology, University of Toronto; Deputy Chief Microbiologist-in-Chief, Mount Sinai Hospital, Toronto, Ontario, Canada

Laboratory Diagnosis of Infection Due to Viruses, Chlamydia, Chlamydophila, and Mycoplasma

Kathleen A. McGann MD, Vice Chair of Pediatrics for Education, Dr. Glen and Muriel Kiser Professor of Pediatrics, Duke University Medical Center; Attending Physician, Infectious Diseases, Duke Children's Hospital, Durham, North Carolina

Respiratory Tract Symptom Complexes

Kenneth McIntosh MD, Professor of Pediatrics, Harvard Medical School, Children's Hospital Boston, Boston, Massachusetts

Pneumonia in the Immunocompromised Host

Lucy A. McNamara PhD, MS, Epidemiologist, Meningitis and Vaccine Preventable Diseases Branch, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Principles of Epidemiology and Public Health

Michal Meir MD, Attending Physician, Pediatric Infectious Diseases, Ruth Rappaport Children's Hospital, Rambam Health Care Campus, Haifa, Israel

Immunologic Development and Susceptibility to Infection

Debrah Meislich MD, Assistant Professor of Pediatrics, Cooper Medical School of Rowan University; Division of Infectious Diseases, Children's Regional Hospital-Cooper, Camden, New Jersey

Anaerobic Cocci; *Anaerobic Gram-Positive Nonsporulating Bacilli (Including Actinomyces)*

H. Cody Meissner MD, Professor of Pediatrics, Tufts University School of Medicine; Director, Division of Pediatric Infectious Disease, Tufts Medical Center, Boston, Massachusetts

Passive Immunization; *Bronchiolitis*; *Respiratory Syncytial Virus*

Elissa Meites MD, MPH, Medical Officer, Division of Viral

Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Trichomonas vaginalis

Asunción Mejías MD, PhD, MSCS, Associate Professor of Pediatrics, Division of Infectious Diseases, The Ohio State University College of Medicine; Principal Investigator, Center for Vaccines and Immunity, The Research Institute at Nationwide Children's Hospital, Columbus, Ohio

Serratia Species; *Parainfluenza Viruses*

Jussi Mertsola MD, Professor of Pediatrics, Turku University Hospital, Turku, Finland

Bordetella pertussis (Pertussis) and Other Bordetella Species

Kevin Messacar MD, Assistant Professor of Pediatrics, University of Colorado School of Medicine; Division of Infectious Diseases, Children's Hospital Colorado, Aurora, Colorado

Introduction to Picornaviridae; *Enteroviruses and Parechoviruses*

Mohammed Nael Mhaissen MD, Pediatric Infectious Disease Specialist, Valley Children's Hospital, Madera, California

Cryptosporidium Species; *Cystoisospora (Isospora) and Cyclospora Species*; *Microsporidia*

Marian G. Michaels MD, MPH, Professor of Pediatrics and Surgery, University of Pittsburgh School of Medicine; Division of Pediatric Infectious Diseases, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pennsylvania

Eosinophilic Meningitis; *Infections in Solid Organ Transplant Recipients*

Melissa B. Miller PhD, D(ABMM), Professor of Pathology and Laboratory Medicine, University of North Carolina School of

Medicine; Director, Clinical Molecular Microbiology Laboratory; Associate Director, Clinical Microbiology-Immunology Laboratory, University of North Carolina Hospitals, Chapel Hill, North Carolina

Mechanisms and Detection of Antimicrobial Resistance

Eric D. Mintz MD, MPH, Team Lead, Global Epidemiology, Waterborne Diseases Prevention Branch, Division of Foodborne, Waterborne, and Environmental Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Vibrio cholerae (Cholera)

John F. Modlin MD, Deputy Director, Polio, Bill and Melinda Gates Foundation; Professor Emeritus of Pediatrics and Medicine, Geisel School of Medicine at Dartmouth, Seattle, Washington

Introduction to Picornaviridae; Enteroviruses and Parechoviruses

Parvathi Mohan MD, MBBS, Professor of Pediatrics, George Washington University School of Medicine & Health Sciences; Interim Chief and Director of Hepatology, Pediatric Gastroenterology, and Hepatology, Children's National Health System, Washington, District of Columbia

Chronic Hepatitis

Susan P. Montgomery DVM, MPH, Epidemiology Team Lead, Parasitic Diseases Branch, Centers for Disease Control and Prevention, Atlanta, Georgia

Diphyllobothrium, Dipylidium, and Hymenolepis Species; Blood Trematodes: Schistosomiasis

José G. Montoya MD, FACP, FIDSA

Professor of Medicine, Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine, Stanford, California;

Director, Palo Alto Medical Foundation Toxoplasma Serology Laboratory, National Reference Center for the Study and Diagnosis of Toxoplasmosis, Palo Alto, California

Toxoplasma gondii (Toxoplasmosis)

Pedro L. Moro MD, MPH, Epidemiologist, Immunization Safety Office, Division of Healthcare Quality Promotion, National Center for Zoonotic and Emerging Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Echinococcus Species: Agents of Echinococcosis

Anna-Barbara Moscicki MD, Professor of Pediatrics, David Geffen School of Medicine at The University of California Los Angeles; Chief, Adolescent and Young Adult Medicine, Department of Pediatrics, The University of California Los Angeles, Mattel Children's Hospital UCLA, Los Angeles, California

Human Papillomaviruses

R. Lawrence Moss MD, E. Thomas Boles, Jr. Professor of Surgery, The Ohio State University College of Medicine; Surgeon-in-Chief, Nationwide Children's Hospital, Columbus, Ohio

Peritonitis; *Appendicitis*; *Intra-Abdominal, Visceral, and Retroperitoneal Abscesses*

Angela L. Myers MD, MPH, Associate Professor of Pediatrics, University of Missouri-Kansas City School of Medicine; Division of Infectious Diseases, Pediatric Infectious Diseases Fellowship Program Director, Children's Mercy Hospital Kansas City, Kansas City, Missouri

Abdominal and Retroperitoneal Lymphadenopathy; *Localized Lymphadenitis, Lymphadenopathy, and Lymphangitis*

Simon Nadel MRCP, MRCPCH, FRCP, Consultant and Adjunct Professor in Paediatric Intensive Care, St. Mary's Hospital and Imperial College, London, United Kingdom

Acute Bacterial Meningitis Beyond the Neonatal Period

Michael N. Neely MD, MSc, FCP, Associate Professor and Clinical Scholar, Division of Infectious Diseases, Department of Pediatrics, Keck School of Medicine, University of Southern California; Director, Laboratory of Applied Pharmacokinetics and Bioinformatics, The Saban Research Institute, Children's Hospital Los Angeles, Los Angeles, California

Pharmacokinetic-Pharmacodynamic Basis of Optimal Antibiotic Therapy

Karen P. Neil MD, MSPH, Epidemic Intelligence Service Officer, Division of Foodborne, Waterborne, and Environmental Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Enteric Diseases Transmitted Through Food, Water, and Zoonotic Exposures

Joanna Nelson MD, Clinical Assistant Professor, Stanford University School of Medicine, Division of Infectious Disease, Stanford University Medical Center, Stanford, California

Entamoeba histolytica (Amebiasis); *Other Entamoeba, Amebas, and Intestinal Flagellates*; *Naegleria fowleri*; *Acanthamoeba Species*

Noele P. Nelson MD, PhD, MPH, Medical Epidemiologist, Division of Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, Georgia

Hepatitis A Virus

William L. Nicholson MS, PhD, Research Microbiologist and Chief, Pathogen Biology and Ecology Activity, Rickettsial Zoonoses Branch, Centers for Disease Control and Prevention, Atlanta, Georgia

Family Anaplasmataceae (Anaplasmosis, Ehrlichiosis, Neorickettsiosis, and Neoehrlichiosis)

Victor Nizet MD, Professor of Pediatrics and Pharmacy, University of California San Diego, La Jolla, California

Pharyngitis; *Streptococcus pyogenes (Group A Streptococcus)*

Amy Jo Nopper MD, Professor of Pediatrics, University of Missouri-Kansas City School of Medicine; Director, Division of Pediatric Dermatology, Children's Mercy Hospital Kansas City, Kansas City, Missouri

Superficial Bacterial Skin Infections and Cellulitis

Theresa J. Ochoa MD
Associate Professor of Pediatrics, Tropical Medicine Institute, Universidad Peruana Cayetano Heredia, Lima, Peru;
Associate Professor of Epidemiology, School of Public Health, University of Texas Health Science Center at Houston, Houston, Texas

Yersinia Species

Walter A. Orenstein MD, DSc (Hon), Professor of Medicine, Pediatrics, Global Health and Epidemiology, Department of Medicine, Division of Infectious Diseases, Emory University School of Medicine, Atlanta, Georgia

Active Immunization

Miguel O'Ryan MD, Professor and Faculty of Medicine of Microbiology and Mycology Program, Institute of Biomedical Sciences, University of Chile, Santiago, Chile

Yersinia Species; *Aeromonas Species*

Christopher D. Paddock MD, MPHTM, Medical Officer, Rickettsial Zoonoses Branch, Centers for Disease Control and Prevention, Atlanta, Georgia

Rickettsia rickettsii (Rocky Mountain Spotted Fever)

Harpreet Pall MD, Associate Professor of Pediatrics, Drexel University College of Medicine; Chief, Section of Gastroenterology, St. Christopher's Hospital for Children, Philadelphia, Pennsylvania

Inflammatory Enteritis

Suresh Kumar Panuganti DCH, DNB (Pediatrics), Fellowship in Pediatric Critical Care, St. Mary's Hospital & Children's Acute Transport Services, London, United Kingdom

Acute Bacterial Meningitis Beyond the Neonatal Period

Diane E. Pappas MD, JD, Professor of Pediatrics, University of Virginia School of Medicine; University of Virginia Health System, Charlottesville, Virginia

The Common Cold; *Rhinoviruses*

Robert F. Pass MD, Beth Gordy Dubina Professor of Pediatrics, University of Alabama at Birmingham School of Medicine; Director, Pediatric Hospital Medicine, Children's Hospital of Alabama, Birmingham, Alabama

Viral Infections in the Fetus and Neonate; *Cytomegalovirus*

Thomas F. Patterson MD, Professor of Medicine, Chief, Division of Infectious Diseases; Director, San Antonio Center for Medical Mycology, The University of Texas Health Science Center at San Antonio, San Antonio, Texas

Classification of Fungi; *Agents of Hyalohyphomycosis and Phaeohyphomycosis*; *Agents of Mucormycosis*; *Malassezia Species*; *Sporothrix schenckii Complex (Sporotrichosis)*; *Cryptococcus Species*

Monica E. Patton MD, Division of Sexually Transmitted Disease Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia

Skin and Mucous Membrane Infections and Inguinal Lymphadenopathy

Stephen I. Pelton MD, Professor of Pediatrics and Epidemiology, Boston University Schools of Medicine and Public Health; Chief, Section of Pediatric Infectious Diseases, Boston Medical Center, Boston, Massachusetts

Otitis Media

Brett W. Petersen MD, MPH, Medical Officer, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Poxviridae

Larry K. Pickering MD, Adjunct Professor of Pediatrics, Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia

Active Immunization

Swetha Pinninti MD, Assistant Professor of Pediatrics, University of Nebraska Medical Center, Omaha, Nebraska

Viral Infections in the Fetus and Neonate

Paul J. Planet MD, Assistant Professor of Pediatrics, The Perelman School of Medicine at the University of Pennsylvania; Attending Physician, Division of Infectious Diseases, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

Pseudomonas aeruginosa

Andrew J. Pollard BSc, MBBS, MRCP(UK), MA, DIC, PhD, FRCPCH, FMedSci, Professor of Paediatric Infection and Immunity, Department of Paediatrics, University of Oxford; Honorary Consultant Paediatrician, Children's Hospital, Oxford, United Kingdom

Neisseria meningitidis

Klara M. Posfay-Barbe MD, MS, Head of Pediatric Infectious Diseases, Children's Hospital of Geneva, University Hospitals of Geneva, Geneva, Switzerland

Eosinophilic Meningitis

Casper S. Poulsen MSc, Doctoral Student, Research Group for Genomic Epidemiology, Technical University of Denmark, Lyngby, Denmark

Endolimax nana

Susan M. Poutanen MD, MPH, FRCPC, Associate Professor of Laboratory Medicine and Pathobiology & Medicine, University of Toronto; Microbiologist & Infectious Disease Physician, University Health Network & Mount Sinai Hospital, Toronto, Ontario, Canada

Human Coronaviruses

Ann M. Powers PhD, Chief, Virology Activity, Arboviral Diseases Branch, Division of Vector-Borne Diseases, Centers for Disease Control and Prevention, Fort Collins, Colorado

Togaviridae: Alphaviruses

Charles G. Prober MD, Professor of Pediatrics, Microbiology, and Immunology, Senior Associate Dean for Medical Education, Stanford University School of Medicine, Stanford, California

Introduction to Herpesviridae; *Herpes Simplex Virus*

Octavio Ramilo MD, Henry G. Cramblett Chair in Infectious Diseases, Professor of Pediatrics, The Ohio State University College of Medicine; Chief, Division of Infectious Diseases, Nationwide Children's Hospital; Principal Investigator, Center for Vaccines and Immunity, The Research Institute at Nationwide Children's Hospital, Columbus, Ohio

Parainfluenza Viruses

Shawn J. Rangel MD, Associate Professor of Surgery, Harvard Medical School; Department of Pediatric Surgery, Boston Children's Hospital, Boston, Massachusetts

Peritonitis

Suchitra Rao MBBS, Assistant Professor of Pediatrics (Infectious Diseases, Hospital Medicine, and Epidemiology), University of Colorado School of Medicine; Sections of Infectious Diseases and

Hospital Medicine, Children's Hospital Colorado, Aurora, Colorado

BK, JC, and Other Human Polyomaviruses

Sarah A. Rawstron MBBS, Clinical Associate Professor of Pediatrics, Icahn School of Medicine at Mount Sinai; Pediatric Residency Program Director, The Brooklyn Hospital Center, Brooklyn, New York

Treponema pallidum (Syphilis); *Other Treponema Species*

Jennifer S. Read MD, MS, MPH, DTM&H, Associate Director for Clinical Research/Division of Allergy, Immunology, and Transplantation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland

Epidemiology and Prevention of HIV Infection in Children and Adolescents

Michael D. Reed PharmD, FCCP, FCP, Professor of Pediatrics, Case Western Reserve University School of Medicine; Director, Rainbow Clinical Research Center, Rainbow Babies and Children's Hospital, University Hospitals Cleveland Medical Center, Cleveland, Ohio

Pharmacokinetic-Pharmacodynamic Basis of Optimal Antibiotic Therapy

Ryan F. Relich PhD, D(ABMM), MLS(ASCP)CMSMCM, Assistant Professor of Clinical Pathology and Laboratory Medicine, Indiana University School of Medicine; Associate Medical Director, Division of Clinical Microbiology, Indiana University Health Pathology Laboratory, Indianapolis, Indiana

Laboratory Diagnosis of Infection Due to Bacteria, Fungi, Parasites, and Rickettsiae

Megan E. Reller MD, PhD, MPH, DTM&H, Instructor, Duke University School of Medicine, Division of Infectious Diseases, Duke Children's Hospital, Durham, North Carolina

Salmonella Species

Neil Rellosa MD, Assistant Professor of Pediatrics, Drexel University College of Medicine; Attending Physician, Sections of Infectious Diseases and Immunology, St. Christopher's Hospital for Children, Philadelphia, Pennsylvania

Fusobacterium Species

Katherine A. Rempe PhD, Molecular Microbiology Fellow, Actelion Clinical Research, Cherry Hill, New Jersey

Classification of Bacteria; *Haemophilus influenzae*

Melissa A. Reyes MD, MPH, Staff Dermatologist, Palo Alto Medical Foundation, Dublin, California

Purpura

Samuel E. Rice-Townsend MD, Assistant Professor of Surgery, Harvard Medical School, Department of Pediatric Surgery, Boston Children's Hospital, Boston, Massachusetts

Peritonitis

Frank O. Richards Jr., MD, Director, River Blindness Elimination Program, Lymphatic Filariasis Elimination Program, and Schistosomiasis Control Program, The Carter Center, Atlanta, Georgia

Diphyllobothrium, Dipylidium, and Hymenolepis Species; *Blood Trematodes: Schistosomiasis*

José R. Romero MD, FAAP, FIDSA, FPIDS, Professor of Pediatrics, University of Arkansas for Medical Sciences; Horace C. Cabe Endowed Chair in Infectious Diseases, Director, Pediatric Infectious Diseases Section, Arkansas Children's Hospital, Little Rock, Arkansas

Aseptic and Viral Meningitis

David A. Rosen MD, PhD, Instructor in Pediatrics, Washington University School of Medicine & Health Sciences; Division of Pediatric Infectious Diseases, St. Louis Children's Hospital, St. Louis, Missouri

Infectious Complications in Special Hosts

Christina A. Rostad MD, Instructor in Pediatrics, Emory University School of Medicine; Division of Infectious Diseases, Emory Children's Center, Atlanta, Georgia

Myocarditis; *Pericarditis*

G. Ingrid J.G. Rours MD, PhD, Department of Medical Microbiology and Infectious Diseases, Department of Paediatrics, Erasmus Medical Center, Rotterdam, Netherlands

Chlamydia trachomatis

Janell A. Routh MD, MHS, Medical Officer, Viral Vaccine Preventable Diseases Branch, Division of Viral Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Vibrio cholerae (Cholera)

Anne H. Rowley MD, Professor of Pediatrics and Microbiology/Immunology, Northwestern University Feinberg School of Medicine; Attending Physician, Division of Infectious Diseases, The Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois

Kawasaki Disease

Lorry G. Rubin MD

Professor of Pediatrics, Hofstra Northwell School of Medicine, Hempstead, New York;
Director of Pediatric Infectious Diseases, Steven and Alexandra Cohen Children's Medical Center of New York, New Hyde Park, New York

Capnocytophaga Species; *Francisella tularensis (Tularemia)*; *Legionella Species*; *Streptobacillus* *moniliformis (Rat-Bite Fever); Other Gram-Negative Coccobacilli*

Edward T. Ryan MD, Professor of Medicine, Harvard Medical School; Professor of Immunology & Infectious Diseases, Harvard School of Public Health; Director, Global Infectious Diseases, Division of Infectious Diseases, Massachusetts General Hospital, Boston, Massachusetts

Antiparasitic Agents

Lisa Saiman MD, MPH, Professor of Pediatrics, Columbia University Medical Center, Division of Infectious Diseases, Morgan Stanley Children's Hospital of New York-Presbyterian, New York, New York

Endocarditis and Other Intravascular Infections

Julia S. Sammons MD, Assistant Professor of Clinical Pediatrics, University of Pennsylvania School of Medicine; Division of Infectious Diseases, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

Clinical Syndromes of Device-Associated Infections

Laura Sass MD, Assistant Professor of Pediatrics, Eastern Virginia Medical School; Attending Physician, Division of Pediatric Infectious Diseases, Children's Hospital of The King's Daughters, Norfolk, Virginia

Healthcare-Associated Infections in the Neonate

Jason B. Sauberan PharmD, Clinical Research Pharmacist, Neonatal Research Institute, Sharp Mary Birch Hospital for Women and Newborns, San Diego, California

Antimicrobial Agents

Sarah Schillie MD, MPH, MBA, Medical Epidemiologist, Division of Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, Georgia

Hepatitis B and Hepatitis D Viruses

Grant S. Schulert MD, PhD, Instructor, University of Cincinnati College of Medicine; Division of Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

Fever and the Inflammatory Response

Jennifer E. Schuster MD, MSCI, Assistant Professor of Pediatrics, University of Missouri-Kansas City School of Medicine; Division of Infectious Diseases, Children's Mercy Hospital Kansas City, Kansas City, Missouri

Human Metapneumovirus

Kevin L. Schwartz MD, MSc, Public Health Ontario, Toronto, Ontaraio, Canada

Protection of Travelers

Bethany K. Sederdahl BS, Research Coordinator, Emory University School of Medicine; Division of Pediatric Infectious Diseases, Children's Healthcare of Atlanta, Atlanta, Georgia

Other Campylobacter Species

Jose A. Serpa MD, MS, Assistant Professor of Medicine, Baylor College of Medicine; Director of Infectious Diseases Fellowship Training Program, Texas Children's Hospital, Houston, Texas

Taenia solium, Taenia asiatica, and Taenia saginata: Taeniasis and Cysticercosis; Taenia Multiceps (multiceps) and Taenia serialis: Coenurosis

Kara N. Shah MD, PhD, Associate Professor of Pediatrics and Dermatology, University of Cincinnati College of Medicine; Medical Director, Division of Dermatology, Cincinnati Children's Hospital, Cincinnati, Ohio

Urticaria and Erythema Multiforme

Samir S. Shah MD, Professor of Pediatrics, University of

Cincinnati College of Medicine; Attending Physician, Divisions of Infectious Diseases and Hospital Medicine; James M. Ewell Endowed Chair, Director, Division of Hospital Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

Chlamydophila (Chlamydia) pneumoniae; *Mycoplasma pneumoniae*; *Other Mycoplasma Species*; *Ureaplasma urealyticum*

Andi L. Shane MD, MPH, MSc, Associate Professor of Pediatrics, The Marcus Professor of Hospital Epidemiology and Infection Prevention, Emory University School of Medicine; Division of Infectious Diseases, Children's Healthcare of Atlanta, Atlanta, Georgia

Infections Associated With Group Childcare; *Approach to the Diagnosis and Management of Gastrointestinal Tract Infections*

Eugene D. Shapiro MD, Professor of Pediatrics, Epidemiology, and Investigative Medicine, Yale University Schools of Medicine, Public Health, and Graduate School of Arts and Sciences; Attending Pediatrician, The Children's Hospital at Yale-New Haven, New Haven, Connecticut

Fever Without Localizing Signs; *Leptospira Species (Leptospirosis)*; *Borrelia burgdorferi (Lyme Disease)*; *Other Borrelia Species and Spirillum minus*

Jana Shaw MD, MPH, Associate Professor of Pediatrics, State University of New York; Division of Infectious Diseases, Golisano Children's Hospital, Syracuse, New York

Infections of the Oral Cavity

Avinash K. Shetty MD, Associate Dean for Global Health, Professor of Pediatrics, Wake Forest School of Medicine; Chief, Division of Pediatric Infectious Diseases, Brenner Children's Hospital, Winston-Salem, North Carolina

Rubella Virus; Mumps Virus; Rubeola Virus: Measles and Subacute Sclerosing Panencephalitis

Linda M. Dairiki Shortliffe, MD, Stanley McCormick Memorial Professor of Urology Emerita, Stanford University School of Medicine, Stanford, California

Urinary Tract Infections, Renal Abscess, and Other Complex Renal Infections

George Kelly Siberry MD, MPH, Medical Officer, Maternal Pediatric Infectious Disease Branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland

Management of HIV Infection

Jane D. Siegel MD, Former Professor of Pediatrics, Division of Infectious Diseases, University of Texas Southwestern Medical Center, Dallas, Texas

Pediatric Healthcare Epidemiology

Robert David Siegel MD, PhD, Professor of Microbiology and Immunology, Stanford University School of Medicine, Stanford, California

Classification of Human Viruses

Kari A. Simonsen MD, Associate Professor of Pediatrics and Public Health, Chief, Pediatric Infectious Diseases, University of Nebraska Medical Center, Omaha, Nebraska

Infectious Complications of Corticosteroid Therapy

Nalini Singh MD, MPH, Professor of Pediatrics, Global Health, and Epidemiology, George Washington University School of Medicine & Health Sciences; Division of Infectious Diseases, Children's National Health System, Washington, District of Columbia

Clostridium difficile

Upinder Singh MD, Associate Professor of Medicine and Microbiology and Immunology, Stanford University School of Medicine, Division Chief of Infectious Diseases and Geographic Medicine, Stanford University Medical Center, Stanford, California

Entamoeba histolytica (Amebiasis); *Other Entamoeba, Amebas, and Intestinal Flagellates*; *Naegleria fowleri*; *Acanthamoeba Species*

P. Brian Smith MD, MPH, MHS, Professor of Pediatrics, Division of Neonatology, Duke University Medical Center, Duke Clinical Research Institute, Durham, North Carolina

Candida Species

John D. Snyder MD †, Professor of Pediatrics, George Washington University School of Medicine & Health Sciences; Chief, Gastroenterology, Hepatology, and Nutrition, Children's National Health System, Washington, District of Columbia

Acute Hepatitis; *Chronic Hepatitis*

Eunkyung Song MD, Assistant Professor of Pediatrics, The Ohio State University College of Medicine; Division of Infectious Diseases, Nationwide Children's Hospital, Columbus, Ohio

Serratia Species

Jennifer L. Sorrell MD, Clinical Assistant Professor of Dermatology and Pediatrics, Departments of Dermatology and Pediatrics, Stanford University School of Medicine, Palo Alto, California

Papules, Nodules, and Ulcers

Emily Souder MD, Clinical Instructor of Pediatrics, Drexel University College of Medicine; Section of Infectious Diseases, St. Christopher's Hospital for Children, Philadelphia, Pennsylvania

Other Haemophilus Species and Aggregatibacter Species

Joseph W. St. Geme III, MD, Chair, Department of Pediatrics, The Perelman School of Medicine at the University of Pennsylvania; Chair, Department of Pediatrics, Physician-in-Chief, Children's Hospital of Philadelphia; Philadelphia, Pennsylvania

> *Classification of Bacteria*; *Classification of Streptococci*; *Enterococcus Species*; *Viridans Streptococci, Abiotrophia and Granulicatella Species, and Streptococcus bovis Group*; *Groups C and G Streptococci*; *Other Gram-Positive, Catalase-Negative Cocci: Leuconostoc and Pediococcus Species and Other Genera*; *Haemophilus influenzae*

Mary Allen Staat MD, MPH, Professor of Pediatrics, University of Cincinnati College of Medicine; Director, International Adoption Center, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

> *Infectious Diseases in Refugee and Internationally Adopted Children*

J. Erin Staples MD, PhD, Medical Epidemiologist, Arboviral Diseases Branch, Division of Vector-Borne Diseases, Centers for Disease Control and Prevention, Fort Collins, Colorado

> *Coltivirus (Colorado Tick Fever)*; *Togaviridae: Alphaviruses*

Jeffrey R. Starke MD, Professor of Pediatrics, Baylor College of Medicine; Infection Control Officer, Texas Children's Hospital, Houston, Texas

> *Mycobacterium tuberculosis*

William J. Steinbach MD, Professor of Pediatrics, Molecular Genetics, and Microbiology; Chief, Division of Pediatric Infectious Diseases, Duke University Medical Center, Durham, North Carolina

> *Candida Species*; *Aspergillus Species*; *Antifungal Agents*

Christen R. Stensvold PhD, MSc, Senior Scientist, Department of Microbiology and Infection Control, Statens Serum Institut, Copenhagen, Denmark

Balantioides coli (Formerly Balantidium coli); *Blastocystis*; *Endolimax nana*

Bradley P. Stoner MD, PhD, Associate Professor of Anthropology and Medicine, Washington University School of Medicine & Health Sciences, St. Louis, Missouri

Klebsiella granulomatis: Granuloma Inguinale

Raymond A. Strikas MD, MPH, Medical Officer, Immunization Services Division, Centers for Disease Control and Prevention, Atlanta, Georgia

Active Immunization

Jonathan B. Strober MD, Professor of Neurology and Pediatrics, University of California San Francisco; Director of Pediatric MDA Clinic, Director of Ambulatory Services, Pediatric Brain Center and Division of Child Neurology, University of California San Francisco Benioff Children's Hospital, San Francisco, California

Parainfectious and Postinfectious Neurologic Syndromes

Paul K. Sue MD, CM, Assistant Professor of Pediatrics, Division of Pediatric Infectious Diseases, University of Texas Southwestern Medical Center, Dallas, Texas

Immunologic Development and Susceptibility to Infection

Deanna A. Sutton PhD, Professor of Pathology, University of Texas Health Science Center at San Antonio, San Antonio, Texas

Classification of Fungi; *Agents of Hyalohyphomycosis and Phaeohyphomycosis*; *Agents of Mucormycosis*; *Malassezia Species*; *Sporothrix schenckii Complex*

(Sporotrichosis)

Douglas Swanson MD, Associate Professor of Pediatrics, University of Missouri-Kansas City School of Medicine; Attending Physician, Pediatric Infectious Diseases, Children's Mercy Hospital Kansas City, Kansas City, Missouri

Chronic Meningitis

Jacqueline E. Tate PhD, Epidemiologist, Division of Viral Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Astroviruses

Marc Tebruegge DTM&H, DLSHTM, MRCPCH, MSc, FHEA, MD, PhD

Honorary Clinical Senior Lecturer, Department of Paediatrics, The University of Melbourne, Parkville, Victoria, Australia;
NIHR Clinical Lecturer in Paediatric Infectious Diseases & Immunology, Faculty of Medicine, The University of Southampton, Southampton, United Kingdom

Infections of the Upper and Middle Airways;
Mycobacterium Nontuberculosis Species

Eyasu H. Teshale MD, Medical Epidemiologist, Division of Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, Georgia

Hepatitis E Virus

Amelia B. Thompson MD, MPH, Clinical Fellow, Division of Pediatric Infectious Diseases, Emory University School of Medicine, Atlanta, Georgia

Trypanosoma Species (Trypanosomiasis)

George R. Thompson III, MD, Associate Professor of Medicine, Department of Medical Microbiology and Immunology, Division of Infectious Diseases, University of California Davis, Davis, California

Cryptococcus Species; Coccidioides immitis and Coccidioides posadasii (Coccidioidomycosis)

Robert Thompson-Stone MD, Assistant Professor of Neurology and Pediatrics, University of Rochester School of Medicine and Dentistry, Division of Neurology, Golisano Children's Hospital, Rochester, New York

Neurologic Symptom Complexes

Richard B. Thomson Jr., PhD, D(ABMM), Clinical Professor of Pathology, The University of Chicago Pritzker School of Medicine; Division Head of Clinical Pathology, Medical Microbiologist and Director, Microbiology Laboratories, Department of Pathology, NorthShore University HealthSystem, Chicago, Illinois

Nocardia Species

Emily A. Thorell MD, MSCI, Assistant Professor of Pediatrics, University of Utah; Attending Physician, Pediatric Infectious Diseases, Director, Antimicrobial Stewardship Program, Associate Hospital Epidemiologist, Primary Children's Hospital, Salt Lake City, Utah

Cervical Lymphadenitis and Neck Infections

Nicole H. Tobin MD, Adjunct Associate Professor of Pediatrics, David Geffen School of Medicine at The University of California Los Angeles, Los Angeles, California

Immunopathogenesis of HIV-1 Infection

Philip Toltzis MD, Professor of Pediatrics, Case Western Reserve University School of Medicine; Department of Critical Care Medicine, Rainbow Babies and Children's Hospital, Cleveland, Ohio

Staphylococcus epidermidis and Other Coagulase-Negative Staphylococci

James Treat MD, Associate Professor of Clinical Pediatrics and

Dermatology, The Perelman School of Medicine at the University of Pennsylvania; Fellowship Director, Pediatric Dermatology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

Vesicles and Bullae

Stephanie B. Troy MD, Medical Officer, Center for Drug Evaluation and Research, Division of Antiviral Products, United States Food and Drug Administration, Silver Spring, Maryland

Polioviruses

Russell B. Van Dyke, MD, Professor of Clinical Pediatrics, Section of Infectious Diseases, Tulane Health Sciences Center, New Orleans, Louisiana

Infectious Complications of HIV Infection

Louise Elaine Vaz MD, MPH, Assistant Professor of Pediatrics, Oregon Health & Science University, Portland, Oregon

The Systemic Inflammatory Response Syndrome (SIRS), Sepsis, and Septic Shock

Jennifer Vodzak MD, Assistant Professor of Pediatrics, University of Missouri-Kansas City School of Medicine; Division of Pediatric Infectious Diseases, Children's Mercy Hospital Kansas City, Kansas City, Missouri

Other Haemophilus Species and Aggregatibacter Species; *Fusobacterium Species*; *Laboratory Manifestations of Infectious Diseases*

Ellen R. Wald MD, Professor and Chair of Pediatrics, University of Wisconsin School of Medicine & Public Health; Physician-in-Chief, American Family Children's Hospital, Madison, Wisconsin

Mastoiditis; *Sinusitis*; *Preseptal and Orbital Infections*

Rebecca Wallihan MD, Department of Pediatrics, The Ohio State University College of Medicine; Physician, Division of Infectious Diseases, Nationwide Children's Hospital, Columbus, Ohio

Less Commonly Encountered Enterobacteriaceae

Zoon Wangu MD, Assistant Professor of Pediatrics, University of Massachusetts Medical School; Division of Pediatric Infectious Diseases and Immunology, UMass Memorial Children's Medical Center, Worcester, Massachusetts; Clinical Faculty, Ratelle STD/HIV Prevention Training Center, Massachusetts Department of Public Health, Boston, Massachusetts

Neisseria gonorrhoeae; Other Neisseria Species

Matthew Washam MD, MPH, Department of Pediatrics, The Ohio State University College of Medicine; Fellow, Pediatric Infectious Diseases, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

Giardia intestinalis (Giardiasis)

Joshua R. Watson MD, Department of Pediatrics, The Ohio State University College of Medicine; Physician, Division of Infectious Diseases, Nationwide Children's Hospital, Columbus, Ohio

Less Commonly Encountered Enterobacteriaceae

Rachel L. Wattier MD, MHS, Assistant Professor of Pediatrics, Division of Pediatric Infectious Diseases, University of California San Francisco, San Francisco, California

Antifungal Agents

Geoffrey A. Weinberg MD, FAAP, FIDSA, FPIDS, Professor of Pediatrics, University of Rochester School of Medicine and Dentistry; Director, Pediatric HIV Program, Division of Pediatric Infectious Diseases, Golisano Children's Hospital, Rochester, New York

Neurologic Symptom Complexes

A. Clinton White Jr., MD, Professor of Medicine, University of Texas Medical Branch, Galveston, Texas

Taenia solium, Taenia asiatica, and Taenia saginata:

Taeniasis and Cysticercosis; *Taenia Multiceps (multiceps) and Taenia serialis: Coenurosis*

Harold C. Wiesenfeld MD, Associate Professor of Obstetrics, Gynecology, and Reproductive Science Division, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Pelvic Inflammatory Disease

John V. Williams MD, Professor of Pediatrics, University of Pittsburgh School of Medicine; Chief, Division of Pediatric Infectious Diseases, Children's Hospital of Pittsburgh/UPMC, Pittsburgh, Pennsylvania

Human Metapneumovirus

Rodney E. Willoughby Jr., MD, Professor of Pediatrics, Medical College of Wisconsin; Division of Infectious Diseases, Children's Hospital of Wisconsin, Milwaukee, Wisconsin

Rabies Virus

Sarah L. Wingerter MD, Assistant Professor of Pediatrics, Boston University School of Medicine, Pediatric Emergency Medicine, Boston Medical Center, Boston, Massachusetts

Infection Following Trauma; *Infection Following Bites*

Robert R. Wittler MD, Professor of Pediatrics, Kansas University School of Medicine-Wichita; Consultant, Pediatric Infectious Diseases, Wesley Medical Center and Via Christi Medical Center, Wichita, Kansas

Persistent and Recurrent Pneumonia

Karen K. Wong MD, MPH, Medical Officer, Enteric Diseases Epidemiology Branch, Division of Foodborne, Waterborne, and Environmental Diseases, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Other Vibrio Species

Kimberly A. Workowski MD, Professor of Medicine, Division of Infectious Diseases, Emory University School of Medicine; Division of Sexually Transmitted Disease Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia

Skin and Mucous Membrane Infections and Inguinal Lymphadenopathy; *Trichomonas vaginalis*

Terry W. Wright PhD, Associate Professor of Pediatrics, Microbiology, and Immunology, University of Rochester School of Medicine and Dentistry, Rochester, New York

Pneumocystis jirovecii

Pablo Yagupsky MD, Professor of Pediatrics and Clinical Microbiology, Ben-Gurion University of the Negev; Director of Clinical Microbiology Laboratory, Soroka University Medical Center, Beer-Sheva, Israel

Kingella Species

Catherine Yen MD, MPH, Medical Officer, Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Rotaviruses

Jumi Yi MD, Assistant Professor of Pediatrics, Emory University School of Medicine; Attending Physician, Pediatric Infectious Diseases, Children's Healthcare of Atlanta, Atlanta, Georgia

Approach to the Diagnosis and Management of Gastrointestinal Tract Infections; *Campylobacter jejuni and Campylobacter coli*

Jonathan S. Yoder MSW, MPH, Medical Officer, Division of Foodborne, Waterborne, and Environmental Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Enteric Diseases Transmitted Through Food, Water, *and Zoonotic Exposures*

Edward J. Young MD, Professor of Medicine, Michael E. DeBakey VA Medical Center, Baylor College of Medicine, Houston, Texas

Brucella Species (Brucellosis)

Andrea L. Zaenglein MD, Professor of Dermatology and Pediatrics, Penn State/Hershey Medical Center, Hershey, Pennsylvania

Erythematous Macules and Papules

Kanecia Zimmerman MD, MPH, Assistant Professor of Pediatrics, Duke University School of Medicine; Department of Pediatrics, Duke University Medical Center, Duke Clinical Research Institute, Durham, North Carolina

Necrotizing Enterocolitis

[†] Deceased.

[†] Deceased.

PART I

Understanding, Controlling, and Preventing Infectious Diseases

OUTLINE

A Epidemiology and Control of Infectious Diseases
B Prevention of Infectious Diseases
C Host Defenses Against Infectious Diseases

A

Epidemiology and Control of Infectious Diseases

OUTLINE

1 Principles of Epidemiology and Public Health
2 Pediatric Healthcare Epidemiology
3 Infections Associated With Group Childcare
4 Infectious Diseases in Refugee and Internationally Adopted Children

1

Principles of Epidemiology and Public Health

Lucy A. McNamara, Stacey W. Martin

Epidemiology is the study of the distribution and determinants of disease or other health-related states or events in specified populations and the application of this study to the control of health problems.[1] The key component of this definition is that epidemiology focuses on populations, an emphasis that distinguishes epidemiology from clinical case studies, which focus on individual subjects.

Health events can be characterized by their distribution (descriptive epidemiology) and by factors that influence their occurrence (analytic epidemiology). In both descriptive and analytic epidemiology, health-related questions are addressed using quantitative methods to identify patterns or associations from which inferences can be drawn and interventions developed, applied, and assessed.

Descriptive Epidemiology

Surveillance

The goals of descriptive epidemiology are to define the frequency of health-related events and determine their distribution by person, place, and time. The foundation of descriptive epidemiology is surveillance, or case detection. Retrospective surveillance identifies health events from existing data, such as clinical or laboratory records, hospital discharge data, and death certificates. Prospective surveillance identifies and collects information about cases as they occur, for example, through ongoing laboratory-based reporting.

With *passive surveillance,* case reports are supplied voluntarily by clinicians, laboratories, health departments, or other sources. The completeness and accuracy of passive reporting are affected by whether reporting is legally mandated, whether a definitive diagnosis can be established, illness severity, interest in and awareness of the medical condition among the public and the medical community, and whether a report will elicit a public health response. Because more severe illness is more likely to be diagnosed and reported, the severity and clinical spectrum of passively reported cases are likely to differ from those of all cases of an illness. Passively collected reports of nationally notifiable diseases are tabulated in the *Morbidity and Mortality Weekly Report* (http://www.cdc.gov/mmwr/).

In *active surveillance,* an effort is made to ascertain all cases of a condition occurring in a defined population. Active case finding can be prospective (through routine contacts with reporting sources), retrospective (through record audit), or both. Population-based active surveillance, in which all cases in a defined geographic area are identified and reported, provides the most complete and unbiased ascertainment of disease and is optimal for describing the rate of a disease and its clinical spectrum. By contrast, active surveillance conducted at only one or several participating facilities can yield biased information on disease frequency or spectrum based on the representativeness of the patient population and the size of the sample obtained.

Case Definition

Establishing a standard case definition is an important first step for surveillance and description of the epidemiology of a disease or health event.[2] Formulation of a case definition is important, particularly when laboratory diagnostic testing results are not definitive. More restrictive case definitions minimize misclassification, but they can exclude true cases and are most useful when investigating a newly recognized condition, in which the ability to determine etiology, pathogenesis, or risk factors is decreased by inclusion of noncases in the study population. A more inclusive definition can be important in an outbreak setting to detect potential cases for further investigation or when preventive interventions can be applied. Multiple research or public health objectives can be addressed by developing a tiered case definition that incorporates varying degrees of diagnostic certainty for definite and probable cases.

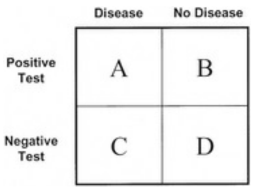
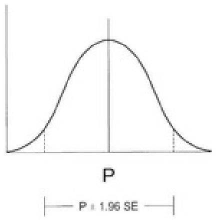
Sensitivity, Specificity, and Predictive Value

Sensitivity, specificity, and predictive values can be used to quantify the performance of a case definition or the results of a diagnostic test or algorithm (Table 1.1). Unlike sensitivity and specificity, predictive values vary with the prevalence of a condition within a population. Even with a highly specific diagnostic test, if a disease is uncommon among those people tested, a large proportion of positive test results will be false positive, and the positive predictive value will be low (Table 1.2). If the test is applied more selectively such that the proportion of people tested who truly have disease is greater, the test's predictive value will be improved. Thus, sensitivity and specificity are characteristics of the test, whereas predictive values depend both on test sensitivity and specificity and on the disease prevalence in the population in which the test is applied. Often, the sensitivity and specificity of a test are inversely related. Selecting the optimal balance of sensitivity and specificity depends on the purpose for which the test is used. Generally, a screening test should be highly sensitive, whereas a follow-up confirmatory test should be highly specific.

TABLE 1.1

Definitions and Formulas for the Calculation of Important Epidemiologic Parameters

Measures of test	*Sensitivity:* Proportion of	A/(A + C)	

accuracy	true positive (diseased) with a positive test result		 Disease No Disease Positive Test Negative Test A B C D
	Specificity: Proportion of true negative (nondiseased) with a negative test result	D/(B + D)	
	Positive predictive value (PPV): Proportion of positive test results that are true positives	A/(A + B)	
	Negative predictive value (NPV): Proportion of negative test results that are true negatives	D/(C + D)	
Measures of data dispersion and precision	*Variance:* Statistic describing variability among individual members of a population	$[1/(n-1)]\left[(x_1-\bar{x})^2+(x_2-\bar{x})^2+\ldots+(x_n-\bar{x})^2\right]$	
	Standard error (SE): Statistic describing the variability of sample-based point estimates (P) around the true population value being estimated	$\sqrt{\text{Variance}}$	
	Confidence interval: A range of values that is believed to contain the true value within a defined level of certainty	—	

	(usually 95%)		

TABLE 1.2

Positive and Negative Predictive Values for a Hypothetical Diagnostic Test Having a Sensitivity of 90% and a Specificity of 90%

Proportion With Condition	Positive Predictive Value	Negative Predictive Value
1%	8%	>99%
10%	50%	99%
20%	69%	97%
50%	90%	90%

Incidence and Prevalence

Characterizing disease frequency is one of the most important aspects of descriptive epidemiology. Frequency measures typically include a count of new or existing cases of disease as the numerator and a quantification of the population at risk as the denominator. *Cumulative incidence* is expressed as a proportion and describes the number of new cases of an illness occurring in a fixed at-risk population over a specified period of time, generally 1 year unless otherwise stated. *Incidence density* is the rate of new cases of disease in a dynamic at-risk population; the denominator typically is expressed as the population-time at-risk (e.g., person-time).

Because the occurrence of many infections varies with season, extrapolating annual incidence from cases detected during a short observation period can be inaccurate. In describing the risk of acquiring illness during a disease outbreak, the *attack rate,* defined as the number of new cases of disease occurring in a specified population and time period, is a useful measure. Finally, the *case-fatality rate*, or proportion of cases of a disease that result in death, is used to quantify the mortality resulting from a disease in a particular population and time period.

Prevalence refers to the proportion of the population having a condition at a specific point in time. As such, it is a better measure of disease burden for chronic conditions than is incidence or attack rate, which identify only new (incident) cases. Prevalent cases of disease can be ascertained in a cross-sectional survey, whereas determining incidence requires longitudinal surveillance. When disease prevalence (P) is low and incidence (I) and duration (D) are stable, prevalence is a function of disease incidence multiplied by its average duration ($P = I \times D$).

Describing Illness by Person, Place, and Time

Characterizing disease by person, place, and time is often useful. Demographic variables, including age, sex, socioeconomic status, and race or ethnicity, often are associated with the risk of disease. Describing a disease by place can help define risk groups, for example, when an illness is caused by an environmental exposure or is vector borne, or during an outbreak with a point source exposure. Time also is a useful descriptor of disease occurrence. Evaluating longterm (secular) trends provides information that can be used to identify emerging health problems or to assess the impact of prevention programs. The timing of illness in outbreaks can be displayed in an epidemic curve and can be useful in defining the mode of transmission of an infection or its incubation period and in assessing the effectiveness of control measures.

Analytic Epidemiology

Study Design

The goal of analytic studies is to identify predictors of an outcome. This goal can be addressed in experimental or epidemiologic (observational) studies. In addition, ecologic or trend studies can be used to assess predictors when the frequency or distribution of an outcome has changed over time or differs among populations.

In *experimental studies,* hypotheses are tested by systematically allocating an exposure of interest to subjects in separate groups to achieve the desired comparison. Such studies include randomized, controlled, double-blind treatment trials, as well as laboratory experiments. By carefully controlling study variables, investigators can restrict differences among groups and thereby increase the likelihood that the observed differences are a consequence of the specific factor being studied. Because experiments are prospective, the temporal sequence of exposure and outcome can be established, making it possible to define cause and effect.

By contrast, *epidemiologic studies* test hypotheses using observational methods to assess exposures and outcomes among individual subjects in populations and to identify statistical associations from which inferences regarding causation are drawn. Although observational studies cannot be controlled to the same degree as experiments, they are practical in circumstances in which exposures or behaviors cannot be assigned. Moreover, the results often are more generalizable to a real population having a wide range of attributes. The 3 basic types of observational studies are cohort studies, cross-sectional studies, and case-control studies (Table 1.3). Hybrid study designs, incorporating components of these 3 types, also have been developed.[3] In planning observational studies, care must be taken in the selection of participants to minimize the possibility of bias. Selection bias results when study subjects have differing probabilities of being selected and the probability of selection is related to the risk factors or outcomes under evaluation.

TABLE 1.3

Types of Observational Studies and Their Advantages and Disadvantages

Type of Study	Design and Characteristics	Advantages	Disadvantages
Cohort	Prospective or retrospective	Ideal for outbreak investigations in defined populations	Unsuited for rare diseases or those with long latency
	Select study group	Prospective design ensures that exposure preceded disease	Expensive
	Observe for exposures and disease	Selection of study group is unbiased by knowledge of disease status	Can require long follow-up periods
	Outcome measures used: Relative risk (RR) or hazard ratio (HR) of disease given exposure	RR and HR accurately describe risk given an exposure	Difficult to investigate multiple exposures
Cross-sectional	Nondirectional	Rapid, easy to perform, and inexpensive	Timing of exposure and disease can be difficult to determine
	Select study group	Ideal to determine knowledge, attitudes, and behaviors	Biases can affect recall of past exposures
	Determine exposure and disease status		
	Outcome measures used:		

	Prevalence ratio for disease given exposure		
Case-control	Retrospective	Rapid, easy to perform, and inexpensive	Timing of exposure and disease can be difficult to determine
	Identify cases with disease	Ideal for studying rare diseases, those with long latency, new diseases	Biases can occur in selecting cases and controls and determining exposures
	Identify controls without disease		OR only provides an estimate of the RR if disease is rare
	Determine exposures in cases and controls		
	Outcome measures used: Odds ratio (OR) for an exposure given disease		

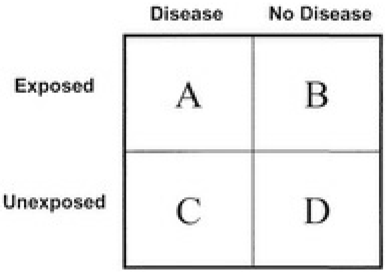
In contrast to experimental or observational studies that analyze information about individual subjects, *ecologic studies* draw inferences from data on a population level. Inferences from ecologic studies must be made with caution because populations differ in multiple ways and because relationships observed on a population level do not necessarily apply on the individual level (a problem known as the *ecologic fallacy*). Because of these drawbacks, ecologic studies are suited best for generating hypotheses that can be tested using other study methods.

Cohort Studies

In a *cohort study,* subjects are categorized based on their exposure to a suspected risk factor and are observed for the development of disease. Associations between exposure and disease are expressed by the *relative risk* of disease, or *risk ratio,* in exposed and unexposed groups (Table 1.4). Cohort studies typically are prospective, with exposure defined before disease occurs. However, cohort studies also can be retrospective, in which the cohort is selected after the outcome has occurred. In this case, exposures are determined from existing records that preceded the outcome, and thus the directionality of the exposure-disease relationship is still forward. Characterizing exposures before development of disease is a major benefit of cohort studies because this approach minimizes selection bias and simplifies inference of cause and effect. Another advantage of cohort studies is that they can be used to assess multiple potential outcomes resulting from an exposure. However, in a cohort study it can be difficult to investigate multiple exposures as risk factors for a single outcome. Cohort studies also are impractical for studying rare diseases or conditions with a long latent period between exposure and the onset of clinical illness. In general, cohort studies are unsuited for investigating risk factors for new or rare diseases or for generating new hypotheses about possible exposure-disease relationships.

TABLE 1.4

Measures of Association, Risk, and Impact

Absolute measures of association and risk	*Absolute risk reduction* (ARR), *excess risk*, or *attributable risk:* Difference in the incidence of the outcome between exposed and unexposed	(A/(A + B)) – (C/(C + D))	 Disease No Disease Exposed A B Unexposed C D
	Number needed to treat (NNT): Number of individual subjects who must receive an intervention (or exposure) to prevent one negative outcome	1/ARR	
Relative measures of association and risk	*Relative risk* or *risk ratio* (RR): Risk (probability) of a health event in those with a given exposure divided by the risk in those without the exposure	$\frac{A/(A+B)}{C/(C+C)}$	
	Odds ratio (OR): Odds of a given exposure among those with a health event divided by odds of exposure among those without the health event	AD/BC	
Measure of impact	*Population attributable fraction:* The proportion of	$[P_e\ (RR-1)]/[1 + P_e\ (RR-1)]$ [Proportion exposed, P_e = (A	

	disease in a population that results from the specific exposure	+ B)/(A + B + C + D)]	
	Vaccine efficacy (VE): The percentage of reduction in incidence of a disease among persons who have received a vaccine compared with the incidence in persons who have not received the vaccine	(1 − RR) × 100 or (1 − OR) × 100	

Cohort studies provide data not only on whether an outcome occurs but also, for those experiencing the outcome, on when it occurs. Analysis of time-to-event data for outcomes such as death or illness is a powerful approach to assess or compare the impacts of preventive or therapeutic interventions. The probability of remaining event-free over time can be expressed in a *Kaplan-Meier survival curve* where the event-free probability is initially 1 and declines in a step-function as the outcomes of interest occur (Fig. 1.1A). Time-to-event data also can be displayed as the *cumulative hazard* of an event occurring among members of a cohort that increases from 0 at enrollment (Fig. 1.1B). These 2 approaches are related in that the hazard reflects the incident event rate, whereas survival reflects the cumulative nonoccurrence of that outcome.[4,5] With time-to-event analysis, the association between exposure and disease often is expressed as a hazard ratio. Like relative risk, hazard ratio is a comparative measure of risk between exposed and unexposed groups. The primary difference is that the hazard ratio compares event experience over the entire time period, whereas the relative risk compares event occurrence only at the study endpoint.[6]

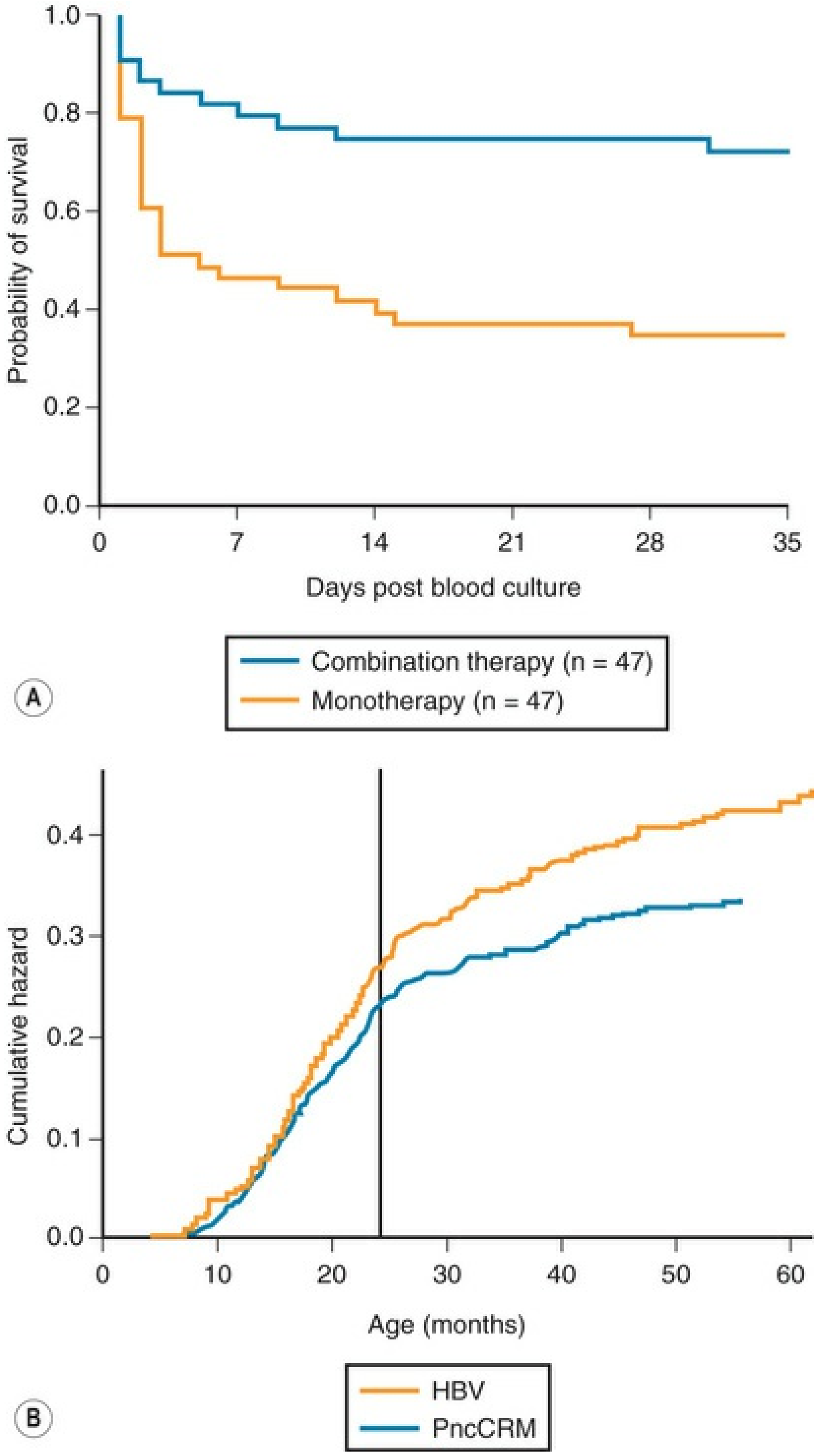


FIGURE 1.1 **Example of Kaplan-Meier and cumulative hazard curves. (A) Survival plot for critically ill patients with *Streptococcus pneumoniae* bacteremia treated with monotherapy or combination therapy. (B) Cumulative hazard of tympanostomy tube placement from 2 months until 4 to 5 years of age in children who received pneumococcal conjugate vaccine (PncCRM) or a control vaccine (hepatitis B vaccine [HBV]).** **([A] Redrawn from Baddour LM, Yu VL, Klugman KP, et al. Combination antibiotic therapy lowers mortality among severely ill patients with pneumococcal bacteremia. Am J Respir Crit Care Med 2004;170:440–444. [B] Redrawn from Palmu AAI, Verho J, Jokinen J, et al. The seven-valent pneumococcal conjugate vaccine reduced tympanostomy tube placement in children. Pediatr Infect Dis J 2004;23:732–738.)**

Cross-Sectional Studies

In a *cross-sectional study,* or survey, a sample is selected, and at a single point in time exposures and outcome are determined. Outcomes can include disease status or behaviors and beliefs, and multiple exposures can be evaluated as explanations for the outcome. Associations are characterized by the *prevalence ratio*, similar to the risk ratio in cohort studies. Because neither exposures nor outcomes are used in selection of the study group, prevalence is an estimate of that in the overall population from which the sample was drawn. National survey data characterizing health status, behaviors, and medical care are available from the National Center for Health Statistics (http://www.cdc.gov/nchs/index.htm).

Case-Control Studies

In a *case-control study,* the investigator identifies a group of people with a disease or outcome of interest (cases) and compares their exposures with those in a selected group of people who do not have disease (controls). Differences between the groups are expressed by an *odds ratio,* which compares the odds of an exposure in case and control groups (see Table 1.4). The odds ratio is not the same as a risk ratio; however, it provides an estimate of the risk ratio if the disease or outcome in question is rare. Case-control studies are retrospective in that disease status is known and serves as the basis for selecting the 2 comparison groups; exposures are then determined by reviewing available records or by interview.

A major advantage of case-control studies is their efficiency in studying uncommon diseases or diseases with a long latency. Case-control studies also can evaluate multiple exposures that may contribute to a single outcome; study subjects frequently can be identified from existing sources (e.g., hospital or laboratory records, disease registries, or surveillance reports) and, after identification of suitable control subjects, data on previous exposures can be collected rapidly. Case-control studies also have several drawbacks. Bias can be introduced during selection of cases and controls and in determining exposures retrospectively, and inferring causation from statistically significant associations can be complicated by difficulty in determining the temporal sequence of exposure and disease.

Causal Inference and the Impact of Bias

The impact of potential bias is particularly important in observational studies. The *validity* of a study is the degree to which inferences drawn from a study are warranted. *Internal validity* refers to the correctness of study conclusions for the population from which the study sample was drawn, whereas *external validity* refers to the extent to which the study results can be generalized beyond the population sampled. The validity of a study can be affected by bias, or *systematic error,* in selecting the study participants (sampling), in ascertaining their exposures, or in analyzing and interpreting study data. For errors to result in bias, they must be systematic, or directional. *Nonsystematic error* (random misclassification) decreases the ability of a study to identify a true association but does not result in detection of a spurious association.

Several sources of bias can occur in selection of study participants (Box 1.1).[7] *Diagnosis bias* results when persons with a given exposure are more likely to be diagnosed as having disease than are people without the exposure; this can occur because diagnostic testing is more likely to be done or because the interpretation of a test may be affected by knowledge of exposure status. For hospital-based studies, differential referral also can bias selection of a study sample. This bias would occur if, for example, the frequency of an exposure varied with socioeconomic status and a hospital predominantly admitted persons from either a high-income group or a low-income group. Bias also can occur when eligible subjects refused to participate in a study as cases or controls.

Box 1.1

Potential Sources of Bias in Observational Studies[a]

Bias in Case Ascertainment and Case/Control Selection

Surveillance bias: differential surveillance or reporting for exposed and unexposed

Diagnosis bias: differential use of diagnostic tests in exposed and unexposed

Referral bias: differential admission to hospital based on an exposure or a variable associated with exposure

Selection bias: differential sampling of cases based on an exposure or a variable associated with exposure

Nonresponse bias: differential outcome or exposures of responders and nonresponders

Survival bias: differential exposures between those who survive to be included in a study and those who die following an illness

Misclassification bias: systematic error in classification of disease status

Bias in Estimation of Exposure

Recall bias: differential recall of exposures based on disease status

Interviewer bias: differential ascertainment of exposures based on disease status

Misclassification bias: systematic errors in measurement or classification of exposure

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[a] A more complete listing is provided by Sackett.[7]

Determination of exposures can be affected by several types of bias. Recall of exposures can be different for persons who have had an illness compared with people who were well. This bias occurs in either direction: patients may be more likely to remember an exposure that they associate with their illness (e.g., what was eaten before an episode of diarrhea) or less likely to recall an exposure if a severe illness affected memory. Interviewers can introduce bias by questioning cases and controls differently about their exposures. Misclassification of exposures can result from errors in measurement such as can occur with the use of an inaccurate laboratory test. Although systematic misclassification can result in bias, misclassification of exposure often is random rather than systematic.

Even a carefully designed study that minimizes potential biases can lead to erroneous causal inferences. An exposure can falsely appear to be associated with disease because it is closely linked to the true, but undetermined, risk factor. Race often is found to be associated with the risk of a disease, whereas the true risk factor may be an unmeasured variable that is linked to race, such as socioeconomic status. The risk of making incorrect inferences can be minimized by considering certain general criteria for establishing causation. These criteria include the strength of an association, the presence of a dose-response effect, a clear temporal sequence of exposure to disease, the consistency of findings with those of other studies, and the biologic plausibility of the hypothesis.[8]

Statistical Analysis

Characteristics of Populations and Samples

Whereas epidemiologic analysis seeks to make valid conclusions about populations, the entire population rarely is included in a study. An assumption underlying statistical analysis is that the sample evaluated was selected randomly from the population. Often, this criterion is not met and calls into question the appropriateness and interpretation of statistical analyses.

The mean, median, and mode describe central values for samples and populations. The arithmetic *mean* is the average, determined by summing individual values and dividing by the sample size. When data are not normally distributed (skewed), calculation of a geometric mean can limit the impact of outlying values. The geometric mean is calculated by taking the nth root of the *product* of all the individual values, where n is the total number of individual values. For example, immunogenicity of vaccines is usually expressed by the geometric mean titer. The *median,* or middle value, is another way to describe nonnormally distributed data. The *mode,* or most commonly occurring value in a sample, rarely is used.

Several measures can be used to describe the variability in a sample. The *range* describes the difference between the highest and lowest value, whereas the *interquartile range* defines the difference between the 25th and 75th percentiles. Variation among individual elements most often is characterized by the variance or standard deviation. The *variance* is the mean of the squared deviation of each observation from the sample's mean. The *standard deviation* is the square root of the variance (see Table 1.1). For a normally distributed population, 68% of values fall within 1 standard deviation of the mean, and 95% of values fall within 1.96 standard deviations. The *standard error* represents a type of standard deviation and is used to describe the standard deviation of an estimate (e.g., mean, odds ratio, relative risk).

When analyzing a sample, the mean or other statistics describing the sample represent a *point estimate* of that parameter for the entire population. If another random sample were drawn from the same population, the point estimate for the parameter of interest likely would be different, depending on the variability in the population and the sample size selected. A *confidence interval* defines a range of values that includes the true population value, within a defined level of certainty. Most often, the 95% confidence interval is presented (see Table 1.1).

Absolute and Relative Measures of Association

Measures of association are used to assess the strength of an association between an exposure and an outcome. In a cohort study, the *absolute risk reduction* (also known as *excess risk, attributable risk,* or *risk difference*) is the difference in the incidence of the outcome between exposed and unexposed subjects. The *number needed to treat* (NNT) is a measure of the number of individual subjects who must receive a treatment to prevent a single negative outcome and is calculated as the reciprocal of the *absolute risk reduction*. In addition to absolute measures, relative measures also are useful for describing the strength of an association. In a cohort study or survey, the relative risk or risk ratio compares the risk of disease for subjects with versus subjects without an exposure (see Table 1.4). In case-control studies, association is assessed by the odds ratio, which compares the odds of exposure among subjects with and without a disease or health outcome; when disease is uncommon (<10%) in both exposed and unexposed groups, the odds ratio approximates the relative risk. For time-to-event analyses, the comparative risk is expressed as the *hazard ratio.* Odds ratios, relative risks, and hazard ratios greater than 1 signify increased risk given exposure, and values less than 1 suggest that exposure decreases the risk of an outcome. Because observational studies generally do not include all members of a population, these measures of association represent an estimate of the true value within the entire population. Statistical analyses can help guide investigators in making causal inferences based on point estimates of these measures of association.

Statistical Significance

Statistical tests are applied to assess the likelihood that the study results were obtained by chance alone rather than representing a true difference within the population. Most investigators consider a P value <0.05 as being *statistically significant*, indicating a less than 5% risk that the observed association is the result of chance alone (designated a *type I error*, the probability of which is the *alpha level*). Although use of this cutoff for significance testing has become conventional, ignoring higher P values can lead to missing a real and important association, whereas blind faith in the significance of lower P values can lead to erroneous conclusions. Statistical testing should contribute to, but not replace, criteria for evaluating possible causation.

Statistical significance also can be defined based on 95% confidence intervals, which approximately correspond to a P value of 0.05. An odds ratio, relative risk, or hazard ratio is considered statistically significant if the 95% confidence interval does not include 1. An advantage of using confidence intervals to define statistical significance is that they provide information on whether a finding is statistically significant and on the possible range of values for the point estimate in the population, with 95% certainty.

One pitfall in interpreting statistical significance is ignoring the *magnitude* of an effect in favor of its "significance." A very large study can identify as significant a small, perhaps trivial, difference among study groups. Some epidemiologists have proposed that, despite statistical significance, odds ratios less than 2 or 3 in an observational study should not be interpreted because unidentified bias or confounding could have accounted for a difference of this magnitude.[9] Conversely, the relative risk or odds ratio associating an exposure and outcome can be large, but if the exposure is uncommon in both groups, it cannot explain most cases of illness. The public health importance of an exposure can be described by the *population-attributable fraction*, or the proportion of the disease in a population that is related to the exposure of interest.

Sample Size

A study can fail to identify a true risk factor as statistically significant because the sample size was too small (designated a *type II error,* the probability of which is the *beta level*). Statistical power is defined as 1 − β and is the complement of type II error; that is, power is the probability of correctly identifying a difference of specified size among groups, if such a difference truly exists. The problem of inadequate sample size in clinical studies was highlighted in an analysis of “negative” randomized controlled trials reported in 3 leading medical journals between 1975 and 1990. Of 70 reports, only 16% and 36% had sufficient statistical power (80%) to detect a true 25% or 50% relative difference, respectively, among treatment groups.[10]

In calculating sample sizes for testing hypotheses, investigators must select type I and type II errors and define the magnitude of the difference that is deemed clinically important. Often, the type II error is set at 0.2, indicating acceptance of a 20% likelihood that a true difference exists but would not be identified by the study. Sample size calculations can be performed using a range of computer software. The program Epi-Info can be used to perform sample size calculations as well as other statistical functions and is available at no charge from the Centers for Disease Control and Prevention (www.cdc.gov/epiinfo/).

Ensuring an adequate sample size is particularly important for studies attempting to prove *equivalence* or *noninferiority* of a new treatment compared with standard therapy. Food and Drug Administration guidance recommends that noninferiority trials adopt a null hypothesis that a difference exists among treatments; this hypothesis is rejected if the lower 95% confidence limit for the new treatment is within a specified margin of the point estimate for standard therapy. Because the null hypotheses can never be proven or accepted, the failure to reject a null hypothesis of no difference among treatments or exposure does not prove equivalence. The importance of this distinction is illustrated by an analysis of 25 studies claiming equivalence of therapies for pediatric bacterial meningitis. Twenty-three studies claimed equivalence based on a failure to detect a significant difference among treatment groups.

However, only 3 of these trials could exclude a 10% difference in mortality, thus showing that many studies potentially missed a clinically significant difference.[11]

In some situations, an investigator would want to detect a significant difference among study groups as soon as possible, for example, when a therapeutic or preventive intervention could be applied once a risk group is identified or when concerns exist about the safety of a drug or vaccine. One approach to this situation is to include in the study design an *interim analysis* after a specified number of subjects are evaluated. Because the likelihood of identifying chance differences as significant increases with the number of analyses, it is recommended that the threshold for defining statistical significance should become more stringent as the number of planned analyses increases.[12] If each interim analysis can lead the investigators to stop the trial, this study design is considered a group sequential method.[13] Another example of a group sequential design is when concordance or discordance in outcome is tabulated for each matched set exposed to alternate treatments. Results for each set are plotted on a graph, and data collection continues until a preset threshold for a significant difference among study groups is crossed or no significant difference is detected at a given power.[12]

Statistical Inference

Statistical testing is used to determine the significance of differences among study groups, and thus it provides guidance on whether to accept or reject the null hypothesis. Although providing details of specific statistical tests is outside the scope of this chapter, Table 1.5 gives examples of statistical tests that can be applied in analyzing different types of exposure and outcome variables.

TABLE 1.5

Types of Statistical Tests Used to Evaluate the Significance of Associations Among Categorical and Continuous Variables

Independent Variable (Exposure, Risk Factor)	**Dependent Variable (Disease, Outcome)**	
	Categorical and Dichotomous	**Continuous**
CATEGORICAL		
Dichotomous	Chi-square test	Student t-test (parametric)

	Fisher exact test	Wilcoxon rank sum test (nonparametric)
>2 categories	Chi-square test	Analysis of variance (parametric)
		Kruskal-Wallis test (nonparametric)
CONTINUOUS		
	Logistic regression	Linear regression
		Correlation (Pearson: parametric; Spearman: nonparametric)

Using appropriate analytic and statistical methods is important in identifying significant predictors of an outcome (i.e., risk factors) correctly. *Confounding variables* are associated with the disease of interest and with other exposure variables that are associated with the disease and are not part of the causal pathway (Fig. 1.2). For example, if recent antimicrobial use is associated with childcare attendance, failure to adjust for recent antimicrobial use as a confounding variable could result in overestimating the relationship between childcare and antibiotic-resistant pneumococcal carriage. *Effect modifiers* interact with risk factors to affect their impact on outcome but may or may not themselves affect outcome. Frequently, age is an effect modifier, with an exposure associated significantly with an outcome in one age group but not in another.

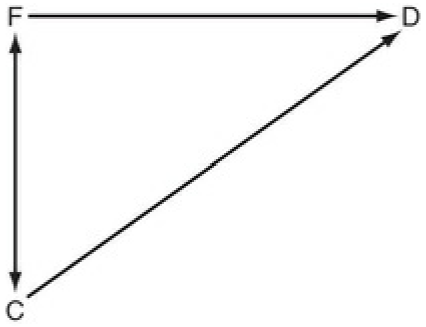

FIGURE 1.2 Path diagram illustrating associations among a confounding variable (*C*), another risk factor (*F*), and the disease outcome (*D*).

Several approaches are used to control for confounding variables and effect modifiers. In study design, an extraneous variable can be controlled for by randomization, restricting sampling to one category of the variable or by *frequency matching* to obtain similar proportions of cases and controls in each stratum of the variable. A more extreme form of matching is to select control subjects who are similar to individual cases for extraneous variables (e.g., age, sex, underlying disease) and to analyze whether exposures are concordant or discordant within matched sets. A newer approach to study design is the *case-crossover*[14] or *case series*[15] analysis. In this method, exposures occurring in a defined risk period before the outcome are compared with exposures occurring outside the risk window for the same individual subjects. This approach has been adapted to the study of adverse events after vaccination. If the vaccine causes the event, the rate of the event will be greater within a defined risk window than predicted by chance alone based on the expected distribution of the event.[16] The strength of this approach is that each subject, or case, serves as his or her own control, thereby decreasing confounding.

At the analysis stage, the impact of confounding variables and effect modifiers can be limited by performing a stratified analysis or using a multivariable model. In a *stratified analysis,* the possible association between a risk factor and an outcome is determined separately within different categories, or strata, of the extraneous variable. Stratum-specific estimates can be combined into a single estimate using an appropriate statistical test (e.g., a *Mantel-Haenszel odds ratio*). If a stratification variable is an effect modifier, the relative risk or odds ratio will differ substantially among the strata; for example, an exposure can be a strong risk factor in one age group but not another. In this setting, a summary statistic should not be presented, and results for each stratum should be presented separately. When the extraneous variable is confounding, an unstratified analysis can identify an exposure as a significant risk factor, whereas stratifying analysis by the confounding variable abolishes the apparent association in each stratum and indicates that the exposure is not an independent risk factor for disease.

Because stratified analyses become confusing rapidly as the number of strata increases, techniques of *mathematical modeling* have been developed that permit simultaneous control of multiple variables. Significant risk factors determined in a *multivariable model* are interpreted as each contributing independently and significantly to the outcome, thus controlling for confounding. Effect modification can be taken into account by including terms expressing the interaction between a risk factor and effect modifier in the model. Various multivariable models are appropriate for discrete, continuous, and time-dependent outcomes. A limitation of multivariable modeling is *multicollinearity,* which occurs when 2 or more explanatory variables of interest are highly correlated, and it can result in inaccurate measures of association and decreased statistical power. The risk of multicollinearity can be reduced by assessing correlations among potential risk factors and selecting which variables to include in the model. Various methods to identify and minimize multicollinearity have been developed.[17]

Vaccine Efficacy Studies

Most prelicensure efficacy studies are experimental, randomized, double-blind, controlled trials in which *vaccine efficacy* (VE) is calculated by comparing the attack rates (AR) for disease in the vaccinated and unvaccinated groups: $\text{VE (\%)} = (\text{AR unvaccinated} - \text{AR vaccinated}) / \text{AR unvaccinated}) \times 100$; or $(1 - \text{RR}) \times 100$.

After licensure, conducting controlled studies, which requires withholding vaccine from a control group, is no longer ethical. Therefore further studies of efficacy must be observational rather than experimental, by comparing persons who have chosen to be immunized with those who have not. In *case-control efficacy studies,* vaccination status of persons with disease is compared with vaccination status of healthy control subjects. The number of vaccinated and unvaccinated cases and controls is included in a 2×2 table, and vaccine efficacy is calculated as 1 minus the odds ratio: $\text{VE (\%)} = (1 - \text{OR}) \times 100$. When the proportion of cases vaccinated is less than the proportion of vaccinated controls, the odds ratio is <1, and the point estimate for efficacy indicates that immunization is protective. The precision of the estimate is expressed by the 95% confidence interval. A lower 95% confidence limit that is greater than 0% indicates statistically significant protection; often investigators set power of vaccine efficacy studies so that the expected lower confidence limit is much greater than 0 and consistent with meaningful levels of protection. The most important component of a case-control efficacy study is selecting control subjects who have the same opportunity for immunization as do cases. If cases have less opportunity to be immunized, results will be biased toward showing protection. Factors such as low socioeconomic status, which can increase the risk of disease and decrease the chance of being immunized, are potential confounding variables and can be controlled for by matching control subjects to cases for those factors.

Cohort studies also can be used to determine vaccine efficacy after licensure. A study design called the *indirect-cohort method* was developed by researchers at the Centers for Disease Control and Prevention to evaluate the efficacy of the pneumococcal polysaccharide vaccine by using data collected by disease surveillance.[18] The study cohort included persons identified with invasive pneumococcal infections. The study hypothesis was that if vaccine was protective, the proportion of vaccinated persons infected with pneumococcal serotypes that are included in the vaccine formulation would be less than the proportion of unvaccinated persons infected with vaccine-type strains. Vaccine efficacy was calculated from the relative serotype distributions overall and for each individual serotype. In a study of pneumococcal polysaccharide vaccine efficacy that used this approach, the point estimate of efficacy for preventing invasive infection was 57% (95% confidence interval, 45% to 66%)[19]; this estimate is similar to that obtained in a case-control efficacy study.[20]

Disease Control and Public Health Policy

Outbreak Investigations

Outbreak investigations require knowledge of disease transmission and use of descriptive and analytic epidemiologic tools. Possible outbreaks can be identified from surveillance data showing an increased rate of an infection or an unusual clustering of infection in person, place, and time. Comparing the incidence rate of disease with a baseline rate from a previous period is helpful in validating the occurrence of an outbreak. Other explanations for changes in the apparent rate of disease occurrence, such as diagnostic error, seasonal variations, and changes in reporting, must be considered. Using sensitive molecular methods to assess similarities among isolates from cases can be helpful in documenting that an apparent cluster of cases represents an outbreak because most outbreaks are caused by a single strain.

After establishing the presence of an outbreak, the next steps of an investigation are to develop a case definition, identify cases, and characterize the descriptive epidemiology. An *epidemic curve* depicts the number of cases over time and can provide information on possible transmission. In an outbreak with a *point source exposure,* an index case may be identified, with other cases occurring after an incubation period or at multiples of an incubation period (Fig. 1.3). Plotting the location of cases on a spot map can be helpful in determining possible exposures. Describing patients' characteristics can be important in identifying at-risk populations for further investigation or targeting control measures, as well as for developing hypotheses that can be investigated in an analytic study.

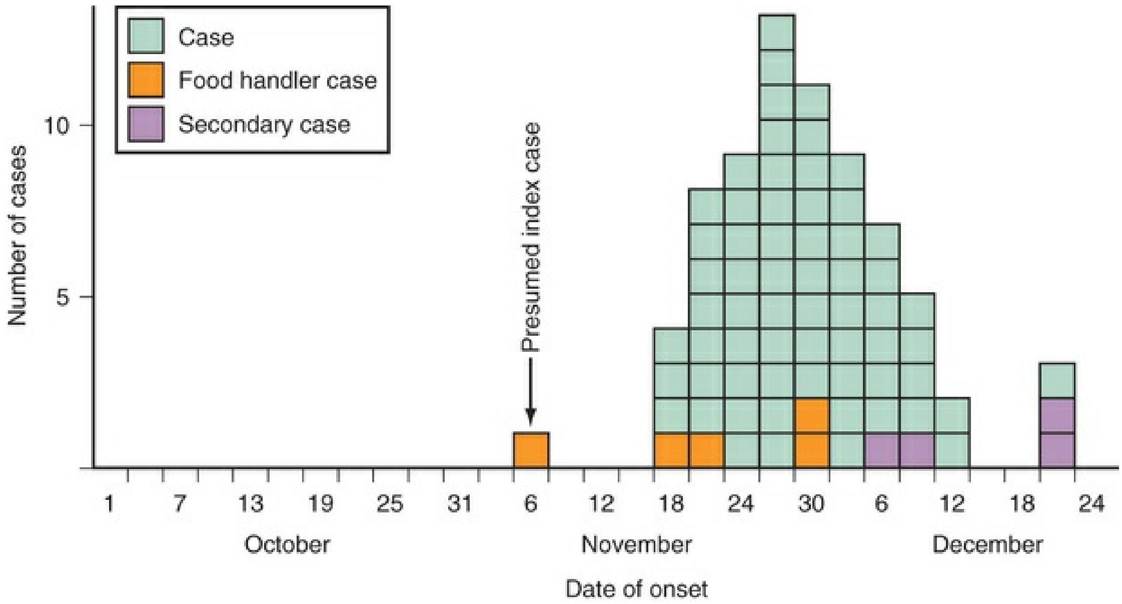

FIGURE 1.3 **Example of an epidemic curve for a common source outbreak with continuous exposure. Cases of hepatitis A by date of onset in Fayetteville, Arkansas, from November to December 1979.**

(From Centers for Disease Control and Prevention, unpublished data.)

Not all outbreaks can be traced to a point source exposure. Outbreaks and epidemics also can result from increased transmission of an *endemic* disease (i.e., a disease or condition that normally occurs in a specific population or area). In this situation it can be challenging to determine when an increase in disease constitutes an outbreak rather than a normal fluctuation in disease incidence. To determine whether an outbreak is occurring, the current incidence of the disease must be compared with the baseline disease incidence in that area. Often, no standard definition exists for when an increase in endemic disease incidence constitutes an outbreak or epidemic. For instance, in US pertussis epidemics the threshold for declaring an epidemic has varied by state. In California in 2010 and 2014, an epidemic was declared when the statewide case counts had reached 5 times the number of cases observed in a year with baseline pertussis incidence. By contrast, in Washington State in 2012, an epidemic was declared when the incidence of pertussis reached 2 standard deviations above the statewide 10-year average (Fig. 1.4).

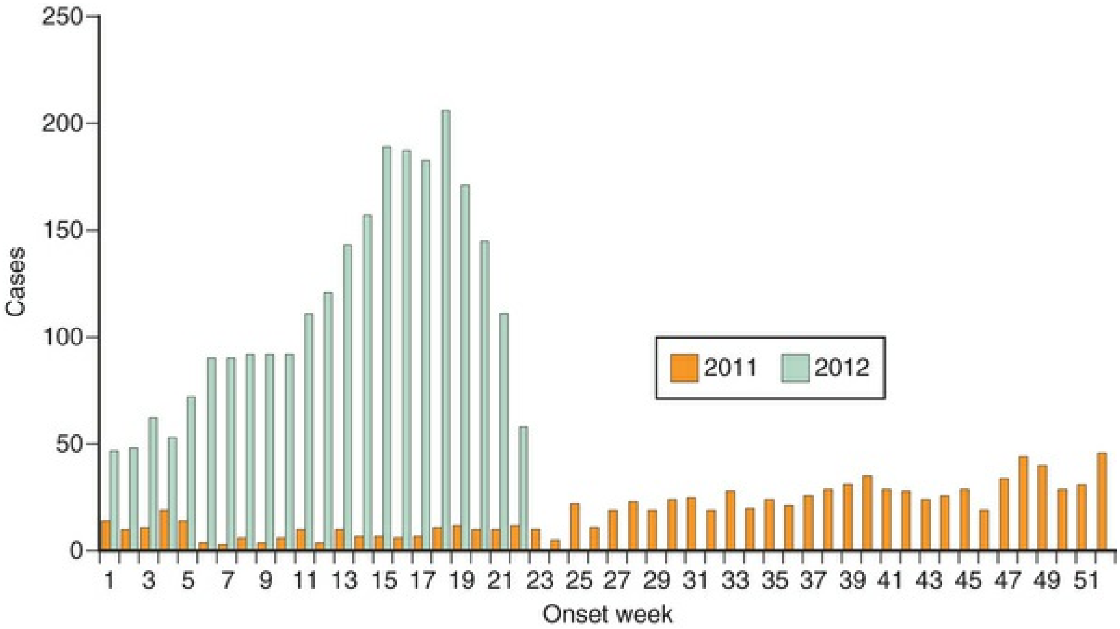

FIGURE 1.4 **Example of an epidemic curve for an epidemic of an endemic disease. Reported confirmed and probable pertussis cases by week of onset in Washington State, from January 1, 2011 to June 16, 2012.** (Redrawn from Centers for Disease Control and Prevention. Pertussis epidemic — Washington, 2012. MMWR Morb Mortal Wkly Rep 2012;61:517–522.)

Cohort studies are optimal for investigating outbreaks that occur in small, well-defined populations, including in schools, childcare settings, social gatherings, and hospitals. In populations that are not well defined, a case-control study is the most feasible approach. It is important to select control subjects who had an opportunity equal to that of cases for exposure to potential risk factors and development of disease. When the number of cases is relatively small, enrolling multiple control subjects per case increases the power of the study to find significant risk factors. After a standard questionnaire is administered, significant risk factors are determined by comparing exposures of cases and controls. The results of analyses can lead to inferences of causation and development of prevention and control strategies or to further hypotheses that can be evaluated later. The impact of intervention can be determined by ongoing surveillance and continued plotting of additional cases on the epidemic curve.

Impact and Economic Analysis of Disease Prevention

Assessing health and economic impacts of public health interventions is important in developing or supporting policy decisions. Health impacts can be expressed directly as cases of disease, deaths, and sequelae prevented. Vaccine efficacy is a specific example of the *prevented fraction* (PF), where $\mathrm{PF} = P\,(1 - \mathrm{RR})$, with P representing the proportion exposed to an intervention. Secondary measures of health impact include *years of potential life lost (YPLLs)* or *quality-adjusted life-years (QALYs)* lost, which quantify the impact of death, or death and disability, respectively, based on the age at which these events occur.[21] A measure of the efficiency of an intervention is the *number needed to treat,* which describes how many persons must be exposed to an intervention to avoid a single case of adverse health outcome.

Cost-effectiveness analyses determine the cost per health outcome achieved, such as the cost per death or complication averted, and it permits comparison of an intervention with other potential users of resources. In a cost-effectiveness formula, costs appear in the numerator, and health benefits appear in the denominator. The numerator includes expenditures for the prevention program from which cost savings occurring with disease prevention are subtracted. In addition to direct costs averted (e.g., savings from decreased medical care), indirect cost savings occur from increased productivity of people who do not become ill or miss time from work while receiving care or caring for ill family members. *Cost-utility* calculations are similar to cost-effectiveness but assess cost per quality-adjusted life-years saved or years of potential life lost averted.

Cost-benefit analyses differ from cost-effectiveness analyses in that the calculation is made entirely in economic terms. Health benefits are assigned an economic value, and expenditures are compared with savings. One problem with this approach lies in the difficulty of assigning an economic value to a health effect. For example, the value of a life saved may be quantified as the estimated value of a person's earnings over his or her lifetime, forgone earnings as a result of premature death, or by a standard amount; both economic and ethical issues can be raised by the choice of approach. Because the parameters used in economic analyses often are uncertain or based on limited data, and because choices made by the investigator (e.g., regarding the value of life) can be influential to the analysis, *sensitivity analyses* often are performed in which parameters are varied across a range of potential values. In addition to defining a range of possible economic outcomes, sensitivity analyses can identify the factors that most strongly influence the results, thus elucidating where further studies may be important.

Evaluating the Medical Literature

Steps in reviewing published medical research are shown in Box 1.2.[22] The ability to assess published studies carefully often is limited by the information presented in the report. To improve reporting of randomized controlled trials, a group of investigators and editors developed the Consolidated Standards of Reporting Trials (CONSORT)[23] (http://www.consort-statement.org/) and later extended these recommendations to reporting randomized trials of noninferiority and equivalences.[24] Reporting often still does not adhere to the quality standards proposed.[25,26] Although the guidelines refer to experimental rather than observational studies, most criteria apply to observational studies as well.

Box 1.2

Steps in the Critical Evaluation of Epidemiologic Literature

1. Consider the research hypothesis

2. Consider the study design

- Type of study

- Selection of study participants
- Selection and definition of outcome variables
- Selection and definition of exposure (predictor) variables
- Sample size and power

3. Consider the analysis

- Complete accounting of study subjects and outcomes
- Appropriateness of statistical tests
- Potential sources and impact of bias
- Potential impact of confounding and effect modification

4. Consider the interpretation of results

- Magnitude and importance of associations
- Study limitations
- Ability to make causal inferences

From Greenberg RS. Medical Epidemiology. Norwalk, CT, Appleton and Lange, 1993.

In assessing the medical literature, it is important to examine all published work on a particular topic rather than relying on a single report and to evaluate the strength of the combined evidence from these reports. One framework for evaluating the literature on a topic is the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, adopted by the US Advisory Committee on Immunization Practices (ACIP) in 2010 (www.cdc.gov/vaccines/acip/recs/GRADE/about-grade.html). In GRADE, the strength of evidence for the relationship between a particular intervention or exposure and an outcome is categorized into 4 hierarchical levels, from greatest to least[27]:

1. Randomized controlled trials, or overwhelming evidence from observational studies

2. Randomized controlled trials with important limitations, or exceptionally strong evidence from observational studies

3. Observational studies, or randomized controlled trials with notable limitations

4. Clinical experience and observations, observational studies with important limitations, or randomized controlled trials with several major limitations

To minimize *publication bias* (i.e., the tendency to submit or publish reports of effectiveness versus noneffectiveness of a treatment), many countries require all clinical trials to be officially registered so that a record shows that the study was conducted even if the results are never published. Reviewing information on all registered clinical trials on a topic in addition to reviewing the published literature can provide a more complete picture of the effect of a particular intervention or exposure. In the United States, all clinical trials must be registered at clinicaltrials.gov; similar sites exist for other countries.

Understanding a Medical or Epidemiologic Study

Assessing the *research hypothesis* allows readers to determine the relevance of the study to their practice and to judge whether the analyses were done to test the hypothesis or to identify other associations of interest. The ability to make causal inferences from a confirmatory study that tests a single hypothesis is greater than from an exploratory study in which multiple exposures are considered as potential explanations for an outcome.

Several components of *study design* are important to consider. Details should be presented regarding the criteria for selecting the cohort or cases and controls. *Exposure* and *outcome variables* should be clearly defined, and the potential for misclassification and its impact should be considered. Quantifying exposure can be important to establish a dose-response relationship. S*ample size estimates* should be presented, making clear the magnitude of difference among study groups considered clinically meaningful and the type I and type II error levels.

In the *analysis*, it is important that outcomes for all study subjects are reported, even if that outcome is "lost to follow-up." *Intent-to-treat* analyses consider outcomes for all enrolled subjects, whether or not they completed the therapy (e.g., subjects who were nonadherent to therapy or who received only part of a vaccination series). By contrast, *per protocol* analyses include only those subjects who followed the study protocol throughout the full study duration. Usually, an intent-to-treat analysis is considered more conservative than a per protocol analysis, but this is not necessarily the case for noninferiority trials.

The appropriateness of the statistical tests should be assessed; for example, if data are not normally distributed, they can be transformed to a scale that is more normally distributed (e.g., geometric mean titers), or nonparametric statistical tests should be used. In assessing a multivariable model, the reader should critically evaluate the type of model chosen, the variables included, and whether interaction terms were considered. Missing data pose a particular problem in modeling in that study subjects can be included only if data are available for each variable in the model; thus the power of a multivariate model can be much less than that predicted in a sample size calculation.

Bias can have an important impact on study results and must be carefully considered. Approaches to minimize bias should be described clearly. The direction and potential magnitude of remaining bias should be estimated and its impact on results considered. Potential confounding, the presence of important unmeasured variables, and possible effect modification can have a major impact on the results. Investigators should openly discuss the potential limitations of the investigation and describe the strategies applied to overcome those limitations.

Interpretation of study results includes assessing the magnitude of the associations, their relevance to practice, and the likelihood that the relationships observed are causal. The importance of an exposure in explaining an outcome can be expressed by the attributable proportion. However, the *external validity* of the results and the potential impact on one's own patient population still must be assessed.

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2

Pediatric Healthcare Epidemiology

Jane D. Siegel, Judith A. Guzman-Cottrill

The reduction of healthcare-associated infections (HAIs) is an important component of patient safety programs. Five of the 16 Hospital National Patient Safety Goals for 2016 of The Joint Commission (formerly the Joint Commission on Accreditation of Healthcare Organizations) target prevention of HAIs.[1] Hospitals have learned from high-reliability organizations (e.g., the aviation industry) the importance of adopting changes that include the leadership's commitment to achieving zero patient harm, a fully functional culture of safety throughout the organization, and the widespread deployment of highly effective process improvement tools.[2] Involvement of new stakeholders for improving patient safety and outcomes related to HAIs (e.g., Children's Hospitals' Solutions for Patient Safety, Children's Hospital Association, individual states' mandatory HAI public reporting programs, the Centers for Medicare and Medicaid Services, The Joint Commission) has broadened the arena for HAI prevention efforts. Knowledge of the complexities of prevention and control of HAIs in children is critical to many different leaders of children's healthcare facilities. One framework for patient safety in children's hospitals that includes infection prevention and control (IPC) was developed by the Ohio Children's Hospital Solutions collaborative and demonstrates the effectiveness of hospitalwide collaboration.[3] As more disciplines in healthcare become engaged in prevention of

HAIs as well as antimicrobial stewardship, it is the responsibility of the healthcare epidemiologist and the IPC staff (infection preventionists, healthcare epidemiologists) to educate the facility leadership on the discipline of IPC.

IPC for the pediatric population is a unique discipline that requires understanding of various host factors, sources of infection, routes of transmission, behaviors required for care of infants and children, pathogens and their virulence factors, treatments, preventive therapies, and behavioral theory. Although the term *nosocomial* still applies to infections that are acquired in acute care hospitals, the more general term, *healthcare-associated infections* (HAIs), is preferred because much care of high-risk patients, including patients with medical devices (e.g., central venous catheters, ventilators, ventricular shunts, peritoneal dialysis catheters), has shifted to ambulatory settings, rehabilitation or chronic care facilities, and the home; thus, the geographic location of acquisition of the infection often cannot be determined.

The principles of transmission of infectious agents in healthcare settings and recommendations for prevention are reviewed in the Healthcare and Infection Control Practices Advisory Committee (HICPAC) Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings, 2007[4] and in the Management of Multidrug Resistant Organisms in Healthcare Settings, 2006 document.[5] As new pathogens emerge, epidemiologists will continue to learn more about preventing transmission; therefore, for such pathogens, the most up-to-date guidance posted on the Centers for Disease Control and Prevention (CDC) or the World Health Organization (WHO) website should be consulted. The experience treating Ebola virus disease (EVD) in the United States in 2014 is the most recent example of changes in the usual infection prevention paradigm that were required, with emphasis on the hierarchy of controls[6] and donning and doffing of personal protective equipment (PPE) with trained observers.[7] A detailed discussion of HAIs can be found in Chapters 99 and 100. This chapter focuses on the components of an effective pediatric hospital epidemiology program.

Risk Factors for Healthcare-

Associated Infections in Children

Unique aspects of HAIs in children are summarized in the following sections. Specific risks and pathogens are addressed in several other chapters in this textbook.

Host or *Intrinsic* Factors

Intensive care units (ICUs), oncology services, and gastroenterology services caring for patients with short gut syndrome who are dependent on total parenteral nutrition (and lipids) have the highest rates of bacterial and fungal infection associated with central venous catheters. A newer definition of mucosal barrier injury laboratory-confirmed bloodstream infection (MBI-LCBI) currently is used by the National Healthcare Safety Network (NHSN) of the CDC to distinguish bacteremia that represents translocation of gut microorganisms related to mucosal barrier injury in patients with oncologic conditions, hematopoietic stem cell transplantation (HSCT), and intestinal failure from bacteremia associated with central venous catheters.[8] HAIs can result in substantial morbidity and mortality, as well as lifetime physical, neurologic, and developmental disabilities. Host (i.e., intrinsic) factors that make children particularly vulnerable to infection include immaturity of the immune system, congenital abnormalities, and congenital or acquired immunodeficiencies. Children with congenital anomalies have a high risk of HAI if their unusual anatomic features predispose them to contamination of normally sterile sites. Moreover, these children require prolonged and repeated hospitalizations, undergo many complex surgical procedures, and have extended exposure to invasive supportive and monitoring equipment.

Innate deficiencies of the immune system in prematurely born infants, who may be hospitalized for prolonged periods and exposed to intensive monitoring, supportive therapies, and invasive procedures, contribute to the relatively high rates of infection in the neonatal ICU (NICU). All components of the immune system are compromised in neonates, and the degree of deficiency is proportional inversely to gestational age (see Chapter 9). The underdeveloped skin of the very low birth weight (<1000 g) infant provides another mode of pathogen entry.

Populations of immunosuppressed children have expanded with the advent of more intense immunosuppressive therapeutic regimens used for oncologic conditions, HSCT, solid-organ transplantation, and rheumatologic conditions and inflammatory bowel disease for which immunosuppressive agents and tumor necrosis factor-α–inhibiting agents (infliximab [Remicade]) and other immune modulators are used. Genetic mutations in the genes for the transmembrane conductance regulator (CFTR) in children with cystic fibrosis result in thick secretions, chronic endobronchial infections, and gastrointestinal malabsorption. Knowledge of the epidemiology of infection of patients with cystic fibrosis and effective methods to prevent patient-to-patient transmission have expanded with the use of newer molecular diagnostic methods, resulting in a 2013 update in the Infection Prevention and Control Guideline for Cystic Fibrosis.[9] Fortunately, the population of children with perinatally acquired human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) has decreased dramatically since 1994, but new cases of sexually transmitted HIV infection continue to be diagnosed in teens who receive care in children's hospitals. Finally, young infants who have not yet been immunized, or immunosuppressed children who do not respond to vaccines or who lose antibody during disease or treatment (e.g., patients with nephrotic syndrome), have increased susceptibility to vaccine-preventable diseases.

Sources or *Extrinsic* Factors

The source of many HAIs is the endogenous flora of the patient. An asymptomatically colonizing pathogen can invade a patient's bloodstream or be transmitted to other patients on the hands of healthcare personnel (HCP) or on shared equipment. Other important sources of HAIs in infants and children include the mother in the case of neonates, invasive monitoring and supportive equipment, blood products, total parenteral nutrition fluids, lipids, infant formula and human milk, HCP, and other contacts, including adult and sibling visitors. Maternal infection with *Neisseria gonorrhoeae, Treponema pallidum,* HIV, hepatitis B virus, parvovirus B19, *Mycobacterium tuberculosis,* herpes simplex virus, or group B

Streptococcus, or colonization with multidrug-resistant organisms (MDROs), pose substantial threats to the neonate. During perinatal care, procedures such as fetal monitoring using scalp electrodes, fetal transfusion and surgical procedures, umbilical cannulation, and circumcision are potential risk factors for infection. Intrinsically contaminated powdered formulas and infant formulas prepared in contaminated blenders or improperly stored or handled have resulted in sporadic and epidemic infections in the nursery (e.g., *Cronobacter* [formerly *Enterobacter*] *sakazakii*), but such infections have become less frequent since the pathogenesis was defined and contamination reduced.[10] Human milk that has been contaminated by maternal flora or by organisms transmitted through breast pumps has caused isolated serious infections and epidemics. The risks of neonatal hepatitis, cytomegalovirus (CMV) infection, and HIV infection from human milk warrant further caution for handling and use of banked breast milk. With increasing numbers of procedures being performed by pediatric interventional radiologists,[11] an understanding of appropriate aseptic technique, as well as prevention and management of infectious complications, by interventional radiologists is important.[12]

Construction, renovation, demolition, and excavation in and near healthcare facilities are important sources of environmental fungi, (e.g., *Aspergillus* spp., agents of mucormycoses, *Fusarium* spp., *Scedosporium* spp., *Bipolaris* spp.).[13] Immunocompromised patients and patients in the pediatric ICU (PICU) and NICU are at greatest risk for fungal infection, and case fatality rates can be ≥50%, especially if diagnosis and treatment are delayed.

Practices Related to Care of Infants and Young Children.

Several practices must be evaluated with respect to the potentially associated risk of infection. A significant association between reduced levels of nurse staffing and appropriately trained nurses has been demonstrated to increase risk of infection in many studies in both children and adults.[4,14,15] Theoretical concerns exist that infection risk also will increase in association with the innovative practices of co-bedding of twins and kangaroo care in the NICU because of increased opportunity for skin-to-skin exposure of multiple-gestation infants to each other and to their mothers, respectively. Neither the benefits nor the safety of co-bedding multiple-birth infants in the hospital setting has been demonstrated.[16] Overall, the infection risk is reduced with kangaroo care, but transmission of tuberculosis and respiratory syncytial virus (RSV) has occurred in kangaroo mother care units in South Africa.[17] Parents providing kangaroo care should be monitored for the presence of skin infections.

Antimicrobial Selective Pressure.

Exposure to vancomycin and to third-generation cephalosporins contributes substantially to the increase in infections caused by vancomycin-resistant *Enterococcus* (VRE)[18] and multidrug-resistant gram-negative bacilli, including extended spectrum β-lactamase (ESBL)–producing organisms[19] and carbapenem-resistant Enterobacteriaceae[20] (CRE) in children. Additionally, exposure to third-generation cephalosporins also is a risk factor for the development of invasive candidiasis in low birth weight infants in the NICU.[21] Studies of the human microbiome using culture-independent methods have demonstrated the bacterial community diversity on mucosal surfaces and the profound suppressive effect of antimicrobial agents on the population of protective bacteria, *Firmicutes,* thus increasing the risk of colonization and subsequent invasive disease caused by pathogenic bacteria.[22]

Transmission

Routes

The principal modes of transmission of infectious agents are direct and indirect contact, droplet, and airborne.[4]

Contact.

Most infectious agents are transmitted by the contact route on the hands of HCP or through shared items; many pathogens can be transmitted by more than 1 route. Viruses, bacteria, and *Candida* spp. can be transmitted horizontally. Toddlers often share waiting rooms, playrooms, toys, books, and other items and therefore have the potential of transmitting pathogens directly and indirectly to one another. Contaminated bath toys were implicated in an outbreak of multidrug-resistant *Pseudomonas aeruginosa* in a pediatric oncology unit.[23] Although the source of most *Candida* HAIs is the patient's endogenous flora, horizontal transmission, most likely through HCP hands, has been demonstrated in studies using typing by pulsed gel electrophoresis in the NICU and in a pediatric oncology unit.[24,25] Newer molecular diagnostic methods (e.g., whole genome sequencing) are more sensitive and specific than pulsed gel electrophoresis and have proven to be valuable in identifying outbreaks of a variety of pathogens in both pediatric and adult settings.[26,27]

Droplet.

Infectious respiratory droplets >5 μm in diameter are generated from the respiratory tract by coughing, sneezing, or talking or during such procedures as suctioning, intubation, chest physiotherapy, or pulmonary function testing. Transmission of infectious agents by the droplet route requires exposure of mucous membranes to large respiratory droplets within 3 to 6 feet (1 to 2 m) of the infected person. Large respiratory droplets do not remain suspended in the air for prolonged periods, and they settle on environmental surfaces. The dynamics of infectious aerosols can be affected by a variety of factors including characteristics of specific strains of bacteria, temperature, humidity, and number of air exchanges in a room. Adenovirus, influenza virus, and rhinovirus are transmitted primarily by the droplet route, whereas RSV is transmitted primarily by the contact route.[28] Although influenza virus can be transmitted by the airborne route under unusual conditions of reduced air circulation or low absolute humidity, ample evidence indicates that transmission of influenza is prevented by droplet precautions and, in the care of infants, the addition of contact precautions.[29]

Airborne.

Droplet nuclei that arise from desiccation of respiratory droplets and are <5 μm in diameter and contain infectious agents remain suspended in the air for prolonged periods and travel long distances on air currents.[4] Susceptible persons who have not had face-to-face contact or been in the same room as the source person can inhale such infectious particles. *M. tuberculosis,* varicella-zoster virus (VZV), and rubeola virus are the agents most frequently transmitted by the airborne route. Although transmission of *M. tuberculosis* by the airborne route can occur rarely from an infant or young child with active tuberculosis, the more frequent source is the adult visitor with active pulmonary tuberculosis that has not yet been diagnosed; thus screening of visiting family members is an important component for control of tuberculosis in pediatric healthcare facilities.[30]

Some agents (e.g., severe acute respiratory syndrome–coronavirus [SARS-CoV]) can be transmitted as small-particle aerosols under special circumstances of aerosol-generating procedures (e.g., endotracheal intubation, bronchoscopy); therefore, an N95 or higher respirator is indicated for persons in the same airspace when these procedures are performed, but an airborne infection isolation room (AIIR) may not always be required. Roy and Milton[31] proposed the following classification for aerosol transmission when evaluating routes of SARS-CoV transmission:

1. *Obligate:* Under natural conditions, disease occurs following transmission of the agent only through small-particle aerosols (e.g., tuberculosis).

2. *Preferential:* Natural infection results from transmission through multiple routes, but small-particle aerosols are the predominant route (e.g., measles, varicella).

3. *Opportunistic:* Agents naturally cause disease through other routes, but under certain environmental conditions they can be transmitted by fine-particle aerosols.

This conceptual framework can explain rare occurrences of airborne transmission of agents that are transmitted most frequently by other routes (e.g., smallpox, SARS, influenza, noroviruses). Concern about airborne transmission of influenza arose during the 2009 influenza A (H1N1) pandemic. However, the conclusion from all published experiences during the pandemic was that droplet transmission is the usual route of transmission, and surgical masks were noninferior to N95 respirators in preventing laboratory-confirmed influenza in HCP.[32,33] Concerns about unknown or possible routes of transmission of agents that can cause severe disease and have no known treatment often result in more extreme prevention strategies. Therefore, recommended precautions could change as the epidemiology of emerging agents is defined and these controversial issues are resolved. Although no evidence supports airborne transmission of the Ebola virus under usual circumstances in the field, the aerosolization of body fluids that contain high titers of Ebola virus requires additional protection.[34]

Healthcare Personnel

Transmission of microbes between children and HCP is a risk because of the very close contact that occurs during care of infants and young children and is facilitated by overcrowding, understaffing, and too few appropriately trained nurses in pediatric facilities.[4,14] Staffing levels and composition are important components of an effective IPC program. HCP rarely are the *source* of outbreaks of HAIs caused by bacteria and fungi, but when they are, certain factors are usually present that increase the risk of transmission (e.g., sinusitis, draining otitis externa, respiratory tract infections, dermatitis, onychomycosis, wearing of artificial nails).[35–37] Persons with direct patient contact who were wearing artificial nails have been implicated in outbreaks of *P. aeruginosa* and ESBL-producing *Klebsiella pneumoniae* in NICUs; therefore, the use of artificial nails or extenders is prohibited in persons who have direct contact with high-risk patients.[4] Several published studies have shown that infected pediatric HCP, including resident physicians, transmitted *Bordetella pertussis* to other patients and can be the source of other vaccine-preventable infections in healthcare.[38,39]

Pathogens

Although no agreed-on definition for what constitutes an “epidemiologically important organism” has yet been established, the following characteristics apply and are presented for guidance to infection control staff in the 2007 HICPAC Guideline for Isolation Precautions in Healthcare Settings[4]:

1. A propensity for transmission within healthcare facilities based

on published reports and the occurrence of temporal or geographic clusters of infection in >2 patients (e.g., VRE, methicillin-resistant *Staphylococcus aureus* [MRSA], and methicillin-susceptible *S. aureus* [MSSA], *Clostridium difficile,* norovirus, RSV, influenza, rotavirus, *Enterobacter* spp., *Serratia* spp., group A *Streptococcus*). A single case of healthcare-associated invasive disease caused by certain pathogens (e.g., group A *Streptococcus* postoperatively or in burn units; *Legionella* sp.; *Aspergillus* sp.) should trigger an investigation.

2. Association with antimicrobial resistance (e.g., MRSA, VRE, ESBL-producing gram-negative bacilli (GNB), CRE, *Burkholderia cepacia, Ralstonia* spp., *Stenotrophomonas maltophilia,* and *Acinetobacter* spp.). Infections caused by intrinsically resistant GNB also suggest possible contamination of water or medication.

3. Association with serious clinical disease and increased morbidity and mortality (e.g., MRSA and MSSA, group A *Streptococcus*).

4. A newly discovered or reemerging pathogen (e.g., vancomycin-intermediate or vancomycin-resistant *S. aureus* [VISA, VRSA], *C. difficile*).

Pathogens associated with HAIs in children differ from those in adults in that respiratory viruses are more frequently associated with transmission in pediatric healthcare facilities. Respiratory viruses (e.g., RSV, parainfluenza, adenovirus, human metapneumovirus) have been implicated in outbreaks in high-risk units. As more respiratory viruses and gastrointestinal pathogens are identified by using highly sensitive molecular methods, epidemiologic studies will be required to define further the risk of transmission in healthcare facilities and the clinical significance of positive antigen detection test results.[40,41] Healthcare-associated outbreaks of varicella, measles, and rotavirus infection now are rare events because of the consistent use of vaccines by children and HCP.

The emergence of community-associated MRSA isolates characterized by the unique scc *mec* type IV element was first observed among infants and children. As rates of colonization with community-associated MRSA at the time of hospital admission increased, so did transmission of community strains, most often

USA 300, within the hospital and especially within the NICU, thus making prevention especially challenging. Other MDROs (e.g., VRE, ESBLs, and CRE, especially *K. pneumoniae*) have emerged as the most challenging healthcare-associated pathogens in both pediatric and adult settings, and otherwise healthy children in the community can be colonized asymptomatically with these MDROs.[42] GNB, including ESBL and other multidrug-resistant isolates, are more frequent than MRSA and VRE in many PICUs and NICUs. Patients who are transferred from chronic care facilities may be colonized with MDR GNB at the time of admission to the PICU. Trends in targeted MDROs are tracked in the National Nosocomial Infections Surveillance system (NNIS), now NHSN ICUs. HAIs caused by MDROs are associated with increased length of stay, increased morbidity and mortality, and increased cost, in part because of the delay in initiating effective antimicrobial therapy.[43,44] Although the prevalence of specific MDROs is lower in pediatric institutions, the same principles of target identification and interventions to control MDROs apply in all settings.

C. difficile is an important pathogen in children, as it is in adults, especially in children receiving chemotherapy. Testing for *C. difficile* in the first year of life is not advised because of the high asymptomatic colonization rate with toxigenic strains in this age group.

Candida spp. are the third most frequent pathogens associated with bloodstream infections in US NICUs. There is considerable center-to-center variability in both the incidence of invasive candidiasis and the proportion of *Candida* infections caused by *Candida* non-*albicans* spp., most of which are resistant to fluconazole. Risk factors for *Candida* infections include prolonged length of stay in an ICU, use of central venous catheters, intralipids, histamine (H_2)-blocking agents, and exposure to third-generation cephalosporins. GNB and *Candida* spp. are especially important pathogens for HAIs in patients with intestinal failure who are receiving total parenteral nutrition, and these organisms can cause repeated episodes of sepsis. The incidence of *Candida* infections had increased in incidence in most PICUs and NICUs during the 1990s, but the rate of *C. albicans* and non-*albicans* central line–associated bloodstream infections decreased by 75% in all birth weight categories from 1999 to 2009,[45] likely a result of improved infection control practices, antimicrobial stewardship, and use of fluconazole prophylaxis in the very low birth weight preterm infants. The most recently published clinical practice guidelines of the Infectious Diseases Society of America (IDSA) recommend the use of oral or intravenous fluconazole prophylaxis in infants weighing <1000 g at birth in NICUs with high rates (>10%) of invasive candidiasis, based on high quality of evidence to support efficacy and safety.[46] Additionally, empiric antifungal therapy in preterm infants of ≤1000 g birth weight is associated with improved survival rates without adverse outcomes.[47] The staff members of each NICU first must optimize infection control practices and then assess the remaining risk of *Candida* infections. Finally, environmental fungi (e.g., *Aspergillus, Fusarium, Scedosporium, Bipolaris,* agents of mucormycosis) are important sources of infection for severely immunocompromised patients; meticulous attention to the conditions of the internal environment of any facility that provides care for severely immunocompromised patients is required, as well as prevention of possible exposure to construction dust in and around healthcare facilities.[13] With the advent of more effective and less toxic antifungal agents and improved outcomes, it is important to identify promptly the infecting agent by obtaining tissue samples and to determine susceptibility to candidate antifungal agents.

Prevention Programs

Prevention remains the mainstay of infection control and requires special considerations in children. The goals of IPC are to prevent the transmission of infectious agents among individual patients or groups of patients, visitors, and HCP who care for them. As new pathogens emerge, new strategies for prevention emerge. The experience treating EVD in the US in 2014 and 2015 is the most recent example of changes in the usual infection prevention paradigm that were required, with a renewed emphasis on the 3 tiers of the hierarchy of controls (e.g., engineering, administration, and PPE), donning and doffing of PPE, and use of trained observers.[6,7] If prevention cannot always be achieved, the strategy of early diagnosis, treatment, and containment is critical.

A series of IPC guidelines have been developed and updated at varying intervals by the HICPAC/CDC, IDSA, Society for

Healthcare Epidemiology of America (SHEA), American Academy of Pediatrics, Association for Professionals in Infection Control and Epidemiology, and others to provide evidence-based and rated recommendations for practices that are associated with reduced rates of HAIs, especially those infections associated with the use of medical devices and surgical procedures. Recommended isolation precautions by infectious agent also can be found in the most recent edition of the *Red Book Report of the Committee on Infectious Diseases* of the American Academy of Pediatrics.

Prevention *bundles* are groups of 3 to 5 evidence-based "best practices" with respect to a process that individually improve care, but when applied together result in substantially greater reduction in infection rates. Adherence to the individual measures within a bundle is readily measured. Bundled practices are used most frequently for prevention of device- or procedure-related HAIs, but they can be applied to prevention of any type of HAI.

Administrative Factors

The importance of certain administrative measures for a successful IPC program has been demonstrated. A white paper published by SHEA summarizes the necessary infrastructure for an effective IPC program in modern times. The paper addresses the expansion of IPC responsibilities from a relatively narrow focus on acute infectious disease events in the acute care hospital, surveillance, and implementation of recommended isolation precautions to a broader set of activities across the continuum of care requiring team work within and beyond individual facilities, usually including large networks.[48] Because IPC comprises one component of the institutional culture of safety, it is critical to obtain support from the senior leadership of healthcare organizations to provide necessary fiscal and human resources for a proactive, successful IPC program. Critical elements requiring administrative support include access to the following: (1) appropriately trained healthcare epidemiologists and IPC personnel; (2) clinical microbiology laboratory services needed to support infection control outbreak investigations, including ability to perform molecular diagnostic testing; (3) data-mining programs and information technology specialists; (4) multidisciplinary programs to ensure judicious use of antimicrobial agents and control of resistance; (5) development of effective educational information for delivery to HCP, patients, families, and visitors; and (6) local and state health department resources for preparedness. Provision of adequate numbers of well-trained infection preventionists and bedside nursing staff is critical for success.

Infection Prevention and Control Team

An effective IPC program improves safety of patients and HCP and decreases short-term and long-term morbidity, mortality, and healthcare costs.[49] The IPC committee of a facility establishes policies and procedures to prevent or reduce the incidence and costs associated with HAIs. This committee should be one of the strongest and most accessible committees in the facility; committee composition should be considered carefully and limited to active, authoritative participants who have well-defined committee responsibilities and who represent major groups within the hospital. The chairperson should be a good communicator with expertise in IPC issues, healthcare epidemiology, and clinical pediatric infectious diseases. Important functions of the IPC committee are regular review of IPC policies and development of new policies as needed. Annual review of all policies is required by The Joint Commission and can be accomplished optimally by careful review of a few policies each month. With the advent of unannounced inspections, a constant state of readiness is required.

The hospital epidemiologist or medical director of the pediatric IPC department usually is a physician with training in pediatric infectious diseases and dedicated expertise in healthcare epidemiology. In multispecialty medical centers where infants and children comprise a small proportion of patients, pediatric infectious disease experts should be consulted for management of pediatric IPC issues and report to the broader IPC leadership. The skillsets, training, and competencies needed for success as a healthcare epidemiologist were summarized in another white paper published by the SHEA.[50] Certification for healthcare epidemiologists has not yet been developed.

Infection preventionists are specialized professionals with advanced training, and preferably certification, in IPC. Although most infection preventionists are registered nurses, other professionals, including microbiologists, medical technologists, pharmacists, and epidemiologists, are successful in this position. Pediatric patients should have infection preventionist services provided by professionals with expertise and training in the care of children. In a large, general hospital, at least 1 infection preventionist should be dedicated to IPC services for children. The responsibilities of infection preventionists have expanded greatly and include the following:

1. Surveillance and IPC in facilities affiliated with primary acute care hospitals (e.g., ambulatory clinics, day-surgery centers, long-term care facilities, rehabilitation centers, home care) in addition to the primary hospital

2. Oversight of occupational health services related to IPC (e.g., assessment of risk and administration of recommended prophylaxis following exposure to infectious agents, tuberculosis screening, influenza and pertussis vaccination, respiratory protection fit testing, administration of other vaccines as indicated during infectious disease crises such as preexposure smallpox vaccine in 2003 and pandemic influenza A [H1N1] vaccine in 2009)

3. Preparedness planning for annual influenza outbreaks, pandemic influenza, SARS, Middle East respiratory syndrome (MERS), bioweapons attacks, and EVD

4. Adherence monitoring for selected IPC practices

5. Oversight of risk assessment and implementation of preventive measures associated with construction, renovation, and other environmental conditions associated with increased infection risk

6. Participation in antimicrobial stewardship programs, focusing on prevention of transmission of MDROs

7. Evaluation of new products and medical devices that could be associated with increased infection risk (e.g., endoscopes,[51] contaminated injectable medications[52]) and introduction and assessment of performance after implementation of modified

products

8. Mandatory public reporting of HAI rates in states according to enacted legislation

9. Increased communication with the public and with local public health departments concerning infection control–related issues

10. Participation in local and multicenter reporting and research projects

IPC programs must be adequately staffed to perform all the foregoing activities. Thus the ratio of 1 infection preventionist to 250 beds that was associated with a 30% reduction in the rates of nosocomial infection in the Study on Efficacy of Nosocomial Infection Control (SENIC) performed in the 1970s no longer is sufficient because the complexity of patient populations and responsibilities have increased. Many experts recommend that a ratio of 1 infection preventionist to 100 beds is more appropriate for the current workload, but no study has been performed to confirm the effectiveness of that ratio. No information is available on the number of IPC personnel required outside acute care, but it is clear that persons well trained in IPC must be available for all sites where healthcare is delivered. Data collected from a member workforce survey conducted in 2015 by the Association for Professionals in Infection Control and Epidemiology are expected to help determine the optimal number of infection preventionists for different healthcare settings based on the current responsibilities and demographics of infection preventionists.

Surveillance

Facilitywide or Systemwide Surveillance

Surveillance for HAIs consists of a systematic method of determining the incidence and distribution of infections acquired by hospitalized patients. The CDC recommends the following: (1) prospective surveillance on a regular basis by trained infection preventionists, using standardized definitions; (2) analysis of infection rates using established epidemiologic and statistical methods (e.g., calculation of rates using appropriate denominators that reflect duration of exposure; use of statistical process control charts for trending rates); (3) regular use of data in decision making; and (4) employment of an effective and trained healthcare epidemiologist who develops IPC strategies and policies and serves as a liaison with the medical community and administration.[53–55] The CDC has established a set of standard definitions of HAIs that have been validated and accepted widely with updates posted on the CDC NHSN website. Standardization of surveillance methodology has become especially important with the advent of state legislation for mandatory reporting of HAI rates to the public. The NHSN now receives, analyzes, and reports data from >17,000 healthcare facilities in the US. A standardized infection ratio (SIR) that takes into account differences in risk among healthcare settings, unit types, procedures, and patient populations has been included in summary reports of HAI rates since 2009.[56] The Centers for Medicare and Medicaid Services and most states use the NHSN data for public reporting of HAI rates on their websites. Although much effort has been directed toward making these data understandable and useful to consumers, interpretation of these data by the public remains difficult, and more research is needed to optimize methods of data display to the public.[57] New York State is the first state to have published an improvement in process and outcomes of central line–associated bloodstream infection rates in NICUs following implementation of a public reporting program.[58]

Although various surveillance methods are used, the basic goals and elements are similar and include using standardized definitions of infection, finding and collecting cases of HAIs, tabulating data, using appropriate denominators that reflect duration of risk, analyzing and interpreting the data, reporting important deviations from endemic rates (epidemic, outbreaks) to the bedside care providers and to the facility administrators, implementing appropriate control measures, auditing adherence rates for recommended processes, and assessing efficacy of the control measures. Medical centers can use different methods of surveillance, as outlined in Box 2.1. Most experts agree that a combination of methods enhances surveillance and reliability of data, and some combination of clinical chart review and database retrieval is important. Whatever data collection systems are used, validation is required. Administrative databases created for the purposes of billing should not be used as the sole source to identify HAIs because of overestimates and underestimates that result from inaccurate coding of HAIs.[59] Use of software designed specifically for IPC data entry and analysis facilitates real-time tracking of trends and timely intervention when clusters are identified. The IPC team should participate in the development and update of electronic medical record systems for a healthcare organization, to ensure that surveillance needs will be met.

Box 2.1

Sources of Data for Surveillance

Clinical rounds with physicians or nurses, or both

Review of:

- Patients' orders
- Radiology reports and databases
- Pharmacy reports and databases
- Operating room diagnoses and procedures
- Microbiology: bacteriology, virology, mycology, mycobacteriology, serology reports, autopsy reports, data-mining reports

Postdischarge surveillance, especially for surgical site infections

Public health surveillance

Review of:

- Employee health reports
- Admission diagnoses

- Outpatient diagnoses
- Administrative databases, but these should not be used as a sole source because of inaccurate coding of healthcare-associated infections

Targeted Pathogen-Specific Active Surveillance Cultures

Controversy has surrounded the role of obtaining active surveillance cultures from all patients admitted to an acute care hospital, especially to an ICU, to detect asymptomatic colonization with MRSA or VRE and then placing those persons on Contact Precautions in an endemic setting, a practice referred to as a *vertical* approach.[60,61] More recently published experiences demonstrate the benefits of a *horizontal* approach to reduce the risk of transmission of a broader variety of pathogens,[61] and a framework for a less restrictive approach has been published.[62] Contributing factors to the benefits of the horizontal approach include the following: (1) widespread implementation of bundled prevention practices, including limiting use of unnecessary medical devices; (2) improved understanding and more consistent implementation of Standard Precautions, especially hand hygiene; (3) establishment of the safety and efficacy of universal decolonization using chlorhexidine bathing in ICUs[63,64] and NICUs for infants weighing >1000 g at birth[65]; (4) improving environmental cleaning; and (5) promoting antimicrobial stewardship. A program of active surveillance cultures and Contact Precautions is best reserved for implementation in a targeted fashion (i.e., in units with an indication of ongoing transmission of MRSA, VRE, or other MDROs) according to 2006 guidelines, if transmission continues after standardized horizontal interventions have been completely implemented.[5] At this time, no formal recommendation has been made to discontinue routine use of Contact Precautions for patients with asymptomatic colonization with MRSA or VRE in an endemic setting; thus each IPC program must determine practice based on local conditions and follow with close auditing and surveillance for potential adverse outcomes.

The microbiology laboratory can provide online culture information about individual patients, outbreaks of infection, antibiograms (antibiotic susceptibility patterns of pathogens summarized periodically), and employee infection data. The laboratory also can assist with surveillance cultures and facilitation of molecular typing of isolates during outbreak investigations. Rapid diagnostic testing of clinical specimens for identification of respiratory and gastrointestinal tract viruses and *B. pertussis* is especially important for pediatric facilities. The IPC division and the microbiology laboratory must communicate daily because even *requests* for cultures or other diagnostic testing from physicians (e.g., *M. tuberculosis, Neisseria meningitidis, C. difficile*) can identify patients early who are infected, are at high risk of infection, or require isolation. If microbiology laboratory work is outsourced, it is important to ensure that the services needed to support effective ICP be available, as delineated in a 2013 guideline developed by the IDSA and the American Society for Microbiology.[66]

Control of unusual infections or outbreaks in the community generally is the responsibility of the local or state public health department; however, the individual facility must be responsible for preventing transmission within that facility. Public health agencies can be helpful, particularly in alerting hospitals of community outbreaks so that outpatient and inpatient diagnosis, treatment, necessary isolation, and other preventive measures are implemented promptly to avoid further spread. Conversely, designated persons in the hospital must notify public health department personnel of reportable infections to facilitate early diagnosis, treatment, and infection control in the community. Benefits of community or regional collaboratives of individual healthcare facilities and local public health departments for prevention of HAIs, especially those caused by MDROs, have been demonstrated, and this collaboration should be encouraged.[4,67]

Antimicrobial Stewardship

The rapid increase of MDROs is a public health threat. Between 20% and 50% of antibiotics prescribed in US hospitals are either inappropriate or unnecessary.[68] In 2014, the President's Council of Advisors on Science and Technology submitted a 78-page *Report to* *the President on Combating Antibiotic Resistance* that raised awareness of antimicrobial resistance to a national level.[69] A National Action Plan based on this report was released in March 2015, and funding was made available for its implementation.

Antimicrobial stewardship was defined in a consensus statement by the IDSA, SHEA, and Pediatric Infectious Diseases Society in 2012 as "coordinated interventions designed to improve and measure the appropriate use of antibiotic agents by promoting the selection of the optimal antibiotic regimen, including dosing, duration and route of administration."[70] Antimicrobial stewardship programs are collaborative partnerships among infection preventionists, healthcare epidemiologists, clinical pharmacists, and microbiologists. Hospital administrative support for the infrastructure required for ongoing measurement and reporting of antimicrobial use and other related outcome measures, including feedback to prescribers, is a critical component of a successful antimicrobial stewardship program. An antimicrobial stewardship program can optimize clinical outcomes while decreasing unintended consequences of antimicrobial use, including the emergence of resistant organisms. Additionally, use of specific antimicrobial agents can alert the IPC program to the presence of potentially infectious patients (e.g., with pulmonary tuberculosis, MDROs). National guidelines exist for developing and implementing an institutional antimicrobial stewardship program, including core components for acute care hospitals and for long-term care facilities.[68,70] The Natinal Quality Forum and its partners have also developed a Playbook that provides additional guidance for implementation of antimicrobial stewardship programs in acute care. The knowledge and skills required for antimicrobial stewardship leaders also have been defined.[50,71]

The effectiveness of antimicrobial stewardship programs in achieving improved patient outcomes is evident in pediatric acute care hospitals,[72,73] including the NICU,[74,75] in ambulatory settings, and in long-term care facilities. The area of antimicrobial stewardship, however, requires additional research to establish optimal methods in various pediatric specialty populations. One practice from the CDC GET SMART program that can be implemented by each prescriber in most settings is the antibiotic "time out" that consists of reviewing patient data at 48 to 72 hours of treatment to determine which of the following is indicated: (1) continue antibiotic treatment; (2) change to a narrower-spectrum agent; (3) change from a parenteral to an oral agent; or (4) shorten or conclude therapy.[68]

Isolation Precautions

Isolation of patients with potentially transmissible infectious diseases is a strategy proven to prevent transmission of infectious agents in healthcare settings. Many published studies, performed in both adult and pediatric settings, provide a strong evidence base for most recommendations for isolation precautions and for limiting outbreaks. However, controversies exist concerning the most clinically and cost-effective measures for preventing certain HAIs, especially those associated with MDROs. As discussed earlier in the section on surveillance, a call has gone out to reconsider recommendations for isolation of patients who are asymptomatically colonized with MRSA or VRE, but no definite recommendation has been made by the HICPAC/CDC, SHEA, or Association for Professionals in Infection Control and Epidemiology.

Since 1970, the guidelines for isolation developed by CDC have responded to the needs of the evolving US healthcare systems. For example, universal precautions became a required standard in response to the HIV epidemic that emerged in the 1980s and the need to prevent acquisition of bloodborne pathogens (e.g., HIV, hepatitis B and C viruses) by HCP through skin, eye, mucous membrane, or parenteral contact with blood or other potentially infectious materials from persons not known to be or suspected of being infected. Universal precautions were modified and have been known as Standard Precautions since publication of the 1996 Guideline for Isolation. The federal Needlestick Safety and Prevention Act, signed into law in November 2000, authorized the Occupational Safety and Health Administration's revision of its Bloodborne Pathogens Standard more explicitly to require the use of safety-engineered sharp devices.[76]

Evidence and recommendations are provided for the prevention of transmission of MDROs such as MRSA, VRE, VISA, VRSA, and GNB.[4,5] The components of a protective environment for prevention of environmental fungal infections in HSCT recipients are summarized.[4] Finally, evidence-based, rated recommendations for administrative measures that are necessary for effective prevention of infection in healthcare settings are provided.

Standard Precautions

The most recent Guideline for Isolation Precautions published in 2007[4] reaffirms *Standard Precautions*, a combination of universal precautions and body substance isolation, as the foundation of transmission prevention measures. Critical thinking is required for HCP to recognize the importance of body fluids, excretions, and secretions in the transmission of infectious pathogens and take appropriate protective precautions by using PPE (e.g., masks, gowns, gloves, face shields, or goggles) and safety devices when exposure is likely even if an infection is not suspected or known. In addition, these updated guidelines provide recommendations for Standard Precautions in all settings in which healthcare is delivered (acute care hospitals, ambulatory surgical and medical centers, long-term care facilities, and home health agencies). The components of Standard Precautions are summarized in Table 2.1. In the most recent HICPAC/CDC isolation guideline,[4] safe injection practices are included as a component of Standard Precautions. Despite the emphasis on safe injection practices, transmission of hepatitis B and C viruses continues to be reported in ambulatory care settings as a result of failure to follow recommended practices, thus indicating a need to reiterate the established effective practices.[77] During 2008 to 2014, 45 outbreaks (≥2 cases) of viral hepatitis related to healthcare were reported to the CDC; of these, 42 (95%) occurred in nonhospital settings. A review of clusters of transmission of hepatitis C virus in dialysis centers from 2005 to 2015 identified the following potential infection control breaches: (1) use of multidose vials for heparin or saline administration; (2) poor compliance with hand hygiene before and after patient contacts or after touching a possibly contaminated surface; (3) failure to change gloves between patient contacts or after contact with a potentially contaminated surface; (4) failure to disinfect environmental surfaces adequately; (5) unsafe injection practices; (6) failure to disinfect shared equipment between patient uses; (7)

lack of a separate area for medication preparation; and (8) failure to have clean and dirty utility rooms clearly separated.[78]

TABLE 2.1

Recommendations for Application of Standard Precautions for the Care of All Patients in All Healthcare Settings

Component	Recommendations for Performance
Hand hygiene	Perform before touching patients and before donning gloves; after touching blood, body fluids, secretions, excretions, contaminated items; immediately after removing gloves; between patient contacts. Alcohol-containing antiseptic hand rubs preferred except when hands are visibly soiled with blood or other proteinaceous materials or if exposure to spores (e.g., *Clostridium difficile, Bacillus anthracis*) is likely to have occurred
Gloves	Use for touching blood, body fluids, secretions, excretions, contaminated items; for touching mucous membranes and nonintact skin
Gown	Wear during procedures and patient care activities when contact of clothing or exposed skin with blood or body fluids, secretions, and excretions is anticipated
Mask,[a] eye protection (goggles), face shield	Wear during procedures and patient care activities likely to generate splashes or sprays of blood, body fluids, secretions (especially suctioning, endotracheal intubation) to protect healthcare personnel. For patient protection, the person inserting an epidural anesthesia needle or performing myelograms should use a mask when prolonged exposure of the puncture site is likely to occur
Soiled patient-care equipment	Handle in a manner that prevents transfer of microorganisms to others and to the environment; wear gloves if equipment is visibly contaminated; perform hand hygiene
Environmental control	Develop procedures for routine care, cleaning, and disinfection of environmental surfaces, especially frequently touched surfaces in patient care areas
Textiles and laundry	Handle in a manner that prevents transfer of microorganisms to others and to the environment
Safe injection practices (use of needles and other sharps)	Do not recap, bend, break, or hand-manipulate used needles; if recapping is required, use a one-handed scoop technique only; use needle-free safety devices when available; place used sharps in a puncture-resistant container. Use a sterile, single-use, disposable needle and syringe for each injection given. Single-dose medication vials are preferred when medications are administered to >1 patient
Patient resuscitation	Use a mouthpiece, resuscitation bag, or other ventilation device to prevent contact with mouth and oral secretions
Patient placement	Prioritize for a single-patient room if the patient is at increased risk of transmission, is likely to contaminate the environment, does not maintain appropriate hygiene, or is at increased risk of acquiring infection or developing adverse outcome following infection
Respiratory hygiene and cough etiquette[b]	Instruct symptomatic persons to cover the mouth or nose when sneezing or coughing; use tissues and dispose in no-touch receptacle; observe hand hygiene after soiling of hands with respiratory secretions; wear a surgical mask if tolerated or maintain spatial separation, >1–2 m (3–6 feet) if possible

[a] During aerosol-generating procedures on patients with suspected or proven infections transmitted by aerosols (e.g., severe acute respiratory syndrome), wear a fit-tested N95 or higher respirator in addition to gloves, gown, and face and eye protection.

[b] Source containment of infectious respiratory secretions in symptomatic patients, beginning at the initial point of encounter (e.g., triage and reception areas in emergency departments and physician offices).

Modified with permission from Siegel JD, Rhinehart E, Jackson M, et al. Guideline for isolation precautions: preventing transmission of infectious agents in healthcare settings, 2007. Am J Infect Control 2007;35(Suppl 2):S65–S164.

Two additions were made to Standard Precautions in 2007: (1) *respiratory hygiene or cough etiquette* for source containment by people with signs and symptoms of respiratory tract infection and (2) *use of a mask* by personnel inserting an epidural anesthesia needle or performing a myelogram when prolonged exposure of the puncture site is likely. Both components have a strong evidence base.

Implementation of Standard Precautions requires the availability of PPE in proximity to all patient care areas. HCP with exudative lesions or weeping dermatitis must avoid direct patient care and handling of patient care equipment. Persons having direct patient contact should be able to anticipate exposure incurring risks and steps to take if a high-risk exposure occurs. Exposures of concern are as follows: exposures to blood or other potentially infectious material defined as an injury with a contaminated sharp object (e.g., needlestick, scalpel cut); a spill or splash of blood or other potentially infectious material onto nonintact skin (e.g., cuts, hangnails, dermatitis, abrasions, chapped skin) or onto a mucous membrane (e.g., mouth, nose, eye); or blood exposure covering a large area of normal skin. Patient-related duties that do *not* constitute high-risk exposures include handling food trays or furniture, pushing wheelchairs or stretchers, using restrooms or telephones, having personal contact with patients (e.g., giving information, touching intact skin, bathing, giving a back rub, shaking hands), or performing clerical or administrative functions for a patient.

If hands or other skin surfaces are exposed to blood or other potentially infectious material, the area should be washed immediately with soap and water for at least 10 seconds and rinsed with running water for at least 10 seconds. For an eye, nose, or mouth splash with blood or body fluids, the area should be irrigated immediately with a large volume of water. If a skin cut, puncture, or lesion is exposed to blood or other potentially infectious material, the area should be washed immediately with soap and water for at least 10 seconds and rinsed with 70% isopropyl alcohol. Any exposure incident should be reported immediately to the occupational health department to determine whether blood samples are required from the source patient and the exposed person and if immediate prophylaxis is indicated.

All HCP should know where to find the exposure control plan specific to each place of employment, whom to contact, where to go, and what to do if inadvertently exposed to blood or body fluids. Important resources include the occupational health department, the emergency department, and the infection control or hospital epidemiology division. The most important recommendation in any accidental exposure is to seek advice and intervention immediately because the efficacy of recommended prophylactic regimens is improved with shorter intervals after exposure, such as for hepatitis B immune globulin administration after exposure to hepatitis B virus or for antiretroviral therapy after percutaneous exposure to HIV. Chemoprophylaxis following exposure to HIV-infected material is most effective if it is initiated as soon as possible, but within hours of exposure.[79] The current guidelines recommend using ≥3 drugs for postexposure prophylaxis of HIV independent of the severity of exposure. Updates are posted on the CDC website as they are developed. Reporting a work-related exposure is required for subsequent medical care and workers' compensation.

Transmission-Based Precautions

Transmission-Based Precautions are designed for patients with documented or suspected infection with pathogens for which additional precautions beyond Standard Precautions are needed to prevent transmission. The 3 categories of Transmission-Based Precautions are *Contact Precautions, Droplet Precautions,* and *Airborne Precautions,* and they are based on the likely routes of transmission of specific infectious agents. Transmission-based precautions are combined for infectious agents that have more than 1 route of transmission. When used singly or in combination, such precautions always are used in addition to Standard Precautions. Transmission-based precautions applied at the time of initial contact, based on the clinical presentation and the most likely pathogens are referred to as *Empiric Precautions* or *Syndromic*

Precautions. This approach is useful especially for emerging agents (e.g., SARS-CoV, avian influenza, pandemic influenza), for which information concerning routes of transmission is evolving. The categories of clinical presentation are as follows: diarrhea, central nervous system, generalized rash or exanthem, respiratory, skin or wound infection. Single-patient rooms always are preferred for children needing Transmission-Based Precautions. If single-patient rooms are unavailable, cohorting of patients, and preferably of staff, according to clinical diagnosis is recommended. The experience of treating EVD in the US in 2014 led to the development of special precautions after viral transmission to 2 nurses occurred as a result of patients' extraordinarily high viral loads and large volumes of emitted body fluids.[6] PPE for all transmission-based precautions is donned *upon entry* into the room to protect against acquisition of pathogens from contaminated surfaces, even if direct contact with the patient is not intended.

Although targeted Contact Precautions and universal gowning and gloving are effective for preventing transmission of infectious agents, potential adverse effects in patients placed on Contact Precautions have been described (e.g., depression, fewer visits from the healthcare team, increased rates of hypoglycemia or hyperglycemia, increased falls).[80] Additionally, adherence to Contact Precautions decreases as the number of patients on Contact Precautions increases.[81] Finally, a simulation study demonstrated contamination of HCP skin and clothing during doffing of gowns and gloves[82]; this study effectively demonstrated the PPE lessons learned during the SARS and EVD experiences. Evidence supports the importance of applying Contact Precautions only when indicated, obtaining training on the use of PPE, having effective PPE readily available, and practicing consistent and precise use of PPE.[83]

Table 2.2 lists the 3 categories of isolation based on routes of transmission and their necessary components. Table 2.3 lists precautions by syndromes, to be used when a patient has an infectious disease and the agent is not yet identified. For infectious agents that are more likely to be transmitted by the droplet route (e.g., pandemic influenza), droplet precautions (with use of surgical mask) are appropriate; however, during an aerosol-generating procedure, N95 or higher respirators are indicated.[84]

TABLE 2.2

Transmission-Based Precautions[a]

Component	Contact	Droplet	Airborne
Hand hygiene	Per Standard Precautions Perform 5 moments of hand hygiene, and ***upon entry*** into room Soap and water preferred over alcohol hand rub for *Clostridium difficile, Bacillus anthracis* spores	Per Standard Precautions Perform 5 moments of hand hygiene, and ***upon entry*** into room	Per Standard Precautions Perform 5 moments of hand hygiene, and ***upon entry*** into room
Gown	Yes; don before or ***upon entry*** into room	Per Standard Precautions Add to droplet precautions for infants, young children, or presence of diarrhea	Per Standard Precautions and, if infectious, draining skin lesions present
Gloves	Yes; don before or ***upon entry*** into room	Per Standard Precautions. Add for infants, young children and/or presence of diarrhea	Per Standard Precautions Add for infants, young children or presence of diarrhea
Mask	Per Standard Precautions	Yes; don before or ***upon entry*** into room	Don N95 particulate respirator or higher ***before entry*** into room
Goggles or face shield	Per Standard Precautions	Per Standard Precautions Always for SARS, avian influenza	Per Standard Precautions Always for SARS, avian influenza
N95 or higher respirator (Always don *before entry* into room)	When aerosol-generating procedures performed for influenza, SARS, VHF[b]	When aerosol-generating procedures performed for influenza, SARS, VHF	Yes; don ***before entry*** into room
Room placement	Single-patient room preferred Cohort similar infections if single-patient rooms unavailable	Single-patient room preferred Cohort similar infections if single-patient rooms unavailable	Single-patient room Negative air pressure; 12 air changes/hr for new construction, 6 air changes/hr for existing rooms
Environmental measures	Increased frequency, especially in the presence of diarrhea, transmission of *C. difficile*, norovirus Bleach for VRE, *C. difficile*, norovirus	Routine	Routine
Transport	Mask patient if coughing Cover infectious skin lesions PPE not routinely required for transporter	Mask patient	Mask patient Cover infectious skin lesions

[a] In addition to Standard precautions, use Transmission-Based Precautions for patients with highly transmissible or epidemiologically important pathogens for which additional precautions are needed.

[b] Includes Ebola virus. Consult most recent Centers for Disease Control and Prevention and World Health Organization guidelines for recommended infection control precautions for Ebola virus disease.

PPE, personal protective equipment; SARS, severe acute respiratory syndrome; VHF, viral hemorrhagic fever; VRE, vancomycin-resistant *Enterococcus*.

Modified with permission from Siegel JD, Rhinehart E, Jackson M, et al. Guideline for isolation precautions: preventing transmission of infectious agents in healthcare settings, 2007. Am J Infect Control 2007;35(Suppl 2):S65–S164.

TABLE 2.3

Clinical Syndromes or Conditions Warranting Empiric Transmission-Based Precautions in Addition to Standard Precautions Pending Confirmation of Diagnosis[a]

Clinical Syndrome or Condition[b]	Potential Pathogens[c]	Empiric Precautions (Always Includes Standard Precautions)
DIARRHEA		
Acute diarrhea with a likely infectious cause in an incontinent or diapered patient	Enteric pathogens[d]	Contact Precautions (pediatrics and adult)
MENINGITIS	*Neisseria meningitidis*	Droplet Precautions for first 24 hr of antimicrobial therapy; mask, face, and eye protection for intubation
	Enteroviruses	Contact Precautions for infants and children
	Mycobacterium tuberculosis	Airborne Precautions if pulmonary infiltrate
		Airborne Precautions plus Contact Precautions if potentially infectious draining body fluid present
RASH OR EXANTHEMS, GENERALIZED, ORIGIN UNKNOWN		
Petechial or ecchymotic exanthem with fever (general)	*N. meningitidis*	Droplet Precautions for first 24 hr of antimicrobial therapy
If traveled in an area with an ongoing outbreak of viral hemorrhagic fever in the 10 days before onset of fever	Ebola, Lassa, Marburg viruses	Airborne Precautions plus Contact Precautions, with face and eye protection, emphasizing safety sharps and barrier precautions when blood exposure likely In the United States, asymptomatic persons can be managed in Ebola assessment centers. Transfer symptomatic persons with infection to biocontainment units Use a single-use fluid-resistant or impermeable gown that extends to at least midcalf or a coverall without an integrated hood. Two pairs of gloves should be worn. Use a single-use fluid-resistant or impermeable boot cover. A single-use fluid resistant or impermeable apron

		should be worn to cover the torso if the patient has vomiting or diarrhea Consult CDC, WHO websites for current recommendations
Vesicular	Varicella-zoster, herpes simplex, variola (smallpox), vaccinia viruses	Airborne plus Contact Precautions Contact Precautions only if herpes simplex, localized zoster in an immunocompetent host, or vaccinia viruses most likely
Maculopapular with cough, coryza, and fever	Rubeola (measles) virus	Airborne Precautions
RESPIRATORY INFECTIONS		
Cough, fever, or upper-lobe pulmonary infiltrate in an HIV-negative patient or a patient at low risk for HIV infection	*M. tuberculosis,* respiratory viruses, *Streptococcus pneumoniae, Staphylococcus aureus* (MSSA or MRSA)	Airborne Precautions plus Contact Precautions until *M. tuberculosis* ruled out Droplet Precautions if respiratory viruses most likely
Cough, fever, or pulmonary infiltrate in any lung location in an HIV-infected patient or a patient at high risk for HIV infection	*M. tuberculosis,* respiratory viruses, *Streptococcus pneumoniae, Staphylococcus aureus* (MSSA or MRSA)	Airborne Precautions plus Contact Precautions Use eye and face protection if aerosol-generating procedure performed or contact with respiratory secretions anticipated If tuberculosis is unlikely and no AIIRs or respirators are available, use Droplet Precautions instead of Airborne Precautions Tuberculosis more likely in HIV-infected than in HIV-uninfected persons
Cough, fever, or pulmonary infiltrate in any lung location in a patient with a history of recent travel (10–21 days) to a country with an outbreak of SARS or avian influenza	*M. tuberculosis,* severe acute respiratory syndrome virus–coronavirus (SARS-CoV), avian influenza	Airborne Precautions plus Contact Precautions in addition to eye protection If SARS and tuberculosis unlikely, use Droplet Precautions instead of Airborne Precautions
Respiratory infections, particularly bronchiolitis and pneumonia, in infants and young children	Respiratory syncytial virus, parainfluenza virus, adenovirus, influenza virus, human metapneumovirus	Contact Precautions plus Droplet Precautions Droplet Precautions can be discontinued when adenovirus and influenza have been ruled out
SKIN OR WOUND INFECTION		
Abscess or draining wound that cannot be covered	*Staphylococcus aureus* (MSSA or MRSA), group A streptococcus	Contact Precautions Add droplet precautions for the first 24 hr of appropriate antimicrobial therapy if invasive group A streptococcal disease is suspected

[a] Infection control professionals should modify or adapt this table according to local conditions. To ensure that appropriate empiric precautions are always implemented, hospitals must have systems in place to evaluate patients routinely according to these criteria as part of preadmission and admission care.

[b] Patients with the syndromes or conditions listed may have atypical signs or symptoms (e.g., neonates and adults with pertussis may not have paroxysmal or severe cough). The clinician's index of suspicion should be guided by the prevalence

of specific conditions in the community, as well as clinical judgment.

[c] The organisms listed under the column "Potential Pathogens" are not intended to represent the complete, or even most likely, diagnoses, but rather possible etiologic agents that require additional precautions beyond standard precautions until they can be excluded.

[d] These pathogens include enterohemorrhagic *Escherichia coli* O157:H7, *Shigella* spp., hepatitis A virus, noroviruses, rotavirus, and *Clostridium difficile.*

AIIR, airborne infection isolation room; CDC, Centers for Disease Control and Prevention; CoV, coronavirus; HIV, human immunodeficiency virus; MRSA, methicillin-resistant *Staphylococcus aureus;* MSSA, methicillin-susceptible *Staphylococcus aureus;* SARS, severe acute respiratory syndrome; VHF, viral hemorrhagic fever; WHO, World Health Organization.

Environmental Measures

Contaminated environmental surfaces and noncritical medical items have been implicated in transmission of several infectious agents, including VRE, *C. difficile, Acinetobacter* spp., MRSA, and RSV in healthcare settings.[4,85,86] Pathogens on surfaces are transferred to the hands of HCP and are then transferred to patients or items to be shared. Occupying a room previously occupied by a patient with a key pathogen is a risk factor for acquiring that pathogen during a hospital stay. Most often, the failure to follow recommended procedures for cleaning and disinfection contributes more than does the specific pathogen to the environmental reservoir during outbreaks. Education of environmental services personnel combined with direct observation and feedback was associated with a persistent decrease in VRE acquisition in a medical ICU. Use of a standardized cleaning checklist and implementation of monitoring for adherence to recommended environmental cleaning practices are important determinants of success. Visual markers (e.g., invisible fluorescein powder) and adenosine triphosphate bioluminescence technologies are also useful for monitoring effective environmental cleaning and providing immediate feedback to workers.[87] A program of environmental cleaning should be developed collaboratively by the IPC and environmental services departments. Certain infectious agents (e.g., rotavirus, noroviruses, *C. difficile*) can be resistant to some routinely used hospital disinfectants; thus when ongoing transmission occurs despite appropriate cleaning procedures, a 1 :

10 dilution of 5.25% sodium hypochlorite (household bleach) or other special disinfectants are indicated.

"No-touch" automated room decontamination technologies have been developed and added to room turnover procedures in some facilities. Ultraviolet light irradiation and hydrogen peroxide vapor systems have been shown to reduce surface contamination with common pathogens and decrease the risk of acquiring HAIs caused by those pathogens when these systems are added to a terminal cleaning regimen.[85–87] At specific wavelengths, ultraviolet light breaks the molecular bonds in DNA, thus destroying the organisms. Ultraviolet technology also has been considered as a method of disinfecting PPE, as a risk mitigation strategy for HCP caring for patients with EVD.[88] These technologies supplement, but do not replace, standard cleaning and disinfection because surfaces must be physically cleaned of particulate matter and debris. Other disadvantages of these systems are that they cannot be used when people are in the rooms, room turnover is delayed, and the systems are expensive to purchase. No recommendations have been made for routine use or specific indications because research on antimicrobial effectiveness, cost effectiveness, and feasibility of these systems is ongoing.

Self-disinfecting surfaces can be created by altering the structure of the surface material or by incorporating a material that has antimicrobial activity.[85–87] Copper has antimicrobial activity against a wide range of organisms including bacteria and fungi. Thus, incorporating copper into high-touch surfaces such as toilet seats, bed rails, door handles, or countertops is a novel infection prevention strategy that has been shown to reduce bacterial colony counts compared with control surfaces in healthcare settings.[89] However, no recommendation for routine use has yet been made.

Disinfection, Sterilization, and Removal of Infectious Waste

Disinfection and sterilization as they relate to IPC have been reviewed,[90] and the HICPAC/CDC developed comprehensive guidelines in 2008.[91] *Cleaning* is the removal of all foreign material from surfaces and objects. This process is accomplished using soap and enzymatic products. Failure to remove all organic material from items before disinfection and sterilization reduces the effectiveness of these processes. *Disinfection* is a process that eliminates all forms of microbial life except the endospore. Disinfection usually requires liquid chemicals. Disinfection of an inanimate surface or object is affected adversely by the following: the presence of organic matter; a high level of microbial contamination; use of too dilute germicide; inadequate disinfection time; an object that can harbor microbes in protected cracks, crevices, and hinges; and pH and temperature.

Sterilization is the eradication of all forms of microbial life, including fungal and bacterial spores. Sterilization is achieved by physical and chemical processes such as steam under pressure, dry heat, ethylene oxide, and liquid chemicals. The Spaulding classification of patient care equipment as *critical, semicritical,* and *noncritical* items with regard to sterilization and disinfection is used by the CDC. *Critical items* require sterilization because they enter sterile body tissues and carry a high risk of causing infection if they are contaminated; *semicritical items* require disinfection because they may contact mucous membranes and nonintact skin; and *noncritical items* require routine cleaning because they come in contact only with intact skin. If noncritical items used on patients requiring Transmission-Based Precautions, especially Contact Precautions, must be shared, these items should be disinfected between uses. Guidelines for specific objects and specific disinfectants are published and updated by the CDC. Multiple published reports and manufacturers similarly recommend the use and reuse of objects with appropriate sterilization, disinfection, or cleaning recommendations. Recommendations in guidelines for reprocessing endoscopes to avoid contamination focus on training of personnel, meticulous manual cleaning, high-level disinfection followed by rinsing and air-drying, and proper storage.[92] However, outbreaks of MDR GNB infections associated with exposure to duodenoscopes used for retrograde cholangiopancreatography that have been reprocessed according to recommendations suggest a need for new endoscope reprocessing technologies.[51,93] These endoscopes have a complex design with long, narrow channels, crevices that are difficult to access with a cleaning brush, right-angle turns, and heavy microbial contamination following procedures. Until new methods are developed, meticulous adherence to recommended processes with enhancements should be followed. Medical devices that are designed for single use (e.g., specialized catheters, electrodes, biopsy needles) must be reprocessed by third parties or hospitals according to the guidance issued by the Food and Drug Administration (FDA) in August, 2000 with amendments in September, 2006; such reprocessors are considered and regulated as "manufacturers." Available data show that single-use devices reprocessed according to the FDA regulatory requirements are as safe and effective as new devices.

Deficiencies in disinfection and sterilization leading to infection have resulted either from failure to adhere to scientifically based guidelines or failures in the disinfection or sterilization processes. When such failures are discovered, an investigation must be completed, including notification of patients and, in some cases, testing for infectious agents. A guidance document for risk assessment and communication to patients in such situations is published.[94]

Healthcare facility waste is all biologic or nonbiologic waste that is discarded and not intended for further use. *Medical waste* is material generated as a result of use with a patient, such as for diagnosis, immunization, or treatment, and it includes soiled dressings and intravenous tubing. *Infectious waste* is that portion of medical waste that potentially could transmit an infectious disease. Microbiologic waste, pathologic waste, contaminated animal carcasses, blood, and sharps are all examples of infectious waste. Methods of effective disposal of infectious waste include incineration, steam sterilization, drainage to a sanitary sewer, mechanical disinfection, chemical disinfection, and microwave treatment. State regulations guide the treatment and disposal of regulated medical waste. Recommendations are available for developing and maintaining a program within a facility for safe management of medical waste.[95]

Visitation Policies

Special visitation policies are required in pediatric units, especially the high-risk units, because acquisition of a seemingly innocuous viral infection in neonates and in children with underlying diseases can result in unnecessary evaluations and empiric therapies for suspected septicemia as well as serious, life-threatening disease. All visitors with signs or symptoms of respiratory or gastrointestinal tract infection should be restricted from visiting patients in healthcare facilities. Increased restrictions may be required during a community outbreak (e.g., SARS, pandemic influenza, enterovirus D68). During respiratory virus season, the number of visitors can be limited and the age restriction increased. It is preferred for all visitors to be immunized against influenza during influenza season. Several children's hospitals provide influenza vaccine or tetanus, diphtheria, and acellular pertussis (Tdap) vaccine, or both, to household contacts at no charge, thereby supporting the cocooning strategy endorsed by the Advisory Committee on Immunization Practices and the American Academy of Pediatrics.[96]

For patients requiring Contact Precautions, the use of PPE by visitors is determined by the nature of the interaction with the patient and the likelihood that the visitor will frequent common areas on the patient's unit or interact with other patients and their families. It is important to distinguish parents or guardians from nonhousehold visitors when determining whether the visitor should wear PPE. The risk-benefit decision should weigh not only the specific pathogen in question, but also the effect of parental or guardian PPE on breastfeeding, bonding, and family participation in the child's medical care. For family members who are rooming in with children who have prolonged hospitalizations, restriction of visitation to other patients is emphasized. A SHEA expert guidance document has been published to summarize the principles to follow to prevent transmission of infectious agents by visitors to patients because few data are available to inform evidence-based recommendations.[97]

Although most pediatricians encourage visits by siblings in inpatient areas, the medical risk must not outweigh the psychosocial benefit. Families favorably regard sibling visitation, and no evidence indicates increased bacterial colonization or subsequent bacterial infection in the neonate or older child who has been visited by siblings. Strict guidelines for sibling visitation should be established and enforced in an effort to maximize visitation opportunities and minimize risks of transmission of infectious agents, most frequently viruses. The following recommendations regarding visitation can guide policy development:

1. Sibling visitation is encouraged in the well-child nursery and NICU, as well as in areas for care of older children.

2. Before visitation, parents should be interviewed by a trained staff nurse concerning the current health status of the sibling. Siblings should not be allowed to visit if they are delinquent in recommended vaccines, have fever or symptoms of an acute illness, or are within the incubation period following exposure to a known infectious disease. After the interview, the physician or nurse should place a written consent for sibling visitation in the patient's permanent record and a name tag indicating that the sibling has been approved for visitation for that day.

3. Asymptomatic siblings who recently were exposed to varicella but who previously were immunized can be assumed to be immune.

4. The visiting sibling should visit only his or her sibling and not be allowed in playrooms with groups of patients.

5. Visitation should be limited to periods of time that ensure adequate screening, observation, and monitoring of visitors by medical and nursing staff members.

6. Children should perform hand hygiene before and after contact with the patient or upon entry and departure from the patient's room.

7. During the entire visit, sibling activity should be supervised by parents or another responsible adult.

Animals in Healthcare Facilities

Animal-assisted therapy can be of substantial clinical benefit to the child hospitalized for prolonged periods; therefore it is important for healthcare facilities to provide guidance for safe visitation. Many zoonoses and infections are attributable to animal exposure (see Chapter 89). Most infections result from inoculation of animal flora through a bite or scratch or self-inoculation after contact with the animal, the animal's secretions or excretions, or contaminated environment. Although few data support a true evidence-based guideline for animal visitation (including personal pets) in healthcare facilities, updated expert guidance is provided in the SHEA Expert Guidance on Animals in Healthcare Facilities: Recommendations to Minimize Potential Risk, which includes a review of the literature related to animal-assisted activities.[98]

Prudent visitation policies should limit visitation to animals that: (1) are domesticated; (2) do not require a water environment; (3) do not bite or scratch; (4) can be brought to the hospital in a carrier or easily walked on a leash; (5) are trained to defecate and urinate outside or in appropriate litter boxes; (6) can be bathed before visitation; and (7) are known to be free of respiratory, dermatologic, and gastrointestinal tract disease. Despite the established risk of salmonellosis associated with reptiles (e.g., turtles, iguanas), many reports of outbreaks of invasive disease associated with reptiles continue to be published[99]; reptiles should be excluded from pet visitation programs, and families should be advised not to have pet reptiles in the home with young infants or immunocompromised persons. Exotic animals that are imported should be excluded because of unpredictable behavior and the potential for transmission of unusual pathogens (e.g., monkeypox in the US in 2003).[100,101] Visitation should be limited to short periods and confined to designated areas. Visiting pets must have a certificate of immunization from a licensed veterinarian. Children should observe hand hygiene after contact with animals. Most pediatric facilities restrict pet interaction with severely immunosuppressed patients and patients in ICUs.

Occupational Health

Occupational health and student health collaboration with the IPC department of a healthcare facility is required by the Occupational Safety and Health Administration. HCP are at increased risk of infection in hospitals caring for children because (1) children have a high incidence of infectious diseases, (2) personnel can be susceptible to many pediatric pathogens, (3) pediatric care requires close contact, (4) children lack good personal hygiene, (5) infected children can be asymptomatic, and (6) HCP are exposed to multiple family members who also may be infected.

The occupational health department is an educational resource for information on infectious pathogens in the healthcare workplace. In concert with the IPC service, occupational health provides preemployment education and respirator fit testing and annual retraining for all employees regarding routine health maintenance, available recommended and required vaccines, Standard and Transmission-Based Precautions, and exposure control plans. Screening for tuberculosis at regular intervals, as determined by the facility's risk assessment, can use either tuberculin skin testing or interferon-γ release assays.[102] With new pathogens being isolated, new diseases and their transmission described, and new prophylactic regimens and treatment available, it is mandatory that personnel have an up-to-date working knowledge of IPC and know where and what services, equipment, and therapies are available for HCP.

All HCP should be screened by history or serologic testing, or both, to document their immune status to specific agents, and immunization should be provided for the following for all employees who are nonimmune and who do not have contraindications to receiving the vaccine: diphtheria toxoid, hepatitis B virus, influenza (yearly), mumps, poliomyelitis, rubella, rubeola, varicella, and Tdap. The 2006 Advisory Committee on Immunization Practices recommendation to administer a single dose of Tdap to certain HCP was amended in 2011 to have no restriction based on age or time interval since the last Td dose. Providing vaccines at no cost to HCP increases acceptance.

Influenza vaccine coverage among HCP has increased over time to 77% overall for the 2014 to 2015 influenza season, with the highest coverage rate of 90% in HCP working in hospitals and the lowest rate of 64% in long-term care settings.[103] Although mandatory influenza vaccination programs for all employees in healthcare facilities are endorsed by many professional societies,[104,105] some facilities have had success using novel strategies that include incentives, without a mandate.[106] Publications from several large institutions, including children's hospitals, indicate that mandatory programs with only medical and religious exemptions are well received, and only rare employees are terminated for failure to be vaccinated.[107,108]

Special Concerns of Healthcare Personnel

HCP who have common underlying medical conditions should be able to obtain general information on wellness and screening when needed from the occupational health service. HCP with direct patient contact who have infants <1 year of age at home often are concerned about acquiring infectious agents from patients and transmitting them to their susceptible children. An immune healthcare worker who is exposed to VZV does not become a silent "carrier" of VZV. However, pathogens to which the healthcare worker is partially immune or nonimmune can cause a severe, mild, or asymptomatic infection in the employee that can be transmitted to family members. Examples include influenza, pertussis, RSV and other respiratory viruses, norovirus, and tuberculosis. Important preventive procedures for HCP with infants at home or who are pregnant are as follows: (1) consistent training and observance of Standard Precautions, Transmission-Based Precautions, and especially hand hygiene according to published recommendations; (2) annual influenza and 1-time Tdap immunization (unless pregnant, when a Tdap immunization during each pregnancy is recommended); (3) routine tuberculosis screening; (4) assurance of immunity or immunization against poliomyelitis, measles, mumps, hepatitis B, and rubella; (5) early medical evaluation for acute infectious illnesses; (6) routine, on-time immunization of infants; and (7) prompt initiation of prescribed prophylaxis or therapy following exposure or development of certain infections.

HCP who are, could be, or anticipate becoming pregnant should feel comfortable working in the healthcare workplace. In fact, with Standard Precautions and appropriate adherence to environmental cleaning and isolation precautions, vigilant HCP can be at less risk than a preschool teacher, childcare provider, or mother of children with many playmates in the home. Pathogens of potential concern to pregnant HCP include cytomegalovirus, hepatitis B virus, influenza, measles, mumps, parvovirus B19, rubella, VZV, *M. tuberculosis*, and, since 2015, Zika virus. The causal association between Zika virus and microcephaly and other neurodevelopmental abnormalities[109] has led to recommended precautions. Although Zika virus is more frequently acquired outside of healthcare, pregnant HCP are advised to follow safe injection practices for prevention of exposure to infectious blood.[4] Pregnancy is an *indication* for influenza vaccine to prevent the increased risk of serious disease and hospitalization that occurs in women who develop influenza in the second or third trimester of pregnancy. In 2011, the CDC recommended universal immunization with Tdap (if previously not immunized with Tdap) for pregnant women after 20 weeks of gestation, and since 2012, the CDC recommends a dose of Tdap with each pregnancy.[110] Pregnant workers should assume that all patients potentially are infected with cytomegalovirus and other "silent" pathogens and should use hand hygiene and gloves when handling body fluids, secretions, and excretions. Table 2.4 summarizes information about infectious agents that are relevant to the pregnant woman working in healthcare. Chapters on each agent may be consulted for more specific information.

TABLE 2.4

Pregnant Healthcare Personnel: Guide to Management of Occupational Exposure to Selected Infectious Agents

Agent or Disease	In-Hospital Source	Potential Effect on the Fetus	Perinatal Transmission	Maternal Screening
Bordetella pertussis **Pertussis ("whooping cough")**	Respiratory droplets from a coughing patient, HCP, visitor	No congenital syndrome	Maternal respiratory secretions	Documenta of date of vaccination Tdap Tdap recommen during eac pregnancy. Past histor pertussis d is *not* prote and does n replace vac
Cytomegalovirus (CMV)/congenital infection syndrome[a], hearing loss	Patient populations: neonates, toddlers in childcare, hemodialysis patients, immunocompromised hosts, transplant recipients HCP acquisition during pregnancy unlikely to be occupational	Symptomatic congenital infection syndrome[a] 5%–10%; hearing loss 10%–15%; asymptomatic congenital infection; hepatitis, anemia, thrombocytopenia Hearing loss can have later onset	Primary infection 25%–50% Recurrent infection or second infection with new strain: 69% reduction in risk of transmission	Routine screening n recommen Preexisting maternal antibody incomplete protective fetus

	Urine, saliva, blood, semen, vaginal secretions, breast milk, respiratory secretions if pneumonia present		Symptomatic <5%–15%	
Ebola virus	Blood and body fluids from infected, clinically ill patients, especially large-volume diarrhea	Spontaneous abortion, stillbirth Neonatal survival rare.	Data on perinatal transmission limited and anecdotal; likely very high because Ebola virus is present in products of conception when tested	Routine screening n recommenc but a low threshold f diagnosing in the preg woman is recommenc PCR on blo the recommenc diagnostic Case fatalit of EVD in pregnant women is 9
Hepatitis A virus (HAV)	Feces (most common), highest titer just before onset of jaundice; blood *very* rare Transmission in healthcare settings rare	None; transmission can occur at the time of delivery if mother still in the infectious phase and can cause hepatitis in infant	None	Routine screening n recommenc
Hepatitis B virus (HBV)	Blood, body fluids, vaginal secretions, semen	Hepatitis; if acquired perinatally or at young age, increased risk for hepatocellular carcinoma	HBeAg$^-$ and HBsAg$^+$ (10%) HBeAg$^+$ and HbsAg$^+$ (90%)	Routine H testing adv Documenta of vaccinati
Hepatitis C virus (HCV)	Blood, body fluids	Hepatitis	Transmission 5% (range 0% –25%)	Screening c risk factors present: illi drug user (mother or

				partner wh illicit IV dr user); histo organ trans transfusion blood or bl products be 1992; hemodialys HBV or HI infection; unexplaine elevation o serum hepa enzymes; h of tattooing with histor percutaneo exposure to blood test f HCV antibo positive, H RNA)
Herpes simplex virus (HSV) **Fever blisters, cold sores, genital ulcers, encephalitis**	Vesicular fluid, oropharyngeal and vaginal secretions, amniotic fluid	Sepsis, encephalitis, meningitis, mucocutaneous lesions, congenital malformation (rare)	Primary genital infection 33%–50% Recurrent genital infection 1%–2%	Routine antibody te minimally useful Maternal ty specific ser for HSV-1 a HSV-2 antibodies should be considered when evalu an asymptoma neonate following vaginal or cesarean delivery to women wit genital lesio that are characterist HSV
Human immunodeficiency virus (HIV) **Acquired immunodeficiency syndrome (AIDS)**	Blood, body fluids, vaginal secretions, semen	No congenital syndrome Transmission primarily during delivery If infected, onset of symptoms usually at 12–18 months of age	Risk of transmission determined by maternal HIV viral load, duration of exposure to maternal blood, body fluids (including breast milk),	Routine pre screening advised wi repeat at er pregnancy high-risk behaviors HIV-expose infants who receive AR from birth: repeated sc

			and use of ART during pregnancy, labor, and postnatally in the infant If no ART: maternal viral load <1000 copies/mL virus, rate of 2%; if load ≥10,000, rate up to 25% Rate reduced to <3% with perinatal and neonatal ART	during firs HIV antibo screen wit fourth-generation if positive, quantitativ PCR
Influenza virus **Influenza (flu)**	Respiratory droplets or sneezing; coughing patient, HCP, visitor	No congenital syndrome Influenza in mother can cause fetal hypoxia, premature labor, and fetal death Increased morbidity during third trimester of pregnancy Increased morbidity and mortality in pregnant women with 2009 influenza A (H1N1)	Maternal respiratory secretions	Documenta of vaccine received du current sea

Measles (rubeola)	Respiratory secretions, coughing patient	Prematurity, spontaneous abortion; no congenital syndrome	Rare	Serology (I question af exposure, b not routine checked if adequate documenta provided Provider-documente disease or 2 doses meas containing vaccine ≥12 months of a
***Mycobacterium tuberculosis*, active disease (tuberculosis [TB])**	Sputum, skin lesions, CSF if meningitis present	Neonatal tuberculosis; liver most frequently infected	Rare	PPD, IGRA (interferon-release assa e.g., Quantiferoı Gold, T-Spo Chest radiograph indicated clinically or past known positive PP IGRA resul
***Neisseria meningitidis*, meningococcal disease, meningococcal meningitis, sepsis**	Blood, respiratory secretions	No congenital syndrome Fetus at risk if mother develops severe disease during pregnancy	Rare	No routine screening
Parvovirus B19 Fifth disease (slapped cheeks), anemia, fetal	Respiratory secretions; blood of immunocompromised patients and patients	Fetal hydrops, stillbirth No congenital syndrome	Rare	No routine screening. Parvovirus DNA can b

hydrops	with sickle cell disease during aplastic crisis Patient with Fifth disease no longer contagious once rash appears	Approximately 25% Fetal death <10%		detected in serum, leukocytes, respiratory secretions, tissue speci Specific Ig IgG if expo has occurre
Rubella	Respiratory secretions	Congenital infection syndrome[a] 90% affected in first trimester 40%–50% affected overall	Rare	Documenta of 2 doses rubella-containing vaccine beforepreg Routine ru IgG testing during pregnancy Preconcept screening recommen
Syphilis **Rash, skin and genital lesions, central nervous system disease**	Blood, lesion (especially large bullae of congenital syphilis), amniotic fluid	Congenital infection syndrome[a] Variable 10%–90%; depends stage of maternal disease and trimester of the infection	Transmission possible, related to contagiousness of maternal lesions	Serum VD RPR Serum FTA
Varicella zoster virus (VZV) **Chickenpox, shingles**	Respiratory secretions, vesicle fluid	Congenital infection syndrome Malformations, skin, limb, CNS, eye: chickenpox zoster	High risk of infection and severe disease if maternal varicella within 5 days	Varicella Ig serology Past history chickenpox unreliable

		Congenital syndrome 2%	before or 2 days after delivery	
Zika virus	Blood, body fluids of infected patients; mosquitoes in endemic area. Acquisition in the community more likely than in healthcare settings	Microcephaly, other neurodevelopmental abnormalities	Undefined at time of publication	rt-PCR on Serum IgG,

[a] Congenital syndrome: varying combinations of jaundice, hepatosplenomegaly, microcephaly, thrombocytopenia, anemia, retinopathy, skin and bone lesions, and “blueberry muffin spots” (extramedullary hematopoiesis).

[b] Live virus vaccine given before or after pregnancy.

ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; CNS, central nervous system; CSF, cerebrospinal fluid; EVD, Ebola virus disease; FTA-ABS, Fluorescent treponema antigen-antibody test; HBeAg, hepatitis B e antigen; HBIG, hepatitis B immune globulin; HBsAg, hepatitis B surface antigen; HCP, healthcare personnel; IgG, immunoglobulin G; IgM, immunoglobulin M; IGIV, immune globulin intravenous; IM, intramuscular; IV, intravenous; PCR, polymerase chain reaction; PPD, purified protein derivative; RPR, rapid plasma reagin test; Tdap, tetanus-diphtheria-acelluar pertussis; VDRL, Venereal Disease Research Laboratory test; WHO, World Health Organization.

Infection Prevention and Control in the Nonacute Care Setting

The risk of HAIs in pediatric ambulatory settings is substantial, and it usually is associated with lack of adherence to routine IPC practices and procedures, especially disinfection, sterilization, and hand hygiene. Respiratory viral agents and *M. tuberculosis* are noteworthy pathogens transmitted in ambulatory settings. Transmission of RSV in an HSCT outpatient clinic has been demonstrated using molecular techniques.[111] Crowded waiting rooms, toys, furniture, lack of isolation of children, unwell children, contaminated hands, contaminated secretions, and susceptible HCP are only some of the factors that result in sporadic and epidemic illness in outpatient settings. The association of community-associated MRSA in HCP working in an outpatient HIV clinic with environmental community-associated MRSA contamination of that clinic indicates the potential for transmission in this setting.[112] Patient-to-patient transmission of *Burkholderia* species and *P. aeruginosa* in outpatient clinics for patients with cystic fibrosis has been confirmed and prevented by implementing recommended IPC methods.[9] IPC guidelines and policies for pediatric outpatient settings, including office practices, were published by the American Academy of Pediatrics in 2007,[113] reaffirmed in 2015, and are updated currently. Prevention strategies include definition of policies, education, and strict adherence to guidelines. In pediatrics, among the most important interventions are separation of children with respiratory tract illnesses from well children and consistent implementation of respiratory etiquette or cough hygiene. A guideline for IPC for outpatient settings with a checklist and a guideline for outpatient oncology settings can be found on the CDC website.[114] Principles and recommendations for Safe Living after HSCT[115] and for patients with cystic fibrosis[9] are valuable contributions to management of infectious risks for specific populations in the ambulatory setting. A guideline based on data and expert consensus opinion for IPC in residential facilities for pediatric patients and their families provides practical guidance for settings where high-risk patients live with their families for varying periods of time.[116] IPC challenges now are being addressed in long-term care facilities for children.[117] More data are needed to determine the most effective and least restrictive practices.

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3

Infections Associated With Group Childcare

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On average, 12.5 million (61%) of the 20.4 million children in the United States who are younger than 5 years of age were enrolled in a regular childcare arrangement during the spring of 2011.[1] Group childcare settings can increase the frequency of certain infectious diseases and amplify outbreaks of illness (Table 3.1). Aggregation of young children potentiates transmission of organisms that can produce disease in other children, adult care providers, parents, and community contacts. Children newly entered into group childcare are at especially high risk of enteric and respiratory tract infections. However, mothers whose children were enrolled in group childcare before 2.5 years of age reported their children had less frequent respiratory and gastrointestinal tract infections and episodes of otitis media during elementary school years.[2] A longitudinal repeated-event analysis of 3963 newborns followed for 8 years found that children who were enrolled in childcare at <2 years of age had more episodes of wheezing in the first years of life; however, among those children without older siblings, wheezing episodes and steroid use between ages 4 and 8 years were reduced compared with children who were not enrolled in childcare at an early age. Overall, early childcare was not found to be protective against asthma symptoms, airway hyperresponsiveness, or allergic sensitization when children were assessed at 8 years of age.[3] An increase in antibiotic use as an attempt to facilitate earlier return to care enhances the potential for emergence of resistant organisms, thus resulting in an increased economic burden to individual persons and society.[4–6] Despite the challenges of frequent respiratory and gastrointestinal illness exacerbations among children enrolled in group childcare, these arrangements facilitate opportunities for socialization and enable primary caregivers to be employed outside the home.

TABLE 3.1

Association of Infectious Diseases With Group Childcare Settings

Disease or Infection	**Risk Factors and Association With Outbreaks**
Enteric	Close person-to-person contact, fecal-oral contact, suboptimal hand hygiene and food preparation practices
Viral	
Rotaviruses, enteric adenoviruses, astroviruses, noroviruses, hepatitis A virus (HAV)	Commonly associated with outbreaks; HAV and rotavirus vaccine preventable
Bacterial	
Shigella spp., *Escherichia coli* O157:H7	Commonly associated with outbreaks
Campylobacter spp., *Salmonella* spp., *Clostridium difficile*	Less commonly associated with outbreaks
Parasitic	
Giardia intestinalis	Commonly associated with outbreaks
Cryptosporidium parvum	
Respiratory tract (acute upper and lower respiratory tract infections and invasive disease)	Aerosolization and respiratory droplets, person-to-person contact, suboptimal hand hygiene
Bacterial	
Haemophilus influenzae type b (Hib)	Few outbreaks; vaccine preventable
Streptococcus pneumoniae	Few outbreaks; vaccine preventable; invasive *S. pneumoniae* caused by serotypes not in vaccine
Group A streptococcus	Few outbreaks and low risk of secondary cases
Neisseria meningitidis	Few outbreaks; some serogroups vaccine preventable
Bordetella pertussis	Increasingly associated with outbreaks in childcare centers and schools; vaccine preventable
Mycobacterium tuberculosis	Occasional outbreaks, usually as a result of contact with an infectious adult care provider
Kingella kingae	Outbreaks rare; oropharynx usual habitat; usually manifest as arthritis and osteomyelitis
Viral	
Rhinoviruses, parainfluenza, influenza, respiratory syncytial virus (RSV), respiratory adenoviruses, influenza, metapneumoviruses, bocavirus	Disease usually caused by same organisms circulating in the community; influenza vaccine preventable in children ≥6 months of age

Multiple organ systems	
Cytomegalovirus	Prevalent; asymptomatic excretion with transmission from children to providers
Parvovirus B19	Outbreaks reported; risk to susceptible pregnant women and immunocompromised
Varicella-zoster virus (VZV)	Outbreaks in childcare centers occur; vaccine preventable in children ≥12 months of age; zoster lesions present low risk of infection
Herpes simplex virus (HSV)	Low risk of transmission from active lesions and oral secretions
Hepatitis B virus	Rarely occurs in childcare centers; vaccine preventable
Hepatitis C virus	No documented cases of transmission in the childcare setting
Human immunodeficiency virus (HIV)	No documented cases of transmission in the childcare setting
Skin	Close person-to-person contact
Staphylococcal and streptococcal impetigo	Transmission increased by close person-to-person contact with lesions; outbreaks less likely with decreased incidence of varicella infections; methicillin-resistant *Staphylococcus aureus* (MRSA) infection common
Scabies	Outbreaks in group childcare reported
Pediculosis	Common in children attending group childcare
Ringworm	Tinea corporis and tinea capitis outbreaks associated with childcare
Conjunctiva	Outbreaks in group childcare reported with both bacterial and viral causes

Childcare Settings

Quantifying the number of children participating in each type of childcare setting is challenging because of different ascertainment methods used in several data sources. Types of facilities can be classified by size of enrollment, age of enrollees, and environmental characteristics of the facility. Grouping of children by age varies by setting, but in organized care facilities children usually are separated into the following groups: infants (6 weeks through 12 months), toddlers (13 through 35 months), preschoolers (36 months through 59 months), and school-aged children (5 through 12 years). These designations have relevance to infectious disease epidemiology as well as regulation and monitoring. Most nonrelative care provided in an organized care facility is subject to state licensing and regulation, whereas care by a relative in a child's or provider's home is usually not subject to state regulations and monitoring.

The United States Census Bureau conducts the Survey of Income and Program Participation (SIPP), which collects information about childcare arrangements for children <15 years of age. In 2011, 51% of children <5 years of age with working mothers were cared for by a relative, 33% were in organized care including center-based care or family childcare homes, 27% had multiple arrangements, and 11% did not have a regular childcare arrangement, with some survey respondents selecting more than 1 option.[1]

Epidemiology and Etiology of Infections

Although most infectious organisms can be associated with outbreaks in settings that do not involve childcare, many agents have the propensity to propagate in childcare settings (see Table 3.1.)

Enteric Infections

Enteric viruses are the predominant cause of diarrheal syndromes among children in group childcare.[7] Outbreaks of diarrhea occur at a rate of approximately 3 per year per childcare center and are associated most frequently with organisms that cause infection after ingestion of a low inoculum. These organisms generally are transmitted from person to person and include rotavirus, norovirus, sapovirus, astrovirus, enteric adenovirus, *Giardia intestinalis, Cryptosporidium, Shigella* spp., *Escherichia coli* O157:H7, other Shiga toxin–producing *E. coli* (STEC), *E. coli* O114, and enteropathogenic *E. coli.* These fecal coliforms and enteric viruses contaminate the environment with greater frequency during outbreaks of diarrhea. In a prospective study of acute gastroenteritis in childcare centers, viruses isolated from the stool of children with diarrhea also were detected on environmental surfaces in 45% of outbreaks.[8] The inoculum associated with diarrhea, the attack rates, and the frequency of asymptomatic excretion of organisms for common enteric infections in childcare settings are shown in Table 3.2. Reported attack rates depend on several factors, including methods used for organism detection.

TABLE 3.2

Organism	Inoculum Required to Cause Diarrhea in Adult Volunteers	Attack Rate in Enrollees (%)	Secondary Attack Rate in Family Members (%)	Asymptomatic Excretion in Enrollees
Rotavirus	18–1000 virions	50	15–80	Common
Enteric adenovirus	Unknown	40	Unknown	Common
Astrovirus	Unknown	50–90	Unknown	Common
Calicivirus	Unknown	50	Unknown	Common
Giardia intestinalis	10^{1-2} cysts	17–54	15–50	Common
Cryptosporidium	132 oocysts	33–74	25–60	Common
Shigella	10^{1-2}	33–73	25–50	Uncommon
Escherichia coli	10^{8}			
O157:H7		29, 34	Unknown	Uncommon
O114:NM		67	Unknown	Uncommon
O111:K58		56, 94	Unknown	Uncommon
Clostridium difficile	Unknown	32	Unknown	Common

Organisms generally associated with foodborne outbreaks, including *Salmonella* spp. and *Campylobacter jejuni,* are infrequently associated with diarrhea in the childcare setting. However, reports of childcare outbreaks of diarrhea in association with ingestion of fried rice contaminated with *Bacillus cereus,*[9] and of norovirus infection in association with frozen strawberries,[10] highlight the issue that foodborne outbreaks can occur in the childcare setting, especially when food is prepared and served at the childcare center.

Spread of diarrheal pathogens from index cases in the childcare setting to family members has been reported for many enteropathogens (see Table 3.2), with secondary attack rates ranging from 15% to 80%. During outbreaks of diarrhea in childcare centers, asymptomatic excretion of enteropathogens is frequent (see Table 3.2). In a longitudinal study of serial stool samples collected from 82 children <2 years of age in a childcare center, enzyme immunoassay revealed that 21 of 27 (78%) children from whom *G. intestinalis* was detected and 19 of 37 (51%) children from whom rotavirus was detected were asymptomatic.[11] A point-prevalence evaluation of 230 asymptomatic preschool children attending childcare in southwest Wales and inner London demonstrated a 1.3% fecal colonization rate with both *Cryptosporidium* and *Giardia* spp.[12] The role that asymptomatic excretion of enteropathogens plays in spread of disease is unknown.

Acute infectious diarrhea is 2 to 3 times more common in children enrolled in out-of-home childcare than in age-matched children cared for at home.[13–15] Approximately 20% of outpatient visits for acute diarrheal illness among children younger than 3 years of age are attributable to childcare attendance.[13] In addition, the incidence of diarrheal illness is threefold higher among children during their first month in out-of-home childcare compared with children cared for at home.[13,16,17]

Diarrhea occurs 17 times more frequently in diapered children than in toilet-trained children.[17] Higher attack rates among diapered children may represent exposure of a younger, nonimmune cohort. In contrast, in a multicommunity group childcare outbreak of *Shigella sonnei*, the highest attack rates were noted in rooms where both toilet-trained and diapered children were co-mingled (14%) compared with rooms with toilet-trained children only (9%) and rooms with diapered children only (5%), despite comparable availability of sinks and toilets.[18] The likely reason for this finding was that the toilet-trained children were acquiring continence, and the diarrhea resulting from their shigellosis made them incontinent. Investigators in North Carolina demonstrated that adherence to proper diapering and hand hygiene practices and use of dedicated food preparation equipment decreased the incidence of diarrheal illness among children and staff in out-of-home childcare centers.[19]

Enteric Viral Infections

Rotavirus.

In the prerotavirus vaccine era, rotaviruses were the most common cause of significant symptomatic diarrhea in children <2 years of age. Person-to-person transmission by the fecal-oral route predisposes nonimmune infants and young children and their childcare providers to rotavirus infection. Because rotavirus can be isolated from human stools for approximately 21 days after illness onset and rotavirus RNA can be detected on toys and surfaces in childcare centers, this organism has been associated with outbreaks of diarrhea in the childcare setting.[20]

Primary prevention of rotavirus in all settings is accomplished with the completion of an oral rotavirus vaccine series. The universal uptake of rotavirus immunization in the US has changed the epidemiology of rotavirus infections and has resulted in a greatly reduced burden of disease and consequently fewer childcare-associated outbreaks.[21] Pediatric rotavirus immunization has also provided indirect protection to adults, with a decline in peak prevalence by nearly 50% in 1 study.[22] Rotavirus-immunized childcare enrollees can therefore provide indirect protection to rotavirus-nonimmune childcare providers, thus reducing opportunities for person-to-person transmission.

Norovirus.

In the postrotavirus vaccine era, norovirus has become the leading cause of acute gastroenteritis in young children. A population-based surveillance study of children younger than 5 years of age with acute gastroenteritis who presented for medical care in 3 counties surrounding Nashville, Tennessee, Cincinnati, Ohio, and Rochester, New York in 2009 and 2010 detected norovirus in 278 (21%) of 1295 stool specimens, compared with rotavirus in 152 (12%).[23]

Several features of norovirus facilitate its spread, including the low inoculum required for transmission (approximately 18 to 1000 virions), asymptomatic shedding that can precede and extend beyond symptom duration (in up to 30% of infections), tolerance to a wide range of temperatures that facilitates persistence on environmental surfaces, and strain-specific immunity.[24] Outbreaks can occur in a variety of settings including childcare centers, long-term care facilities, hospitals, restaurants, and cruise ships. Two epidemiologic studies of norovirus gastroenteritis in Germany and Japan found that genogroup GII strains predominated in outbreaks associated with childcare facilities while these strains were circulating in the community.[25,26]

Hepatitis A Virus.

Hepatitis A virus (HAV) infections usually are mild or asymptomatic in children, and outbreaks in childcare centers generally are not recognized until illness becomes apparent in older children or adults. The first outbreak of HAV infection in a childcare center was reported in 1973 in North Carolina,[27] with subsequent outbreaks recognized throughout the US.[28] Before routine immunization of children with hepatitis A vaccines in the

US, approximately 15% of HAV infections were estimated to be associated with childcare centers. Uptake of universal hepatitis A immunization in children has correlated with a decreasing proportion of outbreaks among children in childcare and elementary school settings, as well as among adults who have contact with children enrolled in childcare centers.[29,30]

Peak viral titers in stool and greatest infectivity with hepatitis A occur during the 2 weeks before onset of symptoms. HAV infections are transmitted in the childcare setting by the fecal-oral route and occur more frequently in settings that include diapered children. The mainstays of prevention of HAV infection include maintenance of personal hygiene, hand hygiene, disinfecting procedures, and immunization.

The US Centers for Disease Control and Prevention (CDC) recommend hepatitis A vaccine for all children beginning at 1 year of age, with the 2 doses administered 6 to 18 months apart.[31] Administration of hepatitis A vaccine to unimmunized, immunocompetent people 12 months through 40 years of age also is recommended for postexposure prophylaxis (PEP).[32,33] The CDC advises that vaccine PEP be administered to all previously unvaccinated staff and attendees of childcare centers or homes when 1 or more HAV infections are identified in children or employees or when an HAV infection is recognized in 2 or more households of center attendees. In centers that provide care only to toilet-trained children, PEP need be administered only to unimmunized classroom contacts of the index child. If an HAV infection is identified in 3 or more households, PEP should be considered for members of households with diapered children attending the childcare center.[34] Standard immune globulin (IG) is no longer recommended for HAV PEP in the US in most situations. Despite the decline in the incidence of HAV, continued education, training, and monitoring of staff regarding appropriate hygienic practices are essential components of any prevention plan.

Enteric Bacterial Infections

Escherichia coli.

Bacterial pathogens that have the potential to cause severe systemic infections, including *E. coli* O157:H7 and other Shiga toxin–

producing *E. coli* (STEC) strains, have been associated with fecal-oral transmission in group childcare settings. An epidemiologic study of non–O157 STEC outbreaks in the US found that 15 (39%) occurred through person-to-person transmission, with 13 (87%) of those occurring in childcare centers.[35] In an outbreak of *E. coli* O157:H7 infection in a childcare center in Bronx, New York, 11 of 45 attendees tested positive for *E. coli* O157:H7 by stool culture or Shiga-like toxin assay.[36] The original source of the outbreak was not determined; however, multiple sanitary violations were identified, including improper disinfection of diaper changing tables, lack of sanitary distribution of food, and inadequate exclusion of attendees who had diarrheal illnesses. After 2 cases of STEC were identified at a childcare center in Norway, an outbreak investigation found 9 additional cases among the 91 children enrolled and 1 case among the 41 employees; no evidence of common exposures was found, and person-to-person transmission was determined to be likely. Three of the persons with cases were asymptomatic, a finding that raises important questions regarding the utility of exclusion policies and screening of asymptomatic contacts.[37]

Shigella sonnei.

S. sonnei causes periodic multicommunity outbreaks in group childcare settings. Childcare attendance and age <60 months were associated with illness in a community outbreak of *S. sonnei* among traditionally observant Jewish children in New York City in 2000.[38] Multiple illnesses in a single household were determined to result from intrahousehold secondary transmission. A multicommunity outbreak of more than 1600 culture-confirmed cases in the greater metropolitan area of Cincinnati, Ohio in 2001 had an overall mean attack rate of 10% among childcare center enrollees. The highest attack rates occurred among newly or incompletely toilet-trained enrollees, and the lowest attack rates were noted among diapered children. The attack rate was 6% among staff members. Secondary transmission was facilitated by poor hygiene practices, including inaccessible handwashing supplies and incomplete diaper disposal practices, as well as through recreational activities involving water.[18] A prolonged multistate increase of shigellosis caused by organisms with similar biochemical and genetic profiles occurred in the South and mid-Atlantic areas in 2001 to 2003. A substantial proportion of infections was associated with group childcare.[39] In 2005, 639 cases of multidrug-resistant *S. sonnei* were reported in northwest Missouri. A case-control investigation of 39 licensed childcare centers demonstrated that centers with ≥1 sink or a diapering station in each room were less likely to have cases, thus reinforcing the importance of environmental design and hygiene in reducing the propagation of shigellosis in childcare centers.[40] An observational study following a shigellosis outbreak in St. Louis, Missouri examined the utility of requiring a second negative convalescent stool culture among those excluded from work or childcare. Of the 172 people who submitted at least 2 follow-up cultures, the probability that *S. sonnei* was isolated from a second culture after being isolated from a first culture was 7%. All (100%) of the second cultures from people who had a first negative follow-up culture result were without growth of *S. sonnei*, a finding suggesting that a single negative convalescent culture result is sufficient to document clearance.[41]

Respiratory Tract Infections

Organisms responsible for respiratory tract infections in childcare settings are similar to organisms that circulate in the community and include respiratory syncytial virus (RSV), parainfluenza viruses, adenovirus, rhinovirus, coronavirus, influenza viruses, human metapneumovirus, bocavirus, parvovirus B19, and *Streptococcus pneumoniae.*

Children <2 years of age who are attending childcare centers have an increased number of upper and lower respiratory tract infections, including acute otitis media and pneumonia, compared with age-matched children cared for at home. Approximately 10% to 17% of respiratory tract infections in US children <5 years of age are attributable to childcare attendance.[42,43] A prospective cohort study found that 89% of disease episodes among children attending a childcare center are respiratory tract infections.[44] Another prospective cohort study following 119 childcare attendees through 24 months of age demonstrated a mean annual incidence of 4.2 respiratory tract infections per child during the first year of childcare enrollment and 1.2 per child during the second year of childcare enrollment. One or more viruses were detected by real-time reverse transcriptase polymerase chain reaction (real-time RT-PCR) from two thirds of the children with respiratory tract infections.[45] Molecular-based diagnostics have increased the yield of virus detection in children with respiratory tract infections. An epidemiologic study of childcare attendees with new-onset respiratory illness detected at least 1 virus in 84% and multiple viruses in 46% of cases using PCR. Children with multiple viruses detected at the onset of illness were less likely to have fever (odds ratio [OR] 0.6; 95% confidence interval [CI], 0.4–0.9) but more likely to have symptoms lasting >7 days (OR 1.9; 95% CI, 1.2–3.14).[46]

A national registry-based study of Danish children from birth to 5 years of age revealed that the first 6 months of enrollment in group childcare among children enrolled at ≤1 year of age were associated with a 69% higher incidence of hospitalizations for acute respiratory tract infections compared with age-matched children in home care. The incidence of hospitalization decreased after 6 months of group childcare enrollment and was comparable to that of children in home care after >12 months of enrollment.[47] A prospective study comparing children enrolled in childcare in the first year of life with those who were not found that childcare attendees had more episodes of physician-diagnosed upper respiratory tract infections and acute otitis media in their first year of life. Additionally, although the 2 groups had similar rates of illness over the entire 6-year study period, childcare attendees had increased visits to their general practitioner and an increased risk of specialist referral.[48]

The risk of acute otitis media is increased among children enrolled in childcare, especially those <2 years of age. In 1 study, the incidence of otitis media was 1.5 times higher among children enrolled in childcare compared with children in home care.[43] Acute otitis media is the most common reason for antibiotic use in children <3 years of age in the childcare setting. Childcare attendance has been associated with increased risk of recurrent acute otitis media (>6 episodes in 1 year) and chronic otitis media with effusion persisting for more than 6 months. After controlling for the total size of the childcare group for children younger than 12 months of age, the previously established relationship between attending out-of-home childcare and frequent ear infections was reduced from an OR of 3.2 (95% CI, 1.5–6.7) to and OR of 1.34 (not significant; P = 0.60).[49] Because acute otitis media usually is diagnosed empirically, the relative contribution of bacterial versus viral causes is largely unknown.

Handwashing decreases the frequency of acute respiratory tract infections in childcare.[50,51] A randomized controlled trial that included training childcare staff regarding handwashing, transmission modes of infection, and aseptic techniques related to nose wiping demonstrated a significant reduction in upper respiratory tract infections among enrollees <24 months of age.[50] A study to assess the potential role of clothing as a source of transmission of human rhinovirus found that teachers' clothing is unlikely to facilitate the transmission of rhinovirus in childcare settings. Symptomatic teachers are more likely to have rhinovirus in their nasal mucus and on clothing.[52] Because most infectious agents are communicable for a few days before and after symptoms, exclusion of children and teachers based on upper respiratory tract symptoms is unlikely to decrease transmission, and the continued practice of respiratory and hand hygiene is likely to be more effective in preventing spread.

Respiratory Viral Infections

Influenza Virus.

Rates of seasonal influenza are highest among children <2 years of age and older adults, and rates of complications are greatest among children of all ages with predisposing or underlying medical conditions. Among preschool-aged children with influenza virus infections, hospitalization rates range from 100 to 500 per 100,000 children, with the highest hospitalization rates among children from <1 year of age.[53] Influenza viruses are spread from person to person primarily through large respiratory tract droplets, either directly or by secondary contact with objects that are contaminated with infectious droplets. Children shed virus for several days before the onset of clinical symptoms and are contagious for >10 days following symptom onset. Transmission of infections can be increased by close contact among children who are not able to contain their secretions.

Annual vaccination of all people ≥6 months old is the primary method of preventing seasonal influenza infections.[54] A randomized controlled trial conducted during the 1996 to 1997 influenza season in 10 childcare centers in San Diego, California found that vaccinating children against influenza reduced influenza-related illness among their household contacts.[55–57] In addition to preventing respiratory tract illness, influenza vaccine prevents acute otitis media among children attending childcare, as shown by several studies.[50,51,58,59]

Routine use of intranasal influenza vaccine among healthy children can be cost effective and can be maximized by using group-based vaccination approaches. A prospective study of intranasal influenza vaccine in healthy children 15 through 71 months of age demonstrated clinical and economic efficacy when vaccination efforts were focused on children in group childcare settings.[60] Vaccinating children has been associated with indirect protection of older people as well.[60,61]

Mandatory influenza vaccination before childcare attendance can increase immunization coverage and consequently decrease infection. In 2010, Connecticut became the second state, after New Jersey, to require all children 6 to 59 months of age in licensed childcare programs to receive at least 1 dose of seasonal influenza vaccine annually.[62] Seasonal influenza vaccination rates among children 6 to 59 months of age in Connecticut increased from 68% in 2009 to 2010 to 84% in 2012 to 2013. Connecticut also was compared with the 10 other sites participating in the CDC Emerging Infections Program, none of which had an influenza vaccine mandate for childcare centers at the time. Between the 2007 to 2008 and the 2012 to 2013 seasons, Connecticut had the highest percentage of decrease in influenza-associated hospitalization rates; 9 of 10 sites without mandated influenza immunization for childcare attendees reported increasing influenza-associated hospitalization rates over this time period.

Childcare center closure as a strategy to prevent and monitor community spread of influenza was considered during the 2009 H1N1 influenza pandemic. Extrapolating to school-aged children, 58% of families of 402 students in Perth, Australia who were affected by pandemic-related school closures reported a substantial disruption of daily schedules. Almost one half of the parents had work absences, and 35% made alternative childcare arrangements. Children affected by the school closures were more likely to report out-of-home activities during the school closure period. Fewer than one half (47%) of the parent respondents believed that the school closures were an effective response in reducing the potential for community transmission.[63]

Respiratory Syncytial Virus.

RSV is among the most common causes of serious lower respiratory tract infections in young children, with an estimated 55,000 to 125,000 related hospitalizations and 200 to 500 RSV-related deaths annually in the US.[64] Attack rates as high as 98% have been reported after first exposure among children at risk for infection, with frequent reinfection (65% to 75%) on reexposure to RSV in the 2 years after initial exposure.[65]

A prospective cohort study of children 4 weeks to 30 months of age who were attending full-time childcare detected RSV by RT-PCR from 59 (11%) of the children with respiratory illnesses and multiple viruses in 42 (71%) of the patients with RSV. This study also found longer duration of symptoms and increased frequency of healthcare visits in RSV-positive children compared with RSV-negative children. Additionally, 2 clusters of RSV infection resulted in 50% of enrolled children infected within 6 days of the index case in each room. When molecular sequencing was performed in 1 cluster, the same strain of RSV was isolated in 5 (38%) of 13 illness episodes, a finding suggesting rapid child-to-child transmission.[66]

Respiratory Bacterial Infections

Pertussis.

Infections caused by *Bordetella pertussis* in the US have increased dramatically since 2000; 7867 cases were reported in 2000, 27,550 cases in 2010, and 28,660 cases in 2014.[67,68] Several pertussis epidemics have occurred since 2000, including outbreaks in Washington State in 2012 and in California in 2014.[69,70] These outbreaks have been attributed to inadequate vaccine coverage and waning immunity related to universal use of acellular pertussis vaccines.

Incompletely immunized infants often experience severe clinical disease from pertussis. In many group childcare settings, adolescents and adults with mild to moderate illnesses can be the source cases of pertussis. An outbreak of pertussis occurring in a childcare center in northern Israel with 88% immunization coverage resulted in *B. pertussis* detected by a positive culture or PCR result in all unvaccinated children and in 7% of vaccinated children.[71] In 2005, the CDC recommended that postpartum women and other contacts of newborn infants receive tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) vaccine to protect infants from pertussis exposure, a strategy known as cocooning.[72] In 2011, the CDC recommended that unvaccinated pregnant women receive a dose of Tdap to protect infants by transplacental maternal antibody transfer.[73] In 2012, the CDC expanded this recommendation to administration of Tdap immunization during the third trimester of every pregnancy.[74] Childcare providers of any age with routine contact with infants <12 months of age should receive a single dose of Tdap.[72]

Tuberculosis.

An adult or adolescent often is the index case for *Mycobacterium tuberculosis* infections in a group childcare setting; child-to-child transmission occurs infrequently. An outbreak of tuberculosis (TB) associated with a private-home childcare facility in San Francisco, California occurred between 2002 and 2004. Of 11 outbreak cases, 9 (82%) occurred in children <7 years of age; all these children had extensive contact through childcare in a private home, where the adult index patient spent considerable time. Isolates from 4 of the pediatric patients and 2 of the adult patients had identical molecular patterns. Additionally, 36 children and adult contacts had latent TB infection.[75] In an outbreak of TB following prolonged contact with a provider with cavitary disease in a childcare center in Sweden, 17 children had radiographic evidence of pulmonary disease; 1 child had miliary disease, and 17 had latent TB infection.[76] These outbreaks demonstrate that detection and contact investigations in childcare centers are paramount in reducing TB infection.

Group A *Streptococcus.*

Outbreaks of group A *Streptococcus* (GAS) infection among children and adult staff in childcare settings have been reported. In a study of prevalence of GAS conducted in a childcare center after a fatal case of invasive GAS disease, 25% of 258 children and 8% of 25 providers had GAS isolated from throat culture. Risk of carriage was increased in children who shared a room with the index case (OR, 2.7; 95% CI, 0.8–9.4).[77] Perianal GAS infection and infection associated with varicella also have been reported.[78,79] A clone of GAS (*emm* type 4) was responsible for a community outbreak of streptococcal toxic shock syndrome among children attending a childcare center in northern Spain. In this situation, the outbreak-associated strains were not isolated from pharyngotonsillar swabs of staff, childcare, or household contacts of the colonized and infected children.[80]

Invasive Bacterial Infections

Haemophilus influenzae Type b.

Studies conducted before routine use of *Haemophilus influenzae* type b (Hib) conjugate vaccine in the US showed that the risk of developing primary invasive Hib infection was higher among children attending childcare centers than in children cared for at home, independent of other possible risk factors. Incorporation of Hib conjugate vaccines into the routine immunization schedule of children in the US dramatically reduced the frequency of invasive Hib disease. Oropharyngeal carriage of *H. influenzae* non–type b was associated with childcare attendance exceeding 15 hours per week in an epidemiologic study in Minnesota from 2008 to 2009.[81] Despite its rising prevalence in other settings, nontypable *H. influenzae* has not been associated with childcare outbreaks.

Neisseria meningitidis.

Risk of disease caused by *Neisseria meningitidis* can be increased in group childcare settings. Using space-time cluster analysis of invasive infections during 9 years of surveillance from 1993 to 2001 in the Netherlands, researchers noted that clustering beyond chance occurred at a rate of 3% and concluded that this rate was likely the result of direct transmission. Childcare center attendance was reported as the likely exposure for 8 of 40 (20%) clusters, thus accounting for 13 of 82 (16%) cases of invasive disease with multiple serosubtypes.[82] For children 2 through 10 years of age, routine immunization with meningococcal conjugate vaccine is recommended only for those children at continued increased risk of invasive disease, a risk that does not include out-of-home childcare.[83]

Streptococcus pneumoniae.

Incorporation of heptavalent (7-valent) pneumococcal conjugate vaccine (PCV7) into the routine childhood immunization schedule in the US in 2000 resulted in dramatic reductions of both the frequency of invasive pneumococcal disease and the frequency of PCV7-containing serotypes.[84] Universal uptake of PCV7 also was associated with a decline in national rates of outpatient visits for acute otitis media in children <2 years old.[85] Serotype 19A was among the replacement serotypes associated with invasive disease in many communities,[86] as well as in childcare.[87] In 2010, introduction of a 13-valent pneumococcal conjugate vaccine (PCV13) replaced PCV7,[88] thus resulting in further declines in invasive pneumococcal disease among all age groups[89]; vigilance for possible serotype replacement is ongoing.

Before the introduction of the PCVs, the risks of invasive pneumococcal disease, *S. pneumoniae* nasopharyngeal carriage, and carriage of antibiotic-resistant *S. pneumoniae* were increased in children attending childcare. This observation has not been fully explored in the postvaccine era. However, a French study of nasopharyngeal carriage of *S. pneumoniae* in childcare attendees found stable carriage rates, a decrease in all vaccine serotypes except 19A, and decreased antibiotic resistance from 1999 to 2012.[90] Secondary spread of *S. pneumoniae* in the childcare setting has been reported, but the risk has not been characterized.

Kingella kingae.

Kingella kingae colonizes the oropharynx and respiratory tracts of young children and has been associated with invasive disease. Multiple childcare-associated outbreaks of *K. kingae* have been reported, primarily involving osteoarticular infections; endocarditis also has been described.[91–95]

Invasive Viral Infections

Echovirus.

During an outbreak of echovirus 30 infection in children and care providers in a childcare center, and in exposed parents, infection occurred in 75% of children and 60% of adults; aseptic meningitis was more frequent in infected adults (12 in 65; 18%) than in children (2 in 79; 3%).[96] A retrospective cohort study of echovirus infections in 4 childcare centers in Germany revealed that 42% of childcare attendees, 13% of their household contacts, 5% of childcare center employees, and 2% of employees' household contacts were ill over a 31-day period. Thirteen percent (12 of 92) of childcare attendees had meningitis. This outbreak likely began among children enrolled in group childcare, with secondary cases occurring among their household contacts.[97] An association with childcare also was noted in an outbreak of echovirus 18 meningitis that occurred in a rural Missouri community with an attack rate of 1 per 1000 people; contact with childcare was noted as the most common risk factor among ill people.[98]

Parvovirus B19.

Parvovirus B19, the agent of erythema infectiosum (fifth disease), can cause arthropathy, transient aplastic crisis, persistent anemia in immunocompromised hosts, and nonimmune fetal hydrops. It spreads through contact with respiratory or oropharyngeal secretions. Serologic evidence of past infection has been reported to be 30% to 60% in adults, 15% to 60% in school-aged children, and 2% to 15% in preschool-aged children.[99] The virus is endemic among young children and has caused outbreaks of disease in the childcare setting.[100,101] In an outbreak during which more than 571 school and childcare personnel were tested serologically, the highest attack rate (31%) occurred among childcare personnel.[100] A cross-sectional study of 477 childcare staff members revealed a seroprevalence of parvovirus B19 immunoglobulin G antibodies of 70%. Seropositivity was associated with age and, among staff members <40 years of age, with length of group childcare contact.[102]

A concern exists that a previously nonimmune pregnant childcare provider could be exposed and infected during her childcare responsibilities, thus resulting in transplacental transmission leading to fetal hydrops. Estimates of the risk of fetal loss when a pregnant woman of unknown antibody status is exposed are 3% for fetal death after household exposure and 2%

after occupational exposure in a school.[103] The American Academy of Pediatrics does not recommend exclusion of pregnant women from the workplace when erythema infectiosum is occurring. This recommendation is based on low rates of adverse effects on the fetus and high community prevalence of parvovirus B19 infection. Routine infection control practices, including hand hygiene and proper disposal of used facial tissues, are recommended to prevent transmission.[104]

Cytomegalovirus.

Young childcare attendees shed cytomegalovirus (CMV) intermittently in their saliva and urine after acquisition, and they often transmit virus to other children and adults with whom they have close daily interaction. Transmission is thought to occur through direct person-to-person contact and from contaminated toys, hands of childcare providers, or classroom surfaces. Prevalence studies have shown that 10% to 70% of children <3 years of age (peak, 13 through 24 months) in childcare are shedding CMV in their urine or saliva.[105–107] Nonimmune childcare providers and mothers acquire CMV at annual rates of 8% to 20% while caring for CMV-infected children. In comparison, acquisition rates of 1% to 3% were noted among nonimmune childcare providers and mothers caring for CMV-uninfected children.[108–110] Given that care providers of young children are at increased risk of acquiring CMV, women of childbearing age should be educated about the risks of acquiring CMV, potential effects on the fetus, and methods to prevent transmission including hand hygiene after changing diapers or contact with saliva.[111]

Bloodborne Viral Pathogens

Concern about the potential for spread of bloodborne organisms in the childcare setting has focused on transmission of hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV). Universal immunization of infants with HBV vaccine in 1991 has reduced to negligible the potential for horizontal HBV transmission in the childcare setting. Because the highest concentrations of HBV in infected people are found in blood and blood-containing body fluids, the most common and efficient routes of transmission are through percutaneous blood exposure, by sexual exposure, and perinatally. However, high levels of HBV DNA have been detected in the saliva of hepatitis B e antigen (HBeAg)–positive children, a finding suggesting that exposure to saliva could be a means of horizontal transmission.[112] Thus, if a known hepatitis B surface antigen (HBsAg) carrier bites and breaks the skin of a hepatitis B–unimmunized child, hepatitis B immune globulin and the HBV vaccine series should be administered to the hepatitis B–unimmunized child.[113] The transmission risk of HCV infection in childcare settings is unknown. The general risk of HCV infection from percutaneous exposure to infected blood is estimated to be 10 times greater than that of HIV but less than that of HBV. Rates for percutaneous exposure to HCV-containing saliva are unknown.

No cases of HIV infection are known to have resulted from transmission of the virus in out-of-home childcare. The risk of transmission of HIV by percutaneous body fluid exposure, such as biting, is low. Complete evaluation of the source and extent of exposure should be undertaken to assess the possible risk of HIV transmission and the need for PEP.[113]

Precautions for prevention of HBV, HCV, and HIV infections should be directed toward preventing transfer of blood or secretions from person to person. Childcare providers should be educated about modes of transmission of bloodborne diseases and their prevention, and each center should have written policies for managing illnesses and common injuries, such as bite wounds.[114] Standard precautions for handling blood and blood-containing body fluids should be practiced in all childcare settings. Children known to be infected with HIV or HCV or children who are HBsAg carriers should be included in childcare activities. Decisions regarding attendance at childcare and the optimal childcare environment for these children should be made jointly by the child's physician and parents after considering the risks and benefits.

Skin Lesions

The magnitude of skin infections or infestations and the rates of occurrence in children in group childcare compared with rates in age-matched children not in group childcare are not known. The most frequently recognized non–vaccine-preventable conditions are impetigo or cellulitis caused by *Staphylococcus aureus* or GAS, pediculosis, and scabies. Other conditions with skin manifestations that occur in childcare attendees include molluscum contagiosum, head lice, ringworm, herpes simplex virus (HSV) infection, and varicella.

Molluscum Contagiosum.

Molluscum contagiosum is a benign, superficial infection of the skin caused by a poxvirus. It is manifest by the presence of small, 2- to 5-mm painless skin-colored papules with central umbilication and typically resolves spontaneously within 6 to 12 months. The virus is spread by direct contact or by fomites, and humans are the only source. Infectivity is low, but outbreaks have been reported. Keeping skin lesions covered can help to prevent transmission.

Varicella-Zoster Virus.

Since 2006, the CDC has recommended a 2-dose varicella-zoster virus (VZV) vaccination program for children, with the first dose administered at 12 through 15 months and a second dose at 4 through 6 years of age.[115] Children entering childcare or starting school should be required to have age-appropriate VZV vaccination status or other evidence of immunity to chickenpox.[116] As of January 2015, 47 states required VZV vaccination for childcare and school attendance; 1 state (Montana) requires vaccination only for childcare attendance, and 2 states (South Dakota and Ohio) require vaccination only for school attendance.[117] Unimmunized children in childcare settings are susceptible to VZV infection; most reported cases occur in children <10 years of age. Universal VZV immunization has reduced cases of clinical disease among children in group childcare.[115] However, several outbreaks of chickenpox have been reported among childcare attendees in the postvaccine era, often in the setting of inadequate vaccination coverage.[115,118–122]

Herpes Simplex Virus.

Clusters of primary HSV infections occur in children in childcare, and these infections most frequently manifest as gingivostomatitis. In a study conducted in a childcare center, restriction endonuclease analysis of HSV DNA revealed that a single strain of HSV-1 had been transmitted among children.[123] A longitudinal study of 115 childcare attendees followed from early infancy found that 37% of children had evidence of HSV-1 infection by 5 years of age based on virus isolation or seroconversion, or both. The highest incidence of infection occurred among children 1 to 2 years of age.[124] Children with severe HSV-1 infections should be excluded from childcare facilities if excess drooling and secretions are present.

Methicillin-Resistant *Staphylococcus aureus*.

The emergence of community-acquired methicillin-resistant *S. aureus* (MRSA) and its predisposition for people in crowded conditions where sharing of fomites and skin-to-skin contact occurs make childcare exposure a potential risk factor. A molecular epidemiologic study of MRSA prevalence among 104 children, 32 employees, and 17 household contacts of attendees affiliated with a university medical center's childcare facility in Texas noted an overall 7% colonization rate with MRSA. Molecular typing revealed closely related, mostly community-associated isolates from 1 employee (3%), 6 (35%) family members, and 4 (2%) environmental samples. Macrolide antibiotics and asthma medications were associated with MRSA colonization.[125] An epidemiologic study of 1163 children attending 24 childcare centers in North Carolina and Virginia found that 18% were colonized with *S. aureus* and 1% with MRSA; genotyping did not indicate classroom transmission in the 2 centers that had multiple children who were colonized with the bacterium.[126] A draining wound is a reason for exclusion of a child from a childcare setting; MRSA colonization is not.

Scabies.

Scabies is caused by a hypersensitivity reaction to the adult female mite of *Sarcoptes scabiei* subspecies *hominis*, which burrows in the upper epidermis of the skin. This infestation manifests as a pruritic, erythematous papular eruption, especially in skinfolds. Transmission occurs through prolonged close contact. Children with scabies should be excluded from childcare or school until treatment is completed, and household contacts of infected children should also be treated to prevent reinfection.[127] Prophylactic treatment for childcare providers and other contacts who have had prolonged skin-to-skin contact with an infected child should also be considered because symptoms can take 4 to 6 weeks to develop in persons who have not had a previous infection. Additionally, because transmission of crusted scabies—characterized by widespread, hyperkeratotic crusted lesions—can occur after minimal contact, treatment of all close contacts of patients with such cases is recommended.

Pediculosis.

Head lice are cosmetically unappealing, but they do not transmit disease. The incidence of pediculosis capitis (head lice) among children in childcare facilities was 0.02 per 100 child-weeks in Seattle[128] and 0.03 per child-year in San Diego.[129] Because head lice are transmitted by direct head-to-head contact, childcare centers with shared sleeping areas can facilitate transmission. Treatment of infested children and their contacts with pediculicides can be considered as control measures.[130]

Tinea Capitis.

An outbreak of tinea capitis and tinea corporis secondary to *Trichophyton tonsurans* was reported at a childcare center in the United Kingdom, with infection of 12 children and 7 staff members over a 12-month period. Control of the outbreak was accomplished through use of oral antifungal agents and antifungal shampoo, exclusion of persons with cases for a short period, removal of shared items from the center, and enhanced decontamination of fomites.[131]

Vaccine-Preventable Diseases

In the US, children should be immunized against the following 16 diseases or pathogens, unless medical contraindications exist: diphtheria, tetanus, pertussis, Hib, poliomyelitis, measles, mumps, rubella, varicella, *S. pneumoniae,* HBV, HAV, influenza, rotavirus, human papillomavirus, and meningococcal disease.[31,132] Immunization of children and childcare providers should be a priority because high rates of immunization benefit children in childcare settings and their care providers. Laws requiring age-appropriate immunizations of children attending licensed childcare programs exist in almost all states. As of January 2015, vaccine mandates for HBV were active in 41 (82%) states, for HAV in 20 (40%) states, for pneumococcus in 38 (76%) states, for varicella in 48 (96%) states, and for influenza in 4 (8%) states.[133] In a study of exemptions to immunizations, children 3 through 5 years of age with immunization exemptions were 66 times more likely to acquire measles and 17 times more likely to acquire pertussis than were age-matched immunized children.[134]

Infections Associated With Animals

Animal exposure has been associated with sporadic zoonotic infections as well as outbreaks, injuries, and allergies, most notably in children <5 years of age. The increased prevalence of infections in this age group likely reflects compromised hand hygiene resulting in transmission of pathogens from animal to child. Animal interaction can occur in locations where childcare is provided, with a resident pet or visiting animal, or in public venues where children visit, including petting zoos, aquariums, county fairs, parks, carnivals, circuses, or farms. Guidelines to reduce opportunities for transmission and infection have been developed to prevent disease transmission in many of these settings.[135,136] Inadequate hand hygiene, suboptimal supervision of children's activities following animal contact, and hand-to-mouth activities following animal contact are risk factors for infection. Organisms that have been associated with close contact with animals include *E. coli* O157:H7, Shiga toxin–producing *E. coli* (STEC), *Salmonella enterica* serotype Typhimurium, *Cryptosporidium parvum, C. jejuni,* and *G. intestinalis.* In addition to enteric infections, animal exposure can result in transmission of ectoparasites and endoparasites, *M. tuberculosis* in certain settings, and local or systemic infections as a consequence of bites, scratches, stings, and other injuries.

Contact with animals within the childcare environment should occur only where control measures are established to reduce the risk of injuries and disease. Supervision of children during animal contact, strict hand hygiene after direct animal contact or contact with animal products or environment, designation of areas for animal contact that are separate from areas in which food or drink are consumed, and disinfection and cleaning of all animal areas should be observed. Amphibians, reptiles, and weasels (ferrets and mink) should be housed in cages and not handled by children. Wild or exotic animals, nonhuman primates, mammals with a high risk of transmitting rabies, wolf-dog hybrids, aggressive wild or domestic animals, stray animals, venomous or toxin-producing spiders, insects, reptiles, and amphibians should not be permitted in the group childcare setting.[137,138]

Infectious Diseases in Adults

Parents of children who attend a childcare facility and people who provide care to these children have an increased risk of acquiring infections such as CMV, parvovirus B19, HAV, and infectious diarrhea. A retrospective cohort study of children 12 to 60 months of age attending childcare in and around Quebec City, Canada found that transmission of acute gastroenteritis and acute respiratory illness from children to their parents occurred in about 1 in every 3 episodes of infection.[139] During outbreaks of diarrhea in childcare centers, 40% of childcare providers developed diarrhea.[17] During a multicommunity outbreak of shigellosis, the overall median attack rate among employed staff members of childcare centers was 6%, with a range of 0% to 17%.[18] In outbreaks of group A *Streptococcus* and echovirus 30 infection in childcare centers, adult providers and parents were affected.[96] Similar prevalence rates of pneumococcal colonization (5% among adult employees of childcare centers with child contact and 5% among nonclinical employees at a tertiary care center) were noted in a study performed in 2003 in Galveston, Texas; these data suggest that childcare providers are not at an increased risk for pneumococcal colonization in the universal PCV era.[140] Compared with nonproviders, childcare providers have a significantly higher annual risk of at least 1 infectious disease and loss of workdays as a result of infectious disease.[141] Childcare providers should receive all immunizations routinely recommended for adults.[142]

Economic Impact of Group Childcare

Illness

The economic burden of illness associated with group childcare was estimated at $1.8 billion annually adjusted to 2015 US dollars.[143,144] Precise estimates of illness burden and methods for evaluating the effectiveness of infection control interventions are limited by the multiple challenges associated with performing such assessments.[145] Attributing an outbreak to group childcare is challenging; although these settings can promote transmission of infection, childcare attendees and staff members interact with household contacts external to the childcare arrangement, thus facilitating secondary spread. A prospective evaluation of 208 families with at least 1 childcare enrollee that was conducted from November 2000 to May 2001 in the Boston area documented 2072 viral illnesses over 105,352 person-days. Among the 834 subjects, 1683 upper respiratory tract infections and 389 gastrointestinal tract illnesses were reported during the study period, with a total mean cost of $49 per respiratory tract infection and $56 per gastrointestinal illness. Decreased parental productivity during missed days of work to care for a child who had to be withdrawn from childcare accounted for a significant proportion of the nonmedical cost.[143] Another prospective study of 381 children attending childcare centers in Sydney, Australia in 2010 found that the mean cost of an influenza-like illness was AU$626 (95% CI, AU$484–768); independent drivers of cost were both parents being employed and longer duration of illness.[146]

Prevention

Specific standards should be established for hand hygiene, maintenance of current immunization records of children and providers, exclusion policies, environmental cleaning, and appropriate handling of food and medication. In studies in which improved infection control measures were implemented and monitored, both upper respiratory tract illness and diarrhea were reduced in childcare centers that received infection control interventions.[50,147] Because asymptomatic excretion and potential for transmission precede the onset of clinical symptoms in many childcare-associated infectious diseases, strategies that involve prevention are most efficacious.

Educational sessions on health topics by healthcare professionals were found to have the most impact in simultaneous surveys of licensed childcare center directors, parents, and health providers in Boston.[148] A prospective observational study of a convenience sample of 134 childcare centers in Pennsylvania noted that suburban, nonprofit, parent-funded centers had improved health and safety practices compared with centers that were located in urban areas, received their funding through state subsidies, or were designated as for profit.[149]

Local health authorities should be notified about cases of communicable diseases involving children or care providers in the childcare setting. The American Academy of Pediatrics Healthy Child Care America Child Care & Health Partnership sets standards regarding quality early education and childcare.[150] Additional resources include information about group childcare infection rates,[151] as well as guidance for preparation of childcare programs for pandemic response.[152]

Infection prevention, including reinforcement of meticulous personal hygiene, maintenance of immunization status, and efforts to reduce environmental contamination, ensures that both childcare attendees and childcare providers reduce opportunities for exposure and transmission. Controlling clusters and outbreaks of infectious diseases in the childcare setting can involve approaches that include cohorting of functional but symptomatic children and providers to minimize exclusion and economic loss. Provider and parental familiarity with guidelines and policies developed in collaboration with public health authorities and pediatric infectious disease physicians aids in the implementation of best practices.

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4

Infectious Diseases in Refugee and Internationally Adopted Children

Mary Allen Staat

In this chapter, the infectious disease issues of 2 groups of immigrants are discussed: refugees and internationally adopted children. Refugees are noncitizen immigrants who are unable or unwilling to return to their country of origin because of persecution or a fear of persecution.[1] Internationally adopted children are immigrants who are classified as orphans; most are not truly orphaned but have been abandoned by or separated from both parents.

Since 2004 the number of refugee arrivals to the United States has ranged from 41,094 to 74,602 per year, with 69,933 arriving in 2013.[1] Of these, 26,316 (38%) were <20 years of age, and 75% were ≥5 years of age. Although refugees came from more than 62 countries, 81% of the arriving refugees in 2013 came from just 5 countries: Iraq (28%), Burma (23%), Bhutan (13%), Somalia (11%), and Cuba (6%), with some variation in the top countries since 2004.[1]

Since 1999, more than 250,000 children have been internationally adopted in the US, with a peak of 22,990 children adopted in 2004.[2]

Since 2004, the numbers have steadily declined, with only 6574 children adopted in 2013, and a significant shift has occurred in the source countries and the ages of children adopted over this period. In 2004, 83% of adopted children came from 5 countries: China (31%), Russia (26%), Guatemala (14%), South Korea (8%), and Kazakhstan (4%), and only 14% of children were ≥5 years of age. In 2013, 82% of children adopted came from 13 countries: China (34%), Ethiopia (14%), the Ukraine (5%), Haiti (5%), Uganda (4%), Russia (4%), the Democratic Republic of the Congo (3%), South Korea (3%), Philippines (2%), Ghana (2%), Bulgaria (2%), Colombia (2%), and India (2%).[1] In 2013, 39% of children were ≥5 years of age.[2] In addition, nearly all children from China in recent years have significant medical or developmental special needs, whereas in 2004 most children adopted from China were relatively healthy.

Because refugees and internationally adopted children come from resource-limited countries, healthcare providers should be cognizant of the global prevalence of infectious diseases that are seen less commonly in native-born North Americans. Both types of immigrant groups are at increased risk for common infectious diseases such as tuberculosis (TB), intestinal parasites, dermatologic infections, and infestations. In addition, infections with hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and *Treponema pallidum* (syphilis) are far more prevalent in the countries of immigrants where resources for screening and prevention are scarce compared with the US.

Refugee and internationally adopted children differ in terms of the general medical screening they receive before arrival in the U.S.[3–8] First, most refugees are subjected to organized screening evaluations, including a physical examination, before emigration visas are issued. For children >15 years of age, predeparture screening includes serologic testing for HIV and syphilis and a chest radiograph to assess for evidence of TB. In contrast, only adoptees from certain countries with high rates of TB (e.g., China and Ethiopia) have been required to undergo this organized screening procedure for TB.[5,7] Second, because medical screening for refugees usually is sponsored by responsible medical organizations, results of such testing typically are accurate. For international adoptees, results of serologic test for HIV, syphilis, and HBV from country of origin typically are provided. When tests from countries with established screening programs (e.g., China and Ethiopia) have been repeated in the US, previous results generally have proven to be accurate. However, the accuracy of testing for children from other countries is not known. Third, preventive measures such as immunizations, vitamin supplementation, and dental care are undertaken for most refugees, whereas in adoptees, preventive care is inconsistent. Finally, differences in the types of infectious diseases also may distinguish refugees from adopted children. Although both populations are susceptible to a variety of infectious agents, because the countries of origin and the existing living conditions differ, refugee children are more likely to have been exposed to infections such as typhoid fever, malaria, filariasis, flukes, or schistosomiasis, which occur less commonly in internationally adopted children from countries outside Africa.

Guidelines for Evaluation

Because of the preeminence of infectious diseases in resource-limited countries, recommendations for screening tests are weighted toward infectious disease processes, but aspects of general health, including vision, hearing, dental, developmental and mental health screenings, also should be included.[3–8] Despite the healthy appearance of many immigrant children, children should be evaluated by a healthcare professional within 2 weeks after arrival to ensure that they have been or are screened properly and receive preventive healthcare services. Table 4.1 outlines the recommended screening tests for infectious diseases for refugee and internationally adopted children. The reader also is referred to pathogen-specific chapters.

TABLE 4.1

Recommended Tests for Refugee and Internationally Adopted Children

Test	Refugee Children	Internationally Adopted Children
Tuberculin skin test (TST)	All	All[a]
Hepatitis B virus serologic testing	All	All
Hepatitis B surface antigen (HBsAg)[a]		

Hepatitis B surface antibody (anti-HBs)		
Hepatitis B core antibody (anti-HBc)		
Hepatitis C virus serologic testing	Some	Some[a]
Human immunodeficiency virus 1 and 2 serologic testing	≥15 years of age	All[a]
Syphilis serologic testing		
Nontreponemal test (RPR, VDRL, or ART)	≥15 years of age	All
Treponemal test (TPPA, MHA-TP, or FTA-ABS)	Not recommended	All
Stool examination		
Microscopic evaluation for ova and parasites (3 specimens)	All[b]	All
Giardia intestinalis and *Cryptosporidium* antigen (1 specimen)	All[b]	All
Complete blood count	All	All
Urinalysis	All	Not recommended

[a] Consider reassessing 6 months after arrival.

[b] All should be screened if no presumptive treatment occurred before arrival to the United States. See Centers for Disease Control and Prevention: http://www.cdc.gov/immigrantrefugeehealth/guidelines/domestic/intestinal-parasites-domestic.html.

ART, automated reagin test; FTA-ABS, fluorescent treponemal antibody absorption; MHA-TP, microhemagglutination-*Treponema pallidum*; RPR, rapid plasma reagin; TPPA, Treponema pallidum particle agglutination; VDRL, Venereal Disease Research Laboratory.

Hepatitis A

Virtually all inhabitants of resource-poor countries will have contracted hepatitis A virus (HAV) by early adulthood. Now that HAV vaccine is recommended for all US children ≥12 months of age,[9] immunoglobulin G (IgG) anti-HAV testing in children >1 year of age should be considered for all immigrants to determine which children should be immunized.[10] Screening for immunoglobulin M (IgM) anti-HAV can be useful to identify the child with acute HAV infection so that secondary prevention through HAV vaccine can be provided to unvaccinated family members and close contacts. Because HAV infection is anicteric in young children,[9] and because most young children are asymptomatic, the only way to identify children who may shed HAV for months is by screening with an IgM anti-HAV test. Even in the absence of jaundice, symptoms of HAV infection should prompt evaluation for viral hepatitis in recently arrived immigrants or adoptees.[9]

Hepatitis B

Routine screening for HBV infection is recommended for all refugees and internationally adopted children.[4–8] Early identification of HBV infection is important to provide appropriate management and to initiate vaccination of household contacts and caregivers. The prevalence of chronic HBV infection varies by region, and the rates of infection in refugee and internationally adopted children mirror the rates of infection in their country of origin. Children typically acquire HBV by vertical transmission, although bloodborne infection and horizontal transmission also can have occurred.[11–28] In international adoptees, the prevalence of chronic HBV infection was 20% in Romanian adoptees from the early 1990s[14–16]; however, more recent studies have consistently shown a prevalence of 1% to 5%.[17–25]

HBV screening tests, including the HBV surface antigen (HBsAg) and antibodies to surface (anti-HBs) and core (anti-HBc) antigens, are recommended in the medical evaluation of internationally adopted children and refugees.[4–8] All 3 tests should be performed to determine whether the child is immune as a result of immunization, has recovered from infection, or has acute or chronic hepatitis B. Common patterns of the hepatitis B serology profile are shown in Chapter 213. In a child who is found to be HBsAg positive, testing should be repeated 6 months later; if HBsAg persists for ≥6 months, the child has chronic hepatitis B. If the child no longer has HBsAg and has developed anti-HBs, the child had acute infection, has recovered, and is no longer able to transmit HBV to others. Children with acute or chronic HBV infection (positive HBsAg) can transmit HBV to others and should have additional tests performed, including HBV e antigen (HBeAg), HBV e antibody (HBeAb), quantitative HBV polymerase chain reaction (PCR), α-fetoprotein, and serum hepatic enzyme levels. HBsAg-positive children should be followed by a hepatologist for management. For children with negative test results initially, some experts recommend repeat testing for HBV approximately 6 months after arrival in the US to exclude infection just before arrival[8,25] In addition, children with acute or chronic HBV infection also should have serologic testing for HAV (to determine the need for vaccination) and HCV (for management and treatment considerations).

Vaccination of household contacts of children with acute or chronic HBV (HBsAg-positive children) must occur promptly. Epidemiologic studies have demonstrated that up to 20% of unvaccinated household contacts of HBV cases become HBsAg positive within ≥5 years of exposure within the home,[26,27] and transmission of HBV from newly adopted children to their parents is well documented.[26–28]

Hepatitis C

Until more is known regarding the incidence and prevalence of HCV infection in refugee and internationally adopted children, screening for this virus is not recommended routinely.[4–8] However, if the child has a history of specific risk factors such as current or former injection drug use, receipt of blood products, or residence in settings with a documented high prevalence of HCV, testing should be performed.[29] These risk factors often are difficult to ascertain in either group of children. One study reported that the prevalence of HCV antibody in internationally adopted children was <1%.[21] Recommendations may change in the near future because curative treatment is now available. Antibody testing is performed initially, and if the antibody test result is positive, HCV PCR is performed to confirm infection. Nonimmune or unimmunized children with HCV infection should be immunized for HAV and HBV and should be referred to a hepatologist for further management of HCV.

Human Immunodeficiency Virus-1 and Human Immunodeficiency Virus-2 Infection

Refugees ≥15 years of age routinely are tested for HIV before coming to the US.[5] Children <15 years of age are not tested unless they are in a high-risk situation. Otherwise, for refugee children not tested abroad, routine testing is not recommended for refugees unless indicated clinically. In contrast, most internationally adopted children have been tested for HIV-1 anti-IgG by enzyme immunoassay (EIA) in their birth country. Although reports of HIV infection in internationally adopted children are rare,[16,21] routine screening by EIA is recommended for all internationally adopted children on arrival in the US.[7,8] Positive or indeterminate results should be resolved with use of HIV DNA PCR. If clinical suspicion of HIV infection exists, HIV DNA PCR testing should be considered if the result of antibody testing by EIA is negative. Antibody retesting ≥6 months after arrival in the US should be considered.[8] Families are now permitted to adopt children with HIV infection. Thus clinicians should be prepared to provide care and resources for children arriving in the US with HIV infection.

Preadoptive testing for HIV-2 infection is not performed routinely. HIV-2 infection is prevalent in some African nations and is now recognized on several other continents; perinatal transmission appears to be limited. Symptoms suggestive of HIV infection in a child with negative EIA results for HIV-1 should prompt testing for HIV-2.

Tuberculosis

TB is highly prevalent in the countries of origin for both refugees and internationally adopted children; therefore, screening on arrival to the US is recommended for both groups.[4–8] In 2015, 66% of the 9563 persons with active TB cases in the US were foreign born.[30] The incidence in foreign-born persons (15.1 cases per 100,000) was more than 13 times the incidence among US-born persons (1.2 cases per 100,000) during 2013 to 2015.[30] In 2015, among foreign-born persons with reported TB in the US, Asians had both the highest case count (3007 cases) and the highest incidence (28.2 cases per 100,000 persons). The top 5 countries of origin for foreign-born persons with TB were Mexico (n = 1250; 19.7%), the Philippines (n = 819; 12.9%), India (n = 578; 9.1%), Vietnam (n = 513; 8.1%), and China (n = 424; 6.7%).[30] In addition, in 2014, 88% of the 91 multidrug-resistant TB cases in the US occurred in foreign-born persons. One study reported that TB rates were 32 times higher in foreign-born children and 6 times higher in US-born children with foreign-born parents compared with rates in US-born children with US-born parents.[31]

Both refugees and internationally adopted children are at increased risk for *Mycobacterium tuberculosis* infection. High proportions of immigrants and refugees are found to have latent TB infection (LTBI), with rates ranging from 20% to 76%.[32–36] One study found that 7% of immigrants had active pulmonary TB.[36] The rate of LTBI is lower in internationally adopted children compared with refugees, ranging from 14% to 21%,[37–39] and TB disease rarely has been reported.[40,41] Retesting children at least 3 months after arrival in the US has been supported by data from 2 studies, in which children with initially negative tuberculin skin test (TST) results had repeat TST >3 months later, with positive TST results in 13% to 20% of these children.[38,39]

In the past, refugees ≥15 years of age and children <15 years of age with concern about TB exposure or disease were screened with a chest radiograph before arriving in the US. If the chest radiograph findings were abnormal, microscopic evaluation of sputum or gastric aspirate for acid-fast bacilli was performed. Sputum-positive people are banned from entry into the US until sputum smears are negative. The overseas screening requirements for TB for immigrants and refugees bound for the US underwent a major revision in 2007, including TB screening for all people.[42] These requirements are still in the process of being implemented. International adoptees from certain countries with high rates of TB (China and Ethiopia) now fall under the same requirements as other immigrants and refugees.[42] For other adoptees, screening in the country of origin is performed inconsistently, and results generally are documented only in older children.

For both refugees and internationally adopted children, screening for TB should be performed at the initial assessment by placement of a TST (5 tuberculin units [TU] purified protein derivative) or interferon-γ release assay (IGRAs), such as QuantiFERON-TB Gold (Cellestis Limited, Carnegie, Australia) and T-SPOT (Oxford Immunotec, Marlborough, Mass), for children ≥5 years of age.[5–8,43] For TB disease, the sensitivity of IGRAs is reported to be comparable to that of the TST. For LTBI, IGRA specificity is higher than that of the TST, but sensitivity is not known. For immunocompetent children ≥5 years of age, IGRAs can be used in place of a TST to confirm cases of active TB or LTBI. The TST should be read 48 to 72 hours later by a healthcare professional. A reading of ≥10 mm of induration is considered positive for both refugees and internationally adopted children. A reading of ≥5 mm is considered positive if the child has known contact with a person with active TB, an abnormal chest radiograph, signs or symptoms suggestive of TB, or evidence of immunosuppression. Children with a positive TST or IGRA result should have a thorough physical examination and chest radiograph performed to assess for *M. tuberculosis* disease. If findings are normal, the diagnosis of LTBI is made, and treatment with a 9-month course of isoniazid is begun. Retesting of children ≥6 months after arrival should be considered for all children with negative test results, given the high rate of false-negative TST results shortly after arrival to the US; retesting by IGRAs has not been reported in this population of children.[38,39] A negative result on the TST or IGRA does not rule out *M. tuberculosis* infection definitively.

Although most refugees and internationally adopted children with *M. tuberculosis* infection have LTBI, disease should be considered in children with pneumonia or nonspecific symptoms such as fever, malaise, growth delay, weight loss, cough, night sweats, or chills. Pulmonary TB is the most common site of infection in children, followed by lymphatic TB. Chest radiographs can reveal hilar or mediastinal lymphadenopathy, segmental or lobar infiltrates, or pleural effusion. Cavitary lesions and miliary disease are less common. Extrapulmonary manifestations in the central nervous system, middle ear and mastoids, lymph nodes, bone, joints, and skin can be seen. Recovery of the responsible organism is paramount because many children arrive from countries in which drug-resistant *M. tuberculosis* is common. Gastric aspirates or bronchoscopy, or both, can be useful adjuncts in a child too young or too ill to expectorate sputum.[43]

Vaccination with bacille Calmette-Guérin (BCG) is common in most resource-poor countries, but it is not a contraindication to the use of a TST.[8,43] Previous studies demonstrated that TST after BCG vaccination does not elicit induration of ≥10 mm, and thus a history of BCG vaccination does not affect interpretation of the TST.[44,45]

BCG vaccination can be recognized by a 2- to 4-mm scarification, typically on the left deltoid. Occasional complications include enlargement of the regional lymph nodes or nodularity or ulceration at the vaccination site. The granuloma typically is located in the deltoid region and may or may not be draining and can be associated with regional or distant sites of infection (Fig. 4.1). Culture of the drainage yields *Mycobacterium bovis*. No consensus exists on the management of this condition. Some lesions resolve without treatment, whereas others require excision or treatment with isoniazid, erythromycin, or clarithromycin.[43,46,47]

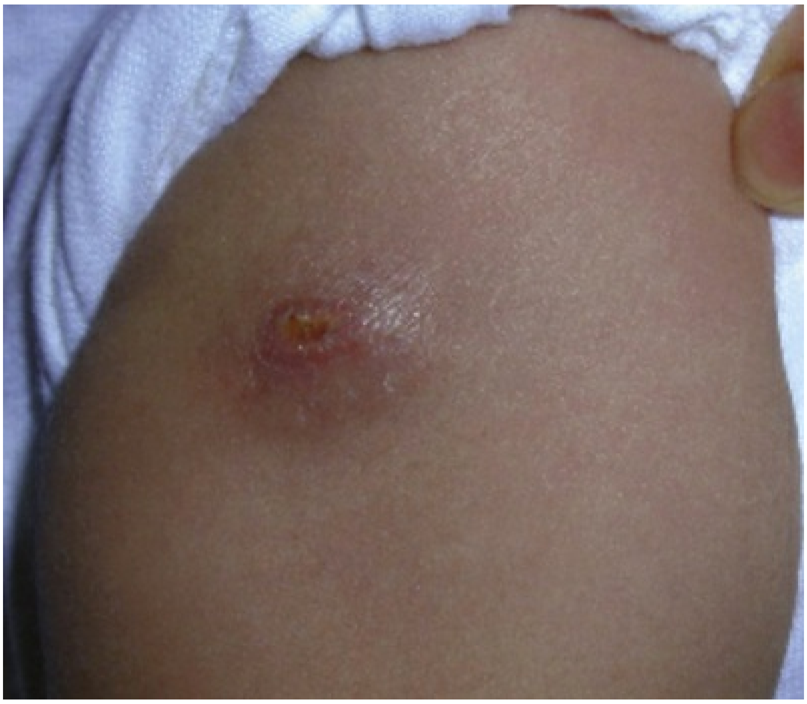

FIGURE 4.1 **Child with granuloma caused by *Mycobacterium bovis* at site of bacille Calmette-Guérin vaccination.**

Enteric Infections

Intestinal parasites are common in both refugee and internationally adopted children; infection rates vary by age and country of origin.[12–14,17–24,48–52] Although most children will not have had testing before coming to the US, presumptive treatment of refugees from certain regions of the world is recommended before departure to the US.[53] All refugees from the Middle East, South Asia, and Southeast Asia are recommended to receive albendazole for roundworm infestation and ivermectin for *Strongyloides stercoralis*. African refugees also should receive presumptive treatment for *Strongyloides,* and for refugees originating from areas endemic for schistosomiasis, treatment with praziquantel should be given. In African countries where microfilarial *Loa loa* infection is endemic, ivermectin should not be given for *Strongyloides* because treatment with ivermectin in the presence of *Loa loa* has been associated with encephalopathy; instead, a 7-day course of albendazole is given.

Additional details of country-specific recommendations, timing, dosing, and duration of treatment can be found in the Centers for Disease Control and Prevention (CDC) guidelines for refugee and immigrant care, available on the CDC website (http://www.cdc.gov/immigrantrefugeehealth/guidelines/domestic/i parasites-domestic.html).[53]

Many different parasites, both pathogenic and nonpathogenic (Table 4.2), can be seen in both groups of immigrants. Refugees compared with internationally adopted children are more likely to have nematodes and trematodes. In adoptees, the prevalence of intestinal parasites varies from 9% to 51%, depending on the child's age and country of origin; older children and children originating from countries other than Korea have higher rates.[17–24,52] One study in internationally adopted children found that the overall prevalence of intestinal parasites was 29%; 19% had *Giardia intestinalis,* and <1% had helminths.[52] A higher prevalence was found in older children, but there was no increased risk with the presence of malnutrition or gastrointestinal symptoms.[52,53] In contrast, in refugees, 17% of children had *Giardia,* whereas 19% had helminths.[51]

TABLE 4.2

Pathogenic and Nonpathogenic Intestinal Parasites

Parasite Type	Pathogens	Nonpathogens
Protozoa	*Giardia intestinalis*	*Endolimax nana*
	Entamoeba histolytica	*Entamoeba coli*
	Dientamoeba fragilis[a]	*Entamoeba gingivalis*
	Balantidium coli	*Entamoeba hartmanni*
	Blastocystis hominis[a]	*Entamoeba polecki*
	Cystoisopora belli	*Iodamoeba butschlii*
	Cryptosporidium parvum	*Chilomastix mesnili*
	Cyclospora cayentensis	*Enteromonas hominis*
	Microsporidium species	*Retortamonas intestinalis*
		Trichomonas hominis
		Trichomonas tenax
Helminths		
Nematodes (roundworms)	*Ascaris lumbricoides* (roundworm)	
	Trichuris trichiura (whipworm)	
	Strongyloides stercoralis (threadworm)	
	Enterobius vermicularis (pinworm)	
	Necator americanus (hookworm)	
	Ancyclostoma duodenale (hookworm)	
Cestodes (tapeworms)	*Hymenolepis* species	
	Taenia saginata (beef tapeworm)	

	Taenia solium (pork tapeworm)	
	Schistosoma species	

[a] Controversy exists regarding the pathogenicity of this organism.

Both refugees (who cannot be presumed to have been treated) and adoptees should be screened for intestinal parasites on arrival to the US.[5–8] The diagnosis is made by examination of preserved stool for ova and parasite testing; testing multiple specimens increases the sensitivity,[52,54,55] with a yield of 79% for 1 specimen, 92% for 2 specimens, and an additional 8% for a 3rd specimen.[52] One stool specimen also should be evaluated for *G. intestinalis* and *Cryptosporidium parvum* by using antigen testing.[8] Repeat stool samples are essential to assess the effectiveness of treatment for the identified parasite and to determine the presence of new (or newly found) pathogens. If the child remains persistently symptomatic, additional stool examinations are warranted, and testing for other parasites such as *Cyclospora* and *S. stercoralis* should be considered. In adoptees, screening for parasitosis with eosinophil counts is not indicated because most infections are caused by protozoa *(G. intestinalis)* and nonmigrating nematodes (pinworms), which do not elicit peripheral blood eosinophilia.[8] However, for either group, for children with negative stool ova and parasite examinations and eosinophilia (absolute eosinophil count exceeding 450 cells/mm^3), additional serologic testing should be done.[4,5,8] In this case, serologic testing for *S. stercoralis* should be performed, regardless of country of origin. Moreover, children with eosinophilia who are from sub-Saharan Africa, Southeast Asia, or areas of Latin America where schistosomiasis is endemic should have serologic testing for *Schistosoma* species. Similarly, testing for filariasis should be performed in children with eosinophilia who come from areas where filariasis is endemic. Because a variety of parasites can cause filariasis (see Chapter 278), if test results are positive, consultation with an infectious disease specialist with expertise in this disease is recommended to ensure that correct treatment is given.

Bacterial enteric pathogens appear to be less common than intestinal parasites in immigrants and adoptees; however, most studies have not assessed these groups systematically for bacterial causes. Children with bloody diarrhea or diarrhea associated with high fever should have stool examined for bacterial enteropathogens (e.g., *Salmonella, Shigella, Yersinia, Campylobacter*) as part of the initial evaluation.[8]

Chagas Disease (American Trypanosomiasis)

Chagas disease, caused by *Trypanosoma cruzi,* is endemic throughout much of Mexico, Central America, and South America. The risk of Chagas disease varies by region within endemic countries. Although the prevalence of Chagas disease in refugees or internationally adopted children is unknown, screening is warranted because treatment of infected children is highly effective compared with treatment in adults.[8] Serologic testing should be performed only in children ≥12 months of age because of the potential presence of maternal antibody.

Syphilis

Refugees ≥15 years of age routinely are screened for syphilis before resettlement.[5] Although refugees are not screened routinely upon arrival in the US, refugees of any age should be tested if there is clinical suspicion for syphilis or there is evidence or concern for sexual exposure.

Most internationally adopted children have documentation of syphilis screening in their birth country; syphilis rarely has been reported after arrival in the US.[17–24] In children with a history of syphilis, it often is difficult to obtain the details of the birth mother's history, treatment, and management. In addition, in children with suspected *T. pallidum* exposure, details of the evaluation and prescribed treatment regimens often are incomplete or uninterpretable. For internationally adopted children, screening with both a nontreponemal test and a treponemal test is recommended.[8] A positive treponemal test result warrants a complete and thorough evaluation to document the extent of the disease and to provide optimal treatment.

Other Testing

A complete blood count is recommended for refugees and internationally adopted children.[5–8] The hemoglobin and red blood cell indices can identify children with anemia, iron deficiency, hemoglobinopathies, or malaria. A low white blood cell count and lymphopenia can indicate HIV infection or malnutrition. Eosinophilia is common among refugees and suggests parasitic infection.[4–8,53] For refugees, a urinalysis is recommended to assess for hematuria and pyuria.[4,53] Hematuria can indicate schistosomiasis, and pyuria can reflect a urinary tract infection or renal TB. Routine screening for malaria is not recommended, but malaria should always be considered in children with fever who come from endemic areas.[5]

Elevated blood lead levels have been reported in internationally adopted children, and lead testing is recommended for all international adoptees.[56] No formal recommendation exists for refugees; however, it is likely that they could benefit from screening.

Other Infections

Dermatologic Infections.

Lice, scabies, tinea, and molluscum contagiosum are common in both refugees and internationally adopted children. The incidence of these conditions has not been well documented. The physical examination should include careful skin evaluation so that appropriate treatment is given.

Upper Respiratory Tract Infections.

Upper respiratory tract infections occur frequently in adopted children within the 1st month of arrival.[57] Because the past history of otitis media often is unknown and because many children have language delays, referral to an otolaryngologist for hearing test evaluation should be considered for children with otitis media and language delays.

Other Less Common Infections.

Clinicians should be aware of other potential diseases and clinical manifestations that can be seen in refugees and internationally adopted children. These diseases are less prevalent than those discussed and do not have readily available screening tests. In addition, some diseases (e.g., neurocysticercosis) can have long incubation periods, as long as several years. In most cases, however, the longer the interval is from arrival in the US to the development of a clinical syndrome, the less likely it is that the syndrome will be attributed to a pathogen acquired in the country of origin. Population-specific health profiles can be found on the CDC's website at www.cdc.gov/immigrantrefugeehealth/profiles/index.html.

Preventive Measures

Immunizations

Both refugees and adoptees can arrive in the US without a complete immunization record, thus making the approach to optimizing immunizations challenging. The Immigration and Nationality Act of 1996 requires immigrant visa applicants to provide proof of vaccination with receipt of at least the 1st dose of the Advisory Committee on Immunization Practices (ACIP)–recommended vaccines before entry into the US.[5,6] These regulations apply to most immigrant children entering the US; however, internationally adopted children who are ≤10 years of age can obtain an exemption from these requirements; adoptive parents are required to sign a waiver indicating their intention to comply with the ACIP immunization requirements within 30 days after the child's arrival in the US. Refugees are not required to meet immunization requirements of the Immigration and Nationality Act at the time of entry into the US but must show proof of immunization when they apply for permanent residency, typically 1 year after arrival.

Refugee Children.

If immunization documents exist, they should be reviewed and can be accepted as valid if the immunizations were provided at ages and intervals acceptable to US standards.[5–8,58,59] The clinical diagnosis of vaccine-preventable diseases may not be reliable, especially for rubella and mumps; vaccine should be given. History of varicella infection may be unavailable or unreliable in these populations; therefore, children should be immunized for varicella or have antibody testing performed.

Refugees who have no records or who have incomplete immunizations should receive vaccines at their 1st visit. Guidelines for routine and catch-up immunizations should be followed.[6,58,59] Few data are available on verifying immunization status by antibody testing in refugees; however, a study found that screening for varicella was more cost effective than providing immediate vaccine for people >5 years of age.[60]

International Adoptees.

Several studies have used antibody testing to verify the immunization status of internationally adopted children.[20–24,61–69] Results differ; some studies showed inadequate protection, whereas others found good protection. Differences in study design, laboratory methods, and definitions of protection likely account for the differences. Currently, 2 acceptable approaches are recommended to ensure that internationally adopted children are protected against vaccine-preventable diseases.[8,58,59] The 1st approach is to reinitiate immunizations regardless of documentation, and the 2nd approach is to use serologic testing to determine which immunizations are needed. Because antibody testing for a single vaccine-preventable disease may not be predictive of others, a combination of reimmunization and antibody testing can be used. Serologic testing is available for most vaccine antigens (Table 4.3). For children ≥5 months of age, testing for diphtheria, tetanus, poliomyelitis, *Haemophilus influenzae* type b (Hib), and HBV can be performed. Testing for measles, mumps, rubella, varicella, and HAV antibodies can be considered only in children ≥12 months of age because of the possible presence of maternal antibody. For varicella, testing is performed to verify whether the child had previous infection because varicella immunization is not available in most countries from which children are adopted.

TABLE 4.3

Serologic Testing Available for Verifying Immunization Status

Children ≥5 Months of Age	Children ≥12 Months of Age
Diphtheria IgG EIA	Diphtheria IgG EIA
Tetanus IgG EIA	Tetanus IgG EIA
Poliovirus serotypes 1–3 neutralizing antibody	Poliovirus serotypes 1–3 neutralizing antibody

Haemophilus influenzae type b-PRP	*Haemophilus influenzae* type b-PRP
Hepatitis B surface antibody	Hepatitis B surface antibody
	Rubeola (measles) antibody
	Mumps antibody
	Rubella antibody
	Varicella antibody
	Hepatitis A antibody

EIA, enzyme immunoassay; IgG, immunoglobulin G; PRP, polyribosylribitol phosphate antibody.

Providing care for new immigrants can be rewarding. Application of directed screening tests on arrival yields incalculable dividends for prevention and for the welfare of adoptees, refugees, and their families.

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B

Prevention of Infectious Diseases

OUTLINE

5 Passive Immunization
6 Active Immunization
7 Antimicrobial Chemoprophylaxis
8 Protection of Travelers

5

Passive Immunization

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Passive immunization provides persons with exogenous, preformed antibodies that can prevent or treat infectious diseases. In the early 20th century, hyperimmune animal sera were produced to treat specific infections. After human plasma fractionation was developed (during World War II), immune globulin (human) (IG) became available for passive immunization. Although this development was a major breakthrough, intravenous (IV) infusion of the product was found to evoke a variety of severe adverse reactions. Therefore, the IV route of administration was precluded, and IG largely was limited to intramuscular (IM) injection. For some indications, this route was not a disadvantage. However, for treatment of a primary immunodeficiency disorder, it became clear that the volume (and hence the amount of immunoglobulin G [IgG]) that could be administered by the IM route was suboptimal. In 1981, the Food and Drug Administration (FDA) approved the first United States–licensed (human) IGIV. IGIV enables administration of large doses of IgG with minimal discomfort and to produce an immediate rise in both total plasma IgG concentration and titers of specific antibodies.

The products available for passive immunization can be grouped into 4 categories: (1) standard IG for IM administration (hepatitis A, measles, rubella); (2) hyperimmune globulins that can be administered by the IM route (hepatitis B IG [HBIG], rabies IG, tetanus IG [TIG], varicella IG) or by the IV route (cytomegalovirus [CMV], vaccinia, botulism IGs); (3) IGIV; and (4) monoclonal antibodies (mAbs) (Table 5.1). In addition, 2 antitoxins of animal origin are available for limited distribution.

TABLE 5.1

Immune Globulins Prepared From Human Plasma

Nonproprietary Name	Abbreviation
FOR INTRAMUSCULAR ADMINISTRATION	
Standard immune globulin (human)	IG
Hepatitis B immune globulin (human)	HBIG
Rabies immune globulin (human)[a]	RIG
Tetanus immune globulin (human)	TIG
Varicella-zoster immune globulin (human)[b]	VariZIG
FOR INTRAVENOUS ADMINISTRATION	
Immune globulin intravenous (human)	IGIV
Cytomegalovirus immune globulin intravenous (human)	CMV-IGIV
Botulism immune globulin intravenous (human)	BIG-IGIV
Vaccinia immune globulin intravenous (human)	VIG-IGIV
Anthrax immune globulin intravenous (human)	AIG-IGIV

[a] As much of the dose as possible should be instilled around the wound.

[b] See text.

Passive immunization is used for a variety of clinical indications, including the following: (1) treatment of a primary immunodeficiency and, in certain cases, a secondary immunodeficiency; and (2) prophylaxis against infections with specific organisms. IG is less useful for treatment of established infections. However, the use of IGIV for the treatment of various conditions that involve immune dysregulation, such as immune thrombocytopenic purpura (ITP) and Kawasaki disease, has become routine.

In the following sections, the various products and their uses are discussed. Pathogen-specific and disease-specific chapters should be consulted. An effort has been made to use nonproprietary product names as they appear in the labeling, but for brevity, abbreviations are used liberally. Emphasis is placed on FDA-approved indications (i.e., those that appear in the product package inserts). In the case of IGIV, not all products have been approved or studied for all indications (Table 5.2). Moreover, in contrast to IG for IM administration, IGIV products are produced by a variety of manufacturing processes, they use several different stabilizers and excipients, various concentrations, and physical states, and they can differ in subtle ways (e.g., IgA content).

TABLE 5.2

Available Immune Globulin Intravenous Products in the United States

Product Registered Name	Manufacturer	FDA-Approved Indication
Bivigam	Biotest Pharmaceuticals	PID
Gammaplex	Bio Products Laboratory	ITP, PID
Carimune NF	CSL Behring	ITP, PID
Privigen	CSL Behring	PID, chronic ITP
Flebogamma DIF 5%, 10%	Instituto Grifols, SA	PID
Gammagard Liquid (IV, SC)	Baxter Healthcare	PID, MMN
Gammagard S/D	Baxter Healthcare	CLL, ITP, KD, PID
Gamunex-C (IV, SC)	Grifols Therapeutics, Inc.	ITP, PID, CIDP
Octagam	Octapharma USA	PID
GamaSTAN S/D (IM)	Grifols Therapeutics, Inc.	Hepatitis A, measles, varicella prophylaxis
Vivaglobulin (SC)	CSL Behring	PID
Hizentra (SC)	CSL Behring AG	PID
HYQVIA (SC)	Baxter Healthcare	PID
WinRho SDF	Cangene	Chronic or acute ITP and HIV-immune related conditions

CIDP, chronic inflammatory demyelinating polyneuropathy; CLL, chronic lymphocytic leukemia; FDA, Food and Drug Administration; HIV, human immunodeficiency virus; IM, intramuscular; ITP, immune thrombocytopenia purpura; IV, intravenous; KD, Kawasaki disease; PID, primary immunodeficiency; MMN, multifocal motor neuropathy; SC, subcutaneous.

Immune Globulin (Human)

IG is prepared by cold alcohol fractionation of pooled human plasma. It is formulated as a 16.5% protein solution. At least 96% of the total protein is IgG, but small quantities of IgM and IgA may be present. Each lot represents the pooled plasma of at least 1000 donors to provide a wide diversity of antibodies. In practice, however, each lot represents many more donors (up to 60,000). Individual donations of the plasma, like those used as the source for all human plasma derivatives, are screened for markers of certain viruses (hepatitis B, hepatitis C, human immunodeficiency viruses 1 and 2 [HIV-1 and [HIV-2], human T-lymphotropic virus 1 and 2 [HTLV-1 and HTLV-2], West Nile virus), as well as *Trypanosoma cruzi* and *Treponema pallidum*, to minimize the potential for transmission. Other steps taken to minimize such transmission are noted at the end of this chapter.

Hepatitis A

A major use of standard IG is for postexposure prophylaxis of hepatitis A virus (HAV) in susceptible persons.[1] When injected deep into a large muscle mass within 14 days of exposure, IG is 80% to 90% effective in preventing clinical hepatitis. IG is most effective when administered early in the incubation period. When administered later in the incubation period, IG may only attenuate the severity of HAV disease expression. The usual dose is 0.02 mL/kg, given as soon as possible after exposure. For persons 12 months through 40 years of age, HAV vaccine is preferred for postexposure prophylaxis. IG is recommended for people >40 years of age because of the absence of data regarding vaccine use in adults >40 years of age and the severity of HAV infection in older adults. Children <12 months of age, immunocompromised people, people with chronic liver disease, and others who may have a diminished response to vaccine should receive IG.[2]

IG may be effective for preexposure prophylaxis in travelers to areas where HAV is prevalent. However, for travelers who are ≥1 year old and whose departure is not imminent, HAV vaccine largely has replaced IG. The dose of IG depends on the age of the traveler and the length of stay. For a child <1 year old, the dose is 0.02 mL/kg if the anticipated stay is 2 months or less and 0.06 mL/kg if longer. In older persons whose departure is imminent, the dose of IG is 0.02 mL/kg, concomitant with the first dose of vaccine, for a stay of up to 5 months, and 0.06 mL/kg, concomitant with the first dose of vaccine, for a longer stay.

For people ≥12 months of age for whom IG is given for preexposure or postexposure prophylaxis, hepatitis A vaccine is given simultaneously, at a separate site and using a separate syringe.[3]

Measles

Vaccination is the major strategy for achieving protection against measles. More than 98% of persons who receive 2 doses of measles vaccine (with the first dose administered no earlier than the first birthday and the second dose administered at least 28 days after the first dose) develop serologic evidence of immunity.[4] Nonetheless, measles postexposure prophylaxis with IG is important for children <12 months of age (for age 6 to 11 months, measles, mumps, and rubella [MMR] vaccine can be substituted for IG if within 72 hours of exposure), seronegative persons who cannot be vaccinated within 72 hours of exposure, seronegative pregnant women, and immunocompromised children who are not receiving routine immunoglobulin replacement therapy. Prophylaxis is indicated for susceptible household or hospital contacts of a case. A single dose of 0.5 mL/kg administered within 6 days of exposure may prevent or modify disease and provide temporary protection. Immunocompromised children should receive 0.5 mL/kg. In either case, no more than 15 mL should be injected, and small children should be given no more than 3 mL at any single site. Manufacturers' instructions should be consulted for maximum volume injected into a single muscle. A child who is receiving routine IgG replacement therapy is likely to have a protective concentration of measles-neutralizing antibody. If the child is ≥12 months of age, live measles vaccine should be administered approximately 6 months after IG administration if no contraindication exists. For children 6 through 11 months of age who are traveling to areas where measles is endemic, MMR vaccine (rather than IG) should be administered; this dose is not counted in the required 2-dose series at ≥12 months of age. IGIV is recommended for seronegative pregnant woman and for persons who are severely immunocompromised.[5]

Rubella

IG can be considered for prophylaxis of rubella-susceptible women who are exposed to rubella early in pregnancy. As many as 85% of infants born to mothers who are infected in the first trimester of pregnancy will have signs of congenital rubella syndrome. The IG option is recommended only for women if termination of pregnancy is declined. Limited data indicate that IM IG in a dose of 0.55 mL/kg may decrease clinically apparent infection, virus shedding, and rates of viremia in infected susceptible people. Theoretically, the reduction in viral replication may decrease the likelihood of fetal infection. The absence of clinical signs in a woman who has received IG does not guarantee that fetal infection has been prevented. Infants with congenital rubella have been born to mothers who received IG shortly after exposure.

Specific Immune Globulins for Intramuscular Administration

Specific hyperimmune IGs for IM use are IgG preparations produced from plasma that is selected by screening donations or collected from donors who have been purposefully immunized or who have received a booster. Either approach can ensure the presence of high concentrations of antibody directed against 1 or more specific antigens. The manufacturing process is essentially the same as that used to prepare IG. The protein concentration differs for individual products and may be found in the package insert. Specific products available for IM administration are listed in Table 5.1. Hyperimmune IM globulins are used to prevent hepatitis B, rabies, tetanus, and varicella-zoster virus (VZV) infection.

Hepatitis B Immune Globulin

All pregnant women should be tested for circulating hepatitis B surface antigen (HBsAg). Infants born to women who are HBsAg positive (either acutely or chronically infected with hepatitis B virus [HBV]) are at high risk of developing acute and chronic HBV infection. The HBV vaccination series accompanied by a single dose of HBIG is 85% to 95% effective in preventing HBV infection in the infant. Infants born to an HBsAg-positive mother should receive HBIG (0.5 mL) within 12 hours of birth. The first of 3 doses of HBV vaccine should be given at the same time as HBIG but at a different site.

In general, HBIG is not recommended if the mother's HBsAg status is not known, but HBV vaccination series should be begun within 12 hours of birth. Ideally, in such a case, the mother should be tested for HBsAg as soon as possible after delivery. If the test result is positive, the infant should receive 0.5 mL of HBIG IM as soon as possible (within 12 to 24 hours) and if delay is unavoidable, at least within 7 days of birth; vaccination series should be completed according to schedule. Preterm infants (<2 kg) constitute a special class. If the mother's HBsAg status is unknown and cannot be determined within 12 hours, the neonate should be given 0.5 mL of HBIG as well as vaccine, because the premature infant may respond suboptimally to HBV vaccine.

After a percutaneous (needlestick, laceration, or bite) or mucosal exposure that contains or may contain HBV, blood should be obtained from the person who was the source of the exposure (if possible) to determine his or her HBsAg status. Management of the exposed person depends on the HBsAg status of the source and the vaccination and anti-HBs response status of the exposed person. Recommended postexposure prophylaxis for different situations has been outlined by the Centers for Disease Control and Prevention (CDC).[6]

Human Rabies Immune Globulin

Rabies IG (human) (HRIG) is always used in association with rabies vaccine.[7] HRIG is administered to previously unvaccinated persons to provide rabies virus-neutralizing antibody until the patient responds to vaccination by actively producing virus-neutralizing antibodies. HRIG is administered once at the same time postexposure prophylaxis is initiated with the human rabies vaccine.[7,8]

The dose of HRIG is 20 IU/kg. If anatomically feasible, the dose should be infiltrated around the wound, and any remaining dose should be administered by the IM route at an anatomic site distant from the vaccine administration. HRIG is supplied in 2-mL (300 IU) and 10-mL (1500 IU) vials with an average potency of 150 IU/mL. Thus the contents of a 2 mL vial can be used to treat a child of up to 15 kg; for larger children, additional vials are required. A 10-mL vial is sufficient to treat a 75-kg adult and as a result is less suitable for pediatric use. However, if the smaller vials are not available, an appropriate portion can be withdrawn to treat a child. The product contains no preservative; once a vial has been entered, the contents should be administered promptly, and the remainder should be discarded.

Tetanus Immune Globulin

TIG is the oldest of the specific IGs. TIG is recommended for the treatment of tetanus and for prophylaxis in certain circumstances. Tetanus is so rare in persons whose immunization history includes at least 3 doses of tetanus toxoid that TIG is not recommended for such persons. The need for active immunization with or without passive immunization depends on the condition of the wound and the patient's immunization history. Specific guidance has been provided by the Advisory Committee on Immunization Practices.[9] Persons with wounds that are neither clean nor minor and who have had 0 to 2 previous doses of tetanus toxoid or have an uncertain history of previous doses should receive TIG, as well as diphtheria and tetanus toxoids (DT), tetanus and diphtheria toxoids (Td), diphtheria and tetanus toxoids and acellular pertussis (DTaP), or tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap), depending on age and other needed vaccines. TIG can neutralize only unbound tetanus toxin; it cannot affect toxin bound to nerve endings. A single IM dose of 3000 to 5000 units TIG is generally recommended for treatment of children and adults, with part of the dose infiltrated around the wound (250 units is maximum used for prophylaxis). IGIV contains tetanus antitoxin and can be used if TIG is not available.

Varicella-Zoster Immune Globulin

Postexposure prophylaxis should be targeted toward patients without evidence of immunity to varicella who are at high risk for severe disease and complications and who have been exposed to and likely infected by VZV. Such persons include the following: (1) immunocompromised people; (2) nonimmune pregnant women; (3) neonates whose mothers develop signs and symptoms of varicella within 5 days before delivery to 48 hours after delivery; (4) premature infants born at 28 weeks of gestation or later who are exposed in the neonatal period and whose mothers do not have evidence of immunity; (5) premature infants born before 28 weeks of gestation or who weigh <1000 g at birth and are exposed during the neonatal period regardless of maternal history of varicella disease or vaccination (because transfer of maternal antibody may not have occurred). Significant exposure can occur through residence in the same household, close contact with a playmate, proximity to a contagious patient, or contact with a contagious visitor or hospital staff member.

In December 2012, the FDA approved VariZIG, a varicella-zoster IG preparation (Cangene Corporation, Winnipeg, Canada) for postexposure prophylaxis for persons at high risk of severe disease who lack evidence of immunity to varicella and for whom varicella vaccine is contraindicated. VariZIG is a lyophilized product and after reconstitution is administered IM. VariZIG is approved for administration as soon as possible following VZV exposure, ideally within 96 hours (4 days) for greatest effectiveness, but if it is administered within 10 days, it may result in disease attenuation. The dose is 125 U (1 vial)/10 kg body weight up to a maximum of 625 IU (5 vials). The minimum dose is 125 IU, or 62.5 IU if weight is ≤2 kg.[10]

If VariZIG cannot be obtained within 96 hours after exposure, IGIV can be given at a dose of 400 mg/kg. Although licensed IGIV preparations are known to contain varicella antibody, the titer of any specific lot is uncertain. An alternative to postexposure prophylaxis with VariZIG or IGIV is administration of oral acyclovir, which should be started 7 to 10 days after exposure and continued for a total of 7 days. This approach can be considered in immunocompetent, seronegative people with significant exposure who cannot be vaccinated. The oral acyclovir dose for adults is 800 mg given 4 times a day. If a child requires acyclovir preemptively, the dose is 40 to 80 mg/kg per day, divided into 4 doses. As an alternative, exposed immunocompetent children and adults can be given varicella vaccine within 3 to 5 days of exposure if they have not previously received 2 doses of vaccine and have no contraindication.

Immune Globulin Intravenous

(Human)

IGIV, like IG, is prepared from large pools of plasma derived from as many as 60,000 donors. The early steps in its manufacture are similar to those used for preparing IG. Further processing of individual products is performed by a variety of techniques, including steps such as polyethylene glycol precipitation, ion exchange chromatography, and exposure to low pH. This variation reflects, in part, the lack of consensus on the optimal procedure for preparing IGIV on a commercial scale in a form that is safe for IV administration. Final formulations are diverse, such as freeze-dried or in solution, different protein concentrations of the solution, different pH, and various stabilizers and other excipients that can be used in several different combinations. The product package label should be consulted for a brief synopsis of the product's preparation and properties.

Each lot of IGIV must contain minimum levels of antibodies to certain infectious organisms or toxoids (measles, poliovirus, and diphtheria). These concentrations were established to ensure lot-to-lot consistency rather than to match the clinical indications for individual products. Even though the use of large plasma pools enhances consistency, IGIV products differ in sources of plasma. As a result, antibody titers to other bacterial and viral pathogens can vary significantly among preparations and lots.[11,12] In addition, processing steps can alter functional capabilities of IgG or change the relative distribution of immunoglobulin subclasses. These changes may or may not be reflected in antibody titers measured by nonfunctional assays. In addition, individual products have undergone clinical trials for only a certain subset of indications. Even when several IGIV products carry the same indication, direct comparisons of the efficacy of multiple products in a single clinical trial are uncommon. For all these reasons, IGIV cannot be considered a uniform generic product. Available products in the US are shown in Table 5.2. Certain physiologic properties intrinsic to IGIV preparations (and variable among products) should be considered in all persons for whom administration is considered and especially in persons who have underlying conditions. Such considerations include the following: high volume load, sodium content, and osmolality, especially in neonates and young children, as well as in patients with cardiac disease, renal impairment, or thromboembolic risk; 2% to 10% carbohydrate content in children with diabetes or renal impairment; low pH in neonates; and average IgA content (<2 to 720 μg/mL) in persons with anti-IgA antibodies.

Approved Indications

Current FDA-approved available IGIV products in the US have the following 6 indications: (1) replacement therapy for primary immunodeficiency disorders associated with defects in humoral immunity; (2) treatment of ITP to induce a rapid rise in platelet count when needed to prevent or control bleeding; (3) prevention of coronary artery aneurysms associated with Kawasaki disease; (4) prevention of bacterial infections in patients with hypogammaglobulinemia associated with B-cell chronic lymphocytic leukemia; and (5) maintenance therapy to improve muscle strength in adults with multifocal motor neuropathy; (6) improvement of neuromuscular disability and maintenance therapy to prevent relapse of chronic inflammatory demyelinating polyneuropathy (Table 5.3). Previous products were approved for prevention of infection and graft-versus-host disease in adult bone marrow transplant recipients and for prevention of infection in children with HIV infection.

TABLE 5.3

Approved Indications for Immune Globulin Intravenous Therapy

Indications	Dosage	Comments
REPLACEMENT THERAPY		
Primary immunodeficiency	~400 mg/kg q4wk (average dose)	Adjust dose according to individual response
Chronic lymphocytic leukemia	400 mg/kg q3–4 wk	Cost effectiveness questioned
Bone marrow transplantation	500 mg/kg q1wk	Other anti-infective therapies also effective
Human immunodeficiency virus infection in children	400 mg/kg q2–4 wk	Useful in selected symptomatic patients
IMMUNE MODULATION		
Idiopathic thrombocytopenic purpura	400 mg/kg daily for 5 days, *or* 1 g/kg single dose	Useful in acute and chronic cases
Kawasaki disease	2 g/kg single dose	10%–20% of patients may need a second dose
Multifocal motor neuropathy	400 mg/kg daily for 5 days	Repeat doses dependent on

		clinical response
Chronic inflammatory demyelinating polyneuropathy	400 mg/kg daily for 5 days	Repeat doses dependent on clinical response

Primary Immune Deficiencies

IGIV is standard replacement therapy in primary immunodeficiency, and all IGIV products include this indication.[13] Clinical experience with IGIV in many different types of primary immunodeficiency has been favorable. Patients with the following primary immunodeficiencies have associated hypogammaglobulinemia and may benefit from replacement IGIV therapy: X-linked agammaglobulinemia, common variable immunodeficiency, severe combined immunodeficiency, hyper-IgM syndrome, congenital agammaglobulinemia, and Wiskott-Aldrich syndrome.

The objective of replacement therapy is to determine the dose and frequency that will result in freedom from serious infections. Monitoring the trough levels of IgG in parallel with the patient's clinical course has been helpful in accomplishing this objective. A range of effective doses, dosing schedules, and trough levels has been observed. The usual schedule for IGIV infusion is once every 3 or 4 weeks, and the typical dose is 400 mg/kg (range, 300 to 800 mg/kg). Trough concentrations of IgG should be maintained in the range of 400 to 500 mg/dL.[14] In 2006, IG subcutaneous (Vivaglobulin, CSL Behring) was FDA approved for people with primary immunodeficiency. It is the first subcutaneous IG approved that can be self-administered weekly (158 mg/kg) by using a portable pump, and it has gained favor for this reason.

Secondary Immune Deficiencies

Chronic lymphocytic leukemia and the immune suppression that occurs in patients undergoing bone marrow transplantation result in quantitative and qualitative humoral immunodeficiency. Although IGIV reduces infections in these conditions, unresolved issues are selection of patients most likely to benefit, optimal timing and duration of administration, and the relative effectiveness of IGIV and other anti-infective therapies.

Infection with HIV causes dysregulation of humoral immunity with impaired functional antibody activity. Some HIV-infected children have fewer bacterial infections while they are receiving IGIV; hence IGIV may benefit selected patients. With the use of combined antiretroviral therapy, antimicrobial prophylaxis (e.g., trimethoprim-sulfamethoxazole), and vaccination, the need for IGIV has decreased, but it can be considered in patients with recurrent serious bacterial infections and IgG ≤400 mg/dL or evidence of functional antibody deficiency.[15]

Immunomodulation

Mechanism of immunomodulation by IGIV and its use in treatment of inflammatory and autoimmune diseases have been reviewed.[16] Potential anti-inflammatory mechanisms include neutralization of pathologic autoantibodies, enhanced clearance of autoantibodies, inhibition of phagocytosis by effector cells, altered complement deposition, altered cytokine expression, neutralization of superantigens, and modulation of lymphocyte function.[17] Because immunomodulation does not appear as a separate category in the labeling of IGIV, the labeled indications in this category are considered individually in this discussion.

Immune Thrombocytopenic Purpura.

ITP can follow viral infections. Antibodies that are specific for or that cross-react with platelet surface antigens coat the cell surface and promote increased clearance of platelets by the spleen. In patients with ITP, IGIV can effect a rapid increase in platelet counts (often within 24 hours of infusion) and thereby avert life-threatening bleeding. One hypothesis is that IgG in IGIV interacts with phagocytic Fc receptors, thus blocking clearance of platelets and allowing them to enter or remain in the circulation[18] However, the mechanism likely is more complex.[18]

Many different IGIV products are useful for the treatment of ITP, although few direct comparisons of effectiveness exist, and no tests predict efficacy. IGIV has been studied in acute and chronic ITP in adults and children. Not all patients respond, but children do so more frequently than adults, and the increase in platelet count is more prolonged in children treated for acute ITP. Because acute ITP can resolve spontaneously, especially in young children, it is important to consult a hematologist during planning of the therapeutic approach.[19] In general the IGIV dose used is 0.8 to 1 g/kg.[20,21]

Kawasaki Disease.

Immune dysregulation may play a role in diseases for which a specific cause has not been identified. Kawasaki disease is an acute inflammatory condition with multisystem vasculitis that can result in arterial aneurysms, particularly of the coronary vessels. Several IGIV preparations have been studied for the treatment of this condition. IGIV administered concurrently with aspirin rapidly downregulates the inflammatory response. IGIV in combination with aspirin reduces the incidence of coronary artery aneurysms from 20% to 25% to <5%. IGIV should be administered within the first 10 days of illness and within 7 days of onset of symptoms if possible; a single dose of 2 g/kg infused over 10 to 12 hours is recommended.[22] Patients with Kawasaki disease that is diagnosed after 10 days of fever also should receive aspirin and IGIV promptly, although benefit has not been studied in this setting.

Children who have persistent or recrudescent symptoms may benefit from a second dose of IGIV 2 g/kg. Inasmuch as the cause of Kawasaki disease is unknown, it is possible that not all IGIV preparations (or all lots) are equally effective.[22]

Bone Marrow Transplantation.

IGIV may reduce the risk of infection in recipients of bone marrow transplants. In addition, several studies have reported IGIV to lower the incidence of acute graft-versus-host disease, but in one study this result only was observed in patients who were >20 years of age. Increased doses of IGIV have been associated with veno-occlusive disease.[23,24] A meta-analysis concluded that prophylaxis did not affect mortality rates or infection-related outcomes.[25]

Chronic Idiopathic Demyelinating Polyneuropathy and Multifocal Motor Neuropathy.

IGIV is thought to compete with pathologic autoantibodies.[26] The dose of IGIV used to treat multifocal motor neuropathy is 0.5 g/kg per day for 5 consecutive days once a month for 3 months. Subcutaneous IG has been shown to elicit a response comparable to that of IGIV.[27] In addition, chronic idiopathic demyelinating polyneuropathy can be responsive to plasma exchange and corticosteroid therapy, whereas multifocal motor neuropathy is unresponsive or even worsens.[28]

Other Uses

The number of clinical conditions for which IGIV is used exceeds its approved indications, and the off-label use of IGIV has been implicated in shortages of IGIV. This section includes some of the more frequent off-label uses of IGIV.

Toxic Shock Syndrome.

IGIV has been used an adjuvant for the treatment of toxic shock syndrome associated with staphylococcal and streptococcal disease. IGIV typically contains antibodies against superantigen toxins (including toxic shock syndrome toxin-1, staphylococcal enterotoxins, and streptococcal exotoxins) produced by both these organisms.[29] Furthermore, the anti-inflammatory properties of IGIV may help ameliorate the exaggerated cytokine response induced by superantigens. Animal studies and human case reports suggest the utility of IGIV as adjuvant therapy for the treatment of toxic shock syndrome.[30,31] The efficacy of IGIV as adjunctive therapy in streptococcal toxic shock syndrome was studied in a double-blind, placebo-controlled trial, but the trial ended prematurely because of poor patient accrual. Although statistical significance was not evident, results suggested a 3.6-fold higher mortality rate in placebo recipients. A retrospective review of streptococcal toxic shock did not show a difference in mortality rates or hospital length of stay, whereas a comparative observational study demonstrated improved survival.[32,33] Because most patients respond rapidly to fluids, vasopressor therapy, and antimicrobial therapy, some experts reserve IGIV for patients who do not respond to initial therapy. The typical dose of IGIV for this purpose is 1 g/kg given once, although a range of doses has been used.

Neonates.

Because of the high morbidity and mortality rates in preterm infants, the effects of IGIV in this population have been studied extensively.[34] Despite enthusiasm and the apparent logic of replacing missing antibodies, studies to date have shown minimal benefit, and routine use is not indicated.[34,35]

Parvovirus B19.

Most parvovirus B19 infections are mild and do not require treatment. However, anemia can be prolonged in patients with a variety of immunodeficiencies. IGIV (400 mg/kg daily for 5 days) has been reported to reduce the viral load and to restore erythropoiesis in selected patients. An alternate dosing regimen of 2 g/kg over fewer days has been used.[36,37,38] Anemia, hydrops, and persistent neonatal infection also can occur with intrauterine infection. In conjunction with intrauterine transfusions of red blood cells, IGIV may be helpful in ameliorating anemia associated with congenital parvovirus B19 infection.[37,39,40]

Immune-Mediated Cytopenias.

Patients with a variety of immune-mediated cytopenias, including anemia, thrombocytopenia, and neutropenia, have been treated with IGIV.[41,42] In autoimmune neutropenia, IGIV has been shown to cause a transient rise in neutrophil count that may be beneficial in instances of severe infection, with recombinant human granulocyte colony-stimulating factor typically used for sustaining counts.[42,43] Published reports support the use of IGIV in HIV-infected persons with ITP, although antiretroviral agents comprise the primary therapy.[44]

Guillain-Barré Syndrome.

Guillain-Barré Syndrome (GBS) is an acute, immune-mediated, inflammatory polyneuropathy. IGIV and plasma exchange represent the main methods of treatment. Large, randomized controlled trials of IGIV versus placebo in children with GBS are not available.[45,46] Results from small trials in children with GBS are consistent with data from larger randomized trials in adults, thus suggesting that IGIV therapy can shorten the time to recovery.[47] The mechanism of IGIV in GBS is uncertain.[48,49]

Specific Immune Globulins for

Intravenous Administration

Currently, 5 specific, plasma-derived hyperimmune polyclonal products for IV administration are approved for prophylaxis or therapy of infectious disease (see Table 5.1).

Cytomegalovirus Immune Globulin.

CMV-IGIV (human) is used for prophylaxis of CMV disease associated with stem cell or solid-organ transplantation, typically in conjunction with antiviral prophylaxis.[50–54] The use of CMV-IGIV for prophylaxis of CMV disease varies among transplant centers. Factors that influence the susceptibility of transplant recipients to CMV disease include organ type, immunosuppressive regimen, and the CMV status of the donor and recipient. CMV-negative transplant recipients who receive an organ from a CMV-positive donor are at highest risk for CMV disease and typically receive some form of CMV prophylaxis. CMV-IGIV for in utero CMV infection is not recommended; a randomized controlled trial showed no benefit over placebo.[55–58] Of concern in a randomized trial was that CMV-IGIV recipients had higher obstetric complications.[58]

Botulism Immune Globulin.

Botulism IGIV (human) (BIG-IV) was approved by the FDA in 2003 under the orphan drug program. It is indicated for infants <12 months of age for treatment of botulism suspected to be caused by either toxin type A or toxin type B. Produced by immunization of healthy adults, BIG-IV is available under the trade name BabyBIG, only through the California Department of Health Services (510-231-7600, all days and hours). A 5-year randomized, placebo-controlled treatment trial demonstrated the safety and efficacy of BIG-IV in reducing the mean hospital stay per case from approximately 5.5 weeks to 2.5 weeks, as well as a reduced mean hospitalization cost per case by approximately $90,000. Treatment with BIG-IV should be initiated as soon as possible to neutralize toxin and should not be delayed for laboratory confirmation of a suspected case.[59] BabyBIG is not indicated for foodborne or wound botulism. In 2013 the FDA-approved heptavalent equine botulism antitoxin (HBAT) containing antitoxin to types A, B, C, D, E, F, and

G replaced previous A, B, and E products as the only products available in the US for naturally occurring noninfant botulism; HBAT is available only through the CDC (770-488-7100 all hours and days).[60]

Vaccinia Immune Globulin.

Vaccinia IG (human) (VIG) was developed in the 1960s for ameliorating side effects associated with smallpox (vaccinia) immunization, including eczema vaccinatum, generalized vaccinia, and progressive vaccinia.[61] The original preparation contained a high proportion of protein aggregates and thus was administered by the IM route and is no longer available. Vaccinia IGIV (VIG-IV) is the only product currently available for treatment of complications of vaccinia vaccination. Supplies of VIG-IV are stored in the Strategic National Stockpile. Release of VIG-IV from the stockpile requires CDC approval.

Anthrax Immune Globulin Intravenous.

Anthrax IGIV (human) (AIG-IV) was FDA approved in March 2015 for inhalational anthrax treatment in adult and pediatric patients in combination with antibacterial drugs. It is manufactured from the plasma of persons who received anthrax vaccine. It is stored in the US Strategic National Stockpile to be available in response to an anthrax emergency.

Monoclonal Antibodies

The development of hybridoma technology in the 1970s permitted the production of essentially unlimited supplies of any mAb. The effectiveness of mAbs that either block bacterial components or modify proinflammatory cytokines has been studied in septic shock syndrome. The mAbs directed against endotoxin in the treatment of gram-negative bacillary septicemia were not beneficial.[62,63] The advantages of mAbs include the avoidance of a requirement for a large IV infusion over several hours, a predictable supply of a highly standardized product, elimination of concern about adventitious agents, and avoidance of unwanted antibody in a polyclonal product that could interfere with a live virus vaccine.[64]

Palivizumab is a humanized murine mAb directed against the surface fusion glycoprotein of respiratory syncytial virus. After monthly IM administration of palivizumab, the risk of hospitalization for respiratory syncytial virus infection among high-risk infants was reduced from 10.6% among placebo recipients to 4.8% among prophylaxis recipients.[65] Guidance for use of palivizumab prophylaxis provided by the American Academy of Pediatrics has become increasingly restrictive based on data published since licensure in 1998 that now indicate little benefit from monthly prophylaxis for infants and young children at increased risk of hospitalization.[66]

Raxibacumab is a recombinant human IgG1λ mAb that binds and neutralizes the free protective antigen (PA) component of *Bacillus anthracis* toxin. Antibiotics aid in controlling infection, but they do not clear toxins present in the bloodstream. The effectiveness of raxibacumab is based on animal models (rabbits and monkeys) of inhalational anthrax. This is the first mAb approved using the FDA Animal Efficacy Rule (well-controlled animal studies when human studies are not ethical of feasible). Guidance is available for management of pediatric systemic illness.[67] Currently, anthrax IG or raxibacumab antitoxin is indicated in patients with anthrax systemic disease. Raxibacumab is also approved for prophylaxis of inhalational anthrax if other alternatives are not available or are contraindicated. Because inhalational anthrax is a possible bioterrorist threat, doses of raxibacumab are stored in the US Strategic National Stockpile.

Immunoglobulin Products Prepared From Animal Plasma

In the past, several approved animal-derived immunoglobulin products were available for treating various infectious agents or their toxins. Few of these agents are in use currently. Most have been supplanted by analogues of human origin (e.g., RIG, TIG) or by other therapeutic modalities. The only available products in this category are botulism antitoxin and diphtheria antitoxin. They can be obtained from the CDC for emergency use in the treatment of foodborne botulism and diphtheria, respectively. These equine immunoglobulin products are provided only when specifically indicated. Because immediate anaphylaxis and delayed serum sickness are possible adverse reactions, these products should be used only when their lifesaving potential outweighs their risks. Procedures for skin testing and desensitization are readily available, and the physician should always be prepared to treat any adverse event.[68]

Adverse Reactions to Immune Globulins Prepared From Human Plasma

The most common adverse reaction to IM-administered IGs is pain at the injection site. Local or facial flushing can occur, as can headache, chills, or nausea, but these symptoms are less common. Severe systemic reactions are rare.

Infusion-Related Reactions

Reactions such as fever, headache, myalgia, chills, nausea, and vomiting often are related to the rate of IGIV infusion and usually are mild to moderate and self-limited (Box 5.1). These reactions may result from formation of IgG aggregates during manufacture or storage. Product-to-product variations in adverse effects may occur among individual patients. An isoimmune hemolytic reaction has been described rarely, especially if large doses of IGIV are infused. Less common but severe reactions include the following: hypersensitivity and anaphylactoid reactions marked by flushing, changes in blood pressure, and tachycardia; thromboembolic events; aseptic meningitis; and renal insufficiency. The causes of these reactions are unknown. The incidence of adverse events often can be decreased by following the package insert for the individual product with regard to the rate of administration. Aseptic meningitis associated with pleocytosis can occur, especially among patients receiving high doses of IGIV (2 g/kg).[69] Acute renal failure has been reported rarely following IGIV infusions, particularly among patients with preexisting renal disease who receive IGIV products containing sucrose.

Box 5.1

Adverse Effects of Immune Globulin Intravenous Therapy

Minor Systemic Reactions

Headache, back or hip pain, fever, dizziness or lightheadedness, nausea, flushing

Pyrogenic Reactions

High fever and systemic symptoms

Vasomotor or Cardiovascular Manifestations

Changes in blood pressure and heart rate

Infrequent, Serious Reactions

Aseptic meningitis[a]

Acute renal failure

Hypersensitivity reactions[b]

Anaphylaxis

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[a] Aseptic meningitis may be more common in adults or children with specific underlying conditions.

[b] Reaction reports are more common for products that contain sucrose.

Anaphylactic reactions induced by anti-IgA can occur in patients with primary antibody deficiency who have a total absence of circulating IgA and who develop IgG antibodies to IgA. IgE anti-IgA is less common.[70,71] These reactions are rare in patients with panhypogammaglobulinemia and are more common in patients with selective IgA deficiency and subclass IgG deficiencies. In the rare instances in which reactions related to anti-IgA antibodies have occurred, use of IgA-depleted IGIV preparations may decrease the likelihood of further reactions. Because of the rarity of these reactions, screening for IgA deficiency and anti-IgA antibodies is not recommended routinely.

Interference With Active Immunization

Antibodies present in IGs can interfere with the immune response to vaccines. Provided the 2 products are administered with separate syringes at different sites, this is rarely a problem when the vaccine is an inactive substance such as a toxoid, a polysaccharide, or a killed virus preparation, even when the vaccine is given simultaneously with the IG. However, antibodies in IG can interfere with viral replication after administration of live virus vaccines and thus can prevent successful immunization. The effect on the immune response to measles immunization has been demonstrated, but in principle, similar interference could occur with any live virus vaccine. Measles, mumps, rubella, or varicella vaccine should not be given in the 2 weeks before or 3 months after a patient receives any IgG preparation or whole or fractionated blood. Because high doses of IGIV can inhibit the response to measles vaccine for extended periods, longer intervals are required as the IGIV dose is increased (up to 11 months after 2 g/kg IGIV as for Kawasaki disease) to provide sufficient time for passively acquired antibodies to wane.[72]

Transmission of Infectious Agents

Although IGs prepared from human plasma are biologic products and hence must always be considered to carry a theoretic risk for transmission of viruses, they have a remarkable record of safety. Even IGIV, which is administered directly into the bloodstream, often in large quantities, has been extremely safe. Investigations have revealed no documented case of transmission of hepatitis by US-licensed IGs for IM use. Similarly, no evidence indicates transmission of HIV by US-licensed IGs for either IM or IV administration.[73,74]

Several cases of non-A, non-B hepatitis were associated with IGIV administration between 1983 and 1987.[75] These cases involved sources of IGIV that were not commercial lots available in the US.

In February 1994, however, a worldwide recall of US-licensed IGIV products manufactured by Baxter Healthcare Corporation was initiated because of hepatitis C virus transmissions.[76] Cases of hepatitis C occurred in several countries, including the US, among persons who received these products between April 1, 1993, and February 23, 1994, after which they were removed from the market.[77]

Concern regarding the potential transmission of prion disease by IG products has been raised. These concerns are highlighted by the lack of serologic assays to screen blood products for prions. The findings of several studies suggested that the likelihood of prion transmission through plasma products is exceedingly small. These findings include the observations that very low levels of prions are found in the plasma of affected persons and that the processing of plasma for the production of IGs typically inactivates prions.[78,79] To date, no case of prion disease has been linked to IG therapy.

Laboratory studies have shown that many manufacturing steps that are intrinsic to the process of preparing IgG greatly lower viral and prion burden. For example, alcohol fractionation of plasma partitions virus and prions away from the IgG fraction.[80] If the alcohol concentration at a particular manufacturing step is sufficiently high and the virus is sufficiently labile (e.g., HIV), alcohol is viricidal.[80] Other precipitating agents, such as polyethylene glycol, can achieve similar partitioning of viruses. Incubation at low pH, either in the presence or absence of enzymes, has a strong antiviral effect.[81,82]

Solvent-detergent treatment has been added to purification procedures to enhance viral inactivation in various IGs. This treatment destroys enveloped viruses such as HBV, hepatitis C virus, and HIV.[83] Another viral inactivation step used for some products is heat treatment, which can be performed in the presence of stabilizers to prevent denaturation of the IgG.[84] Purification processes now include nanofiltration, that is, filtration of the product through membranes with pore dimensions that permit the passage of proteins but not viruses.

Product Shortages

Periodic shortages of certain IGIV products have occurred, for multiple reasons. In some cases, production problems have occurred. Increased use of IGIV is another contributing factor. Use of IGIV in the US has increased by approximately 10% each year, and production has not kept pace. Off-label use of IGIV contributes to shortages. A study of 12 academic health centers revealed that 52% of IGIV prescribed was used for off-label indications.[85] In response to these shortages, some hospitals have developed committees to review and restrict use of IGIV.

The Future

In the future, new IGIV products as well as additional mAbs are likely to become available. Several mAbs have been licensed for use for noninfectious indications, including those for the following: (1) organ transplantation (through inhibition of cytokine activity or depletion of lymphocyte subsets); (2) treatment of malignant diseases (i.e., lymphoma, colon cancer, and breast cancer); and (3) immunologic modulation (i.e., asthma and Crohn disease). The mAbs used for the treatment and prevention of infectious diseases in clinical development include the following: *Clostridium difficile, Staphylococcus aureus*, HIV, rabies virus, West Nile virus, Shiga toxin–producing *Escherichia coli,* and *Candida albicans.*[86,87] Multiple other mAbs are being studied for the prevention and treatment of infection.[86,88–91] Other advances include alterations to extend the half-life of palivizumab.[87,89] The Ebola epidemic demonstrated the benefit of rapid development of mAbs.[92,93]

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6

Active Immunization

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Vaccines are among the most effective means of preventing disease, disability, and death. The use of vaccines, initiated by Jenner in 1796 with demonstration that inoculation of material from cowpox lesions could prevent smallpox, predates the germ theory of disease. The profound impact of vaccines on disease incidence is a result of both the availability of safe and effective vaccines and effective strategies and programs to deliver vaccines to target groups. Eradication of smallpox in 1977, one of the greatest public health achievements, required both disease surveillance and containment with a highly effective vaccine.[1] Similarly, global efforts to eradicate poliomyelitis involve comprehensive disease control strategies, including national and multicountry mass vaccination campaigns, intensive surveillance for wild poliovirus, and house-to-house vaccination programs. These programs have succeeded in terminating transmission of wild poliovirus in the Americas, the Western Pacific, Europe and Southeast Asia, and gains are being made in the remaining endemic countries of Pakistan, Afghanistan, and Nigeria (www.polioeradication.org).[2–4] Efforts to reduce or even eliminate measles and neonatal tetanus, 2 of the major causes of childhood fatality worldwide, also are progressing, although cases of measles continue to occur worldwide.[5,6] Gavi, the vaccine alliance, a collaboration among organizations in the public and private sectors, provides support for introduction of vaccines in the world's poorest countries (≤$1580 per capita income per year) that previously could not support their use. (www.gavi.org).

Benefits of successful vaccines include not only reductions in disease incidence, disability, pain, and suffering, but also savings in healthcare costs in both the economically developed and developing world. Studies in the United States have reaffirmed benefits of childhood immunization.[7–8] A cost-benefit analysis covering vaccine-preventable diseases of childhood, including diphtheria, tetanus, pertussis, poliomyelitis, hepatitis A, hepatitis B, *Haemophilus influenzae* type b (Hib) infection, measles, mumps, rubella, rotavirus infection, pneumococcal disease, and varicella, estimated that routine childhood immunization among members of the 2009 US birth cohort will prevent approximately 42,000 early deaths and 20 million cases of disease, with net savings of $13.5 billion in direct costs and $68.8 billion in total societal costs, respectively.[7]

Immunization and Vaccines: Overview

Immunization is the process of artificially inducing immunity or providing protection from disease. *Active immunization* is the process of stimulating the body to produce antibody and other immune responses (e.g., cell-mediated immunity) through administration of a vaccine or toxoid. *Passive immunization* is provision of temporary immunity by administration of preformed antibodies derived from humans or animals (see Chapter 5).

Vaccine Content

Biologic agents used to induce active immunization include vaccines and toxoids. Traditionally, a *vaccine* is defined as a suspension of live (usually attenuated) or inactivated microorganisms, or fractions thereof, which is administered to induce immunity and prevent infectious disease or its sequelae; efforts to develop vaccines to increase immune response to cancers or to treat diseases including diabetes mellitus necessitate rethinking of this definition. *Live, attenuated* vaccines traditionally have been developed by means of serial passage (in culture or animals) of an initially pathogenic bacteria or virus strain with selection for strains that are less pathogenic for humans but that induce protective immunity (e.g., measles, mumps, and rubella

[MMR] vaccine). Live, attenuated vaccines also can be developed with use of reassortants of attenuated animal or human virus strains with virus coat antigens from pathogenic strains (e.g., cold-adapted influenza, rotavirus vaccine). *Inactivated* vaccines can consist of the following: (1) whole organisms inactivated by heat, formalin, or other agents (e.g., polio, hepatitis A, rabies vaccines); (2) purified protein (e.g., acellular pertussis, influenza, and meningococcal serogroup B vaccines) or polysaccharide antigens (e.g., pneumococcal, meningococcal, and intramuscular typhoid vaccines) from whole organisms; (3) purified antigens produced by genetically altered organisms (e.g., hepatitis B and human papillomavirus [HPV] vaccines produced by yeast); or (4) chemically modified antigens, such as polysaccharides conjugated to carrier proteins to increase immune response (e.g., conjugated Hib, pneumococcal, and meningococcal vaccines). *Toxoids* are bacterial toxins produced in bacterial culture that have been rendered nontoxic but retain the ability to stimulate formation of antitoxin.

Vaccine and toxoid preparations also contain other constituents intended to enhance immunogenicity and stability but that can be responsible for adverse reactions.[9] Such constituents include the following: (1) suspending fluid, which can be saline or complex fluids containing constituents derived from the biologic system or medium in which the vaccine is produced (e.g., egg or serum proteins); (2) preservatives, stabilizers, or antimicrobial agents, which are used to inhibit bacterial growth in viral cultures or the final product or to stabilize antigens (e.g., mercurials, phenols, albumin, glycine, neomycin); and (3) adjuvants, which enhance response to inactivated antigens (e.g., aluminum phosphate, aluminum hydroxide, amorphous aluminum hydroxyphosphate sulfate and monophosphoryl lipid A [ASO_4]). Concern about the possibility of adverse effects from cumulative exposure to mercury in the environment has led to removal of thimerosal as a preservative from most US vaccines recommended for infants.[10] The only vaccines administered to infants that contain thimerosal as a preservative are some influenza vaccines (multidose vials) and diphtheria-tetanus (DT) vaccine. Physicians should be knowledgeable about the constituents of each vaccine, which are described in vaccine information package inserts.

Vaccine Development, Licensure, and Approval

Immunologic Basis of Response to Vaccines

The 2 major approaches to active immunization are (1) live, attenuated vaccines and (2) inactivated or detoxified agents or their purified components. For some diseases, such as poliomyelitis and influenza, both approaches have been used.

Live, attenuated vaccines have the advantage of producing a complex immunologic response simulating natural infection. Because replication of the organism and processing of antigens mimic those of the natural pathogen, both humoral and cell-mediated responses can be generated to a variety of antigens. Generally, immunity induced by a single dose of a live, attenuated vaccine is long-lasting, possibly lifelong. However, the strength of response, particularly the humoral response, usually is less robust than the response following natural infection, and detectable antibodies can wane with time, resulting in some potential loss of protection. Induction of immunity by live vaccines can be inhibited by passive antibody, whether from transplacental acquisition from the mother or receipt of immunoglobulin-containing blood products. Thus optimal response depends on ensuring that passive antibody levels have declined (e.g., primary measles vaccination at 12 months of age instead of earlier, delay of measles vaccination after administration of blood products). In addition, because response may be only 90% to 95% after a single dose, a 2-dose or multiple-dose regimen can be necessary to induce higher levels of protection in the community and prevent spread of disease if the population is exposed (community protection).

Inactivated or purified antigen vaccines induce response only to components present in the vaccine. Generally, multiple doses, usually 3 or more, are necessary to induce satisfactory antibody levels that persist for long periods of time; booster doses at longer intervals (e.g., 10 or more years for tetanus and diphtheria toxoids) sometimes are required to ensure lasting protection. The nature of vaccine responses depends on antigen type. Protein and glycoprotein antigens usually induce both humoral immunity and memory (response through helper T lymphocytes) after multiple doses, as evidenced by more rapid, broad, and intense (anamnestic) response to successive doses. Polysaccharide antigens by themselves induce only humoral antibody without T-lymphocyte stimulation and fail to induce an anamnestic response with repeated antigenic challenge. This limitation can be overcome by conjugation of polysaccharides to protein carriers to induce both a stronger immune response in younger children and immunologic memory.

Immune Response to Active Immunization

The general mechanism by which a long-term protective memory immune response is induced requires activation of T lymphocytes by antigen-presenting cells, which then provide help to B lymphocytes to develop into antibody-producing plasma cells (i.e., T-lymphocyte–dependent response).[11,12] Polysaccharide antigens bypass T-lymphocyte help (i.e., T-lymphocyte–independent response) and induce B-lymphocyte differentiation directly, but they do not induce immunologic memory. Initiation of a T-lymphocyte–dependent antibody response occurs by activation of naïve CD4$^+$ helper T lymphocytes in response to antigen-presenting cells, generally dendritic cells. This interaction occurs through recognition of the major histocompatibility complex (MHC) on the antigen-presenting cells by the T-lymphocyte receptor and by secretion of cytokines that are necessary for maturation of naïve CD4$^+$ helper T lymphocytes to differentiate toward a helper T-lymphocyte 1 (Th1) or Th2 response.[13] Th1 responses are predominantly cell mediated, whereas Th2 responses are predominantly humoral. In the presence of interleukin-12 (IL-12), Th1 response is differentiated and is associated with secretion of IL-2 and interferon γ (IFNγ). In the presence of IL-4, Th2 response is differentiated and is associated with secretion of IL-4 and IL-5. These 2 cytokines are essential for differentiation and maturation of B lymphocytes into antibody-secreting plasma cells. A small subset of CD4$^+$ T lymphocytes does not differentiate into effector cells; instead, these T lymphocytes mature to become long-lived memory cells, which form the nucleus of the secondary immune response on reexposure to antigen. The overall response is regulated by a further class of CD4+ T lymphocytes (Treg).[14]

In a primary response, naïve B lymphocytes recognize a specific antigenic epitope on native antigen through the immunoglobulin receptor on their surface, and they differentiate into antibody-secreting cells in response to help from CD4+ Th2 lymphocytes. A given B lymphocyte is activated by a T lymphocyte responding to the same antigen. B-lymphocyte proliferation and maturation then occur in a clonal manner, and during this process, immunoglobulin (Ig) class switching (from IgM to IgG and IgA) and affinity maturation also occur. Antigen-specific plasma cells develop and secrete large amounts of clonal antibody.

The polyclonal response to a given immunogen reflects the sum of the multiple individual clonal B-lymphocyte responses that make up an antibody response. A few activated B lymphocytes mature into long-lived memory B lymphocytes, which form the basis of the rapid secondary response on the next encounter with antigen. Some plasma cells acquire the capacity to migrate toward long-term survival niches mostly located within the bone marrow, from where they may produce antibodies during extended periods.[15,16] The duration of antibody responses reflects the number or quality, or both, of long-lived plasma cells generated by immunization.[16] The mechanism of maintenance of these lymphocytes is an area of active research because the ability to mount a strong secondary response after many years is a critical component of the adaptive immune response.

Initiation of the specific immune response to a pathogen depends on the innate immune response, which is rapid, does not exhibit memory, and historically has been considered nonspecific. However, discovery of germline-encoded pattern recognition receptors has led to an understanding that specific molecular structures are recognized by pathogen-associated molecular patterns. These specific structures include toll-like receptors (TLRs), which are membrane associated, and nucleotide-binding oligomerization domain (NOD)-like receptors, which are found in the cytoplasm and include the NALP family of receptors (member of the nucleotide-binding domain and leucine-rich repeat containing gene family) and others, all of which contribute to immune activation by inducing proinflammatory cytokines, which in turn modulate the adaptive immune response. TLRs and NOD-like receptors are found on antigen-presenting cells and recognize a wide variety of molecules commonly found in pathogens. TLR4 binds lipopolysaccharide, and TLR5 binds flagellin, both common bacterial components. The NALP3 inflammasome is activated by aluminum and has been shown to be the pathway through which aluminum adjuvants enhance immunogenicity.[17]

Antibodies produced in response to immunization can mediate protection by a variety of extracellular mechanisms including (1) direct neutralization of bacterial toxin, (2) facilitation of intracellular digestion of bacteria by phagocytes (opsonization), (3) initiation of or combination with the complement pathway to cause lysis, or (4) sensitization of macrophages to promote phagocytosis. Antibodies cannot readily reach the intracellular space, which is the site of viral and some bacterial replication. However, antibodies are effective against many viral diseases by interacting with a virus before initial intracellular penetration occurs (neutralization) and by preventing locally replicating virus from disseminating from the site of entry to an important target organ, as in spread of poliovirus from the gut to the central nervous system or spread of rabies from a puncture wound to peripheral neural tissue. Antigen-specific cytotoxic T-lymphocyte–mediated responses are important components of the response to viral infections.[12]

The cell-mediated immune response also has an innate and memory effector arm. Natural killer (NK) cells recognize virally infected cells in a nonspecific manner, without generation of memory. Activated NK cells secrete a variety of soluble mediators, including IFNs that kill virus-infected cells and ILs that modulate differentiation and response of $CD4^+$ helper T lymphocytes. Cytotoxic $CD8^+$ T lymphocytes require the help of $CD4^+$ T lymphocytes (generally Th1) to differentiate and mature. $CD8^+$ cytotoxic T lymphocytes are an important part of the immune response to intracellular bacteria and viruses.[12] As viruses replicate in a cell, viral proteins are processed and presented on the cell surface as an MHC class I/peptide complex. The complex is recognized by cytotoxic T lymphocytes. As with $CD4^+$ T lymphocytes, a small subset develops into long-lived memory $CD8^+$ T lymphocytes capable of rapid reactivation as part of a secondary immune response.

Rarely, vaccination can result in immune responses that alter the course of natural infection detrimentally. For example, killed measles vaccine, a formalin-inactivated vaccine administered to some children in the United States from 1963 to 1967, sensitized some vaccine recipients so that when exposed to wild virus, they developed an atypical infection with enhanced severity of disease. The prevailing theory has been that failure of formalin-inactivated vaccine to produce response to the measles virus fusion protein led to altered immune response and atypical disease on subsequent challenge. More recent theories suggest that killed measles virus failed to induce high-avidity antibody, and immune-complex deposition was the major determinant of atypical measles.[18]

Following primary immunization with inactivated antigens, antibody response develops in 2 to 6 weeks but can be incomplete even after 2 doses; after effective priming, booster responses occur within 4 to 14 days. The initial response usually is IgM antibodies, followed within weeks by IgG antibodies. Response to live vaccines requires 1 incubation period, followed by several weeks to months for development of a strong immune response. Response to measles vaccination usually is maximal by 6 weeks, but in younger children, antibody levels can continue to rise for several months. However, protection against measles begins much earlier, and some evidence suggests that disease can be prevented even when vaccine is administered within 72 hours of exposure.

Determinants of Response

Vaccine immunogenicity and response are determined by characteristics of the vaccine and the host. Vaccine dose, presence of an adjuvant, route and site of administration, timing of doses, and vaccine handling can affect response. Vaccine doses are adjusted before licensure to ensure a high level of response (generally >90% of subjects); adjuvants permit a better response with a lower dose of inactivated antigen. The routes of administration (e.g., intradermal, subcutaneous, intramuscular, and mucosal) can determine the strength and nature of the immune response. Mucosal administration (intranasal or oral) stimulates higher levels of mucosal IgA antibodies that can inhibit disease transmission with greater effectiveness than parenteral administration, which induces limited or no mucosal response.[19] Intradermal vaccination with lower antigen doses can induce antibody responses similar to responses induced by intramuscular or subcutaneous administration of recommended doses, but intradermal vaccine is more difficult to deliver precisely and, in practice, achieves less predictable responses.

Sites of Administration

Intramuscular injections should be given in the anterior thigh (infants and toddlers) or deltoid muscle (children and adults); injection into the buttocks can produce lower antibody response, which has been documented for hepatitis B and rabies vaccines in adults, probably as a result of delivery of vaccine into adipose tissue.[20,21] Vaccines with adjuvants should be given in deep muscle because subcutaneous or intradermal injection can induce local inflammation, granuloma formation, or necrosis.[22] Timing of doses of killed vaccines is important; a minimal interval of 1 month between primary doses is usual,[8] as is delay of a 4th or reinforcing dose for 10 months or longer after the first dose to enhance response and duration of antibody persistence. The recommended routes and sites of administration and timing of doses are devised to ensure optimal effectiveness in disease prevention and should be used.

Host Factors

Intrinsic factors in the host that affect immune response include genetic factors, age, nutritional or disease status, primary or secondary immunodeficiency, sex, pregnancy, and smoking.[11,23–26] Although genetic factors such as MHC polymorphism are known to affect both cellular and humoral immune response at a molecular level for some vaccines, the precise mechanisms are unknown.[23–26] Evaluating how host genetic markers alter vaccine response could identify differences that predict successful or adverse vaccine outcome. Studies of the expression of genetic information modified on a molecular level can reveal how environmental influences affect innate and adaptive immune responses.[26] This work, combined with system vaccinologic approaches, may lead to better understanding of these immune responses.[11,12,27] Age is an important factor in response to immunization.[12] With killed vaccines, neonates generally do not develop as brisk a response as older infants or children (e.g., hepatitis B), and with certain vaccines, too early immunization can result in poor response or development of tolerance or interference (diphtheria and tetanus toxoids and acellular pertussis [DTaP]; inactivated poliovirus vaccine [IPV]; Hib conjugates). For live (and some killed) vaccines, inhibition of response by maternal antibodies determines the optimal timing for vaccination in early childhood (measles, hepatitis A). Generally, response to all vaccines is excellent in young children, adolescents, and young adults but diminishes with increasing age.[12] In adults, smoking decreases response to hepatitis B vaccine.[20,22] Extreme debilitation, primary or secondary immunodeficiency disorders (including diseases or treatments that cause immunosuppression), and some chronic diseases (renal disease, diabetes mellitus) can diminish immune response. For people with such conditions, inactivated vaccines can be recommended, although higher or more frequent doses may be required; live vaccines often are contraindicated because of the risk of disseminated disease and possible death caused by the vaccine organism.[22,28]

Measurement of Response

Ideally, reliable laboratory tests should be available to measure the presence and strength of each of the major effectors of protection against the disease for which the vaccination is administered. In routine practice, many different tests are available to assess the presence, absence, and level of antibodies. These include enzyme immunoassay (EIA), complement fixation, and immunofluorescent techniques. Assays for functional antibody, such as neutralization or opsonophagocytosis, generally are performed in reference or research laboratories, as are tests for T-lymphocyte function. $CD4^+$ Th1 and Th2 lymphocytes and $CD8^+$ lymphocytes generally are characterized by their cytokine profiles by using assays such as enzyme-linked immunospot (ELISpot) or intracellular cytoplasmic staining.

For certain diseases, such as hepatitis B, poliovirus, rubella, and measles, reliable tests exist, and antibody levels that correlate with protection are known. For some diseases, such as pertussis and HPV infection, no serologic correlate of protection has been defined. Development of improved laboratory methods to measure protection and to permit rapid diagnosis of acute disease continues to be a priority of vaccine-preventable disease control programs.

Vaccine Licensure and Approval

Before US Food and Drug Administration (FDA) licensure, a new vaccine generally requires 10 to 15 years of preclinical testing and clinical trials. Before testing a vaccine in humans, a manufacturer files an investigational new drug (IND) application with the FDA, followed by 3 phases of clinical trials that are performed to study vaccine safety, immunogenicity, and efficacy.[29,30] On completion of the prelicensure clinical trials, the following steps generally occur for a vaccine to become available and used: (1) the manufacturer applies for a Biologics Licensure Application (BLA) with the FDA; (2) the FDA licenses the vaccine; (3) the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics (AAP)[31] and other professional medical societies make recommendations for use of the vaccine; and (4) financing is secured for the public and private sectors (Fig. 6.1).

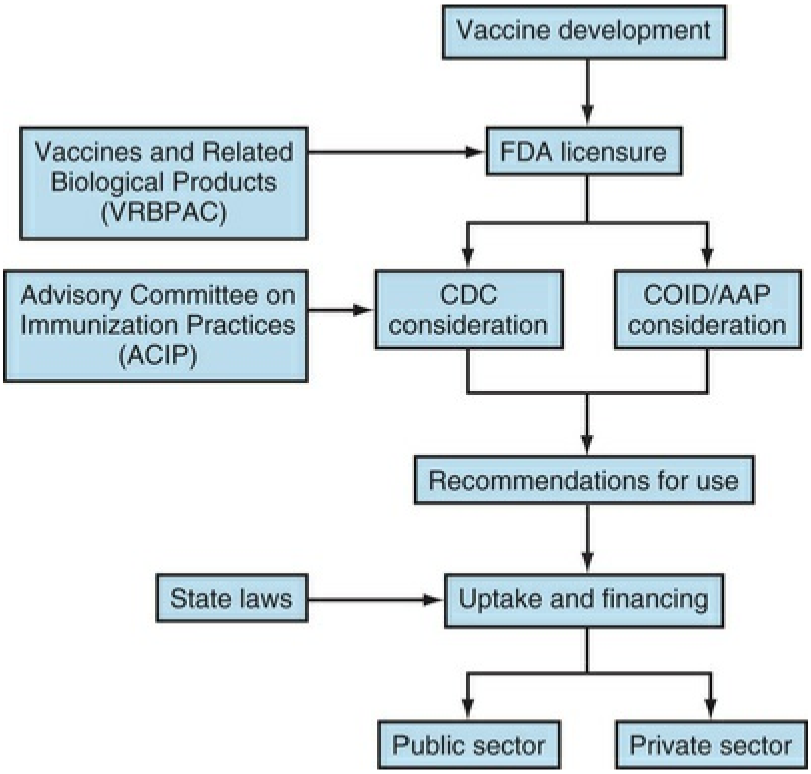


FIGURE 6.1 **Development of pediatric vaccine recommendations and policies. AAP, American Academy of Pediatrics Board of Directors; CDC, Centers for Disease Control and Prevention; COID, Committee on Infectious Diseases; FDA, Food and Drug Administration; VRBPAC, Vaccines and Related Biological Products Advisory Committee.** (Redrawn from Pickering LK, Orenstein WA. Development of pediatric vaccine recommendations and policies. Semin Pediatr Infect Dis 2002;13:148–154.)

Following FDA licensure of a new vaccine, information about the vaccine is reviewed by the ACIP. ACIP consists of 15 voting, nongovernment members appointed by the US Department of Health and Human Services for 4-year terms. In addition, many professional medical and public health societies and organizations and industry representatives participate in ACIP discussions, but they do not vote. To formulate recommendations, the ACIP establishes subject-specific work groups to review and synthesize data months to years before presentation to the ACIP, where votes are taken on vaccine use. Data considered in making recommendations are subjected to the GRADE process (http://www.cdc.gov/vaccines/acip/recs/grade/index.html). ACIP recommendations are not official until approved by the CDC director and published in the *Morbidity and Mortality Weekly Report (MMWR)* (http://www.cdc.gov/vaccines/acip/committee/charter.html) Given that new vaccines and updated recommendations appear often, the reader is advised to follow the ACIP website for new recommendations at http://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/index.html.

Following vaccine licensure, monitoring for rare adverse events continues for some vaccines through formal phase IV trials conducted by the manufacturer, which often are required and monitored by the FDA. In addition, postmarketing surveillance for adverse events is performed and permits detection of new or unanticipated adverse events. Physician and manufacturer reporting of certain adverse events observed after vaccine administration is required by the National Childhood Vaccine Injury Act for vaccines covered under the Vaccine Injury Compensation Program.[32] The importance of postmarketing surveillance was demonstrated following licensure and wide use of tetravalent rhesus rotavirus vaccine in the US for infants in 1999. Surveillance of adverse events detected cases of intussusception within 1 week after receipt of the first or second doses of the rhesus rotavirus vaccine. Follow-up studies determined that risk of intussusception was 1 case per 10,000 doses of vaccine administered.[33] Subsequently, the vaccine was withdrawn from distribution, and recommendation for universal use in infants in the US was withdrawn.

Principles of Immunization Programs

Disease Reduction

Childhood immunization programs have reduced substantially the occurrence of vaccine-preventable diseases in the US (Table 6.1).[34–37] Declines exceed 95% for all diseases for which universal vaccination has been well implemented, with the exception of hepatitis B, which remains a common clinical disease in adults not reached by universal vaccine programs, and pertussis.[38,39] Smallpox has been eradicated, poliomyelitis resulting from indigenous wild poliovirus has not occurred since 1979 in the US, and endemic rubella has been declared eliminated in the US.[40,41] Fewer than 10 cases each of diphtheria and tetanus in children are now reported each year, and indigenous transmission of measles has been interrupted. Wide use of Hib conjugate vaccines has reduced Hib disease by >98% in the

US and in some European countries.[42–44] Use of pneumococcal conjugate vaccines (PCVs) has led to marked reductions in invasive pneumococcal disease (IPD) among vaccinated children as well as unvaccinated young infants, adolescents, and adults.[44–47] Building on the success of the program to date, the US Public Health Service established 2010 goals to eliminate indigenous transmission of measles, rubella and congenital rubella syndrome, mumps, diphtheria, poliomyelitis, Hib disease in children <5 years of age, and tetanus in people <35 years of age, and to reduce hepatitis B in people 2 to 18 years old by 90%.[48] These goals were achieved for diphtheria, measles, rubella, congenital rubella, poliomyelitis, and hepatitis B. The new Healthy People 2020 objectives include specific goals for the vaccination of adolescents, including the following: 1 dose of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap); 1 dose of meningococcal conjugate vaccine (MCV); 3 doses of HPV vaccine; and ≥2 doses of varicella vaccine (http://www.healthypeople.gov/2020/topics-objectives/topic/immunization-and-infectious-diseases/objectives).[48]

TABLE 6.1

Reported Morbidity of Selected Vaccine-Preventable Diseases and Vaccine Coverage Levels: United States, 20th Century and 2015

Disease	United States, 20th-Century Annual Morbidity[a]	United States, 2015 Morbidity[b]	Vaccine Coverage Levels, 2015 %[c]	Healthy People 2020 Coverage Level Goals (%)	Reduction in Morbidity (%)
Diphtheria	21,053	0	85 (≥4 doses)	90	100
Tetanus	580	25	85 (≥4 doses)	90	96
Pertussis	200,752	18,166	85 (≥4 doses)	90	90.6
Poliomyelitis (paralytic)	16,316	0	94[d] (≥3 doses)	90	100
Measles	530,217	189	92 (≥1 dose)	90	99.8
Mumps	162,344	1,057	92 (≥1 dose)	90	99.3
Congenital rubella	152	1	92 (≥1 dose)	90	99.9
Acquired rubella	47,745	5	92 (≥1 dose)	90	99.9
Haemophilus influenzae type b and unknown; <5 years of age	20,000	23[e]	94 (≥2 or 3 doses, depending on brand)	90	99.9
Varicella	4,085,120	8,370	92 (≥1 dose)	90	99.8

[a] Roush SW, Murphy TV; Vaccine-Preventable Disease Table Working Group. Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States. JAMA. 2007;298(18):2155–2163

[b] Centers for Disease Control and Prevention. MMWR 2016;64(51):ND923-940

(MMWR provisional data).

[c] Centers for Disease Control and Prevention. Vaccination coverage among children aged 19–35 months—United States, 2015. MMWR 2016; 65(39);1065–1071.

[d] Inactivated poliovirus vaccine.

[e] Haemophilus influenzae type b (Hib) < 5 years of age.

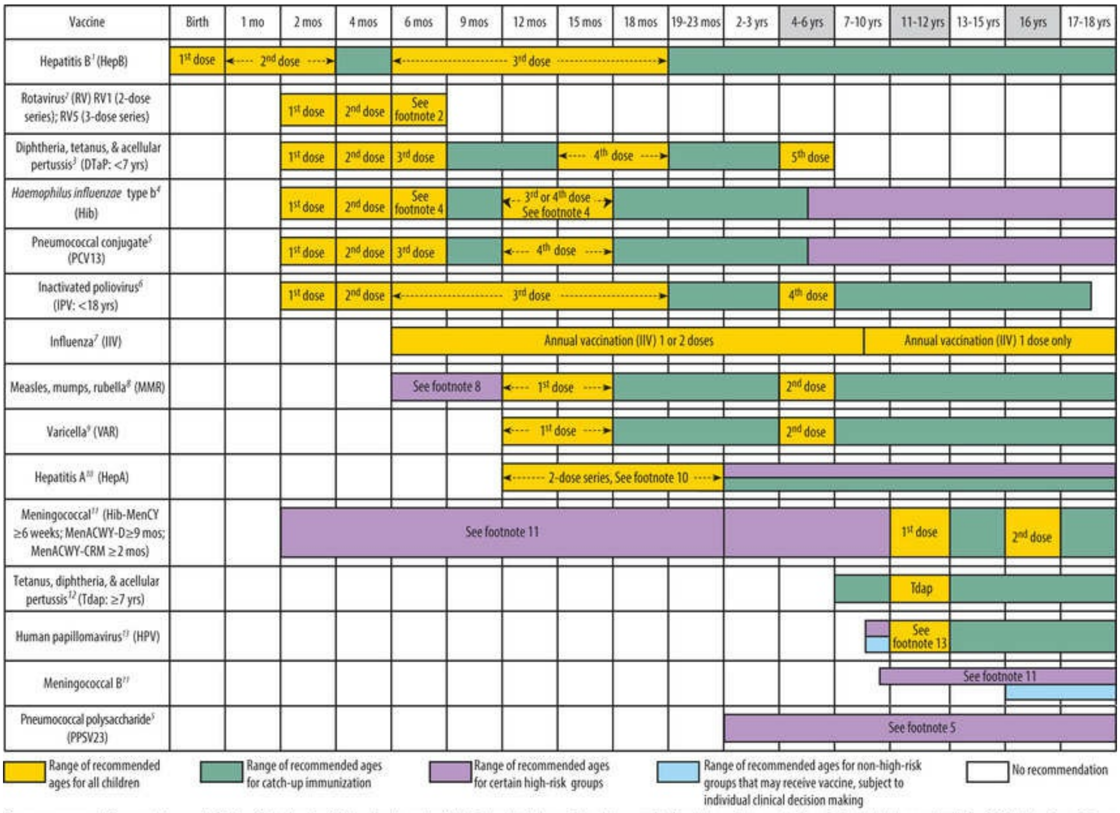
Immunization Coverage

Immunization coverage among preschool children has increased steadily after the measles resurgence that began in 1989 and stimulated unprecedented efforts to improve delivery of immunization. In 2014, coverage with 3 doses of DTaP, poliovirus, and hepatitis B virus (HBV) vaccines and 1 dose of MMR and varicella vaccines among children 19 through 35 months of age each reached or exceeded 91%.[49] Among school-aged children, coverage with the recommended series of DTaP and 2 doses of varicella and MMR vaccines exceeded 93% in 2014 and 2015, likely as a result of enforcement of comprehensive state immunization laws requiring receipt of specified vaccines for school attendance.[50] School laws often expand to include newly recommended vaccines.[51] In 2014, 87% of adolescents received 1 dose of Tdap, 79% received 1 dose of MCV4, and 40% of adolescent girls and 22% of adolescent boys received 3 doses of HPV vaccine.[52]

Vaccine Administration

Vaccine Schedules

The CDC, AAP, American Academy of Family Physicians (AAFP), and American College of Obstetricians and Gynecologists (ACOG) annually publish harmonized childhood and adolescent immunization schedules.[8] The ACIP, AAFP, ACOG, American College of Nurse Midwives (ACNM), and American College of Physicians also publish an annual adult immunization schedule (www.cdc.gov/vaccines).[53] The ACIP, with input from many liaison organizations, periodically reviews the schedules to ensure consistency with new vaccine developments and policies. The first harmonized childhood immunization schedule was published in 1995 and recommended 6 vaccines containing antigens against 9 infectious diseases.[54] Since November 2010, vaccines have been recommended universally in the childhood and adolescent immunization schedule to protect against 16 infectious diseases (Figs. 6.2 to 6.4). The harmonized schedule specifies the recommended and acceptable timing for each dose of universally recommended vaccine and for vaccines recommended for children and adolescents in selected high-risk populations.



Vaccine	Birth	1 mo	2 mos	4 mos	6 mos	9 mos	12 mos	15 mos	18 mos	19-23 mos	2-3 yrs	4-6 yrs	7-10 yrs	11-12 yrs	13-15 yrs	16 yrs	17-18 yrs
Hepatitis B[1] (HepB)	1st dose	←---- 2nd dose ----→	🟨	🟩	←------------------ 3rd dose ------------------→	🟨	🟨	🟨	🟨	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩
Rotavirus[2] (RV) RV1 (2-dose series); RV5 (3-dose series)			1st dose	2nd dose	See footnote 2												
Diphtheria, tetanus, & acellular pertussis[3] (DTaP: <7 yrs)			1st dose	2nd dose	3rd dose	🟩	🟩	←---- 4th dose ----→	🟨	🟩	🟩	5th dose					
Haemophilus influenzae type b[4] (Hib)			1st dose	2nd dose	See footnote 4	🟩	←-- 3rd or 4th dose --→ See footnote 4	🟨	🟩	🟩	🟩	🟩🟪	🟪	🟪	🟪	🟪	🟪
Pneumococcal conjugate[5] (PCV13)			1st dose	2nd dose	3rd dose	🟩	←---- 4th dose ----→	🟨	🟩	🟩	🟩	🟩🟪	🟪	🟪	🟪	🟪	🟪
Inactivated poliovirus[6] (IPV: <18 yrs)			1st dose	2nd dose	←------------------ 3rd dose ------------------→	🟨	🟨	🟨	🟨	🟩	🟩	4th dose	🟩	🟩	🟩	🟩	🟩
Influenza[7] (IIV)					Annual vaccination (IIV) 1 or 2 doses	🟨	🟨	🟨	🟨	🟨	🟨	🟨	🟨 Annual vaccination (IIV) 1 dose only	🟨	🟨	🟨	🟨
Measles, mumps, rubella[8] (MMR)					See footnote 8	🟪	←---- 1st dose ----→	🟨	🟩	🟩	🟩	2nd dose	🟩	🟩	🟩	🟩	🟩
Varicella[9] (VAR)							←---- 1st dose ----→	🟨	🟩	🟩	🟩	2nd dose	🟩	🟩	🟩	🟩	🟩
Hepatitis A[10] (HepA)							←------- 2-dose series, See footnote 10 ----→	🟨	🟨	🟨	🟪 🟩	🟪 🟩	🟪 🟩	🟪 🟩	🟪 🟩	🟪 🟩	🟪 🟩
Meningococcal[11] (Hib-MenCY ≥6 weeks; MenACWY-D≥9 mos; MenACWY-CRM ≥2 mos)			See footnote 11	🟪	🟪	🟪	🟪	🟪	🟪	🟪	🟪	🟪	🟪	1st dose	🟩	2nd dose	🟩
Tetanus, diphtheria, & acellular pertussis[12] (Tdap: ≥7 yrs)													🟩	Tdap	🟩	🟩	🟩
Human papillomavirus[13] (HPV)													🟪 🟦	See footnote 13	🟩	🟩	🟩
Meningococcal B[11]													🟪	See footnote 11	🟪	🟪 🟦	🟪 🟦
Pneumococcal polysaccharide[5] (PPSV23)											See footnote 5	🟪	🟪	🟪	🟪	🟪	🟪

🟨 Range of recommended ages for all children

🟩 Range of recommended ages for catch-up immunization

🟪 Range of recommended ages for certain high-risk groups

🟦 Range of recommended ages for non-high-risk groups that may receive vaccine, subject to individual clinical decision making

☐ No recommendation

These recommendations must be read with the footnotes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the *green bars* in Fig. 6.2. To determine minimum intervals between doses, see the catch-up schedule (Fig. 6.3). School entry and adolescent vaccine age groups are shaded in *gray*.

Footnotes — Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger, UNITED STATES, 2017

For further guidance on the use of the vaccines mentioned below, see: www.cdc.gov/vaccines/hcp/acip-recs/index.html.
For vaccine recommendations for persons 19 years of age and older, see the Adult Immunization Schedule.

Additional information

- For contraindications and precautions to use of a vaccine and for additional information regarding that vaccine, vaccination providers should consult the ACIP General Recommendations on Immunization and the relevant ACIP statement, available online at www.cdc.gov/vaccines/hcp/acip-recs/index.html.
- For purposes of calculating intervals between doses, 4 weeks = 28 days. Intervals of 4 months or greater are determined by calendar months.
- Vaccine doses administered ≤ 4 days before the minimum interval are considered valid. Doses of any vaccine administered ≥ 5 days earlier than the minimum interval or minimum age should not be counted as valid doses and should be repeated as age-appropriate. The repeat dose should be spaced after the invalid dose by the recommended minimum interval. For further details, see Table 1, *Recommended and minimum ages and intervals between vaccine doses, in MMWR, General Recommendations on Immunization and Reports / Vol. 60 / No. 2,* available online at www.cdc.gov/mmwr/pdf/rr/rr6002.pdf.
- Information on travel vaccine requirements and recommendations is available at wwwnc.cdc.gov/travel/.
- For vaccination of persons with primary and secondary immunodeficiencies, see Table 13, *Vaccination of persons with primary and secondary immunodeficiencies,* in *General Recommendations on Immunization* (ACIP), available at www.cdc.gov/mmwr/pdf/rr/rr6002.pdf.; and Immunization in Special Clinical Circumstances, (American Academy of Pedatrics). In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 report of the Committee on Infectious Diseases. 30th ed.* Elk Grove Village, IL: American Academy of Pediatrics, 2015:68-107.
- The National Vaccine Injury Compensation Program (VICP) is a no-fault alternative to the traditional legal system for resolving vaccine injury petitions. Created by the National Childhood Vaccine Injury Act of 1986, it provides compensation to people found to be injured by certain vaccines. All vaccines within the recommended childhood immunization schedule are covered by VICP except for pneumococcal polysaccharide vaccine (PPSV). For more information; see www.hrsa.gov/vaccinecompensation/index.html.

1. **Hepatitis B (HepB) vaccine. (Minimum age: birth)**
   Routine vaccination:
   At birth:
   - Monovalent hepatitis B vaccine should be administered within 24 hours of birth for medically stable infants weighing ≥ 2000 g born to hepatitis B surface antigen (HBsAg)-negative mothers.
   - Preterm infants weighing <2000 g born to HBsAg-negative mothers should receive the first dose of vaccine 1 month after birth or at hospital discharge.
   - For infants born to hepatitis B surface antigen (HBsAg)-positive mothers, administer HepB vaccine and 0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours of birth. These infants should be tested for HBsAg and antibody to HBsAg (anti-HBs) at age 9 through 12 months (preferably at the next well-child visit) or 1 to 2 months after completion of the HepB series if the series was delayed.
   - If mother's HBsAg status is unknown, within 12 hours of birth, administer HepB vaccine regardless of birth weight. For infants weighing less than 2,000 grams, administer HBIG in addition to HepB vaccine within 12 hours of birth. Determine mother's HBsAg status as soon as possible and, if mother is HBsAg-positive, also administer HBIG to infants weighing 2,000 grams or more as soon as possible, but no later than age 7 days.

   Doses following the birth dose:
   - The second dose should be administered at age 1 or 2 months. Monovalent HepB vaccine should be used for doses administered before age 6 weeks.
   - Infants who did not receive a birth dose should receive 3 doses of a HepB-containing vaccine on a schedule of 0, 1 to 2 months, and 6 months, starting as soon as feasible (see Fig. 6.3).
   - Administer the second dose 1 to 2 months after the first dose (minimum interval of 4 weeks); administer the third dose at least 8 weeks after the second dose AND at least 16 weeks after the **first** dose. The final (third or fourth) dose in the HepB vaccine series should be administered **no earlier than age 24 weeks**.
   - Administration of a total of 4 doses of HepB vaccine is permitted when a combination vaccine containing HepB is administered after the birth dose.

   Catch-up vaccination:
   - Unvaccinated persons should complete a 3-dose series.
   - A 2-dose series (doses separated by at least 4 months) of adult formulation Recombivax HB is licensed for use in children aged 11 through 15 years.
   - For other catch-up guidance, see Fig. 6.3.
2. **Rotavirus (RV) vaccines. (Minimum age: 6 weeks for both RV1 [Rotarix] and RV5 [RotaTeq])**
   Routine vaccination:
   Administer a series of RV vaccine to all infants as follows:
      1. If Rotarix is used, administer a 2-dose series at ages 2 and 4 months.
      2. If RotaTeq is used, administer a 3-dose series at ages 2, 4, and 6 months.
      3. If any dose in the series was RotaTeq or vaccine product is unknown for any dose in the series, a total of 3 doses of RV vaccine should be administered.

   Catch-up vaccination:
   - The maximum age for the first dose in the series is 14 weeks, 6 days; vaccination should not be initiated for infants aged 15 weeks, 0 days, or older.
   - The maximum age for the final dose in the series is 8 months, 0 days.
   - For other catch-up guidance, see Fig. 6.3.

For further guidance on the use of the vaccines mentioned below, see: www.cdc.gov/vaccines/hcp/acip-recs/index.html.

3. **Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine. (Minimum age: 6 weeks. Exception: DTaP-IPV [Kinrix, Quadracel]: 4 years)**

   Routine vaccination:
   - Administer a 5-dose series of DTaP vaccine at ages 2, 4, 6, 15 through 18 months, and 4 through 6 years. The fourth dose may be administered as early as age 12 months, provided at least 6 months have elapsed since the third dose.
   - Inadvertent administration of fourth DTaP dose early: If the fourth dose of DTaP was administered at least 4 months after the third dose of DTaP and the child was 12 months of age or older, it does not need to be repeated.

   Catch-up vaccination:
   - The fifth dose of DTaP vaccine is not necessary if the fourth dose was administered at age 4 years or older.
   - For other catch-up guidance, see Fig. 6.3.

4. ***Haemophilus influenzae* type b (Hib) conjugate vaccine. (Minimum age: 6 weeks for PRP-T [ActHIB, DTaP-IPV/Hib (Pentacel), Hiberix, and Hib-MenCY (MenHibrix)], PRP-OMP [PedvaxHIB])**

   Routine vaccination:
   - Administer a 2- or 3-dose Hib vaccine primary series and a booster dose (dose 3 or 4, depending on vaccine used in primary series) at age 12 through 15 months to complete a full Hib vaccine series.
   - The primary series with ActHIB, MenHibrix, Hiberix, or Pentacel consists of 3 doses and should be administered at ages 2, 4, and 6 months. The primary series with PedvaxHIB consists of 2 doses and should be administered at ages 2 and 4 months; a dose at age 6 months is not indicated.
   - One booster dose (dose 3 or 4, depending on vaccine used in primary series) of any Hib vaccine should be administered at age 12 through 15 months.
   - For recommendations on the use of MenHibrix in patients at increased risk for meningococcal disease, refer to the meningococcal vaccine footnotes and also to *MMWR* February 28, 2014 / 63(RR01):1–13, available at www.cdc.gov/mmwr/PDF/rr/rr6301.pdf.

   Catch-up vaccination:
   - If dose 1 was administered at ages 12 through 14 months, administer a second (final) dose at least 8 weeks after dose 1, regardless of Hib vaccine used in the primary series.
   - If both doses were PRP-OMP (PedvaxHIB or COMVAX) and were administered before the first birthday, the third (and final) dose should be administered at age 12 through 59 months and at least 8 weeks after the second dose.
   - If the first dose was administered at age 7 through 11 months, administer the second dose at least 4 weeks later and a third (and final) dose at age 12 through 15 months or 8 weeks after second dose, whichever is later.
   - If first dose is administered before the first birthday and second dose administered at younger than 15 months, a third (and final) dose should be administered 8 weeks later.
   - For unvaccinated children aged 15–59 months, administer only 1 dose.
   - For other catch-up guidance, see Fig. 6.3. For catch-up guidance related to MenHibrix, see the meningococcal vaccine footnotes and also *MMWR* February 28, 2014 / 63(RR01):1-13, available at www.cdc.gov/mmwr/PDF/rr/rr6301.pdf.

   Vaccination of persons with high-risk conditions:

   Children aged 12 through 59 months who are at increased risk for Hib disease, including chemotherapy recipients and those with anatomic or functional asplenia (including sickle cell disease), human immunodeficiency virus (HIV) infection, immunoglobulin deficiency, or early component complement deficiency, who have received either no doses or only 1 dose of Hib vaccine before 12 months of age, should receive 2 additional doses of Hib vaccine, 8 weeks apart; children who received 2 or more doses of Hib vaccine before 12 months of age should receive 1 additional dose.
   - For patients younger than age 5 years undergoing chemotherapy or radiation treatment who received a Hib vaccine dose(s) within 14 days of starting therapy or during therapy, repeat the dose(s) at least 3 months following therapy completion.
   - Recipients of hematopoietic stem cell transplant (HSCT) should be revaccinated with a 3-dose regimen of Hib vaccine starting 6 to 12 months after successful transplant, regardless of vaccination history; doses should be administered at least 4 weeks apart.
   - A single dose of any Hib-containing vaccine should be administered to unimmunized* children and adolescents 15 months of age and older undergoing an elective splenectomy; if possible, vaccine should be administered at least 14 days before procedure.
   - Hib vaccine is not routinely recommended for patients 5 years or older. However, 1 dose of Hib vaccine should be administered to unimmunized* persons aged 5 years or older who have anatomic or functional asplenia (including sickle cell disease) and unimmunized* persons 5 through 18 years of age with HIV infection.

   ** Patients who have not received a primary series and booster dose or at least 1 dose of Hib vaccine after 14 months of age are considered unimmunized.*

5. **Pneumococcal vaccines. (Minimum age: 6 weeks for PCV13, 2 years for PPSV23)**

   Routine vaccination with PCV13:
   - Administer a 4-dose series of PCV13 at ages 2, 4, and 6 months and at age 12 through 15 months.

   Catch-up vaccination with PCV13:
   - Administer 1 dose of PCV13 to all healthy children aged 24 through 59 months who are not completely vaccinated for their age.
   - For other catch-up guidance, see Fig. 6.3.

   Vaccination of persons with high-risk conditions with PCV13 and PPSV23:
   - All recommended PCV13 doses should be administered prior to PPSV23 vaccination if possible.
   - For children aged 2 through 5 years with any of the following conditions: chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure); chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy); diabetes mellitus; cerebrospinal fluid leak; cochlear implant; sickle cell disease and other hemoglobinopathies; anatomic or functional asplenia; HIV infection; chronic renal failure; nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease; solid organ transplantation; or congenital immunodeficiency:
     1. Administer 1 dose of PCV13 if any incomplete schedule of 3 doses of PCV13 was received previously.
     2. Administer 2 doses of PCV13 at least 8 weeks apart if unvaccinated or any incomplete schedule of fewer than 3 doses of PCV13 was received previously.
     3. The minimum interval between doses of PCV13 is 8 weeks.
     4. For children with no history of PPSV23 vaccination, administer PPSV23 at least 8 weeks after the most recent dose of PCV13.
   - For children aged 6 through 18 years who have cerebrospinal fluid leak; cochlear implant; sickle cell disease and other hemoglobinopathies; anatomic or functional asplenia; congenital or acquired immunodeficiencies; HIV infection; chronic renal failure; nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease; generalized malignancy; solid organ transplantation; or multiple myeloma:
     1. If neither PCV13 nor PPSV23 has been received previously, administer 1 dose of PCV13 now and 1 dose of PPSV23 at least 8 weeks later.
     2. If PCV13 has been received previously but PPSV23 has not, administer 1 dose of PPSV23 at least 8 weeks after the most recent dose of PCV13.
     3. If PPSV23 has been received but PCV13 has not, administer 1 dose of PCV13 at least 8 weeks after the most recent dose of PPSV23.
   - For children aged 6 through 18 years with chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure), chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy), diabetes mellitus, alcoholism, or chronic liver disease, who have not received PPSV23, administer 1 dose of PPSV23. If PCV13 has been received previously, then PPSV23 should be administered at least 8 weeks after any prior PCV13 dose.
   - A single revaccination with PPSV23 should be administered 5 years after the first dose to children with sickle cell disease or other hemoglobinopathies; anatomic or functional asplenia; congenital or acquired immunodeficiencies; HIV infection; chronic renal failure; nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease; generalized malignancy; solid organ transplantation; or multiple myeloma.

6. **Inactivated poliovirus vaccine (IPV). (Minimum age: 6 weeks)**

   Routine vaccination:
   - Administer a 4-dose series of IPV at ages 2, 4, 6 through 18 months, and 4 through 6 years. The final dose in the series should be administered on or after the fourth birthday and at least 6 months after the previous dose.

   Catch-up vaccination:
   - In the first 6 months of life, minimum age and minimum intervals are only recommended if the person is at risk of imminent exposure to circulating poliovirus (i.e., travel to a polio-endemic region or during an outbreak).
   - If 4 or more doses are administered before age 4 years, an additional dose should be administered at age 4 through 6 years and at least 6 months after the previous dose.
   - A fourth dose is not necessary if the third dose was administered at age 4 years or older and at least 6 months after the previous dose.
   - If both OPV and IPV were administered as part of a series, a total of 4 doses should be administered, regardless of the child's current age. If only OPV was administered, and all doses were given prior to 4 years of age, 1 dose of IPV should be given at 4 years or older, at least 6 months after the last OPV dose.
   - IPV is not routinely recommended for U.S. residents aged 18 years or older.
   - For other catch-up guidance, see Fig. 6.3.

7. **Influenza vaccines. (Minimum age: 6 months for inactivated influenza vaccine [IIV], 18 years for recombinant influenza vaccine [RIV])**

   Routine vaccination:
   - Administer influenza vaccine annually to all children beginning at age 6 months. For the 2016–17 season, use of live attenuated influenza vaccine (LAIV) is not recommended.

   For children aged 6 months through 8 years:
   - For the 2016–17 season, administer 2 doses (separated by at least 4 weeks) to children who are receiving influenza vaccine for the first time or who have not previously received ≥2 doses of trivalent or quadrivalent influenza vaccine before July 1, 2016. For additional guidance, follow dosing guidelines in the 2016–17 ACIP influenza vaccine recommendations (see *MMWR* August 26, 2016;65(5):1-54 , available at www.cdc.gov/mmwr/volumes/65/rr/pdfs/rr6505.pdf).
   - For the 2017–18 season, follow dosing guidelines in the 2017–18 ACIP influenza vaccine recommendations.

   For persons aged 9 years and older:
   - Administer 1 dose.

8. **Measles, mumps, and rubella (MMR) vaccine. (Minimum age: 12 months for routine vaccination)**

   Routine vaccination:
   - Administer a 2-dose series of MMR vaccine at ages 12 through 15 months and 4 through 6 years. The second dose may be administered before age 4 years, provided at least 4 weeks have elapsed since the first dose.
   - Administer 1 dose of MMR vaccine to infants aged 6 through 11 months before departure from the United States for international travel. These children should be revaccinated with 2 doses of MMR vaccine, the first at age 12 through 15 months (12 months if the child remains in an area where disease risk is high), and the second dose at least 4 weeks later.
   - Administer 2 doses of MMR vaccine to children aged 12 months and older before departure from the United States for international travel. The first dose should be administered on or after age 12 months and the second dose at least 4 weeks later.

   Catch-up vaccination:
   - Ensure that all school-aged children and adolescents have had 2 doses of MMR vaccine; the minimum interval between the 2 doses is 4 weeks.

9. **Varicella (VAR) vaccine. (Minimum age: 12 months)**

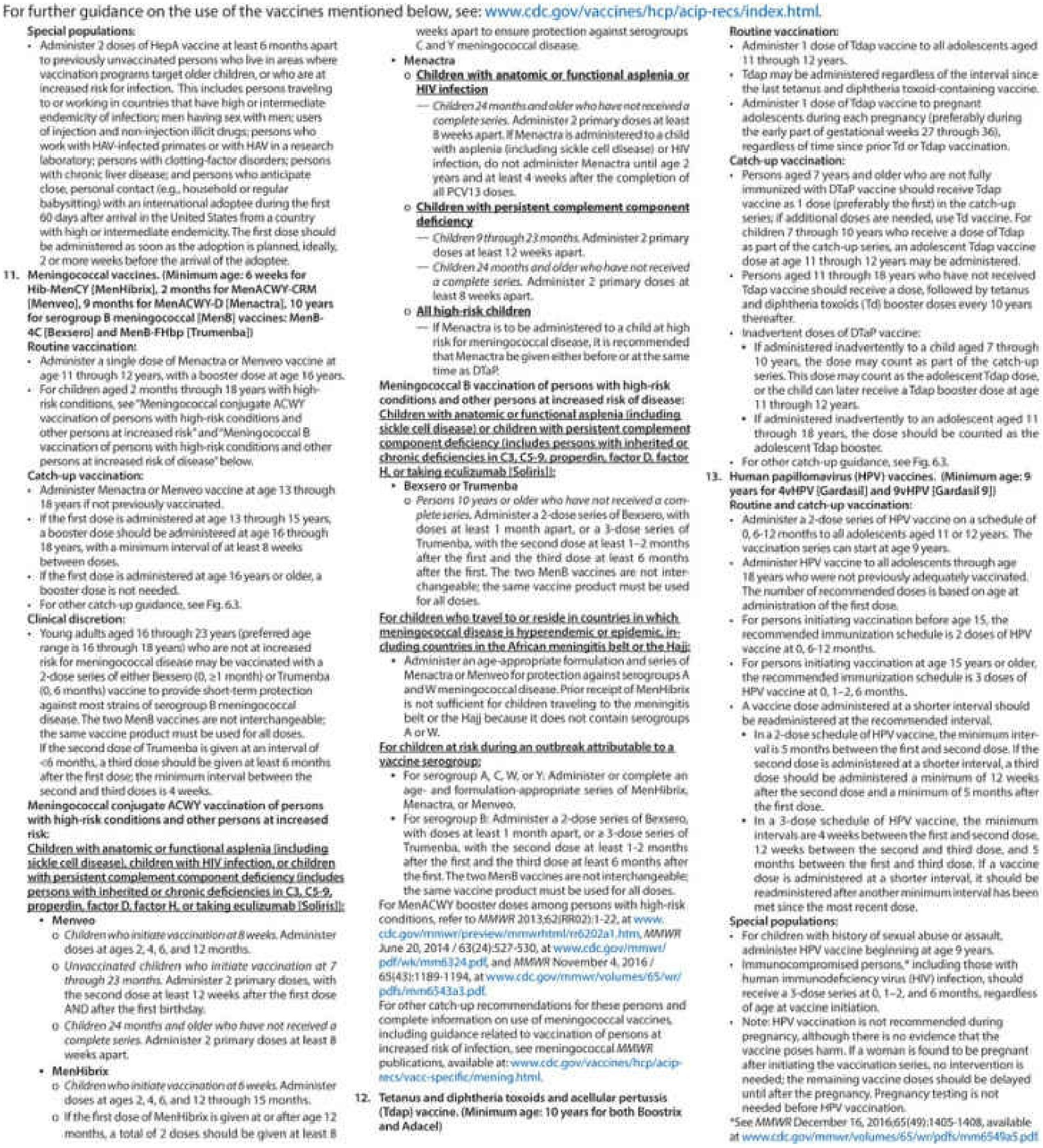
   Routine vaccination:
   - Administer a 2-dose series of VAR vaccine at ages 12 through 15 months and 4 through 6 years. The second dose may be administered before age 4 years, provided at least 3 months have elapsed since the first dose. If the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid.

   Catch-up vaccination:
   - Ensure that all persons aged 7 through 18 years without evidence of immunity (see *MMWR* 2007;56[No. RR-4], available at www.cdc.gov/mmwr/pdf/rr/rr5604.pdf) have 2 doses of varicella vaccine. For children aged 7 through 12 years, the recommended minimum interval between doses is 3 months (if the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid); for persons aged 13 years and older, the minimum interval between doses is 4 weeks.

10. **Hepatitis A (HepA) vaccine. (Minimum age: 12 months)**

    Routine vaccination:
    - Initiate the 2-dose HepA vaccine series at ages 12 through 23 months; separate the 2 doses by 6 to 18 months.
    - Children who have received 1 dose of HepA vaccine before age 24 months should receive a second dose 6 to 18 months after the first dose.
    - For any person aged 2 years and older who has not already received the HepA vaccine series, 2 doses of HepA vaccine separated by 6 to 18 months may be administered if immunity against hepatitis A virus infection is desired.

    Catch-up vaccination:
    - The minimum interval between the 2 doses is 6 months.



For further guidance on the use of the vaccines mentioned below, see: www.cdc.gov/vaccines/hcp/acip-recs/index.html.

Special populations:

- Administer 2 doses of HepA vaccine at least 6 months apart to previously unvaccinated persons who live in areas where vaccination programs target older children, or who are at increased risk for infection. This includes persons traveling to or working in countries that have high or intermediate endemicity of infection; men having sex with men; users of injection and non-injection illicit drugs; persons who work with HAV-infected primates or with HAV in a research laboratory; persons with clotting-factor disorders; persons with chronic liver disease; and persons who anticipate close, personal contact (e.g., household or regular babysitting) with an international adoptee during the first 60 days after arrival in the United States from a country with high or intermediate endemicity. The first dose should be administered as soon as the adoption is planned, ideally, 2 or more weeks before the arrival of the adoptee.

11. **Meningococcal vaccines. (Minimum age: 6 weeks for Hib-MenCY [MenHibrix], 2 months for MenACWY-CRM [Menveo], 9 months for MenACWY-D [Menactra], 10 years for serogroup B meningococcal [MenB] vaccines: MenB-4C [Bexsero] and MenB-FHbp [Trumenba])**

Routine vaccination:

- Administer a single dose of Menactra or Menveo vaccine at age 11 through 12 years, with a booster dose at age 16 years.
- For children aged 2 months through 18 years with high-risk conditions, see "Meningococcal conjugate ACWY vaccination of persons with high-risk conditions and other persons at increased risk" and "Meningococcal B vaccination of persons with high-risk conditions and other persons at increased risk of disease" below.

Catch-up vaccination:

- Administer Menactra or Menveo vaccine at age 13 through 18 years if not previously vaccinated.
- If the first dose is administered at age 13 through 15 years, a booster dose should be administeed at age 16 through 18 years, with a minimum interval of at least 8 weeks between doses.
- If the first dose is administered at age 16 years or older, a booster dose is not needed.
- For other catch-up guidance, see Fig. 6.3.

Clinical discretion:

- Young adults aged 16 through 23 years (preferred age range is 16 through 18 years) who are not at increased risk for meningococcal disease may be vaccinated with a 2-dose series of either Bexsero (0, ≥1 month) or Trumenba (0, 6 months) vaccine to provide short-term protection against most strains of serogroup B meningococcal disease. The two MenB vaccines are not interchangeable; the same vaccine product must be used for all doses.
  If the second dose of Trumenba is given at an interval of <6 months, a third dose should be given at least 6 months after the first dose; the minimum interval between the second and third doses is 4 weeks.

Meningococcal conjugate ACWY vaccination of persons with high-risk conditions and other persons at increased risk:

Children with anatomic or functional asplenia (including sickle cell disease), children with HIV infection, or children with persistent complement component deficiency (includes persons with inherited or chronic deficiencies in C3, C5-9, properdin, factor D, factor H, or taking eculizumab [Soliris]):

- **Menveo**
  - *Children who initiate vaccination at 8 weeks.* Administer doses at ages 2, 4, 6, and 12 months.
  - *Unvaccinated children who initiate vaccination at 7 through 23 months.* Administer 2 primary doses, with the second dose at least 12 weeks after the first dose AND after the first birthday.
  - *Children 24 months and older who have not received a complete series.* Administer 2 primary doses at least 8 weeks apart.
- **MenHibrix**
  - *Children who initiate vaccination at 6 weeks.* Administer doses at ages 2, 4, 6, and 12 through 15 months.
  - If the first dose of MenHibrix is given at or after age 12 months, a total of 2 doses should be given at least 8 weeks apart to ensure protection against serogroups C and Y meningococcal disease.
- **Menactra**
  - **Children with anatomic or functional asplenia or HIV infection**
    - — *Children 24 months and older who have not received a complete series.* Administer 2 primary doses at least 8 weeks apart. If Menactra is administered to a child with asplenia (including sickle cell disease) or HIV infection, do not administer Menactra until age 2 years and at least 4 weeks after the completion of all PCV13 doses.
  - **Children with persistent complement component deficiency**
    - — *Children 9 through 23 months.* Administer 2 primary doses at least 12 weeks apart.
    - — *Children 24 months and older who have not received a complete series.* Administer 2 primary doses at least 8 weeks apart.
  - **All high-risk children**
    - — If Menactra is to be administered to a child at high risk for meningococcal disease, it is recommended that Menactra be given either before or at the same time as DTaP.

Meningococcal B vaccination of persons with high-risk conditions and other persons at increased risk of disease:

Children with anatomic or functional asplenia (including sickle cell disease) or children with persistent complement component deficiency (includes persons with inherited or chronic deficiencies in C3, C5-9, properdin, factor D, factor H, or taking eculizumab [Soliris]):

- Bexsero or Trumenba
  - *Persons 10 years or older who have not received a complete series.* Administer a 2-dose series of Bexsero, with doses at least 1 month apart, or a 3-dose series of Trumenba, with the second dose at least 1–2 months after the first and the third dose at least 6 months after the first. The two MenB vaccines are not interchangeable; the same vaccine product must be used for all doses.

For children who travel to or reside in countries in which meningococcal disease is hyperendemic or epidemic, including countries in the African meningitis belt or the Hajj:

- Administer an age-appropriate formulation and series of Menactra or Menveo for protection against serogroups A and W meningococcal disease. Prior receipt of MenHibrix is not sufficient for children traveling to the meningitis belt or the Hajj because it does not contain serogroups A or W.

For children at risk during an outbreak attributable to a vaccine serogroup:

- For serogroup A, C, W, or Y: Administer or complete an age- and formulation-appropriate series of MenHibrix, Menactra, or Menveo.
- For serogroup B: Administer a 2-dose series of Bexsero, with doses at least 1 month apart, or a 3-dose series of Trumenba, with the second dose at least 1-2 months after the first and the third dose at least 6 months after the first. The two MenB vaccines are not interchangeable; the same vaccine product must be used for all doses.

For MenACWY booster doses among persons with high-risk conditions, refer to *MMWR* 2013;62(RR02):1-22, at www.cdc.gov/mmwr/preview/mmwrhtml/rr6202a1.htm, *MMWR* June 20, 2014 / 63(24):527-530, at www.cdc.gov/mmwr/pdf/wk/mm6324.pdf, and *MMWR* November 4, 2016 / 65(43):1189-1194, at www.cdc.gov/mmwr/volumes/65/wr/pdfs/mm6543a3.pdf.

For other catch-up recommendations for these persons and complete information on use of meningococcal vaccines, including guidance related to vaccination of persons at increased risk of infection, see meningococcal *MMWR* publications, available at: www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/mening.html.

12. **Tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccine. (Minimum age: 10 years for both Boostrix and Adacel)**

Routine vaccination:

- Administer 1 dose of Tdap vaccine to all adolescents aged 11 through 12 years.
- Tdap may be administered regardless of the interval since the last tetanus and diphtheria toxoid-containing vaccine.
- Administer 1 dose of Tdap vaccine to pregnant adolescents during each pregnancy (preferably during the early part of gestational weeks 27 through 36), regardless of time since prior Td or Tdap vaccination.

Catch-up vaccination:

- Persons aged 7 years and older who are not fully immunized with DTaP vaccine should receive Tdap vaccine as 1 dose (preferably the first) in the catch-up series; if additional doses are needed, use Td vaccine. For children 7 through 10 years who receive a dose of Tdap as part of the catch-up series, an adolescent Tdap vaccine dose at age 11 through 12 years may be administered.
- Persons aged 11 through 18 years who have not received Tdap vaccine should receive a dose, followed by tetanus and diphtheria toxoids (Td) booster doses every 10 years thereafter.
- Inadvertent doses of DTaP vaccine:
  - If administered inadvertently to a child aged 7 through 10 years, the dose may count as part of the catch-up series. This dose may count as the adolescent Tdap dose, or the child can later receive a Tdap booster dose at age 11 through 12 years.
  - If administered inadvertently to an adolescent aged 11 through 18 years, the dose should be counted as the adolescent Tdap booster.
- For other catch-up guidance, see Fig. 6.3.

13. **Human papillomavirus (HPV) vaccines. (Minimum age: 9 years for 4vHPV [Gardasil] and 9vHPV [Gardasil 9])**

Routine and catch-up vaccination:

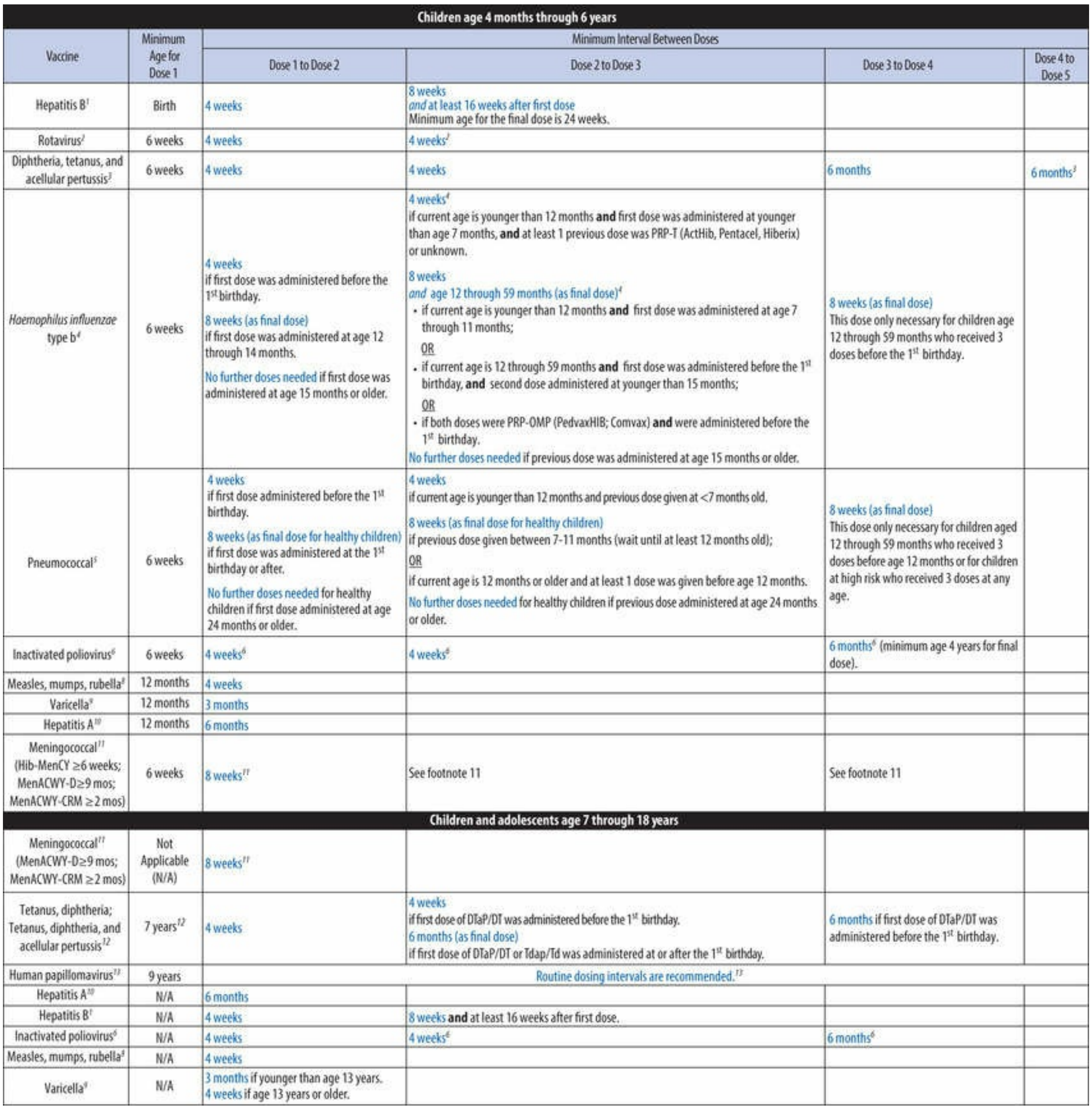
- Administer a 2-dose series of HPV vaccine on a schedule of 0, 6-12 months to all adolescents aged 11 or 12 years. The vaccination series can start at age 9 years.
- Administer HPV vaccine to all adolescents through age 18 years who were not previously adequately vaccinated. The number of recommended doses is based on age at administration of the first dose.
- For persons initiating vaccination before age 15, the recommended immunization schedule is 2 doses of HPV vaccine at 0, 6-12 months.
- For persons initiating vaccination at age 15 years or older, the recommended immunization schedule is 3 doses of HPV vaccine at 0, 1–2, 6 months.
- A vaccine dose administered at a shorter interval should be readministered at the recommended interval.
  - In a 2-dose schedule of HPV vaccine, the minimum interval is 5 months between the first and second dose. If the second dose is administered at a shorter interval, a third dose should be administered a minimum of 12 weeks after the second dose and a minimum of 5 months after the first dose.
  - In a 3-dose schedule of HPV vaccine, the minimum intervals are 4 weeks between the first and second dose, 12 weeks between the second and third dose, and 5 months between the first and third dose. If a vaccine dose is administered at a shorter interval, it should be readministered after another minimum interval has been met since the most recent dose.

Special populations:

- For children with history of sexual abuse or assault, administer HPV vaccine beginning at age 9 years.
- Immunocompromised persons,* including those with human immunodeficiency virus (HIV) infection, should receive a 3-dose series at 0, 1–2, and 6 months, regardless of age at vaccine initiation.
- Note: HPV vaccination is not recommended during pregnancy, although there is no evidence that the vaccine poses harm. If a woman is found to be pregnant after initiating the vaccination series, no intervention is needed; the remaining vaccine doses should be delayed until after the pregnancy. Pregnancy testing is not needed before HPV vaccination.

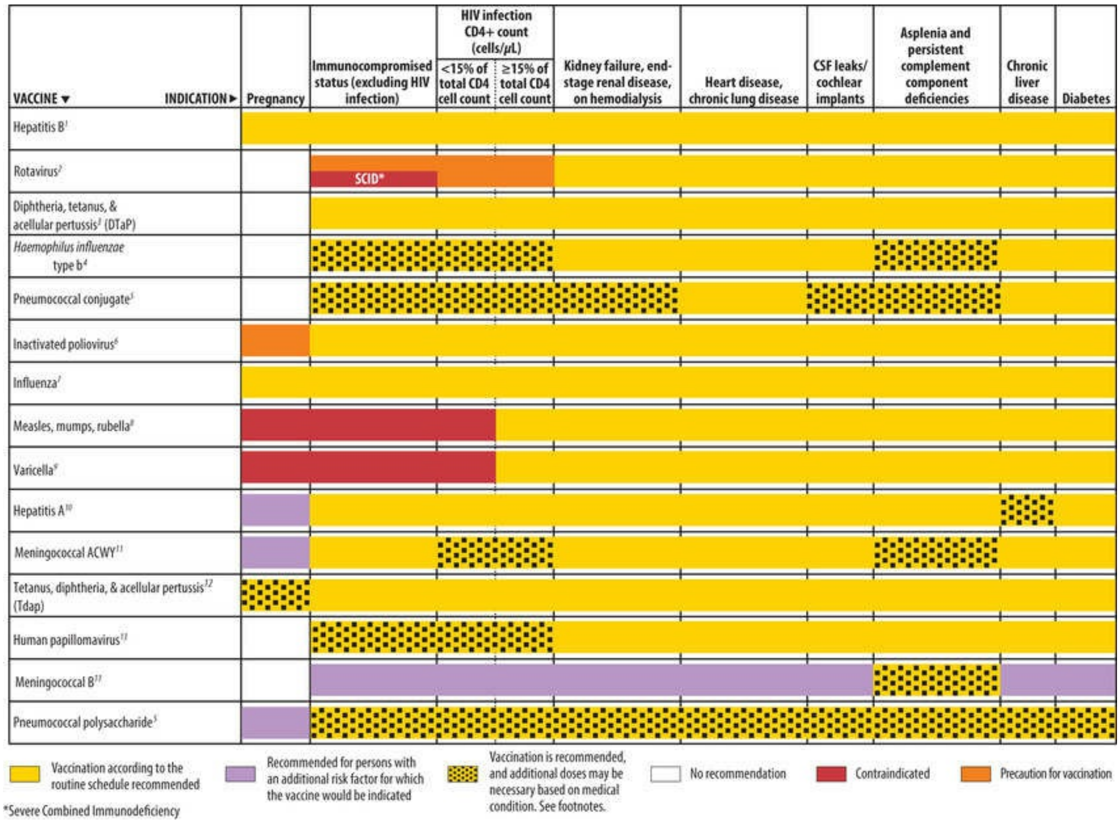
*See *MMWR* December 16, 2016;65(49):1405-1408, available at www.cdc.gov/mmwr/volumes/65/wr/pdfs/mm6549a5.pdf

FIGURE 6.2 **Recommended immunization schedule for persons 0 through 18 years of age: United States, 2017. For those who fall behind or start late, see the catch-up schedule (Fig. 6.3).** **(Modified from the National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Ga.)**



Children age 4 months through 6 years					
Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to Dose 2	Dose 2 to Dose 3	Dose 3 to Dose 4	Dose 4 to Dose 5
Hepatitis B[1]	Birth	4 weeks	8 weeks *and* at least 16 weeks after first dose Minimum age for the final dose is 24 weeks.		
Rotavirus[2]	6 weeks	4 weeks	4 weeks[2]		
Diphtheria, tetanus, and acellular pertussis[3]	6 weeks	4 weeks	4 weeks	6 months	6 months[3]
Haemophilus influenzae type b[4]	6 weeks	4 weeks if first dose was administered before the 1st birthday. 8 weeks (as final dose) if first dose was administered at age 12 through 14 months. No further doses needed if first dose was administered at age 15 months or older.	4 weeks[4] if current age is younger than 12 months **and** first dose was administered at younger than age 7 months, **and** at least 1 previous dose was PRP-T (ActHib, Pentacel, Hiberix) or unknown. 8 weeks *and* age 12 through 59 months (as final dose)[4] • if current age is younger than 12 months **and** first dose was administered at age 7 through 11 months; OR • if current age is 12 through 59 months **and** first dose was administered before the 1st birthday, **and** second dose administered at younger than 15 months; OR • if both doses were PRP-OMP (PedvaxHIB; Comvax) **and** were administered before the 1st birthday. No further doses needed if previous dose was administered at age 15 months or older.	8 weeks (as final dose) This dose only necessary for children age 12 through 59 months who received 3 doses before the 1st birthday.	
Pneumococcal[5]	6 weeks	4 weeks if first dose administered before the 1st birthday. 8 weeks (as final dose for healthy children) if first dose was administered at the 1st birthday or after. No further doses needed for healthy children if first dose administered at age 24 months or older.	4 weeks if current age is younger than 12 months and previous dose given at <7 months old. 8 weeks (as final dose for healthy children) if previous dose given between 7-11 months (wait until at least 12 months old); OR if current age is 12 months or older and at least 1 dose was given before age 12 months. No further doses needed for healthy children if previous dose administered at age 24 months or older.	8 weeks (as final dose) This dose only necessary for children aged 12 through 59 months who received 3 doses before age 12 months or for children at high risk who received 3 doses at any age.	
Inactivated poliovirus[6]	6 weeks	4 weeks[6]	4 weeks[6]	6 months[6] (minimum age 4 years for final dose).	
Measles, mumps, rubella[8]	12 months	4 weeks			
Varicella[9]	12 months	3 months			
Hepatitis A[10]	12 months	6 months			
Meningococcal[11] (Hib-MenCY ≥6 weeks; MenACWY-D≥9 mos; MenACWY-CRM ≥2 mos)	6 weeks	8 weeks[11]	See footnote 11	See footnote 11	
Children and adolescents age 7 through 18 years					
Meningococcal[11] (MenACWY-D≥9 mos; MenACWY-CRM ≥2 mos)	Not Applicable (N/A)	8 weeks[11]			
Tetanus, diphtheria; Tetanus, diphtheria, and acellular pertussis[12]	7 years[12]	4 weeks	4 weeks if first dose of DTaP/DT was administered before the 1st birthday. 6 months (as final dose) if first dose of DTaP/DT or Tdap/Td was administered at or after the 1st birthday.	6 months if first dose of DTaP/DT was administered before the 1st birthday.	
Human papillomavirus[13]	9 years	Routine dosing intervals are recommended.[13]			
Hepatitis A[10]	N/A	6 months			
Hepatitis B[1]	N/A	4 weeks	8 weeks **and** at least 16 weeks after first dose.		
Inactivated poliovirus[6]	N/A	4 weeks	4 weeks[6]	6 months[6]	
Measles, mumps, rubella[8]	N/A	4 weeks			
Varicella[9]	N/A	3 months if younger than age 13 years. 4 weeks if age 13 years or older.			

FIGURE 6.3 **Catch-up immunization schedule for persons 4 months through 18 years of age who start late or who are more than 1 month behind: United States, 2017. The figure provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child's age. Always use this table in conjunction with the accompanying childhood and adolescent immunization schedule (see Fig. 6.2) and the respective footnotes (see Fig. 6.2 footnotes).** (Modified from the National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Ga.)



VACCINE ▼ INDICATION ▶	Pregnancy	Immunocompromised status (excluding HIV infection)	HIV infection CD4+ count (cells/μL) <15% of total CD4 cell count	HIV infection CD4+ count (cells/μL) ≥15% of total CD4 cell count	Kidney failure, end-stage renal disease, on hemodialysis	Heart disease, chronic lung disease	CSF leaks/ cochlear implants	Asplenia and persistent complement component deficiencies	Chronic liver disease	Diabetes
Hepatitis B[1]	🟨	🟨	🟨	🟨	🟨	🟨	🟨	🟨	🟨	🟨
Rotavirus[2]	☐	🟧 🟥 SCID*	🟧	🟧	🟨	🟨	🟨	🟨	🟨	🟨
Diphtheria, tetanus, & acellular pertussis[3] (DTaP)	☐	🟨	🟨	🟨	🟨	🟨	🟨	🟨	🟨	🟨
Haemophilus influenzae type b[4]	☐	▨	▨	▨	🟨	🟨	🟨	▨	🟨	🟨
Pneumococcal conjugate[5]	☐	▨	▨	▨	▨	🟨	▨	▨	🟨	🟨
Inactivated poliovirus[6]	🟧	🟨	🟨	🟨	🟨	🟨	🟨	🟨	🟨	🟨
Influenza[7]	🟨	🟨	🟨	🟨	🟨	🟨	🟨	🟨	🟨	🟨
Measles, mumps, rubella[8]	🟥	🟥	🟥	🟨	🟨	🟨	🟨	🟨	🟨	🟨
Varicella[9]	🟥	🟥	🟥	🟨	🟨	🟨	🟨	🟨	🟨	🟨
Hepatitis A[10]	🟪	🟨	🟨	🟨	🟨	🟨	🟨	🟨	▨	🟨
Meningococcal ACWY[11]	🟪	🟨	▨	▨	🟨	🟨	🟨	▨	🟨	🟨
Tetanus, diphtheria, & acellular pertussis[12] (Tdap)	▨	🟨	🟨	🟨	🟨	🟨	🟨	🟨	🟨	🟨
Human papillomavirus[13]	☐	▨	▨	▨	🟨	🟨	🟨	🟨	🟨	🟨
Meningococcal B[11]	☐	🟪	🟪	🟪	🟪	🟪	🟪	▨	🟪	🟪
Pneumococcal polysaccharide[5]	🟪	▨	▨	▨	▨	▨	▨	▨	▨	▨

🟨 Vaccination according to the routine schedule recommended
🟪 Recommended for persons with an additional risk factor for which the vaccine would be indicated
▨ Vaccination is recommended, and additional doses may be necessary based on medical condition. See footnotes.
☐ No recommendation
🟥 Contraindicated
🟧 Precaution for vaccination

*Severe Combined Immunodeficiency

FIGURE 6.4 Vaccines that might be indicated for persons aged 0 through 18 years based on medical indications. These recommendations must be read along with the footnotes of this schedule found in Fig. 6.2.

Since its inception, the US immunization program has focused on immunization of infants and young children. In 1996, following growing concern about morbidity associated with vaccine-preventable diseases in the difficult-to-reach adolescent population, the ACIP recommended expanding efforts to immunize adolescents by establishing a routine vaccination visit at 11 to 12 years of age.[55] In addition to providing Td and previously missed vaccinations, the report emphasized that this visit should be used to provide other important preventive health services. The addition of several newer vaccines for adolescents (i.e., MCV4, Tdap, and HPV) stimulated a reappraisal of approaches that will most effectively and efficiently increase the proportion of adolescents who receive newly recommended vaccines and develop ways to integrate these approaches into other adolescent health, education, and development programs.[56]

Vaccine Spacing

Minimal spacing of vaccine doses generally is 1 month for the initial doses of killed vaccines; longer intervals are needed for booster doses to provide optimal responses.[8] For children with delayed initiation of immunization (after 6 months of age), an accelerated schedule is recommended (see Fig. 6.3).[8,57] To optimize adherence to the schedule in this circumstance, visits should be scheduled at 1-month intervals, and all recommended vaccines should be given at each visit. No need exists to restart any of the vaccine series in people with long delays between doses. The minimal spacing between nonsimultaneously administered live virus vaccines (e.g., MMR, varicella, and live, attenuated influenza) or repeated dose of the same live virus vaccine is 28 days.

Simultaneous Administration

All childhood vaccines can be administered simultaneously. This practice is based on extrapolation of data from multiple studies showing that most vaccines can be administered at the same time without compromising safety or immunogenicity.[58] Thus DTaP, Hib, IPV, HBV, PCV, MMR, varicella, and rotavirus vaccines can be administered simultaneously, and for inactivated vaccines within any interval of one another when otherwise indicated.[8,57] Lower geometric mean concentrations (GMCs) of IgG antibodies to some pneumococcal serotypes were observed compared with corresponding IgG GMCs when 7-valent PCV (PCV7) was administered alone. It is possible that the Menactra MCV4 (Sanofi Pasteur, Swiftwater, Pa) vaccine interferes with the immune response to 13-valent PCV (PCV13). Because of high risk for invasive pneumococcal disease, children with functional or anatomic asplenia or HIV infection should not be immunized with MenACWY-D (Menactra) before 2 years of age to avoid interference with the immune response to the PCV series.[59,59a] Data suggest possible immunologic interference in the meningococcal human complement serum bactericidal assay (hSBA) responses, resulting in decreased titers when MenACWY-D is administered 30 days after Daptacel (DTaP, Sanofi Pasteur). In contrast, coadministration of MenACWY-D and Daptacel was not associated with reduced hSBA responses to all four meningococcal serogroups. Available data do not allow evaluation of potential interference from other DTaP-containing vaccines on meningococcal seroresponse rates. If MenACWY-D is to be administered to a child at increased risk for meningococcal disease, the CDC recommends MenACWY-D be given either before or concomitantly with DTaP.[59a] Interference between live virus vaccines other than oral poliovirus vaccine (OPV) and rotavirus (e.g., MMR and varicella) theoretically can occur if they are given within a short interval; live virus vaccines should be given either simultaneously or at least 1 month apart. Vaccines should not be mixed in the same syringe unless specifically licensed for such use. Interference has been found between certain vaccines (cholera and yellow fever [YF]).

Spacing of Antibody-Containing Products and Vaccines

Immunoglobulins or blood products containing immunoglobulins inhibit response to certain live-virus vaccines (MMR and possibly varicella). The duration of inhibition of response is related to the dose of immunoglobulin delivered, and algorithms for calculating appropriate delays of MMR after receipt of such products are available.[22,57,60] In general, MMR vaccines should be delayed 3 months or longer after administration of usual doses of immunoglobulin (e.g., to prevent hepatitis A) or blood products and for longer periods after higher doses (e.g., 11 months after 2 g/kg immune globulin intravenous administered for treatment of Kawasaki disease).

Interchangeability of Vaccines

Available data support interchangeability of most vaccines produced by different manufacturers to prevent the same disease. Studies indicate that response to a 3-dose series using different Hib conjugate vaccines equals or exceeds that when the same vaccine is used for all doses.[61] The ACIP and AAP recommend that, when feasible, the same vaccine should be used for the primary series but that 3 doses of any vaccine are sufficient.[8,57] Data are limited regarding safety, immunogenicity, and efficacy of using acellular pertussis (as DTaP) vaccines from different manufacturers for successive doses of the pertussis series. Data suggest that 2 of the current DTaP preparations can be used interchangeably for the first 3 doses of the DTaP series without affecting safety or immunogenicity.[62] When the specific product is not known or available, any DTaP vaccine should be used to continue or complete the series. Similarly, any HPV vaccine can be used in populations for whom the vaccine is licensed to complete a series and protect against serotypes 16 and 18.[63]

Vaccine Safety and Compensation for Vaccine Injury

In 1986, the National Childhood Vaccine Injury Act was enacted to create a compensation program for families affected by childhood vaccine-associated adverse events and help ensure safety of the vaccine supply (Table 6.2).

TABLE 6.2

Outcomes From the National Childhood Vaccine Injury Act, 1986

National Vaccine Injury Compensation Program	• Limits manufacturer liability • Provides payments to families of children who sustain documented injuries following routine immunization
Vaccine Information Statement (VIS)	• A VIS must be given with every vaccination including each dose in a multidose series. Each VIS contains a brief description of the disease as well as the risks and benefits of the vaccine. The CDC develops VISs and distributes them to state and local health departments as well as individual providers
National Vaccine Program Office	• Develops and coordinates a comprehensive national vaccine plan
Advisory Commission on Childhood Vaccines	• Advises the Secretary of Health and Human Services on injury compensation program
National Vaccine Advisory Committee	• Advises the Secretary of Health and Human Services on national vaccine policy
Federal excise tax on childhood vaccines	• 1987 amendment to the Compensation Act • Proceeds used to finance payments to families of children affected by a vaccine-associated adverse event
Vaccine Adverse Events Reporting System	• Healthcare providers required to report certain adverse events (health effects occurring after immunization that may or may not be related to the vaccine)
Committee from the Institute of Medicine (IOM) to review literature on vaccine reactions	• IOM identified the following problems: 1. Limited understanding of biologic processes that underlie adverse events 2. Incomplete and inconsistent information from individual reports 3. Poorly constructed research studies (not enough people enrolled for the period of time) 4. Inadequate systems to track vaccine side effects 5. Few experimental studies published in the medical literature

CDC, Centers for Disease Control and Prevention.

Data from Schwartz B, Orenstein WA. Vaccination policies and programs: the federal government's role in making the system work. Prim Care 2001;28:697–711; and http://www.cdc.gov/vaccinesafety/ensuringsafety/history/index.html.

Studies of Vaccine Safety

As many vaccine-preventable diseases approach or reach elimination in the US, continuing to balance the risks and benefits of each vaccine becomes increasingly important.[64] For example, OPV was formerly recommended for routine use in the US but was associated with vaccine-associated paralytic poliomyelitis (VAPP) in 1 case per 2.5 million vaccine doses distributed. This rare adverse event was no longer considered acceptable following elimination of poliomyelitis in the US, and in 2000, the ACIP recommended using IPV for all doses of poliovirus vaccine.[65] Public perceptions of vaccine safety are a challenge to the continued success of the vaccination program. New parents and younger physicians grew up without appreciating the morbidity and mortality of several vaccine-preventable diseases. Therefore risk or perception of risk for adverse events becomes an important concern.

In the early 1990s, the Institute of Medicine (IOM) reviewed available information regarding the possible causality of serious adverse events after administration of each of the then licensed childhood vaccines.[66–68] These reviews were updated in 2011.[67] For many events, information was considered insufficient to determine causality. For some events, however, the investigating panels classified events more definitively, as follows: (1) evidence establishes definitively that vaccine plays a causal role; (2) evidence supports a causal role for the vaccine; and (3) evidence indicates that the vaccine definitely does not play a causal role. These events are summarized in Table 6.3. These investigations represented a comprehensive compilation of data on vaccine safety, although controversy persists regarding certain events. Reanalysis of available data on the occurrence of type 1 diabetes mellitus after MMR or DTaP vaccination suggests that evidence favors rejection of a causal relationship.[69]

TABLE 6.3

Summary of Institute of Medicine and Agency for Healthcare Research and Quality Findings on the Relationship of Adverse

Events With Individual Vaccines

Vaccine	Established Causation/Convincingly Supports	Favors Causation/Acceptance	Favors Rejection of Causation
DT/Td/TT	Anaphylaxis	GBS[a] Brachial neuritis	Encephalopathy Type 1 diabetes Infantile spasms Death from SIDS
DTaP, Tdap (acellular pertussis)	—	—	Type 1 diabetes
DTP (whole cell pertussis)	Anaphylaxis; protracted, inconsolable crying	Acute encephalopathy Shock and unusual shock-like state (hypotonic-hyporesponsive episode) Chronic encephalopathy (after acute encephalopathy)	Infantile spasms Hypoarrhythmia Reye syndrome SIDS
Influenza	Anaphylaxis AHRQ: GBS (after 2009 monovalent H1N1 vaccine only)	Oculorespiratory syndrome Febrile seizures	(Inactivated) Bell palsy Asthma exacerbation or reactive airway episodes in children and adults (Inactivated) Cardiovascular and cerebrovascular events in older adults; serious adverse events in renal disease
IPV	—	—	—
Hepatitis B	Anaphylaxis	—	—
Hib (conjugate)	—	—	Early-onset *Haemophilus influenzae* b disease
HPV	Anaphylaxis	—	Type 1 diabetes, juvenile rheumatoid arthritis, GBS, appendicitis, seizures, stroke, syncope, venous thromboembolism
Measles	Death from measles vaccine strain in primarily immunocompromised persons Measles inclusion body encephalitis in persons with	Anaphylaxis	—

	immunodeficiencies		
Meningococcus	Anaphylaxis	—	—
MMR	Anaphylaxis Thrombocytopenia Febrile seizures	—	Autistic spectrum disorders Type 1 diabetes
Mumps (see MMR)	—	—	—
OPV	Poliomyelitis Death from polio vaccine strain, mainly in immunocompromised people	GBS[a]	—
Pneumococcal (conjugate)	—	Febrile seizures	—
Rotavirus	—	Intussusception	—
Rubella[b] (see MMR)	Anaphylaxis	Transient arthralgia in women Transient arthralgia in children	—
Varicella	Disseminated Oka VZV with (only in persons with immunodeficiencies) and without other organ involvement, e.g., pneumonia, meningitis, hepatitis) Vaccine strain viral reactivation without and with subsequent infection (meningitis, encephalitis) Anaphylaxis	—	—

[a] The Advisory Committee on Immunization Practice of the United States Public Health Service disagreed with these IOM findings (see reference 39).

[b] Data were reviewed by an earlier IOM committee. Initial report categories corresponding to those table headings were “Evidence indicates a causal relationship, Evidence is consistent with a causal relationship,” and “Evidence does not indicate a causal relationship.”

AHRQ, Agency for Healthcare Research and Quality; DT, diphtheria and tetanus toxoids; DTaP, diphtheria and tetanus toxoids and acellular pertussis; DTP, diphtheria and tetanus toxoids and pertussis (whole cell) vaccine; GBS, Guillain-Barré syndrome; Hib, *Haemophilus influenzae* type b conjugate vaccine; HPV, human papillomavirus; IOM, Institute of Medicine; IPV, inactivated poliovirus vaccine; MMR, measles, mumps, and rubella vaccine; OPV, live oral poliovirus vaccine; SIDS, sudden infant death syndrome; Td, tetanus and diphtheria toxoids; TT, tetanus toxoid; VZV, varicella-zoster virus.

Data from references 66 to 72.

As a result of continued concerns about vaccine safety, in 2000 the CDC and the National Institutes of Health commissioned the IOM to convene an Immunization Safety Review Committee.[70] Between 2001 and 2011, this independent expert committee published 9 reports related to various immunization safety concerns. The Committee has made recommendations in the areas of public health response, policy review, research, and communications for each of the 8 subjects reviewed (Box 6.1). The IOM concluded that the body of epidemiologic evidence favors rejection of a causal relationship between MMR vaccine and autism and concluded that no relationship exists between thimerosal-containing vaccines and autism.[70] None of the 9 IOM reports recommended a policy review of the current vaccine recommendations or change in the immunization schedule.[71] The most recent review by the IOM was charged to (1) review scientific findings and stakeholder concerns related to the safety of the recommended childhood immunization schedule and (2) identify potential research approaches, methodologies, and study designs that could inform this question, considering strengths, weaknesses, as well as the ethical and financial feasibility of each approach. The report concluded that the

Box 6.1

Institute of Medicine Immunization Safety Review Committee Reports and Dates of Release, 2001 to 2013

- Measles-Mumps-Rubella Vaccine and Autism (April 2001)
- Thimerosal-Containing Vaccines and Neurodevelopmental Disorders (October 2001)
- Multiple Immunizations and Immune Dysfunction (February 2002)
- Hepatitis B Vaccine and Demyelinating Neurological Disorders (May 2002)
- SV40 Contamination of Polio Vaccine and Cancer (October 2002)
- Vaccinations and Sudden Unexpected Death in Infancy (March 2003)
- Influenza Vaccines and Neurological Complications (October 2003)
- Vaccines and Autism (May 2004)

- Adverse Effects of Vaccines: Evidence and Causality (August 2011)
- Childhood Immunization Schedule and Safety: Stakeholder Concerns, Scientific Evidence, and Future Studies (January 2013)

Data from (1) http://nationalacademies.org/hmd/activities/publichealth/immunizationsafety.aspx; (2) http://nationalacademies.org/hmd/reports/2002/immunization-safety-review-sv40-contamination-of-polio-vaccine-and-cancer.aspx; (3) http://nationalacademies.org/hmd/reports/2002/immunization-safety-review-multiple-immunizations-and-immune-dysfunction.aspx; (4) http://nationalacademies.org/hmd/reports/2001/immunization-safety-review-measles-mumps-rubella-vaccine-and-autism.aspx; (5) http://nationalacademies.org/hmd/reports/2001/immunization-safety-review-thimerosal—containing-vaccines-and-neurodevelopmental-disorders.aspx; (6) http://nationalacademies.org/hmd/reports/2002/immunization-safety-review-hepatitis-b-vaccine-and-demyelinating-neurological-disorders.aspx; and (7) references 69–71.

> *… committee's efforts to identify priorities for recommended research studies did not reveal … evidence suggesting that the childhood immunization schedule is linked to autoimmune diseases, asthma, hypersensitivity, seizures or epilepsy, child developmental disorders, learning disorders or developmental disorders, or attention deficit or disruptive behavior disorders. While the committee found that there is no scientific evidence to justify the majority of safety concerns, perceptions dictate parental support and actions. Therefore further study of the full immunization schedule as well as further study to understand stakeholder perceptions and how they are formed can help improve awareness and education efforts.*[71]

In addition, the Agency for Healthcare Research and Quality commissioned an assessment of vaccine safety that evaluated evidence on the safety of vaccines recommended for routine use among adults, children, and pregnant women as of 2011.[72] This report included an extensive literature search for clinical trials and observational studies with strong study designs and analysis methods: cohort studies comparing vaccinated and unvaccinated groups, case-control studies, self-controlled case series, and designs using multivariate risk factor analyses. The results support most findings of the 2011 IOM report for vaccines routinely recommended for children, with some additional findings:

- “There is insufficient evidence to determine any potential association between trivalent inactivated vaccine and asthma exacerbation, acute disseminated encephalomyelitis, and transverse myelitis.
- Febrile seizures have been reported after DTaP, MMR, measles, mumps, rubella, and varicella (MMRV), inactivated influenza vaccine (IIV), and PCVs.[73,74] An analysis suggests that for DTaP, influenza, and PCV vaccines, only PCV vaccine is likely to cause febrile seizures when given alone or when given concomitantly with influenza or DTaP vaccines.[75]
- A large US postlicensure study found associations between both Rotarix and RotaTeq and intussusception in the short term following vaccination; patient-related risk factors were not reported.
- Strong evidence for a lack of association of HPV vaccines with several serious medical conditions (juvenile rheumatoid arthritis, type 1 diabetes, Guillain-Barré syndrome [GBS]) has been found in large postlicensure studies.
- Insufficient evidence has been found regarding other serious conditions such as multiple sclerosis, chronic inflammatory demyelinating polyneuropathy, amyotrophic lateral sclerosis, and pancreatitis.
- Insufficient evidence has been found to determine the possible association, if any, between vaccines such as DTaP, meningococcal vaccine, and varicella vaccine and the onset of nervous system conditions such as acute disseminated encephalomyelitis, transverse myelitis, multiple sclerosis, and GBS. Because these medical conditions are extremely rare, it may not be possible to reach a level of evidence beyond insufficient.”[72]

Monitoring of Vaccine Safety

A robust infrastructure consisting of several systems has been established to monitor vaccine safety following licensure. The Vaccine Adverse Event Reporting System (VAERS), operated jointly by the CDC and the FDA, is a national passive surveillance system used to detect early warning signals and generate hypotheses about possible new vaccine adverse events or changes in frequency of recognized events.[76] Intussusception associated with receipt of rhesus rotavirus vaccine and leading to its withdrawal from the market in 1999 was detected by the VAERS.[77,78] Physicians and vaccine manufacturers should report all suspected adverse reactions after vaccination to the VAERS and are required to report certain events.[31,76] Family members, patients, and others also can report adverse events to the VAERS. VAERS reports can be submitted electronically through a secure website at http://vaers.hhs.gov. A second CDC system is the Vaccine Safety Datalink (VSD), which consists of large, linked databases from integrated healthcare systems.[64,77,79] Associations between medically attended health events and immunizations can be evaluated through the VSD. A third system is the Clinical Immunization Safety Assessment (CISA) Centers network, which consists of selected clinical academic medical centers that work in partnership with the CDC to study the pathophysiology of vaccine reactions and develop clinical management protocols for affected patients. In addition, the FDA uses a sentinel surveillance program to study adverse events reported after vaccination, drug use, and use of medical devices. These systems are crucial to the vitality and strength of the US immunization program.

Compensation Program for Adverse Events After Immunization

In addition to mandating the review of causality of adverse events and creating a unified reporting system for adverse events after vaccination, the National Childhood Vaccine Injury Act established a program to provide compensation to people who experience permanent injury after vaccination.[31] A table of injuries eliciting automatic compensation was developed and has been revised on the basis of the findings of the IOM studies; in addition, any person who shows medical evidence of causality may be compensated. This program is funded by a special excise tax on each dose of vaccine ($0.75 per disease prevented) to which the program applies (i.e., diphtheria, tetanus, pertussis, Hib infection, poliomyelitis, measles, mumps, rubella, hepatitis A, hepatitis B, IPD, varicella, rotavirus infection, meningococcal disease, HPV infection, and influenza).

Vaccination in Special Situations

Infants Who Weigh Less Than 2000 Grams

Studies show that infants with birth weights of <2000 g may have a diminished response after administration of HBV vaccine at birth.[78] However, by 1 month chronologic age, all preterm infants, regardless of gestational age or weight at birth, are as likely to respond as older and larger infants.[22,57] Preterm infants born to hepatitis B surface antigen (HBsAg)–positive mothers and mothers with unknown HBsAg status should receive immunoprophylaxis with HBV vaccine and hepatitis B immunoglobulin (HBIG) within 12 hours of birth. If these infants weigh <2000 g at birth, the initial vaccine dose should not be counted toward completion of the HBV vaccine series, and 3 additional doses of vaccine should be administered, beginning when the infant is 1 month of age. Preterm infants weighing <2000 g and born to HBsAg-negative mothers should receive the first dose of the HBV vaccine series at 1 month of postnatal age (if medically stable) or at hospital discharge if the infant is younger than 1 month of age at discharge.

Pregnant Women

Risk of vaccination during pregnancy is largely theoretical. The benefit of vaccinating a pregnant woman outweighs the risk when the risk for disease exposure is high, infection may harm the mother or infant, and the vaccine is unlikely to cause harm. Tdap and influenza vaccines are indicated for all pregnant women. One randomized controlled trial conducted in Bangladesh that provided IIV to pregnant women during the third trimester demonstrated that infants born to vaccinated women had a 63% reduction in laboratory-confirmed influenza illness during the first 6 months of life, compared with pregnant women receiving 23-valent pneumococcal polysaccharide vaccine.[80] Maternal influenza vaccination during pregnancy was associated with significantly reduced risk for influenza virus infection (relative risk, 0.59; 95% confidence interval [CI], 0.37–0.93) and hospitalization for influenza-like illness (relative risk, 0.61; 95% CI, 0.45–0.84) among infants <6 months old in a nonrandomized prospective cohort study.[81] Women's healthcare providers should provide a maternal Tdap vaccination for every pregnant women during each pregnancy. Studies have demonstrated no statistically significant differences in rates of medically attended acute adverse events or adverse birth outcomes in pregnant women related to timing since previous tetanus-containing vaccination.[82,83] To maximize the maternal antibody response and passive antibody transfer to the infant, optimal timing for Tdap administration is early during the period of gestational weeks 27 through 36, regardless of time since prior Td or Tdap vaccination. For women not previously vaccinated with Tdap, if Tdap is not administered during pregnancy, Tdap should be administered immediately post partum.[84] Hepatitis B, hepatitis A, meningococcal, and pneumococcal vaccines can be given to pregnant women at high risk for these diseases.

The greatest concerns have been raised about live vaccines. MMR vaccine is contraindicated in pregnant women on theoretical grounds; however, because no case of congenital rubella syndrome has been reported after MMR vaccination among susceptible women exposed to rubella virus through MMR vaccine, inadvertent vaccination is not a reason to interrupt pregnancy. Varicella-containing vaccines also are contraindicated in pregnant women because of the theoretical risk that they can cause birth defects. Although the manufacturer's pregnancy registry closed in 2013, reporting of inadvertent immunization with a varicella-containing vaccine during pregnancy is encouraged.[85] Merck (Kenilworth, NJ) will continue to monitor pregnancy outcomes after inadvertent exposures to varicella-zoster virus–containing vaccines during pregnancy or within 3 months before conception. The CDC and FDA will continue to monitor adverse events after vaccination with varicella-zoster virus–containing vaccines through the VAERS. New cases of exposure immediately before or during pregnancy or other adverse events after vaccination with varicella-containing vaccines, should be reported to Merck (telephone: 877-888-4231) and to the VAERS (https://vaers.hhs.gov/index). Pregnancy in a household member is not a reason to postpone vaccination of other family members. In fact, vaccination of family members can be the best way to protect a pregnant mother from being exposed to natural infection. Breastfeeding does not adversely affect the responses to live or killed vaccines; breastfed infants should be vaccinated according to the recommended childhood and adolescent immunization schedule.[8]

Immunocompromised People

People with altered immunocompetence require special considerations for vaccination because they can be at increased risk for serious adverse consequences of disease or vaccination or poor response to vaccination.[22,28,57,86,87] The safety and efficacy of vaccines in people with immunodeficiencies are determined by the nature and degree of immunosuppression. Immunodeficiency conditions can be grouped into primary and secondary (acquired) disorders. Primary disorders of the immune system generally are inherited as single-gene disorders, can involve any part of the immune system, and share the common feature of susceptibility to infection with various organisms, depending on the specific deficiency. Categories of immunocompromised people with acquired immunodeficiency disorders include people with the following conditions: human immunodeficiency virus (HIV) infection; hematopoietic or solid-organ transplants; malignant diseases; immunosuppression resulting from administration of chemotherapy, systemic corticosteroids, radiation, monoclonal antibodies, or other drugs with significant side effects; and other chronic conditions, including splenectomy. People in these categories can be vaccinated safely with killed vaccines, which usually are recommended in the same doses and on the same schedules as for immunocompetent people. Response to both killed and live vaccines can be suboptimal, and higher doses or additional doses may be needed to ensure protection. Live vaccines generally are not recommended for any of these groups because of known or theoretical risks of disseminated infection resulting from the vaccine. Exceptions are MMR and varicella vaccines, which are either recommended or can be considered for susceptible people with HIV infection with $CD4^+$ T-lymphocyte counts ≥15% expected for age and no or mild symptoms of disease.[22,57,86,87] Table 6.4 shows recommendations for immunization of children and adolescents with primary and secondary immunodeficiencies.

TABLE 6.4

Vaccination of Children and Adolescents With Primary and Secondary Immunodeficiencies

Type of	Specific	Contraindicated	Risk-Specific	Effectiver

Type of Immunodeficiency	Specific Immunodeficiency	Contraindicated Vaccines[a]	Recommended Vaccines[a]	Effectiver Comment
PRIMARY				
B-lymphocyte (humoral)	Severe antibody deficiencies (e.g., X-linked agammaglobulinemia and common variable immunodeficiency)	OPV[b] Smallpox LAIV BCG Ty21a (live typhoid) Yellow fever Measles Mumps Rubella Varicella	Pneumococcal	The effect any vacci uncertain depends humoral (e.g., PPS MPSV4) IGIV inter the immu to measles and possi vaccine
	Less severe antibody deficiencies (e.g., selective IgA deficiency and IgG subclass deficiency)	OPV[b] BCG Yellow fever Other live vaccines appear to be safe	Pneumococcal Hib (if unimmunized)[c]	All vaccin effective; response attenuate
T-lymphocyte (cell-mediated and humoral)	Complete defects (e.g., SCID disease, complete DiGeorge syndrome)	All live vaccines[d,e,f]	Pneumococcal	Vaccines ineffective
	Partial defects (e.g., most patients with DiGeorge syndrome, Wiskott-Aldrich syndrome, ataxia-telangiectasia)	All live vaccines[d,e,f,g]	Pneumococcal Hib (if not administered in infancy)	Effectiven vaccine d degree of immunos
Complement	Persistent complement, properdin, or factor B deficiency	None	Pneumococcal Meningococcal conjugate ACWY, and B vaccines Hib (if unimmunized)[c]	All routin likely effe
Phagocytic function	Chronic granulomatous disease, leukocyte adhesion defect, and myeloperoxidase deficiency	Live bacterial vaccines[d]	Pneumococcal[h]	All inacti vaccines s likely effe Live viral likely safe effective
SECONDARY	HIVc/AIDS	OPV[b] Smallpox BCG LAIV Meningococcal conjugate ACWY Withhold MMR and varicella in severely immunocompromised persons Yellow fever vaccine may have a contraindication or a precaution depending on clinical parameters	Pneumococcal Hib (if unimmunized[c])	MMR, va rotavirus, inactivate including effective[i]

		of immune function		
	Malignant neoplasm, transplantation, immunosuppressive or radiation therapy	Live viral and bacterial, depending on immune status[d,e]	Pneumococcal Hib	Effectiven vaccine d degree of immunos
	Asplenia	LAIV	Pneumococcal Meningococcal conjugate ACWY, and B vaccines Hib (if unimmunized[c])	All routin likely effe
	Chronic renal disease	LAIV	Pneumococcal Hepatitis B[j]	All routin likely effe
	After allogeneic or autologous hematopoietic stem cell transplantation	LAIV Rotavirus	IIV Pneumococcal Hib	All other recomme inactivate should be administe Rubin LG Ljungmar 2013 IDS practice g vaccinatic immunoc host. Clin 2014;58:e4 detailed s

[a] Other vaccines that are universally or routinely recommended should be given if not contraindicated.

[b] OPV is no longer available in the United States.

[c] Children who have not received a primary series and booster dose or at least 1 dose of Hib vaccine after 14 months of age are considered unimmunized.

[d] Live bacterial vaccines: BCG and oral Ty21a *Salmonella typhi* vaccine.

[e] Live viral vaccines: MMR, MMRV, OPV, LAIV, yellow fever, zoster, rotavirus, varicella, and vaccinia (smallpox). Smallpox vaccine is not recommended for children or the general public.

[f] Regarding T-lymphocyte immunodeficiency as a contraindication for rotavirus vaccine, data exist only for SCID.

[g] Children with partial DiGeorge syndrome should undergo immune system assessment of lymphocyte subsets and mitogen responsiveness to determine whether they should be given live viral vaccines. Those with ≥500 CD3 T lymphocytes/mm^3, ≥200 CD8 T lymphocytes/mm^3, and normal mitogen response should receive MMR and varicella vaccines.

[h] Pneumococcal vaccine is not indicated for children with chronic granulomatous disease beyond age-based universal recommendations for PCV. Children with chronic granulomatous disease are not at increased risk for pneumococcal disease.

[i] HIV-infected children should receive IG after exposure to measles and can receive varicella and measles vaccine if CD4$^+$ T-lymphocyte count is ≥15%.

[j] Indicated based on the risk from dialysis-based bloodborne transmission.

[j] Indicated based on the risk from dialysis-based bloodborne transmission.

[k] Symptomatic HIV infection or CD4$^+$ T-lymphocyte count of <200/mm^3 or <15% of total lymphocytes for children <6 years of age is a contraindication to yellow fever vaccine administration. Asymptomatic HIV infection with CD4$^+$ T-lymphocyte count of 200 to 499/mm^3 for persons ≥6 years of age or 15% to 24% of total lymphocytes for children <6 years old is a precaution for yellow fever vaccine administration. Details of yellow fever vaccine recommendations are available from the Centers for Disease Control and Prevention.[226]

AIDS, acquired immunodeficiency syndrome; BCG, bacille Calmette-Guérin; Hib, *Haemophilus influenzae* type b; HIV, human immunodeficiency virus; IG, immunoglobulin; IgA, immunoglobulin A; IgG, immunoglobulin G; IGIV, immune globulin intravenous; IIV, inactivated influenza vaccine; LAIV, live, attenuated influenza vaccine; MMR, measles, mumps, and rubella; MPSV4, quadrivalent meningococcal polysaccharide vaccine; OPV, oral poliovirus vaccine (live); PCV, pneumococcal conjugate vaccine; PPSV, pneumococcal polysaccharide vaccine; SCID, severe combined immunodeficiency.

Data from Centers for Disease Control and Prevention. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2011;60:2; and Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014;58:e44–e100.

International Travelers

International travelers frequently have increased risk of exposure to vaccine-preventable diseases, even in economically developed countries. Parents and physicians of children and adolescents planning international travel should ensure that all routine childhood and adolescent immunizations are up to date and that adults are up to date on their immunizations. Infants ≥6 months of age should be given MMR vaccine. The need for other vaccines should be determined through consultation with specific guidelines for travelers.[88] Additional information for international travelers can be found on the CDC website at www.cdc.gov/travel or the World Health Organization (WHO) website at www.who.int/ith/en.

Immigrants

The immunization status of all children emigrating from other countries should be reviewed on entry of these children into the US, and necessary vaccinations should be administered. Since 1996, the Immigration and Naturalization Act has required that people seeking permanent US residency show proof of having received the immunizations that are documented on an immunization record generally can be presumed to have been effective. Doses that are consistent in initial timing and intervals with US recommendations can be considered acceptable, and only doses required to comply with US recommendations for age need be given.[8] If a child has no immunization record, the immunization series should be initiated; the most significant risk of serious reaction may be to the tetanus component of DTP or DTaP, for which immunization in the presence of high levels of antibody resulting from previous undocumented immunization can cause serious local Arthus-type reactions.[57]

International Adoptees

Studies have shown that immunization records for international adoptees from some areas (e.g., Eastern Europe, the former Soviet Union, and China), especially children from orphanages, may not accurately reflect protection because of inaccurate or unreliable records, lack of vaccine potency, poor nutritional status, or other problems. For any international adoptee, if a question exists about whether vaccines were administered or were immunogenic, the best course is to administer all vaccines recommended by age. If avoiding unnecessary injections is desired, the judicious use of serologic testing can help to determine which injections can be avoided (see Chapter 4).

Other Programmatic Issues

Responsibility for ensuring that children and adolescents are immunized adequately lies with parents and primary care providers. For children and adolescents without primary healthcare providers, public and hospital-based clinics provide immunizations through federal- and state-funded programs. Each child's immunization status should be assessed every time the child is seen for healthcare, whether for preventive care or curative treatment. Physicians should ensure that each child has an immunization record and that the record is updated each time an immunization is given.[89] Parents should be encouraged to bring the immunization record for each healthcare visit. Immunization information systems (i.e., immunization registries) are intended to compile and make record for each healthcare visit. Immunization information systems (i.e., immunization registries) are intended to compile and make available to all providers the immunization records of all children in a city or state. These registries will provide a system whereby reminders about impending or missed immunizations can be generated and providers can gain access to a reliable record for mobile children.[90]

Clinical Practice Guidelines for Child and Adolescent Immunization

The Infectious Diseases Society of America (IDSA) developed specific guidelines for child and adolescent immunization practices to help providers maintain practices that optimize the immunization status of children and adults.[89] These are guidelines for appropriate clinical practices, including identification of appropriate contraindications to immunization (www.cdc.gov/vaccines/hcp/admin/contraindications-vacc.html), use of tracking systems, and avoidance of missed opportunities. The Task Force for Community Preventive Services extensively reviewed the scientific literature regarding best practices to improve immunization of young children.[91–94] The most effective and most strongly recommended interventions are divided into the following categories: (1) interventions that increase community demand for vaccines (client reminder-recall systems, education, and vaccination requirements for school, childcare, and college attendance); (2) interventions that enhance access to vaccination services (reducing out-of-pocket costs for vaccination and expanding access in medical or public health settings); and (3) interventions that use provider-based interventions (reminder-recall and assessment and feedback for vaccine providers). Conducting audits of patients' immunization records in both public clinics and private providers' offices is recommended to educate providers about the immunization status of patients, as well as to identify practices that can be changed to improve immunization coverage. Routine use of audits in public clinics has reduced missed opportunities for immunization and markedly improved immunization coverage. Self-assessment methods are available from the CDC and AAP.

immunization programs. The National Childhood Vaccine Injury Act mandated that parents should be provided with written materials for vaccines covered by the Vaccine Injury Compensation Program that describe the diseases that vaccines are intended to prevent, the risks and benefits of the vaccines, and the procedure for reporting adverse events and seeking compensation for vaccine-related injury.[31] Vaccine information statements are available at http://www.cdc.gov/vaccines/hcp/vis/index.html.

Vaccine Shortages

In addition to the rising cost of vaccines, unparalleled numbers of vaccine shortages in the US have had a substantial impact on vaccine delivery. From 2000 through 2010, vaccine shortages, vaccine supply issues, and changes in routine recommendations occurred for almost all vaccines in the childhood and adolescent immunization schedule.[95–102] The shortages affected millions of children and their healthcare providers and even triggered suspension of school entry requirements for vaccines.[102–104]

The causes of these widespread vaccine shortages are multifactorial, but an important factor is the decrease in the number of manufacturers of childhood vaccines. In 1993, 6 manufacturers produced the 6 vaccines. Currently, although several vaccines (PCV13, varicella, influenza, Tdap, rotavirus, MMRV, hepatitis A, herpes zoster, MCV, and HPV) have been added to the recommended schedules, the number of manufacturers has increased to only 8. In addition, many of the childhood and adolescent vaccines (MMR, MMRV, varicella, and PCV13) have a single manufacturer. In response to concerns over the fragility of the US vaccine supply, the General Accounting Office and National Vaccine Advisory Committee both conducted in-depth reviews of the vaccine shortages, concluded that future disruptions in vaccine supply are likely to continue, and proposed several solutions.[95,105] The current status of vaccine shortages in the US can be found at www.cdc.gov/vaccines/hcp/clinical-resources/shortages.html.

Handling and Storage of Vaccines

Vaccines are perishable products that require specific care in

Vaccines are perishable products that require specific care in handling and storage; ensuring that a vaccine maintains potency and safety is a responsibility shared by the manufacturer and all people handling the vaccine. Live, attenuated vaccines are more susceptible to degradation when exposed to temperature extremes, and inactivated vaccines (particularly those containing adjuvants) and toxoids must be protected from freezing to ensure potency.[22] Vaccines that are exposed to damaging environmental conditions can suffer loss of potency without a change in appearance. A vaccine quality control program should be established in each clinical practice and should focus on education of personnel, maintenance of equipment, and adherence to established daily monitoring of vaccines.[31] Recommendations and materials about vaccine storage and handling can be accessed at www.cdc.gov/vaccines/hcp/admin/storage/index.html.

Vaccine Financing

Ensuring that all children and adolescents, regardless of health insurance status or income level, have access to recommended vaccines requires a complex system of financing that includes private and public funding mechanisms (Table 6.5). In 2013, 53% of US children received vaccines purchased through the public sector, and 47% received vaccines purchased through the private sector. Most of the public-purchase vaccines are financed through the Vaccines for Children (VFC) program, an entitlement program established in 1994 as part of the Social Security Act.[31] Other government funding mechanisms include federally purchased vaccines through the discretionary Immunization Program, authorized under Section 317 of the Public Health Service Act of 1962, and state and local government funding. These programs support states to provide immunizations to children and adults who do not qualify for the VFC program but who are not covered by private insurance. Several states use a combination of federal and state funding to purchase and distribute vaccines recommended for children to all immunization providers in private and public sectors. Insurance programs provide vaccines for children in the private sector. The Affordable Care Act requires insurers to cover ACIP-recommended vaccines at in-network (http://www.hhs.gov/healthcare/facts-and-features/fact-sheets/aca-and-immunization/index.html). Thus, all children with insurance should not have financial barriers to access if they seek vaccinations at in-network providers.

TABLE 6.5

Major Financing Programs for Childhood Immunization

Variable	Vaccines for Children Program	Section 317 Immunization Grant Program	State/Local Government	Private Insurance
Financing source	Entitlement funded through Medicaid trust fund	Annual discretionary appropriation by Congress	Appropriations through state or local legislatures	Employer-based insurance
Eligibility	Age <19 years and membership in ≥1 of the following categories: Medicaid-eligible; uninsured; Alaska Native or American Indian; or underinsured at a federally qualified health center or rural health clinic	No federal eligibility restrictions	Varies by state or local area	Persons covered by private insurance, including Employee Retirement Income Security Act (ERISA) plans
Financing of new vaccines and recommendations	Vote of ACIP and establishment of a federal contract; funds are approved by the Office of Management and Budget	Funding appropriated by Congress annually	Funding must be sought from state legislatures	As of September 2010, new health plans must cover ACIP-recommended vaccines with no copay or deductible when provided by an in-network provider
Proportion of childhood vaccine market purchased	46%	4%	3%	47%

ACIP, Advisory Committee on Immunization Practices.

Surveillance for Vaccine-Preventable Diseases

Surveillance for vaccine-preventable diseases is mandated by each

Surveillance for vaccine-preventable diseases is mandated by each state, and data are compiled in the CDC National Notifiable Disease Surveillance System and available at www.cdc.gov/mmwr.[106] These data are monitored to assess the effectiveness of vaccines and vaccination programs. For each reported case of disease, confirmation of disease by laboratory testing and documentation of the patient's vaccination status are critical to determining whether continued occurrence of disease is the result of failure to deliver vaccine or failure of vaccine. As programs approach elimination of indigenous transmission, determining chains of disease transmission, as well as whether the case is indigenous or imported, and rapid implementation of control measures also become critical. All physicians are urged to report all suspected cases of vaccine-preventable diseases promptly to their local and state health departments.

Routine Childhood and Adolescent Vaccines

Diphtheria and Tetanus Toxoids and Pertussis Vaccines

In 1980, cutaneous diphtheria was no longer a nationally notifiable disease in the US. Between 1980 and 2014, 57 cases of respiratory tract diphtheria were reported.[107,108] From 2001 through 2014, 397 cases of tetanus were reported in the US, with a peak of 41 cases in 2006.[36,108] Since 2003, the number of reported cases of pertussis has increased each year through 2012, with a peak of 48,277 cases in 2012.[109] More than 28,000 cases were reported in each of 2013 and 2014, and 18,166 were reported in 2015.[109] Changes in pertussis vaccine recommendations for the newer Tdap vaccine were published between 2010 and 2012.[84,110,111] Although infants have the highest incidence of pertussis and morbidity associated with pertussis, adolescents and adults account for the majority of reported cases.[112]

Immunization of children and adolescents to prevent diphtheria, tetanus, and pertussis usually is completed with a vaccine composed of diphtheria and tetanus toxoids combined with an acellular pertussis component.[110,113–115] Diphtheria and tetanus toxoids are purified preparations of formalin-inactivated diphtheria and tetanus toxins, respectively. Table 6.6 shows the composition and recommended use of vaccines with tetanus toxoid, diphtheria toxoid, and acellular pertussis components licensed in the US for children <7 years of age and people ≥7 years of age. Whole cell DTP was the only pertussis vaccine available from 1948 through 1992; because of its relatively high rate of adverse reactions compared with the newer acellular pertussis vaccines, DTP is no longer used in the US.[113] Whole cell DTP continues to be the most frequently used pertussis-containing vaccine worldwide.

TABLE 6.6

Composition of Selected Vaccines With Tetanus Toxoid, Diphtheria Toxoid, and Acellular Pertussis Components Licensed

in the United States, 2015

Vaccines for Children <7 Yr of Age	**Trade Name**	**PT (µg/dose)**	**FHA (µg/dose)**	**PRN (µg/dose)**	**FIM (µg/dose)**	**Recommended Use**
DTaP	Infanrix	25	25	8	—	All 5 doses
DTaP-IPV-HepB	Pediarix	25	25	8	—	First 3 doses
DTaP	Daptacel	10	5	3	5	All 5 doses
DTaP-IPV/Hib	Pentacel	20	20	3	5	First 4 doses
DTaP-IPV	Kinrix	25	25	8	—	Fifth dose only
DTaP-IPV	Quadracel	20	20	3	5	Fifth dose only
DT	No trade name	—	—	—	—	Use instead of DTaP if pertussis contraindicated
Vaccines for People ≥7 Yr of Age						
Tdap	Boostrix	8	8	2.5	—	Single dose indicated for people 10 yr of age and older
Tdap	Adacel	2.5	5	3	5	Single dose indicated for people 11–64 yr of age
Td	Several	—	—	—	—	Every 10 yr

DT, diphtheria and tetanus toxoids; DTaP, diphtheria and tetanus toxoids and acellular pertussis for use <7 years of age; FHA, filamentous hemagglutinin antigen; FIM, fimbriae; HepB, hepatitis B; IPV, inactivated poliovirus vaccine; PRN, pertactin; PT, pertussis toxoid, Td, tetanus and diphtheria toxoids for use ≥7 years of age; Tdap, tetanus toxoid, and reduced diphtheria toxoid, and acellular pertussis vaccine for use in adolescents.

Recommendations for DTaP Immunization for Children Younger Than 7 Years of Age

Immunization with DTaP vaccine is recommended for all children <7 years of age. Primary vaccination consists of 3 doses of DTaP vaccine given at 2, 4, and 6 months of age; the minimal age for initiating vaccination is 6 weeks, and the minimal interval between doses is 4 weeks (see Fig. 6.2).[113–115] To ensure protection, a reinforcing dose of DTaP is given at 15 to 18 months of age and at school entry (4 through 6 years of age). Diphtheria and tetanus (DT) toxoids are used in children for whom pertussis vaccination is contraindicated. If the schedule is interrupted, the series does not need to be restarted.

The vaccination advisory bodies consider data insufficient to support expression of a preference among the different acellular pertussis vaccines.[113] Whenever feasible, the same brand of DTaP vaccine should be used for all doses of the primary vaccination series (3 doses on a standard schedule), although data suggest that the 2 available preparations can be used interchangeably for the first 3 doses of the series.[62] If the provider does not know or does not have available the type of DTaP vaccine previously administered, any of the DTaP vaccines can be used to complete the series. DTaP vaccines can be given simultaneously with other recommended childhood vaccines (HBV, Hib, IPV or OPV, PCV13, rotavirus) at 2, 4, and 6 months of age, and they can be given with these vaccines as well as with MMR, varicella, and HAV vaccines at 15 through 18 months of age. DTaP is not licensed for use in adults or in children ≥7 years of age. Vaccination to prevent diphtheria and tetanus is recommended for previously unvaccinated children (≥7 years of age and in whom pertussis vaccine is contraindicated) and adults. Children 7 through 10 years of age who are not fully immunized with DTaP against pertussis should receive a single dose of Tdap.[8,110]

Immunity often wanes in the few years following vaccination with acellular pertussis vaccines.[116,117] Thus clinicians should suspect pertussis in persons with clinically compatible symptoms. At present, no recommendations for additional boosters with Tdap exist for the general population with the exception of pregnant women, for whom Tdap is recommended during each pregnancy.

Use of tetanus toxoid–containing preparations, with or without tetanus immunoglobulin, can be indicated after penetrating or other types of injuries in people who are not adequately vaccinated.[115] For any such person who has not previously received the 3-dose primary series, initiation or continuation of the primary vaccination appropriate for age (DTaP, Tdap, DT, or Td) is recommended after any wound. Vaccination is not necessary in people who have received 3 previous doses of tetanus vaccine, except in the following circumstances: (1) the last vaccination occurred more than 10 years previously (5 years for wounds, other than clean and minor wounds); or (2) only 3 doses of fluid (nonadjuvant) tetanus toxoid were received, in which case 1 dose of Td vaccine should be given (see Chapter 188).[115]

Precautions and Contraindications.

Vaccination with any pertussis-containing vaccine is contraindicated in any child who has had an anaphylactic reaction to any component of the vaccine or has experienced acute encephalopathy not attributable to another identifiable cause within 7 days of administration of a previous dose.[113] The following events are considered precautions to pertussis immunization: (1) temperature ≥40.5°C within 48 hours of a previous dose not attributed to another cause; (2) collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of DTP or DTaP administration; (3) persistent, inconsolable crying (≥3 hours) within 48 hours of administration of DTP or DTaP; and (4) convulsions with or without fever within 3 days of immunization. When these events occur, the physician can elect to continue vaccination if the benefits are judged to outweigh the risks, such as when a pertussis outbreak is occurring in the community. DTaP immunization should be deferred in children with evolving neurologic disorders until the situation is clarified; when the condition is stable, the child should be given DTaP vaccine. Decisions about pertussis vaccination of such children should be made before the first birthday. If pertussis vaccine is not used, pediatric DT should be administered.

Recommendations for Tdap Immunization for Adolescents 11 Through 18 Years of Age

Adolescents 11 through 18 years of age should receive a single dose of Tdap instead of Td for booster immunization against tetanus, diphtheria, and pertussis if they have completed the recommended childhood DTP/DTaP vaccination series and have not received Tdap.[8] The preferred age for Tdap vaccination is 11 to 12 years of age (see Fig. 6.2).

Adolescents 11 through 18 years of age who received Td, but not Tdap, are encouraged to receive a single dose of Tdap to provide protection against pertussis if they have completed the recommended childhood DTP/DTaP vaccination series.[84,110] If more doses of tetanus and diphtheria toxoids are needed to complete the primary series (after 1 dose of Tdap) in such older children, Td should be used.

Contraindications, Precautions, and Reasons to Defer Tdap

or Td Among Adolescents 11 Through 18 Years of Age.

Contraindications to Tdap include a history of serious allergic reaction (i.e., anaphylaxis) to vaccine components or encephalopathy (e.g., coma or prolonged seizures) not attributable to an identifiable cause within 7 days of administration of a vaccine with pertussis components. This is a contraindication to use of the pertussis components; Td can be used.

Precautions and reasons to defer Tdap include the following: GBS occurring <6 weeks after a previous dose of a tetanus toxoid–containing vaccine; progressive neurologic disorder, including progressive encephalopathy, or uncontrolled epilepsy, until the condition has stabilized (these conditions are precautions for the pertussis components; Td can be used); moderate or severe acute illness; and history of an Arthus reaction after a tetanus toxoid–containing or diphtheria toxoid–containing vaccine administered <10 years previously.

Special Situations for Tdap (Single-Dose) and Td Use Among Adolescents 11 Through 18 Years of Age.

If simultaneous vaccination is not feasible, inactivated vaccines can be administered at any time before or after a different inactivated or live vaccine. The ACIP recommends that Tdap (or Td) and MCV4 vaccines (which all contain diphtheria toxoid) can be administered using any sequence and timing.[8,39,110] The following situations for administration of Tdap should be considered:

- Use of Td when Tdap is not available. When Tdap is indicated but not available, vaccine providers should administer Td if the last pediatric DTP, DTaP, DT, or Td dose was >10 years earlier, to provide protection against tetanus and diphtheria.
- Tetanus prophylaxis in wound management. Adolescents who require a tetanus toxoid–containing vaccine as part of wound management should receive a single dose of Tdap instead of Td if they previously have not received Tdap; if Tdap is not available or previously was administered, adolescents who need a tetanus toxoid–containing vaccine should receive Td, and if Td is not available, adolescents who previously received Tdap should receive Tdap.
- History of pertussis. Adolescents who have a history of pertussis

generally should receive Tdap according to the routine recommendations.

- No history of pertussis vaccination. Adolescents who have not received vaccines with pertussis components but who have completed the recommended tetanus and diphtheria vaccination series with pediatric DT or Td should generally receive Tdap according to the routine recommendations if they do not have a contraindication to the pertussis components.
- No history of pediatric DTP/DTaP or Td/Tdap vaccination. Adolescents who have never received tetanus-diphtheria-pertussis vaccination should receive a series of 3 vaccinations. The preferred schedule is a single Tdap dose, followed by a dose of Td ≥4 weeks after the Tdap dose and a second dose of Td 6 to 12 months after the earlier Td dose. Tdap can be substituted for any 1 of the 3 Td doses in the series.
- Use of Td and Tdap in pregnant adolescents. See the earlier section on pregnant women. Manufacturers of Boostrix (GlaxoSmithKline Biologicals, Philadelphia; telephone: 888-825-5249), and Adacel (Sanofi Pasteur; telephone: 800-822-2463) maintain pregnancy registries for Tdap as required by the FDA at licensure. Providers can report Tdap administrations to the appropriate manufacturer.[39,84]

Haemophilus influenzae Type b Conjugate Vaccines

Before introduction of conjugated Hib vaccines in 1987, the incidence of invasive Hib diseases among children <5 years of age was estimated to be 1 cases in 1000. In 2014, 472 cases of invasive disease caused by *H. influenzae* were reported in children <5 years of age; of these cases, 9% were type b, and 92% were of unknown serotype.[36,108] In 2015, 23 cases of *H. influenzae* type b disease were reported.[117a]

Hib conjugate vaccines, first licensed for 18-month-old children in 1987 and for infants 2 months of age and older in 1990, have replaced the polysaccharide vaccines available from 1985 to 1989.[118] Hib conjugate vaccines contain Hib polysaccharide covalently linked with a protein carrier, which induces a T-lymphocyte–

dependent immune response and immune memory not induced by polysaccharide (polyribosylribitol phosphate [PRP]) vaccine alone. The carrier protein for the vaccines licensed for infants is either tetanus toxoid (PRP-T) or the outer membrane protein (OMP) of *Neisseria meningitidis* (PRP-OMP). Two combination vaccines containing either PRP-OMP or PRP-T are available.

When given as a 2-dose (PRP-OMP) or 3-dose (PRP-T) primary series to infants, Hib vaccine induces a high level of antibody to Hib polysaccharide that wanes over the next 6 through 15 months; a booster dose is therefore needed at 12 through 15 months of age. PRP-OMP induces a substantial response after a single dose and may be preferred for populations at highest risk of infant infection (Native Americans, including Alaska Natives); PRP-T vaccines require 3 doses for optimal response in infants.[118] Controlled trials showed 93% to 100% efficacy for PRP-OMP in infants in the US; licensing of PRP-T was based on comparable immunogenicity and 95% efficacy data from a British trial.[118] Several studies have shown that giving different Hib vaccines during the primary series induces a response similar to that induced by a primary series with the same vaccine and that booster doses with different vaccines induce strong responses.[61,118]

Recommendations for Immunization

Hib vaccination is recommended for all infants, starting at 6 weeks to 2 months of age (see Fig. 6.2).[8,57,86,118] For PRP-T, the primary series consists of 3 doses and should be administered at 2, 4, and 6 months of age. The primary series with PRP-OMP consists of 2 doses and should be administered at 2 and 4 months of age; a dose at age 6 months is not indicated. One booster dose (dose 3 or 4, depending on the vaccine used in the primary series) of any Hib vaccine should be administered at age 12 through 15 months. When primary immunization is delayed, the number of doses is reduced; for children vaccinated beginning at 7 through 11 months of age, 2 primary doses are recommended with a 1-month interval, followed by a booster at 12 through 15 months of age, at least 2 months after the second dose. If vaccination is initiated at 12 through 14 months of age, 2 doses with an 8-week interval are indicated. For initiation of vaccination in children 15 through 59 months of age, a single dose of any of the licensed vaccines is recommended. Although the primary series ideally should be completed with the same vaccine, 3 doses of any vaccine are recommended if the initial vaccine is not available or is unknown. Booster doses can consist of any of the licensed vaccines. Hib vaccines can be given simultaneously with all other childhood vaccines, including DTaP, IPV or OPV, hepatitis B, PCV13, MMR, varicella, hepatitis A, and rotavirus vaccines.[118]

Children considered at high-risk for Hib disease include the following: children with sickle cell disease, splenectomy, HIV infection, immunoglobulin deficiency (including immunoglobulin G_2 subclass deficiency), or early component complement deficiency; recipients of a hematopoietic stem cell transplant; and those receiving chemotherapy or radiation therapy for malignant neoplasms; these children may need additional doses of Hib vaccine, but the vaccine may not be as highly immunogenic as in healthy children.[23,57,86,118] Hematopoietic stem cell transplant recipients should be revaccinated with a 3-dose regimen of Hib vaccine starting 6 to 12 months after successful cell transplantation, regardless of vaccination history; doses should be administered at least 4 weeks apart.[28,118] Children 12 through 59 months of age who have received either no doses or only 1 dose of Hib vaccine before 12 months of age should receive 2 additional doses of Hib vaccine 8 weeks apart; children who received 2 or more doses of Hib vaccine before 12 months of age should receive 1 additional dose. For children <5 years of age undergoing chemotherapy or radiation treatment who received Hib vaccine within 14 days of starting therapy or during therapy, repeat the dose or doses at least 3 months following therapy completion. A single dose of any Hib-containing vaccine should be administered to unimmunized (has not received a primary series and booster dose or at least 1 dose of Hib vaccine after 14 months of age) children and adolescents 15 months of age and older who are undergoing elective splenectomy; if possible, vaccine should be administered at least 14 days before the procedure. Unimmunized children aged 5 years old or older who have anatomic or functional asplenia (including sickle cell disease) and unvaccinated children 5 through 18 years of age with HIV infection should receive a single dose of any Hib-containing vaccine.[28,118]

Immunization is indicated in children with previous Hib disease during the first 2 years of life, in whom adequate immunity may not develop after infection, but it is not necessary in older children who have had Hib disease. These children should receive primary vaccination or revaccination with a second primary series beginning 4 weeks after the onset of disease.

Contraindications and Precautions

The only known common adverse events following administration of Hib vaccines are fever and local reactions, observed in <4% of recipients; serious reactions are uncommon.[119] The only contraindication to Hib vaccine is an anaphylactic reaction to a previous dose of the same vaccine.

Hepatitis B Vaccine

Between 2000 and 2014, the number of acute hepatitis B cases reported annually declined by 67%.[108,120] This steady decline coincides with implementation of a national strategy to eliminate transmission of HBV. The primary elements of this strategy are as follows: (1) screening of all pregnant women for HBV infection with the provision of postexposure prophylaxis to infants born to infected women; (2) routine vaccination of all infants and children <19 years of age; and (3) vaccination of others at increased risk for hepatitis B, including healthcare personnel (HCP), men who have sex with men, injection drug users, household and sexual contacts of people with chronic HBV infection, and adults with diabetes.[38,121–123]

In 2014, the incidence of hepatitis B cases among children and adolescents ≤19 years of age was 0.02 per 100,000 population, representing a 95% decline for that age group from 2000 to 2014.[120] During that time, the disparity between the population with the highest (black, non-Hispanics) and the lowest (whites) incidence has been reduced by approximately 90%. Among adults, 38% of cases occur in people in identified risk groups (i.e., injection drug users, men who have sex with men, and people with multiple sex partners), thus indicating a need to strengthen efforts to reach these populations with this vaccine.[38,120]

Recommendations for Immunization

Hepatitis B vaccine consists of purified HBsAg particles produced through recombinant DNA technology in yeast. Table 6.7 shows vaccine products that contain hepatitis B antigen and that are licensed in the US. This vaccine is usually given as a 3-dose series; doses 2 and 3 are administered 1 and 6 months, respectively, after the first dose. In the United States, monovalent hepatitis B vaccine is recommended as the first dose of the series for all newborns within 24 hours of birth if they are medically stable, born to HBsAg negative mothers, and ≥2000 g. Preterm infants weighing <2000 g and born to HBsAg-negative mothers should receive the first dose of vaccine 1 month after birth or at hospital discharge. Additional detail regarding hepatitis B vaccination of infants born to HBsAg-positive mothers or mothers whose hepatitis B status is unknown can be found in the ACIP hepatitis B recommendation (https://www.cdc.gov/mmwr/PDF/rr/rr5416.pdf). Alternative schedules include the following: 0, 1, 4 months; 0, 2, 4 months; and a schedule that includes 4 doses, with doses 2, 3, and 4 given at 1, 2, and 12 months, respectively, after the first. Schedules that vary the timing of the second and third doses to permit integration into the recommended childhood and adolescent immunization schedule have resulted in high immunogenicity. The final (third or fourth) dose in the hepatitis B series should be administered no earlier than 24 weeks after the first. A 2-dose schedule (second dose given 4 to 6 months after the first) has been approved for adolescents 11 through 15 years of age for a specific hepatitis B vaccine. Dosages vary by age, vaccine, and whether the child is born to an HBsAg-positive mother; dosages for infants and children are half of those required for adults. Minimal intervals between doses should be 1 month between the first 2 doses, and 2 months, but preferably 4 to 6 months or more, between the second and third doses; lapsed immunization does not necessitate restarting the vaccine series.[8] Three products that combine HBV vaccine with other vaccine antigens are licensed for use at various ages (see Table 6.7).

TABLE 6.7

Hepatitis B–Containing Vaccines Licensed in the United States

Vaccine	Antigen Content	Recommended Age Group
Recombivax HB	Hepatitis B	All age groups
Engerix-B	Hepatitis B	All age groups
Comvax[a]	Hepatitis B and Hib conjugate	6 wk–71 months

Pediarix	Hepatitis B + DTaP + IPV	6 wk–6 yr
Twinrix	Hepatitis B + hepatitis A	≥18 yr

[a] No longer manufactured; all doses of Comvax expired by August 19, 2016.

DTaP, diphtheria and tetanus toxoids and acellular pertussis; Hib, *Haemophilus influenzae* type b; IPV, inactivated poliovirus vaccine.

Response to a 3-dose series is excellent in all age groups; this series produces anti-HBV antibodies (anti-HBs) in 85% to 99% of recipients, and response is highest in children 2 through 18 years of age.[38,121] People with immunocompromising conditions, such as renal failure, have a poorer response, and higher doses are recommended. Vaccine efficacy measured in placebo-controlled trials in both high-risk children (infants of HBsAg-positive mothers) and adults has shown a short-term efficacy of 80% to 95%. Long-term follow-up of children and adults has demonstrated protection against serious consequences of infection (chronic carriage and chronic liver disease) in almost all people who show response to the initial series (anti-HBs level of ≥10 mIU/mL), but continued studies are needed. Booster doses of hepatitis B vaccine are not recommended for any age group; however, the need for a booster continues to be evaluated. HBV vaccine can be given simultaneously with all other childhood vaccines.

Contraindications and Precautions

Hepatitis B vaccination is contraindicated for people with a history of hypersensitivity to yeast or to any vaccine component. Despite a theoretical risk for allergic reaction to vaccination in people with allergy to *Saccharomyces cerevisiae* (baker's yeast), no evidence exists for adverse reactions after vaccination of people with a history of yeast allergy.

People with a history of serious adverse events (e.g., anaphylaxis) after receipt of hepatitis B vaccine should not receive additional doses. As with other vaccines, immunization of people with moderate or severe acute illness, with or without fever, should be deferred until the acute phase of the illness resolves. Immunization is not contraindicated in people with a history of multiple sclerosis, GBS, autoimmune disease (e.g., systemic lupus erythematosus or rheumatoid arthritis), or other chronic diseases.[69,70,121] Pregnancy is not a contraindication to vaccination. Limited data indicate no apparent risk for adverse events to developing fetuses when hepatitis B vaccine is administered to pregnant women.

Measles, Mumps, and Rubella Vaccine

Vaccination programs have reduced the incidence of disease caused by measles, mumps, and rubella viruses in the US.[37] Implementation of these strategies has resulted in interruption of measles transmission in the US and an all-time low number of 37 measles cases reported in 2004, 27 of which were imported and resulted in 6 secondary cases.[124] However, measles cases continue to occur in the US as a result of importation and transmission to mostly unvaccinated persons. In 2008, multiple outbreaks of measles occurred in the US, totaling 140 cases.[125] These cases resulted from importation into community clusters with large proportions of unvaccinated persons. Subsequently, in 2011, the US had 220 cases as more than 30 countries in the WHO European Region reported an increase in measles, and France was experiencing a large outbreak. Most of the cases that were brought to the US in 2011 came from France. The US reported 184 cases and 11 outbreaks in 2013.[126] In 2014, the US experienced 628 cases in 23 measles outbreaks, including a large outbreak of 383 cases, occurring primarily among unvaccinated Amish communities in Ohio. This total case count was the highest in the US since 1994. Many of the cases in the US in 2014 were associated with cases brought in from the Philippines, which experienced a large measles outbreak.[125,127] In 2015 the United States reported 189 measles cases, including many from a large, multistate measles outbreak linked to an amusement park in California. The outbreak likely started from a traveler who became infected overseas with measles and then visited the amusement park while infectious; however, no source was identified. Analysis by CDC scientists showed that the measles virus type in this outbreak (B3) was identical to the virus type that caused the large measles outbreak in the Philippines in 2014.[125]

From 1989 through 1991, there was a resurgence of rubella, primarily because of outbreaks among unvaccinated adolescents and young adults who initially were not recommended for vaccination and in religious communities with low rubella vaccination coverage. As a result of the rubella outbreaks, two clusters of approximately 20 CRS cases arose. Outbreaks during the mid-1990s occurred in settings where young adults congregated and involved unvaccinated persons who belonged to specific racial/ethnic groups. Further declines were observed as rubella vaccination efforts increased in other countries in the WHO Region of the Americas. From 2001 through 2004, reported rubella and CRS cases were at an all-time low, with an average of 14 reported rubella cases a year, four CRS cases, and one rubella outbreak (defined as three or more cases linked in time or place).[127a] In 2004, a 9-person independent panel unanimously agreed that rubella is no longer endemic in the US.[40] During 2004 to 2015, 99 cases of rubella and 9 cases of congenital rubella syndrome were reported in the US.[117a,128]

The incidence of reported cases of mumps in the US had been decreasing until 2006, when an outbreak involving several thousand people occurred.[129] Between 229 (in 2011) and 1057 (in 2015) cases of mumps have occurred.[130] Protection against measles, mumps, and rubella is provided by the combined MMR and MMRV vaccines.[8,73] Measles vaccine is a live, attenuated virus vaccine produced from the Moraten strain of measles virus, which was derived from the Edmonston B strain. Mumps vaccine is a live, attenuated vaccine derived from the Jeryl Lynn strain of mumps virus. Rubella vaccine is a live, attenuated vaccine derived from the RA27/3 strain of rubella virus that was grown on human diploid cells. Other rubella strains, with slightly different safety and efficacy profiles, were used in the US before 1979.

Recommendations for Immunization

A single dose of measles vaccine given to children ≥12 months of age induces antibody and produces protection in 95% to 98% of recipients. Protection is long-lasting, and waning of immunity, although documented in several studies, appears to be uncommon and plays a minimal role in measles outbreaks, which occur in the US because of importation and spread to unimmunized people.[73,124–127] Nevertheless, because infrequent vaccine failure with a single dose led to frequent measles outbreaks among schoolchildren, a second dose of MMR vaccine is now recommended for all children. In most studies, the second dose increases measles antibody response to >99%, whether the dose is given within 3 months of the initial dose or years later on a child's entry to primary or middle school. Additionally the booster dose can induce antibody increases in people with low levels of antibody, but the increases appear to be short-lived. Evaluation of actual clinical observational studies of measles vaccine effectiveness showed a median protection level of 93% for 1 dose and 97% after 2 doses.[73]

A single dose of mumps vaccine given at 12 through 15 months of age induces detectable antibodies in 80% to 85% of recipients. Median vaccine effectiveness has been estimated at 78% after 1 dose of vaccine and 88% after 2 doses.[73] Immunity is long-lasting, possibly lifelong, but waning immunity (or possibly primary vaccine failure) has been suggested as a contributing cause in some mumps outbreaks in highly vaccinated school populations. A large mumps outbreak that began in Iowa in December 2005 and spread to several other states prompted a change in recommendations for use of mumps-containing vaccines.[131] In addition to routine immunization, CDC recommends MMR vaccine for people born in 1957 or later who do not have a history of physician-diagnosed mumps infection, laboratory evidence of immunity, or immunity through vaccine, which the ACIP has redefined as 1 dose of mumps vaccine for preschool children and adults not at high risk, and 2 doses for children in kindergarten through 12th grade and adults at high risk (HCP, international travelers, and post high-school students).

During an outbreak, a second dose of mumps vaccine should be considered for all adults and children 1 through 4 years of age who have not received 2 doses; the second dose is given at least 28 days after the first dose. The CDC suggests that unvaccinated HCP born before 1957 who do not have other evidence of immunity also should receive 2 doses of the vaccine during an outbreak.

Currently, data are insufficient to recommend for or against the use of a third dose of MMR vaccine for mumps outbreak control. The CDC has issued guidance for considerations for use of a third dose in specifically identified target populations along with criteria for public health departments to consider for decision making. During mumps outbreaks, public health authorities may administer a third dose of MMR vaccine for specifically identified target populations. Criteria to consider prior to administering a third dose in a target *population for mumps outbreak control include:*

- *High two-dose vaccination coverage (i.e., vaccination coverage >90%)*
- *Intense exposure settings likely to facilitate transmission (e.g., schools, colleges, correctional facilities, congregate living facilities) or healthcare settings;*
- *High attack rates (i.e., >5 cases per 1,000 population); and evidence of ongoing transmission for at least two weeks in the target population (i.e., population with the high attack rates)*

Additional data on the effectiveness and impact of a third dose of MMR vaccine for mumps outbreak control are needed to guide control strategies in future outbreaks.[131a]

Rubella vaccine induces a primary response in 95% to 98% of children vaccinated at 12 months of age or older; protection is long-lasting, with >90% of recipients protected against clinical disease and viremia for >15 years. Median vaccine effectiveness has been estimated at 97% after 1 dose of vaccine.[73] In contrast to mumps and measles, in which vaccine failure has played a role in transmission, rubella vaccine failure has not played an important role in rubella outbreaks.

Vaccination to prevent measles, mumps, and rubella is recommended for all children and adolescents.[8,73] Measles vaccination and now mumps vaccine are recommended in a 2-dose series, given as MMR or MMRV, for all susceptible people. MMRV vaccine is indicated for simultaneous immunization against measles, mumps, rubella, and varicella among children 12 months through 12 years of age; MMRV is not licensed for people outside this age group.[73] For infants and young children, the first dose should be given at 12 through 15 months of age, and the second should be given at 4 through 6 years of age.[73] The timing of the first dose is based on the likelihood that maternal antibody does not persist during the second year of life; in the past, persistence of maternal antibody accounted for lower efficacy when vaccine was given at 12 through 14 months of age. Later studies have shown that younger mothers, who have acquired antibody through vaccination, may transfer less measles antibody to their infants (because vaccine induces lower titers than natural measles infection), who then become susceptible at a younger age.[132] During outbreaks that affect children <1 year of age (and for international travel to areas where measles is endemic), the age of measles vaccination should be lowered to 6 months; children vaccinated before 12 months of age still should be vaccinated with 2 doses of MMR or MMRV at the recommended ages.[73,133]

For dose 1 of the 2-dose MMR series, the risk of febrile seizures is increased in children who received MMRV compared with children who received simultaneous but separate MMR and varicella vaccines. For first dose at ages 12 through 47 months, either MMR and varicella vaccines or MMRV vaccine can be used. However, unless the parent prefers MMRV as a single injection, the CDC recommends that MMR and varicella vaccines should be given separately (but simultaneously) for the first dose. No evidence indicates an increased risk of febrile seizures with MMRV when it is used for dose 2 of the 2-dose series; MMRV is preferred over separate MMR and varicella vaccines for dose 2.[73]

Recommendations for timing of the second dose of MMR are based on (1) the major benefit of the second MMR in reducing the proportion of children who remain susceptible to measles because of failure of the primary vaccine and (2) the ease of implementation by using the preschool immunization visit. All children should be given the second dose of MMR vaccine at school entry if it was not given previously. The ACIP recommends that all children entering school have received 2 doses of MMR after the first birthday.[73] Receipt of 2 doses of MMR vaccine also is recommended for all people entering or enrolled in college; many states now implement prematriculation requirements, which have been shown to reduce the risk of measles outbreaks in these populations.

Rubella vaccination is recommended for all susceptible adults.[73] Adolescents and adults should be considered susceptible to rubella and should be vaccinated unless they have a history of ≥1 dose of vaccine or have serologic evidence of immunity. Ensuring rubella immunity is especially important in women of childbearing age. A clinical history of rubella is not sufficiently reliable. Delivery of rubella vaccine to adults is more successful in programs that do not use prevaccination screening because screening requires a second visit for susceptible people to be vaccinated.

Programs to ensure immunity to measles, mumps, and rubella are recommended for all HCP and for international travelers, who may be exposed to these diseases in countries with less effective control programs.[73] Among people born after 1956, measles immunity should be based on receipt of 2 doses of measles vaccine or serologic evidence of immunity. Acceptable presumptive evidence of immunity to mumps includes 1 of the following: (1) documentation of adequate vaccination; (2) laboratory evidence of immunity; or (3) birth before 1957. Evidence of immunity through documentation of adequate vaccination is now defined as 1 dose of a live mumps virus–containing vaccine for preschool-aged children and adults not at high risk and 2 doses for school-aged children (i.e., grades K through 12) and for adults at high risk (i.e., HCP, international travelers, and students at post–high school educational institutions).

Contraindications and Precautions

Measles, MMR, and MMRV vaccines produce minor reactions, including fever ≥39.4°C in 5% to 15% and transient rash in 15% of recipients. Fever and rash occur between 4 and 14 days after vaccination and last for several days. More serious reactions include febrile convulsions, in 1 in 3000 to 4000 recipients 1 to 2 years of age; the risk is higher in people with a personal or family history of convulsions.[73,134] Thrombocytopenia, which usually is transient, can occur in 1 in 30,000 recipients of MMR vaccine, and anaphylaxis, more rarely.[73] Three published reports of persons with immunodeficiencies described measles inclusion body encephalitis after measles vaccination, documented by intranuclear inclusions corresponding to measles virus or the isolation of measles virus from the brain.[73] The time from vaccination to development of measles inclusion body encephalitis for these patients was 4 to 9 months, consistent with development of measles inclusion body encephalitis after infection with wild measles virus. In 1 case, the measles vaccine strain was identified.[73] Available data do not support a relationship between measles-containing vaccine and subacute sclerosing panencephalitis (SSPE); in fact, widespread use of measles vaccines virtually has eliminated SSPE; no case of SSPE confirmed to be caused by vaccine virus has been reported.[67,69,73,135] The IOM rejected a hypothesized causal relationship between MMR vaccine and autism spectrum disorders.[70] Uncommon adverse events after mumps vaccines include aseptic meningitis, parotitis, orchitis, and low-grade fever. Reactions are expected to be less frequent among recipients of the second dose.

Adverse events after rubella vaccination include fever and mild rash in 5% to 10% of recipients, as well as joint pain, generally without arthritis. The frequency of arthritis increases with age of vaccination, particularly for recipients >15 years of age, and it can reach 40% in older women.[69,73] The rate of acute arthritis is lower than that observed for natural rubella in the same age group.[66,69] The IOM has concluded that evidence is insufficient to conclude that rubella-containing vaccines can cause chronic arthritis or arthralgia in children or adults.[69] Other studies have found no evidence for a risk of onset of chronic arthropathy after rubella vaccination, and a randomized trial found only a small risk of persistent joint pains.[136,137] The RA 27/3 rubella vaccine has not been linked to radiculoneuritis or neuropathy.

Vaccination with MMR or any component vaccine is contraindicated in pregnant women, in people with anaphylaxis from any vaccine component including neomycin or gelatin, and in people who are immunocompromised because of the following: (1) persons with primary or acquired immunodeficiency, including persons with immunosuppression associated with cellular immunodeficiencies, hypogammaglobulinemia, dysgammaglobulinemia, or AIDS or severe immunosuppression associated with HIV infection; (2) persons with blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic system; (3) persons who have a family history of congenital or hereditary immunodeficiency in first-degree relatives (e.g., parents and siblings), unless the immunocompetence of the potential vaccine recipient has been substantiated clinically or verified by a laboratory; or (4) persons receiving systemic immunosuppressive therapy, including corticosteroids ≥2 mg/kg of body weight or ≥20 mg/day of prednisone or equivalent for persons who weigh >10 kg, when the drugs are administered for ≥2 weeks.[73] Rarely, disseminated infection and death resulting from measles encephalitis have been reported in immunocompromised people who were inadvertently given measles vaccine.[67,69] MMR or MMRV vaccination is indicated for people with asymptomatic HIV infection because measles can be severe in such people and vaccine can induce immunity; vaccination should be considered for symptomatic HIV-infected people if they do not have evidence of severe immunocompromise and they lack measles immunity.[28,86] Data show that even people with severe egg allergy can be vaccinated. Most anaphylactic reactions appear to be related to other vaccine components (e.g., gelatin).[138]

Rubella vaccine virus is able to cross the placenta and cause fetal infection; however, no case of congenital rubella syndrome resulting from vaccine virus was reported in infants of 680 susceptible women who received rubella vaccine within 3 months of conception and who carried their pregnancies to term.[73,139] The ACIP recommends that rubella vaccination not be considered a reason to interrupt pregnancy, but also that rubella vaccine not be given knowingly to a pregnant woman. A reasonable approach is to ask women whether they are pregnant now or may become pregnant within the next 28 days after immunization and to vaccinate only women who answer negatively.

Pneumococcal Conjugate and Polysaccharide Vaccines

Before the use of PCV7, *Streptococcus pneumoniae* was the most common bacterial cause of acute otitis media and invasive bacterial infections in children, with >17,000 cases of invasive disease occurring annually in the US in children <5 years of age. After the introduction of routine PCV7 immunization, the incidence of IPD declined dramatically, especially in children <2 years of age.[140–142] US population-based active surveillance data show that within 2 years of PCV7 licensure, the rate of IPD in children <2 years of age declined by 69%.[143] In tandem with the decrease in IPD, data suggest that the incidence of pneumococcal noninvasive disease in children, including otitis media, also decreased, as did antibiotic prescriptions.[144–146] In addition to decreasing the burden of pediatric pneumococcal disease, PCV7 may have had an impact on decreasing disease caused by *S. pneumoniae* in adults.[44–47]

In 2010, PCV13 was licensed. PCV13 contains the 7 serotypes included in the previously licensed PCV7 (4, 6B, 9V, 14, 18C, 19F, and 23F) and 6 additional serotypes (1, 3, 5, 6A, 7F, and 19A) each conjugated to cross-reactive material (CRM) 197, a nontoxic variant of diphtheria toxin. By 2008, 8 years after licensure of PCV7, 3 serotypes contained in PCV13 (3, 7F, and 19A) accounted for >90% of cases of IPD caused by the 6 additional serotypes.[140] PCVs induce a T-lymphocyte–dependent response that includes a primary response in infants and an anamnestic response to booster doses. Three doses of vaccine in infants induce significant increases in serum antibody concentrations to all 13 serotypes. PCV13 has reduced IPD across all age groups including adults since it has been used routinely in children in the US. These findings provide reassurance that, similar to PCV7, PCVs with additional serotypes can also prevent transmission to unvaccinated populations.[147,148]

Pneumococcal polysaccharide vaccine (PPSV23) consists of purified capsular polysaccharides of 23 serotypes of *S. pneumoniae,* which represented approximately 72% of strains isolated from cases of IPD in the US in immunocompromised children 6 through 18 years of age from 2007 through 2009.[149] PPSV23 vaccine induces increased antibodies to pneumococcal polysaccharides in 80% of healthy young adults after a single dose.[150] Initial studies showed high effectiveness in young, healthy adults; subsequent studies have shown approximately 60% effectiveness against IPD in adults at risk for disease but lower effectiveness in adults who are immunocompromised, who have cirrhosis or renal failure, or who are older.[151] Efficacy in children has not been measured, and the vaccine is not immunogenic in children <2 years. PPSV23 does not induce immunologic memory.

Recommendations for Immunization

Pneumococcal vaccination with PCV13 is recommended for all children <2 years of age.[140] The vaccine is given to infants as a 4-dose series at 2, 4, 6, and 12 through 15 months of age. Catch-up immunization is recommended for all children through 59 months of age, with fewer doses used depending on age. For high-risk children, catch-up is recommended through 71 months of age. Providers should give a dose of PCV13 to children at extremely high risk of invasive disease (functional or anatomic asplenia, immunosuppression [e.g., HIV infection], cochlear implant, and cerebrospinal fluid leaks), between the ages of 6 years and 18 years if they have not previously received PCV13.[149]

PPSV23 is given in a single dose to high-risk children ≥2 years of age.[140,149,150] PPSV23 is recommended for children at increased risk of pneumococcal disease irrespective of PCV receipt because PPSV23 provides protection against additional serotypes. One-time revaccination is recommended for people who are at highest risk of invasive disease (asplenia, immunosuppression, nephrotic syndrome) if 5 years have elapsed since the last dose. No more than 2 doses of PPSV23 are recommended. Children ≥2 years of age with high-risk conditions should first receive PCV13, followed by PPSV23 ≥8 weeks later (see Chapter 123).

Contraindications and Precautions

Adverse events after PCV13 administration are minor; examples are as follows: injection site erythema, swelling, and soreness, which occur in 35% to 49% of recipients; low-grade fever in approximately 40%; and higher fever (>39°C) in 5%.[140] Simultaneous administration of IIV and PCV13 has been associated with a transient increased risk of fever compared with administration of either vaccine alone in children 6 months through 4 years of age.[74,75,152] An increased risk of febrile seizures after simultaneous IIV and PCV13 administration was detected in the 2010 to 2011 influenza season, but not in the 2011 to 2012 and 2012 to 2013 seasons.[74] After evaluating data on febrile seizures from these 3 influenza seasons, and taking into consideration benefits and risks of vaccination, no policy change was recommended for use of IIV or PCV13. Surveillance for febrile seizures after IIV is ongoing through the VAERS.[74] No serious adverse events have been associated with use of PCV13. Use of PCV13 is contraindicated in people who have had anaphylactic reactions to a previous dose or to a vaccine component. Safety during pregnancy has not been evaluated. Systemic reactions to PPSV23 are uncommon, but mild local reactions occur in approximately one half of recipients and can be worse in people revaccinated within 5 years of initial vaccination.[140,150] PPSV23 vaccine is contraindicated in people who have had previous anaphylactic reactions to the vaccine or to vaccine components.

Poliovirus Vaccines

Through the use of OPV, the last case of indigenously transmitted poliomyelitis in the US occurred in 1979. In 2005 in the US, poliovirus infections occurred in 4 children who were not vaccinated for religious reasons.[153] All 4 children were asymptomatic and were infected with a poliovirus derived from viruses found in attenuated OPVs used in much of the world. In another report, an unimmunized 22-year-old woman acquired VAPP from a child immunized with OPV in Central America.[154] This was the first case of paralytic poliomyelitis identified in the US. since 1999 and the first imported VAPP case ever documented in the US. In 2008, a 44-year-old woman who was immunosuppressed because of common variable immunodeficiency acquired VAPP and died of complications of her chronic illness, including neurologic sequelae.[155] In 2013, an infant 7 months of age who recently immigrated to the US from India developed left leg paralysis after receiving OPV vaccination in India and was diagnosed with VAPP; further evaluation revealed the presence of severe combined immunodeficiency (SCID) syndrome.[156] These reports raise concerns about transmission of both vaccine-derived and wild polioviruses and the risk of a polio outbreak occurring in the US. Worldwide, poliomyelitis remains endemic in only 3 countries (Afghanistan, Nigeria, and Pakistan).[4]

Enhanced IPV is the only poliovirus vaccine now available in the US.[156a] IPV is derived from 3 wild strains of poliovirus (types 1, 2, and 3), which are inactivated by formalin. The quantity of antigen is measured in D antigen units, and IPV contains 40, 8, and 32 D antigen units for types 1, 2, and 3, respectively. Until 2000, when recommendations were made for exclusive use of IPV for routine immunization, live, attenuated OPV was available in the US. OPV is still the most commonly used poliovirus vaccine in the world. OPV is constituted from 2 Sabin strains of polioviruses (1 and 3), in concentrations of 1,000,000, 100,000, and 600,000 tissue culture infective doses ($TCID_{50}$) per vaccine dose, respectively.[157] Both IPV and OPV, when given as 3-dose primary series, induce protective antibody to each type of poliovirus in 95% to 99% of recipients. Antibody levels decline gradually, and booster doses of each vaccine are recommended at school entry. OPV induces higher levels of intestinal immunity than IPV and thus provides greater protection against infection because OPV better prevents replication and shedding of wild-type poliovirus in the intestine. In developing countries, OPV has lower per-dose effectiveness than in industrialized countries. Therefore, more doses are required to reach the immunity thresholds in the community to terminate transmission than would be needed in developed countries.

Vaccination against poliovirus is recommended for all children. With the progress in global poliomyelitis eradication and the continued risk of VAPP after OPV vaccination (approximately 8 cases per year from 1980 to 1994), the US vaccination policy was modified, first to a sequential schedule of 2 doses of IPV followed by 2 doses of OPV in 1997 and subsequently to a schedule of all IPV in the year 2000.[156a,158,159]

Recommendations for Immunization

IPV is recommended to be given at 2, 4, and 6 through 18 months of age, simultaneously with other childhood vaccines. Vaccination can be given at 6 weeks of age, and 4-week minimal intervals are acceptable for the interval between dose 1 and 2 and between dose 2 and 3.[156a] The interval between the next-to-last and last dose should be 6 months, and this booster dose is recommended at school entry and must be after the fourth birthday.[158] No need exists to restart the series if it is interrupted. OPV can be used in the same schedule, but OPV is no longer produced in the US and, for practical purposes, is no longer available. OPV continues to be the preferred vaccine in countries where poliomyelitis is or recently was endemic. However, with progress in global poliomyelitis eradication and the need to stop the use of OPV because it can rarely cause poliomyelitis, the Strategic Advisory Group of Experts (SAGE) of the WHO recommended that all countries add at least 1 dose of IPV to their immunization schedules.[2,156a,158,159]

Contraindications and Precautions

IPV is contraindicated only in children who have experienced a severe allergic reaction to a previous dose of IPV or to streptomycin, polymyxin B, or neomycin. OPV is contraindicated in children who have immunosuppressive conditions resulting from congenital immunodeficiency (agammaglobulinemia or hypogammaglobulinemia), cancer (leukemia or lymphoma), immunosuppressive chemotherapy, or AIDS.[28,156a] OPV also is contraindicated for family and other close contacts of immunocompromised people because of the risk of transmission of OPV to the affected person. Vaccination in pregnancy should be avoided on theoretical grounds, but, if necessary, IPV can be given.

No significant adverse reactions have been observed after administration of IPV. The major adverse reaction to OPV is VAPP, which develops at a rate of 1 in 2.5 million vaccine doses.[161] Before the policy change in the US, healthy vaccine recipients represented approximately 40% of cases of VAPP, contacts of recipients represented approximately 40% of cases, and immunosuppressed people represented 20%. The highest risk is associated with receipt of the first vaccine dose (1 in 700,000 recipients) and is 10-fold lower for subsequent doses. The risk in people with congenital immunodeficiency is approximately 2000-fold higher than in healthy recipients. The risk of VAPP appears to be raised by receipt of multiple doses of injectable antibiotics 1 to 30 days after immunization.[162] OPV rarely can cause disseminated infection and death in immunocompromised people.[67]

Varicella Vaccine

Live, attenuated varicella virus vaccine was licensed for use in US children and adults in 1995. By 2015, 92% of children 19 through 35 months of age were immunized with at least 1 dose of varicella vaccine.[163–164] Varicella vaccine, developed in Japan from the Oka strain of varicella virus, is >95% effective in protecting against severe disease with 1 dose and 85% effective against all varicella for children vaccinated at 1 to 2 years of age for at least 7 to 9 years after vaccination.[163a–165] Vaccinated children and adults who experience breakthrough infection with wild varicella-zoster virus usually have mild disease, with an average of <50 lesions (compared with >250 lesions observed in typical varicella).

Recommendations for Immunization

In 2006, the ACIP made policy changes for use of live, attenuated varicella-containing vaccines for prevention of varicella.[164] A routine 2-dose schedule of varicella vaccination of children is now recommended along with a second-dose catch-up varicella vaccination for children, adolescents, and adults who previously had received only 1 dose. The basis for these changes was as follows: (1) vaccine failures are recognized to occur after a first dose; (2) outbreaks of varicella had been reported in populations with high coverage with 1 dose of vaccine; (3) emergency revaccination during outbreaks, which previously had been recommended, was difficult and costly; and (4) evidence showed that a second dose could decrease vaccine failure rates and is associated with improved protection or efficacy. The ACIP also expanded recommendations for varicella-containing vaccines to promote wider use of the vaccine for adolescents, adults, and HIV-infected children and approved new criteria for evidence of immunity to varicella. Specific recommendations are as follows:

- All children <13 years of age routinely should receive 2 doses of varicella-containing vaccine, with the first dose administered at 12 through 15 months of age and the second dose at 4 through 6 years of age (i.e., before a child enters kindergarten or first grade). The second dose can be administered at an earlier age provided the interval between doses 1 and 2 is at least 3 months. However, if the second dose is administered at least 28 days following the first dose, the second dose does not need to be repeated.[8,164]
- A second catch-up dose of varicella-containing vaccine is recommended for children, adolescents, and adults who previously have received 1 dose, to improve individual protection against varicella and for more rapid impact on school outbreaks. Catch-up vaccination can be implemented during routine health provision visits and through school and college entry requirements. For persons age <13 years, a catch-up second dose can be administered at any interval ≥3 months after the first dose (see Figs. 6.2 and 6.3).[164] The minimum 3-month interval is the package insert allowance based on studies of the second dose. Future research may evaluate intervals as short as 1 month. The 2-dose varicella vaccination schedule is similar to the MMR vaccination schedule. MMRV vaccine is licensed and indicated for simultaneous vaccination against measles, mumps, rubella, and varicella among children 12 months through 12 years of age. MMRV is associated with an increased risk of febrile seizures following the first dose in people 12 through 23 months of age. Unless a parent prefers MMRV, separate simultaneous

administration of MMR and varicella vaccines is preferred to the combination vaccine for the first dose if the dose is given at 12 through 47 months of age. For second doses at any age or first doses administered at 48 months of age or older, the combination product generally is preferred, but providers need to consider the number of injections, the availability of vaccines, the timeliness of series completion, the potential of patients' return, storage and cost considerations, patients' choice, and the potential of adverse events. Students at all grade levels (including college) and children in childcare facilities should be protected against varicella.

HIV-infected children >12 months of age with $CD4^+$ T-lymphocyte counts of ≥15% of expected for age and without evidence of varicella immunity should be considered for vaccination with 2 doses of single-antigen varicella vaccine at a minimum interval of 3 months. Because data are not available on safety, immunogenicity, or efficacy of MMRV vaccine in HIV-infected children, MMRV vaccine should not be administered as a substitute for the component vaccines when vaccinating HIV-infected children.[164]

Women should be assessed prenatally for evidence of varicella immunity. On completion or termination of their pregnancies, women who do not have evidence of varicella immunity should receive the first dose of varicella vaccine before discharge from the healthcare facility. The second dose should be administered 4 to 8 weeks later (at the postpartum or other healthcare visit). To ensure administration of varicella vaccine, standing orders are recommended for healthcare settings where completion or termination of pregnancy occurs.[164]

Varicella vaccine previously was recommended for people ≥13 years of age without evidence of immunity who (1) have close contact with people at high risk for severe disease (HCP and family contacts of immunocompromised people) or (2) are at high risk for exposure or transmission. The ACIP now recommends that all people 13 years of age and older without evidence of immunity be vaccinated with 2 doses of varicella-containing vaccine at an interval of at least 4 weeks between doses or a second dose (catch-up dose) if they have received only 1 dose. The vaccine can be offered during routine healthcare visits.[164]

During a varicella outbreak, people who have received 1 dose of varicella vaccine should receive a second dose (including preschool-aged children who, according to the routine vaccination schedule, are recommended to have 1 dose of vaccine only), provided the appropriate vaccination interval has elapsed since the first dose (3 months for people 12 months through 12 years of age and at least 4 weeks for people ≥13 years of age).[164]

Revised criteria for evidence of immunity to varicella include any of the following: (1) documentation of age-appropriate vaccination (1 dose for preschool-aged children ≥12 months of age and 2 doses for school-aged children, adolescents, and adults); (2) laboratory evidence of immunity or laboratory confirmation of disease; (3) birth in the US before 1980 (although for HCP, pregnant women, and immunocompromised persons, birth before 1980 should not be considered evidence of immunity); (4) a healthcare provider diagnosis of varicella or a healthcare provider verification of history of varicella disease; and (5) a healthcare provider diagnosis of herpes zoster or a healthcare provider verification of a history of herpes zoster.[164]

Varicella vaccine can be given simultaneously with all other childhood vaccines. The vaccine also is recommended for postexposure prophylaxis of susceptible people up to 5 days after exposure to varicella and can be used for outbreak control.[164]

Contraindications and Precautions

Varicella vaccine induces mild varicelliform rash and fever in 5% to 10% of recipients.[164] Vaccine virus rarely can be transmitted from healthy people who experience rash. More serious adverse events (e.g., encephalitis, ataxia) have been reported rarely, at rates lower than expected after natural varicella and lower than background rates in the community. Varicella vaccine is contraindicated in people who have a blood dyscrasia, in people with primary or acquired immunodeficiency (including immunodeficiency from HIV infection), in pregnant women, and in people who have had an anaphylactic reaction to varicella vaccine or any component, including gelatin. However, vaccine can be given to people with humoral immunodeficiency and should be considered for people with asymptomatic or mildly symptomatic HIV infection with age-specific $CD4^+$ T-lymphocyte counts >15%, after the risks and benefits have been weighed.[164] As with measles-containing vaccines, vaccination should be delayed for ≥3 months after receipt of immunoglobulin or blood products because response to vaccine administered within this interval is unknown. Although varicella vaccine virus rarely has been isolated from patients with herpes zoster, the risk of clinical herpes zoster after varicella vaccination appears to be substantially lower among children than the risk after natural varicella infection.

Hepatitis A Vaccine

Hepatitis A childhood immunization has been implemented incrementally, starting with the ACIP recommendation in 1996 to vaccinate children living in communities with the highest disease rates and continuing in 1999 with the ACIP recommendations for vaccination of children living in states, counties, and communities with consistently elevated hepatitis A rates.[166,167] The strategy was expanded in 2005 to include routine vaccination nationwide of children 12 through 23 months of age.[168,169] In 2014, the incidence was estimated at 0.4 cases per 100,000, with 1239 cases reported.[120]

Recommendations for Immunization

Hepatitis A vaccines are produced in tissue culture and purified and inactivated with formalin; 2 vaccines have been licensed for use in the US since 1995.[169] These vaccines are highly immunogenic and are >95% effective in preventing HAV infection when given as a 2-dose series to children or adults.[169,171] Hepatitis A vaccine also can provide protection after exposure and can be useful in controlling hepatitis A outbreaks in well-defined populations. Hepatitis A vaccines are licensed for use in children ≥12 months of age.[169] A combination product consisting of hepatitis A and B vaccines given on a 0-, 1-, and 6-month schedule is licensed for people ≥18 years of age.

Hepatitis A vaccine is given as a 2-dose series, with doses separated by 6 to 18 months.[171] Recommendations for use of hepatitis A vaccine in children are as follows:

- All children should receive hepatitis A vaccine at 1 year of age (i.e., 12 through 23 months). Vaccination should be completed according to the licensed schedules and integrated into the recommended childhood immunization schedule. Children who are not vaccinated by 2 years of age can be vaccinated at subsequent visits.

- States, counties, and communities with existing hepatitis A vaccination programs for children 2 through 18 years of age are encouraged to maintain these programs. In these areas, new efforts focused on routine vaccination of children 1 year of age should enhance, not replace, ongoing programs directed at a broader population of children.
- In areas without existing hepatitis A vaccination programs, catch-up vaccination of unvaccinated children 2 through 18 years of age can be considered. Such programs may be warranted, especially in the context of increasing incidence or ongoing outbreaks among children or adolescents.

In addition, high-risk groups recommended to receive hepatitis A vaccine include men who have sex with men, users of illicit drugs, people with cirrhosis or clotting factor disorders, previously unvaccinated persons who anticipate close personal contact (e.g., household contact or regular babysitting) with an international adoptee from a country of high or intermediate endemicity during the first 60 days following arrival of the adoptee in the US, and people traveling to or working in countries where hepatitis A is highly endemic.[169,172]

Contraindications and Precautions

Adverse reactions to hepatitis A vaccine appear to be limited to pain at the injection site. The only contraindication to the vaccine is a severe reaction to a previous dose of the vaccine or to 1 of its components (alum or phenoxyethanol). Because hepatitis A vaccine is inactivated, no special precautions need to be taken when immunizing immunocompromised people.

Influenza Vaccines

Since the worldwide influenza pandemic of 1918 that caused an estimated 25 to 50 million deaths, the control of influenza circulation has been a major challenge to clinicians and public health experts. During 1976 to 2007, annual estimates of influenza-associated deaths from respiratory and circulatory causes ranged from 3349 (in 1986 to 1987) to 48,614 (in 2003 to 2004). During seasons when influenza A (H3N2) circulating strains were prominent, 2.7 times more deaths occurred compared with seasons when influenza A (H3N2) was not prominent.[173] The 2009 H1N1 influenza pandemic, which caused an estimated 12,469 deaths, renewed awareness of influenza.[174] Eighty-seven percent of the deaths occurred in people <65 years of age, with children and working adults having risks of hospitalization and death 4 to 7 times and 8 to 12 times greater, respectively, than estimates of impact from seasonal influenza covering the years 1976 to 2001. Additionally, influenza causes >200,000 hospitalizations annually.[175,176] Because of the frequent antigenic changes in influenza viruses, the antigenic content of influenza vaccine can be changed annually to optimize protection against influenza type A and B strains expected to circulate during the following winter and spring. Influenza viruses of type A (H1N1 and H3N2) and B are selected on the basis of immunologic match with circulating strains. Most vaccines in use in the US are made from viruses that are grown in chicken embryos and combined into a single vaccine containing components of all these strains. However, in recent years, vaccines grown in cell culture (ccIIV3) and made through recombinant DNA in baculoviruses have become available (RIV3). The efficacy of vaccine is related to the degree of match between the vaccine and circulating influenza viruses. Major antigenic drift in the circulating strain or strains is associated with seasonal epidemics because the population may have little immunity to the drifted strain from previous infection and the vaccine's effectiveness may be reduced substantially. Annual vaccination is necessary because immunity wanes over time and to optimize protection against each year's influenza strains.[177,178]

Recommendations for Immunization

Two types of influenza vaccines are licensed for use in the US: (1) IIV, which is either trivalent or quadrivalent, purified, split with a detergent, and inactivated with formalin; and (2) a quadrivalent cold-adapted, live, nasally administered vaccine (live, attenuated influenza vaccine [LAIV]). In 2010, the ACIP and AAP recommended expansion of annual influenza vaccination to all people 6 months of age and older. IIV can be used for all people without contraindications. In light of low effectiveness against influenza A(H1N1)pdm09 in the US during the 2013–2014 and 2015–2016 seasons, for the 2016–2017 season, ACIP made the interim recommendation that LAIV4 should not be used. Because LAIV4 is still a licensed vaccine that might be available and that some providers might elect to use, for informational purposes, reference is made to previous recommendations for its use. ACIP will re-review this decision in 2017.[179]

Some children 6 months through 8 years of age require 2 doses of vaccine. For 2015 to 2016, those who received ≥2 doses before July 1, 2015 required only 1 dose; for other children, 2 doses of vaccine, given at 4-week intervals, were recommended. For other groups, only a single dose is necessary. These guidelines can change each year, and so the most recent guideline should be consulted. All licensed influenza vaccines are included on a table published by the CDC that is updated whenever a new vaccine is licensed or a change in recommendations occurs (see http://www.cdc.gov/flu/protect/vaccine/vaccines.htm)

Contraindications and Precautions

IIV should not be administered to people known to have had a severe allergic reaction to any vaccine component, including egg protein. People with egg allergy who experienced only hives should receive influenza vaccine (IIV or RIV3) with in-office observation for 30 minutes.[180] People who report having had a severe reaction (e.g., anaphylaxis) can receive RIV3 if they are ≥18 years old, or they can receive IIV administered by a physician with experience in recognition and management of severe allergic conditions. Chemoprophylactic use of antiviral agents is an option for preventing influenza for persons who cannot receive vaccine.[181] Regardless of allergy history, all vaccines should be given in settings with the availability of appropriate resuscitative equipment. When vaccine supply is limited, efforts should focus on vaccinating those persons with conditions that put them at higher risk of influenza complications. The list of children and adolescents with high-risk conditions includes the following:

- Children 6 months through 4 years of age
- People who have chronic pulmonary (including asthma),

cardiovascular (except isolated hypertension), renal, hepatic, neurologic, hematologic, or metabolic (including diabetes mellitus) disorders

- People who are immunosuppressed (including immunosuppression caused by medications or by HIV)
- People who are or will be pregnant during the influenza season
- People who are 6 months through 18 years of age and are receiving long-term aspirin therapy and who therefore may be at risk for Reye syndrome after influenza virus infection
- Residents of nursing homes and other long-term care facilities
- American Indians and Alaska Natives
- People who are morbidly obese (body-mass index ≥40)

People with moderate to severe acute febrile illness usually should not be immunized until their symptoms have resolved. However, minor illnesses with or without fever do not contraindicate use of influenza vaccine, particularly among children with mild upper respiratory tract infection or allergic rhinitis.

Approximately 3% to 5% of recipients experience local tenderness or fever after vaccination. The occurrence of GBS within 6 weeks of influenza vaccination was observed in adults after the swine influenza vaccine program campaign in 1976 but was not observed subsequently until 1990, when a case-control study suggested a slightly elevated risk in persons 18 through 64 years of age but not in people ≥65 years of age.[177] Given the substantial benefits of influenza vaccination among the target populations, the risk of GBS, if any, is exceeded by the benefits.

LAIV should not be used in people of the following ages or with the following conditions: (1) age <2 years or ≥50 years, (2) those with contraindications listed in the package insert, (3) children 2 through 17 years old who are receiving aspirin or aspirin-containing products, (4) persons who have experienced severe allergic reactions to the vaccine or any of its components or to a previous dose of any influenza vaccine, (5) pregnant women, (6) immunosuppressed persons, (7) persons with a history of egg allergy, (7) children 2 through 4 years old who have asthma or who have had a wheezing episode noted in the medical record within the past 12 months or whose parents report that an HCP stated that they had wheezing or asthma within the last 12 months, and (8) persons who have taken influenza antiviral medications within the previous 48 hours. In addition to the groups for whom LAIV is not recommended, the "Warnings and Precautions" section of the LAIV package insert indicates that persons of any age with asthma may be at increased risk for wheezing after administration of LAIV and notes that the safety of LAIV in persons with other underlying medical conditions that could predispose them to complications after wild-type influenza infection (e.g., chronic pulmonary, cardiovascular [except isolated hypertension], renal, hepatic, neurologic, hematologic, or metabolic [including diabetes mellitus] disorders) has not been established. These conditions, in addition to asthma in persons aged ≥5 years, should be considered precautions for the use of LAIV.[179]

Meningococcal Vaccines

Rates of meningococcal disease have been declining in the US since the late 1990s. Fewer than 600 cases are now reported each year. In 2014, 433 invasive meningococcal cases were reported.[108] Meningococcal disease is seasonal: the number of cases generally peaks each year in January and February. The overall case-to-fatality ratio for meningococcal disease is approximately 10% to 15% and is somewhat higher in adolescents. Severe sequelae (e.g., hearing loss, neurologic disability, limb or digit loss, and skin scarring) occur in approximately 11% to 19% of survivors.[182] Infants have the highest rates of meningococcal disease, generally from serogroup B. Approximately three fourths of cases among adolescents and young adults are caused by serogroups B, C, or W. Serogroup A accounts for epidemics outside the US. Evidence demonstrates that college freshmen living in dormitories have historically had a modestly increased risk of meningococcal disease (4.6 cases in 100,000) compared with other people of the same age.[182]

Recommendations for Immunization

In the US, 4 meningococcal vaccines are licensed for use in children and adults against serogroups A, C, Y, and W, and 2 vaccines are licensed for people 10 years through 25 years of age against serogroup B.[182–184] A meningococcal polysaccharide (MPSV4) vaccine, containing antigens of serogroups A, C, W, and Y was licensed in the US in 1981 and was used until conjugated meningococcal vaccines were licensed.

By using the same technology used to develop PCV7, a meningococcal serogroup C conjugate vaccine was licensed in the United Kingdom in 1999. The vaccine was introduced into the routine infant schedule, with catch-up vaccination for older children and adolescents. In the 2 years after introduction of this vaccine, the incidence of serogroup C meningococcal disease declined by 87% in vaccinated people.[182] Substantial reductions in disease also occurred in unvaccinated populations as a result of community protection.

In the US, 3 MCVs are licensed for use. MenACWY-D (Menactra), a quadrivalent vaccine that includes serogroups A, C, W, and Y, is licensed for children from 9 months through 55 years of age. MenACWY-CRM (Menveo) includes the same 4 serogroups and is licensed for use from 2 months through 55 years of age. Hib-MenCY-TT (MenHibrix) contains meningococcal serogroups C and Y, in addition to Hib, and is licensed by the FDA as a 4-dose series for children 6 weeks through 18 months of age. These MCVs are recommended for use only in children <11 years of age who are at increased risk of meningococcal disease, including children with persistent terminal complement component deficiency, functional or anatomic asplenia, HIV infection, or during a community outbreak attributable to a vaccine serogroup (see Fig. 6.2).[59,59a] Each of the polysaccharides is linked to a diphtheria toxoid, CRM 197, or tetanus toxoid. Because MenACWY induces T-lymphocyte–mediated immunity and higher-quality immune responses, the duration of protection is thought to be longer than immunity produced by MPSV4.[182]

Current recommendations for use of MenACWY were published by the CDC in 2013 and 2014.[182,183] The first dose is recommended to be administered at age 11 to 12 years, and a booster dose should be administered at 16 years. A dose of MenACWY administered at 10 years of age can be counted as the 11- to 12-year dose. Doses administered before age 10 years are not counted as part of the routine adolescent MenACWY series. Adolescents who receive their first dose at 13 through 15 years of age should receive a booster dose at 16 through 18 years of age. The minimum interval between doses of MenACWY is 8 weeks. Adolescents who receive a first dose after their 16th birthday do not need a booster dose unless they become at increased risk for meningococcal disease. Persons 19 through 21 years of age are not recommended routinely to receive MenACWY. MenACWY can be administered up to age 21 years as catch-up vaccination for those who have not received a dose after their 16th birthday. HCP should use every opportunity to provide the booster dose when indicated, regardless of the vaccine brand used for the previous dose or doses. The minimum interval between doses is 8 weeks.

For people 9 months through 55 years old with HIV infection, persistent complement component deficiency, or asplenia (functional or anatomic), a 2-dose primary series should be given separated by 2 months. Routine booster doses should be given thereafter. If the most recent dose was received before 7 years of age, a booster should be administered 3 years later; otherwise, the interval is 5 years, with continued boosters every 5 years thereafter. For people without persistent complement component deficiency, and without asplenia (functional and anatomic), who may have received a first dose of MenACWY at 2 through 10 years of age (e.g., for international travel), the next dose should be administered at the following interval if the child remains at risk: after 3 years if the first dose was given at 2 through 6 years or after 5 years if the first dose was given at 7 years of age or older.[182]

Two meningococcal B vaccines have been licensed by the FDA for use in the US and approved for use in persons aged 10 to 25 years of age: MenB-FHbp (Trumenba, Pfizer, New York, NY) and MenB-4C (Bexsero, Novartis Vaccines). MenB-FHbp is licensed as a 2-dose series at 0 and 6 months. If the second dose is given <6 months after the first dose, a third dose should be given at least 6 months after the first dose; the minimum interval between the second and third doses is 4 weeks. MenB-4C is licensed as a 2-dose series, with doses administered at least 1 month apart, although in some studies, MenB-4C doses were administered up to 6 months apart. The 2 meningococcal B vaccines are not interchangeable; the same vaccine product must be used for all doses. The ACIP recommended that these vaccines be used for persons 10 years of age and older who are at increased risk of meningococcal disease, including (1) persons with persistent complement component deficiencies (including inherited or chronic deficiencies in C3, C5-9, properdin, factor D, factor H, or taking eculizumab [Soliris]), (2) persons with anatomic or functional asplenia (including sickle cell disease), (3) microbiologists routinely exposed to isolates of *Neisseria meningitidis,* and (4) persons identified to be at increased risk because of a serogroup B meningococcal disease outbreak.[184] The ACIP and CDC also have recommended that the serogroup B meningococcal vaccine series can be administered to adolescents and young adults 16 through 23 years of age to provide short-term protection against most strains of serogroup B meningococcal disease. The preferred age for MenB vaccination is 16 through 18 years.[185] The current low prevalence of disease, coupled with the lack of availability of important data for making policy recommendations for MenB vaccines, led the ACIP to determine that insufficient evidence exists to make a routine public health recommendation that all adolescents be vaccinated with MenB vaccine. Given the seriousness of meningococcal disease and the availability of licensed vaccines, the ACIP agreed that sufficient evidence exists to encourage individual clinical decision making.[185]

Precautions and Contraindications

Vaccination should be deferred for people with moderate or severe acute illness until their condition improves. MenACWY vaccination is contraindicated among people known to have a severe allergic reaction to any component of the vaccine, including diphtheria toxoid (for MenACWY), or to dry natural rubber latex. Because both MCVs are inactivated vaccines, they can be administered to people who are immunosuppressed as a result of disease or medications; however, response to the vaccine may be less than optimal.

To date, no randomized, controlled clinical trials have been conducted to evaluate use of MPSV4 or MenACWY vaccines in pregnant or lactating women. VAERS reports of exposure to MPSV4 or MenACWY-D during pregnancy have not identified adverse effects among either pregnant women or newborns of women vaccinated during pregnancy. Pregnancy should not preclude vaccination with MenACWY or MPSV4, if indicated. Women of childbearing age who become aware that they were pregnant at the time of MenACWY vaccination should contact their

HCP or the vaccine manufacturer so that their experience can be captured in the manufacturer's registry of vaccination during pregnancy.[182,186,187] The MenB vaccines are recommended by their manufacturers to be used during pregnancy only if clearly needed.[186,187]

Rotavirus Vaccine

Rotavirus is the most common cause of severe gastroenteritis in infants and young children worldwide. In developing countries, rotavirus gastroenteritis is a major cause of childhood death and is responsible for more than half a million deaths per year in children <5 years of age.[188,189] Before the routine use of rotavirus vaccines, rotavirus gastroenteritis resulted in relatively few childhood deaths in the US (approximately 20 to 70 per year). However, nearly every child in the US was infected with rotavirus by 5 years of age and most developed gastroenteritis, leading to >400,000 physician visits, >200,000 emergency department visits, 55,000 to 70,000 hospitalizations each year, and direct and indirect costs of approximately $1 billion.[189]

A live, attenuated tetravalent rotavirus vaccine prepared from rhesus rotavirus type 3 and human-rhesus reassortant types 1, 2, and 4 was licensed in 1999 for use in infants in the US. In prelicensure controlled trials, this vaccine was shown to be safe and highly effective, and it prevented >90% of hospitalizations for rotavirus diarrhea.[190] Following licensure, the vaccine was recommended for use in infants in March 1999. By June of that year, reports of adverse events suggested that cases of intussusception followed rotavirus vaccination. Subsequent studies demonstrated that children given this rotavirus vaccine had a relative risk of intussusception of 24.8 during the 3 to 7 days after the first dose, with an estimated risk of 1 case in 10,000 vaccinated infants.[32] On the basis of these data, the ACIP and AAP rescinded the recommendation for routine use of rotavirus vaccine in the US, and the manufacturer withdrew the vaccine from distribution.

The next generation of rotavirus vaccines licensed by the FDA includes 2 products. The ACIP states no preference between the 2 products. The first vaccine is a pentavalent reassortant vaccine (RV5, or Rotateq, Merck) that was licensed by the FDA in 2006. This vaccine is a live oral vaccine that contains 5 reassortant rotaviruses (G1, G2, G3, G4, and P1A) developed from human and bovine parent rotavirus strains.[191] Data from prelicensure trials showed immunogenicity of 93% to 100% and efficacy of 74% against rotavirus gastroenteritis of any severity and 98% against severe gastroenteritis.[192] The incidence of serious adverse events, intussusception, fever, and irritability was similar among RV5 and placebo recipients.[189,193] The second vaccine is a monovalent rotavirus vaccine based on an attenuated human rotavirus strain of P1A[8]G1 specificity, RIX 4414 (RV1, or Rotarix, GlaxoSmithKline Biologicals), licensed in 2008. This orally administered vaccine, given in 2 doses, has shown good clinical efficacy, and no increase in intussusception was noted among recipients of the vaccine versus placebo in a trial of >60,000 infants.[194,195] In postlicensure studies in Mexico and Brazil, RV1 prevented approximately 80,000 hospitalizations and 1300 deaths annually and was associated with a short-term risk of intussusception in approximately 1 in 51,000 to 68,000 vaccinated infants.[196] More recent studies in the US demonstrated a small increased risk of intussusception following rotavirus vaccination. Approximately 1 in 20,000 to 1 in 100,000 US infants who receive rotavirus vaccine may develop intussusception within a week of receiving the vaccine.[197,198]

Introduction of RV5 and RV1 has been associated with a dramatic reduction in rotavirus-associated hospitalizations, office visits, and overall burden of disease from rotavirus in the US.[199–203] In 2010, a virus or parts of a virus called porcine circovirus was found in both rotavirus vaccines. This virus does not cause disease in humans and is not thought to be a safety or efficacy concern.[204,205]

Recommendations for Immunization

All infants should be immunized routinely with 3 doses of RV5 administered orally at 2, 4, and 6 months of age or 2 doses of RV1 administered orally at 2 and 4 months of age. The first dose should be administered between 6 weeks and 14 weeks 6 days of age. Subsequent doses should be administered at 4- to 10-week intervals, and all doses of vaccine should be administered by 8 months 0 days of age. RV can be administered together with other childhood vaccines indicated at the same visits.

Premature infants (i.e., infants born at <37 weeks' gestation) can be immunized if they are at least 6 weeks of age, are being or have been discharged from the hospital nursery, and are clinically stable. Infants living in households with people who have or are suspected of having an immunodeficiency disorder or impaired immune status can be vaccinated, including infants living in households with pregnant women.

Readministration of a dose of RV to an infant who regurgitates, spits out, or vomits during or after administration of vaccine is not recommended. The infant should receive the remaining recommended doses of RV at appropriate intervals. If a recently vaccinated child is hospitalized for any reason, no measures other than routine universal precautions need be taken to prevent the spread of vaccine virus in the hospital setting.

Contraindications and Precautions

Contraindications for use of RV include a history of severe hypersensitivity to any component of the vaccine, a history of serious allergic reaction to a previous dose of vaccine, a history of intussusception, or a history of SCID.[206] SCID is a contraindication because 8 cases of SCID have been diagnosed in infants who received RV vaccine with evidence of gastrointestinal tract symptoms presumably caused by vaccine virus.[207,208]

Human Papillomavirus Vaccine

More than 150 types of papillomaviruses have been recognized on the basis of DNA sequence analyses, more than 40 of which infect the genital area.[209,210] HPV is associated with a variety of clinical conditions that range from benign skin and mucous membrane lesions to cancer. Clinical manifestations with the most frequently associated HPV types include skin warts (types 1, 2, 3, and 10), recurrent respiratory papillomatosis (types 6 and 11), condyloma acuminata (types 6 and 11), and cervical, anal, and oropharyngeal cancer (types 16, 18, 31, 33, 45, 52, and 58). The CDC estimated that approximately 30,700 new cancers were attributable to HPV annually between 2008 and 2012, including 19,200 among females and 11,600 among males.[208a] HPV is one of the most common causes of sexually transmitted infections in the US and worldwide, and it causes almost all the morbidity and mortality associated with cervical cancer.[209] Based on the association of HPV with cervical cancer and precursor lesions, HPV can be grouped into low-risk and high-risk HPV types. In the US and Europe, HPV-16 accounts for approximately 50% of cases of cervical cancer, with types 18, 31, and 45 accounting for an additional 25% to 30% of cases.[209,210]

Vaccination against high-risk HPV types could substantially reduce the incidence of cervical cancer. Administration of vaccine protecting against HPV-16 has been shown to reduce the incidence of HPV-16 infection and HPV-related cervical intraepithelial neoplasia.[211,212] In addition, a bivalent HPV vaccine was efficacious in preventing persistent cervical infections with HPV-16 and HPV-18 and associated cytologic abnormalities and lesions.[213] Three HPV vaccines are licensed in the US: (1) a 9-valent vaccine (9vHPV) containing virus-like particles of serotypes 6, 11, 16, 18, 31, 33, 45, 52, and 58; (2) a quadrivalent vaccine (4vHPV) containing virus-like particles of serotypes 6, 11, 16, and 18; and (3) a bivalent vaccine (2vHPV) containing virus-like particles of serotypes 16 and 18.[63,210] 2vHPV, 4vHPV, and 9vHPV all protect against HPV-16 and HPV-18, types that cause approximately 66% of cervical cancers and the majority of other HPV-attributable cancers in the US. 9vHPV targets 5 additional cancer-causing types, which account for approximately 14% of HPV-associated cancers in girls and women and 4% of HPV-associated cancers in boys and men. 4vHPV and 9vHPV also protect against HPV-6 and HPV-11, types that cause genital warts.

Recommendations for Immunization

HPV vaccination is recommended for girls, women, boys, and men. Routine HPV vaccination should be initiated at age 11 or 12 years but can be started beginning at age 9 years. Vaccination also is recommended for girls and women 13 through 26 years old and for boys and men 13 through 21 years old who have not been vaccinated previously or who have not completed the 3-dose series.[63] Men 22 through 26 years old can be vaccinated. Vaccination of girls and women is recommended with 4vHPV (as long as this formulation is available) or 9vHPV. Vaccination of boys and men is recommended with 4vHPV (as long as this formulation is available) or 9vHPV (see Fig. 6.2).

For persons initiating vaccination before their 15th birthday, the recommended immunization schedule is 2 doses of HPV vaccine. The second dose should be administered 6 to 12 months after the first dose (0, 6 to 12 month schedule). For persons initiating vaccination on or after their 15th birthday, the recommended immunization schedule is 3 doses of HPV vaccine. The second dose should be administered 1 to 2 months after the first dose, and the third dose should be administered 6 months after the first dose (0, 1 to 2, 6 month schedule).[210a] HPV vaccine can be administered at the same visit as other age-appropriate vaccines, such as Tdap and MCV4. Cervical cancer screening recommendations have not changed for girls and women who receive HPV vaccine because approximately up to 30% of cervical cancers are caused by HPV types not in the vaccine.[210]

HPV vaccine is not recommended for use in pregnancy. The vaccine has not been associated causally with adverse outcomes of pregnancy or adverse events to the developing fetus. However, data on vaccination in pregnancy are limited. A registry for girls and women inadvertently vaccinated during pregnancy was established by the manufacturer as part of its postlicensure commitment to the FDA.[210] More than 2800 girls and women who received vaccine within 1 month before their last menstrual period or anytime during pregnancy were enrolled in the registry. Rates of spontaneous abortions and major birth defects were not greater than those of a comparison unexposed population. The registry was terminated at the end of 2012 with concurrence from the FDA. The CDC will continue to monitor pregnancy outcomes through reports to the VAERS) and through studies in the Vaccine Safety Datalink. Any exposure to vaccine in pregnancy should also be reported to the relevant vaccine manufacturer (Merck: 800-986-8999; GlaxoSmithKline: 888-452-9622).

Both 9vHPV and 4vHPV vaccines are licensed for boys and men 9 through 26 years of age.[63,210] The 4vHPV vaccines has been shown to be effective for prevention of genital warts, and the 9vHPV vaccine is presumed to be similarly effective from immunobridging data.[214] These HPV vaccines have been licensed by the FDA for prevention of anal cancer and genital warts and are recommended for boys and men 11 through 21 years of age and for men 22 through 26 years of age who are immunosuppressed, have HIV infection, or are men who have sex with men. Either of these HPV vaccines can be given to boys 9 through 10 years of age and men 22 through 26 years of age at the provider's discretion.

Contraindications and Precautions

HPV vaccine is contraindicated for people with a history of immediate hypersensitivity to any vaccine component. Quadrivalent HPV vaccine is produced in yeast cells. Bivalent HPV vaccine is produced using a baculovirus-infected insect cell line. HPV vaccine can be administered to people with minor acute illnesses. Vaccination of people with moderate or severe acute illnesses should be deferred until after the illness improves.

Selected Other Vaccines That Can Be Used in Children and Adolescents

Bacille Calmette-Guérin Vaccine

A live, attenuated vaccine prepared from the Calmette-Guérin bacillus (bacille Calmette-Guérin [BCG]) strain of *Mycobacterium bovis* is intended to prevent serious *Mycobacterium tuberculosis* disease (tuberculosis [TB]).[215] The vaccine is used routinely throughout most of the developing world but only in restricted situations in the US. Data regarding the efficacy of BCG are highly variable and conflicting. Meta-analyses suggest that a single dose of BCG vaccine given at or soon after birth is approximately 50% effective in preventing the most severe outcomes of *M. tuberculosis* infection (disseminated or miliary TB).[215–217] Vaccine efficacy data in adults, such as HCP, are inconclusive. BCG vaccine can cause reactivity of the tuberculin skin test and thus reduce the test's utility for monitoring for *M. tuberculosis* infection and aiding in the decision whether preventive antimicrobial therapy is indicated.

In the US, BCG vaccine should be considered only for tuberculin-negative infants and children who continually are exposed and cannot be separated from adults who (1) are untreated or ineffectively treated for TB (if the child cannot be given long-term treatment for infection) or (2) have TB caused by strains resistant to isoniazid and rifampin.[215–217] Information about BCG vaccine can be found at www.cdc.gov/tb/publications/factsheets/prevention/BCG.htm/.

Vaccines for Travelers

Cholera Vaccine

A live, oral cholera vaccine, VAXCHORA, was licensed in the US in June, 2016. It is licensed for persons 18 through 64 years of age traveling to cholera-affected countries. VAXCHORA is a vaccine indicated for active immunization against disease caused by *Vibrio cholerae* serogroup O1. The effectiveness of VAXCHORA has not been established in persons living in cholera-affected areas, nor in persons who have preexisting immunity due to previous exposure to *V. cholerae* or receipt of a cholera vaccine. VAXCHORA has not been shown to protect against disease caused by *V. cholerae* serogroup O139 or other non-O1 serogroups (see http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/A for additional information). Two types of oral cholera vaccines are available in other countries: (1) Dukoral and (2) Shanchol and mORCVAX. The latter 2 are identical vaccines in terms of strains but are formulated by different manufacturers using different methods. Another cholera vaccine may be licensed soon in the US (see http://www.paxvax.com/cholera). These vaccines are not currently recommended for travelers.[218,219]

Japanese Encephalitis Vaccine

Japanese Encephalitis (JE) virus, a mosquito-borne flavivirus, is the most common vaccine-preventable cause of encephalitis in Asia. Among an estimated 35,000 to 50,000 annual cases, 20% to 30% of patients die, and 30% to 50% of survivors have neurologic or psychiatric sequelae. No treatment exists. For most travelers to Asia, the risk for JE is very low, but it varies on the basis of destination, duration, season, and activities.[220]

JE vaccine is recommended for travelers who plan to spend a month or longer in endemic areas during the JE virus transmission season and for laboratory workers with a potential for exposure to infectious JE virus.[220] The vaccine should be considered for the following: (1) short-term (<1 month) travelers to endemic areas during the JE virus transmission season if they plan to travel outside an urban area and will have an increased risk for JE virus exposure as a result of itinerary, activities, or accommodations; (2) travelers to an area with an ongoing JE virus outbreak; and (3) travelers to endemic areas who are uncertain of specific destinations, activities, or duration of travel. JE vaccine is not recommended for short-term travelers whose visit will be restricted to urban areas or times outside a well-defined JE virus transmission season.[220]

Inactivated Vero cell culture–derived JE vaccine (JE-VC [Ixiaro]) is the only JE vaccine licensed and available in the US.[220,221] JE-VC is licensed for use in adults and in children ≥2 months of age. The primary series consists of 2 intramuscular doses administered 28 days apart. For children 2 months through 2 years of age, each dose is 0.25 mL, and for adults and children ≥3 years of age, each dose is 0.5 mL. For persons ≥17 years of age, the ACIP recommends that if the primary series of JE-VC was administered >1 year previously, a booster dose can be given before potential JE virus exposure.[222] Data on the need for and timing of additional booster doses are not available. Data on the need for a booster dose following a primary series of JE-VC in children also are not yet available. An inactivated mouse brain–derived vaccine (JE-MB) previously was available and recommended for use in adults and children ≥1 year of age but is no longer being produced.

Typhoid Fever Vaccine

Two typhoid vaccines are available in the US: (1) a purified capsular polysaccharide parenteral vaccine prepared from the typhoid Vi antigen; and (2) an oral live, attenuated vaccine (*Salmonella typhi* Ty21a strain).[223,224] The inactivated Vi vaccine is given as a single dose, with booster doses at 2-year intervals if exposure continues. The oral vaccine is given as a 4-dose series of enterically coated capsules at 2-day intervals, taken before meals; the manufacturer recommends booster doses every 5 years if continued or renewed exposure to *Salmonella* serotype Typhi is expected. Both vaccines have efficacy of 50% to 80%. The minimal recommended ages for use of these vaccines are 2 years for the inactivated Vi vaccine and 6 years for the oral vaccine.

Typhoid vaccination is indicated for people who potentially will be exposed to contaminated food and water while traveling to areas in which typhoid is endemic (see http://wwwnc.cdc.gov/travel), for laboratory workers exposed to the organism, and for people exposed to typhoid carriers in the household. Inactivated Vi vaccine produces local reactions (swelling, induration) in 7% and fever or headache in fewer than 3% of recipients. Oral typhoid vaccine produces only minor adverse events, including nausea, vomiting, and abdominal discomfort. Oral typhoid vaccine should not be given to immunocompromised people (including people with HIV infection).

Yellow Fever

YF is a vector-borne disease transmitted to a human from the bite of an infected mosquito. YF is endemic to sub-Saharan Africa and tropical South America and is estimated to cause 200,000 cases of clinical disease and 30,000 deaths annually. Infection in humans is capable of producing hemorrhagic fever and is fatal in 20% to 50% of people with severe disease.[225] No treatment exists for YF disease. A traveler's risk for acquiring YF virus is determined by multiple factors, including immunization status, location of travel, season, duration of exposure, occupational and recreational activities while traveling, and local rate of virus transmission at the time of travel.

All travelers to countries in which YF is endemic should be advised of the risks for contracting the disease and available methods to prevent it, including use of personal protective measures and receipt of vaccine.[226] Administration of YF vaccine is recommended for people ≥9 months of age who are traveling to or living in areas of South America and Africa where a risk exists for YF virus transmission. Because serious adverse events can occur following YF vaccine administration, HCP should vaccinate only people who are at risk for exposure or who require proof of vaccination for entry into a country. To minimize the risk for serious adverse events, HCP should observe the contraindications, consider the precautions to vaccination before administering vaccine, and issue a medical waiver if indicated.[226] The YF vaccine is available in the US only from providers certified by state health departments (wwwnc.cdc.gov/travel/yellow-fever-vaccination-clinics/search.htm).

YF vaccine is contraindicated in people who have anaphylactic allergy to eggs, infants <6 months of age, and people with altered immune status as a result of a thymus disorder, immunodeficiency, or immunosuppressive or immunomodulating therapies.[226] Age 6 to 8 months and ≥60 years, asymptomatic HIV infection with moderate immunosuppression, pregnancy, and breastfeeding are precautions for YF vaccine administration. If travel to YF-endemic areas cannot be avoided or postponed for groups with a precaution for vaccination, the risk for YF virus exposure needs to be weighed against the possible risk for serious adverse events following vaccination.[226,227]

A single primary dose of YF vaccine provides long-lasting protection and is adequate for most travelers.[228] Additional doses of YF vaccine are recommended for certain populations (i.e., pregnant women, hematopoietic stem cell transplant recipients, and HIV-infected persons) who may not have as robust or sustained an immune response to YF vaccine compared with other recipients. Additional doses also can be given to certain groups believed to be at increased risk for YF disease either because of their location and duration of travel or because of more consistent exposure to virulent virus (e.g., laboratory workers).

Sources of Information on Vaccines

Important sources for information about vaccines are as follows:

Official Package Information Insert.

Manufacturers provide product-specific information for each vaccine; some of these are reproduced in their entirety in the *Physicians' Desk Reference.*

Centers for Disease Control and Prevention.

Specific information on immunization and vaccine-preventable diseases is available from the CDC website (www.cdc.gov/vaccines/) and the CDC Information Center (800-232-INFO [4636]).

Morbidity and Mortality Weekly Report.

This report, published weekly by the CDC, contains vaccine recommendations, reports of specific disease activity, policy statements, and regular and special recommendations of the ACIP.

Subscription information is available online at www.cdc.gov/mmwr/.

Health Information for International Travel.

Travelers' health information, including requirements and recommendations for specific immunizations and health practices for travel to various countries, can also be obtained through the CDC website (www.cdc.gov/travel) or the CDC information center (800-232-INFO [4636]).

American Academy of Pediatrics *Red Book: Report of the Committee on Infectious Diseases.*

The full report containing recommendations on all licensed vaccines, published by the AAP, is updated every 3 years. The most recent *Red Book* was published in 2015 and can be ordered from the AAP at www.aap.org/bookstore/ or 888-227-1770.

Control of Communicable Diseases in Man.

The American Public Health Association publishes this manual at approximately 5-year intervals. The 20th edition (2014) is available. The manual contains valuable information concerning the following: infectious diseases; their occurrence worldwide; immunization, diagnostic, and therapeutic information; and up-to-date recommendations on isolation and other control measures for each disease presented. The manual can be ordered at https://secure.apha.org/iMIS/APHA/Store.

Health Departments.

Most state and many local health departments provide routine immunizations, immunization cards, and schedules to patients. They also send out routine reports of disease incidence. Many states have print information online to be downloaded. State health department immunization websites can be found at http://www.cdc.gov/vaccines/imz-managers/awardee-imz-websites.html.

World Health Organization.

Additional information about the WHO and international vaccine programs can be found online at http://www.who.int/topics/vaccines/en/.

Gavi: The Vaccine Alliance.

Information on Gavi can be found at the website http://www.gavi.org/

Additional Useful Sources of Information.

Other resources include the following: the Immunization Action Coalition, online at www.immunize.org/; the National Network for Immunization Information, online at www.idsociety.org/; the Vaccine Education Center, online at www.chop.edu/service/vaccine-education-center/home.html; and the Institute for Vaccine Safety, online at www.vaccinesafety.edu.

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7

Antimicrobial Chemoprophylaxis

John S. Bradley

Chemoprophylaxis is prevention of disease by administration of a drug. An antimicrobial agent is given to an individual who is at risk of developing an infection following exposure to bacteria, viruses, fungi, mycobacteria, or parasites, because of exposure to the pathogen. The term “prophylaxis” as used in this chapter does not apply to those situations in which infection is already established; however, for some children who already are infected, the term has been used in situations to denote the prevention of “disease” rather than infection. Other chapters discuss immunoprophylaxis (see Chapters 5 and 6) and barrier prophylaxis (e.g., use of condoms; see Chapters 51 and 52). Specific discussions of the prevention of travelers' diarrhea (see Chapter 8), neonatal conjunctivitis (see Chapter 80), malaria (see Chapter 271), and human immunodeficiency virus (HIV) infection (see Chapter 109) can also be found elsewhere. Similarly, immunoprophylaxis and chemoprophylaxis for immunocompromised hosts, such as solid-organ or bone marrow transplant recipients, or patients being treated for cancer, are not discussed specifically in this chapter.

Ideally, recommendations for antimicrobial prophylaxis should be based on data documenting efficacy in prospective, randomized controlled studies, but most prophylactic regimens are presumed to be efficacious on the basis of small clinical trials, supporting pharmacology and biologic plausibility. In addition, prophylaxis can be justified solely by the severe consequences of possible infection (e.g., infection of implanted neurosurgical or cardiac foreign material).

Chemoprophylaxis of infection in children can be classified as general or specific. Chemoprophylaxis is *general* when all children, regardless of underlying disease or other factors, are at substantial risk of infection following exposure to a pathogen (e.g., *Neisseria meningitidis* in households). Chemoprophylaxis is *specific* when it is administered to certain children who are deemed at special risk for infection because of the presence of an immunodeficient state or anatomic structural anomalies or because these children have undergone procedures or operations that can be associated with a risk of subsequent infection. Chemoprophylaxis should be administered during the entire interval of documented increased risk of infection; the duration of general or specific chemoprophylaxis varies. Prophylaxis can be short term, following a specific exposure (e.g., *N. meningitidis*), more prolonged with ongoing exposure (e.g., malaria), or administered over several years (e.g., rheumatic fever).

The benefits of chemoprophylactic strategies to decrease morbidity and mortality and their attendant costs to the healthcare system should be weighed against potential risks, including drug toxicities, costs, alteration of the host microbiome, and the development and spread of antimicrobial resistance. Every effort should be made to limit the duration of prophylaxis or to find alternative methods to prevent infection (e.g., clean intermittent catheterization of the urinary bladder to prevent urinary tract infections). Recommendations change periodically on the basis of evolving knowledge, changing pathogens, and susceptibility to antimicrobial agents. Updated guidelines for specific infections are published periodically by the Centers for Disease Control and Prevention, by the American Academy of Pediatrics,[1] in the *Medical Letter on Drugs and Therapeutics*,[2] by the American Heart Association,[3] and in peer-reviewed journals.

General Principles

For chemoprophylaxis to be effective, 3 criteria should be met:

1. The antimicrobial drug or drugs used must have activity against the likely infectious agent and attain appropriate tissue-specific drug concentration.

2. The host should have a well-defined increased risk of disease. Other important factors considered in assessing the need for prophylaxis are the likelihood of development of infection following exposure, the severity of infection with associated risk of morbidity or mortality, and communicability to others.

3. The safety of a chemoprophylactic agent must be such that complications of its administration do not outweigh the risks of infection (i.e., an acceptable risk-to-benefit ratio).

Chemoprophylaxis in Healthy Children

Chemoprophylaxis is recommended to prevent surgical and trauma-related infections (Table 7.1), as well as to prevent disease associated with significant morbidity and mortality caused by bacterial, viral, fungal, mycobacterial, and parasitic agents. Pathogen-specific chemoprophylactic agents, doses, and durations as well as alternative regimens are shown in Table 7.2.

TABLE 7.1

Classification of Operative Wounds and Risk of Infection

Classification	Criteria	Risk (%)
Clean	Elective, not emergency, nontraumatic; primarily closed; no acute inflammation; no break in technique; respiratory, GI, biliary, and GU tracts not entered	<2
Clean-contaminated	Urgent or emergency, otherwise clean; elective opening of respiratory, GI, biliary, or GU tract with minimal spill and not infected urine or bile; minor technique break	<10
Contaminated	Nonpurulent inflammation; gross spill from GI tract; entry into biliary or GU tract in the presence of infection; major break in technique; penetrating trauma lasting <4 hr; chronic open wounds to be grafted or covered	~20
Dirty	Purulent inflammation (e.g., abscess); preoperative perforation of respiratory GI or GU tract; penetrating trauma lasting >4 hr	~40

GI, gastrointestinal; GU, genitourinary.

TABLE 7.2

Chemoprophylaxis for Healthy Children Exposed to Specific Pathogens[a]

Pathogen or Disease	Prophylactic Agent	Dose/Day	Maximum Daily Dose	Divided Doses	Duration
Bordetella pertussis[b]	Erythromycin	40–50 mg/kg	2 g	4	14 days
	Azithromycin	10 mg/kg	500 mg	1	5 days
	or				
	Clarithromycin	15 mg/kg	1 g	2	7 days
***Haemophilus influenzae* type b**	Rifampin	20 mg/kg	600 mg	1	4 days
Corynebacterium diphtheriae	Erythromycin	40–50 mg/kg	2 g	4	7 days
	or				
	Benzathine penicillin	600,000 units (IM) if <30 kg 1.2 million units (IM) if ≥30 kg			Once
Neisseria meningitidis	Rifampin	20 mg/kg	1.2 g	2	2 days
	or				
	Ceftriaxone	125 mg (IM) if <12 yr 250 mg (IM) if ≥12 yr			
	or				
	Ciprofloxacin	500 mg if ≥18 yr	Once		
***Yersinia pestis* (pneumonic)**	Sulfonamide	40 mg/kg if <8 yr		2	7 days
	or				
	TMP-SMX	8 mg/kg TMP if <8 yr		2	7 days
	Tetracycline	15 mg/kg if ≥8 yr	1 g	4	7 days
Vibrio cholerae[c]					
<8 years	TMP-SMX	8 mg/kg TMP		2	3 days
8–17 years	Tetracycline	50 mg/kg	2 g	4	3 days
≥18 years	Ciprofloxacin	15 mg/kg	1 g	2	3 days
Streptococcus agalactiae	Ampicillin (maternal intrapartum)		2 g; then 1 g (IV) q4 h		Until delivery
	or				
	Penicillin G (maternal intrapartum)		5 million units; then 2.5 to 3 million q4h		Until delivery
***Mycobacterium leprae* (borderline or lepromatous)**	Dapsone	1 mg/kg	100 mg	1	3 yr
Herpes simplex virus[d]	Acyclovir (preemptive	60 mg/kg (IV)		3	10 days for preemptive

	following perinatal exposure for the neonate; see text)				
	Acyclovir (suppression of active infection in neonates with CNS infection; see text)	300 mg/m^2/dose		3 times/day	6 months
	Acyclovir (suppression of oral, genital or ocular infection)	10–20 mg/kg	800	2–4	Up to 12 months or longer
Influenza A[e]					
	Oseltamivir	By body weight, children ≥12 months: >40 kg: 75 mg; >23–40 kg: 60 mg; >15–23 kg: 45 mg Infants 9–11 months: 3.5 mg/kg Term infants 0–8 months: 3 mg/kg Preterm infants[f]	75 mg	1	See text
	Zanamivir inhaled (for prophylaxis for children ≥5 yr)	2 inhalations (5 mg per inhalation, 10 mg total per dose)	2 inhalations total	1	See text
Scabies	5% permethrin	Topically			Once
Neisseria gonorrhoeae					
Ophthalmia neonatorum	0.5% erythromycin	Topically			Once
Sexual exposure					Once
<45 kg	Ceftriaxone	25-50 mg/kg (IM)	125 mg		
45 kg and ≥8 years	Ceftriaxone plus	250 mg (IM)	250 mg		Once
	azithromycin	1 g orally in a single dose			
	or				
	Cefixime plus	400 mg			Once
	azithromycin	1 g orally in a single dose			
Chlamydia trachomatis					
<8 years	Erythromycin	50 mg/kg	2 g	4	7 days
≥8 years	Doxycycline	4 mg/kg	200 mg	2	7 days
	or				
	Azithromycin	1 g			Once
Treponema pallidum	Benzathine penicillin G	50,000 units/kg (IM)	2.4 million units (IM)	2	Once
	Alternative[a]				
	Doxycycline if ≥8 yr	4 mg/kg	200 mg		14 days
	Alternative				

	Azithromycin	2 g			Once
Klebsiella granulomatis	Doxycycline if ≥8 yr	4 mg/kg	200 mg	2	3 weeks
	or				
	TMP-SMX	8 mg/kg TMP	320 mg TMP	2	3 week

[a] Alternative drugs used only if other cannot be used; listings are not exhaustive. Some regimens are not of proven benefit. Administration is oral except as noted.

[b] See Chapter 162 for doses by age. Azithromycin dose for immunized at age ≥6 months is 10 mg/kg once followed by 5 mg/kg on subsequent 4 days (or maximum 500 mg, followed by 250-mg doses)

[c] Resistance of isolate requires revision of chemoprophylactic regimen.

[d] Based on current American Academy of Pediatrics recommendations for neonates and young infants.[13–14]

[e] Oseltamivir not recommended for routine prophylaxis for infants younger than 3 months of age because of the lack of safety data in that age group. Prophylaxis is indicated in very young infants when benefits outweigh possible risks.

[f] Oseltamivir dosing for preterm infants. The weight-based dosing recommendation for preterm infants is lower than for term infants. Preterm infants can have lower clearance of oseltamivir because of immature renal function, and doses recommended for full-term infants can lead to very high drug concentrations in this age group. Limited pharmacokinetic data provide the basis for once-daily dosing for prophylaxis of preterm infants using postmenstrual age (gestational age + chronologic age): 1.0 mg/kg per dose, orally, for those <38 weeks of postmenstrual age; 1.5 mg/kg per dose, orally, for those 38 through 40 weeks of postmenstrual age; 3.0 mg/kg per dose, orally, for those >40 weeks of postmenstrual age. For extremely premature infants (<28 weeks), please consult a pediatric infectious diseases physician.

CNS, central nervous system; IM, intramuscularly; IV, intravenously; SMX, sulfamethoxazole; TMP, trimethoprim.

Specific Pathogens With a Defined Point of Exposure

Neisseria meningitidis

The reported secondary attack rates for meningococcal disease among household contacts of index cases range from 0.25% in adults to 10% for infants younger than 1 year of age. Prophylaxis is reviewed in Chapter 125. Regimens using rifampin, ciprofloxacin, and ceftriaxone are effective in eliminating nasopharyngeal carriage of *N. meningitidis*.[4] The largest experience in children is with the use of rifampin. Prophylaxis should be instituted as soon as possible (preferably within 24 hours) for contacts in households and childcare centers, for close school contacts, as well as for persons who have had contact with infected oral secretions. Rifampin alters the metabolism of some drugs, including oral contraceptives, phenytoin, phenobarbital, carbamazepine, warfarin compounds, and other agents using the hepatic cytochrome P450 enzyme system. Safety of rifampin in pregnancy has not been established. Alternative agents include ceftriaxone and ciprofloxaxin.[4] Ceftriaxone requires injections, but compliance and antimicrobial exposure are ensured. Ciprofloxacin has been evaluated in adults and documented to eradicate carriage; fluoroquinolone agents have a relative contraindication in pregnant women, and prepubertal children out of concern for possible arthropathy. However, additional safety data on fluoroquinolones in children suggest that a single 10-day treatment course is unlikely to lead to long-term injury[5]; arthropathy is highly unlikely to occur with a single dose used for prophylaxis.

Haemophilus influenzae Type B

Prophylaxis against *Haemophilus influenzae* infections is discussed in Chapter 172. Infection caused by *H. influenzae* type b (Hib) is exceedingly rare in adequately immunized children. Rifampin is approximately 95% effective in the eradication of nasopharyngeal carriage of Hib in children.[6]

Group B *Streptococcus*

Early-onset disease caused by group B *Streptococcus* (*Streptococcus agalactiae)* can be prevented by intrapartum administration of ampicillin or penicillin[7] (see Chapter 119). Intrapartum administration of antibiotics does not prevent disease in infants who were infected before therapy was started, nor does it prevent late-onset group B *Streptococcus* infections.

Human Immunodeficiency Virus

Perinatal or intrauterine transmission of HIV is diminished by the administration of zidovudine and other anti-HIV retroviral therapy to the mother during pregnancy, with continued treatment of the infant for various periods of time after delivery, depending on the regimen used. This is an area of active investigation, and the most current information on treatment and prophylaxis is posted on the AIDSinfo website of the National Institutes of Health (http://aidsinfo.nih.gov/). Specific, current recommendations on regimens to prevent neonatal HIV infection can be found at: http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf. Current HIV maternal and neonatal prophylactic regimens with zidovudine and other agents or cesarean deliveries have reduced the rate of transmission in worldwide studies to <2% (see Chapter 109).[8] For recommendations for healthcare worker exposure[9] or sexual or injection-drug nonoccupational HIV exposure,[10] detailed antiviral drug recommendations based on risks of transmission balanced by risks of antiviral drug toxicity with chemoprophylaxis also are provided on the AIDSinfo website. The risk of HIV infection can be decreased after exposure, particularly if antiviral prophylaxis is provided within 12 to 24 hours of exposure (see Chapter 109).

Herpes Simplex Virus

Neonatal herpes simplex virus (HSV) infection usually results from exposure and transmission at the time of labor and delivery (see Chapter 204). With vaginal delivery during maternal primary genital infection, the rate of transmission of HSV to the infant can exceed 50%, whereas delivery during maternal reactivation disease carries a risk of less than 3% to 5%. It can be difficult to determine whether an active HSV infection is primary or recurrent because primary genital infection often is asymptomatic. Diagnostic tests for maternal HSV infection, including specific tests for HSV-1 and HSV-2, and rapid polymerase chain reaction testing for HSV DNA from mucosal surfaces, aid in defining the neonate's risk of infection, although many of these tests are not widely or rapidly available in hospitals to help with management decisions. For pregnant women, data on the efficacy of preventing infection by using antiviral prophylaxis with acyclovir or valacyclovir in patients with a history of genital HSV have prompted the use of antiviral agents during the last month of pregnancy. Prophylaxis can prevent recurrent infection at the time of delivery, although the impact of prophylaxis on preventing neonatal infection has not yet been demonstrated.[11,12]

For the neonate potentially exposed to a mother with recurrent genital HSV infection at the time of delivery, current guidance recommends cultures (e.g., cultures of the conjunctiva, mouth, nasopharynx, and rectum) and blood polymerase chain reaction at 12 to 24 hours of age in all infants who are asymptomatic without starting antiviral therapy,[13] whereas other experts consider that documented exposure to virus at the time of vaginal delivery constitutes sufficient risk to the infant to begin intravenous acyclovir therapy to prevent symptomatic infection. Positive results from culture specimens taken 24 hours or more after delivery are more likely to indicate infection, with a higher risk of developing symptomatic disease, thus leading the American Academy of Pediatrics to recommend intravenous acyclovir therapy when cultures are positive, to prevent symptomatic infection.[13]

For neonates with documented central nervous system HSV-2 infection, oral acyclovir prophylaxis to prevent symptomatic infection for the first 6 months of life has been associated with a modest benefit in improved cognitive development at 5 years of age, compared with children who did not receive prophylaxis.[14]

Acyclovir and valacyclovir prophylaxis to prevent recurrent symptomatic disease has been used to reduce the number of recurrent genital and oral-cutaneous HSV infections in adolescents and adults with frequent recurrences. In addition, acyclovir has been used prophylactically in children younger than 3 years of age who were exposed to HSV infections in daycare nursery outbreaks (30 to 60 mg/kg/day in 3 to 5 divided doses).[15] Some experts also recommend acyclovir prophylaxis following ocular HSV infections (recurrent HSV keratitis or recurrent infection of skin adjacent to the eye) to prevent corneal ulcerations and scarring. However, no data exist on the safety and efficacy of prophylaxis for children, and epidemiologic data document the increase in acyclovir resistance with long-term prophylaxis for keratitis[16] (see Chapter 295).

Respiratory Tract Bacterial and Viral Pathogens

Mycobacterium tuberculosis.

Isoniazid (INH) is effective in preventing symptomatic tuberculosis in latently infected asymptomatic children when the drug is given for 9 months (daily, or twice weekly with observed therapy), and INH is believed to be effective in preventing *Mycobacterium tuberculosis* infection in uninfected children following close exposure.[17,18] For children suspected of or documented to have latent tuberculosis infection caused by INH-resistant strains, rifampin should be administered for 4 months. Data suggest that a 12-dose, weekly administered regimen of combination of rifapentine and INH is as effective as INH alone, and this regimen has improved adherence compared with daily INH for 9 months.[19] Treatment of latent tuberculosis infection actually is therapy rather than prophylaxis because drug administration eradicates inapparent, ongoing latent infection and thereby prevents the progression to symptomatic disease (see Chapter 134).

Bordetella pertussis.

Macrolide agents are likely to be effective in preventing the transmission of *Bordetella pertussis* and in halting the development of clinical pertussis in household contacts before symptoms occur. Most *Bordetella* isolates are macrolide susceptible.[20–22] Both 5 days of azithromycin and 7 days of clarithromycin administration in older children and adults should be as effective as 14 days of erythromycin to prevent disease following exposure. Of the effective macrolides, azithromycin is the best tolerated and therefore the preferred agent. Given the association of idiopathic hypertrophic pyloric stenosis with administration of erythromycin to neonates, azithromycin also is the preferred agent for newborns. However, the safety profile of azithromycin in the newborn is not well defined, and cases of idiopathic hypertrophic pyloric stenosis following azithromycin have been reported. The risk for severe or fatal pertussis following exposure in neonates warrants administration of azithromycin, with close observation for the development of disease. Infants and children older than 2 months of age who are intolerant of macrolides should be given trimethoprim-sulfamethoxazole for 14 days as postexposure prophylaxis.

Influenza Virus.

Protection against influenza in high-risk patients, such as those with underlying cardiac or pulmonary disease, is best achieved by annual immunization. However, when this is not possible or is delayed, antiviral prophylaxis to prevent infection following an exposure until immunization can be completed is an appropriate strategy.[23,24] Prophylaxis should also be considered for immunocompromised children (for whom active immunization may not be protective) during periods of widespread influenza activity when exposures are likely. Neuraminidase inhibitors (zanamivir and oseltamivir) are effective for treatment and prophylaxis of both influenza A and influenza B virus infections. Although oseltamivir is approved by the Food and Drug Administration for treatment of infants 2 weeks of age and older, limited clinical information on safety exist for infants less than 3 months of age for whom prophylaxis is not recommended routinely.[23,25,26] Since 2005 to 2006, influenza A viruses have demonstrated widespread resistance to both amantadine and rimantadine, and influenza B virus is intrinsically resistant to these agents. Healthcare providers should follow annual recommendations by the Centers for Disease Control and Prevention and the American Academy of Pediatrics for optimal prophylaxis strategies, particularly for winter seasons in which vaccine strains of influenza are not well matched with circulating strains. Prophylaxis decreases but does not eliminate the risk of influenza infection.

Unusual Pathogens

Prophylaxis is recommended for several infrequent infections (see Table 7.2), including diphtheria, plague, cholera, and leprosy. Consultation with public health or infectious disease experts is recommended for dealing with these unusual infections in the United States.

Sexually Transmitted Pathogens

Prophylaxis is recommended after exposure to certain sexually transmitted agents. Despite the lack of evidence, prophylaxis is justified because (1) transmission rates of disease after exposure are high and (2) the diagnosis of infection can be difficult until active disease develops. Identification and treatment of index cases and contacts are critical to decreasing transmission in the community. Therefore, for certain infections that can be asymptomatic and for which transmission rates exceed 50%, such as gonorrhea, *Chlamydia* *trachomatis* infection, and syphilis, it is reasonable to provide therapy on an empiric basis, as outlined by the Centers for Disease Control and Prevention[27] (see Table 7.2). Guidelines also exist for evaluation and treatment of sexually abused children and adolescents[27] (see Chapter 54). Infants born to mothers who have untreated gonorrhea are at high risk of infection and should be given ceftriaxone, 25 to 50 mg/kg intravenously or intramuscularly once, not to exceed 125 mg; for premature infants and those with hyperbilirubinemia, ceftriaxone should be given cautiously because of concerns for bilirubin displacement from albumin binding sites caused by ceftriaxone. Additionally, ceftriaxone should not be administered concurrently with calcium-containing fluids because fatal calcium precipitation in the pulmonary vasculature can occur. No other regimens have been proven effective, and dual therapy with ceftriaxone and azithromycin is not currently recommended for newborns. If ceftriaxone cannot be used, please consult an infectious disease or public health specialist regarding the use of cefotaxime in neonates with gonorrhea.[27]

Chemoprophylaxis for Surgical Procedures and Trauma

Surgical procedures (see Chapter 100) and traumatic injuries (see Chapter 86) are associated with variable risks for infection. Studies documenting the efficacy of systemic prophylaxis of surgical wound infections have been performed primarily in adults, but the pathogenesis of such infections is assumed to be similar in children. The risk of infection can be estimated by categorizing the type of surgical procedure as clean, clean-contaminated, contaminated, or dirty, yielding a risk of infection from less than 2% up to approximately 40% (see Table 7.1).[28] Further assessment of risk is based on patients' characteristics.[29] Antibiotic prophylaxis is warranted in all patients who undergo procedures that are clean-contaminated, contaminated, or dirty (see Chapters 65, 66, 86, and 100).

Principles

During surgical procedures, the time of maximum risk of infection is relatively finite, and therefore chemoprophylactic regimens should be limited in duration. A single dose of antimicrobial agent given 60 minutes before the initial incision usually provides adequate tissue concentrations.[29–33] When an operation is prolonged, major blood loss occurs, or the agent used has a short half-life (e.g., 1 to 2 hours), additional dosage is advisable during the procedure.[29,32]

Surgical prophylaxis should be reserved for use in situations in which (1) the risks of infection outweigh the risks of toxicity of antibiotic therapy or the development of antibiotic resistance and (2) infection would have major consequence (e.g., when foreign material such as a ventriculoperitoneal shunt is implanted). The choice of antibiotic is based on its spectrum of activity against the most likely pathogens and the penetration at the site of interest. Periodic consensus recommendations for prophylaxis during surgical procedures are published by professional societies and in the *Medical Letter on Drugs and Therapeutics*.[2,29] Quality standards for prophylaxis in surgical procedures have been proposed.[34] Insufficient data exist on improved outcomes with the addition of vancomycin to standard preoperative regimens to prevent surgical site infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA); routine use of vancomycin is therefore not recommended.[29] However, for selected patients known to be colonized with MRSA, particularly patients who are to undergo extensive operations and for procedures involving the placement of foreign material, preoperative skin decontamination should be performed, and anti-MRSA perioperative prophylaxis should be considered.[2,29]

Surgical Procedures

Neurosurgery.

Placement of a ventriculoperitoneal shunt is classified as a clean procedure. However, the morbidity associated with infection of ventriculoperitoneal shunts is high. A favorable role has been demonstrated for prophylactic antibiotic therapy.[29,35,36]

Head and Neck Surgery.

For clean-contaminated surgical procedures involving the head and neck, prospective studies in adults with cancer suggest that more prolonged antimicrobial therapy beyond 24 hours is not associated with lower infection rates.[37] A meta-analysis of studies investigating antimicrobial prophylaxis for tonsillectomy demonstrated decreased fever, but no consistent benefit in rates of secondary hemorrhage or pain.[38]

Noncardiac Thoracic Surgery.

Studies in adults undergoing chest procedures document a decrease in surgical site infections with antimicrobial prophylaxis.[29,39] Although documented rates of infection are lower with video-assisted thoracoscopic surgery compared with open procedures, prophylaxis also is recommended for video-assisted thoracoscopic surgery.[29]

Cardiac Surgery.

In cardiovascular surgery, antibiotic prophylaxis is the standard of care. Even with a small risk of perioperative infection, the high morbidity of infection has justified its use as currently proposed in surgical infection guidelines.[2,29,40–42] Antibiotic treatment for 24 hours is likely to provide maximum benefit with acceptable risks; treatment for longer than 24 to 48 hours is not likely to provide additional benefit. For operations that last longer than 400 minutes, patients who were given a second dose of cefazolin demonstrated a statistically significant decrease in infections compared with patients who were not (7.7% vs. 16%).[42]

A prospective study of antimicrobial prophylaxis during implantation of pacemakers in adults demonstrated a significant reduction in the incidence of infection.[43] Routine antimicrobial prophylaxis was recommended for all patients receiving cardiovascular implantable electronic devices in the 2010 American Heart Association guidelines.[44] Antimicrobial prophylaxis for placement of ventricular assist devices in adults has not been standardized or well studied, and wide variation in practice has been documented.[45] However, national guideline recommendations suggest that prophylaxis be used as for other cardiac procedures.[29]

Abdominal Surgery.

Many studies performed in adults document the efficacy of antimicrobial prophylaxis in abdominal surgical procedures, particularly for colorectal procedures and appendectomy when perforation has occurred.[29] Prophylactic agents should have activity against common flora of the gastrointestinal tract, especially gram-negative enteric bacilli and anaerobic bacteria. For an appendectomy for acute appendicitis (including ruptured appendix), a Cochrane meta-analysis demonstrated that prophylaxis improved outcomes compared with placebo.[46] However, for nonperforated appendicitis, a single preoperative antibiotic dose was as effective as either 24 hours or 5 days of antibiotic prophylaxis.[47]

Orthopedic Surgery.

Clean procedures that do not involve implantation of foreign materials do not require antimicrobial prophylaxis.[29] Prophylactic antibiotics (particularly antistaphylococcal agents) reduce the incidence of infection after several orthopedic procedures, particularly when foreign material (e.g., an artificial joint or internal fixation device with plates or screws) is implanted. Efficacy of prophylaxis has been demonstrated most strikingly in joint replacement procedures in adults.[48] Current regimens most commonly use single-dose or short-course (24 hours or less) cefazolin or a similar agent with good antistaphylococcal activity, with a caution to screen patients for MRSA colonization and if the patient is already known to be colonized or infected with MRSA, to use vancomycin prophylaxis.[2,29]

Genitourinary Surgery.

Prophylactic antibiotics are not routinely required for cystoscopy in a patient who does not have an indwelling catheter and whose urine is documented to be sterile, although in some prospective controlled trials in adults, the rate of bacteriuria following a procedure was decreased from 9% to 3% to 5% with antibiotic prophylaxis.[49] If the urine is not sterile or is not known to be sterile (e.g., a culture has not been performed), a single dose of prophylactic antibiotic is recommended before the procedure. If the procedure is more invasive and involves ureteroscopy or the implantation of prosthetic material, antibiotic prophylaxis also is recommended.[2,29]

Trauma

Traumatic injury has, understandably, a higher risk for infection than controlled surgical procedures, but the risk varies by the extremely heterogeneous types and locations of injury, as well as by the characteristics of penetrating injury and environmental contamination of the wound (see Chapters 86 and 88). Trials of prophylactic antibiotics after significant trauma have inconsistently demonstrated a benefit in preventing infection, but they cannot always adequately identify the population most likely to benefit. Practice guidelines have been created that stratify risk of open fractures by type of injury, and they appear to have successfully matched prophylactic antibiotic recommendations with risk.[50]

Mammalian Bite Wounds

Antimicrobial prophylaxis or early treatment of animal bite wound injuries is controversial (see Chapter 88). A meta-analysis of studies of antibiotic prophylaxis of mammalian bite wounds suggested a benefit for antibiotics when the bite was caused by a human and when the mammalian bite occurred on the hand.[51] High-quality, prospective comparative studies of antimicrobial prophylaxis in which the severity and location of the bite and surgical management are standardized are needed. Amoxicillin clavulanate in the 4:1 formulation (20 to 40 mg/kg/day of the amoxicillin component in 3 divided doses for 5 to 7 days) provides the best spectrum of activity for both animal and human bites, considering the most frequently responsible pathogens: *Pasteurella multocida* (in cat and dog bites), *Eikenella corrodens* (in human bites), anaerobic bacteria, streptococci, and *S. aureus.* Alternative prophylaxis could be needed if MRSA was known to have caused previous infections in the child with a bite, but no regimen has been studied.

Antimicrobial prophylaxis also is recommended following a dog or cat bite in patients who are immunocompromised or have asplenia, advanced liver disease, preexisting or resultant edema of the affected area, moderate to severe injuries (especially to the hand or face), or injuries that may have penetrated the periosteum or joint capsule.[52]

Chemoprophylaxis in Special Situations and in Children With Conditions Predisposing to Infection

Children predisposed to development of infection by virtue of an underlying condition, such as an immunodeficient state, or an underlying anatomic defect (congenital or acquired) may benefit from chemoprophylaxis (Table 7.3). Prophylaxis is required over a prolonged period of risk, and strict compliance with regimens is critical to preventing “breakthrough” infections.

TABLE 7.3

Chemoprophylaxis in Special Situations

Disorder	Prophylactic Agents	Doses	Duration
Previous RF	Benzathine penicillin G	1.2 million units every 4 wk (every 3 wk if high-risk)	RF without carditis: 5 yr after episode, or 21 yr of age, whichever is longer
	or		
	Penicillin V	250 mg twice daily	RF with carditis, without regurgitation (clinical or echocardiographic): 10 yr after episode, or well into adulthood, whichever is longer
	or		
	Sulfisoxazole	500 mg if ≤27 kg (60 lb); 1 g if >27 kg; once daily	
	or		
	Erythromycin	250 mg twice daily	RF with carditis, with regurgitation: 10 yr after episode, or at least 40 yr of age, sometimes lifelong
Asplenic states[a]	Penicillin V	125 mg twice daily if <5 yr 250 mg twice daily if ≤5 yr	At least until 5 yr of age or 5 yr after surgical removal, whichever is longer; see text
Recurrent otitis media	Sulfisoxazole	50 mg/kg at bedtime	3–6 months
	or		
	Amoxicillin	20 mg/kg at bedtime	3–6 months
Recurrent urinary tract infection	TMP-SMX	2 mg/kg TMP once daily	Variable
	or		
	Nitrofurantoin	1–2 mg/kg once daily	

Endocarditis	Standard:		
Dental, oral, or upper respiratory tract procedures	Amoxicillin (PO)	50 mg/kg (maximum 2 g) procedure; then 25 mg/kg 6 hr after initial dose	Once 30 to 60 min before the procedure
	Penicillin-allergic:		
	Clindamycin (PO)	20 mg/kg (maximum 600 mg)	
	Oral medication impossible:		
	Ampicillin (IM or IV)	50 mg/kg (maximum 2 g)	
	Cefazolin	50 mg/kg (maximum 1 g)	Once 30 to 60 min before the procedure
	or		
	Ceftriaxone (IM)	25–50 mg/kg (maximum 2 g)	
	or		
	Gentamicin (IM or IV)		2 mg/kg (maximum 80 mg) before procedure; can be repeated 8 hr after initial dose

[a] Asplenic states include congenital and surgical asplenia, and splenic dysfunction associated with hemoglobinopathies; also considered for persons with complement disorders. Vaccinations are also very important. See references 59 to 62.

IM, intramuscularly; IV, intravenously; PO, by mouth; RF, rheumatic fever; SMX, sulfamethoxazole; TMP, trimethoprim.

Previous Rheumatic Fever

Patients who have a well-documented history of acute rheumatic fever (including disease manifested by carditis, arthritis, or chorea) should receive continuous antibiotic prophylaxis to prevent recurrent attacks associated with either symptomatic or asymptomatic group A streptococcal infection. The preferred prophylactic agent is penicillin. To ensure adherence, monthly administration of benzathine penicillin (1.2 million units intramuscularly for children weighing more than 27 kg [60 lb]; 600,000 units for those weighing less than 27 kg) is recommended, but for patients believed to be compliant with oral therapy, continuous prophylaxis with penicillin V (phenoxymethyl penicillin), 250 mg twice daily, should be effective at preventing streptococcal infection if an exposure occurs. For patients receiving monthly intramuscular injections, adequate serum antibiotic levels may not persist beyond 3 weeks, and, in high-exposure situations, recurrences are less likely if intramuscular therapy is provided every 3 weeks rather than every 4 weeks.[53]

The appropriate duration of chemoprophylaxis for rheumatic fever is not known; some studies suggest that treatment can be discontinued in young adults who are at low risk for recurrent episodes of group A streptococcal infection.[54] Current recommendations for minimum duration are 5 years (or until age 21 years) for patients *without* carditis and 10 years (or until age 21 years, whichever is longer) for those *with* carditis, without residual heart disease. For patients with carditis *and* residual heart disease, prophylaxis should continue at least 10 years or until age 40 years (whichever is longer), with consideration given to lifelong prophylaxis[55] (see Table 7.3).

Recommendations for other conditions associated with *Streptococcus pyogenes* are less certain. Most experts recommend antibiotic prophylaxis for children with poststreptococcal Sydenham chorea, similar to that for rheumatic fever. Some experts recommend prophylaxis for 1 year in children who have had an episode of poststreptococcal reactive arthritis but have no evidence of rheumatic fever because reactive arthritis can be an incomplete manifestation of acute rheumatic fever. If no evidence of rheumatic fever is present after 12 months of prophylaxis, therapy can be discontinued, but the child with poststreptococcal reactive arthritis should be followed long term for new evidence of cardiac involvement.[55–58] The cost-to-benefit ratio, safety, and efficacy of prophylaxis of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) have not been established; routine chemoprophylaxis is not recommended.

Asplenia

Children with functional or anatomic asplenic states, particularly sickle cell anemia, have been shown to benefit from continuous penicillin prophylaxis to prevent pneumococcal and other bacterial infections (see Chapter 106). A single prospective controlled study showed an 84% reduction in rate of infection in children younger than 3 years of age who received daily oral penicillin V (125 mg twice daily for children <5 years; 250 mg twice daily for children ≥5 years) compared with children receiving placebo.[59] A follow-up placebo-controlled trial of penicillin prophylaxis beyond 5 years of age in children who were receiving comprehensive care for sickle cell disease showed a low incidence of infection and no significant benefit of antibiotic prophylaxis in preventing pneumococcal bacteremia or meningitis (2% in the penicillin-treated group vs. 1% in the placebo group).[60] Prophylaxis can be discontinued in children older than 5 years of age, provided these children have not previously had invasive pneumococcal infection and are appropriately immunized for age with conjugate and polysaccharide vaccines.

Asplenia from other causes (congenital, surgical, functional) also is associated with an increased risk of fulminant septicemia. Compared with the incidence in healthy children, the incidence of mortality from septicemia is 50-fold higher after splenectomy for trauma (compared with >350-fold higher in children with sickle cell disease). Although the risk is higher in younger children and in the first 5 years after splenectomy, fulminant septicemia has been reported in adults more than 25 years after splenectomy.[61,62] The general consensus is that asplenic children with malignant disease, thalassemia, congenital anomalies, or other diseases with a high risk of fulminant infection should receive daily chemoprophylaxis.[61] Less certainty exists about the need for chemoprophylaxis in otherwise healthy children who undergo splenectomy for trauma. In general, prophylaxis (in addition to appropriate immunization) should be provided to asplenic children younger than 5 years of age and should be considered for older children. For children of any age, prophylaxis should be considered for 1 year after splenectomy.[61] Asplenic children should receive conjugate and polysaccharide pneumococcal vaccines, meningococcal conjugate vaccine (with appropriate boosting), and Hib vaccine, as recommended in Chapter 6.

Underlying Immunocompromising Conditions

The prevention of bacterial, viral, fungal, and mycobacterial infections in immune-compromised hosts is an area of active research. As new regimens for treatment of disease evolve, collaborative guidelines are published by professional organizations to aid the practitioner in decisions regarding prophylaxis for various high-risk populations, including children undergoing cancer chemotherapy,[63] stem cell transplantation,[64] solid-organ transplantation,[65,66] and therapy of HIV infection.[67]

Similarly, as primary immunodeficiencies of cellular or humoral immunity or of phagocytic cell function are increasingly identified and better characterized, a systematic approach to antimicrobial prophylaxis for each entity is considered, based on the expected pathogens and risks of infection (see Chapters 102 to 105).[68,69] Immunization with a protein-conjugate vaccine is likely to be more protective than antibiotic prophylaxis for those immunodeficiencies in which the child can mount an appropriate, protective response to immunization.

Other Underlying Conditions

Recurrent Otitis Media

The widespread use of conjugate pneumococcal vaccines has been associated with a decrease in the incidence of acute and recurrent otitis media. In the past, sulfisoxazole, amoxicillin, and trimethoprim-sulfamethoxazole were shown to be effective for prophylaxis in otitis-prone children, although not all placebo-controlled investigations documented benefit.[70–74] The development of colonization with antibiotic-resistant organisms, as well as transmission of these organisms to contacts (both adults and children), should be considered. No current studies of antibiotic prophylaxis have been performed in the current PCV13 era; therefore, the risks and benefits of tympanostomy tube placement and antimicrobial prophylaxis should be considered for each child based on factors such as age, frequency, and severity of infections.[75,76]

Urinary Tract Infection

Antibiotic prophylaxis is effective in preventing recurrent urinary tract infection and is indicated in children with underlying anatomic abnormalities or neurogenic bladder, which lead to a higher risk of infection, especially in patients with obstructive lesions or high-grade vesicoureteral reflex (grades III to V).[77–79] Prophylaxis is designed primarily to prevent incremental renal damage with each episode of pyelonephritis that may ultimately lead to renal failure later in life. In the past, children without the identifiable increased risk factors listed here who had recurrent infections also were believed to benefit from antibiotic prophylaxis. In this group, documentation of 3 or more urinary tract infections within a 1-year period was considered a reasonable indication for prophylaxis. The benefit of prophylaxis in this group is limited to decreasing the pain and discomfort that accompany urinary tract infections, rather than preventing renal scarring, although even this benefit was questioned in some well-controlled studies. Increased antimicrobial resistance is often associated with prophylaxis.[78,80–84]

Current American Urology Association guidelines for children suggest that more high-quality data are required before recommendations regarding antimicrobial prophylaxis can be made, particularly for specific high-risk groups of children who can benefit most from prevention of recurrent infections.[85]

Nitrofurantoin (1 to 2 mg/kg/day), and trimethoprim-sulfamethoxazole (2 mg/kg/day of the trimethoprim component) are the best-studied regimens in children for prophylaxis.

Prevention of Endocarditis

The American Heart Association periodically publishes guidelines for endocarditis prophylaxis. In 2007, major changes were made based on the Committee's conclusions: (1) extremely small numbers of cases of infective endocarditis would be prevented by antibiotic prophylaxis for dental procedures, even if prophylaxis were 100% protective; (2) prophylaxis should not be recommended solely on the basis of an increased lifetime risk of acquisition of endocarditis; (3) infective endocarditis prophylaxis for dental procedures should be recommended only for people with underlying conditions associated with the highest risk of adverse outcome from infective endocarditis; (4) for patients with these underlying conditions, endocarditis prophylaxis should be given for all dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa.[3] Antibiotic prophylaxis decreases the risk, but it does not always prevent the occurrence of endocarditis in high-risk children. Cardiac conditions associated with the highest risk of adverse outcome from endocarditis for which prophylaxis with dental procedures is recommended are shown in Box 7.1. Antibiotic prophylaxis is no longer recommended for any other form of congenital heart disease, including mitral valve prolapse with regurgitation, acquired valvulopathy, hypertrophic cardiomyopathy, or the presence of cardiac pacemakers or implanted defibrillators, unless the patient has a history of previous endocarditis or placement of a prosthetic valve. Antibiotic prophylaxis is not recommended for shedding of deciduous teeth or bleeding from trauma to the lips or oral mucosa.

Box 7.1

Prophylaxis for Infective Endocarditis According to Cardiac Conditions and Dental Procedures[3]

Cardiac conditions associated with highest risk of adverse outcome from endocarditis for which prophylaxis for dental procedures is recommended:

- Prosthetic cardiac valve
- Previous infective endocarditis
- Congenital heart disease[a]
    - Unrepaired cyanotic congenital heart disease including palliative shunts and conduits
    - Completely repaired congenital heart defect with prosthetic material or device, whether placed surgically or by catheter intervention, during the first 6 months after the procedure[b]
    - Repaired congenital heart disease with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device that inhibit endothelialization
- Cardiac transplantation in which cardiac valvulopathy has developed

Dental procedures for which endocarditis prophylaxis *is* recommended for patients above:

- All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa
- Professional cleaning with gingival probing, biopsies, suture removal, placement of orthodontic bands

Dental procedures for which endocarditis prophylaxis *is not* recommended even for patients above:

- Routine anesthetic injections through noninfected tissue
- Taking of dental radiographs
- Drilling of carious teeth
- Orthodontic or prosthodontic procedures
- Placement or removal of appliances
- Placement of orthodontic brackets
- Adjustment of orthodontic appliances

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[a] Except for conditions listed, antibiotic prophylaxis is no longer recommended for any other form of congenital heart disease.

[b] Prophylaxis is recommended because endothelialization of prosthetic material occurs within 6 months after the procedure.

From Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation 2007;116:1736–1754.

The antibiotics recommended when prophylaxis is appropriate according to Box 7.1 are shown in Table 7.2. A single dose of antibiotic should be administered before the procedure. If the dose was inadvertently omitted, it can be administered up to 2 hours after the procedure.

Antibiotic prophylaxis is not recommended for routine noninvasive respiratory tract, genitourinary, or gastrointestinal procedures.[3] Antibiotic prophylaxis can be considered for patient with conditions listed in Box 7.1 who undergo an invasive procedure that involves incision or biopsy of the respiratory tract mucosa (e.g., tonsillectomy, adenoidectomy, bronchoscopy with incision of the respiratory mucosa) or when the procedure is performed to treat an established infection (e.g., to drain an abscess or empyema). For patients with conditions listed in Box 7.1 who are scheduled for cystoscopy or other urinary tract manipulation and who have an enterococcal urinary tract infection or enterococcal colonization, antibiotic therapy to eradicate or suppress enterococci in the urine before the procedure may be reasonable.[3]

Antibiotic prophylaxis is recommended for procedures on infected skin, skin structures, or musculoskeletal tissue only for patients with conditions listed in Box 7.1. In 2007, the American Heart Association reaffirmed previous recommendations of settings for which endocarditis prophylaxis is *not* indicated (including cardiac catheterization and cesarean delivery) and added the following procedures: ear and body piercing, tattooing, vaginal delivery, and hysterectomy.[3]

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8

Protection of Travelers

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More than 1.1 billion people, including an estimated 60 million children, travel internationally each year.[1–3] Up to 8% of travelers to developing countries seek medical care while abroad or on returning home.[4] Although travel can expose children to some risks, the benefits are many. A careful pretravel evaluation to provide appropriate guidance and preparation is critical to protect pediatric travelers and their families and allow them to enjoy their time abroad.

Preparation for Travel

General Advice

A pretravel evaluation should be performed at least 6 to 10 weeks before travel. The entire itinerary for the trip should be reviewed, including destinations, time and duration of travel, types of accommodation, activities, and potential exposure to insects and animals. The evaluation also should review the medical and immunization history of the child to ensure that appropriate advice is given regarding preventive measures, including necessary vaccines. This evaluation can be accomplished by providing a form for parents to complete and bring to the initial pretravel assessment visit. Particular attention should be given to children of immigrants who are returning to their home countries to visit friends and relatives (VFR) because these children have been shown to be at increased risk for many infectious diseases.[1,5,6] Many excellent resources, most of which are accessible online, provide pretravel advice for pediatricians (Box 8.1).

Box 8.1

Resources and Additional Information for Travelers

- World Health Organization (WHO). International Travel and Health, print version updated biannually, online version updated regularly:www.who.int/ith/
- WHO vaccine summaries: http://www.who.int/immunization/monitoring_surveillance/en/
- Centers for Disease Control and Prevention (CDC). Health Information for International Travel, updated approximately every 2 years (The Yellow Book, Atlanta, GA: US Department of Health and Human Services): http://wwwnc.cdc.gov/travel/page/yellowbook-home-2014
- CDC travel information section: www.cdc.gov/travel/
- CDC *Morbidity and Mortality Weekly Report* (MMWR Morb Mortal Wkly Rep): http://www.cdc.gov/mmwr/
- CDC *Emerging Infectious Diseases Journal:* http://wwwnc.cdc.gov/eid/
- CDC Malaria Hotline: 770-488-7788
- CDC Travelers' Health Automated Information Line (toll-free): 877-FYI-TRIP
- GIDEON (Global Infectious Diseases and EpidemiOlogy Network): www.gideononline.com/
- Pickering LK, Baker CJ, Kimberlin DW, Long SS (eds). Red Book: 2012 Report of the Committee on Infectious Diseases, 29th ed. Elk Grove Village, IL, American Academy of Pediatrics, 2009 (888-

227-1770 Publications); new edition published every 3 years

- Pan American Health Organization, the regional office of the WHO: www.paho.org/
- Immunization Action Coalition: http://www.immunize.org/resources/manufact_vax.asp
- United States State Department Hotline for American Travelers: 202-647-5225
- United States State Department: http://travel.state.gov/content/travel/english.html
- International Association for Medical Assistance to Travellers: www.iamat.org
- Program for Monitoring Emerging Diseases (Pro-MED-mail): www.promedmail.org
- Committee to Advise on Tropical Medicine and Travel (CATMAT): http://www.phac-aspc.gc.ca/tmp-pmv/catmat-ccmtmv/index-eng.php
- Travax (NHS National Services Scotland): www.travax.scot.nhs.uk/
- United States: American Society for Tropical Medicine and Hygiene travel health: www.astmh.org
- International Society for Travel Medicine: www.istm.org
- United Kingdom (TravelHealth): www.travelhealth.co.uk/diseases/travelclinics.htm
- Canada Public Health Agency: www.travelhealth.gc.ca

Travel health guidance should be provided regarding safety issues and infectious diseases.[7–9] Motor vehicle crashes are the most common cause of death among travelers; therefore, particular attention must be given to use of seat belts and car seats as recommended according to the age and size of the child.[10] Car seats may not be readily available at the destination and should accompany the family. Other injury concerns for children include drowning, falls from unprotected balconies or windows, and electrical injuries from unprotected outlets. Children and adolescents who participate in extreme sports and outdoor activities while traveling also should be informed of the potential risks. A parent traveling alone with children should have notarized documentation authorizing him or her to travel with the children.

Advice regarding food and water precautions and insect avoidance should be reviewed thoroughly. Skin protection is an important topic and includes both the risk of serious sunburn and the avoidance of infectious diseases. For sunblock, 30 is the minimum sun protection factor (SPF) recommended for children. Sunblock should be applied 30 minutes before exposure and always before insect repellent is applied where both are needed. Adolescent travelers should be counseled regarding safer sex practices and risks of body piercing and tattooing in less developed countries. Freshwater exposure of any kind should be avoided in areas that are endemic for schistosomiasis or where *Leptospira* species can contaminate the water. Exposure to infected stool of animals or humans can result in several types of parasitic infection either directly (e.g., hookworm) or through fecal-oral exposure (e.g., *Toxocara* spp.). Shoes provide more protection than sandals for children exposed to contaminated environments. Animal bites can result in injury, bacterial infection at the site, or rabies; therefore, children should be cautioned to avoid unknown animals while traveling. Because disposable diapers may not be available in some countries, parents should be aware that cloth diapers must be ironed after washing to kill eggs and larvae deposited on clothing by the tumbu fly, the vector of myiasis, in parts of Africa.

A travel medical kit should be assembled before travel and carried with the family at all times (Box 8.2). As at home, medications should be stored in childproof containers out of reach of children. A discussion of travel health insurance and what to do in the event of illness should be included in the evaluation. In addition, written material summarizing the pretravel advice can be helpful for families.

Box 8.2

Pediatric Travel Medical Kit

Nonprescription Items

- Personal information card: name, birth date, chronic medical conditions, regular medications, allergies, blood type, vaccination record, emergency contact information
- First aid supplies: bandages, adhesive tape, gauze, antiseptic cleaning solution, commercial suture or syringe kit (with letter from physician)
- Thermometer
- Analgesics or antipyretics: acetaminophen, ibuprofen
- Skin care products: sunscreen (sun protection factor [SPF] ≥30), barrier ointment/cream, topical corticosteroid cream, disinfectant solution (e.g., chlorhexidine)
- Antihistamine (e.g., diphenhydramine)
- Insect repellent (diethyltoluamide [DEET]), insecticide (permethrin)
- Water purification system
- Oral rehydration packets
- Antimotility agent (e.g., loperamide) if older child (≥2 years)
- Extra pair of prescription glasses

Prescription Items

- Currently prescribed medications
- Antimalarial prophylaxis
- Antibiotic for severe travelers' diarrhea (see text)
- Topical antibacterial ointment or cream

- Topical antifungal ointment or cream
- Topical ophthalmic and otic antibiotic solution

Immunizations Overview

Although immunization rates have been increasing in the United States, significant numbers of children are underimmunized.[11] Many countries with low immunization rates have ongoing transmission of vaccine-preventable illnesses that rarely are seen in North America. Consequently, children who travel must have up-to-date immunization coverage to minimize their risk of contracting vaccine-preventable diseases. Country-specific vaccine-preventable disease statistics and immunization schedules can be found on the World Health Organization (WHO) website, and a listing of international vaccine names also is available online.[12,13]

Travel vaccines are divided into the categories of routine, required, and recommended. *Required* travel vaccines are needed by travelers to cross international borders according to health regulations at the destination. Proof of yellow fever vaccination may be required for entry into or travel from countries where yellow fever is endemic. Vaccinations against meningococcus, influenza virus, and polio virus are required for travelers to the Hajj in Saudi Arabia.[14] *Recommended* travel vaccines include vaccines that should be considered according to the risk of infection during travel.

During the pretravel evaluation, some children may need to receive vaccines in the routine childhood and adolescent immunization schedule administered in an accelerated manner to complete their primary series, catch up with vaccinations, or complete the recommended pretravel vaccine series before departure (Table 8.1).[15–17] The routine or catch-up schedule for immunizations should be continued when the child returns.

TABLE 8.1

Acceleration of Routine Vaccine Schedule for Travel[a]

Vaccine	Earliest Age for First Dose	Minimum Interval Between Doses
Combined hepatitis A	1 yr	1 wk, 2 wk between second and third doses (booster after 1 yr)

and B[b]		
Hepatitis A	1 yr	6 months[c]
DTaP	6 wk	4 wk, 6 mo between third and fourth doses
IPV	6 wk	4 wk
OPV	Birth	4 wk
Hib (conjugate)	6 wk	4 wk (booster after 12 months of age)
Hepatitis B	Birth	4 wk, 8 wk between second and third doses (third dose should be given ≥16 weeks after first dose)
PCV13	6 wk	4 wk, 8 wk between third and fourth doses (after 12 mo of age)
Measles	6 mo followed by MMR at 12 mo and at 4 to 6 yr of age	4 wk
MMR	12 mo	4 wk
Rotavirus[d]	6 wk	4 wk
Varicella	12 mo	4 wk if ≥13 yr of age 3 mo if <13 yr of age

[a] Regular immunization schedule should be reinstituted on return from the endemic area.

[b] Combined hepatitis A and B accelerated schedule is an off-label use for children.

[c] Hepatitis A booster does not need to be given as an accelerated schedule because the seroconversion rate following the first dose is high. The second dose can be given any time after 6 months to induce long-lasting immunity.

[d] For rotavirus vaccine, the maximum age for the first dose is 14 wk and 6 days, and the maximum age for the last dose is 8 months and 0 days.

DTaP, diphtheria and tetanus toxoids and acellular pertussis; Hib, *Haemophilus influenzae* type b; IPV, inactivated poliovirus vaccine; MMR, measles, mumps, rubella; OPV, oral poliovirus vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.

Two or more inactivated vaccines or an inactivated and a live vaccine can be administered simultaneously or at any interval. In general, 2 parenterally administered live vaccines should be administered either simultaneously or at least 28 days apart.[18] Caution must be used when scheduling live vaccine administration following immune globulin (IG) administration because decreased immunogenicity of the vaccines can result.[16] This is particularly true of measles and varicella vaccines. Measles- and varicella-containing vaccines should be deferred from 3 to 11 months after IG administration depending on the indication and dose of IG required (see Chapter 5). Although the effect of IG administration on the immunogenicity of varicella vaccine is unknown, the current recommendation is to use the same guidelines for varicella vaccine and IG as are used for measles-containing vaccines.[19] IG administration does not interfere with the immune response to yellow fever vaccine, oral poliovirus vaccine (OPV), rotavirus vaccines, or any inactivated vaccines. IG should not be given <14 days after administration of a live vaccine.

Routine Immunizations

Most North American vaccine-preventable diseases are endemic globally; therefore, a child's routine vaccination schedule should be brought up to date before travel.[15] In particular, the primary series of vaccines, including at least 3 doses of diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine, should be administered by standard or accelerated schedules (see Table 8.1). The tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) adolescent preparation vaccine should be used as the adolescent booster beginning at 11 years of age.[20] People 7 through 10 years of age who are not fully immunized against pertussis should receive a single dose of Tdap. Tdap can be administered regardless of the interval since the last tetanus- and diphtheria-containing vaccine. Underimmunized children <6 years of age also should receive the conjugate *Haemophilus influenzae* type b (Hib) vaccine before travel.

Although global poliomyelitis eradication had been targeted for 2005, poliomyelitis remains endemic in 3 countries: Afghanistan, Nigeria, and Pakistan.[21] OPV, although widely used in the WHO Expanded Programme on Immunization-Plus (EPI-PLUS), is not available in the US. An accelerated schedule for inactivated poliovirus vaccine (IPV) should be initiated if required, with the first dose given at 6 weeks of age and subsequent doses given at least 4 weeks apart.[15] If a child is traveling in the first few weeks of life and OPV is available, vaccination with OPV can be initiated at birth, with subsequent doses at 4-week intervals.[17] A booster dose of IPV should be given at 4 to 6 years of age and at least 6 months following the previous dose.

Approximately 400 children die of measles every day; children <1 year of age have the highest risk of severe disease.[22] Suboptimal immunization rates raise the risk of transmission within the US, as evidenced by the 2015 outbreak linked to undervaccinated children at a California amusement park.[23] Moreover, the risk of subacute sclerosing panencephalitis is related to acquisition of measles virus at a young age. Maternal antibodies generally protect infants for <6 months. Children between 6 and 12 months of age who are traveling to countries where measles is endemic (including all countries where measles vaccination is not universal) should receive 1 dose of measles, mumps, rubella (MMR) vaccine before travel. Only doses given at or after 12 months of age count as part of the routine US immunization schedule. Children >12 months of age should receive 2 doses of MMR given at least 28 days apart before travel.

Hepatitis B is part of the routine immunization schedule in the US.[24] Children who have not completed their routine hepatitis B series should receive hepatitis B vaccine before travel to highly endemic areas. The hepatitis B series can be accelerated with doses given at 0, 1, and 2 months, followed by a fourth dose at 12 months. A hyperaccelerated schedule of 0, 7, and 21 days with a fourth dose at 12 months can be used if necessary. Although this schedule is not licensed by the US Food and Drug Administration, it is used widely in travel clinics. A 2-dose schedule of adult Recombivax HB (Merck, Whitehouse Station, NJ) at 0 and 4 to 6 months is licensed in the US for adolescents 11 through 15 years of age.[24]

Hepatitis A vaccine, recommended universally for US children, should be given as a 2-dose schedule beginning at 12 to 24 months of age with the second dose 6 months later.[25] Children who have not received the hepatitis A vaccine series should be vaccinated before travel to developing countries. Most hepatitis A cases imported into the US by travelers are related to travel to Mexico and Central America.[25] Although hepatitis A generally causes asymptomatic or mild infection in young children, such children can shed the virus for prolonged periods. Consequently, vaccination of young travelers is recommended to protect both the recipient and any contacts. Children from birth to <12 months of age who are at high risk of exposure to hepatitis A can be given 0.02 mL/kg of IG intramuscularly as passive hepatitis A prophylaxis.[25] For travel lasting longer than 3 months, a larger dose of 0.06 mL/kg should be used.

Twinrix (GlaxoSmithKline, Philadelphia) is a combined hepatitis A and B vaccine that is licensed for people ≥18 years of age.[17,24] Twinrix-Junior is not licensed in the US but is available widely in Europe and Canada for children 1 through 15 years of age. These vaccines are given in a 3-dose schedule at 0, 1, and 6 months. For last-minute travel they can be accelerated in a schedule of 0, 7, and 21 days with a booster given at 1 year.[26] In Canada and parts of Europe, 2 *adult* doses of the vaccine administered 6 months apart have been approved for children 1 through 15 years of age.[27,28]

Varicella vaccine is recommended for all susceptible children and is given in the US for children from 12 months through 12 years of age. For children <13 years of age, a second dose should be given 3 months after the first. For adolescents 13 years of age and older, 2 doses are required with an interval of at least 4 weeks between doses.[19]

The 13-valent pneumococcal conjugate vaccine (PCV13) is part of the routine childhood immunization schedule and should be given as a 4-dose series at 2, 4, 6, and 12 through 15 months of age, although the schedule can be accelerated (see Chapter 123).[29]

Two quadrivalent conjugate meningococcal vaccines for serogroups A/C/Y/W-135 (MCV) are licensed in the US for children. Menactra (Sanofi Pasteur, Swiftwater, Pa) is licensed as a 2-dose series between the ages of 9 and 23 months, whereas Menveo (GlaxoSmithKline) is licensed as a 4-dose series starting at 2 months of age. Both vaccines are recommended for persons at increased risk of meningococcal disease, including travelers to countries with hyperendemic or epidemic meningococcal disease.[30] In addition, MCV is recommended routinely for use in all children 11 to 12 years of age, with a booster dose at 16 years of age. Administer 1 dose at 13 through 18 years of age if the patient is not previously vaccinated (see Chapter 125).[31] As of January 2015, 2 novel vaccines for serogroup B have been approved in the US for persons 10 to 25 years of age in response to an outbreak in university students.[32] Bexero (GlaxoSmithKline) has been approved for use in Canada for children 2 months of age and older.[33] However, this vaccine is generally not recommended for travel unless someone is traveling to an area with an ongoing outbreak of serogroup B meningococcal disease.

Influenza vaccine is recommended for all people without medical contraindications 6 months of age and older.[34] The influenza season occurs from April to September in the southern hemisphere and year-round in the tropics. Influenza outbreaks have occurred on cruise ships and organized group tours in any latitude and season.[35]

Rotavirus vaccine is recommended for all US children starting at 2 months of age in a 2- or 3-dose schedule depending on which of the 2 licensed vaccines is used.[36] Rotavirus vaccine can be given in an accelerated dosing schedule, if needed (see Table 8.1).

Two human papillomavirus (HPV) vaccines are licensed in the US and Canada and are recommended for use in all girls at 11 to 12 years of age.[37] HPV4 vaccine is recommended for boys and girls at 11 to 12 years of age. HPV vaccines in children are administered in a 2- or 3-dose schedule, the second and third dose 2 and 6 months after the first dose or a single 6-month dose. The first dose can be given as early as 9 years of age.

Required and Recommended Vaccines for Travel

Table 8.2 provides details regarding travel vaccines recommended for children.

TABLE 8.2

Schedule and Dosing for Travel Vaccines

Vaccine	Schedule	Minimum Age	Dose (mL)	Route	Booster Dose
BCG (live, attenuated)	1 dose	Birth	<1 yr: 0.05 mL ≥1 yr: 0.1 mL	Intradermal preferred but subcutaneous acceptable	None
Hepatitis A/B, combined (inactivated/recombinant)	3 doses: 0, 1, and 6 mo	1 yr	0.5 mL	Intramuscular	None
Meningococcal A/C/Y/W-135 (conjugated polysaccharide)	2–6 mo = 4 doses: 0, 2, 4, 12 mo 7–23 mo = 2 doses: 0, 3 mo >23 mo = 1 dose	2 mo	0.5 mL	Intramuscular	<7 yr: 3 yr ≥7 yr: 5 yr
Rabies (inactivated cell culture)	3 doses: 0, 7, 21 or 28 days	Birth	1.0 mL	Intramuscular	Consider at 2 yr if high-risk
Typhoid, Ty21a (live, attenuated)	4 doses: alternate days	6 yr	1 capsule	Oral	5 yr
Typhoid, Vi (capsular polysaccharide)	1 dose	2 yr	0.5 mL	Intramuscular	2 yr
Yellow fever (live,	1 dose	9 mo	0.5 mL	Subcutaneous	10 yr

attenuated)					
Japanese encephalitis (inactivated cell culture)	2 doses: 0 and 28 days	2 mo	<3 yr = 0.25 mL ≥3 yr = 0.5 mL	Intramuscular	1 yr

BCG, bacille Calmette-Guérin.

Cholera Vaccine

The risk of cholera is low for travelers. Cholera vaccines are not available in the US. However, they are licensed in some countries: WC/rBS (Dukoral, SBL Vaccines, Solna, Sweden) and 2 closely related bivalent cholera vaccines Shanchol (Shantha Biotec, Hyderabad, India) and mORCVAX (Vabiotech Vietnam).[38] Dukoral is licensed for children ≥2 years of age. Cholera vaccine is not required for entry into any country. The WHO recommends use of cholera vaccine only for travelers at high risk such as emergency or relief workers who plan to work in refugee camps or as healthcare personnel in endemic areas.[39]

Typhoid Vaccine

Typhoid vaccine is recommended for pediatric travelers to the Indian subcontinent and other developing countries in Central and South America, the Caribbean, Africa, and Asia.[40] Children are particularly at risk of developing typhoid and of becoming chronic carriers. Two vaccines are available for prevention of typhoid: a live, attenuated oral vaccine (Ty21a), which can be used in children ≥6 years of age; and a purified Vi capsular polysaccharide vaccine that is delivered intramuscularly to children ≥2 years of age. The efficacy of both vaccines is approximately 50% to 70%; receipt of the vaccine does not eliminate the need for food and water precautions.[41–43] If exposure continues, revaccination is recommended every 2 years for the polysaccharide vaccine and every 5 years for the oral Ty21a vaccine.

The Ty21a vaccine is available only in capsules in the US, thus limiting usefulness in younger children. The Ty21a vaccine must be refrigerated and taken with cool liquids approximately 1 hour before eating. The Ty21a vaccine should not be taken concurrently with the antimalarial proguanil, and antibiotics should not be used from the day before the first capsule until 7 days after completing the vaccine course. Clinical trials of a Vi conjugate vaccine demonstrating safety, efficacy, and immunogenicity in infants and children are ongoing.[44–46]

Yellow Fever Vaccine

Yellow fever vaccine is a live, attenuated vaccine that may be required or recommended for travel to central South America and sub-Saharan Africa. Some countries in Africa require an international certificate of vaccination (or a physician's waiver letter) against yellow fever for all entering travelers; other countries may require evidence of vaccination for travelers coming from or traveling through endemic areas. The vaccine is recommended for all children ≥9 months of age traveling to endemic areas. A single dose of yellow fever vaccine confers lifelong immunity; therefore, boosters are not required for protection. However, a booster may be required every 10 years by some countries.[47] Risks and benefits of yellow fever vaccination and likelihood of infection must be considered carefully in pregnant women and in people who are immunocompromised.[48] Yellow fever vaccine contains egg protein; therefore, people with previous anaphylaxis in response to eggs should not receive the vaccine. The vaccine is only available in the US from providers certified by state health departments.[49]

A yellow fever vaccine–associated encephalitis syndrome has been reported in young infants at a rate of 0.5 to 4 per 1000 infants vaccinated.[17] Neurologic symptoms occur 7 to 21 days after immunization; disease is related to reversion of vaccine virus to wild-type neurotropic virus. Consequently, the vaccine is contraindicated in infants <6 months of age. For infants 6 to 9 months of age who cannot avoid travel to a yellow fever–endemic area, consultation with an expert in the field is recommended. Yellow fever vaccine–associated viscerotropic disease, a severe systemic illness that can result in fatal organ failure, rarely has been reported.

Rabies Vaccine

Rabies is highly endemic in Africa, Asia (particularly India, China, and Indonesia), and parts of Latin America, but the risk to travelers is low. Preexposure rabies immunization is recommended for travelers with an occupational risk of exposure, for people planning extended stays in endemic areas where medical care is limited, and for outdoor travelers.[50] However, studies suggest that animal bites often occur during short-term travel.[51] Given that children are more likely to interact with animals and not report an animal bite, rabies preexposure vaccination should be considered for children traveling to endemic countries for at least 1 month.[52] The preexposure vaccine is 3 doses of 1.0 mL each given intramuscularly at 0, 7, and 21 or 28 days.[50] The series can be administered using either of the 2 licensed vaccines in the US: human diploid cell vaccine (HDCV) or purified chick embryo cell vaccine (PCECV). If a vaccinated child is bitten or sustains a skin-penetrating scratch by a potentially rabid animal, the wound must be washed thoroughly, and 2 additional doses must be completed as soon as possible (given 3 days apart); rabies IG is not required.[53] Without preexposure immunization, rabies IG and 4 doses of an approved vaccine (given over 14 days) are required; however, rabies IG is often not available in many developing countries.[53]

Japanese Encephalitis Virus Vaccine

Japanese encephalitis, an arboviral infection transmitted by night-biting *Culex* mosquitoes, is endemic in rural areas of Asia, although occasional epidemics occur in periurban areas. In temperate regions, transmission occurs from April to November, but disease occurs year-round in tropical and subtropical areas. The disease is uncommon in travelers.[54] Although most cases are subclinical, half of patients with clinical disease have persistent neurologic abnormalities, and the case fatality rate is 20% to 30%.[54] The vaccine is recommended for all travelers who are traveling in endemic areas for at least 1 month. Vaccination also should be considered for shorter-term travelers with increased risk of Japanese encephalitis virus exposure. One Japanese encephalitis vaccine (JE-VC [IXIARO], Valneva Austria, Vienna, Austria, distributed by Intercell USA, Gaithersburg, Md) is licensed in the US for people ≥2 months of age.[54] Two doses of JE-VC are administered 1 month apart. For adults at ongoing risk of exposure, a booster dose of JE-VC is recommended at 1 to 2 years after the primary series.[54] For children, the duration of immunity is unknown.

Meningococcal Vaccine

Five serogroups of *Neisseria meningitidis* (A, B, C, Y, and W135) are responsible for most meningococcal disease. The epidemiology of serogroups responsible for disease is changing worldwide; B, C, and Y are most prevalent in the US, whereas A, C, and W135 cause most epidemic disease in sub-Saharan Africa. The incidence in the US is 0.3 cases in 100,000, and in sub-Saharan Africa it can be as high as 800 cases in 100,000 annually.[30,32]

Meningococcal vaccine is required for travelers to the Hajj and also is recommended for people traveling to the "meningitis belt" in equatorial Africa during the dry season from December to June, where serogroup A accounts for 85% of all cases. One of the quadrivalent conjugate vaccines for serogroups A/C/Y/W-135 (MCV4) can be given to children beginning at 2 months of age. Children who received the conjugate or polysaccharide meningococcal vaccine before 7 years of age should be revaccinated within 3 years if they remain at risk.[31] Novel serogroup B meningococcal vaccines have been approved for use in the US[32] and Canada.[33]

Tickborne Encephalitis Virus Vaccine

Tickborne encephalitis virus is transmitted by *Ixodes ricinus* ticks in the forests of central and eastern Europe during the summer months.[55] Two vaccines are licensed in Europe for use in children ≥1 year of age (FSME-IMMUN, Baxter Vaccine, Vienna, Austria; and Encepur, Novartis, Germany. According to CDC's *Yellow Book,* neither is licensed in the US.[3,43]

Bacille Calmette-Guérin Vaccine

Bacille Calmette-Guérin (BCG) vaccine is part of the routine vaccination schedule in many developing countries where tuberculosis (TB) is highly endemic. BCG does not prevent TB infection but has been shown to decrease the incidence of severe TB disease such as miliary TB and TB meningitis. Vaccination with BCG is generally not recommended in the US; however, it can be considered in selected children after consultation with a TB expert. In addition, children who do not receive BCG and who have traveled to a country with a high TB burden should have a tuberculin skin test before and 3 months after returning from travel.[56]

Malaria

Malaria is caused by infection with *Plasmodium* species, most commonly through the bite of an infected female *Anopheles* mosquito. Malaria is a leading cause of death among children <5 years of age worldwide, and it causes approximately 200 million infections and more than 500,000 deaths each year.[57] Young children, pregnant women, and people who previously have not been exposed to malaria have the highest risk of severe disease. Although malaria is endemic throughout the tropics, the highest risk for malaria infection in travelers occurs in sub-Saharan Africa, Papua New Guinea, the Solomon Islands, and Vanuatu.[52,58] No vaccine is available for prevention of malaria infection in travelers; therefore, families traveling with children must be provided with advice regarding personal protective measures and malaria chemoprophylaxis if they are traveling to endemic areas.

Chemoprophylaxis

The type of chemoprophylaxis recommended depends on the likelihood of drug resistance, potential adverse reactions, cost, and convenience. In addition, characteristics of the individual traveler, including age, ability to swallow tablets, and any specific contraindications, are relevant.[59] Breastfeeding infants require prophylaxis because antimalarial drugs do not reach high enough levels in human milk. Several medications are recommended for prevention of malaria in children: chloroquine, mefloquine, doxycycline, and atovaquone/proguanil.[59,60] Chloroquine is inexpensive and well tolerated, but it is of limited efficacy because of resistance to *Plasmodium falciparum* in all regions except parts of the Caribbean and Central America. Atovaquone/proguanil is typically the best tolerated, but it is the most expensive. It is approved for children >5 kg and comes as pediatric tablets. Mefloquine is safe for use in pregnancy and neonates and has the convenience of weekly dosing. Adult tablets need to be broken and compounded into a liquid. Neuropsychiatric side effects limit its tolerability, and increasing resistance is reported in Southeast Asia.[60] Doxycycline is contraindicated in children <9 years of age because of dental staining. Primaquine is recommended as a primary agent in areas with a high incidence of *Plasmodium vivax*, such as Central America, and as a second-line agent in other areas when other antimalarial drugs cannot be used (see Chapter 271).[61] Chloroquine should be initiated 1 to 2 weeks before travel and preferably 4 weeks before travel for mefloquine; doxycycline, atovaquone/proguanil, and primaquine can be started 1 day before exposure. Most chemoprophylactic agents must be continued for 4 weeks after departure from malaria-endemic areas except for atovaquone/proguanil and primaquine, which must be continued for only 1 week after exposure. However, in an atovaquone/proguanil prophylaxis study in 485 Israeli subjects, 87% discontinued the drug 1 day after travel; no cases of malaria occurred, suggesting a shorter duration after travel can be adequate.[62] Updated guidelines from national organizations such as the Centers for Disease Control and Prevention (CDC) and the Committee to Advise on Tropical Medicine and Travel (CATMAT) can be found online (see Box 8.1).

Protective Measures

Because no malaria chemoprophylaxis is 100% effective, personal protective measures, such as barrier and chemical protection and exposure avoidance, should be used to minimize risk of contact with mosquitoes. These protective measures also can decrease the risk of other vector-borne diseases, such as dengue and other arboviruses.

Because *Anopheles* species mosquitoes that transmit malaria bite from dusk to dawn, children must have adequate protection during these hours. The *Culex* species mosquitoes that transmit Japanese encephalitis virus also bite primarily between dusk and dawn, whereas the *Aedes* species mosquitoes that transmit dengue, chikungunya, and yellow fever viruses bite primarily during the day. When a risk of insect exposure exists, children should be dressed in light-colored clothing that covers their arms and legs. Other measures to avoid insect bites include staying in air-conditioned or well-screened accommodation or using insecticide-treated bed nets.

Chemical protection provides additional defense against insect-borne diseases. The safest and best studied is *N,N*-diethyl-meta-toluamide (DEET).[59] Although adverse reactions, such as encephalopathy and rashes, have been described with excessive or prolonged use of high concentrations of DEET in children, this compound is considered safe when used appropriately according to product label instructions (Box 8.3).[58,63] The concentration of DEET correlates with the duration of protection; therefore, products with lower concentrations must be reapplied. DEET is recommended by the American Academy of Pediatrics in concentrations up to 30% for children as young as 2 months of age; in standard preparations, this concentration provides 4 to 6 hours of protection.[64] Non–DEET-containing repellents such as picaridin, IR3535, and oil of lemon eucalyptus appear to be safe and well tolerated but must be reapplied more frequently.[61] Oil of lemon eucalyptus is not recommended in children <3 years of age.

Box 8.3

Precautions for Use of Diethyltoluamide

- Use repellents containing ≥30% DEET only.
- Apply sparingly to exposed skin.
- Apply only to intact skin.
- Apply to face by wiping; avoid eyes and mouth; do not spray directly on face.
- Wash off with soap and water when coming indoors.
- Do not inhale or ingest repellent.
- Do not apply on hands or other areas that are likely to come in contact with the eyes or mouth.
- Do not allow children younger than 10 years of age to apply DEET themselves. Apply to your own hands and then apply to the child.
- Do not use on children less than 2 months of age.

DEET, diethyltoluamide.

Permethrin (a safe chrysanthemum derivative) is a contact insecticide that can be used for treatment of bed nets and clothing.[60] Permethrin-treated fabric has a duration of efficacy between 2 weeks and 6 months depending on the method of treatment. The best chemical protection against mosquito bites is use of a combination of permethrin-treated clothing and an effective insecticide on exposed skin.

Travelers' Diarrhea

Travelers' diarrhea is one of the most common illnesses among travelers, and it affects 22% to 39% of children who travel.[65,66] Both the incidence and the severity of travelers' diarrhea are age dependent, with the highest rates, longest duration, and greatest severity occurring in infants and children younger than 3 years of age.[67,68] Children's stools normally can be quite variable; consequently, travelers' diarrhea is defined as a twofold or greater increase in the frequency of unformed stools, lasting at least 2 to 3 days. The infectious causes of travelers' diarrhea in children and adults predominantly are bacterial and include enterotoxigenic *Escherichia coli* (ETEC), which is the most common cause, enteroaggregative *E. coli* (EAEC), *Salmonella, Campylobacter, Shigella,* enteropathogenic *E. coli* (EPEC), and, rarely, shigatoxin-producing *E. coli* (STE). Viral and parasitic infections are less common causes of pediatric travelers' diarrhea, although rotavirus, *Cryptosporidium parvum, Giardia lamblia,* and *Entamoeba histolytica* also account for a small proportion of diarrhea cases in young travelers. Studies show that 15% or more of cases of travelers' diarrhea may be caused by norovirus.[69,70]

The risk of developing travelers' diarrhea depends on the travel destination, with rates as high as 73% among children traveling to North Africa and 61% among children visiting India.[67] Travel to Southeast Asia, Latin America, and other African countries has been associated with rates of approximately 40%. Although travelers' diarrhea generally is a self-limited infection, it can cause significant morbidity, particularly if it results in moderate to severe dehydration. Parents must be counseled regarding the symptoms and signs of dehydration, as well as the approach to oral rehydration and when to seek medical attention.[71]

Preventive Measures

Because no vaccines are licensed in the US for prevention of travelers' diarrhea in children, counseling regarding food and water precautions is the most important preventive measure. Vaccines are in development in preclinical and clinical phases against ETEC, *Shigella* spp., and *Campylobacter jejuni*. A cholera vaccine that also provides short-term protection against ETEC is licensed in Canada and Europe for children ≥2 years of age.[72]

General rules regarding food and water precautions when traveling apply to both children and adults; however, young children are more likely to explore the environment with their hands and mouths, thus creating opportunities for infection and increasing their risk of diarrhea.[52] Frequent handwashing with soap and water is critical, particularly before eating, although alcohol-based handwashes can be used when water is not available.

Children must be reminded to use safe water sources for all drinking, tooth brushing, and food preparation. Safe water sources include bottled water from a trusted source or water that has been boiled, chemically treated, or filtered. Combination chemical and filter pumps can provide the best protection because filters vary in the size of microbes that are removed.[73] Water should be boiled for at least 1 minute at altitudes <2000 m and 3 minutes at >2000 m.[56] Carbonated drinks also are considered safe for drinking, but water used to make ice can be contaminated. For infants, breastfeeding is the safest form of nutrition. In addition to its many health benefits, breastfeeding does not require a source of clean water, unlike the use of formula, both in its preparation and in the cleaning of bottles.

The selection and preparation of foods are important during travel to minimize the risk of travelers' diarrhea. Although the advice to "boil it, cook it, peel it, or forget it" frequently is given, this often is not practical to follow. If possible, only steaming-hot, freshly made food should be consumed. Families traveling with children should have a ready supply of snacks and avoid buying food from street vendors (Box 8.4).

Box 8.4

Prevention of Travelers' Diarrhea in

Children

Do

- Eat only thoroughly cooked food served hot.
- Peel fruit.
- Drink only bottled, carbonated, boiled, chemically treated, or filtered water.
- Prepare all beverages and ice cubes with boiled or bottled water.
- Wash hands before eating or preparing foods.
- Continue breastfeeding throughout travel period.

Do Not

- Eat raw vegetables or unpeeled fruit.
- Eat raw seafood or shellfish or undercooked meat.
- Eat food from street vendors.
- Drink tap water
- Consume milk or dairy products unless labeled as pasteurized or irradiated.

Additional food and water precautions can decrease risk of other infectious diseases while traveling. These include avoidance of unpasteurized dairy products to eliminate the risk of brucellosis and other bacterial infections. Raw or undercooked meat and fish should not be consumed because of the risk of parasitic infections. Avoiding undercooked seafood can decrease the risk of hepatitis A. In developing countries, raw vegetables and fruit that cannot be self-peeled should be avoided.

Chemoprophylaxis for travelers' diarrhea generally is not advised in children.[67] However, short-term prophylaxis (<3 weeks) could be considered for children with increased susceptibility to travelers' diarrhea, such as children with achlorhydria or children in whom travelers' diarrhea could have significant medical consequences (e.g., children with chronic renal failure, congestive heart failure, diabetes mellitus, or inflammatory bowel disease).[74]

Treatment

Treatment of travelers' diarrhea in children must include close attention to hydration status, and parents should be counseled regarding early signs of dehydration. Oral rehydration therapy using a homemade or commercially prepared oral rehydration solution (ORS) can be used to prevent dehydration associated with diarrheal disease. Commercial ORS should be used to treat mild to moderate dehydration; severe dehydration can require intravenous fluid resuscitation.[75,76] ORS packets should be part of a family's travel medical kit. Locally made preparations can be used early in therapy, although they differ in composition from the reduced-osmolarity ORS recommended by the WHO (Table 8.3).[75] For infants, breastfeeding should be continued, along with oral rehydration and solid food intake, although foods high in simple sugars should be avoided because the increased osmotic load can worsen fluid losses.

TABLE 8.3

Formulation of Oral Rehydration Solution

World Health Organization	Home Formula
NaCl 2.6 g/L (75 mmol/L sodium)	6 level teaspoons sugar
KCl 1.5 g/L (20 mmol/L potassium)	1/2 teaspoon salt
Trisodium citrate, dihydrate 2.9 g/L (10 mmol/L citrate)	1 L water
Glucose, anhydrous 13.5 g/L (75 mmol/L glucose)	A splash of lemon juice (for taste)

KCl, potassium chloride; NaCl, sodium chloride; $NaHCO_3$, sodium bicarbonate.

Loperamide generally is used in combination with antibiotics for treatment of travelers' diarrhea in adults; however, the role of loperamide in pediatric travelers' diarrhea remains controversial, even though this drug is licensed for use in children ≥2 years of age. Although loperamide has been shown to decrease the duration and severity of acute diarrhea in children, it has been associated with significant side effects in children and is not recommended for children <3 years of age.[76–78] Zinc supplementation has been associated with improved outcomes in diarrheal disease in children in developing countries, but zinc supplementation is not recommended in treatment of travelers' diarrhea.[76]

Empiric treatment with antimicrobial agents can be considered in pediatric travelers' diarrhea. However, treatment should be confined to moderate to severe diarrhea, given data that show a marked increased carriage of extended spectrum β-lactamase (ESBL)–producing Enterobacteriaceae with antibiotic use.[79] Azithromycin often is used as the first choice for treatment of pediatric travelers' diarrhea, especially in areas with a high prevalence of fluoroquinolone-resistant *Campylobacter* species (e.g., South and Southeast Asia), because the drug is given once a day and has a known safety profile in children. A dose of 10 mg/kg once daily for 3 days (maximum dose of 500 mg) is appropriate.[67] In adults, a single dose of antibiotic has been shown to be as effective as 3 days of treatment; therefore, in children a full 3-day course may not be necessary.[80,81]

Fluoroquinolones for 1 to 3 days are the drug of choice for adults with travelers' diarrhea that is moderate to severe, persistent (>3 days), or associated with fever or bloody stools. Although concerns exist regarding the potential for development of arthropathy and antimicrobial resistance with fluoroquinolone use in children, the US Food and Drug Administration has approved ciprofloxacin for anthrax and as a second-line agent for the treatment of urinary tract infections in children from 1 through 17 years of age.[82] Therefore, fluoroquinolones could be considered safe in children for the short course required for travelers' diarrhea. A 1- to 3-day course of ciprofloxacin at a dose of 30 mg/kg/day divided twice daily with a maximum dose of 500 mg twice daily is recommended for children with moderate to severe or bloody diarrhea.[67]

Rifaximin (Xifaxan), a nonabsorbed rifamycin derivative, has been approved in the US for treatment and prevention of travelers' diarrhea for people ≥12 years of age.[83] A liquid preparation is available in some countries for pediatric use. The drug is indicated for the management of noninvasive diarrheas such as those seen in ETEC infection, cholera, or EAEC infection when fever and bloody diarrhea are absent.

If travelers' diarrhea does not respond to a course of antimicrobial therapy, medical attention should be sought to investigate other possible causes of the diarrhea. Postinfectious irritable bowel syndrome is well recognized in adults as well as in children.

Emerging Infectious Diseases

Several infectious agents, such as Ebola virus, severe acute respiratory syndrome (SARS) and Middle Eastern respiratory syndrome (MERS) coronaviruses, chikungunya virus, Zika virus, the H5N1 strain of avian influenza virus, and the pandemic (H1N1) 2009 influenza virus have emerged as potentially widespread health threats. Given the constantly changing epidemiology of infectious diseases, pediatricians who advise families regarding travel health must keep informed of the current status of emerging infectious diseases that can pose a threat to the traveler. Several websites provide up-to-date information regarding such infections, including those of the WHO and the CDC (see Box 8.1).

Immunocompromised Travelers

Children with immunodeficiencies require special consideration at their pretravel evaluation because of increased risk of travel-related illness.[84] Most patients with an altered immune system, particularly people with decreased T-lymphocyte immunity, should not receive live vaccines because of risk of developing clinical illness from the vaccine strain.[84] IPV should be given instead of OPV to all members in the family of an immunocompromised person, and Vi typhoid vaccine should be administered instead of the Ty21a vaccine to an immunocompromised child, although the patient is not at risk if family members receive the live oral vaccine.[16,85] However, MMR, varicella, and yellow fever vaccines should be considered for human immunodeficiency virus (HIV)–seropositive children who are not severely immunocompromised (see Chapters 205 and 227). Killed or subunit vaccines can be administered to children with altered immunity, although responses to the vaccines can be diminished.[85] Asplenic patients may respond poorly to polysaccharide vaccines in particular. Patients with certain B-lymphocyte deficiencies, such as X-linked agammaglobulinemia and common variable immunodeficiency, should avoid OPV, vaccinia, and live bacterial vaccines, although other patients with humoral immunodeficiencies, including selective immunoglobulin (Ig) A and IgG subclass deficiency, must avoid only OPV; other live vaccines can be considered.

Some travel-associated illnesses can be more severe in immunocompromised travelers. Asplenic travelers are at greater risk of severe babesiosis and malaria, and organ and stem cell transplant recipients are more likely to develop bacteremia associated with gastroenteritis from *Salmonella* or *Campylobacter* spp.[86] HIV-seropositive travelers with low $CD4^+$ lymphocyte counts must be particularly conscious of risk factors associated with opportunistic infections such as *Toxoplasma gondii, Cystoisospora* (previously *Isospora*) *belli, Salmonella* spp., and *C. parvum,*[86] and therefore they must be particularly cautious regarding food, water, and animal exposures. In addition, because of the risk of disseminated strongyloidiasis in immunocompromised hosts, closed footwear should be encouraged strongly in such travelers.

Return From Travel

Routine posttravel screening generally is not required for asymptomatic, short-term travelers, although screening can be considered for long-term travelers, expatriates, adventure travelers, and people who have experienced significant illness while traveling.[4] If posttravel screening is indicated, the tests required should be determined by the potential exposures associated with the travel itinerary and any symptoms, if present.

Children who develop fever after travel should seek immediate medical attention, and parents must inform physicians caring for them of their travel itinerary. This is particularly critical if the itinerary has included a malaria-endemic area given that chemoprophylaxis cannot prevent all cases of malaria. Because malaria can manifest with nonspecific symptoms in children, any symptoms of fever, rigors, headache, malaise, abdominal pain, vomiting, diarrhea, poor feeding, or cough following travel to an endemic country should be evaluated promptly by a physician.[52,87]

Travel-related illness has been shown to be highly dependent on itinerary. In a report of disease and relation to place of exposure among ill returned travelers, significant regional differences in proportionate morbidity were reported.[4] Typhoid fever was seen most frequently in travelers returning from South Asia. Malaria was the most frequent cause of febrile illness among travelers returning from sub-Saharan Africa, whereas dengue was a more frequent cause of fever in most other areas. Rickettsial infections, primarily tickborne spotted fever, occur more frequently than malaria or dengue among travelers returning from South Africa.[4]

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C

Host Defenses Against Infectious Diseases

OUTLINE

9 Immunologic Development and Susceptibility to Infection
10 Fever and the Inflammatory Response

9

Immunologic Development and Susceptibility to Infection

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The human immune system has evolved to protect the individual person from infectious microbes. It does this by using a complex interactive network of cells, proteins, and organs. Experiments of nature in humans, such as those recognized as the inherited disorders of immune function,[1–3] have taught us that despite the apparent redundancy of the system, quantitative and qualitative defects in individual components or pathways, or both, result in abnormal function and susceptibility to particular infections.

This chapter provides a general overview of the development of innate and adaptive immune responses, addresses some immunologic developmental characteristics unique to the fetus and newborn, and addresses susceptibility to pathogens in general terms.

Innate Immune Response

The innate immune system represents the first line of host defense against infection and includes the following: (1) antimicrobial products and physical barriers such as skin and mucosal surfaces; (2) receptors for pathogens, including toll-like receptors (TLRs), C-type lectin receptors, nucleotide-binding oligomerization domain (NOD) proteins, leucine-rich repeat–containing receptors (NLRs), and retinoic acid–inducible gene I protein (RIG-I) helicase receptors, which recruit immune cells to sites of infection[4]; (3) phagocytic cells such as neutrophils and macrophages; (4) dendritic cells (DCs); (5) complement proteins; and (6) natural killer cells.

Antimicrobial Products, the Skin, and Mucosal Barriers

In mammals, epithelial cells are capable of secreting antimicrobial peptides such as defensins and cathelicidins. Defensins contribute to host defense by disrupting the cytoplasmic membranes of microbes and inducing DC and lymphocyte chemotaxis. The α-defensins are produced by neutrophils, monocytes, and Paneth cells of the gut, whereas β-defensins are produced by epithelial cells. Cathelicidins exhibit both antimicrobial and immunomodulatory activity in the setting of injury and infection, and they are expressed by epithelial and peripheral blood cells. The sole cathelicidin expressed in humans, hCap18/LL-37, stimulates angiogenesis; it also induces chemotaxis of neutrophils, monocytes, and lymphocytes and demonstrates neutralizing capability against lipopolysaccharide (LPS).[5–9]

The skin's tight junctions between epithelial cells, thickness, and dry environment offer a shield against microbes. Loss of skin integrity, as occurs with wounds, burns, and inflammation, allows pathogens to breach this barrier. Antimicrobial peptides decrease the susceptibility to infection when skin barriers are compromised. Psoriasis and atopic dermatitis (AD), which are inflammatory skin conditions associated with skin disruption, demonstrate the role of these molecules in modulating infection risk. Although infection rarely is associated with psoriasis, patients with AD commonly are infected with *Staphylococcus aureus*. Human β-defensin 2 (HBD2) and the cathelicidin LL-37 appear to be strongly expressed in psoriasis and not in eczematous skin. Interleukin-13 (IL-13), produced under atopic conditions, suppresses the induction of these antimicrobial peptides.[10,11]

Intrauterine expression of antimicrobial peptides provides a robust defense against potential pathogens during fetal development. The α-defensin human neutrophil peptide (HNP) is detected in the cervical mucus plug, and placental and fetal membranes express HBD1 to HBD3.[12,13] During the third trimester of pregnancy, the fetus becomes covered by the vernix caseosa that contains antimicrobial peptides including α-defensins, cathelicidin LL-37, and psoriasin, a calcium-binding protein upregulated in psoriasis. Vernix extracts have antibacterial activity against gram-negative bacteria and antifungal properties against *Candida albicans*, whereas amniotic fluid–derived proteins and peptides show only the former activity.[14] At the level of the mucosal-epithelial interface, the expression of IL-17 by Th17 cells and the synthesis of defensins by keratinocytes also prevent invasion by *Candida* spp. Experimental models of mucocutaneous candidiasis have shed light on the pathogenesis of *Candida* infections in patients with hyperimmunoglobulinemia E (hyper-IgE), the autoimmune polyendocrinopathy syndrome, in patients with ectodermal dysplasia (APECED), and in patients with defects in the caspase recruitment domain-9 (CARD-9) protein.[15–20]

The more common entry pathway for pathogens is through the mucosal barrier. Mucosal epithelial cells secrete mucus that contains antimicrobial peptides. Mucus coats pathogens, thus allowing antimicrobial peptides to exert their action, and provides a vehicle for particles and pathogens to be cleared by the action of cilia. Within the respiratory tract, cilia move the mucus toward the upper airways, where it is either expelled by cough mechanism or swallowed. Ineffective clearance, as seen in patients with immotile cilia syndrome or cystic fibrosis and after lung transplantation, favors pathogen colonization. Cathelicidin LL-37 promotes bacterial phagocytosis by macrophages and thereby contributes to pathogen clearance; evolving therapeutic approaches using novel antimicrobial peptides in the setting of decreased mucosal clearance show promise.[21,22]

Surfactant-associated proteins, specifically surfactant protein A (SP-A) and surfactant protein D (SP-D), contribute to innate immune responses in the lung. Produced by type II pneumocytes and nonciliated respiratory epithelial cells, SPs belong to the family of proteins called collectins. SP-A and SP-D can interact with microorganisms, modulate local inflammatory responses, modulate neutrophil responses in vitro, and participate in clearance of pollens and other complex organic antigens.[23] In patients with severe, treatment-resistant asthma, SP-D levels in bronchoalveolar lavage fluids decline, whereas serum concentrations increase.[24] Potentially in the near future, this defective innate immune response within the airways may benefit from administration of recombinant SP-D.[25] Lysozyme, lactoferrin, histatins, and phospholipase A2 in tears and saliva also are potent antibacterial enzymes.[26,27] The gastrointestinal tract is protected by digestive enzymes, bile salts, fatty acids, and lysolipids. Paneth cells in the human gut secrete α-defensins and influence the virulence of orally ingested bacteria. Thus children and adults with infections caused by *Shigella* or virulent *Salmonella* strains have demonstrably decreased synthesis of HBD1 and cathelicidin LL-37 by colonic enterocytes. HBD2 expression also is reduced in enterocytes of patients with Crohn disease, and gastric mucosa–derived β-defensins are decreased in *Helicobacter pylori* infections. In vitro, *H. pylori* is susceptible to HBD2.

Endogenous antimicrobial peptides also appear to play a role in the regulation of host commensal bacteria and in the composition of gut microbiota. Decreased α-defensin expression in knockout murine models is associated with changes in the gut microbiome, with fewer Bacteroidetes and more Firmicutes.[28]

Pathogen Receptors and Toll-Like Receptors

Pathogen-associated molecular patterns (PAMPs) represent pathogen-specific carbohydrates and lipoproteins or nucleic acids expressed as part of their life cycle (i.e., bacterial DNA as unmethylated repeats of dinucleotide CpG, double-stranded [ds] or single-stranded [ss] RNA). Host proteins capable of recognizing such specific microbial patterns are called pathogen recognition receptors (PRRs). An example is mannose-binding lectin (MBL), a circulating soluble protein that binds mannose or fucose, residues on microbes and facilitates phagocytosis. Macrophages carry a C-type lectin, called macrophage mannose receptor (MMR), which binds carbohydrate moieties found on the surface of bacteria and also recognizes viruses such as the human immunodeficiency virus (HIV) and fungi.[29,30]

Toll-like receptors are a type of PRR capable of linking the innate and adaptive immune systems (see Chapter 10). These proteins are present on many cells including airway and gut epithelial cells, antigen presenting cells (B lymphocytes, macrophages, DCs, monocytes), hematopoietic stem cells, mast cells, regulatory T lymphocytes (Tregs), natural killer (NK) cells, and endothelial cells.[31] A total of 10 different TLRs have been identified in humans: TLR1, TLR2, TLR4, TLR5, TLR6, and TLR10 are found on cell surfaces, whereas TLR3, TLR7, TLR8, and TLR9 are localized within the endosomes. TLR11 has been found only in mice, appears to be a specific receptor for *Toxoplasma gondii,* and contributes to control of encephalitis in these animals.[32] TLR2 is involved in responses to gram-positive bacteria (peptidoglycans and lipoproteins) and yeast.[33] TLR4 mediates the interaction of gram-negative bacteria by transducing signals derived from LPS. A mouse model for TLR4 mutations renders the animal resistant to endotoxin but highly susceptible to gram-negative infection.[34] All TLRs are capable of interacting with different ligands (see Table 10.1 in Chapter 10). Respiratory syncytial virus (RSV) F protein, LPS, and *Pseudomonas* exoenzyme S have been shown to interact with TLR4, whereas flagellin is recognized by TLR5.[35] TLR2 recognizes envelope proteins of herpes simplex virus (HSV), whereas TLR9 identifies CpG motifs within the viral genome.[36]

TLR recognition of microbial products triggers the activation of downstream signaling pathways where myeloid differentiation factor 88 (MyD88) and toll–IL-1 receptor domain containing adaptor-inducing interferonβ (IFNβ) (TRIF) lead to activation of NF-κB and subsequent transcription of proinflammatory cytokines: tumor necrosis factor-α (TNF-α), IL-1, and IL-6. MyD88 recruits the IL-1R–associated kinase (IRAK) family of proteins: IRAK1 and IRAK4. Humans and mice with deficiencies in IRAK4 or MyD88 demonstrate severe impairment of IL-1 and TLR downstream signaling and are susceptible to recurrent and severe bacterial infections.[37–39] TRIF signaling results in activation of IFN regulatory factor-3 (IRF-3) and induction of type 1 IFN genes such as IFNα and IFNβ,[40] thus enhancing viral clearance.

TLR polymorphism can be linked to diseases such as asthma[41] and atherosclerosis.[31] TLR-9 has been linked to hepatic injury following severe renal ischemia reperfusion,[42] and a deletion of the signaling domain of TLR5 has been found to increase susceptibility to Legionnaire disease.[43] Finally, toll signaling pathways have been implicated in the pathogenesis of sepsis and shock.[44–46] Defects in TLR3 have identified inherited susceptibility to HSV encephalitis.[47–51] The stage of human development in which toll receptors appear is not clearly established. However, evidence indicates that TLR2 is developmentally expressed during fetal life from the early pseudoglandular to canalicular stages of human lung development[52] (see Chapter 11).

Phagocytes

The major phagocytic cells are neutrophils and macrophages. In humans, myeloid precursors are found in the yolk sac by day 19 of development, 2 days before the onset of blood circulation. Hematopoiesis then shifts to the fetal liver and finally to the bone marrow. In the bone marrow phagocyte development is under the control of multiple growth factors, including IL-3, granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), and macrophage colony-stimulating factor (M-CSF). The marrow pool of neutrophils in adults is 20 times the number of neutrophils in circulation. The mechanisms responsible for the release of neutrophils from the marrow are complex. In familial neutropenias associated with maturational arrest, genes such as *HAX-1*,*CSF3R*, *ELANE*, and *WAS* have been identified as essential for neutrophil development.[53–57] The release or retention of neutrophils within the marrow compartment also is regulated by the interaction of signaling proteins on the cell surface, called chemokines, which interact with their ligands on bone marrow stromal cells. An example is the CXCR4/CXCL12 pair that permits retention of neutrophils in the marrow.[58,59] Mutations in CXCR4 lead to a rare condition called WHIM syndrome, for warts, hypogammaglobulinemia, immunodeficiency and myelokathexis. Myelokathexis indicates that neutrophils are retained in the marrow compartment, unable to be released, causing peripheral neutropenia. Once in the circulation neutrophils circulate for a few hours and then move into the tissues where they are active for 2 to 6 days.

At term, the neonatal peripheral neutrophil count is higher than that of adults, but reserved capacity to respond with an outpouring of phagocytic cells, which often are immature, appears to be minimal during infection. Newborn infants with septicemia often have severe neutropenia and depletion of phagocytic storage pools, a finding associated with high mortality rates.[60] The cause of this rapid depletion remains unknown, but the condition is likely exacerbated by the relative paucity of progenitor reserves in newborns' marrow. It is possible that decreased numbers of neutrophils at the site of infection contribute to the susceptibility of neonates to pneumonia and skin infection and to the development of multiple sites of infection after bacteremia or fungemia.[61] Lack of adequate numbers of cells at the site of infection can cause or result in functional deficiencies.

Monocytes also move from the circulation to tissue spaces, where they develop into macrophages, live for 2 to 3 months, and assume specialized characteristics generally determined by their location (e.g., lung, liver, or spleen). Circulating monocytes also have chemotactic and phagocytic activities and have receptors for immunoglobulin G (IgG) Fc domains (FcR), complement, and TLRs 2 to 9 along with CD14, an important molecule that mediates TLR4 activation by LPS.[62,63]

The function of phagocytes, which are particularly important in defense against bacteria and fungi, requires not only sufficient numbers of cells but also adequate ability to sense and migrate toward the site of infection (chemotaxis) and to ingest and kill microorganisms (phagocytosis). These processes are mediated by the expression of adhesion molecules, opsonins (complement and antibodies), and chemoattractants, IL-8 is the most important chemokine that attract neutrophils. At the site of infection, neutrophils engulf microbes and particulate matter by the mechanism of phagocytosis and kill the pathogen. Additionally, neutrophils secrete chemokines, release NETS (neutrophil extracellular traps), and die by apoptosis once their mission is accomplished. Macrophages subsequently clear any cellular debris. Monogenic defects at different stages of this process define unique syndromes (Fig. 9.1).

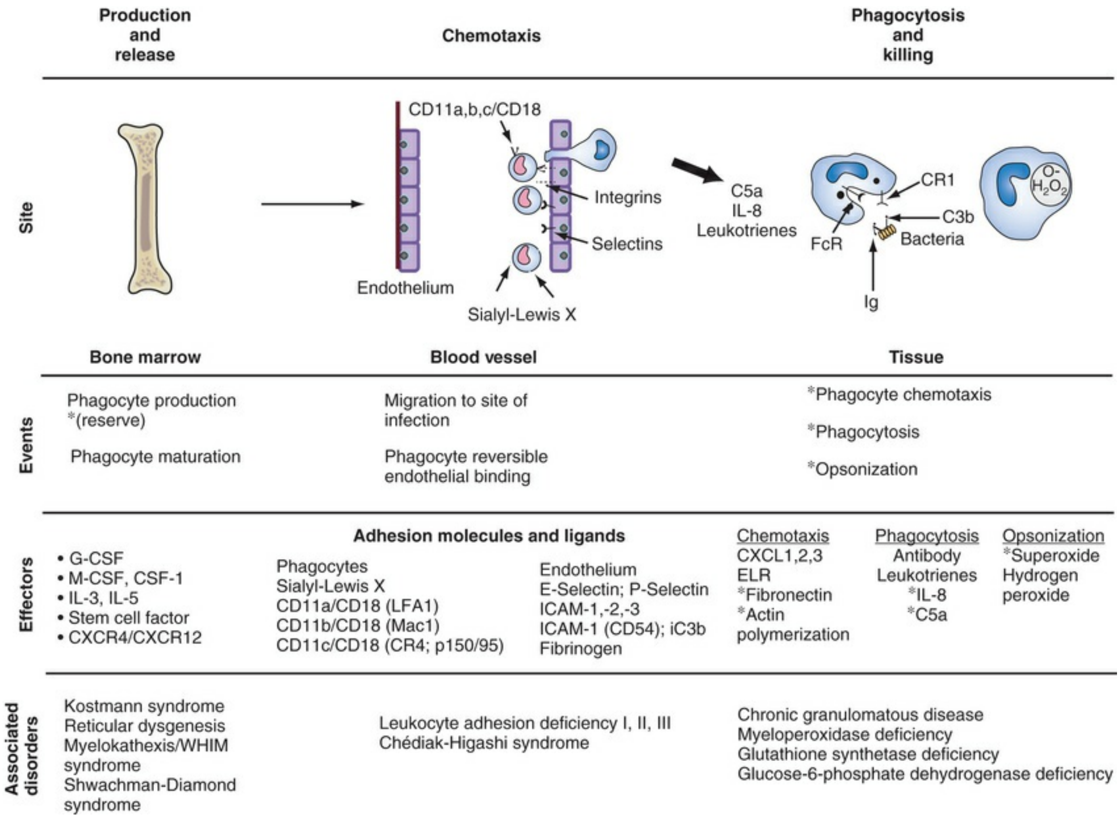

FIGURE 9.1 **Aspects of immunologic function. The *asterisks* indicate aspects that are immature or defective in the neonatal period. C, complement; CD, cluster of differentiation; CR, complement receptor; CXCL, CXC chemokine ligand; FcR, Fc receptor; G-CSF, granulocyte colony-stimulating factor; ICAM, intercellular adhesion molecule; Ig, immunoglobulin, IL, interleukin; M-CSF, macrophage colony-stimulating factor; WHIM, warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis.**

Chemotaxis is the process by which phagocytes reach the site of infection. As a result of a local inflammatory response, endothelial cells within local vessels express adhesion molecules called selectins (CD62E, CD62P). These molecules reversibly bind to ligands on neutrophils (sialyl-Lewis X and PSGL1) and consequently make the neutrophil slow down and “roll” along the endothelium. Subsequently, another group of adhesion molecules, called integrins, is upregulated on the surface of neutrophils. Integrins are composed of one of three different α chains: CD11a, CD11b (CR3), or CD11c (CR4); they are noncovalently linked to a β chain, CD18, thus forming a CD11a/CD18 or LFX1, CD11b/CD18 or MAC-1, and CD11c/CD18 or p150,95 integrin complex. Integrin molecules “stop” the neutrophil, which then undergoes skeletal changes and migrates through the vascular lumen into the extravascular space by adhering to intracellular adhesion molecules (ICAMs). The sialic constituent of the group B *Streptococcus* (GBS) capsular polysaccharide mimics the human Lewis X antigen, thus making this a poor immunogen, and perhaps renders the neonate especially susceptible to this organism.[64] Defects in the expression of adhesion molecules have been described in humans: leukocyte adhesion defect (LAD) types 1, 2, and 3. Lack of integrin expression causes LAD-1, lack of sialyl-Lewis X expression causes LAD-2, and defects of integrin activation cause LAD-3. Patients have persistent leukocytosis, delayed separation of the umbilical cord, skin ulcers, periodontitis, and delayed wound healing.[65–67] L-selectin (CD62L) levels on fetal and immature infant neutrophils are comparable to those of adults. However, L-selectin expression is downregulated in the term neonate and is further diminished during acute bacterial infection in vivo.[68] Other defects in chemotaxis have been described.[65,69–72] In the newborn, defects in chemotaxis have been linked to decreased expression of Rac2, a signaling molecule, on umbilical cord blood neutrophils.[61]

Phagocytosis is an active process by which a previously bound pathogen is engulfed by a phagocyte in a membrane-bound vesicle called a phagosome. Both macrophages and neutrophils contain lysosomes, which are membrane-bound acidic organelles containing proteolytic enzymes and are capable of producing toxic products: nitric oxide (NO), superoxide anion (O_2^-), and hydrogen peroxide (H_2O_2). Fusion of the lysosome and phagosome membranes is necessary to kill the organism. Within azurophilic granules, a bactericidal/permeability-increasing protein (BPI) binds to bacterial LPS and kills gram-negative bacteria. BPI has been implicated in both neonatal sepsis[73,74] and chronic *Pseudomonas* infection in patients with cystic fibrosis.[75]

Production of O_2^- and H_2O_2 depends on the reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme complex (see Chapter 104). Defects in the different components of this enzyme complex result in the immunodeficiency known as chronic granulomatous disease. Affected patients are susceptible to infections with catalase-producing organisms, *Aspergillus* and *Nocardia* species. Because phagocytes are unable to kill the microbes, the host tries to contain the infection by calling in more macrophages and lymphocytes, with resulting granuloma formation. Once bacteria are killed, neutrophils die, whereas macrophages can generate new lysosomes. Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency and glutathione synthetase deficiency also have neutrophil dysfunction and can have clinical features similar to those of chronic granulomatous disease.[76,77]

No well-described phagocytic defects have been reported in the developing human embryo. The capability of the newborn for nonopsonic adherence to organisms and phagocytosis is nearly equal to that of adult cells. However, deficiencies in chemotaxis and O_2^- production have been described.[64,78–81] Bacterial killing of umbilical cord blood phagocytes is effective against *Escherichia coli* and *Streptococcus pyogenes* and is similar to bacterial killing of phagocytes in adults, but it appears abrogated against GBS.[82] Abnormalities in chemoattractants (IL-8, complement fragment C5a, fibronectin)[83,84] and defective expression of complement receptors, such as C5a receptor, caused by C5a-mediated exocytosis of myeloperoxidase[85] also have been described. Defects in membrane fluidity and cytoskeletal changes can contribute to neutrophil motility defects as well.[86]

Dendritic Cells

DCs are the prototypic antigen-presenting cell. In humans, $CD34^+$ hematopoietic stem cells (HSCs) capable of generating DCs are detected in the fetal liver at 20 weeks of gestation, after which they are found mainly in the bone marrow. After birth, 1% to 3% of umbilical cord blood cells express CD34. During differentiation, these $CD34^+$ cells lose CD34 expression and express CD4, CD45RA, IL-3R, and major histocompatibility complex (MHC) class II antigens.[87,88] A class of DCs called Langerhans cells (LCs) was first described in 1868. It is difficult to identify the lineage ontogeny of human DCs. Bone marrow differentiation studies of DCs suggest a dual origin of DCs: myeloid and lymphoid.[89,90] LCs can derive from blood DCs.[91] Although lineage-specific markers are still being defined, transcription factors have been shown to regulate DC development. For example, transcription factor PU.1 is important for myeloid-derived DCs,[92] RelB is associated with DC activation,[93] and Ikaros proteins are transcriptional activators that influence chromatin remodeling and histone deacetylation.[94]

DCs are capable of regulating both innate and adaptive immune responses. With unique morphologic characteristics when activated, several pathogen receptors have been identified. Examples include TLRs that appear to be involved in DC maturation and scavenger receptors that mediate bacterial internalization, such as MAC-1 (CD11b/CD18) and the CR3 complex.[95,96] DCs induce antiviral cytotoxic T-lymphocyte responses producing IL-12 and IL-15, 2 cytokines critical for cytotoxic $CD8^+$ T-lymphocyte differentiation. Other DC subsets activate $CD4^+$ T lymphocytes through MHC II activation. Furthermore, activated DCs can promote B-lymphocyte proliferation into plasma cells by releasing soluble factors or by direct cell-cell interaction.[97]

In the skin, DCs are localized to the basal and suprabasal layers of the epidermis; in the murine gut, DCs are found in the Peyer patches; and in the human lungs they can be found within the airway epithelium, alveolar septa, visceral pleura, and vascular walls.[98–101]

While surveying the tissue environment, DCs can be recognized by an "immature" phenotype ($CD11b^{bright}$, $CD11c^{mo}$d, $CD86^{low}$, $ClassII^{low}$, $CD4^-$). On uptake of antigen or microbial products by different mechanisms of phagocytosis, DCs migrate through the afferent lymphatics to the regional lymph node, where they arrive as mature, nonphagocytic DCs ($CD40\ ^{high}$). These DCs can produce inflammatory cytokines and chemokines. Bacterial uptake of *Mycobacterium tuberculosis*, bacille Calmette-Guérin (BCG), *Saccharomyces cerevisiae*, *Corynebacterium parvum*, *S. aureus*, *Leishmania* spp., and *Borrelia burgdorferi* has been demonstrated in vitro.[102–105]

Complement

The complement system comprises a series of serum proteins that function in host defense as an enzymatic cascade (see Chapter 103). When microorganisms invade the host, activation of complement occurs locally by 1 of 3 pathways that converge at the stage of the formation of the enzyme C3 convertase. This enzyme cleaves complement component C3 into C3b and C3a. C3b, the major effector molecule of the complement system, binds to the bacterial cell membrane. This important molecule functions as an opsonin (to facilitate phagocytosis) and also helps cleave C5 into C5a and C5b.

C5a is a potent chemoattractant, and C5b is an integral part of the membrane-attack complex along with other terminal components: C6, C7, and C9. One pathway (classical) is activated by antibody-antigen complexes and thus depends on and enhances specific humoral immunity. A second pathway (alternative) can be activated by direct binding to the surface of some microorganisms and thus functions to provide innate (nonspecific) immunity. A third pathway (the MBL pathway) is initiated by the binding of MBL on mannose- and fucose-containing surfaces of bacteria and viruses, favoring their phagocytosis.

Until 18 months of age, the concentration of most complement proteins is lower than that in adults, with the exception of C7. Between 28 and 33 weeks of gestation, little development of the complement system appears to occur. Both the levels and function of the classical complement pathways are reduced in preterm neonates who are <34 weeks of gestational age, with C8 and C9 as the most markedly reduced at all gestational ages.[106] Deficiencies of complement activation in both classical and alternative pathways have been described.[107,108] Low levels of total hemolytic complement activity are significant predictors of death in neonates with septicemia.[108]

The molecular basis for defects in complement function in neonates and the details of the consequences are only partially understood. For example, a possible defect has been described in formation of a reactive thioester bond on C3 that is essential for opsonic and covalent binding of C3b to bacteria.[109] Inefficient killing of *E. coli* by neonatal sera appears to correlate with low concentrations of C9,[110] and it can be overcome by adding C9 to ampicillin-treated serum from neonates in vitro.[111] Deficient formation of C5a also can increase the neonate's risk of infection. Although levels of C5 are similar in adult and neonatal sera, neonatal sera form significantly less C5a on exposure to GBS type III.[112] This deficiency was apparent in newborn sera with antibody levels similar to those of adults and could be corrected by in vitro addition of C3. Finally, circulating serum MBL concentrations also can play a role in complement activity, with decreased serum concentrations associated with increased risk for neonatal sepsis.[113]

Hemolytic uremic syndrome occurs in childhood and frequently is preceded by a diarrheal illness caused by *E. coli* O157:H7. Plasma protein factor H and plasma serine protease I, regulatory proteins of the alternative complement pathway, have been associated with the nondiarrheal form of hemolytic uremic syndrome.[114,115] A study of 120 patients with nondiarrheal hemolytic uremic syndrome found that 10% of patients had mutations in the membrane cofactor protein (MCP; CD46). The onset typically was in early childhood, and most patients did not develop end-stage renal failure.[116]

Natural Killer Cells

NK cells form a subgroup of lymphocytes that exhibit cytolytic activity against tumor cells or cells infected with viruses (Table 9.1). In humans, NK cells are similar to cytotoxic $CD8^+$ T lymphocytes in their effector function, but they lack the T-lymphocyte receptor–CD3 complex and express the low-affinity Fc receptor for IgG (CD16, FcγRIII). NK cells comprise up to 10% of peripheral blood lymphocytes (PBLs) in adults.

TABLE 9.1

Comparison of Natural Killer Cells and Cytotoxic T Lymphocytes

Characteristic	Natural Killer Cell	Cytotoxic T Lymphocyte
Identification of target for kill	Nonspecific killing of virus-infected cells *or* Binding to antibody-coated cells by CD16 (ADCC)	TCR specifically identifies viral peptide within MHC class I molecule on surface of infected cell
Surface markers	CD16 and/or CD56	CD3/CD8
Signal(s) for activation	IFNα, IFNβ, IL-12	IL-2 and antigen (on surface of antigen-presenting cell)
Onset of function	1–6 days after infection	5–10 days after infection
Mechanism of killing	Granule exocytosis and secretion of toxin	Granule exocytosis and secretion of toxin

ADCC, antibody-dependent cell-mediated cytotoxicity; IFN, interferon; IL, interleukin; MHC, major histocompatibility complex; TCR, T-cell receptor.

NK cells appear in substantial numbers by 6 to 9 weeks of gestation in the embryonic liver and later in the fetal liver, thymus, and spleen. After birth, NK cells develop primarily from HSCs in the marrow and are driven to maturity by cytokines, in particular IL-15. IL-15 has the same intracellular signaling molecule, the common γ chain (γC), as other cytokines (IL-2, IL-4, IL-7, IL9, and IL-21). Mutations in γC are responsible for the X-linked form of severe combined immunodeficiency (SCID) that lacks both T and NK cells ($T^-NK^-B^+$ SCID).

Unlike cytotoxic T lymphocytes (CTLs), NK cells do not require MHC class I antigens to recognize their targets, do not recognize particular viral antigens, and can be activated by cytokines without previous exposure to the antigen, thereby making this cell an important contributor to innate responses.[117] However, NK cells can function with some degree of antigenic specificity because they can lyze cells that have been previously coated with specific antibody molecules. This process is called antibody-dependent cell-mediated cytotoxicity (ADCC). Both NK cells and CTLs mediate cytolysis in a similar manner because these 2 cell populations contain lytic granules composed of cytolytic proteins (perforin) and enzymes (granzymes). Perforin polymerizes when in contact with the target cell plasma membrane, thus creating pores; granzyme introduced through these pores induces target cell apoptosis.[118] Defects in the lytic granule content, priming, docking, and membrane fusion have been described in patients with hemophagocytic lymphohistiocytosis syndromes (see Chapter 12). In addition, defects in NK cell number or function have been recognized in many different human congenital deficiencies of immune function.[119]

NK cell activity in umbilical cord blood from infants born between 32 and 36 weeks of gestation is low compared with activity in infants born after 36 weeks. Antenatal glucocorticoid therapy for preterm labor can accelerate maturation of NK cells.[120] Compared with adult NK cells, neonatal NK cells have decreased cytotoxic activity and diminished ADCC until at least 6 months of age.[121] Conversely, when interferons (IFNs), IL-2, IL-12, and IL-15 are added to cultured neonatal NK cells, they can respond like adult cells.[122]

Neonatal HSV infection and severe recurrent herpesvirus infections in adults along with discoveries of genetic defects that cause NK deficiency provide evidence of the importance of NK cells in host defense.[119]

Adaptive Immune Response

The adaptive immune response is essential for host defense, as demonstrated by the increasingly recognized congenital deficiency syndromes. Specificity and immunologic memory are the most important consequences of adaptive immunity. Specificity is determined by the vast range of molecular diversity of antigen receptors. Immunologic memory is the ability to respond rapidly and effectively to pathogens previously encountered. The effector cells of the adaptive immune response are T and B lymphocytes, which develop from bone marrow–derived HSCs (Fig. 9.2). Lymphopoiesis is a tightly regulated sequence of events that leads to the expression of a functional antigen receptor on the surface of the lymphocyte. For B lymphocytes, it is the B-cell receptor (BCR) that represents surface immunoglobulin molecule, and for T lymphocytes, it is the T-cell receptor (TCR) complex. Cellular microenvironment, transcription factors, and posttranscriptional regulators such as microRNAs, cytokines, and chemokines, along with silencing or activation of certain genes at different stages of lineage commitment, are some of the multiple factors contributing to a successful and mature lymphocyte.[123,124]

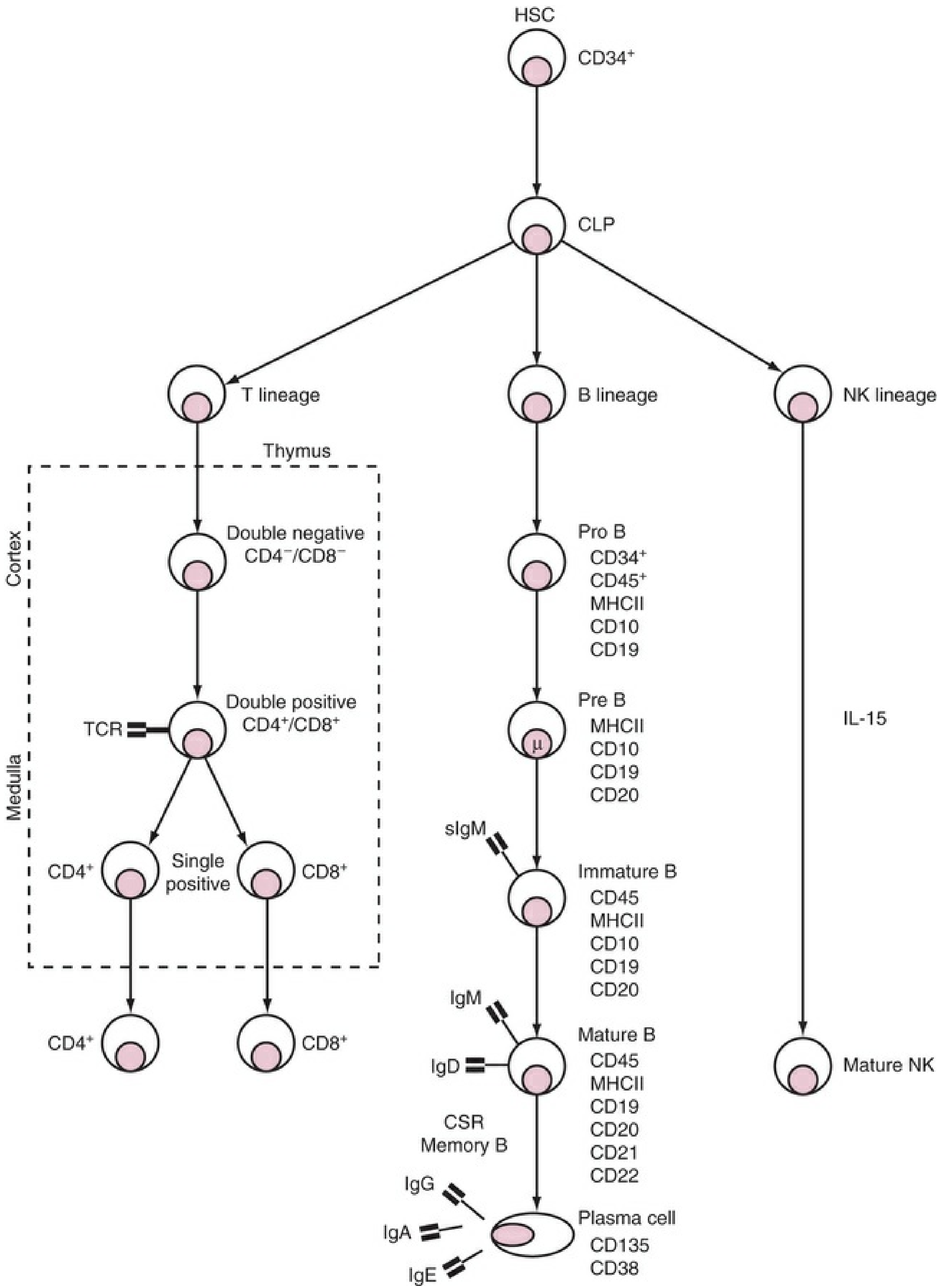

FIGURE 9.2 Schematic representation of normal lymphocyte development. B, B lymphocyte; CD, cluster of differentiation; CLP, common lymphoid precursor; CSR, class switch recombination; HSC, hematopoietic stem cell; Ig, immunoglobulin; IL, interleukin; NK, natural killer lymphocyte; MHC, major histocompatibility complex; sIg, secretory immunoglobulin; T, T lymphocyte; TCR, T-cell receptor.

B Lymphocytes

B lymphocytes play a critical role in pathogen-specific immunity by producing antibodies. B lymphocytes recognize soluble antigens through immunoglobulins anchored on their surface and differentiate into antibody-producing cells, called plasma cells, capable of secreting immunoglobulins. These proteins function alone (neutralization) or with complement or phagocytes to inactivate microorganisms.

The B-lymphocyte system is fully developed at birth. The origin of the human B lymphocyte is not well defined, but fetal B lymphocytes can be recognized in the yolk sac, omentum, and fetal liver. After birth, B-lymphocyte development takes place in the bone marrow. The ordered steps of B-lymphocyte development are marked by rearrangement of the immunoglobulin genes (see Fig. 9.2). Recombinase-activating genes *RAG1* and *RAG2*, transcription factors, and signaling molecules are required for normal B-lymphocyte development. Defects in B-lymphocyte development result in the classic X-linked Bruton agammaglobulinemia secondary to mutations in Bruton tyrosine kinase (BTK) or autosomal recessive forms of agammaglobulinemia.[125] A mature B lymphocyte can be identified by cell surface molecules: CD19, CD20, CD21 (the Epstein-Barr virus receptor) and CD40 (ligand for CD154, also called CD40LG, which is defective in hyper-IgM syndrome) among others. All these B-lymphocyte surface molecules are lost when the cell reaches the mature plasma cell state. Thus the monoclonal antibody anti-CD20, used for management of B-lymphocyte CD20$^+$ lymphomas and autoimmune conditions, does not deplete the plasma cell pool.

Flow cytometry analysis of circulating B lymphocytes has long allowed the identification of unique functional subsets within the B-lymphocyte compartment. A unique subset, known as B1 cells, plays a critical role in neonatal immunity. Although restricted in their repertoire, these B lymphocytes serve as the primary source of T-lymphocyte–independent antibody production and in experimental models, important in *Streptococcus pneumoniae* control.[126] Class-switched memory B lymphocytes, defined by the expression of cell surface markers CD27$^+$IgM$^-$IgD$^-$, have allowed for classification of patients with the primary immunodeficiency called common variable immunodeficiency (CVID), thereby providing insights into the pathogenesis of this heterogeneous disorder.[127]

Finally, regulatory B (Breg) lymphocytes are critical for controlling the inflammatory response by releasing anti-inflammatory mediators including IL-10.[128]

Passively Acquired Antibodies.

Neonates have a limited serum antibody repertoire (at least 10^{11}) of actively formed, self-produced antibodies because they have not had the opportunity to encounter pathogens. This limitation is alleviated by transplacental transfer of maternal antibody, which occurs by a selective, active process, starting at approximately 20 weeks of gestation but more consistently after 35 weeks of gestation. Only IgG transport occurs and is mediated by the neonatal Fc receptor (FcRn). At birth, term infants have serum IgG levels that are equal to or exceed maternal levels by 5% to 10%. Because most antibody transfer occurs during the third trimester of pregnancy, preterm infants can have very low levels. For example, most infants born at 32 weeks of gestation or earlier have serum IgG levels lower than 400 mg/dL. Transplacentally acquired antibody disappears rapidly after birth and reaches a nadir at 3 months (Table 9.2). However, these low levels of maternal IgG antibody at 3 months of age appear to be associated with less risk of infection than would be expected. A longitudinal study of the ability of preterm infants to form specific antibodies provides a partial explanation for this low risk. By approximately 9 months of age, infants have formed specific IgG antibodies in response to immunizations, and their antibodies have functional opsonic activity against *E. coli* and coagulase-negative staphylococci.[129–132]

TABLE 9.2

Concentration of Serum Immunoglobulin G in Term and Premature Infants

Postnatal Age	Gestational Age: Mean Serum IgG (mg/dL)		
	25–28 wk[a]	**29–32 wk**[a]	**Term**[b]
1 wk	251	368	1,031
3 months	60	104	430
6 months	159	179	427

[a] Data for premature infants based on samples at 1 wk, 3 months, and 6 months of age.[147]

[b] Data for term infants based on umbilical cord blood and samples at 1 to 3 months

and 4 to 6 months of age.[148]

IgG, immunoglobulin G.

The maternal repertoire of specific antibodies is critical for protection of the newborn infant from commonly encountered pathogens. In a landmark report, Baker and Kasper[133] demonstrated that a concentration of ≤2 μg/mL of serum antibody to GBS type III in umbilical cord blood correlated with susceptibility to invasive disease. Evidence of the protective effect of maternal antibodies against herpesviruses such as HSV and varicella-zoster virus is well established.[134] Many gram-negative organisms require IgM antibodies and complement for efficient opsonization. Because IgM does not cross the placenta, neonatal sera opsonize these organisms poorly. The apparent protective role of transplacental IgG antibodies has led to extensive attempts to prevent or treat neonatal sepsis with passively administered antibodies. In a randomized treatment trial involving 3493 neonates, no effect of IgG therapy on mortality rates or major disability at age 2 years was observed.[135] This trial and previous studies underscore complex mechanisms necessary for the newborn to clear pathogens

Active Production of Antibodies.

The ability of newborn infants to produce an active antibody response to antigenic stimulation develops in an orderly fashion. An adult pattern of antibody responses is not acquired until 4 to 5 years of age. Analysis of the factors responsible for this developmental pattern is complex because production of antibody depends not only on B-lymphocyte maturity but also on interactions with other cells that mature at different rates (Fig. 9.3). After birth, active production of IgG slowly increases, with IgG being the last isotype to achieve adult concentrations. Postmortem studies of fetuses suggest that secretory IgA (sIgA)–containing epithelial cells appear at 20 to 21 weeks of gestation, and their number increases from 2.5 cells/10,000 μm at 23 to 26 weeks to 8 cells/10,000 μm at 36 to 40 weeks. In fetuses with pneumonia or sepsis, sIgA-containing epithelial cells in the trachea, bronchi, and intrahepatic duct decrease and, at times, completely disappear. This finding suggests that sIgA is an important component of mucosal immunity as early as 20 weeks of gestation.[136,137]

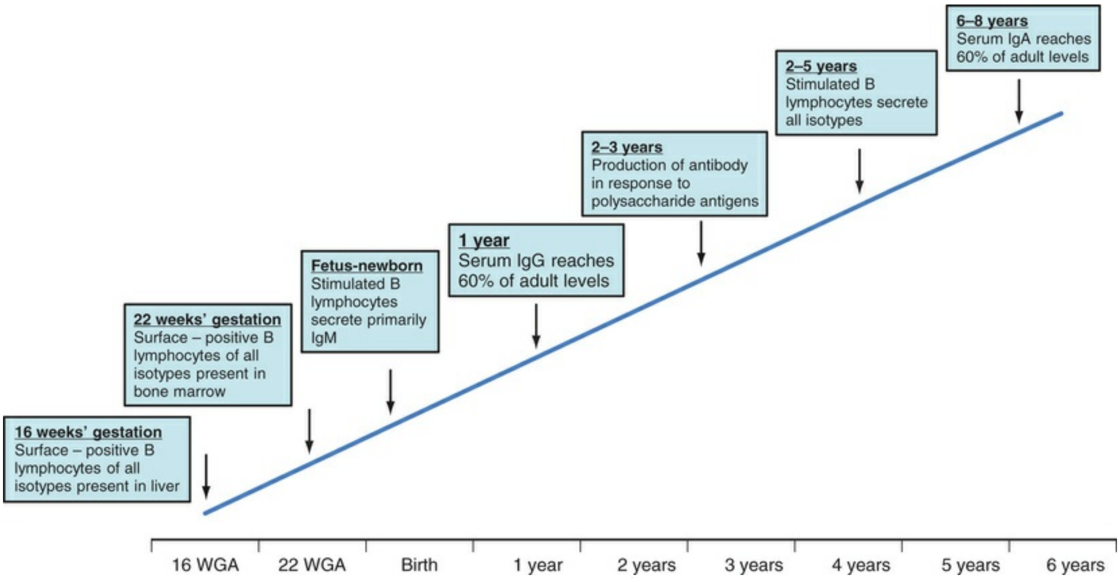
6–8 years
Serum IgA reaches 60% of adult levels
2–5 years
Stimulated B lymphocytes secrete all isotypes
2–3 years
Production of antibody in response to polysaccharide antigens
1 year
Serum IgG reaches 60% of adult levels
Fetus-newborn
Stimulated B lymphocytes secrete primarily IgM
22 weeks' gestation
Surface – positive B lymphocytes of all isotypes present in bone marrow
16 weeks' gestation
Surface – positive B lymphocytes of all isotypes present in liver
16 WGA
22 WGA
Birth
1 year
2 years
3 years
4 years
5 years
6 years

FIGURE 9.3 **Developmental milestones of humoral immunity. Ig, immunoglobulin; WGA, weeks' gestational age.**

Fetuses can produce IgM antibodies, predominantly in response to intrauterine infection. Preterm infants respond nearly as well as term infants to immunization beginning at 2 months with diphtheria and tetanus toxoids and pertussis (DTP), diphtheria and tetanus toxoids and acellular pertussis (DTaP), poliovirus, and hepatitis B vaccines. Term infants immunized or infected during the first few days of life usually produce protective antibody responses, although at somewhat lower levels than adults.

The presence of fetal bone marrow B-lymphocyte pools similar in size to those of adults and with comparable isotype diversity suggests that B-lymphocyte functional deficits may reflect a developing memory repertoire with increased specificity to antigen or the need to generate T lymphocytes capable of producing strong B-lymphocyte signals, rather than inherent B-lymphocyte immaturity as a sole factor. Studies of B-lymphocyte activation have revealed much about the complexities of B-lymphocyte signaling and suggest possible mechanisms for deficits of B-lymphocyte function that can be examined in healthy neonates.

In contrast to the early development of antibody responses to most protein antigens, responses to thymus (T)–independent antigens, such as polysaccharides, develop later. The basis for this process remains unclear. Umbilical cord blood B lymphocytes are capable of activation in vitro with T-independent activators. This finding suggests that signal transduction pathways within the B lymphocyte are normal. However, the mechanism of B-lymphocyte activation by polysaccharides differs from protein antigens in that it involves co-stimulation through a B-lymphocyte surface molecule called CD21 and can be influenced by the expression of yet another B-lymphocyte surface molecule: CD22. Both CD21 and CD22 were noted to be reduced on stimulation of neonatal B lymphocytes, thus suggesting a unique role for these molecules in antibody production to polysaccharide antigens. However, normal functional antibody responses to Pneumovax (Merck, Whitehouse Station, NJ), a pure polysaccharide pneumococcal vaccine, has been reported in children as young at 12 months.[138,139]

Although the extent to which neonatal deficiencies of neutrophil function, complement, or antibody contribute to the increased risk of infection is unknown, these factors are important in vitro in the opsonophagocytic killing of *E. coli*, GBS, and *Candida* species. The combined effects of these deficiencies undoubtedly contribute to the increased risk of serious infection with these pathogens in neonates.[140]

T Lymphocytes

T lymphocytes play a central role in regulation of antigen-specific immune responses, by modulating the function of antigen-presenting cells, B lymphocytes, and other T lymphocytes, both through contact with (receptor binding) and secretion of cytokines and by direct killing of target cells. HSC progenitors migrate to the thymus where, similar to B lymphocytes, T lymphocytes rearrange their TCR genes by somatic recombination (see Fig. 9.2). In contrast to BCRs, TCRs do not diversify their variable (V) region genes through somatic hypermutation. Moreover, unlike B lymphocytes, T lymphocytes develop into 2 populations: αβ T lymphocytes (the most abundant, 95% of the circulating pool) or γδ T lymphocytes (approximately 5% to 10% of the circulating pool). Maturing T lymphocytes move within the thymus in a directed manner from the cortex to the medulla (see Fig. 9.2). The expression of surface molecules identifies their state of maturity. Thus T lymphocytes start as double-negative ($CD4^-/CD8^-$) stage → double-positive ($CD4^+/CD8^+$) → single-positive $CD4^+$ or $CD8^+$ just before being released into the periphery. During maturation in the thymus, T lymphocytes are selected to proceed to the next developmental stage in response to the interactions of a successfully assembled TCR with self-MHC–self-peptide complexes. As with B lymphocytes, *RAG1* and *RAG2* genes and their products are identified during early stages of development, and the expression of transcription factors and signaling events drive clonal commitment.[141]

Understanding normal human T-lymphocyte development in the thymus led to the identification of T-lymphocyte receptor excision circles (TRECs) as biomarkers for T-lymphocyte lymphopoiesis that defined naïve T lymphocytes coming out of the thymus.[142] Because TRECs can be quantitated by polymerase chain reaction, DNA isolated from dried blood spots collected for newborn screening provided an opportunity to identify infants born with absent or very low number of T lymphocytes as a result of SCID. In 2010 the US Department of Health and Human Services Secretary recommended that SCID be added to the newborn screening panel. It is now recognized that the prevalence of SCID in the United States is estimated to be 1 in 58,000 live births, and screening has permitted the initiation of lifesaving therapies for these infants before the onset of infections.[143]

Umbilical cord blood has an increased absolute number of naïve T lymphocytes, compared with the peripheral blood of older children and adults (Table 9.3). The mean peripheral T-lymphocyte counts in newborn infants, children, and adults vary with age and are highest in healthy infants. The ratio of $CD4^+$ to $CD8^+$ lymphocytes in umbilical cord blood is the same as that in adults (1.2), but it is increased to 1.9 from birth through 11 months of life.[144,145] Although the absolute number of circulating T lymphocytes decreases beyond the neonatal period, the percentage of T lymphocytes among the total lymphocyte population increases. Advances in flow cytometry have permitted the identification of different subsets of circulating T lymphocytes. Naïve $CD4^+$ T lymphocytes can differentiate into distinct subpopulations with a variety of different functions. The main functional classes are Th1, Th2, Th17, and Treg. In addition, T-follicular helper lymphocytes (T_{FH}) provide help to B lymphocytes in the lymphoid follicles.

TABLE 9.3

Comparison of Newborn and Adult T Lymphocytes

Characteristics	**Newborn**	**Adult**
Repertoire of TCR binding specificity	Unknown	Broad
Mean T-lymphocyte count	3100/mm^3	1400/mm^3
CD4$^+$/CD8$^+$ ratio	1.2	1.2
Proliferation (mitogen-stimulated)	Good	Good
Proliferation (antigen-stimulated)	Poor	Good
Ability to provide help to B lymphocytes	Poor	Good
CD45RA$^+$ (naïve CD4$^+$ T lymphocytes)	90%	48%
Production of cytokines	Decreased IFNγ, IL-4, G-CSF, GM-CSF, IL-3	Multiple

G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; TCR, T-cell receptor.

Most mature T lymphocytes (95%) recognize antigen through a TCR. Contrary to B lymphocytes, T lymphocytes can recognize only those antigens that are displayed on cell surfaces. These antigens can be derived from pathogens that replicate within the cell such as viruses or intracellular bacteria or products internalized from the extracellular space. T lymphocytes recognize intracellular pathogens because infected cells display on their surface fragments or peptides derived from the pathogens' proteins. The molecules responsible for holding these peptides within their groove are the MHC molecules. Two classes of MHC molecules are recognized: class I, which include human leukocyte antigen-A (HLA-A), HLA-B, and HLA-C; and class II: HLA-DR, HLA-DQ, and HLA-DP. MHC class I molecules are present on all nucleated cells, whereas MCH class II are present on antigen-presenting cells and other specialized cells. Peptide–MCH class I complexes (MHC I) present antigen to cytotoxic T lymphocytes (CD8$^+$), and peptide–MHC class II complexes (MHC II) present antigen to helper T lymphocytes (Th1/CD4$^+$).

Cytosolic peptides derived from vaccinia virus, influenza virus, rabies virus, and *Listeria* are coupled to MHC I molecules on the surface of the infected cell. These peptide–MHC I complexes then can be recognized by cytotoxic CD8$^+$ cells that kill the targeted infected cell. *Mycobacterium tuberculosis*, *Mycobacterium leprae*, *Leishmania donovani*, and *Pneumocystis jirovecii* are localized within macrophage vesicles, and their derived peptides are coupled to MHC II molecules on their surfaces. Peptide–MHC II complexes are recognized by CD4$^+$ (Th1) cells. These activated T lymphocytes then produce IFNγ, which recruits more macrophages; a granuloma is formed, and the activated macrophage kills its intracellular pathogen by releasing the antimicrobial products within its vesicles. *Clostridium tetani*, *S. aureus*, *S. pneumoniae*, polioviruses, *P. jirovecii*, and *Trichinella spiralis* require both humoral and cellular immune response for effective killing.[146,147] It is therefore understandable that defects in antigen processing, presentation, and both T-lymphocyte and B-lymphocyte effector functions make the individual person susceptible to pathogens that require a particular pathway for clearance.

Proliferative Responses.

Neonatal T lymphocytes proliferate normally in response to phytohemagglutinin (PHA) and allogeneic cell stimulation, but they have a limited ability to develop immunologic memory.[148–150] Umbilical cord blood cell populations have been shown to contain large numbers of naïve T lymphocytes (CD45RA$^+$) versus memory T lymphocytes (CD45RO$^+$).[151,152] This proportion declines slowly to 61% by 7 years of age as naïve lymphocytes are replaced by memory lymphocytes, a process that probably represents an intrinsic maturation of T lymphocytes as a consequence of antigenic stimulation.[153,154]

Cytokine Production.

The predominant naïve phenotype of newborn T lymphocytes may further account for differences in cytokine production. Neonatal T lymphocytes produce less INFγ, IL-2, IL-4, IL-10, and TNF-α than adult T lymphocytes in response to various stimuli. Modest reduction of GM-CSF and decreased G-CSF and IL-3 production and gene expression also are described.[154–158] Dysregulation of various immunoregulatory and cytokine genes in umbilical cord blood mononuclear cells could explain the apparent immaturity of neonatal cell-mediated immunity.[159]

T lymphocytes influence the functional activity of many other cell types. Decreased T-lymphocyte function in neonates is likely to increase susceptibility to infection by many pathogens. For example, decreased T-lymphocyte help for antibody production and isotype switching by CD40L-CD40 interaction,[160] along with decreased phagocytic function, probably contributes to increased susceptibility to bacterial infection. Susceptibility to viral infection and other intracellular pathogens, such as *T. gondii* and *Listeria*, probably results from decreased cytolytic activity of T lymphocytes and decreased IFNγ.[154] The specific role of T-lymphocyte immaturity in severe clinical HSV infection in neonates is suggested by the observation that neonates infected with HSV showed decreased antigen-specific cellular responses (decreased proliferation and IFNγ production) compared with adults who had primary HSV infection.[161]

Interrelationships and the Future

Humans resist infection in several ways. The innate defense mechanisms act first and may be capable of eliminating the pathogen completely. If not, adaptive responses are initiated and put in place by releasing clonally expanded effector T and B lymphocytes to the sites of infection. The mechanisms that regulate the final clearance depend on the pathogen itself. For certain pathogens, an effective adaptive immune response leads to a state of protective immunity. However, many pathogens evolve mechanisms that permit evasion from an effective immune response. Since Edward Jenner's studies of cowpox more than 200 years ago, vaccination has become a successful application of our interpretation of nature's experiments. Furthermore, the study of patients with primary immunodeficiency not only has provided a better understanding of biologic systems as they relate to humans but also has offered therapeutic options for this group of patients as well as for others. Only through the understanding of the basic intrinsic mechanisms that regulate immunity will further pathogenic mechanisms be elucidated and therapies developed.

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10

Fever and the Inflammatory Response

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Fever

Pathogenesis

Fever is defined as a centrally mediated rise of body temperature higher than the normal daily variation in response to a variety of pathologic insults.[1] The rise in body temperature is a regulated process triggered by the elevation of the thermoregulatory center set point, located in the hypothalamus, caused by pyrogenic substances. Various microbial products, including endotoxins and exotoxins, are exogenous pyrogens. Although these molecules can act directly to induce fever, evidence indicates that they stimulate host cells to secrete mediators known as endogenous pyrogens including cytokines produced during the inflammatory response, most notably tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-6, and, to a lesser degree, the interferons (IFNs).[2–4] Fever is more likely to be caused by infection, but any inflammatory, neoplastic, immunologic, or traumatic event also can generate fever.

Once pyrogenic cytokines are produced, they enter the systemic circulation and stimulate the rich vascular network surrounding the preoptic area of the hypothalamus (thermoregulatory center). Here they activate phospholipase A_2, which liberates plasma membrane arachidonic acid as a substrate for the cyclooxygenase pathway.[5,6] Some cytokines can increase cyclooxygenase expression directly and cause liberation of the arachidonate metabolite prostaglandin (PG) E_2 (PGE_2). Because this small lipid molecule diffuses easily across the blood-brain barrier, some investigators believe PGE_2 to be the local mediator that activates thermoregulatory neurons, which in turn raise the thermostat set point (Fig. 10.1). Although the blood-brain barrier prevents migration of large proteins such as circulating cytokines, the presence of pyrogenic substances has been demonstrated at the circumventricular organs, which lack a blood-brain barrier.[6]

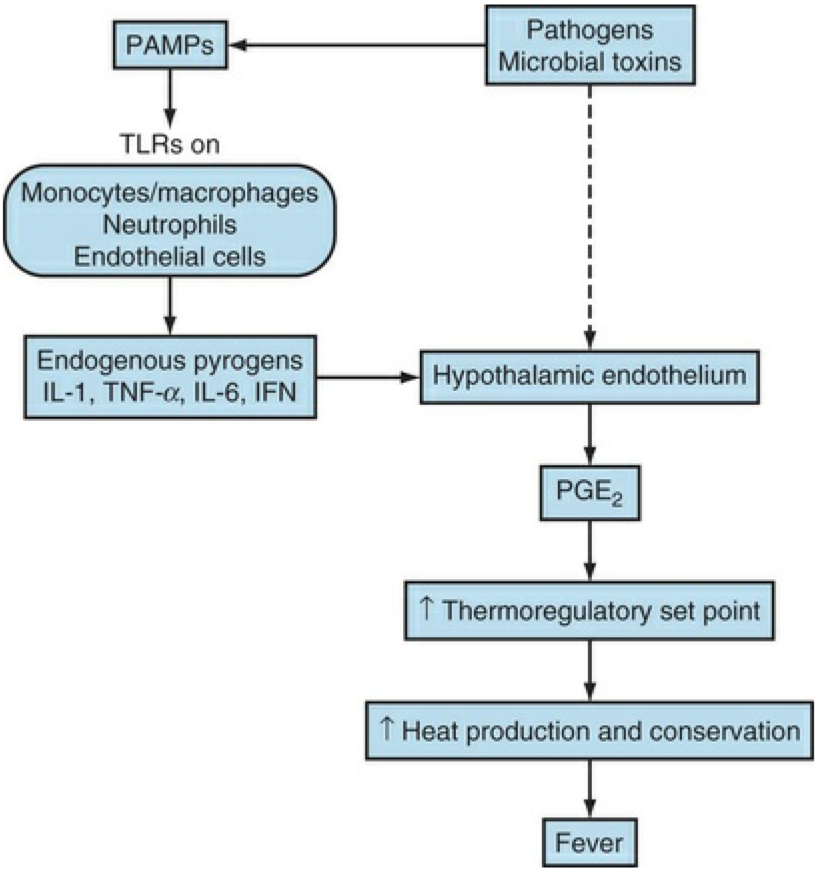

FIGURE 10.1 **Induction of fever: central and peripheral mechanisms. IFN, interferon; IL, interleukin; PAMPs, pathogen-associated molecular patterns; PGE_2, prostaglandin E_2; TLRs, toll-like receptors; TNF-α, tumor necrosis factor-α.**

As a result, activation of peripheral mechanisms that stimulate the sympathetic chain and terminal adrenergic efferent nerves leads to vasoconstriction (heat conservation) and muscle contraction (heat production), which generate fever. Autonomic (decreased sweating) and endocrine (decreased vasopressin secretion to reduce amount of body fluid to be heated) pathways contribute to thermoregulation.[6] Conservation and production of heat continue until the temperature of the blood bathing the hypothalamic neurons matches the new elevated setting. When cytokine stimulation ceases, the hypothalamic set point is reset downward, and the process of heat loss through vasodilation and sweating is initiated. In addition to these thermoregulatory mechanisms, certain areas in the cerebral cortex are stimulated to promote behavioral changes designed to help control temperature, such as the heat-saving behavior of desiring extra blankets during a shaking chill and the heat loss behavior of removing clothing.

Fever must be distinguished from hyperthermia, which is an uncontrolled increase in the body temperature. Hyperthermia typically develops when exogenous heat exposure or endogenous heat production exceeds the body's ability to lose heat. This condition occurs despite a normal hypothalamic set point.

Clinical Aspects

Body temperature varies with age, physical activity, and time of day; it fluctuates from less than 37°C in the early morning to up to 38°C in the late afternoon. Normal diurnal fluctuation also is exhibited in febrile patients. In general, values higher than 37.8°C are considered to be fever, although single elevations do not always imply a pathologic process. Very young infants tend to have blunted fever rises more often than older children in response to the same antigenic stimulus. In clinical practice, core temperature is measured best by a rectal thermometer; oral temperatures can be influenced by previous ingestion of hot or cold foods and are reduced in the presence of open-mouth breathing in patients with tachypnea. Axillary readings are less reliable and typically are 0.5°C lower than oral values and 1°C lower than rectal readings. In theory, the tympanic membrane is an ideal site for measuring core body temperature because the membrane is perfused by a tributary artery supplying the body's thermoregulatory center. Unfortunately, numerous studies using different instruments have shown that although convenient, tympanic membrane thermometers give highly variable readings compared with simultaneously obtained oral or rectal readings.[7,8]

Antipyretic Therapy

Substantial evidence suggests that fever is more beneficial than harmful for the host.[9] High temperatures interfere with the replication and virulence of certain pathogens and may speed the recovery of infected patients. In addition, some immunologic responses (e.g., leukocyte migration and phagocytosis, as well as IFN production) are enhanced by temperature elevation. Fever also induces stress responses in microbes, thus leading to increased production of pathogen-associated molecular patterns (PAMPs) that further enhance the immune response (see later).[10] Moreover, fever serves to attenuate immune responses by promoting caspase cleavage and accelerating leukocyte apoptosis.[11,12] As such, although short courses of standard antipyretic drugs carry a low risk of toxicity, and most have analgesic properties as well, these agents may prolong an illness or diminish a vaccine response. Nonspecific suppression of fever also may eliminate an important clue for the need for further diagnostic investigations or for changes in therapy

Because fever is generated after local hypothalamic stimulation by PGs, inhibitors of the cyclooxygenase enzyme system are potent antipyretics. Although acetaminophen is a poor cyclooxygenase inhibitor in peripheral tissue, acetaminophen is oxidized in the brain, and the resulting compound inhibits cyclooxygenase activity. Aspirin inhibits PG synthetase in a wide variety of tissues, and its antipyretic effect is equivalent to that of acetaminophen. Because these drugs are broad cyclooxygenase inhibitors, they have many side effects. The potential association between aspirin therapy in children with influenza or varicella and the development of Reye syndrome precludes the use of this drug in children with these conditions. Although several nonsteroidal anti-inflammatory drugs (NSAIDs; e.g., ibuprofen, naproxen) have antipyretic effects similar to those of aspirin and acetaminophen, NSAIDs are anti-inflammatory and are associated with more adverse effects than is acetaminophen. NSAID use for treatment of simple fever is ill advised and should be restricted for conditions requiring an anti-inflammatory agent.

Corticosteroids are among the most potent antipyretic drugs because they inhibit the activity of phospholipase A_2, thereby interfering with arachidonic acid metabolism and PG synthesis, and they also block the production of pyrogenic cytokines (i.e., TNF, IL-1, and IL-6) at a proximal step in the genesis of a febrile response. Similarly, IL-1 blockade, most notably with the recombinant IL-1 receptor antagonist anakinra, is highly efficacious for treating fever. However, these agents should not be used in management of simple fever or infectious episodes without specific indications (see Chapter 15).[13]

The use of a cooling blanket or water-alcohol bathing as an attempt to accelerate peripheral heat losses is uncomfortable, and water-alcohol bathing can lead to alcohol toxicity. Peripheral cooling, in the absence of pharmacologic downregulation of the hypothalamic set point can be counterproductive because cold receptors in the skin send signals to the spinal cord and brain that induce reactive vasoconstriction and shivering, thus increasing heat conservation and eliciting oxygen consumption and heat production.

Inflammatory Response

The body has a sentinel system that maintains immunologic surveillance to avoid pathogen-induced derangements of homeostasis. Once this background activity is circumvented, a host inflammatory response ensues. The *inflammatory response* is a complex reaction involving the migration of elements of the immune system into sites of tissue injury or microbial invasion.[14] In most clinical situations, the inflammatory response, with or without the aid of antimicrobial therapy, is effective in resolving the infection and contributes to tissue remodeling. If the infection is not brought under control, however, the infectious stimulus gains access to the circulation and stimulates the release of a cascade of systemic and local effector molecules. This host reaction, called the systemic inflammatory response syndrome, can be caused by a variety of immunologic, traumatic, surgical, or drug-induced insults; most often, however, an infectious agent is the trigger (see

Chapter 11). The sum of the balance of the microbial damage–host response framework can result in host damage caused by the microbe, the host, or both.

Overview of the Innate and Adaptive Immune Systems

The immune response to infection and cellular injury can be broadly divided into 2 categories: innate and adaptive immunity.[15] The initial immune response is mounted by the innate immune system, involving neutrophils, monocytes and macrophages, dendritic cells, and natural killer (NK) cells. These cells use pattern recognition receptors (PRR) to mount an immediate response associated with the production of IL-1, IL-6, and TNF-α. PRRs have broad specificity for highly conserved and often integral microbial structures called PAMPs, as well as endogenous ligands released as a result of tissue damage called damage-associated molecular patterns (DAMPs). In addition to inflammatory cytokines, many other pathways are activated, including synthesis of degradative enzymes and enzymes responsible for production of small molecule mediators of inflammation such as arachidonic acid derivatives (Fig. 10.2).

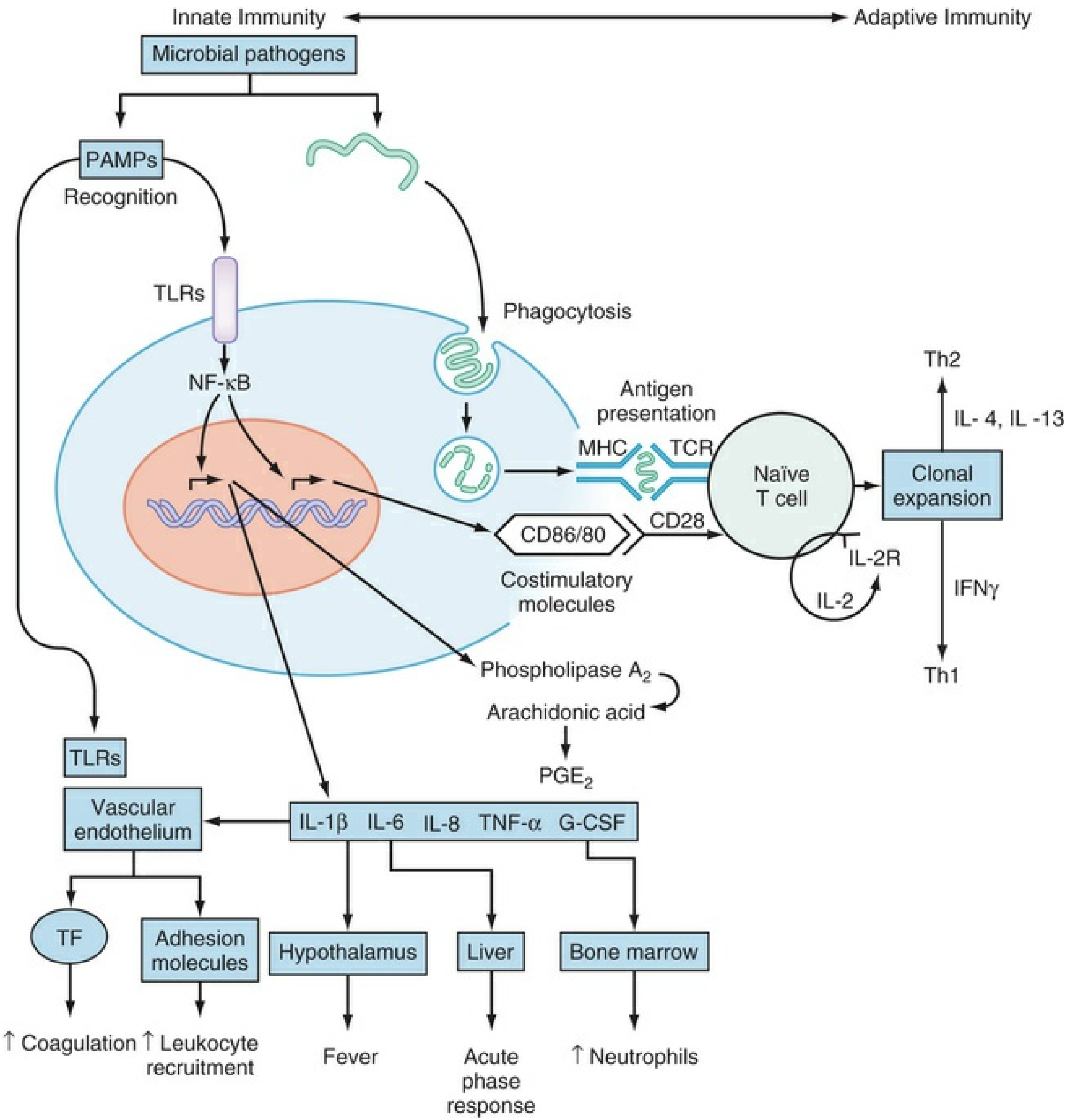

FIGURE 10.2 Induction of the innate and adaptive immune responses. The recognition of pathogen-associated molecular patterns (PAMPs) by toll-like receptors (TLRs) results in the activation of intracellular signaling pathways leading to the activation of the transcription factor nuclear factor-κB (NF-κB). The translocation of NF-κB into the nucleus leads to upregulation of expression of genes encoding proinflammatory cytokines interleukin-1 (IL-1), IL-6, tumor necrosis factor-α (TNF-α), and colony-stimulating factors (CSFs). It also leads to increased expression of costimulatory molecules involved in antigen presentation and induction of the adaptive immune responses. The cytokines IL-1, IL-6, TNF, and granulocyte CSF (G-CSF), through their effects on hypothalamus, bone marrow, liver, and vascular endothelial cells, initiate the inflammatory cascade. CD, cluster of differentiation; IFN, interferon; IL-2R; interleukin-2 receptor; MHC, major histocompatibility complex; PGE_2, prostaglandin E_2; TCR, T-cell receptor; TF, tissue factor; Th1 and Th2, helper T lymphocyte, subtypes 1 and 2.

The contribution of the adaptive immune system becomes important at later stages of the immune response. The adaptive immune response is mediated by T and B lymphocytes and is distinguished from innate immunity by high specificity and long-lasting memory. The adaptive immune response is influenced by the generation of helper T-lymphocyte subsets (Th) and the subsequent production of "effector" cytokines by these cells. Naïve T lymphocytes recognize antigen encountered by antigen-presenting cells (APCs), undergo activation and expansion, and can differentiate into 2 subsets determined by the cytokine milieu. The IFNs and IL-12 drive Th1 differentiation, and these cells secrete IFNγ and promote mainly cellular immunity. In contrast, IL-4 induces Th2 differentiation, leading to production of IL-4, IL-5, IL-10, and IL-13 and the promotion of humoral immunity.[16] Infection by intracellular pathogens induces primarily a Th1-dominated response that protects against the majority of microorganisms, whereas some parasitic infections induce a Th2 response that is associated with resistance to helminths.

In addition to instructive cytokines, APCs use several costimulatory molecules, including CD80 and CD86, to signal T lymphocytes and induce their clonal expansion. Antigen presentation in the absence of costimulatory molecules leads to cell anergy. Because the engagement of the innate receptors on APCs leads to upregulation of expression of the costimulatory molecules and enhances antigen presentation, the interaction between the innate and adaptive systems at this step becomes very important.[15]

Receptors of the Innate Immune System

The PRRs that initiate the innate immune response detect infectious agents by recognizing PAMPs, which are shared by large groups of microorganisms but are not present in mammalian cells.[15] Probably the best-known PAMPs are lipopolysaccharides (LPSs) from the outer membrane of gram-negative bacteria. LPS administration induces local and systemic inflammation and tissue damage similar to that observed in infection caused by gram-negative bacteria themselves. For this reason, the LPS-induced response has been used for several decades as a model of inflammation. In 1998, the principal component of the human LPS receptor was identified as toll-like receptor 4(TLR4). The term is based on structural similarities with the *Drosophila* protein "toll," which is required for the normal development of the flies and protection against the fungus *Aspergillus*.[17,18] At least 9 other human TLRs have been identified, each of which appears to recognize a distinct set of PAMPs (Table 10.1). It is becoming clear that, collectively, TLRs can detect most (if not all) microbes,[15,19–21] including protozoa, bacteria, viruses, and fungi. In addition, TLRs also may recognize endogenous ligands such as degradation products of various extracellular matrix components released as a result of tissue damage called DAMPs. The recognition of DAMPs by TLRs may contribute to the development of inflammation and in some infections may lead to a greatly exaggerated inflammatory response. For instance, TLR4 increases the severity of the inflammatory response to H5N1 influenza virus infection by recognizing a DAMP rather than the virus itself. More specifically, acute lung injury caused by H5N1 virus produces endogenous oxidized phospholipids, which stimulate TLR4.[22] TLRs are expressed in different and important cells of the innate immune system including monocytes and macrophages, dendritic cells, neutrophils, vascular endothelial cells, and epithelial cells lining mucosal surfaces. Although some TLRs (e.g., TLR1, TLR2, TLR4, TLR5, and TLR6) are expressed on the cell surface, others (TLR3, TLR7, and TLR9) are found almost exclusively in intracellular compartments such as endosomes.[21]

TABLE 10.1

Toll-Like Receptors and Their Microbial Ligands

TLR	Ligand	Microbial Source
TLR1/TLR2 TLR2/TLR6	Lipoproteins Peptidoglycan Lipopolysaccharide Zymosan	Bacteria Gram-positive bacteria *Leptospira* Yeast
TLR3	Double-stranded RNA	Viruses
TLR4	Lipopolysaccharide	Gram-negative bacteria
TLR5	Flagellin	Various bacteria
TLR7/8	Single-stranded RNA	Viruses
TLR9	CpG DNA	Bacteria, protozoa

TLR, toll-like receptor.

Pathogens that have evaded cell surface or endosomal TLRs and have gained access to the cytosol are recognized by another group of PRRs called nucleotide-binding and oligomerization domain

(NOD) receptors and NOD-like receptors (NLRs).[23,24] Similar to TLRs, these receptors bind a variety of microbial products, including flagellin, bacterial exotoxins, and viral and bacterial DNA. Activation of NLRs is believed to require 2 signals and integrate the recognition of PAMPs with detection of cellular damage or stress (DAMPs). The activation of at least some of the NLRs induces assembly of a macromolecular inflammasome and activation of caspase 1, which catalyzes the proteolytic processing of pro-IL-1β to into mature active IL-1β.

The binding of microbial molecules to PRRs leads to the activation of intracellular signaling pathways. The predominant pathway used by TLRs leads to the activation of nuclear factor-κB (NF-κB), a nuclear transcription factor that initiates rapid changes in expression of several groups of genes (see Fig. 10.2). Most important are those encoding the following:

- Cytokines and chemokines (including the pyrogenic cytokines TNF-α, IL-1, IL-6, as well as IL-8; colony-stimulating factors; platelet-activating factor; among others)
- Enzymes involved in the degradation of extracellular matrix proteins
- Enzymes responsible for the production of small molecule mediators of inflammation such as arachidonic acid derivatives
- Proteins involved in microbial killing mechanisms

A subset of TLRs comprising TLR3, TLR7, and TLR9 recognizes nucleic acids derived mainly from viruses. In addition to production of proinflammatory cytokines, activation of these TLRs also leads to the production of type I IFNs that can induce proteins that interfere with viral replication.[21]

The engagement and activation of TLRs expressed on vascular endothelial cells also lead to increased expression of chemokines and adhesion molecules (selectins and integrin ligands).[25,26] Combined with the simultaneous upregulation of selectin ligands and integrins on leukocytes (also stimulated by TLR engagement), the result is adhesion of leukocytes to the vascular endothelium. Once these cells are firmly attached, they transmigrate across endothelial surfaces (i.e., extravasation) to the sites of inflammation. During extravasation, neutrophil degranulation occurs with the release of several proteolytic enzymes and toxic oxygen radicals that contribute to increased vascular permeability. Furthermore, activation of the complement system (classical and alternative pathways) and coagulation cascades (intrinsic and extrinsic pathways) occurs concurrently with cytokine stimulation. Release of the anaphylatoxins C3a and C5a promotes vascular abnormalities and neutrophil activation.

The cytokines and chemokines whose production is stimulated by PRR engagement in turn further amplify the inflammatory response:

- The cytokines IL-1, TNF-α, and IL-6 stimulate metabolism of arachidonic acid to form leukotrienes, thromboxane A_2, and prostaglandins (especially PGE_2 and PGI_2).
- IL-1, TNF-α, and IL-6 increase PGE_2 synthesis in the vascular and perivascular cells of hypothalamus, thus leading to generation of fever.[2–4]
- Granulocyte colony-stimulating factor increases production and release of neutrophils from the bone marrow to replace those consumed by inflammation, often leading to an increase in absolute neutrophil counts.
- IL-1 and TNF-α stimulate endothelial cells to synthesize secondary factors that contribute to the inflammatory process, including endothelial cell adhesion molecules, chemokines (IL-8, macrophage inflammatory protein-1α), and hemostatic tissue factor, as well as IL-1, PGI_2, and granulocyte-macrophage colony-stimulating factor.

The release of the hemostatic tissue factor by endothelial cells and macrophages appears to be pivotal in the activation of the coagulation cascade, which in turn can trigger further activation of the complement system. Together, the dysregulated activation of these pathways can lead to the disseminated intravascular coagulation seen in the systemic inflammatory response syndrome.[27] Platelets also are primed to interact with endothelium and aggregate in dense masses that interfere with tissue blood supply. Generalized endothelial cell activation is central to the pathogenesis of vascular injury and capillary permeability associated with acute inflammation that, when uncontrolled, can progress to shock and multiorgan dysfunction.[27]

Acute Phase Response

Primarily in response to IL-1 and IL-6, a structurally and functionally heterogeneous group of proteins known as acute phase response proteins changes their concentration in peripheral blood.[1,28] Some of these are *positive acute phase proteins* because they increase in concentration after antigenic stimuli. These proteins are synthesized mainly by the liver, and they include C-reactive protein (CRP), serum amyloid A, α_1-acid glycoprotein, α_1-antitrypsin, haptoglobin, ceruloplasmin, and fibrinogen. Other acute phase proteins are *negative acute phase proteins* because their plasma concentrations are reduced. Examples include albumin, prealbumin, retinol-binding protein, and transferrin. The exact functions of the acute phase proteins are not understood completely. CRP appears to be a pattern recognition molecule that typically binds to molecular configurations that either are exposed during cell death or are found on the surface of certain pathogens such as *Streptococcus pneumoniae*.[29] Ligand-bound or aggregated CRP efficiently activates the classical complement pathway through direct interaction with C1q and stimulates phagocytosis. This finding raises the possibility that CRP is involved in clearing of cellular debris from necrotic and apoptotic cells, but CRP also may give additional protection against certain microbes.

The acute phase responses provide a guide to the intensity of inflammation or the extent of tissue involvement. For instance, the rise in fibrinogen causes erythrocytes to form stacks (rouleaux) that sediment more rapidly than do individual erythrocytes. This is the basis for measuring erythrocyte sedimentation rate as a simple test for the magnitude of systemic inflammatory response regardless of the initiating stimuli.

The acute phase response also is associated with profound alterations in the use of carbohydrates, proteins, lipids, and minerals. These diverse cellular stressors may be advantageous during an infection by preferentially harming pathogens rather than the host.[30] The best-documented alterations in mineral use are decreased serum concentrations of iron and zinc caused by the uptake in hepatocytes and phagocytes, thus limiting their availability to pathogens.[31] Because of hypoferremia, reduction of red blood cell synthesis, and decreased red blood cell life span, mild but reversible anemia usually accompanies a significant acute inflammatory response.[1,32,33] The hypermetabolic state typically seen in patients with the systemic inflammatory response syndrome requires massive use of carbohydrate and lipid stores to meet energy needs, as well as use of amino acids from muscle tissue by the liver to produce glucose (gluconeogenesis). These changes are presumably provoked by cytokine-induced production of cortisol, insulin, glucagon, and growth hormone. Clinically, these abnormalities manifest as reactive hyperglycemia, substantial fluctuation in plasma concentrations of free fatty acids, hypertriglyceridemia, and negative nitrogen balance resulting from catabolism of amino acids. Many of these effects are mediated by TNF-α.

Regulatory Anti-Inflammatory Pathways

Excessive activation of the inflammatory responses described earlier can lead to extensive tissue damage and vascular injury, disseminated intravascular coagulation, and shock. To attenuate potential damage to the host, the inflammatory cascade stimulates modulating pathways that involve anti-inflammatory cytokines such as transforming growth factor-β (TGF-β), IL-4, and IL-10. TGF-β also stimulates production of extracellular matrix proteins and contributes to tissue remodeling after the resolution of inflammation. Natural inhibitors of inflammatory cytokines also exist.[34] For instance, many inflammatory cells including neutrophils and macrophages can shed their TNF receptors, which then bind free TNF and neutralize its proinflammatory activity. Similarly, the IL-1 system has unique pathways of negative regulation involving natural IL-1 receptor antagonists and the type II decoy receptor. Some anti-inflammatory cytokines (e.g., IL-4, IL-10) can simultaneously inhibit the production of IL-1 and stimulate the production of receptor antagonists and the decoy receptor. Thus an intricate network of positive and negative biofeedback loops operates during the course of a systemic inflammatory response, and the net balance determines the clinical expression and severity of disease.

Interaction of Innate and Adaptive Immune

Responses

In summary, the *immediate* inflammatory response to microbial invasion and tissue injury is controlled mainly by the innate immune system. This innate response is triggered by the binding of PAMPs and DAMPs to the PRRs (i.e., TLRs and NLRs) expressed in host cells. The subsequent intracellular signaling in host cells leads to increased expression of several groups of genes including those encoding pyrogenic and proinflammatory cytokines TNF-α, IL-1, and IL-6. TLR activation also causes upregulation of expression of the costimulatory molecules involved in antigen presentation (i.e., CD80/CD86). This leads to the enhancement of adaptive immunity that becomes more important in *later stages* of the inflammatory response. Anti-inflammatory pathways are activated simultaneously, and the net balance between proinflammatory and anti-inflammatory stimuli determines the magnitude and the outcome of the inflammatory response. Basic mechanisms of the inflammatory response are similar regardless whether the response is systemic or local. For instance, in bacterial meningitis, local production of cytokines within the subarachnoidal space in response to the presence of bacteria, or their cell wall components, induces disruption of the blood-brain barrier, increased vascular permeability, and chemotactic attraction of neutrophils to the meningeal site of microbial invasion.[35]

The effective coordination of adaptive and innate immunity eventually leads to the elimination of invading microbes. The absence of microbial stimulation causes cessation of the proinflammatory response and resolution of inflammation. At this stage, several cytokines and growth factors (including TGF-β) contribute to the repair of the damaged tissues. This process allows the host to return to and maintain a relative state of homeostasis until the next microbial challenge.

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PART II

Clinical Syndromes and Cardinal Features of Infectious Diseases: Approach to Diagnosis and Initial Management

OUTLINE

A Septicemia, Toxin, and Inflammation-Mediated Syndromes
B Cardinal Symptom Complexes
C Oral Infections and Upper and Middle Respiratory Tract Infections
D Lower Respiratory Tract Infections
E Cardiac and Vascular Infections
F Central Nervous System Infections
G Genitourinary Tract Infections
H Gastrointestinal Tract Infections and Intoxications
I Intra-Abdominal Infections
J Skin and Soft Tissue Infections
K Bone and Joint Infections
L Eye Infection
M Infections Related to Trauma
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P Infections and Cancer
Q Infections Associated With Hospitalization and Medical Devices
R Infections in Patients With Deficient Defenses
S Human Immunodeficiency Virus and the Acquired Immunodeficiency Syndrome

A

Septicemia, Toxin, and Inflammation-Mediated Syndromes

OUTLINE

11 The Systemic Inflammatory Response Syndrome (SIRS), Sepsis, and Septic Shock

12 Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome

11

The Systemic Inflammatory Response Syndrome (SIRS), Sepsis, and Septic Shock

Judith A. Guzman-Cottrill, Louise Elaine Vaz

Sepsis remains a major cause of morbidity and mortality among children.[1-4] While the prevalence of pediatric sepsis has risen,[5,6] sepsis-associated mortality in children has decreased from 97% in 1966[7] to 8% to 12% by 2012.[5,6] In the United States, the estimated incidence annually is 0.89 cases per 1000 persons.[6] Although this represents a significant improvement over past decades, severe sepsis remains one of the leading causes of death in children.[7,8] A recent study estimates a median hospital stay of 17 days and total hospitalization cost of $77,446,[5] and $14.6 billion in health care expenditures in the US.[6]

In a seminal study, Watson and colleagues[9] analyzed the effects of age, birth weight, underlying disease, and microbiologic etiology on the incidence, mortality, and hospital costs of children who develop septicemia using 1995 hospital discharge and population data from seven states. Using the same databases, Hartman updated these estimates in 2005.[6] The incidence is highest in newborns (9.70 per 1000) and falls significantly in older children (0.48 per 1000 in 10- to 14-year-olds). An increase in prevalence among very low birth weight infants was noted from 1.8 cases per 1000 births in 1995 to 4.6 cases per 1000 in 2005. Underlying comorbidities varied by age; however, neuromuscular, cardiovascular, and respiratory were the most common comorbidities in all years. Endocarditis and central nervous system infections had the highest case-fatality rates (16.7% and 15.2%, respectively), whereas genitourinary and wound and soft tissue infections had the lowest (3.7% and 3.9%, respectively).[6]

Global estimates for sepsis are limited; however, the Sepsis Prevalence, Outcomes, and Therapies (SPROUT) study recently used prospective point prevalence estimates among 128 sites in 26 countries.[10] Prevalence was noted to be 8.2%, with hospital mortality of 25%, and did not differ by age or between developed and resource limited countries. Additional patient characteristics from this international study are noted in Table 11.1.

TABLE 11.1

Characteristics of Patients with Severe Sepsis

Characteristic	**Value**
Age in years	3.0 (0.7–11.0)
Male sex, *n* (%)	302 (53.3%)
Race/ethnicity, *n* (%)	
White	245 (43.2)
Hispanic	97 (17.1)
Black	79 (13.9)
Asian	75 (13.2)
Other	39 (6.9)
Unknown	32 (5.6)
Comorbid condition(s), *n* (%)	
Respiratory	172 (30.3)
Gastrointestinal	141 (24.9)
Cardiovascular	136 (24.0)
Genetic	115 (20.3)
Hematologic/immunologic	114 (20.1)
Neuromuscular	97 (17.1)
Neoplastic	80 (14.1)
Prematurity	76 (13.4)
Metabolic	62 (10.9)
Renal	55 (9.7)
Solid organ/stem cell transplant	54 (9.5)
Organ dysfunction present at screening, *n* (%)	

Respiratory	469 (82.7)
Cardiovascular	398 (70.2)
Hematologic	175 (30.9)
Hepatic	143 (25.2)
Neurologic	119 (21.0)
Renal	93 (16.4)

Modified from Weiss SL, Fitzgerald JC, Pappachan J, et al. Global epidemiology of pediatric severe sepsis: the sepsis prevalence, outcomes, and therapies study. Am J Respir Crit Care Med 2015;191:1147−1157.

Definitions

An international panel of experts in the fields of adult and pediatric septicemia and clinical research in 2005 proposed the first set of specific definitions and criteria for the components of the sepsis continuum that can be applied consistently in the pediatric population.[11] These definitions were used again in the international guidelines for management of sepsis and septic shock.[12] The consensus definitions for systemic inflammatory response syndrome (SIRS), infection, sepsis, severe sepsis, septic shock, and multiple organ dysfunction syndrome in children are listed in Box 11.1 and Table 11.2. It is important to recognize that these definitions were meant for use in the design, conduct, and analysis of large, multicenter, international therapeutic trials rather than as a clinical tool at the bedside. It is clear that, given the intraindividual and interindividual differences in the time course of disease progression, these definitions often have limited clinical utility.[13] Other vital sign ranges (such as used by the Pediatric Advanced Life Support septic shock guidelines) may be clinically useful to help guide diagnostic and therapeutic decisions.[14]

Box 11.1

Definitions of Systemic Inflammatory Response Syndrome, Infection, Sepsis, Severe Sepsis, and Septic Shock[1]

Systemic Inflammatory Response Syndrome (SIRS)

Presence of two or more of the following criteria, one of which must be abnormal temperature or leukocyte count:

- Core temperature by rectal, oral, or central catheter probe of >38.5°C or <36°C

- Tachycardia, defined as a mean heart rate >2 SD above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise unexplained persistent elevation over a 0.5- to 4-hour time period or for children <1 year old: bradycardia, defined as a mean heart rate <10th percentile for age in the absence of external vagal stimulus, β-blocker drugs, or congenital heart disease; or otherwise unexplained persistent depression over a 0.5-hour time period

- Mean respiratory rate >2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia

- Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) or >10% immature neutrophils

Infection

Suspected or proven (by positive culture, tissue stain, or polymerase chain reaction test) infection caused by any pathogen or a clinical syndrome associated with a high probability of infection

Evidence of infection includes positive findings on clinical examination, imaging, or laboratory tests (e.g., white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans)

Sepsis

SIRS in the presence of or as a result of suspected or proven infection

Severe Sepsis

Sepsis plus the following: cardiovascular organ dysfunction, acute respiratory distress syndrome (ARDS), or two or more other organ dysfunctions

Septic Shock

Sepsis and cardiovascular organ dysfunction

Distributive (Warm) Shock

Decreased systemic vascular resistance and elevated cardiac output noted by fast capillary refill, bounding pulses, warm and dry extremities, and wide pulse pressure

Cold Shock

Increased systemic vascular resistance with decreased cardiac output noted by delayed capillary refill, diminished pulses, and mottled and cool extremities

Modified from Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 2005;6:2–8.

TABLE 11.2

Age-Specific Abnormal Vital Signs and Laboratory Values[a]

Age Group	Heart Rate (beats/min)		Respirations (breaths/min)	Systolic Blood Pressure (mm Hg)	Peripheral Leukocyte Count (Leukocytes × $10^3/mm^3$)
	Tachycardia	Bradycardia	Tachypnea	Low	High/Low
0 days to 1 wk	>180	<100	>50	<65	>34

1 wk to 1 mo	>180	<100	>40	<75	>19.5 or <5
1 mo to 1 yr	>180	<90	>34	<100	>17.5 or <5
2 to 5 yr	>140	NA	>22	<94	>15.5 or <6
6 to 12 yr	>130	NA	>18	<105	>13.5 or <4.5
13 to <18 yr	>110	NA	>14	<117	>11 or <4.5

[a] Lower values for heart rate, leukocyte count, and systolic blood pressure are for the 5th percentile, and upper values for heart rate, respiration rate, or leukocyte count are for the 95th percentile.

NA, not applicable.

Modified from Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 2005;6:2–8.

Etiology

Several factors influence the potential pathogens causing septicemia in children, including age, host immune status, presence of an indwelling catheter, and geographic location at the time of infection. In addition, organisms causing community-onset infections differ from those acquired in the hospital setting. During the neonatal period, common bacterial causes include group B *Streptococcus* and enteric bacilli, such as *Escherichia coli.* Other less common pathogens include enterococci, *Listeria monocytogenes, Staphylococcus aureus* (including methicillin-resistant *Staphylococcus aureus* [MRSA]), nontypable *Haemophilus influenzae,* and *Streptococcus pneumoniae*. Advances in neonatology and survival of very low birth weight infants affect the epidemiology of hospital-associated neonatal sepsis. The use of central venous lines and other foreign bodies further predisposes these already compromised neonates to pathogens such as coagulase-negative staphylococci, *S. aureus* (including MRSA), other gram-negative bacilli, and *Candida* spp. Rigorous application of bundles of infection control practices can reduce dramatically the incidence of coagulase-negative staphylococci bloodstream infection in neonatal intensive care[15] (see Chapter 100). Viral neonatal sepsis may be clinically indistinguishable from bacterial disease. Viral pathogens include herpes simplex virus, adenovirus, enteroviruses, respiratory syncytial virus, and influenza virus.

Beyond the neonatal period, *S. pneumoniae* and *Neisseria* *meningitidis* are common causes of sepsis in otherwise healthy children. *Haemophilus influenzae* type b (Hib) should be considered in the incompletely vaccinated child. Before the Hib vaccine, there were estimates of 20,000 cases per year. This has since been reduced to less than 700 per year, with the largest burden in children younger than 5 years and adults 65 years and older.[16,17] Since the routine administration of the heptavalent pneumococcal conjugate vaccine (PCV7) in 2000, the overall incidence of invasive pneumococcal disease due to vaccine serotypes in children younger than 5 years declined by 97%.[18] Universal infant immunization with PCV13 in 2010 further reduced invasive pneumococcal disease, without evidence to date of replacement serotype invasive disease.[19] Remaining cases of invasive pneumococcal disease currently are occurring disproportionately in children with underlying conditions and with a variety of nonvaccine serotypes.[20]

Other organisms causing sepsis include *S. aureus* and *Streptococcus pyogenes*, which also can cause toxic shock syndrome, as well as *Salmonella* spp. and rickettsiae in certain geographic regions (e.g., Rocky Mountain spotted fever). Malaria and dengue fever also can cause sepsis. In hospitalized infants and children with indwelling central venous lines, coagulase-negative staphylococci, *S. aureus*, gram-negative bacilli, and *Candida* spp. are important causes of sepsis related to central-line–associated bloodstream infection. Infections with multidrug-resistant organisms are an increasing, particularly those due to gram-negative organisms (carbapenemase-resistant strains, extended-spectrum β-lactamase [ESBL] strains,) and enterococci (vancomycin resistant).

Children with underlying immunodeficiency can have septicemia caused by the same pathogens as healthy children; however, some conditions predispose the immunocompromised host to additional organisms. Neutropenic oncology patients with mucositis are at risk for sepsis due to the Enterobacteriaceae (or other gram-negative bacilli such as *Pseudomonas aeruginosa*) and gram-positive organisms, including α-hemolytic streptococci. Viridans group streptococci are an important cause of sepsis in the neutropenic oncology population, often with associated acute respiratory distress syndrome (ARDS).[21,22] Prolonged neutropenia and recent antibiotic use can increase the risk for fungal sepsis. As most oncology patients have an indwelling central venous catheter, they also remain at risk for the typical central-line–associated bloodstream infection pathogens. Patients with acquired immunodeficiency syndrome (AIDS) are at higher risk for bacteremia due to *S. pneumoniae, P. aeruginosa, S. aureus,* and typable *H. influenzae*. Patients with anatomic or functional asplenia (including sickle cell disease) are at increased risk for sepsis caused by encapsulated organisms such as *S. pneumoniae, Salmonella* spp., *H. influenzae, N. meningitidis,* and *Capnocytophaga canimorsus* (associated with dog or cat exposure).

Culture-negative sepsis occurs in 30% to 75% of children with sepsis, reflecting a host response to bacterial components, a result of antibiotic treatment before obtaining cultures, or uncultivated organisms (e.g., rickettsiae, certain fungi, and viruses). Newer multiplex polymerase chain reaction assays may improve the rate of organism detection.[23,24]

Pathophysiology

If a microbe gains access to the intravascular compartment, the host activates defensive mechanisms. Transient bacteremia without significant clinical consequences occurs commonly in healthy children. Depending on the age and immunocompetence of the patient, the virulence and number of pathogens in the blood, and the timing and nature of a therapeutic intervention, the host's systemic inflammatory response ensues and can progress independently despite successful eradication of the microbe. Although infection is a major cause of SIRS, a number of other entities, including trauma, ARDS, neoplasm, burn injury, and pancreatitis, also are recognized causes.

Most pathophysiologic consequences of the sepsis syndrome result from an imbalance between proinflammatory and anti-inflammatory mediators in combination with microbial toxins.[25] In children, severe sepsis arises from coordinated activation of the innate immune response.[26] This response, triggered by diverse pathogens, is multifaceted.[25-27] When triggered, the response leads to secretion of proinflammatory and anti-inflammatory cytokines, activation and mobilization of leukocytes, activation of coagulation and inhibition of fibrinolysis,[28,29] and increased apoptosis.[30] As a result of coagulation activation, generation of thrombin promotes fibrin deposition in the microvasculature and also exacerbates ongoing inflammation by direct and indirect mechanisms.[25] Although evolutionarily designed to limit microbial dissemination, overly exuberant innate inflammatory processes can be detrimental, resulting in cardiac dysfunction, vasodilation, capillary injury, and microvascular and macrovascular thromboses. Despite antimicrobial therapy and intensive supportive care, these processes frequently lead to organ dysfunction, thrombotic complications, longterm neurologic morbidity, or death.[1,31]

The clinical manifestations are the result of systemic inflammation and include abnormal temperature regulation, flushed warm skin, widened pulse pressure, tachycardia, tachypnea, metabolic acidosis (elevated serum lactate, decreased base excess), renal or hepatic dysfunction, thrombocytosis, and leukocytosis. As the syndrome progresses, multiorgan failure, including acute respiratory failure, hypotension, myocardial failure, decreased neurologic function, oliguric or anuric renal failure, hepatic failure, leukopenia, anemia, and thrombocytopenia, can ensue and can lead to death.

Clinical and Laboratory Findings

Fever, tachycardia, and tachypnea are the most common physiologic abnormalities associated with sepsis, even though they are insensitive and nonspecific. Other clinical signs include decreased tone, diminished activity, pale or grey skin color, prolonged capillary refill time, and poor feeding or sucking.[32] Biochemical markers of inflammation may one day prove to be more objective and reliable than physiologic findings; however, no biochemical marker has been confirmed to be robust enough to use for the definitive diagnosis of sepsis or for tracking response to therapy and disease progression. In terms of septic shock, early recognition should be done by clinical examination because there are no reliable biochemical tests available to date.[12] Nonetheless, a rapid and reliable clinical or biologic marker would be invaluable because early treatment with antibiotics and fluid resuscitation has been clearly demonstrated to reduce both morbidity and mortality.[12,33]

Clinical Signs

The earliest clinical sign of infection is age-dependent change in body temperature.[34] In immune-competent children, the earliest sign is fever. In immune-compromised children and premature infants, the earliest sign can be hypothermia or fever.[34] Fever in association with changes in a child's behavior, such as an infant's loss of smiling or playfulness (especially after fever has been controlled with antipyretic therapy), is a sign of serious infection, which can benefit from antibacterial, antiviral, or antifungal therapy.[35-37]

Tachycardia is a useful sign of sepsis in the neonate born at term,[38] as is tachycardia or tachypnea in older children.[34] Fever can account for some tachycardia, as each 1°C increase can result in an increase in heart rate of 10%; however, the heart rate and respiratory rate should become normal for age when fever is controlled with antipyretic therapy or falls spontaneously.[34] Heart rate higher than 150 beats/min in children and higher than 160 beats/min in infants and respiratory rates higher than 50 breaths/min in children and higher than 60 breaths/min in infants are associated with increased mortality risk and commonly presage the development of septic shock.[11] A minimal mean arterial pressure of more than 30 mm Hg is considered the absolutely lowest tolerable blood pressure in the extremely premature infant.[12,39] Specific hemodynamic abnormalities in the emergency department have been associated with increasing mortality (percentages in parenthesis): eucardia (1%), tachycardia/bradycardia (3%), hypotension with capillary refill less than 3 seconds (5%), normotension with capillary refill greater than 3 seconds (7%), and hypotension with capillary refill greater than 3 seconds (33%).[12,14]

Laboratory Findings

Numerous biologic markers of sepsis in children have been studied, but none has made its way to complete acceptance in clinical practice based on prospective clinical trials and evidence-based criteria.[34,40,41] Biomarkers that are commonly used diagnostically, clinically, and prognostically include the total peripheral white blood cell count,[42] platelet count, erythrocyte sedimentation rate, lactate,[43,44] procalcitonin,[45-48] C-reactive protein,[49-52] interleukin-6,[53-56] base excess/base deficit, glucose, and organ-specific markers (e.g., blood urea nitrogen, creatinine, alanine aminotransferases, coagulation). None is completely sensitive or specific.[57,58] There are many types of biologic markers currently under development that may prove to be more accurate in screening, diagnosing, and determining the response to therapy during infection and sepsis. These include tests such as serum amyloid A level,[57] rapid antigen assays,[59] polymerase chain reaction,[60-62] genomic testing (for guiding therapy and determining host response),[63-65] and proteomic profiling (for identification of differentially expressed proteins and peptides).[66-69] Combinations of markers may improve sensitivity and specificity.[70] A pediatric sepsis biomarker risk model (PERSEVERE), using a combination of biomarkers, recently has been shown to identify children with septic shock at risk for death and more severe illness.[71-73]

Management

Antimicrobial Therapy

Empiric therapy for suspected sepsis should be targeted toward the likely causative pathogens (Table 11.3). Important considerations when selecting a regimen include the child's age, community versus hospital acquisition, host immune status, and penetration into tissues and compartments (such as central nervous system). Knowledge of bacteria susceptibility patterns in the community and institution is essential; in US cities, rates of community-acquired MRSA isolates can be as high as 76%.[74] Vancomycin should be included in the empiric regimen if the clinical syndrome is compatible with staphylococcal infection and MRSA is recovered more than sporadically in the geographic area. If *E. coli* or *Klebsiella* spp. (or other gram-negative bacilli in certain hospital settings) is isolated, the organism should be tested for ESBL production. Carbapenems are the treatment of choice for serious infections with ESBL-producing organisms.[75] Infections caused by carbapenem-resistant Enterobacteriaceae are increasing worldwide and have been reported in pediatric populations.[76,77] Continued local and regional surveillance for these multidrug-resistant pathogens is critical at the local, regional, and national level.

TABLE 11.3

Suggested Initial Antimicrobial Agents for Empiric Therapy in Infants and Children with Suspected Sepsis

Age or Clinical Situation	**Antimicrobial Agents**[a]
Neonate (community onset)	Ampicillin *plus* gentamicin
Neonate (hospital onset)	Vancomycin, *plus* gentamicin *or* cefotaxime
Neonatal HSV infection	Acyclovir
Child (community onset)	Cefotaxime *or* ceftriaxone, *plus* vancomycin
Child (hospital onset)	Vancomycin, *plus* antipseudomonal penicillin *or* ceftazidime *or* cefepime *or* carbapenem[b]
Coverage for intra-abdominal or genitourinary sources	Cefepime, ceftazidime, ciprofloxacin *or* levofloxacin, *plus* metronidazole *or* piperacillin-tazobactam *or* carbapenem
Skin or soft tissue involvement	Vancomycin *or* semisynthetic penicillin, *plus* clindamycin
Toxic shock syndrome	Vancomycin *or* semisynthetic penicillin, *plus* clindamycin
Immunosuppressed, cystic fibrosis	Vancomycin *plus* cefepime *or* ceftazidime, *plus* gentamicin *or* carbapenem (if ESBL-producing organism suspected)
Immunocompromised with persistent fever	*Add* liposomal amphotericin *or* echinocandin *or* voriconazole
Tick-borne diseases: Rocky Mountain spotted fever, ehrlichiosis	Doxycycline (for any age)

[a] Antimicrobial therapy should be modified as laboratory data are available and based on clinical course.

[b] Antimicrobial therapy should be based on patient-specific risk factors and local antimicrobial susceptibility therapy patterns (see text).

ESBL, extended spectrum β-lactamase; HSV, herpes simplex virus.

When the causative organism is isolated and antibiotic susceptibilities are available, antimicrobial therapy should be adjusted appropriately. When possible, broad-spectrum agents (such as vancomycin and carbapenems) should be discontinued to minimize the emergence of multidrug-resistant organisms.

Prompt initiation and appropriate choice of antibiotics are critical in the management of sepsis, and both concepts have been shown to improve outcomes in adults.[12,78-80] A recent pediatric study identified delayed antimicrobial therapy as an independent risk factor for mortality and prolonged duration of organ dysfunction. Weiss and associates determined that more than a 3-hour delay from sepsis recognition to initiation of therapy and first appropriate antimicrobial therapy was associated with higher mortality[81]; the odds ratio for pediatric intensive care unit mortality was 3.92 (95% confidence interval [CI], 1.27–12.06) and 3.59 (95% CI, 1.09–11.76), respectively.

Supportive Care

Effective treatment of sepsis and septic shock is dependent on prompt recognition and initiation of supportive as well as specific therapy. The basic principles of initial critical care include ensuring adequate airway patency, gas exchange (breathing), and circulation (the so-called ABCs). The interventions required to achieve these goals depend on the specific physiologic state of the patient at the time of presentation. Shock that occurs during sepsis results from decreased intravascular volume, maldistribution of intravascular volume, or impaired myocardial function, all of which can occur at different times during the course of septic shock.[82] Children with sepsis who receive early aggressive fluid resuscitation (>40 mL/kg in the first hour with isotonic intravenous fluids) demonstrate improved survival without increased risk for noncardiogenic pulmonary edema or ARDS.[83,84]

Determination of when, what type of, and how much pharmacologic support is needed in a patient with septic shock requires careful consideration of many factors. These factors include the patient's clinical state (e.g., capillary refill time, urine output, peripheral versus core temperature gradient), information obtained from monitoring devices (heart rate, blood pressure, central venous pressure, pulmonary artery pressure, cardiac output, stroke volume, and systemic vascular resistance), and knowledge of basic drug effects (including dopamine, norepinephrine, epinephrine, and phenylephrine) in the setting of septic shock.

Septic shock causes multisystem organ dysfunction, and it is important to evaluate and manage abnormalities in other organ systems, including the kidney and gastrointestinal tract. Patients with acute renal failure may require renal replacement therapy. The gastrointestinal tract is vulnerable to disturbances such as hemorrhage, ileus, brush border atrophy, and translocation of enteric organisms into the blood. Additionally, early institution of nutritional support, particularly enteral feeding, can ameliorate gastrointestinal atrophy and improve function of multiple organ systems.[85]

Maintaining tight control of blood glucose level has been shown to be beneficial in some studies in critically ill adult patients, but the current evidence does not adequately address this issue in the pediatric population.[86,87]

Intravenous Immunoglobulin Therapy

Immunoglobulin for intravenous use (IGIV) can be regarded as a treatment method that seeks to improve host defense. Although plasma immunoglobulin concentration can be reduced in patients with sepsis, the use of IGIV therapy is not supported by randomized clinical trials. A small nonblinded study of 21 patients with streptococcal toxic shock syndrome showed a reduced mortality (6% versus 34%, $P = 0.02$).[88] Results of the International Neonatal Immunotherapy Study, which enrolled 3493 infants, also demonstrated no effect on the outcomes of suspected or proven neonatal sepsis; these results are echoed in a *Cochrane Review*.[89-92] For patients with toxic shock syndrome, IGIV may have clinical utility.

Corticosteroids

Adrenal failure is common in critical illness and in particular in vasopressor-dependent septic shock. High baseline total serum cortisol, together with a low response to a corticotropin stimulation test, is correlated with a poor outcome in sepsis.[93] Several studies in children and adults with septic shock have demonstrated abnormalities of control of adrenal corticosteroid secretion over the course of illness.[94,95]

Various randomized controlled trials comparing administration of hydrocortisone to placebo have been performed in septic shock. There is general agreement that hydrocortisone supplementation improves the hemodynamic condition of vasopressor-dependent septic shock.[96] What remains more controversial is the definition of adrenal insufficiency, the optimal dose and timing of steroid supplementation, whether this should then be tapered slowly, and the effect of steroid supplementation on outcome.[97] Although evidence is lacking regarding how to measure adrenal insufficiency in children, it is advised to obtain a baseline serum cortisol or adrenocorticotropin hormone stimulation test before steroid administrations.[97] A multicenter, randomized, placebo-controlled trial of 499 patients with septic shock[98] found that hydrocortisone did not improve survival overall or in the subgroup of patients who did not have a response to corticotropin, although shock was reversed more quickly in the hydrocortisone-treated group than in the placebo group.

Future Considerations

The publication of the human genome will allow for rapid advances in genomics and proteomics. The possibilities for individualized drug treatment of patients with sepsis, related to their genotype, may become reality. New innovations, such as the pediatric sepsis biomarker risk model (PERSEVERE),[71,72] may allow for targeted therapy and improved early risk stratification of children with sepsis.

Current research focused on sepsis management includes anticytokine therapy such as anti–tumor necrosis factor-α,[99,100] anticoagulant therapies such as antithrombin,[101] and hemofiltration through continuous renal replacement therapy. The recently completed IVOIRE (hIgh VOlume in Intensive Care) hemofiltration study is a prospective randomized multicenter trial comparing two treatments in adults with septic shock complicated with acute renal failure.[102] One group will be treated by early high volume hemofiltration (70 mL/kg/h) and the second group by standard volume hemofiltration (35 mL/kg/h), with one-month mortality as the primary outcome measured. The results of this study may clarify the value of continuous renal replacement therapy in sepsis and acute kidney injury.

The development of an antiendotoxin vaccine targeted against core lipopolysaccharide structures of gram-negative bacteria has not led to protective efficacy for sepsis.[103,104] Because antibiotic resistance among gram-negative bacteria has reached critical levels (and development of novel therapeutics is lagging), antiendotoxin vaccines against sepsis should be readdressed.[105] Until then, sepsis management remains dependent on early administration of appropriate antimicrobial therapy, resuscitation by a practiced protocol, and “source control” when identified.[12]

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12

Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome

Hayley A. Gans, David B. Lewis

Hemophagocytic Lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) is a clinical syndrome characterized by the accumulation of activated T lymphocytes and well-differentiated macrophages (histiocytes) in the bone marrow, lymph nodes, liver, spleen, and, often, the central nervous system (CNS). HLH is typified by fever, hepatosplenomegaly, peripheral blood cytopenias, and, most characteristically, hemophagocytosis, that is, the presence of intact red blood cells, leukocytes, platelets, or their precursors within infiltrating macrophages of the liver, spleen, bone marrow, and the CNS.[1,2] Most cases of HLH appear to be due to lymphocyte hyperactivation, particularly $CD8^+$ T lymphocytes,[3] with cytokine hypersecretion resulting in systemic mononuclear phagocyte activation, inflammation, coagulopathy, and, potentially, multiorgan failure.

HLH is divided into primary and secondary forms.[4] In the primary form, HLH is the predominant presenting feature of a small group of genetic disorders, including familial hemophagocytic lymphohistiocytosis (FHL).[3] Systemic infections are a precipitant of the hemophagocytic syndrome in many primary cases.[1,5] Secondary HLH encompasses all other causes and also most often is triggered by systemic infections, especially in immunocompromised hosts,[6–8] or by untreated hematologic malignancies.[4] The macrophage activation syndrome (MAS), which occurs in rheumatologic autoinflammatory and autoimmune disorders, has some pathologic similarities to HLH[9] but is treated differently and is discussed at the end of this chapter.

Etiology and Incidence

Primary Hemophagocytic Lymphohistiocytosis

Classic FHL, which was first reported in 1952,[10] accounts for approximately 25% of all HLH cases worldwide. FHL is estimated to affect 1 in 50,000 live births in northern Europe[1] and likely occurs at a higher frequency in countries where consanguinity is common.[11] One study estimated the overall prevalence of HLH to be 1.07 per 100,000 persons younger than 18 years.[12] There are five types of FHL but only four genetically defined autosomal recessive (AR) causes of FHL[3,13] (accounting for 90% of FHL cases) due to mutations in the genes (indicated in italics) encoding perforin (*PRF1*; FHL2, 20% to 40% of FHL), Munc13-4 (*UNC13D*; FHL3, 20% to 25% of FHL), syntaxin 11 (*STX11*; FHL4, 14% to 21% of FHL), and syntaxin-binding protein 2 (*STXB2*; FHL5) (Table 12.1), all of which play critical roles in cell-mediated cytotoxicity.[14–20] The AR genetic defect for FHL1 is unknown.[13] In FHL, HLH typically is fulminant and develops in the first few months of life or even in utero.[21] HLH rarely can manifest first in adulthood, especially in cases in which hypomorphic FHL mutations preserve some protein function.[13] In addition to HLH, FHL5 can manifest with hypogammaglobulinemia, bleeding, or colitis.[22]

TABLE 12.1

Classification of Pediatric Hemophagocytic Lymphohistiocytosis

PRIMARY HLH		
Familial HLH	**Chromosome**	**Protein/Gene**
FHL1	9q21.3-22	Unknown
FHL2	10q22	Perforin IPRF1
FHL3	17q25.1	MUNC13-4/*UNC13D*
FHL4	6q24	Syntaxin-11/*STX11*
FHL5	19p13.3-p13.2	MUNC18-2/*STXBP2*
Immunodeficiency Disease		
CHS-1	1q42.1-q42.2	*LYST*
XLP disease		
(XLP1)	Xq25	SAP/*SH2D1A*
(XLP2)	Xq25	XIAP/*BIRC4*
HPS	5q14.1	*AP3B1*
GS type 2	15q21	*RAB27A*
ITK	5q31-q32	*ITK*/ITK
CD27 deficiency	12p13	*CD27*/CD27
SECONDARY HLH		
Infections	**Frequent Inciting Agents**	
Viral	Adenovirus, enteroviruses, herpesviruses (EBV, CMV, HSV, HHV-6, HHV-8, VZV), HIV (including acute infection), influenza (including H5N1), measles, parvovirus B19	
Bacterial	*Mycobacterium tuberculosis*, *Brucella*, *Coxiella*, rickettsioses, gram-negative or gram-positive bacteremia	
Parasitic	*Plasmodium* spp., *Leishmania* spp.	
Fungal	*Histoplasma capsulatum*, *Penicillium* sp., *Fusarium* sp.	
Noninfectious Categories		
Therapy	ART, phenytoin, other anticonvulsants, BMT, solid organ transplant, chemotherapy	
Oncologic (as presenting feature)	Lymphomas, pre–B-cell ALL	
Rheumatologic	JIA, SLE, Kawasaki disease	

ALL, acute lymphoblastic leukemia; BMT, bone marrow transplantation; CHS, Chédiak-Higashi syndrome; CMV, cytomegalovirus; EBV, Epstein-Barr virus; FHL, familial hemophagocytic lymphohistiocytosis; GS, Griscelli syndrome; ART, antiretroviral therapy; HIV, human immunodeficiency virus; HHV-6, human herpesvirus 6; HHV-8, human herpesvirus 8; HLH, hemophagocytic lymphohistiocytosis; HPS, Hermansky-Pudlak syndrome; HSV, herpes simplex virus; JIA, juvenile idiopathic arthritis; SLE, systemic lupus erythematosus; XLP, X-linked lymphoproliferative syndrome; VZV, varicella-zoster virus.

Adapted from Janka G, Zur Stadt U. Familial and acquired hemophagocytic lymphohistiocytosis. Hematol (Am Soc Hematol Educ Program) 2005;82–88; Janka G, Imashuku S, Elinder G, et al. Infection- and malignancy-associated hemophagocytic syndromes. Secondary hemophagocytic lymphohistiocytosis. Hematol Oncol Clin North Am 1998;12:435–444; and Janka G, Lehmberg K. Hemophagocytic syndromes: an update. Blood Rev 2014;28:135-42.

Several primary immunodeficiency disorders are associated with high rates of HLH, which all have in common defects in genes encoding proteins involved with cytotoxicity (see Table 12.1). In addition, a susceptibility to Epstein-Barr virus (EBV) disease and HLH is seen specifically with four mutations. First is X-linked lymphoproliferative (XLP) disease, which has two subsets.[23] XLP1 disease (SAP/*SH2D1A* deficiency) only affects males and usually presents in association with primary EBV infection, with about 60% of cases developing fulminant HLH.[24] In contrast to FHL, hypogammaglobulinemia, often present before EBV infection,[24] is frequent, as is the rapid development of EBV-related lymphoproliferative disease or lymphomas. XLP2 disease (XIAP/*BIRC4* deficiency)[25,26] only affects males and can manifest similarly to FHL. XLP2 also can have a more delayed, mild, or recurrent course, with recovery without cytotoxic chemotherapy.[26] In contrast to XLP1 disease, EBV-related lymphoproliferative disease or lymphoma is infrequent, and it is not clear whether hypogammaglobulinemia frequently occurs before the onset of HLH.[25,26]

Analysis of a cluster of EBV-driven HLH cases lead to the discovery of interleukin-2–inducible T-cell kinase *(ITK)* gene mutations in several individuals, which was associated with a poorer survival despite therapy.[27] In addition, defects in CD27, a member of the tumor necrosis factor receptor family, have also been reported in several patients with EBV-associated HLH.[28]

Unrelated to EBV susceptibility are a group of primary immunodeficiencies that have defects that predispose to HLH. These include Griscelli syndrome type 2 (AR *RAB27A* gene deficiency), which typically manifests as early-onset HLH in manner indistinguishable from FHL.[29] Melanosome transport also is defective, resulting in partial albinism and the hair having a characteristic silvery sheen.[3] In addition, in Chédiak-Higashi syndrome (AR *LYST* gene deficiency), HLH frequently develops during infancy or childhood.[30] Chédiak-Higashi syndrome readily is distinguished from other forms of primary HLH by oculocutaneous albinism, dysfunctional neutrophils with giant inclusions, and platelet dysfunction.[31]

Among the same family as Griscelli and Chédiak-Higashi syndromes is Hermansky-Pudlak syndrome type 2 (*AP3B1* gene deficiency), which has been described in 3 patients and includes oculocutaneous albinism, bleeding, recurrent infection, and neutropenia, and was accompanied by lethal HLH in 1 patient.[32]

Secondary Hemophagocytic Lymphohistiocytosis

The incidence of secondary HLH has not been defined but is likely underreported. Secondary HLH most often is triggered by severe or prolonged infections in immunocompromised patients (see Table 12.1), particularly those with severe acquired immunodeficiency,[33] such as that due to HIV/AIDS,[34] cancer chemotherapy,[35] or potent immunosuppression. However, secondary HLH is reported in immunocompetent hosts and also can be a complication of severe infection in patients with primary immunodeficiencies other than those that are causes of primary HLH, including chronic granulomatous disease,[36,37] severe combined immunodeficiency,[38,39] DiGeorge syndrome (22q11.2 deletion),[40] Wiskott-Aldrich syndrome,[41] and X-linked agammaglobulinemia.[42] In the immunocompetent host, secondary HLH originally was considered to be mainly a complication of primary EBV infection in previously healthy older children; however, it is now appreciated that HLH can occur in all ages in association with severe infections with a wide variety of pathogens (see Table 12.1).[7,8,43] Common non-EBV viral triggers include infections with other herpesviruses (e.g., cytomegalovirus, human herpesvirus type 6 [HHV-6], HHV-8), adenovirus, dengue, enterovirus, influenza A,[44] and parvovirus B19. There are case reports of many other types of viral infection that also have been associated with HLH, suggesting that HLH potentially can complicate any severe systemic viral infection. Severe bacterial infections, particularly those involving the reticuloendothelial system (e.g., typhoid fever, rickettsial diseases, brucellosis, and disseminated *Mycobacterium tuberculosis*)[8] are frequent precipitants of HLH, and systemic fungal infections (e.g., *Histoplasma* and *Penicillium* spp. infection) are recognized causes. Visceral leishmaniasis, which has been misdiagnosed as FHL,[45] and malaria are frequent protozoal triggers.[8] As the recognition of HLH increases, so do the reports of infectious associations. This indicates that the disorder can be the end result of marked immune activation from any inciting event.

Rarer noninfectious conditions associated with secondary HLH in children (see Table 12.1) include lymphoid malignancies,[46,47] antiretroviral therapy for HIV, antiepileptic drug therapy, acute allograft rejection, graft-versus-host disease (GvHD; including by maternal T-lymphocyte engraftment in infants with severe combined immunodeficiency),[39] hemolytic anemia, and certain inherited metabolic disorders (e.g., lysinuric protein intolerance).

Pathogenesis

In primary HLH, most of the identified genetic defects compromise the ability of T lymphocytes and natural killer (NK) cells to kill target cells through the usual pathway of the secretion of perforin and granzymes from intracellular cytotoxic granules (Fig. 12.1). Under normal conditions, antigenically naïve $CD8^+$ T lymphocytes acquire their cytotoxic granules after activation and differentiation into effector cells, whereas newly produced NK cells emerge from the bone marrow containing these granules. Cytotoxic granules are released by $CD8^+$ T lymphocytes after their surface αβ T-cell receptors (TCRs) are engaged by antigenic peptide–major histocompatibility (MHC) complexes on the infected target cell, whereas NK-cell granule release occurs when the NK cells encounter infected target cells that lack MHC class I expression. Cell-mediated cytotoxicity requires the concerted activity of the LYST, Rab27a, MUNC13-4, syntaxin 11, and MUNC18-2 proteins for the intracellular maturation, trafficking, prerelease priming, and exocytosis of cytotoxic granules. The end result is apoptosis and clearance of the infected cell and microbe-derived antigen and termination of the immune response; genetic mutations encoding these proteins result in ineffective cell clearance and persistent immune activation in Chédiak-Higashi syndrome, Griscelli syndrome type 2, FHL3, FHL4, and FHL5, respectively.[3] The release of perforin, which is defective in FHL2, perforates the target cell membrane, allowing the cytoplasmic entry of granzymes that trigger target cell apoptosis (see Fig. 12.1).[48,49] It is not yet known how XIAP deficiency promotes HLH.

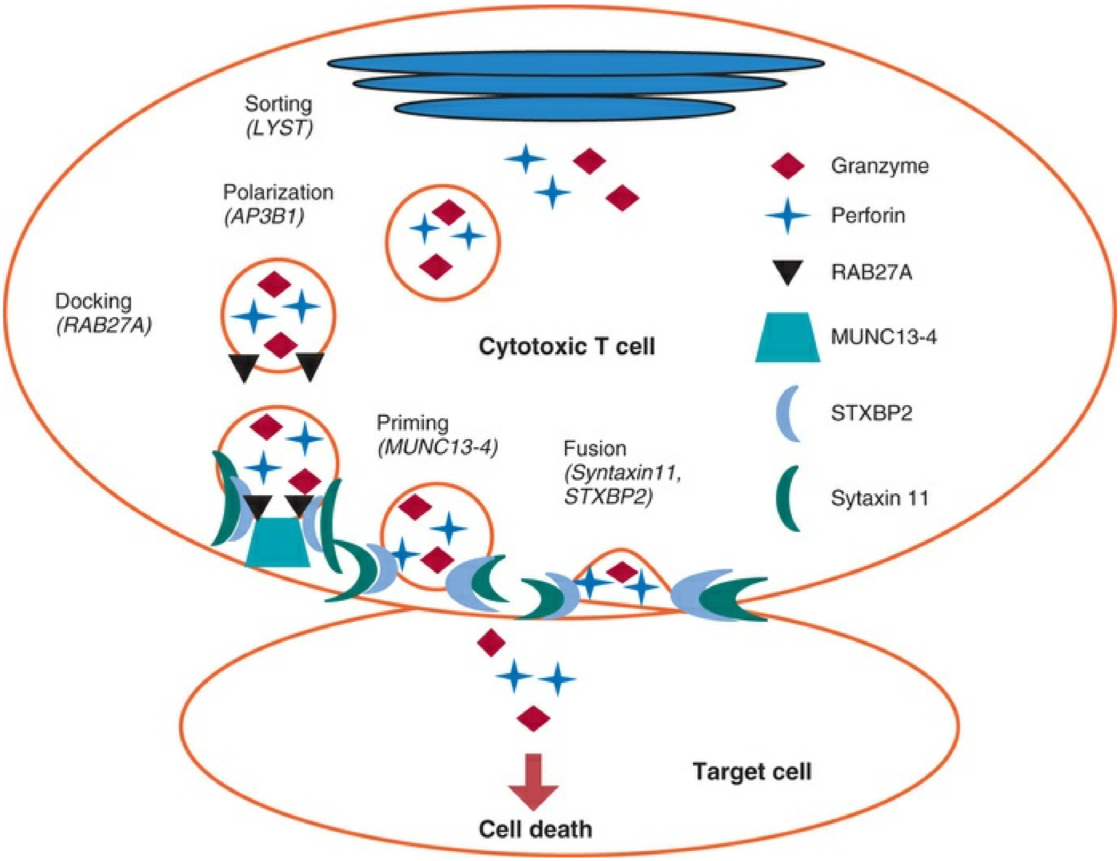

FIGURE 12.1 Steps in cytotoxic T-lymphocyte function leading to target cell death. Proteins involved with loading, moving, priming, and docking of the cytotoxic granules are shown in parenthesis, defects in the genes encoding these proteins leads to hemophagocytic lymphohistiocytosis (HLH). (Adapted from Filipovich AH, Chandrakasan S. Pathogenesis of hemophagocytic lymphohistiocytosis. Hematol Oncol Clin North Am 2015;29:895−902; and Madkaikar M, Shabrish S, Desai M, et al. Hemophagocytic lymphohistiocytosis: advances in pathophysiology, diagnosis, and treatment. J Pediatr 2013;163:1253−1259.)

Activated CD8$^+$ T lymphocytes and NK cells also release large amounts of interferon γ (IFNγ) and tumor necrosis factor-α, which potently activate macrophages and dendritic cells. A plausible scenario for primary HLH occurring in association with viral infection is that T lymphocytes and NK cells are activated by severe infection to secrete cytotoxins and cytokines, but cytotoxicity is ineffective in killing and eliminating the viral antigenic stimulus. This results in prolonged and persistent lymphocyte activation and cytokine secretion that, in turn, persistently activates macrophages and dendritic cells, leading them to become hemophagocytic[4,33,50] and to secrete additional proinflammatory cytokines. This combined lymphocyte and mononuclear phagocyte “cytokine storm” appears to be a common final pathway for HLH pathogenesis,[4,51] accounting for fever, hyperlipidemia, endothelial activation, coagulopathy, tissue infiltration of T lymphocytes and macrophages, CNS vasculitis and demyelination, marrow hyperplasia or aplasia, and multiorgan dysfunction and failure. In XLP1 disease, SAP deficiency selectively impairs recognition and killing of EBV-infected B lymphocytes by CD8$^+$ T lymphocytes and NK cells,[52,53] resulting in a high EBV viral load; other forms of activation and cytokine secretion by CD8+ T lymphocytes and NK cells are intact and driven by the persistent viral load. However, cases of HLH can occur in FHL without apparent associated infections, and these observations, along with studies in animals, suggest that perforin-dependent cell-mediated cytotoxicity, in addition to its antimicrobial role, also directly regulates lymphocyte activation and homeostasis.[3]

Secondary HLH most commonly occurs when overwhelming infection in an immunocompromised host triggers marked or prolonged T-lymphocyte and NK-cell activation and hypercytokinemia. Lymphocyte and mononuclear phagocyte-derived hypercytokinemia also is likely the cause of HLH in untreated leukemia and lymphoma, GvHD, or HLH after chemotherapy.

More enigmatic is the basis for HLH and hypercytokinemia after primary EBV infection in previously healthy children because only a minority of cases are accounted for by primary HLH genetic disorders.[54] In EBV-associated HLH and in EBV infection complicating primary HLH, there often are high levels of EBV genomes in circulating T lymphocytes,[55,56] but the importance of this T-lymphocyte tropism of EBV in HLH pathogenesis remains unclear.

Clinical and Radiologic Features

Primary and secondary HLH cannot be distinguished reliably on the basis of clinical, laboratory, or histopathologic features. Prolonged high fever, hepatosplenomegaly, and cytopenias generally are hallmarks of HLH. Rash, lymphadenopathy, respiratory tract and gastrointestinal symptoms, failure to thrive, and irritability are frequent (Table 12.2).[57–61] Clinical and laboratory abnormalities often peak at days 6 to 10 of illness, although there is substantial variability.[57]

TABLE 12.2

Clinical Manifestations of Hemophagocytic Lymphohistiocytosis

Symptoms	Present at Time of Diagnosis (%)
Fever	91–100
Hepatomegaly	89–97
Splenomegaly	61–98
Lymphadenopathy	17–52
Skin rash	6–65
Respiratory distress	33–88
Hypotension	85
Jaundice	72
Gastrointestinal	44
Neurologic	20–47

Adapted from references 57 to 61.

Systemic Manifestations

Fever, often prolonged, is present in all patients. HLH is an important diagnostic consideration in fever of unknown origin.[57] Organomegaly, often pronounced and progressive, is found in more than 90% of cases. A diffuse erythematous maculopapular or petechial rash may transiently appear with high fevers.[57] Respiratory tract symptoms are frequent and can vary from mild cough to acute respiratory distress syndrome requiring ventilatory support.[57] Cardiovascular collapse and renal failure can occur.[57] Lymphadenopathy, often prominent, is frequent (50% to 70% of patients).[57] Gastrointestinal symptoms, including vomiting, diarrhea, and abdominal pain, occur in about 40% of patients.

Central Nervous System Manifestations

Most HLH patients have neurologic symptoms or cerebrospinal fluid (CSF) abnormalities (mononuclear pleocytosis or elevated protein) at the time of diagnosis.[62] Rarely, hemophagocytosis of white blood cells of the CSF can be observed,[2] a finding that is specific for HLH. Neurologic symptoms can be the presenting feature, preceding clinical HLH by 2 or more years,[63] or can develop only later in the course.[2] Seizures, meningismus, and irritability are present commonly.[64] Cranial nerve palsies, ataxia, nystagmus, disturbances of gait and vision, hemiplegia or tetraplegia, delayed psychomotor development, and increased intracranial pressure have been reported. Frequent findings on magnetic resonance imaging or computed tomography include multiple nodular or ring-enhancing parenchymal lesions in the cerebrum and cerebellum, leptomeningeal enhancement, confluent parenchymal lesions with or without hemorrhage, and ventriculomegaly, which can be due to cerebral atrophy or hydrocephalus.[62,65] Demyelination can occur and mimic acute disseminated encephaloymyelitis.[66] Definitive diagnosis of CNS disease may require biopsy of the meninges and white matter.[67]

Hemophagocytic Lymphohistiocytosis in the Fetus and Neonate

HLH manifesting with liver failure[68,69] is more common in the fetus and neonate than in older children. Nonimmune hydrops fetalis[68,70] can be a presentation of HLH due to either FLH[21] or congenital infections, such as syphilis or rubella. Neonates and young infants with severe herpesvirus (herpes simplex virus, cytomegalovirus, or HHV-8) or enteroviral infections,[71] or bacterial or fungal sepsis[72] can develop secondary to HLH. This may be a more common complication of severe infection than in older, immunocompetent children, most likely because of developmental limitations in fetal and neonatal host defense mechanisms.[73]

Laboratory and Pathologic Findings

General

Characteristic laboratory abnormalities include pancytopenias, hypertriglyceridemia, hyperferritinemia, hyperbilirubinemia, transaminemia, and hypofibrinogenemia, but none is specific for HLH (Table 12.3).[1,57] Platelets are the most consistently depressed blood lineage, and thrombocytopenia may be a useful indicator of disease activity.[74] Approximately 80% to 90% of patients have two depressed blood cell lineages at presentation.[57] Neutrophils often are the last line to become depressed. Hypofibrinogenemia occurs in most patients and can occur in the absence of disseminated intravascular coagulation. Serum ferritin level is consistently elevated, and in approximately 90% of cases, this concentration exceeds 4000 μg/L. A ferritin level higher than 10,000 μg/L is 90% sensitive and 96% specific for HLH.[75] Hyponatremia and low serum protein and albumin concentrations are common.[57]

TABLE 12.3

Laboratory Findings in Hemophagocytic Lymphohistiocytosis

Laboratory Finding	Present at Time of Diagnosis (%)
Anemia	89–94
Thrombocytopenia (<100,000 platelets/mm^3)	82–100
Neutropenia (<1000 cells/mm^3)	58–100
Leukopenia	39–87
Hypertriglyceridemia	80–100
Hypofibrinogenemia	65–85
Elevated serum alanine aminotransferase level	33–92
Hyperbilirubinemia	33–74
Hyponatremia	79
Cerebrospinal fluid pleocytosis	52–91

Adapted from Aricò M, Janka G, Fischer A, et al. Hemophagocytic lymphohistiocytosis. Report of 122 children from the International Registry. FHL Study Group of the Histiocyte Society. Leukemia 1996;10:197–203; Henter JI, Elinder G, Soder O, et al. Incidence in Sweden and clinical features of familial hemophagocytic lymphohistiocytosis. Acta Paediatr Scand 1991;80:428–435; and Janka GE. Familial hemophagocytic lymphohistiocytosis. Eur J Pediatr 1983;140:221–230.

Clinical Immunology

In primary HLH due to FHL, Griscelli syndrome type 2, and Chédiak-Higashi syndrome, a functional defect in killing by CD8$^+$ T lymphocytes and NK cells occurs, and the circulating levels of CD4$^+$ and CD8$^+$ T lymphocytes and NK cells usually are normal or elevated.[33,76] NK-cell–mediated cytotoxicity is decreased only moderately or even is normal in some cases of primary HLH, including FHL,[77] whereas CD8$^+$ T-lymphocyte–mediated cytotoxicity is more uniformly impaired. In cases of secondary HLH, such as from severe EBV infection, the circulating number of NK cells often is reduced; most patients have transiently reduced NK-cell activity if blood is used as a source of NK cells for the assay.[9] The reason for this depression of circulating NK-cell numbers is unclear but may reflect NK-cell sequestration in the tissues away from the circulation. Circulating invariant NK T lymphocytes, which have features of NK cells and T lymphocytes, are absent in XLP1 disease[78] but are present in normal numbers in patients with XLP2 disease.[79] A decreased number of B lymphocytes is common in HLH, including from secondary causes,[80] which can pose challenges in diagnosing certain primary immunodeficiency disorders.[39] There are no consistent abnormalities of quantitative immunoglobulin levels.

Although cytokine assays are not routinely used diagnostically, HLH patients tend to have marked elevations of IFNγ, interleukin-10 (IL-10), and IL-18, and only moderately increased IL-6, whereas patients with bacterial septicemia often have markedly elevated levels of IL-6 and only moderate elevations of IL-10, IL-18, and IFNγ.[81]

Pathology

The classical histopathology is diffuse infiltration of the bone marrow, liver, spleen, lymph nodes, lungs, and brain with $CD8^+$ T lymphocytes and activated non-Langerhans (lacking expression of CD1a) histiocytes that are actively phagocytosing blood cells. Hepatic portal and sinusoidal infiltration with $CD8^+$ T lymphocytes expressing granzyme B, and with $CD68^+$ $CD1a^+$ histiocytes, is found characteristically in children with primary HLH. The degree of infiltration correlates with clinical disease severity.[82] Bile duct damage and endothelialitis with preservation of the hepatic parenchyma are frequent.[82] CNS tissue typically shows lymphohistiocytic infiltration of the parenchyma and perivascular space and hemophagocytosis in the leptomeninges, choroid plexus, or perivascular areas.[1] Importantly, the characteristic pathologic findings may not be present on an initial biopsy, and the demonstration of hemophagocytosis is not required to make the diagnosis (see later section, “Diagnosis”).

Evaluation for Infectious Diseases

Initial evaluations should include bacterial and fungal cultures of blood, urine, and in most cases, CSF; throat and rectal swabs for viral culture; and a chest radiograph. Serologic evaluation for viruses and fungi should be pursued, although these may not be sensitive in immunocompromised hosts. Polymerase chain reaction −based nucleic acid tests for EBV, CMV, parvovirus B19, HHV-6, and HIV infection should be performed; an elevated viral load supports the diagnosis of a poorly controlled viral infection. Specific epidemiologic factors, such as exposure to tuberculosis, travel, and animals, should guide further testing given the broad range of pathogens associated with HLH.

Diagnosis and Differential Diagnosis

The diagnosis requires either confirmation of primary HLH (e.g., by genomic DNA sequencing or flow cytometry) *or* presence of more than 5 of the 8 clinical criteria presented in Box 12.1. Hemophagocytosis may not be evident in bone marrow biopsies obtained early in the disease, and repeat bone marrow aspirates or analysis of other tissues may be required.[1,33] The diagnosis is supported by CSF mononuclear cell pleocytosis and elevated protein or a liver biopsy showing chronic persistent hepatitis. Other findings that are suggestive include meningitis or cerebritis, lymphadenopathy, elevation of serum hepatic enzymes, jaundice, edema, hypoproteinemia, hyponatremia, increased serum level of very low density lipoproteins, and decreased level of high-density lipoproteins.[1]

Box 12.1

Diagnostic Criteria for Hemophagocytic Lymphohistiocytosis (HLH)

The diagnosis of HLH can be established by either a molecular diagnosis consistent with HLH *or* fulfillment of ≥5 of 8 diagnostic criteria:

Original Diagnostic Criteria

Clinical

1. Fever

2. Splenomegaly

Laboratory

3. Cytopenia (≥2 cell lineages in the peripheral blood)

- Hemoglobin <9 g/dL (<10 g/dL if <4 weeks of onset)
- Platelets <100,000/mm^3
- Neutrophils <1000/mm^3

4. Hypertriglyceridemia and/or hypofibrinogenemia

- Fasting triglycerides ≥265 mg/dL
- Fibrinogen ≤150 mg/dL

Histopathologic

5. Hemophagocytosis in bone marrow, spleen, or lymph nodes without evidence of malignancy

New Diagnostic Criteria

Laboratory

6. Low or absent natural killer cell activity

7. Ferritin >500 μg/L

8. Soluble interleukin-2 receptor α chain (CD25) ≥2400 U/mL

Adapted from Henter JI, Samuelsson-Horne A, Aricò M, et al. Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. Blood 2002;100:2367–2373 and HLH-2004 protocol: www.histio.org/society/protocols/trails-protocols.html.

NK-cell cytotoxicity, in which peripheral blood mononuclear cells containing NK cells are incubated with chromium-labeled K562 erytholeukemia target cells, should be evaluated in inflammatory conditions. NK-cell cytotoxicity is markedly decreased or undetectable in most cases of primary or secondary HLH.[9,76,80] Circulating NK cells ($CD56^+/CD16^+/CD3^-$ lymphocytes) usually are present in normal or elevated numbers but functionally are defective in patients with primary HLH.[83] In secondary HLH, particularly in association with EBV infection, the numbers of NK cells often are depressed markedly, accounting for impaired cytotoxicity[9]; activity may return to normal with the recovery of NK-cell numbers. Normal or borderline low NK-cell activity can occur in certain forms of FHL and some cases of XLP disease. Flow cytometric evaluation for cytotoxic granule release based on surface staining of lymphocytes for the CD107a/b proteins[13] may be particularly useful in classifying FHL cases.[3,13]

Clinical flow cytometry assays are available for the determination of T-lymphocyte and NK-cell intracellular perforin, SAP, and XIAP, which are encoded by genes that are mutated in FHL2, XLP1 disease, and XLP2 disease, respectively.[13,84] Genomic DNA sequencing is important in the initial evaluation for primary HLH because normal flow cytometric protein assays do not exclude the diagnosis (see http://www.ncbi.nlm.nih.gov/sites/GeneTests; Fig. 12.2).[49,85] Clinical FHL can occur in the absence of any of the known genetic causes of primary HLH, suggesting that other genetic etiologies remain to be defined. Thus, without a previous family history or genetic confirmation, the diagnosis of primary HLH is provisional, and it is essential to exclude malignancy and autoimmune disease as precipitants.

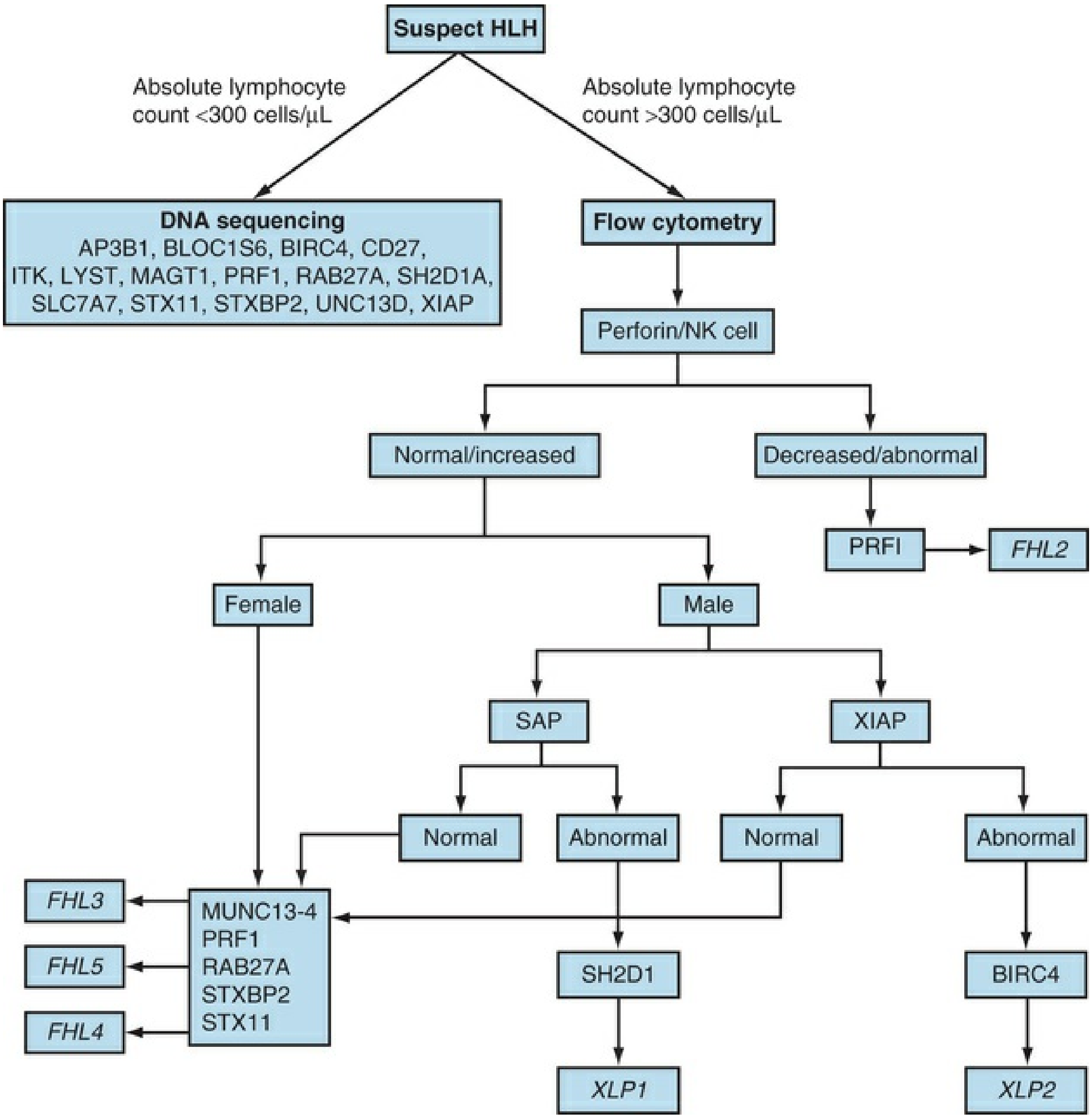

FIGURE 12.2 Diagnostic evaluation for suspected hemophagocytic lymphohistiocytosis (HLH) including genetic and immune testing. (Adapted from Filipovich AH, Chandrakasan S. Pathogenesis of hemophagocytic lymphohistiocytosis. Hematol Oncol Clin North Am 2015;29:895−902; and Madkaikar M, Shabrish S, Desai M. Current updates on classification, diagnosis and treatment of hemophagocytic lymphohistiocytosis [HLH]. Indian J Pediatr 2016;83:434−443.)

The nonspecific nature of the most prominent features of HLH (i.e., fever, hepatosplenomegaly, and cytopenias) leads to a broad differential diagnosis, which includes leukemia, lymphoma, aplastic anemia, myelodysplasia, and Langerhans cell histiocytosis. In the fetus and neonate, other etiologies of liver failure, hepatitis, and hydrops fetalis should be considered. Differential diagnosis of neurologic disease includes autoimmune and acute disseminated encephalomyelitis, other CNS demyelinating disease,[66] and vasculitis.

Treatment

Advances have been made in the treatment of HLH over the past two decades due in large part to the guidelines put forth by the Histiocyte Society in 1994 and 2004.[1,74] HLH previously was a fatal disease, but the survival of HLH patients has improved to more than 60% with the use of chemoimmunotherapy combined with hematopoietic stem cell transplantation (HSCT). Aggressive supportive care with transfusions, antibiotics, and nutrition typically is indicated. An integrated team approach of experts in hematology-oncology, immunology, infectious diseases,[57] critical care, neurology, and nephrology is ideal. Close monitoring for secondary bacterial and fungal infections and for adequate hemostasis is important because infections and bleeding are important causes of HLH mortality.[86]

Immunosuppression and Chemotherapy

First-line treatment is focused on suppressing the hyperimmune state. Aggressive immunotherapy of primary HLH, before definitive genetic diagnosis, which may take months, may be necessary because a delay can have adverse consequences.[5] The natural course of untreated primary HLH is progressive multiorgan failure and CNS disease, with a mean survival of only 2 months.[74] Secondary HLH also can have a high mortality, especially if EBV induced,[33] although some cases can resolve spontaneously without therapy.[87] The type of treatment for children with HLH is determined by disease severity, age at onset, and history of familial disease.[1,88] The updated 2004 HLH protocol serves as a treatment guide for cases of primary HLH and severe, persistent, or recurrent secondary HLH, particularly EBV-associated HLH.[1,5,89] The therapeutic goals are to induce remission and to bridge to HSCT when indicated. For patients with primary HLH or severe secondary disease, especially EBV-associated HLH, treatment includes etoposide, corticosteroids, and cyclosporine for 8 weeks. For all cases of primary HLH and for secondary HLH that does not respond to initial therapy, intrathecal methotrexate may be used. If neurologic symptoms persist, recur, or progress, intrathecal glucocorticoid therapy may be useful. These agents help control HLH by inducing apoptosis of lymphocytes and histiocytes (mainly an effect of etoposide) and by inhibiting cytokine and chemokine production (mainly an effect of glucocorticoids and cyclosporine). Relapses are common as treatment is reduced, especially in FHL, and may require reescalation of therapy.[1] Etoposide usually is not used in cases of secondary HLH complicating HIV infection or iatrogenic immunosuppression. Etoposide therapy often results in prolonged neutropenia and is associated with a later risk for acute myeloid leukemia. FHL has been treated with etoposide-free regimens, such as the combination of antithymocyte globulin, glucocorticoids, cyclosporine, and intrathecal methotrexate.[90] Severity of HLH may dictate individualized treatment protocols, and for some less severe cases, corticosteroids may be sufficient, but disease progression and relapse must be monitored very carefully.

For EBV-associated HLH, which can have a highly variable course,[87] relatively conservative therapies, such as glucocorticoids and cyclosporine, with or without immune globulin intravenous, can be considered, reserving etoposide for nonresponsive cases.[91] In EBV-associated HLH and primary HLH in XLP disease, rituximab (CD20 monoclonal antibody) has been used.[92,93]

Overall, complete response to initial HLH treatment is only seen in 50% to 75% of individuals, with inactive disease at 8 weeks correlating with survival.[94]

Hematopoietic Stem Cell Transplantation

Patients with primary HLH ultimately require allogeneic HSCT for cure.[1] Reduced intensity nonmyeloablative conditioning regimens have had particularly favorable results.[95] Patients with primary HLH who have early relapse of HLH or persistent CNS involvement may benefit from early HSCT.[96] HSCT also has been used for EBV-associated HLH, particularly for those with recurrent disease.[97] The timing of the transplantation is important; patients with active HLH at transplantation tend to have worse outcomes compared with patients with inactive disease because active disease increases graft failure.[94]

Prognosis

If untreated, primary HLH, particularly FHL, is almost uniformly fatal.[1] Increased survival is associated with prompt response to initial therapy and with older age at presentation.[98] Secondary HLH can be a self-limited process, with recovery after only supportive measures. Longterm remission is uncommon in patients with CNS disease and in those older than 30 years[99]; early aggressive therapy for severe or recurrent cases appears to be beneficial.[100] A soluble CD25 serum level of 10,000 U/mL[101] or greater also has been associated with mortality.[51] HLH patients who have a 96% or more drop in serum ferritin with therapy have a reduced risk for mortality.[102]

Macrophage Activation Syndrome

Systemic-onset juvenile idiopathic arthritis (sJIA) is a frequent cause of MAS in childhood,[103] and the presence of defective NK-cell function due to NK-cell lymphopenia is similar to that associated with other causes of secondary HLH.[103,104] Clinical and laboratory findings of MAS include persistent fever, hepatosplenomegaly, neurologic abnormalities, marked cytopenias, and coagulopathy.[9] Because some diagnostic criteria for HLH also can occur with exacerbations of sJIA (lymphadenopathy, splenomegaly, and hyperferritinemia), a marked elevation of serum CD25 and CD163 levels[105] can help make the diagnosis of MAS in this context. In an attempt to increase the specificity and sensitivity of diagnostic criteria, a new set of clinical and laboratory criteria have been put forth that improve on the HLH-2004 protocol in diagnosing MAS.[106] This study showed low sensitivity and specificity of clinical criteria but strong predictions for the presence of three or more laboratory studies including, among others, platelets count ($\leq$211,000/mm^3), lactate dehydrogenase level (>882 U/L), total protein ($\leq$6.3 g/dL), albumin ($\leq$2.9 g/dL), aspartate transaminase (>59.7 U/L), fibrinogen ($\leq$180 mg/dL), and ferritin (>400 μg/L).[106] MAS can be managed in most cases using immunosuppression without chemotherapy. The optimal regimen remains controversial and may depend on the underlying disorder; for example, IL-1 and IL-6 appear to play a central role in sJIA inflammation and MAS,[107] which may account for some patients responding to inhibitors of IL-1 (e.g., anakinra) or IL-6.[107]

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B

Cardinal Symptom Complexes

OUTLINE

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13

Mucocutaneous Symptom Complexes

Sarah S. Long, Ishminder Kaur

Generally, in differentiating between bacterial and viral causes of febrile illnesses in children, the more mucous membranes involved in the patient's illness (e.g., conjunctiva, throat, respiratory, gastrointestinal tract), the more likely the cause is viral. When multiple mucous membranes are involved and an exanthem (i.e., mucocutaneous complex) is present, a self-limited viral cause is likely, but other important diagnoses must be considered. These commonly include inflammatory or immunologically mediated conditions, such as Kawasaki disease (KD), Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN), drug hypersensitivity, and bacterial toxin-mediated diseases, including staphylococcal and streptococcal toxic shock, streptococcal scarlatiniform disorders, and staphylococcal exfoliative toxin syndromes or staphylococcal scalded-skin syndrome. A best, if not the definitive, diagnosis can be deduced through careful assessment of (1) the dominant features of the illness; (2) prodromal events and exposures; (3) specific characteristics of the exanthem and abnormality at each affected mucous membrane; and (4) the cadence of the developing constellation. Laboratory features are of secondary importance, heightening or diminishing the fitness of the clinical assessment.

Table 13.1 shows useful differentiating features of commonly considered causes of mucocutaneous symptom complexes. Features distinguishing streptococcal toxic shock due to streptococcal pyrogenic exotoxin (SPE) A or B from staphylococcal toxic shock associated with toxic shock syndrome toxin-1 (TSST-1) are shown in Table 13.2 and are described in the discussion where pertinent. SJS and TEN are considered ends of the same disease spectrum, whereas erythema multiforme (EM) is a separate entity distinct from SJS and TEN. EM is characterized by target lesions, whereas the skin lesions of SJS and TEN are widespread and consist of blistering on erythematous or purpuric macules. Table 13.3 shows differentiating features of EM, SJS, and TEN.[1,2]

TABLE 13.1

Differentiating Among Causes of Mucocutaneous Symptom Complexes

	Kawasaki Disease	Toxic Shock[a]	Staphylococcal Exfoliative Toxin Syndromes	Streptococcal Scarlatina	Steve Synd
CLINICAL FEATURES					
Fever	+++	+++	+	+	++
	≥5 days	<2 days	2–3 days	2–3 days	5 day
Conjunctiva	+++	+++	++	−	++
	Bilateral hyperemia (bulbar > palpebral); anterior uveitis	Bilateral hyperemia (bulbar > palpebral)	Unilateral or bilateral purulent conjunctivitis (palpebral > bulbar); or normal	Normal	Bilate conju chem kerat pano
Lips	+++	++	−	−	+++
	Erythema, fissures	Erythema	Normal or desquamation	Normal, with circumoral pallor	Eryth edem denu bleed escha
Oropharynx	+++	++	−	++	++
	Mucosal erythema; strawberry tongue	Mucosal erythema; strawberry tongue	Normal, or mucosal erythema	Tonsillar erythema, exudate; palatal petechiae; strawberry tongue	Pann eryth confl ulcer denu pseu
Exanthem	+++	++	+++	+++	+++
	Polymorphous, nonvesicular,	Erythroderma	Indurative or papular	Papular erythroderma	Eryth multi

	vasoactive and changing; morbilliform, symmetric; exaggerated or solely in groin		erythroderma; tender; Nikolsky sign and desquamation during acute phase	(sandpaper); Pastia sign	polyr fixed,
Extremities	++	++	–	–	–
	Symmetric, indurative edema distally; painful erythema, palms and soles; stocking-glove distribution; occasional digital cyanosis	Symmetric distally; erythema on palms and soles	Normal, or edema contiguous with exanthem	Normal	Norm edem conti exant
Other	+++	+++	+	+	++
	Unremitting crankiness; cervical lymphadenopathy; arthralgia, arthritis; meningismus, cranial nerve palsy; abdominal pain, distention, tenderness; hydropic gallbladder	Profuse prodromal diarrhea; dizziness, headache, confusion; hypotension, shock; hydropic gallbladder	Infected tissue site	Sore throat, odynophagia; cervical lymphadenitis; malaise, vomiting	Mala arthr ureth ulcer symp abdo diarr
Predominant feature(s)	+++	+++	+++	++	+++
	Persistent fever and unremitting crankiness	Fever and prostration	Desquamating skin lesions	Exanthem and sore throat	Edem bloo oral pseu
Convalescent clinical features	+++	+++	+++	+++	++
	Desquamation periungually to palms and soles (full thickness); minimal desquamation elsewhere; hair loss, nail abnormalities; coronary artery aneurysms and thrombosis	Desquamation hands and feet (full thickness); mild desquamation elsewhere; hair loss, nail abnormalities	Desquamation extensive during acute and convalescent periods	Desquamation hands and feet (full thickness); desquamation extensive elsewhere	Desq sites lips, recur seriou ophth seque
LABORATORY FEATURES					
	Elevated peripheral neutrophils, platelets, sedimentation rate; anemia, hypoalbuminemia; sterile pyuria; ± electrocardiographic or echocardiographic abnormalities	Thrombocytopenia, left shift of neutrophils; coagulopathy; hyponatremia; multiorgan dysfunction related to hypoperfusion; acute respiratory distress syndrome	Left shift of neutrophils; hypovolemia in young infant; bacteremia or septicemia related to infected site	Elevated peripheral neutrophils	Eleva perip neutr sedin rate

DIAGNOSIS					
	Clinical, with exclusion of others and supportive laboratory findings; response to IGIV; ectasia, aneurysm, or thrombosis of coronary arteries	TSST-1 producing *Staphylococcus aureus* recovered (from mucosa or infected site); response to aggressive fluid support, antibiotic	Exfoliative toxin (ETA and ETB) producing *S. aureus* recovered (usually not from the skin lesions but from the primary site of infection[19]); response to antibiotic	Erythrogenic toxin-producing *Streptococcus pyogenes* recovered (usually from throat); response to antibiotic	Clini impr recur
TREATMENT					
	IGIV 2 g/kg Aspirin (high dose followed by low dose)	Crystalloid, colloid, then pressor agents; penicillinase-resistant antibiotic (or vancomycin) plus clindamycin; IGIV not proved (see text)	Penicillinase-resistant antibiotic (consider adding vancomycin or clindamycin); supportive fluids	Penicillin	Supp disco inciti cortic IGIV

[a] Features of staphylococcal toxic shock (i.e., related to TSST-1); see text and Table 13.2 for differences in streptococcal toxic shock.

IgE, immunoglobulin E; IGIV, immune globulin intravenous; TSST, toxic shock syndrome toxin; +++, prominent, expected finding; ++, frequent finding; +, variable finding; −, not present.

TABLE 13.2

Comparative Features of Toxic Shock Syndrome[a]

Feature	Staphylococcal Toxic Shock	Streptococcal Toxic Shock
Primary toxin	TSST-1	SPEA, B
Prodrome	Vomiting, diarrhea	Flu-like illness
Duration prodrome	Hours	Hours to days
Severity prodrome	+++	+
Focal infection	+	++
Extreme pain and hyperesthesia at focal site	−	+++
Rash	Erythroderma	Scarlatina or none
Shock	Predictable	Unpredictable, related to clotting
	Treatable	Sometimes untreatable
Multiorgan failure	Predictable, related to blood pressure	Unpredictable
	Treatable	Sometimes untreatable
Positive blood culture	−	++
Coagulopathy	+	+++
Complicated hospitalization	+	+++
Gangrene	±	+++

Mortality	+	++

[a]Differences represent general comparisons rather than clinical findings or outcomes in individual patients.

SPE, streptococcal pyrogenic exotoxin; TSST, toxic shock syndrome toxin; ±, not an expected occurrence; +, occurs, but infrequently; ++, occurs with some frequency; +++, occurs commonly; −, does not occur.

TABLE 13.3

Differentiating Features of Erythema Multiforme (EM) Minor, EM Major, Stevens–Johnson Syndrome (SJS), and Toxic Epidermal Necrolysis (TEN)

	Skin Lesions	Distribution of Skin Lesions	Mucosal Involvement	Detachment Skin (% TBSA)	Systemic Symptoms	Pathology	Pre Fac
EM minor	Typical target lesions[a] ± atypical papular target lesions[b]	Extremities and face > trunk	Absent or mild if present	None	Absent	Nonspecific, including apoptotic keratinocytes and dermal inflammation	Her sim viru Oth infe age
EM major	Similar to EM minor with occasional bullous lesions	Similar to EM minor	Present	Occasional, minimal	Present	Similar to EM minor	Sim EM
SJS	Lesions are widespread with blistering on erythematous or purpuric macules; atypical macular target lesions[c]	Trunk and face > extremities	Present	Confluence of blisters results in epidermal detachment of <10% TBSA[d]	Present	Apoptotic keratinocytes; subepidermal cleavage; keratinocyte necrosis; dermal inflammation	Dru occ infe age
TEN	Similar to SJS	Similar to SJS	Present	Confluence of blisters results in epidermal detachment of >30% TBSA[d]	Present	Similar to SJS	Sim SJS

[a]Typical target lesions are <3 cm with regular round shape, well-defined borders, and 3 distinct zones.

[b]Atypical papular target lesions are round, edematous, and palpable with 2 zones or indistinct border.

[c]Atypical macular lesions are nonpalpable targets (with exception of central blister) with round shape and 2 zones or indistinct border.

[d]Overlap SJS-TEN: confluent blisters result in detachment of 10% to <30% TBSA.

TBSA, total body surface area.

Modified from Auquier-Dunant A, Mockenhaupt M, Naldi L, et al; SCAR Study Group. Severe cutaneous adverse reactions. Correlations between clinical patterns and causes of erythema multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis: results of an international prospective study. Arch Dermatol. 2002;138:1019−1024; and French LE, Prins C. Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis. In: Bolognia JL, Jorizzo JL, Schaffer JV (eds). Dermatology, 3rd ed. St. Louis, Elsevier, 2012:319−333.

Less common conditions share certain clinical features of the mucocutaneous syndromes shown in Table 13.1 but usually can be distinguished on the basis of circumstances of occurrence, such as recurrences and periodicity of febrile episodes in periodic fever with aphthous stomatitis, pharyngitis, and adenitis (the PFAPA syndrome)[3] and chronicity and additional findings in Behçet disease.[4] Although the ulcerative gingivitis and pseudomembrane of mucositis associated with neutropenia and anticancer chemotherapy[5] can be indistinguishable from the confluent denuding ulcers of SJS, the clinical setting of the former, as well as the absence of conjunctivitis and rash, distinguishes mucositis from SJS. Most commonly, SJS is associated with antibiotics or anticonvulsant drugs or with *Mycoplasma* infection.[6–8] Medications strongly associated with SJS and TEN include sulfonamides, phenobarbital, lamotrigine, and carbamazepine. Reports of cases and case series, however, implicate a myriad of medications, including acetaminophen and ibuprofen.[9] Paraneoplastic vasculitis complicating myeloproliferative disorders can manifest with urticaria, EM, or palpable purpura. This diagnosis is suspected because of the associated malignancy and is confirmed by skin biopsy.[10]

Rocky Mountain spotted fever (RMSF), an infective vasculitis caused by *Rickettsia rickettsii,* shares many features of other mucocutaneous syndromes (i.e., high fever, progressive serious illness, conjunctival hyperemia and suffusion, peripheral edema despite hypovolemia, and hyponatremia), but the presence of unremitting headache, peripheral petechial rash, season (illness onset during summer), and exposure to ticks usually sets RMSF apart.[11] Ehrlichiosis and anaplasmosis occur in a similar setting; leukopenia may be a clue.[12] Empiric treatment for RMSF or ehrlichiosis with doxycycline regardless of age sometimes is required because the diagnoses cannot be reasonably or quickly excluded. Leptospirosis is indistinguishable from RMSF, except possibly for a biphasic illness and disproportionate kidney or liver involvement in leptospirosis.[13] Drug hypersensitivity reactions can manifest a variety of mucocutaneous abnormalities, including immediate immunoglobulin E (IgE)-mediated rashes and delayed reactions, SJS, TEN, drug rash with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP).[14–16] DRESS is characterized by diverse cutaneous eruptions (often evolving into indurated edematous erythroderma), with or without mucosal involvement, and systemic involvement that can include hematologic, hepatic, renal, pulmonary, cardiac, neurologic, gastrointestinal, or endocrine abnormalities.[17] The exanthem of AGEP is generalized with multiple sterile, nonfollicular pustules accentuated in the skinfolds, and it typically spares mucous membranes.[15]

For the previously healthy child or adolescent who comes to medical attention in shock, the following must be considered: septic shock from unrecognized ruptured appendix, urosepsis, invasive meningococcal or pneumococcal infection (especially if petechiae, purpura, or purpura fulminans is present), and septic or toxic shock from disseminated staphylococcal and group A streptococcal infection. *Streptococcus pneumoniae* and group B streptococcus also can cause toxic shock–like manifestations, which probably are related to cytokine stimulation.[18]

Specific Distinguishing Characteristics

Fever and Prodrome

The patient's duration of fever and sequence of clinical events provide useful clues to diagnosis. Although children with KD and bacterial toxin-mediated syndromes ultimately share many mucocutaneous features, the cadence of the prodrome is distinct. The child with staphylococcal toxic shock usually has profuse diarrhea and severe prostration within hours of onset of fever.[19,20] KD begins with fever and crankiness, sometimes with unilateral cervical lymphadenitis, the concern for diagnosis arising only when fever and crankiness persist and the symptom complex evolves rather than abates.[21,22] An important exception occurs in less than 10% of children with KD, who have rapidly progressive disease with hypotension requiring admission to an intensive care unit and who frequently are misdiagnosed as having septic or toxic shock.[23] The young child with staphylococcal exfoliative toxin syndrome can manifest rapidly progressive and dramatic skin manifestations, before or without severe systemic illness.[24,25]

Enteroviruses and respiratory viruses that cause mucocutaneous findings evolve over 3 to 5 days; nasal symptoms, rhinorrhea, hoarseness, or cough is present in more than 75% of cases, distinguishing these viral infections from KD. High fever (≥39.2°C) or persistent fever (≥5 days) does not eliminate viral etiology because viruses commonly considered in such patients (adenovirus, influenza A and B viruses) typically cause high fever and at least one third of affected children have fever beyond 5 days.[26–28]

Conjunctiva

To ascribe conjunctival findings accurately, the examiner must pay particular attention to (1) presence of inflammation and exudate versus erythema alone; (2) relative involvement of bulbar versus palpebral and tarsal sites; (3) presence or absence of photophobia, pain on movement, and itching; and (4) presence of uveitis, destructive keratitis, and panophthalmitis versus superficial inflammation.

Ocular manifestations of many infectious, inflammatory, allergic, and toxin-mediated conditions begin with bilateral conjunctival erythema.[29] The earliest ocular findings of KD, measles, SJS, RMSF, and leptospirosis, for example, cannot be distinguished. However, in KD, toxic shock syndromes, leptospirosis, and many cases of RMSF, nonedematous, nonexudative erythema of bulbar conjunctivae bilaterally is the complete evolution. In sharp contrast, adenoviral conjunctivitis is unilateral in 65% of cases, is predominantly palpebral (frequently with follicular lymphoid hyperplasia), and is associated with keratitis, purulent exudate, and photophobia in approximately one half of cases and with concurrent pharyngitis in 55%.[30] Conjunctivitis due to other viruses usually is bilateral, palpebral, and exudative.

Bacterial conjunctivitis (especially that due to nontypable *Haemophilus influenzae, S. pneumoniae,* or *Staphylococcus aureus*) is purulent, and bilateral usually; other mucocutaneous symptoms are not present (except with exfoliative toxin-producing *S. aureus* infection). Concurrent acute otitis media is common when nontypable *H. influenzae* is causative.[31] Orbital and periorbital cellulitis manifest predominantly with eyelid edema, erythema, and chemosis. Ocular itching, tearing, and photophobia accompany the "red eye" of allergic disorders; papillary hypertrophy of the palpebral conjunctivae is characteristic.

The findings of light sensitivity, ocular pain, and decreased vision suggest uveitis, which is characteristic of juvenile idiopathic arthritis (JIA) and Behçet disease. Such forms of JIA generally are not associated with fever and rash. Anterior uveitis is common in KD, being present in 83% of children examined in the first week and in 66% examined after the first week in one study.[32] Unlike other causes of uveitis, the inflammation in KD is mild and transient and is associated with minimal photophobia or pain. SJS frequently is associated with severe anterior-segment involvement, with exudative conjunctival discharge and sloughing of epithelium as well as pseudomembrane formation, and has the potential to cause subsequent severe corneal and eyelid scarring.[33] Anterior uveal inflammation can occur with measles and leptospirosis but is not expected with other mucocutaneous syndromes (e.g., streptococcal or staphylococcal toxin-mediated diseases, enteroviral or adenoviral infection, rickettsial diseases). Ophthalmologic evaluation with slit-lamp examination is valuable in children with evolving conjunctival findings and a mucocutaneous syndrome to uncover intraocular disease, and to aid in the diagnosis and sometimes sight-sparing management of SJS.

Lips

In infants, the lips (and frequently the ears) are brightly colored when fever is high, returning to normal with even transient defervescence. The lips infrequently are involved in mucocutaneous syndromes due to viruses, except during primary herpes simplex stomatitis, when diagnosis is apparent. Measles and influenza may be other exceptions, in which lips can be red, edematous, and cracked after several days of high fever.[34] The lips are noticeably red and occasionally are cracked and fissured in KD and toxic shock. The swollen, denuded, bleeding lips with black eschar of SJS (Fig. 13.1) are pathognomonic—involving the mucocutaneous junctions of lips, conjunctivae, urethra, and anus.

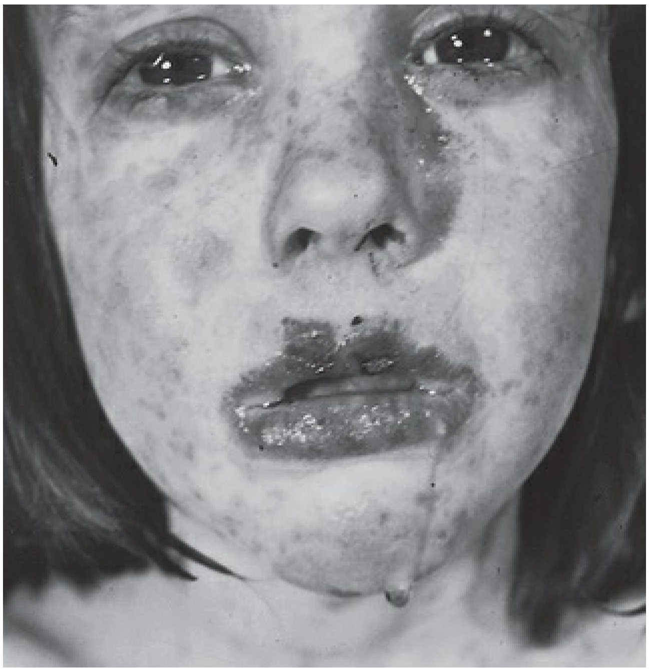

FIGURE 13.1 Ten-year-old girl with Stevens-Johnson syndrome and characteristic denudation of mucocutaneous junctions of the lips.

Oropharynx

Examination is performed to detect (1) diffuse erythema, sometimes with uvulitis (KD and toxic shock); (2) hypertrophied or dilated papillae on the tongue to give the appearance of a strawberry tongue (KD, toxic shock, streptococcal scarlatina); (3) confluent buccal and gingival ulceration with pseudomembrane formation (SJS and mucositis of neutropenia and antineoplastic drug therapy); (4) palatal petechiae (*Streptococcus pyogenes* and Epstein-Barr virus); (5) discrete ulcers (enteroviruses, herpes simplex virus); (6) Koplik spots (rubeola); and (7) exudative enanthem (*S. pyogenes,* respiratory tract viruses, Epstein-Barr virus). The singular (or few) deep, large ulcerative lesions of aphthous stomatitis and Behçet disease characteristically are found on the buccal or lingual mucosa or the lateral tongue.

Exanthem

The exact characteristics, distribution, pattern of evolution, and timing and manner of resolution of exanthematous lesions have differentiating features. Vesicular skin eruptions are almost unique to herpesviruses and enteroviruses.[35] Bullae are the typical initial lesions of staphylococcal exfoliative toxin syndrome, as is sloughing of sheets of epidermis with gentle tangential pressure or minor trauma on erythematous skin—Nikolsky sign. Nikolsky sign also can be elicited in SJS and TEN and in autoimmune bullous skin diseases, such as bullous pemphigoid.[15,36] Localized hemorrhagic bullae can form in the skin overlying necrotizing cellulitis, myositis, or fasciitis, especially due to toxin-producing *S. pyogenes.*[37] Blistering erythema, the hallmark of SJS, occurs first in localized areas (usually on the head and trunk), evolves to confluence over days, then appears and subsequently evolves at other sites (see Table 13.3; see also Chapter 70). The histology of skin lesion shows full-thickness epidermal necrosis with subepidermal cleavage in SJS and TEN compared with intraepidermal cleavage without keratinocyte necrosis in staphylococcal exfoliative toxin syndrome.[1,2]

Vesicular, bullous, or petechial lesions are distinctly rare in KD. The rash of KD is polymorphous (patchy macular, maculopapular, infrequently papular) and is indistinguishable in individual cases from the exanthem of viral infection, drug or food allergy, SJS, or toxin-mediated disease; however, characteristically, the rash in KD is fiery red, morbilliform (confluent), symmetric (when involving hands, feet, knees, and elbows), and changeable from hour to hour, rather than fixed as in viral infection or SJS. Although urticarial and EM-like lesions can occur in KD, they are not fixed. Rashes in KD characteristically spare the head, whereas exanthems in many viral infections, SJS, and staphylococcal toxin diseases commonly begin on, or involve, the face. Exaggeration or confinement of exanthem at the groin is characteristic of KD[38] but also can occur in streptococcal scarlatiniform eruptions, staphylococcal exfoliative toxin syndrome, influenza,[34] and bacterial cellulitis in the neonate.

Erythema, induration of the scrotum, and pain in the testicles can occur in KD and RMSF; a hydrocele can appear acutely.[39]

Viral exanthems are not painful or tender. The skin of children with diffuse staphylococcal exfoliative toxin syndrome, however, is erythematous and edematous, sometimes has a sandpaper quality, and usually is painful and tender.[40] In KD, specific sites of exanthem are not painful except on the hands and feet, where edema frequently leads to refusal to bear weight. If the patient complains of exquisite pain, sometimes with hyperesthesia or hypoesthesia out of proportion to local findings, toxin-producing streptococci (usually β-hemolytic group A streptococci, but also groups B, C, and G on occasion, and *S. pneumoniae,* the last especially in individuals with connective tissue diseases)[41] and necrotizing *S. aureus* infections must be considered.[37,42]

Epidemiologic features, such as season, exposure, incubation period, and associated findings, frequently are more helpful in distinguishing viral infections than is the exanthem itself. Enteroviruses are the leading cause of exanthematous diseases, with more than 30 types associated with rash illnesses, some of which also cause mucosal lesions.[35,43,44] Although neonates and young infants can have diffuse macular or blotchy rashes, exanthem at peak ages for enteroviral exanthematous diseases (especially due to echoviruses 4, 9, and 16 as well as coxsackieviruses A9 and B5) usually consists of rubelliform (maculopapular discrete, nonconfluent) lesions beginning on the face and upper trunk and spreading to the extremities.[44] An important exception is hand-foot-mouth disease (usually due to coxsackievirus A16, followed by A5, A6, A9, A10, B1, and B3, and enterovirus 71), in which buttock and peripheral distribution of vesicular or rubelliform lesions is characteristic. The exanthem of coxsackievirus A6 can be more widespread and varied with vesiculobullous, petechial, or eczema herpeticum−like presentation termed *eczema coxsackium*.[45] Rashes during viral infections due to influenza A and B, parainfluenza, and respiratory syncytial virus (especially in young children) probably occur more than occasionally, always are rubelliform, are frequently present for less than 24 hours, and spread from the head to the trunk and extremities.[35]

Rash occurs in 2% to 8% of adenoviral infections, and adenovirus types 1, 2, 3, 4, 7, and 7a have been isolated most frequently[44];

lesions are distributed as with influenza and usually are rubelliform, occasionally are morbilliform (maculopapular confluent patches), and rarely are EM like. Mucocutaneous and systemic manifestations of measles can simulate KD, the rash being least differentiating; prominent cough, coryza, and eventual purulent conjunctivitis distinguish measles. Similarly, the prominent respiratory tract symptoms caused by *Mycoplasma pneumoniae* distinguish this infection; maculopapular rashes (5% to 15% of cases), consisting of vesicular or bullous, papular, petechial, urticarial, or EM-like lesions have been described.[46]

Classically, staphylococcal toxic shock is associated with diffuse erythroderma, with a flushed, sunburned appearance (without discrete lesions, tenderness, or induration) especially on the face, trunk, and proximal extremities. Streptococcal scarlet fever or scarlatina is associated with a diffuse, fine maculopapular rash, which is palpable, sandpaper like, and prominent on the trunk and proximal extremities; exaggeration of erythema in skinfolds (Pastia sign) is characteristic and is dramatic in the groin when present. Children with staphylococcal exfoliative toxin syndrome commonly have crusted, exudative, infective conjunctivitis, or paranasal lesions, in addition to generalized nonexudative exfoliation (Fig. 13.2). Frequently, toxin-mediated exanthems overlap, presumably because more than one toxin is encoded.

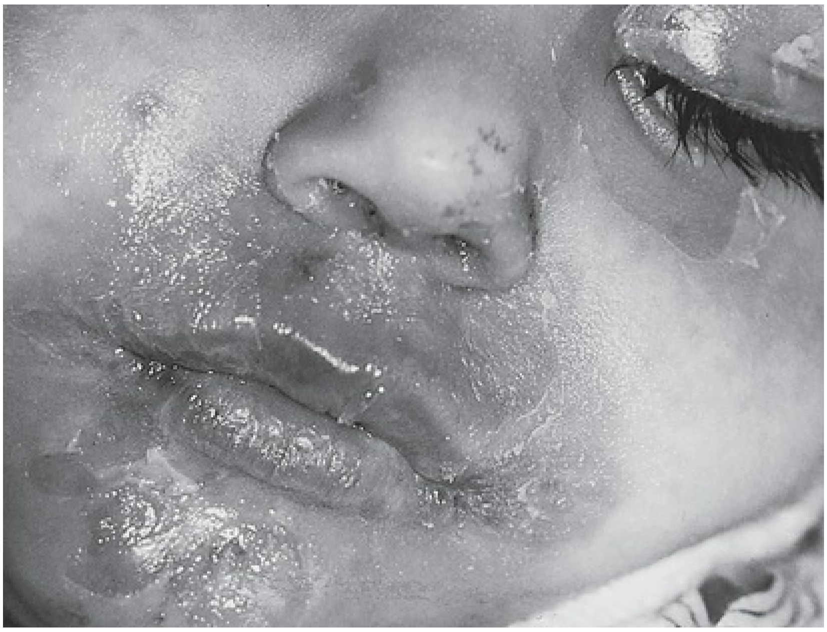

FIGURE 13.2 Four-year-old boy with staphylococcal

exfoliative toxin disease. Note characteristic paper-thin desquamation of skin on eyelid and impetiginous infection around the nose and chin.

Extremity Changes

Indurative erythroderma with frank edema of the distal extremities probably is the most helpful differentiating physical finding in some mucocutaneous syndromes, reflecting inflammatory vasculitis (KD), vascular dilation (toxic shock syndromes), or infective vasculitis (RMSF). Indurative erythroderma occurs in viral infections or SJS but is confined to contiguous sites of obvious exanthem. The demarcated, socks or gloves distribution of erythema and induration in KD is dramatic on occasion, as are digital cyanosis and gangrene (Fig. 13.3). When toxic or septic shock leads to peripheral ischemia, low blood pressure, weak pulse, and pale, cool extremities are expected. Parvovirus B19 and some herpesviruses also cause socks and gloves syndrome (especially in older children), with initial erythema and edema of dorsum and palms and soles with progression to papules and purpura, which is well demarcated at ankles and wrists.[47]

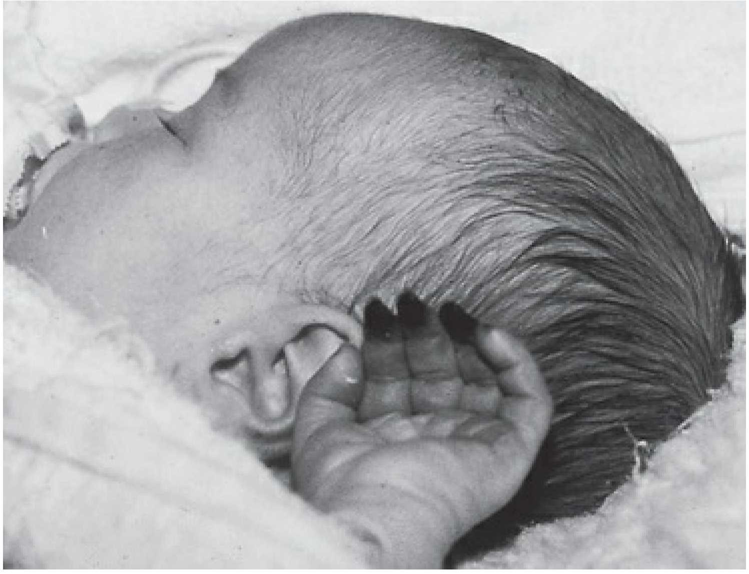

FIGURE 13.3 Six-week-old boy with the infantile polyarteritis nodosa form of Kawasaki disease. Note the dusky fingers with distal gangrene.

Evolution and Resolution

The exanthem of KD evolves, with waning, waxing, and migrating over days; that of toxic shock and exfoliative syndromes is rapidly progressive; and viral exanthems characteristically appear days after onset of systemic illness and evolve at one site while progressing to others. Desquamation occurs during the crescendo phase of staphylococcal exfoliative toxin syndromes, but during the decrescendo phase of KD, and only during the convalescent phases of staphylococcal and streptococcal toxic shock and scarlet fever. Desquamation of palms and soles is likely to be a full-thickness loss (as if molted) after KD, streptococcal scarlet fever, and toxic shock. In KD, unlike bacterial toxin-mediated diseases, total body desquamation does not occur or is fine and superficial, occurring in only about 10% of patients, particularly in the groin and perineal area. Hair loss and nail bed deformities (i.e., grooves [Beau lines], pits, and transverse [red] lines) are well described after KD but can occur after other highly febrile illnesses, after coxsackievirus A6,[45] or with hypotension or ischemia, such as invasive bacterial infection, toxic shock, and RMSF.

Other Clinical Features and Cardinal Feature

Clinical features other than mucocutaneous signs or symptoms, alone or in combination, can provide valuable clues to diagnosis. A partial listing is given in Table 13.1. Inflammation at multiple sites is typical of KD, anterior uveitis being quite specific among diagnoses considered. Transient hydrops of the gallbladder manifesting as right upper quadrant abdominal pain, tenderness, and fullness is a common finding in KD but is nonspecific, also described with staphylococcal toxic shock,[19] streptococcal scarlet fever,[48] enteric fever,[49] leptospirosis, Epstein-Barr virus mononucleosis,[50] neonatal group B streptococcal septicemia, and asphyxia, and during parenteral alimentation.[51]

Infants younger than 6 months with KD are especially prone to a rapidly progressive course and severe vascular complications[21,52,53] and can lack classical features, such as exanthem and erythematous conjunctivae. Extremely high fever, inconsolable irritability, respiratory distress, and cardiac gallop murmur with hepatomegaly can be clues. Aneurysmal dilation of multiple vessels can occur;

pulsatile masses in the axillae or groin can sometimes be detected within days of onset of fever.

Delineating the predominant complaint, or cardinal feature, of the child's illness aids in establishment of a correct diagnosis (see Table 13.1). Prodromal fever, diarrhea, and then profound prostration and hypotension are predominant in staphylococcal toxic shock but also can occur in streptococcal toxic shock. Streptococcal toxic shock frequently has a specific prodrome; the clinical picture can be dominated by extremely painful but apparently minor soft tissue infection, followed by sudden inexorable shock and coagulopathy.

Children with staphylococcal exfoliative toxin syndrome have variable degrees of illness, depending on age and presence of bloodstream or focal infection; the rapidly evolving exanthem with loss of skin in sheets as well as purulence around eyelids and nose dominate the clinical picture. Edematous, bleeding, black eschar on the lips, and oral mucosal denudation are dramatic findings in SJS; in some cases, inflammatory necrosis of respiratory or intestinal tract mucosa causes wheezing, odynophagia, and other symptoms. In viral illnesses, the mucocutaneous features broaden the differential diagnosis, but other symptoms (such as cough, hoarseness, sore throat) commonly dominate the patient's or parent's complaints; general debilitation usually is modest, and the epidemiologic setting heightens the likelihood of a specific diagnosis.

Table 13.2 summarizes the differentiating features of classic staphylococcal toxic shock (associated with TSST-1 and enterotoxin B) and streptococcal toxic shock (associated with SPE A or B and, possibly, bacterial proteases). Although these syndromes are similar superficially, the evolution of clinical symptoms, complications, and outcomes frequently is distinctive. Staphylococcal toxic shock usually has a dramatic onset and rapid progression. Focal infection is present in most nonmenstrual pediatric cases but can be relatively minor (e.g., sinusitis, surgical wound).[54,55] Streptococcal toxic shock usually has a less abrupt onset of symptoms, with initial malaise and myalgia and then complaints of severe pain, hyperesthesia, or hypoesthesia at an apparently minor soft tissue site of infection.[41,42,56] Nonexudative pharyngitis is the occasional primary site of streptococcal infection, with a complaint of sore throat out of proportion to the findings.[57] Many children with streptococcal toxic shock have been brought for medical attention one or more times before the onset of catastrophic multiorgan system failure and shock.[58] A possible potentiating role of nonsteroidal anti-inflammatory drugs in invasive streptococcal disease has been questioned[59] and not excluded by case-control studies.[60,61]

Diagnosis and Empiric Therapy

The best working diagnosis, barring the presence of pathognomonic features, is made on clinical grounds. Laboratory findings infrequently confirm a diagnosis at the time therapy must be given. Brisk elevations of acute-phase reactants are supportive laboratory findings in KD (and are variably present in SJS); white blood cell count less than 15,000/mm^3, erythrocyte sedimentation rate less than 40 mm/hour, C-reactive protein less than 3 mg/dL, or platelet count less than 200,000/mm^3 are negative indicators for KD[21] (with important exception of low platelets in patients with severe shock-like presentation[23]). Leukemoid reaction with neutrophil count exceeding 30,000/mm^3 frequently occurs in very young infants with the infantile polyarteritis presentation of KD; anemia is universal.[52] These can be important clues to the diagnosis when mucocutaneous features are absent.

Leukocytosis is not expected in enteroviral infections. Leukocyte counts are less than 15,000/mm^3 in 90% of children hospitalized with influenza; leukopenia occurs in approximately 25%.[27,34] In a study of 105 children hospitalized with adenoviral infection, the mean peripheral leukocyte count was 13,300/mm^3 (10% had counts >20,000/mm^3), and almost 30% had an erythrocyte sedimentation rate higher than 40 mm/hour.[62]

Thrombocytosis is expected in KD but only in the second week of illness. Thrombocytopenia is described in rare cases of KD, usually unassociated with consumption coagulopathy.[23,63] Thrombocytopenia is common in invasive bacterial infection and toxic shock syndromes and occurs early in RMSF and ehrlichiosis[12]; modest thrombocytopenia can occur with uncomplicated enteroviral infections. A normal or low, rather than high, neutrophil count with extreme left shift is a typical effect of bacterial toxins[64];

thrombocytopenia and consumption coagulopathy (with extremely low erythrocyte sedimentation rate) also are common. Pyuria without hematuria is common in KD but infrequent in other conditions except SJS.

Empiric therapies are shown in Table 13.1, and conditions other than SJS are discussed in specific chapters. Prompt and aggressive antibiotic and supportive therapies are lifesaving in invasive bacterial infections and in staphylococcal exfoliative toxin syndrome in young infants. Antibiotic therapy may be beneficial in staphylococcal toxic shock, especially to treat focal infection and to prevent recurrence, but aggressive reversal of hypovolemia and cardiovascular shock is paramount. The important challenges in streptococcal toxic shock are (1) halting microbial replication and toxin production; (2) reversing tissue ischemia, acidosis, hypovolemia, and hypotension; and (3) supporting multiorgan failure related to diffuse thromboemboli. Data from animal models of streptococcal necrotizing myositis, as well as clinical observations, suggest that clindamycin is superior to β-lactam agents for treatment.[57,65]

Corticosteroid therapy should not be initial treatment for KD, is not indicated in staphylococcal exfoliative toxin syndrome or in staphylococcal or streptococcal toxic shock, and is controversial in SJS.[66] Aggressive care in burn units for children with SJS or toxic epidermal necrolysis with more than 10% skin loss improves outcome.[67] Many experts would give a 5-day trial of corticosteroids to a subset of children with SJS who are toxic and have mucosal involvement in addition to the mouth, skin eruption for 3 days or less, and less than 20% skin denudation.[25] Excess rate of infections[68] and mortality in drug-induced toxic epidermal necrolysis[67] have been reported with use of corticosteroids in uncontrolled studies. Patients with SJS or TEN onset in the setting of prior exposure to corticosteroids might have prolonged latency to disease onset and longer duration of disease progression.[69]

Therapy with immune globulin intravenous (IGIV) is critical for optimal outcome in patients with KD[21,22] and is lifesaving for very young infants.[52] No randomized prospective study with adequate power has been performed to evaluate IGIV therapy in staphylococcal or streptococcal toxic shock. Case reports and retrospective, matched case-control studies in adults suggest a potential benefit. Dosage used was 500 mg/kg/day × 5 days for staphylococcal disease and 2 g/kg once for streptococcal disease.[70] A European randomized, double-blind, placebo-controlled trial of IGIV (1 g/kg on day 1 followed by 500 mg/kg on days 2 and 3) for streptococcal toxic shock[71] showed trend of benefit,[72] but a multicenter retrospective study in US children did not.[73] Another European prospective comparative observational study in adults demonstrated improved survival in streptococcal toxic shock syndrome with use of either IGIV or clindamycin, but groups were not similar in severity of infection.[74] Anecdotal reports and predominantly retrospective case series of use of IGIV for severe SJS suggest possible beneficial effect but are conflicting.[66,75,76]

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14

Fever Without Localizing Signs

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Most young children with fever and no apparent focus of infection have self-limited viral infections that resolve without treatment and are not associated with significant sequelae. However, a small proportion of young children with fever who do not appear to be seriously ill may be seen early in the course of a bacterial infection that could progress to bacteremia or meningitis. Despite numerous studies that have attempted to identify the febrile child who appears well but has a serious infection and to assess the effectiveness of potential interventions, no clear answers have emerged.[1–4] Studies show that parents usually are more willing than physicians to assume the small risk of serious adverse outcomes in exchange for avoiding the short-term adverse effects of invasive diagnostic tests and antimicrobial treatment.[5,6] The best approach to the treatment of the febrile child combines informed estimates of risks, careful clinical evaluation and follow-up of the child, and judicious use of diagnostic tests.[7]

Etiologic Agents

The list of microbes that cause fever in children is extensive. Relative importance of specific agents varies with age, season, and associated symptoms. The goal of this chapter is to assist in identifying the febrile child with a serious bacterial infection (SBI).

Table 14.1 shows the most common causes of SBI in children younger than 3 months.[8–12] The division at 1 month is not absolute; considerable overlap exists. Receipt of vaccines typically administered at 2 months also reduces the risk of SBI. Certain viruses, notably herpes simplex, influenza, and enteroviruses, can cause serious infections in neonates, mimicking septicemia and beginning as fever with no apparent focus of infection. Less serious viral infections are the most common causes of fever in children of all ages.

TABLE 14.1

Age-Related Causes of Serious Bacterial Infections in Very Young Infants

Age Group	Causative Bacteria
BACTEREMIA OR MENINGITIS	
<1 month	*Escherichia coli* Other enteric gram-negative bacilli
	Group B *Streptococcus*
	Streptococcus pneumoniae
	Staphylococcus aureus
	Salmonella spp. *Neisseria meningitides*
	Streptococcus pneumoniae *Listeria monocytogenes*
1–3 months	*Escherichia coli* Other enteric gram-negative bacilli Group B *Streptococcus*
	Salmonella spp.
	Neisseria meningitides
OSTEOARTICULAR INFECTIONS	
<1 month	Group B *Streptococcus*
	Staphylococcus aureus
1–3 months	*Staphylococcus aureus*
	Group B *Streptococcus*
	Streptococcus pneumoniae
URINARY TRACT INFECTION	
0–3 months	*Escherichia coli*
	Other enteric gram-negative bacilli
	Enterococcus species

In children between 3 and 35 months of age, most bacterial infections with no apparent focus are caused by *Streptococcus pneumoniae* (in unimmunized children), *Neisseria meningitidis,* or *Salmonella* spp. infection (which often is associated with symptoms of gastroenteritis). Because universal administration of pneumococcal and *Haemophilus influenzae* type b (Hib) conjugate vaccines, Hib has become rare, and the incidence of infection with *S. pneumoniae* has fallen substantially.[13,14] Other common causes of invasive bacterial infections in these children, such as *Staphylococcus aureus,* are usually associated with identifiable focal infections.

Epidemiology

Children Younger Than 3 Months

The risk of serious bacterial infection varies with age. Although longitudinal studies have shown that only 1% to 2% of children are brought to medical attention for fever during the first 3 months of life, a greater proportion of febrile infants has serious bacterial infections than older children.[15–18] Risk is greatest during the immediate neonatal period and through the first month of life, and risk is heightened for infants born prematurely.

In a prospective study conducted by investigators at the University of Rochester, factors were identified that indicate a low risk of serious bacterial infection in febrile infants younger than 3 months.[19] Among 233 infants who were born at term with no perinatal complications or underlying diseases, who had not received antibiotics, and who were hospitalized for fever and possible septicemia, 144 (62%) were considered unlikely to have a serious bacterial infection and fulfilled all of the following criteria: no clinical evidence of infection of the ear, skin, bones, or joints; white blood cell (WBC) count between 5000 and 15,000/mm^3; less than 1500 band cells/mm^3; and normal urinalysis results. Only 1 (0.7%) of the 144 infants had a serious bacterial infection (i.e., *Salmonella* gastroenteritis), and none had bacteremia. In contrast, among the 89 infants who did not meet these criteria, 22 (25%) had a serious bacterial infection ($P < 0.0001$) and 9 (10%) had bacteremia ($P < 0.0005$).

Many studies have largely corroborated results of the Rochester study.[11,12,20–25] Although investigators have used slightly different criteria to define young febrile infants at low risk for serious bacterial infection (and some investigators excluded children younger than 1 month old), all found that the risk of a serious bacterial illness in the group defined as being at low risk is very low. Approximately 10% of young febrile infants have urinary tract infections (UTIs), largely due to *Escherichia coli*, and 10% of this group (1% overall) have concomitant bacteremia or meningitis.[11,12,26]

In a meta-analysis of studies of febrile children younger than 3 months, the risks of serious bacterial illness, bacteremia, and meningitis were 24.3%, 12.8%, and 3.9%, respectively, for high-risk infants and 2.6%, 1.3%, and 0.6%, respectively, for low-risk infants.[15] The negative predictive value (NPV) for serious bacterial illnesses among infants fulfilling low-risk criteria ranged from 95% to 99%, and the NPV was 99% for bacteremia and 99.5% for meningitis.[15] Although the risk of serious bacterial infection is high among febrile infants younger than 3 months of age with no apparent focus of infection, clinical and laboratory assessment can identify the slightly more than 50% of infants at very low risk.

An observational study of more than 3000 infants younger than 3 months of age with fever greater than 38°C treated by practitioners and reported as part of the Pediatric Research in Office Settings Network found that 64% were not hospitalized.[4,27] Practitioners individualized management and relied on clinical judgment; guidelines were followed in only 42% of episodes.[4,27,28] Outcomes of the children were excellent. If the guidelines had been followed, outcomes would not have improved, but there would have been substantially more laboratory tests performed and more hospitalizations.[4]

Risk of serious bacterial illness in young infants has fallen further due to the marked reduction in early-onset group B streptococcal infections because of the effectiveness of peripartum antimicrobial prophylaxis of pregnant women with positive screening test results for colonization with group B S*treptococcus*.[29] In febrile children younger than 3 months of age who have an identified viral infection such as influenza, respiratory syncytial virus (RSV), or enteroviruses, the risk of a serious bacterial infection other than a UTI falls to almost zero.[24,30–33]

Children Older Than 3 Months

In the 1970s and 1980s, there was concern about occult bacteremia in febrile children between 3 months and 24 to 36 months of age.[34] Studies performed in that era showed that some children 3 months of age or older with fever who did not appear to be toxic and who had no apparent focus of infection had bacteremia, most often due to *S. pneumoniae* but occasionally due to Hib or *N. meningitidis.*[34–41] In some instances, serious focal infections such as meningitis developed in children with occult bacteremia.

The concern about progression to focal infections resulted in protocols being developed to identify and intervene for infants at high risk. Protocols emphasized routine blood cultures and empiric antibiotic administration for many febrile children in this age group.[28] These practices discounted several facts. First, most children with occult bacteremia have transient infection and recover without antimicrobial therapy and without developing a serious complication (e.g., meningitis, septic shock).[28,42,43] Second, risk of meningitis complicating occult bacteremia varies with bacterial species (*N. meningitidis* ≫ Hib ≫> *S. pneumoniae*).[35] Third, universal vaccination against Hib led to elimination in vaccinated infants of the most concerning occult bacteremia, and subsequent use of conjugate pneumococcal vaccine eliminated almost all other cases of occult bacteremia.[44–49]

The risk of UTI in well-appearing febrile children in this age group has not changed significantly over the years. Several studies have shown that the rate of UTI varies among different populations (e.g., girls vs. boys, uncircumcised vs. circumcised) within this age group and varies with height and duration of fever. UTI should be considered as a potential source of SBI in these patients.[44,50]

Laboratory Findings and Diagnosis

Various diagnostic tests to quantify the risk of bacteremia and its complications have been assessed. They include the WBC count and differential count, microscopic examination of buffy coat of blood, erythrocyte sedimentation rate, C-reactive protein, procalcitonin, morphologic changes in peripheral blood neutrophils, and quantitative cultures of blood.[28,51–58] Clinical scales have been developed to help identify the febrile child with a serious illness.[59]

Unfortunately, no test has sufficient sensitivity and positive predictive value (PPV) or NPV to be clinically useful for an individual patient. In the era before conjugate vaccinations for Hib and *S. pneumoniae,* several studies examined the risk of bacteremia among children with a temperature higher than 40°C and in those with fever and a WBC count of at least 15,000/mm.[3,41,51,60] The PPV of the tests for bacteremia was only about 15%. In the current era of low incidence and unconfirmed predictive value of WBC for remaining pathogens, laboratory testing no longer is justified.[1,7,45,47]

Making a laboratory-confirmed diagnosis of a viral infection significantly reduces the likelihood that a febrile infant has a concomitant bacterial infection (with the exception of a UTI). This currently holds true for influenza, RSV, and enterovirus, and in the future, it will likely be true for many other respiratory viruses (e.g., human metapneumovirus, parainfluenza virus, coronavirus) that are being diagnosed with multiplex polymerase chain reaction (PCR) technology. One study showed that incorporating viral diagnostics into the initial evaluation of febrile infants reduced the length of hospitalization and healthcare costs.[61]

Management

Although there is no single correct approach to the management of febrile infants without localizing signs who appear well, studies have provided data based on which informed decisions can be made.[7] There is general agreement that febrile children who are very young (i.e., variously considered to be younger than 3, 2, or 1 month of age) should be managed differently from older children.

Children Younger Than 3 Months

Because of the substantially greater risk of serious infections in very young infants with fever and the difficulty in assessing the degree of wellness accurately, pediatricians have approached the management of these cases conservatively. Some clinicians adhere to a protocol of treating all young infants with fever and no apparent focus of infection with broad-spectrum antimicrobial agents administered intravenously in the hospital until the results of cultures of the blood, urine, and cerebrospinal fluid (CSF) are known.[62] Although perceived as the safe approach, it incurs considerable financial cost and risk of iatrogenic complications and of diagnostic misadventures associated with hospitalization.[63–65] These risks include errors in the type and dosage of drugs, complications of venous cannulation (e.g., phlebitis, sloughing of the skin), and nosocomial infections. Hospitalization of a young infant is a major disruption for the family and may potentiate development of the vulnerable child syndrome.[66]

Investigators have found that selected young infants with fever can be treated expectantly without hospitalization.[4,7,19,21,27,67] Consequently, many experts think that febrile infants between 4 and 12 weeks of age with no apparent focus of infection who appear well or have a laboratory-documented viral infection can be treated without additional laboratory tests or hospitalization, provided that careful follow-up is ensured.[7] Others prefer to confirm laboratory criteria that predict low risk (sometimes including a normal CSF analysis result). Some providers observe the patient very closely without giving antimicrobial therapy; others treat all such infants for 2 days with a single daily dose of ceftriaxone (50 mg/kg) administered parenterally while awaiting the results of blood, urine, and CSF cultures. Either approach, if careful and vigilant, is defensible.

Before an antimicrobial agent is administered, cultures of the blood, urine, and CSF should be obtained. Rapid tests for specific viral pathogens are widely available, can aid decisions about managing patients, and can reduce the duration of hospitalization or eliminate the need.[7,31–33,68] Febrile infants at low risk for serious bacterial infection for whom adequate home observation and follow-up cannot be ensured should be hospitalized and can be observed without antimicrobial treatment. If the child appears well, doing so is reasonable and avoids the adverse side effects of antimicrobial agents and intravenous cannulation, shortens the duration of hospitalization, and saves money without placing the child at significant risk for complications.[21,27,67]

Most infants with fever who are younger than 1 month should be hospitalized and treated with antimicrobial therapy (with or without acyclovir for herpes simplex virus), although in selected instances, hospitalization without antimicrobial treatment or outpatient management after laboratory evaluations, including CSF analysis, may be reasonable. If a decision is made to administer antimicrobial agents intravenously, ampicillin (100 to 200 mg/kg per day every 6 hours) plus gentamicin (7.5 mg/kg per day every 8 hours) or a third-generation cephalosporin (e.g., ceftriaxone, 50 mg/kg per day in one dose; cefotaxime, 150 mg/kg per day every 8 hours) could be chosen. Ampicillin and gentamicin is a well-established combination with narrower spectrum of antimicrobial activity than ceftriaxone and excellent effectiveness against group B *Streptococcus*, *Listeria monocytogenes,* and many enteric gram-negative rods. Because of the rising incidence of ampicillin-resistant *E. coli* and the rarity of listeriosis in recent large studies, a regimen with a third-generation cephalosporin without ampicillin offers coverage for the few infants who have bacteremia or meningitis with a UTI due to ampicillin-resistant *E. coli*.[11,12,25] No study has directly assessed the relative risks and benefits of either regimen. Before initiating antimicrobial treatment with any regimen, cultures of the blood, urine (obtained by urethral catheterization or suprapubic aspiration of the bladder), and CSF should be obtained.

Children 3 Months of Age and Older

Children 3 months of age and older who appear well and have no apparent focus of infection can be evaluated clinically without laboratory tests or treatment with antimicrobial agents, with the exception of examination of the urine. In the current conjugate vaccine era, blood culture isolates are substantially more likely to be contaminants than to be pathogens.[7] Substantial evidence suggests that obtaining blood cultures routinely from these children has little impact on outcome, although false-positive blood culture results lead to substantial unnecessary costs.[69,70]

The following approach seems appropriate. The febrile child should be carefully assessed for a focus of infection, including UTI, and if a focus is found, the child should be treated according to likely pathogens. If the child appears toxic, appropriate cultures and diagnostic tests should be performed, and antimicrobial treatment (usually with cefotaxime, 150 mg/kg per day in divided doses every 8 hours, or ceftriaxone, 50 mg/kg once daily) should be initiated; some physicians add vancomycin (40 mg/kg per day in divided doses every 6 to 8 hours). Most of these children should be hospitalized.

If no focus is found and the child does not appear toxic, no diagnostic tests are indicated routinely. Parents should be instructed to look for signs that a more serious problem is developing (e.g., persistent irritability or lethargy, inattentiveness to the environment). Serial observations should be planned that permit subsequent clinical and laboratory evaluation and antimicrobial treatment as indicated. If a practitioner encounters a febrile child older than 4 months of age who is unimmunized or partially immunized, a more aggressive plan for evaluation and management may be warranted.

Other Considerations

This chapter focuses on invasive bacterial infections, particularly bacteremia, as a cause of fever without apparent focus. Although other serious illnesses such as autoimmune diseases and inflammatory bowel disease can manifest as fever without a focus of infection, they are rare and come to attention because of persistence or recurrence of fever (see Chapter 15).

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15

Prolonged, Recurrent, and Periodic Fever Syndromes

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Diagnosing and treating patients with prolonged, recurring, or periodic fever requires extensive review of signs and symptoms to establish the onset and cardinal features of illness, to define the exact fever pattern, and to understand the context of illness within the patient's family. It also requires comprehensive medical and family histories.

Defining fever patterns (Box 15.1) is essential in prioritizing the differential diagnosis and investigation.[1] A comprehensive physical examination can identify target organ abnormalities of potential infectious and noninfectious diseases. In children with prolonged fever, laboratory testing should include simple screening, and targeted investigation then is performed for specific organ systems as identified by the history, physical examination, exposures, or prioritized clinical differential diagnosis (Box 15.2).[1] For children with periodic fever, the main goal of performing screening laboratory tests is to confirm normal organ system function, direct the clinician to a specific disorder (e.g., recurrent urinary tract infection), or support the diagnosis of a noninfectious periodic fever syndrome. In evaluating children with any fever pattern, casting a broad net of serologic testing for unusual infectious agents is rarely fruitful in the absence of a specific exposure history or compatible clinical findings.

Box 15.1

Fever Patterns of Illness Used for Establishing a Diagnosis

Prolonged fever: A single illness in which the duration of fever exceeds that expected for the clinical diagnosis (e.g., >10 days for viral upper respiratory tract infections; >3 weeks for mononucleosis)

or

A single illness in which fever was an initial major symptom and subsequently is low grade or only a perceived problem

Fever of unknown origin: A single illness of at least 3 weeks′ duration in which fever >38.3°C occurs on most days and the diagnosis remains uncertain after 1 week of intense evaluation

Recurrent fever: A single illness in which fever and other signs and symptoms wax and wane (sometimes in relation to discontinuation of antimicrobial therapy)

or

Repeated unrelated febrile infections of the same organ system (e.g., sinopulmonary, urinary tract)

or

Multiple illnesses occurring at irregular intervals and involving different organ systems in which fever is one variable component

Periodic fever: Recurring episodes of illness for which fever is the cardinal feature, other associated symptoms are similar and predictable, and the duration of episodes is days to weeks, with intervening weeks to months of complete well-being; episodes can have clockwork or irregular periodicity

Box 15.2

Physical Examination and Screening Laboratory Testing for Children With Prolonged, Recurrent, or Periodic Fever

Physical Examination

- Growth chart
- Thorough general examination
- Careful organ-specific examination
- Notation of mouth ulcers, exanthem, joint abnormalities, and lymph nodes

Tests

- Complete blood count with manual differential count of white blood cells[a]
- Erythrocyte sedimentation rate and C-reactive protein[a]
- Screening serum chemistry tests (and lactate dehydrogenase and uric acid levels for prolonged fever)
- Serum quantitative immunoglobulin levels
- Urinalysis
- Urine culture
- Chest plain radiograph (for prolonged fever)
- Other imaging only as directed by examination and other screening tests
- Blood culture (for prolonged fever)
- Serologic testing only as directed by examination, other screening tests and exposures
- Complete blood count performed during episode and wellness interval for periodic fever

Fever of Unknown Origin

Definition

The three criteria for fever of unknown origin (FUO) in Petersdorf and Beeson's landmark study of adults in 1961[2] were illness of more than 3 weeks duration, fever higher than 38.3°C on several occasions, and an uncertain diagnosis after 1 week of study in the hospital. A prospective, population-based study conducted in the 1990s with adults in the Netherlands used fixed epidemiologic entry criteria and a specific diagnostic protocol.[3,4] The classic definition of FUO was adjusted; immunocompromised patients were excluded, and 1 week of hospitalization was replaced with 1 week of intensive evaluation (usually including computed tomography [CT] of the abdomen), and pursuit of potential diagnostic clues.

In pediatrics, studies of FUO have used various definitions, with temperature thresholds between 38.0°C and 38.9°C and durations of fever ranging from 14 to 21 days.[5–9] Some required daily fever, but others required fever on multiple occasions. For purposes of our definition, FUO in children is considered only after a minimum of 14 days of daily documented temperature of 38.3°C or greater without apparent cause after performance of repeated physical examinations and screening laboratory tests. This definition assumes exclusion of protracted but waning symptoms from acute, self-limited respiratory tract infections, well-documented periodic fever, and repeated but unrelated episodes of fever with identifiable causes.

Almost one-half of children referred for FUO do not meet fever and exclusion criteria. The method of temperature measurement and the frequency and timing of fever must be carefully investigated. Temperature is interpreted with the use of norms for age and sex (Fig. 15.1).[10] At 18 months of age, mean rectal temperature for boys is 37.7°C with a standard deviation (SD) of 0.38°C; a rectal temperature of 38.5°C is less than 2 SD above the mean. Normal body temperature fluctuates on average by 0.5°C in adults and by as much as 1.5°C in children, and it typically peaks in the late afternoon or evening.[11,12] An asymptomatic toddler with low-grade fever in the evenings with normal physical examination findings may have a normal body temperature.

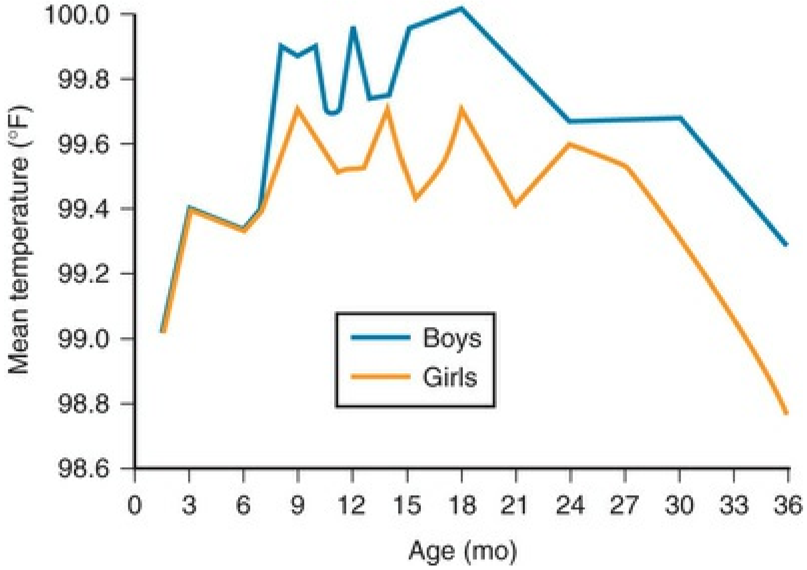

FIGURE 15.1 The normal mean rectal temperatures for boys and girls through 36 months of age are shown (100°F = 37.8°C). (Data from Bayley M, Stolz HR. Maturational changes in rectal temperature of 61 Infants from 1 to 36 months. Child Dev 1937;8:195.)

Etiology

In Petersdorf and Beeson's original paper, a high incidence of serious disease was found, with infections accounting for 36% of cases, neoplasms for 19%, collagen vascular diseases for 13%, and no diagnosis found in 7% of cases.[2] In a separate assessment of individuals with fever that did not exceed 38.3°C (even if protracted), diagnosis of significant illness was rare, and 30% of patients had no diagnosis, three-fourths of whom recovered spontaneously. In studies of FUO in children, decreasing stringency of entry criteria also correlated with increased likelihood of self-limited conditions.[5,9,13–17] When fever approaches 4 weeks' duration without a definable source, the rate of life-altering diagnoses such as malignancy and autoimmune or autoinflammatory disease rose to 40% in some series.[5,14,15]

In recent studies of FUO, probably because earlier diagnoses are made with imaging, serologic, or molecular diagnostic tests, a large proportion of patients who fulfill criteria have no identified diagnosis.[18] In a prospective, multicenter study of adults in the

Netherlands in 2007, 51% of patients had no cause of FUO found.[19] A similar trend has been seen in pediatrics.[18,20] In pediatric studies, 42% to 47% of patients with prolonged fever or FUO had no identified cause.[9,21] Most patients had spontaneous resolution of fever without sequelae.[5,6,21] In most recent decades, patients fulfilling criteria for FUO also are less likely to have serious, life-altering diagnoses.[6,21]

Limitations of published case series of FUO in children include small numbers; variations in the definition of FUO and investigation of subjects, study methodologies, and years and sites of study; and subspecialty referral biases.[22] A systematic review published in 2011 of 18 pediatric studies involving 1638 children divided studies into those performed in developed countries (i.e., 8 studies from three countries, all published more than 1 decade ago) and developing countries (i.e., 10 studies, with 8 published since 2000).[22] Overall, categories of diagnoses in developed and developing countries were remarkably similar: infection in 51%, malignancy in 6%, autoimmune or autoinflammatory diseases in 9%, miscellaneous noninfectious conditions in 11%, and no diagnosis in 23% of cases. Infectious causes were slightly more common in developing countries (56% vs. 42%), whereas finding no cause was more common in developed countries (31% vs. 18%). The infections diagnosed in 832 children included in the systematic review are shown in Table 15.1.[22]

TABLE 15.1

Reported Infectious Causes of Fever of Unknown Origin in 832 Children in Developed and Developing Countries

Infectious Cause	Developed Countries[a] (*N* = 275)	Developing Countries[b] (*N* = 557)	Most Common Agents and Infections in Descending Order of Frequency
Bacteria	56%	61%	Developed: urinary tract, osteomyelitis, tuberculosis, *Bartonella*, septicemia (not specified), *Salmonella*, *Brucella*
			Developing: *Brucella*, urinary tract, *Salmonella*, tuberculosis, abscess (not specified), septicemia (not specified)
Viruses	15%	3%	Developed: Epstein-Barr virus, cytomegalovirus, enterovirus
			Developing: Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus
Fungi	1%	0.2%	Developed: *Blastomyces*, *Histoplasma*

Parasites	2%	14%	Developed: *Leishmania*
			Developing: *Leishmania, Plasmodium*
Infectious syndrome without pathogen	26%	22%	Developed: viral syndrome (not specified), pneumonia, meningitis
			Developing: pneumonia, respiratory tract (not specified), infectious mononucleosis, viral syndrome (not specified)

[a] United States, Germany, and Spain.

[b] Tunisia, India, Turkey, Poland, Argentina, Serbia, Georgia, and Kuwait.

From Chow A, Robinson JL. Fever of unknown origin in children: a systematic review. World J Pediatr 2011;7:5–10.

Children younger than 6 years of age are more likely to have an infectious cause of fever than older children, who are more likely to have autoimmune and autoinflammatory disorders.[8] In older pediatric studies of FUO, bacterial pathogens and respiratory tract infections were responsible for a larger portion of disease compared with more recent studies.[9,20,21] Epstein-Barr virus (EBV), *Bartonella henselae,* urinary tract infections, and osteomyelitis (especially of spine and pelvic bones) are the most common infections identified in recent studies.[7,9,21] Agents that produce granulomatous infections (i.e., *Bartonella, Mycobacterium, Salmonella, Histoplasmosis, Brucella,* and *Francisella* spp.) cause FUO disproportionately and frequently involve the visceral organs, reticuloendothelial system, and bone marrow.[23]

Box 15.3 summarizes noninfectious causes of FUO. Leukemia and lymphoma are the most common malignancies diagnosed, and juvenile idiopathic arthritis, inflammatory bowel disorders, and systemic lupus erythematosus are the most common autoinflammatory and autoimmune disorders, but they may be variously classified.[22] Kawasaki disease is the most common miscellaneous diagnosis in developed countries.[22] Table 15.2 shows some discriminating features of infectious and noninfectious causes of FUO.[24–63] For infections, the agents, sites, and clinical manifestations are typical but are subtle and overlooked or are associated with an insidious or prolonged course.[1,23,64]

Box 15.3

Noninfectious Causes of Fever of Unknown Origin

Kawasaki disease

Autoimmune diseases

Autoinflammatory disorders

Inflammatory bowel disease

Malignancy

Drugs, other medicinal and nutritional products

Munchausen syndrome by proxy

Dysautonomia

Central thermoregulatory disorder

Diabetes insipidus

Anhidrotic ectodermal dysplasia

Hyperthyroidism

Hematoma in a closed space

Pulmonary embolus

TABLE 15.2

Discriminating Features of Infectious and Noninfectious Causes of Fever of Unknown Origin

Causes of Fever	Exposure or Condition	Features	Diagnostic Method
INFECTIOUS CAUSES			
Salmonella spp.[24–27]	Exposure to endemic pathogen; immigration; turtles and other animals; foods	High spiking fever; overlooked or mild abdominal pain	Culture blood, stool; culture bone marrow (especially if antibiotic given)
Bartonella henselae[9,28–31]	Kittens; healthy and immunocompromised people	Mild abdominal complaints, headache; lymphadenopathy usually absent; hepatic, splenic, or bone marrow granulomas	Serology; histology
Epstein-Barr virus[9,32]		Typhoidal course without classic mononucleosis symptoms or signs;	Serology; plasma PCR

		malaise; pneumonia	
Yersinia enterocolitica[33]	Animals, especially pigs; pork chitterlings	Abdominal pain; hepatic or splenic granulomas or abscesses; exanthems	Culture blood, stool, biopsy specimen; serology
Mycobacterium tuberculosis[34–36]	Exposure to symptomatic adults; endemic; immigration; HIV	Extrapulmonary, miliary, disseminated disease	Chest radiograph; tuberculin skin test or interferon-γ release assay; culture gastric aspirate, bone marrow, or biopsy specimen
Nontuberculous mycobacteria[37]	HIV, malignancy, cystic fibrosis; occasionally healthy toddlers	Respiratory or gastrointestinal symptoms; mediastinal lymphadenopathy	Culture gastric aspirate, blood, stool, mediastinal or enteric biopsy specimen; histology
Plasmodium spp.[22,24]	Exposure to mosquitoes in endemic areas; rare in United States from mosquitos or blood transfusions	Persistent (early) or remitting spiking fever, splenomegaly; anemia	Wright stain blood smears, rapid malaria antigen detection test
Brucella spp.[38,39]	Unpasteurized dairy products; farm animals	High spiking fever, arthralgia, hepatomegaly; elevated hepatic transaminases; Coombs-positive anemia	Serology
Coxiella burnetii[40]	Unpasteurized dairy products; aerosol from parturient cats	Fever persistent 5–10 days or relapsing over months; elevated levels of hepatic transaminases	Serology
Francisella tularemia	Ticks, fleas, mites, deer flies; airborne or direct contact with animals	Ulceroglandular, typhoidal, pleuropneumonia	Serology
Leptospira spp.	Rodents, domestic animals	Persistent or biphasic fever, aseptic meningitis; hepatitis	Serology
Leishmania	Exposure to endemic pathogen; immigration	Insidious onset (2–6 months); hepatosplenomegaly; Coombs-positive anemia	Giemsa or Wright stain biopsy or aspirate specimen; culture bone; serology
Rickettsia, Ehrlichia, Anaplasma[9]	Exposure to ticks in endemic areas	Absent or atypical rash; headache	Serology; PCR; Wright stain of blood or CSF (morulae of *Anaplasma, Ehrlichia*)
Neisseria meningitidis (chronic)		Petechial exanthema	Culture of blood
Toxocara canis, T. cati	Dog and cat feces; pica	Hepatosplenomegaly; eosinophilia; hypergammaglobulinemia	Serology
HIV	Sexual or vertical	Hepatosplenomegaly;	PCR; serology

	acquisition	mononucleosis syndrome; hypergammaglobulinemia	blood or saliva
Endocarditis	Congenital or acquired heart disease, central venous catheter; occasionally no underlying condition found	Splenomegaly, new heart murmur; immune complex exanthems; anemia; HACEK organism from blood culture; persistently positive blood culture	Blood culture; echocardiogram; consideration of uncultivatable pathogens
Intra-abdominal or retroperitoneal abscess[22,41–43]	Appendicitis; surgery; urinary tract infection; *Staphylococcus aureus* bloodstream infection	Localized pain or tenderness; elevated inflammatory markers; positive blood culture	Computed tomography
Pelvic or vertebral osteomyelitis		Localized pain or tenderness; elevated inflammatory markers; positive blood culture	Magnetic resonance imaging
Odontogenic infection[44]	Dental caries	Painful teeth, discomfort with chewing or biting on tongue depressor; lung abscess; submandibular or submental lymphadenopathy; swelling, tenderness of face or jaw	Dental radiography
Kikuchi-Fujimoto disease[45,46]		Regional or generalized lymphadenopathy; elevated inflammatory markers	Biopsy or histology
Inflammatory pseudotumor[47–49]	History of nonspecific illness (presumed host-controlled infection)	Insidious; malaise, weight loss, vague abdominal pain or tenderness; anemia; elevated inflammatory markers	Abdominal computed tomography; biopsy or histology
NONINFECTIOUS CAUSES			
Kawasaki disease (incomplete)[50,51]		Asynchronous or incomplete features Kawasaki disease; elevated inflammatory markers; thrombocytosis	Clinical constellation; echocardiogram
Juvenile idiopathic arthritis[16,52]	Familial, sporadic	Hepatosplenomegaly, lymphadenopathy, exanthem; anemia, elevated inflammatory markers	Clinical constellation
Systemic lupus erythematosus	Familial, sporadic	Malaise, weight loss; then multisystem involvement (kidneys, joints, skin)	Serum antinuclear antibody, anti–double-stranded DNA, anti–smooth muscle antibody
Hemophagocytic lymphohistiocytosis[53,54]	Virus associated; familial; rheumatologic disorder	Severe, rapidly progressive illness; hepatomegaly, lymphadenopathy, exanthem; cytopenias; extreme elevations of inflammatory markers	Ferritin, triglyceride levels, other diagnostic criteria; macrophage phagocytosis blood cells; natural killer

			cell, CD8$^+$ T lymphocyte dysfunction
Vasculitis syndromes	Familial, sporadic	Specific hallmarks (renal, neurologic, stomatitis or perianal ulcers, uveitis, pulmonary)	Clinical constellation; specific autoantibodies; biopsy or histology
Sarcoidosis[55]	Geography; race	Fatigue, weight loss, leg pain; anemia, elevated inflammatory markers; mediastinal lymphadenopathy; uveitis	Clinical constellation; biopsy or histology; soluble interleukin-2 receptor level
Inflammatory bowel disease	Familial; sporadic	Linear growth failure, subtle gastrointestinal symptoms or abdominal tenderness; perirectal skin tag; iron deficiency anemia; elevated inflammatory markers	Abdominal computed tomography; barium study
Lymphoreticular malignancy[22,56–59]		Weight loss, fatigue; nonarticular bone pain; lymphadenopathy; cytopenias	Bone marrow or tissue biopsy
Drug hypersensitivity[60]	Prescription or nonprescription drug exposure	Preserved sense of well-being; exanthems; eosinophilia; organ dysfunction (renal, cardiac, pulmonary)	Clinical constellation; withdrawal of drug
Factitious fever or Munchausen syndrome by proxy[61]	Predisposing parent-patient dynamic	Discordant temperature and vital signs; discordant parent-measured temperature and urine temperature; normal inflammatory markers	Clinical constellation; medical validation temperature
Hypothalamic dysfunction, diabetes insipidus, dysautonomia, or absent corpus callosum[62,63]	Underlying condition; genetic syndrome; anatomic abnormality	Normal inflammatory markers; hypernatremia; no response to nonsteroidal anti-inflammatory drugs	Clinical constellation; laboratory tests and imaging

CSF, Cerebrospinal fluid; HACEK, *Haemophilus*, *Aggregatibacter* (previously *Actinobacillus*), *Cardiobacterium*, *Eikenella*, and *Kingella* genera; HIV, human immunodeficiency virus; PCR, polymerase chain reaction.

Approach to the Workup

For those with FUO, careful reassessment of the history and physical examination findings often reveals diagnostic clues that should be pursued with targeted testing (see Table 15.2).[5,6,65] FUO is more likely an unusual presentation of a common disease than an uncommon disease.[66] The workup typically is done in phases, the pace of which is determined by the progression and severity of symptoms and laboratory test results. Screening tests are performed on all patients, and specific serologic tests are guided by exposure histories and examination findings. Serology for EBV and *B. henselae* typically are sent early in the workup in patients with compatible clinical presentations due to the high frequency of these diagnoses.[7,9,65]

A chest radiograph should be performed for all patients regardless of symptoms. Other imaging is obtained selectively based on symptoms, physical examination findings, and test results. Abdominal ultrasound usually is performed for patients with abdominal symptoms, with abnormal levels of serum hepatic enzymes, or in whom hepatosplenic cat-scratch disease is suspected, but it may also have diagnostic utility for patients without localizing symptoms.[7,9]

CT of the sinuses is viewed as an early study for patients with symptoms of sinusitis. Chest CT may be indicated when granulomatous or embolic disease is suspected. For 28 children with prolonged fever, an abdominal CT scan was abnormal for 86% of the children in whom clinical features directed suspicion to the abdomen; the yield of the procedure for others was low.[67] In another study of 109 children with FUO, multiple modalities, including radioisotope scans and bone marrow biopsies, rarely led to a diagnosis.[7] Performing imaging studies in the absence of signs or symptoms of involvement of an organ system usually is not helpful. A definite normal interpretation of imaging studies is unusual, and any abnormal finding often leads to further studies, which can divert focus from a correct diagnosis.

Fluorodeoxyglucose position-emission tomography (FDG-PET) was thought to be a useful early test for adults in the Netherlands and in one meta-analysis in 2011.[19,68] However, FDG-PET has not been adequately studied in children with FUO. In a rigorously conducted, prospective study of FUO in adults for whom no potentially diagnostic clues were gleaned from the history or physical examination, scintigraphy, other imaging modalities, liver or bone marrow biopsy, and screening for endocrine abnormalities were not revealing of pathology.[4] The investigators recommended repeating a thorough history, physical examination, and first-level laboratory tests and waiting for diagnostic clues to appear.[4] This approach also is appropriate for children unless there is progression of weight loss or an abnormality found on examination or simple screening tests.

Prolonged Insignificant Fever, Prolonged Illness With Resolved Fever, and Fatigue of Deconditioning

One of the most frequent referrals to pediatric infectious disease subspecialists for prolonged fever is an adolescent with low-grade or falsely perceived fever or one whose fever has resolved but feels unwell and is unable to attend school and social activities. These patients require the same disciplined performance of history and examination as those with true FUO. For the subspecialist to offer a definitive opinion, the family must perceive that a thorough and thoughtful consultation has occurred. All laboratory test results, imaging studies, and biopsy slides should be reviewed. The findings listed in Box 15.4, evaluation of complaints, review of systems, and laboratory studies must suggest that no cryptogenic infection or serious medical condition is present.[1]

Box 15.4

Typical Findings for Patients With Fatigue of Deconditioning

Age older than 12 years

High level of achievement before illness

Family expectations high

Acute febrile illness with onset easily dated

Family and outside attention high

Multiple but vague complaints

Odd complaints of brief duration (<1 minute) (e.g., shooting pains at multiple sites; blindness; stereotypic, sporadic, unilateral tremors, jerks, or paralysis)

Tiredness but no daytime sleep or reversal of daytime and nighttime sleep

Model of chronic illness in family, recent loss of important person, change in family dynamic

Unusual cooperation and interest during interview and examination or unusual fearfulness and dependency on parent

Preserved or increased weight

Normal physical and neurologic examination findings

Normal results of screening laboratory tests

Discordance of a lengthy list of complaints with the normal findings of examination and laboratory tests is typical. The family's modus operandi centers on the patient. Prodded recitation of a typical 24-hour period of activity reveals a feeling of tiredness but no prolongation of time asleep. There is frequently a parental model of chronic illness or a recent change in extended-family dynamics (e.g., divorce, serious medical diagnosis, death). Deconditioning (i.e., diminution of physical strength, stamina, and vitality), loss of self-esteem, fear of failure to perform at the level of previous expectations, and secondary gain may contribute to the clinical state. The patient should be queried privately about potential abuse and for other informative insights.

Depression should be considered. Clues in depressed individuals include a feeling of persistent sadness, lack of self-worth, dislike of or wanting to hurt oneself, anger, marginalization, and a feeling of being disliked by others.[69] Fatigued individuals usually do not have these feelings, but they instead have increased somatic complaints and a tendency to internalize stress.[70]

In the past decade, neurally mediated hypotension and postural tachycardia have been postulated as mechanisms of persistent fatigue. Two studies of adults published in 2005 suggest that orthostatic instability is a common finding in healthy and fatigued individuals[71] and that among military recruits with orthostatic intolerance, endurance exercise training significantly improved the physiologic findings and symptoms.[72] In a formal study of 14 adolescents with orthostatic hypotension, symptoms and findings were attenuated by use of a static hand grip[73] (see Chapter 200).

Management of fatigue of deconditioning begins with a precise review of findings and conclusions about what the diagnosis is and is not.[1] Management is outlined in Box 15.5. It is a disservice to diagnose chronic fatigue syndrome, support home tutoring, or refer the patient to additional subspecialists for minor findings. The primary care pediatrician should set the tempo for reconditioning and monitoring. A personal fitness trainer may introduce a new positive relationship with the patient that separates the patient effectively from illness-enabling family dynamics.

Box 15.5

Management of the Patient With Fatigue of Deconditioning

Patient

- Validate symptoms as accurate.
- Explain that there is no serious disease.
- Prescribe incremental, forced return to school.
- Prescribe exercise.
- Predict increased symptoms in the process of reconditioning.
- Disallow school absence without examination that day by primary care provider.
- Reassure that there will be no expectation of achievement from performance.

Family

- Validate their concerns.
- Explain that symptoms could have been clues to serious conditions.

- Validate their medical pursuit.
- Describe organ-based normal findings in history, examination, and screening laboratory tests.
- Advise change of family focus from illness to health.
- Advise family to avoid asking, “How do you feel?”
- Elicit promise to patient of no expectation of achievement or performance.

Primary Physician

- Set the pace of reconditioning and monitoring.
- Continue to perform examination to ensure normal findings.

Recurrent Fever and Periodic Fever Syndromes

Recurrent Fever

When a history is carefully obtained, most children who are referred to subspecialists for recurrent fever have multiple self-limited infections. Healthy children 2 to 3 years of age can have up to 10 self-limited illnesses per year, and children who attend childcare can have more.

In the absence of respiratory tract symptoms, fever that abates repeatedly during antibiotic therapy occasionally can result from endocarditis, renal infection, central nervous system ventricular shunt infection, or pneumonia in predisposed hosts. Relapsing infections such as *Borrelia recurrentis, Brucella,* and malaria are unusual or rare causes of recurring fevers distinguished by their unique exposures.[74] Autoimmune disorders and certain autoinflammatory disorders with prominent adaptive immune involvement (e.g., inflammatory bowel disease, systemic-onset juvenile rheumatoid arthritis) can also manifest with recurrent fever.[75] Fig. 15.2 shows an approach to analyzing patients with recurrent fever.

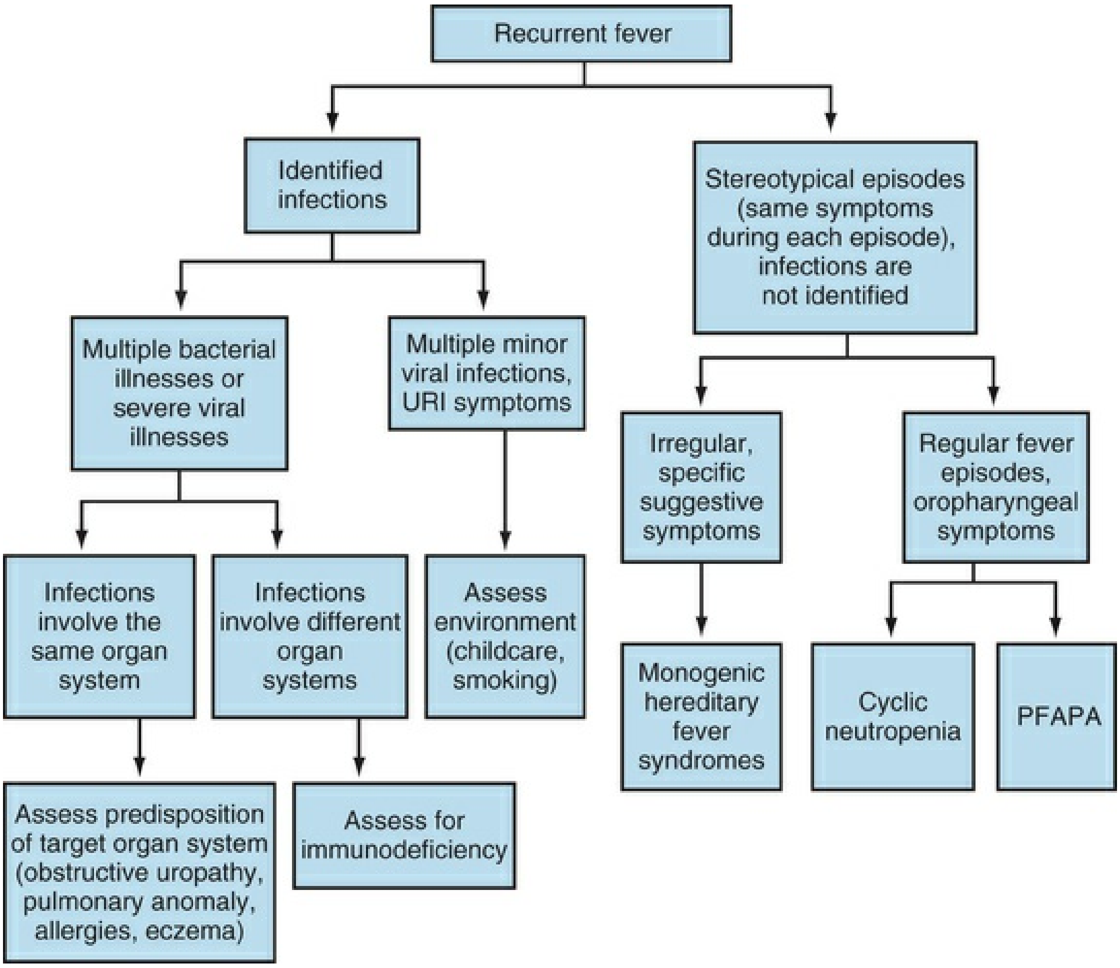
Recurrent fever
Identified infections
Stereotypical episodes (same symptoms during each episode), infections are not identified
Multiple bacterial illnesses or severe viral illnesses
Multiple minor viral infections, URI symptoms
Irregular, specific suggestive symptoms
Regular fever episodes, oropharyngeal symptoms
Infections involve the same organ system
Infections involve different organ systems
Assess environment (childcare, smoking)
Monogenic hereditary fever syndromes
Cyclic neutropenia
PFAPA
Assess predisposition of target organ system (obstructive uropathy, pulmonary anomaly, allergies, eczema)
Assess for immunodeficiency

FIGURE 15.2 Approach to recurrent fever. *PFAPA*, Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis; *URI*, upper respiratory tract infection. (Data from Long SS. Distinguishing among prolonged, recurrent, and periodic fever syndromes: approach of a pediatric infectious disease subspecialist. Pediatr Clin North Am 2005;52:811–835; Marshall GS. Prolonged and recurrent fevers in children. J Infect 2014;68:S83–S93.)

Periodic Fever

Periodic fever refers to recurring episodes of illness in which fever is the cardinal feature, episodes have a predictable symptom complex and duration, and episodes are separated by symptom-free intervals. Some syndromes are characterized by clockwork periodicity (i.e., multiple recurrences with the same episode duration and same interval between episodes), whereas others have irregular episode timing. Features of several periodic fever syndromes are shown in Table 15.3. Those with identified causative gene mutations are called *hereditary periodic fever syndromes*.

TABLE 15.3

Differentiating Features of Periodic Fever Syndromes

Feature	**PFAPA**	**Cyclic Neutropenia**	**FMF**	**MVK Deficiency**	**TRAPS**
OMIM identifier	—	162800	249100	260920	142680
Usual inheritance pattern	Not identified	Autosomal dominant	Autosomal recessive	Autosomal recessive	Autosoma dominant
Genetic locus/gene	—	19p13/*ELANE*	16p13/*MEFV*	12q24/*MVK*	12q13/*TN*
Protein	—	Neutrophil elastase	Pyrin/marenostrin	Mevalonate kinase	TNFR1
Onset <5 years	Usual	Usual; often <1 year old	Common; peak onset middle of first decade	Expected; median 6 months	Variable; form <1 y
Length of fever episode	3–4 days	5–7 days	1–3 days	4–7 days	7–21 days
Periodicity of episodes	q3–6 wk (mean, 28 days)	q14–28d (most, 21 days)	Irregular intervals: weeks, months, or occasionally years	q4–8 wk or irregular intervals; immunization trigger	Irregular intervals: to years
Associated symptoms and signs	Pharyngitis, aphthous stomatitis, cervical adenopathy, headache (each in more than two-thirds of cases); abdominal pain, nausea, vomiting (each in about one-	Ulcers, gingivitis, periodontitis; otitis media, sinusitis, cellulitis; rare peritonitis; rare gram-negative bacillary or *Clostridial* septicemia	Polyserositis; erysipelas-like rash; scrotal pain and swelling	Lymphadenopathy, headache, chills, abdominal pain, vomiting, diarrhea; arthralgia; small macules, papules, nodules, especially on extremities; splenomegaly	Migratory myalgia a pseudocel conjunctiv periorbita edema

	third)				
Laboratory findings	Mild neutrophilia, elevated acute phase reactants	Absolute neutrophil count <200 cells/mm^3 for 3–5 days in cycle (just before fever)	Elevated acute phase response	Elevated acute phase response; variable decreased serum cholesterol and elevated IgA and IgD	Elevated a phase resp
Treatment	Cimetidine	Recombinant G-CSF; aggressive periodontal care; aggressive treatment of suspected septicemia	Colchicine	Anti–IL-1	Anti-TNF
	Corticosteroids			Anti-TNF	Anti-IL-1
	Tonsillectomy			Corticosteroids	

CAPS, Cryopyrin-associated periodic syndrome; FCAS, familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; G-CSF, granulocyte colony-stimulating factor; Ig, immunoglobulin; IL-1, interleukin-1; MVK, mevalonate kinase; MWS, Muckle-Wells syndrome; NOMID, neonatal-onset multisystemic inflammatory disease syndrome; OMIM, Online Mendelian Inheritance in Man database; PFAPA, periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis; TNF, tumor necrosis factor; TNFR1, tumor necrosis factor-α receptor 1; TRAPS, tumor necrosis factor receptor–associated periodic fever syndrome.

The term *autoinflammatory syndrome* was used in the late 1990s to describe a group of systemic inflammatory diseases distinct from infectious, autoimmune, allergic, and immunodeficiency-associated diseases.[76,77] Unlike autoimmune disorders that involve adaptive immune pathways (i.e., development of autoantibodies and activation of T lymphocytes), autoinflammatory diseases result from dysregulation of innate immune signaling. Patients have seemingly unprovoked episodes of systemic or localized inflammation. In addition to the hereditary periodic fever syndromes, Crohn disease; chronic, recurrent, multifocal osteomyelitis; and Behçet disease are considered autoinflammatory diseases,[78] and some also include periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome.[75]

Autoinflammatory conditions known to result from gene mutations are registered in the Online Mendelian Inheritance in Man (OMIM) database (http://www.ncbi.nlm.nih.gov/sites/entrez?db=OMIM).[79] Diagnostic genetic testing for hereditary autoinflammatory diseases is available commercially (http://www.genedx.com or http://www.aruplab.com). Sequence variants involved in hereditary fever syndromes are collected in the

Infevers database (http://fmf.igh.cnrs.fr/infevers),[80,81] which was established in 2002 and expanded in 2009 to an international Eurofever Registry (http://www.printo.it/eurofever/) that includes 67 centers in 31 countries.

In a European study of 228 patients with a history of periodic fever, genetic screening was performed to detect mutations in *MVK, TNFRSF1A,* and *MEFV* genes.[82] The diagnostic Gaslini score was developed by comparing clinical features of mutation-positive and -negative patients. The Gaslini score can be calculated using an online tool (https://www.printo.it/periodicfever/index.asp). Younger age at onset, family history of periodic fever, abdominal pain, thoracic pain, diarrhea, and lack of aphthous stomatitis were significantly associated with identification of gene defects and are used in the Gaslini score.[82]

Clinical syndromic classification is useful (see Table 15.3). PFAPA is by far the most commonly encountered periodic fever syndrome. The likelihood of seeing a patient with a hereditary periodic fever syndrome among those with presumed PFAPA is small (<5% in practice) but can be higher depending on the patient population served and referral patterns.[83–86] In an Italian study of 210 children who met the diagnostic criteria for PFAPA syndrome, 43 children had diagnostic mutations (*MVK,* 33; *TNFRSFIA,* 3; *MEFV,* 7).[87] Mutation-positive patients had a significantly higher frequency of abdominal pain, vomiting, diarrhea, rash, and arthralgia, whereas mutation-negative patients had higher rates of exudative pharyngitis.[87] In this population, the Gaslini score correctly identified 91% of patients with a mutation.

We perform genetic testing for hereditary autoinflammatory diseases for any of the following: onset in patients younger than 6 months or older than10 years of age, prolonged episode duration (>7 days), highly irregular episode timing and durations, positive family history for recurrent fever, migratory rash, arthritis, prominent arthralgia, prominent abdominal pain, or substantial vomiting or diarrhea with episodes. We evaluate for cyclic neutropenia with serial complete blood cell counts or genetic testing in patients with suggestive clinical clues (e.g., gingivitis, minor recurring infections such as cellulitis or otitis media, invasive infections) or laboratory clues (e.g., low absolute neutrophil count during an episode). Because hereditary autoinflammatory diseases have symptom complexes that evolve with age, continued follow-up of children with a diagnosis of PFAPA is important.

The goals of diagnosing hereditary periodic fever syndromes are to intervene to relieve symptoms and to prevent amyloidosis and renal failure. These complications are not seen with PFAPA.

In addition to the periodic fever syndromes discussed in this chapter, several other hereditary autoinflammatory syndromes have been described. Some have significant bone and joint involvement, including pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome, Majeed syndrome, and deficiency of the interleukin-1β (IL-1β) receptor antagonist (DIRA). Many patients with periodic fever do not conform phenotypically to described syndromes and do not have identified causal mutations.[75]

Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Cervical Adenitis

Epidemiology and Cardinal Clinical Features

PFAPA was first described in 1987 in 12 children from Tennessee and Alabama.[83] More than 700 cases from many continents and racial backgrounds have been reported; undoubtedly, exponentially more cases go unreported or undiagnosed. PFAPA is the most common periodic fever syndrome in children.[21] Between 6% and 10% of patients report a family history of PFAPA,[84,88] but the family history of recurrent fevers or PFAPA-like illnesses can be as high as 45% to 60%.[89,90]

The numerous reported familial cases suggest that affected patients may have predisposing genetic factors.[91–94] Studies investigating polymorphisms in inflammasome-related genes have been small and have not shown a consistently higher prevalence of polymorphisms in affected individuals.[89,95,96] However, PFAPA patients with mutations in *MEFV* have shorter episode duration and more irregularity in episode timing compared with those without the mutations.[97,98] During flares, patients with PFAPA have heightened expression of complement, IL-1β– and IL-18–related genes, and interferon-induced genes compared with asymptomatic periods in PFAPA patients and healthy controls.[89,99] Multiple studies attempting to identify a causative infectious pathogen in

PFAPA have had negative results.

The original diagnostic criteria for PFAPA included five features: regularly recurring fevers (>38.3°C), usually with an early age of onset; constitutional symptoms in the absence of upper respiratory tract infection with at least one symptom being aphthous stomatitis, cervical adenitis, or pharyngitis; exclusion of cyclic neutropenia and other intermittent fever syndromes on the basis of history or laboratory test results; asymptomatic intervals between episodes; and normal growth and development.

Table 15.4 shows features of PFAPA patients followed through a Nashville registry.[84] There are no recognizable triggers for episodes, but many patients have fatigue or irritability a few hours before fever onset. Abrupt onset of fever greater than 39°C, which persists at that level for most of the duration of the episode, is a cardinal feature. Respiratory symptoms are absent. Typically, mouth ulcers are small, shallow, scattered or solitary, and frequently noticed in episodes only after questioning. Pharyngitis usually includes tonsils that are moderately enlarged and erythematous and sometimes have exudate.[85,87,100] Cervical lymph nodes are tender and increase in size bilaterally with episodes but are not erythematous or larger than 3 to 4 cm. Patients frequently also have myalgia, arthralgia, abdominal pain, and headache during episodes.[84,101]

TABLE 15.4

Characteristics at Diagnosis of Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Cervical Adenopathy

Demographic and Clinical Features	**Mean (Range)**	**Signs and Symptoms During Episodes**[a]	**Percentage of Patients**
Male-to-female ratio	1.2	Fever + >1 cardinal feature	97
Onset of PFAPA	2.8 years (2.4–3.3 years)[b]	Cervical lymphadenopathy	77
Maximum temperatures	40.5°C (40.4–40.6°C)	Aphthous stomatitis	67
Duration of fever	3.8 days (3.5–4.1 days)	Pharyngitis	65
Duration of episode	4.8 days (4.5–5.1 days)	Chills	80
Episodes/year	11.5 (10.5–12.5)	Headache	65
Wellness interval	28.2 days (26.0–30.4 days)	Nausea	52
Mean white blood cell count at episode	13,000/mm^3 (2–37 × 10^3)	Abdominal pain	45
Mean erythrocyte	41 mm/hour (5–190	Diarrhea	30

sedimentation rate at episode	mm/hour)		
		Coryza	18
		Rash	15

[a]Although 94 children were included in the original registry, parents did not always answer all queries (frequently citing inability to assess because of age).

[b]Mean (95% confidence interval).

PFAPA, Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenopathy.

Modified from Thomas KT, Feder HM, Lawton AR, et al. Periodic fever syndrome in children. J Pediatr 1999;135:15–21.

Clockwork periodicity of episodes is typical of the syndrome. However, alternating periods of remission and relapses have been seen in some patients, and the natural history of the disease is that episode frequency declines over time.[88,102] Descriptions of the syndrome are similar across countries and have not changed over 2 decades.[83,88,103–105]

Absent or minimal response to acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), or antibiotics is typical of PFAPA. One or two doses of a corticosteroid abruptly abort an episode. This response sometimes is used as a diagnostic test, but it must be interpreted in the context of the patient's clinical features because patients with mevalonic kinase deficiency (formerly hyperimmunoglobulinemia D syndrome), tumor necrosis factor receptor–associated periodic fever syndrome (TRAPS), and many infectious diseases can have similar responses to corticosteroids.[106] Children with PFAPA are completely well and fully energetic between episodes and grow and gain milestones normally.

Episodes usually begin at 2 to 3 years of age.[83,103] However, 10% of patients have episode onset after 5 years of age.[101] In Israel, 14 adults were reported to have PFAPA-like conditions starting in adolescence or early adulthood; all responded to a single dose of prednisone.[107]

Treatment and Outcome

The longest follow-up study of PFAPA reported the outcomes of 60 children followed for 12 to 21 years.[88] In this study, 85% had complete resolution of PFAPA episodes (mean duration, 6.3 years). Lengthening of the intervals between fevers frequently preceded resolution of PFAPA in these patients. The remainder (15%) continued to have persistent PFAPA episodes for a mean duration of 18 years (range, 14 to 25 years). In those with persistent fever, the duration of fever declined from 3.6 to 1.8 days and symptom-free intervals increased from 29 to 159 days over time.

Patients with PFAPA usually do not develop other diagnoses or long-term serious consequences of the illness. Of the 60 patients described, 1 patient was diagnosed with Behçet disease and another with familial Mediterranean fever.[88] More than one-third of patients had recurrent aphthous stomatitis, often after cessation of fever episodes. With time, episodes of PFAPA typically retain the same symptoms as at diagnosis. Families should be questioned at follow-up about development of additional features. If they are reported, the diagnosis should be reconsidered.

When given daily as prophylaxis, cimetidine therapy is associated with resolution or amelioration of fever attacks in approximately one-third of patients.[84] Prednisone can be given in a dose of 1 to 2 mg/kg and characteristically aborts an attack of PFAPA within 2 to 12 hours[84,88,103]; 18% of patients may need a second dose.[103] In a single medical center's experience, a lower dose of prednisone (mean, 0.6 mg/kg per day) also was effective.[102] Corticosteroid use may lead to increased frequency of episodes in 7% to 50% of patients,[84,88,102,103] and frequent, repeated use can have detrimental side effects.

Tonsillectomy was first found to be curative in patients with PFAPA in 1989.[108] In a 2011 systematic review of tonsillectomy for PFAPA, 15 studies were identified involving a total of 149 children.[109] Thirteen of the studies were observational and noncomparative, and two were prospective, randomized, controlled trials (RCTs).[110,111] Comparisons of these studies were limited by variations in diagnostic criteria for PFAPA, type of surgical procedure performed (i.e., tonsillectomy with or without adenoidectomy), and duration of follow-up. For all studies combined, 83% (95% confidence interval [CI], 77%–89%) of patients had resolution of episodes after surgery. The odds ratio for complete resolution after surgery in the two RCTs was 13 (95% CI, 4–43).[109] Another study from a single U.S. center reported that 99 of 102 patients who underwent tonsillectomy for PFAPA had complete resolution of fever episodes when followed for an average of 43 months.[112]

Anakinra and colchicine have been used in patients with PFAPA.

In an Israeli study, 9 patients with frequent episodes (≤14 days apart) were given daily colchicine prophylaxis. The patients had an increase in the average interval between episodes (1.7 to 8.4 weeks).[113] Anakinra, an IL-1β receptor antagonist, was shown in a small group of patients to abort fever episodes, but some patients needed multiple doses during each episode to achieve fever control.[99]

We discuss these options with parents at the time of diagnosis, assess with them the degree to which the episodes interfere with the child's and family's quality of life, recommend commencement of a diary to accrue a history of episodes, and attempt medical management before a surgical decision is made. With this approach, some patients do not have PFAPA-fulfilling courses, many families are comfortable with following the natural history, and a few evolve to symptoms of a hereditary autoinflammatory disease.

Cyclic Neutropenia

Epidemiology and Etiology

Cyclic neutropenia is an autosomal dominantly inherited hematologic disorder, not an autoinflammatory disorder, characterized by regular cycling of the peripheral blood neutrophil count to a nadir of less than 500 cells/mm^3 (usually <200 cells/mm^3) and a symptom complex manifesting during the neutrophil nadir. Most patients with cyclic neutropenia have mutations in the *ELANE* gene (formerly called *ELA2)*, which encodes neutrophil elastase. Many patients with severe congenital neutropenia also have mutations in *ELANE.*[114,115] In some cases, particular mutations are associated with cyclic neutropenia, but others are associated with congenital neutropenia; however, individuals with both disorders have been reported to have the same mutation.[116] The favored hypothesis is that mutations in neutrophil elastase (i.e., protease) lead to destabilization of a proteoglycan, which induces unfolding and increases the transcription of endoplasmic reticulum–associated protein degradation and proapoptotic genes that ultimately lead to neutrophil apoptosis in bone marrow.[117]

Cardinal Clinical Features

The diagnosis of cyclic neutropenia usually is established in infancy.[118] Cardinal features are recurrent fever with clockwork periodicity (typically a 21-day cycle), pharyngitis, mouth ulcers, and lymphadenopathy. Untreated individuals often have oropharyngeal inflammation, including gingivitis, periodontitis, and tooth abscesses, which often persist into the second week after a fever episode. Periodontal disease can lead to deciduous tooth loss in childhood. Mouth ulcers are deep and painful. Recurrent bacterial infections, such as cellulitis (especially at sites of minor trauma), otitis media, sinusitis, and pharyngitis, differentiate cyclic neutropenia from the periodic autoinflammatory syndromes. Some patients have few or relatively minor bacterial infections, whereas others can have spontaneous bacterial peritonitis, overwhelming gram-negative or *Clostridium* septicemia, or septic shock resulting from ileocolonic ulceration during neutropenic episodes. Although oral manifestations may linger, these children usually are well between episodes.

During the neutropenic period, peripheral blood neutrophils characteristically fall to less than 200 cells/mm^3 for 3 to 7 days.[119] The absolute neutrophil count then rises and remains at approximately 2000 cells/mm^3. At the time that clinical symptoms of fever appear, neutropenia may be resolving, typically with immature myelocytic cells found in peripheral blood. Monocyte counts may cycle in the opposite direction of neutrophils. Children with clockwork periodicity of fevers plus any familial or clinical features (as previously described) compatible with cyclic neutropenia should have complete blood cell counts performed two or three times weekly during the interval of wellness and continuing through the next febrile episode. Alternatively or additionally, genetic testing for *ELANE* mutations can be performed. Although the inheritance pattern is autosomal dominant, manifestations can be mild, and parental inheritance may be unrecognized. Severity of symptoms declines with age.[119]

Course, Treatment, and Outcome

Granulocyte colony-stimulating factor (G-CSF) administered subcutaneously daily is effective treatment for cyclic neutropenia. G-CSF is thought to affect intracellular signaling and stimulate neutrophil production. Doses are titrated to achieve an absolute neutrophil count of 1500 cells/mm or higher.[115]

Familial Mediterranean Fever

Epidemiology and Etiology

Familial Mediterranean fever (FMF) is the most common hereditary periodic fever syndrome. In 1997, mutations in a single gene *(MEFV)* on the short arm of chromosome 16 were implicated as the cause of FMF.[120,121] *MEFV* encodes a protein product called *pyrin* (from the Greek *pyrus* ["fever"]). Pyrin is a member of the death domain superfamily, which is part of critical pathways of apoptosis and innate immunity. There is general consensus that through complex intracellular mechanisms, pyrin plays a role in modulating caspase 1 activity and subsequent IL-1β release.[122] Particular ethnic groups, including Sephardic and Ashkenazi Jewish, Middle Eastern Arab, Armenian, Italian, North African, and Turkish populations, have a high carrier frequency of MEFV mutations (up to one in three people).[123] FMF is more prevalent but not exclusively found in these populations.

More than 50 disease-associated mutations have been identified, and most are nucleotide substitutions in exon 10. FMF is considered to have autosomal recessive inheritance, but in an Israeli population, as many as 30% of patients with clinical symptoms of FMF were heterozygous for *MEFV* mutations, and 28% had no mutation in *MEFV*.[124] M694V is the most commonly identified mutation and is associated with young age at episode onset, a severe course, and a high risk of amyloidosis.[124] Other common pathogenic mutations include M694I, M680I, and V726A.

Cardinal Clinical Features

FMF flares are characterized by short episode duration (lasting 12 to 72 hours) and typical painful symptoms, including serositis involving the synovia, pleura, or peritoneum. Approximately 90% of patients have recurring abdominal pain, and 40% have thoracic pain.[125] Many patients have an erysipelas-like rash. Disease onset occurs before 10 years of age in 25% to 60% of cases and before 20 years of age in 64% to 90% of cases. The mean delay in diagnosis is 7 years.[125]

Episodes typically do not have clockwork periodicity with weeks to years between episodes and can be triggered by stress or minor trauma. Abdominal pain (i.e., sterile peritonitis) ranges from mild and localized to severe and diffuse with abdominal rigidity, which may be mistaken for appendicitis. Well-demarcated erysipelas-like lesions are distinctly associated with FMF and typically develop bilaterally or unilaterally below the knees anterior to the dorsum of the feet.[126] Histologic examination reveals dermal infiltration of neutrophils. Children also may exhibit purpuric lesions of the face, trunk, and extremities.[127] Arthritis usually is monoarticular, involving the knee, ankles, or hips; synovial fluid pleocytosis is neutrophilic. Children are well between episodes.

Course, Treatment, and Outcome

The most serious complication of FMF is amyloidosis. Serum amyloid A is an acute phase reactant that can deposit in many organs, including the kidney, leading to organ failure. Before colchicine therapy, end-stage renal disease occurred in many FMF patients by the age of 40 years. Oral colchicine is the treatment of choice for children and adults, reducing the frequency and severity of attacks and the risk of amyloidosis.[128]

Pyrin interacts with tubulin and colocalizes with microtubules, suggesting a rationale for the high efficacy of colchicine, a microtubular-destabilizing agent.[129] In those who cannot tolerate colchicine, IL-1β blockade with anakinra, an IL-1β receptor antagonist; canakinumab, and anti–IL-1β monoclonal antibody; or rilonacept, a fusion protein targeting IL-1β has been beneficial.[130]

Mevalonate Kinase Deficiency

Epidemiology and Etiology

Hyperimmunoglobinemia D and periodic fever syndrome (HIDS) was first described in several Dutch patients in 1984.[131] In 1999, the causative *MVK* gene was localized on the long arm of chromosome 12.[132,133] *MVK* encodes the enzyme mevalonate kinase (MVK), and MVK deficiency is a more accurate name for the condition; additionally, not all patients have elevated levels of IgD. The HIDS registry in the Netherlands has data on more than 200 patients worldwide. Although most patients are from northern Europe, some have been from the Mediterranean basin and Asia.[125]

MVK deficiency is an autosomal recessively inherited disorder. More than 35 pathogenic mutations have been reported. Most patients are compound heterozygotes for missense mutations, resulting in residual *MVK* activity that is 1% to 8% of normal. Mutations in *MVK* also are responsible for mevalonic aciduria, in which mutations cluster around the active sites of the enzyme and result in total absence of enzyme activity and a catastrophic disease characterized by dysmorphic features, failure to thrive, mental retardation, ataxia, recurrent fever attacks, and death in early childhood. Rare patients with MVK deficiency have neurologic signs, suggesting that these may be overlapping syndromes.[134]

MVK is an essential enzyme in the isoprenoid biosynthesis pathway and cholesterol cascade. The pathogenic mechanisms leading to autoinflammatory disease are not well understood. Lack of isoprenoids, which are metabolic products downstream from MVK, rather than an excess of mevalonate leads to caspase 1 activation, which cleaves pro–IL-1β to its active form.[135] Stimuli such as infection or vaccination that activate the inflammasome to produce pro–IL-1β also trigger episodes.

Cardinal Clinical Features

Clinical features and longterm follow-up of 103 patients from 18 different countries from the HIDS registry have been reported.[136] The median age of the first attack was 6 months (range, 0–120 months), and almost 70% of patients had their first attack before the age of 12 months. The median time from disease onset to diagnosis was 9.9 years.

A typical attack starts with prodromal symptoms such as malaise and headache, followed by a rapid rise in temperature (often >40°C), chills, enlargement of and pain in cervical lymph nodes, abdominal pain, vomiting diarrhea, and arthralgia of large peripheral joints (with arthritis in 50%). Skin lesions occur during attacks in more than two-thirds of patients. Although small macules, papules, and nodules are the usual exanthem, urticaria, purpura, and erythema nodosum have been reported.[126,137] Histology of lesions ranges from mild vasculitis to dense dermal infiltrate of neutrophils.[127] Oral aphthous ulcers with or without genital ulcers are reported in almost one-half of patients.[136] One-third to one-half of patients have splenomegaly during attacks.[127,136]

In the HIDS registry, childhood vaccinations induced the first attack in two-thirds of patients.[125] Injury, physical exercise, or emotional stress can also trigger attacks.[127] MVK deficiency and PFAPA have similar episode frequency and duration, and patients are well between episodes. Differentiating features of MVK deficiency, such as severe headache, gastrointestinal complaints, rash, genital ulceration, and arthralgia, can evolve years after the onset of febrile episodes. Almost one-fourth of patients with MVK deficiency report decreases in episode duration and severity in response to brief corticosteroid use, making differentiation from infections or PFAPA problematic.[136]

Although the original disease name suggests that patients have elevated serum IgD levels, 22% of patients have normal IgD levels,[136] especially children younger than 3 years of age.[138] Most patients with elevated IgD levels and no *MVK* mutation have no definite diagnosis.[139] Elevated IgA levels have been reported for 64% of MVK-deficient patients.[140] Mevalonic acid concentrations in urine are elevated during febrile episodes, but testing is not readily available. Genetic testing for *MVK* mutations is the best confirmatory test, and V377I and I268T are the most commonly identified mutations. However, some patients with typical symptoms are heterozygotes with only one identified mutation.

Course, Treatment, and Outcome

Patients have decreasing frequency of attacks with age; 44% had more than 12 attacks per year in their first decade of life, 30% in their second decade, and 18% in their 20s.[136] Amyloidosis occurred in 3 (3%) of 103 patients in the HIDS registry, and all of these patients had episodes for more than 20 years before manifesting amyloidosis. Abdominal adhesions and joint contractures also were reported.

Statin therapy has had mixed results. In the Eurofever registry, NSAIDs were frequently used, with 64% of patients having partial responses and 13% having complete responses.[130,141] Corticosteroids reduced the severity and duration of episodes (i.e., 24% had complete responses, and 67% had partial responses).[141] Anakinra resulted in at least partial remission in 89% of patients, whereas etanercept, a tumor necrosis factor-α (TNF-α) receptor fusion protein, was efficacious in 65% of patients.[141]

Tumor Necrosis Factor Receptor–Associated Periodic Fever Syndrome

Epidemiology and Etiology

In 1982, a large Irish family with recurrent episodes of fever, myalgia and rash was described and this fever syndrome was called familial Hibernian fever.[142] This syndrome is now referred to as tumor necrosis factor receptor–associated periodic fever syndrome (TRAPS). Since the original description, cases have been reported in a wide range of ethnic groups, including people of African American, Mexican, Mediterranean, and European origin.[143] TRAPS is an autosomal dominant disease with variable penetrance.

In 1998, linkage studies placed the susceptibility locus in chromosome 12,[76,144] and within a year, mutations in the *TNFRSF1A* gene were determined to be causative.[145] The exact pathophysiology of TRAPS remains unclear. *TNFRSF1A* encodes the TNF-α receptor 1 protein (TNFR1). TNF-α binds and stimulates TNFR1, which recruits several proteins to form a complex that ultimately activates nuclear factor-κB (NF-κB) and the apoptosis pathway. Some mutations in TNFR1 impair metalloprotease cleavage of the receptor, leading to defective shedding at the cell surface. The soluble receptor acts as a decoy for TNF-α, and lack of receptor shedding in TRAPS leads to proinflammatory signals. In other patients, the mutant TNFR1 is unable to traffic appropriately from the endoplasmic reticulum to the cell surface. Mutant TNFR1 also may result in prolonged survival of inflammatory cells through impaired TNF-mediated apoptosis.[146]

Cardinal Clinical Features

TRAPS is characterized by recurrent attacks of fever, migratory myalgia, tender erythematous plaques, abdominal pain, and periorbital edema or other ocular complaints due to conjunctivitis, uveitis, or iritis.[75,143] Chest pain due to pleuritis or pericarditis and mouth ulcers occur in less than 20% of patients. Ocular manifestations and migrating myalgias are distinguishing features of TRAPS.[143] Disease manifestations also can be milder and vary among family members.

Almost two-thirds of patients develop distinctive cutaneous lesions of localized erythematous macules or patches.[126,137] Lesions appear to undergo a set progression from solitary or grouped macules and papules to lesions that expand and coalesce, resulting in annular and serpiginous patches and plaques that migrate distally. Skin lesions overlie areas of myalgia.[127,137] A third of cutaneous lesions resolve with an ecchymotic appearance. Microscopy of skin lesions reveals superficial and deep perivascular infiltrates of lymphocytes and monocytes.[127]

Compared with other periodic fever syndromes, TRAPS flares are longer, typically lasting 7 to 21 days. Injury, immunizations, and stress can trigger episodes. In one study, the mean age at onset was 18 months for severe TRAPS and 58 months for mild TRAPS.[147]

Course, Treatment, and Outcome

The most severe complication of TRAPS is amyloidosis, occurring in 8% to 10% of patients.[127,143] In the Eurofever registry, etanercept, which binds serum TNF-α and prevents its engagement with the cell surface TNFR1, had some benefit in 86% patients, but only 30% had complete remission, and the response can decrease with time.[141,146] Anakinra produced complete remission in 79% of patients, which supports its increasing use as a first-line agent.[141,147,148] For some patients, treatment with infliximab, which is a monoclonal antibody that binds TNF-α, led to worsening of symptoms.[149]

Cryopyrin-Associated Periodic Syndrome

Epidemiology and Etiology

Cryopyrin-associated periodic syndrome (CAPS) includes three disorders: familial cold autoinflammatory syndrome (FCAS), previously called familial cold urticarial (FCU) syndrome; Muckle-Wells syndrome (MWS); and neonatal-onset multisystemic inflammatory disease syndrome (NOMID), also known as chronic infantile neurologic, cutaneous, and articular (CINCA) syndrome. These three syndromes represent a spectrum of disorders that share characteristics of episodic fever, urticaria-like rash, and joint involvement. FCAS is considered the mildest, MWS is intermediary, and NOMID is the most severe.[127,146,150] These syndromes have autosomal dominant inheritance patterns, but many de novo cases have been reported, particularly of NOMID.[151] Although most reported cases are from the United States and Europe (predominantly northern Europe), patients from other regions, including the Mediterranean, have been described.[152]

Linkage studies placed the susceptibility locus for MWS and FCAS on chromosome 1, and mutations were identified in the cold-induced autoinflammatory syndrome 1 gene (*CIAS1)*, which is now designated as *NLRP3*.[153–155] In 2002, mutations in the same gene were identified in NOMID.[151,156] *NLRP3* encodes the protein cryopyrin, which is part of a macromolecular complex called the inflammasome.[146] Inflammasome assembly leads to activation of caspase 1, which cleaves pro–IL-1β into its bioactive form. Patients with CAPS have a gain of function mutation in cryopyrin, leading to constitutive inflammasome activation. More than 50 missense mutations in *NLRP3* have been identified in patients with CAPS; some are unique to particular disorders, and others are found in several disorders. Of 18 U.S. patients with the clinical diagnosis of NOMID, 40% did not have *NLRP3* mutations despite having indistinguishable phenotypes from those with mutations.[156]

Cardinal Clinical Features

CAPS episodes are characterized by fever, urticaria-like rash, and joint pain. Onset of CAPS usually occurs in the first 6 months of life.

FCAS episodes are induced by generalized exposures to cold temperatures but not necessarily by contact with cold objects or drinking cold liquids.[75] Symptoms often are delayed an average of 2.5 hours after exposure and last approximately 12 hours.

MWS is not necessarily triggered by changes in temperature and episodes last longer (1–days). Microscopic examination of skin lesions reveals perivascular infiltrate of neutrophils without vasculitis, mast cells, or mast cell degranulation.[127] Lesions usually are not pruritic. Systemic symptoms of fever, headache, nausea, sweating, drowsiness, extreme thirst, conjunctivitis, blurred vision, ocular pain, and polyarthralgia can occur during episodes. Patients with MWS often have progressive sensorineural hearing loss in childhood.

NOMID manifests within the first 6 weeks of life with fever, urticaria-like rash, chronic arthritis, and a characteristic bony overgrowth predominantly involving the knees.[157] Central nervous system manifestations include chronic aseptic meningitis, increased intracranial pressure, cerebral atrophy, ventriculomegaly, chronic papilledema, optic atrophy and loss of vision, mental retardation, seizures, and sensorineural hearing loss.

Course, Treatment, and Outcome

Patients with FCAS have normal lifespan, but 20% of those with NOMID die before adulthood.[157] Amyloidosis occurs in a substantial percentage of patients with CAPS.

Corticosteroids can alleviate symptoms but not disease progression. IL-1β inhibition agents have been successful in treating all three syndromes. In a study of 18 patients with NOMID, anakinra therapy resulted in complete remission of central nervous system inflammation in most patients. Discontinuation of therapy resulted in rapid relapse, and reintroduction produced remission.[157] All 14 patients in an Italian registry of CAPS had significant and persistent improvement in clinical manifestations and quality of life with anakinra.[158] In a randomized, placebo-controlled trial, 15 patients who received canakinumab had complete remission compared with 19% of those receiving placebo.[159]

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16

Lymphatic System and Generalized Lymphadenopathy

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Anatomy and Function of Lymphoid Tissue

The lymphoid system is composed of an extensive capillary network that drains lymph into elaborate systems of collecting vessels. The collecting vessels merge and empty lymph into the bloodstream by way of the thoracic duct at its entry into the left subclavian vein or by the right lymphatic duct, which empties into the right subclavian vein. Specialized lymphatic structures interspersed along the collecting vessels include the tonsillar tissues of the Waldeyer ring, the thymus, the spleen, mucosa-associated lymphoid nodules, and lymph nodes (Table 16.1).

TABLE 16.1

Anatomic Types of Lymphoid Tissue

Type of Tissue	Location	Distinguishing Features
Discrete lymph	Occipital, preauricular, postauricular, submandibular, submental, facial,	Nodes have discrete capsules; afferent lymphatic flow enters from periphery;

node groups	parotid, cervical, supraclavicular, para-aortic, axillary, epitrochlear, inguinal, iliac, popliteal, mediastinal, hilar, pelvic, mesenteric, celiac	efferent lymphatic flow exits and blood vessels enter and exit through hilum of node
Waldeyer ring	Pharyngeal (adenoid), palatine (faucial), lingual and tubal (Gerlach) tonsils; lateral pharyngeal bands; posterior pharyngeal granulations	Aggregates of lymphoid nodules are partially encapsulated; no afferent lymphatics and no lymphoid sinuses; efferent lymphatic flow is not as structured as for lymph nodes
Lymphoid nodules	Small, submucosal lymphoid collections throughout the intestinal (i.e., Peyer patches), respiratory, and genitourinary tracts (i.e., mucosa-associated lymphoid tissue [MALT])	Lymphatic flow is not encapsulated or structured; tissue responds to mucosal antigens with phagocytosis and immunoglobulin A production
Thymus	Anterior mediastinum	Organ is composed of lymphoid and epithelial cells; no afferent lymphatic vessels; protected from antigen; essential for development and maturation of peripheral lymphoid tissues
Spleen	Abdomen	Lymphatic tissue is uniquely specialized to filter blood; largest lymphatic organ in the body; no afferent lymphatic vessels and no lymphatic vessels within spleen; sinusoid structure is similar to lymph node but lymph empties into splenic vein

The Waldeyer ring of lymphoid tissue that surrounds the oropharyngeal isthmus and the opening of the nasopharynx into the oropharynx is uniquely positioned to interact with foreign material entering the nose or mouth. The ring is formed superiorly by the midline pharyngeal (adenoid) tonsil, which is located in the roof of the nasopharynx, and inferiorly by the lingual tonsils in the posterior third of the tongue. On either side of the pharynx, the lateral pharyngeal bands of lymphoid tissue connect the adenoid to the tubal tonsils of Gerlach at the openings of the eustachian tubes and to the faucial (palatine) tonsils. Smaller aggregates of lymphoid tissue in this area include the posterior pharyngeal granulations and the lymphoid tissue within the laryngeal ventricle.

Small submucosal lymphoid nodules located throughout the respiratory, gastrointestinal, and genitourinary tracts are composed of phagocytic and lymphoid cell collections without a connective tissue capsule. These nodules are ideally situated to respond to mucosal antigens.

The thymus, which is located over the superior vena cava in the anterior mediastinum, is relatively protected from antigens. Surrounded by a thin connective tissue capsule, the thymus is uniquely composed of epithelial and lymphatic elements.

The spleen is the largest lymphatic organ in the body and the only lymphatic tissue specialized to filter blood. Similar to the lymph nodes, the spleen is a component of the peripheral lymphoid system and is composed of red pulp (i.e., red blood cells) and an interior of white pulp, which contains lymphoid nodules with germinal follicles.

Normal lymph nodes are small, oval or bean-shaped bodies that are strategically located along the course of lymphatic vessels to filter lymph on its way to the bloodstream. Lymphatic vessels enter around the periphery of the nodes. Lymph filters through the cortex to the medulla of the node and exits through the hilum. Blood vessels enter and leave through the hilum, which is connected to capillaries that course through the node. During this process, lymphocytes can leave the blood and re-enter the lymphatic circulation.

Nodes are densely packed with lymphocytes that are organized loosely into cortical nodules and medullary cords by connective tissue trabeculae and lymphatic sinuses. The juxtaposition of phagocytic cells, antigen-processing cells, and lymphocytes in an area of sluggish blood flow is ideally suited to provide the first line of defense against pathogens. As lymph slowly filters through the rich reticular network, organisms are trapped and can be ingested by phagocytic cells, stimulating the release of cytokines, which recruits lymphocytes for immunologic responses. The lymph node groups in the body can be divided into the superficial and peripheral nodes, which usually are easily palpable, and the deeper groups adjacent to major vessels and viscera (see Table 16.1).

Developmental Changes

Lymphoid tissue, including the thymus, forms a significantly larger percentage of total body weight in infants and children than in adults. Considerable lymphoid activity is present at birth, and continuing exposure to environmental antigens results in an increase in lymphoid mass that reaches a peak between the ages of 8 and 12 years. Atrophy of lymphoid tissue begins during adolescence. In children, the thymus can weigh 40 g; in adults, the thymus is replaced by fibrous and fatty tissue and can weigh only 10 g. By adult standards, almost all children have lymphadenopathy because palpable nodes, particularly in the cervical, axillary, and inguinal areas, are common in children of all ages, including neonates (Table 16.2). Prominent palatine tonsils are common in preadolescent children, whereas in infants younger than 1 year of age and adults, the palatine tonsils usually are not visible.

TABLE 16.2

Frequency and Location of Palpable Peripheral Lymph Nodes in Healthy Children

Palpable Node	Neonate[a]	Age <2 Years[b]	Age >2 Years[b]
Cervical	+	++	++
Postauricular	−	+	−
Occipital	−	++	+
Submandibular	−	+	++
Supraclavicular	−	−	−
Axillary	+	+++	+++
Epitrochlear	−	−	−
Inguinal	+	+++	+++
Popliteal	−	−	−
None	++	++	++

[a] Data from Bamji M, Stone RK, Kaul A, et al. Palpable lymph nodes in healthy newborns and infants. Pediatrics 1986;78:573.

[b] Data from Herzog LW. Prevalence of lymphadenopathy of the head and neck in infants and children. Clin Pediatr 1983;22:485.

+++, Normally found in less than 50% of children; ++, normally found in 25% to 50%; +, normally found in 5% to 25%; −, normally found in less than 5%.

Because of their normally hyperplastic nodes, the response of children to antigenic, infectious, or neoplastic stimuli is much more rapid, prolific, and exaggerated than that in adults. Lymph nodes can increase in size as much as 15-fold within 5 to 10 days of antigen exposure. Increased size of mediastinal and mesenteric nodes can be particularly pronounced.

Characteristics of Lymphadenopathy

Lymphadenopathy (i.e., enlarged lymph nodes) can be characterized by size, location, consistency, rate of growth, tissue inflammation, and fixation. In all ages and lymph node groups, a node is considered enlarged if it measures (in the longest diameter) greater than 10 mm. There are two exceptions to this rule. In the epitrochlear region, nodes greater than 5 mm are abnormal, and in the inguinal region, only nodes greater than 15 mm are considered abnormal.

Most children examined when healthy have palpable lymph nodes.[1] In healthy neonates, lymph nodes ranging from 3 to 12 mm in the longest diameter can be found in the cervical, axillary, and inguinal regions.[2] In children younger than 2 years, palpable nodes can be found at any peripheral location, except in the epitrochlear, supraclavicular, and popliteal areas, where palpable lymph nodes always are abnormal. In children older than 2 years, palpable lymph nodes in these areas and in the posterior auricular and suboccipital areas are considered abnormal.

Characteristics of lymph nodes are determined by palpation (Table 16.3). Soft, discrete, nontender, small (<2 cm) nodes that are found bilaterally or usually with no periadenitis, cellulitis, or abscess formation typically result from hyperplasia due to viral infection. Unilateral, large (>2 cm), warm, tender, poorly defined nodes with surrounding edema, erythema, or abscess formation usually are infected with pyogenic bacteria. Moderately large, unilateral nodes with discrete margins and minimal inflammation that progress slowly to become erythematous (but not warm), fluctuant, and adherent to overlying skin are characteristic of chronic, usually bacterial infections.

TABLE 16.3

Characteristics of Enlarged Lymph Nodes According to Cause

Characteristic	Causes of Enlargement			
	Acute Bacterial	Chronic Bacterial	Acute Viral	Malignant
Large size	+++	+++	+	++/+++
Erythema	+++	++	−	−
Tenderness	+++	++	+	++
Consistency	Soft or firm	Firm	Soft	Firm or rubbery
Discrete	++	+++	+++	+++
Matted	++	++	−	++
Fixed	+++	+	−	−
Fluctuant	+++	+++	−	−
Associated with cellulitis	+++	+	−	−
Unilateral	+++	+++	−	+

+++, Common finding; ++, less common finding; +, occasional finding; −, rare.

Enlarged nodes resulting from lymphoma usually are firm, discrete, freely movable, nontender, and rubbery, and they have no surrounding inflammation. Nodes increase in size over time, and adjacent nodes can become matted together and lose individual characteristics. Suppuration and fixation to skin or deeper structures, as seen in inflammatory lymphadenopathy, are not expected in lymphoma. Lymphomatous nodes can wax and wane in size over weeks to months, and lymphomatous changes can develop or become more apparent in nodes for which a biopsy specimen initially showed only hyperplasia.[1–3] Enlarged nodes that result from metastatic tumors are hard and bound to each other and to surrounding tissues.

Enlarged nodes can be single or multiple and contiguous. When confined to one region, the condition is referred to as *regional lymphadenopathy*. Enlargement of a single node or regional nodes can be the result of localized disease or the first manifestation of generalized lymphadenopathy. *Generalized lymphadenopathy* is defined as the simultaneous occurrence of two or more enlarged nodes in noncontiguous groups; enlargement need not be identified in every body site. Concurrent mesenteric and hilar adenopathy is considered generalized lymphadenopathy. Splenomegaly also can occur but is not included in the definition.

Pathogenesis of Lymphadenopathy and Lymphadenitis

Microorganisms reach lymph nodes directly by lymphatic flow from the inoculation site or by lymphatic spread from adjacent nodes. If initial involvement of regional nodes does not contain infection adequately, organisms can reach noncontiguous nodes by hematogenous spread. Lymph node enlargement can result from a variety of mechanisms (Box 16.1).

Box 16.1

Mechanisms of Lymph Node Enlargement

Cells within the node replicate in response to antigenic stimuli or as a result of malignant transformation.

Cells exogenous to the node, such as neutrophils or metastatic neoplastic cells, enter the node in large numbers.

Foreign material is deposited within histiocytic cells of the node (e.g., lipid storage diseases).

Local cytokine release leads to vascular engorgement and edema.

Tissue necrosis leads to suppuration.

In acute pyogenic lymphadenitis, the initial inflammatory response in the node, including complement activation and cytokine release, causes recruitment of neutrophils and mononuclear phagocytes. Vascular engorgement, intranodal edema, and cellular replication in response to the antigenic stimulus lead to rapid enlargement of the node. Involvement of adjacent lymph nodes and surrounding soft tissues, including skin, can result in cellulitis, suppuration, necrosis, and fixation to adjacent tissues. After purulence occurs, lymph node architecture and antibiotic access are destroyed. Healing occurs by fibrosis.

For microorganisms that cause subacute or chronic granulomatous changes, the increase in node size and tenderness and adjacent inflammatory response usually are modest. Formation of granulomas and, in some cases, caseating necrosis also destroy nodal architecture; drainage or removal may be required to relieve pain or hasten resolution.

With local or generalized viral infections, the nodal response primarily is one of hyperplasia without necrosis. This resolves as infection abates without sequelae.

Enlarged lymph nodes, lymphoid nodules, or lymphoid tissue such as the Waldeyer ring can result in obstruction, compression, or erosion of important structures, rupture of nodal contents, or inflammation of adjacent structures. Generalized hyperplasia of the Waldeyer ring can result in obstruction of the posterior nares, eustachian tube, or oropharynx. Extensive mediastinal lymphadenopathy can lead to obstruction or erosion of the airways, esophagus, superior vena cava, recurrent laryngeal nerve, or lymphatics (see Table 18.3). Gastrointestinal inflammation of Peyer patches (e.g., *Salmonella* Typhi infection) can lead to intestinal perforation and hemorrhage or serve as the lead point for intussusception. Infectious mesenteric lymphadenitis can lead to an intra-abdominal abscess. Perinodal inflammation of muscles in the neck results in torticollis, and spread of infection in the neck can lead to deep fascial space infections.

Histopathology of Lymphadenitis

Nonspecific hyperplasia is the most common histopathologic finding in biopsy specimens of enlarged lymph nodes. The cause is not determined in most children, and the condition usually resolves. For 17% to 25% of cases, however, a pathologic process ultimately develops, most often a lymphoreticular disease.[3–5]

In acute pyogenic infection, lymph nodes are filled with neutrophils, microorganisms, edema, and necrotic debris. Granuloma formation along with caseating necrosis is typical of infections caused by *Mycobacterium tuberculosis, Histoplasma capsulatum, Coccidioides immitis,* and some nontuberculous mycobacteria. Stellate abscesses surrounded by palisading epithelioid cells are typical for lymphogranuloma venereum (caused by *Chlamydia trachomatis*) and infections caused by *Bartonella henselae* and *Francisella tularensis* (with more extensive granuloma formation in the latter). Toxoplasmosis produces characteristic nodal histologic findings of reactive follicular hyperplasia with scattered clusters of epithelioid histiocytes in cortical and paracortical zones, blurring of margins of germinal centers, and focal distention of subcapsular and trabecular sinuses by monocytoid cells. *Yersinia* spp. can cause necrotizing lymphadenitis in cervical, mediastinal, and mesenteric nodes. Brucellosis is characterized by noncaseating granulomas that are indistinguishable from those of sarcoidosis.

Lymphocutaneous and Oculoglandular Syndrome

For several infections resulting in regional and, with extension, generalized lymphadenopathy, a characteristic and often granulomatous inflammatory reaction develops at the site of inoculation. Regional adenopathy often develops from lymphatic spread of organisms before the inoculation site has healed. When the initial inoculation site is in the conjunctiva, the constellation is the Parinaud oculoglandular syndrome, and when in the skin, it is the lymphocutaneous syndrome. Organisms that cause these syndromes are shown in Box 17.1 in Chapter 17.

Infectious Causes of Generalized Lymphadenopathy

Local or generalized lymph node enlargement due to self-limited conditions must be differentiated from potentially life-threatening disorders such as a neoplasm, histiocytic proliferation, or autoimmune disease.[6,7] The distinctions usually can be made on the basis of history, lymph node examination (see Table 16.3), other systemic manifestations, and a limited number of laboratory tests (Box 16.2).

Box 16.2

Steps in Evaluating the Child With Generalized Lymphadenopathy

Take a careful history, paying attention to epidemiologic features, including travel, animal exposures, tick bite, unpasteurized milk consumption, immunization status, blood transfusion, drug exposures, and review the HIV risk factors for the mother and child.

Consider whether the child appears ill or well to determine the pace of evaluation and differential diagnosis.

Identify associated signs and symptoms, including fever and weight loss, and perform a thorough review of symptoms.

Identify the location and characteristics of lymph nodes, associated organomegaly, musculoskeletal findings, and rash.

Perform a laboratory evaluation, including CBC, CRP, ESR, serum hepatic enzymes, LDH, ferritin, and blood cultures, and obtain a chest radiograph.

Perform serologic testing based on clinical risk; consider EBV, CMV, HIV, *Mycoplasma*, *Treponema*, *Brucella*, *Bartonella*, *Histoplasma, Francisella,* HHV-6, HHV-8. Perform tuberculin skin testing.

Consider a lymph node biopsy, and plan specific testing of the specimen.

CBC, Complete blood cell count; CMV, cytomegalovirus; CRP, C-reactive protein; EBV, Epstein-Barr virus; ESR, erythrocyte sedimentation rate; HHV, human herpesvirus; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase.

Systemic infections are the most common causes of generalized lymphadenopathy. Many conditions characterized by generalized adenopathy also cause hepatic or splenic enlargement or initially cause regional adenopathy. Differentiating features of characteristic syndromes are listed in Table 16.4.

TABLE 16.4

Causes of Generalized Lymphadenopathy and Predominant Regional Involvement

Disease	Organism	Lymphadenopathy			
		Generalized	**Hepatosplenomegaly**	**Mediastinal**	**Cer**
SPIROCHETAL SYNDROMES					
Syphilis, secondary	*Treponema pallidum*	++++	—	+	++
Leptospirosis	*Leptospira* spp.	++++	++++	—	++
Lyme disease	*Borrelia burgdorferi*	+	+ (H)	—	—
BARTONELLA **SYNDROMES**					
Bartonellosis (Oroya fever; verruga peruana)	*Bartonella bacilliformis*	++++	—	—	—
Cat-scratch disease	*Bartonella henselae*	+	+ (S)	++	+++
MESENTERIC LYMPHADENOPATHY SYNDROMES					
Typhoid fever	*Salmonella* Typhi	++++	++++ (S)	+	+
Yersiniosis	*Yersinia enterocolitica*	+	—	+	+
PULMONARY SYNDROMES					
Mycoplasma infection	*Mycoplasma pneumoniae*	+	—	++	++
Legionnaire disease	*Legionella pneumophila*	+	+(S)	—	—
Primary tuberculosis	*Mycoplasma tuberculosis*	++	++++	++++	++
Histoplasmosis	*Histoplasma*	+	++++	+++	++

(disseminated)	*capsulatum*				
Coccidioidomycosis (disseminated)	*Coccidioides immitis*	+	—	++	—
Paracoccidioidomycosis	*Paracoccidioides brasiliensis*	++++	++	+++	+++
MISCELLANEOUS BACTERIAL SYNDROMES					
Scarlet fever	*Streptococcus pyogenes*	+	+	—	+++
Brucellosis	*Brucella melitensis*	+++	+++	—	++
Tularemia	*Francisella tularensis*	++	++	—	+++
EXANTHEMATOUS SYNDROMES					
Measles	Measles virus	+++	++ (S)	+++ (A)	+++
Rubella	Rubella virus	++	+ (S)	—	+++
Chickenpox	Varicella-zoster virus	++	—	—	—
MONONUCLEOSIS SYNDROMES					
	Epstein-Barr virus	++++	+++	+	+++
	CMV	+++	+++	—	+++
	HIV	++++	+++	+	++
	HHV-6	++++	+++	—	++
	Parvovirus B19	++	++	—	—
	Hepatitis A virus	+	+++ (H)	—	+++
	Toxoplasma gondii	++	+	—	+++
CASTLEMAN DISEASE					
Disease of lymph nodes and related tissues	HIV, HHV-8	++++	+++	+++	+++
MISCELLANEOUS VIRAL SYNDROMES					
Pharyngoconjunctival fever	Adenovirus	++	+++	—	+++
Nonspecific febrile illness	Enterovirus	+	+	—	+
RICKETTSIA* AND *CHLAMYDIA					
Scrub typhus	*Rickettsia tsutsugamushi*	++++	+++	—	+++
Ehrlichiosis	*Ehrlichia chaffeensis*	+++	—	—	—
Neorickettsiosis	*Neorickettsia sennetsu*	++++	—	—	—
Lymphogranuloma venereum	*Chlamydia trachomatis*	+	—	—	—
TROPICAL SYNDROMES					
Chagas disease (American trypanosomiasis)	*Trypanosoma cruzi*	++++	++	—	+
African sleeping sickness (African trypanosomiasis)	*Trypanosoma brucei*	++	++	—	+++
Kala-azar (leishmaniasis)	*Leishmania* spp.	++	++++	—	+
Filariasis	*Wuchereria bancrofti* and	+++	—	—	—
		+++			

	Brugia spp.				
Schistosomiasis (Katayama fever)	*Schistosoma* spp.	+++	+++	—	+
Dengue fever	Dengue virus	++	+	—	+
Chikungunya disease	Chikungunya virus	+++	—	—	+++
Lassa and Ebola fevers	Lassa and Ebola viruses	+++	++	—	—
West Nile fever	West Nile virus	++	—	—	—
CONGENITAL SYNDROMES					
AIDS	HIV	++++	+++	—	+++
Rubella	Rubella virus	+++	++++	—	—
Mononucleosis, other	CMV	+	++++	—	—
Toxoplasmosis	*Toxoplasma gondii*	+++	++++	—	+
Syphilis	*Treponema pallidum*	+++	++++	—	+++
Chagas disease	*Trypanosoma cruzi*	+++	++++	—	—
MISCELLANEOUS SYNDROMES					
IAHS	Various	++++	++++	—	+++
Sarcoidosis	—	++++	+++	+++	+++
Gianotti-Crosti syndrome	—	++++	++++	—	+
Chronic granulomatous disease	—	+++	++	++	+++
Chronic atopic eczema	—	++	+	—	+++
Typhoid immunization	*Salmonella* Typhi (inactivated)	++	—	—	++

[a] Other includes particularly axillary, inguinal, epitrochlear, mesenteric, occipital, and supraclavicular adenopathy, depending on disease (see text for details for specific diseases).

A, Atypical; CMV, cytomegalovirus, H, predominantly hepatomegaly; HHV, human herpesvirus; HIV, human immunodeficiency virus; IAHS, infection-associated hemophagocytic syndrome; S, predominantly splenomegaly; ++++, characteristic association; +++, frequent association; ++, occasional association; +, rare association; —, not applicable or unknown.

Congenital Syndromes.

One-third of infants who have congenital toxoplasmosis show signs and symptoms of acute infection. Many infants have splenomegaly (90%), hepatomegaly (70%), or generalized adenopathy (68%). Hepatosplenomegaly is diagnosed in 50% to 75% and generalized lymphadenopathy in 20% to 50% of infants with congenital rubella. These manifestations usually resolve over a few weeks. Generalized lymphadenopathy is uncommon in congenital herpes simplex and CMV infections. Infants with intrauterine HIV infection have generalized, painless lymphadenopathy. Lymph node biopsy results can demonstrate a variety of patterns, including follicular hyperplasia, angioimmunoblastic changes, and atrophy.

Hepatosplenomegaly occurs in almost all infants with early congenital syphilis. Generalized lymphadenopathy is described in 50% of patients. Nodes can be 1 cm or larger and usually are nontender. Enlarged epitrochlear nodes are relatively unique to congenital syphilis.

Spirochetal Infections.

Rash and generalized, painless lymphadenopathy occur in 90% of patients with secondary syphilis. Enlargement of the epitrochlear nodes is a unique and common finding. In 70% of patients, rash and lymphadenopathy are accompanied by constitutional symptoms of fever, malaise, anorexia, and weight loss.

In leptospirosis, generalized lymphadenopathy, hepatosplenomegaly, and constitutional symptoms of muscle tenderness, conjunctival injection, and rashes are seen in the first septicemic stage. The first clinical manifestation of Lyme disease is the typical annular rash, erythema migrans. Untreated, almost 25% of patients have dissemination that leads to secondary lesions of erythema migrans. Patients also complain of fever, headache, myalgia, malaise, and arthralgia, and they can have nontender regional or generalized lymphadenopathy.

Rickettsia, *Ehrlichia*, and *Anaplasma* Infections.

After an incubation period of 1 to 2 weeks, the initial mite bite lesion and necrotic eschar can be seen in patients with scrub typhus. This coincides with the onset of the main characteristic features of the disease, which are fever, headache, rash, and generalized lymphadenopathy. Lymphadenopathy is particularly prominent in the axilla, neck, and inguinal areas. Hepatosplenomegaly and conjunctival injection are common.

Sennetsu fever caused by *Neorickettsia sennetsu* has been found in Japan and Southeast Asia. The infection is likely acquired from eating raw fish.[8] Abrupt onset of fever, chills, headache, malaise, sore throat, and muscle and joint pains is accompanied by hepatosplenomegaly and generalized, tender lymphadenopathy. Posterior auricular and posterior cervical adenopathy are particularly prominent. Generalized lymphadenopathy is not found in other rickettsial infections (e.g., *Rickettsia rickettsii* infection) and occurs inconsistently in *Ehrlichia* and *Anaplasma* infections.

Bartonella Infections.

In the mountain valleys of Peru, Ecuador, and southwest Colombia, between the altitudes of 500 and 3400 m, *Bartonella bacilliformis* infection can be transmitted by the sandfly vector or by blood transfusion, causing Oroya fever. In the acute stage, cells of the reticuloendothelial system contain many organisms after phagocytosis and destruction of infected, deformed red cells. Fever, headache, and muscle and joint pain are accompanied by anemia and generalized, painless lymphadenopathy. Splenomegaly occurs only in patients with intercurrent infection.

B. henselae infection most commonly is associated with prominent regional lymphadenopathy related to the site of inoculation during a cat's scratch. Cat-scratch disease occasionally manifests with generalized lymphadenopathy, splenomegaly, and granulomatous hepatitis, especially in the immunocompromised host. In most instances of generalized lymphadenopathy, only two or three sites are involved, suggesting that separate inoculations might have occurred in some cases.

Enteric Infections.

Enteric fever caused by *Salmonella* spp. primarily affects the lymphoid tissue in Peyer patches in the ileum, the lymphoid follicles of the cecum, and the mesenteric nodes. About 50% of patients have hepatosplenomegaly. Occasionally, patients have generalized lymphadenopathy, particularly involving cervical nodes. Lymphoid tissue undergoes consecutive stages of hyperplasia, necrosis, ulceration, and healing. Suppurative lymphadenitis has been described.

Yersinia pseudotuberculosis and *Y. enterocolitica* infections have been associated with terminal ileitis and mesenteric adenitis, in which mesenteric lymph nodes are enlarged and can become necrotic and intensely suppurative. Concurrently enlarged inguinal and, rarely, cervical and hilar nodes have been described.

Pulmonary Infections.

Although rare, legionellosis in children can manifest with nonspecific symptoms and occasionally with findings of rash, splenomegaly, and lymphadenopathy. Pneumonia caused by *Mycoplasma pneumoniae* infection is accompanied by lymphadenopathy, particularly cervical, in about 25% of cases; mediastinal and hilar lymphadenopathy also can occur.

Tuberculosis usually is characterized by mediastinal and occasionally by cervical lymphadenopathy. Protracted hematogenous disease can cause high fever, hepatosplenomegaly, and generalized lymphadenopathy.

Rarely, symptomatic, disseminated coccidioidomycosis occurs within weeks or months after the initial localized pulmonary infection; most frequently, extrapulmonary spread is to bone, soft tissue, lymph nodes, and meninges. Tissue reaction primarily is granulomatous but can be accompanied by acute inflammation.

In acute disseminated histoplasmosis in infants, the reticuloendothelial system has a high density of yeast forms compared with mycelial forms. Hepatosplenomegaly and intra-abdominal lymphadenopathy are common, and one-third of patients have peripheral lymphadenopathy. In acute pulmonary histoplasmosis, lymphohematogenous spread involves lymph nodes in the neck (where suppuration of supraclavicular or cervical nodes can occur), mediastinum, liver, and spleen.

Paracoccidioidomycosis is endemic in most countries of Latin America, particularly Brazil. The disease almost always is disseminated, with a predilection for the reticuloendothelial system. Peripheral lymphadenopathy occurs in 75% of children with the acute or subacute forms. Cervical, inguinal, mesenteric, or mediastinal lymphadenopathy is almost universal. Lymph nodes vary in size, number, and consistency, Over time, abscesses and fistulas form. Masses of lymph nodes (frequently with caseation) can be seen, and patients usually have hepatosplenomegaly.

Other Bacterial Infections.

Acute onset of symptoms occurs in 50% of patients with brucellosis. As organisms are ingested by mononuclear phagocytes, disease is localized primarily in the lymph nodes, liver, spleen, and bone marrow. Noncaseating granulomas that are indistinguishable from sarcoidosis are the usual finding in liver biopsy specimens.

Lymphadenitis is a common manifestation of tularemia. Although regional involvement (with the site depending on whether acquisition was oropharyngeal or tick related) is the most common presentation, multiple sites can be involved. Hepatosplenomegaly was diagnosed in 35% of infected children in one series.[9]

Generalized lymphadenopathy is rarely described as a feature of scarlet fever. It may be more typical of the severe toxic form of the disease.

Exanthematous Syndromes.

Studies of rubella virus inoculation in adolescents and young adult volunteers demonstrated that suboccipital and posterior auricular lymphadenopathy is most characteristic, but generalized involvement can occur.[10] Pharyngitis and cervical lymphadenopathy are common in measles during the exanthematous period. Generalized lymphadenopathy with suboccipital, posterior auricular, and mediastinal involvement and splenomegaly are also common.

Generalized lymphadenopathy is an uncommon manifestation of varicella-zoster viral infection. It is more often related to secondary bacterial infections.

Clinically, parvovirus B19 infection most often causes erythema infectiosum. However, a mononucleosis-like syndrome with generalized lymphadenopathy and hepatosplenomegaly also has been described.

Mononucleosis Syndromes.

Lymphadenopathy in Epstein–Barr virus (EBV)–associated mononucleosis most prominently involves anterior and posterior cervical nodes, but diffuse lymphadenopathy often involves the occipital, supraclavicular, axillary, epitrochlear, inguinal, and mediastinal lymphatic chains. Enlarged nodes usually are nontender or minimally tender and have no overlying erythema, and they are most prominent during the second to fourth week of illness. Splenomegaly occurs in 50% and hepatomegaly in 30% to 50% of cases.

In children, cytomegalovirus (CMV) is a less common cause of mononucleosis than EBV, but lymphoid manifestations are similar.

In one study of 124 children with the mononucleosis syndromes, fever, hepatosplenomegaly, rashes, and upper airway obstruction were found with equal frequency in infections caused by EBV or CMV. Cervical lymphadenopathy was more common with EBV (93% of cases) than CMV (75%).

Clinical disease caused by human immunodeficiency virus (HIV) in infants and young children is characterized by generalized lymphadenopathy, hepatosplenomegaly, failure to thrive, intermittent fever, chronic or recurrent diarrhea, parotitis, chronic dermatitis, and recurrent infections. In older children and adults, a mononucleosis-like syndrome (i.e., seroconversion syndrome) can occur weeks after HIV infection and includes generalized lymphadenopathy, fever, malaise, myalgia, headache, sore throat, diarrhea, and rash. Lymphadenopathy can involve several sites and can persist for months. Lymph nodes are discrete, nontender, and nonsuppurative; biopsy reveals follicular hyperplasia. With progression to acquired immunodeficiency syndrome (AIDS), lymphocyte depletion occurs. A biopsy specimen from rapidly enlarging nodes should be examined to exclude malignancy. Multicentric Castleman disease can occur in HIV-infected patients (discussed later).

Patients with anicteric hepatitis A or B can manifest a mononucleosis-like syndrome, commonly characterized by posterior cervical lymphadenopathy. Generalized lymphadenopathy is unusual; splenomegaly occurs in 15% of cases.

The most common findings in symptomatic acquired toxoplasmosis are fatigue and lymphadenopathy without fever. Nodes are discrete, may or may not be tender, and do not suppurate. The cervical, suboccipital, supraclavicular, axillary, and inguinal nodes are most often involved. Lymphadenopathy can be localized or generalized, including involvement of the retroperitoneal and mesenteric nodes. Lymphadenopathy can simulate lymphoma.

Miscellaneous Viral Infections.

The usual onset of adenoviral pharyngoconjunctival fever is abrupt, with sore throat, headache, generalized aches and pains, eye irritation or pain, and fever. Some degree of anterior and posterior cervical lymphadenopathy occurs in most patients. Preauricular lymphadenopathy is surprisingly uncommon, and generalized lymphadenopathy is found in 10% to 20% of patients. Hepatosplenomegaly is common. Generalized lymphadenopathy occasionally occurs in nonspecific illnesses caused by enteroviruses.

Tropical Syndromes.

During the acute phase of symptomatic Chagas disease (caused by *Trypanosoma cruzi*), patients have generalized lymphadenopathy, moderate hepatosplenomegaly, rash, vomiting, diarrhea, and neurologic and cardiac changes. At various stages of African trypanosomiasis, the hemoflagellate trypanosomal protozoans *(Trypanosoma brucei rhodesiense* and *T.b. gambiense)* can be found in lymphatics and lymph nodes. Patients can have fever, posterior cervical lymphadenopathy, and local chancre.

In visceral leishmaniasis (i.e., kala-azar), the principal histopathology is the result of macrophage infection and reticuloendothelial hyperplasia. Patients have massive splenomegaly and generalized lymphadenopathy with pancytopenia.

In filarial infections, lymphangitis with involvement of regional nodes is more common than generalized lymphadenopathy. Hematogenous dissemination by way of the thoracic duct, however, can lead to generalized adenopathy.

Katayama fever (i.e., acute schistosomiasis) occurs with severe schistosomal infestation. Generalized, nontender lymphadenopathy, splenomegaly, and hepatomegaly with tenderness are common findings in addition to fever, headache, myalgia, weakness, and gastrointestinal symptoms.

Generalized lymphadenopathy is an integral part of several tropical viral hemorrhagic fever syndromes (see Table 16.4).

Other Causes of Generalized Lymphadenopathy

Drug-Induced Hyperplasia Related to Hypersensitivity.

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is recognized as a great clinical mimicker because the major clinical features also occur in other systemic disorders.[11] Localized or generalized lymphadenopathy can appear 1 to 2 weeks after beginning phenytoin or other anticonvulsant medications such as carbamazepine. A severe, pruritic, maculopapular rash with fever, hepatosplenomegaly, jaundice, anemia, leukopenia, and plasmacytosis in blood and bone marrow occurs concurrently with or after lymphadenopathy. Other agents that have been associated with generalized lymphadenopathy or DRESS syndrome, or both, include pyrimethamine, antileprosy and antithyroid drugs, isoniazid, aspirin, barbiturates, penicillin, minocycline, iodides, sulfonamides, abacavir, nevirapine, allopurinol, and phenylbutazone.

Inherited Immunodeficiency Syndromes.

Generalized lymphadenopathy often is characteristic of inherited immunodeficiency syndromes (e.g., Wiskott-Aldrich syndrome, common variable immunodeficiency) (see Box 16.4). Detection of dysregulated lymphoproliferation in these patients with underlying chronic generalized lymphadenopathy can be difficult. More than 5% of patients with Chédiak-Higashi syndrome have an accelerated phase of disease with generalized lymphadenopathy and hepatosplenomegaly.

Lymphadenopathy with or without dermatitis is a common early feature of chronic granulomatous disease and occurs in almost all patients. Although cervical lymphadenopathy is most common, femoral, inguinal, hilar, mediastinal, and generalized adenopathy also are observed. Typically, early signs of inflammation such as fever, pain, and local inflammation are lacking, and affected nodes suppurate chronically (i.e., cold abscesses). The nodes have caseating or noncaseating granulomas with central necrosis, a reaction to inadequate killing of intracellular and extracellular organisms.

Hodgkin and Non-Hodgkin Lymphoma.

Lymphadenopathy can result from malignant transformation of cells intrinsic to the node or from metastatic spread of cells extrinsic to the node (Box 16.3). Primary neoplasms of lymph nodes include the lymphomas and histiocytosis.[12] Data from the American Cancer Society for 2014 show that lymphomas account for approximately

10% of cancers in children younger than 15 years of age, and leukemia and central nervous system tumors account for 30% and 21%, respectively.

Box 16.3

Noninfectious Causes of Generalized Lymphadenopathy

Inherited immunodeficiency syndromes

- Chronic granulomatous disease
- Wiskott-Aldrich syndrome
- Chédiak-Higashi syndrome

Papular acrodermatitis (i.e., Gianotti-Crosti syndrome)

Sarcoidosis

Hyperthyroidism

Drug-induced hyperplasia or hypersensitivity

Autoinflammatory and autoimmune disorders

Lipid storage diseases

Other lymphoid hyperplasia syndromes

- Hemophagocytic lymphohistiocytosis
- Rosai-Dorfman disease
- Kikuchi-Fujimoto disease
- Multicentric Castleman disease

Cancers

- Primary lymphomas and metastatic neoplasms
- Non-Hodgkin lymphoproliferative disorders
- Childhood histiocytoses

Hodgkin lymphoma (HL) in children younger than 16 years accounts for 10% to 15% of the approximately 7880 HL cases diagnosed annually in the United States. Non-Hodgkin lymphoma (NHL) in children makes up about 5% of the 53,370 cases of NHL diagnosed each year. Among childhood NHL cases, lymphoblastic lymphomas (20%), Burkitt lymphoma (19%), anaplastic large cell lymphoma (10%), and diffuse large B-cell lymphoma (22%) are most common. The cure rate for pediatric lymphoma is as high as 90% for certain categories. Lymphoma is among the most curable of all cancers, which emphasizes the importance of early diagnosis.

The most common first clinical manifestation of HL and NHL is painless lymph node enlargement, most often in the cervical (60% to 90% of cases) or supraclavicular chains. Onset of HL typically is subacute and prolonged, but NHL onset can occur rapidly over a few days or weeks. HL is primarily a disease of adolescents and young adults. Of childhood cases, 60% occur in children 10 to 16 years of age, and less than 3% of cases occur in children younger than 5 years.

Constitutional symptoms of fever, weight loss, drenching night sweats, generalized pruritus, and pain affect only 30% of children at the time of presentation. For patients with HL, 90% come to medical attention with an unusual mass or swelling and enlarged, painless supraclavicular or cervical nodes. Up to 70% of patients have mediastinal lymphadenopathy at presentation, making a chest radiograph valuable if the diagnosis is suspected. Involvement of the Waldeyer ring should be considered if high cervical nodes are enlarged.

Hepatosplenomegaly occurs in patients with advanced disease. Left-sided or bilateral cervical or supraclavicular involvement is more common in extramediastinal para-aortic and splenic spread. Mediastinal disease more often accompanies right-sided cervical or supraclavicular disease.

Other Lymphoproliferative Disorders.

Children with congenital or acquired immunodeficiency syndromes (including HIV infection and immunosuppression after organ transplantation) have a risk of developing lymphoproliferative disorders that is 100 to 10,000 times that of age-matched controls. The lymphoproliferative disorders are a heterogeneous group of B-lymphocyte proliferations that range from polyclonal hyperplasia to true monoclonal malignant lymphoma. The child's underlying condition (i.e., inherited, iatrogenic, or acquired) permits expansion of lymphoid cell populations that are more strictly regulated in the healthy child. Defects in immune regulation and surveillance result in unchecked proliferation of subpopulations of cells with new, irreversible cytogenetic aberrations, sometimes eventuating in NHL (Box 16.4). Lymphoproliferative disorders can manifest with a syndrome of fever, pharyngitis, and generalized lymphadenopathy, which in the early stages strongly resembles acute mononucleosis. EBV infection plays an etiologic role.

Box 16.4

Lymphoproliferative Disorders Associated With Immunodeficiency

Inherited immunodeficiency syndromes

- Ataxia-telangiectasia syndrome
- Wiskott-Aldrich syndrome
- Combined immunodeficiency syndromes
- X-linked lymphoproliferative syndrome

Immunodeficiency resulting from solid organ and stem cell transplantation

Viral infections causing immunodeficiency syndromes

- Epstein-Barr virus infection

- Retrovirus infection

Metastatic Neoplasms.

Metastatic involvement of lymph nodes occurs in a variety of nonlymphomatous cancers, including neuroblastoma, the leukemias, and malignancies of the head and neck (i.e., rhabdomyosarcoma, lymphosarcoma, and sarcoma of the parotid gland, thyroid, and nasopharynx).

Histiocytosis.

Childhood histiocytoses are a rare and diverse group of disorders that can cause generalized lymphadenopathy. Diagnosis and treatment are difficult. The histiocytoses are characterized by infiltration and accumulation of macrophages formed from histiocytic stem cells. Cells of the histiocytic system consist of antigen-processing (phagocytic) and antigen-presenting (dendritic) cells. Both are found in normal and reactive lymph nodes. Langerhans dendritic cells primarily are located in the skin but can be found in lymph nodes. Sinus histiocytes are the principal cells involved in phagocytosis of foreign particulate matter, and they are primarily located in lymph node sinuses.

The pathophysiology of histiocytoses is thought to be uncontrolled immunologic stimulation of normal antigen-processing cells rather than malignant transformation. Lymphadenopathy is a frequent manifestation.

Hemophagocytic Lymphohistiocytosis.

Hemophagocytic lymphohistiocytosis (HLH) is characterized by reactive histiocytic hyperplasia with leukoerythrophagocytosis in a variety of organs. HLH can be inherited or occur sporadically. Genetic and sporadic forms can be triggered by infection and in the setting of other immune dysregulation, including autoimmune disorders and malignancies.

Children with HLH frequently become critically ill, with fever, pancytopenia, generalized lymphadenopathy, and hepatosplenomegaly.[13,14] Laboratory abnormalities include cytopenia; disseminated intravascular coagulation; elevated levels of tissue enzymes, ferritin, and triglycerides; and extremely high levels of cytokines.[15] Bone marrow examination reveals excessive proliferation of benign-appearing histiocytes that are phagocytosing white blood cells, red blood cells, and platelets.

HLH can be triggered by bacteria, fungi, parasites, and most prominently viruses, especially EBV, although the pathophysiology is incompletely understood. Outcomes vary, and they can be poor depending on the type of HLH and underlying conditions. When related to infection other than EBV, recovery rates can be as high as 60% to 70% with treatment of the infection and supportive care[16] (see Chapter 12).

Sinus Histiocytosis With Massive Lymphadenopathy.

Sinus histiocytosis with massive lymphadenopathy (i.e., Rosai-Dorfman disease) is characterized by generalized proliferation of sinusoidal histiocytes.[17] It is a rare disease that occurs in the first 2 decades of life, and the cause of Rosai-Dorfman disease is unknown but thought to be the result of a dysregulated immune system or a response to a presumed infectious agent, or both.

All patients have a history of bilateral cervical lymphadenopathy, often of several months' duration. Lymphadenopathy can be asymmetric, and in 80% of patients, it involves other nodal groups, including the axillary, inguinal, hilar, and mediastinal nodes. In 30% of patients, extranodal disease occurs and involves the nasal and oral cavities, salivary glands, pharynx, tonsils, paranasal sinuses, trachea, orbit, bone, or skin. Systemic manifestations usually include fever, anemia, leukocytosis, an elevated sedimentation rate, and hypergammaglobulinemia. The course usually is indolent with spontaneous regression, but immune-modulating therapy may be required for extensive or progressive disease.

Histiocytic Necrotizing Lymphadenitis.

Histiocytic necrotizing lymphadenitis (Kikuchi-Fujimoto disease) is a benign cause of lymphadenopathy, which is accompanied in 20% of patients by systemic symptoms such as fever, nausea, weight loss, night sweats, arthralgia or hepatosplenomegaly, and leukopenia.[18] The most common manifestation is regional or generalized lymphadenopathy, with or without fever.

The median age of onset is 30 years, but the disease has occurred in children 2 to 18 years of age. Lymph node histologic examination reveals reactive histiocytes and large immunoblastic lymphoid cells. Focal necrotic lesions occur in the paracortical areas of lymph nodes.

The cause is thought to be dysregulation of a disordered immune system. The prognosis is excellent. Spontaneous resolution of lymphadenopathy occurs within 4 months.

Multicentric Castleman Disease.

Castleman disease is an atypical lymphoproliferative disorder characterized histologically by hyperplasia of lymph nodes with plasma cell predominance and marked capillary proliferation. Castleman disease can be a localized, indolent disease that can be cured by local excision or, particularly in HIV-infected individuals, can be a rapidly progressive disease with a poor prognosis. The multicentric form has been associated strongly with HIV and human herpesvirus 8 (HHV-8).[19,20]

Symptoms include fever, myalgia, and weight loss. Patients have diffuse lymphadenopathy, splenomegaly, and rhabdomyolysis. A pilot study suggested some efficacy for zidovudine and valganciclovir against Castleman disease in HIV-infected adults receiving antiretroviral therapy.[21]

Autoinflammatory and Autoimmune Disorders.

Forty percent of children with juvenile idiopathic arthritis of systemic onset have generalized lymphadenopathy, often preceding joint involvement. Patients have splenomegaly and, less often, hepatomegaly. Seventy percent of children with systemic lupus erythematosus have lymphadenopathy, which is generalized in one-third of them. Hepatosplenomegaly is common. Serum sickness (i.e., hypersensitivity reaction to foreign proteins, often drugs) is characterized by fever, urticaria, edema, polyarthralgia, and generalized lymphadenopathy.

In Sjögren syndrome, a rare disease in children, lymphadenopathy and splenomegaly can be accompanied by parotid and lacrimal gland involvement. Lymphadenopathy in Kawasaki disease usually is not generalized.

Papular Acrodermatitis.

Papular acrodermatitis of childhood (i.e., Gianotti-Crosti syndrome) is a distinctive eruption observed in children 6 months to 12 years of age. It is associated with malaise, low-grade fever, generalized lymphadenopathy, and hepatomegaly (when accompanied by hepatitis B viremia). The discrete, 1- to 5-mm, flat-topped, firm papules that appear in groups on the face, buttocks, limbs, palms, and soles resolve spontaneously within 3 weeks, whereas lymphadenopathy and hepatomegaly can persist for months. The eruption has been associated with several viral syndromes, notably hepatitis B and C infection.

Sarcoidosis.

Sarcoidosis is a multisystem granulomatous disease of unknown cause. It affects young adults, and most commonly manifests as asymptomatic, bilateral hilar and paratracheal adenopathy, often with parenchymal lung involvement. Generalized lymphadenopathy with prominent cervical involvement is the most common finding in children. Enlarged nodes are discrete, painless, and freely movable.

Characteristic histologic findings are epithelioid cell tubercles with little or no necrosis. Other findings result from local granuloma formation and include changes in the eyes, skin, liver, spleen, and parotid glands. Biopsy results of a supraclavicular node are diagnostic in 85% of cases.

Lipid Storage Diseases.

In Niemann-Pick, Gaucher, Wolman, and Farber diseases, lipid-laden histiocytes accumulate in the lymph nodes, liver, or spleen, resulting in detectable enlargement. Diagnosis typically is established by some combination of biopsy, genetic testing, and enzyme assays.

Miscellaneous Disorders.

Hyperthyroidism is associated with generalized lymphoid hyperplasia. Beryllium exposure can result in granulomatous lymphadenopathy, which can be generalized.

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17

Cervical Lymphadenitis and Neck Infections

Emily A. Thorell

Epidemiology

Neck masses in children, unlike those in adults, seldom represent ominous disease. Most (95%) masses are enlarged or inflamed lymph nodes and are acute in nature. In one series, 44% of children younger than 5 years had palpable lymph nodes.[1] Other masses are congenital cysts and sinuses (3%), vascular malformations, salivary and thyroid anomalies, benign and malignant neoplasms, traumatic injuries, and nonlymphatic infections. Malignancy accounts for 10% to 15% of children hospitalized for evaluation of a persistent neck mass.[2-4] Although malignancy is uncommon, prompt diagnosis is crucial. Recent US trends show that the incidence of head and neck malignancies among children younger than 15 years increased at a greater rate than childhood cancer in general.[5]

Cervical lymphadenopathy (enlargement) and lymphadenitis (inflammation) are very common; only a few primary studies of etiology are recent and represent a minority of cases. Attempts to delineate the causes and causative agents of acute lymphadenitis have been based on analysis of specimens obtained through needle aspiration and surgical biopsy, or by serologic testing.

Staphylococcus aureus or *Streptococcus pyogenes* is isolated from 40% to 80% of culture-positive cases after aspiration of acutely inflamed, unilaterally inflamed nodes.[6,7] Community-acquired methicillin-resistant *S. aureus* (CA-MRSA) has emerged in more recent years.[8,9] Anaerobic organisms outnumber aerobic and facultative organisms in normal oropharyngeal flora by more than 10:1. In a study from 1980, anaerobic bacteria were isolated in 38% of cases when careful attention was paid to specimen collection and culture.[10] A 2013 study showed that anaerobic organisms were isolated in only 2% of anaerobic cultures in 277 patients requiring surgical intervention; however, 32% of cultures had no isolate.[11] Depending on many factors, especially pretreatment with antimicrobial therapy, no pathogen is isolated in at least 25% of cases of acutely inflamed nodes.[7,10]

For persistent cervical masses, biopsy may be needed for diagnosis. One large study from 1963 examined the biopsy results of persistent cervical masses in 267 children.[3] Congenital cyst or cystic hygroma was found in 60%, malignant tumors in 16%, benign tumors in 7%, nonspecific lymphoid hyperplasia in 10%, and tuberculous granuloma in 7%. The 46 malignant tumors were as follows: 20 lymphosarcoma or Hodgkin disease, 11 neurogenic tumors (neuroblastoma, neurofibroma, neurofibrosarcoma), 11 thyroid tumors, and 4 parotid tumors.

In a review of peripheral lymph node excisional biopsies performed in 239 children, a specific cause was found in only 41% of cases.[12] Of all excised nodes, 76% were located in the neck. Reactive hyperplasia accounted for 52% of cases, granulomatous diseases for 32%, neoplasia for 13% (cases suggestive of lymphoma before biopsy were excluded), and chronic lymphadenitis for 3%. Of the 31 cases of malignancy, Hodgkin lymphoma and non-Hodgkin lymphoma (NHL) accounted for 24, neuroblastoma for 4, and rhabdomyosarcoma for 3 cases. In this series, generalized lymphadenopathy was associated most often with reactive hyperplasia. Close follow-up of patients with a diagnosis of nonspecific reactive hyperplasia is important because studies indicate that up to 25% of such patients ultimately develop life-threatening lymphoreticular disease.[2,8,13,14]

The use of polymerase chain reaction (PCR) testing of surgical specimens has improved diagnostics in persistent, culture- or serology-negative cases. In a 2009 study of 60 children treated surgically for suspected infectious persistent cervical lymphadenitis, an etiology was identified in 82%.[15] Methods combining conventional stain and culture with PCR to amplify the eubacterial 16S ribosomal RNA followed by more specific pathogen amplification were used. Organisms identified were both tuberculous and nontuberculous *Mycobacterium* spp. (62%), followed by *Bartonella* spp. (10%) and *Legionella* spp. (10%). Interestingly, this is the first case series describing *Legionella* as a cause of persistent cervical lymphadenitis; diagnosis was made by PCR testing. As molecular diagnostics become more available, spectrum of causative agents of adenitis likely will increase.

Surgical biopsy results from children in developing countries show a slightly different spectrum of disease. A review of 1332 patients younger than 15 years over a 23-year span in South Africa showed 48% reactive nodes, 25% *Mycobacterium tuberculosis,* 11.6% neoplasm, and 11.5% chronic granuloma. Miscellaneous etiologies included syphilis, yaws, toxoplasmosis, sinus histiocytosis, and Kaposi sarcoma.[16]

Age is useful in predicting etiology of infection (Table 17.1). Group B *Streptococcus* is a common cause of lymphadenitis in young infants; *S. aureus* in infants and children; and *S. pyogenes, S. aureus,* and nontuberculous *Mycobacterium* (NTM) spp. in children 1 to 4 years old. Acute cervical lymphadenitis may be more common in the young child because of an inability to localize the organism to the initial nasal or pharyngeal site of attachment. In children aged 5 to 15 years and adults, anaerobic infection, toxoplasmosis, cat-scratch disease, and tuberculosis are important considerations.

TABLE 17.1

Age-Specific Causes of Cervical Lymphadenitis

	Patient Age			
Organism	**Neonate**	**2 Months–1 Year**	**1–4 Years**	**5–18 Years**
Group A *Streptococcus*	–	–	+	++
Group B *Streptococcus*	++	+	–	–
Staphylococcus aureus	+	++	++	++
Nontuberculous *Mycobacterium*	–	–	++	+
Bartonella henselae	–	+	++	++
Toxoplasma gondii	–	–	+	+
Anaerobic bacteria	–	–	+	++

++, Frequent cause; +, occasional cause; –, rare cause or never a cause.

Lymphatic Flow and Fascial Spaces of the Head and Neck

A complex and efficient lymphatic system has evolved to defend against microbial invasion of the head, neck, nasopharynx, and oropharynx, as shown in Table 17.2 and Fig. 17.1. There are three interrelated lines of defense. The ring of Waldeyer is composed of a circle of adenoidal, tonsillar, and lingual lymphoid tissue (see Chapter 16). A collar of superficial satellite lymph nodes runs along the lower margins of the jaw and encircles this ring. This outlying collar of nodes of the head consists of the occipital, postauricular, preauricular, parotid, and facial groups. Nodes of the neck are the salivary gland–associated submaxillary and submental nodes and the vertically oriented superficial and deep cervical chains.

TABLE 17.2

Physiology of Lymph Flow in the Head and Neck

Lymph Node Group	Areas Drained
HEAD	
Postauricular (mastoid)	Temporal and parietal scalp; posterior wall of ear canal; upper half of pinna
Occipital	Posterior scalp; skin of upper, posterior side of neck
Preauricular	Anterior and temporal regions of scalp; anterior ear canal and pinna; lateral conjunctivae
Parotid	Root of nose; eyelids; temporal scalp; exterior auditory meatus; parotid glands; middle ear; floor nasal activity; posterior palate
Facial	Eyelids, conjunctivae; skin and mucous membranes of nose and cheek; nasopharynx
NECK	
Submental	Central lower lip; floor of mouth; skin of chin; tongue tip
Submandibular (submaxillary)	Buccal mucosa; side of nose; medial palpebral commissure; upper lip; lateral part of lower lip; gums, anterior part of tongue margin, teeth
Superficial cervical	Anterior: superficial anterior neck tissues including skin, lower larynx, thyroid, cranial trachea
	Posterior: lower ear canal; parotid region
Superior deep cervical	Tonsil, adenoid; posterior scalp and neck; tongue, larynx, palate; thyroid; nose, nasopharynx; esophagus; paranasal sinuses; all nodes of head and neck except inferior deep cervical
Inferior deep cervical (scalene, supraclavicular)	Dorsal scalp and neck; superficial pectoral region of arm; superior deep cervical nodes; larynx, trachea; thyroid
	Right: left lower lobe, lingula, right lung and pleura
	Left: left upper lobe; entire abdomen

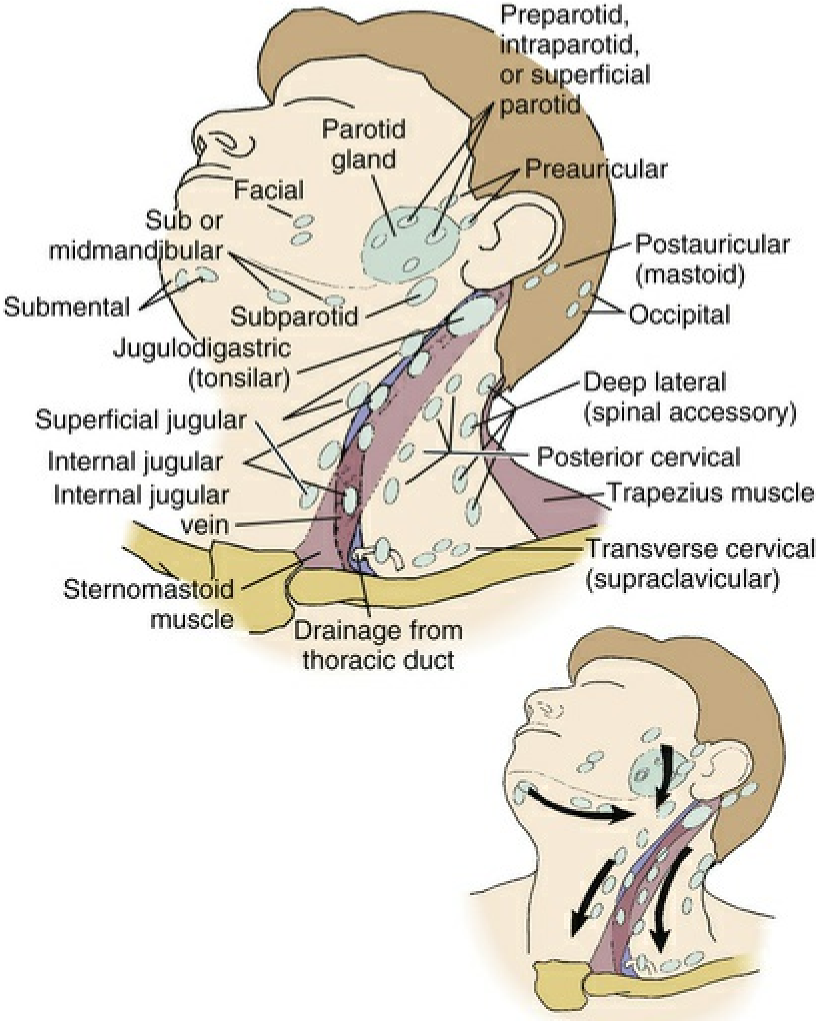


FIGURE 17.1 Lymphatic flow in the head and neck.

Occipital nodes often are enlarged when generalized lymphadenopathy is present; regional enlargement is almost always infectious and is due to tinea capitis, pediculosis capitis, seborrheic dermatitis, or scalp cellulitis or abscess. Enlargement of preauricular nodes reflects local skin or conjunctival infection. Asymptomatically enlarged parotid glands raise the possibility of malignancy.

Specific Lymph Node Groups

Superficial Cervical Nodes

The superficial cervical nodes in the neck are a disparate group composed roughly of three vertical chains. The *deep lateral or spinal* *accessory chain* runs behind the posterior border of the sternocleidomastoid (SCM) muscle and along the spinal accessory nerve. The *superficial cervical chain* follows the external jugular vein, which runs obliquely across the surface of the SCM muscle to empty into the subclavian vein in the supraclavicular triangle. The superficial *anterior chain* runs in the midline from the chin to the suprasternal notch and comprises, in descending order, the infrahyoid, prelaryngeal, pretracheal, and anterior cervical nodes. The term *posterior cervical nodes* is nonspecific, referring to nodes of the spinal accessory chain and those of the superficial cervical chain that lie over and behind the SCM muscle; lymph nodes anterior to the SCM muscle are designated as in the anterior triangle and those behind as in the posterior triangle.

Deep Cervical Nodes

The *deep cervical chain* of lymph nodes runs from the base of the skull to the root of the neck in close approximation to the internal jugular vein on the carotid sheath, and under the SCM muscle. This chain contains numerous large nodes and is divided into superior and inferior deep cervical groups. The *superior group* is above and the *inferior group* is below the point low in the neck where the omohyoid muscle crosses the internal jugular vein. The lymphatic channels and nodes in the head and neck connect, and ultimately all empty into the thoracic duct on the left or the lymphatic duct on the right, each of which in turn immediately empties into the respective subclavian vein.

The tonsillar or jugulodigastric node, which drains the palatine tonsil, belongs to the superior deep cervical group and lies at the angle of the mandible just below the posterior belly of the digastric muscle. Other deep cervical nodes lying under the SCM muscle along the internal jugular vein drain the adenoid, larynx, trachea, thyroid, palate, esophagus, paranasal sinuses, nasopharynx, occipital scalp, back of the neck, pinna, and much of the tongue. The large jugulo-omohyoid node that drains the tongue lies just above the omohyoid muscle where it crosses the internal jugular vein, which separates the superior and inferior deep cervical nodes.

Because most lymphatics of the head and neck drain to the submandibular and deep cervical nodes, these nodes are involved in more than 80% of cases of cervical lymphadenitis in young children.

The inferior deep cervical nodes lie low in the neck, below the omohyoid muscle and under and posterior to the anterior clavicular insertion of the SCM muscle. They lie in close approximation to the brachial plexus and to the entrance sites of the thoracic duct and right lymphatic duct into the left and right subclavian veins. All lymph from the head and neck, arms, superficial thorax, lungs, mediastinum, and abdomen passes through these nodes. The left supraclavicular nodes (Virchow-Troisier nodes) drain the left upper lobe of the lung, left mediastinum, stomach, small intestine, kidney, and pancreas. Enlargement of these nodes in the absence of cervical adenopathy suggests intra-abdominal tumor or inflammation (Troisier sign) or intrathoracic disease. The right supraclavicular nodes drain the left lingula and lower lobes as well as the entire right lung, pleura, and right mediastinum. Enlargement of these nodes most often indicates thoracic lesions, especially Hodgkin lymphoma and NHL. Prompt biopsy is indicated in the absence of easily documented pulmonary or cervical infection.

Deep Neck Infections

The fascial system of the neck is complex, but a general anatomic description is useful to understand the deep neck infections. The neck fascia is divided into two layers: the superficial layer and the deep layer. The deep fascia is further divided into the superficial, middle, and deep layers of the deep fascia (Fig. 17.2). The 11 *deep neck spaces* interconnect and include the lateral pharyngeal (parapharyngeal), retropharyngeal, prevertebral, "danger," masticator, submandibular, carotid, pretracheal, peritonsillar, parotid, and temporal spaces.[17]

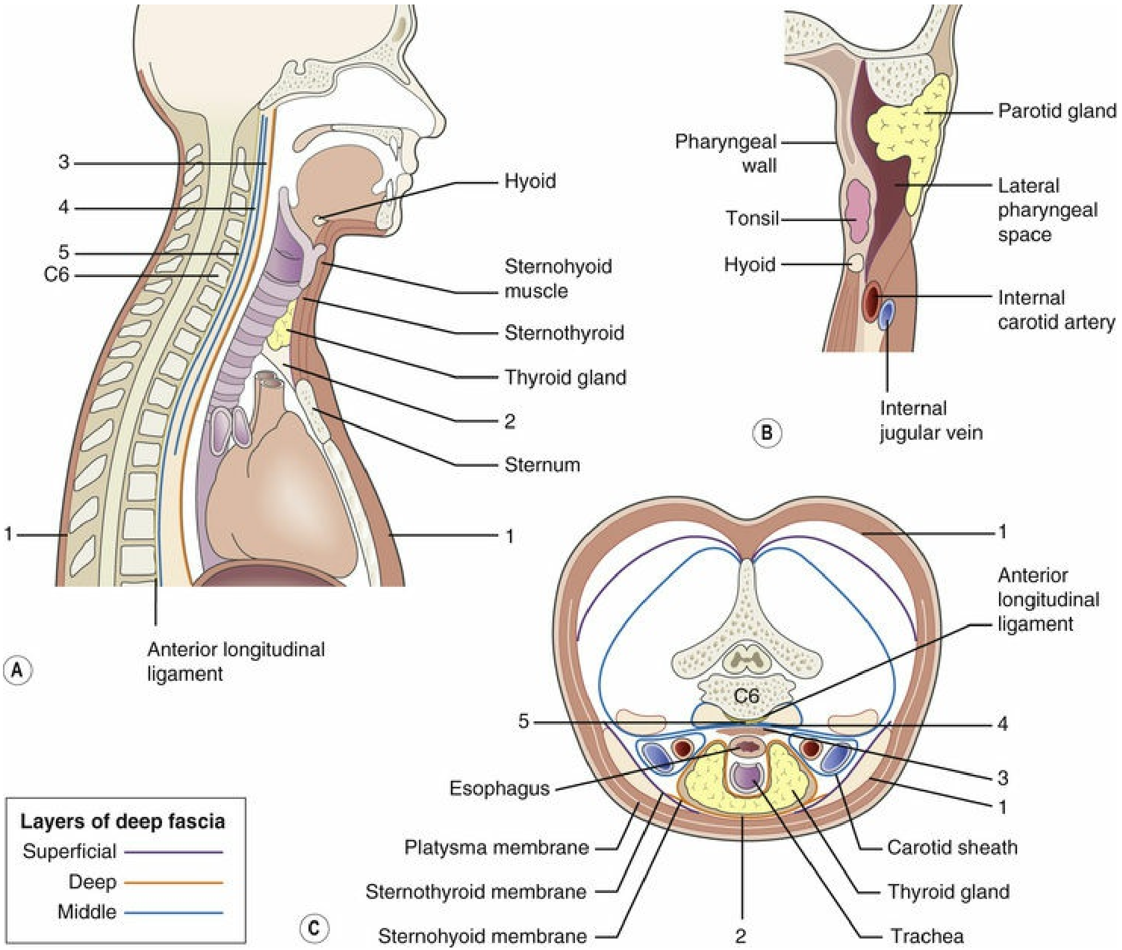


FIGURE 17.2 **Relation of the lateral pharyngeal, retropharyngeal, and prevertebral spaces to the posterior and anterior layers of the deep cervical fascia. (A) Midsagittal image of the head and neck. (B) Coronal image in the suprahyoid region of the neck. (C) Cross section of the neck at the level of the thyroid isthmus. In all illustrations, 1: superficial space; 2: pretracheal space; 3: retropharyngeal space; 4: danger space; 5: prevertebral space.** (From Mandell GL. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Disease. 7th ed. St. Louis, Elsevier, 2009. Reproduced with permission of Elsevier.)

The most clinically relevant deep neck spaces include the *submandibular*, *peritonsillar*, *retropharyngeal*, and *lateral pharyngeal spaces*. Infection in the submandibular space is known as *Ludwig angina*. Ludwig angina is a bilateral, brawny cellulitis that originates in the floor of the mouth. Infection of the retropharyngeal space is most common in children aged 2 to 4 years because the several small lymph nodes and space atrophy by adolescence. Infection in this space in older children and adults usually is secondary to direct trauma rather than to lymphatic spread. Cervical adenitis is not a common manifestation because these nodes drain into the prevertebral space; however, mediastinitis and empyema can occur. The peritonsillar space surrounds the palatine tonsil. Peritonsillar abscess is the most common deep neck infection, accounting for 50% of cases, and is more common in adolescents and young adults. Abscess usually is unilateral but can be bilateral. Cervical and submandibular adenopathy also can occur from drainage of the superior deep cervical nodes.[18,19]

The lateral pharyngeal space is a central connection for all other neck spaces, and thus infections can follow infection at various sites; presentation with unilateral cervical adenitis is common. The lateral pharyngeal space is divided into anterior and posterior compartments. Suppurative jugular thrombophlebitis (Lemierre syndrome) is a well-described complication of *Fusobacterium* infection of the posterior compartment, most commonly spread from primary tonsillitis. Along with sepsis because of proximity to the carotid sheath, swelling around the SCM muscle or "bull neck," neck pain and stiffness, and torticollis are common.[18,19] More detailed descriptions regarding neck space infections are found in Chapters 25 and 28.

Oculoglandular Syndrome of Parinaud

The oculoglandular syndrome of Parinaud consists of unilateral, chronic granulomas or ulcers of the conjunctivae associated with preauricular and submaxillary lymphadenitis.[20] Causes are listed in Box 17.1. *Bartonella henselae* infection is most common. Primary conjunctival inoculation causes grey or yellow granulomatous nodules or areas of focal necrosis, often surrounded by significant conjunctival chemosis and palpebral inflammation. Recovery without sequelae (except for occasional mild conjunctival scarring) occurs within 2 to 3 months. Antimicrobial therapy usually is given but has not been proved to hasten resolution.[21]

Box 17.1

Organisms Associated With Lymphocutaneous and Oculoglandular (Parinaud) Syndromes

Viruses

Herpes simplex

Bacteria

Treponema pallidum

Mycobacterium tuberculosis

Nontuberculous *Mycobacterium* spp.

Bartonella spp.

Francisella tularensis

Corynebacterium diphtheria

Spirillum minor

Chlamydia trachomatis

Bacillus anthracis

Nocardia brasiliensis

Yersinia spp.

Listeria monocytogenes

Fungi

Histoplasma capsulatum

Coccidioides immitis

Paracoccidioides spp.

Sporothrix schenckii

Parasites

Trypanosoma spp.

Rickettsia

Rickettsialpox

Rickettsia spp.

Infectious Causes of Lymphadenitis

For purposes of predicting etiology, most cases of infectious cervical lymphadenitis can be divided into the following three categories (with some overlap): (1) acute bilateral lymphadenitis; (2) acute unilateral lymphadenitis; and (3) subacute (chronic) lymphadenitis.

Acute Bilateral Lymphadenopathy/Lymphadenitis

Acute bilateral lymphadenopathy (less commonly lymphadenitis) most often is a localized response to acute pharyngitis or part of a generalized lymphoreticular response to systemic infection in older children. Usually, lymph nodes are small and soft, may or may not be tender, and are not associated with erythema or warmth of the overlying skin. Viral upper respiratory tract infection is the most common cause, followed by pharyngitis due to *S. pyogenes* and *Mycoplasma pneumoniae.*

Epstein-Barr Virus.

Although generalized lymphadenopathy is common in Epstein-Barr virus (EBV) infection, cervical adenopathy is most prominent and is present in 93% of infected children.[22] Enlargement usually is bilateral and most prominent in the posterior cervical chain, followed by the anterior cervical chain. Lymph nodes are enlarged singly or in groups; vary from 5 to 25 mm in diameter; and are firm, discrete, and minimally tender. Moderate splenomegaly occurs in 75% of patients. Significant enlargement of the lymphoid tissue in Waldeyer ring can result in nasopharyngeal and oropharyngeal airway obstruction.

Cytomegalovirus.

Mononucleosis due to cytomegalovirus (CMV) is similar to that due to EBV, although it is more frequent in children younger than 4 years.[22] Cervical adenopathy is less common in CMV infection (75%) than in EBV (95%) infection. Tonsillopharyngitis and sore throat are more common in EBV infection, whereas hepatosplenomegaly, upper airway obstruction, and rashes are more common in CMV infection.

Herpes Simplex Virus Infections.

Cervical, submaxillary, and submental nodes frequently are enlarged and tender during the course of primary gingivostomatitis due to herpes simplex virus (HSV). Primary infections of the conjunctivae and lids are accompanied by preauricular adenopathy. Localized or regional necrotizing lymphadenitis from primary HSV infection also has been reported as a rare occurrence.[23]

Adenoviral Syndromes.

Pharyngoconjunctival fever due to adenovirus is characterized by abrupt onset of fever, pharyngitis, and granular conjunctivitis (unilateral or bilateral). Hyperplasia of the tonsillar, adenoidal, and pharyngeal lymphoid tissue is present. A study from Spain showed that 32% of children with positive pharyngeal cultures for adenovirus had cervical node enlargement.[24] Preauricular adenopathy is surprisingly infrequent. Generalized adenopathy is present in 10% to 20% of patients with pharyngoconjunctival fever, and hepatosplenomegaly is common.

Preauricular adenitis occurs in 90% of patients with epidemic keratoconjunctivitis. One half of patients with the usually unilateral, acute, follicular conjunctivitis also have pharyngitis and rhinitis.[25]

Acute respiratory disease due to adenoviruses generally has significant constitutional as well as localized respiratory symptoms. Bilateral cervical adenopathy is expected.

Enteroviruses.

Nonspecific febrile illness due to coxsackieviruses and echoviruses generally has an abrupt onset. Manifestations include fever, malaise, sore throat, nausea, vomiting, and abdominal pain. Minimal conjunctival and pharyngeal erythema with bilateral cervical adenopathy is present.

Human Herpesvirus 6 and 7 (Roseola).

In one reported series of human herpesvirus 6 (HHV-6) infections in 688 children, mild bilateral cervical adenopathy was present in 31% of cases. Typically, the occipital, posterior auricular, and posterior cervical nodes are involved, but enlargement is modest.[26] HHV-7 also can cause roseola; however, the complete clinical picture of disease has not been defined.[27]

Human Herpesvirus 8.

HHV-8 generally is the etiologic agent of Kaposi sarcoma in severely immunosuppressed patients with human immunodeficiency virus infection. HHV-8 also has been associated with primary effusion lymphoma and multicentric Castleman disease. Primary infection in immunocompetent children, however, can cause fever, sore throat, morbilliform rash, and cervical lymphadenopathy.[28,29]

Rubella Virus.

In patients with experimentally induced rubella, lymph node enlargement begins as early as 7 days before the onset of the rash. Although generalized lymphadenopathy occurs, the nodes most commonly involved are the posterior auricular, suboccipital, and cervical nodes. Tenderness and swelling are most severe on the first day of the rash. Although tenderness of nodes subsides within 1 to 2 days, enlargement persists for weeks.

Parvovirus B19.

A mononucleosis-like syndrome due to parvovirus B19 infection can be associated with bilateral cervical and intraparotid lymphadenopathy. Generalized lymphadenopathy and hepatosplenomegaly also can be present. Facial palsy and parotitis can accompany intraparotid lymphadenopathy.[30]

Mycoplasma pneumoniae.

Physical examination of children and adults with pneumonia due to *M. pneumoniae* reveals cervical adenopathy in 25%, pharyngitis in

50%, and auscultatory findings in 75%. In patients in whom pharyngitis is the major manifestation, 43% have exudative tonsillitis and 50% have cervical adenopathy.

Corynebacterium diphtheriae.

Cervical adenitis is variable in tonsillar and pharyngeal diphtheria. In some cases, adenitis is associated with edema of the soft tissues of the neck ("erasive edema") so severe as to appear as to cause a bull-neck appearance. In other cases, lymphadenitis is minimal.

Acute Unilateral Lymphadenitis.

Table 17.3 summarizes clinical clues to and diagnostic tests for selected causes of unilateral cervical lymphadenitis.

TABLE 17.3

Clinical Clues and Diagnostic Tests for Selected Causes of Unilateral Cervical Lymphadenitis

Organisms	Clinical Clues	Diagnostic Tests
Staphylococcus aureus *Streptococcus pyogenes*	Acute unilateral adenitis; ages 1–4 years; 2- to 6-cm nodes, frequent associated cellulitis; 25%–33% become fluctuant For *S. aureus*, suppuration is rapid; without therapy, 85% of nodes suppurate	Throat culture for *S. pyogenes;* needle aspirate of node for Gram stain and culture
Group B *Streptococcus*	Ages 2–6 weeks; cellulitis-adenitis syndrome; facial or submandibular cellulitis; ipsilateral otitis media	Blood culture and aspirate of node or soft tissue for Gram stain and culture CSF evaluation if cellulitis-adenitis syndrome
Anaerobic bacteria	Older children; dental caries; periapical or periodontal disease present, Lemierre syndrome	Needle aspiration of node for Gram stain and culture; blood culture
Bartonella henselae	Most common cause of chronic unilateral adenopathy; contact with kittens; oculoglandular syndrome; inoculation papule present	Serologic analysis; culture of tissue with granulomas with stellate abscesses on biopsy, PCR
Nontuberculous *Mycobacterium*	Age 1–5 years; no systemic symptoms; no exposure to TB; unilateral submandibular node: normal chest radiograph and ESR; TST usually <15 mm	Characteristic granulomatous reaction; culture of excised node, PCR
Mycobacterium tuberculosis	Age >5 years; systemic symptoms with history of exposure to TB; bilateral lower cervical node involvement; elevated ESR	Positive TST and chest radiograph; culture of gastric aspirate, PCR
Toxoplasma gondii	Fever, fatigue, myalgia, sore throat; discrete <3 cm localized anterior cervical, suboccipital, or supraclavicular nodes; ± mediastinal adenopathy	Serologic analysis (laboratory with special expertise)

CSF, cerebrospinal fluid; ESR, erythrocyte sedimentation rate; PCR, polymerase chain reaction; TB, tuberculosis; TST, tuberculin skin test.

Staphylococcus aureus and *Streptococcus pyogenes*.

S. aureus or *S. pyogenes* infections account for 40% to 80% of cases of acute unilateral cervical lymphadenitis.[6,7] Typically, the patient is a 1- to 4-year-old child with a history of recent upper respiratory tract symptoms (sore throat, earache, coryza) or impetigo and signs of pharyngitis, tonsillitis, or acute otitis media. Few clinical findings distinguish streptococcal from staphylococcal infection.

The infected nodes, usually in the submaxillary or superior deep cervical chain, are 2.5 to 6 cm in diameter and tender, and often the overlying skin is erythematous and warm. Systemic symptoms, bacteremia, or metastatic foci of infection can occur. Occasionally, suppuration and periadenitis are so severe that torticollis is present and individual nodes cannot be palpated. Systemic symptoms such as high fever, toxicity, tachycardia, and flushed facies may be present. In up to one third of cases that come to medical attention, lymph node suppuration and fluctuation develop. Infection caused by *S. aureus* tends to have a longer duration of disease before diagnosis, a higher likelihood of suppuration, and slower resolution (Fig. 17.3).

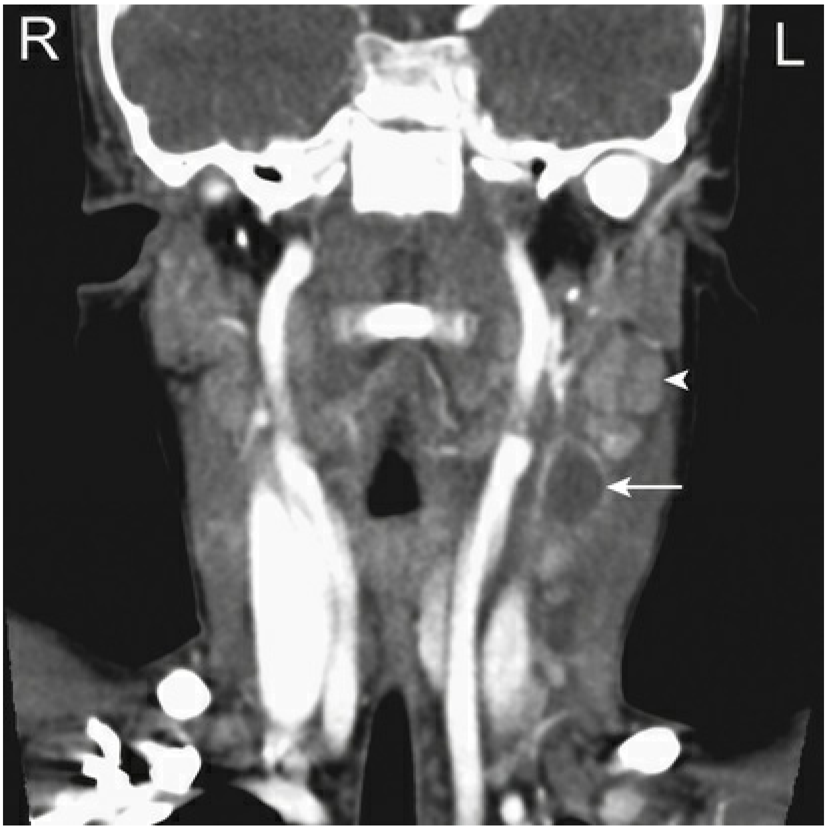


FIGURE 17.3 ***Staphylococcus aureus*** **neck infection. Note multiple left-sided inflamed nodes (*arrow*) and (*arrowhead*) abscess at the level of the hyoid.**

The role of *S. aureus* alone as a cause of acute unilateral lymphadenitis has been questioned. In a study from 1979, node aspirates from 65% of the patients yielded pure growth of *S. aureus*; 41% of these patients exhibited an immune response to one or more of the extracellular antigens of *S. pyogenes*.[31] Additionally, it has been observed that many children improve clinically with penicillin or ampicillin therapy alone, which would not be effective against β-lactamase−producing *S. aureus*. Recent studies suggest a predominant role of *S. aureus* (including CA-MRSA) compared with *S. pyogenes* when etiology is confirmed; however, recent serologic studies have not been performed.[8,9,32]

Streptococcus agalactiae (Group B *Streptococcus*).

Typically, the young infant with group B streptococcal cellulitis-adenitis (submandibular/cervical) syndrome has abrupt onset of fever, poor feeding, and irritability associated with unilateral facial or submandibular swelling that is erythematous and tender.[33] Bacteremia usually is present, and the organism is isolated from the aspirate of cellulitis or a lymph node. Ipsilateral otitis media is common. Meningitis is present in as many as 24% of infants with cellulitis-adenitis.[34] Suppurative submandibular lymphadenitis caused by *S. aureus* sometimes is distinguishable because of manifestation as a discrete mass and the propensity for suppuration.

Anaerobic Bacteria.

In older children with the acute onset of unilateral adenitis, an anaerobic infection secondary to periodontal or dental abscesses should be considered. Such infection can lead to septic thrombophlebitis of the jugular vein, septic pulmonary emboli, and central nervous system infection (Lemierre syndrome; see Chapters 25 and 28). Presentation is with bull neck, severe inflammatory response, systemic toxicity, and several positive blood cultures with isolation of *Fusobacterium* spp. or, less commonly, viridans streptococci.

Francisella tularensis.

Cervical lymphadenopathy alone or concurrent with other regional adenopathy was common in tularemia. In one series, lymphadenopathy (especially cervical nodes) was the most common manifestation, being present in 96% of patients; in 4 of 28 children, cervical nodes were the only enlarged nodes (Fig. 17.4).[35] One third of the children had late suppuration after antibiotic therapy. In untreated cases, the skin over the involved nodes is inflamed, and about 50% of nodes suppurate and drain. In the remainder of cases, the nodes remain firm, enlarged, and tender for several months.

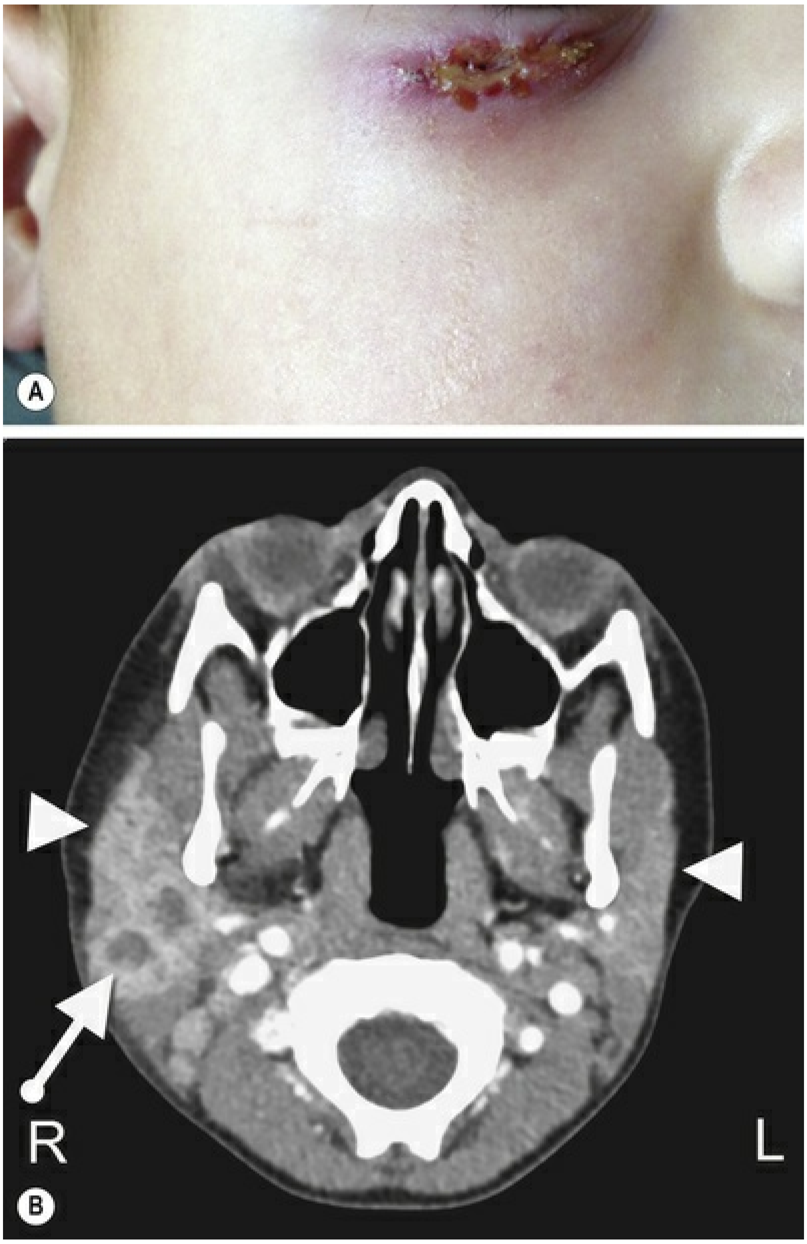


FIGURE 17.4 **Ulceroglandular tularemia in a 6 year old. (A) Ulcer at the site of inoculation with surrounding erythema. (B) Right-sided acute inflammatory parotitis with multiple suppurative lymph nodes within the parotid. Note normal parotid gland on the left.**

In oculoglandular tularemia, the eyelids become edematous, and the conjunctivae are inflamed and painful, with nodules and ulcers. Preauricular, submaxillary, and cervical nodes are enlarged, tender, and painful.

Pasteurella multocida.

After an animal bite or scratch on the head, neck, or upper chest, acute unilateral cellulitis due to *P. multocida* can be associated with tender cervical lymphadenitis.

Yersinia pestis.

Fleas from wild mammals, cats, and dogs in the western United States serve as the vectors for *Y. pestis* (bubonic plague). Organisms are carried in lymphatics to the nearest node, usually causing acutely enlarged, edematous, exquisitely tender, unilateral lymphadenitis with overlying erythema (bubo). Because animal bites occur more commonly on the extremities than around the head and neck, cervical adenopathy is the third most common site of involvement. Fever and other systemic manifestations accompany the appearance of buboes. Untreated, the nodes suppurate and ulcerate.

Unusual Organisms.

Rarely, gram-negative bacilli, *Streptococcus pneumoniae*, group C streptococci, *Nocardia brasiliensis, Yersinia enterocolitica, Staphylococcus epidermidis*, α-hemolytic streptococci, *Legionella* spp., or endemic fungi such as *Histoplasma* or *Coccidioides* spp. are isolated from a node. Immunodeficiencies such as Job syndrome and chronic granulomatous disease should be considered if a catalase-producing gram-positive or gram-negative organism is causative.

Subacute or Chronic Unilateral Lymphadenitis

Mycobacterial infections, cat-scratch disease, and toxoplasmosis are most commonly associated with subacute lymphadenitis. Typical finding is a painless or minimally tender, unilateral, swollen cervical or submaxillary node. If the lymph nodes enlarge and the disease progresses, the overlying skin becomes taut and effaced, with pinkish discoloration (although there is no increase in skin temperature). Skin becomes attached to the underlying mass. If the infection is untreated, fluctuation and spontaneous drainage (with or without formation of sinus tracts) usually follow. Suppuration from toxoplasmosis is rare.

Cat-Scratch Disease.

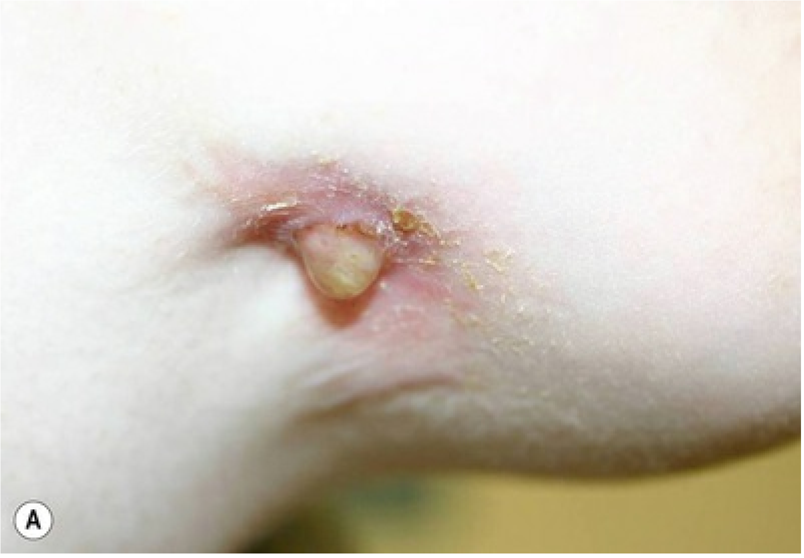
Cat-scratch disease is regional lymphadenitis that follows inoculation of *B. henselae* into damaged skin or mucosal membrane. The most common sites of lymphadenopathy are the axilla (52%) and neck (28%), presumably from scratches on the extremities and cuddling an animal, respectively. Adenopathy can begin 5 days to 2 months after inoculation. Generally, the affected node is solitary, often more than 4 cm in diameter, and tender. Constitutional symptoms usually are mild and include fever in up to 25% of cases. Overlying skin is not red or warm, but suppuration occurs in 30% to 50% of patients brought to medical attention. The oculoglandular syndrome of Parinaud, initially described in cat-scratch disease, is common.[16] Supraclavicular nodes can be involved from scratches on the neck or upper chest. Nonsuppurative nodes diminish in size after 4 to 6 weeks. Treatment probably aborts suppuration of larger nodes (see Chapter 160).

Toxoplasmosis.

In the 10% of patients with acquired toxoplasmosis who are symptomatic, lymphadenopathy and fatigue without fever are the most common manifestations.[36] The nodes most commonly involved are the cervical, suboccipital, supraclavicular, axillary, and inguinal. The involved nodes are discrete, may or may not be tender, and do not suppurate. Adenopathy is localized or involves multiple areas.

Nontuberculous *Mycobacterium.*

Infection due to NTM occurs in children 1 to 4 years old, and cervical adenitis is the most common manifestation in this age group. Organisms are ubiquitous in soil and probably are ingested; infection is localized to a submandibular or single tonsillar node. Bilateral involvement is rare. A recognizably enlarged node is usually the superficial marker of a large, deeper cluster. Initial appearance can be rapid (over 24 hours), with gradual increase in node size over 2 to 3 weeks. Most enlarged nodes are 3 cm or less in diameter, although enlargement to more than 5 cm can occur. Pain, tenderness, and constitutional illness are minimal. Approximately 50% of children with recognized lymphadenitis have fluctuant lesions, and in 10%, spontaneous drainage and sinus tract formation occur (Fig. 17.5A). The skin changes from pink to a distinctive lilac red, with the overlying skin developing a thin, parchment-like quality. In some cases, fluctuation without skin changes develops. Signs and symptoms of *M. tuberculosis* adenitis and NTM adenitis are identical (Fig. 17.5B). Other clinical and epidemiologic features are distinctive. Chest radiograph is normal in children with NTM infection, and an intermediate Mantoux tuberculin skin test results in less than 15 mm induration (usually 5 to 9 mm). Surgical excision generally is recommended unless proximity to nerves is concerning or cosmetic outcome is undesirable. Careful attention must be paid to the facial nerve location because more than 30% of patients have been reported to have some facial nerve injury postoperatively.[37] Incisional drainage is not recommended because the development of sinus tracts is possible. Therapy with antimicrobial agents active against NTM as adjunctive therapy may be useful in some situations[38-40] (see Chapter 135).



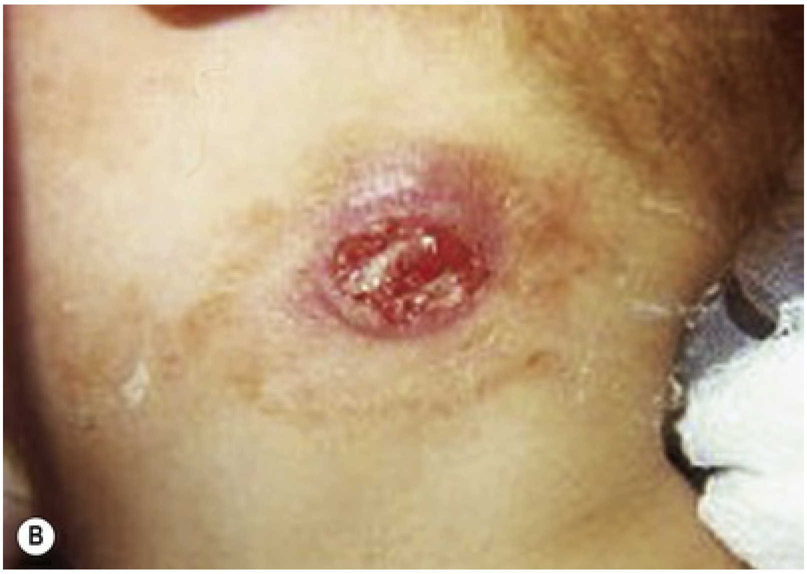


FIGURE 17.5 (A) Draining lymph node due to nontuberculous *Mycobacterium* infection. (B) Draining lymph node due to *Mycobacterium tuberculosis* infection. These are clinically indistinguishable. (A, Courtesy of J. Christenson, Indianapolis, IL.)

Mycobacterium tuberculosis.

Striking enlargement of the superficial regional lymph nodes is an integral part of the primary lower respiratory tuberculous complex. Involvement of the cervical nodes is most often the result of extension from the paratracheal nodes to the tonsillar and submaxillary nodes or from the apical pleurae and upper lung fields by direct spread to the inferior deep cervical (supraclavicular) nodes. Rarely, superficial lymph nodes are enlarged secondary to generalized adenopathy during the course of lymphohematogenous spread of infection (see Fig. 17.5B). Reactivation of quiescent tuberculous infection can manifest initially as localized or generalized adenopathy.

When superficial nodes are involved early in the infection, nodes usually are enlarged, painless, and rubbery.[41] Bilateral enlargement is the rule, but right-sided involvement can predominate. Acute nontuberculous respiratory tract infections can precipitate or aggravate tuberculous lymphadenitis, resulting in local pain and perilymphadenitis. Rarely, the patient is seen with a fluctuant mass and shiny, erythematous overlying skin. These nodes can rupture and drain chronically. Secondary infection with other pyogenic bacteria can occur. In general, clinical features do not distinguish tuberculous and nontuberculous mycobacterial infections, and diagnosis may be difficult if exposure to *M. tuberculosis* is suspected.[41] Surgical excision frequently is avoided with infection due to *M. tuberculosis* because infection usually extends into the mediastinum and responds to antituberculous therapy.

Actinomyces and *Nocardia* Species.

In cervicofacial actinomycosis, *Actinomyces israelii* causes a chronic, granulomatous suppurative infection of the soft tissues in and around the mandible. Although lymph nodes usually are not involved, chronic tissue induration can mimic chronic lymphadenopathy. Tissue destruction can be considerable without proper therapy.

The lymphocutaneous syndrome due to *Nocardia* spp. in children begins with a facial papular lesion followed by fever and an enlarged, tender, unilateral, submaxillary gland.[42] *N. brasiliensis* is the most common species causing the skin and lymph node cervicofacial syndrome. Lymphadenitis was associated with skin lesions in 58% of children in Texas with nocardiosis.[43] Lymphocutaneous nocardiosis can occur in healthy children, and an exhaustive search for an immunodeficiency is not necessary if there is a prompt response to trimethoprim-sulfamethoxazole therapy.

Calmette-Guérin Bacillus Vaccination.

When vaccination using Calmette-Guérin bacillus is given, painless enlargement of regional nodes (axillary, rarely cervical) can occur and presumably is due to multiplication of bacilli and formation of granulomas. Calcification or abscess formation with breakdown can occur, particularly in infants.[44] Rarely, regional adenitis can develop years after vaccination, especially if the individual becomes immunocompromised. Treatment is controversial, and spontaneous resolution of nonsuppurative lesions generally occurs without antimicrobial therapy in young children.[45]

Donovanosis.

Vertical transmission of *Klebsiella granulomatis* (granuloma inguinale or donovanosis) subacute cervical adenitis has also been described in two infants with concomitant otitis media and skin lesions. One child also had meningitis. Untreated vaginal ulcers were documented in both mothers during pregnancy[46,47] (see Chapter 139).

Noninfectious Causes of Lymphadenopathy

Kawasaki Disease.

Lymph node swelling is the least common of the principal diagnostic criteria of Kawasaki disease, occurring in 50% to 75% of patients. Lymphadenitis, one of the earliest manifestations, usually is unilateral and confined to the anterior triangle; the node is moderately tender. The enlarged node or mass of nodes usually is more than 1.5 cm in diameter and nonfluctuant, sometimes with overlying erythema. The ultrasound or computed tomography appearance of an acutely enlarged node due to Kawasaki disease differs from that of bacterial lymphadenitis and can be a useful diagnostic tool. In Kawasaki disease, suppuration does not occur, and edema of surrounding tissue is not pronounced.[48,49] Adenopathy of Kawasaki disease usually resolves early in the course of disease.

Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Cervical Adenitis (PFAPA).

First described in 1987,[50] PFAPA usually affects children younger than 5 years. Bilateral, modestly enlarged and tender cervical nodes are typical during febrile episodes; other lymph nodes are not affected.

Sarcoidosis.

The most common physical finding in children with sarcoidosis is peripheral lymphadenopathy. Involved cervical nodes are enlarged bilaterally and are discrete, firm, and rubbery. More than 80% of children have involvement of the supraclavicular nodes; bilateral hilar adenopathy is almost always present, along with nonspecific symptoms and other multisystem manifestations.

Sinus Histiocytosis With Massive Lymphadenopathy (Rosai-Dorfman Disease).

Rosai-Dorfman disease is a rare non−Langerhans cell histiocytosis that manifests in the first decade of life with mobile, discretely and asymmetrically enlarged lymph nodes, initially usually located in the neck.[51] With progression, the nodes become massively enlarged bilaterally and are painless and adherent to surrounding tissues. Other nodal groups (e.g., axillary, inguinal, and hilar nodes) and extranodal sites can be involved. Systemic manifestations of fever, leukocytosis, neutrophilia, anemia, elevated inflammatory markers, and hypergammaglobulinemia frequently are present. Histopathologic analysis demonstrates florid follicular hyperplasia, marked histiocytic proliferation, and prominent plasmacytosis. Resolution occurs spontaneously after 6 to 9 months, but therapy may be required for extensive or progressive disease.

Histiocytic Necrotizing Lymphadenitis (Kikuchi-Fujimoto Disease).

Kikuchi-Fujimoto disease is a benign, rare entity of unknown etiology that manifests in older children with bilaterally enlarged, firm, painful cervical nodes, most often in the posterior cervical triangle, which are unresponsive to antibiotic therapy. Perinodal inflammation is common. Associated findings in 50% of patients include skin lesions, fever, leukopenia with atypical lymphocytosis, and an elevated erythrocyte sedimentation rate. Those with prolonged fever are more likely to develop leukopenia.[52] Splenomegaly, nausea, weight loss, and night sweats can be present. Nodal histology showing necrosis and exuberant histiocytic infiltration is characteristic but can be confused with that of malignant lymphoma. No other diagnostic test is available. Symptoms resolve in most patients a few days after excisional biopsy. Viral etiology is suspected based on a few reports of serologic studies suggesting EBV, CMV, human T-lymphotropic virus, HHV-6, and parvovirus B19 infection.[53] Kikuchi-Fujimoto disease also has been shown to occur in association with or preceding systemic lupus erythematosus in some cases. In most cases the prognosis for spontaneous resolution of Kikuchi-Fujimoto disease is excellent.[54,55]

Kimura Disease.

Kimura disease is a chronic, benign, but potentially disfiguring unilateral, localized cervical lymphadenopathy of Asians, most often males of Chinese or Japanese descent. Insidious onset of painless, subcutaneous nodules overlying the affected lymph nodes occurs. Eosinophilia and a marked increase in serum immunoglobulin E are present. Renal involvement can occur, with proteinuria present in 12% to 16% of cases.[56] Resection, irradiation, or corticosteroid therapy can be associated with recurrences.[57,58]

Neck Masses Not Involving Lymph Nodes

Tumors of the Head and Neck

The differential diagnosis of neck masses includes congenital cysts and sinuses, vascular malformations, salivary and thyroid anomalies, and benign and malignant neoplasms of nonsquamous origin.

Malignancy should be considered, particularly in older children with a painless, firm, cervical mass more than 3 cm in diameter that is fixed to the deep cervical tissues, has grown rapidly, or is located in the supraclavicular area or posterior triangle of the neck. Such masses can be multiple and can extend across the anterior and posterior triangles. The incidence of all pediatric cancer has increased in the past few decades; however, the incidence of pediatric neck masses over the same timeframe has increased at a greater rate. Teenagers 15 to 18 years old are the most frequently affected (39%), followed by children aged 4 years and younger (27%).[5]

Fifty percent of masses in the posterior triangle are malignancies, most of lymphoid origin. Fifty percent of all malignant neck masses in children are Hodgkin lymphoma or NHL; neuroblastoma is the next most common, accounting for 15%, followed by thyroid tumors. Soft tissue sarcomas, including primary rhabdomyosarcoma and carcinoma of salivary glands and the nasopharynx, also occur. Age is predictive of diagnosis; in children younger than 6 years, the most common malignancies, in order of decreasing frequency, are neuroblastoma, NHL, rhabdomyosarcoma, and Hodgkin lymphoma. In patients 7 to 15 years old, Hodgkin lymphoma and lymphosarcoma occur with equal frequency, followed by thyroid carcinoma, rhabdomyosarcoma, and parotid adenocarcinoma.

Soft tissue sarcomas manifesting in the neck are primary rhabdomyosarcoma and undifferentiated sarcomas. Rhabdomyosarcoma accounts for 18% of all solid carcinomas in children; of these, 36% manifest in the head and neck region, usually as an asymptomatic mass or with symptoms related to location.

Hodgkin lymphoma most commonly manifests as an asymptomatic cervical or supraclavicular mass. Upper cervical nodes are three to four times more likely to be involved than supraclavicular nodes. NHL is more likely to be associated with systemic symptoms, including fever and leukocytosis with pronounced neutrophilia, and cervical lymph node involvement, which can be unilateral and associated with massive swelling. Cervical adenopathy is a primary symptom in only 11% to 35% of patients with Hodgkin lymphoma, and extranodal head and neck masses are unusual.[59]

Congenital Cysts and Sinuses

Multiple congenital cysts and sinuses related to embryologic development can manifest as infection or as the sudden appearance of a mass as if infected.[60] Recurrence of a suppurative mass in exactly the same location should lead to evaluation for an underlying congenital lesion.[61] Table 17.4 delineates noninfectious causes of neck masses in children.

TABLE 17.4

Noninfectious Causes of Neck Masses[a]

Condition	Comments
CONGENITAL ANOMALIES	
Thyroglossal duct cyst	Most common congenital neck mass; discrete 1-cm midline nodule that may elevate with tongue protrusion; elective excision best; may contain only existing thyroid tissue
Second pharyngeal (branchial) cleft	Second most common congenital neck mass; anterior to upper or middle one third of sternomastoid muscle; external sinus opens anterior

anomaly	to sternal head of muscle; tract needs to be excised; cyst associated with lymphatic tissue
Cystic hygroma	Third most common congenital neck mass; occurs along jugular lymphatic chain in posterior supraclavicular fossa; failure of mesenchymal clefts to fuse; varies from few centimeters to massive collar-like lesions; may extend into mediastinum
Dermoid or epidermoid cysts	Midline, deep to mylohyoid muscle; soft, fluid-filled midline mass; may elevate with tongue protrusion; contain caseous material or epithelial debris
NONLYMPHOMATOUS MALIGNANCIES	
Neuroblastoma	Second most common malignant neck mass in children (first in younger children)
Thyroid cancer	Third most common neck malignancy (first in 11–18 years); high incidence of malignancy in thyroid nodules; prompt biopsy required
Rhabdomyosarcoma	Most common nasopharyngeal malignancy in children
Nasopharyngeal carcinoma	Cervical adenopathy often initial and only symptom; arises most often in fossa of Rosenmüller
Parotid tumors	Vascular anomalies most common; asymptomatic node may be malignant and should be excised
MISCELLANEOUS	
Sternocleidomastoid tumor	Fibrous mass within muscle; detected at 2–4 weeks of age in 0.4% of infants; head turned away from mass; ipsilateral facial hypoplasia
Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease)	Bilateral, painless cervical nodes; generalized lymphadenopathy may develop; systemic manifestations include fever and hypergammaglobulinemia; self-limited
Giant lymph node hyperplasia (Castleman disease)	Asymptomatic lymphadenopathy in mediastinum or neck; systemic symptoms include fever and hypergammaglobulinemia; surgical removal curative (see Chapter 18)
Histiocytic necrotizing lymphadenitis (Kikuchi-Fujimoto disease)	Asymptomatic cervical or generalized adenopathy; skin lesions, fever, and leukopenia; spontaneous resolution; recurrences possible
Kimura disease	Benign, chronic, unilateral lymphadenopathy; adjacent subcutaneous nodules, peripheral eosinophilia and increased serum immunoglobulin E, proteinuria and renal involvement possible

[a] For review of lymphomas, see Chapters 16 and 18.

Branchial Cleft Cysts and Sinuses.

During the fifth week of embryologic development, four endodermal pharyngeal pouches fuse with four ectodermally derived clefts and are obliterated. Rarely, they are not completely obliterated, and persistence of the cleft can result in a cystic mass or sinus tract that is prone to infection. Persistence of the first pharyngeal cleft results in a sinus tract opening just behind the ramus of the mandible. Cystic components of the tract, which extends to the external ear canal, often are more extensive than is apparent clinically. Persistence of the second cleft is most common, the opening of which is just anterior to the sternal attachment of the SCM muscle. The unseen tract extends the length of the SCM muscle, beginning at the tonsillar bed. Cysts, with potential for acute enlargement, can occur anywhere along the length of the tract. Anomalies of the second and third cleft are indistinguishable. Because the thymus also is derived from the third cleft, thymic duct remnants can be seen as soft, fluctuant, mobile paratracheal masses low in the neck. Surgery usually is required to remove the sinus tract or cyst to prevent recurrences.

Midline Sinuses and Cysts.

Dermoid or epidermoid cysts are embryologic defects in fusion. They occur as painless, soft, fluid-filled midline masses.

Thyroid tissue originates embryologically at the base of the tongue and descends the thyroglossal duct to its usual site anterior to the proximal end of the trachea. Although the tract usually is obliterated, cysts can form along its course, appearing as 1-cm midline nodules. Retaining attachment to the base of tongue, such cysts elevate on tongue protrusion. It is important to determine the presence and position of thyroid tissue, because cysts may contain the only functional gland. Nodules within the thyroid gland have a high incidence of malignancy in children. A thyroid mass in the neonate most often is a congenital goiter or a teratoma.

Lymphangiomas.

In the sixth embryologic week, clefts develop in the cervical mesenchyma, which subsequently fuse to form lymph channels and lymph nodes. Sequestration, or failure to communicate with the rest of the lymphatic system, leads to tumor-like masses of lymph channels most commonly found along the external jugular chain of lymphatics in the lateral cervical region. Lymphatic masses vary in size from a few centimeters to massive collar-like lesions with extension into the mediastinum. In the larger lesions, lymphatic channels dilate into cystic spaces, and the lesion is called a *cystic hygroma*. Most cystic hygromas are posterior to the sternomastoid muscle in the supraclavicular fossa. Sixty-five percent are present at birth and gradually increase in size as a result of obstructed flow or bleeding; the remainder almost always appear before age 2 years (Fig. 17.6).

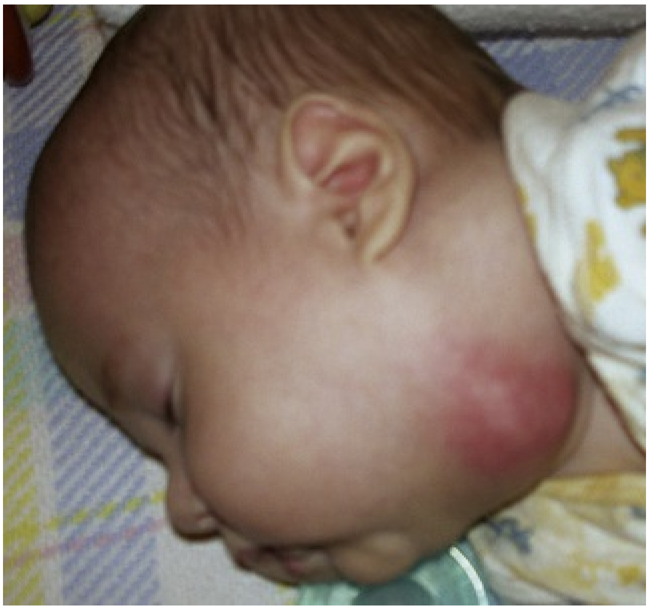


FIGURE 17.6 Cystic hygroma in a 2-month-old child, infected secondarily with group B *Streptococcus*.

Salivary and Thyroid Gland Masses

Parotid Gland Masses.

Parotid tumors are rare. The most common parotid masses are vascular anomalies, usually capillary hemangiomas and rarely cavernous hemangiomas. Large cavernous hemangiomas can disfigure and destroy tissue, whereas capillary hemangiomas usually resolve by the age of 4 or 5 years without any permanent findings. Parotid gland enlargement in childhood can result from calculus formation or recurrent sialectasia, in which case the parotid gland becomes rubbery, firm, and tender but has no signs of inflammation. Parotid infections are discussed in Chapter 25.

Thyroiditis.

Infection of the thyroid gland is rare but potentially is life threatening. Infection can arise by the hematogenous route or directly from an adjacent fascial space infection, from a patent foramen cecum and infected thyroglossal duct cyst, or from anterior esophageal perforation. Suppuration usually results from infection of pyriform sinus fistula or thyroglossal duct remnant. The most common aerobic pathogens are *S. aureus,* group A streptococci, pneumococci, and viridans streptococci. Anaerobic bacteria also are isolated, with the most common being gram-negative bacilli including *Prevotella* spp. and *Peptostreptococcus* spp. Other pathogens are *Haemophilus influenzae, Eikenella corrodens,* and *Actinomyces* spp., with rare reports of enteric gram-negative bacilli, mycobacteria, and fungi.[62,63]

History and physical examination identify acute onset of fever, chills, sore throat, dysphagia, hoarseness, and an extremely tender, red, warm, and enlarged gland. Involvement can be unilateral or bilateral; pain can be referred to the ear or chest. Results of thyroid function tests usually are normal. Laboratory investigation of thyroiditis should include ultrasonography, radionuclide scan, or computed tomography to detect paratracheal extension; needle aspiration is performed for diagnostic microbiology. With prompt and aggressive therapy, complete resolution without abscess formation is expected.

Subacute (de Quervain) thyroiditis is a poorly defined, self-limited condition characterized by an insidious onset with tenderness and marked induration of the gland. The sedimentation rate is high, and biopsy reveals acute and chronic inflammation with granulomatous changes. In most cases, the cause is a virus, such as mumps virus, influenza virus, enterovirus, adenovirus, echovirus, EBV, or, rarely, St. Louis encephalitis virus.[63] Mild and transient manifestations of hypermetabolism and elevated thyroid hormone levels can be present. Differentiation from bacterial thyroiditis can be difficult.

Diagnostic Approach to Cervical Lymphadenopathy

The assessment and specific evaluation and management of cervical lymphadenopathy and lymphadenitis are directed by integration of the history and initial examination (Table 17.5). In young infants with acute unilateral involvement and systemic manifestations, causative agents can be expected to be *S. aureus,* group B *Streptococcus,* or gram-negative organisms. Blood, as well as aspirate of the node or cellulitis, is obtained for culture. Examination of cerebrospinal fluid should be considered in young infants if the etiology is group B *Streptococcus*. Isolated finding of discrete small cervical nodes in a healthy infant is likely to be normal (see Table 17.1). Associated findings may lead to evaluation for congenital infection in other patients.

TABLE 17.5

Mode of Onset and Characteristics of Lymph Nodes Infected by Selected Organisms

	Mode of Onset		Characteristics		
Pathogen	**Acute**	**Subacute/Chronic**	**Suppuration**	**Cellulitis**	**Generalized Adenopathy**
BACTERIA					
Staphylococcus aureus	++++	–	++++	++++	–
Streptococcus pyogenes	++++	–	+++	++++	+
Anaerobic bacteria	+++	–	+++	++	–
Bartonella henselae	–	++++	+++	+	+
Francisella tularensis	+++	++	+++	+++	–
Yersinia enterocolitica	++	++	+++	+	+
Pasteurella multocida	+++	–	+	+++	–
Yersinia pestis	++++	–	++++	++	–
Nontuberculous *Mycobacterium*	+	++++	+++	+	–
Mycobacterium tuberculosis	+	++++	+++	+	+++
Group B *Streptococcus*	+++	–	+	+++	–
Calmette-Guérin bacillus	+	++	++	–	–
Mycoplasma pneumoniae	+	+	–	–	–
Nocardia brasiliensis	++	++	++	–	–
Actinomyces israelii	–	++	++	–	–
VIRUSES					
Epstein-Barr	+++	++	–	–	++++
Cytomegalovirus	++	++	–	–	+++
Hepatitis A, B	+	+	–	–	+
Herpes simplex	++++	–	–	++	–
Human immunodeficiency	–	++	–	–	+++
Adenovirus	+++	–	–	–	+
Rubella	+++	–	–	–	+++
Rubeola	+++	–	–	–	+++
Influenza	+++	–	–	–	
Human herpesvirus 6	++	–	–	–	–
Enterovirus	++	–	–	–	+
Parvovirus B19	+++	–	–	–	+++
PROTOZOA					
Toxoplasma gondii	++	+++	–	–	+

++++, Characteristic; +++, frequently associated; ++, occasionally associated; +, rarely associated; –, not known to be associated.

The older child with bilateral, soft, discrete, minimally tender, and minimally enlarged (<2 cm) nodes high in the neck who has had respiratory tract symptoms and fever usually has a viral infection, or may have streptococcal pharyngitis or *M. pneumoniae* infection. In roseola, rubella, adenoviral, or enteroviral infections, cervical adenopathy is frequently in the suboccipital, posterior auricular, or superficial posterior cervical areas (Table 17.6).

TABLE 17.6

Associations of Selected Organisms With Involvement of Specific Lymph Node Groups in the Neck

	Lymph Node Group					
Pathogen	**Preauricular**	**Postauricular**	**Occipital**	**Submaxillary**	**Tonsillar**	**Anteric Cervica**
BACTERIA						
Staphylococcus aureus	–	–	++	++	++++	+++
Streptococcus pyogenes	–	–	++	++	++++	+++
Anaerobic bacteria	–	–	–	++++	++	++
Arcanobacterium haemolyticum	–	–	–	+	+++	+++
Mycoplasma pneumoniae	–	–	–	++	++	++
Francisella tularensis	++	–	–	++	+	++
Mycobacterium tuberculosis	–	–	–	+++	+++	–
Nontuberculous *Mycobacterium*	++	–	–	+++	+++	–
Bartonella henselae	++++	–	–	+	+++	+++
Nocardia brasiliensis	–	–	–	++++	+	–
VIRUSES						
Herpes simplex	–	–	–	+++	+++	+
Rubeola	–	++	++	–	–	–
Rubella	–	+++	+++	–	–	–
Human herpesvirus 6	–	++	++	–	–	++
Epstein-Barr	–	–	++	++	++	++
Keratoconjunctival fever	++++	–	–	–	–	–
Pharyngoconjunctival fever	±	–	–	–	–	++
Parvovirus B19	++	–	–	+	+	+
PROTOZOA						
Toxoplasma gondii	–	–	–	–	–	–
Trypanosoma cruzi	+	–	–	–	–	–
FUNGI						
Tinea capitis	–	+	++++	–	–	–
Histoplasma capsulatum	–	–	–	–	–	++
Coccidioides immitis	–	–	–	–	–	–

++++, Characteristic site of adenopathy; +++, additional site, often associated; ++, occasional site; +, rare site; –, not described.

If nodes are large and minimally tender, with no overlying cellulitis, mononucleosis due to EBV or CMV is likely. For protracted or unusual cases, sarcoidosis, Kikuchi-Fujimoto and Rosai-Dorfman diseases are considered.

When acute unilateral or bilateral adenopathy is associated with an obvious site of infection, diagnostic studies are focused on the site. Obvious sites of infection include herpes simplex ulcerations, infected abrasions, scalp infections, animal bites or scratches, and conjunctival granulomas.

Acutely inflamed, unilateral, tender large nodes with associated periadenitis and cellulitis, fever, and constitutional symptoms, often with poor node definition and torticollis, are usually due to *S. aureus* or *S. pyogenes* in the young child[64] (see Tables 17.3 and 17.5). In older children and adolescents, a dental focus with resulting anaerobic infection should be considered. Failure to respond to antibiotic therapy after 48 hours leads to evaluation for antimicrobial resistance, an abscess or a more unusual cause such as Kawasaki disease, and infected or uninfected congenital cysts and sinuses.

The most challenging problem is the patient with a unilateral, asymptomatic, initially noninflamed, nontender, firm node of acute or subacute onset. Some such nodes become fluctuant and develop the characteristic findings of cat-scratch disease or nontuberculous mycobacterial disease, whereas others do not change over time.

It is important to identify toxoplasmosis, tuberculosis, and lymphoma or another malignancy as soon as possible to initiate appropriate therapy if indicated. Accurate measurements of the size and consistency of such nodes should be performed once or twice a week to determine whether malignancy should be considered. The presence of systemic symptoms, hepatosplenomegaly, pneumonia, or mediastinal adenopathy is suggestive of tuberculosis or malignancy.

Guidance for biopsy of lymph nodes to rule out a malignancy is provided in Box 17.2. If an excisional biopsy is performed and nonspecific hyperplasia is reported, the patient must be followed carefully because 25% of patients with such findings are ultimately found to have a lymphoreticular malignancy.

Box 17.2

Settings That Prompt Early Consideration of

Biopsy of Enlarged Cervical Lymph Node to Rule Out Malignancy

Site

Supraclavicular

Posterior cervical (particularly with extension across sternomastoid muscle to involve anterior and posterior triangles)

Deep to fascia

Size

>2 cm diameter

Continued enlargement after 2 weeks

No significant decrease in size after 4–6 weeks

Not normal in size after 8–12 weeks

Consistency

No inflammation

Nontender (unless rapidly enlarging)

Firm, rubbery, or matted (may be fixed to underlying structures)

Ulceration

Potential Local or Systemic Spread

Mediastinal or generalized adenopathy

Bone marrow involvement

Fever, weight loss, hepatosplenomegaly

Recurrent epistaxis, progressive nasal obstruction, facial paralysis, or otorrhea

No Evidence to Support an Infectious Etiology

Negative results of evaluation for infectious causes

No response to empirically chosen antibiotics

Needle Aspiration

Needle aspiration of the infected node is a valuable diagnostic tool for acute and subacute lymphadenitis and also can be therapeutic. In 60% to 90% of patients with acute cervical lymphadenitis in whom needle aspiration is performed for bacterial and mycobacterial culture, an etiologic agent is recovered.[6,7,13,65] The procedure is safe and easy to perform and has no serious complications. Controversy exists as to whether a persistently draining fistula is precipitated by aspiration if the lymphadenitis is due to mycobacterial infection. The preponderance of data suggests that aspiration (unlike incision and drainage) is not contraindicated and is greatly useful to direct definitive therapy. Because tuberculous and nontuberculous diseases are difficult to distinguish clinically, fine-needle aspiration is a useful diagnostic tool if *M. tuberculosis* exposure is possible. Rapid identification by molecular methods also is being used as a diagnostic tool using needle aspiration samples.[66,67]

The specimen is obtained from the largest and most fluctuant node. If no material is aspirated, saline is injected into the node and repeat aspiration performed. Gram and acid-fast stain should be performed, and the specimen should be inoculated onto media for growth and isolation of anaerobic and aerobic bacteria, fungi, and mycobacteria. If no visible specimen is obtained, the needle and syringe can be flushed into a blood culture flask.

Lymph Node Biopsy

If the diagnosis remains in doubt and the enlarged lymph node fails to regress, enlarges further, is hard, or is fixed to adjacent structures, biopsy should be performed. An accelerated schedule for biopsy is appropriate in the presence of persistent fever or weight loss (in the absence of confirmed diagnosis) or if firm lymph nodes are found in the posterior cervical triangle or supraclavicular area (if *M. tuberculosis* and *B. henselae* are excluded). These settings are associated with greater possibility of malignancy.

Excisional biopsy (to establish lymph node architecture and complete histologic character) is preferred to incisional biopsy of lymph nodes, although some studies support the use of fine-needle aspiration as an initial diagnostic mechanism; negative or nonspecific findings do not exclude malignancy.[68,69] Yield from biopsy is maximized through careful choice of tissue site and proper handling of resected tissue. Generally, the largest, firmest nodes should be excised. Whenever possible, more than one node should be obtained. When several groups of nodes are involved, biopsy specimens taken from the lower neck and supraclavicular area (or a region other than the neck) have higher diagnostic yield than those taken from high cervical nodes. If EBV or toxoplasmosis is expected, biopsy is carefully considered because of the difficulty of discrimination of such diseases from malignancy and the ability to confirm both diagnoses by serologic testing. If lymphoma is suspected, needle biopsy or frozen section is unreliable for excluding the diagnosis. When nontuberculous mycobacterial infection is suspected and surgery is required for diagnosis and therapy, excisional dissection of deep nodes may be necessary. The individual situation dictates specific evaluations of excised tissue, but evaluation commonly consists of flow cytometry; special stains, including Giemsa, periodic acid–Schiff, methenamine silver, and Warthin–Starry silver stains; and, in selected cases, testing by in situ hybridization, PCR, or electron microscopy. Culture for facultative and anaerobic bacteria, mycobacteria, and fungi is appropriate.

Many reactive processes simulate malignant histology and may make definitive diagnosis impossible. Examples are dysregulated inflammatory responses as with rheumatoid arthritis, phenytoin-induced adenopathy, dermatopathic adenitis, and infections such as toxoplasmosis and EBV mononucleosis. A thorough history and a second series of evaluations, including serologic tests, are essential for making a correct diagnosis of these cases.

Management

Initial Therapy

Children with bilaterally enlarged cervical lymph nodes (<3 cm in size) that are not erythematous or exquisitely tender are observed without evaluation or therapy. If the initial findings are typical of acute bacterial lymphadenitis (unilateral node, >2 to 3 cm, erythematous, and tender) without systemic symptoms, empiric therapy is given for *S. aureus* and *S. pyogenes* infection unless the course or findings are typical for *S. pyogenes* (Table 17.7). Therapy usually is given for 10 days or at least 5 days beyond resolution of acute signs and symptoms, whichever is longer. Knowledge of local resistance patterns of *S. aureus* is important when choosing empiric therapy. Antimicrobial resistance or alternative pathogens should be considered if empiric antimicrobial therapy fails. If a primary focus of infection is identified elsewhere, the mode and duration of therapy are directed in reference to that site as well. Impetigo and other skin infections usually are caused by *S. aureus* and *S. pyogenes.* Dental or periodontal disease leads to lymphadenitis due to anaerobic bacteria. A culture should be obtained from suppurative sites whenever possible. Aspiration of the inflamed site should be performed if moderate to severe adenitis with cellulitis and constitutional symptoms is present or if no improvement occurs after 48 to 72 hours of therapy. In the latter instance, additional diagnoses are considered, including viral infection, Kawasaki disease, nontuberculous mycobacterial infection, and more unusual causes of adenitis. If cat-scratch disease is suspected, *Bartonella*-specific antimicrobial therapy is given if a node is larger than 3 cm, in an attempt to avoid abscess formation (see Chapter 160).

TABLE 17.7

Treatment of Acute Bacterial Cervical Lymphadenitis

Presumed Pathogen and Setting	**Empiric Therapy (Consult Local Antibiogram)**	**Route/Duration**	**Diagnostic Tests**
STAPHYLOCOCCUS AUREUS* OR *STREPTOCOCCUS PYOGENES			
No prominent systemic symptoms, cellulitis, or suppuration	Amoxicillin-clavulanate, cephalexin, or clindamycin (TMP-SMX if MRSA known, not for *S. pyogenes*)	PO/10 days or 5 days past resolution of symptoms, whichever is longer	Routine culture (+ PCR for MRSA)
With cellulitis, marked	Nafcillin, cefazolin, or clindamycin; vancomycin	IV/10 days or 5 days past resolution of	Routine culture (+ PCR for MRSA)

enlargement, moderate or severe symptoms	or clindamycin for MRSA	symptoms, whichever is longer. Consider PO after clinical improvement	
With suppuration	Needle aspiration if no improvement after 48 hours, consider parenteral antibiotics as above and incision and drainage	IV/10 days or 5 days past resolution of symptoms, whichever is longer. Consider PO after clinical improvement	Routine culture (+ PCR for MRSA)
GROUP B *STREPTOCOCCUS* OR *STAPHYLOCOCCUS AUREUS*			
Infant <2 months with cellulitis with or without systemic symptoms or adenitis	Nafcillin or oxacillin	IV/10–14 days	Routine culture (+ PCR for MRSA)
	Vancomycin if MRSA rates high (evaluate for meningitis if group B *Streptococcus*)		
ANAEROBIC BACTERIA			
Associated dental or periodontal disease, bull neck	Clindamycin or penicillin plus metronidazole	PO or IV, depending on anatomic locations and severity of disease	Anaerobic culture
	(Alternative piperacillin/tazobactam or carbapenem if severe disease)		
BARTONELLA HENSELAE			
Fluctuant or draining node; systemic manifestations	Needle aspiration of node; consider use of azithromycin, rifampin, ciprofloxacin, TMP-SMX, or gentamicin (see Chapter 160)	PO, IV/optimal duration not known	Serologic analysis, PCR, granulomas on tissue, Warthin-Starry silver stain of tissue
NONTUBERCULOUS *MYCOBACTERIUM*			
TB ruled out; node not draining	Excision of node or see Chapter 135		TST, mycobacterial culture, tissue PCR, granulomatous reaction
Mycobacterium tuberculosis	See Chapter 134		TST, mycobacterial culture, tissue PCR, granulomatous reaction, Interferon-γ release assays
FRANCISELLA TULARENSIS			
Acute onset, fever; diagnosis reasonably certain	Streptomycin (gentamicin/amikacin) Alternative: ciprofloxacin, doxycycline; see Chapter 171	IM, IV/10 days or longer for severe illness	Serologic analysis, PCR, culture of blood or tissue (alert laboratory personnel with clinical suspicion)
PASTEURELLA MULTOCIDA			
Onset within 24 hours of animal bite	Amoxicillin-clavulanate or nafcillin until diagnosis confirmed; then penicillin	PO, IV depending on severity/7–10 days for local infections and 10–14 days for severe infections	Routine culture

IM, intramuscular; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; PCR, polymerase chain reaction; PO, oral; TB, tuberculosis; TMP-SMX, trimethoprim-sulfamethoxazole; TST, tuberculin skin test.

Routine antituberculous therapy generally is ineffective for nontuberculous mycobacterial infections. In cases in which removal of the node is not advised (e.g., because of size or proximity to the facial nerve), combination therapy for NTM generally is given (see Chapter 135).

Patients with marked lymph node enlargement, moderate to severe systemic symptoms, and cellulitis frequently require parenteral therapy for the first several days. This route provides a higher concentration of drug in inflamed tissue, halts bacteremia if present, and may promote more rapid localization. Although a decrease in fever, inflammation, and tenderness is expected within 48 to 72 hours after appropriate treatment of bacterial lymphadenitis, lymph node regression may be slow, requiring 4 to 6 weeks, and suppuration despite appropriate therapy is not unusual.

Abscess Drainage

Ultrasonography or computed tomography can be helpful in cases in which abscess is suspected in the absence of fluctuation on physical examination.[59] For abscesses due to *S. aureus* or *S. pyogenes*, incision and drainage are the procedures of choice. Needle aspiration can be therapeutic. For abscesses from suspected mycobacterial or *Bartonella* infection, aspiration (with an 18- or 19-gauge needle) initially is preferred to avoid fistula formation. Installation of saline may facilitate aspiration when pus is very thick. Surgical excision is required infrequently for cat-scratch disease.

Surgical Excision and Long-Term Therapy

Surgical excision is the most effective treatment for nontuberculous mycobacterial cervical adenitis.[37,70,71] Excision of the largest and necrotic mass or masses usually is adequate because the remaining adenopathy resolves spontaneously over ensuing months. Excision of all affected nodes (especially as documented by imaging studies) requires extensive and difficult surgery and is not warranted as a first procedure; adjunctive antimicrobial therapy usually is given. When infection has ruptured into soft tissue, resection of inflamed overlying skin and sinus tracts, followed by primary closure without leaving a drain, is advocated. A decision to begin combination therapy for *M. tuberculosis* infection is based on the clinical setting and tuberculin skin test results. The clinical response of *M. tuberculosis* infection to antituberculous therapy usually is rapid, with resolution of symptoms and marked regression of the lymph nodes within 3 months; prolonged therapy is required. *Actinomyces* infections of the neck require very prolonged antimicrobial therapy; osteomyelitis of the jaw may require aggressive debridement as well.

Complications

Complications of pyogenic neck infections, such as mediastinal abscess, purulent pericarditis, thrombosis of the internal jugular vein, and pulmonary emboli or disseminated septic emboli, have become uncommon since the availability of effective antimicrobial therapy. *Fusobacterium* spp. infection is an exception. Rapid progression or failure to treat adenitis due to *S. aureus* or *S. pyogenes* can result in cellulitis, bacteremia, septicemia, or toxin-related symptoms. Poststreptococcal acute glomerulonephritis occurs occasionally.

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18

Mediastinal and Hilar Lymphadenopathy

Mary Anne Jackson, J. Christopher Day

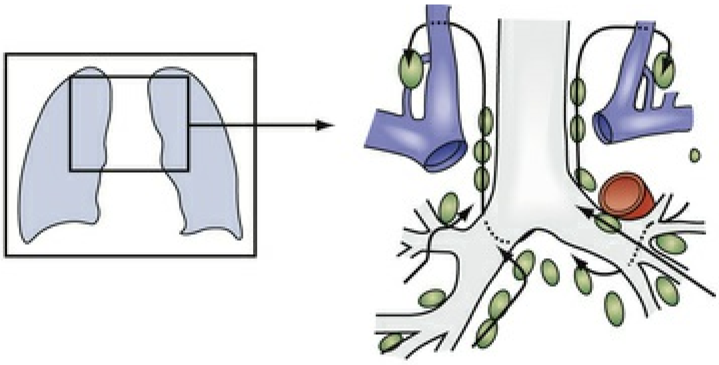
Anatomy of the Mediastinum

The mediastinum is the space between the pleural cavities that contains the heart and all chest viscera except the lungs. Consisting of loose areolar tissue and organs, the mediastinum is more a potential space than an actual body cavity. It is bounded laterally by the parietal pleurae, anteriorly by the sternum, posteriorly by the ribs and paravertebral gutters, superiorly by the thoracic inlet, and inferiorly by the diaphragm. The *anterior mediastinum* contains everything anterior and superior to the heart, including the thymus, aortic arch and its major branches, innominate veins, and lymphatic tissue (nodes and vessels). Most masses here are of thymic origin—teratomas, lymphomas, or angiomatous tumors. The *middle mediastinum* is triangular with the apex at the fourth thoracic vertebra. It contains the heart, pericardium, trachea, pulmonary hilar and mediastinal lymph nodes and vessels, and phrenic and vagus nerves. Masses in this compartment usually are infectious or are malignant lesions of lymph nodes. The *posterior mediastinum* extends from the first rib to the diaphragm, behind the heart and lung roots. It contains the esophagus, descending aorta, paravertebral lymph nodes, lower portion of the vagus nerve, and sympathetic nerve chains. Neurogenic tumors and duplication cysts are the most common lesions encountered.

Although the delicacy of mediastinal tissue planes offers little resistance to the spread of disease between compartments, tumors and inflammation tend to extend within compartments. Infections within the mediastinum are relatively uncommon, but their proximity to many vital structures makes accurate diagnosis essential.

Lymphatic Drainage of the Lungs and Pleura

As shown in Fig. 18.1, lymph from the thoracic viscera (heart, pericardium, lungs, pleura, thymus, and esophagus) traverses one of three possible sets of nodes before entering the thoracic duct or right lymphatic duct. Anterior mediastinal nodes are located anterior to the aortic arch, innominate veins, and large arterial trunks leading from the aorta. They receive afferents from the thymus and pericardium, the sternal nodes, and the thyroid gland.



Lymph drainage patterns

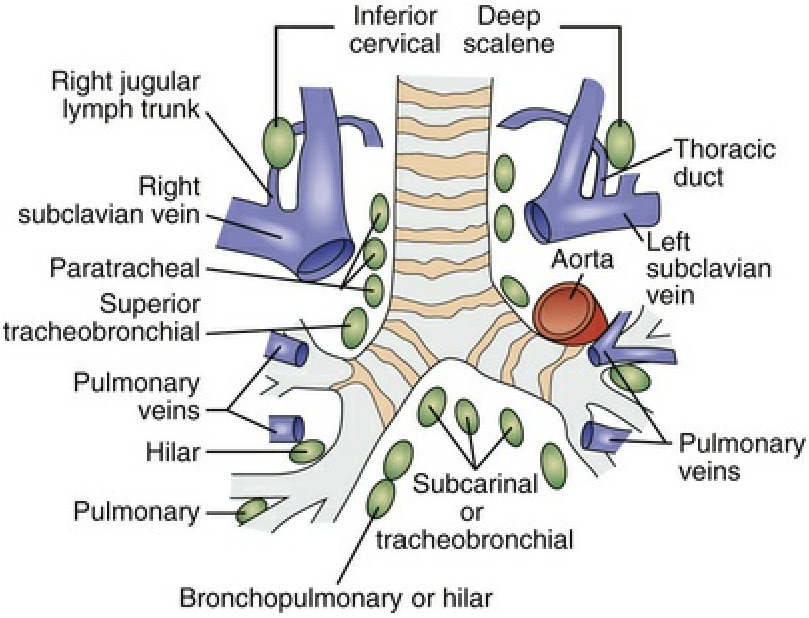


FIGURE 18.1 Lymphatic drainage of the thorax.

Posterior mediastinal nodes lie dorsal to the pericardium and adjacent to the esophagus and descending aorta. They receive afferents from the esophagus, dorsal pericardium, diaphragm, and convex surface of the liver. Middle or mediastinal nodes drain the lungs and pleura. Lymphatic drainage of the lungs is composed of superficial and deep plexuses. The superficial plexus lies beneath the visceral pleura. Lymph flows around the border of the lung to enter the bronchopulmonary (hilar) nodes. The deep plexus accompanies branches of the pulmonary vessels and ramifications of the bronchi throughout the lungs.

Lymphatic drainage of the lung passes through four sets of lymph nodes (Table 18.1). Intrapulmonary lymph nodes are located within the lung, chiefly at the bifurcations of the larger bronchi. Bronchopulmonary or hilar nodes are located at the pulmonary hilus at the site of entry of the main bronchi and vessels. Tracheobronchial nodes are divided into superior and inferior groups. The superior group lies in the obtuse angle between the trachea and bronchi on both sides. The inferior, or subcarinal, group lies under the carina at the tracheal bifurcation. The fourth group, the tracheal or paratracheal nodes, lies beside and somewhat anterior to the trachea. A fifth group of lymph nodes of importance in the drainage of the lungs is the inferior deep cervical (scalene or supraclavicular) chain, which is located over the lower portion of the internal jugular vein, just above the clavicle and usually under the scalenus anterior muscle. The apical pleurae drain directly to these deep cervical nodes, as do the paratracheal chains. A finding of supraclavicular lymphadenopathy should lead to investigation for intrathoracic or intra-abdominal pathology.

TABLE 18.1
Lymphatic Drainage of the Lung and Pleura

Lymph Node Group	Areas Drained
Intrapulmonary	Pulmonary vessels, bronchi, and parenchyma
Hilar (bronchopulmonary)	Intrapulmonary nodes and superficial plexus of visceral pleural lymphatics
Tracheobronchial: superior and inferior (subcarinal)	
Right side	All hilar nodes of right lung and hilar nodes of left lower lobe and lingula
Left side	Left upper lobe hilar nodes
Paratracheal	
Right side	Right tracheobronchial nodes
Left side	Left tracheobronchial nodes
Supraclavicular	
Right side	Right apical pleura, right paratracheal nodes, head, neck, arms, and upper thorax
Left side (Virchow node)	Left apical pleura, left paratracheal nodes, intra-abdominal nodes, head, neck, arms, and upper thorax

Ultimately, all lymph from the lungs and pleurae reaches the tracheobronchial and paratracheal lymph nodes. Generally, lymph from the lungs flows from left to right, a probable explanation for the preeminence of right upper paratracheal and supraclavicular lymphadenopathy in infectious pulmonary processes, particularly tuberculosis. Lymph from the left lower lobe (and usually also the lingula) flows from the hilar nodes to the lower tracheobronchial nodes, and then to the right paratracheal nodes. Lymph from the right hilar nodes travels to the right paratracheal nodes (see Table

18.1).

Lymph vessels from the paratracheal nodes join with lymph trunks from the anterior mediastinum to form the right and left bronchomediastinal trunks. These trunks then join with the lymphatic trunks from the supraclavicular nodes to form the right lymphatic duct and left thoracic duct.

Epidemiology

At least one third of all mediastinal masses occur in children younger than 15 years; one half of such masses are symptomatic. Among children with mediastinal masses, 50% who present with symptoms of airway compression have malignant tumors, whereas 90% of those who have noncompressive symptoms have nonmalignant conditions. The greater proportion of symptomatic masses in children compared with adults may be due to smaller thoracic size, resulting in symptoms of compression, or to a higher frequency of malignant lesions.[1] The overall incidence of tumors (excluding metastatic disease) and cysts in the mediastinum is 1 per 100,000 people.

In a series of biopsies of only anterior and middle mediastinal masses in children (thus excluding neurogenic tumors), 1% to 57% are reported to be due to histoplasmosis. This extreme variance in rate is due to prevalences of *Histoplasma capsulatum* in the geographic areas in which studies are done. For example, at St. Jude Children's Research Hospital in Memphis, histoplasmosis was a relatively common complication in children with cancer, and a reason for referral of children without cancer.[2] Fever with pulmonary infiltrates (frequently nodular) and hilar or mediastinal mass and lymphadenopathy were the usual presentation. Blastomycosis, coccidioidomycosis, and tuberculosis also are associated with infectious mediastinal disease. A variety of other pathogens, including *Pneumocystis jirovecii* and *Mycoplasma* spp., can lead to mediastinal lymphadenitis associated with pulmonary infiltrates. Cysts and tumors predominate as the cause of posterior mediastinal lymphadenopathy (Table 18.2). Generally, neurogenic tumors are the most common cause of mediastinal masses; lymphomas are second, and germ cell tumors are third in frequency.

TABLE 18.2

Relative Frequencies of Noninfectious Mediastinal Masses in Children[a]

	Study			
	Silverman and Saleiston[31]	**Filler et al.[32]**	**Woods et al.[15]**	**Gaebler et al.[33]**
Number of children	437	429	68	37
FREQUENCY OF MASS (%)				
Neurogenic tumor	40	33	—	—
Lymphoma	18	14	68	43
Leukemia	—	—	17	—
Germ cell tumor	11	9.8	—	—
Mesenchymal tumor	7	6.8	—	—
Bronchogenic cyst	7	7.5	—	—
Lymph node infection	—	4.4	9	57
Other cysts or malignancy	14	25	6	—

[a] Anterior and middle mediastinal masses only.

Characteristics of Lymphadenopathy

Lymph nodes are readily identifiable on computed tomography (CT) and can be categorized according to size, shape, coalescence, replacement by tumor mass, presence of calcium, abscess cavities, and parenchymal lung involvement. Most authorities use a 10-mm diameter as the upper limit of normal size for lymph node.[3,4] Mediastinal lymph nodes larger than 20 mm virtually are always abnormal; this statement may not be true for hilar nodes. Mediastinal nodes have the potential to become much larger than any other nodes in the body.

Densely calcified bilateral nodes are typical of histoplasmosis and, occasionally, of blastomycosis, coccidioidomycosis, or sarcoidosis. Unilateral densely calcified nodes are typical of prior or late-diagnosed tuberculosis. Benign mediastinal tumors also can be calcified (i.e., teratoma, cystic thymoma, and thyroid adenoma). Childhood lymphomas can cause bilateral hilar adenopathy but usually do not become calcified until after therapy.

In general, mediastinal mass lesions require a tissue diagnosis. Situations in which a biopsy may not be necessary include (1) certain granulomatous lesions that show dense calcification and are not increasing in size, as shown by consecutive imaging studies; (2) lymphomatous lesions diagnosed by biopsy of tissue outside the thorax; and, most important, (3) tuberculosis or histoplasmosis, which should be confirmed with other diagnostic testing.

Clinical Manifestations

Mediastinal lymphadenopathy frequently is asymptomatic until compression or erosion through a mediastinal structure occurs. Table 18.3 delineates findings associated with mediastinal disease. Respiratory symptoms result from airway obstruction or erosion. If the obstruction is significant enough, distal obstructive emphysema, atelectasis, pneumonia, or chronic, recurrent respiratory tract infections can result. Obstruction of the superior vena cava is a rare complication most commonly associated with rapidly growing malignant mediastinal tumors. The superior vena cava is particularly vulnerable to obstruction because of its thin wall, low intravascular pressure, and confinement by lymph nodes and other rigid structures. Older children with mediastinal masses may describe feeling intrathoracic discomfort or pain, which probably is due to pressure on intercostal nerves or pleura. Vertebral erosion secondary to posterior mediastinal tumors can cause a boring, interscapular pain. Most children with mediastinal disease caused by histoplasmosis present with chest pain or cough.

TABLE 18.3

Symptoms of Compression Resulting From Mediastinal Adenopathy

Structure	Symptom or Sign
Airway	Cough, wheezing; recurrent respiratory infections, bronchitis, atelectasis, unresolved pneumonia; hemoptysis; chest pain, sudden death
Esophagus	Dysphagia (interruption of peristalsis); hematemesis (fistula formation)
Superior vena cava	Dilation of collateral veins of the neck and upper thorax; chemosis of conjunctiva; edema of face, neck, upper chest, and arm; cyanosis; headaches, visual disturbances; epistaxis, tinnitus
Lymphatic channels	Pleural effusion
Recurrent laryngeal nerve	Hoarseness, inspiratory stridor (paralysis of vocal cord)
Phrenic nerve	Paralysis of left diaphragm

Sympathetic ganglia	Horner syndrome
Vertebrae, ribs	Pain secondary to bony erosion; symptoms of spinal cord compression

The finding of mediastinal widening, regardless of symptoms, leads to evaluation by CT. The diagnosis of lymphoma is considered first. If granulomatous lung disease is present, the diagnosis of tuberculosis is considered, as is histoplasmosis in endemic regions. History of travel, foreign birth, consumption of unpasteurized milk, or farm or bird exposure is sought.

Diagnosis

Historically, the differential diagnosis of mediastinal masses evident on chest radiograph was considered according to location within one of the four mediastinal compartments. Use of CT has largely supplanted the need for this classification because distinct tissue groups are now defined: fat, lymph nodes, vessels, airways, thymus, esophagus, and paraspinal tissues.

Imaging Studies

CT is the imaging study of choice for children with mediastinal mass. Unenhanced CT augments recognition of calcification. CT with administration of contrast material is useful to define anatomy better and distinguish vessels from lymph nodes. Identification of a solid, homogeneously enhancing soft tissue mass distinguishes lymphoma from cavitating lesions of histoplasmosis and tuberculosis, which are peripherally enhancing with low attenuation centrally. With the widespread use of multidetector helical CT, multiplanar imaging now is routine and allows definition of mediastinal structures in all planes. Magnetic resonance imaging (MRI) is required infrequently to evaluate the mediastinum because most lesions are visualized well on multidetector helical CT. In addition, MRI usually requires sedation (which can be dangerous in the presence of intrathoracic mass) and cooperation of the child to hold the breath (lest there be motion artifact). MRI is used for specific problem solving, such as evaluation of soft tissue masses of the chest wall, and when neurogenic lesions are suspected, to evaluate extension into the spinal canal.

Although CT and MRI are highly sensitive in detecting enlarged lymph nodes, neither reliably distinguishes between benign and malignant causes. Both can show displacement or compression of trachea or esophagus, but neither distinguishes invasion. MRI has the limitation of not being able to demonstrate calcium and is highly sensitive to motion (breathing or heart contraction) artifact.

Tissue Diagnosis and Biopsy

In general, mediastinal mass lesions require a tissue diagnosis because of likely causes and their proximity to vital structures. In some cases, diagnosis can be made without obtaining mediastinal tissue. Supraclavicular nodes (whether enlarged or not) or other enlarged extrathoracic nodes can provide diagnostic tissue. In one half of children with mediastinal malignancy, at least one lymph node in the cervical, supraclavicular, or infraclavicular or axillary area is larger than 2 cm and can be biopsied. Tissue biopsy from other sites, along with serologic testing, can confirm sarcoidosis. Bronchoscopy with bronchoalveolar lavage or gastric aspirates may identify an infectious cause.

Infectious Causes

Table 18.4 shows differentiating features of the causes of mediastinal lymphadenopathy. Mycobacteria and the endemic fungal organisms, *Histoplasma* and *Coccidioides,* commonly cause hilar and mediastinal adenopathy. Although mediastinal infection without significant pulmonary infection is rare, the degree of adenopathy frequently is disproportionate to degree of parenchymal involvement. Pneumonia due to *Mycoplasma pneumoniae, Bartonella henselae, Yersinia enterocolitica,* or *Francisella tularensis* can be associated with hilar adenopathy, as can bronchiectasis and cystic fibrosis. Adenopathy is rare in other acute bacterial and viral pneumonias.

TABLE 18.4

Causes of Mediastinal Lymphadenopathy

Etiology	**Frequency**	**Associated Pneumonia**	**Node Abscess**	**Node Calcification**	**Method of Diagnosis**
INFECTIOUS CAUSES					
Bacteria					
Mycobacterium tuberculosis	++	++	++	++	Tuberculin skin test; chest radiograph; culture and nucleic acid amplification of gastric aspirate or bronchial washing
Nontuberculous mycobacteria	+	–	+	–	Culture and histopathologic analysis of tissue
Mycoplasma pneumoniae	+	++	–	–	Serology
Bartonella henselae	+	–	+	–	Serology; culture; histopathology
Yersinia enterocolitica	+	–	+	–	Culture; serology
Actinomyces species	+	–	+	–	Culture; histopathology
Melioidosis	±	–	+	–	Culture
Fungus					
Histoplasma spp.	++	+	+	++	Serology; antigen detection; culture
Coccidioides spp.	+	+	+	+	Serology; culture
Blastomyces spp.	+	++	+	+	Culture
Paracoccidioides spp.	+	+	++		Culture
Cryptococcus spp.	+	+	–	–	Culture
Viruses					
Epstein-Barr virus	+	–	–	–	Serology
Protozoa					
Toxoplasma spp.	±	–	–	–	Serology
Chronic Infection					
Cystic fibrosis	++	++	+	–	Sweat test; gene identification
Bronchiectasis	+	+	+	–	Radiograph; culture
Lung abscess	±	+	–	–	Radiograph
NONINFECTIOUS CAUSES					
Malignancy					
Hodgkin lymphoma	++	±	–	+[a]	Biopsy
Non-Hodgkin lymphoma	++	–	–	+[a]	Biopsy
Leukemia	+	–	–		Bone marrow
Other					
Chronic granulomatous disease	+	+	++	–	Neutrophil function assay
Sarcoidosis	++	–	–	–	Biopsy
Rosai-Dorfman disease	+	–	–	–	Biopsy; histopathology
Castleman disease	+	–	–	–	Biopsy; histopathology
Lymphoproliferative syndromes	++	–	–	–	Epstein–Barr virus serology; biopsy
Graves disease	±	–	–	–	Thyroid hormone measurement

[a] After treatment.

++, Frequent; +, occasional; ±, rare, consider under special circumstances.

Bacterial Causes

Mycobacterium tuberculosis.

Primary pulmonary infection with *M. tuberculosis* has the following three elements: the primary parenchymal focus, intraparenchymal lymphangitis, and regional lymphadenitis (Figs. 18.2 and 18.3). At least 70% of primary pulmonary foci are subpleural, with spread through lymphatics to the regional lymph nodes. After several weeks, hypersensitivity develops, with regional node enlargement and the potential for caseating necrosis. Caseating lesions have a high density of actively multiplying bacilli, which spread rapidly to adjacent lymphatics. The hallmark of early tuberculosis is excessive unilateral mediastinal lymphadenitis compared with the relatively insignificant focus in the lung. Hilar adenopathy is unilateral in 80% or more of cases of tuberculosis.

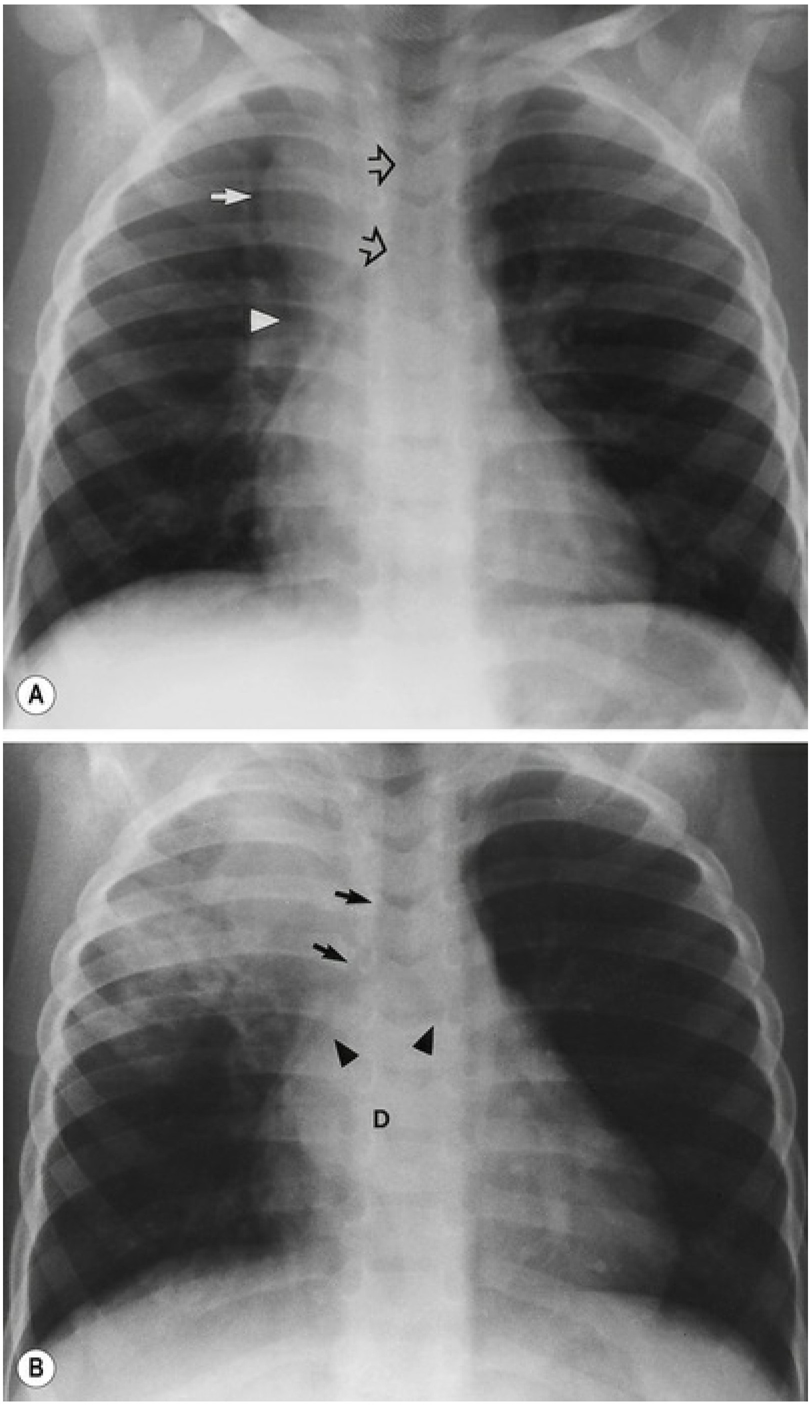


FIGURE 18.2 (A) Chest radiograph of a child with tuberculosis shows right paratracheal adenopathy (*closed arrow*) and right tracheobronchial adenopathy (*arrowhead*), causing effacement of the right lateral aspect of trachea (*open arrows*). (B) Chest radiograph of the same patient 4 months later (without therapy) shows right upper lobe pneumonia with subtle effacement of the right lateral aspect of the trachea and right mainstem bronchus, indicating right hilar and right paratracheal adenopathy (*arrows*). There is splaying of the carina (*arrowheads*) and double density

(*D*) of the lower mediastinum centrally, indicating subcarinal adenopathy.

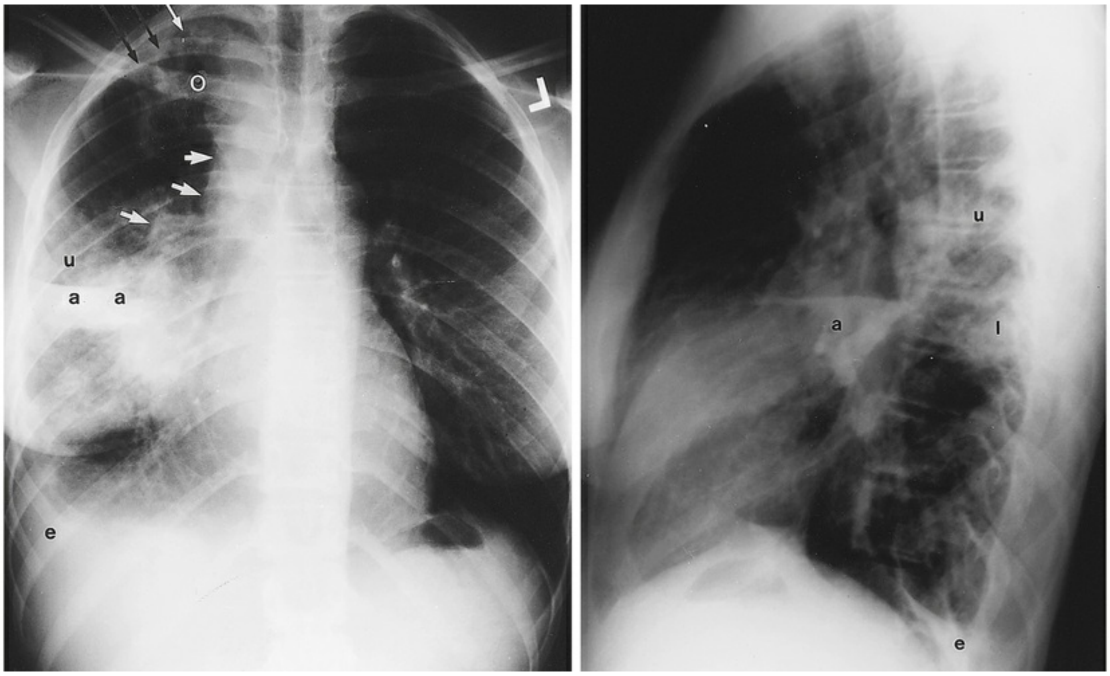


FIGURE 18.3 Chest radiographs of a child with reactivated tuberculosis show cystic changes in the apex of the right upper lobe (*open circle*) and pleural thickening in the superior hemithorax (*long arrows*). There is a right pleural effusion (e); right paratracheal, tracheobronchial, and hilar adenopathy (*short arrows*); and atelectasis or pneumonia in the right middle lobe (a), right upper lobe (u), and right lower lobe (l).

Infection can spread beyond the hilar and tracheobronchial nodes to the more distant right upper paratracheal nodes (the ones most often affected) and deep cervical (supraclavicular) nodes.[5] Additionally, apical subpleural primary infections can drain directly to the supraclavicular nodes. In one series of patients, 14 of 54 patients with a primary lesion in the right upper lobe had ipsilateral enlargement of deep cervical nodes.[6]

Enlargement of hilar nodes adjacent to bronchi can cause bronchial obstruction with the collapse or consolidation or fan-shaped segmental lesion typical of childhood tuberculosis. Infection and inflammation of the bronchial wall can occur, and obstruction of the lumen rarely can result in sudden death or in obstructive hyperaeration, segmental atelectasis, or secondary pneumonia. Multiple segmental lesions can occur, usually in the same lung.

Calcification follows caseous necrosis and occurs more often in children and in the regional lymph nodes than in the primary pulmonary focus. Extensive calcification is uncommon with early treatment, which prevents caseation.

In one series of CT performed in 23 young adults presenting with tuberculous mediastinal or hilar lymphadenitis, pulmonary involvement was demonstrated in 14 patients.[7] There was remarkable preponderance of involvement of the right paratracheal and tracheobronchial nodes. Nodes larger than 20 mm in diameter invariably showed central areas of relatively low density and peripheral rim enhancement that was irregular in thickness.

Nontuberculous Mycobacteria.

In immunocompromised children (and occasionally in healthy young children), nontuberculous mycobacteria can cause (1) extensive hilar and paratracheal lymphadenopathy with or without parenchymal disease and (2) endobronchial disease with atelectasis.[8] In all reported patients in one series, the organism was isolated from lymph node, lung, or bronchoalveolar lavage. Lymphadenopathy can be unilateral or bilateral, and nodes undergo extensive caseating necrosis.

Mycoplasma pneumoniae.

Radiographic findings in 56 patients with pneumonia (21 younger than 20 years) due to *M. pneumoniae* revealed that 22% of patients had hilar or paratracheal node enlargement, and 14% had pleural effusion.[9,10]

Bartonella henselae.

A few patients with cat-scratch disease have been described with mediastinal and peripheral lymphadenopathy. Mediastinal node biopsy in one patient revealed granuloma with microabscesses.[11]

Yersinia enterocolitica.

Significant bilateral self-limited hilar adenopathy without pneumonia due to *Y. enterocolitica* has been described in several adults. All patients recovered without therapy. The diagnosis was based on results of culture or serum agglutination titers.[12]

Lung Abscess.

Lung abscess frequently is associated with anaerobic infections but can occur in the course of any necrotizing pneumonia. Mediastinal lymphadenopathy is not unusual.

Bronchiectasis.

In children and adults, bronchiectasis of any etiology (e.g., associated with congenital anomaly, foreign body), and especially that associated with cystic fibrosis in children, can cause mediastinal lymphadenopathy. In one study of CT in patients with bronchiectasis, mediastinal lymphadenopathy (nodes >10 mm in diameter) was present in 29% of patients.[13]

Fungal Causes

Histoplasma capsulatum.

Infection due to *Histoplasma capsulatum* can take multiple clinical forms (Figs. 18.4 and 18.5). In the immunocompetent host, histoplasmosis most frequently is subclinical, recognized incidentally. In symptomatic infection, cough or chest pain is most common. Mediastinal lymphadenopathy, an uncommon finding in disseminated infection, is the most common manifestation in healthy children with self-limited infection. Of 35 children hospitalized with histoplasmosis between 1968 and 1988, 29 (83%) had pulmonary infection, mediastinal infection, or both. Chest radiograph was abnormal in 31 (91%), revealing adenopathy in 25 (74%) and infiltrates in 19 (56%).[14] Isolated mediastinal adenopathy can be difficult to distinguish from lymphoma.[15,16] Rarely, massive inhalation of fungus causes disseminated, symptomatic primary infection with fever, cough, and massively enlarged mediastinal lymph nodes. The differentiation is important because histoplasmosis is mild and self-limited in most immunocompetent people. Antifungal therapy is used in those with acute diffuse pulmonary infection, chronic pulmonary infection, progressive disseminated disease, and mediastinal adenitis associated with obstructive symptoms.

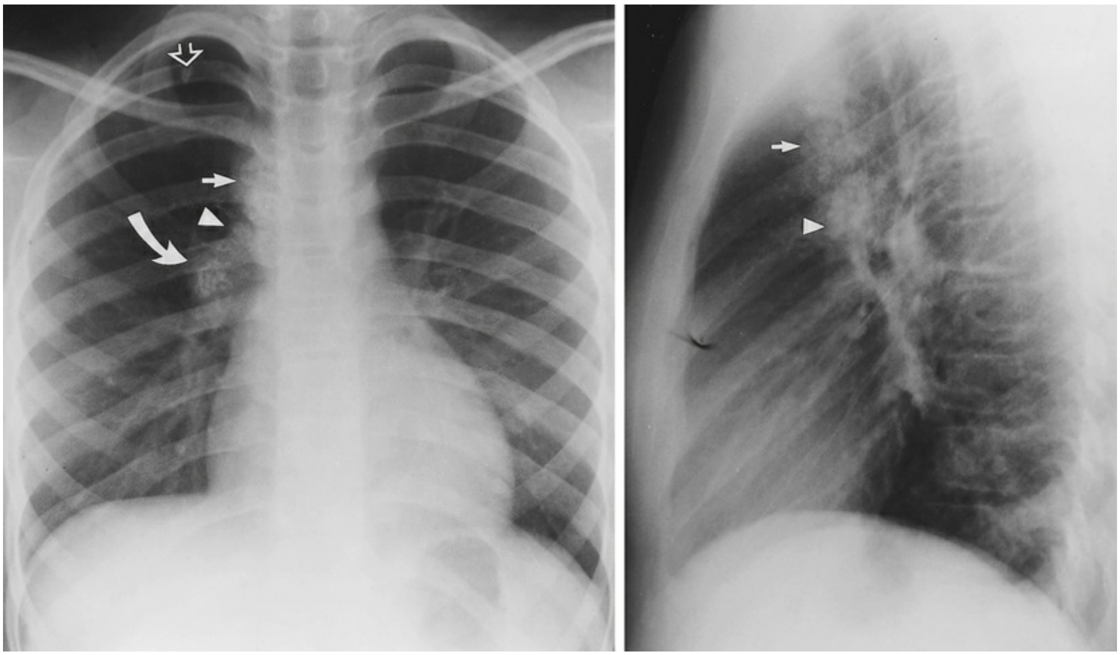


FIGURE 18.4 Chest radiographs of a child with healed histoplasmosis shows granuloma in right upper lobe (*open arrow*), calcified paratracheal nodes (*straight arrow*), tracheobronchial nodes (*arrowhead*), and calcified right hilar nodes (*curved arrow*).

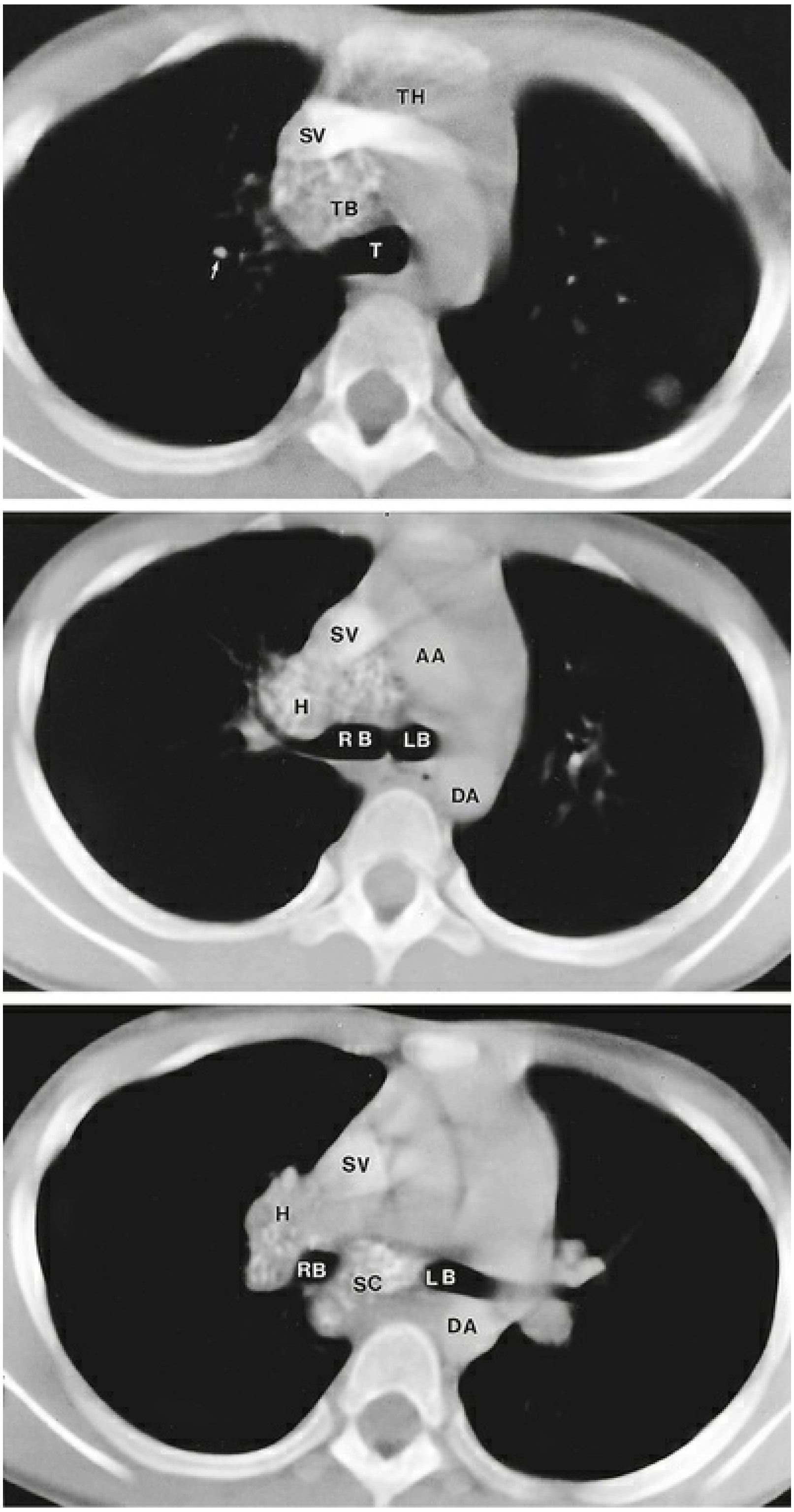


FIGURE 18.5 Enhanced computed tomography scan of the patient in Fig. 18.4 shows extensive right tracheobronchial, right hilar, and subcarinal lymphadenopathy. Particulate calcification within the nodes is characteristic of healed histoplasmosis. *Arrow* indicates calcified granuloma in right upper lobe. AA, ascending aorta; DA, descending aorta; H, calcified right hilar node; LB, left mainstem bronchus; RB, right

mainstem bronchus; SC, calcified subcarinal nodes; SV, superior vena cava; T, trachea; TB, calcified tracheobronchial nodes; TH, thymus.

In the otherwise healthy host, marked enlargement of mediastinal lymph nodes can cause obstruction of bronchi, the superior vena cava, or the esophagus. Additionally, a group of large nodes can become necrotic and matted to form a large single mediastinal mass known as an acute mediastinal granuloma. Most such masses resolve spontaneously; the effect of antifungal therapy has not been studied.

In the populations with deficiencies in cellular immunity, pulmonary histoplasmosis can be a difficult diagnosis, mainly because it is not often considered. Histoplasmosis generally occurs sporadically, manifesting as a prolonged febrile illness with subacute pulmonary symptoms.[17] Disseminated histoplasmosis, both in transplant recipients and in patients with an underlying condition treated with anti−tumor necrosis factor-α therapy, is well described. Symptoms frequently are nonspecific, and signs of respiratory infection may be absent. Diagnosis in this setting requires detection of *Histoplasma* antigen in the serum and urine.[18] Disseminated disease once noted frequently in people living in endemic areas with advanced human immunodeficiency virus (HIV) infection is rarely seen now owing to the early diagnosis and treatment of HIV infection.

Coccidioidomycosis immitis.

Coccidioidomycosis occurs primarily in the southwestern United States. It is subclinical in children in 60% of cases. An insignificant flu-like illness or severe respiratory infection with lobar pneumonia and pleural effusions can occur. Radiographic findings are nonspecific; bronchopneumonic infiltrates often are associated with enlargement of hilar nodes. Cavitation, nodule formation, or calcification occurs in a minority of patients.

Parenchymal infiltrates commonly are associated with hilar lymphadenopathy. More extensive mediastinal adenopathy is not considered part of the primary complex and may represent dissemination. Rarely, bilateral hilar adenopathy occurs without apparent pulmonary disease.

Paracoccidioides brasiliensis.

A progressive chronic disease due to *P. brasiliensis,* paracoccidioidomycosis preferentially involves the lungs and reticuloendothelial system. It occurs predominantly in a few Latin American countries. Only about 2% of cases occur in children. Pulmonary lesions can be infiltrative, fibrotic, fibrocaseous, or cavitary. Enlargement of hilar and mediastinal lymph nodes is observed. Enlargement of liver, spleen, and other lymph nodes (e.g., cervical, inguinal, and mesenteric) also occurs. Complications include suppuration and fistula formation and scarring of affected nodes with residual pulmonary fibrosis.

Pneumocystis jirovecii.

A patient with acquired immunodeficiency syndrome and *P. jirovecii* pneumonia with calcified hilar and mediastinal nodes has been reported.[19]

Other.

An immunocompetent child with fever, pneumonia, and a posterior mediastinal mass with hilar and subcarinal lymphadenopathy was originally thought to have lymphoma, but at biopsy, a granuloma with broad septated fungal hyphae with right-angle branching compatible with zygomycosis was found.[20]

Viral Causes

Epstein-Barr Virus.

Generalized lymphadenopathy secondary to extensive lymphocytic hyperplasia can include the mediastinum.[21,22] In transplant recipients undergoing immunosuppression, manifestations of lymphoproliferative disease related to Epstein-Barr virus can include generalized or localized adenopathy, including involvement of the mediastinal nodes.

Rubeola.

Pulmonary infiltrates and hilar adenopathy appearing early in the course of measles are well described. In one series of 130 children with measles, 55% had pulmonary infiltrates and 74% had hilar adenopathy.[23]

Noninfectious Causes

Malignancy

Lymphomas (Figs. 18.6 and 18.7) characteristically occur in the anterior and middle mediastinum and are the third most common cause of mediastinal masses in children. The most common manifestation of Hodgkin lymphoma or non-Hodgkin lymphoma is painless lymph node enlargement, most often in the cervical or supraclavicular chains. Of patients with Hodgkin lymphoma, 50% to 60% have mediastinal lymphadenopathy (usually bilateral) and evidence of tracheobronchial compression at the time of diagnosis. Involved nodes are hilar (≥25%), subcarinal (22%), posterior mediastinal (5%), and cardiophrenic angle (8%). Ipsilateral pulmonary parenchymal involvement is present in 10% of patients.

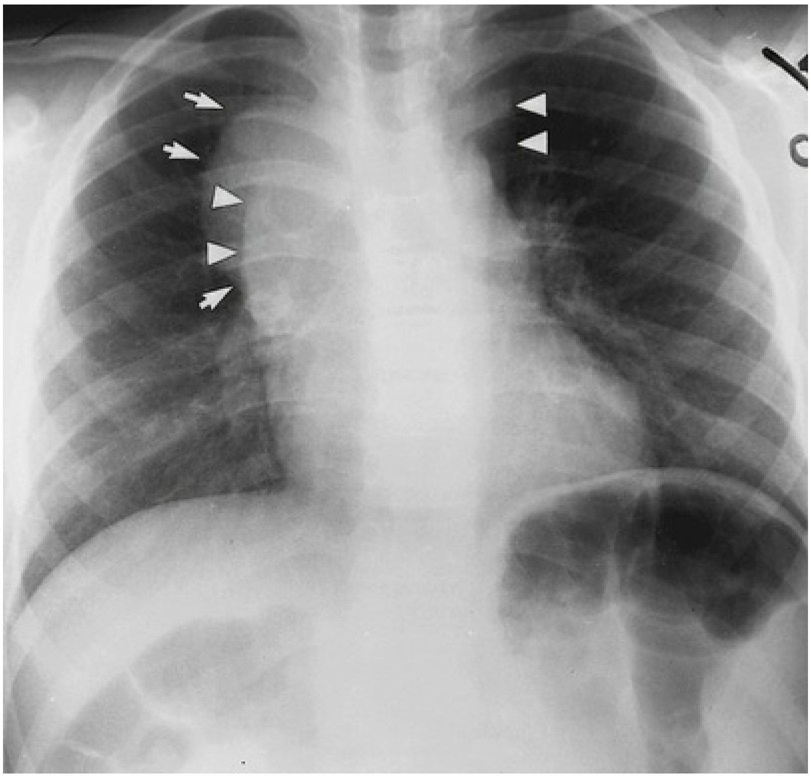


FIGURE 18.6 Chest radiograph of a child with mixed-cell Hodgkin disease shows right paratracheal (*arrows*) and tracheobronchial lymphadenopathy (*arrows*). The superior mediastinum is widened on the left as well,

indicating enlargement of anterior mediastinal nodes (*arrowheads*).

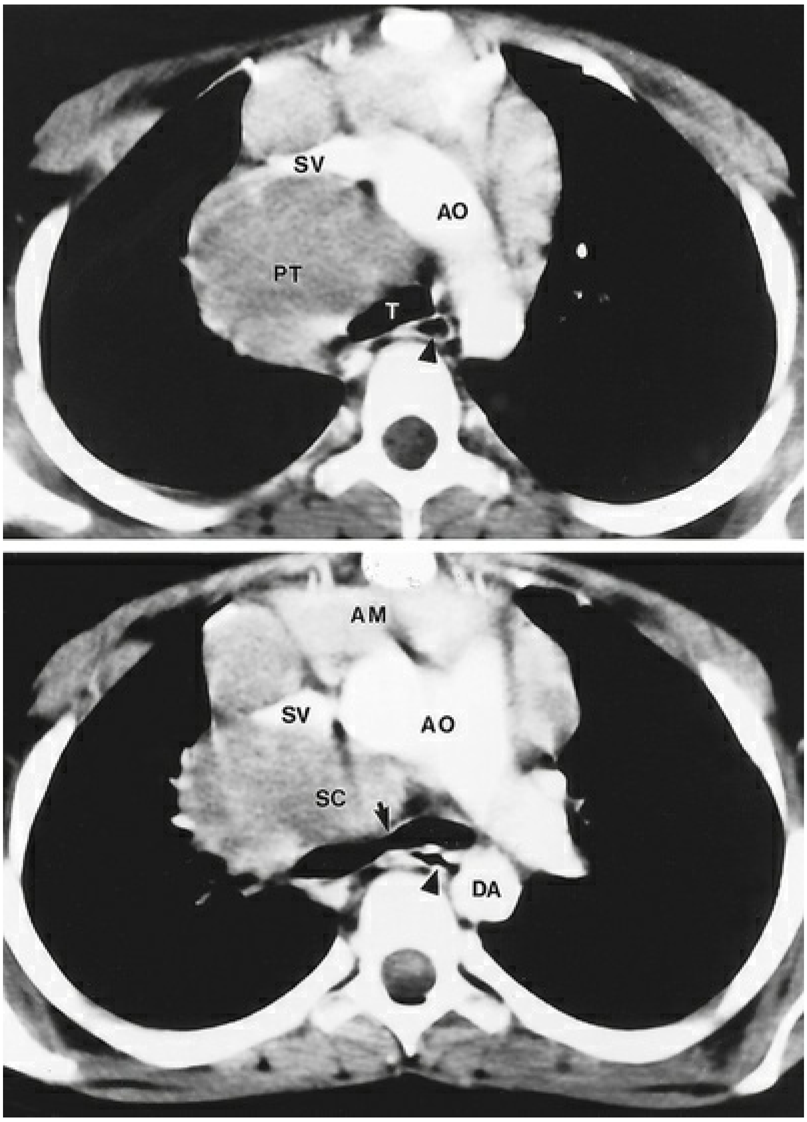


FIGURE 18.7 Enhanced computed tomography scans of a child with mixed-cell Hodgkin disease show extensive mediastinal adenopathy. *Arrow* indicates carina, and *arrowhead* indicates esophagus containing air. AM, anterior mediastinal nodes; AO, aortic arch; DA, descending aorta; SC, subcarinal nodes; SV, superior vena cava; T, trachea.

Childhood non-Hodgkin lymphoma is a rapidly proliferating malignancy, usually affecting adolescent males and often with a duration of symptoms of only 4 to 6 weeks. Lymphoblastic lymphoma and the closely related acute lymphoblastic leukemia often manifest indistinguishably, with mediastinal adenopathy and compression. Dissemination is present in 70% of children at the time of diagnosis. Non-Hodgkin lymphoma can arise in any lymphoid tissue and in numerous extralymphatic sites. Painless, rapidly progressive enlargement of cervical, supraclavicular, and axillary nodes is a common presenting complaint. With involvement of these nodes, an anterior mediastinal tumor is common (50% to 70%), as are pleural effusions.

Other Causes

Sarcoidosis.

Sarcoidosis is a multisystem granulomatous disease of unknown cause that is relatively uncommon in children. The incidence appears to become more significant beginning at about 13 years of age.[24] Sarcoidosis most commonly involves the lungs, lymph nodes, eyes, skin, liver, and spleen. Nonspecific symptoms consist of fever, weight loss, cough, fatigue, lethargy, lymphadenitis, visual disturbances, and rashes. In large series of children and adults, 90% of patients have bilateral involvement of the lungs and hilar lymph nodes.[25,26] In children, bilateral hilar lymphadenopathy, occasionally involving the paratracheal nodes, was associated with parenchymal involvement in 50% of cases.[26] Patients should be evaluated for ocular involvement as well as other visceral sites of disease.

Giant Lymph Node Hyperplasia (Castleman Disease).

Castleman disease, a rare disease in children younger than 14 years, can manifest as an asymptomatic mass in the mediastinum or neck, along the aorta or in the abdomen.[27,28] Some patients have prolonged fever, anemia, weight loss, splenomegaly, hypergammaglobulinemia, elevated erythrocyte sedimentation rate (ESR), bone marrow plasmacytosis, and a poor outcome. Microscopically, the large, well-circumscribed ovoid nodes 3 to 8 cm long are characterized by lymphoid follicular hyperplasia with and without germinal center formation and marked capillary proliferation with endothelial hyperplasia. Human herpesvirus 8 has been found in the nodes of affected patients. Surgical removal of localized nodes for diagnosis and therapy may relieve systemic symptoms. Recurrences have not been reported in children. Pilot study data suggest that valganciclovir-zidovudine combination therapy was effective in HIV-infected adults taking highly active antiretroviral therapy.[29]

Wegener Granulomatosis.

Mediastinal adenopathy with tracheal and bronchial stenosis associated with Wegener granulomatosis has been reported rarely in children. In these cases, disease was limited to the airways and sinuses.

Chronic Granulomatous Disease.

Hilar adenopathy in association with pneumonia raises suspicion of chronic infection or granuloma formation. Patients with chronic granulomatous disease frequently have mediastinal adenopathy in conjunction with pneumonia.

Graves Disease.

Thymic enlargement simulating an anterior mediastinal mass has been noted in adults and adolescents with Graves disease. In such cases, thyrotropin receptor autoantibodies stimulate the thyroid and some extrathyroid tissues including the thymus. Clinical findings of hyperthyroidism may be subtle but measurement of thyroid hormone levels are diagnostic.[30]

Diagnostic Approach

The diagnostic approach depends on the age of the patient, exposures, presence and progression of symptoms, associated physical findings, and specific abnormalities of imaging studies (see Table 18.4). Results of serologic tests (e.g., for *Bartonella, Mycoplasma, Histoplasma* infection) and the tuberculin skin test may confirm the diagnosis, averting the need for tissue biopsy. *H. capsulatum* antigen detection is most sensitive for disseminated disease but can be negative in pulmonary histoplasmosis. *Histoplasma* antigen found in serum, urine, or bronchoalveolar lavage fluid, however, can confirm the diagnosis if all symptoms and signs are compatible. Rapidly enlarging masses, in the absence of a confirmed, compatible diagnosis, require prompt biopsy. Optimal therapy depends on rapid and accurate diagnosis.[31,32]

Subacute infections associated with hilar lymphadenopathy can be difficult to distinguish from lymphoreticular malignancy. In one study of 37 children with anterior and middle mediastinal masses, 16 had lymphomas and 21 had histoplasmosis.[33] The two entities could not be distinguished on the basis of patient age or sex, fever, weight loss, duration of illness, anemia, ESR, or lung infiltrates and calcifications. Anterior mediastinal masses were due to lymphoma in 81% of cases and histoplasmosis in 5%. Of the patients with lymphomas, only 7% had *Histoplasma* complement fixation titers of 1 : 8 or higher, but 67% of patients with histoplasmosis had titers of 1 : 32 or higher. The authors of this study concluded that biopsy of anterior mediastinal masses should be performed. Immunodiffusion testing for *H. capsulatum,* however, is highly specific. The finding of H bands is highly suggestive of acute infection (see Chapter 250).

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19

Abdominal and Retroperitoneal Lymphadenopathy

Angela L. Myers

Lymphadenopathy, the abnormal enlargement of lymph nodes, can result from a wide variety of infectious and noninfectious causes. Acute enlargement of superficial lymph nodes caused by infection can occur over a period of days, accompanied by pain and tenderness to palpation, resulting in lymphadenitis. Alternatively, the enlargement of nodes can occur over weeks to months, with little tenderness, representing a more chronic inflammatory process. Abdominal and retroperitoneal lymphadenopathy is a diagnosis made by imaging techniques such as ultrasonography (US), computed tomography (CT), or magnetic resonance imaging (MRI). Without sequential imaging studies, it can be unclear whether enlargement represents a new, rapidly evolving process or a more prolonged, chronic, relatively stable one. Without the ability to examine the lymph nodes directly, the clinician must rely on clues from the history and physical examination to formulate a diagnosis.

Inflammation in lymph nodes may be the direct result of infection in the tissues (or other lymph nodes) that the nodes drain or a consequence of dissemination of an organism through the bloodstream. Tissues and organs of the abdomen and retroperitoneal space can be infected by a variety of pathogens and through various routes (see Chapters 66 and 67).

Epidemiology and Differential Diagnosis

Abdominal and retroperitoneal lymphadenopathy in children can have infectious and noninfectious causes. Malignant processes and serious infection are the primary concerns; although incidental lymphadenopathy also is found in asymptomatic children.[1-8] A systematic approach to evaluation for infection requires consideration of selected factors from the history and clinical examination (Box 19.1).

Box 19.1

Evaluation of Patients With Lymphadenopathy of Suspected Infectious Etiology

Symptoms

Duration of symptoms: acute (days) or chronic (weeks to months)

Presence of weight loss, fever, night sweats

Presence of organ system–specific symptoms: diarrhea, abdominal pain, jaundice, dysuria, flank pain, hip pain, back pain

Exposures

Exposure to animal bites or scratches: cats, rodents, farm animals, ticks

Travel to areas endemic for enteric bacteria, parasites, or fungal pathogens: *Histoplasma, Coccidioides, Mycobacterium*, or *Plasmodium* spp.

Ingestion of unpasteurized dairy products

Risk factors for HIV infection

Underlying Disorders

Concomitant infection elsewhere in the patient

History of previous or chronic infection of liver or gallbladder, spleen, pancreas, bowel, kidney or ureters, bladder, ovaries or uterus, iliopsoas muscle, or vertebral bodies

Presence of underlying immunocompromising disorders: malignant tumors, chemotherapy, corticosteroid therapy, HIV infection

Congenital immunodeficiencies: chronic granulomatous disease, severe combined immunodeficiency

Transplantation: immunodeficiency and posttransplantation lymphoproliferative disorders

Crohn disease

Celiac disease

Gaucher disease[64]

Physical Examination

Lymphadenopathy: focal versus regional or systemic

Evidence of infection in tissues or organs drained by lymph nodes

Evidence of systemic infection: Epstein-Barr virus infection, cat-scratch disease, tuberculosis, *Yersinia* spp., salmonellosis

HIV, human immunodeficiency virus.

Regional lymph nodes that drain the organs and tissues from the abdomen, retroperitoneal space, and lower extremities are shown in Fig. 19.1.[4,9] Focal, deep lymphadenopathy suggests infection in the adjacent draining structures or lymph node groups; generalized adenopathy suggests a disseminated process that is likely to involve other lymph nodes, superficial ones that may be palpably enlarged, as well as the liver and spleen.

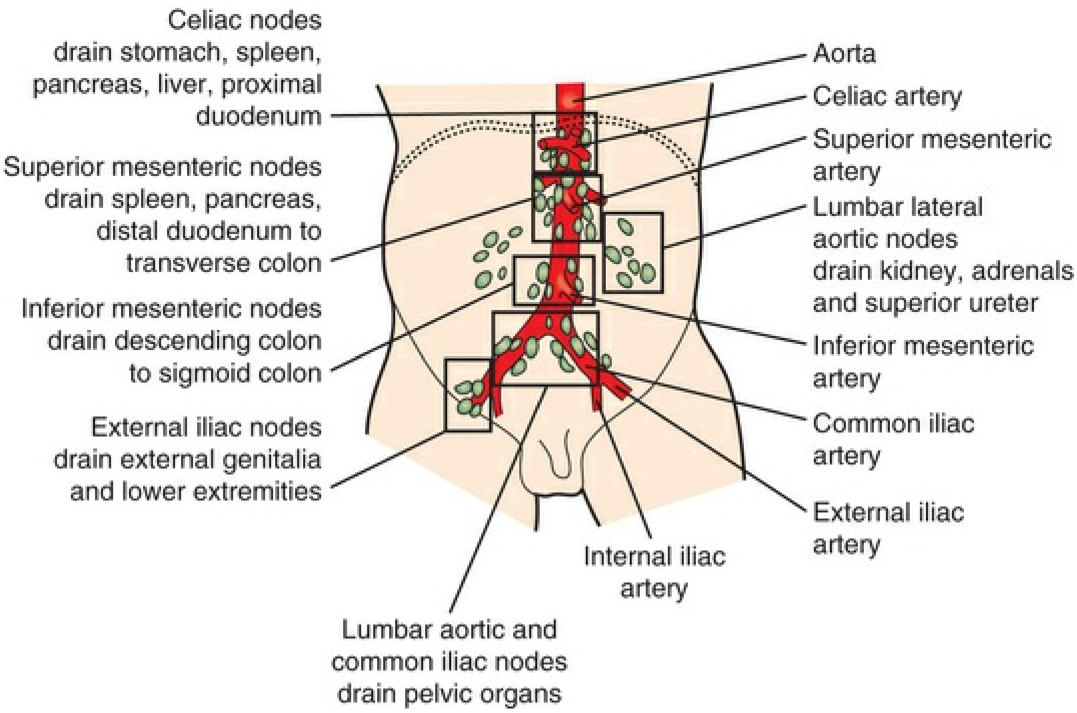
Celiac nodes drain stomach, spleen, pancreas, liver, proximal duodenum
Superior mesenteric nodes drain spleen, pancreas, distal duodenum to transverse colon
Inferior mesenteric nodes drain descending colon to sigmoid colon
External iliac nodes drain external genitalia and lower extremities
Aorta
Celiac artery
Superior mesenteric artery
Lumbar lateral aortic nodes drain kidney, adrenals and superior ureter
Inferior mesenteric artery
Common iliac artery
External iliac artery
Internal iliac artery
Lumbar aortic and common iliac nodes drain pelvic organs

FIGURE 19.1 Location and drainage patterns of deep abdominal lymph nodes.

Infectious causes of enlarged superior or inferior mesenteric lymph nodes include most of the bacterial, viral, and parasitic pathogens that cause gastroenteritis. Mesenteric lymph node enlargement in association with an acute, symptomatic febrile illness that most often manifests as abdominal pain is referred to as *mesenteric lymphadenitis*. *Yersinia, Salmonella,* and *Shigella* spp., *Escherichia coli,* adenoviruses, enteroviruses, and *Entamoeba histolytica* are important causes of mesenteric lymphadenitis, and each has a characteristic constellation of clinical and laboratory findings (see Chapter 66).[4,9-16] Associated inflammation of the terminal ileum and ileocecal junction suggests infectious causes, such as *Yersinia,*[11,17] *Mycobacterium tuberculosis* or *M. bovis,* as well as Crohn disease.[13,18,19] *M. tuberculosis* is considered especially if the child was born in an endemic region, has traveled to tuberculosis-endemic areas, or may have ingested contaminated food products (e.g., homemade unpasteurized cheese).[18,20-22]

Epstein-Barr virus (EBV) and *Bartonella henselae* infection are the most commonly reported infectious causes of abdominal lymphadenopathy in otherwise healthy children. In mononucleosis, the accompanying malaise, pharyngitis, systemic lymphadenopathy, and hepatosplenomegaly often lead to the diagnosis.[23] Peripheral findings of a papule at the site of inoculation and of regional peripheral lymphadenopathy frequently are present in patients with cat-scratch disease. However, fever, with or without abdominal pain, in the absence of peripheral findings, can be the presentation of *B. henselae* infection in the liver, spleen, or abdominal lymph nodes.[24-27] Other less common systemic infections include malaria, toxoplasmosis, and pentastomiasis.[28-31]

Tuberculosis in children can manifest with abdominal lymphadenopathy as the sole anatomic manifestation of systemic infection. Lymphadenopathy can occur during primary infection or during reactivation of a previous infection. Both *M. tuberculosis* and *M. bovis* can cause symptomatic infection of the intestines, lymph nodes, peritoneum, omentum, liver, or spleen.[20-23,32,33] Additionally, a recently recognized mycobacterium species, *M. gastri,* has been reported to cause disseminated infection with extensive abdominal lymphadenopathy.[34] Children can have symptoms of weight loss, fatigue, and intermittent abdominal pain in the absence of abdominal physical findings. The clinical presentation can mimic inflammatory bowel disease.[35] Because low numbers of organisms typically are present, polymerase chain reaction (PCR) of biopsy specimen is a more reliable test than mycobacterial stain or culture. If the infection is caused by *M. tuberculosis,* hilar adenopathy also may be detected on chest radiograph, but, in most cases, abdominal tuberculosis occurs in the absence of pulmonary disease.

Lymphoproliferative syndromes caused by EBV and characterized by abdominal lymphadenopathy have been well described.[24,36-38] At one center, approximately 8% of pediatric transplant recipients developed lymphoproliferative syndrome.[36] Approximately one half of children with an EBV-related abdominal lymphoproliferative disorder have abdominal pain; one fourth have enlarged liver or spleen or manifest an abdominal mass. Evidence of EBV infection of B lymphocytes usually is present.

In children with symptomatic human immunodeficiency virus (HIV) infection, abdominal lymphadenopathy can signify the underlying HIV infection, an HIV-related cancer, or secondary infection.[2,39] In particular, *M. avium* complex (MAC) infection can cause massive systemic lymphadenopathy, including the mesenteric and retroperitoneal lymph nodes.[40] Congenital immunodeficiencies, such as chronic granulomatous disease, also rarely can be characterized by mesenteric lymphadenopathy.[41]

Mesenteric lymphadenopathy can accompany noninfectious inflammation of the bowel, such as that due to Crohn disease[14] or celiac disease.[42,43] Abdominal lymphadenopathy can be a systemic manifestation of a number of disorders of unknown cause, including sarcoidosis,[44] Castleman disease,[45] Rosai-Dorfman disease,[3] or familial Mediterranean fever.[46]

Diagnostic Tests

Imaging Studies

US has been used to assess the significance and degree of abdominal lymphadenopathy in both infectious and noninfectious conditions,[7,47,48] including cat-scratch disease[49] and abdominal tuberculosis.[50,51] Subtle differences detectable by US can help differentiate between infectious causes of enlarged nodes. In studies in which US and CT have been compared, CT is more sensitive for detecting abdominal lymphadenopathy,[50,52] aiding in the diagnosis of both abdominal and retroperitoneal lymphadenopathy.[14,20,53] MRI has been used to evaluate lymphadenopathy in both the abdominal and retroperitoneal spaces, has advantages over other imaging techniques for the detection of vascular lesions and tumors, and appears to be at least equivalent to CT in intra-abdominal infection.[22,54-56]

Clinical Findings and Laboratory Tests

Clues to the cause of lymphadenopathy are based on physical findings that can include systemic lymphadenopathy or hepatosplenomegaly. Other physical findings of infection of the respiratory tract, gastrointestinal tract, skin, skeletal system, cardiovascular system, or genitourinary system also can provide clues to the primary site of infection.

In the immunocompetent child, a tuberculin skin test (TST) remains one of the most sensitive and specific techniques for diagnosis of infections caused by *M. tuberculosis* or *M. bovis* in young children. However, shortages of purified protein derivative may hinder the use of TST.[57] Additionally, false-negative test results have been seen in conjunction with disseminated tuberculosis and immunocompromising conditions. Diagnostic assays based on production of interferon γ (IFNγ) by cultured peripheral blood lymphocytes after in vitro exposure to purified proteins from *M. tuberculosis* are useful in adults, but may not be reliable in children younger than 5 years.[58–60] For older children, IFNγ release assays may have equal or improved senstitivity compared with traditional TST, when used in the appropriate clinical setting.[61,62] Further, these tests can differentiate *M. tuberculosis* infection from *M. bovis*, bacille Calmette-Guérin, and most nontuberculous mycobacterial infections.

Biopsy

Many infections that lead to abdominal lymphadenopathy can be detected by specific serologic tests, including infections caused by *B. henselae,* EBV, cytomegalovirus, *Toxoplasma* spp., and HIV. The types of cultures obtained from blood, urine, stool, or biopsy specimens should be directed toward the suspected pathogens, noting the particular lymph node group affected, pertinent history and clinical findings, and associated or underlying diseases.

When tissue samples are required for accurate diagnosis, particularly in the case of tumors, the techniques discussed in Chapter 67 are useful for the diagnosis not only of organ disease but also of lymph node disease. Options include open surgical biopsy and laparoscopic biopsy or fine-needle biopsy, directed by US or CT. Considerations for choosing the optimal technique in individual cases include the volume of tissue required for diagnosis, the urgency for arriving at a diagnosis, institutional procedural experience, and the ancillary support services available. In general, histologic diagnosis of specific tumors requires larger amounts of tissue than are required for diagnosis of infection.

Special stains, cultures, and PCR assays can be used to identify bacteria, fungi, mycobacteria, or viruses. Biopsy samples are examined histologically for evidence of acute or chronic inflammation, abscess or granuloma formation, or primary or metastatic tumors. Pathogens generally produce characteristic histopathologic findings. For example, caseating granuloma characterizes tuberculosis, but stellate granuloma is more suggestive of infection due to *B. henselae.*

Therapy

Treatment of abdominal and retroperitoneal lymphadenopathy is dependent on the underlying etiology. Although many infectious causes are benign and self-limited, antimicrobial therapy can be beneficial depending on the pathogen implicated (e.g., *Salmonella Typhi*). Chapters that discuss specific pathogens should be reviewed. Treatment of abdominal lymphadenopathy caused by posttransplantation lymphoproliferative disorder ranges from reduction of immune suppression alone to courses of chemotherapy in those with malignant transformation.[37] Immune modulators are the primary modality of treatment in patients with inflammatory bowel disease who are unresponsive to conventional therapies.[63]

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20

Localized Lymphadenitis, Lymphadenopathy, and Lymphangitis

Angela L. Myers

Lymphadenopathy and Lymphadenitis

Lymphadenopathy is defined as disease of the lymph nodes, but the term is more commonly used to denote lymph node enlargement. Enlarged lymph nodes can arise in association with a wide variety of infectious, inflammatory, or neoplastic disease processes. *Lymphadenitis* refers to a localized inflammatory process, usually bacterial, within a lymph node or group of nodes. Lymphadenitis can develop acutely or chronically and can be pyogenic or granulomatous in nature.

Other chapters in this textbook are devoted to the evaluation and management of generalized lymphadenopathy (see Chapter 16) and lymphadenopathy of the cervical nodes (see Chapter 17), hilar nodes (see Chapter 18), inguinal nodes (see Chapter 50), and abdominal nodes (see Chapter 19). This chapter focuses on regional lymph node disease encountered in the remaining superficial locations.

Pathogenesis

Enlarged lymph nodes can result from intrinsic proliferation of lymphocytes or reticuloendothelial cells or from infiltration by cells from an extrinsic source. Lymphocytes or lymphoblasts proliferate in response to antigenic stimuli, producing lymph node enlargement, which recedes after antigen clearance. Pathogens that are able to survive intracellularly can provide persistent stimuli and can be associated with chronic lymphatic cellular hyperplasia. Extrinsic invasion of lymph nodes occurs by neutrophils in response to bacteria and bacterial toxins, by histiocytes in histiocytosis and certain storage diseases, and by malignant cells in leukemia, lymphoma, and metastatic solid tumors.

Etiologic Agents

The pyogenic bacteria *Staphylococcus aureus* and *Streptococcus pyogenes* account for more than 80% of acute bacterial lymphadenitis.[1] Lymph node infection usually can be attributed to spread from an adjacent skin infection or inoculation site; occasionally, no clear origin is evident. Acute localized lymphadenitis with or without overlying cellulitis can develop in an infant as a manifestation of late-onset bacteremic group B streptococcal disease.[2,3] Subacute development of localized lymph node enlargement in healthy children occurs with cat-scratch disease (i.e., *Bartonella henselae* infection) and with nontuberculous mycobacterial infection. Adenitis with fungal pathogens such as *Aspergillus* or *Candida* can occur in immunosuppressed patients, including those with primary immune deficiency (e.g., chronic granulomatous disease) and those who are undergoing chemotherapy for an oncologic diagnosis.[4–6] Unusual pathogens can produce lymphadenitis in otherwise healthy people after specific environmental exposures (e.g., *Francisella tularensis* after a tick bite or animal skinning, *Corynebacterium pseudotuberculosis* in sheep handlers).

History and Clinical Findings

Certain clinical features may be useful in guiding the evaluation of localized lymph node infections (Table 20.1). Small inguinal, cervical, or axillary lymph nodes can be palpated in about one third of healthy infants.[7] Subsequent antigenic stimulation leads to steady enlargement of lymphoid tissue from infancy through puberty, and most healthy children have palpable cervical, inguinal, and axillary nodes.[8] In contrast, other peripheral node groups (e.g., posterior auricular, supraclavicular, epitrochlear, iliac, popliteal), if palpable, are always considered abnormal.[9]

TABLE 20.1

Infections Associated With Localized Lymphadenopathy

Lymph Node Group	Area of Drainage	Palpable Nodes	Infectious Causes	
			Common	Less Common
Occipital	Back of scalp and neck	5% of healthy children	Impetigo Pediculosis (head lice) Tinea capitis Seborrheic dermatitis	Rubella Toxoplasmosis
Preauricular	Lateral portion of eyelids Lateral conjunctivae Skin above cheek, temple	Only with disease	Adenoviral conjunctivitis Parinaud syndrome due to cat-scratch disease	*Chlamydia* conjunctivitis Parinaud syndrome due to tularemia or herpes simplex virus infection
Axillary	Hand and arm	70%–90% of healthy children	Local pyogenic infection	Calmette-Guérin bacillus vaccine, fever, tuberculosis (scrofuloderma), hidradenitis suppurativa
	Chest wall, breast Upper lateral abdominal wall	—	Cat-scratch disease	—
Epitrochlear	Ulnar aspect of hand and forearm	Only with disease	Local pyogenic infection	Tularemia, cat-scratch disease, secondary or congenital syphilis
Iliac	Lower abdominal viscera Urinary and genital tract Lower extremities	Only with disease	Abdominal infection such as appendicitis, abdominal trauma, urinary tract infection	Pyogenic infection of lower extremity
Popliteal	Skin of	Only	Severe local pyogenic	—

	lateral foot and lower leg, knee joint	with disease	infection	

A careful history must be obtained regarding the time of onset and rate of lymph node enlargement (Box 20.1). The skin and soft tissue areas drained by the enlarged nodes are examined for signs of infection and disruption. History of exposure to animals is detailed. Occurrence of bites (including tick bites) or traumatic scratches or other papular or ulcerative skin lesions is elicited. Weight loss, protracted fever, rash, generalized lymphadenopathy, and hepatosplenomegaly suggests a systemic disease.[10]

Box 20.1

Clinical Clues to the Cause of Lymphadenopathy

History

Associated symptoms and duration of illness

Ingestion of unpasteurized milk or undercooked meat

Dental problems

Skin lesions or trauma with or without foreign body exposure

Animal exposures; flea or tick bites

Contact with tuberculosis

Drug usage (especially phenytoin)

Physical Examination

Dental disease

Ocular, otic, or oropharyngeal lesions

Skin lesions

Noncervical adenopathy

Hepatomegaly or splenomegaly

Lymph nodes associated with viral infection tend to be small, bilateral, freely mobile, and variably tender.[11] Erythema, warmth, and tenderness overlying a node typically indicate a pyogenic acute inflammatory response related to a bacterial pathogen. Fluctuation of the lymph node suggests acute pyogenic bacterial adenitis but also can be seen with more indolent pathogens, including nontuberculous mycobacteria (NTM), and an overlying violaceous hue raises suspicion of NTM (Fig. 20.1). Most acutely infected lymph nodes in children have a rubbery or firm consistency and are freely mobile. Fixation of nodes to underlying tissue or matting to each other can occur with bacterial adenitis but raises concern about a neoplastic process. Absence of fixation does not exclude malignancy, especially not lymphoma.

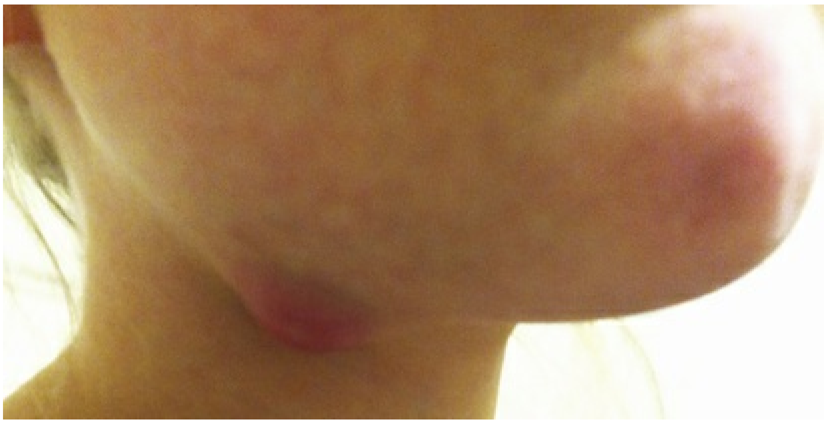


FIGURE 20.1 A 6-year-old girl has a violaceous submandibular lymph node consistent with nontuberculous mycobacterial infection. The lymph node was resected, and necrotizing granulomas with rare acid-fast bacteria were found on pathology review. (Courtesy of J. Christopher Day, MD, Children's Mercy Hospital, Kansas City, Missouri.)

Differential Diagnosis

Knowledge of lymphatic drainage patterns is essential for identification of the primary focus of infection and the most likely etiologic agents in the child with localized lymphadenopathy. The regions drained by specific lymph node groups are listed in Table 20.1, along with the associated infections encountered.

Occipital Nodes

The occipital lymph nodes drain the posterior scalp and can become enlarged by diseases such as impetigo, pediculosis capitis, tinea capitis, and inflamed seborrheic dermatitis. Tularemia often involves occipital nodes because a common site for tick bite in children is on the parieto-occipital scalp. Occurrence of the tick bite itself may be unknown or forgotten; it may have occurred a week or more earlier. A history of exposure to a tick-infested area should raise suspicion. The scalp should be inspected carefully for a papule or an ulcer because ulceroglandular tularemia is more common than glandular disease, and it is most common in those younger than 2 years of age.[12,13] Less often, rubella infection or toxoplasmosis can produce isolated occipital lymphadenopathy.

Preauricular Nodes

Preauricular nodes drain the lateral eyelid and conjunctivae, along with skin overlying the cheek and temple. Severe conjunctivitis associated with ipsilateral preauricular lymphadenopathy is known as Parinaud or oculoglandular syndrome. Oculoglandular syndrome is a relatively common complication of *B. henselae* infection (i.e., cat-scratch disease), affecting approximately 8% of symptomatic patients (Fig. 20.2).[14] The differential diagnosis also includes tuberculosis, tularemia, and nontuberculous lymph node infection. Chlamydial neonatal inclusion conjunctivitis can appear 5 to 10 days after birth, and lymph node enlargement helps to distinguish it from gonococcal ophthalmia neonatorum.[15]

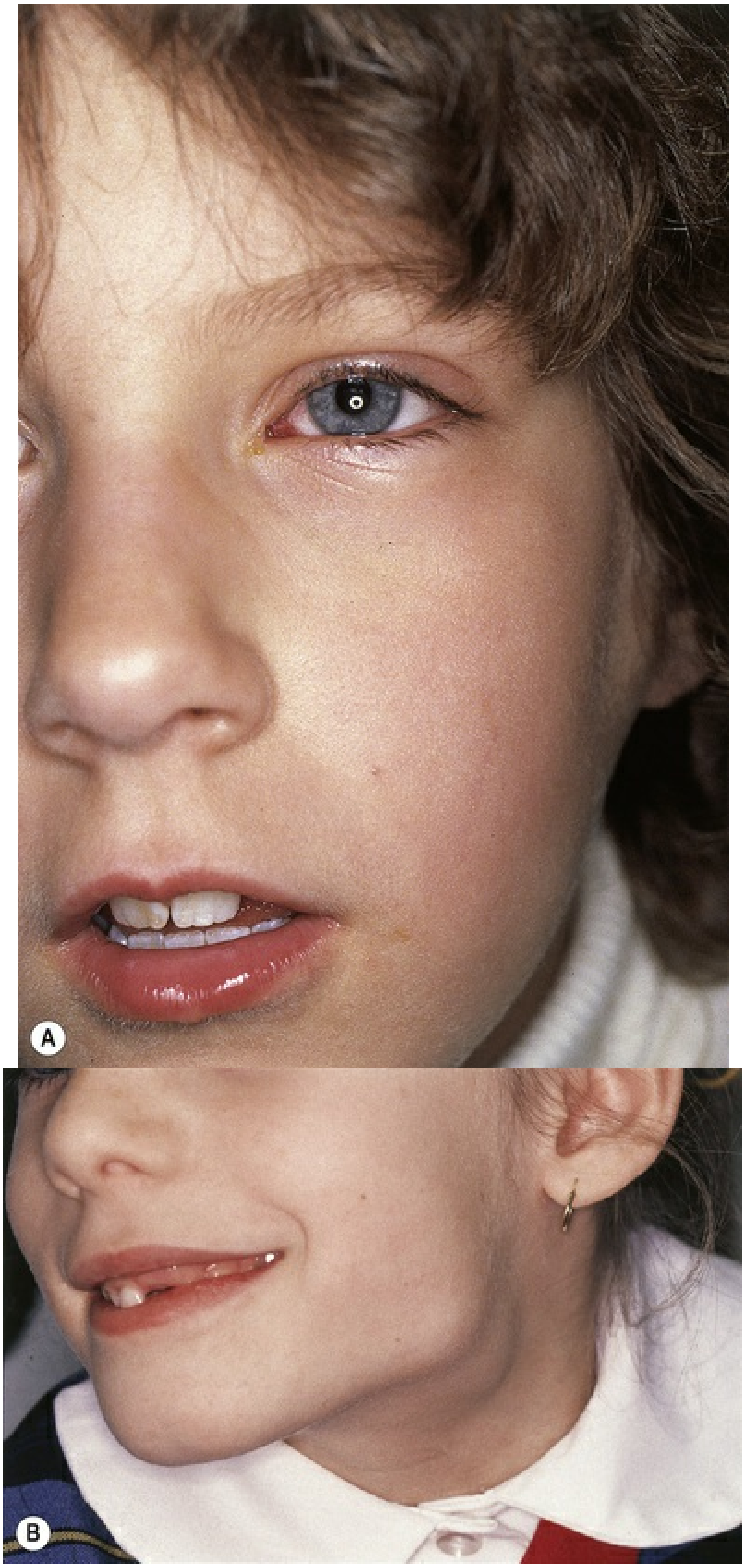


FIGURE 20.2 Two school-aged girls have granulomatous conjunctivitis and lymphadenopathy due to *Bartonella henselae* infection. One girl has associated preauricular lymphadenopathy (A), and the

other has facial and anterior cervical lymphadenopathy (B). (Courtesy of Sarah Long, MD, St. Christopher's Hospital, Philadelphia, Pennsylvania.)

Trachoma, which is a chronic form of chlamydial eye infection, causes an oculoglandular syndrome that can result in blindness. It is rare in the United States but endemic in many developing countries. Epidemic keratoconjunctivitis[16] and pharyngoconjunctival fever[17] are adenoviral infections that can be associated with preauricular adenopathy.

Axillary Nodes

The axillary nodes drain the upper extremity, chest wall, and upper lateral abdominal wall. Localized axillary lymphadenopathy most often represents a response to a pyogenic infection of the upper extremity. *B. henselae* infection is commonly associated with localized axillary lymphadenopathy after a cat scratch on the arm, and rat-bite fever due to *Spirillum minus* can cause axillary node enlargement and tenderness.[18] Regional cutaneous tuberculosis (i.e., scrofuloderma) can be associated with axillary node enlargement.[19,20]

The most common complication of bacille Calmette-Guérin (BCG) vaccination is granulomatous lymphadenitis of the ipsilateral axillary region, which sometimes heals spontaneously but can have a protracted course. Disease responds poorly to isoniazid therapy and can require surgical excision.[21–23] The diagnosis should be considered when evaluating internationally adopted children.

Hidradenitis suppurativa is a defect of terminal follicular epithelium that often affects obese adolescent girls and can lead to recurrent polymicrobial axillary node abscesses, fistulas, and scarring.[24,25] Although gram-positive organisms predominate as causes of axillary skin and lymph node abscesses, *Proteus mirabilis* was an unexpected pathogen in 28% of axillary skin abscesses in adolescent girls in a single-center study.[26]

Noninfectious causes of axillary lymphadenopathy must be considered, because steadily enlarging nodes in the absence of an obvious focus can raise concerns about lymphoma or other neoplasms. Rheumatologic diseases with inflammation of the wrists or finger joints can produce axillary lymph node swelling, although lymphadenopathy usually affects more than the axillary nodes alone.

Epitrochlear Nodes

The epitrochlear nodes drain the distal arm and the middle, ring, and fifth fingers. Isolated enlargement typically results from a local skin lesion infected with *Staphylococcus* or *Streptococcus.* Epitrochlear lymphadenopathy also can follow cutaneous inoculation of *B. henselae, F. tularensis,* or (rarely) *Sporothrix schenckii.* Chronic enlargement of epitrochlear nodes can occur in cases of secondary syphilis and can be a clue to congenital syphilis. Hodgkin disease can manifest with epitrochlear adenopathy.[27]

Iliac and Femoral Nodes

Enlarged iliac nodes can be detected by deep palpation over the inguinal ligament, and enlarged femoral nodes can be detected by deep palpation below the inguinal ligament on the leg in the fossa between the adductor and rectus muscles. Suppurative iliac lymphadenitis is an important cause of retroperitoneal abscess and can result from abdominal trauma, appendicitis, urinary or genital tract infection, or infections of the lower extremity.[28,29] Femoral lymphadenitis results from superficial or deep infection of the lower extremity. *S. aureus* and *S. pyogenes* are implicated most commonly, but *B. henselae* also can cause prominent femoral or iliac lymphadenitis. *Yersinia enterocolitica, Salmonella,* and tickborne *F. tularensis* can infect the inguinal nodes.

The child with iliac lymphadenitis can have fever, a limp, abdominal or hip pain, and spasm of the psoas muscle. The patient typically prefers to lie with the hip flexed and the thigh abducted, because hip extension is extremely painful. Differentiation of iliac lymphadenitis from appendicitis is facilitated by the lack of nausea and vomiting and from pyogenic arthritis by demonstration of a fuller range of motion of the hip on examination.[30] Computed tomography is the favored imaging modality when more extensive evaluation of iliac lymph node abnormalities is required.

Popliteal Nodes

The popliteal lymph nodes are difficult to palpate unless they are substantially enlarged. Consequently, popliteal lymphadenopathy is appreciated only when associated with severe pyogenic infections of the distal lower extremity or knee joint or noninfectious diseases of the reticuloendothelial system.

Management and Therapy

Definitive therapy for localized lymphadenopathy or lymphangitis requires identification of the most likely pathogen involved. A history of antecedent trauma, presence of a skin lesion or infection in the region drained by the involved node or nodes, and rapid development of a large, warm, tender mass is highly suggestive of acute pyogenic lymphadenitis. Needle aspiration of a fluctuant node can provide therapeutic benefit, rapid presumptive diagnosis (with use of Gram stain), and a sample for culture and antibiotic susceptibility testing. Children with nonfluctuant nodes whose symptoms are otherwise consistent with acute bacterial infection can be treated empirically and closely monitored for clinical response. Timely needle aspiration is increasingly important with the rise in community-associated methicillin-resistant *S. aureus* (CA-MRSA) infection. The child with significant fever or systemic symptoms should be further evaluated with a blood culture, complete blood cell count, and measurement of inflammatory markers (e.g., C-reactive protein).

Treatment of acute lymphadenitis should be based on the presumed etiologic agent (Box 20.2). A specimen from the node should be obtained to guide definitive therapy. Because acute pyogenic lymphadenitis can be staphylococcal or streptococcal in origin, the use of a cephalosporin (e.g., cephalexin, 50 mg/kg/day) or clindamycin (30 to 40 mg/kg/day) is appropriate initial therapy for an outpatient. Local prevalence of CA-MRSA and clindamycin resistance by MRSA, methicillin-susceptible *S. aureus* (MSSA), and *S. pyogenes* should be considered.[31–34] Linezolid should be reserved for MRSA infection that is clindamycin resistant. Trimethoprim-sulfamethoxazole is inappropriate for treatment of *S. pyogenes* infection.[35]

Box 20.2

Treatment of Common Infections Associated With Isolated Lymphadenitis

Empiric Therapy

Nafcillin, Cefazolin, Cephalexin, cefadroxil, clindamycin (consider local *Staphylococcus aureus* antibiogram)

Periodontal Abscess

Penicillin V, ampicillin and sulbactam, or clindamycin

Cat-Scratch Disease

Macrolides, rifampin, trimethoprim-sulfamethoxazole (TMP-SMX)

Tularemia

Gentamicin, doxycycline (high relapse rate), ciprofloxacin

Macrolide antibiotics such as erythromycin and azithromycin should not be used to treat acute bacterial adenitis because of the high rate of resistance of *S. aureus,* occasional resistance of *S. pyogenes,* and lack of data supporting use for deeper infections. Azithromycin is an option if cat-scratch infection is considered likely.[36] For patients who appear systemically ill and for young infants at higher risk for a bloodstream infection (BSI), initiation of parenteral therapy with similar agents (e.g., nafcillin or clindamycin, or both, in areas where MRSA and clindamycin resistance of MSSA are prevalent) is indicated.

Nodes with significant suppurative changes are likely to respond more promptly to therapy after percutaneous aspiration or incision and drainage. A total antibiotic (i.e., parenteral plus oral) course of 2 to 3 weeks' duration is often required for complete resolution of bacterial lymphadenitis. In the setting of bacteremia or for life-threatening disease, vancomycin (60 mg/kg/day) should be given, provided normal renal function, in addition to an antistaphylococcal β-lactam and clindamycin after collection of specimens likely to yield a microbiologic diagnosis.[37]

Localized lymph node enlargement lacking the characteristic features of acute pyogenic lymphadenitis and enlarged nodes that do not respond to antibiotic therapy merit further careful evaluation. Any clue regarding possible exposure to unusual pathogens should be pursued diagnostically. A tuberculin skin test (TST) should be performed, realizing that *Mycobacterium tuberculosis* and nontuberculous mycobacterial (NTM) strains can be associated with a positive test result; the latter typically is an intermediate response.

The interferon γ release assay (IGRA) can be used to differentiate between infection due to *M. tuberculosis* and that due to NTM; the test result is negative in the latter case.[38] However, the IGRA is approved for use only in children 5 years of age or older and may not differentiate between *M. tuberculosis* and certain NTM strains, such as *M. kansasii*.[38,39]

B. henselae infection can be evaluated by serologic testing. Cat-scratch lymphadenitis typically is a self-limited infection requiring no antibiotic therapy, but in some cases, antibiotic therapy is beneficial, and aspiration of suppurative nodes may be required. Follow-up is important because unusual systemic complications, such as hepatic involvement and encephalopathy, can occur.[40]

Tularemia can be diagnosed by serologic testing, and initial testing usually is diagnostic if lymphadenopathy has been present for ≥2 weeks (Fig. 20.3). Hidradenitis suppurativa can be temporized by antibiotic therapy such as clindamycin and rifampin, although wide surgical excision is considered most effective, and healing by granulation follows.[41,42]

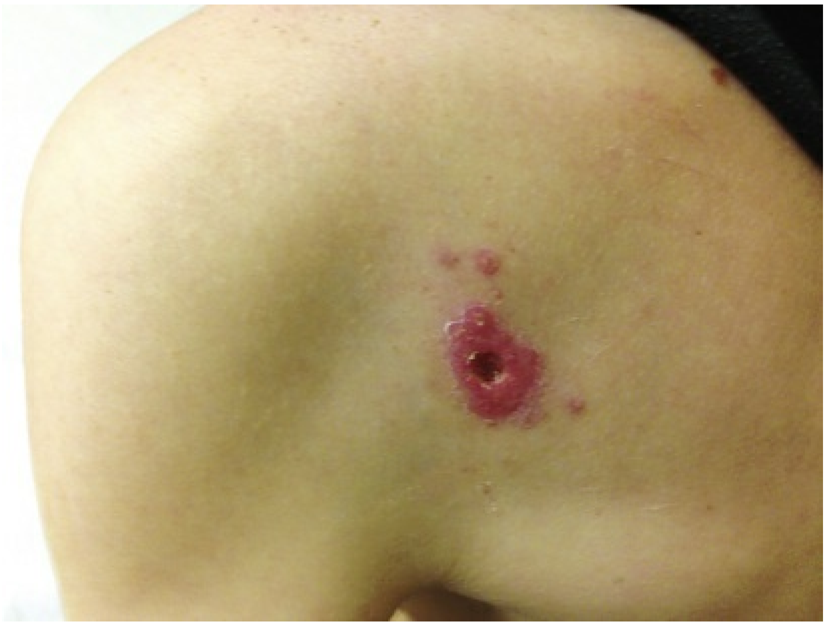


FIGURE 20.3 The shoulder and back of an 8-year-old

boy with ulceroglandular tularemia of the left scapular region and associated axillary lymphadenopathy. The patient had a history of a tick bite of the left scapula. The diagnosis was made by serology. (Courtesy of James Christopher Day, MD, Children's Mercy Hospital, Kansas City, Missouri.)

Biopsy is indicated for patients for whom the history, associated physical findings, and screening laboratory tests fail to lead to a diagnosis, especially when suspicion of a neoplasm or an unusual infection is high. In a series of 75 children who underwent excisional biopsy of a peripheral lymph node, nonspecific reactive hyperplasia was found in 55%, noncaseating granuloma (e.g., cat-scratch disease) in 21%, lymphoreticular malignancy in 17%, and caseating granuloma in 7%.[43] Studies also suggest that fine-needle aspiration, perhaps guided by ultrasound, is a safe and effective alternative to excisional biopsy for discriminating infection from malignancy in the lymph nodes of children; one study found a diagnostic sensitivity of 86% and specificity of 96%.[44–46] However, excisional biopsy should be used in the setting of suspected malignancy and inconclusive aspiration results, and it is the preferred method of therapy in the setting of suspected or presumed NTM infection.[47]

Any specimen from an excised node or needle aspirate should be submitted for Gram staining, acid-fast staining, and culture for bacteria (except when tularemia is suspected and culture poses risk for laboratory personnel), mycobacteria, and fungi. Staining with Warthin-Starry reagents for *Bartonella* is sometimes performed, but a positive result is not specific.

Lymphangitis

Lymphangitis refers to inflammation of subcutaneous lymphatic channels, typically in an extremity. It can manifest an acute bacterial infection or a more chronic, indolent process due to a fungal, mycobacterial, or parasitic pathogen.

Etiologic Agents

Infections that cause lymphangitis are summarized in Table 20.2. *S. pyogenes* is the leading cause of acute lymphangitis. Less commonly, *S. aureus* or other streptococci can cause lymphangitis, as can *Pasteurella* spp. after a cat or dog bite and *S. minor* after a rat bite. When inoculated cutaneously, several organisms can produce chronic, nodular lymphangitic infection.[48,49] Organisms include the dimorphic fungus *Sporothrix schenckii*, *Nocardia* spp., *Mycobacterium marinum*, and certain other mycobacteria, and *Leishmania* spp.[50] In the case of *Nocardia* or NTM, an antecedent history of trauma often is elicited. A foreign body, often wood, can be identified. Arthropod-borne filariasis due to *Wuchereria bancrofti* or *Brugia* spp., which is endemic in the tropics and subtropics, manifests as acute lymphangitic inflammation or chronic lymphatic obstruction with lymphedema.

TABLE 20.2

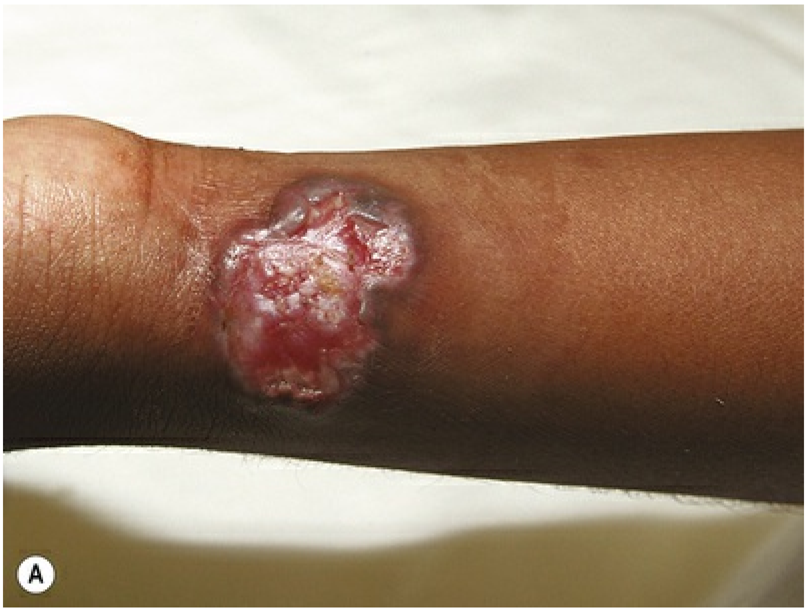
Causes of Lymphangitis

Etiologic Agent	Exposure	Onset	Clinical Features
ACUTE BACTERIAL LYMPHANGITIS			
Streptococcus pyogenes (less commonly, *Staphylococcus aureus*)	Localized skin infection	Acute (<24–48 hr)	Red streaking, tender regional nodes, fever, chills, malaise
Pasteurella multocida	Dog or cat bite	Acute (<24–48 hr)	Red streaking, tender regional nodes, fever, chills, malaise
Spirillum minus	Rat bite	Acute, after incubation period 1–3 wk	Red streaking, tender regional nodes, fever, chills, malaise, headache
NODULAR LYMPHANGITIS (LYMPHOCUTANEOUS SYNDROME)			
Sporothrix schenckii (sporotrichosis)	Soil, peat moss, thorned flowers	Insidious, incubation period 1–12 wk	Inoculation site papule, proximal spread of reddish nodules, systemic symptoms rare
Mycobacterium marinum (occasionally *Mycobacterium chelonae*)	Fish, shellfish, aquariums, ponds	Insidious, incubation period 2–4 wk	Nontender nodules at inoculation site and spreading proximally, systemic symptoms rare
Nocardia brasiliensis	Soil botanicals	Insidious, incubation period 1–2 wk	Localized chronic granuloma with nodular spread, drainage with "sulfur granules," regional adenopathy
Leishmania brasiliensis (also *Leishmania mexicana*)	Travel to endemic area, sandfly bite	Insidious, incubation period 2–8 wk	Primary ulcer with surrounding nontender nodules, no adenopathy or systemic symptoms
Wuchereria bancrofti (also *Brugia* spp.)	Travel to endemic area, mosquito bite	Acute or chronic	Acute: red streaking, adenopathy, fever rare Chronic: lymphatic obstruction, elephantiasis

Clinical Manifestations

Acute bacterial lymphangitis can accompany cellulitis or can occur in association with minor or inapparent skin infection. Lymphangitis is recognized from the rapid appearance of tender, red, linear streaks proceeding from the site of cutaneous (frequently minor) infection toward the regional lymph nodes. Tender lymphadenopathy is typical, as are systemic symptoms such as fever, chills, and malaise. BSI occurs in approximately 5% of patients.[51]

Nodular lymphangitis (i.e., lymphocutaneous syndrome) has distinctive clinical features and expected pathogens.[50] Infection most often manifests on the hands and upper extremities. Sporotrichosis is the prototypical lymphocutaneous infection (Fig. 20.4). The disease often begins with a shallow ulcer at the site of inoculation. Subcutaneous nodules 2 to 20 mm in diameter appear indolently as the infection advances along the course of the lymphatic channel. The nodules are small and freely mobile or adhere to the superficial skin. Larger nodules often exhibit overlying erythema, but they rarely are painful. Nodules sometimes ulcerate, releasing serosanguineous fluid.



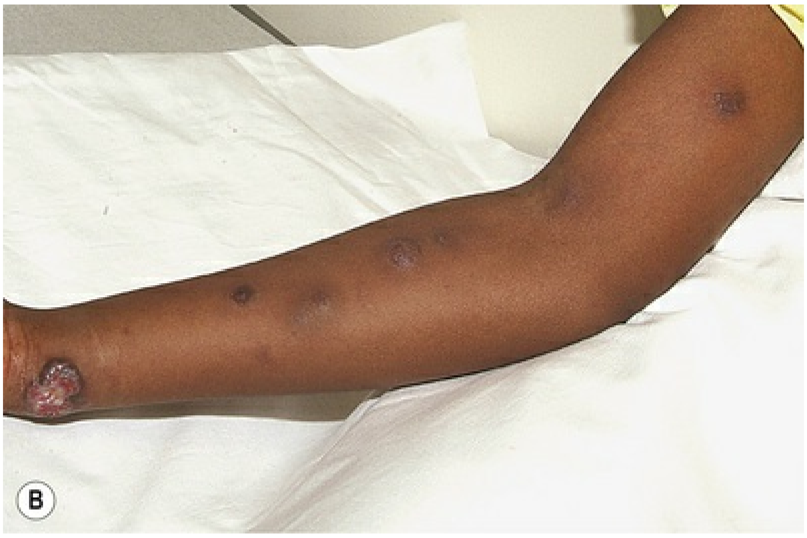


FIGURE 20.4 An adolescent girl had a 4-month history of an ulcerating skin lesion on her wrist (A) and nodular lymphangitis (B). *Sporothrix schenckii* was isolated. Her only exposure to roses was from a florist. (Courtesy of Sarah Long, MD, St. Christopher's Hospital, Philadelphia, Pennsylvania.)

In contrast to acute bacterial lymphangitis, systemic symptoms of infection and regional adenopathy typically are absent in chronic nodular lymphangitis. Most patients do not come to medical attention until several weeks into the clinical illness. Biopsy and culture of lesions establish the diagnosis.

Differential Diagnosis

Acute lymphangitis is a clinical diagnosis made for the febrile patient with tender, linear, red streaking that extends proximally from a site of peripheral infection or traumatic inoculation. Thrombophlebitis is the major differential diagnostic consideration, but it lacks the characteristic inciting lesion unless it is associated with an intravascular cannula and the tender regional lymphadenopathy associated with acute lymphangitis.

The precise etiologic agent (usually *S. pyogenes*) can be identified with a Gram stain and culture of a specimen from the cutaneous lesion or by culture of the blood.[51] Acute lymphangitis develops in about 20% of patients with animal bites infected with *Pasteurella canis* (dogs) or *P. multocida* (cats).[52,53] *S. minus* infection should be considered in a child living in a crowded urban dwelling that is prone to rat infestation because the superficial bite wound often completely heals during the 1- to 3-week incubation period before development of acute lymphangitis.

The origin of nodular lymphangitis usually is established through a careful history of potential exposure to causative pathogens. The incubation period between inoculation and development of lymphangitic nodules can vary from 1 to 8 weeks, depending on the infecting organism.[49,54] *S. schenckii* is found in soil and botanical debris, and infection follows contact with thorned material such as rose bushes or with sphagnum moss.[55] *M. marinum* is a ubiquitous organism in marine and freshwater environments, aquariums, and swimming pools. A reddish blue primary lesion develops at the site of trauma (e.g., fingers and hands in fish-handlers′ granuloma, elbows or knees in swimming-pool granuloma). Ulceration with purulent drainage can occur, and the disease can spread centripetally to produce sporotrichoid-like nodular lymphangitis.[56] The rapidly growing soil and water mycobacterium *M. chelonae* can produce a similar constellation.[57]

Nocardia brasiliensis can gain access to lymphatics through minor wounds contaminated with soil and can produce nodular lymphangitis with suppurative ulceration, occasionally accompanied by regional adenopathy and systemic symptoms.[58] New World cutaneous leishmaniasis is a protozoal disease seen in travelers to rural Central or South America who encounter its sandfly vector. After development of a shallow ulcer at the location of the insect bite, nodular lymphatic spread with superficial scale, discharge, and crusting is common.[59]

The histopathologic changes associated with chronic nodular lymphangitis typically are granuloma formation with epithelioid and giant cells and various degrees of neutrophilic infiltration. Diagnosis of sporotrichosis is made by identification of fungal spores surrounded by eosinophilic material (i.e., asteroid bodies) or inoculation of a specimen from tissue drainage on Sabouraud agar. *M. marinum* often is not detected on acid-fast staining of lymphatic biopsy specimens, but culture on appropriate media incubated at 30°C is highly sensitive. *Nocardia* species appear as delicate, beaded, branching, gram-positive bacilli that can be grown on simple media but may take several days to display characteristic colonial morphology.[60] Pathognomonic sulfur granules are sometimes seen in exudate from lesions. Diagnosis of cutaneous leishmaniasis is made by direct visualization of amastigotes within histiocytes from a biopsy specimen or scraping.

Therapy

Because *S. pyogenes* is the predominant cause of acute lymphangitis, penicillin is the preferred initial treatment. Children with mild disease can be treated with oral penicillin V (50 mg/kg/day). Patients with *S. pyogenes* disease and concurrent BSI should be treated with intravenous penicillin G (100,000 to 400,000 U/kg/day), depending on illness severity; resistance to penicillin has never been documented. Penicillin is also the drug of choice for *Pasteurella* lymphangitis and *S. minus* rat-bite fever. Those with prominent systemic symptoms and unknown or possible bacteremia should receive intravenous therapy with an antibiotic that also provides adequate coverage for *S. aureus*.

Lack of familiarity with the syndrome of nodular lymphangitis often leads to delays in the correct diagnosis and inappropriate antibiotic therapy directed at pyogenic bacteria. Conservative measures, such as local application of a heating pad, may contribute significantly to resolution of lesions associated with sporotrichosis, *M. marinum* infection, or cutaneous leishmaniasis. Itraconazole (100 to 200 mg/day) is the drug of choice for lymphocutaneous sporotrichosis, supplanting saturated solution of potassium iodide (SSKI) because of lower toxicity.[54] Treatment should be continued for 4 weeks beyond resolution of lesions (i.e., 2 to 3 months total).

Antimicrobial agents (e.g., trimethoprim-sulfamethoxazole, minocycline, rifampin plus ethambutol) are variably effective against *M. marinum* lymphangitis, and surgical excisional debridement often is required. *Nocardia* infection usually responds readily to a sulfa drug; amoxicillin-clavulanate is an option for patients allergic to sulfa, and linezolid has been used successfully in some cases. Cutaneous leishmaniasis often heals spontaneously with topical care, but therapy with pentavalent antimony should be used if lesions evolve to the mucocutaneous form.

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21

Respiratory Tract Symptom Complexes

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Mucopurulent Rhinorrhea

Mucopurulent rhinorrhea (i.e., purulent nasal discharge) denotes nasal discharge that is thick, opaque, and colored.[1] It occurs at any age and usually is a manifestation of a self-limited and uncomplicated viral upper respiratory tract infection (URI). Mucopurulent rhinorrhea is most problematic in children younger than 3 years because of a protracted course and frequent recurrence, especially in those in out-of-home childcare[2]; parental concern and misperception about the cause; and overprescription of antibiotics by healthcare providers.[3–5] Occasionally, this symptom is a clue to the diagnosis of a treatable bacterial infection or underlying condition.

Acute, sporadic mucopurulent rhinorrhea has an infectious cause and almost always is the manifestation of a viral upper respiratory tract infection or the uncomplicated common cold due to rhinoviruses, coronaviruses, human metapneumovirus (MPV), influenza, enteroviruses, parainfluenza, respiratory syncytial virus (RSV), or other circulating viruses.[6,7] When the problem is chronic or recurrent or persistent and unilateral, broader underlying anatomic, obstructive, immunologic, and allergic disorders are considered (Table 21.1).[8–10] Onset in an infant younger than 3 months heightens suspicion of an anatomic anomaly, ciliary dyskinesia, or cystic fibrosis. Accompanying sinusitis, otitis media, or pneumonia at this young age prompts consideration of an immunologic deficiency, especially humoral immunodeficiency (e.g., hypogammaglobulinemia, agammaglobulinemia, human immunodeficiency virus [HIV] infection); neutrophil defect; cystic fibrosis; or ciliary dyskinesia. URIs are conspicuously severe in such instances, with recrudescence occurring almost immediately after discontinuation of antibiotic therapy. Unilateral nasal discharge and obstruction should prompt investigation for a foreign body, mass lesion, or unilateral posterior choanal atresia.

TABLE 21.1
Causes of Mucopurulent Rhinorrhea

Acute	Chronic or Recurrent	
	Underlying Conditions	**Obstructing Lesions**
Viral nasopharyngitis Bacterial sinusitis Acute otitis media Streptococcal nasopharyngitis Anaerobic bacterial nasopharyngitis (nasal foreign body) Adenoiditis Syphilis Pertussis Cerebrospinal fluid rhinorrhea[b]	Allergy[a] Medications or rhinitis medicamentosa[a] (antihypertensive drugs, oral estrogens, α_1-adrenergic agonists, aspirin and nonsteroidal anti-inflammatory drugs) Cocaine use[a] Pregnancy[a] Hypothyroidism[a] Immunoglobulin deficiency Human immunodeficiency virus (HIV) infection Cystic fibrosis Ciliary dyskinesia	Polyps Congenital nasal anomalies (choanal atresia or stenosis, Tornwaldt cyst, deviated septum) Neuroembryonal mass (dermoid, encephalocele, glioma, teratoma) Tumor (hemangioma, angiofibroma, neurofibroma, lipoma, craniopharyngioma) Neoplasm (lymphoma, rhabdomyosarcoma, nasopharyngeal carcinoma)

[a] Rhinorrhea is characteristically clear, but an opaque, white discharge is not unusual.

[b] Rhinorrhea is characteristically clear.

Table 21.2 shows differentiating features of important or common causes of acute mucopurulent rhinorrhea. Allergic rhinitis is included because of its place in the differential diagnosis for older children and adolescents.

TABLE 21.2
Differentiating Among Causes of Nasal Discharge

Characteristic	Viral Nasopharyngitis	Acute Bacterial Sinusitis	Streptococcal Nasopharyngitis	Foreign Body–Related Bacterial Rhinitis	Allergic Rhinitis
HISTORY					
Peak age	Peak in first 2 yr after enrollment in childcare or school	Any	<3 yr	<3 yr	>2 yr
Onset	Acute; dryness, burning in nose or nasopharynx	Insidious with cough day and night or with secondary fever or worsening upper respiratory tract infection symptoms; occasionally, acute, febrile, toxic	Insidious; occasionally acute, febrile, toxic	Insidious	Can be sea or perenni precipitant often ident
Associated symptoms	Nasal congestion, sneezing, malaise	Malodorous breath; head or facial pain, edema		Malodorous breath ± hyponasal voice	Sneezing; congestion nasal itchi postnasal drip/coug allergic conjunctiv with itchi and tearin
Fever	Yes/no	No/yes	Low/high	No	No
Duration of discharge	3–15 days	≥10 days	>5 days	Chronic	Seasonal o perennial
PHYSICAL EXAMINATION					
Associated findings	Red, excoriated nares; sometimes acute otitis media	Periorbital swelling, facial tenderness; mucopurulent postnasal discharge	Anterior cervical lymphadenitis; impetiginous lesions below nose	Mouth-breathing	Transverse nasal or lo eyelid crea infraorbita edema and darkening, conjunctiv cobbleston of conjunc or posterio pharynx
Character of discharge	Clear or colored, watery or thick	Thick, colored	Thick, colored	Unilateral, purulent, putrid bloodstained	Watery, cl
Rhinoscopy	Hyperemic mucosa; dry or glazed early, edematous later; crusted discharge	Normal mucosa; discharge from middle meatus	Normal, hyperemic, or excoriated mucosa	Identifiable object (button, pit, nut), boggy mass (vegetable), or rhinolith	Pale or blu edematous turbinates
DIAGNOSIS					

Diagnostic tests	None; nasal smear shows neutrophils and mononuclear cells ± inclusion bodies, pyknotic epithelial cells	None unless suppurative complications suspected	Nasopharyngeal culture for *Streptococcus* only	Rhinoscopy	Positive allergen sk tests or ser IgE levels, rhinoscop nasal smea rare cases
ETIOLOGY					
Causes	Multiple agents, depending on age and season	*Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*	*Streptococcus pyogenes*	Normal nasopharyngeal facultative and anaerobic bacteria	Allergens
TREATMENT					
Therapies	Saline nasal drops, humidification; antibiotic only for secondary bacterial infection (acute otitis media or sinusitis)	Amoxicillin; amoxicillin-clavulanate (14:1 formulation), 90 mg/kg/day of amoxicillin component	Penicillin V	Removal of obstruction; amoxicillin-clavulanate for tissue or sinus complication	Allergen avoidance; glucocorti nasal spra antihistam antihistam nasal spra leukotrien receptor antagonist nasal salin irrigation, allergen immunoth

Causes

Viral Nasopharyngitis

In uncomplicated viral nasopharyngitis or rhinitis, the nasal discharge initially is clear but can become white, yellow, or green due to mucous secretions, dryness, blood, exfoliation of damaged epithelial cells and cilia, and a leukocytic inflammatory response. High fever and persistence of discharge can be seen, depending on the specific viral agent, but they are more common in uncomplicated infection than generally perceived.

In a study of hospitalized children, more than 50% with uncomplicated adenovirus, influenza, parainfluenza, or RSV infection had temperatures greater than 39°C, and 12% had temperatures greater than 40°C; the height of fever in these children was not different from that in children with serious bacterial infection.[11] Fever persisted for 5 or more days in 37% of the children in the study; 20% to 30% of those with adenovirus or influenza A infection had fever for ≥7 days. In another study, nasal discharge or congestion associated with uncomplicated URI persisted for 6.6 days in 1- to 2-year-old children who were in home care and for 8.9 days in children younger than 1 year in out-of-home childcare.[1] In a systematic review of studies on the common cold and nonspecific URIs in children, symptoms resolved in 50% by day 10 and 7, respectively, and in 90% by days 15 and 16.[12,13]

The bacteriology of nasopharyngeal flora in children with uncomplicated viral respiratory illnesses, mucopurulent rhinorrhea, acute otitis media, and sinusitis has been evaluated and compared with that in healthy children.[6,14–21] Viral infection is associated with acquisition of new serotypes of *Streptococcus pneumoniae* and with temporally increased risk of acute otitis media.[20] Quantitative and some qualitative differences in nasopharyngeal flora have been found in children with purulent nasopharyngitis during uncomplicated viral URIs, with excessive isolation rates reported for *S. pneumoniae* and *Haemophilus influenz*ae, *Peptostreptococcus* spp., *Fusobacterium* spp., and *Prevotella melaninogenica.*[14,18,19] Differences may reflect new bacterial acquisition or exuberant proliferation in virus-induced inflammatory mucus or availability of a more robust specimen than in healthy subjects. A high rate (25%–46%) of isolation of *S. pneumoniae* does not exceed that in healthy young children when fastidious technique is used.[21]

In a prospective study, there was no difference in the duration of illness or complications in children with clear or purulent nasal discharge.[15] A large Cochrane meta-analysis concluded no benefit of antibiotic therapy in children with URI or cough.[5,22] In a placebo-controlled, blinded study of 142 children 3 months to 3 years old with mucopurulent rhinorrhea of any duration, antibiotic therapy (e.g., cephalexin) or systemic use of an antihistamine-decongestant, or both, had no effect on the course or complications of mucopurulent rhinorrhea.[14] In a meta-analysis of randomized, controlled trials assessing the effect of probiotics on URIs in children and adults, significantly fewer days of illness and absences from childcare, school, or work occurred in those receiving a probiotic (i.e., *Lactobacillus* or *Bifidobacterium* strains) compared with placebo.[16]

Acute bacterial adenoiditis has been postulated as a cause of purulent nasal discharge when tympanic membranes are normal, *S. pyogenes* is not found in culture specimens, and radiographs show an enlarged adenoid shadow but no sinus abnormality.[23] No study has been performed to validate this entity. Mucopurulent rhinorrhea plus additional clinical features, such as prolonged or new fever, cough or ill appearance; stridor or auscultatory abnormalities can indicate another diagnosis.

Bacterial Sinusitis

Bacterial sinusitis reportedly complicates 5% to 10% of viral upper respiratory tract infections in children.[24] In a prospective study of 236 children 4 to 7 years of age, 8.8% of symptomatic URIs were complicated by sinusitis using the definitions that follow; all episodes met one of the first two definitions.[13] Mucopurulent rhinorrhea or daytime cough (which frequently is worse at night), or both, of 10 or more days′ duration without improvement, worsening symptoms (i.e., recrudescence after improvement or new onset of fever), or severe onset of symptoms with fever of 39°C or higher and purulent nasal discharge for at least 3 consecutive days strongly suggests paranasal bacterial sinusitis and response to antibiotic therapy.[25–27]

Guidelines on the diagnosis and management of acute bacterial rhinosinusitis have been published.[24,26,27] Sinus radiographs show significant abnormalities in almost 90% of children 2 to 6 years old and many older children with uncomplicated upper respiratory tract illness, supporting a clinical approach to diagnosis without imaging.

Streptococcal Nasopharyngitis

In children younger than 3 years of age, *S. pyogenes* can be associated with high fever, toxicity, and rhinorrhea or indolent infection with irregular fever and purulent nasal discharge, sometimes with associated excoriation of nares or tender anterior cervical lymphadenitis.[13,18,25] In a streptococcal outbreak studied in a childcare facility for school-aged and young children, 26% of children younger than 3 years of age were affected, but pharyngitis was predominant, with no case of nasal streptococcosis.[28]

Other Infectious Causes

Bacterial nasopharyngitis associated with a nasal foreign body is typified by the young age of the patient and putrid, commonly bloodstained, unilateral nasal discharge. Fever is unusual unless infection has spread to contiguous sinuses or distant sites. *Prevotella, Fusobacterium,* and *Peptostreptococcus* spp., as well as facultative flora, are responsible. Nasal discharge can be the first manifestation of congenital syphilis and a later finding in nasal diphtheria, in which discharge is putrid and sanguineous with pieces of pseudomembrane.

Allergic Rhinitis

Allergic rhinitis is uncommon before 2 years of age. Diagnosis can be suspected because of the season, environmental precipitants, personal and family history of allergy or atopy, other associated symptoms, physical findings, and the response to specific interventions, such as avoidance or pharmacotherapy (see Table 21.2). Nasal secretions typically are clear.

Management

For most children with purulent nasal discharge (even if thick and green) of up to 1 week's duration, the history and setting of illness, associated symptoms, and physical findings suggest an uncomplicated viral URI. Antimicrobial therapy is inappropriate unless acute otitis media or sinusitis is diagnosed from additional findings.[5] Symptomatic therapy with saline nose drops or lavage facilitates expulsion of secretions and provides humidification. Its effectiveness reduces parental pressure to prescribe an antibiotic.[29] Over-the-counter medications should be avoided for children, especially those younger than 6 years of age. Antipyretic or analgesic medication is appropriate for the treatment of fever and discomfort.

If mucopurulent rhinorrhea persists for more than 5 days, especially if the epidemiology or certain findings (e.g., anterior cervical lymphadenopathy, scarlatiniform rash, excoriation around nostrils) heighten the likelihood of streptococcal disease, nasopharyngeal specimens should be obtained for the culture of *S. pyogenes* only. If the culture is positive, penicillin V is given for 10 days. Routine culture for or recovery of *S. pneumoniae, H. influenzae, Moraxella catarrhalis,* or *Staphylococcus aureus* has no meaning and can result in misinterpretation.

If mucopurulent rhinorrhea persists for 10 or more days without diminution, especially if other symptoms are present, paranasal sinusitis is likely. Nasal mucosa is examined after use of a single or second (i.e., 5 minutes after the first) application of a topical vasoconstrictor such as oxymetazoline. If purulent secretions flow from the middle meatus, the diagnosis of acute sinusitis is confirmed. Signs of allergic rhinitis can also be confirmed. An imaging study such as contrast-enhanced computed tomography is performed if suppurative complication of sinusitis is suspected.[26,27]

Patients fulfilling a definition of sinusitis are treated with a high-dose (90 mg/kg/day) of amoxicillin with or without clavulanate as first-line therapy, which has been shown to decrease the duration of symptoms.[30] When antimicrobial therapy is effective, substantial improvement of symptoms is expected within 48 to 72 hours. Therapy is continued for 10 to 14 days in children and at least 1 week after resolution of symptoms.[26]

Stridor

Characteristics

Stridor is a rough, high-pitched, monophonic sound caused by passage of air through a narrowed upper airway, which includes the extrathoracic trachea, larynx, and hypopharynx. Because the extrathoracic airway normally narrows during the inspiratory phase of respiration, stridor due to upper-airway disease occurs during inspiration or is more pronounced during inspiration if severe narrowing causes obstruction during inspiration and expiration. Because the intrathoracic trachea normally narrows during expiration, obstruction of the intrathoracic trachea, as occurs with extrinsic compression from a vascular ring or sling or intraluminal obstruction from a foreign body, inflammation, or tracheomalacia, causes a loud noise that is acoustically like stridor and heard during both phases of respiration, but it is more pronounced on expiration. Extrathoracic obstruction (i.e., inspiratory stridor) is associated with prolonged inspiration and underaeration of the chest, whereas intrathoracic obstruction (i.e., expiratory stridor or wheezing) is associated with prolonged expiration and an overinflated chest.

Stridor can be associated with mild tachypnea, but a respiratory rate higher than 50 breaths/min should not be ascribed to upper airway obstruction alone. The degree of obstruction associated with stridor can range from minimal to life-threatening.[31]

The timbre of the stridulous sound provides a clue to the cause. For example, a high-pitched, fixed, dry sound is associated with congenital subglottic stenosis; a wet, rhonchal changing sound with inflammatory laryngotracheitis; and a low-pitched, vibratory, positionally variable sound with laryngomalacia. Associated voice changes also are useful in specifying disease. Vocal cord paralysis causes a weak, dysphonic cry, supraglottic obstruction causes a muffled voice, and laryngotracheitis causes hoarseness or aphonia, frequently with a barking cough.

Etiology

Categorization of the setting and duration of stridor as acute, persistent, or recurrent/episodic provides a framework for considering likely causes (Table 21.3).[31–34] Infections cause most acute upper airway obstruction by means of intraluminal, epithelial inflammation or by encroachment on the airway by reactive or infected lymphoid tissue in parapharyngeal or paratracheal spaces. Viral laryngotracheitis is the most common cause of abrupt-onset stridor in young children.[31] Fungal or viral tracheobronchitis must be considered when stridor occurs in an immunocompromised child; odynophagia and dysphagia also are common.[32]

TABLE 21.3

Causes of Upper-Airway Obstruction and Stridor

Acute	Persistent
INFECTIOUS	**CONGENITAL**
Viral laryngotracheitis (croup) Bacterial tracheitis Epiglottitis, supraglottitis Peritonsillar, retropharyngeal, or parapharyngeal abscess Tracheobronchitis associated with immunodeficiency	Laryngotracheal web, cleft, cyst, hemangioma Tracheal stenosis Vascular ring or sling Laryngotracheal malacia Neuromuscular disorder Cystic hygroma
NONINFECTIOUS	**ACQUIRED**
Angioedema Anaphylaxis	Posttraumatic tracheal stenosis Subglottic stenosis

Foreign body Necrotizing tracheobronchitis in neonates Recurrent/episodic spasmodic croup Caustic burns Gastroesophageal reflux	Foreign-body aspiration Mediastinal mass (tumor, lymphatic, vascular) Papilloma (perinatally acquired) Posttraumatic spinal cord, vagal or glossopharyngeal nerve, or vocal cord damage Vocal cord dysfunction or paralysis Bulbar neuropathy (infectious, postinfectious, malignant) Eosinophilic esophagitis

Congenital anatomic abnormalities should be considered, especially for infants whose persistent stridor began neonatally. Acquired obstruction can have an abrupt onset and an obvious cause (e.g., foreign body aspiration, necrotizing tracheobronchitis in ventilated neonates) or more insidious onset and an inapparent cause (e.g., expanding laryngotracheal papillomas or hemangioma, an extrinsic compressing mass). The younger the infant, the more likely that sudden obstruction, apnea, or feeding difficulties overshadow a singular complaint of stridor.

Clinical Features of Acute Infectious Causes

Recognition, avoidance of precipitating sudden airway occlusion, and urgent, expert intervention to establish an airway when indicated are paramount to avert disastrous outcomes of acute upper airway obstruction. Table 21.4 shows characteristic features of infectious causes of stridor and acute airway obstruction.[35–42] Viral laryngotracheitis (i.e., infectious croup) or laryngotracheobronchitis due to parainfluenza viruses, especially type 1, is by far the most common.[35,36] Influenza viruses, RSV, adenoviruses, measles, MPV, and other viruses typically cause symptomatic disease elsewhere in the respiratory tract, but during epidemic seasons, stridor is the predominant feature in a minority of infected children.

TABLE 21.4

Differentiating Infectious Causes of Upper Airway Obstruction

Characteristic	Viral Laryngotracheitis	Epiglottitis or Supraglottitis	Bacterial Tracheitis	Retropharyngeal Abscess
HISTORY				
Peak age	6–36 mo	<6 yr, any	2–4 yr, any	2–4 yr
Peak season	Late fall, late spring	Any	Fall, winter; any	Any
Prodrome	Viral illness	Uncommon	Viral illness	Uncommon

Onset of stridor	Gradual	Abrupt	Abrupt	Abrupt
PHYSICAL EXAMINATION				
Peak temperature (°C)	38–39	>39	>39	>39
Predominant findings	Brassy or barking cough, stridor	Toxicity, stridor	Toxicity, stridor	Toxicity, stridor
Associated findings	Bark, rhinorrhea	Sore throat, odynophagia, dysphagia, anxiety, drooling	Brassy cough, anxiety	Lethargy, dysphagia, drooling, trismus
Voice	Hoarse, raspy	Normal, muffled, mute	Hoarse, raspy	Muffled, mute
Position	Any; thrashing	Tripod or sniffing position; stillness; refusing to lie flat	Any; thrashing	Sniffing position; stillness; reluctance to move neck
Airway occlusion	Predictable from degree of stridor	Sudden	Sudden	Sudden
Response to racemic epinephrine	Yes, with rebound	No	No or partial	No
LABORATORY TESTS				
Peripheral neutrophils	Normal or low	High	Immature	Immature
RADIOGRAPHY				
Hypopharynx	Distended	Distended	Distended	Anteriorly displaced
Airway	Subglottic narrowing steeple sign; edema cords	Enlarged epiglottis (thumb sign) and aryepiglottic folds	Subglottic narrowing; irregular trachea ± intraluminal membranes	Prevertebral soft tissue mass with anterior displacement of airway (not valid sign for expiratory film, flexed neck)
ENDOSCOPY				
Examination findings	Red, edematous subglottis and lateral tracheal walls; crusting pseudomembrane	Red, edematous supraglottic structures	Red, edematous, eroded trachea and bronchi; thick purulence, pseudomembrane	Bulging mass in posterior pharyngeal wall; purulence
ETIOLOGY				
Agents	Parainfluenza viruses, especially type 1 (epidemic); other viruses (sporadic)	*Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Haemophilus influenzae* b and other *Haemophilus* spp., *Staphylococcus aureus*	*Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*	*Streptococcus pyogenes*; *Staphylococcus aureus*; rare *Streptococcus pneumoniae*; other oral flora

Bacterial tracheitis usually is a complication of viral laryngotracheitis (with concordant peak age and season) but can occur at any age or as a complication of oropharyngeal surgery.[43] *S. aureus* is the most common cause, followed by *S. pyogenes;* the role of anaerobic bacteria is less clear.[41,43] With the universal use of *H. influenzae* b vaccine, epiglottitis is a rare cause of stridor; current cases of supraglottitis are more likely to affect the aryepiglottic region and to be caused by streptococci and staphylococci. Other agents, including *Fusobacterium* spp. and other anaerobes that can cause parapharyngeal and retropharyngeal infections in children, must be considered because the incidence is increasing[42,44,45] (see Chapter 28).

The history surrounding the onset of stridor and the patient's age and examination findings are the most helpful clues to the likely site and cause of infection. The child with viral laryngotracheitis usually has had 2 to 3 days of a typical URI when cough worsens and stridor begins. The child with bacterial tracheitis usually has had a similar background illness and then has sudden onset of high fever, toxicity, and rapid progression to airway obstruction. The young child with retropharyngeal abscess or adolescent with peritonsillar abscess has less stridor but refuses to swallow and has a muffled voice, reluctance to move the neck, and a guarded posture to maximize oropharyngeal airway patency. Trismus is an expected and useful finding in patients with peritonsillar abscess and some lateral pharyngeal space infections of odontogenic origin.[38] Epiglottitis and supraglottitis cause the patient to guard anxiously in a sitting posture with arms back, jaw forward, and chin raised (i.e., sniffing position) to maximize lift of the epiglottis away from the airway. In contrast, subglottic, tracheal obstruction cannot be lessened by position; patients with laryngotracheitis or bacterial tracheitis thrash about with the anxiety of suffocation.

The expected course[36,46,47] and sequelae of acute infectious airway obstruction are shown in Table 21.5. Children with viral laryngotracheitis are less prone to sudden complete obstruction; the hourly course is predictable by degree of stridor and adequacy of aeration. The response to racemic epinephrine and dexamethasone therapy usually averts intubation.[48] In a systematic review of children with croup, symptoms resolved in 2 days for 90%.[12] Establishment of an artificial airway is urgently required for almost all patients with stridor due to acute supraglottitis and bacterial tracheitis and for many with retropharyngeal infection. The course of disease in children with bacterial tracheitis can be further complicated because infection (and obstructive consequences) commonly extends the length of the trachea and below.

TABLE 21.5

Expected Course and Sequelae of Acute Infectious Upper Airway Obstruction

Characteristic	Viral Laryngotracheitis	Supraglottitis, Epiglottitis	Bacterial Tracheitis	Retropharyngeal Abscess
Artificial airway (% of cases)	<1	>90	>75	<50 to >75[a]
Median intubation period	4 days	2 days	6 days	2 days
Airway occlusion after intubation	Rare	No	Yes	No
Death during hospitalization	No	No	Yes	No
Airway sequelae (% of cases)	<3	Rare	<3	No

[a] Varies according to age and site (e.g., higher retropharyngeal; lower in older, parapharyngeal and surgical drainage)

Cough

Characteristics

Cough is a critical protective mechanism to expel particulate matter from the larynx and trachea and is a cardinal sign of infectious and noninfectious respiratory tract and nonrespiratory tract disorders. Occasional acute, life-threatening infectious and noninfectious causes may be overlooked unless the clinician adopts a disciplined diagnostic approach. Careful assessment of a pathologic cough—its onset, duration, clinical context, association with other findings, specific timbre, pattern, and productivity—frequently predicts the site of pathophysiology and narrows the differential diagnosis to a limited number of entities.

Cough usually is defined as acute (<3 weeks), subacute (3–8 weeks), or chronic (>8 weeks). A wet or moist cough in children, frequently referred to as *productive*, is associated with detectable secretions by bronchoscopy and can be reported accurately by parents and clinicians.[47]

Etiology

A dry cough is expected in allergic rhinitis/sinusitis and asthma, and a wet cough is typical in infectious sinusitis, bronchiolitis, bronchiectasis, and pneumonia. In a systematic review of self-limited URIs, acute cough symptoms resolved by day 10 after onset in 50% and by day 25 after onset in 90% of children.[12] Isolated subacute cough (in absence of other symptoms), which usually is dry and follows a viral infection, frequently is related to increased cough receptor sensitivity.[49] Chronic cough (≥8 weeks) is pathologic. If the durations of 4 to 8 weeks are included, many coughs are postinfectious and resolve spontaneously.[50–52]

The differential diagnosis can be focused by age, history, and clinical findings. The algorithms for sequential evaluation and management sometimes are complex[50,51,53,54] and best performed by a pediatric pulmonologist. Most common causes of chronic cough in older children are allergic or nonallergic rhinitis and sinusitis, asthma, protracted bacterial bronchitis, and gastroesophageal reflux disease.[50–56] An important minority of children have cystic fibrosis, non– cystic fibrosis bronchiectasis, immunodeficiency disorders, or ciliary dyskinesia. These diagnoses are considered especially in the preschool-age child with chronic cough.[53]

Management focuses on determining the cause. No evidence supports the use of medications aimed at symptomatic relief of acute or chronic cough, and some data suggest harmful effects are possible.

Cough should not be accepted as a sign of a self-limited URI in infants younger than 3 months of age. The mnemonic CRADLE, which is used to recall the differential diagnoses for cough in infants,[57] refers to cystic fibrosis (C); respiratory tract infections (R), especially pneumonia and pertussis; aspiration (A) due to swallowing dysfunction, gastroesophageal reflux, or tracheoesophageal fistula; ciliary dyskinesia (D); lung, vascular, or airway malformations (L); and edema (E) due to heart failure or pulmonary lymphangiectasia.

Table 21.6 provides a framework for consideration of cough illnesses. There is considerable overlap in symptoms of cough caused by certain infectious agents, such as *Bordetella pertussis* or *Mycoplasma pneumoniae* in adolescents[58] because of a common tracheobronchial site of pathophysiology and frequent dual infections.[59] *B. pertussis* causes a dramatic, debilitating, paroxysmal cough without airway or lower tract abnormalities (unless secondary pneumonia occurs, leading to fever and toxicity), whereas *Chlamydia trachomatis* causes pneumonia with prominent tachypnea: the cough is important only because it brings the child to medical attention (see Chapters 162 and 167). Diagnosis of pneumonia is based on signs of lower respiratory tract involvement, such as tachypnea and retractions, in addition to cough, and the likely causative agent is determined from the constellation of clinical findings (Tables 21.7 and 21.8).

TABLE 21.6
Differentiating Among Causes of Cough

Cause	Peak Age	Nature of Cough	Cough as Dominant Feature	Anticipated or Associated Findings
INFECTIONS OF THE RESPIRATORY TRACT				
Viral laryngotracheitis	<5 yr	Brassy, painful	Yes	Hoarse, raspy voice; viral URI complex[a]
Viral laryngotracheitis or laryngotracheobronchitis	6–36 mo	Barking, brassy	Codominant with stridor	Stridor, hoarseness, viral URI complex[a]
Mycoplasma pneumoniae	Adolescent	Hacking, paroxysmal, painful	Yes	Prodromal, fever, headache, myalgia; then gradual worsening cough; crackles
Pertussis	Infancy, adolescence	Sudden paroxysm of explosive, machine-gun bursts (15–30 per breath) when beyond neonatal age	Yes	Bulging, watering eyes during paroxysm, posttussive emesis; skin and conjunctival hemorrhages; afebrile, without lower respiratory tract symptoms or symptoms between paroxysms
Chlamydia trachomatis pneumonia	1–3 mo	Staccato, dry (single cough per breath)	Yes	History can include prior/concurrent conjunctivitis; afebrile, tachypnea, crackles
Bronchiolitis	4 mo–2 yr	High-pitched or grunt	No	Wheezing, rhinorrhea, respiratory distress; ± fever
Pneumonia (bacterial or viral)	Any	Wet, productive or nonproductive	Codominant with respiratory distress	Tachypnea, rales, respiratory distress; fever
Pleurodynia	Any	Inspiratory hitch; expiratory grunt	Codominant with chest pain	Chest pain; costochondral tenderness

Sinusitis	Any	Irritative; occurs during day and worsens at night	Sometimes	Mucopurulent rhinorrhea, postnasal discharge; facial pain, swelling, or tenderness; headache; ± fever
Tracheoesophagitis (fungal or viral)	Any	Irritative	No	Odynophagia or dysphagia; immune-compromised host; hoarseness; oropharyngeal lesions
Cystic fibrosis	<2 yr; any	Wet, productive; paroxysmal, hacking	Sometimes	Poor growth; persistent and recurrent sinusitis, pneumonia; digital clubbing
Protracted bronchitis	Any; mean, 8–9 yr	Wet, productive; >8 wk	Yes	Bronchoscopy; neutrophils, bacteria, cytokines; response to antibiotic
OTHER CONDITIONS				
Purulent pericarditis	Any	Grunt	Sometimes	Fever, toxicity, respiratory distress or dyspnea; displaced point of maximum impulse; muffled heart sounds
Myocarditis	Any	Grunt	Sometimes	Fatigue, dyspnea, tachypnea; ± fever
Congestive heart failure	Any	Grunt, wet, or brassy	Sometimes	Fatigue, dyspnea, sweating, tachycardia, tachypnea; ± fever; distended neck veins, liver
NONINFECTIOUS AIRWAY ABNORMALITIES				
Gastroesophageal reflux	6 wk–6 mo	High-pitched, dry	Codominant with other symptoms	Stridor, choking, gagging, irritability, arching (Sandifer syndrome) ± regurgitation, pneumonia
Reactive airway, asthma	6 mo–adolescence	Irritative dry, repetitive (not paroxysmal); night especially	Sometimes	Atopic, precipitants, seasonal; ± wheezing; response to β-agonist
Congenital vascular rings, pulmonary sling	Infancy	Brassy	No	Stridor; onset of symptoms in first month of life
Compression on airway or glossopharyngeal or phrenic nerve	Any	Irritative, dry	Sometimes initially	Can be positional (tumors, other masses), associated with other neuropathies, stridor, changes in phonation
Habit cough	Adolescence	Vibratory, low-pitched, honking; disappears with sleep	Yes, sole feature	"La belle indifference"; family dynamics and other somatization

[a] Viral upper respiratory tract infection (URI) complex consists of fever, rhinorrhea,

sore throat, conjunctivitis, exanthem, and enanthem.

TABLE 21.7

Symptoms and Signs of Pneumonia

Symptoms	Signs	Physical Examination Findings
Fever	Fever	Crackles (rales)
Cough	Cough	Wheezes (depending on cause)
Rapid breathing	Tachypnea	Diminished breath sounds
Difficulty breathing	Dyspnea	Bronchial (tubular) breath sounds
Vomiting	Retractions	Dullness to percussion
Poor feeding	Nasal flaring	Decreased tactile and vocal fremitus
Irritability	Grunting	Meningismus (upper lobe, bacterial)
Lethargy	Splinting	Ileus (lower lobe, bacterial)
Chest pain	Apnea	Pleural friction rub (pleural fluid)
Abdominal pain		
Shoulder pain		

TABLE 21.8

Clinical Features of Pneumonia in Infants Younger Than 3 Months

Characteristic	Respiratory Syncytial Virus	Other Respiratory Viruses	*Chlamydia trachomatis*	Pertussis[a]
HISTORY				
Season	Winter	Unique to each	Any	Any; peak July–October
Onset	Acute, days	Acute, days	Insidious	Progressive, days
Illness in others	URI	URI, flu, croup	No	Cough
Fever	Half of cases	Most cases	No	No
Cough	Yes	Yes	Yes/staccato	Yes/paroxysmal
Associated features	Apnea, URI	URI, croup, conjunctivitis	Conjunctivitis (prior or current)	Apnea, cyanosis, posttussive emesis
PHYSICAL EXAMINATION				
Predominant feature	Respiratory distress	Respiratory distress	Cough	Cough
General appearance	Ill, not toxic	Ill, not toxic	Well, tachypneic	Well between paroxysms
Degree of illness: respiratory findings	Degree of illness = findings	Degree of illness = findings	Findings > degree of illness	Ill only during cough
Auscultation	Wheezes, coarse crackles	Crackles, wheezes	Diffuse crackles	Clear
LABORATORY STUDIES				
Chest radiograph	Hyperaeration, subsegmental atelectasis, peribronchial	Hyperaeration, ± peribronchial thickening, ± diffuse interstitial infiltrates	Hyperaeration, diffuse alveolar and interstitial infiltrates	Normal or perihilar infiltrate

	cuffing			
White blood cell count	Normal or lymphocytosis	Normal, lymphocytosis, neutropenia	Eosinophilia	Lymphocytosis; no eosinophilia
Other findings	Hypoxemia	—	Increases in IgG, IgA, IgM	—
Diagnostic tests	Nasal wash EIA, DFA, PCR	Nasal wash EIA, DFA, PCR	Conjunctival, NP DFA, EIA	NP, PCR, culture

[a] Pertussis is included in this table because it should be considered in young infants with cough and respiratory distress, although pneumonia is characteristically absent.

DFA, direct fluorescent antibody (test); EIA, enzyme immunoassay; Ig, immunoglobulin; NP, nasopharyngeal specimen; PCR, polymerase chain reaction; URI, upper respiratory tract infection.

Protracted bacterial bronchitis is inadequately studied, but it may be an underdiagnosed cause of chronic wet cough for which antibiotic therapy may be appropriate.[60] Confirmation rests on bronchoscopic findings of dense bacteria and an acute neutrophilic inflammatory response.[61] Because isolated bacteria are those found commonly in oropharyngeal flora, acute otitis media, and sinusitis, some pulmonologists prescribe a diagnostic or therapeutic trial of amoxicillin-clavulanate for 2 weeks for patients with a typical isolated episode of chronic cough.

Tachypnea and Other Signs of Lower Respiratory Tract Disorders

Tachypnea can be a voluntary or involuntary response to anxiety, fright, or pain; an abnormal breathing pattern related to central nervous system dysfunction; or the physiologic response to increased temperature or metabolic state. Most commonly, tachypnea is the response to respiratory acidosis or hypoxemia of acute infection or the attempt to restore pH balance during metabolic acidosis (e.g., diabetes, salicylate poisoning, dehydration). Metabolic causes should not be forgotten while the clinician pursues the much more likely primary pulmonary causes. Tachypnea can result from primary cardiac abnormalities (e.g., congestive heart failure, cyanotic congenital heart disease), pulmonary vascular abnormalities (e.g., cardiac shunts, capillary dilatation, hemorrhage, obstructed return to the heart, infarction), impaired lymphatic flow (e.g., congenital lymphangiectasia, tumor), or pleural fluid collections (e.g., hemorrhagic, purulent, transudative or lymphatic fluid, an infusion from a misplaced vascular catheter).

Clinical practice guidelines for management of community-associated pneumonia in infants and children by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America include an excellent literature review of clinical findings.[62] Table 21.7 shows symptoms and signs of pneumonia in infants and children. Tachypnea is thought to be the best clinical predictor of lower respiratory tract infection in children. The World Health Organization (WHO) defines pneumonia primarily as cough or difficult breathing and tachypnea. The definition of tachypnea is related to age, with a respiratory rate of >60 breaths/min in infants aged 0 to 2 months, >50 in infants 2 to 12 months, >40 in children 1 to 5 years, and >20 in children older than 5 years of age.[63,64]

Tachypnea has a sensitivity of 50% to 85% for the diagnosis of lower respiratory tract infection and a specificity of 70% to 97%.[65,66] At less than 24 months of age, the younger the patient, the less likely that pneumonia is the diagnosis if tachypnea is absent. In one study, for infants younger than 2 months of age, a respiratory rate of 60 breaths/min, retractions, or nasal flaring had sensitivity for the diagnosis of pneumonia of 91%.[66] In a study from a U.S. emergency department of children younger than 5 years who were undergoing chest radiography for possible pneumonia, respiratory rates in those with or without documented pneumonia did not differ significantly. However, 20% of those with WHO-defined tachypnea had pneumonia confirmed compared with 12% of those who did not.[67]

Obtaining chest radiographs for febrile infants without an apparent focus of infection to exclude pneumonia missed by physical examination has a low yield in the absence of tachypnea.[68,69] Cough is a more sensitive but nonspecific symptom of pneumonia. Other symptoms and signs associated with pneumonia, such as nasal flaring, intercostal retractions, and cyanosis, have lower sensitivity (25%, 9%, and 9%, respectively) but high specificity (87%, 93%, and 94%, respectively).[65] Although fever, cough, and tachypnea are cardinal features, they can be overshadowed or overlooked in patients who come to medical attention for pneumonia-associated stiff neck, abdominal pain, or chest pain or for nonspecific symptoms of illness, such as feeding difficulty in infants. Although a chest radiograph is not routinely needed for children with any of these complaints, it should be considered if the patient has fever and cough or tachypnea.[70,71] Classic symptoms of pneumonia reported in adolescents and adults are fever, chills, pleuritic chest pain, and cough that produces purulent sputum, with less noticeable tachypnea.

Grunting is an expiratory sound produced in the larynx when vocal cords are adducted to generate positive end-expiratory pressure (i.e., self-induced PEEP) and increased resting volume of the lung. Its causes are myriad but never trivial. Grunting can be a sign of surfactant deficiency in the neonate or of pulmonary edema, foreign body aspiration, severe pneumonia, mediastinal mass or severe mediastinal shift from any cause, pleuritic or musculoskeletal chest pain, or myopericarditis or other cardiac abnormalities at any age.[72] Retractions (i.e., intercostal, subcostal, or suprasternal) and grunting have been associated with severe pneumonia, and nasal flaring and head bobbing with hypoxemia.

Adventitial respiratory sounds usually indicate lower respiratory tract disease, pulmonary edema, or hemorrhage. *Wheezes* are continuous musical sounds made predominantly on expiration and are a sign of airway obstruction. Widespread bronchiolar narrowing, as most commonly occurs with the inflammation of virus-associated lower respiratory tract infection, produces heterophonous, high-pitched, sibilant wheezes of variable pitch and presence in different lung fields.[73] Fixed obstruction in a larger airway, as from a foreign body or anomaly, produces a homophonous, monotonous wheeze. The rate of radiographically confirmed pneumonia among children with wheezing is low (<5% overall and 2% in the absence of fever).[70]

Rhonchi, sometimes also called low-pitched wheezes or coarse crackles, are nonrepetitive, nonmusical, low-pitched sounds frequently produced during early inspiration and expiration that usually are a sign of turbulent airflow through secretions in large airways. *Fine crackles,* the term preferred by pulmonologists over *rales* (which has a variety of meanings in different languages) are high-pitched, low-amplitude, end-inspiratory, discontinuous popping sounds indicative of the opening of peripheral air-fluid interfaces. Fine crackle is the auscultatory finding suggesting the diagnosis of pneumonia.

Auscultatory abnormalities of crackles and wheezing have disparate diagnostic usefulness in various studies, depending on the categorization of bronchiolitis. Tachypnea is a more sensitive finding than crackles for bacterial pneumonia; wheezing is more sensitive than tachypnea for bronchiolitis.

Diminished or distant breath sounds, dullness to percussion, and decreased vocal fremitus indicate parenchymal pulmonary consolidation, pleural mass, or fluid collection. *Bronchial* (*tubular*) *breath sounds* have a low-pitched sound of similar intensity throughout inspiration and expiration, as is heard normally in the intrascapular area. Bronchial breath sounds, dullness to percussion, and increased vocal fremitus over an anatomically (tubular) confined lung field indicate parenchymal consolidation, atelectasis, or another continuous tissue or fluid density juxtaposed between a bronchus and the chest wall.

Radiographic infiltrates have been reported in 5% to 19% of children with fever in the absence of symptoms or signs of lower respiratory tract infection.[74,75] Rate of pneumonia deemed occult fell from 15% to 9% after universal vaccination with 7-valent pneumococcal conjugate vaccine (PCV7) in one study.[70] Clinical features associated with occult pneumonia in another study included cough, fever of more than 5 days' duration, fever greater than 39°C, and leukocytosis greater than 20,000 cells/mm^3; only 5% of children without cough had radiographically confirmed pneumonia.[74]

Differentiating Features of Pneumonia

Pneumonia in Young Infants

In young infants, acute infection with bacterial and nonbacterial respiratory tract pathogens frequently leads to lower respiratory tract infection. Except in the first few days of life, when pneumonia predominantly is caused by bacteria acquired from the mother's genital tract or organisms acquired transplacentally, nonbacterial pathogens are overwhelmingly predominant.[72] As perinatally acquired agents persist, community exposures increase, and maternally derived antibody protection wanes, the infant between 3 weeks and 3 months of age is vulnerable to a unique array of lower respiratory tract pathogens.[76]

The clinical setting, specific symptom complex, and severity of illness in proportion to findings on physical examination aid identification of likely causes and guide the diagnostic and therapeutic approach (see Table 21.8). Although the pathogens listed in Table 21.8 frequently are referred to as causing afebrile pneumonia, this is a misnomer because *B. pertussis* infrequently causes lower respiratory tract abnormalities, and RSV and especially other respiratory viruses frequently cause fever.[11,72,77,78] A causal role for *Ureaplasma urealyticum* is not completely defined because the situation is confounded by the asymptomatic presence of this organism in women and young infants. Pneumonia due to *Pneumocystis jirovecii* probably is confined to infants with severe debilitation or immune defects.

Pneumonia in Older Infants, Children, and Adolescents

Table 21.9 categorizes the features of acute pneumonia in older infants, children, and adolescents by cause. No single fact in the medical history or examination finding is unique for any agent, but when taken together, a working diagnosis emerges and guides intervention or further diagnostic testing. Chest radiography and laboratory tests usually are reserved for patients who are ill and hospitalized or whose clinical picture is not compelling for a category of etiologic agents.

TABLE 21.9

Clinical Features of Acute Pneumonia in Children and Adolescents

Characteristic	Bacteria	Virus	Mycoplasma	Tuberculosis
HISTORY				
Age	Any; infants especially	Any	School age	Any; <4 yr and 15–19 yr especially
Temperature (°C)	Most ≥39	Most <39	Most <39	Most <39 (unless empyema)
Onset	Abrupt	Gradual	Worsening cough	Insidious cough
Others in home ill	No	Yes, concurrent; upper respiratory tract infection, rash,	Yes, weeks apart; pharyngitis, flulike illness, cough	Yes, persistent cough

		conjunctivitis		
Associated signs, symptoms	Toxicity, rigors	Myalgia, rash, mucous membrane involvement	Headache, sore throat, chills, myalgia, rash, pharyngitis, myringitis, chest pain	Weight loss, night sweats (late)
Cough	Wet, productive	Nonproductive	Hacking, paroxysmal, usually nonproductive	Irritative or productive
PHYSICAL EXAMINATION				
Predominant feature	Toxicity, respiratory distress	Respiratory distress	Cough	Persistent cough
Degree of illness: respiratory finding	Degree of illness > findings	Degree of illness ≥ findings	Degree of illness < findings	Well: no findings (+ cough); ill with findings
Pleuritic chest pain	No/yes	No	No	No/occasional
Auscultation	Unilateral, anatomically confined crackles or none; dullness, diminished or bronchial/tubular sounds	Diffuse, bilateral crackles, wheezes, rhonchi	Unilateral, anatomically confined crackles; ± wheezes	Most normal; or unilateral crackles ± dullness
LABORATORY STUDIES				
Chest radiograph	Hyperaeration, patchy alveolar infiltrate or consolidation in lobe, segment, subsegment	Hyperaeration, interstitial infiltrate in diffuse or perihilar distribution; "wandering" atelectasis	Patchy alveolar and/or interstitial infiltrate in single or contiguous, usually unilateral lower lobe or lobes; perihilar adenopathy	Patchy alveolar infiltrate in single or contiguous lobes with disproportionate hilar adenopathy; miliary or lobar consolidation
Pleural fluid	No/yes (large)	No/yes (small)	No/yes (small to moderate)	No/yes (small, large)
Peripheral white blood cell count (cells/mm^3)	Most cases >15,000; neutrophils ± bands	Most cases <15,000; lymphocytes	Most cases <15,000; neutrophils	Most cases <15,000; neutrophils, monocytes
Sputum	Copious, purulent; neutrophils, abundant bacteria	Scant mucoid; epithelial, mononuclear cells	Scant mucoid; mixed mononuclear cells/neutrophils	Scant to copious; neutrophils (if copious)
Diagnostic tests	Sputum Gram stain, culture; blood culture	Nasal wash, throat, bronchoscopy specimen for antigen detection, polymerase chain reaction (PCR); acute and convalescent serology	Throat, nasal, bronchoscopy specimen for PCR; cold agglutinins (≥12 years); acute and convalescent serology	Gastric aspirate; sputum stain and culture; tuberculin skin test or interferon γ release assay (IGRA) (≥5 yr old)

Several studies using complex diagnostic methods have confirmed the specific cause of pneumonia in 45% to 85% of cases.[77–81] Viral causes predominate, and most are amenable to diagnosis.[77] The efficacy trial and postmarketing studies of PCV7 infer that *Streptococcus pneumoniae* is a relatively common cause of pneumonia with patchy or consolidative infiltrates.[82,83] Use of the urine antigen detection test in children with lobar pneumonia also supports the important role of *S. pneumoniae*[84]; however, the test is positive for more than 15% of children with asymptomatic colonization and not recommended for diagnosis.[85]

A Cochrane systematic review of clinical symptoms and signs of *Mycoplasma* pneumonia found the absence of wheezing and presence of chest pain were significant associations.[86] Serologic testing for *M. pneumoniae* using an IgM enzyme immunoassay is problematic because of false-positive test results.[62,87] Detection in throat or nasal specimens using polymerase chain reaction methods is highly sensitive, but the meaning requires clinical interpretation and further study. Ascribing a causal role of pneumonia to *Chlamydophila pneumoniae* is confounded by the findings of prolonged asymptomatic carriage and inconsistent serologic results among studies.[88]

Hemoptysis

Hemoptysis, defined as coughing up blood that originated below the larynx, is uncommon in children. More commonly, blood originates from the upper airway due to epistaxis or other sources. Mechanisms of hemoptysis include bleeding from congenital or acquired abnormal bronchial or pulmonary blood flow, venous obstruction, or vascular abnormalities; immune-mediated endothelial damage; or infectious or traumatic erosion of tracheal, bronchial, or bronchiolar epithelium. Hemorrhage can be mild (e.g., tracheitis, tracheobronchitis) or massive (e.g., congenital malformations, foreign body, bronchiectasis, pulmonary hemosiderosis).

Causes of hemoptysis in children are listed in Table 21.10. Infection is a common cause of hemoptysis, including pneumonia from various causes, including tuberculosis and *Aspergillus*. In a 10-year retrospective study from Texas Children's Hospital, cystic fibrosis patients accounted for 68% of hemoptysis episodes overall.[89]

TABLE 21.10

Causes of Hemoptysis in Children

Epithelial Damage	Vascular Abnormality or Damage
Acute infection (bacterial, fungal, mycobacterial) Bronchiectasis (cystic fibrosis, non–cystic fibrosis, immunodeficiency) Foreign body Trauma (airway or chest, suffocation) Tumor (primary airway or pulmonary, metastatic) Miscellaneous (inhalation medications, factitious)	Congenital heart disease or pulmonary vascular anomalies (venous obstruction, arteriovenous fistula) Congenital malformation (pulmonary sequestration) Autoimmune vasculitis (systemic lupus erythematosus, microscopic polyangiitis, granulomatosis with polyangiitis, inflammatory bowel disease, Goodpasture syndrome, Henoch-Schönlein purpura, Churg-Strauss) Idiopathic pulmonary hemosiderosis Nonspecific endothelial damage (chemical, drug) Coagulopathy Tumors

A chest radiograph, bronchoscopy, coagulation studies, and computed tomography are useful diagnostic modalities in most cases of hemoptysis. If negative, a cardiac evaluation including echocardiography and studies for autoimmune vasculitides may be indicated. Digital subtraction angiography, pulmonary arteriography, or lung biopsy may be indicated.

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22

Abdominal Symptom Complexes

Ishminder Kaur

To guide the clinical approach, abdominal pain usually is classified as acute or chronic/recurrent abdominal pain. Acute abdominal pain demands rapid diagnosis and appropriate intervention so that catastrophic outcomes can be avoided.

Acute Abdominal Pain

Signs and symptoms of medical and surgical conditions that cause acute abdominal pain have considerable overlap. Even though Scholer and associates[1] determined that only 1.1% of 1141 nonscheduled healthcare visits for acute abdominal pain (≤3 days' duration) resulted in a surgical diagnosis, rapid diagnosis and intervention always should be a primary goal to avoid adverse outcomes. In a classic monograph, Cope[2] espoused the first principle of approach to the patient with acute abdominal pain is the necessity of coming to a best, albeit not certain, diagnosis because severe abdominal pain of 6 hours' duration occurring in a previously well child frequently is caused by a condition of surgical importance.

History

The history and character of the patient's acute abdominal pain are elicited with specific consideration of anatomy, embryology, and physiology. Diaphragmatic irritation, for example, causes shoulder pain, because the diaphragm, a high thoracic structure embryologically, shares cervical nerve innervation with the shoulder. A history of therapies already provided is elicited, and potential effects are integrated. Anti-inflammatory agents, especially corticosteroids, can alter expected clinical findings substantially, and potent analgesics or pretreatment with antimicrobial agents can mask otherwise clarifying symptoms. Regimentation in history taking is essential. Three features of pain of particular importance are location, migration, and radiation sites.

Location

Pain over the entire abdomen suggests a diffuse peritoneal process. Pain associated with disease in the small intestine is felt chiefly in the epigastric and umbilical areas, and because innervation of the appendix is similarly derived embryologically, the initial pain of acute appendicitis is located periumbilically. Pain caused by disease in the large intestine usually is felt in the hypogastrium or over the site of colonic abnormality. Pain from pelvic structures also is appreciated in the hypogastrium.

Migration and Radiation

Migration of pain and sites of radiation are useful clues.[3] The early epigastric pain of appendiceal obstruction is carried by visceral pain fibers. After the inflamed appendix irritates or adheres to the abdominal wall, affected somatic pain fibers in the parietal peritoneum cause migration of pain to the right lower quadrant. Similarly, biliary colic begins with epigastric pain but migrates to the right upper quadrant when the inflamed gallbladder contacts the parietal peritoneum. Because the eighth thoracic nerve innervates the bile ducts and infrascapular area of the posterior thorax, pain from biliary colic often is perceived just inferior to the right scapula. Renal and ureteral colic radiates to the ipsilateral testicle. Vertebral pain, as in osteomyelitis, radiates to the corresponding site of abdominal innervation.

Associated Symptoms

The presence, timing, and nature of associated symptoms, especially vomiting, provide important clues to the diagnosis. Pancreatitis can cause severe, repeated vomiting because the inflamed pancreas directly irritates the celiac nerve plexus. Bowel obstruction causes vomiting; the more proximal the obstruction, the more severe the vomiting. High small-bowel obstruction causes intractable bilious emesis early in the course, whereas distal small-bowel obstruction is associated with delayed onset of emesis with long periods between episodes (which can progress to feculent emesis).

Large-bowel obstruction is associated with late-onset emesis or no emesis. Incarcerated inguinal hernia can cause abdominal pain, which manifests as irritability in infants, that is associated with decreased appetite and signs of bowel obstruction. Nausea and loss of appetite can replace vomiting as a symptom in patients with less sensitive triggering of emesis. In children with acute abdominal pain, sudden loss of appetite heightens concern, whereas preserved hunger lessens concern.

Character and Relative Severity of Symptoms

The younger the patient, the less helpful the character of the pain. A sense of well-being between waves of pain is helpful, however. The child with crampy pain from gastroenteritis is playful and active intermittently, whereas children with appendicitis, obstruction, or intussusception do not experience complete relief.

Factors that exacerbate or alleviate pain can be useful clues. The relative importance of symptoms also is helpful. Nausea, vomiting, and diarrhea are cardinal features of gastroenteritis, and abdominal pain is secondary. Abdominal pain is the initial and unremitting feature of acute appendicitis or peritonitis, and other symptoms are less significant.

Physical Examination

A complete physical examination must not be supplanted by imaging studies or laboratory tests.

Vital Signs and Habitus

Vital signs often are normal until the pathologic condition causing abdominal pain is advanced; however, an elevated respiratory rate (out of proportion to temperature) is a clue to thoracic causes of pain that is referred to the abdomen. Abdominal processes that cause splinting of the diaphragm lead to shallow tachypnea and the appearance of a respiratory tract condition. Acidosis related to compromised bowel or infection causes increases in the respiratory rate and tidal volume (i.e., Kussmaul breathing). Abdominal pain associated with emesis, Kussmaul breathing, and dehydration should hasten evaluation for diabetic ketoacidosis. Fever is not a discriminating feature, although high temperatures (≥39.5°C) at the onset of abdominal pain in the absence of vomiting and diarrhea suggest a renal or pulmonary process or primary peritonitis. When abdominal pain and high temperature are associated with vomiting or diarrhea, or both, a primary infectious gastrointestinal cause (e.g., norovirus, *Salmonella*, *Shigella*) is a primary consideration.

The patient's preferred position and degree of movement provide diagnostic information. The child with intussusception lies anxiously, anticipating a paroxysm of pain that causes the child to writhe. The patient with pain due to Henoch-Schönlein purpura (HSP) tosses and turns, trying to find comfort, whereas the child with appendicitis flexes at the waist, and the child with peritonitis lies motionless.

Examination of the Abdomen

Observation of the abdomen may reveal distention, swelling, or a mass. Limited diaphragmatic movement implicates an upper abdominal process, including pancreatic or hepatobiliary disease. Meaningful examination usually requires distraction, warmed hands, and gentle palpation, beginning at the site most distant from the reported location of pain. Palpation can reveal a mass (e.g., intussusception, tubal pregnancy, ovarian cyst, malignancy, hydronephrosis) or a site of tenderness, or it can confirm abdominal rigidity (i.e., sign of parietal peritoneal inflammation). Persistent palpation, as an attempt to overcome localized or generalized abdominal rigidity, elicits greater pain and rigidity unless disease is in the thorax. A rectal examination is necessary and can identify heme-positive stool or mucus, a mass, fullness, or localization of tenderness. It also can prompt consideration of gynecologic conditions.

Percussion of the abdomen usually is not helpful in differentiating abdominal processes. However, dullness suggests the presence of peritoneal fluid and helps delineate edges of the liver or spleen. Auscultation identifies ileus but rarely adds diagnostic specificity.

Other Findings

Additional physical findings of importance seek evidence of respiratory distress (e.g., nasal flaring, retractions, adventitial auscultatory findings), an exanthem (e.g., HSP, gonococcemia), vaginal discharge, pelvic girdle tenderness, and hip pain on testing range of motion. The patient with abdominal pain who holds one hip flexed and externally rotated is likely to have acute appendicitis or primary inflammation of the iliopsoas or obturator internus muscle.

Specific Causes and Approach

Conditions in which acute abdominal pain is the cardinal feature are discussed with a focus on an early clinical approach and intervention. Abdominal pain as part of a syndrome of fever of unknown origin is discussed in Chapter 15. Specific diagnostic studies are discussed elsewhere.

Appendicitis

Acute appendicitis in its classic, most common form can be readily diagnosed before appendiceal rupture in patients who seek attention promptly. Wagner and colleagues[4] described the characteristic sequence of symptoms (rather than any particular symptom) and recognized that the sequence reflects pathophysiologic events (Box 22.1). Interruption of this order should increase suspicion of an alternative diagnosis.

Box 22.1

Expected Sequence of Events or Findings in Appendicitis

1. **Pain, usually epigastric or umbilical**

Appendiceal obstruction and distention stimulate visceral afferent nerves of T8 to T10, referring pain to the epigastrium and periumbilical area.

2. **Anorexia, nausea, and vomiting**

Further obstruction and distention of the appendix lead to colicky pain and reverse peristalsis.

3. **Abdominal tenderness**

Serosal inflammation follows, with irritation of the parietal peritoneum. Pain shifts to somatic fibers, resulting in the localization of tenderness to deep palpation and later localization of pain to the right lower quadrant.

4. **Fever**

Arterial supply of the appendix is compromised, leading to gangrene and rupture. Fever precedes rupture and frank peritonitis and usually is mild (<39°C)

5. **Leukocytosis**

Development of localized peritonitis triggers neutrophilia, which is a relatively late event.

Atypical localization of tenderness and pain can occur, depending on the position of the appendix. If the organ lies retrocecally and cephalad, the serosa abuts the iliopsoas muscle, causing pain that results in a preferred position of flexion at the waist with flexion and external rotation of the right hip. If the appendiceal tip is directed inferiorly, pelvic, left lower quadrant, or urinary symptoms can predominate. Occasionally, pelvic appendicitis can inflame rectal tissue and cause painful defecation, spasms of diarrhea, or rectal obstruction. A mass or tenderness elicited on palpation of the right or anterior rectal wall during rectal examination can clarify the diagnosis. Left-sided appendicitis, sometimes associated with thoracic situs inversus, can cause all of the presentations seen in right-sided appendicitis but in mirror image.

Appendicitis usually evolves from first symptoms to rupture in less than 24 hours.[5] The diagnosis remains a clinical one, although ultrasonography (US) can add specificity, and computed tomography (CT) adds sensitivity and specificity.[6] Clinical scoring systems can help identify children at low risk for appendicitis and potentially avoid radiation exposure.[7] Infants and toddlers present a diagnostic challenge; preoperative ruptures occur in more than 50% of these cases because of patients' inability to communicate classic signs or symptoms and because of lack of distinction from acute gastroenteritis, which is common in this age group.[8]

Mesenteric Lymphadenitis

A diagnosis often made by surgeons during an otherwise normal laparotomy performed for suspected appendicitis is mesenteric lymphadenitis, which has been illuminated with the use of improved imaging techniques. Often larger than 1 cm in diameter, inflamed nodes typically cluster in the mesentery in groups of three or more. The mesentery also can be inflamed and thickened.

Mesenteric adenitis manifests clinically as symptoms of severe, localized abdominal pain that mimics pain of other regional pathologic processes. Unfortunately, diagnoses are not mutually exclusive, and the diagnosis of isolated mesenteric adenitis often is one of exclusion despite visualization of nodes by US or CT.[9,10] An improper sequence of symptoms for acute appendicitis, milder pain, disproportionately high fever, and preserved appetite may permit judicious avoidance of surgery. Mesenteric adenitis can be associated with localized or systemic inflammatory process (e.g., appendicitis, inflammatory bowel disease, acute pancreatitis, cholecystitis, connective tissue diseases), malignancy, and multiple enteric and systemic infections (e.g. *Bartonella* infection, *Yersinia* infection, tuberculosis).[10]

Pneumonia

When abdominal pain is associated with high fever, cough, nasal flaring, tachypnea, respiratory distress, and abnormal auscultatory findings, the diagnosis of pneumonia is obvious. More subtle manifestations make differentiation challenging, but careful attention to degree of fever, initial signs, and meticulous auscultation over all lung fields permits differentiation.

The theory of referred abdominal pain due to diaphragmatic irritation has been refuted by reports of isolated upper and middle lobe pneumonia causing similar pain syndromes.[11] Typical bacterial causes of community-acquired pneumonia are expected.

Pyelonephritis

Specificity of symptoms of urinary tract infection (UTI) is age related. In the neonate and infant, the disease can cause decreased appetite alone or intermittent fussiness. Nonblack race, female sex, lack of circumcision in boys, temperature greater than 39°C, fever of 2 or more days' duration, and absence of another source of infection increase the likelihood of UTI in infants.[12] The toddler often has nonspecific abdominal pain (with or without dysuria). The older child and adolescent are most likely to have dysuria, flank pain, tenderness at the costovertebral angle, and hypogastric pain. Pelvic appendicitis or pelvic abscess from any source can cause dysuria and pyuria, mimicking UTI.

Pancreatitis

The incidence of acute pancreatitis in children is rising.[13] Identifiable causes of pancreatitis vary. Systemic illness, biliary disease, trauma, and medications commonly are identified, but many cases are idiopathic.[14,15] Pancreatitis also is associated with endocrinopathies, autoimmune disorders, multiple organ failure, and metabolic disorders. Alcohol consumption is implicated rarely in pediatric cases.

Anatomic relationships predict the symptoms of acute pancreatitis. The gland lies close to the celiac plexus and semilunar ganglion; consequently, pancreatic inflammation causes nausea, intractable vomiting (never feculent), and severe epigastric pain. The head of the pancreas is surrounded by the duodenum, whereas the body overlies the lumbar vertebrae, and the tail reaches the left flank. Inflammation occasionally causes pain only in the left hypochondrium or flank. Because of the organ's proximity to the diaphragm, pain occasionally can be referred simultaneously to the left scapula and the left supraspinous fossa (i.e., phrenic pain).

Fever of 38.5°C to 39.2°C is common but does not presuppose bacterial superinfection. Epigastric tenderness is expected, but muscular rigidity varies. Jaundice is common and usually is caused by swelling of the head of the pancreas rather than obstructing gallstones.

Hemorrhagic pancreatitis, a life-threatening form of pancreatitis, can have one of two pathognomonic signs: bluish discoloration in the flank (i.e., Grey Turner sign) or around the navel (i.e., Cullen sign). Carbohydrate intolerance can occur as pancreatic islet cells are destroyed.

Acute pancreatitis is a clinical diagnosis supported by elevated serum levels of pancreatic amylase and lipase and abnormal US or CT findings. Edema and parapancreatic fluid collections are typical and should not be overinterpreted as abscess. Serum amylase concentration alone is neither sensitive nor specific. Combined use of amylase and lipase tests increases sensitivity and specificity.[15]

Gallbladder Disease

Acute cholecystitis and infection of the gallbladder rarely are seen in children, except when predisposing conditions exist (e.g., portoenterostomy for biliary atresia, obstructing anomalies). Cholelithiasis, the usual antecedent of cholecystitis in adults, typically occurs without cholecystitis in children. In two pediatric series consisting of 85 patients with gallstones, only 2 patients developed cholecystitis.[16,17] Children with cholelithiasis typically have an identifiable precipitating cause, such as hemolysis, total parenteral nutrition, or adolescent pregnancy. Acalculous cholecystitis (i.e. cholecystitis in the absence of gallstones) is described with increasing frequency among children and often is associated with systemic illness or infectious agents, such as *Salmonella*, Epstein-Barr virus, hepatitis A virus, and others.[18]

The usual sequence of symptoms in patients with cholecystitis is fever followed by colicky epigastric abdominal pain that shifts to the right upper quadrant and then tenderness over the right upper quadrant. An elevated serum concentration of γ-glutamyltranspeptidase and bilirubin (out of proportion to elevation of aminotransferase) is expected. *Enterococcus*, *Escherichia coli,* and other Enterobacteriaceae and oropharyngeal flora occasionally are isolated from blood, hepatic biopsy, or an ascitic fluid specimen.

Biliary dyskinesia is increasingly described in the pediatric literature. In one series of consecutive pediatric patients after cholecystectomy, biliary dyskinesia was implicated in 16% of the patients.[19] Biliary dyskinesia is characterized by functional dysmotility of the gallbladder, causing symptoms mimicking those of cholelithiasis, with right upper quadrant pain and fatty food intolerance. The diagnosis is considered when US fails to identify gallstones despite a high clinical suspicion of gallbladder disease. US may demonstrate gallbladder wall thickening or sludge. The diagnosis is confirmed by a hepatobiliary nuclear imaging scan using cholecystokinin stimulation, but the role of scintigraphy in predicting prognosis or gallbladder pathology in children remains unclear.[20,21] The spectrum of disorders of functional motility can blur the separation of acute and recurrent abdominal pain.

Pelvic Inflammatory Disease

Adolescent women are at higher risk of pelvic inflammatory disease (PID) than adult women. Higher infection rates with *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in general, combined with biologic factors such as immaturity of the menstrual cycle, lack of antibodies to sexually transmitted infectious agents, and extent of cervical ectropion, contribute to the higher risk.[22]

Some women with PID are asymptomatic, and others have only mild or nonspecific symptoms or signs (e.g., abnormal bleeding, dyspareunia, vaginal discharge). Because the manifestations vary widely, PID must be considered with mild lower abdominal pain in a sexually active adolescent. Because of the difficulty of confirming PID and the possible consequence of long-term decreased fertility if it is untreated, a low threshold for diagnosis and treatment of PID is recommended. Diagnostic criteria are listed in Box 22.2.[23]

Box 22.2

Criteria for Clinical Diagnosis of Pelvic Inflammatory Disease

Minimum criteria (if no other cause of illness is identified) include one of the following:

- Uterine/adnexal tenderness

Or

- Tenderness on motion of the cervix

Additional supportive criteria (enhancing specificity of minimum criteria):

- Oral temperature >38.3°C
- Abnormal cervical friability or mucopurulent discharge
- Abundant number of white blood cells on saline microscopy of vaginal secretions
- Elevated erythrocyte sedimentation rate or C-reactive protein
- Laboratory documentation of chlamydial or gonococcal infection

Specific criteria:

- Endometrial biopsy showing endometritis
- Transvaginal sonography or magnetic resonance imaging demonstrating thickened, fluid-filled fallopian tubes with or without free pelvic fluid or tubo-ovarian complex or a Doppler study

suggesting pelvic inflammation (e.g., tubal hyperemia)

- Laparoscopic findings consistent with pelvic inflammatory disease

From Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep 2015;64(RR-03):1–137.

Classic physical findings are fever, lower abdominal pain or pelvic tenderness (or both), and vaginal discharge. The constellation of abnormal vaginal discharge, a tender mass on bimanual examination, and an elevated erythrocyte sedimentation rate predicts laparoscopically proven PID; however, only 20% of patients with PID have the triad.

Henoch-Schönlein Purpura

In its most common presentation, four features distinguish HSP: purpura due to leukocytoclastic vasculitis, classically palpable and present below the waist (in young children, especially nonambulatory children, distribution can be atypical and often involves the face and scalp); glomerulonephritis, with a spectrum from microscopic hematuria with or without proteinuria to renal failure with severe hypertension; arthritis affecting larger joints and with pain out of proportion to synovial fluid accumulation; and abdominal pain caused by the leukocytoclastic vasculitis. Abdominal pain usually is midline and colicky. Intestinal mucosal purpura causes gastrointestinal bleeding or can initiate intussusception.

Abdominal pain can precede purpura by days (rarely, weeks) in 14% to 36% of patients.[24] Because many patients with HSP have fever and abdominal pain (which can be severe) at onset, intra-abdominal infections and appendicitis often are considered before the typical purpuric rash appears or is seen when the patient is unclothed below the waist.

Enteric and Other Infections

Enteric infections infrequently cause abdominal pain and fever as cardinal features. In the relative absence of gastrointestinal symptoms, however, *Salmonella, Shigella, E. coli* O157:H7, and *Clostridium difficile* infections can cause severe pain due to intestinal spasm before diarrhea; dysenteric stool with mucus and blood clarifies the pathophysiology. *Campylobacter jejuni* infection can mimic inflammatory bowel disease with myalgia and arthralgia associated with bloody stools.

Infections due to *Yersinia enterocolitica* and *Y. pseudotuberculosis* most closely mimic acute appendicitis when they cause mesenteric adenitis. Appendicitis has been associated with numerous pathogens, including cytomegalovirus, *Shigella* spp, *Schistosoma haematobium*, and *Enterobius vermicularis*.[25]

Typhoid fever, visceral abscesses,[26] peritonitis, intestinal granuloma in chronic granulomatous disease, yersiniosis, visceral *Bartonella henselae* infection, cryptococcosis, toxocariasis and brucellosis can manifest as fever with a predominant complaint of abdominal pain. Acute hepatitis can cause abdominal pain, but disproportionate nausea, right upper quadrant tenderness, and hepatomegaly provide clues to the correct diagnosis. Epstein-Barr virus infection can cause predominant abdominal symptoms with severe splenic enlargement.

Streptococcus pyogenes causing acute pharyngitis can cause abdominal symptoms ranging from pain to nausea and vomiting, which are likely related to extracellular enzymes produced by the organism. One prospective study failed to identify abdominal pain as a positive predictor of *S. pyogenes* infection as a singular symptom or combined with other predictive factors.[27] *S. pyogenes* can cause retroperitoneal abscess, necrotizing fasciitis, puerperal sepsis, bacterial peritonitis, and tubo-ovarian abscess, all of which manifest as severe abdominal pain.

Intussusception

Intussusception in childhood is most often idiopathic, with a peak incidence in the United States at 5 to 9 months of age. Typically, infants have no demonstrable intestinal lead point. Hypertrophy of Peyer patches or mesenteric lymphadenopathy may initiate intussusception. Adenovirus has been recovered in stool or mesenteric node cultures in idiopathic cases.[28] Both U.S. rotavirus vaccines are associated with a small (0.19–1.6 events/100,000 doses administered) but measurable excess cases of intussusception in the 3 to 6 days after immunization.[29] Older children are more likely to have a pathologic lead point, identified in 8% of cases,[30] and the most common identifiable cause is a Meckel diverticulum.[31]

Regardless of cause, the clinical manifestations of intussusception are similar. Midline abdominal pain occurs in paroxysms as each peristaltic wave advances the intussusception. An apathetic presentation is seen in approximately 5% of patients; children appear drugged and inattentive rather than writhing in pain. Primary intracranial disease or intoxication can be incorrectly pursued before a palpable abdominal mass or currant jelly stool focuses attention on the intestinal tract. It has been speculated that this peculiar presentation may result from high levels of endogenous opiates released in response to the painful process of intussusception.

Volvulus

Volvulus, which usually occurs in infants with congenital malrotation, is a life-threatening event. Abdominal pain is unusual without associated emesis, which becomes bilious during the acute presentation. Because of vascular compromise, infection is a common secondary event. Although empiric treatment for septicemia is indicated, interrogation for intestinal obstruction should be pursued in the ill infant with bilious emesis.

Occasionally, postprandial pain can be a prominent feature of the subacute or chronic presentation of volvulus. Volvulus can occur in infants with apparently normal intestinal anatomy and in older children. Volvulus and internal hernia with strangulation also should be considered in children with a history of prior abdominal surgery because adhesions can predispose to these events.

Chronic or Recurrent Abdominal Pain

Chronic abdominal pain (CAP) or recurrent abdominal pain (RAP) requires an inclusive, thorough consideration of the medical, psychosocial, and family history. Both CAP and RAP are a subset of functional gastrointestinal disorders. The term *functional abdominal pain* (FAP) is preferred in recent literature. The approach to patients with CAP, RAP, or FAP can involve days to weeks of data collection with only selective use of laboratory tests. Constipation, a common cause of recurrent abdominal pain, is not discussed here.

RAP, as defined by Apley,[32] requires the occurrence of three episodes of pain severe enough to affect activities over a period of 3 months and occurring during the year leading to investigation. Peak incidence of RAP is in 9- and 10-year-old girls. Pain is characterized as paroxysmal, periumbilical, and lasting less than 60 seconds. Its character often is vague but has been described as dull, crampy, or sharp but not temporally related to activity, meals, stress, or bowel habits. The prevalence of RAP among 1000 unselected schoolchildren was as high as 12% among girls.[33] Family histories of children with RAP show a higher incidence of migraine, psychiatric disorders, and peptic ulcer disease than those of controls.[33] In uncontrolled observations from a wide range of practice settings, socioeconomic status correlates directly with the prevalence of RAP.[34]

In 2006, consensus guidelines for the diagnosis of FAP were published from the Rome III group meeting. These guidelines essentially shorten the duration of symptoms, establishing chronicity to 2 months. Symptoms can be episodic or continuous; lack evidence of an inflammatory, anatomic, metabolic, or oncologic process to explain symptoms; and lack criteria for a more specific functional diagnosis.[35]

Differentiating Causes of Recurring Abdominal Pain

FAP disorders are considered more broadly in the biopsychosocial model. While respecting the complex interplay of genetic, psychological variables (e.g., stress, role modeling, intrinsic and extrinsic supports), and physiologic variables (e.g., inflammatory mediators, motility, hyperresponsiveness of environmental stimuli), the clinician must have a pragmatic approach to the individual patient and family. Preferred diagnostic studies are a thorough history, physical examination (between and during episodes of pain), and simple laboratory tests. Extensive use of laboratory testing usually fails to confirm diagnosis and heightens the family's fear and pursuit of missed disease.

Distinguishing features of nonorganic origin are characteristic enough that the clinical diagnosis is not simply a diagnosis of exclusion (Table 22.1). For children who meet Apley criteria for RAP, an organic disease (which if treated, eliminates the symptoms) is identified in less than 10%. In the largest follow-up study of children with RAP, which tracked 161 patients over 5 years, only 3 of the patients were found eventually to have organic disease, which was Crohn disease in all 3 cases.[36]

TABLE 22.1

Features of Nonorganic Versus Organic Causes of Abdominal Pain

Findings	Nonorganic Causes	Organic Causes
Pain location	Periumbilical	Peripheral
Pain character	Dull, crampy	Colicky, penetrating, burning, boring
Pain pattern	Not progressive Follows precipitating event in one third of cases; normal between events; better on weekends	Progressive Associated with meals, or fluid bolus Nocturnal symptoms, daily, persistent
Associated signs	Normal abdominal examination, little objective findings	Retching, writhing Distended abdomen, abdominal tenderness Mouth ulcers, digital clubbing
Associated symptoms	Multiple, vague, often unrelated Headache, dizzy, fatigue Fever absent	Focused, one or two related symptoms, including fever, weight loss, poor growth, arthritis, diarrhea, vomiting, dysuria
Family history	Can be positive for depression, anxiety, migraine	Can be positive for pancreatitis, peptic ulcer, inflammatory bowel disease
Social history	Frequent school absence; high socioeconomic status	—
Screening laboratory tests	Normal ESR, CRP, complete blood count, and urinalysis	Anemia, high ESR and CRP Stool positive for occult blood Abnormal urinalysis

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Nonorganic Causes

The pain of FAP is located centrally, is most often periumbilical, and is vague in character. Associated phenomena such as headache, diarrhea, nausea, pallor, and sleepiness after attacks are common. Fever may occur with the first painful episode, and a few children have recurrent low-grade fever with episodes. Persistent fever or fevers greater than 38.3°C raise suspicion of possible infection or an inflammatory process. Vomiting is common but only rarely occurs with each episode. Recurrent vomiting with painful episodes, particularly if postprandial and associated with bloating, prompts concern for intermittent volvulus. An imaging study performed at the time of an attack may be the only means of clarifying the diagnosis.

Compared with controls, children with RAP are described as fussy, excitable, anxious, timid, or apprehensive. Patients and their parents are described as overly conscientious. The child is indrawn and is more likely to express features of emotional disturbance.[33] With open-ended history taking, precipitating events can be identified at the onset of RAP in one third of cases. In a study of adults by Campo and associates,[37] 28 former RAP patients were significantly more likely than controls to describe anxiety symptoms and disorders, to demonstrate hypochondriacal beliefs, to have greater perceived vulnerability to physical impairment, to exhibit poor social functioning, to be receiving current treatment with psychoactive drugs, and to have a family history of generalized anxiety. In these studies,[33,37] there were trends suggesting associations between childhood RAP and lifetime psychiatric disorder, depression, family history of depression, and migraine. In a cohort of patients referred for CAP, Bakker and colleagues[38] demonstrated an increased auditory startle reflex compared with controls, supporting a theory of generalized hyperresponsiveness to sensory stimuli even outside of the gastrointestinal tract.

Organic Causes

Table 22.2 lists the organic disorders to be considered in the evaluation of patients with RAP. UTI is the most common organic cause. Obstructive uropathy is less common. When pain in the flank and an abdominal mass are identified, abdominal US should be performed; hydronephrosis is most likely. The absence of hematuria and lateralizing pain has been documented in more than one half of the patients younger than 8 years of age who ultimately had urolithiasis as the cause of their RAP; almost 70% had diffuse or central abdominal complaints.[39]

TABLE 22.2

Expanded Diagnosis for Chronic or Recurrent Abdominal Pain

COMMON CAUSES
Psychophysiologic
Recurrent abdominal pain Irritable-bowel syndrome Conversion reaction Task-induced phobia
Gastrointestinal
Nonulcer dyspepsia Gastroesophageal reflux Constipation
Genitourinary
Urinary tract infection
LESS COMMON CAUSES
Genitourinary
Dysmenorrhea Pelvic inflammatory disease Mittelschmerz
Gastrointestinal
Inflammatory bowel disease
RARE CAUSES
Genitourinary
Urolithiasis Tumors (ovarian, renal) Endometriosis Hematocolpos
Gastrointestinal
Angioedema Malrotation Cystic fibrosis Mesenteric cyst Recurrent pancreatitis Cholelithiasis Gallbladder dysmotility Recurrent intussusception Meckel diverticulum Chronic appendicitis Abdominal wall hernia
Neurologic
Intracranial mass Radiculopathy Spinal cord tumor or injury
Cardiovascular
Chronic dysrhythmias Familial dysautonomia Superior mesenteric artery syndrome
Miscellaneous
Abdominal epilepsy Abdominal malignancy Abdominal migraine Acute intermittent porphyria Addison disease Collagen vascular disease Periodic fever syndromes Heavy metal intoxication Hyperthyroidism Wegener granulomatosis

Modified from McGregor RS. Chronic complaints in adolescence. Chest pain, chronic fatigue, headaches, abdominal pain. Adolesc Med 1997;8:15–31.

Gastroesophageal reflux (GER) has been demonstrated in a few studies to be more prominent than previously thought. A study of patients with atypical RAP demonstrated that 56% of consecutively evaluated patients had significant GER as detected by a pH probe; 71% of cases were responsive to histamine receptor type 2 blocking agents and prokinetic agents.[40] Similarly, a Norwegian study prospectively used a pH probe as part of a diagnostic scheme to evaluate children with RAP and demonstrated GER in 21%.[41]

Peptic ulcer disease can cause RAP. A history of recurrent emesis and a pattern of nocturnal pain that awakens the child suggest peptic ulcer disease.[42] *Helicobacter pylori* is the primary cause of peptic ulcer disease in adults[43] and in children.[44] RAP and *H. pylori*[45] have been linked in some selected populations, in which eradication of *H. pylori* was associated with resolution of RAP.[45,46] However, a systematic review of published evidence showed no evidence of association between RAP and *H. pylori*,[47] and *H. pylori* eradication was not associated with symptomatic improvement in patients with RAP in one randomized, controlled trial.[48]

Inflammatory bowel disease can manifest as RAP. Weight loss, poor linear growth, pubertal delay, digital clubbing, perirectal abnormalities (i.e., fistulas or skin tags), joint symptoms, and nocturnal bowel movements raise suspicion of inflammatory bowel disease. Interruption of linear growth can precede overt gastrointestinal symptoms and signs by years.

Abdominal migraine, although rare and challenging to diagnose, is worth addressing because of evidence-based efficacy of treatment with an antimigraine medication. In one small trial of 14 children, pizotifen therapy was associated with fewer days of abdominal pain.[49]

Chronic pancreatitis, although uncommon, can mimic RAP. Measurement of serum amylase and lipase concentrations is justifiable in the evaluation of RAP. Although celiac disease is included as a cause of RAP, the incidence of positive antibodies was no more frequent among children with RAP than age-matched controls in one study.[50] Recurrent episodes of abdominal pain in the setting of periodic fever is one of the differentiating features of familial periodic fever syndromes.

Approach to Diagnosis and Management

As seen in Table 22.1, the clinical features of RAP of nonorganic origin are sufficiently characteristic that the diagnosis often is established after an open-ended history and thorough physical examination. Screening laboratory tests to eliminate more common organic causes (e.g., UTI, inflammatory bowel disease, pancreatitis) can contribute to physician and family confidence in the diagnosis. Screening tests include urinalysis, urine culture, erythrocyte sedimentation rate, C-reactive protein level, complete blood cell count and differential leukocyte count, stool test for occult blood, and serum concentrations of albumin, amylase, and lipase.

Investigation for gastroesophageal reflux may be moving to first-line evaluation. Endoscopy and radiographic evaluation are performed only to evaluate specific leads from the history, physical examination, or screening laboratory test results or if pain is atypical (e.g., right upper quadrant pain and fatty food intolerance, atypical location of pain).

Systematic reviews of multiple treatment regimens for FAP, including RAP, have failed to demonstrate efficacy. Regimens have included dietary fiber supplements, lactose restriction and probiotic supplementation, and pharmacologic interventions.[51,52] Data support the use of psychological therapies, including cognitive-behavioral therapy and hypnosis.[53]

Management of RAP must involve confirmation of the legitimacy of the patient's complaints, expression of empathy for the family's concerns, reduction of the child's stresses and family's unrealistic expectations, resetting of the family's focus on wellness, and normalization of the patient's activities and the family's response to the pain syndrome. Confident reassurance of the patient and family is the treatment for most children with RAP. Assisting the family to gain insight into psychosocial influences on the patient's symptoms is very important. Nonselective use of multiple consultants may be detrimental. Poor outcomes have been associated with the use of more than three consultants.[54]

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23

Neurologic Symptom Complexes

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The child manifesting symptoms referable to the nervous system is challenging for the clinician and requires a thoughtful approach and evaluation. Often the presence of an infectious disease is not readily apparent. This chapter focuses on the most common presenting neurologic symptoms and features of the history and physical examination that are characteristic of infections, as well as those that distinguish infectious from noninfectious causes. Management, complications, and prognosis are discussed briefly; more details are found in relevant chapters on infectious etiologies.

Headache

Headache occurs in up to 35% to 70% of school-aged children and adolescents.[1–4] Headache is severe enough to be brought to medical attention in a small fraction of cases, although 1% of pediatric emergency department visits are for headaches.[1] Most children evaluated in primary care settings or in a pediatric emergency department with an acute headache and a normal neurologic examination have an acute viral illness, sinusitis, or migraine. Chronic headaches that gradually but progressively worsen in frequency and severity over time are associated with seizures or focal neurologic abnormalities on examination, occur early in the morning or cause awakening at night, or occur in children younger than 3 years are more ominous than acute single or acute recurrent headaches separated by periods of normalcy.[1–4]

History

Important characteristics that aid in differentiating causes of headache are (1) pattern, duration, severity, location, and frequency of pain; (2) associated symptoms, such as fever or purulent rhinorrhea; (3) family history, triggering events, and efficacy of medications; and (4) presence of any underlying condition that predisposes to infection (Table 23.1). Children who have headache coincident with other complaints in which headache is not the cardinal feature rarely have intracranial disease. Although fever is perhaps the most helpful clue in ascribing an infectious origin, its absence does not preclude serious infection. Fever is present in 95% of children with meningitis but in only 30% to 70% of children with a brain abscess.[5,6]

TABLE 23.1

Differentiating Features of Causes of Headaches in Children

Feature	Meningoencephalitis and Meningitis	Brain Abscess	Sinusitis	Brain Tumor	Migraine and Tension	Pseud Cerebr
SYMPTOMS						
Fever	+++	++	++	–	–	–
Onset	Acute	Subacute	Subacute	Subacute	Acute, subacute, or chronic	Subac
Location	Diffuse	Localized to site	Frontal or diffuse	Localized to site	Unilateral, diffuse, or occipital	Diffus
Frequency	Single	Daily	Daily	Daily	Variably recurrent	Daily variabl recurr
Duration	Hours	Weeks	Days	Weeks	Hours	Days–
PREDISPOSING CONDITIONS AND ASSOCIATED FEATURES						
History	Preceding illness; epidemic disease; seasonality	Mastoiditis, otitis, sinusitis; facial cellulitis; cyanotic heart disease; empyema; immunodeficiency; gram-negative bacterial meningitis	Allergic rhinitis	Morning severity; forceful emesis; awakens from sleep; increased severity	Family history; episodic with normalcy in between	Obesit mense vitami cortico Lyme

				with change of position		
PHYSICAL EXAMINATION						
Altered mental status	++[a]	+	–	+	–[b]	–
Focal deficits	++[a]	++	–	+++	–[b]	+[c]
Nuchal rigidity	+++	++	+	–	–	–

[a] In meningoencephalitis.

[b] Can occur with basilar artery or complicated migraine.

[c] Especially abducens nerve palsy or decreased peripheral visual acuity.

+++, Expected; ++, frequent; +, occasional; –, rare or not associated.

Clues to intracranial disease (in approximate order of importance) include (1) abnormal neurologic examination (especially abnormalities in eye movement or gait); (2) papilledema; (3) headache worsened by cough, Valsalva maneuver, or change in position; (4) forceful vomiting after prolonged period of recumbency; (5) headache that awakens the child from sleep or is most severe on awakening; (6) change in prior headache pattern, especially headache of recent onset with progressive severity and frequency; and perhaps (7) lack of family history of migraine. Questions regarding appetite, activity level, hydration, and mental status also may help identify the seriously ill child.

Physical Examination

Physical examination is directed to exclude life-threatening intracranial disease and begins with evaluation of mental status. Nonspecific terms, such as lethargy and fussiness, should be augmented or replaced by notation of interaction with the environment, consolable irritability, verbalization, and sense of well-being. Specific responses to verbal stimulation should be observed and recorded. If the examiner can elicit a smile from an infant or engage an older child in conversation, acute bacterial meningitis or meningoencephalitis is unlikely, although subacute brain abscesses or tumors are possible.

Meticulous attention to abnormalities in vital signs helps assess the diagnosis, pace of illness, and need for immediate intervention. Examples are tachycardia, hypotension, or orthostatic hypotension in the child with moderate to severe dehydration, toxic or septic shock, or the combination of bradycardia, systolic hypertension (wide pulse pressure), and slow, deep, respirations (Cushing triad) indicating increased intracranial pressure (ICP). Overt signs of impending herniation, such as hyperventilation, Cheyne-Stokes respiration (pattern of progressive increase in depth and sometimes rate of breaths followed by apnea) or ataxic respiration (chaotic gasping and apnea), bulging fontanel, fixed pupils, or anisocoria, must be identified quickly. The presence of papilledema is a specific but insensitive sign of raised ICP. It is rare in children with bacterial meningitis, given the relative rapidity of disease, but is notable in 40% to 70% of children with brain abscess.[5,7] Abnormalities of cranial nerve function, asymmetry in strength, tone, or reflexes, gait changes, and papilledema help define an existing lesion; most children with a brain tumor have some abnormality demonstrable on careful neurologic examination.[1–4]

Nuchal rigidity is present in one fourth of patients with brain abscess[7] and in more than 95% of children beyond the neonatal period with meningitis,[8] but can occur with posterior fossa tumors as well. Fever, headache, and nuchal rigidity can occur with acute bacterial pneumonia, especially that involving the upper lobes; tachypnea is almost invariably present but may have been overlooked.

Sinusitis is a relatively uncommon cause of headache in children (10% to 15%)[1]; data from studies of adults reveal that many “sinus headaches” likely are migraine,[9] but in up to 25% of children with sinusitis, headache is the chief complaint. The constellation of fever, purulent nasal discharge, frontal location of dull pain, and sinus tenderness usually identifies patients with sinusitis.[9] In contrast, children with chronic “sinus headaches” as their only complaint most likely have migraines.

Evaluation

If examination reveals overt signs of increased ICP or focal deficits, brain imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) is warranted urgently as the first study. Electroencephalogram is not recommended in the routine evaluation of headaches in children.[3]

Much discussion has centered on whether a brain imaging study must be performed before lumbar puncture in the child with probable bacterial meningitis to diagnose increased ICP that might induce brain herniation after lumbar puncture.[10] Herniation after lumbar puncture for bacterial meningitis has been reported, but such reports are retrospective in design or anecdotal and often involve a study population including the most critically ill patients, who sometimes have had herniation even without lumbar puncture.[8,10–18] Thus the published incidence of herniation in bacterial meningitis of 4% to 6% is likely biased by both study design and publication bias.[10–12,14,16] It is clear that increased ICP accompanies bacterial meningitis, but in general, the diffusely increased ICP of meningitis, with or without performance of lumbar puncture, is much less likely to lead to brain herniation than the differentially increased (focal) ICP associated with intracranial mass lesions. Unfortunately, even a normal result of brain imaging study does not exclude the uncommon to rare likelihood of herniation.[16,18] A large prospective study of the utility of brain imaging in adults with suspected meningitis showed that imaging is overused and that clinical features alone may suffice to choose which patients can proceed to lumbar puncture without imaging.[19,20] Similar prospective pediatric data are lacking, but several case series show that clinical signs are more accurate than head imaging in prediction of impending herniation in children. In current practice, few children with suspected bacterial meningitis have ICP measured at the time of lumbar puncture; recent data suggest that the normal ranges of pressure are wider than once thought.[10,21]

Thus, in general, if meningitis is suspected in a child without papilledema or focal neurologic findings, a lumbar puncture can be performed without obtaining brain imaging.[8,10,13] Additional important but less common contraindications to lumbar puncture include clinically important cardiorespiratory compromise in a neonate or older child; infection in the skin, soft tissue, or epidural area overlying lumbar puncture site; and severe bleeding diathesis.[8,13]

In the uncommon child with suspected bacterial meningitis and signs of impending herniation or focal neurologic signs, blood cultures are obtained, antibiotics are administered, and an imaging study of the brain is performed urgently. Lumbar puncture is postponed until signs of herniation (as judged by both imaging studies and physical examination) have resolved.

A written and videographic review of lumbar puncture methods is available.[22]

Therapy

Antibiotic therapy for infectious causes of headaches is that which is appropriate for the relevant infection (e.g., sinusitis, meningitis, or brain abscess). In addition, brain abscesses larger than 2.5 cm generally require therapeutic drainage procedures beyond simple diagnostic aspiration.

Altered Mental Status

Diagnostic evaluation of the child with altered mental status focuses on quickly identifying the likely cause or causes and initiating appropriate treatment, which usually is determined empirically. The causes of altered mental status in children are shown in Table 23.2, and differentiating features in Table 23.3. Diagnostic evaluation in the emergency department typically involves rapid testing for hypoglycemia, abnormalities of electrolytes or renal function, and, perhaps, intoxications. The differential diagnosis at the time of infectious diseases consultation usually has been narrowed beyond these noninfectious illnesses.

TABLE 23.2

Causes of Altered Mental Status

Intracranial	Systemic
Infection	**Metabolic encephalopathy**
Meningitis	Endogenous
Viral meningoencephalitis	• Hypoglycemia
Bartonella encephalopathy	▪ Hyperammonemia
Mycoplasma pneumoniae encephalopathy	▪ Hypercarbia
Brain abscess	▪ Hypoxia
Autoimmune, post-para infectious	▪ Uremia
Autoimmune disseminated encephalomyelitis	▪ Hypernatremia or hyponatremia
NMDAR antibodies	▪ Endocrinologic disturbance
CNS vasculitis	▪ Vitamin deficiency (B_{12})
Vascular	Exogenous
Ischemic stroke	• Acute poison ingestion

Primary brain hemorrhage	• Chronic heavy metal exposure
Seizure-related	**Intussusception**
Complex partial status epilepticus	**Hypotension**
Postictal state	**Trauma**
Intracranial mass	

CNS, central nervous system; NMDA, *N*-methyl-D-aspartate receptor.

TABLE 23.3

Differentiating Features of Causes of Altered Mental Status in Children

Feature	**Encephalitis**	**Toxic Ingestion**	**Space-Occupying Lesion**	**Reye Syndrome**
Predominant age	Variable	Toddlers, adolescents	Variable	1–14 yr
Fever	++	+	+	–
Prodrome	Headache, fever, irritability, personality change	–	Headache	Upper respiratory tract infection days before protracted vomiting, stupor, coma
Seizures	++	+	++	–[a]
Focal neurologic signs	++	–	++	–
Other associated findings	Rhinorrhea, rash	Altered pupils or vital signs ↑, ↓ sweating ↑, ↓ saliva		Hepatomegaly

[a] Can occur with markedly increased intracranial pressure.

++, Frequent; +, occasional; –, rare; ↑, increased; ↓, decreased.

Encephalitis or meningoencephalitis in the United States most often is caused by viruses, especially enteroviruses, parechovirus, arboviruses (including St. Louis encephalitis virus, California group encephalitis viruses, eastern equine encephalitis virus, and in the older child and adult, West Nile virus), Epstein-Barr virus, varicella-zoster virus, and herpes simplex virus (HSV, being the one agent clearly treatable with antiviral therapy).[23–28] Bacterial causes of encephalitis or meningoencephalitis include *Bartonella henselae* (cat-scratch disease encephalopathy), *Mycoplasma pneumoniae* (although somewhat controversial because diagnosis has often relied on imperfect immunoglobulin M antibody assays), and rarely, *Listeria monocytogenes*.[13,29–31] Other notable infectious causes of pediatric acute encephalitis or meningoencephalitis of unknown origin include influenza virus, rotavirus, bacteremia, toxic shock syndrome, and rabies (see Chapter 44).

Acute disseminated encephalomyelitis (ADEM) is a presumed postinfectious inflammatory demyelinating illness with acute or subacute onset, which affects multiple areas of the central nervous system (CNS).[32–35] ADEM appears to be more common in children than in adults. Clinical symptoms most often include behavioral changes, alterations in consciousness, and focal neurologic deficits (e.g., limb weakness, ataxia, cranial nerve dysfunction). The cerebrospinal fluid (CSF) protein and white cell count generally are both mildly elevated. Cranial MRI usually reveals large, multifocal, hyperintense lesions on fluid-attenuated inversion recovery or T2-weighted images in the white matter of the brain, but also often affects the thalamus and basal ganglia as well. However, published consensus definitions have emphasized diagnosis based more on clinical changes than on MRI abnormalities[36,37] (see Chapter 45).

Recently, it has become clear that autoimmune-paraneoplastic encephalitides occur more commonly than once thought, and the most common is caused by the presence of autoantibodies to the neuronal cell membrane *N*-methyl-D-aspartate receptor (NMDAR).[38–40] Encephalitis with NMDAR antibodies originally was described to occur primarily in young women with ovarian teratomas, but it is now known that more than 50% of cases of NMDAR encephalitis in children occur in patients without associated tumors. The characteristic illness consists of the acute onset of behavioral and neuropsychiatric changes and seizures, followed by progressive coma, orofacial and upper limb choreoathetoid movement disorder, and dysautonomia. Laboratory findings include CSF lymphocytic pleocytosis (70% to 90% of patients), CSF oligoclonal bands (40% of patients), and abnormal electroencephalogram findings (50% to 100% of patients), yet rather unremarkable MRI of the head (70% to 80% of MRIs normal)—all in association with elevated serum and CSF anti-NMDAR antibodies.[38–40]

History

Important features in the history of altered mental status include age, past medical history, presence of fever, convulsions, symptoms of focal neurologic dysfunction, antecedent illness, immunizations, length and progression of illness, medications in the home, length of time the child or adolescent was unobserved before the change in mental status, and, for adolescents, any recent change in disposition at home or school.

Physical Examination

The degree of alteration in consciousness should be measured specifically. Coma scales, particularly the Glasgow Coma Scale, at times fall short in assessing consciousness in children because the scales require an adult level of neurodevelopment and often have a high degree of interobserver variability.[41] Delineation of the patient's neurologic examination is most useful. Identifying signs of increased ICP or focal neurologic deficit are of utmost importance. A record of normal blood pressure is important and excludes hypertensive encephalopathy.

The remainder of the physical examination focuses on recognition of a toxic syndrome or identification of a systemic illness. Toxic ingestion is supported by abnormalities in vital signs, skin (flushing or sweating), mucous membranes (sparse or excessive saliva), and pupillary size and reactivity. Physical examination of the child with hepatic encephalopathy usually reveals other obvious signs, most notably icterus and decreased liver span, and, in the case of Reye syndrome, hepatomegaly without icterus. Infants with intussusception can come to attention with remarkable lethargy, fluctuating consciousness, or hypotonia instead of, or in addition to, the more familiar features of severe, paroxysmal, colicky abdominal pain and bloody stools, perhaps secondary to release of neuroactive endotoxins or central endorphins.[42] Neuropsychiatric changes and seizures can mark HSV encephalitis or NMDAR encephalitis.

An infectious etiology of altered mental status is likely if there is fever with systemic signs, such as involvement of multiple mucous membranes (e.g., conjunctivitis, mucositis, or pharyngitis), diarrhea, abnormal lung findings, or rash.

Evaluation

Unless steps taken to this point determine a likely extracranial cause of the altered mental status, a brain imaging study is performed to identify focal lesions or evidence of intracranial hypertension and to assess the size of ventricles. MRI is superior to CT in making an earlier diagnosis of HSV encephalitis and in assessing the white matter for changes indicative of ADEM. Lumbar puncture is performed if no mass lesion is identified; opening pressure is measured, and specimens of CSF are sent for multiple tests (see Chapter 44). Not infrequently, these study findings also are normal or show only a mildly elevated CSF protein concentration and mononuclear pleocytosis; the remaining differential diagnosis still may include toxic encephalopathy and encephalitis. Electroencephalography may be helpful in determining a seizure focus and identifying periodic lateralizing epileptiform discharges (a finding that increases the likelihood of but is not pathognomonic for HSV encephalitis) or focal slowing; however, absence of abnormality does not narrow the differential diagnosis significantly. It is noteworthy that complex partial status epilepticus can manifest with only alteration in mental status. Normal values of serum hepatic enzymes and ammonia exclude Reye syndrome (which virtually has disappeared since routine aspirin use in children was halted).[43–45] Close monitoring of neurologic status to recognize the necessity to intervene to manage intracranial hypertension and monitoring of cardiac function for dysrhythmia associated with intoxications are indicated.

Therapy

Infectious causes of altered mental status in which antimicrobial therapy is critical include HSV encephalitis, listeriosis, bacterial meningitis, and brain abscess (along with surgical intervention if large). Empiric therapy for HSV encephalitis is given if no other diagnosis is likely, after appropriate specimens have been collected for culture and molecular identification. Delay in obtaining CSF for polymerase chain reaction testing for HSV does not reduce its sensitivity. Antimicrobial therapy sometimes is given for possible *Bartonella* and *Mycoplasma* encephalopathy or encephalitis, although the effect of antimicrobial therapy in these conditions is unproved.[13] ADEM, NMDAR encephalitis, and CNS vasculitis are treated with anti-inflammatory medications, generally glucocorticoids (along with removal of ovarian tumor if present in NMDAR). Enterovirus and West Nile virus encephalitis are treated with supportive therapy.

Ataxia

Ataxia is a disorder of impaired balance and poor coordination of intentional movement. Ataxia results from cerebellar or brainstem dysfunction due to damage either to the afferent sensory nerve pathways to the cerebellum or to the motor fibers to or from the cerebellum. The differential diagnosis of ataxia in children is broad and includes infectious etiologies primarily when onset is acute or subacute (see Chapters 44 and 132). Before universal childhood immunization against varicella, acute cerebellar ataxia was recognized to be a not infrequent complication of chickenpox. Other uncommon viral causes of acute cerebellar ataxia include Epstein-Barr virus and mumps virus.[32,46] *Listeria* CNS infection sometimes causes rhomboencephalitis (i.e., brainstem encephalitis) with prominent ataxia. Whether postinfectious acute cerebellar ataxia is actually a form of ADEM is uncertain.[32] Differentiating features of acute ataxia are shown in Table 23.4. Benign paroxysmal vertigo of childhood and "basilar migraine" can cause recurrent episodes of acute ataxia with normalcy in between. These entities are considered by most to be migraine-variant conditions.

TABLE 23.4

Differentiating Features of Causes of Acute Ataxia in Children

Feature	Infectious or Postinfectious Cerebellitis	Toxic Ingestion	Neuroblastoma	Basilar Artery Migraine	Benign Paroxysmal Vertigo
Predominant age	<10 yr	Toddler	<5 yr	Any	<4 yr
Fever	– to ++	–	+	–	–
Onset	Acute to subacute	Acute	Subacute	Acute	Acute
Frequency	Single	Single	Single	Recurrent	Recurrent
Duration	Days–weeks	Hours	Months	Minutes–hours	Seconds–minutes
Associated symptoms and signs	Resolving antecedent illness (e.g.,	Altered mental status	Opsoclonus, myoclonus	Disturbed vision; vomiting; headache; vertigo;	Suddenly reaches for support;

	chickenpox)			ataxia; dysarthria	refuses to walk
Results of evaluation	Normal or modest ↑ protein, cells in CSF	Abnormal serum, urine toxin screen	↑ Urine HVA, VMA; abnormal imaging of abdomen and chest		

CSF, cerebrospinal fluid; HVA, homovanillic acid; VMA, vanillylmandelic acid; ++, frequent; +, occasional; –, absent; ↑, increased.

History

History for a patient with ataxia focuses on (1) the child's age; (2) presence of fever, recent illness, immunization, trauma, medications in the home, and ingestion or intoxication; (3) progression, duration, and frequency of the ataxia if intermittent; (4) presence of constitutional symptoms; and (5) family history of migraine headache. Fever and ataxia have only rarely been reported as sole findings in patients with acute bacterial meningitis.[47]

Physical Examination

In considering the differential diagnosis, the clinician should first distinguish cerebellar dysfunction and ataxia from other disorders of gait (e.g., weakness from muscular or neuromuscular disorders, primary hip or limb disease, chorea). The verbal child with middle-ear or inner-ear disease leading to disequilibrium complains of dizziness; this is not usually the case in the child with ataxia due to cerebellar or posterior column disease. The ataxic child generally is not weak, and the Romberg test is positive with eyes both opened and closed. Ataxia due to posterior column disease is associated with a positive Romberg test result only when the eyes are closed.

When disease is localized to the cerebellum, initial evaluation targets life-threatening causes. CNS tumor, particularly brainstem glioma, usually is associated with chronic, intermittent ataxia but rarely can cause acute ataxia. Signs of increased ICP can be but are not invariably present. On the other hand, increased ICP from whatever cause can manifest initially as ataxia.

The general physical examination should be thorough and should be directed at distinguishing etiologies (see Table 23.4). Fever and new or healing rash (e.g., chickenpox) can be clues to acute infectious or postinfectious cerebellitis. Careful examination of skin and scalp for ticks (wood or dog ticks) is warranted because the initial signs of tick paralysis are ataxia and nystagmus; motor weakness and ascending paralysis follow within 48 hours.[48,49] Middle-ear disease can result in vestibular dysfunction and ataxia (with complaints of dizziness and vertigo). The paraneoplastic syndrome of opsoclonus-myoclonus-ataxia occurs in only 2% to 3% of all children with neuroblastoma, but 50% to 80% of children identified with opsoclonus-myoclonus-ataxia are found to have neuroblastoma.[50] Despite a relative increase in survival with treatment of children with neuroblastoma, chronic ataxia and severe neurodevelopmental delay usually persist.[50]

Unless the ataxia is of very short duration, as with basilar artery migraine syndrome and benign paroxysmal vertigo, further evaluation (including cranial imaging, followed by lumbar puncture and perhaps other studies) is necessary, as summarized in Table 23.4 (see also Chapter 45).

Therapy

Empiric therapy with ampicillin for *Listeria* is considered depending on the clinical setting and CSF findings. Postinfectious acute cerebellar ataxia generally resolves spontaneously. Tick paralysis and its initial ataxia are rapidly reversed by removal of attached ticks.

Hypotonia and Weakness

Tone and strength are distinctly different, but intimately related, properties of skeletal muscle. Muscle tone is the least resistance generated against passive movement of the muscle and is best evaluated in the wakeful, relaxed state. Strength is the greatest force that a muscle can generate actively against an opposing force and requires the patient's maximal effort.

Weakness can be associated with both upper motor neuron (i.e., CNS) and lower motor neuron (i.e. peripheral nervous system) diseases. With upper motor neuron conditions (e.g., cerebral palsy or subacute stroke), the weakness is typically accompanied by hypertonia. With a lower motor neuron condition (e.g., spinal muscular atrophy or muscular dystrophy), the child exhibits hypotonia. In infants, CNS disorders can also cause hypotonia without accompanying weakness, and hypotonia is a cardinal feature of disease, whereas weakness is a complaint more often found in the toddler and older child. The spectrum of disease-causing abnormalities in tone and strength varies within these age groups and includes infectious,[26,27,51] postinfectious,[52–55] malignant, and other causes. For these reasons, the features and causes of hypotonia and weakness are considered separately in Tables 23.5 and 23.6.

TABLE 23.5

Differentiating Features of Causes of Hypotonia in Infancy

Feature	**Infant Botulism**	**Myasthenic Syndromes**	**Spinal Muscular Atrophy**	**CNS Injury/Genetic Syndrome**	**Myopathy**
SITE OF DISEASE	Neuromuscular junction	Neuromuscular junction	Anterior horn cell	Central nervous system	Muscle
HISTORY					
Prenatal, perinatal	Normal	Decreased fetal movement, polyhydramnios; short umbilical cord, abnormal fetal lie, low Apgar scores can occur in all			
Onset	1–12 mo	Birth	Birth; more obvious with time	Birth	Variable; more obvious with time
Course	Deficits peak at 1–5 days	Deficits peak at birth	Death in infancy	Not progressive	Some are progressive
	Recovery 3–12 wk	Recovery in passive form			
Family history	–	Myasthenic mother in passive form	Autosomal recessive	Variable	Variable
Other	Breastfed; constipation; loss of facial expression; poor suck; weak cry	Fatigability; loss of facial expression; poor suck	Preserved facial expression	–	–
PHYSICAL EXAMINATION					
General	Normal to flushed skin; ptosis; poor suck; weak cry; poor head control	–	Paucity of movement; frog leg position; expressive face	Abnormal head size; dysmorphic features	–[a]
Cognition	Normal	Normal	Normal	Abnormal	Normal
Strength	↓	↓	↓	Normal-↓	↓
Reflexes	Normal–↓	Normal–↓	↓–Absent	↑–Normal	Normal–↓
Muscle bulk	Normal	Normal	Proximal	Normal-↓	Proximal

			atrophy		atrophy
Fasciculations	–	–	++	–	–
Sensation	Normal	Normal	Normal	Normal	Normal
Other	Oculomotor ↓; bulbar findings; descending symmetric paralysis, always including cranial nerves; autonomic signs	Oculomotor ↓; bulbar findings; fatigability	Facial muscles, diaphragm spared	Apnea; seizures; abnormal fundi	Facial diplegia
EVALUATION	Stool toxin assay	EMG Edrophonium chloride	EMG Muscle biopsy *SMN* gene testing	Brain imaging Genetic testing Metabolic screen	EMG Muscle biopsy

[a] Hepatomegaly in Pompe disease (glycogen storage disease IIa).

CNS, central nervous system; EMG, electromyography; ++, frequent; +, occasional; –, absent; ↑, increased; ↓ decreased.

TABLE 23.6

Differentiating Features of Causes of Weakness in Older Children and Adults

Feature	**Guillain–Barré Syndrome**	**Transverse Myelitis**	**Paralytic Poliomyelitis**[b]	**West Nile Virus Acute Flaccid Paralysis**	**Brain, Spinal Tumors**
SITE OF DISEASE	Peripheral nerve and roots	Spinal cord	Anterior horn cell	Anterior horn cell	Spinal
HISTORY					
Onset	Subacute	Subacute (50 hr to maximum deficit)	Acute or subacute	Acute	Insidiou
Progression	Ascending	Paresthesias, leg weakness	Biphasic paralysis 3–5 days after fever	Acutely progressive with febrile meningoencephalitis	Weeks–months
Duration	Weeks–months	Weeks–months	Days–weeks	Weeks–months	Variabl
Recovery	+++	66%–75% of cases	Dependent on degree/extent of paralysis	+	Depend on tum type, locatio interve
Predominant age	Adolescence	Adolescence	Any	Predominantly adults	Any
Paresthesias	++++	+++	++	–	++, if d column involve

Back pain	+	+++	20%	–	++ Dull, aching
PHYSICAL EXAMINATION					
Autonomic dysfunction	60%	++	20%	–	+
Fever	+	+++	+++	+++	+
Distribution	Ascending, symmetric[a]	Usually symmetric; motor/sensory level	Patchy	Asymmetric	Variabl
Bowel, bladder dysfunction	+	95%	20%	+++	+++
Sensation abnormality	+ (proprioception)	95% (pain and temperature)	+	–	++++
Reflexes	Absent	30% ↑ initially; 65% ↓ overall	↓ or absent on affected side	↓	↑ if corticos tract involve
ASSOCIATED FEATURES	Antecedent URI or diarrheal illness (e.g., *Campylobacter*)	Abdominal pain; antecedent trauma 30%; URI 30%	Intense muscle pain; URI symptoms; nuchal rigidity; headache	Headache; dyskinesia (e.g., parkinsonism); meningoencephalitis	Change posture Valsalv accentu pain; abnorm gait
CSF	↑ Protein	↑ Protein	↑ Protein	↑ Protein	Not applica
	0–few cells	↑ Cells	↑ Cells	↑ Cells	

[a] The less common Miller-Fisher variant consists of ophthalmoplegia, ataxia, areflexia, and weakness that is less pronounced than in the classic form.

[b] Paralytic poliomyelitis-like syndrome can also occur with other enteroviruses, especially enteroviruses EVD-68, EV 71.

CSF, cerebrospinal fluid; URI, upper respiratory tract infection; ++++, expected; +++, frequent; ++, occasional; +, rare; –, absent; ↑, increased; ↓, decreased.

Therapy

Infant botulism is treated with botulism-specific human immune globulin (see Chapter 189). Guillain-Barré syndrome and transverse myelitis generally are treated with immune globulin intravenous (IGIV) and glucocorticoids (see Chapter 45).[52–55]

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24

Musculoskeletal Symptom Complexes

C. Buddy Creech

Musculoskeletal pain is a common presenting complaint in young children and adolescents. The usual cause of musculoskeletal pain is trauma or strain to joint, bone, or muscle. Often, the etiology is never determined and symptoms resolve with symptomatic treatment. The challenge for the clinician is to rule out serious disease, including infection, as a cause of symptoms. This chapter focuses on the illnesses responsible for three different categories of musculoskeletal symptoms—extremity pain, back pain, and chest pain—and the distinguishing features of each of these illnesses.

History

Because the differential diagnosis of musculoskeletal pain is extensive, a comprehensive history must be obtained. Important information includes the acuity of onset of illness and presence or absence of fever. Symptoms that are acute, persistent, and accompanied by fever are more likely to be caused by infection. Chronic or subacute symptoms often are the result of noninfectious illnesses.

Important information obtained in the history of the present illness includes the onset and location, description of the progression and severity of the musculoskeletal pain, and whether pain medication has been used and has been helpful. History is elicited of change in gait, ability to bear weight or move the affected area, joint or soft tissue swelling, and presence of induration, erythema, and warmth. A history of trauma, previous or recent illnesses, growth and development, travel, animal exposures, and medication use is important. A review of systems, including history of fever, skin or mucous membrane lesions, pharyngitis, eye inflammation, lymphadenopathy, respiratory or cardiac symptoms, abdominal pain, vomiting or diarrhea, recent sexually transmitted diseases, or neurologic symptoms, is crucial in determining whether the musculoskeletal abnormalities are associated with systemic disease.

Physical Examination

The primary focus of the physical examination is on pinpointing the location of symptoms in order to generate an accurate differential diagnosis and facilitate diagnostic testing. Examination of infants or young children is difficult because they are unable to verbalize the exact location of discomfort. Because musculoskeletal pain can be due to disease affecting a variety of structures, including joints, bones, muscles, nerves, or blood vessels, careful examination of each of these systems is necessary.

Vital signs document the presence or absence of fever, hypothermia, or cardiovascular instability. Height, weight, head circumference, and general appearance of the child should be noted. Poor growth or weight loss could be consistent with inflammatory bowel disease (IBD) or other chronic inflammatory processes, malignancy, or chronic infections such as tuberculosis. Examination of the eyes may reveal conjunctival hyperemia consistent with Kawasaki disease. Mucous membranes are examined for the presence of ulcers (IBD, Behçet disease, systemic lupus erythematosus [SLE]), an enanthem (group A streptococcal infection, enterovirus infection), or hyperemia (Kawasaki disease). Lymphadenopathy can be seen in juvenile idiopathic arthritis (JIA), malignancy, and Kawasaki disease. The chest is palpated for bone tenderness (malignancy, multifocal osteomyelitis, pleurodynia) and for decreased (pleural effusion) and increased (consolidated lung) tactile fremitus during vocalization; the chest is also percussed for dullness (pleural effusion or consolidation). Auscultation can reveal rales, rhonchi, or wheezing (pneumonia associated with hematogenous dissemination of bacteria to bones, joints, or muscles) or decreased breath sounds such as in pleural effusion (occasionally seen with JIA and SLE). Cardiac examination may reveal a new murmur (endocarditis or acute rheumatic fever [ARF]) or muffled heart sounds (pericarditis). The abdomen should be assessed for tenderness, masses (psoas abscess, tumor), hepatomegaly, or splenomegaly (JIA, malignancy, endocarditis). The skin is evaluated carefully for rash (viral infections, associated bacterial infections or intoxications, Kawasaki disease).

Careful examination of bones, joints, muscles, and nervous system is particularly important. The examiner should note how the patient holds the affected limb and whether areas of skin or soft tissue appear swollen or red. Gait and stance are observed. The bones and muscles in the affected limb should be palpated, and passive and active range of motion of joints evaluated. Pain in the lower extremities can be referred from the back, pelvis, abdomen, or hip. A careful examination of the back and pelvis is necessary to rule out diskitis, vertebral osteomyelitis, pelvic osteomyelitis, or abscess. Bones of the spine and pelvis are palpated, and the spine is assessed for abnormalities in flexion or extension. Skin overlying the vertebral bodies should be examined for the presence of a hemangioma, hair, pit, or mass associated with spinal dysraphism. Infection or structural abnormalities of the hip can cause pain referred to the knee. Examination of the hip joint should be performed in all children with a symptom or sign referable to the lower extremity. Neurologic examination includes evaluation for presence and symmetry of deep tendon reflexes, evaluation for clonus, and sensory examination and estimation of muscle strength. Foot deformities may suggest underlying neurologic conditions.

Laboratory Evaluation and Imaging

The laboratory and radiologic evaluation of patients with musculoskeletal pain is guided by findings on history and physical examination. If infection is suspected, attempts should be made to obtain blood cultures and joint, bone, or tissue culture (depending on location of disease) before initiation of antibiotic therapy.

Synovial fluid cell count and cultures are recommended, particularly for patients with monoarticular arthritis, fever, and no other sites or signs of systemic disease. Inflammatory markers (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]) and white blood cell (WBC) counts can be abnormal with infection, inflammatory disease, and hematologic malignancy. Use of other diagnostic tests depends on the differential diagnosis generated on the basis of the history and physical examination.

If a bone or joint disease is suspected, a plain radiograph of the affected area generally is indicated. Both anteroposterior and lateral views should be obtained because abnormalities sometimes can be missed with a single view. Depending on suspected site of the problem, specialized views sometimes are required (Fig. 24.1). Plain radiographs can identify fracture, chronic bone infection, joint effusion, soft tissue swelling, tumor, and structural abnormalities of bone. Ultrasound is useful in identifying joint effusions, particularly in the hip, although a normal ultrasound does not exclude infectious or inflammatory changes in the joint. Magnetic resonance imaging (MRI) or radionuclide scans may be necessary to diagnose bone infections, particularly in the acute phase. These scans also are useful in establishing the diagnosis and extent of bone involvement with malignancies. Radionuclide bone scans are most useful when multifocal disease is suspected.

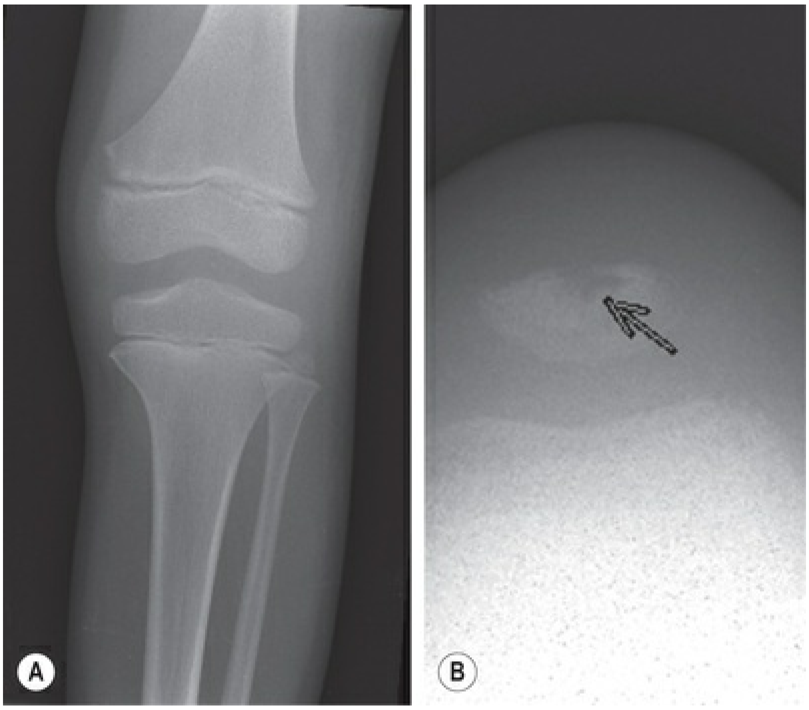

FIGURE 24.1 Radiographs of an 8-year-old boy with fever, limp, and anterior knee pain. Routine posteroanterior view (A) is normal, with lytic lesion of patellar osteomyelitis seen on the sunrise view (B). *Arrow* shows lytic lesion. (Courtesy of Feja KN and Tolan RW, Jr, The Children's Hospital at Saint Peter's University Hospital, New Brunswick, NJ, reprinted with permission of *Pediatrics in Review*.)

Limb Pain

The causes of limb pain in children are extensive and include the broad categories of infection, inflammatory disease, malignancy, trauma, and "orthopedic" problems (Box 24.1). These conditions may involve the joints, bones, muscles, or soft tissue of the affected limb.

Box 24.1

Causes of Limb Pain or Limp in Children

Infectious Diseases

Bacterial arthritis

Viral arthritis

Mycoplasma arthritis

Mycobacterial arthritis

Fungal arthritis

Lyme disease

Disseminated *Neisseria gonorrhoeae*

Hepatitis B infection

Subacute bacterial endocarditis

Psoas or obturator internus muscle abscess

Spinal or paraspinal infection

Osteomyelitis

Skin or soft tissue infection

Postinfectious and Reactive Diseases

Acute rheumatic fever

Enteric or sexually transmitted infection

Neisseria meningitidis

Immunization (rubella vaccine, in particular)

Transient (toxic) synovitis

Neoplastic Diseases

Bone or soft tissue tumors

Leukemia or lymphoma

Metastatic neuroblastoma

Hematologic Diseases

Sickle cell anemia

Hemophilia

Rheumatic Diseases

Juvenile idiopathic arthritis

Systemic lupus erythematosus

Spondyloarthropathy

Dermatomyositis

Vasculitis

Henoch-Schönlein purpura

Serum sickness

Kawasaki disease

Orthopedic Conditions

Trauma

Congenital hip dislocation or dysplasia

Slipped capital femoral epiphysis

Legg-Calvé-Perthes disease

Osgood-Schlatter disease

Chondromalacia patellae

Osteochondritis dissecans

Foreign-body synovitis

Physical overuse syndromes

Miscellaneous Conditions

Inflammatory bowel disease

Reflex sympathetic dystrophy

Familial Mediterranean fever

Behçet disease

Sarcoidosis

Neurologic or neuromuscular disease

Fibromyalgia syndrome

Psychogenic disorders

Disease Involving the Joints

Arthritis is a common cause of limb pain in children and can have multiple etiologies (Table 24.1). Infection of the joints can be caused by bacterial and, less often, viral or fungal infection.

TABLE 24.1

Diseases Associated With Joint Pain

Etiology	Joints Involved	Associated Findings	Laboratory Studies	Ancillary Studies
Pyogenic arthritis	Any joint, more often joints of lower extremities, usually monoarticular	Fever, joint pain, redness, swelling, decreased range of motion	Elevated WBC, CRP, ESR. Synovial fluid WBC >50,000/mm^3, predominantly PMN. Blood or joint fluid cultures may be positive	Joint space widening. US shows fluid in joint space
Transient synovitis	Unilateral hip	Recent viral infection, afebrile or low-grade fever, decreased range of motion of hip joint	CBC <12,000/mm^3. ESR <40 mm/hour. CRP <2 mg/dL	US shows fluid in joint space, cannot differentiate infected versus noninfected fluid

Reactive arthritis	Usually large joints of lower extremities, occasionally small joints, wrists, and elbows. Sacroiliac joint involvement in adults	Enteric infection, sexually transmitted diseases, occasionally *Streptococcus pyogenes, Neisseria meningitidis.* Urethritis, mucous membrane ulcers, conjunctivitis may be present	Elevated ESR, CRP. Synovial fluid WBC <50,000 cells/mm^3	HLA-B27 positive
Juvenile idiopathic arthritis				
Systemic	Large or small joints, symmetrically	High fever, evanescent rash, hepatosplenomegaly, lymphadenopathy	Elevated WBC, ESR, and CRP RF and ANAs are negative	
Oligoarthritis	Involvement of ≤4 joints within the first 6 mo of illness	Iridocyclitis can be present.		
Polyarthritis	Involvement of >4 joints within the first 6 mo of illness		Subdivided into RF-positive and RF-negative forms	
Systemic lupus erythematosus	Painful symmetric arthritis involving 2 or more joints, may be migratory	Fever, malar or discoid rash, photosensitivity, oral ulcers, serositis, neurologic abnormalities	Abnormal urinalysis (casts, proteinuria), leukopenia, anemia, thrombocytopenia. Positive anti-DNA or anti-Sm antibody	Radiograph can show pleural effusion ECG can show pericardial effusion
Acute rheumatic fever	Painful, migratory polyarthritis	Fever, carditis, erythema marginatum, chorea, subcutaneous nodules	Elevated ESR, CRP. Evidence of *Streptococcus pyogenes* infection (positive culture, ASO titer, or anti-DNase)	Abnormal ECG

ANA, antinuclear antibody; anti-Sm, anti−smooth muscle; CRP, C-reactive protein; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; HLA, human leukocyte antigen; PMN, polymorphonuclear cells; RF, rheumatoid factor; US, ultrasound; WBC, white blood cell count.

Pyogenic Arthritis

Pyogenic arthritis usually is the result of hematogenous dissemination of bacteria to the joint space, and less likely the result of direct extension from infected bone, soft tissue, or muscle. The usual bacterial causes vary depending on age (see Chapter 77); *Staphylococcus aureus* is the most common cause of pyogenic arthritis in all age groups. Pathogens typically causing infection in neonates (e.g., group B *Streptococcus* and enteric gram-negative organisms) should be considered in infants younger than 2 months. *Neisseria gonorrhoeae* should be considered in sexually active adolescents. Arthritis caused by *Borrelia burgdorferi* is considered in children who live in or who have traveled to areas where Lyme disease is endemic. Bacterial arthritis can affect any joint, but the joints of the lower extremity are involved most commonly. Pyogenic arthritis typically is monoarticular, but *N. gonorrhoeae* and occasionally *S. aureus* can infect multiple joints. Infants are particularly at risk for infection of multiple joints. Pyogenic arthritis in children is characterized by acute onset of fever, joint pain, redness, and swelling. Physical examination shows markedly decreased range of motion of the affected joint, except in Lyme disease, when effusions characteristically are large and range of motion is relatively preserved.

Pyogenic arthritis of the hip may be difficult to diagnose because associated overlying redness and swelling frequently are not apparent. Pain often is referred to the groin, thigh, or knee. To decrease intracapsular hip joint pressure, the child prefers to hold the affected leg in a flexed, abducted, and externally rotated position. Examination for prone internal rotation is helpful in diagnosing intra-articular hip pathology.[1] The child is placed in a prone position with the pelvis flat on the table and with the knees and ankles flexed and falling away from the body. The examiner tests for pain and limitation of internal rotation. Prompt diagnosis of pyogenic arthritis of the hip is necessary to prevent vascular compromise to the femoral head due to increased intracapsular pressure. Joint effusion can be detected by ultrasonography. If pyogenic hip arthritis is suspected, prompt surgical drainage of infected fluid is indicated.

Transient Synovitis

Transient synovitis is a common cause of limp and hip pain in children 18 months to 12 years of age (mean age, 5 to 6 years) and typically involves a hip joint unilaterally (see Chapter 79). Transient synovitis often occurs in association with a viral respiratory or gastrointestinal illness and may be the result of either direct viral infection of the synovium or a postinfectious response. Although illness is self-limited, resolving with supportive therapy, differentiation from pyogenic arthritis can be challenging. Typically, children with pyogenic arthritis are more likely to have a history of fever, are unable to bear weight, have modestly elevated ESR, CRP, or WBC count, and may have increased hip joint space (>2 mm) on plain radiographs or fluid identified by ultrasonography.[2,3] Because there is overlap in clinical and laboratory findings between transient synovitis and pyogenic arthritis, especially in Lyme disease[4] and *Kingella* infection,[5] careful clinical reassessment is necessary when transient synovitis is suspected.

Other Noninfectious Causes

Reactive arthritis is inflammation of the joint space that occurs in response to an infection elsewhere in the body. Noninfectious inflammatory causes of arthritis generally are more subacute or chronic in presentation. The usual organisms associated with noninfectious reactive arthritis include gastrointestinal pathogens such as *Salmonella* spp., *Campylobacter* spp., *Shigella* spp., *Yersinia* spp., *Clostridium difficile,* sexually transmitted infections such as *Chlamydia trachomatis* and *N. gonorrhoeae,* and occasionally *Streptococcus pyogenes*.

JIA is considered in children younger than 16 years when symptoms of joint inflammation have been present for 6 weeks or more and other causes have been excluded.[4] Categories of JIA include systemic arthritis, oligoarthritis, and polyarthritis.[5] Systemic JIA typically manifests with high fever, an evanescent rash, hepatosplenomegaly, generalized lymphadenopathy, and occasionally pleuritis and pericarditis. These symptoms can precede joint involvement by several weeks to months. Symmetric involvement of large or small joints is typical. The WBC, ESR, and CRP usually are elevated. Rheumatoid factor and antinuclear antibodies usually are not present. Oligoarthritis is characterized by involvement of 1 to 4 joints within the first 6 months of disease, often in association with iridocyclitis. Polyarthritis is inflammation of 5 or more joints during the first 6 months of illness and is further divided into rheumatoid factor–negative and rheumatoid factor –positive forms. SLE is a multisystem autoimmune disease often associated with arthralgia and arthritis. Although children of any age can develop SLE, it most commonly develops in females around the time of puberty or during pregnancy. Children and adolescents can come to medical attention with constitutional symptoms of fatigue, weight loss, hair loss, lymphadenopathy, and hepatosplenomegaly. Nonerosive painful and symmetric arthritis involving two or more joints are seen commonly. Criteria for diagnosis of SLE include the presence of at least 4 of 11 findings: malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis (pleural or pericardial effusion), renal dysfunction (proteinuria or cellular casts), neurologic derangement, hematologic disorder (anemia, leukopenia, lymphopenia, or thrombocytopenia), presence of anti-DNA antibody or anti–smooth muscle antibody, and presence of antinuclear antibody.[6,7]

ARF is a nonsuppurative complication of *S. pyogenes* infection.[8,9] Diagnosis is based on clinical and laboratory findings. Exquisitely painful migratory polyarthritis typically involving the elbows, knees, and ankles is a major criterion for diagnosis of ARF. Arthritis occurs early in the course of illness and does not result in chronic joint disease. Other major criteria of ARF include carditis, erythema marginatum, chorea, and subcutaneous nodules. Minor criteria of ARF include fever, arthralgia, elevated ESR or CRP, and prolonged PR interval on electrocardiogram. Two major criteria of ARF or one major and two minor criteria plus laboratory evidence of a preceding *S. pyogenes* infection are necessary to establish the diagnosis of ARF. Chorea alone can be used to diagnose ARF if other causes have been excluded.

Hip and knee pain also can be the result of noninfectious and noninflammatory structural abnormalities. Hip pain in boys 2 to 12 years old (mean, 7 years) can be secondary to Legg-Calvé-Perthes (LCP) disease. LCP disease occurs when blood supply to the proximal femoral epiphysis is disrupted, resulting in necrosis and infarction of the femoral epiphysis. Predisposing factors are not completely known, but cardiolipin antibodies and thrombophilic coagulation disorders increase the risk for LCP.[10] The most common clinical complaint is limp or vague chronic pain in the groin or anterior thigh. Findings include antalgic gait (shortened stance and prolonged swing phase), muscle spasm, and mild limitation range of motion of the hip. Diagnosis is made by plain radiographs of the hip and pelvis.

Slipped capital femoral epiphysis (SCFE) also must be considered as a cause of hip and knee pain.[11] SCFE occurs when there is displacement of the proximal femoral head anterolaterally and superiorly. Sometimes there is a history of associated trauma or chronic pain. Pain often is referred to the anterior thigh or knee. Affected adolescents often are obese, but SCFE can occur in children of normal weight. Both hips are involved in a substantial number of cases. Physical signs of an acute slip include severe pain when range of motion is attempted. A child with a chronic stable SCFE complains of vague intermittent dull aching pain involving the hip and groin over a period of several weeks. Diagnosis is made by plain radiographs of the hips and pelvis.

Knee pain can be caused by a variety of processes, including Osgood-Schlatter disease, patellofemoral pain syndrome, and osteochondritis dissecans. Osgood-Schlatter disease is an inflammatory disorder of the proximal tibial physis in which the patellar tendon inserts on the tibia. Pain is most pronounced over the tibial tubercle. Osteochondritis dissecans of the knee occurs when an area of bone adjacent to cartilage separates. The cause is unclear but may be related to repetitive trauma.[12] Children complain of nonspecific aching knee pain exacerbated by exercise. Tenderness of the anterior medial aspect of the knee can be noted. Plain radiography shows lesions most often in the medial distal femoral condyle. Patellofemoral knee syndrome is one of the most common causes of knee pain. Pain may be the result of trauma to the patella or peripatellar tissues, overuse, or abnormal patellar tracking. Risk factors include quadriceps weakness and tightness of patellar soft tissue.[13] Symptoms include dull aching pain during activity and with prolonged sitting, joint stiffness, and crepitus. Diagnosis is based on physical examination.

Other causes of joint pain in children include hematologic malignancies and trauma.

Diseases Involving Bone

Infectious Causes

Osteomyelitis is an important cause of limb pain in children (see Chapter 76). Osteomyelitis in children generally is caused by hematogenous dissemination of bacteria to the bony metaphysis. Infection usually is well localized. Multifocal bone involvement sometimes is reported in infants. Most cases of osteomyelitis involve the long bones; however, a substantial number of infections involve bones in the pelvis. Pelvic osteomyelitis can be difficult to diagnose because pain often is poorly localized and may be referred to the hip, groin, or buttock.[14] Onset of fever and bone pain generally is acute, although in some cases fever can be low grade, with intermittent bone pain evolving over a few weeks. Children can come to medical attention with limp or extremity pain. Physical examination can reveal tenderness, redness, warmth, and swelling over the affected bone. Children with pelvic osteomyelitis have pain on compression of the bones of the pelvis. A draining fistula can occur in patients with chronic osteomyelitis. Plain radiographs in acute osteomyelitis show deep soft tissue swelling within a few days after onset of symptoms. Changes consistent with bone destruction typically are not visible for 2 or 3 weeks after onset of symptoms. Bone scan or MRI is useful for early diagnosis of osteomyelitis. WBC, CRP, and ESR frequently are elevated and blood cultures frequently are positive.

Noninfectious Causes

Noninfectious causes of bone pain include trauma, stress fracture, “growing pains,” malignancy, and hemoglobinopathies. Trauma generally is diagnosed by history. “Growing pains,” the cause of which is poorly understood, are characterized by bilateral leg pain typically occurring at night, with no symptoms during the day. Malignant tumors associated with bone pain include osteosarcoma, Ewing sarcoma, and hematologic malignancies such as lymphoma and leukemia.[15,16] Night pain severe enough to awaken a child from sleep, diffuse or migratory bone pain, and pain out of proportion to findings on physical examination raise concern for a malignant process. Vaso-occlusive crises in patients with sickle cell disease manifest with fever and bone pain and can be difficult to differentiate from osteomyelitis. Rarely, chronic recurrent multifocal osteomyelitis (CRMO) can be a cause of limb pain. CRMO is characterized by periodic episodes of fever and bone pain, often involving the jaw, clavicle, and calcaneus. CRMO can be associated with febrile neutrophilic dermatosis and pustulosis palmaris or plantaris.[17]

Muscle Diseases

Infectious Causes

Pyomyositis is a bacterial infection of skeletal muscle that can cause limb pain, particularly in the lower extremities.[18,19] Muscle infection probably occurs when hematogenous bacteria are seeded to injured muscle. The most common bacterial causes of pyomyositis are *S. aureus* and *S. pyogenes*, although a number of gram-negative and anaerobic organisms also can infect muscle. Presentation can be subacute, and symptoms include fever, pain, swelling of the affected extremity, and limp if the lower extremity is involved. Initial symptoms of pyomyositis include malaise and cramping muscle pain. The overlying skin can appear normal; the muscle involved feels firm on palpation. As the infection progresses, abscesses form in the muscle, and the affected area becomes tender, red, and swollen. Untreated, pyomyositis can progress to septicemia, shock, and, rarely, death. The WBC, ESR, and CRP generally are elevated. The causative bacteria are usually isolated from abscess culture; blood cultures also can be positive. Persistent bloodstream infection can occur, especially with *S. aureus*. Ultrasound, computed tomography (CT), and MRI can be used to diagnose and determine the extent of infection. The differential diagnosis of pyomyositis includes cellulitis, fasciitis, osteomyelitis, pyogenic arthritis, thrombophlebitis or deep vein thrombosis (which can coexist with pyomyositis), muscle strain, malignancy, or compartment syndrome.

Viral infection of muscles also can cause inflammation and severe pain. Viruses most commonly reported include influenza (particularly influenza B), enteroviruses, and human immunodeficiency virus. Myositis associated with influenza infection manifests as acute pain and tenderness of the gastrocnemius and soleus muscles, making it difficult for the patient to walk.[20,21] On physical examination, localized tenderness and swelling of calf muscles are noted. Serum creatinine kinase levels are elevated. Rhabdomyolysis occurs in rare circumstances and is more common in girls and after influenza A infection.

Parasitic causes of myositis include *Trichinella* spp., *Taenia solium* (cysticercosis), and *Toxoplasma gondii*[22] (see Chapter 75).

Noninfectious Causes

Noninfectious illnesses that are associated with muscle inflammation generally present less acutely than infections of muscles. Dermatomyositis is nonsuppurative inflammation of striated muscle and is the most frequently diagnosed inflammatory myopathy in children.[23,24] Onset of illness is insidious, and symmetric weakness of proximal muscle groups, rather than pain, usually is the presenting symptom. The illness is associated with a characteristic malar rash and blue purple discoloration of the upper eyelids. The skin over extensor surfaces of joints can be scaly and erythematous. Affected muscles often are stiff and tender to palpation. Associated clinical findings include joint contractures, dysphagia, and cardiac arrhythmias. Serum creatinine kinase levels are elevated. Diagnosis is confirmed by electromyography; muscle biopsy typically reveals perivascular inflammation.

Fibromyalgia syndrome is a chronic pain syndrome characterized by chronic musculoskeletal pain in the absence of any other underlying medical condition or elevation of serum inflammatory markers.[25] Criteria for diagnosing fibromyalgia syndrome are not well defined in children or adolescents. In adults, symptoms include diffuse musculoskeletal pain in at least three areas of the body for at least 3 months, accompanied by pain over at least 11 of 18 previously defined trigger points. Associated symptoms include nonrestorative sleep, fatigue, chronic anxiety, chronic headache, the feeling of soft tissue swelling, irritable bowel syndrome, extremity numbness, and modulation of pain by stress, weather, or physical activity.

Diseases of Soft Tissue and Fascia

Limb pain can be the result of cellulitis or infections involving the deeper levels of the dermis and superficial muscle fascia. The most serious of these infections is necrotizing fasciitis.[26–29] Necrotizing fasciitis is a bacterial infection that spreads rapidly along fascial planes, causing necrosis, thrombosis, and extensive tissue damage. Bacterial causes of necrotizing fasciitis include methicillin-susceptible and methicillin-resistant *S. aureus, S. pyogenes,* gram-negative bacteria, and anaerobic organisms, including *Clostridium* spp. and *Bacteroides* spp. Infection can be polymicrobial.

Predisposing factors include trauma, burns, omphalitis, varicella infection, and immunosuppression. Most patients with *S. aureus* or *S. pyogenes* previously were healthy. Symptoms are rapid in onset, and the patient often appears to have pain out of proportion to findings on physical examination. The patient can have high fever and tachycardia and appear very uncomfortable. Blisters or bullae can be present over the affected area, skin can appear dusky, and the underlying tissue is exquisitely tender. Crepitus is present in some cases. Untreated, infection spreads rapidly, progressing to hypotension, shock, and multisystem organ failure. Diagnosis requires a high index of suspicion. WBC count higher than 15,000 cells/mm^3 and serum sodium concentration less than 135 mmol/L may help distinguish necrotizing fasciitis from cellulitis.[30] One group of investigators has developed a laboratory scoring system of risk indicators for necrotizing fasciitis using CRP, WBC, hemoglobin, serum sodium levels, serum creatinine, and glucose to estimate risk for necrotizing fasciitis.[31] This scoring system has not yet been adequately validated in prospective studies and should not be used to exclude necrotizing fasciitis in a patient. MRI is the preferred imaging modality for ascertaining involvement of the fascia. CT is somewhat less sensitive but may be more readily available, facilitating expeditious evaluation of a critically ill patient.[28] Biopsy of the affected area is useful in determining depth of infection. Management of necrotizing fasciitis involves surgical debridement, empiric broad-spectrum antibiotics, and supportive care in an intensive care unit. The differential diagnosis includes pyomyositis and cellulitis.

Back Pain

Back pain is a common complaint in children, particularly in adolescents,[32,33] and can have multiple etiologies, including uncommon but serious problems such as primary infection or tumor (Box 24.2). Infection can be present in the disk space, vertebral body, epidural space, or a paravertebral or psoas muscle (Table 24.2). Upper-back or neck pain can be associated with meningitis, retropharyngeal abscess, or Ludwig angina.

Box 24.2

Causes of Back Pain in Children

Infectious Diseases

Diskitis

Vertebral osteomyelitis

Spinal epidural abscess

Sacroiliac joint infection

Paraspinal myositis or abscess

Rheumatic Diseases

Juvenile ankylosing spondylitis

Mechanical Disorders

Muscle strain

Spondylolysis or spondylolisthesis

Scheuermann disease

Herniated nucleus pulposus

Hamartomatous and Neoplastic Diseases

Osteoid osteoma

Osteoblastoma

Aneurysmal bone cyst

Hemangioma

Eosinophilic granuloma

Ewing sarcoma

Lymphoma, leukemia

Glioma

Neurofibroma

Ganglioneuroma

Neuroblastoma

TABLE 24.2

Diseases Associated With Back Pain

	Clinical Features	Clinical Findings	Laboratory Studies	Ancillary Studies
Diskitis	Children <6 yr. Subacute presentation. Nonspecific signs: refusal to walk, difficulty sitting, abdominal pain	Low-grade fever, limp, pain with hip flexion, loss of normal spine lordosis	Elevated ESR and CRP. Blood cultures or disk space cultures are rarely positive	After 2–4 wk, plain radiographs show narrowing of disk space and irregularity of vertebral end plate
Vertebral osteomyelitis	Older children. Signs can be subacute	Fever, pain in back, chest, abdomen; tenderness over involved vertebral body variable, paraspinous muscle spasm variable; loss of normal spine curvature; neurologic deficits in 15%–20%	Elevated ESR and CRP. Blood cultures positive in 30%	Plain radiographs show narrowing of affected disk space and lucency of the affected vertebral bodies on either/both sides. MRI delineates extent of disease
Spinal epidural abscess	Anterior abscess results from spread of vertebral body or disk space infection. Posterior abscess results from hematogenous source. History can include surgery to spine, trauma, immune dysfunction, congenital anomaly of spine	Fever, back pain, malaise, limp; as infection progresses: radicular nerve pain, muscle weakness, bowel and bladder dysfunction; soft tissue swelling over back	Elevated WBC, ESR and CRP. Blood and abscess cultures positive	MRI delineates extent of abscess, bone, or muscle involvement
Psoas muscle abscess	Primary abscess results from hematogenous source. Secondary abscess results from underlying bowel pathology	Fever, abdominal pain, hip pain, limp, and back pain; psoas sign; if abscess is large, a mass may be palpated in the	Elevated WBC, ESR, and CRP	Abdominal US or CT can confirm the diagnosis

		abdomen		

CRP, C-reactive protein; CT, computed tomography; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; US, ultrasound; WBC, white blood cell count.

Infectious Causes

Diskitis

Diskitis is inflammation of the intervertebral disk and the vertebral body end plates (see Chapter 78). Children younger than 6 years are affected most often.[34] The rich vascular anastomosis between vertebral bodies in the young child may account for the higher incidence of inflammation localized to the disk space and vertebral end plates, with relative sparing of vertebral body. Infection and destruction of the vertebral body are more frequent in older patients. Diskitis usually involves the lower thoracic or lumbar spine. Cultures for bacteria usually are negative. *S. aureus* is most frequently isolated when cultures are positive. Other bacteria that have been isolated occasionally from blood or disk space cultures include *Kingella kingae,* enteric gram-negative bacteria, and *S. pneumoniae*. Clinical findings in children with diskitis vary depending on age. Symptoms are subacute and increase in severity over several days. The young child is likely to manifest nonspecific signs of irritability or refusal to walk.[35] Older children may localize pain to their back or complain of abdominal symptoms, leg pain, or hip pain. On physical examination, the child may refuse to walk or walk with a limp. Hip flexion causes pain. Loss of normal lordosis of the spine is typical. Plain radiographs of the back are normal initially, but after approximately 2 to 4 weeks, narrowing of the affected disk and irregularity of the vertebral end plates are observed. ESR and CRP usually are elevated modestly.

Vertebral Osteomyelitis

Infection of the vertebral bodies is relatively rare in children compared with adults.[36] Infection is the result of hematogenous seeding or spread from contiguous infection of muscle, soft tissue, or the gut.[37] *S. aureus* is isolated most commonly, although infections with gram-negative enteric bacteria are reported. If the process appears chronic, infection with *Mycobacterium tuberculosis* should be considered. Children with vertebral osteomyelitis generally have fever but can come to attention primarily for back pain (Fig. 24.2). Pain can be localized to the affected area of the back or referred to the chest, abdomen, and legs. Spasm of paraspinous muscles often is present, as is loss of normal curvature of the spine. The neurologic examination is abnormal in some cases. Blood culture is positive in 30% of cases, and WBC, ESR, and CRP often are elevated. Plain radiographs or MRI shows involvement of the disk space and also destruction of adjacent vertebral bodies. If the blood culture is negative, biopsy of the affected vertebral body should be considered.

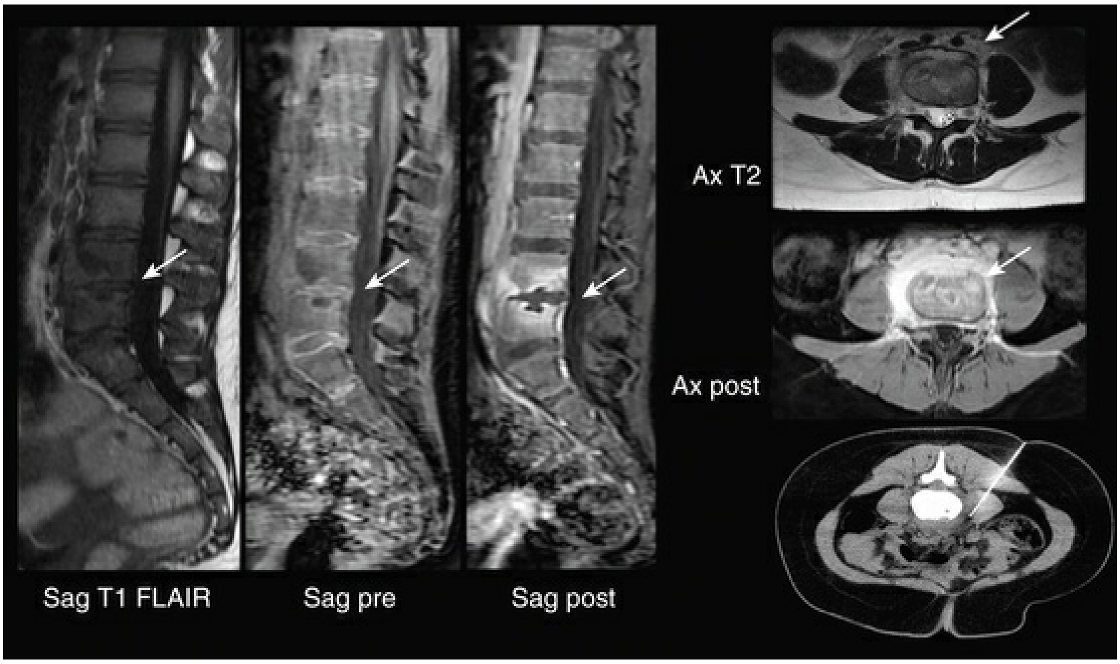

FIGURE 24.2 Magnetic resonance imaging (MRI) in a 12-year-old girl with progressive lower back pain over 4 weeks, which began 4 weeks after returning from the Dominican Republic where she had a 5-day febrile illness. She was afebrile at presentation and had pain only when standing, which was worse on bending forward. There was no tenderness over her spine; C-reactive protein was mg/dL, and erythrocyte sedimentation rate was 62 mm/hour. Vertebral osteomyelitis and anterior paraspinal abscess were best seen on postcontrast sagittal and corresponding axial MRI. Biopsy at the site shown revealed *Salmonella* serotype Typhi. (Case and images courtesy of Long SS and Faerber EN, St. Christopher's Hospital for Children, Philadelphia, PA.)

Spinal Epidural Abscess

Spinal epidural abscess is a rare but potentially catastrophic infection in children.[38] Most epidural abscesses are located posteriorly in the thoracic and lumbar spine and result from hematogenous seeding.[39] Anterior epidural spinal abscesses can result from extension of infection from a vertebral body or disk space, or from the retropharyngeal or retroperitoneal space. Predisposing factors include trauma, previous spinal surgery, and immunodeficiency. Epidural abscesses have been reported in young children with congenital abnormalities such as a neuroenteric fistula[40] or Currarino triad (congenital sacral abnormality, anorectal malformation, and a presacral mass).[41] *S. aureus* is most often isolated, but other gram-positive, gram-negative, and anaerobic organisms have been identified from culture of abscess material.

Initial clinical findings include back pain, malaise, fever, and difficulty walking. As the abscess increases in size, sensory and motor abnormalities typically appear. Untreated, radicular nerve pain, muscle weakness, and bladder or bowel dysfunction can develop. Local tenderness may be noted and, in young children, soft tissue swelling over the lower back may be observed. Blood cultures are positive in 60% of cases, and the WBC count usually is elevated. Diagnosis is made by gadolinium-enhanced MRI. Patients should be managed with a pediatric neurosurgeon because urgent surgical decompression usually is necessary to prevent neurologic sequelae.

Muscle Abscess

Psoas muscle abscess can cause back pain, limp, hip pain, or abdominal pain.[42,43] Psoas muscle abscess is classified as primary or secondary. Primary abscess is more common in children compared with adults and occurs without an obvious intra-abdominal focus of infection. Most primary psoas muscle abscesses are caused by *S. aureus,* although older reports emphasize the importance of *M. tuberculosis.* Secondary psoas abscesses arise as a complication of gastrointestinal conditions (e.g., appendicitis or IBD) or pelvic, renal, or urologic infection. Inflammation of the psoas muscle can result in pain elicited on extension of the thigh (“psoas sign”). This sign is not present consistently, particularly in the young, frightened, irritable child.[42] If the abscess is large, an abdominal mass can be palpable. Inflammatory markers and WBC count generally are elevated. Diagnosis can by confirmed by ultrasound or CT.

Noninfectious Causes

Spondylosis is a defect in the lamina of the vertebra between the posterior articular facets, usually at L4 or L5.[44,45] This defect may occur as a result of trauma or genetic predisposition. When the defect is bilateral, the vertebral body can slip forward (spondylolisthesis). Patients complain of lower back pain and leg pain. Lumbar flexion and extension are limited, and hyperextension of the lumbar spine exacerbates pain. Muscle spasm of the hamstring and paravertebral muscles can be present. Standing lateral and supine oblique radiographs of the lower back are diagnostic.[45]

Scheuermann kyphosis manifests in late childhood and is hypothesized to result from defects in ossification of the anterior portion of the vertebral body or vertebral body wedging due to abnormal biomechanical stress.[46] Progressive wedging of the vertebral body produces kyphosis. Back pain is more common in adults than in adolescents. On physical examination an angular deformity of the back is noted when the patient bends forward. With postural kyphosis, the back deformity is more rounded and less angular. Diagnosis is made by anteroposterior and lateral radiographs of the back.

Children with malignant spinal cord tumors present with back pain that typically is worse at night,[33,35] abnormal gait, and scoliosis. Tumors are classified by location. Intramedullary tumors generally are located in the cervical region of the spinal cord. Lymphoma, neuroblastoma, and sarcomas can metastasize to extramedullary sites, in either intradural or extradural locations. Neurologic abnormalities, including muscle weakness and sensory deficits, commonly are seen.[35,47] Deep tendon reflexes can be diminished at the level of tumor infiltration and increased below the level of the lesion. Bowel and bladder function can be impaired. Although plain radiographs show vertebral body destruction, MRI generally is used for diagnosis.

Chest Pain

Most children who present with chest pain either have a musculoskeletal cause of pain or the etiology is never determined (Box 24.3).[48–50] Musculoskeletal symptoms often are a result of trauma or strain. Infection involving the muscles or bones of the chest wall, lungs, heart, or mediastinum can cause chest pain. Less common causes of chest pain include pulmonary disease, gastrointestinal disease, and, in fewer than 10% of cases, cardiac disease (Table 24.3).

Box 24.3

Causes of Chest Pain in Children

Musculoskeletal Disorders

Costochondritis

Muscle strain or trauma

Slipping-rib syndrome

Tietze syndrome

Precordial catch

Gynecomastia

Cardiac Diseases

Myocarditis

Pericarditis

Endocarditis

Dysrhythmia

Mitral valve prolapse

Hypertrophic cardiomyopathy

Aortic stenosis

Coronary arteritis

Coronary artery anomaly

Coronary artery atherosclerosis

Respiratory Disorders

Pneumonia

Pleuritis

Pleural effusion

Asthma

Pneumomediastinum

Pneumothorax

Cough

Gastrointestinal Disorders

Gastroesophageal reflux

Esophagitis

Gastritis

Esophageal spasm

Esophageal foreign body

Caustic ingestion

Miscellaneous Conditions

Shingles (varicella zoster)

Pleurodynia

Sickle cell crisis

Hyperventilation

Cocaine abuse

Psychogenic

Idiopathic

TABLE 24.3

Diseases Associated With Chest Pain

	Clinical Features	Clinical Findings	Laboratory Studies	Laboratory Studies
Osteomyelitis	Infection of the ribs or sternum uncommon; can result from contiguous infection from lungs (fungal or actinomycoses), or previous surgery or trauma	Fever, tenderness, erythema, and warmth over affected bone, sinus tract, or poorly healing surgical site	Elevated WBC, ESR, CRP. Blood or tissue cultures can be positive	Plain radiographs show bone destruction. Bone scan can be useful if multifocal disease suspected
Pleurodynia	Acute onset of sharp chest or upper abdominal pain. Preceding respiratory or enteric illness	Fever, pain worse on inspiration, mild chest wall tenderness	Enterovirus can be identified in respiratory secretions or stool	
Costochondritis	Acute or subacute onset of anterior chest wall pain	Tenderness over the costochondral or costosternal junctions (usually 2nd to 5th costal cartilages); unilateral	Elevated ESR in some patients	Radiograph normal; occasionally soft tissue swelling at costochondral junction or cartilage calcification
Pneumonia	Acute onset. Preceding URI, cough	Fever, hypoxia, tachypnea, decreased breath sounds, dullness to percussion, rales, rhonchi	Elevated WBC, ESR, CRP. Blood and sputum cultures can be positive	Radiograph abnormal
Pulmonary embolus	Risk factors include the presence of a central venous catheter,	Tachypnea, tachycardia, rales, loud S_2	Positive D-dimers	Radiograph nonspecifically abnormal

	immobility (and other, discussed in text). Acute onset of dyspnea, pleuritic chest pain, cough	and S_4		
Pericarditis	Precordial pain, can be referred to neck or arm	Fever, distant heart sounds, pericardial friction rub; relief of pain if patient bends forward		ST segment elevation, PR segment depression, T wave changes, low voltage with effusion. Radiograph can show increased heart size
Myocardial infarction	Rare in children, usually underlying anatomic heart disease or acquired heart disease (Kawasaki disease)	Hypotension, shortness of breath, cyanosis, anxiety	Elevated cardiac enzymes (reliability in children not well evaluated)	ECG changes: arrhythmias, ST segment changes, wide Q waves
Aortic dissection	Patient may have clinical features of Marfan disease. Acute onset of pain that can radiate to the back	Tachycardia, soft murmur over the aorta, hypotension	Echocardiogram confirms diagnosis	

CRP, C-reactive protein; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; URI, upper respiratory tract infection; WBC, white blood cell count.

Bony and Cartilaginous Causes

Osteomyelitis of the ribs or sternum is uncommon but causes chest pain. Extension of infection from the lung with organisms such as *Aspergillus* spp. *or Actinomyces* spp. occasionally can cause infection of the contiguous bones and soft tissue.

Bacterial pyomyositis and necrotizing fasciitis occasionally involve muscle and fascial tissue of the chest wall.

Enterovirus infection (usually coxsackieviruses or echoviruses) can cause inflammation of the intercostal muscles, upper abdominal muscles, and pleura. The patient often has nonspecific symptoms of a viral illness, fever, and acute onset of sharp chest or abdominal pain. Pain is worse with inspiration and cough. Diagnosis is made by identifying virus in respiratory secretions.[51,52]

Costochondritis is an inflammatory process involving the costochondral or costosternal joints. Rarely, biopsy and culture of cartilage reveal a bacterial pathogen. Patients manifest anterior chest wall pain and tenderness over the costochondral junction of affected ribs. In contrast to Tietze syndrome (described later), swelling, erythema, and warmth generally are not noted. The sedimentation rate can be elevated. Plain radiographs are normal or show soft tissue swelling, and occasionally cartilage calcification and destruction.

Tietze syndrome is distinguished from costochondritis by the presence of swelling in the area of pain.[53] It is not often reported in children. The etiology is unknown, and symptoms resolve over time with supportive care. Usually only one site of swelling and tenderness is noted. Because of the rarity of this diagnosis in children, other causes of anterior chest pain and swelling, such as tumor, soft tissue infection, or osteomyelitis, must be excluded.

Pulmonary Causes

Pulmonary causes of chest pain include pneumonia[54] and reactive airways disease. Patients with pneumonia usually are febrile and tachypneic, and they may have pleural effusion, pneumothorax, or pneumomediastinum. Signs and symptoms of pulmonary disease include decreased breath sounds, dullness to percussion, rales, rhonchi, wheezes, and, rarely, chest wall crepitus.

Pulmonary embolus is rare but should be suspected in patients with any predisposing factor: central venous catheter, methicillin-resistant *S. aureus* infection, obesity, surgery, trauma, cancer, pregnancy, use of oral contraceptives, or inherited hypercoagulable state.[55,56] History of previous venous thrombosis also is a risk factor. Symptoms of pulmonary embolus include sudden onset of dyspnea, pleuritic chest pain, cough, and hemoptysis. Findings on physical examination include tachypnea and tachycardia, rales, and an audible S_4 with a loud S_2 heart sound. Chest radiographic findings are nonspecific. A number of tests have been used to diagnose pulmonary embolus, including serum D-dimer levels, ventilation-perfusion scanning, pulmonary angiography, helical CT, and magnetic resonance angiography.

Cardiac Causes

Pericarditis with pericardial effusion caused by bacterial, viral, fungal, or inflammatory disease is often associated with chest pain.

Pain can be located over the precordium or referred to the neck, shoulder, or left arm. Pain often is relieved when the patient bends forward. Physical examination may reveal distant heart sounds and a pericardial friction rub. Pulsus paradoxus is seen with cardiac tamponade. Echocardiogram is used to assess pericardial disease.

Myocardial infarction is rare in childhood.[57] Myocardial ischemia may occur as a result of anatomic or acquired heart lesions or arrhythmias. Anatomic lesions are often associated with a heart murmur. Myocardial ischemia can be seen with acquired heart disease caused by ARF, endocarditis, or viral myocarditis, trauma, or cocaine abuse. Children with Kawasaki disease and coronary artery aneurysms are at risk for coronary artery thrombosis with subsequent myocardial infarction. Presenting symptoms may include shock, vomiting, irritability, dyspnea, or abdominal pain. Older children are more likely to complain specifically of squeezing chest pain that may or may not radiate and shortness of breath. Diagnosis is made by electrocardiogram changes that include ventricular arrhythmias, ST-segment changes, and wide Q waves. Elevation of cardiac enzymes is noted in most cases, but is not as reliable an indicator of myocardial ischemia in children as in adults.

Other Causes

Gastrointestinal causes of chest pain include gastrointestinal reflux, presence of an esophageal foreign body, and caustic ulceration from oral medications (especially tetracyclines and nonsteroidal anti-inflammatory drugs) taken without sufficient fluid or just before lying down.

Marfan disease is an inherited disorder of connective tissue. Associated clinical findings include a history of subluxation of the lens of the eye, increased height and arm span, narrow fingers and toes, hypermobility of the joints, anterior chest wall deformities, and scoliosis. The most common cardiovascular complication is progressive enlargement of the aortic root predisposing to aortic aneurysm, dissection, or rupture.[58] Symptoms of a dissecting aortic aneurysm include sudden onset of substernal chest pain that radiates to the back or shoulders. Findings on physical examination can include a soft murmur over the aorta, tachycardia, hypotension, and poor perfusion. Echocardiography establishes the presence of dilation of the aortic root and ascending aorta and aortic or mitral valve insufficiency. Spontaneous pneumothorax also can be a feature of Marfan disease and an additional cause of chest pain.

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Oral Infections and Upper and Middle Respiratory Tract Infections

OUTLINE

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25

Infections of the Oral Cavity

Jana Shaw

Immediately following birth, the mouth has a substantial microflora living in symbiosis with a healthy host.[1,2] Molecular methods of 16S DNA amplification reveal a tremendously diverse bacterial environment, largely uncharacterized.[2]

Odontogenic Infections

Tooth Infections

In health, *Streptococcus*, *Peptostreptococcus*, and *Veillonella* spp. and diphtheroids account for more than 80% of the total recoverable flora of the oral cavity. Quantitative studies indicate that anaerobes outnumber facultative bacteria 8-fold. Facultative gram-negative bacilli are uncommon in the healthy child but may become prominent in seriously ill patients.[3] Certain sites tend to adhere certain bacteria. For example, *Streptococcus salivarius* and *Veillonella* spp. have a predilection for the tongue and buccal mucosa and predominate before eruption of teeth.[4] In contrast *Streptococcus sanguinis, Streptococcus mutans,* and *Actinomyces viscosus* preferentially colonize the tooth surface, whereas *Fusobacterium*, *Prevotella,* and *Porphyromonas* spp. and anaerobic spirochetes are concentrated in the gingival crevices.[4]

Dental Caries

In the United States, caries are the most common chronic disease of childhood and are 5 times more common than asthma.[5] Caries of primary teeth commonly are referred to as *caries of early childhood*.[6] Plaque-related bacteria colonize the tooth surface and produce a weak acid during their carbohydrate metabolism.[7] Acid production lowers local pH and results in demineralization of the tooth with efflux of calcium, phosphorus, and carbonate.[8] Tooth colonization with cariogenic bacteria is a key factor for development of caries. Bacterial 16S sequence analysis has shown association of *S. mutans, S. salivarius, S. sobrinus*, and *S. parasanguinis* with early stages of caries, and *Veilonella* spp. were predictive of future caries among children without history of caries.[9] Lactobacilli are strongly associated with more advanced stages of caries.[10] With progression of caries severity, there is loss of healthy microbial community diversity.[9] The major reservoir from which infants acquire cariogenic bacteria is their primary caregiver, usually the mother.[11] Caries can affect any part of the tooth. In children, coronal caries typically have been found in the pits and fissures of the occlusal surfaces of molars and premolars. Food retention occurs less frequently at interproximal sites and the gingival margins, except in infants who fall asleep with a bottle of milk or juice. In early childhood the disease develops over smooth surfaces. Treatment consists of restoration of the affected tooth augmented by preventive methods such as fluoride treatments, flossing, tooth brushing, meticulous removal of the biofilm, placement of sealants, and avoidance of sugary snacks and drinks.

Pericoronitis

Pericoronitis is an acute localized infection associated with operculum of the gum overlying partially erupted teeth or impacted wisdom teeth. The third molars (wisdom teeth) often are affected, especially when their eruption is hindered by lack of space. The tissue around the tooth becomes red, edematous, and tender to touch, but the underlying bone usually is not involved. The patient reports continuous pain that ranges from dull to throbbing to intense, often radiating to the mouth, ear, throat, or the floor of the mouth. Other symptoms can include swelling of the cheek, trismus, dysphagia, and foul breath smell. Systemic manifestations can include fever, chills, and submandibular, submental, or cervical lymphadenopathy. Treatment consists of gentle debridement, irrigation under the operculum, and a systemic antibiotic effective against mouth flora, along with incision and drainage if infection spreads into soft tissue.[12]

Pulpitis and Periapical Abscess

Pulpal infection most frequently results from caries. Demineralization and destruction of the enamel is followed by invasion of the pulp to produce localized or generalized *pulpitis*. In early stages of infection (*reversible* pulpitis), patients typically complain of tooth sensitivity to percussion and thermal changes, especially cold drinks. Pain stops abruptly when the stimulus is withdrawn. The ongoing inflammation and built up pressure lead to pulp necrosis described as *irreversible pulpitis*.[13] Complications of pulpitis include spread of infection to the adjacent periodontal ligaments and invasion of the alveolar bone condition called *periapical abscess*. Serious complications of periapical infections are rare.[5] However, in some cases infection spreads, causing abscesses in the submaxillary triangle or in the parapharyngeal or submasseteric space.[6] In the maxilla, periapical infection can manifest in the soft tissues of the face. Infection also can extend to the infratemporal space, including the sinuses, and from there to the central nervous system, causing subdural empyema, brain abscess, or meningitis.[14]

The most common organisms isolated from infected pulp include aerobic, facultative anaerobic organisms (i.e., *S. salivarius*, other α-hemolytic streptococci, nonhemolytic streptococci) and anaerobic streptococci, anaerobic gram-negative bacilli, *Actinomyces* spp., *Propionibacterium* spp., *Veillonella* spp., and others.[15] Treatment consists of elimination of infected pulp (root canal treatment) or extraction of the tooth. Cochrane literature review found no evidence to support antibiotic use for treatment of pulpitis alone. There was no difference in pain perception or analgesic use among 40 patients with irreversible pulpitis randomly assigned to penicillin or placebo arm.[13] Antibiotic therapy is indicated if drainage cannot be performed or the infection has spread to surrounding soft tissues. Penicillin usually is adequate; amoxicillin-clavulanate and clindamycin are effective against β-lactamase –producing anaerobic bacteria.

Periodontal Infections

Periodontitis is inflammation that extends deep into the tissues and causes loss of supporting connective tissue (periodontium) and alveolar bone. Severe periodontitis can result in loosening of teeth, impaired mastication, and even tooth loss. Bacterial species reproducibly associated with disease include *Porphyromonas gingivalis, Tannerella forsythia, Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans*, and *Treponema denticola*.[16] Histologically, nonprogressive inflammatory foci tend to be composed predominantly of T lymphocytes and macrophages, suggesting that the cell-mediated response can control disease. Destructive lesions are dominated by B lymphocytes and plasma cells, suggesting that humoral immunity, although documented by elevated immunoglobulin G levels against anaerobic organisms, is not always effective.[2,17]

Early-Onset Periodontitis

Juvenile (aggressive) peridontitis is a particularly destructive form of peridontitis seen in adolescents. Its localized form is characterized by rapid bone loss affecting the first molar and incisor teeth. The generalized form is rapidly progressive, affecting other teeth. Plaque is minimal, and specific defects in neutrophil chemotaxis and phagocytosis were demonstrated among 75% of patients. DNA probes and primers have revealed anaerobic organisms such as *A. actinomycetemcomitans, P. gingivalis, Prevotella intermedia, T. denticola,* and *T. forsythia*.[18] Treatment consists of systemic antibiotics. Narrow-spectrum antibiotics such as penicillin, amoxicillin, cephalexin, and macrolides are not effective against increasing number of β-lactamase–producing anaerobes. Antibiotics that include a β-lactamase inhibitor (i.e., clavulanate sulbactam) or clindamycin offer excellent coverage against most aerobic and anaerobic oral pathogens. The decision whether to use a narrow- or broad-spectrum antibiotic should be individualized.

Mucosal Infections

Gingivitis

Gingivitis is the most common periodontal disease during childhood with peak incidence near adolescence.[19] Inflammation is initiated by local irritation and bacterial invasion.[20] Bleeding of the gums after eating or brushing and fetor oris can be early signs of gingivitis. There usually is no pain. Treatment consists of plaque removal and good oral hygiene.[12]

Other Oral Infections and Conditions

Differentiating features of oral infections and other conditions encountered frequently are shown in Tables 25.1 and 25.2.

TABLE 25.1

Viral Infections of the Oral Cavity in Immunocompetent Individuals[a]

Agent	Acquisition	Usual Intraoral Site	Oral Manifestations
HERPES SIMPLEX VIRUS (HSV) TYPES 1 AND 2			
Primary gingivostomatitis	Saliva; direct contact with active lesions (oral, perioral, genital)	Anterior gingiva and mucosa, hard palate, tongue, lips	Vesicles, ulcers covered with yellowish exudates; gingival edema or erythema
Herpes labialis	Saliva; direct contact with active lesions (oral, perioral, genital)	Lips	Vesicles, ulcers and crusting
Recurrent intraoral herpes	HSV reactivation	Gingiva, hard palate	Vesicles, ulcers
Erythema multiforme	HSV reactivation	Buccal and labial mucosa, tongue, lips	Erythematous macules, vesicles, ulcers
VARICELLA-ZOSTER VIRUS (VZV)			
Chickenpox	Saliva, direct contact with active lesions	Hard and soft palate, buccal mucosa, tongue, lips	Vesicles, ulcers
Zoster	VZV reactivation	Palate, lips, tongue, buccal mucosa, gingiva	Unilateral vesicles, ulcers, bone necrosis, tooth exfoliation; pain along trigeminal nerve
EPSTEIN-BARR VIRUS (EBV)			
Infectious mononucleosis	Saliva	Hard and soft palate, gingiva	Lymphadenopathy, palatal petechiae, gingival necrosis, ulcers, edema of uvula
Oral hairy leukoplakia	Established EBV	Lateral borders of	Vertical white,

	infection	the tongue	hyperkeratotic lesions
Burkitt lymphoma	Not known	Maxilla, molar-premolar area	Tumors; loosening and displacement of teeth
Nasopharyngeal carcinoma	Not known	Nasopharynx	Keratinizing squamous carcinoma; nonkeratinizing squamous carcinoma; undifferentiated carcinoma
CYTOMEGALOVIRUS	Congenital; breastfeeding; saliva	Teeth	Enamel hypoplasia, dental attrition, discoloration
HUMAN HERPESVIRUS 8	Possibly sexual transmission	Hard and soft palate	Kaposi sarcoma
COXSAKIEVIRUSES			
Hand-foot-and-mouth disease	Saliva	Buccal and labial mucosa, tongue	Vesicles, ulcers
Herpangina	Saliva	Soft palate	Vesicles, ulcers
HUMAN PAPILLOMAVIRUSES			
Condyloma acuminata	Direct contact with lesions	Tongue, gingiva, labial mucosa, palate	Soft, broad-based papules with a pebble-like surface
Focal epithelial hyperplasia (Heck disease)	Direct contact with lesions; self-inoculation	Alveolar mucosa, lips	Soft, flat, nonpedunculated papules, usually with a pebble-like surface
Squamous cell papilloma	Transformation chronic infection	Uvula, hard and soft palate, tongue, frenulum, lips, buccal mucosa, gingival	Soft, pedunculated, exophytic papules with cauliflower-like surface
Verruca vulgaris	Direct contact with lesions, self-inoculation	Lips, tongue, labial mucosa, gingiva	Firm, broad-based elevated papules with cauliflower-like surface
MOLLUSCUM CONTAGIOSUM	Direct contact with lesion	Lips	Waxy, dome-shaped papules
MEASLES	Saliva, respiratory droplets	Buccal and labial mucosa; teeth	Bluish-white macules surrounded by erythema (Koplik spots); pitted enamel
MUMPS	Saliva, respiratory droplets	Salivary glands	Swelling of salivary glands; erythema and edema of Wharton and Stensen duct openings; oral dryness
RUBELLA	Saliva, respiratory droplets	Hard and soft palate	Petechiae; small dark-red papules (Forchheimer sign)
HEPATITIS C VIRUS	Blood, sexual transmission	Buccal mucosa	Lichen planus

[a] Reproduced from Glick M, Siegel MA. Viral and fungal infections of the oral cavity in immunocompetent patients. Infect Dis Clin North Am 1999:13;817–831.

TABLE 25.2

Oral Mucosal Manifestations of Local and Systemic Infection and Other Conditions

Cause	Lesion	Site	Disease Course/Comment
BACTERIA			
Scarlet fever *(Streptococcus pyogenes)*	Strawberry tongue	Tongue	Reddened edematous papillae project through white coating; coating peels off to leave red glistening tongue with prominent papillae
	Punctiform and petechial lesions	Palate	Intraoral erythema; uvula and free margin of soft palate red and edematous; lips uninvolved
Toxic shock syndrome *(Staphylococcus aureus)*	Intraoral erythema, edema, and desquamation	Lips, all intraoral mucous membranes	Can progress to painful desquamation
Treponema pallidum	Painless ulcer with rolled edges	Anywhere on oral mucous membranes	Primary chancre heals over 5–10 days; followed by systemic manifestations if untreated
Gingivitis	Edema, thickening, erythema, and easy bleeding; usually painless	Gingiva and interdental papillae	Subgingival plaque always present; common in children, particularly during puberty
Acute necrotizing ulcerative gingivitis	Pseudomembranes (necrosis of papillae)	Gingiva	Necrosis of interdental papillae results in marginated, punched-out, eroded appearance; grey necrotic pseudomembranes; fusiform bacilli and spirochetes consistently found
Cystic gingival lesions	Red, cystic lesion, 4–10 mm	Gingival ridge	Infants <10 mo with pneumococcal bacteremia
Glossitis	Swollen, red, painful	Tongue	*Streptococcus pyogenes, Staphylococcus aureus, Haemophilus influenzae* b
Uvulitis	Red, edematous	Uvula	*Streptococcus pyogenes, Haemophilus influenzae* b; can cause respiratory compromise
FUNGUS			
***Candida* spp.**	Pseudomembranes of creamy white plaques on erythematous mucosa	Tongue, gingiva, buccal mucosa; rarely, pharynx, larynx, esophagus; cheilitis	Lesions can be painless, can burn, or can feel sore or dry
Histoplasma capsulatum	Ulcers	Oropharynx	Occurs with subacute or chronic disseminated disease
UNKNOWN			
Kawasaki disease	Strawberry tongue; mucosal erythema; erythema, cracking peeling, bleeding lips	Tongue, oropharynx, lips	Mucosal erythema present in all but atypical forms
Recurrent oral ulcerations (aphthous stomatitis)	Shallow, circular painful ulcer <5 mm on erythematous base with pseudomembrane	Nonkeratinized movable labial and buccal mucosa; tongue and floor of mouth	Healing occurs after 4 days; common (incidence 20%); recurrences 12 times/yr; etiology unknown; symptomatic therapy

	Deep ulcers of >5 mm diameter; painful	All areas of oral cavity	Lasts 6 wk–3 mo; heals with scarring (Sutton scarring aphthae)
	Small cluster of vesicles; extremely painful; no erythematous border	Tip and lateral margins of tongue	Herpetiform ulcers with no relationship to HSV
PFAPA syndrome	Small ulcers	Oral mucosa	Syndrome of recurrent fever, aphthous stomatitis, pharyngitis, and cervical adenitis; affects children <5 yr; recurrence every 2–9 wk
Gangrenous stomatitis (noma)	Focal, destructive lesions	Gingiva and deeper structures	Rare, acute, fulminating in severely debilitated and malnourished children; spirochetes and other anaerobic bacteria may be involved
Cyclic neutropenia and agranulocytosis	Small ulcers	Oral mucosa	
Drug- or radiation-induced stomatitis	Ulcers and pseudomembrane formation; painful	Nonkeratinized labial and buccal mucosae; soft palate; floor of mouth; ventral and lateral tongue surfaces	Microbiologic diagnosis important to rule out viral reactivation or bacterial superinfection
Behçet syndrome	Ulcers	Oral mucosa	Multisystem disease that can involve many mucous membranes
Stevens-Johnson syndrome	Macules, papules, vesicles, bullae	Buccal mucosa and vermilion border of the lips; relative sparing of gingivae	Erythema multiforme exudativum; 25% of cases confined to oral mucosa; lesions appear in crops; complete healing 4–6 wk; can cause recurrent stomatitis and labiitis
Inflammatory bowel disease	Ulcers (aphthous-like)	Oral mucosa	Manifestation of multisystem disease

PFAPA, periodic fever with aphthous stomatitis, pharyngitis, and adenitis.

Herpes Simplex Virus Gingivostomatitis

Herpes simplex virus (HSV) gingivostomatitis is the most recognized viral infection of the oral cavity. Primary infection with HSV-1 occurs throughout childhood, most commonly between the ages of 6 months and 5 years, and during adolescence and results in seropositivity in up to 90% of adults.[21,22] Up to 90% of children with primary HSV infections are symptom free.[23] After primary infection, the virus remains dormant in trigeminal ganglion and reactivates after stressful stimuli (i.e., cold, trauma, sunlight, intercurrent illness). Recrudescent disease has been estimated to occur in up to 40% of seropositive individuals.[24] HSV infection is ubiquitous and transmitted from symptomatic and asymptomatic people with primary or recurrent infection. Infections with HSV-1 usually result from direct contact with infected oral secretions. The incubation period for HSV infection beyond the neonatal period is usually 2 days to 2 weeks.[25] In primary infection, vesicles appear on the first day of illness in 85% of affected children and can persist for 7 to 18 days.[26] Primary symptomatic infections are accompanied by fever, lymphadenopathy, malaise, pharyngitis, and anorexia. Gingiva are red, swollen, and bleeding. Small vesicles surrounded by a red halo on the gingiva and anterior lingual and buccal mucosa rapidly rupture and coalesce, giving rise to ulcerations. HSV gingivostomatitis is painful, and children commonly refuse to swallow, resulting in drooling. Differential diagnosis includes coxsackievirus infection (herpangina), erythema multiforme, pemphigus vulgaris, acute necrotizing ulcerative gingivitis, and most commonly aphthous stomatitis.

Complications of HSV gingivostomatitis include dehydration, herpetic whitlow or herpetic keratitis from autoinoculation, and secondary bacteremia with oral flora.[27,28] Recurrent HSV orolabial lesions occur in one third of individuals with prior HSV infection. Reactivation lesions typically are found around the gingiva, hard palate, and vermilion border of the lip ("cold sore"). A prodrome of tingling, burning, and itching occurs 12 to 36 hours before the eruption of the vesicles. Viral shedding persisted for a mean of 7 days (range, 2–12 days) among 36 untreated immunocompetent children in one study.[29]

Treatment of HSV gingivostomatitis usually is palliative, with hydration and pain control. Topical application of diphenhydramine, simethicone (Maalox), bismuth subsalicylate (Kaopectate), or viscous lidocaine is frequently prescribed; however, their usefulness and benefit have been questioned.[29] A randomized, double-blind treatment trial in children using oral acyclovir during early stages reduced the duration of symptoms, improved healing, and reduced infectivity[30] (see Chapter 204). A systematic review showed weak evidence that oral acyclovir offered treatment benefit.[31] In general, most experts would treat patients who come to attention early, within 72 to 96 hours of the onset of symptoms, or who have severe disease. Chronic suppressive therapy can be used to reduce recurrences, such as in patients with facial, periorbital, or ocular lesions or very frequent episodes.[25] Among healthy subjects, combination of early topical acyclovir 5% and hydrocortisone 1% cream (ME-609) was more effective in reducing progression to ulcerative HSV lip lesions and reduced the size of the lesions compare with topical acyclovir or placebo.[32]

Oral Candidiasis

Oral candidiasis usually is caused by *Candida albicans* and has several manifestations such as pseudomembranous candidiasis, angular cheilitis (perlèche) and erythematous atrophic candidiasis (glossitis).

Pseudomembranous Oral Candidiasis (Thrush).

Neonates typically are colonized by *Candida* spp. during passage through the birth canal. Other sources of transmission to neonates include colonized skin of breasts (for breastfed infants) or hands and improperly cleaned bottle nipples. *Candida* spp. are asymptomatically carried in the gastrointestinal tract of many healthy children and premature infants as well as in patients treated with antibiotics and in those who are receiving chemotherapy, radiation therapy, or inhaled glucocorticoids. Thrush that is more than mild, which occurs beyond 6 months of age in the absence of risk factors, should prompt evaluation for human immunodeficiency virus (HIV) infection, cell-mediated immunodeficiency, neutropenia, or other phagocytic defect.[33] The pseudomembranous form of candidiasis is most common and is characterized by white plaques on the buccal mucosa, palate, tongue, or oropharynx. The plaques can be wiped off to reveal a red, raw, painful surface. Many patients with oral candidiasis are asymptomatic. Symptomatic patients can complain of feeling of “cotton” in the mouth, loss of taste, and sometimes pain during eating and swallowing. The diagnosis of pseudomembranous candidiasis usually is suspected clinically and is readily confirmed by scraping the lesions with a tongue depressor and preparing a slide for Gram stain or KOH preparation. Thrush is the most common oral manifestation of HIV, with reported prevalence ranging between 20% and 72%.[34–36] Thrush (which usually is extensive) can be the initial indication of HIV infection in a patient who appears otherwise healthy.[37] Topical agents (nystatin oral suspension or clotrimazole troches or pastilles) are recommended for initial therapy of mild oral candidiasis, including in immunocompromised children. Systemic therapy with fluconazole should be considered for patients with severe disease, immunocompromised patients (including those with HIV), and patients who fail to improve with topical treatment.[38,39] Patients not responding to treatment with oral or intravenous (IV) fluconazole should be treated with voriconazole, posaconazole, itraconazole, or amphotericin.

Patients with candidial angular cheilitis present with painful fissuring of the corner of their mouth. Risk factors for cheilitis include habitual licking of the corners of the mouth or immunosuppression. Other causes of cheilitis include bacterial and viral infections (i.e., *S. aureus*, HSV), nutritional deficiencies, anemia, allergy, and bruxism. Treatment is similar to that for thrush along with behavioral modification to minimize licking.

Erythematous atrophic candidiasis is characterized by red painful flattened tongue papillae in the dorsum of the tongue or erythema of soft and hard palate. This condition most commonly occurs after disruption of the oral mouth microbiota (i.e., after antibiotic use). Treatment is similar to that for other forms of oral candidiasis.

Acute Necrotizing Ulcerative Gingivitis

ANUG, also known as *Vincent disease* or *trench mouth*, has a sudden onset with gingiva showing punched-out crater-like ulcerations, covered with a whitish pseudomembrane, surrounded by a demarcated zone of erythema. Any area of the mouth can be affected. There is spontaneous bleeding, and breath has fetid odor. The patient's chief complaint is pain. Bacterial overgrowth of oral *Treponema* and *Selenomonas* spp., *P. intermidia,* and *Fusobacterium* spp. contribute to the infection.[40] However, other factors are believed to contribute to the disease.[41] Systemic penicillin and metronidazole are commonly used in addition to an oral antiseptic rinse such as chlorhexidine and good mouth care.[42]

Periodontitis, Gingivitis, and Mucositis in Immunocompromised Hosts

HSV infection in immunocompromised hosts has a higher risk for dissemination and a longer duration of outbreaks and is less responsive to therapy.[43] Complications include esophagitis, tracheobronchitis, pneumonitis, bacteremia, hepatitis, and pancreatitis.[26,27,44–46] Among HIV-infected children with orolabial HSV infection, initial therapy with oral acyclovir is recommended. Children with severe HSV disease or immunosuppression (other than HIV) should be treated with IV acyclovir. Children with recurrent HSV orolabial lesions should be treated with short courses of oral acyclovir, valciclovir, or famciclovir. Alternatively, children with severe and frequent HSV orolabial exacerbations may benefit from daily chronic suppressive therapy.[47] Neonatal HSV skin-eye-and-mouth disease is discussed elsewhere.

Chemotherapy- and radiotherapy-induced mucositis is the result of a breakdown of the mucosal epithelium, ulceration, and bacterial overgrowth in the presence of granulocytopenia. Gram-negative bacteria and α-hemolytic streptococci are important causes of complicating septicemia in patients with mucositis.[48] A Cochrane database systematic review and meta-analysis of randomized trials of 9 interventions (allopurinol, aloe vera, amifostine, cryotherapy, IV glutamine, honey, keratinocyte growth factor, laser, and polymixin-tobramycin-amphotericin antibiotic pastille or paste) showed some statistically significant evidence of benefit (albeit weak) for preventing and reducing severity of mucositis in cancer patients.[49] Trial of a novel drug, palifermin, and a randomized control trial of visible-light therapy in hematopoietic stem cell transplant recipients also showed benefit.[50,51] Palifermin is now recommended for prevention and treatment of mucositis for patients undergoing high-dose chemotherapy with or without radiation therapy followed by bone marrow transplantation for hematologic cancers.[52]

Human Immunodeficiency Virus–Associated Oral Lesions

The pathogenesis of oral lesions in children with HIV is not well characterized. The combination of lymphopenia, low $CD4^+$ lymphocyte counts, humoral dysregulation, and phagocytic defect most likely contributes to the array of infectious complications. In 1992 a European and US expert panel developed a classification system and diagnostic criteria for HIV-associated lesions.[53] A simplified summary is provided in Box 25.1.

Box 25.1

Classification of Human Immunodeficiency Virus–Associated Oral Lesions

Lesions Strongly Associated With HIV Infection

- Candidiasis
  - Erythematous
  - Pseudomembranous
- Hairy leukoplakia
- Kaposi sarcoma
- Non-Hodgkin lymphoma
- Periodontal disease
  - Linear gingival erythema
  - Necrotizing ulcerative gingivitis
  - Necrotizing ulcerative periodontitis

Lesions Less Commonly Associated With HIV Infection

- Bacterial infections (*Mycobacterium avium* complex)
- *Mycobacterium tuberculosis*
- Melanotic hyperpigmentation
- Necrotizing (ulcerative) stomatitis
- Salivary gland disease (xerostomia, swelling of major salivary

glands)

Thrombocytopenic purpura

Ulceration (not otherwise specified)

Viral infections (herpes simplex virus, human papillomavirus, varicella-zoster virus)

Modified from Kline WM. Oral manifestations of pediatrics human immunodeficiency virus infection: a review of literature. Pediatrics 1996;97:380–388.

Besides oral candidiasis, parotid enlargement occurs commonly in HIV infection, with prevalence of 47% reported from a large study of HIV-infected children from the US.[54] Periodontal disease, hairy leukoplakia, and aphthous ulcers have been reported rarely.[55] Several forms of periodontal disease, such as linear gingival erythema and necrotizing ulcerative gingivitis, are strongly associated with HIV infection.[38] Treatment of HIV-associated HSV and *Candida* infections was described earlier.

Complications of Odontogenic and Mucosal Infections

Ludwig Angina

The classic description of Ludwig angina includes rapidly spreading indurated cellulitis of the submandibular and sublingual spaces bilaterally without abscess formation. Infection starts in the floor of the mouth. Dental infection is found in 50% to 90% of reported cases.[12,56] Trauma to the oral cavity, piercing, or laceration preceded infection among a number of reported cases. Clinically, patients demonstrate brawny, board-like swelling in the submandibular spaces that does not pit on pressure. The mouth is held open, and the floor is elevated, pushing the tongue to the roof of the mouth. Eating and swallowing are difficult, and respiration can be impaired by obstruction of the tongue. Rapid progression can result in edema of the neck and glottis and can precipitate asphyxiation. Fever and toxicity usually are present. Treatment requires high doses of antibiotics active against oral flora, airway monitoring, early intubation or tracheostomy when required, dental care, soft tissue decompression, and surgical drainage. Systemic penicillin, ampicillin, and amoxicillin are appropriate choices for less severe infection or when susceptibility of the organism is known. However, their utility is limited owing to the production of β-lactamase by many oral anaerobes.[57] Antimicrobial resistance among anaerobes has been steadily increasing, and consequently susceptibility cannot be predicted for some highly virulent isolates (i.e., *Bacteroides, Prevotella, Fusobacterium,* and *Clostridium* spp.). Hence antibiotics containing clavulanate, sulbactam, or tazobactam component or carbapenems are recommended for severe oral infections.

Suppurative Jugular Thrombophlebitis (Lemierre Syndrome)

The incidence of Lemierre syndrome decreased dramatically after its original description by Andre Lemierre in 1936 but has had apparent resurgence.[58] The syndrome includes septic thrombophlebitis of the internal jugular vein, usually secondary to an acute oropharyngeal infection, and frequently is complicated by bloodstream and metastatic infection. The usual agent is *Fusobacterium necrophorum*, but *S. aureus* and *Streptococcus pyogenes* are occasional causes[59] (see Chapter 28). Most cases occur in adolescents and young adults with tonsillopharyngitis as the primary infection. Odontogenic infections, sinusitis, and otitis externa have been reported as primary infections in a few patients with Lemierre syndrome.

Infections of the Salivary Gland

Bilateral asymptomatic enlargement of the parotid gland usually is due to a noninfectious cause. The differential diagnosis includes metabolic and endocrine disorders such as malnutrition (vitamins B_6 and C deficiencies), chronic pancreatitis, obesity, cystic fibrosis, thyroid disease, and diabetes mellitus. Infections of the salivary glands (including the parotid) are discussed later.

Acute Suppurative Sialadenitis

In contrast to adults, children commonly incur repeated episodes of acute sialadenitis.[60] The parotid gland is affected more commonly than the submandibular gland, and more than one gland can be affected during a single episode.[61] Primary etiology appears to be salivary stasis. Predisposing factors may include calculi, duct stricture, dehydration, infancy, autoimmune disease, and congenital sialectasia. Clinical manifestations include local pain, tenderness, and edema of the soft tissue overlying the affected gland. A purulent discharge can be seen draining from the duct of the involved gland. Most children remain nontoxic during acute episodes.[60] Residual induration and enlargement of the gland can persist for months after the initial infection. Treatment consists of systemic antibiotics, local heat and massage, fluids, and sialagogues. *S. aureus* is the most common infectious cause. In addition, direct needle aspiration has confirmed α-hemolytic streptococci, *H. influenzae*, *S. pyogenes*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Escherichia coli*, and anaerobic bacteria as causative.[61,62] Mycobacterial and fungal parotitis cases also have been described rarely. Acute sialadenitis infrequently progresses to abscess formation. The patient should be monitored closely for spread of infection into contiguous fascial spaces of the neck.[63] Recurrent parotitis is associated with poor oral hygiene and underlying disease such as abnormal ductal architecture, allergies, immunoglobulin A deficiency, and HIV.[64–66] *S. pneumoniae* was isolated from parotid gland pus in a patient with HIV infection.[64] Empiric therapy should include a penicillinase-resistant antistaphylococcal antibiotic, as well as consideration of local prevalence of methicillin-resistant *S. aureus*. Purulent discharge from the gland's duct on the buccal mucosa should be cultured to guide antimicrobial therapy.

Neonatal Sialadenitis

Neonatal suppurative sialadenitis is an uncommon but recognizable disease with a prevalence of 3.8 per 10,000 hospital admissions in one report.[67] Neonatal sialadenitis much more commonly affects the parotid gland than the submandibular gland. Presence of calculi or anatomic deformities of the oral cavity, dehydration, and prematurity are established risk factors in sialadenitis in this age group. Ismail and colleagues[68] reviewed case reports since 1970, which included 44 cases of neonatal parotitis. Approximately 32% of neonates with parotitis were born prematurely. The most common causative organism was *S. aureus*. Other organisms identified included viridans streptococci, *E. coli, Pseudomonas aeruginosa*, *M. catarrhalis*, peptostreptococci, *Bacteroides* spp., *Prevotella* spp., and coagulase-negative staphylococci.[68] Salivary secretions should be cultured and Gram stain obtained. Disease usually is limited to one gland, and signs and symptoms of systemic disease may not be present. Physical examination reveals a warm, tender, erythematous mass; pus can be expressed from the parotid or salivary duct. Laboratory test abnormalities are nonspecific. Leukocytosis with neutrophil predominance was found in 69% of the 44 cases. Serum amylase was measured in 16 of 44 cases and was elevated in only 4 (25%) of cases.[68] Adequate hydration and antibiotic therapy was successful in most cases. If prompt clinical improvement does not occur, ultrasonography may reveal the presence of an intraparotid abscess.

Viral Parotitis

The most common cause of viral parotitis is mumps virus. The disease is seen most frequently during spring and winter months. The incubation period is 16 to 18 days, and the contagious period includes 1 to 2 days before until 5 days after the onset of parotid swelling.[69] The prodrome includes malaise, fever, and sore throat with chills. The major salivary glands become tender. The patient may have trismus and difficulty chewing. The duct orifice may be swollen; saliva is clear. The white blood cell count is normal or slightly elevated with lymphocytosis. The diagnosis is based on clinical manifestations, but culture and serologic tests can be used for the diagnosis. Differential diagnosis includes other viral infections such as influenza, parainfluenza virus types 1 and 3, coxsackievirus types A and B, echoviruses, Epstein-Barr virus, cytomegalovirus, lymphocytic choriomeningitis virus, HSV-1, HIV, human herpesvirus 6, and bacterial causes (see earlier). Noninfectious causes of parotitis include Sjögren syndrome and metabolic, endocrine, and neoplastic disorders. People with parotitis without apparent cause should undergo diagnostic testing to confirm mumps infection[69] (see Chapter 224). Early recognition of the disease and outbreaks is important; reverse transcriptase polymerase chain reaction testing for mumps virus is available through many state laboratories.[70,71]

Juvenile Recurrent Parotitis

Juvenile recurrent parotitis (JRP) is the second most common salivary gland disease in children. A variety of causative factors have been proposed, including congenital ductal malformations, hereditary-genetic factors, viral or bacterial infection, allergy, and local manifestation of an autoimmune disease. A review of published literature shows all cases before puberty.[72,73] Clinical symptoms of JRP include recurrent, nonobstructive, nonsuppurative parotid inflammation. JRP usually is unilateral, but bilateral exacerbations can occur. Patients with HIV infection can manifest recurrent or chronic sialadenitis; cytomegalovirus and *S. pneumoniae* have been associated. Treatment of an acute episode generally includes early antibiotic therapy to prevent further parenchymal damage, adequate fluid intake, massage and warm compresses, and use of gum and other sialagogues. Salivary endoscopy affords opportunity for diagnosis and treatment and proved effective among 70 children with JRP with only 5 patients experiencing recurrence.[74] Performing sialography with dilation and hydrocortisone lavage along with parenteral amoxicillin-clavulanate therapy was reported to be useful in relieving symptoms in 26 children with JRP.[73]

Granulomatous Parotitis

Granulomatous diseases can be associated with chronic inflammatory parotitis. Children are affected infrequently.[63] Patients usually have localized nodules, which should be distinguished from malignancy. The mass usually is painless and slowly progressive, and often has no surrounding erythema. Saliva is normal in color. Sialography demonstrates extrinsic pressure on the ductal system without intrinsic abnormalities. Possible causes include sarcoidosis, cat-scratch disease, actinomycosis, tuberculosis, and nontuberculous mycobacterial infection. Excision of the gland is diagnostic and therapeutic. *Mycobacterium tuberculosis* infection of the gland is part of a systemic disease and requires systemic therapy.

Osteomyelitis

Mandibular Osteomyelitis

Osteomyelitis of the mandible is rare. Clinical manifestations include fever, facial swelling, and jaw pain, usually accompanied by the finding of a carious tooth. Surgical drainage of dental abscess, along with antibiotic therapy, usually results in a clinical cure. Treatment is given for a minimum of 4 weeks.[12]

Actinomycosis is an infrequent cause of mandibular osteomyelitis. Compilation of 19 pediatric cases over three decades showed a median age of 7 years, and 58% were females. Nearly 50% of patients had a history of recent tooth extraction, loss of a tooth with periodontitis, tooth abscess, or trauma with a pencil.[75] All cases presented with firm painful mass over the mandible. All cases required at least 1 surgical debridement in addition to prolonged antibiotic courses (several months).[75] Unfortunately, relapses are common. In such instances, additional debridement and cultures should be performed to direct antibiotic therapy. Actinomycosis may resemble a malignant process. Biopsy with anaerobic culture of the properly collected specimen to avoid contamination with commensal oral flora establishes the diagnosis. Microbiology laboratory personnel should be notified when actinomycosis is suspected in order to hold culture specimens under anaerobic conditions for 14 days. High-dose penicillin is the drug of choice; alternatives include clindamycin, erythromycin, and tetracyclines. The duration of antibiotic therapy depends on the extent and severity of infection, with minimum of 6 months.

Infantile Maxillary Osteomyelitis

Infantile maxillary osteomyelitis is rare, usually occurring in infants younger than 12 weeks.[66] It is an acute bacterial infection of the maxilla with necrosis and sequestration of the surrounding structures. Clinical findings can simulate orbital cellulitis, including chemosis, fever, proptosis, and purulence at the inner or outer canthus. The palate on the affected side is swollen, and the alveolar dental ridge is markedly thickened.[76,77] *S. aureus* is the usual pathogen. The condition can be mistaken for orbital cellulitis. Correct diagnosis is imperative for proper management and the prevention of complications, such as extension intracranially, optic nerve damage, disfiguring scarring of the face, and damage to the developing teeth. Surgical drainage and antibiotic therapy are mainstays of management.

Garré Osteomyelitis

Garré osteomyelitis, also known as *nonsuppurative ossifying periostitis* and *periostitis ossificans*, is a chronic nonsuppurative, sclerosing osteomyelitis. This condition usually is associated with a carious tooth, periodontal defect, or other type of low-grade inflammatory process (erupting molars).[78] The disease usually appears as an asymptomatic, unilateral swelling of the mandible in children and young adults. Clinical and radiographic findings, frequently showing laminated or onion skin appearance, are suggestive but not pathognomic. Differential diagnosis includes cortical hyperostosis (Caffey disease), osteosarcoma, and Ewing sarcoma. Histologic examination is necessary to establish a definite diagnosis. In general, the clinical course usually has sudden onset, with progression, spontaneous regression, and remodeling. Resolution is enhanced by the dental extraction and removal of the inflamed tissue.

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26

The Common Cold

Diane E. Pappas

The common cold, also known as upper respiratory tract infection (URI), is an acute, self-limited viral infection of the upper airway that also may involve the lower respiratory tract. The characteristic symptom complex consisting of rhinorrhea, nasal congestion, and sore or scratchy throat is familiar to all adults.

Colds are the most common cause of human illness and are responsible for significant absenteeism from school and work. Children are especially susceptible because they have not yet acquired immunity to many of the viruses, they have poor personal hygiene practices, and they have frequent close contact with other children who are excreting virus.

Etiology

Colds are common because some of the causative viruses do not produce lasting immunity after infection and some viruses have numerous serotypes (Table 26.1). Cold viruses that do not produce lasting immunity include respiratory syncytial virus (RSV), parainfluenza viruses (PIVs), and human coronaviruses (HCoVs). Cold viruses that have numerous serotypes but produce lasting serotype-specific immunity after infection include rhinoviruses, adenoviruses, influenza viruses, and enteroviruses.[1]

TABLE 26.1

Immunity to Common Cold Viruses

Virus	No. of Serotypes
LONG-LASTING IMMUNITY NOT PRODUCED BY INFECTION[a]	
Respiratory syncytial virus (RSV)	1
Parainfluenza virus	4
Human coronavirus	2
IMMUNITY PRODUCED BY INFECTION[b]	
Rhinovirus	>100
Adenovirus	≥33
Influenza	3[c]
Echovirus	31
Coxsackievirus group A	3
Coxsackievirus group B	6

[a] Repeated infection with the same serotype is usual.

[b] Reinfection with the same serotype is uncommon.

[c] Type A subtypes change.

Modified from Hendley JO. Immunology of viral colds. In: Veldman JE, McCabe BF, Huizing EH, et al (eds). Immunobiology, Autoimmunity, Transplantation in Otorhinolaryngology. Amsterdam: Kugler Publications; 1985, pp. 257–260.

With at least 100 serotypes, rhinoviruses are the most common cause of URIs in children and adults. At least 50% of colds in adults are caused by rhinoviruses. Other viruses that cause URIs are HCoVs, RSV, human metapneumovirus, influenza virus, parainfluenza viruses, adenoviruses, echoviruses, and coxsackieviruses A and B. Human bocavirus (HBoV), discovered in 2005, has been reported in children with symptomatic URIs (>10%) but may also occur in asymptomatic children, making its role in causing illness unclear.[2–4]

Some viruses cause characteristic syndromes. For example, RSV causes bronchiolitis in children 2 years or younger, influenza viruses cause febrile respiratory illness with severe lower respiratory tract involvement, adenoviruses cause pharyngoconjunctival fever, parainfluenza viruses cause croup in young children, HBoV is associated with wheezing, and enteroviruses cause a variety of illnesses, including aseptic meningitis and herpangina.

Epidemiology

In temperate climates in the northern hemisphere, the predictable yearly epidemic of colds begins in September and continues unabated until spring. This sustained epidemic curve is a result of successive waves of different respiratory viruses moving through the community (Fig. 26.1). The epidemic begins with a sharp rise in the frequency of rhinovirus infections in September (after children return to school), which is followed by PIVs in October and November. RSV and HCoVs circulate during the winter months, and infection due to influenza virus peaks in the late winter. The epidemic ends with a small resurgence of rhinovirus infections in the spring. Adenovirus infection occurs at a constant rate throughout the cold season.

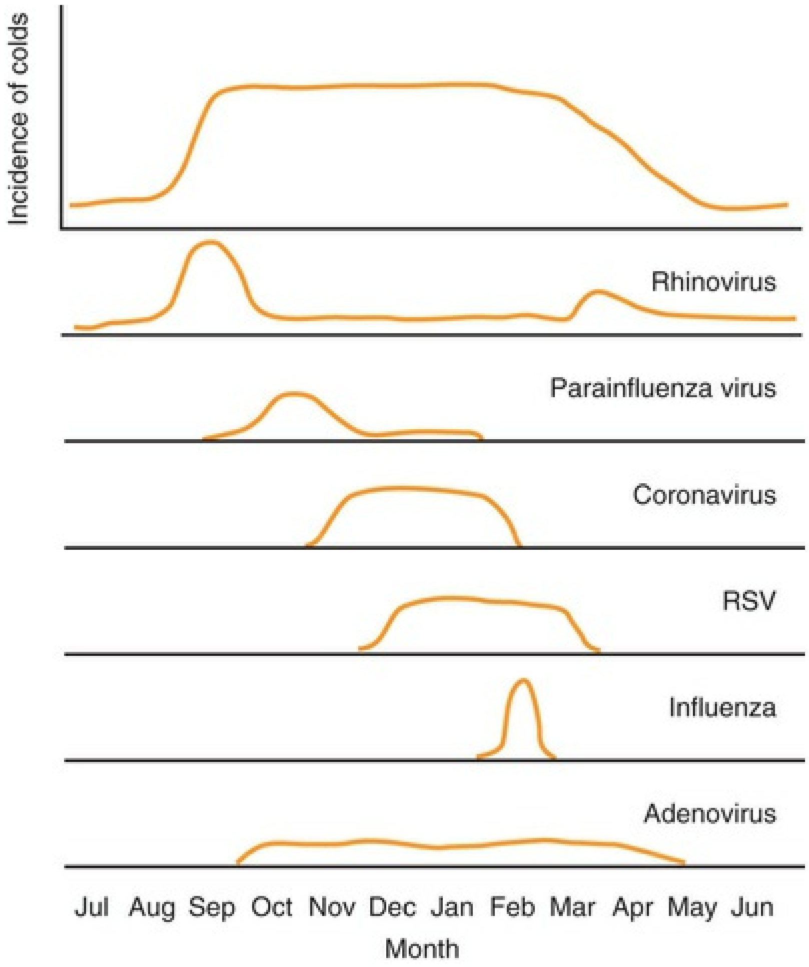

FIGURE 26.1 Schematic diagram of the incidence of colds and frequency of causative viruses. RSV, respiratory syncytial virus. (Modified from Hendley JO. The common cold. In: Goldman L, Bennett JC (eds). Cecil Textbook of Medicine, 21st ed. Philadelphia: WB Saunders; 2000, pp. 1790–1793.)

The frequency of colds varies with age. A 10-year study in the 1970s of families with children who did not attend a childcare facility showed that the peak incidence of colds occurs in preschool children 1 to 5 years old, with a frequency of 7.4 to 8.3 colds per year.[5] In a 52-week longitudinal study of 108 individuals in 26 households in Utah, which included diaries of illness and testing of weekly self-collected or family-collected anterior nares specimens by FilmArray, an automated polymerase chain reaction (PCR) system for virus detection, respiratory symptoms were identified for 38% of person-weeks for children younger than 5 years and 20% for older children and adults. Sixty percent of respiratory illnesses were associated with virus detection, but only approximately 50% of virus detections were associated with symptoms (especially rhinovirus and bocavirus).[6]

Viral transmission occurs primarily in the home setting, although the exact mechanism of spread has not been established. Colds can be spread by a small-particle (<5 μm in diameter) aerosol, which infects when inhaled; by large-particle (>10 μm in diameter) droplets, which infect by landing on nasal or conjunctival mucosa; or by direct transfer through hand-to-hand contact.[7] A small-particle aerosol is an effective method of transfer for influenza virus[8] and coronavirus[9] but not for RSV.[10] Rhinoviruses are most likely spread by large-particle droplets or direct transfer.

Rhinoviruses can survive as long as 2 hours on human hands and up to several days on other surfaces. Studies have shown that infected young adults commonly have rhinovirus on their hands, which can be efficiently transferred to the hands of uninfected individuals during brief contact. Infection results when the uninfected person transfers the virus from the hands on to his or her nasal or conjunctival mucosa. Sneezing and coughing are ineffective modes of rhinovirus transmission,[11] although there is some evidence that the virus also can be transmitted by aerosols generated by coughing, talking, and breathing.[12] Inoculation of the oral mucosa with rhinovirus[13] or RSV[14] does not result in infection.

Pathogenesis

Symptoms of the common cold do not appear to result from destruction of nasal mucosa because nasal biopsy specimens from young adults with natural and experimentally induced colds show intact nasal epithelium during symptomatic illness.[15,16] Study by in situ hybridization of nasal biopsy specimens obtained during rhinovirus infection indicates that replication occurs in only a small number of epithelial cells.[17,18] In vitro studies have shown that rhinovirus and coronavirus produce no detectable cytopathic effect when replicating in a cultured monolayer of nasal epithelial cells, whereas influenza virus A and adenovirus produce obvious damage.[19]

The symptoms of the common cold appear to result from release of cytokines and other mediators from infected nasal epithelial cells and from an influx of polymorphonuclear cells (PMNs). Nasal washings of volunteers experimentally infected with rhinovirus showed a 100-fold increase in PMN concentration 1 to 2 days after inoculation.[20] The influx of PMNs coincides with the onset of symptoms and correlates with a colored nasal discharge.[21] A yellow or white nasal discharge may result from the higher number of PMNs, whereas the enzymatic activity of PMNs (due to myeloperoxidase and other enzymes) may cause a green nasal discharge.

A potent chemoattractant for PMNs is produced by cells in culture infected with rhinovirus.[22] The chemoattractant has been identified as interleukin-8 (IL-8).[23] Elevated levels of IL-8 and other cytokines (e.g., IL-1β, IL-6) also have been demonstrated in the nasal secretions of infected individuals.[24,25] Elevated levels of albumin and kinins (predominantly bradykinin) in nasal secretions coincide with the onset of symptoms in experimental rhinovirus infection.[20] The elevated concentration of albumin and kinins likely results from exudation of plasma proteins due to greater vascular permeability in the nasal submucosa. The method by which viral infection initiates this vascular leak has not been determined. The release of kinins resulting from plasma exudation may augment the symptoms of the cold. Bradykinin alone can cause rhinitis and sore throat when sprayed into the noses of uninfected individuals.[26]

The paranasal sinuses usually are involved during an uncomplicated cold. In one study, CT scans obtained during the acute phase of illness revealed abnormalities of one or more sinuses in 27 (87%) of 31 young adults.[27] Without antibiotic therapy, there was complete resolution or marked improvement of the sinus abnormalities in 11 (79%) of the 14 subjects for whom second CT scans were obtained 2 weeks later. In another study, MRI revealed that 60% of children with URIs had major abnormalities in their paranasal sinuses, which tended to resolve without antibiotic therapy.[28] It is not known whether sinus abnormalities result from viral infection of the sinus mucosa or from impaired sinus drainage due to viral rhinitis. Nose blowing can generate enough pressure to force fluid from the nasopharynx into the paranasal sinuses, suggesting that nose blowing may force mucus containing viruses, bacteria, and inflammatory mediators into the paranasal sinuses during a cold.[29]

The middle ear can be involved during uncomplicated colds. Studies have shown that two thirds of school-aged children develop abnormal middle ear pressures within 2 weeks after the onset of a cold.[30] Otitis media was not diagnosed during the study because ears were not examined, and none of the children sought medical care. It is not known whether the abnormal middle ear pressures result from viral infection of the mucosa of the middle ear and eustachian tube or from viral nasopharyngitis with secondary eustachian tube dysfunction.

Clinical Manifestations

Symptoms of the common cold do not vary by specific causative virus. In older children and adults, rhinorrhea, nasal obstruction, and sore or scratchy throat are typical. The rhinorrhea is initially clear but may become colored as the illness proceeds, and patients can cough or sneeze. Fever (>38°C) is uncommon in adults. Other symptoms are malaise, sinus fullness, and hoarseness. Objective findings are minimal except for mild erythema of the nasal mucosa or pharynx. Symptoms resolve in 5 to 7 days.

Compared with adults, infants and preschool children with colds are more likely to have fever (>38°C) and moderate enlargement of the anterior cervical lymph nodes (Table 26.2).[1] Rhinorrhea may not be noticed until the nasal discharge becomes colored. Nasal congestion can disrupt sleep and lead to fatigue and irritability. The illness often persists in infants and preschool children for 10 to 14 days.[31]

TABLE 26.2

Characteristics of Viral Colds in Adults and Young Children

Characteristic	**Adults**	**Children <6 Years**
Frequency	2–4 per year	One per month, September–April
Fever	Rare	Common during first 3 days
Nasal manifestations	Congestion	Colored nasal discharge
Duration of illness	5–7 days	14 days

Modified from Hendley JO. Epidemiology, pathogenesis, and treatment of the common cold. Semin Pediatr Infect Dis 1998;9:50–55.

Differential Diagnosis

The differential diagnoses of a cold include allergic rhinitis, vasomotor rhinitis, intranasal foreign body, and sinusitis. A diagnosis of allergic rhinitis is suggested by a seasonal pattern of clear rhinorrhea, absence of associated fever, and family history of allergy. Possible associated conditions are asthma and eczema. Physical findings consistent with allergic rhinitis include allergic shiners (i.e., dark circles under the eyes) and nasal salute (i.e., wiping or rubbing the nose with a transverse or upward movement of the hand).

Detection of numerous eosinophils on microscopic examination of the nasal mucus using Hansel stain confirms the diagnosis of allergic rhinitis. A diagnosis of vasomotor rhinitis is suggested by a chronic course without fever or sore throat. The diagnosis of bacterial sinusitis is suggested by persistent rhinorrhea or cough, or both, for more than 10 days.[32]

Clinical Approach

The diagnosis of a cold is based on history and physical examination; typically, laboratory tests are not useful. The rapid test for detecting RSV, influenza, parainfluenza, and adenovirus antigens in nasal secretions can be used to confirm the diagnosis. RSV, rhinovirus, influenza viruses, parainfluenza viruses, and adenoviruses also can be isolated in cell culture. Because HCoVs cannot be detected reliably in cell culture, a serologic titer elevation can be used for diagnosis if necessary.

PCR assays for detection of all the respiratory viruses are available increasingly in clinical laboratories, but there is a lack of standardization and validation for many of the tests offered.

Meaningful interpretation of PCR results remains challenging because PCR detection of virus can occur in several clinical scenarios, including coinfection with multiple viruses, viral detection during the incubation period, subclinical infection, infection with the identified virus, variable duration of viral shedding, and sequential infection with different serotypes of the same species.[33] Other methods of detection can be used but are rarely needed.

Management

No antiviral agents are available that are effective for treatment of the common cold. Although an array of medications may be used to relieve symptoms, there is little scientific evidence to support the use of symptomatic treatments in children. Because the common cold is a self-limited illness with symptomatology that is largely subjective, a substantial placebo effect can suggest that various treatments have some efficacy. Inadequate blinding of placebo recipients in a study can make an ineffective treatment appear effective.

In adults with colds, first-generation antihistamines (e.g., chlorpheniramine) have been shown to provide modest symptomatic relief, with decreases in nasal discharge, sneezing, nose blowing, and duration of symptoms,[34] presumably because of the anticholinergic effects of these medications. A randomized, double-blind, placebo-controlled study of preschool children with URIs showed that treatment with an antihistamine-decongestant combination (i.e., brompheniramine maleate and phenylpropanolamine hydrochloride) produced no improvement in cough, rhinorrhea, or nasal congestion, although a larger proportion of the treated children (47% vs. 26%) were asleep 2 hours after treatment.[35]

Numerous decongestants, antitussives, and expectorants are available over the counter, but there is no evidence to support their use in children. A study of phenylephrine, a topical decongestant, for the treatment children 6 to 18 months old showed no decrease in nasal obstruction with its use during a URI.[36] In a study comparing placebo, dextromethorphan, and codeine for cough suppression in children 18 months to 12 years old, cough decreased in all patients within 3 days, but there was no difference in cough reduction among the three treatment groups.[37] Guaifenesin, an expectorant, has not been shown to change the volume or quality of sputum or the frequency of cough in young adults with colds.[38] Echinacea preparations, often thought to be effective in the treatment of the common cold, have no effect on the prevention or treatment of rhinovirus infection.[39] Similarly, intranasal zinc gluconate has had no effect for the treatment of colds[40] or prevention of experimental rhinovirus colds.[41] In January, 2008, the US Food and Drug Administration issued an advisory strongly recommending that over-the-counter cold and cough medications not be given to infants because of the risk of life-threatening side effects.

Antibiotics have no role in the treatment of uncomplicated URIs in children. Antibiotic therapy does not hasten resolution of the viral infection or reduce the likelihood of occurrence of secondary bacterial infection.[42] Antibiotics are indicated only in cases of secondary bacterial infection, such as sinusitis and acute otitis media.

Supportive measures remain the mainstay of treatment for the common cold in children. Bulb suction with saline drops (i.e., ≈1 teaspoon of salt in 2 cups of water) may help relieve nasal congestion and remove secretions. One study suggests that honey given at bedtime may help reduce cough in children with URIs, although honey is not recommended for children younger than 12 months because of the risk of exposure to *Clostridium botulinum* spores.[43] Vapor rub applied to the chest and neck of children between the ages of 2 and 11 years may help reduce nighttime cough.[44]

Complications

The common cold usually resolves in about 10 to 14 days in infants and children. New-onset fever and earache during this period may herald the development of bacterial otitis media, which occurs in about 5% of colds in preschool children. Persistence of nasal symptoms for longer than 10 days was thought to signify the development of a secondary bacterial sinusitis, but a study found that 20 children hospitalized for preseptal or orbital cellulitis, indicative of bacterial sinusitis, had symptoms of acute respiratory tract infection for 7 or fewer days before hospitalization, suggesting that the complications of rhinosinusitis can occur during the first few days of a cold.[45]

Bacterial pneumonia is an uncommon secondary infection. For children with underlying reactive airways disease, wheezing is common during the course of a viral URI; at least 50% of asthma exacerbations in children are associated with viral infection. Children who experience more than one *lower* respiratory tract infection (e.g., croup, bronchiolitis) during their first year of life have an increased risk of asthma thereafter.[46] Other complications are epistaxis, eustachian tube dysfunction, conjunctivitis, and pharyngitis.

Recent Advances

Symptoms of the common cold appear to result from the effects of inflammatory mediators released in response to the viral infection of the respiratory tract. As the determinants of this process are further elucidated, treatments may be developed that can interrupt or ameliorate release of inflammatory mediators and prevent or reduce the symptoms of the common cold. Vaccines are unlikely to be useful for prevention because of the large number of serotypes of some cold viruses and the lack of lasting immunity to others.

The use of alcohol-based hand gels has been suggested as a means of reducing secondary transmission of respiratory illnesses in the home,[47] but this approach was not shown to be effective in one field trial.[48] Virucidal tissues have been effective in preventing viral passage and transmission and may reduce secondary transmission by about 30%.[49,50] Until new methods are developed, prevention of the common cold is limited to avoiding self-inoculation (i.e., transfer of virus from contaminated fingers to nasal or conjunctival mucosa) by removing virus through handwashing or by killing virus with application of a virucide to the hands.

Acknowledgements

The author wishes to highlight the dominant contribution of J.

Owen Hendley to our understanding of respiratory viruses and to this chapter. The pediatric infectious diseases community recognizes our great loss with his death.

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27

Pharyngitis

John C. Arnold, Victor Nizet

Acute pharyngitis is one of the most common illnesses for which children in the United States visit primary care providers. The diagnoses of acute pharyngitis, acute tonsillitis, or "strep throat" are made more than 12 million times annually.[1,2]

Table 27.1 provides a partial list of etiologic agents for acute pharyngitis. Most cases in children and adolescents are caused by viruses and are benign and self-limited. Group A β-hemolytic *Streptococcus* (GAS) (e.g., *Streptococcus pyogenes*) is the most important bacterial cause. Strategies for the diagnosis and treatment of pharyngitis in children and adolescents depend on differentiating the large group of patients with viral pharyngitis who cannot benefit from antimicrobial therapy from the small group of patients with GAS pharyngitis who can. Distinguishing between groups is important to minimize the unnecessary use of antibiotics in children and adolescents while diagnosing and treating patients for whom benefit is likely.

TABLE 27.1

Causes of Acute Pharyngitis

Etiologic Agents	Associated Disorders or Clinical Findings
BACTERIAL	
Group A *Streptococcus*	Scarlet fever
Groups C and G streptococci	
Mixed anaerobes	Vincent angina
Neisseria gonorrhoeae	
Corynebacterium diphtheriae	Diphtheria
Arcanobacterium haemolyticum	Scarlatiniform rash

Yersinia enterocolitica	Enterocolitis
Yersinia pestis	Plague
Francisella tularensis	Tularemia
Fusobacterium necrophorum	Lemierre syndrome (jugular vein septic thrombophlebitis)
VIRAL	
Rhinovirus	Common cold
Coronavirus	Common cold
Adenovirus	Pharyngoconjunctival fever; acute respiratory disease
Herpes simplex virus types 1 and 2	Gingivostomatitis
Parainfluenza virus	Common cold; croup
Coxsackievirus A	Herpangina; hand-foot-mouth disease
Epstein-Barr virus	Infectious mononucleosis
Cytomegalovirus	Cytomegalovirus mononucleosis
Human immunodeficiency virus (HIV)	Primary HIV infection
MYCOPLASMAL	
Mycoplasma pneumoniae	Acute respiratory disease; pneumonia
CHLAMYDIAL	
Chlamydophila psittaci	Acute respiratory disease; pneumonia
Chlamydophila pneumoniae	Pneumonia
NONINFECTIOUS CAUSES	
Gastroesophageal reflux disease	Heartburn
Laryngopharyngeal reflux	Cough, hoarseness
PFAPA syndrome	Periodic fever, aphthous ulcers, adenitis
Allergic pharyngitis	Scratchy sensation, postnasal drip, hoarseness
Kawasaki disease	Other typical findings (extremity changes, conjunctivitis)

HIV, Human immunodeficiency virus; PFAPA, periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis.

Modified from Bisno AL, Gerber MA, Gwaltney JM, et al. Practice guideline for the diagnosis and management of group A streptococcal pharyngitis. Clin Infect Dis 2002;35:113–125.

Etiology

Viruses are the most common cause of acute pharyngitis in children and adolescents. Respiratory viruses (e.g., influenza virus, parainfluenza virus, rhinovirus, coronavirus, adenovirus, human metapneumovirus, respiratory syncytial virus), enteroviruses (e.g., coxsackievirus, echovirus), herpes simplex virus (HSV), and Epstein-Barr virus (EBV) are frequent causes of pharyngitis. EBV pharyngitis often is accompanied by other clinical findings of infectious mononucleosis (e.g., generalized lymphadenopathy, splenomegaly) and can be exudative and indistinguishable from GAS pharyngitis. HSV pharyngitis often is associated with stomatitis in children and tends to affect the anterior oral mucosa, including the gingiva, buccal mucosa, and tongue. Enteroviral pharyngitis can be an isolated finding (e.g., herpangina) or part of the syndrome of hand-foot-and-mouth disease, and it has a typical appearance. Systemic infections with other viruses (e.g., cytomegalovirus, rubella virus, measles virus) can include pharyngitis.

GAS is the most commonly identified bacterial cause of acute pharyngitis, accounting for 15% to 30% of pediatric pharyngitis. *Fusobacterium necrophorum,* the typical etiologic agent of Lemierre syndrome, is an increasingly reported cause of uncomplicated pharyngitis, especially in older children and young adults.[3,4] Other causes include groups C and G β-hemolytic streptococci (GCS and GGS, respectively). *Arcanobacterium haemolyticum* is a rare cause in adolescents, and *Neisseria gonorrhoeae* can cause acute pharyngitis in sexually active adolescents. Other bacteria such as *Francisella tularensis, Yersinia enterocolitica,* and *Corynebacterium diphtheriae* and mixed infections with anaerobic bacteria (e.g., Vincent angina) are rare causes.

Chlamydophila pneumoniae and *Mycoplasma pneumoniae* have been implicated rarely, particularly in adults. Although bacteria such as *Staphylococcus aureus, Haemophilus influenzae,* and *Streptococcus pneumoniae* frequently are isolated from throat cultures of children and adolescents with acute pharyngitis, their etiologic role is not established. Noninfectious cases of recurrent or prolonged pharyngitis and sore throat include the periodic fever, adenitis, pharyngitis, and aphthous ulcers (PFAPA) syndrome; gastroesophageal or laryngopharyngeal reflux; and allergic rhinitis.

Epidemiology

Most cases of acute pharyngitis occur during the colder months of the year, when respiratory viruses are prevalent. Spread among family members in the home is a prominent feature of the epidemiology of most agents, with children providing the major reservoir. GAS pharyngitis is primarily a disease of children 5 to 15 years of age, and in temperate climates, the prevalence is highest in winter and early spring. Enteroviral pharyngitis typically occurs in the summer and early fall.

Gonococcal pharyngitis occurs in sexually active adolescents and young adults. The usual mode of infection is through orogenital sexual contact. Sexual abuse must be considered strongly when *N. gonorrhoeae* is isolated from the pharynx of a prepubertal child. Widespread immunization with diphtheria toxoid has made diphtheria a rare disease in the United States, with fewer than 5 cases reported annually.

GCS and GGS express many of the same toxins as GAS, including streptolysin S and O. GCS pharyngitis can have clinical features similar to GAS and can cause elevated levels of serum antistreptolysin O (ASO) antibody.[5] GCS is a relatively common cause of acute pharyngitis among college students and adults who seek urgent care.[6,7] Outbreaks of GCS pharyngitis related to consumption of contaminated food products (e.g., unpasteurized cow milk) have been reported in families and schools.[8] Although there also are several well-documented foodborne outbreaks of GGS pharyngitis, the role of GGS in acute, endemic pharyngitis remains unclear. A community-wide outbreak of pharyngitis among children was described in which GGS was isolated from 25% of 222 consecutive children with acute pharyngitis seen in a private pediatric office. Results of DNA fingerprinting suggested that 75% of isolates belonged to the same GGS clone.[9]

The role of GCS and GGS in acute pharyngitis may be underestimated, and many laboratories do not report GCS or GGS even when the organisms are identified in throat cultures. Laboratories may use bacitracin susceptibility to identify GAS; many GCS and GGS are bacitracin resistant. Rapid antigen detection tests (RADTs) recognize the cell wall carbohydrate of GAS but are nonreactive with the carbohydrates of GCS or GGS.[10]

Clinical Manifestations

Group A *Streptococcus*

Certain clinical and epidemiologic findings suggest GAS as the cause of acute pharyngitis (Box 27.1). Patients with GAS pharyngitis commonly have sore throat (usually of sudden onset), severe pain on swallowing, and fever. They also can have headache, nausea, vomiting, and abdominal pain. Examination typically reveals tonsillopharyngeal erythema with or without exudates and tender, enlarged anterior cervical lymph nodes. Other findings can include a beefy, red, swollen uvula; petechiae on the palate; and a scarlatiniform rash. No finding is specific for GAS.

Box 27.1

Clinical and Epidemiologic Characteristics of Group A β-Hemolytic Streptococcal and Viral Pharyngitis

Features Suggesting Group A β-Hemolytic Streptococcus

- Sudden onset
- Sore throat
- Fever
- Scarlet fever rash
- Headache
- Nausea, vomiting, and abdominal pain
- Inflammation of pharynx and tonsils
- Patchy discrete tonsillar exudates
- Tender, enlarged anterior cervical nodes
- Patient 5–15 years of age
- Presentation in winter or early spring
- History of exposure

Features Suggesting Viruses

- Conjunctivitis
- Coryza
- Cough

- Hoarseness
- Myalgia
- Diarrhea
- Characteristic exanthems

Modified from Bisno AL, Gerber MA, Gwaltney JM, et al. Practice guideline for the diagnosis and management of group A streptococcal pharyngitis. Clin Infect Dis 2002;35:113–125.

Many patients with GAS pharyngitis exhibit signs and symptoms that are milder than the classic presentation of illness. Some have bona fide GAS infection (i.e., elevated titers of ASO antibodies), whereas others are merely colonized and have an intercurrent viral infection. GAS naso-pharyngitis in infants (i.e., streptococcosis) is uncommon, and it is difficult to differentiate from viral infections because GAS nasopharyngitis can cause purulent nasal discharge and excoriated nares, and infection can occur without pharyngitis.

Scarlet fever is associated with a characteristic rash that is caused by GAS that produce a pyrogenic exotoxin (i.e., erythrogenic toxin). Scarlet fever occurs in people who lack antitoxin antibodies. Although less common and clinically less severe than in the past, the incidence of scarlet fever is cyclical, depending on the prevalence of toxin-producing strains of GAS and the immune status of the population. The modes of transmission, age distribution, and other epidemiologic features are otherwise similar to those of GAS pharyngitis.

The rash of scarlet fever appears within 24 to 48 hours of the onset of signs and symptoms and can be the first sign. The rash often begins around the neck and spreads over the trunk and extremities. It is a diffuse, finely papular (sandpaper-like), erythematous eruption that produces bright red discoloration of the skin that blanches with pressure. Involvement often is more intense along the creases in the antecubital area, axillae, and groin, and petechiae can occur along the creases (i.e., Pastia lines). The face usually is spared, although the cheeks can be erythematous with pallor around the mouth (Fig. 27.1). After 3 to 4 days, the rash begins to fade and is followed by fine desquamation, first on the face and progressing downward. Occasionally, sheet-like desquamation occurs around the fingernails periungually, the palms, and the soles. Pharyngeal findings are the same as with GAS pharyngitis. The tongue usually is coated, and the papillae are swollen. With desquamation, the reddened papillae are prominent, giving the tongue a strawberry appearance.

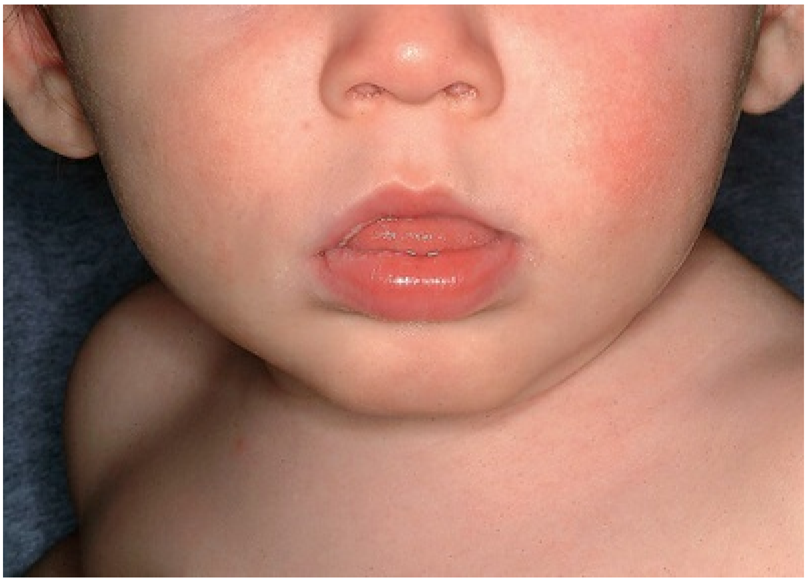


FIGURE 27.1 The child has group A streptococcal pharyngitis and scarlatiniform rash, with characteristic circumoral pallor. (Courtesy of J.H. Brien ©.)

There can be substantial overlap between the findings of scarlet fever and Kawasaki disease. Lack of response to antibiotic therapy for suspected scarlet fever should prompt consideration of Kawasaki disease.

Viruses

Clinical findings such as conjunctivitis, cough, hoarseness, coryza, anterior stomatitis, discrete ulcerative lesions, viral exanthema, myalgia, and diarrhea suggest a virus rather than GAS as the cause of acute pharyngitis (see Box 27.1).

Adenovirus pharyngitis typically is associated with fever, erythema of the pharynx, enlarged tonsils with exudate, and enlarged cervical lymph nodes. Adenoviral pharyngitis can be associated with conjunctivitis, which is referred to as *pharyngoconjunctival fever*. Adenovirus pharyngitis can persist for up to 7 days and conjunctivitis up to 14 days, after which both resolve spontaneously. Outbreaks of pharyngoconjunctival fever have been associated with transmission in swimming pools. Widespread epidemics and sporadic cases also occur.

Enteroviruses (i.e., coxsackievirus, echovirus, and enteroviruses) are associated with erythematous pharyngitis, but tonsillar exudate and cervical lymphadenopathy are unusual. Fever can be prominent. Resolution usually occurs within a few days. Herpangina is a specific syndrome caused by coxsackieviruses A or B or echoviruses. It is characterized by fever and painful, discrete, grey-white papulovesicular or ulcerative lesions on an erythematous base in the posterior oropharynx (Fig. 27.2). Hand-foot-and-mouth disease is characterized by painful vesicles and ulcers throughout the oropharynx associated with vesicles on the palms, soles, and sometimes on the trunk or extremities. Enteroviral lesions usually resolve within 7 days.

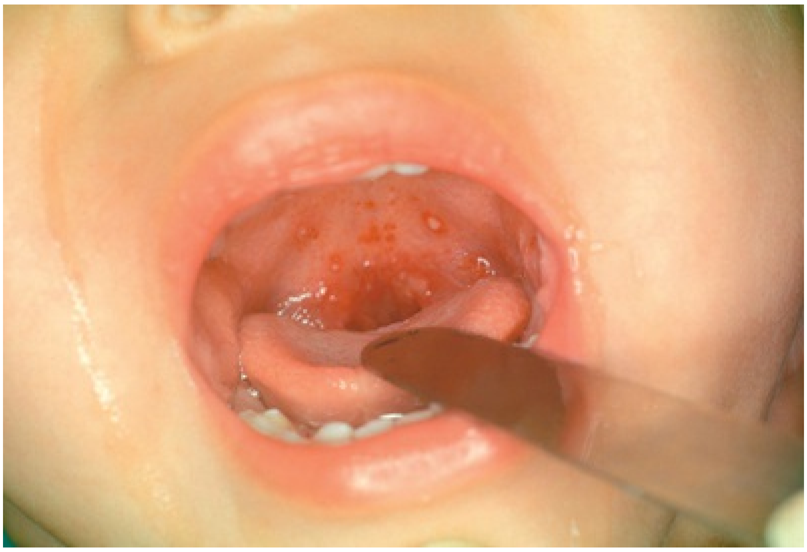
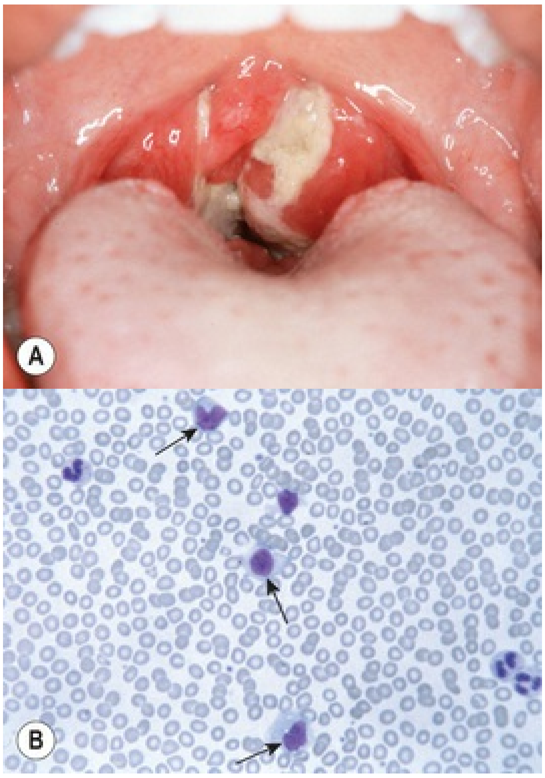


FIGURE 27.2 The child has posterior pharyngeal, grey-white, papulovesicular lesions characteristic of enteroviral herpangina. (Courtesy of J.H. Brien ©.)

Primary oral HSV infections usually occur in young children and typically produce acute gingivostomatitis associated with ulcerating vesicular lesions throughout the anterior mouth and lips, sparing the posterior pharynx. HSV gingivostomatitis can last up to 2 weeks and often is associated with high fever. Pain can be intense, and poor oral intake can lead to dehydration. In adolescents and adults, HSV also can cause mild pharyngitis that may or may not be associated with typical vesicular, ulcerating lesions.

EBV pharyngitis during infectious mononucleosis can be severe, with oral clinical findings identical to those of GAS pharyngitis (Fig. 27.3A). Generalized lymphadenopathy and hepatosplenomegaly also can occur. Posterior cervical lymphadenopathy and presternal and periorbital edema are distinctive findings. Fever and pharyngitis typically last 1 to 3 weeks, whereas the lymphadenopathy and hepatosplenomegaly resolve over 3 to 6 weeks. Laboratory findings include atypical lymphocytosis (see Fig. 27.3B), heterophile antibodies, viremia (detected by polymerase chain reaction [PCR] methods), and specific antibodies to EBV antigens. If amoxicillin has been given, an intense maculopapular rash often occurs (see Fig. 27.3C).



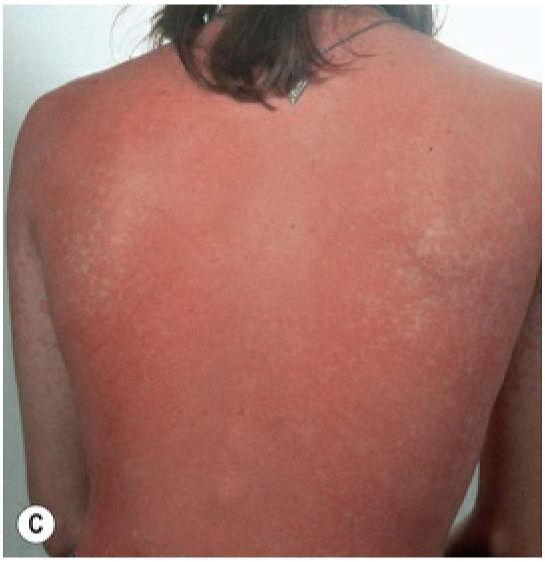


FIGURE 27.3 (A) Pharyngeal erythema and exudate due to Epstein-Barr virus (EBV) infection. (B) Peripheral blood smear shows atypical lymphocytes *(arrows)* in a patient with EBV mononucleosis. Notice the abundant cytoplasm with vacuoles and deformation of cell by surrounding cells. (C) Diffuse. erythematous. raised rash on an adolescent with EBV mononucleosis who received amoxicillin. Notice the predominance of exanthem on the trunk and coalescence of lesions.

(Courtesy of J.H. Brien ©.)

Other Bacteria

A. haemolyticum pharyngitis can resemble GAS pharyngitis, including a scarlatiniform rash. Rarely, *A. haemolyticum* can produce a membranous pharyngitis that can be confused with diphtheria.

Pharyngeal diphtheria is characterized by a greyish brown pseudomembrane that can be limited to one or both tonsils or can extend widely to involve the nares, uvula, soft palate, pharynx, larynx, and tracheobronchial tree. Involvement of the tracheobronchial tree can lead to life-threatening respiratory obstruction. Soft tissue edema and prominent cervical and submental lymphadenopathy can cause a bull-neck appearance.

F. necrophorum can be the cause of pharyngitis in 10% to 20% of adolescents and young adults.[3,11,12] *F. necrophorum* appears to cause the typical signs of bacterial pharyngitis (i.e., high fever, odynophagia, lymphadenopathy, and exudative tonsillitis) and can cause concomitant bacteremia.[13] The frequency of progression from tonsillitis to Lemierre syndrome is unknown.

Diagnosis

Distinguishing between GAS and viral pharyngitis is key to management in US practice. Scoring systems that incorporate clinical and epidemiologic features attempt to predict the probability that the illness is caused by GAS.[14,15] Clinical scoring systems are best aimed to identify individuals at such low risk of GAS infection that a throat culture or RADT usually is unnecessary. In a 2012 systematic review of 34 articles with individual symptoms and signs of pharyngitis assessed and 15 articles with data on prediction rules, no individual or combined symptoms or signs allowed formation of guidelines that could be used to diagnose GAS pharyngitis with a probability of 85% or higher.[16] Similarly, a 2015 review found a range of probability from 64% to 87%. The guidelines from the Infectious Diseases Society of America (IDSA),[17] the American Academy of Pediatrics (AAP),[18] and the American Heart Association (AHA)[19] require microbiologic confirmation with a throat culture or RADT for the diagnosis of GAS pharyngitis.

The decision to perform a microbiologic test on a child or adolescent with acute pharyngitis should be based on the clinical and epidemiologic characteristics of the illness (see Box 27.1). A history of close contact with a documented case of GAS pharyngitis or high prevalence of GAS in the community also can be helpful. More selective use of diagnostic studies for GAS can increase the proportion of positive test results and the tests' positive predictive value (i.e., percentage of patients with positive tests who are infected rather than merely colonized with GAS).

Because adults infrequently are infected with GAS and rarely develop rheumatic fever, in 2001, the Centers for Disease Control and Prevention (CDC), American Academy of Family Physicians (AAFP), and the American College of Physicians with the American Society of Internal Medicine (ACP-ASIM) recommended the use of a clinical algorithm without microbiologic confirmation as an acceptable approach to the diagnosis of GAS pharyngitis in adults only.[20] Although the goal of this algorithm-based strategy was to reduce the inappropriate use of antibiotics, a study intended to assess the impact of six different guidelines on the identification and treatment of GAS pharyngitis in children and adults[21] found that selective use of RADTs with or without throat culture and treatment based only on positive test results significantly reduced the inappropriate use of antibiotics in adults. In contrast, the empiric strategy proposed in the CDC, AAFP, and ACP-ASIM guidelines resulted in the administration of unnecessary antibiotics to an unacceptably large number of adults. Diagnosis of adults only by symptom complex therefore has been discouraged in the latest AHA scientific statement.[19] The ACP-ASIM guideline has been inactivated, and the CDC now recommends diagnostic testing for adults who have symptoms consistent with GAS pharyngitis.[22]

Throat Culture

Culture on sheep blood agar of a specimen obtained by throat swab is the standard laboratory procedure for the microbiologic confirmation of GAS pharyngitis.[23] If performed correctly, a throat culture has a sensitivity of 90% to 95%.[24] A negative result can occur if the patient has received an antibiotic before sampling.

Several variables affect the accuracy of throat culture results. One of the most important is the manner in which the specimen is obtained.[25,26] The surface of both tonsils or tonsillar fossae and the posterior pharyngeal wall should be swabbed. Other areas of the pharynx and mouth (e.g., anterior mucosa, tongue, saliva) are not acceptable sampling sites and should not be touched during the procedure.

Anaerobic incubation and the use of selective culture media can increase the sensitivity of throat cultures for GAS recovery.[27,28] However, data regarding the impact of the atmosphere of incubation and the culture media are conflicting, and in the absence of definite benefit, the increased cost and effort associated with anaerobic incubation and selective culture media are difficult to justify.[28–31]

Duration of incubation can impact the yield of throat cultures. Cultures should be incubated at 35°C to 37°C for at least 18 to 24 hours before reading. Additional overnight incubation at room temperature, however, identifies substantially more positive cultures. In a study of patients with pharyngitis and negative RADT results, 40% of positive GAS cultures were negative after 24 hours of incubation but positive after 48 hours.[32] Although initial therapeutic decisions can be guided by negative results at 24 hours, it is advisable to wait 48 hours for definitive results.

The clinical significance of the number of colonies of GAS growing on inoculated agar is controversial. Although the density of bacteria is likely to be greater for patients with bona fide acute GAS pharyngitis than for GAS carriers, there is too much overlap in the colony counts to permit differentiation on the basis of colony density.[29]

The bacitracin disk test is the most widely used direct microbiologic method for the differentiation of GAS from other β-hemolytic streptococci using growth on sheep blood agar. Presumptive identification is based on the observation that more than 95% of GAS demonstrate a zone of inhibition around a disk containing 0.04 units of bacitracin, whereas 83% to 97% of non-GAS are not inhibited by bacitracin.[29] An alternative and highly specific method for the differentiation of β-hemolytic streptococci is a commercially available, group-specific cell wall carbohydrate antigen detection test applied directly to isolated colonies. Additional expense for the minimal improvement in accuracy may not be justified.[29]

Rapid Antigen Detection Tests and Nucleic Acid Detection

RADTs developed for the identification of GAS directly from throat swabs are more expensive than blood agar cultures, but they offer speed in providing results. Rapid identification and treatment of patients with GAS pharyngitis can reduce the risk of the spread of GAS, speed clinical improvement, and allow the patient to return to school or work sooner.[24,33] In certain environments (e.g., emergency departments), the use of RADTs compared with throat cultures significantly increased the number of patients appropriately treated for GAS pharyngitis.[34,35]

Most RADTs have specificities of 95% or higher compared with blood agar cultures.[36] Therapeutic decisions can be made with confidence on the basis of a positive RADT result. However, the sensitivity of RADTs is between 70% and 90%.[36] Two large meta-analyses, which pooled 55,766 and 23,934 patients, concluded that modern RADTs had a sensitivity in children of 86%.[37,38] Although some patients with positive RADT results merely are GAS carriers, a large proportion are infected with GAS.[39]

The first RADTs used latex agglutination methodology, were relatively insensitive, and had unclear end points.[36] Subsequent tests based on enzyme immunoassay techniques had a more sharply defined end point and increased sensitivity. RADTs using optical immunoassay (OIA), bead concentration of antigens and fluorescent detection, and chemiluminescent DNA probes may be more sensitive than other RADTs, perhaps as sensitive as blood agar plate cultures,[36,40] but because most rapid detection is done by RADTs with marginal sensitivity, advisory groups still recommend a confirmatory blood agar culture for children and adolescents who are suspected on clinical grounds of having GAS pharyngitis and have a negative RADT result. Because of the higher sensitivity of RADTs for adults than children,[38] the IDSA allows for an exclusion of GAS pharyngitis based on a negative RADT result alone, although physicians may continue to use throat culture to achieve maximal sensitivity.[17]

Although nucleic acid detection has superior sensitivity compared with RADT and has sensitivity similar to culture in most circumstances,[41,42] clinical results may not be faster than culture. Although faster technologies are becoming available, with nucleic acid detection in 8 minutes in point-of-care tests,[43] the high cost of new technologies may limit their practical use in primary care settings.

Culture, RADT, and nucleic acid amplification tests cannot accurately differentiate individuals with GAS pharyngitis from carriers. However, definitive testing facilitates nontreatment of most patients (i.e., those without GAS). An estimated 12 to 15 million provider visits for sore throat occur each year in the United States. Antimicrobial therapy historically was prescribed at 60% to 73% of these visits.[2,44] Education can reduce the prescription of antibiotics for children and adolescents with pharyngitis.[45,46] One study documented an overall decrease in prescriptions for children with pharyngitis from 65% in 1998 to 56% in 2010, although the decrease in penicillin prescriptions was offset by an increase in macrolide prescriptions.[2]

Follow-Up Testing

Most asymptomatic people who have a positive throat culture or RADT result after completing a course of appropriate antimicrobial therapy for GAS pharyngitis are GAS carriers,[47] and routine follow-up testing is not indicated. Follow-up throat culture or RADT for asymptomatic individuals should be performed only for those with a history of rheumatic fever and should be considered in patients who develop acute pharyngitis during outbreaks of acute rheumatic fever or poststreptococcal acute glomerulonephritis and for individuals in closed or semiclosed communities during outbreaks of GAS pharyngitis.[47]

Other Diagnostic Considerations

Antistreptococcal antibody titers have no value in the diagnosis of acute GAS pharyngitis, but they are useful in prospective epidemiologic studies to differentiate true GAS infections from GAS carriage. Antistreptococcal antibodies are valuable for confirmation of prior GAS infection in patients suspected of having acute rheumatic fever or other nonsuppurative complications.

The need to definitively diagnose non-GAS causes of pharyngitis occurs rarely and usually only in those who are very ill or have prolonged symptoms. *A. haemolyticum* is not identified using standard culture methods intended to identify only GAS and requires the use of standard respiratory culture methods. *N. gonorrhoeae* can be identified by using selective agar growth media or nucleic acid amplification tests. EBV is routinely diagnosed using the heterophile antibody (i.e., monospot), but low sensitivity in younger children necessitates the use of specific antibody testing or serum PCR methods. Other common viruses such as HSV, adenoviruses, and enteroviruses can be identified in general viral cultures or by PCR, or both.

Pursuit of diagnosis of *F. necrophorum* pharyngitis is controversial.[3] Isolation of this anaerobe requires special laboratory techniques, or detection requires use of molecular techniques. There are no data that treatment of *F. necrophorum* pharyngitis hastens symptomatic relief or prevents Lemierre disease.

Treatment

Antimicrobial therapy is indicated for individuals with symptomatic pharyngitis when GAS is confirmed by RADT or culture.[17] When the clinical and epidemiologic findings strongly suggest GAS, antimicrobial therapy can be initiated while awaiting microbiologic confirmation, provided that therapy is discontinued if the RADT result or culture is negative.

Antimicrobial therapy for GAS pharyngitis shortens the clinical course of the illness.[33] However, GAS pharyngitis usually is self-limited, and most signs and symptoms resolve spontaneously within 3 or 4 days of onset.[48] Initiation of antimicrobial therapy can be delayed for up to 9 days after the onset of GAS pharyngitis and still prevent the occurrence of acute rheumatic fever.[49]

Antimicrobial Agents

Penicillin and its congeners (e.g., ampicillin, amoxicillin) and numerous cephalosporins, macrolides, and clindamycin are effective treatment for GAS pharyngitis. Several advisory groups have recommended penicillin as the treatment of choice.[17,18] GAS has remained exquisitely susceptible to β-lactam agents over 5 decades.[17,18,50] Amoxicillin often is used because of the acceptable taste of the suspension, although efficacy appears to equal penicillin. Orally administered clarithromycin and azithromycin also are effective (discussed later). Sulfa drugs, including trimethoprim-sulfamethoxazole, and tetracyclines are not effective and should not be used to treat GAS pharyngitis.

On the basis of a meta-analysis of 35 clinical trials completed between 1970 and 1999 in which a cephalosporin was compared with penicillin for the treatment of GAS tonsillopharyngitis, authors concluded that cephalosporins should be the treatment of choice for GAS tonsillopharyngitis.[51] However, several methodologic flaws (notably the inclusion of GAS carriers) led to controversy regarding this conclusion.[52] Indirect evidence of the superiority of cephalosporins over penicillins to prevent treatment failures and relapses continues to appear.[53–55] However, there has not been a prospective study to clarify the issue beyond doubt, and eradication of the carrier state confounds many studies. Although the use of cephalosporins for GAS pharyngitis could reduce the number of people (especially chronic carriers) who harbor GAS after completing therapy, empiric first-line use would be associated with substantial economic cost and risk for increased antimicrobial resistance without substantial benefit. There are compelling reasons (e.g., narrow antimicrobial spectrum, low cost, impressive safety profile) to continue to use penicillin as the drug of choice for uncomplicated GAS pharyngitis.

Dosing Intervals and Duration of Therapy

Oral penicillin must be administered many times each day for 10 days to achieve maximal rates of GAS eradication. Attempts to treat GAS pharyngitis with a single daily dose of penicillin have been unsuccessful.[56] Reduced frequency of dosing and shorter treatment courses (<10 days) may result in better patient adherence to therapy. Several antimicrobial agents, including clarithromycin, cefuroxime, cefixime, ceftibuten, cefdinir, and cefpodoxime, are effective in GAS eradication when administered for 5 days or less,[57–62] and effective eradication with once-daily dosing has been described for amoxicillin, azithromycin, cefadroxil, cefixime, ceftibuten, cefpodoxime, cefprozil, and cefdinir.[18,58,61,63–66]

However, the end points of these studies typically are eradication of GAS, not symptomatic improvement or prevention of rheumatic fever, which are the two main clinical reasons for treatment. Many agents have a broader spectrum of activity and, even when administered for short courses, can be more expensive than standard therapy.[58] Additional studies are needed before these short-course or once-daily dosing regimens can be recommended routinely over penicillin.

Table 27.2 gives recommendations for several regimens with proven efficacy for GAS pharyngitis.[14,18] Intramuscular benzathine penicillin G is preferred in patients unlikely to complete a full 10-day course of oral therapy.

TABLE 27.2

Antimicrobial Therapy for Group A β-Hemolytic Streptococcal Pharyngitis

Antimicrobial Agent	Dosage	Duration
ORAL ADMINISTRATION		
Penicillin	Children: 250 mg bid or tid	10 days
	Adolescents and adults: 250 mg tid or qid	10 day
	Adolescents and adults: 500 mg bid	10 days
Erythromycin[a]	Varies with formulation	10 days
First-generation cephalosporins[a,b]	Varies with agent	10 days
INTRAMUSCULAR ADMINISTRATION		
Benzathine penicillin G	600,000 U (for patients ≤27 kg)	1 dose
	1.2 million U (for patients >27 kg)	1 dose
Mixtures of benzathine and procaine penicillin G	Varies with formulation[c]	—

[a] For patients allergic to penicillin.

[b] These agents should not be used to treat patients with immediate-type hypersensitivity to β-lactam antibiotics.

[c] Dose should be determined on basis of benzathine component.

bid, Twice daily; *qid*, four times daily; *tid*, three times daily.

Macrolide and Lincosamide Resistance

Although GAS resistance to penicillin has not occurred anywhere in the world,[67] there are geographic areas with relatively high levels of resistance to macrolide antibiotics.[68,69] The average macrolide resistance in a US multicenter study in 2002 was 6.1% (range, 3%–8.7%).[70] A prospective, multicenter, US community–based surveillance study of pharyngeal GAS isolates recovered from children 3 to 18 years of age during three successive respiratory seasons between 2000 and 2003 found macrolide resistance of less than 5% and clindamycin resistance of 1% and found no evidence of increasing erythromycin minimum inhibitory concentrations over the 3-year study period.[71] There was, however, considerable geographic variation in macrolide resistance rates in each study year and year-to-year variation at individual study sites.

Higher resistance rates have been reported occasionally. For example, 9% of pharyngeal and 32% of invasive GAS strains collected in a San Francisco study during 1994 to 1995 were macrolide resistant.[72] During a longitudinal investigation of GAS disease in a single elementary school in Pittsburgh, investigators found that 48% of isolates of GAS collected between 2000 and 2001 were resistant to erythromycin; none was resistant to clindamycin.[73] Molecular typing indicated that this outbreak was caused by a single strain of GAS. Clinicians should be aware of local rates of resistance and the risk of changes in a short period.

Other Treatment Considerations

There is no evidence from controlled studies to guide therapy of acute pharyngitis when β-hemolytic group C or group G streptococci are isolated. If a physician elects to treat, the regimen should be similar to that for GAS pharyngitis, with penicillin as the antimicrobial agent of choice.[10]

Acyclovir treatment of HSV gingivostomatitis initiated within 72 hours of the onset of symptoms shortens the duration of illness.[74] Although use of antiviral medications for primary EBV pharyngitis can interrupt viral replication temporarily, symptomatic relief is negligible and does not justify the use of acyclovir.

Corticosteroids are recommended for EBV pharyngitis only when tonsillar enlargement threatens airway patency or for other systemic disease such as myocarditis or massive splenomegaly.[18] Several reviews (including a 2012 Cochrane review) of heterogeneous studies of the use of corticosteroids for GAS and non-GAS pharyngitis found a small but measurable benefit in pain reduction, especially when initiated early in the course of severe illness.[75–79] However, an increase in deep neck infections has been temporally associated with increased use of anti-inflammatory medications, including corticosteroids, for pharyngitis.[80] The modest and short-lived benefit of treatment must be weighed against the potential for harm. Use of corticosteroids for pharyngitis is not recommended by the AAP or IDSA.[17]

Treatment Failures, Chronic Carriage, and Recurrences

Antimicrobial treatment failure of GAS pharyngitis can be classified as clinical or bacteriologic failure. The significance of *clinical treatment failure* (i.e., persistent or recurrent signs or symptoms suggesting GAS pharyngitis) is difficult to determine without repeated isolation of the infecting strain of GAS (i.e., true bacteriologic treatment failure).

Bacteriologic treatment failures can be further classified as true or apparent. *True bacteriologic failure* refers to the inability to eradicate the specific strain of GAS causing an acute episode of pharyngitis with a complete course of appropriate antimicrobial therapy. In the absence of penicillin resistance, the following factors have been suggested but not established definitively as causes: penicillin tolerance (i.e., discordance between the concentration of penicillin required to inhibit and to kill the organisms)[81,82]; enhancement of colonization and growth of GAS by pharyngeal flora or inactivation of penicillin by production of β-lactamases[67]; and resistance of intracellular organisms to antimicrobial killing.[83]

Apparent bacteriologic failure can occur when newly acquired GAS isolates are mistaken for the original infecting strain, when the infecting strain of GAS is eradicated but then is rapidly reacquired, or when adherence to antimicrobial therapy is poor. However, most bacteriologic treatment failures are manifestations of the GAS carrier state. *Chronic carriers* have no clinical illness or immunologic response to the organism, can be colonized for 6 to 12 months or longer, are unlikely to spread GAS to close contacts, and are at very low or no risk for developing suppurative or nonsuppurative complications.[84,85]

During the winter and spring in temperate climates, as many as 20% of asymptomatic school-aged children carry GAS.[84] GAS carriers should not be sought or given antimicrobial therapy; the primary approach to the suspected or confirmed carrier is reassurance. A throat culture or RADT should be performed if the patient has symptoms and signs suggesting GAS pharyngitis but should be avoided when symptoms are more typical of viral illnesses (see Box 27.1). Each clinical episode confirmed with a positive culture or RADT should be treated. Identification and eradication of the streptococcal carrier state are desirable in rare specific situations. When antimicrobial therapy is employed, oral clindamycin (30 mg/kg/day up to 900 mg, divided into 3 doses) for 10 days is preferred, but intramuscular benzathine penicillin (alone or in combination with procaine penicillin) plus oral rifampin (20 mg/kg/day divided into 2 doses; maximum dose of 300 mg for 4 days beginning on the day of the penicillin injection[86]) also is effective. Chronic carriage can recur on re-exposure to GAS.

In a patient with symptoms suggesting GAS after treatment, a throat culture or RADT usually is performed. If the result is positive, many clinicians elect to administer a second course of penicillin therapy.

The patient with repeated episodes of acute pharyngitis associated with a positive throat culture or RADT result is a common and difficult problem for the practicing physician. The fundamental question is whether the patient is experiencing repeated episodes of GAS pharyngitis or is a GAS carrier experiencing repeated episodes of viral pharyngitis. The latter situation is by far the more common.

The patient is likely to be a GAS carrier if: (1) clinical and epidemiologic findings suggest a viral cause, (2) there is little clinical response to appropriate antimicrobial therapy, (3) the throat culture or RADT result is positive between episodes of pharyngitis, and (4) there is no serologic response to GAS extracellular antigen (e.g., ASO, anti-deoxyribonuclease B). In contrast, the patient with repeated episodes of acute pharyngitis associated with positive throat cultures or RADT results is likely to be experiencing repeated episodes of GAS pharyngitis if (1) clinical and epidemiologic findings suggest GAS pharyngitis, (2) there is a demonstrable clinical response to appropriate antimicrobial therapy, (3) the throat culture or RADT result is negative between episodes of pharyngitis, and (4) there is a serologic response to GAS extracellular antigens.

If it is determined that the patient is experiencing repeated episodes of true GAS pharyngitis, some physicians have suggested use of oral penicillin V prophylactically. However, the efficacy of this regimen has not been proved, and antimicrobial prophylaxis is not recommended except to prevent recurrences of rheumatic fever in patients who have experienced a previous episode of rheumatic fever. Tonsillectomy may be considered in the rare patient whose symptomatic episodes do not diminish in frequency over time and in whom no alternative explanation for the recurrent GAS pharyngitis is evident. However, tonsillectomy has been beneficial for a relatively small group of these patients, and any benefit is relatively short lived.[87,88] A 2014 Cochrane review found that children who had tonsillectomy had 3 episodes of sore throat in the first year after surgery compared with 3.6 episodes per year for those who did not have tonsillectomy and that children with more severe or more frequent episodes received the largest benefit.[89]

Complications

GAS pharyngitis can be associated with suppurative and nonsuppurative complications (see Chapter 118). Suppurative complications result from the spread of GAS to adjacent structures and include peritonsillar abscess, parapharyngeal and retropharyngeal abscess, cervical lymphadenitis, sinusitis, otitis media, and mastoiditis. Before antimicrobial agents were available, suppurative complications of GAS pharyngitis were common, but antimicrobial therapy has greatly reduced the frequency of these complications.

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28

Infections of the Upper and Middle Airways

Marc Tebruegge, Nigel Curtis

Supraglottic infections comprise peritonsillar abscess, retropharyngeal abscess, parapharyngeal abscess, and epiglottitis. Infections of the middle airways include croup (i.e., laryngotracheitis) and bacterial tracheitis. All of these conditions share the potential for respiratory compromise and airway obstruction. Table 28.1 summarizes the typically affected age groups, common clinical features at presentation, and the most commonly implicated organisms. Differentiation from other airway infections is discussed in Chapter 21 (see Table 21.4).

TABLE 28.1

Clinical Features and Causative Organisms of Infections of the Upper and Middle Airways

Disease	Typical Age Group	Potential Initial Infection	Key Clinical Findings	Typical Organisms
Peritonsillar abscess	Adolescents	Pharyngotonsillitis	Sore throat, odynophagia, dysphagia, peritonsillar swelling, uvular deviation to	*Streptococcus pyogenes*

			contralateral side, muffled voice	
Retropharyngeal abscess	<5 yr	Pharyngitis, tonsillitis, adenitis	Sore throat, odynophagia, dysphagia, neck pain and swelling, limited neck mobility, torticollis	*Streptococcus pyogenes,* viridans streptococci, *Staphylococcus aureus, Haemophilus* and *Neisseria* spp., anaerobic bacteria; often polymicrobial
Parapharyngeal abscess	All age groups	Pharyngitis, tonsillitis, adenitis, otitis media	Sore throat, odynophagia, dysphagia, neck pain and swelling, torticollis, deviation of the lateral wall of the oropharynx to the midline	Same as for retropharyngeal abscess
Lemierre syndrome (primary oropharyngeal infection; septicemia; thrombophlebitis of the internal jugular vein; metastatic infection at distant sites)	Adolescents	Pharyngitis, tonsillitis, adenitis, otitis media, mastoiditis	High-grade fever, neck pain and swelling, dysphagia, nausea and vomiting, hypotension; pulmonary involvement: dyspnea, hemoptysis, pleuritic chest pain	*Fusobacterium necrophorum*
Epiglottitis	In Hib-unimmunized populations: children <4 yr; in Hib-immunized populations: school-age children	—	Unwell looking, high-grade fever, stridor, drooling, muffled voice, tripod position with neck extension	*Haemophilus influenzae* type b
Croup (laryngotracheitis)	6 mo to 2 yr	—	Inspiratory stridor, barking cough, hoarseness; symptoms typically worsen during nighttime	Parainfluenza virus, influenza virus, respiratory syncytial virus
Bacterial tracheitis	2 to 10 yr	—	Moderate- to high-grade fever, cough, stridor, dyspnea, retractions; rapid	*Staphylococcus aureus*

			deterioration is common	

Peritonsillar Abscess

Peritonsillar abscess (i.e., quinsy) is the most common deep oropharyngeal infection.[1] Although rare, it usually is a complication of pharyngotonsillitis. The infection primarily affects adolescents and young adults, but it can occur at any age.

Etiologic Agents.

Streptococcus pyogenes is the most commonly isolated aerobic bacterium in cases with peritonsillar abscess.[2–9] Other streptococci, *Staphylococcus aureus*, and *Haemophilus influenzae* are less frequently implicated. Anaerobic bacteria, including *Prevotella*, *Bacteroides*, and *Peptostreptococcus* species, also are common isolates.[10] Polymicrobial infection occurs in some cases.[10]

Epidemiology and Pathogenesis.

The peak incidence of peritonsillar abscess is in adolescence and early adult life.[1,3,7,11–14] However, although uncommon, peritonsillar abscess can occur in very young children, including infants.[15–17] There is no clear sex predilection.

Peritonsillar abscess traditionally has been thought to result from extension of acute exudative pharyngotonsillitis. However, there is some evidence to suggest that this condition also can result from abscess formation within Weber salivary glands located in the supratonsillar fossa.[18]

Clinical Manifestations and Diagnosis.

At presentation, the patient usually has a severe sore throat and odynophagia.[7,11,13] Difficulty with swallowing often leads to decreased oral intake, which can result in dehydration.[13] Symptoms may worsen, and the patient may become unable to swallow saliva, causing drooling. Fever is reported in most cases, but it is not universal.[13] Common clinical signs at initial presentation include peritonsillar swelling, muffling of the voice, cervical lymphadenopathy, trismus, and uvular deviation toward the contralateral tonsil.[11,13] Bilateral disease is very rare.[12,19]

Inflammatory markers, including the white blood cell (WBC) count and C-reactive protein (CRP) level, are frequently elevated.[11,13] When there is doubt about the diagnosis, transcutaneous or intraoral ultrasound or computed tomography (CT) can be useful for confirmation.[20–23]

Management.

Peritonsillar abscess requires drainage, which can be achieved by needle aspiration, incision and drainage, or tonsillectomy (for quinsy).[13,14] Pus obtained during the procedure should be sent for Gram stain and routine and anaerobic culture. Intervention practices vary widely,[24] and there are no convincing data to suggest that one approach is superior to another.[25–28] Data from a nationwide study of more than 20,000 children with peritonsillar abscess admitted to US hospitals show that approximately half were managed conservatively, whereas incision and drainage was performed in more than one third of cases; fewer than 20% underwent tonsillectomy.[29]

Antibiotic therapy is empiric and should provide sufficient coverage for anaerobic and β-lactamase–producing bacteria. Suggested regimens include penicillin combined with metronidazole, amoxicillin-clavulanate, ampicillin-sulbactam, cefoxitin, and clindamycin.[7,30–34]

The role of adjuvant corticosteroid treatment remains controversial.[11,25,35,36] Data from one randomized, controlled trial (RCT) suggest that corticosteroids may expedite symptomatic improvement in adults.[37] The choice about whether to treat a patient with peritonsillar abscess on an outpatient or inpatient basis should take into account the patient's age, coexisting morbidities, and the need for intravenous hydration, pain control, and airway monitoring.[13]

Complications and Prognosis.

A small proportion of patients require intensive care support, usually for management of airway compromise.[11] The course of the illness can be complicated by contiguous extension of infection to the retropharyngeal or parapharyngeal space.[11,12] Other potential complications include aspiration pneumonia and mediastinitis.

The prognosis for appropriately managed peritonsillar abscess is good. A fatal outcome is rare. Relapse or recurrence occurs in approximately 5% to 10% of cases.[11–13,19]

Retropharyngeal Abscess

The retropharyngeal space extends from the base of the skull to the upper thoracic spine. The anterior border of this space is formed by the constrictor muscles of the pharynx, the lateral borders by the carotid sheaths, and the posterior border by the prevertebral fascia.

Etiologic Agents.

Polymicrobial infection is common; mixed aerobic and anaerobic infection occurs frequently.[38–43] Commonly implicated aerobic bacteria include *S. pyogenes*, viridans streptococci, *S. aureus,* and *Haemophilus* and *Neisseria* species.[a] Methicillin-resistant *S. aureus* (MRSA) as a cause varies geographically.[41,42] A series from Texas highlighted MRSA as a more frequent cause than methicillin-susceptible *S. aureus* (MSSA).[49] Common anaerobic isolates include *Peptostreptococcus*, *Prevotella*, *Bacteroides,* and *Fusobacterium* species.

Epidemiology and Pathogenesis.

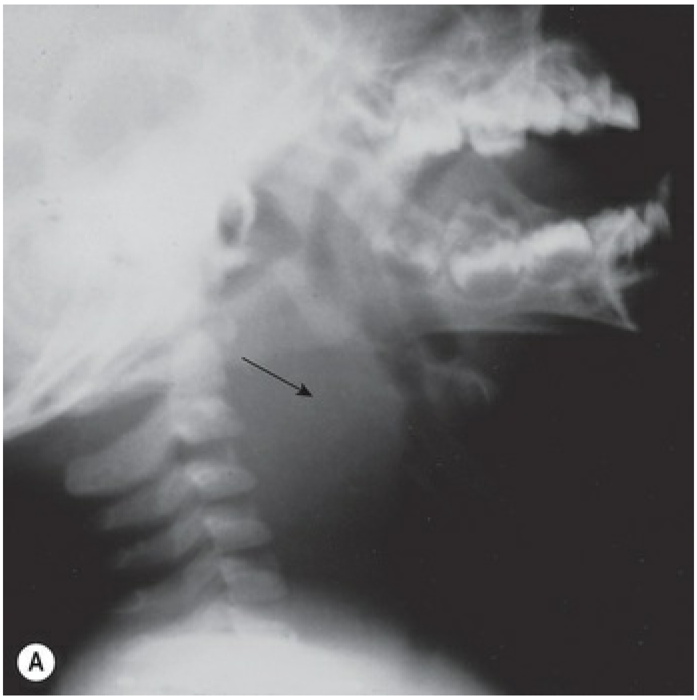
Retropharyngeal abscess can occur at any age, but most commonly affects children younger than 5 years of age.[7,38,45,49–52] In most reports, there is some male predominance.[b] The US incidence peaks during the winter and spring months, and the same has been reported in Europe.[45,46,48,53] Some data suggest that the US incidence of retropharyngeal abscess has increased over the past decade.[38,41,43,49] Similar observations have been reported from the UK.[55]

Retropharyngeal abscess in children predominately results from infection and suppuration of the retropharyngeal chains of lymph nodes, which drain the nasopharynx, the paranasal sinuses, and the adenoids.[38,40–43,46] Common primary infections include pharyngitis, tonsillitis, adenitis, and less frequently, sinusitis, otitis media, mastoiditis, and dental infections. Unlike in adults, local trauma and foreign body ingestion play a relatively minor role in children.[c]

Clinical Manifestations and Differential Diagnosis.

Common presenting features include pyrexia, sore throat, dysphagia, odynophagia, neck pain, neck swelling, limited neck mobility (particularly on extension), and torticollis.[d] Trismus is uncommon, but drooling can occur. Most patients have evidence of pharyngitis or tonsillitis and cervical lymphadenitis on examination.[44,52] In most reports, the proportion of patients with symptoms that indicate airway obstruction, such as difficulty in breathing and stridor, is relatively small.[41,43–46,50,52] Airway obstruction in the context of retropharyngeal abscess predominately occurs in infants and very young children.[41–43]

Peripheral blood leukocytosis is common.[e] The CRP level and erythrocyte sedimentation rate (ESR) usually are elevated.[49,52] In most cases, enlargement of the retropharyngeal space/prevertebral tissue can be seen on plain lateral neck radiographs (Fig. 28.1).[38,43,44,56] However, CT is more sensitive and is the imaging modality of choice.[43,45,50,56–62]



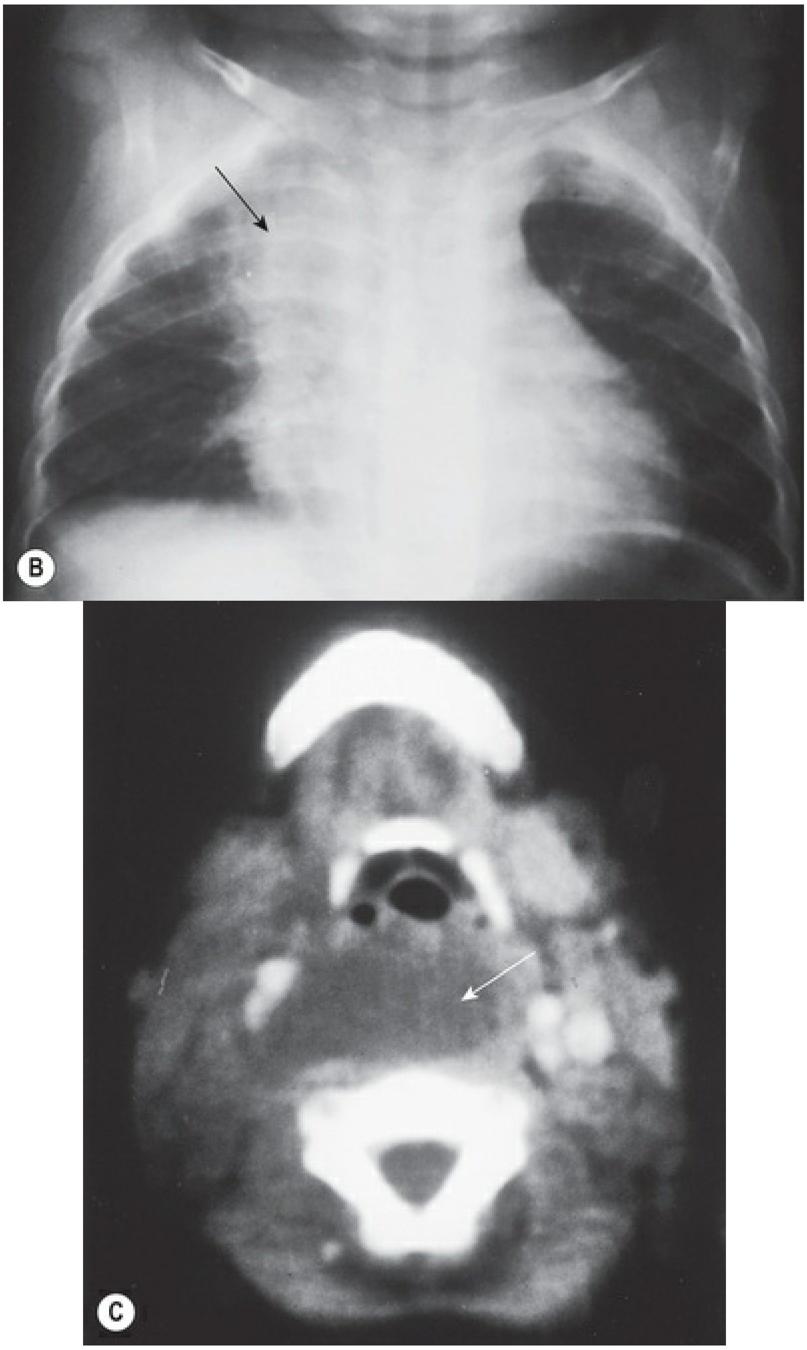


FIGURE 28.1 (A) Lateral neck radiograph of an 18-month-old toddler shows a retropharyngeal abscess due to *Staphylococcus aureus* infection. Notice the marked retropharyngeal soft tissue density *(arrow)* with anterior displacement of the hypopharynx and the laryngotracheal airway and the normal appearance of the epiglottis, glottis, and subglottic airway. (B) The chest radiograph shows an extension of the infection into the mediastinum *(arrow)*. (C) Computed tomography scan without contrast of the upper cervical region shows an abscess in the retropharyngeal space *(arrow)* with anterior displacement and compression of the airway and lateral displacement of the great

vessels. Bony structures are the mandible *(top)*, hyoid bone, and the cervical vertebrae. (Courtesy of Richard H. Schwartz, MD, Vienna, VA.)

Management.

There is no consensus about the optimal empiric antibiotic treatment. Penicillin or ampicillin alone is insufficient because β-lactamase–producing organisms, *S. aureus,* and mixed infections are common. Appropriate empiric antibiotic regimens include a second- or third-generation cephalosporin plus clindamycin or metronidazole, amoxicillin-clavulanate, ampicillin-sulbactam, and piperacillin-tazobactam.[f] Some physicians think that clindamycin alone may be sufficient.[40,54] Local patterns of susceptibility of *S. aureus* and the clinical state of the patient should be taken into account, frequently leading to a combination of antibiotics that includes clindamycin or vancomycin.[49]

The role of surgical drainage remains controversial.[g] Patients with significant respiratory distress require urgent airway management and surgical drainage. However, there is debate about whether a trial of conservative management with intravenous antibiotics for a 24- to 48-hour period in conjunction with close monitoring is appropriate for patients who are stable and have no respiratory distress.[38,44–46,50] The reported success rates with conservative management alone vary considerably between studies, and there have been no randomized trials.[h] Surgical drainage usually is performed using the transoral approach and less commonly using the transcervical route.[i]

Complications and Prognosis.

Potential complications include airway obstruction, internal jugular vein thrombosis, mycotic aneurysm of the carotid artery, aspiration pneumonia, mediastinitis, and sepsis, although these are rare overall.[j] Few patients require repeated surgical intervention.[43,45,49] Most patients have an uncomplicated course and can be discharged on oral antibiotics within a few days.[41,42] Fatal outcomes have been rare in recent studies.

Parapharyngeal Abscess

The lateral pharyngeal space (i.e., parapharyngeal space) is shaped like an inverted cone extending from the base of the skull to the hyoid bone. It is bound medially by the superior pharyngeal constrictor muscle and laterally by the internal pterygoid muscle.[69] The lateral pharyngeal space contains the internal carotid artery, the internal jugular vein, cranial nerves IX to XII, the sympathetic chain, and the lymph nodes. This space is separated from the retropharyngeal space by only the alar fascia, which provides little barrier against the spread of infection.[69] Simultaneous infection of both compartments is common, and some investigators think that a distinction between parapharyngeal and retropharyngeal abscess is not meaningful clinically.[46,65,69–71]

Etiologic Agents, Epidemiology, and Pathogenesis.

The spectrum and frequency of causative organisms are similar to those reported for retropharyngeal abscess.[30,72] Studies of deep neck space infections in children suggest that parapharyngeal abscesses are less common than retropharyngeal abscesses.[7,31,45,52] Unlike retropharyngeal abscess, parapharyngeal abscess occurs in all age groups without a predilection for younger children.[51,73] Parapharyngeal abscess is thought to result primarily from infection and subsequent suppuration of lymph nodes in the lateral pharyngeal space, which are part of the lymphatic drainage of the nasopharynx and middle ear.[73–76] In many cases, there is a history of preceding pharyngitis or tonsillitis.

Clinical Manifestations and Differential Diagnosis.

The clinical features of parapharyngeal abscess closely resemble those associated with retropharyngeal abscess.[69] Fever and neck swelling are common; patients also can have dysphagia, odynophagia, torticollis, or trismus.[k] A common feature distinguishing parapharyngeal abscess from retropharyngeal abscess is deviation of the lateral wall of the oropharynx to the midline on oral inspection.[73,77–79]

Peripheral blood leukocytosis and an elevated CRP level are common.[66,74] Contrast-enhanced CT is the imaging modality of choice for investigating suspected cases.[l] Plain lateral neck radiographs are not useful.[45]

Management, Complications, and Prognosis.

Management of parapharyngeal abscess is similar to that for retropharyngeal abscess. There is ongoing controversy among experts about whether surgery is mandatory in all patients.[m] Traditionally, an external cervical approach has been used for the drainage of parapharyngeal abscesses,[7,60,81] but transoral drainage has been reported to be safe and effective in selected cases with abscess location medial to the great vessels.[69,71,76,77,81] The transoral approach has cosmetic advantages, and the intraoperative time usually is shorter.[81]

Potential complications comprise internal jugular vein thrombosis, erosion of the carotid artery, airway obstruction, aspiration pneumonia, pleural empyema, mediastinitis, pericarditis, and septic shock.[n] Fatal outcomes and long-term sequelae are rare.[31,70,73]

Lemierre Syndrome

The first description of Lemierre syndrome was published in 1900 by Courmont and Cade,[84] followed by a report by Schottmüller in 1918.[85] The clinical syndrome, also referred to as *necrobacillosis*, is named in honor of André Lemierre, who described a series of 20 cases of “postanginal septicemia” in 1920.[86] Lemierre syndrome is characterized by primary infection of the oropharynx, blood culture–confirmed septicemia, evidence of thrombophlebitis of the internal jugular vein, and metastatic infection at one or more distant sites.[87]

Etiologic Agents.

Fusobacterium necrophorum is by far the most commonly implicated etiologic agent in cases of Lemierre syndrome.[87–90] *F. necrophorum* is an obligate anaerobic, gram-negative bacillus that is part of the normal flora of the oral cavity and the gastrointestinal and female genital tract. Most strains are susceptible to second- and third-generation cephalosporins, clindamycin, and metronidazole; a significant proportion of clinical isolates produce β-lactamase.[91–93]

Other causative bacteria associated with Lemierre syndrome include other *Fusobacterium* species, *Bacteroides* species, *Prevotella* species, streptococci (mainly non–group A), and infrequently staphylococci.[87,88,90,94–96] Mixed infections also occur.[89,95]

Epidemiology and Pathogenesis.

Despite the absence of solid epidemiologic data, most experts agree that the incidence of the disease declined considerably during the antibiotic era. Lemierre syndrome currently is uncommon, with an estimated annual incidence of approximately 1 case per 1 million people.[97] However, some data suggest that the incidence has increased in recent years.[98] The disease typically affects teenagers and young adults,[o] although a few cases in infancy have been described.[91,100] There appears to be male predominance.[87,101] Most cases have no predisposing illness.

In most cases, the disease process begins with a primary focus of infection in the oropharynx (e.g., palatine tonsils, peritonsillar tissue). Other infections in the head and neck area, including sinusitis, otitis, mastoiditis, parotitis, and odontogenic infections, are less common sources.[p] The infection subsequently spreads to the lateral pharyngeal space or parapharyngeal space. Further progression results in infectious thrombophlebitis of the internal jugular vein, which causes septic pulmonary emboli and metastatic infection at other distant sites. The lungs are the most commonly involved secondary site, followed by joint and soft tissue infections,[87,88,95,101] Other manifestations, such as skin infection, osteomyelitis, liver abscess, splenic abscess, and meningitis, are rare.[87,91,101,104–107]

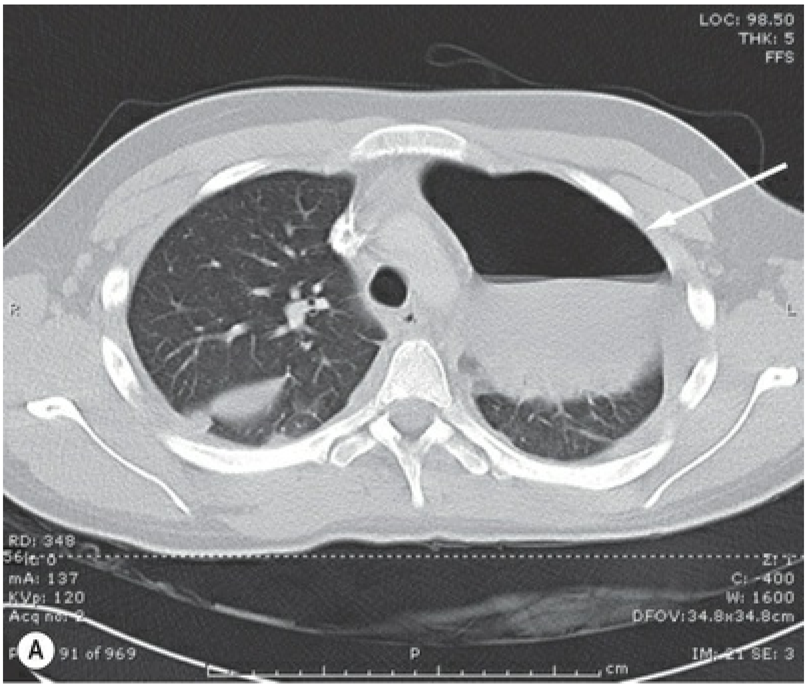
Clinical Manifestations and Differential Diagnosis.

The presenting features of Lemierre syndrome depend partly on the primary site of infection. Most cases are diagnosed within 7 days of onset of the primary infection.[87] In patients with an oropharyngeal source, inspection may reveal exudative tonsillitis, hyperemia, or grayish pseudomembranes. An unremarkable oropharyngeal appearance at the time of septicemia does not rule out Lemierre syndrome.[87,108] Patients with otitis media or mastoiditis as the primary focus can have otorrhea or postauricular fluctuation.[91,109] Most patients have high-grade pyrexia (>39.5°C) at presentation, although fever can be absent. Neck swelling and tenderness is seen in most cases.

Other symptoms and signs include trismus, dysphagia, dyspnea, hemoptysis, pleuritic chest pain, nausea and vomiting, jaundice, hepatomegaly, and hypotension. Severe shock and renal failure are uncommon despite the septicemic state.[87,94] Auscultation and percussion of the chest may reveal crepitations and evidence of pleural effusions in cases with pulmonary involvement.

The WBC count, CRP, and ESR often are markedly elevated.[q] Thrombocytopenia occurs in approximately a quarter of patients.[110] Levels of liver enzymes and bilirubin are sometimes not elevated.[87,95] Blood cultures typically are positive, but they may be sterile in patients who have taken antibiotics before samples were collected for culture.

Contrast-enhanced CT of the neck is the most useful investigation. Possible CT findings include distended neck veins, intraluminal filling defects, and soft tissue swelling.[95,100,111,113,114] Doppler ultrasonography and magnetic resonance imaging are also useful in this setting. The chest radiograph and chest CT may reveal pulmonary infiltrates, pulmonary cavitation, or pleural effusions (Fig. 28.2).



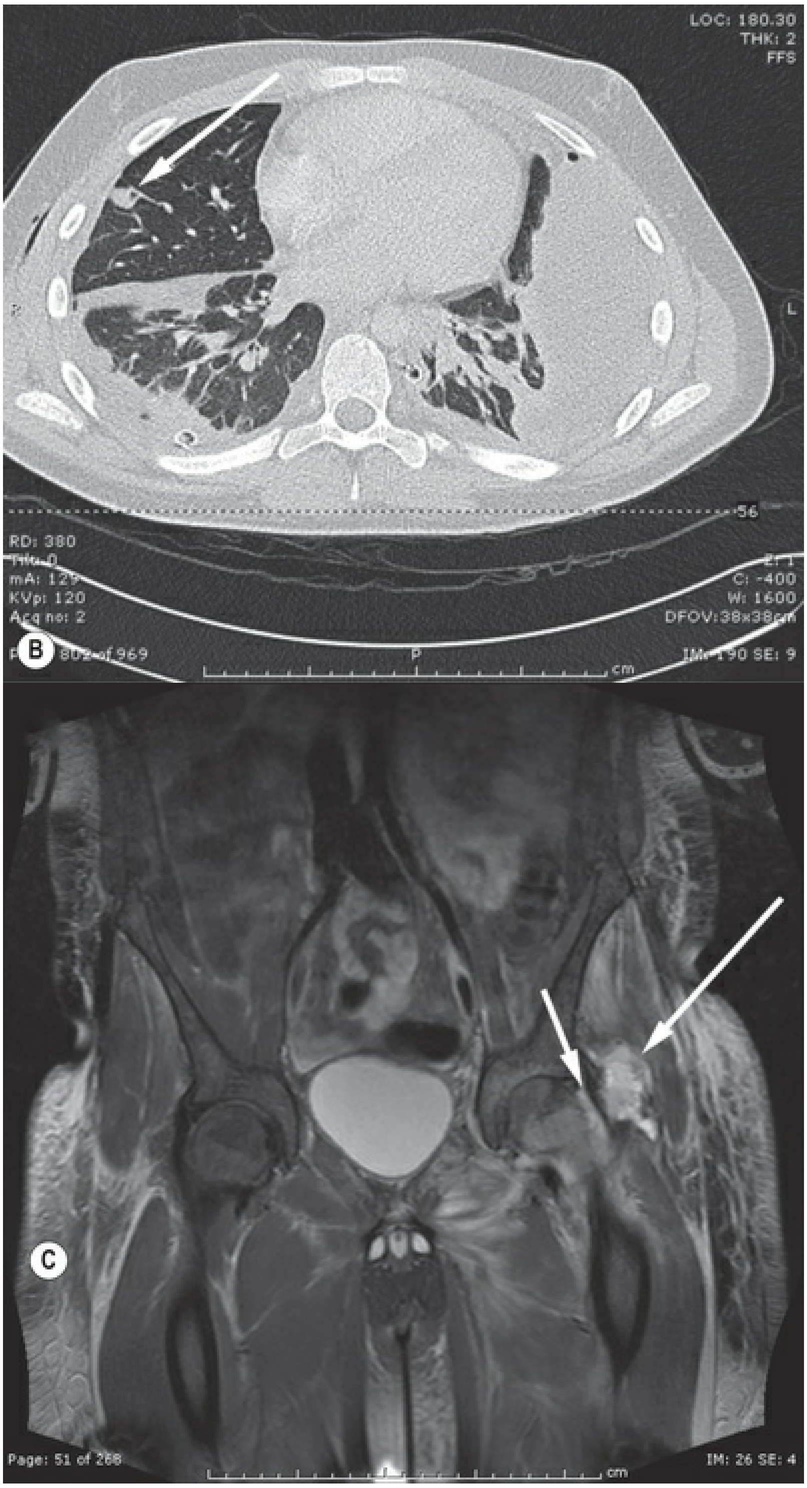


FIGURE 28.2 (A) Chest computed tomography scan of a 16-year-old patient with Lemierre syndrome with marked pulmonary involvement shows a large, left-sided pneumothorax *(arrow)* and adjacent empyema. (B) Chest computed tomography scan of the same patient shows widespread bilateral pulmonary consolidation and nodular foci. The central cavitation in the lesion is marked by an *arrow*. (C) Coronal magnetic resonance image shows the hip region in the same patient, who also developed septic arthritis of the

left hip joint and abscess formation in the adjacent muscles. Notice the synovial enhancement *(small arrow)* and the fluid collection *(large arrow)*, which extended anteriorly between the iliopsoas, the rectus femoris medially, and the gluteus muscles laterally.

Management.

Antibiotic treatment is the mainstay of therapy. Common empiric regimens include high-dose penicillin with metronidazole, clindamycin, ticarcillin-clavulanate, and ampicillin-sulbactam.[r] Due to the endovascular nature of the infection, intravenous therapy is required for several weeks.

Surgical debridement of necrotic tissues and drainage of abscess or empyema often are required in conjunction with medical therapy. Ligation or resection of the internal jugular vein was a common therapeutic intervention in the preantibiotic era. However, this is rarely necessary and should be restricted to unstable patients who fail to respond to conservative therapy.[98,110,111,116] The role of routine anticoagulation therapy in Lemierre syndrome continues to be controversial.[s]

Complications and Prognosis.

Metastatic infections can cause complications depending on their location. Pleural effusions, empyema, lung abscesses, and pulmonary cavitation can occur in patients with Lemierre syndrome. Pneumatocele and pneumothorax can occur. Septic pyogenic arthritis typically affects larger joints, such as the shoulder, elbow, and hip joints (see Fig. 28.2).[87,101] Renal involvement can be associated with proteinuria or hematuria.

In the preantibiotic era, the prognosis was poor, with fatality rates as high as 90% in some historical reports.[86,102] Recent reviews of the literature suggest that fatal outcomes are uncommon, typically between 5% and 10%.[87,88]

Acute Epiglottitis

The incidence of invasive *Haemophilus influenzae* type b (Hib) disease decreased dramatically, and epiglottitis (i.e., supraglottitis) has become a rare disease in countries where Hib vaccines are used routinely.[118–129] Data from England and Wales show that the incidence of invasive Hib disease after 2 decades of routine immunization fell to 0.02 cases per 100,000 inhabitants.[130] Necrotizing epiglottitis is a rare variant, which has been reported predominately among immunocompromised patients.[131]

Etiologic Agents.

Hib infection accounted for approximately 75% to 90% of epiglottitis cases in the pre-Hib vaccination era.[119,126,132] Currently, only rare cases due to vaccination failure are reported.[t] Other organisms implicated in epiglottitis are *S. pyogenes*, *S. pneumoniae*, *S. aureus*, nontypeable *H. influenzae*, *H. parainfluenzae*, *Pseudomonas* species, *Klebsiella* species, and *Moraxella catarrhalis*.[119,126,132,137–140]

Epidemiology and Pathogenesis.

In the pre-Hib vaccination era, the incidence of epiglottitis peaked in early childhood, typically affecting children younger than 4 years of age.[132,137,141] After institution of universal Hib vaccination, the peak incidence shifted toward an older age group, with a simultaneous increase in the proportion of adult cases.[u] Many studies show no sex predominance, while others report some male predominance.[122,132,143–145] There is little seasonal variation in incidence in temperate climates.[129,143–146]

Acute epiglottitis is a localized, invasive bacterial infection of the supraglottic area, comprising the epiglottis, arytenoid cartilages, aryepiglottic folds, and false vocal chords. Inflammation results in airway edema and narrowing, which leads to airway obstruction manifesting as stridor and respiratory distress. The localized infection can evolve into phlegmon and abscess formation. Bacteremia is common in cases caused by Hib, but dissemination to distant sites (e.g., causing septic arthritis or meningitis) is rare.

Clinical Manifestations and Diagnosis.

Children with epiglottitis typically look systemically unwell and have high-grade fever and stridor.[122,137,145] Aphonia, hoarseness, and a muffled, “hot potato” voice are common features.[129,137] Odynophagia is common, and drooling frequently is observed. Most patients assume an upright tripod position with forward leaning and extension of the neck.[147] Cervical lymphadenopathy also is a common feature.[137]

Peripheral blood leukocytosis is present in most cases.[129,137,140,146] Lateral neck radiographs demonstrate epiglottic enlargement with a distended hypopharynx, a classic thumb sign that has high sensitivity (Fig. 28.3). However, this should be attempted only for a stable, cooperative patient in a safe environment because performing radiography in the lateral position can precipitate respiratory arrest from complete airway obstruction, especially if the child's neck is repositioned for optimal results.[133,137]

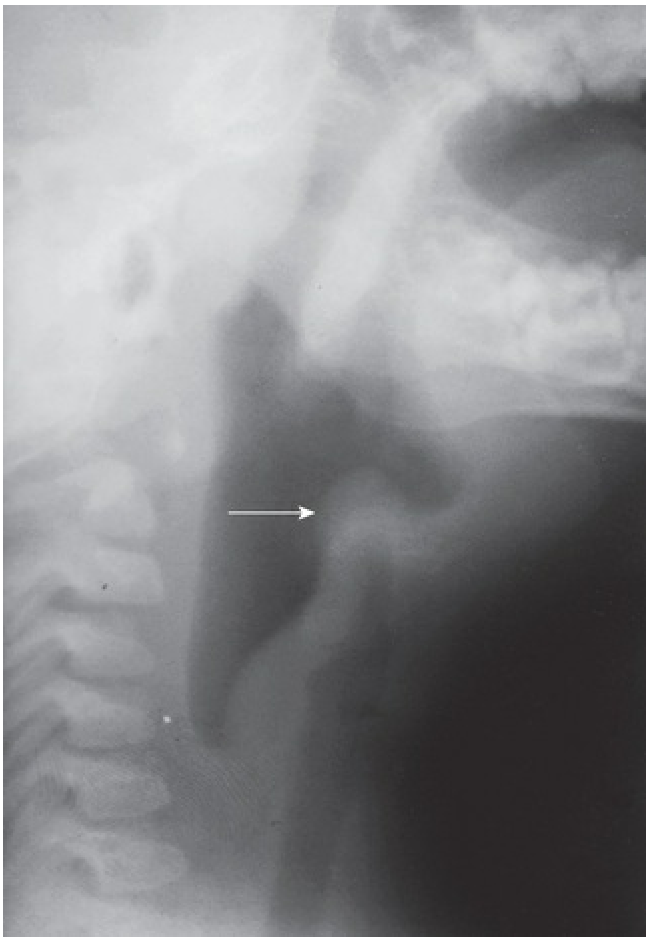


FIGURE 28.3 Lateral neck radiograph of a 4-year-old child with acute epiglottitis shows the characteristically distended hypopharynx and “thumbprint” edematous epiglottis and aryepiglottic folds *(arrow)*. (Courtesy of Richard H. Schwartz, MD, Vienna, VA.)

Management.

Effective airway management is critical. Upsetting the child during attempts to inspect the oropharynx can result in complete airway obstruction. Nebulized epinephrine (i.e., adrenaline) can provide some transient improvement in respiratory distress but also can cause agitation and precipitate airway obstruction. Unstable patients should be urgently intubated by direct laryngoscopy or bronchoscopy in a controlled setting (i.e., operating room or intensive care unit). Although rarely required, facilities to perform a tracheostomy must be available in case attempts to intubate fail.[122,129,137,143] There continues to be controversy about whether cases at the mild end of the disease spectrum without significant respiratory distress can be managed safely without intubation while being closely monitored.[129,137,148]

Blood cultures and throat or epiglottic swabs (in intubated cases) should be obtained for culture and susceptibility testing. Empiric antibiotic therapy, such as a third-generation cephalosporin or ampicillin-sulbactam, should be commenced promptly.[v] The routine use of corticosteroids, which is intended to reduce airway edema, remains controversial, and no RCT has addressed this question.[120,140,148] However, previous, uncontrolled studies have not shown a clear benefit regarding the need for intubation, duration of ventilation, or duration of hospital stay.[137,140,146]

In cases with confirmed Hib epiglottitis, prophylaxis with rifampin should be considered for household contacts according to American Academy of Pediatrics recommendations.[150] The latest UK guidelines also recommend the use of rifampin and suggest ciprofloxacin or azithromycin as an alternative for people who cannot tolerate rifampin or in whom rifampin can interfere with other drugs.[151]

Complications and Prognosis.

Potential complications include complete airway obstruction and cardiac arrest, epiglottic abscess, deep neck infection, pneumonia, and seizures.[122,129,132,137] Most patients require only a short period of intubation and ventilation and can be extubated in 24 to 72 hours.[122,129,132,145] The mortality rate is less than 5% in settings where good intensive care support is available.[129,132,137,141,143]

Croup

Viral croup (i.e., laryngotracheitis) is the most common cause of infectious upper airway obstruction in young children. Some physicians prefer to divide croup into spasmodic croup and laryngotracheitis, also referred to as laryngotracheobronchitis.[152] However, in the clinical setting, this distinction is not particularly meaningful, and *croup* is therefore used in this chapter.

Etiologic Agents and Epidemiology.

Parainfluenza virus types 1, 2, and 3 are the most common causative agents of croup, accounting for 50% to 80% of cases, followed by influenza A, influenza B, and respiratory syncytial virus.[153–159] Less common etiologic agents include adenoviruses, rhinoviruses, coxsackieviruses, and echoviruses.[153,154,158,160] Studies have associated human metapneumovirus, human bocavirus, and human coronavirus NL63 with croup.[160–167] Some data suggest that the clinical course of croup caused by influenza virus is more severe than croup caused by parainfluenza virus.[153]

Epidemiology and Pathogenesis.

Croup is common. One study from Seattle estimated the annual incidence to be as high as 7 cases per 1000 children younger than 6 years of age.[158] The incidence of croup is highest among children between the ages of 6 months and 2 years.[154,156–158] Typical croup symptoms are rarely observed in children older than 6 years of age, likely because of the increase in airway diameter.[157] The incidence is higher among boys.[152–154,156,168] In temperate climates, the incidence typically peaks in late autumn and winter.[154,156,158,168,169]

Inflammatory edema and mucus production result in airway narrowing in the subglottic region, resulting in stridor.[147,152,170,171] Inflammation of the vocal chords results in hoarseness and sometimes in aphonia.

Clinical Manifestations and Differential Diagnosis.

The typical features of croup are inspiratory stridor, a barking cough, and hoarseness. Symptoms often start abruptly and typically worsen during the night.[172] Nonspecific coryzal symptoms frequently precede the illness. Most patients have low-grade or moderate-grade fever.[155,156] Less than 3% of cases in a primary care setting require hospitalization.[155,156]

Infectious and noninfectious causes and clinical features of upper airway obstruction, including croup, are delineated in Chapter 21 (see Tables 21.3–21.5). The noninfectious differential diagnosis includes foreign body aspiration, vocal chord dysfunction, laryngeal webs, allergic or hypocalcemic laryngospasm, subglottic stenosis (e.g., after prolonged intubation), tracheomalacia, H-type tracheoesophageal fistula, gastroesophageal reflux, and vascular ring.[153,172–175] Laryngeal diphtheria, now a rare but potentially life-threatening infection, can begin as severe croup.[172,176, 177]

The diagnosis of croup is made primarily on clinical grounds. Airway or chest radiographs are not indicated in cases with uncomplicated croup.[172,178,179] However, a radiograph showing narrowing of the subglottic airway can be useful if an alternative diagnosis is suspected. Respiratory viral panel testing by PCR can confirm a typical agent but frequently does not aid management.[172]

Management.

Treatment with mist or humidified air has been a key component of croup management for much of the 20th century,[152] although only a few published RCTs have investigated the effectiveness of humidified air in hospitalized patients.[180–183] There are no published data on the effectiveness of warm, humidified air in the home environment—a measure frequently recommended to parents.[184] A Cochrane review that included pooled data from three RCTs found that there was a modest, statistically not significant improvement in the croup severity score of patients receiving humidified air compared with untreated patients during the first hour of treatment; there was no difference between treatment groups for other outcome measures.[184]

Treatment with corticosteroids is routinely indicated.[152] A Cochrane review that included 31 RCTs showed that corticosteroid treatment was associated with significant improvement in the croup severity score at 6 and 12 hours compared with placebo.[185] Corticosteroid treatment was associated with a shorter duration of stay in the emergency department or hospital, fewer admissions, and fewer return visits. However, a range of different corticosteroids (e.g., dexamethasone, budesonide, methylprednisolone, fluticasone), different routes of administration (e.g., oral, intramuscular, inhalation), and doses were used in the trials. Most experts recommend the use of oral or intramuscular dexamethasone (0.6 mg/kg) or nebulized budesonide (2 mg).[152,178,186–188] It remains unclear whether repeated doses over the first 48 hours improve outcome.[189]

Many studies have shown that nebulized epinephrine is effective for achieving symptomatic improvement in children with moderate to severe croup.[190–195] Some data suggest that the use of nebulized epinephrine results in a considerable reduction in the need for intubation or tracheostomy.[196] The drug can be administered as racemic epinephrine (2.25%; 0.5 mL in 2.5 mL of saline) or L-epinephrine (1:1000 solution; 5 mL). A 2013 Cochrane review concluded that the two drugs were equally effective.[197] The treatment is safe, and side effects such as pallor and tachycardia usually are mild and transient.[198]

For children with moderate croup (i.e., stridor and chest wall indrawing at rest) who fail to improve sufficiently within 4 to 6 hours of administration of a corticosteroid, hospitalization should be considered. Children with severe croup should receive a dose of a corticosteroid and be treated with nebulized epinephrine; repeated administration of nebulized epinephrine may be necessary. Intensive care support should be considered if there is an insufficient response. The effect of nebulized epinephrine lasts for only 1 to 2 hours.[190] After that, clinical symptoms can return to baseline or become more severe (i.e., rebound effect).[186]

Children with oxygen saturation below 92% on room air should be given supplemental oxygen. Several reports have described the use of heliox in treating croup with some promising results.[199–201] However, two Cochrane reviews concluded that there was insufficient evidence to support its use in this setting.[202,203]

The use of antitussive and decongestant agents is not recommended.[152,186] Treatment with antibiotics is not indicated unless clinical features or laboratory test results indicate a secondary bacterial infection.[152,173,186] In cases of severe croup caused by influenza A or B virus, treatment with neuraminidase inhibitors should be considered, although there are insufficient efficacy data for this approach in this setting.[152,202–206]

Complications and Prognosis.

Few patients with croup require intubation and ventilation.[153,154] Contiguous spread of the viral infection can occur and can cause otitis media, bronchiolitis, or pneumonia. Bacterial superinfection can lead to bacterial tracheitis (discussed later) or bronchopneumonia.

The prognosis for uncomplicated croup is very good. Symptoms largely resolve within 48 to 72 hours in most patients.[172] A fatal outcome is very rare.

Acute Laryngitis

Isolated, acute laryngitis is primarily a disease described in adolescents and adults.

Etiologic Agents.

Acute laryngitis is caused most commonly by viruses; the spectrum of causative agents is similar to that for croup.[207–211] Bacteria implicated in acute laryngitis include *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*.[212–214]

Clinical Manifestations and Management

The key features of acute laryngitis are a change in the normal pitch of the voice and hoarseness, which typically last for 3 to 7 days. Coexistence of nonspecific upper respiratory tract infection symptoms, such as coryza, sore throat, and cough, is common.

Acute laryngitis in previously healthy people usually is a self-limited viral disease. Treatment with antibiotics is not routinely indicated. A Cochrane review on this topic, which included two RCTs evaluating penicillin V and erythromycin versus placebo, concluded that routine antibiotic treatment has no proven benefit.[215]

Bacterial Tracheitis

The term *bacterial tracheitis* was first used in a publication by Jones and colleagues in 1979.[216] Earlier reports describe cases of *laryngotracheobronchitis* that closely resemble descriptions of bacterial tracheitis, suggesting that this entity was recognized previously.[217,218]

Etiologic Agents.

S. aureus is by far the most common causative organism.[125,219–221] Other bacteria commonly implicated in bacterial tracheitis are *S. pyogenes*, *S. pneumoniae*, *H. influenzae,* and *M. catarrhalis*. Cases attributed to a variety of other bacteria, including *Pseudomonas aeruginosa*, *Bacillus cereus*, *Escherichia coli*, *Prevotella* species, and *Bacteroides* species also have been reported, although they appear to be uncommon.[219–226]

Epidemiology and Pathogenesis.

Bacterial tracheitis is rare, with an estimated annual incidence below 0.1 case per 100,000 children in the United Kingdom and Australia.[220] Incidence data have not been published for other countries. Some data suggest that the incidence peaks during autumn and winter.[220] Bacterial tracheitis predominately affects young children, although a few adult cases have been described.[227–229]

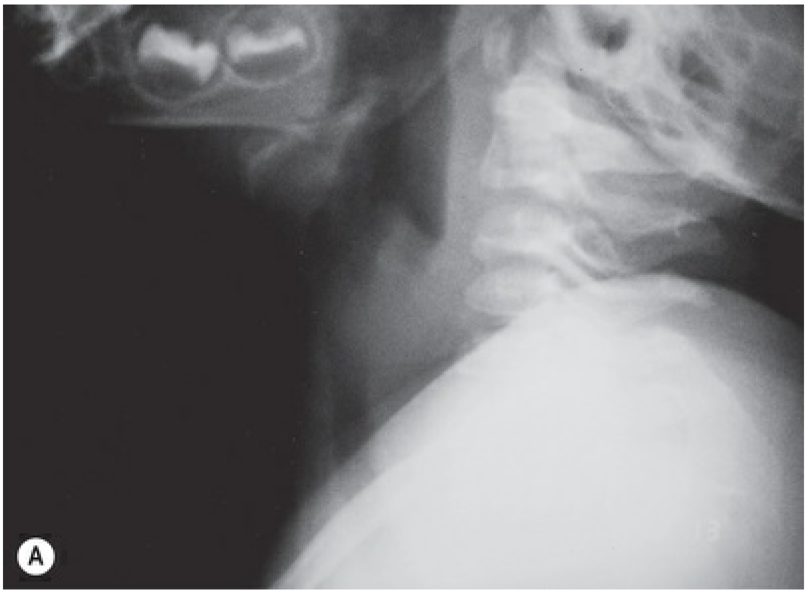
The pathogenesis of bacterial tracheitis remains unclear. It has been postulated that viral infection of the upper respiratory tract may facilitate secondary bacterial infection and invasion of the airways, resulting in inflammation and edema, which ultimately leads to narrowing of the trachea.[219] The peak incidence of bacterial tracheitis coincides with the peak season for viral respiratory pathogens, suggesting synergy. In one large case series, coinfection with influenza virus was identified in almost one third of the cases.[221] Coinfection with parainfluenza virus, respiratory syncytial virus, or adenovirus has been described in other reports.[125,220,223,230]

Clinical Manifestations and Differential Diagnosis.

Most patients with bacterial tracheitis report prodromal symptoms suggestive of a minor upper respiratory tract infection, which typically began 2 to 5 days before the onset of stridor.[219,220] After stridor and dyspnea develop, patients often deteriorate rapidly, frequently requiring intubation within the first 24 hours to overcome increasing upper airway obstruction.[216,220,231–233] Other common features at presentation include fever (often moderate to high grade), hoarse voice or aphonia, cough, and intercostal and subcostal recessions. Drooling is uncommon. Most cases show little or no response to nebulized epinephrine.[234]

The main differential diagnoses are epiglottis and viral croup. Unlike cases of bacterial tracheitis, children with epiglottitis typically refuse to speak, have drooling, and adopt an upright position with extension of the neck. Children with croup typically have only low-grade pyrexia, do not appear toxic, and usually respond to nebulized epinephrine.

An inflammatory response, including an elevated CRP level and WBC count, is seen in most patients at presentation.[220,234] The radiograph may demonstrate narrowing of the tracheal air shadow and intraluminal tracheal membranes, although these are not universal findings (Fig. 28.4).[223,230] Coexisting pulmonary changes, including infiltrates and atelectases, are common.[220,234–237] Direct visualization of the airways reveals an unremarkable or only mildly inflamed epiglottis but shows marked subglottic inflammation, edema of the tracheal mucosa, and copious purulent endotracheal secretions.[216,234] Endotracheal aspirates should be obtained and sent for bacterial culture and susceptibility testing. Blood cultures are rarely helpful, as bacteremia is relatively uncommon in these patients.



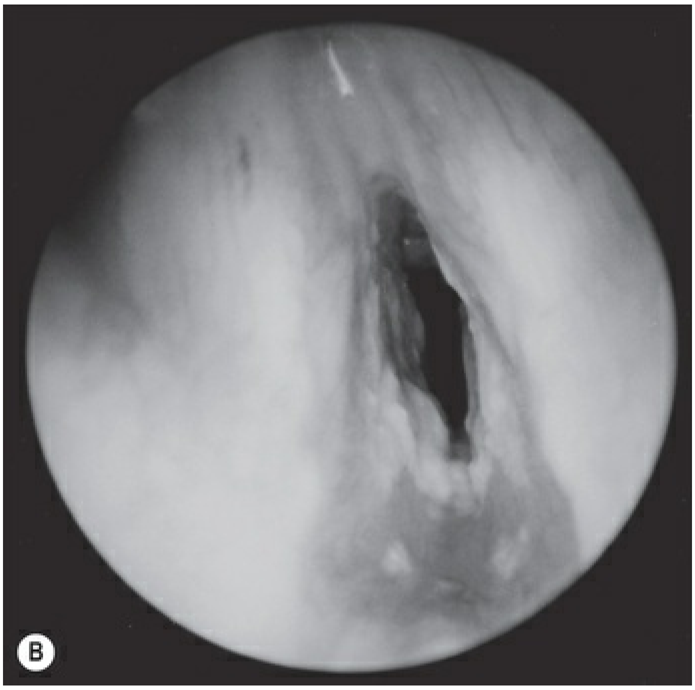


FIGURE 28.4 (A) Lateral neck radiograph of a 22-month-old boy with bacterial tracheitis caused by *Staphylococcus aureus* shows subglottic haziness (similar to croup). (B) Endoscopic view of the trachea shows mucosal denudation, intraluminal debris, and purulent laryngotracheal secretions. (Courtesy of Richard H. Schwartz, MD, Vienna, VA.)

Management.

Proactive airway management is critical in managing bacterial tracheitis to prevent complete airway obstruction and consequent respiratory arrest. In most of the larger published case series, 80% to 100% of patients required intubation or tracheostomy and mechanical ventilation. Intubation usually is challenging and requires the use of an endotracheal tube of considerably smaller diameter than would be expected based on the patient's age. The personnel and equipment for a tracheostomy must be readily available in case conventional intubation fails.

Appropriate empiric antibiotic treatment must include effective antistaphylococcal coverage. A combination of a third-generation cephalosporin (e.g., ceftriaxone, cefotaxime) and a penicillinase-resistant penicillin (e.g., cloxacillin, nafcillin) given intravenously is a suitable choice in areas where community-acquired MRSA infections are unlikely. Otherwise, vancomycin should replace the latter component. Good-quality evidence is lacking, but many centers use systemic corticosteroids in the first few days of the illness with the intention to reduce airway edema.

Most patients require ventilatory support for only 2 to 5 days unless complications occur. The optimal duration of antibiotic treatment is unknown, but most experts recommend a minimum of 10 days of treatment.

Complications and Prognosis.

Complications of bacterial tracheitis include pneumothorax, pneumomediastinum, pulmonary edema, acute respiratory distress syndrome, hypotension, and cardiorespiratory arrest.[230,223,234,238] Cases with concurrent toxic shock syndrome have been described.[230,232,239] Neurologic sequelae are common in patients who experience cardiorespiratory arrest. Subglottic stenosis and subglottic polyps are rare long-term sequelae.[230,240]

Bacterial tracheitis is a potentially life-threatening condition, with some early publications reporting case fatalities in excess of 20%.[230,238] Fatal outcomes have been uncommon in the past decade, likely reflecting improvements in intensive care support.[125,220,221]

Acute Bronchitis

Acute bronchitis predominately occurs in adolescents and adults. Data from the US National Health Interview Survey suggest that approximately 5% of all adults experience one or more episodes of bronchitis per year.[241] The incidence peaks in autumn and winter.[242]

Etiologic Agents.

Most cases of bronchitis are nonbacterial in nature, although no causative organism can be identified in many patients. Viral infections appear to account for most cases.[243,244] Viruses commonly implicated in acute bronchitis include influenza virus, parainfluenza virus, respiratory syncytial virus, rhinovirus, adenovirus, and human metapneumovirus.[243–248] Infection due to bacterial organisms, including *Bordetella pertussis*, *Chlamydophila pneumoniae,* and *Mycoplasma pneumoniae*, is less common.[243–245]

Clinical Manifestations and Management.

Illness typically begins with nonspecific upper respiratory tract infection symptoms, which usually last for a few days. This is followed by a second phase characterized by persistent cough, frequently with sputum production or wheezing, which typically lasts for 1 to 3 weeks.[242,243]

Antibiotic therapy is not routinely indicated for previously healthy people with acute bronchitis.[242,249] A Cochrane review that included nine RCTs showed that antibiotic treatment on average reduced the duration of cough by less than 1 day compared with placebo; adverse effects were significantly more common in the antibiotic-treated patients.[250] The update of this review, which included 17 RCTs, concluded that the benefits of antibiotic treatment in bronchitis were marginal.[251,252] Guidelines for treating acute bronchitis by the American College of Physicians and the American College of Chest Physicians have discouraged the routine use of antibiotics, inhaled bronchodilators, or mucolytic agents.[253,254] However, patients diagnosed with pertussis should receive azithromycin, primarily to limit transmission.[242]

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29

Otitis Media

Stephen I. Pelton

Otitis media is a disease of early childhood. Its relevance to child health in high-income countries has evolved from concern about suppurative complications to concern about prolonged conductive hearing loss, language, and cognitive delays. In low-income settings, acute otitis media (AOM) remains a source of contiguous or hematogenous spread to the mastoids or central nervous system, with potentially fatal outcomes. Although incidence is declining, AOM results in more than 12 million antibiotic prescriptions annually and causes significant family disruption.[1] The impact of universal administration of pneumococcal conjugate vaccine (PCV) on the incidence of AOM and concerns about widespread use of antibiotics for treatment have prompt ongoing re-evaluation of optimal strategies for management.[2]

Acute Otitis Media

Pathogenesis

AOM usually is considered to be a bacterial infection because bacterial otopathogens are isolated from middle ear culture in 70% of cases.[3] AOM usually is a coinfection, with a viral upper respiratory tract infection (URI) enhancing the ability of bacterial otopathogens from the nasopharynx to gain access to the middle ear. Respiratory tract viruses alone occasionally cause AOM (2% to 20%) as proved by tympanocentesis.[4] Eustachian tube dysfunction (i.e., tympanometric measurement of negative pressure) occurs in

75% of children with a viral URI and is a major contributing factor to the development of bacterial AOM.[5] Influenza A infection can suppress neutrophil function[6] and macrophage recruitment, and it likely contributes to the high attack rate for AOM observed among children with influenza A infection.[7] Viral URI in animal models and observed in children enhances the frequency and density of nasopharyngeal colonization with otopathogens.[8–10] Fig. 29.1 synthesizes the important pathophysiologic mechanisms.

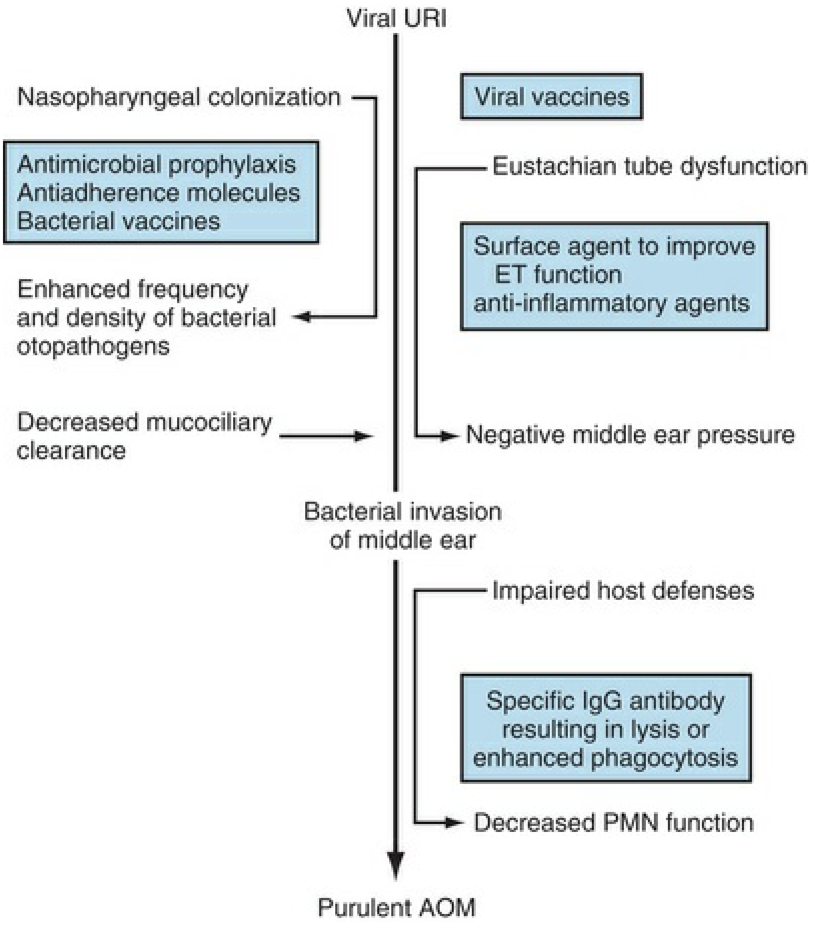
Viral URI
Nasopharyngeal colonization
Viral vaccines
Antimicrobial prophylaxis
Antiadherence molecules
Bacterial vaccines
Eustachian tube dysfunction
Surface agent to improve ET function
anti-inflammatory agents
Enhanced frequency and density of bacterial otopathogens
Decreased mucociliary clearance
Negative middle ear pressure
Bacterial invasion of middle ear
Impaired host defenses
Specific IgG antibody resulting in lysis or enhanced phagocytosis
Decreased PMN function
Purulent AOM

FIGURE 29.1 Schema of events in viral-bacterial pathogenesis of acute otitis media (AOM), with potential intervention strategies (shown in boxes). ET, endotracheal tube; Ig, immunoglobulin; PMN, polymorphonuclear leukocyte; URI, upper respiratory tract infection.

Microbiology and Antimicrobial Susceptibility

A limited number of viral (Table 29.1)[4] and bacterial pathogens are recovered from culture of middle ear fluid. Four bacterial otopathogens—*Streptococcus pneumoniae*, nontypeable *Haemophilus influenzae* (NTHi), *Moraxella catarrhalis,* and *Streptococcus pyogenes* (i.e., group A *Streptococcus* [GAS])—consistently are recovered from children with AOM. Although the proportion of disease due to each pathogen varies with geography and age, remarkable consistency has been observed in microbiologic studies of symptomatic middle ear disease.

TABLE 29.1

Virus Detected Alone or in Combination With Bacterial Pathogens in Middle Ear Fluid in 128 Children With Acute Otitis Media

Virus	No. of Viruses	% Of Total Virus Count
Respiratory syncytial virus	72	49
Parainfluenza virus (types 1, 2, and 3)	20	13.6
Influenza virus (A and B)	19	12.9
Enterovirus	10	6.8
Rhinovirus	10	6.8
Cytomegalovirus	8	5.4
Adenovirus	7	4.8
Herpes simplex virus	1	0.7
Total	147	100

Modified from Chonmaitree T. Viral and bacterial interaction in acute otitis media. Pediatr Infect Dis J 2000;19:S24–S30.

Jacobs and associates[3] described otopathogens recovered from 917 episodes of AOM in Eastern European, Israeli, and US children in 1994 and 1995. After the US introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) in 2000 and the 13-valent vaccine (PCV13) in 2013, the microbiology of AOM evolved, increasing the relative importance of nonvaccine serotypes of *S. pneumoniae* (NV-Sp) and emergence of NTHi as the most common otopathogen in children failing initial therapy.[11–13] Molecular strategies demonstrate an increased identification of NTHi in previous culture-negative cases of recurrent otitis media and when tympanostomy tubes are inserted.[14]

Streptococcus pneumoniae

Pneumococcus is recovered from 30% to 50% of children with AOM.[15–19] Before the US introduction of PCV7, 70% of episodes of pneumococcal AOM were caused by seven serotypes (Fig. 29.2).[20] After universal implementation of PCV7 and PCV13, a shift occurred in serotypes recovered from middle ear cultures of children with AOM, with a progressive decline in V-Sp 19 A cases between 2011 and 2013 and frequent recovery of NV-Sp serotypes, including 6C, 11, 15 A, 15B/C, 21, 23B, and 35.[21,22]

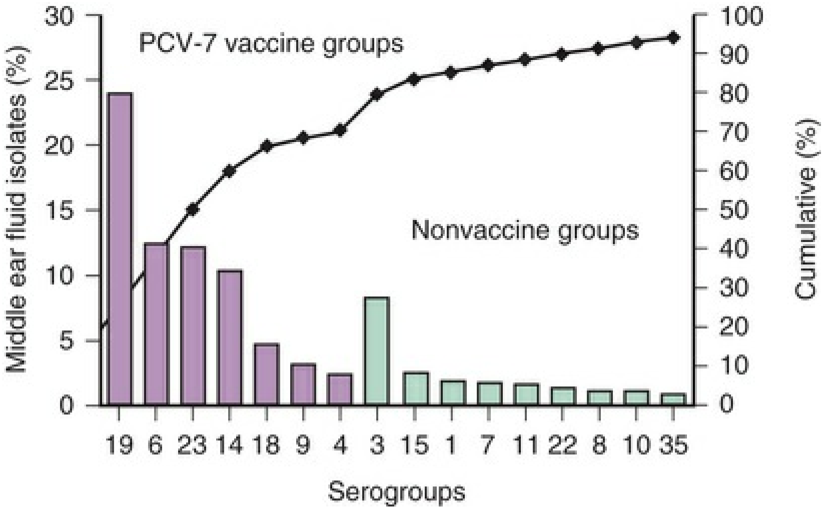

FIGURE 29.2 Serogroups of *Streptococcus pneumoniae* that caused acute otitis media in North American children in 2000. PCV-7, 7-valent pneumococcal conjugate vaccine. (Modified from Hausdorff WP, Bryant J, Kloek C, et al. The contribution of specific pneumococcal serogroups to different disease manifestations: implications for conjugate vaccine formulation and use. Part II. Clin Infect Dis 2000;30:122–140.)

From 1985 through 1999, increasing penicillin and multidrug resistance emerged among isolates of *S. pneumoniae*. Resistance was most common among five to seven of the PCV7 serotypes.[23] Implementation of PCV7 was associated initially with a decrease in penicillin and multidrug resistance, but it was followed by increasing penicillin resistance due to replacement NV-Sp.[2,24] After the PCV13 introduction, colonization and infection due to penicillin-nonsusceptible and multidrug-resistant *S. pneumoniae,* primarily serotype 19A, declined dramatically to current levels of 20% or less. Currently, 30% of *S. pneumoniae* isolates remain resistant to azithromycin, but few isolates have resistance to ceftriaxone or high-level resistance to penicillin.

Haemophilus influenzae

NTHi causes a substantial proportion of cases of AOM in children.[25] A well-recognized clinical syndrome, otitis–conjunctivitis, is associated with recovery of NTHi from the middle ear and conjunctiva.[26] Several investigators have reported an increased proportion of disease due to NTHi among immunized children who have persistent or recurrent disease after initial treatment.[12,13] Most isolates of NTHi produce β-lactamase and are amoxicillin resistant. In Japan and France, isolates of NTHi with high-level resistance to amoxicillin due to alterations in the penicillin-binding proteins have been recovered from children with AOM,[27] but they remain uncommon in the United States.[28]

In the last decade, molecular techniques (PCR amplification) have provided insights into the microbiology of recurrent AOM and persistent otitis media with effusion (OME). Middle ear biofilm formation, most commonly associated with NTHi, is frequent and often recalcitrant to antimicrobial treatment.[29]

Moraxella catarrhalis

M. catarrhalis is a bona fide pathogen in AOM. It is isolated from middle ear culture samples from children with AOM and prompts a humoral immune response.[30] The organism appears to be more prevalent in certain geographic areas and in the first year of life.

Group A *Streptococcus*

Otitis media due to GAS was common in the preantibiotic era. Currently, GAS most often is recovered from school-aged children with AOM. A greater relative importance of GAS is reported in eastern European children than in US children.

Staphylococcus aureus and *Staphylococcus epidermidis*

The role of *Staphylococcus aureus* as a pathogen in AOM remains controversial. In Japan and South Africa, *S. aureus* is reported as a primary pathogen of AOM in children and is recoverable from tympanocentesis fluid.[31] *S. aureus* is recovered from less than 3% of middle ear cultures from US children with AOM and an intact tympanic membrane. Methicillin-susceptible *S. aureus* (MSSA) and community-associated methicillin-resistant *S. aureus* (CA-MRSA) are identified pathogens in children with acute otorrhea associated with a tympanostomy tube.[32,33]

Epidemiology

Otitis media is virtually universal in childhood. Studies of the age-specific incidence of AOM in Denmark between 1996 and 2003 reported that 16% of children had first episodes between 0 and 6 months of age, 44% between 7 and 18 months, and 40% between 19 months and 7 years. Before 7 years of age, 40% had 4 or more episodes.[34]

Risk factors for AOM are young age, exposure to young children (i.e., group childcare attendance or siblings in household), and a positive family history.[35,36] Studies evaluating features such as race, breastfeeding, use of a pacifier, and exposure to cigarette smoke have identified associations with AOM less consistently.[37–40]

Recognition of the otitis-prone child has been important in the development of strategies for reducing the burden of AOM and OME. Onset of disease in the first few months of life is a sentinel event that can result from risk factors and can create enhanced susceptibility to later events. Children who had their first episode before 6 months of age are most likely to develop recurrent AOM. In the past decade, several studies of insurance claims document a decline in the number of AOM-related visits in the US, Canada, and United Kingdom.[41–43] Large studies of US children younger than 7 years of age show a downward trend in otitis media visit rates from 2004 to 2011, with a significant drop that coincided with the introduction of PCV13 in 2010.[41] Other factors that likely contributed are more stringent diagnostic criteria, expanded use of influenza vaccine, and adoption of initial observation for some children.

Studies by Grijalva and colleagues[42] and de Wals and coworkers[43] concluded that the decline in AOM preceded and likely was accelerated by the introduction of PCV7.[42,43] Although clinical trials demonstrated only a modest reduction in AOM episodes, some investigators have hypothesized that substantial reduction in tympanostomy tube insertion is related to prevention of early pneumococcal otitis media and its attendant events.

Management

Many issues influence strategies for the treatment of AOM, including the natural history of AOM, relevance of clinical versus microbiologic end points, antibiotic choices according to current susceptibility patterns of otopathogens, published guidelines for management, and the relative risk of observation versus treatment.

Natural History

In the preantibiotic era, mastoiditis was a common complication of AOM. Antimicrobial therapy for the treatment of AOM has resulted in a dramatic decline in its incidence. Similarly, in certain populations, such as Alaskan Eskimos, chronic otorrhea occurred in about 30% of children before the routine use of antimicrobial therapy.[44] In 1999, Baxter[45] reported a substantial decline in chronic otorrhea cases over a 30-year period that was associated with the introduction of routine antimicrobial therapy for the treatment of AOM. During the same period, socioeconomic conditions also improved, blurring the specific contribution of medical management.

An episode of AOM usually resolves in most children with or without antimicrobial therapy. Antibiotic treatment does not benefit the 20% to 30% of episodes of middle ear disease with negative culture results, and some children with bacterial AOM clear the pathogen spontaneously.[46]

Therapeutic trials that include a placebo group consistently report excess failure rates for children who receive only symptomatic treatment; however, the significance of these differences is debated. Little and coworkers[47] compared the outcomes of children with AOM initially treated with amoxicillin with those of children given a prescription to be filled only if symptoms persisted for 72 hours. Children initially treated with antibiotics improved more quickly.

McCormick and colleagues[48] evaluated the strategy of watchful waiting for children with perceived mild disease as defined by a structured assessment. Children assigned to the delayed treatment group had increased treatment failures and persistent symptoms (Table 29.2). More frequent, mild adverse events and the emergence of multidrug-resistant isolates of *S. pneumoniae* in the nasopharynx occurred in the early-treatment group. Evaluating outcomes within the first 3 to 5 days of treatment provides the best evidence for more rapid resolution in antibiotic-treated compared with placebo-treated cohorts and differences between antibiotic regimens.[49,50] Effective antimicrobial therapy sterilizes the middle ear, resulting in a more rapid resolution of clinical signs (i.e., bulging and erythema) and symptoms (i.e., fever, earache, and irritability).

TABLE 29.2

Clinical Outcomes by Treatment Assignment and Age

Treatment Assignment by Age Cohort	Failure (Day 0–12)		Recurrence (Day 13–33)		Cure	
	No.	%	No.	%	No.	%
<2 YEARS						
Antibiotic immediately	4	6	11	17	50	77
Watchful waiting	12	24	10	20	28	56
Total	16	14	21	18	78	68
>2 YEARS						
Antibiotic immediately	1	2	9	21	34	77
Watchful waiting	9	18	3	6	38	76
Total	10	14	12	16	72	76

From McCormick DP, Chonmaitree T, Pittman C, et al. Nonsevere acute otitis media: a clinical trial comparing outcomes of watchful waiting versus immediate antibiotic treatment. Pediatrics 2005;115:1455–1465.

Two clinical trials described the magnitude of the benefit of antibiotic treatment in children residing in industrialized countries[51,52] One study reported a substantial benefit for amoxicillin-clavulanate compared with placebo for resolution of fever, irritability, decreased activity, and poor appetite.[52] In the other, treatment with amoxicillin-clavulanate was associated with a lower symptom score over the first 7 days.[51] If the outcome of recurrence within 30 days is measured, small but statistically significant differences are reported between children given effective antimicrobial therapy and those given placebo or ineffective therapy.[53]

Between 30% and 50% of children, especially younger children, have persistent OME 30 days after an episode of AOM, long after resolution of the acute signs and symptoms.[54] In a longitudinal study, 40% of children with AOM had OME at 1 month, 20% at 2 months, and 10% at 3 months.[55] OME is associated with conductive hearing loss of up to 50 decibels (dB) during fluid persistence.[56]

Pharmacodynamic Principles of Antimicrobial Selection

In 1992, the Infectious Disease Society of America established guidelines for evaluation of new agents for treatment of AOM,[57] requiring both clinical and microbiologic studies and outcome measures 3 to 5 days after initiation of antimicrobial therapy. Guidelines are consistent with the principles established by Carlin and colleagues[58] and confirmed by Dagan and associates[59] that the middle ear concentration of an antibiotic has a high correlation with clinical success (Table 29.3)

TABLE 29.3

Correlation Between Microbiologic Outcome at Day 4 or 5 and Clinical Outcomes of Patients With Acute Otitis Media

Clinical Outcome	Culture Negative at Day 4 or 5		Culture Positive at Day 4 or 5	
	No.	%	No.	%
Success	236	93	25	62.5
Failure	17	7	15	37.5

Modified from Carlin SA, Marchant CD, Shurin PA, et al. Host factors and early therapeutic response in acute otitis media. J Pediatr 1991;118:178–183.

The selection of antimicrobial therapy should be based on pharmacodynamic principles and results of clinical trials using microbiologic end points. β-Lactam agents and trimethoprim-sulfamethoxazole (TMP-SMX) depend on the time that the drug concentration is above the minimal inhibitory concentration (MIC) for efficacy.[60] Efficacy (i.e., sterilization of middle-ear fluid) of β-lactam agents is predicted when the drug concentration in middle ear fluid exceeds the MIC for about 40% of the dosing interval.[61] For azalides (e.g., azithromycin) and fluoroquinolones, ratios of the area under the antibiotic concentration curve per 24 hours (AUC_{24}) to MIC or the peak concentration to MIC are relevant, and for azithromycin, an AUC_{24} to MIC ratio of 25 predicts efficacy (for pneumococcus).[62]

Although these principles are well established, controversy persists regarding whether extracellular or intracellular concentrations of antibiotics are necessary. For β-lactam agents, there is no enhanced intracellular accumulation. However, for azalides and ketolides, intracellular concentrations of drug exceed extracellular (serum) concentrations up to 100-fold. Results from animal models and clinical trials suggest that extracellular concentrations are the critical correlate.[63]

The acceptance of these principles led the Clinical and Laboratory Standards Institute (CLSI) to identify specific criteria (i.e., breakpoints) for susceptibility or resistance relative to sites of infection. Table 29.4 summarizes the CLSI-specific breakpoints and those derived from pharmacodynamic analysis for *S. pneumoniae* and NTHi.[64]

TABLE 29.4

CLSI and Pharmacodynamic Breakpoints for Selected Antimicrobial Agents and Otopathogens

Antibiotic	CLSI Breakpoints[a] (μg/mL)		Pharmacodynamic Breakpoints[a] (μg/mL)
	Streptococcus Pneumoniae	*Haemophilus Influenzae*	
Amoxicillin	2	4	2
Amoxicillin-clavulanate	2	4	2
Cefuroxime	1	4	1
Cefprozil	2	8	1
Cefixime	0.5	1	1
Cefaclor	1	8	0.5
Loracarbef	2	8	0.5
Azithromycin	0.5	4	0.12
Clarithromycin	0.25	8	0.25

[a] Breakpoint is a concentration used in the interpretation of results of susceptibility testing to define bacterial isolates as susceptible, intermediate, or resistant.

CLSI, Clinical and Laboratory Standards Institute.

Data from National Committee for Clinical Laboratory Standards (NCCLS). Performance Standards for Antimicrobial Susceptibility Testing. Tenth Informational Supplement. Wayne, PA: NCCLS; 2000.

In most cases of AOM, the specific pathogen is unknown, and presumptive therapy is based on the likely pathogens and their in vitro susceptibility. The proportion of isolates of NTHi producing β-lactamase is approximately 40%,[65] and penicillin-nonsusceptible isolates due to altered penicillin-binding proteins is approximately 20%.[66–68] CLSI breakpoints for *S. pneumoniae*, redefining resistant as isolates with a penicillin MIC of 8 μg/mL or greater, are more consistent with pharmacokinetic or pharmacodynamic principles.

Resistance to macrolides and azalides is mediated by an efflux pump mechanism that decreases intracellular accumulation of antibiotic or by a mutation in ribosomal methylase that affects binding between the drug and target site, or both.[69,70] Susceptibility of nasopharyngeal isolates of *S. pneumoniae* in Massachusetts children from 2008 and 2009 and AOM isolates in infants in Rochester, NY, in 2011 and 2012 based on the 2000 CLSI guidelines are shown in Table 29.5 and Table 29.6, respectively. Data from France suggest that the proportion of macrolide-resistant and penicillin-nonsusceptible pneumococcal carriage has declined in the PCV13 era, whereas that of amoxicillin-resistant NTHi remains unchanged.[71] Risk factors for penicillin-nonsusceptible *S. pneumoniae* are age younger than 2 years, recent treatment with antibiotics, season (i.e., late winter to early spring), and attendance in group childcare.[72,73] For most isolates with a penicillin MIC of 2 to 8 µg/mL, a 10-day course of high-dose (90 mg/kg/day) amoxicillin or a three-dose regimen of ceftriaxone (50 mg/kg/day) has proved effective for AOM.[53,74]

TABLE 29.5

Proportion of Antibiotic Resistance Among 2008–2009 Pneumococcal Isolates From Children Younger Than 7 Years in Massachusetts

Antibiotic[a]	Total Isolates (%) (*N* = 290)
PNSP	98 (34)
PCN-I[b]	64 (22)
PCN-R[c]	34 (12)
Erythromycin-NS	83 (29)
Clindamycin-NS	29 (10)
Trimethoprim-sulfamethoxazole-NS	58 (20)
Ceftriaxone-NS	30 (10)
MDR1[d]	81 (28)
MDR2[e]	55 (19)

[a] The following breakpoints were used for PNSP (>0.06), erythromycin-NS (>0.25), clindamycin-NS (>0.5), trimethoprim-sulfamethoxazole-NS, (>0.5), and ceftriaxone-NS (>1.0).

[b] Based on the pre-2008 breakpoint for penicillin intermediate susceptibility (MIC 0.06–1.0 mg/L).

[c] Based on the pre-2008 breakpoint for penicillin resistance (MIC ≥2.0 mg/L).

[d] MDR1 refers to multidrug resistance defined as nonsusceptibility to penicillin plus one other antibiotic class.

[e] MDR2 refers to multidrug resistance defined as nonsusceptibility to three or more classes of antibiotics.

I, Intermediate susceptibility; MIC, minimal inhibitory concentration; MDR, multidrug resistance; NS, nonsusceptible; PCN, penicillin; PNSP, penicillin-nonsusceptible *Streptococcus pneumoniae*; R, resistant.

Modified from Wroe FC, Lee GM, Finkelstein JA, et al. Pneumococcal carriage and antibiotic resistance in young children before 13-valent conjugate vaccine. Pediatr Infect Dis 2012;31:249–254.

TABLE 29.6

Bacteria Causing Acute Otitis Media in Infants in Rochester, New York, During the 2011–2012 Respiratory Season

Pathogen	Proportion of Total Bacterial Pathogens	Proportion That Were Amoxicillin Resistant
Streptococcus pneumoniae	12%	20%
Haemophilus influenzae	56%	50%
Moraxella catarrhalis	22%	100%

Modified from Pichichero ME. Otitis media. *Pediatr Clin North Am.* 2013;60:39.

Pharmacokinetic or pharmacodynamic data and anecdotal evidence support the efficacy of clindamycin for susceptible isolates. Animal studies support the efficacy of linezolid against drug-resistant *S. pneumoniae*.[75] Linezolid, however, has no activity against NTHi.

Defining Clinical Failure, Relapse, and Recurrence

Review of seven clinical trials comparing antibiotic and placebo treatments for AOM identified *treatment failure* (i.e., persistence of symptoms) in 15% of cases at 2 to 3 days, in 10% at 6 to 7 days, and in 9% at 7 to 14 days.[49] The failure of AOM to respond to initial antimicrobial therapy is related to the severity of the initial symptoms and the age of the patient.[59,76] Kaleida and associates[76] observed after 24 hours of therapy that 12% of severely symptomatic patients younger than 2 years but only 4.1% of children 2 years or older with similar severity of symptoms showed no improvement with therapy. Among children with nonsevere AOM, only 6% who were younger than 2 years and less than 1% of those older than 2 years of age had no improvement.

In studies performed before PCV7 became available or in countries where PCV7 immunization is not universal, β-lactamase–positive NTHi was isolated from tympanocentesis specimens in 50% of cases and nonsusceptible *S. pneumoniae* in 25% of cases of high-dose amoxicillin treatment failure.[77] A study conducted during the PCV7 era reported high rates of treatment failure among children younger than 2 years of age (Fig. 29.3) and relatively comparable rates for antimicrobial regimens.[78]

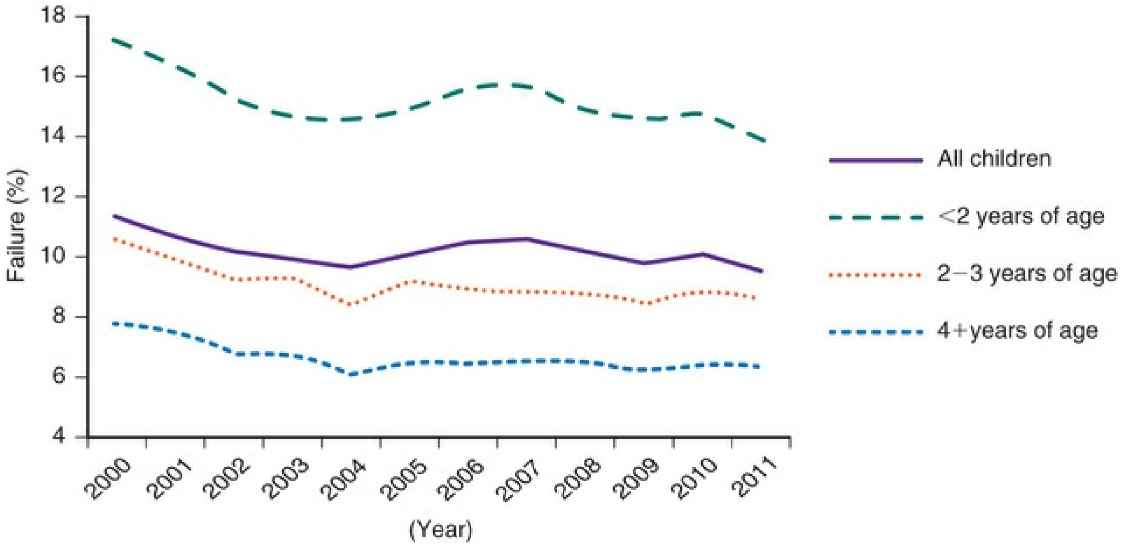

FIGURE 29.3 Rates of antibiotic failure among children with an acute otitis media diagnosis are shown for four age categories from 2000 to 2011. (From McGrath LI, Becker-Dreps S, Pate V, Brookhart MA. Trends in antibiotic treatment of acute otitis media and treatment failure in children, 2000−2011. PLoS One 2013;8:e812107.)

Antimicrobial treatment for these children must include agents active against pneumococcus and NTHi organisms. Ceftriaxone, high-dose amoxicillin-clavulanate, high-dose amoxicillin in combination with cefixime or ceftibuten, and standard-dose amoxicillin in combination with amoxicillin-clavulanate are appropriate. Studies of gatifloxacin and levofloxacin demonstrate in vitro activity against all NTHi and more than 95% *S. pneumoniae.* Clinical trials demonstrate rapid sterilization and clinical resolution of middle ear infection due to either pathogen.[79,80] However, fluoroquinolones are not licensed for use in children for the treatment of AOM.

Universal use of PCV13 has reduced circulation of multidrug-resistant pneumococcus in the community and recovery of such isolates (especially serotype 19A) from children with AOM and mastoiditis.[81] Vancomycin or levofloxacin plus tympanostomy tube insertion or linezolid have provided successful treatment for AOM multidrug-resistant serotype 19A.[82,83]

Relapse and *recurrence* are defined as occurrence of AOM after an initial symptomatic response to antibiotics during treatment or within a defined period after completion of therapy. Differentiating relapse from recurrence requires defining the microbiology of both episodes. Leibovitz and colleagues demonstrated that most relapses that occurred within 1 month after completion of antibiotic therapy were caused by new pathogens or different serotypes of the same pathogen.[77] Other studies showed that ceftriaxone or other β-lactam therapy for AOM eliminated susceptible isolates of *S. pneumoniae* from the nasopharynx but had little effect on resistant strains.[84,85] Beginning as early as 3 to 4 days into the course of treatment, new strains of antibiotic-resistant *S. pneumoniae* are acquired.[86] Recurrent episodes of AOM are more likely to be caused by resistant pathogens.[47]

Fig. 29.4 demonstrates that the likelihood of recovering a penicillin-nonsusceptible pneumococcus correlates with time since last receipt of antibiotics.[87] The data support the recommendation from the American Academy of Pediatrics (AAP) that treatment of recurrent episodes within 30 days of a prior event may necessitate use of antibiotic agents (e.g., ceftriaxone, high-dose amoxicillin-clavulanate) that target resistant otopathogens.[88]

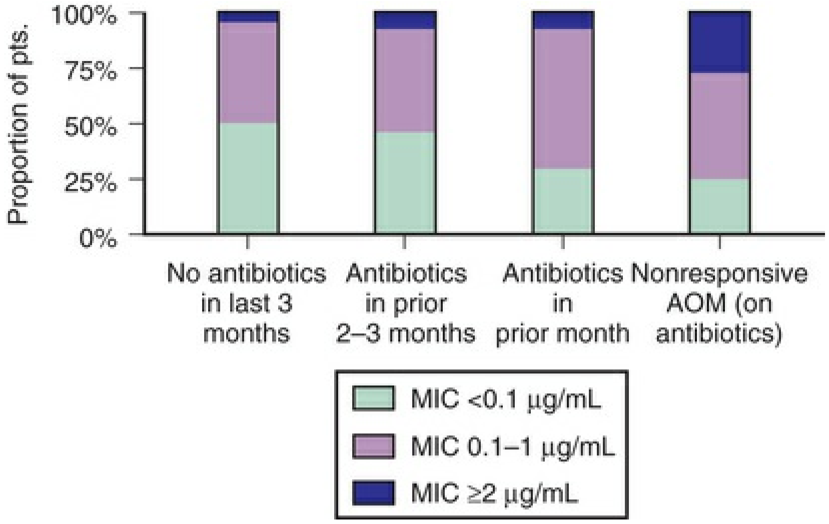

FIGURE 29.4 Correlation between recent antibiotic therapy and likelihood of drug-resistant *Streptococcus pneumoniae* in patients *(pts.)* with acute otitis media *(AOM)*. MIC, Minimum inhibitory concentration. (Modified from Jacobs MR. Increasing antibiotic resistance among otitis media pathogens and their susceptibility to oral agents based pharmacodynamic parameters. Paediatr Infect Dis J 2000;19:S47–S55.)

American Academy of Pediatrics Guidelines for the Diagnosis and Treatment of Acute Otitis Media

The AAP guidelines were published in 2004 and revised in 2013. They define middle ear effusion as detected by physical examination or tympanometry plus an opaque tympanic membrane (i.e., evidence of inflammation) as the critical criterion for the diagnosis of AOM.[88,89] Classification as AOM also requires recent onset of signs and symptoms of acute inflammation such as earache, ear tugging, or a bulging tympanic membrane. The 2013 AAP and American Academy of Family Physicians (AAFP) guideline recommends immediate antibiotic treatment for children younger than 6 months of age, children with severe signs or symptoms (i.e., moderate or severe ear pain, ear pain for ≥48 hours, or temperature ≥39°C [102.2°F]), and children older than 24 months of age with bilateral AOM.[88]

The 2013 AAP/AAFP guideline recommends immediate treatment or observation (with pain control) for children between 6 and 24 months of age with unilateral, nonsevere AOM and for children 24 months or older with unilateral or bilateral, nonsevere AOM. Additional analysis shows a high rate of treatment failure among children younger than 24 months with unilateral, nonsevere AOM,[89] and the observational approach remains controversial.

Amoxicillin remains the first-line therapy for children with AOM who are treated with antibiotics and at low-risk for amoxicillin resistance (Table 29.7).[87,88] Among β-lactam antibiotics, only oral high-dose amoxicillin or intramuscular ceftriaxone achieves middle ear concentrations that fulfill pharmacokinetic or pharmacodynamic requirements for penicillin-nonsusceptible *S. pneumoniae* and β-lactamase–nonproducing NTHi. Cefuroxime axetil, cefprozil, and cefpodoxime are alternatives to high-dose amoxicillin, but each only achieves a sufficient middle ear concentration to be effective against less than 50% of penicillin-nonsusceptible *S. pneumoniae*. Cefprozil has limited activity against NTHi.[90]

TABLE 29.7

Recommendations for Initial or Delayed Treatment of Acute Otitis Media and After Initial Treatment Failure

Initial Immediate or Delayed Antibiotic Treatment		Antibiotic Treatment After 48–72 hr of Failure of Initial Antibiotic Treatment	
Recommended First-Line Treatment	**Alternative Treatment (for Penicillin Allergy)**	**Recommended First-Line Treatment**	**Alternative Treatment**
Amoxicillin (80–90 mg/kg per day in 2 divided doses) *or* Amoxicillin-clavulanate[a] (90 mg/kg/day of amoxicillin with 6.4 mg/kg/day of clavulanate [amoxicillin to clavulanate ratio of 14:1] in 2 divided doses)	Cefdinir (14 mg/kg/day in 1 or 2 doses) *or* Cefuroxime (30 mg/kg/day in 2 divided doses) *or* Cefpodoxime (10 mg/kg/day in 2 divided doses) *or* Ceftriaxone (50 mg/day IM or IV for 1	Amoxicillin-clavulante[a] (90 mg/kg/day of amoxicillin with 6.4 mg/kg/day of clavulanate in 2 divided doses) *or* Ceftriaxone (50 mg/day IM or IV for 3 days)	Ceftriaxone (50 mg/day IM or IV for 3 days) *or* Clindamycin (30–40 mg/kg/day in 3 divided doses) with or without a third-generation cephalosporin After failure of a second antibiotic • Clindamycin (30–40 mg/kg/day in 3 divided doses) plus a third-generation cephalosporin • Consider

	or 3 days)		tympanocentesis and a subspecialty consultation[b]

[a] May be considered in patients who have received amoxicillin in the previous 30 days or who have the otitis conjunctivitis syndrome.

[b] Perform tympanocentesis or drainage if skilled in the procedure, or seek a consultation with an otolaryngologist for tympanocentesis or drainage. If the tympanocentesis reveals multidrug-resistant bacteria, seek an infectious diseases specialist consultation.

IM, intramuscular; IV, intravenous

Modified from Lieberthal AS, Coroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. Pediatrics 2013;131:e964–e969

Macrolide efficacy at the recommended dosage is limited to disease due to susceptible *S. pneumoniae*. Extracellular middle ear fluid concentrations of macrolides are below the MIC for almost all NTHi and *S. pneumoniae* isolates with efflux or a ribosomal mechanism of resistance. Amoxicillin is ineffective against β-lactamase–producing isolates of NTHi. Amoxicillin-clavulanate resists destruction by β-lactamase and effectively eradicates middle ear infection caused by virtually all NTHi. Isolates of NTHi with altered penicillin-binding proteins (i.e., β-lactamase negative, ampicillin-resistant strains) are common in Japan and have been reported rarely in the US,[91] as have isolates with both altered penicillin-binding proteins and β-lactamase production. These isolates can have MICs for amoxicillin that are at the breakpoint for effective eradication even with the recommended high-dose strategy. Amoxicillin-clavulanate is preferred as first-line therapy when children treated for AOM have an increased risk of β-lactam resistance, including having received a β-lactam antibiotic in the previous 30 days, having concomitant purulent conjunctivitis, or having a history of recurrent AOM; NTHi is predominant in the latter two settings.

Initial therapy for the child with a type I (hypersensitivity) allergic reaction to penicillin (i.e., urticaria, laryngeal spasm, wheezing, or anaphylaxis) remains challenging. The choice of alternatives to β-lactams is limited by the substantial prevalence of resistance. Macrolides and lincosamides lack activity against most *H. influenzae* isolates, and approximately one third of pneumococcal isolates are resistant to macrolides. Resistance to TMP-SMX among *S. pneumoniae* and NTHi isolates also is substantial.[87]

Acknowledging potential limitations, the AAP guidelines recommend these agents as the best alternatives. Patients with other types of allergic reactions can be treated with cefdinir, cefpodoxime, cefuroxime, or intramuscular ceftriaxone.

For the allergic child with severe AOM, a combination of agents such as clindamycin and sulfisoxazole may be effective. Unlike macrolides, clindamycin can be effective against isolates of *S. pneumoniae* with the efflux mechanism of resistance and therefore maintains activity against approximately 80% to 90% of *S. pneumoniae* isolates in the US. However, the proportion of isolates of *S. pneumoniae* with ribosomal mechanisms of resistance is increasing, and local or community antimicrobial susceptibility patterns provide the best prediction for the efficacy of clindamycin.[92]

Oral rather than topical therapy is preferred for children with acute otorrhea without a tympanostomy tube. Although topical therapy with a fluoroquinolone otic drop (i.e., ofloxacin or ciprofloxacin) is equivalent to oral therapy for the treatment of otorrhea in children with tympanostomy tubes or chronic suppurative otitis media, topical therapy has not been studied in children with AOM and acute perforation.[88]

The AAP guidelines emphasize that watchful waiting includes providing analgesia for children suffering from AOM. Limited data suggest that ibuprofen or acetaminophen is effective.[93] Topical benzocaine, procaine, or lidocaine (if available) preparations are an alternative for children ≥2 years of age but should not be used in children with a tympanic membrane perforation. Topical benzocaine is avoided in children younger than 2 years of age because of the risk of methemoglobinemia. For children with severe pain, myringotomy is an effective method to attain relief.

Evaluation of the Child With Recurrent Otitis Media

In clinical practice, most children with recurrent otitis media do not have a quantifiable immunologic abnormality.[94,95] When an immune defect is detected, the abnormality usually is limited to IgG subclasses or an IgA deficiency.[94,96] These disorders often are maturational, and repeated testing at 4 years of age or later can show resolution. For children with recurrent serious infections in addition to recurrent otitis media, more serious immunologic defects must be considered.

Recurrent AOM is common in children with Human immunodeficiency virus (HIV) infection.[97–100] Additional signs of immunodeficiency, such as recurrent thrush, lymphadenopathy, hepatomegaly or splenomegaly, failure to thrive, and chronic diarrhea, usually are present, although recurrent AOM can be the presenting or dominant feature early in life.[101] In 60 episodes of AOM in HIV-infected children, *S. pneumoniae,* NTHi, and GAS were recovered from the middle ear in 56% of cases, a proportion similar to that seen in immunocompetent children. *S. aureus* was identified in HIV-infected children with severe immune compromise.

Immunologic evaluation of the child whose recurrent infections are limited to AOM and who does not have failure to thrive, chronic diarrhea, lymphadenopathy, or organomegaly is unlikely to reveal a serious immune deficiency. Kaur and colleagues[102] and Sharma and colleagues[103,104] studied otitis-prone children. They found that reduced memory $CD4^+$ T lymphocyte generation in the circulation of young children may contribute to the condition.[102–104]

Prevention of Recurrent Acute Otitis Media

Decreasing the morbidity of otitis media has implications for decreasing antimicrobial use and the associated emergence of resistance, reducing healthcare costs and surgical procedures, preventing the language and cognitive delays that occur in some children with recurrent AOM, and preventing prolonged conductive hearing loss. In the pre-PCV7 era, Paradise and colleagues observed that approximately 45% of urban children in the first year of life and 30% in the second year spent more than 3 months of each year with middle ear effusion; 10% of children spent more than 50% of each year with middle-ear effusion.[105]

Prevention of recurrent bacterial AOM can be achieved by preventing nasopharyngeal colonization with otopathogens, preventing viral respiratory tract infection, and providing specific antibacterial immunity. Several interventions, including breastfeeding, avoidance of supine bottle feeding and bottle propping, limiting pacifier use, and frequent hand hygiene can have a modest benefit for prevention of respiratory tract infection and AOM. Specific interventions such as insertion of tympanostomy tubes do not reduce the frequency of acute episodes substantially, but they shorten the duration of middle ear effusion.[106]

Antimicrobial prophylaxis lowers the frequency of colonization with respiratory otopathogens and decreases AOM episodes.[107] The greatest benefit occurs for children at highest risk for recurrent AOM (i.e., 6 to 24 months old) and for otitis-prone children who have multiple episodes per year and for whom the problem does not abate with increasing age.

Chemoprophylaxis

Chemoprophylaxis offers only short-term benefits. Most otitis-prone children continue to have recurrent episodes when prophylaxis is discontinued until immunologic and eustachian tube function have matured.[107] Use of a five-carbon sugar alcohol, xylitol, reduced episodes of AOM in group childcare attendees in Finland (3.03 vs. 2.01 episodes per child-year).[108,109] A US study of xylitol administered as a viscous solution at a dose of 5 g three times per day to otitis-prone children failed to reduce the incidence of clinically diagnosed AOM.[110]

Vaccination

Viral respiratory tract illness is a cofactor in the pathogenesis of AOM. Influenza vaccine has been associated with a reduction in AOM episodes, in febrile AOM, and in myringotomy and insertion of tympanostomy tubes over a winter season.[111] A Cochrane review concluded that annual influenza vaccination solely for its modest effect on reducing AOM and attendant antibiotic use was not justified.

Three pneumococcal conjugate vaccines (i.e., PCV_{CRM}, PCV_{OMP}, and PHiD-CV) administered at 2, 4, and 6 months with a booster at 12 to 15 months of age reduced AOM due to vaccine serotypes of *S. pneumoniae* by approximately 60% (Table 29.8).[112–114] However, the overall reduction of 6% to 10% in episodes of AOM was modest in two clinical trials of PCV7.

TABLE 29.8

Efficacy of 7-Valent Pneumococcal Conjugate Vaccine (PCV7) for the Prevention of Pneumococcal Otitis Media

Cross-Reactive Serotypes (6A, 9N, 18B, 19A, 23A)	No. of Episodes		Difference (%)
	PCV7	Control	
All pneumococcal episodes	271	414	↓34
All serotypes included in the vaccine	107	250	↓57
Vaccine serogroups	41	84	↓51
Nonvaccine serogroups	125	95	↑33

Data from Eskola J, Kilpi T, Palmu A, et al. Efficacy of a pneumococcal conjugate vaccine against otitis media. N Engl J Med 2001;344:403–409.

Initial results with an 11-valent pneumococcal polysaccharide vaccine conjugated to protein D from *H. influenzae* (PHiD-CV) demonstrated that protection against AOM could be extended to include NTHi and vaccine serotypes of *S. pneumoniae*.[114] PHiD-CV has been reformulated as a 10-valent pneumococcal vaccine with 8 of the polysaccharides conjugated to protein D. The efficacy of PHiD-CV was 19% (95% confidence interval [CI], 4%–31%) against first episodes of clinically confirmed AOM and 70% (95% CI, 30%–87%) against bacteriologically confirmed AOM caused by vaccine serotypes. In observational studies in Goiânia, Brazil, a 45% reduction in outpatient visits for otitis in 2011–2013 was reported among children younger than 24 months compared with rates before PHiD-CV introduction (2008–2010).[114]

Follow-up studies of cohorts of the original clinical trials of infant immunization with PCV7 in California and Finland identified significant reductions in tympanostomy tube insertions in immunized children.[115,116] Studies of PCV7 immunization in children who already suffer with frequent ROM have failed to demonstrate a significant reduction in episodes.[108] PCV7 postmarketing studies confirmed an increase in AOM due to NV-Sp. and NTHi.[13] Post-PCV13 studies showed a further reduction in healthcare visits for AOM and insertion of tympanostomy tubes.[41] There was concurrently an increased rate of tympanic membrane perforation or otorrhea but substantial declines in mastoiditis.[41] Substantial reduction in pneumococcal AOM with near elimination of cases due to PCV13 serotypes was documented after PCV7/PCV13 introduction in Southern Israel.[117] These studies are unable to delineate a reduction of AOM due to the direct and indirect effects of PCVs from the changes in diagnostic criteria and management of AOM that have occurred over the decade.

Complications of Acute Otitis Media

Perforation of the tympanic membrane is the most common complication of AOM and is observed most frequently in young children. Studies comparing children with AOM managed with antibiotics compared with initial observation demonstrate excess cases of perforation in the observation group.[51,52] AOM in certain ethnic groups, such as Alaskan Eskimos and Native Americans, is associated with a higher incidence of spontaneous perforation. The microbiology of AOM with acute perforation demonstrates a higher proportion of cases due to GAS and *S. aureus*.[33]

The typical natural history of AOM with perforation is complete resolution with healing of the tympanic membrane. A few patients have persistent dry perforation or chronic suppurative otitis media persisting for 6 to 12 weeks. *S. pneumoniae* and NTHi are the most common pathogens in infants and toddlers, whereas *S. aureus* and *Pseudomonas aeruginosa* are frequent pathogens in older children with tympanostomy tubes and during the summer months.[118]

Amoxicillin usually is effective for the treatment of acute otorrhea through a tympanostomy tube, and compared with placebo, it results in rapid clearing of bacterial pathogens and a shortened duration of otorrhea.[119] An alternative to oral antimicrobial therapy is topical otic suspensions of ofloxacin or ciprofloxacin.[120,121] When CA-MRSA is recovered, oral TMP-SMX or topical fluoroquinolone preparations can have transient benefit, but drainage often recurs.[122,123]

Facial palsy is an uncommon complication of AOM.[124] Facial weakness and earache are predominant symptoms. Antibiotic therapy and myringotomy (with or without tube insertion) usually are sufficient to achieve complete resolution.

Mastoiditis, although decreased dramatically since the routine antibiotic treatment of AOM, remains the most common suppurative complication.[125] *S. pneumoniae,* GAS, and NTHi are the most common pathogens in cases of acute mastoiditis but *P. aeruginosa* was found in 29% and *S. epidermidis* in 31% of cases in one large series.[125] These pathogens should be suspected when otorrhea precedes development of acute mastoiditis.

Labyrinthitis develops when AOM spreads through the round window into the cochlear space. The process can be suppurative or serous (due to bacterial toxins). The onset of labyrinthitis often is sudden, with characteristic vertigo and hearing loss. Acute surgical intervention (i.e., myringotomy with tube insertion) plus antimicrobial therapy provide optimal therapy. Additional rare complications of AOM are brain abscess, epidural abscess, and otic hydrocephalus, which can result from transverse, lateral, or sigmoid sinus thrombosis.

Otitis Media With Effusion

OME is a relatively asymptomatic middle ear effusion that often is associated with conductive hearing loss and can persist for months. The pathogenesis most often reflects a postinfectious event that results from local cytokines and other inflammatory mediators. Biofilm formation and persistence by bacterial otopathogens, individually or in combination, have primary pathogenetic importance and are responsible for ongoing inflammation that leads to persistence of the middle ear effusion.[126–128]

In most children, OME resolves without intervention within a few months.[129] When OME persists beyond this period and there is a substantial conductive hearing loss (>20 dB), intervention with tympanostomy tubes and adenoidectomy may be considered. Consequences of tube placement can include recurrent otorrhea, persistent perforation, development of granulation tissue, chronic otitis media, and cholesteatoma.[130] Repeated insertions of tympanostomy tubes also have been associated with mild hearing loss, including a sensorineural component.[131]

Guidelines from the AAP and American Academy of Otolaryngology[129] and their restatement in the 2012 American Academy of Otolaryngology–Head and Neck Surgery Foundation clinical practice guideline[132] stress the need to identify children at risk for speech, language, and cognitive impairment early in the course of disease. The guidelines focus on children with sensory, physical, cognitive, or behavioral features that are likely to increase the risk of developmental difficulties (Box 29.1) and therefore warrant earlier hearing and language assessment and tympanostomy tube insertion. For otherwise healthy children, watchful waiting for up to 6 months with hearing evaluation at 3 months is suggested.

Box 29.1

Comorbid Conditions Associated With Increased Risk of Developmental Difficulties in Children With Otitis Media With Effusion

Permanent hearing loss independent of otitis media with effusion

Suspected or confirmed speech and language delay or disorder

Autism spectrum disorder and other pervasive developmental disorders

Syndromes (e.g., Down) or craniofacial disorders that include cognitive, speech, or language delays

Blindness or uncorrectable visual impairment

From Rosenfeld RM, Schwartz SR, Pynnonen MA, et al. Clinical practice guideline: tympanostomy tubes in children. Otolaryngol Head Neck Surg 2013;149:S1.

The primary intervention for OME is surgical. Antihistamines and decongestants are ineffective, and therapy with antibiotics or corticosteroids does not result in lasting benefit.[133–135]

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Otitis Externa and Necrotizing Otitis Externa

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Otitis Externa

Epidemiology and Clinical Manifestations

Otitis externa is infection of the skin of the hairy and glabrous parts of the ear canal. Acute otitis externa (i.e., swimmer's ear) is usually unilateral and is often associated with head immersion in water. Any source of prolonged ear canal moisture can cause otitis externa, including hearing aid use and drainage from otitis media with a perforated tympanic membrane. Other predisposing factors include radiation exposure and immunocompromise.

In temperate climates, the disease peaks in the summer. When the skin of the ear canal is wet for prolonged periods, local defense mechanisms are impaired. Cerumen, which has antimicrobial properties,[1] is washed away; the thickness of the keratin layer is reduced; the pH of the canal increases; the skin may become macerated; and microscopic fissures develop. This can cause itching of the ear canal that may predispose to further trauma from cotton-tipped buds.[2] Gram-negative bacteria, most commonly *Pseudomonas* spp., flourish in the moist environment and invade superficial layers of skin.[3–5]

The ensuing inflammatory dermatitis progresses through three stages.[6,7] Each is associated with pain and tenderness exaggerated by movement of the tragus or pinna. In *mild otitis externa*, pain is ameliorated by simple analgesics. Skin of the hairy part of the ear canal is erythematous but not edematous.

In *moderate otitis externa*, there is increasing pain. The patient resists insertion of anything into the ear canal. The skin of the hairy part of the ear canal is intensely red under the macerated pieces of desquamated skin. Edema of the canal skin increases, and the canal lumen is narrowed to less than 50% of its normal diameter, obscuring the tympanic membrane.

Severe otitis externa is characterized by intense pain, often requiring narcotics; inflammatory edema, which narrows the external auditory meatus to barely admit a nasopharyngeal swab; and desquamated debris that precludes visualization of the tympanic membrane. Granulation tissue also may be seen in the ear canal. The patient may or may not have otorrhea, and the auricle can be swollen and painful.[7] In advanced cases, tender preauricular or postauricular lymphadenopathy, protrusion of the auricle, and contiguous cellulitis of the skin overlying the mastoid area can be seen. Unlike acute mastoiditis, the entire auricle not only protrudes but also is edematous, and the posterior auricular sulcus is preserved. Suctioning of the ear canal is difficult to perform without adequate analgesia.

Advanced cases of otitis externa are difficult to differentiate from necrotizing otitis externa, which is a perichondritis of the cartilaginous outer third of the ear canal.[8–10] It also can be difficult to distinguish from noninfectious disorders involving the ear canal, including malignancies (e.g., rhabdomyosarcoma), Langerhans cell histiocytosis, and Wegener granulomatosis.

Etiologic Agents

In healthy individuals, the ear canal microflora includes coagulase-negative staphylococci, corynebacteria, and micrococci. With prolonged exposure to water, gram-negative bacteria predominate.[3] *Pseudomonas aeruginosa* is responsible for most cases of otitis externa associated with swimming or due to persistent otorrhea from a patent tympanostomy tube. Other gram-negative bacteria occur less commonly. *Staphylococcus aureus* may be increasing in incidence.[11] *S. aureus* and *Streptococcus pyogenes* are the usual causes of acute otitis externa that occurs as an extension of a focal infection.[12]

Fungi are uncommon causes of otitis externa, in most series comprising less than 5% of cases.[13] However, in some studies, fungi constitute a higher proportion of isolates.[14] *Aspergillus* spp. account for about two thirds, and *Candida* spp. account for the remainder.[15] Prolonged use of topical antibacterials appears to be a risk factor for otomycosis.[15,16]

Viruses rarely cause otitis externa. Reactivation of latent varicella-zoster virus in the seventh cranial nerve results in herpes zoster oticus, which is characterized by unilateral otalgia, auricular vesicles, and hearing and vestibular symptoms. When these findings are associated with a peripheral facial paralysis, the complex is known as Ramsay Hunt syndrome.[17]

Key Points

Diagnosis and Management of Otitis Externa

Epidemiology and Clinical Manifestations

- Commonly associated with swimming
- Any source of prolonged ear canal moisture can lead to otitis externa.
- Manifests with pain on movement of the tragus or pinna

Etiologic Agents

- *Pseudomonas aeruginosa* is the most common cause.
- *Staphylococcus aureus* is also common.

Management

- Mild cases are treated with topical antibiotic drops (with or without glucocorticoids) and analgesics.
- Moderate or severe cases require aural lavage by an

otorhinolaryngologist.

Prevention

- Otitis externa after swimming can be prevented by thorough drying of the ear canal.
- Prompt treatment of acute otorrhea in patients with tympanostomy tubes with antibiotic-glucocorticoid drops can prevent secondary otitis externa.

Management

Mild cases of otitis externa can be treated with instillation of topical otic antibiotic drops. Culture of otorrhea is usually unnecessary. The patient can enter the swimming pool as long as prolonged submersion is avoided. Excess water should be drained from the ear canal and the ear canal dried thoroughly with a hair dryer.

In addition to adequate analgesia, moderate or severe otitis externa usually requires aural lavage of the ear canal to permit contact of the antibiotic drops with infected skin. This is best accomplished by referring the patient to an otorhinolaryngologist. Lavage may be performed daily in some cases, and close follow-up is essential. A wick sometimes is inserted into the canal to allow topical antibiotic drops to remain in contact with the wall, particularly if canal edema makes instillation of drops difficult. Individuals with moderate or severe otitis externa should avoid swimming and maintain dry ear precautions until inflammation subsides, although formal data on the effect of water precautions are lacking.

Available topical otic antibiotic drops include ofloxacin, ciprofloxacin with hydrocortisone or dexamethasone, and polymyxin B–neomycin–hydrocortisone. The use of corticosteroids is empiric. Topical steroid alone is inferior to antibiotic-steroid combinations.[18] A Cochrane database review found that the topical antibiotic preparations available were equally effective and that all were superior to placebo.[19] Systemic antibiotics are unnecessary for uncomplicated cases.[20]

Neomycin, Neosporin

Neomycin is an aminoglycoside and is ototoxic. It should not be administered unless the tympanic membrane is known to be intact. It may also cause a contact dermatitis in some patients. However, in a trial comparing ciprofloxacin-dexamethasone with polymyxin B–neomycin–hydrocortisone, adverse events were uncommon and were not different in the two groups.[21] Polymyxin B–neomycin–hydrocortisone is administered three to four times daily, ciprofloxacin-containing drops are administered twice daily, and ofloxacin drops can be administered once daily with equivalent cure rates.[22] Most patients can be treated with a 7-day course. Symptoms improve within 3 to 6 days of starting therapy. For patients who do not respond, physicians should consider the possibility of necrotizing otitis externa, particularly in immunocompromised hosts. Guidelines for the management of acute otitis externa have been published by the American Academy of Otolaryngology–Head and Neck Surgery Foundation.[23]

For the patient who fails to respond to empiric therapy, fungal infection should be considered. Otomicroscopic examination may reveal fungal elements, and a Gram stain of exudate may reveal the hyphae of *Aspergillus* spp. or the budding yeast of *Candida* spp. A 1% solution of clotrimazole is the most commonly used agent for otomycosis.[24] It has excellent activity against *Aspergillus* and *Candida*.[25] Nontuberculous mycobacteria may rarely be the cause of persistent tympanostomy tube otorrhea.[26] Furunculosis and local cellulitis respond best to the application of warm compresses and an orally administered antibiotic directed against *S. aureus.*

Prevention

After immersion, swimmers prone to recurrent otitis externa may benefit from thorough drying of the ear canals with a hair dryer. The prophylactic instillation of 2% acetic acid can be used to reduce *Pseudomonas* colonization.[27]

Prompt treatment of acute otorrhea in children with tympanic membrane perforation or tympanostomy tubes can prevent the development of secondary otitis externa. In a randomized trial, antibiotic-glucocorticoid drops were superior to oral amoxicillin-clavulanate or observation in resolving otorrhea.[28]

Necrotizing Otitis Externa

Epidemiology and Clinical Manifestations

Necrotizing (i.e., malignant) *otitis externa* results from invasive infection of the cartilage and bone of the external ear canal. A more accurate term is *skull base osteomyelitis due to otitis externa*.[29] Infection begins in the external auditory canal and spreads to the skull base through the fissures of Santorini, small perforations in the cartilaginous portion of the canal.[30] Infection then spreads along venous channels and fascial planes. The compact bone of the skull base becomes replaced with granulation tissue, causing bone destruction. Mastoid involvement is common.

Necrotizing otitis externa occurs most frequently in adults with diabetes mellitus. In a review of 46 adult cases, two thirds of patients were diabetic.[31] In contrast, a series of 14 pediatric cases reported only 21% with diabetes.[32] Other predisposing factors include immune deficiency, especially due to AIDS; chemotherapy-induced neutropenia; and functional neutrophil disorders.[33,34] It can be the presenting manifestation of malignancy.[35] Rarely, patients without risk factors are affected.[36]

The presenting symptoms are severe otalgia and otorrhea; both occur in more than 90% of patients.[31] About 25% of patients have facial nerve palsy at presentation, and children may be at higher risk for facial palsy.[30] This finding indicates further extension of the disease into the skull base, but its prognostic value is unclear.[37,38] Physical examination reveals purulent otorrhea with a swollen, tender external auditory canal. Granulation tissue or exposed bone is seen on the floor of the canal at the bone-cartilage junction.[30] Patients are often afebrile and have a normal leukocyte count, although the erythrocyte sedimentation rate is usually elevated. For children, the presentation is more acute, and they are more often febrile.

The initial manifestations of necrotizing otitis externa can mimic those of otitis externa, and clinicians must be aware of this possibility in the high-risk host. The diagnosis in a patient not known to have risk factors should prompt testing for diabetes and immune deficiency.

Imaging studies used include computed tomography (CT), magnetic resonance imaging (MRI), bone scans, and gallium scans. CT is sensitive in detecting bone erosion and decreased skull base density.[30] It is also sensitive in diagnosing abscess formation and involvement of the mastoid (Fig. 30.1). However, it is inadequate for demonstrating intracranial extension and marrow involvement. MRI is superior in showing soft tissue changes, dural enhancement, and involvement of the medullary bone spaces.[39] A technetium bone scan is highly sensitive, including early in the course of infection, but it is nonspecific and may remain positive for a prolonged period.[40] Gallium scans, which have similar sensitivity, are more useful for monitoring the response to therapy.[40]

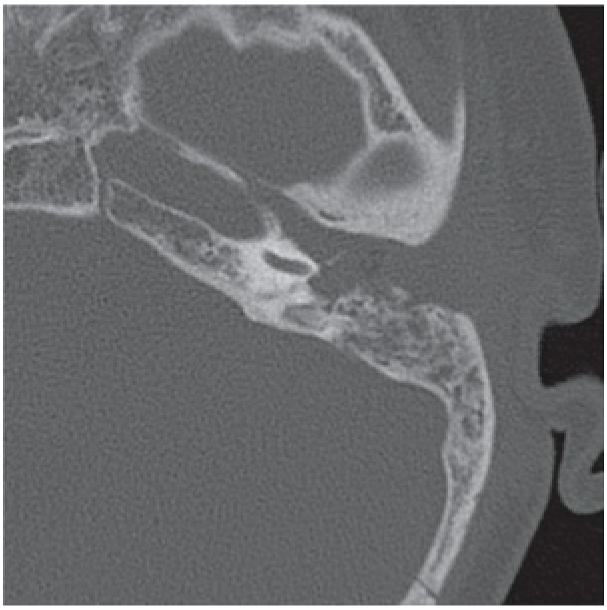

FIGURE 30.1 A 21-year-old man with medulloblastoma and chemotherapy-induced neutropenia had a 10-day history of severe left ear pain, otorrhea, and facial palsy. Axial, noncontrast computed tomography depicts soft tissue opacification of the left external auditory canal and opacification of the left middle ear and mastoid air cells. Irregularity and erosion of the posterior margin of the osseous left external auditory canal suggests osseous invasion and mastoid osteomyelitis consistent with necrotizing otitis externa. Intraoperative cultures of specimens obtained during debridement of the left mastoid grew *Pseudomonas aeruginosa*.

Complications result from contiguous spread to nearby structures. Spread to the stylomastoid foramen results in facial nerve palsy. Less commonly, involvement of the jugular foramen results in palsies of the glossopharyngeal, vagus, and accessory nerves. Septic thrombophlebitis of the internal jugular vein and of the sigmoid sinus may occur. Intracranial extension can result in meningitis, cerebral abscess, or dural sinus thrombosis, all of which portend a poor prognosis.[29]

Etiologic Agents

P. aeruginosa is by far the most common cause of necrotizing otitis externa, especially in patients with diabetes.[31] *S. aureus* is the second most common cause. *Aspergillus* spp., most commonly *A. fumigatis*, are sometimes isolated, particularly in patients with advanced AIDS.[31]

Key Points

Diagnosis and Management of Necrotizing Otitis Externa

Epidemiology and Clinical Manifestations

- Invasive infection of the cartilage and bone of the external ear canal
- Predisposing factors include diabetes mellitus, AIDS, neutropenia, other immune deficiency
- Manifested by severe otalgia and otorrhea; sometimes by facial palsy
- Usually diagnosed by computed tomography or magnetic resonance imaging

Etiologic Agents

- *Pseudomonas aeruginosa* is the most common cause.
- *Staphylococcus aureus* is also common.
- Occasionally, *Aspergillus* spp. are isolated.

Management

- Limited surgery to obtain cultures and to debride necrotic tissue
- Aggressive surgical resection is avoided.
- Empiric parenteral antibiotic therapy (e.g., cefepime, gentamicin) to cover *Pseudomonas*

Management

In the past, necrotizing otitis externa was managed surgically. Currently, most cases are effectively treated with prolonged courses of antibiotics. However, surgery still plays a critical role in two aspects: obtaining tissue samples for culture and histology and for local debridement of necrotic tissue. In contrast, more aggressive surgical resection may propagate infection.

Initial empiric therapy should be directed toward coverage of *P. aeruginosa* and *S. aureus*. Using two agents with antipseudomonal activity, such as cefepime and gentamicin, is prudent initially. Fluoroquinolones should be avoided if the patient recently received topical fluoroquinolone therapy because the incidence of resistance is high.[31,41] Vancomycin can be used for initial staphylococcal coverage. If patients fail to improve on initial therapy and adequate debridement has occurred, imaging to assess extension of infection should be considered. The possibility of infection by a filamentous fungus should be entertained and empiric antifungal therapy started with liposomal amphotericin or voriconazole. The duration of therapy usually is at least 6 weeks, although some patients are switched to oral therapy earlier.[30] Hyperbaric oxygen therapy has been proposed as an adjuvant to antimicrobial therapy, although high-quality data are lacking.[42]

Prognosis

Once a condition with a case-fatality rate of 50%,[43] necrotizing otitis externa is now cured in approximately 95% of patients.[31] Poor prognostic factors include intracranial extension, advanced underlying disease, and infection with *Aspergillus* spp.[29] In contrast to adults with necrotizing otitis externa, facial nerve paralysis in children is usually not reversible. Children are also more likely to experience permanent hearing loss from ossicular destruction.[10,32]

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31

Mastoiditis

Ellen R. Wald, James H. Conway

Acute Mastoiditis

Acute mastoiditis is exclusively a complication of acute otitis media (AOM). Previously, only one third of cases occurred in the context of a first episode of otitis media[1]; more recently, acute mastoiditis has been the first evidence of otitis media in at least 50% of affected children.[2,3]

The incidence of mastoiditis declined remarkably after the introduction of antibiotics. Where antibiotic use for AOM has been systematically restricted, the incidence of acute mastoiditis may be higher, although it remains a relatively unusual occurrence.[4–6] In some settings such as Sweden, where antibiotic therapy for AOM in children younger than 2 years of age may be delayed under a watchful waiting approach with close supervision, no significant increase in acute mastoiditis has been reported.[7] However, when acute mastoiditis cases do occur, intracranial and extracranial complications frequently are observed.[3,8,9]

Pathogenesis

Mastoiditis is inflammation of the mastoid air cells in the temporal bone. Knowledge of the anatomy of the middle ear and mastoid is essential to understand the clinical manifestations of mastoiditis and its complications. Fig. 31.1 shows the relationships among the eustachian tube, middle ear, and mastoid. At birth, the mastoid consists of a single air cell, the antrum, which is connected to the middle ear by a narrow channel, the aditus ad antrum.[10] As the child grows, the mastoid bone becomes pneumatized, resulting in a series of interconnected air cells that are lined by modified respiratory epithelium.

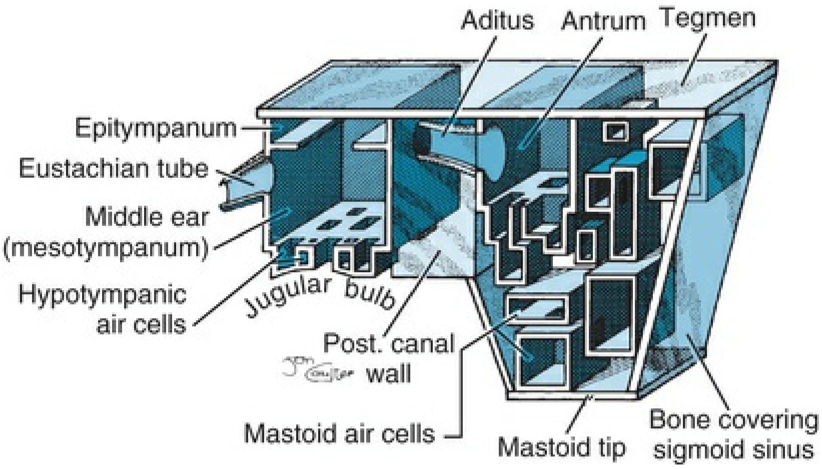

FIGURE 31.1 Schematic representation of the anatomy of the middle ear and mastoid air cell system. The aditus ad antrum is the narrow connection between the two; it may be a site of obstruction inhibiting drainage into the middle ear. (From Bluestone CD, Klein JO. Intratemporal complications and sequelae of otitis media. In: Bluestone CD, Simons JP, Healy GB (eds). Pediatric Otolaryngology, 5th ed. Shelton CT, People's Medical Publishing House-USA, 2014. pp. 781–847.)

When AOM develops as a result of eustachian tube dysfunction, there is an acute inflammatory response of the mucosa lining the middle ear and, in many cases, the mastoid.[11] Most episodes of AOM respond to antibiotic therapy. Eustachian tube dysfunction resolves, and the mucosa of the middle ear and mastoid recovers. In rare cases of newly diagnosed AOM or in cases of inadequate or inappropriate treatment, inflammation of the middle ear and mastoid persists. Histopathologic specimens from children who undergo mastoidectomy for acute or chronic mastoiditis demonstrate similar subacute or chronic infectious changes.[12] Serous and then purulent material accumulates within the mastoid cavities. As the pressure increases, the thin bony septa between air cells may be destroyed (i.e., acute coalescent mastoiditis).[10] This may be followed by formation of abscess cavities and ultimately by the dissection of pus into adjacent areas.

The direction in which purulent material dissects determines the clinical presentation and complications associated with acute mastoiditis (Box 31.1). Pus traversing the aditus ad antrum reaches to the middle ear and empties through the eustachian tube (with resolution of the process) or a perforation of the tympanic membrane. If the pus erodes the lateral cortex of the mastoid, a subperiosteal abscess is produced. The abscess results in swelling or fluctuation above the auricle in infants (when erosion comes from the zygomatic mast cells) or behind the lower earlobe over the mastoid process in older children.[8] Rarely, erosion occurs through the medial aspect of the mastoid tip, resulting in a neck abscess beneath the attachment of the sternocleidomastoid and digastric muscles (i.e., Bezold abscess).[13]

Box 31.1

Complications of Mastoiditis

Extracranial

Subperiosteal abscess

Bezold abscess

Facial nerve paralysis

Osteomyelitis

Deafness

Labyrinthitis

Intracranial

Meningitis

Temporal lobe or cerebellar abscess

Epidural empyema

Subdural empyema

Venous sinus thrombosis

Pus can dissect medially to the petrous air cells (in the 20% of the population in which there is pneumatization), resulting in petrositis, or posteriorly to the occipital bone, resulting in osteomyelitis of the calvarium (i.e., Citelli abscess).[10] Purulent material can spread to the labyrinth and facial nerve. Pus within the mastoid can dissect toward the inner cortical bone, causing suppurative complications in the central nervous system, such as meningitis; epidural, subdural, temporal lobe, or cerebellar abscesses; and venous sinus thrombosis.

Clinical Presentation

The clinical presentation of the patient with mastoiditis depends on the patient's age and the stage of the osteitis (i.e., uncomplicated or already evolved to a subperiosteal abscess). Uncomplicated infection in a child younger than 2 years manifests as fever, otalgia or irritability, retroauricular pain, swelling, erythema, and a downward and outward deviation of the auricle (Fig. 31.2).[8] In most cases, otorrhea or a bulging, immobile, opaque tympanic membrane is observed. There may be sagging of the posterosuperior wall of the external auditory canal. In rare instances with obstruction at the aditus ad antrum, middle ear infection clears through the eustachian tube, but the mastoid, unable to drain, continues to suppurate.

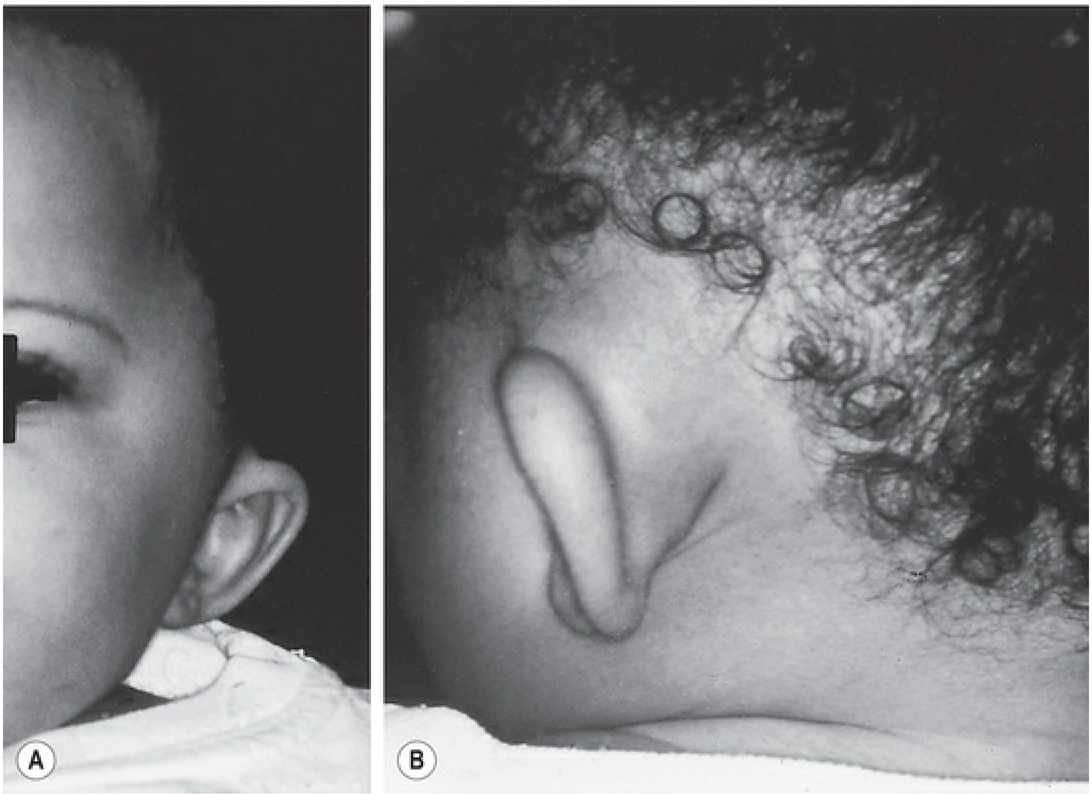

FIGURE 31.2 A 13-month-old toddler with a 10-day history of acute otitis media unresponsive to amoxicillin therapy. (A and B) There is erythema and edema above the left ear with downward, outward, and anterior displacement of the pinna.

In children older than 2 years, the pinna usually is deviated upward and outward because the inflammatory process frequently concentrates over the mastoid process. When subperiosteal pus has accumulated, a fluctuant, erythematous, and tender mass can be found overlying the mastoid bone in all age groups.

Considerable attention has been given in the past 2 decades to the entity called *masked mastoiditis* or *subacute mastoiditis*.[14] The patient typically has had persistent middle ear effusion or recurrent episodes of acute otitis media without sufficient antimicrobial therapy. In either case, there is a low-grade but persistent infection in the middle ear and mastoid with osteitis. Masked mastoiditis can manifest as fever, otalgia, and an abnormal tympanic membrane or occasionally manifest with an extracranial or intracranial complication.

Microbiology

The most recent prospective study of the microbiology of acute mastoiditis in children was published in 1987.[15] Precise delineation of the microbiology has been hampered by routine antibiotic therapy before clinical presentation. Most existing series published in the antibiotic era are retrospective reviews.[1–3,8,14,16–25]

Clinical specimens should be obtained from the middle ear by tympanocentesis or by aspiration through a tympanostomy tube or perforation after careful sterilization of the surrounding structures. Cultures obtained from the external canal without careful sterilization can be contaminated with *Pseudomonas aeruginosa, Staphylococcus aureus,* and other colonizing organisms. Culture of the cerebrospinal fluid is valuable in cases of bacterial meningitis. Blood cultures rarely are positive. Percutaneous aspiration of a subperiosteal abscess should be undertaken, particularly if definitive surgery will be delayed. Materials from abscesses (i.e., brain, epidural, or subdural) that are drained or aspirated should be submitted for Gram stain and aerobic and anaerobic cultures.

In contrast to the usual pathogens that cause AOM (i.e., *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis*),[26] the bacterial species most often implicated in acute mastoiditis are *S. pneumoniae, S. pyogenes, P. aeruginosa,* and *S. aureus* (Table 31.1). *P. aeruginosa* rarely is a true pathogen in acute mastoiditis. Exaggerated rates of recovery may reflect the sampling method for culture from the external canal.[22] Except for a single prospective study in which anaerobic bacteria predominated,[15] *H. influenzae,* Enterobacteriaceae bacteria, mycobacteria, and anaerobic organisms are recovered only occasionally.

TABLE 31.1

Bacteriology of Cases of Acute Mastoiditis in Children (1955–2009)[a]

Bacterial Species	Number	Percentage
Streptococcus pneumoniae	230	32
Streptococcus pyogenes	121	17
Staphylococcus aureus	62	9
Other gram-positive cocci[b]	26	4
Haemophilus influenzae	34	5
Pseudomonas aeruginosa	119	16
Other gram-negative bacilli[c]	29	4
Anaerobic bacteria[d]	72	10
Mycobacterium tuberculosis	31	4
Total isolates	724	100

[a] Many patients received antimicrobial therapy before specimens were obtained for culture. Isolates were obtained from blood, myringotomy aspirate, external auricular drainage, subperiosteal aspirate, cerebrospinal fluid, or surgical specimens.

[b] Viridans streptococci, enterococci, and coagulase-negative staphylococci.

[c] *Citrobacter freundii*, *Escherichia coli*, *Enterobacter* spp., *Acinetobacter* spp., *Klebsiella* spp.

[d] *Bacteroides* spp., *Fusobacterium nucleatum*, and microaerophilic streptococci.

Data from references 1–3, 8, 12, and 16–25.

The introduction of heptavalent pneumococcal conjugate vaccine (PCV7) has not affected the proportion of acute mastoiditis cases caused by *S. pneumoniae*[24] typically related to an increase in serotype 19A as the predominant serotype isolated from mastoid cultures.[27] Although there appeared to be an initial decline in the incidence of acute mastoiditis after the introduction of PCV7 in Australia, Israel, and some areas of the United States, it did not persist, and recent reports suggest that the incidence rates have returned to prevaccination rates.[28–30] The effect of PCV10 and PCV13 on the incidence and microbiology of mastoiditis requires ongoing study.

Diagnosis

The diagnosis of mastoiditis usually is made clinically, without need for imaging studies (Box 31.2). Some studies have shown that outcomes are similar for patients with acute mastoiditis regardless of whether computed tomography (CT) scans are performed.[31] A systematic review of more than 1000 articles identified the clinical signs most frequently used to diagnose acute mastoiditis as postauricular swelling, erythema, tenderness, and protrusion of the auricle.[32] High-grade fevers and elevated inflammatory markers such as absolute neutrophil counts and C-reactive protein levels can suggest more complicated infections.[25]

Box 31.2

Diagnosis of Acute Mastoiditis

Fever, otalgia, postauricular swelling plus redness

- Older child: ear up and out
- Infant: ear down and out

Tympanic membrane: acute otitis media

Radiograph: mastoid air cells coalescent or clouded

Computed tomography, magnetic resonance imaging, or bone scan as needed

If plain radiographs are obtained, they often show clouding of the mastoid or coalescence of air cells (i.e., dissolution of thin bony septa from increased pressure and ischemia). Clouding of the mastoid is not diagnostic of acute mastoiditis and is observed in at least 50% of patients with uncomplicated AOM. Coalescent mastoiditis is a diagnostic radiographic finding, but it is seen in few patients. Plain radiographs in cases of acute and even complicated mastoiditis have been normal.[1,33]

CT imaging usually is more helpful when there are intracranial complications or for patients suspected of having masked mastoiditis.[13,22] CT evidence of mastoiditis consists of haziness or destruction of the mastoid outline and loss of or decrease in sharpness of the bony septa that define the mastoid air cells (Fig. 31.3).[10] Cloudiness in areas normally pneumatized, which can be seen in uncomplicated AOM, is not diagnostic of mastoiditis (Fig. 31.4).

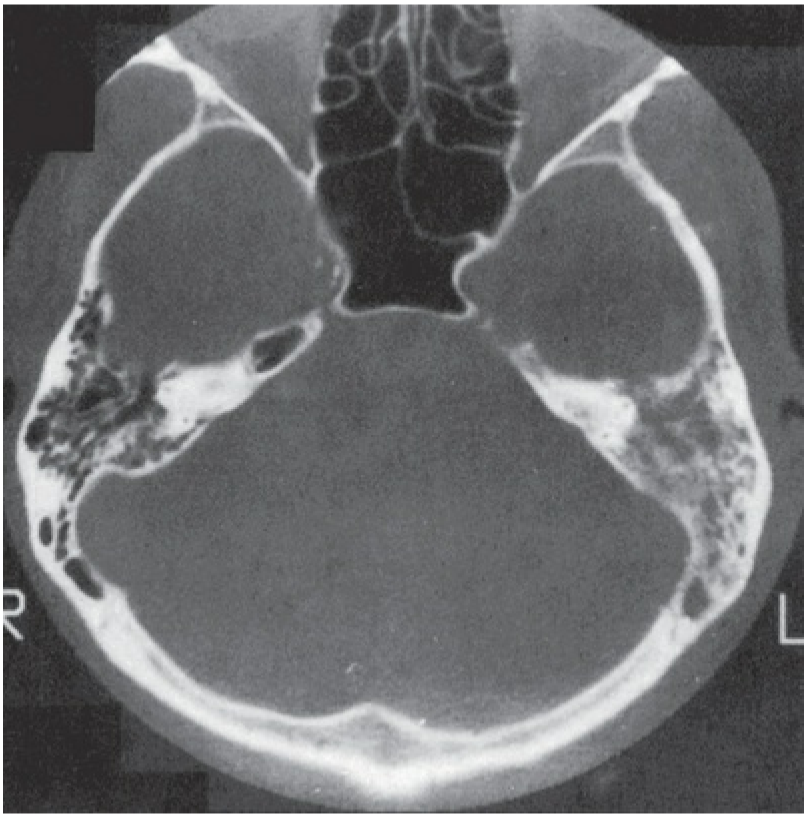

FIGURE 31.3 Computed tomography of a child with acute mastoiditis shows coalescence and destruction of septa between the mastoid air cells.

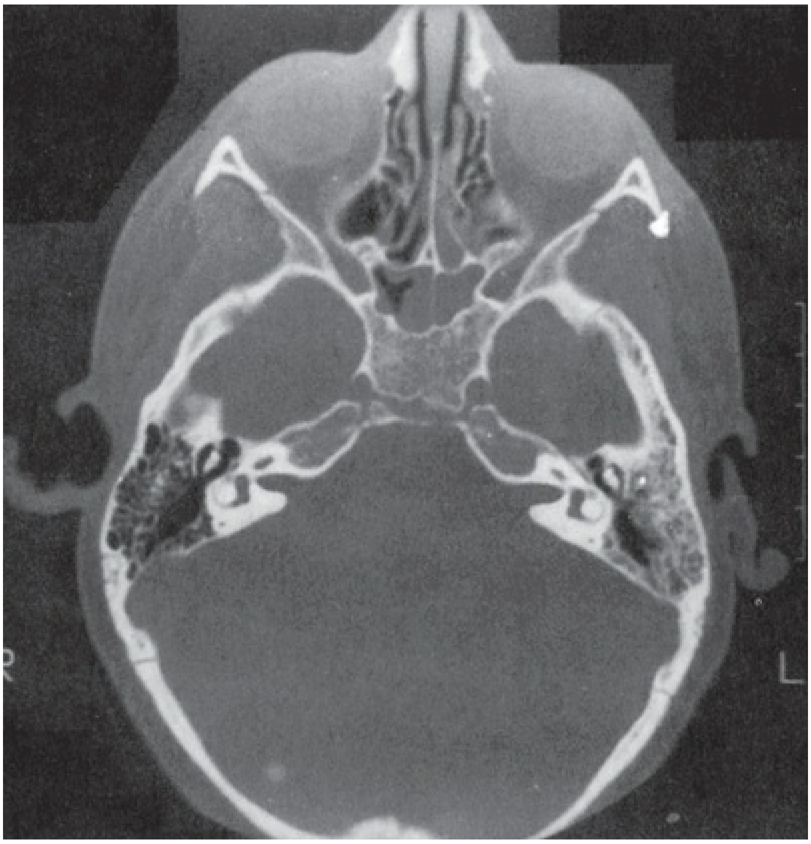

FIGURE 31.4 Computed tomography of a child with acute otitis media shows clouding of the mastoid without bony destruction.

Lytic lesions of the temporal bone and soft tissue abscess sometimes can be seen (Fig. 31.5). For bony destruction to be appreciated, 30% to 50% of bone must be demineralized. When CT shows cloudiness, a technetium-99 bone scan, which is more sensitive to osteolytic changes, may be useful.[34]

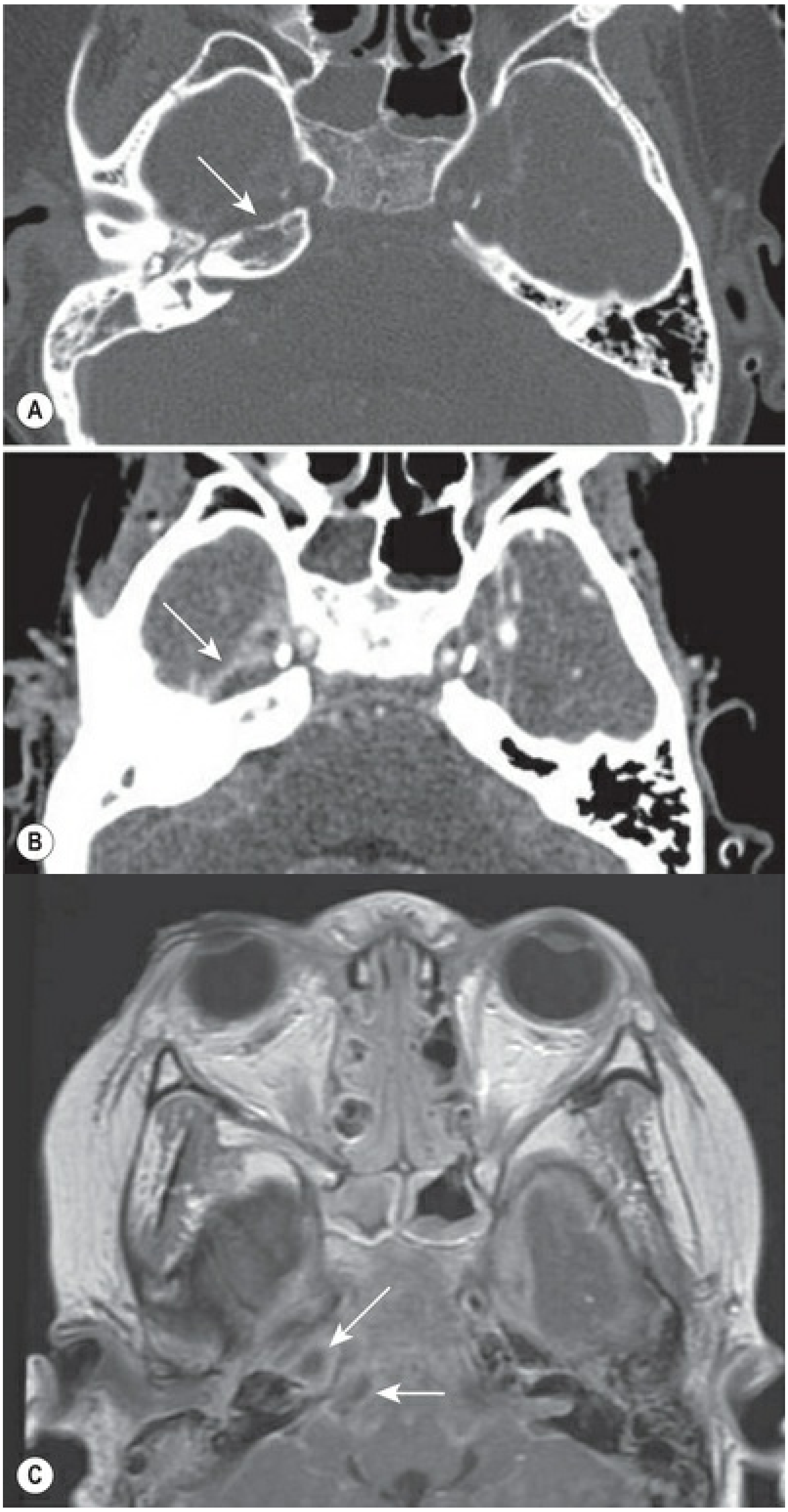

FIGURE 31.5 Case of a 6-year-old boy with Gradenigo syndrome. (A) Noncontrast computed tomography (CT) shows expansion and erosion of the apex of the petrous portion of the right temporal bone *(arrow)* and mastoid coalescence. (B) Contrast-enhanced CT shows an abscess with rim enhancement along the superior border of the petrous apex with an anterior extension *(arrow).* (C) Contrast-enhanced, T1-

weighted, axial magnetic resonance imaging shows hypointense abscesses with rim enhancement around the petrous bone *(long arrow)* and in the right anterior pons *(short arrow)*. (Courtesy of E.N. Faerber, St. Christopher's Hospital for Children, Philadelphia, PA.)

CT with enhancement or magnetic resonance imaging (MRI) is recommended for patients with suspected vascular thrombosis as a complication of mastoiditis. MRI with gadolinium enhancement confirms the diagnosis and delineates the extent of suspected disease[35] because of its higher sensitivity for detection of extra-axial fluid collections and associated vascular complications.[36]

Complications

Complications of mastoiditis are related to the spread of infection or inflammation from the middle ear or mastoid to contiguous structures and occur in 7% to 16% of cases.[18,22] Suppurative labyrinthitis (resulting in deafness), Bezold abscess, and cranial osteomyelitis are infectious complications. Facial paralysis can result from infection or inflammation of the facial nerve as it traverses the petrous bone. If infection spreads to the petrous bone, Gradenigo syndrome can follow, characterized by cranial nerve VI palsy, pain in the distribution of the trigeminal nerve (i.e. eye pain), and otorrhea. Intracranial complications include epidural or subdural empyema, cerebellar or temporal lobe abscess, meningitis, and venous thrombosis.

Management

Treatment of uncomplicated mastoiditis includes intravenous antimicrobial therapy and usually myringotomy, with or without placement of a tympanostomy tube. When possible, tympanocentesis should be performed if there is an intact tympanic membrane to ascertain the microbiologic profile and antimicrobial susceptibility.[10] The same treatment is appropriate when facial paralysis occurs as an isolated complication.[10]

If the child does not improve in 48 hours (i.e., evidenced by diminution of systemic and local findings), a simple mastoidectomy may be required. Simple mastoidectomy in combination with antimicrobial therapy and tympanostomy tube placement usually is indicated as initial management when a subperiosteal abscess exists. Radical mastoidectomy only is performed when there is no response to simple mastoidectomy, as evidenced by continued otorrhea.[10]

This stepwise approach continues to prove effective, and publications support a conservative approach that reserves more invasive surgical procedures for selected patients who are failing to improve. Groups from France, Israel, and Sweden have performed retrospective reviews that endorse a standardized approach to assessment and reserve mastoidectomy for patients who fail to improve or have significant abscesses.[37–39]

Several agents are appropriate for the intravenous treatment of acute mastoiditis. Empiric antibiotic therapy should provide coverage for common bacterial pathogens (see Table 31.1). Cefepime (100–150 mg/kg/day in doses divided every 8–12 hours), ceftazidime (150 mg/kg/day in divided doses every 8 hours), or piperacillin-tazobactam (240 to 300 mg/kg/day [piperacillin component] in divided doses every 6 to 8 hours [not approved for use in patients younger than 12 years]) is suitable. In a penicillin-allergic patient, clindamycin (40 mg/kg/day in divided doses every 6 hours) plus aztreonam (120 mg/kg/day in divided doses every 8 hours) can provide coverage for gram-positive and gram-negative pathogens. The addition of vancomycin (60 mg/kg/day in divided doses every 6 hours) should be considered for children who are severely ill with concerns about secondary bacterial meningitis and for those at high risk for resistant pneumococcal infection caused by penicillin-resistant pneumococci or methicillin-resistant *S. aureus*. Immunization history and consideration of local resistance data are important in determining optimal antibiotic choices.

If the Gram stain of aspirated material demonstrates an unexpected finding, additional antimicrobial agents are considered (e.g., for brain abscess). When results of culture and susceptibility tests are available, therapy is adjusted. Intravenous treatment should be maintained for at least 7 to 10 days. If the clinical response to treatment has been satisfactory, oral antimicrobial therapy can be substituted to complete a 4-week course. Prolonged courses of intravenous therapy usually are unnecessary in the absence of central nervous system extension of infection. Placement and maintenance of indwelling vascular catheters increase the cost of therapy significantly and come with associated risks.[40]

Chronic Mastoiditis

Pathogenesis

Chronic mastoiditis usually is the result of chronic suppurative otitis media (CSOM)[10] and is less frequently the result of inadequate management of acute mastoiditis. CSOM is characterized by long-standing (>3 weeks), painless otorrhea through a nonintact tympanic membrane (i.e., spontaneous perforation or patent tympanostomy tube) that is not responsive to the antibiotics customarily prescribed for patients with AOM (Box 31.3).[10,41] (See Chapter 30).

Box 31.3

Diagnosis of Chronic Mastoiditis

Otorrhea ≥3 wk

Nonintact tympanic membrane (perforation or patent tympanostomy tube)

Nonresponsive to usual antibiotics

Etiology

- Pseudomonads
- Staphylococci
- Other gram-negative bacilli

Complications

- Cholesteatoma
- Progressive mastoiditis

- Deafness (eighth nerve or ossicular)

A nonintact tympanic membrane is essential for pathogenesis, providing microbial species that colonize the external auditory canal access to the middle ear and ultimately the mastoid. These organisms cause a low-grade, persistent inflammatory response that is typically unaltered by conventional therapeutic agents for AOM. Although the inflammatory process is painless and patients rarely are febrile, CSOM can lead to chronic osteitis of the mastoid and complications such as hearing loss, cholesteatoma, facial nerve paralysis, meningitis, and brain abscess.

The microbiology of CSOM and chronic mastoiditis was documented during the 1980s–1990s (Table 31.2).[10,42–46] *P. aeruginosa* is the most common, followed by gram-negative enteric bacilli and *S. aureus. P. aeruginosa* and *S. aureus* occur together frequently.[10,42,47] With the exception of a single study, anaerobic flora are isolated only occasionally.[48] Rarely, *S. pneumoniae* or *H. influenzae* is causative.

TABLE 31.2

Bacteriology of Chronic Suppurative Otitis Media in 200 Children (1983–1992)

Bacterial Species	Number	Percentage
Pseudomonas spp.	176	58
Pseudomonas aeruginosa	171	
Other species	5	
Enteric gram-negative rods	50	16
Escherichia coli	8	
Enterobacter spp.	9	
Proteus spp.	17	
Others	16	
Staphylococcus spp.	41	13
Staphylococcus aureus	38	
Staphylococcus epidermidis	3	
Streptococcus pneumoniae	10	3
Haemophilus influenzae	10	3
Others	19	6

Data from references 42–46.

Mycobacterium tuberculosis was a common cause of mastoiditis in the early 1900s, manifesting as a chronically draining ear. This organism now is recovered very infrequently from patients with long-standing otorrhea.[49] Nontuberculous mycobacteria and *M. bovis* can produce an identical clinical syndrome. Most nontuberculous mycobacterial infections are thought to occur through the introduction of organisms through perforated tympanic membranes, emphasizing the need for good hygiene after tympanostomy tube placement.[50] *M. bovis,* which is not easily distinguished from *M. tuberculosis,* should be considered in patients who consume unpasteurized dairy products.[51]

Diagnosis

The diagnosis of CSOM usually is based on the typical clinical presentation of painless otorrhea unresponsive to conventional antibiotic therapy. The patient with CSOM is readily distinguished from the patient with a spontaneous perforation due to AOM, in whom systemic and local symptoms are prominent, and the response to antimicrobial management is brisk. The CSOM patient also must be differentiated from the child with otorrhea due to otitis externa in whom pressure on or movement of the tragus causes discomfort and the tympanic membrane is normal.

An otomicroscopic examination of the tympanic membrane should be undertaken by the otolaryngologist in the initial evaluation of chronic otorrhea.[47] This procedure, which may require general anesthesia, provides an opportunity to detect a cholesteatoma, retraction pocket, granulation tissue, polyp, or foreign body. A specimen should be obtained from the middle ear cavity without contamination from the external auditory canal and sent for Gram and acid-fast stains and culture for aerobic, anaerobic, and mycobacterial pathogens. A biopsy should be performed of any suspicious tissue protruding through the perforation or tympanostomy tube because rhabdomyosarcoma and neuroblastoma can manifest as CSOM or chronic mastoiditis, usually with associated cranial nerve palsies.[52] The tuberculin skin test (TST) should be performed when CSOM does not respond to standard antimicrobial therapy.

Management

Failure to respond to oral antibiotics is important in defining CSOM and suggests *P. aeruginosa* as the probable cause. Treatment of patients with CSOM often is initiated with topical antimicrobial agents and vigorous aural toilet, which consists of daily suctioning of the external auditory canal to permit delivery of topical therapy. When otorrhea is copious, ototopical therapy cannot be effective unless the external canal is cleared. Topical therapy is chosen because the bacteria isolated from patients with CSOM often are resistant to commonly prescribed oral antibiotics.

Ofloxacin otic solution (0.3%), a topical fluoroquinolone approved for use in children in 1999, has excellent activity against virtually all microbial species likely to be found in patients with CSOM.[41,53] It has shown no ototoxic effects when administered to adults or children.[54] A Cochrane database of systematic reviews performed to assess the effect of topical antibiotics without corticosteroids for patients with chronically draining ears and underlying eardrum perforations found topical quinolones significantly better for CSOM than antiseptics and no drug. Studies were inconclusive regarding differences between quinolone and nonquinolone antibiotics.[55] The aural discharge frequently clears within several days to 1 week after appropriate topical therapy is started.

If the CSOM does not respond to topical therapy, a course of intravenous antimicrobial therapy is appropriate. Comparison of regimens for the treatment of CSOM is confounded by differences in patient selection, causative agents, use of topical agents in conjunction with systemic therapy, frequency of aural toilet, and use of prophylactic antibiotics after completion of initial therapy. An appropriate choice for intravenous therapy is an antipseudomonal penicillin (e.g., piperacillin-tazobactam at 240 to 300 mg/kg/day in divided doses every 6 hours [not approved for use in children younger than 12 years]) or a third- or fourth-generation cephalosporin with antipseudomonal activity, such as ceftazidime (150 mg/kg/day in divided doses every 8 hours) or cefepime (100–150 mg/kg/day in doses divided every 8–12 hours).[41] Daily aural toilet is instituted for debridement and to assess cessation of drainage. Intravenous therapy should be continued at least 1 week after drainage has ceased because the middle ear mucosa is still likely to be inflamed and immediate relapse is possible.[56,57] If otorrhea persists despite parenteral therapy or recurs shortly after the cessation of intravenous therapy, a simple tympanomastoidectomy is required.

Several investigators have reported effectively treating CSOM in children with intravenous or intramuscular antibiotics (e.g., ceftazidime) on an outpatient basis, with daily return to the otolaryngologist for aural toilet.[46] Unfortunately, CSOM remains a neglected and difficult disease. There are few new data on prevention or treatment.[58]

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32

Sinusitis

Ellen R. Wald, Gregory P. DeMuri

Upper respiratory tract infections (URIs) are the most common medical condition evaluated by primary practitioners who care for children. An estimated 5% to 10% of URIs in early childhood are complicated by acute bacterial sinusitis (ABS).[1] Children average 6 to 8 colds per year, and sinusitis is a common problem in clinical practice.

Pathogenesis

The respiratory mucosa that lines the nose is continuous with the mucosa that lines the paranasal sinuses. Secretions produced within the sinus cavities are delivered through the sinus ostia to the nose by normal mucociliary function. The maxillary, anterior ethmoid, and frontal sinuses drain to the middle meatus. The sphenoid and posterior ethmoid sinuses drain to the superior meatus.

Three key elements important to the normal physiology of the paranasal sinuses are patency of the ostia, function of the ciliary apparatus, and integral to the latter, quality of the secretions.[2] Retention of secretions in the paranasal sinuses usually results from one or more of the following conditions: obstruction of the ostia, reduction in the number of or impairment in the function of the cilia, and overproduction of or change in the viscosity of secretions.

Most cases of ABS are thought to be bacterial complications of viral URIs. The viral infection affects the mucosa of the nose, causing rhinitis, and often affects the mucosa of the sinuses. In most instances, the inflammatory response subsides spontaneously. In some cases, however, mucositis results in obstruction of the sinus ostia, impairment of the mucociliary apparatus, and alteration in the volume and quality of secretions.

The narrow caliber of the individual ostia that drain the maxillary and ethmoid sinuses sets the stage for obstruction to occur easily and often during the course of a viral URI. When obstruction occurs, there is a transient increase in intrasinus pressure. This is followed quickly by the development of negative pressure within the sinus cavities as the oxygen component of the intrasinus air is rapidly absorbed by the metabolically active mucosa. When the pressure in the sinuses is negative relative to normal atmospheric pressure in the nose, conditions favor aspiration of mucus heavily laden with bacteria from the nose or nasopharynx into the presumably sterile paranasal sinuses. Under ordinary circumstances, the contaminating bacteria would be swept out again by normal ciliary function. However, when ciliary function is impaired and sinus ostia are obstructed, bacteria multiply to high density and initiate an intense inflammatory response. Sneezing, sniffling, and nose blowing also alter intrasinus pressure and facilitate bacterial contamination of the paranasal sinuses. Intranasal pressures are extremely high during nose blowing, and nasal fluid can enter the maxillary sinus at that time.[3]

The factors predisposing to ostial obstruction can be divided into those that cause mucosal swelling due to systemic illness or local insults and those due to mechanical obstruction (Table 32.1). Although many conditions can lead to ostial closure, viral URI and allergic inflammation are by far the most common and most important.

TABLE 32.1

Factors Predisposing to Sinus Ostial Obstruction

Mucosal Swelling	Mechanical Obstruction
Systemic disorders	Choanal atresia
• Viral upper respiratory tract infection	Deviated septum
• Allergic inflammation	Nasal polyps
• Cystic fibrosis	Foreign body
Immune disorders	Tumor
• Ciliary dyskinesia	Ethmoid bulla
• Local insult	

• Facial trauma	
• Swimming, diving	
• Drug-induced rhinitis	
• Gastroesophageal reflux	

Clinical Manifestations

Viral Upper Respiratory Tract Infections

The course of most uncomplicated viral URIs is 5 to 10 days[4] (Fig. 32.1). Although the patient may not be free of symptoms on the 10th day, respiratory symptoms have peaked in severity on days 3 to 6 and begun to improve. Most patients with uncomplicated viral URIs do not have fever. However, if fever is present, it tends to occur early in the illness, often in concert with other constitutional symptoms such as headache and myalgia. Typically, fever and constitutional symptoms disappear in the first 24 to 48 hours, and respiratory symptoms become more prominent.

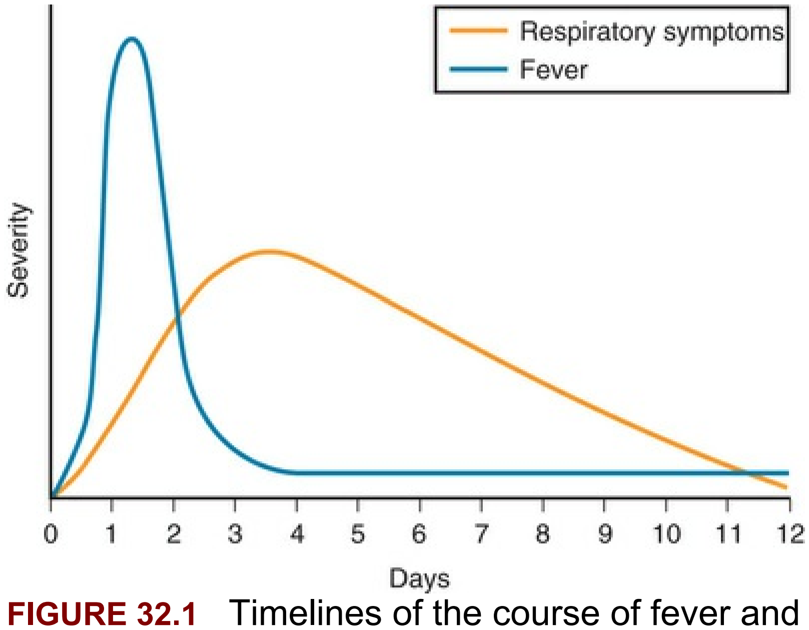

FIGURE 32.1 Timelines of the course of fever and respiratory tract symptoms in uncomplicated viral upper respiratory tract illness.

Viral URIs usually are characterized by nasal symptoms (i.e., discharge and congestion or obstruction) or cough, or both. Patients also may complain of a scratchy throat. The nasal discharge usually begins as clear and watery. Often, the quality of nasal discharge changes during the course of the illness. Typically, the nasal discharge becomes thicker and more mucoid and can become purulent (i.e., thick, colored, and opaque) for several days. The situation then reverses, with the purulent discharge becoming mucoid and then clear again or drying. The transition from clear to purulent to clear again occurs in uncomplicated viral URIs without the intervention of antimicrobial therapy.

Clinical Presentations of Acute Bacterial Sinusitis

Three clinical presentations of ABS can be described (Box 32.1).[5] The most common is onset with persistent symptoms.[6,7] Cardinal features are nasal symptoms (i.e., anterior or posterior nasal discharge, nasal obstruction, or congestion) or cough, or both, for more than 10 but fewer than 30 days and that do not improve. The latter qualifier is extremely important. Some individuals with uncomplicated viral URIs still have residual respiratory symptoms at the 10-day mark. To be considered a sign of ABS, these respiratory symptoms must persist without improvement.

Box 32.1

Clinical Manifestations of Acute Sinusitis

Persistent Symptoms

Nasal discharge and/or cough for >10 days and not improving

Severe Symptoms

High fever (≥39°C) and purulent nasal discharge together for >3 days

Worsening Symptoms

Resolving upper respiratory symptoms

Worsening on day 6 or 7 with new or recurrent fever or exacerbation of nasal symptoms and/or cough

The nasal discharge in patients with persistent symptoms can be of any quality (i.e., thick or thin, serous, mucoid, or purulent), and the cough, which may be wet or dry, must occur during the daytime, although it is often described as worse at night. Malodorous breath often is reported by parents of preschool children. Complaints of facial pain and headache are rare, although painless morning swelling of the eyelids occurs occasionally. The child may not appear very ill, and if fever occurs, it is usually low grade. Persistence rather than severity of symptoms brings the child to attention. Strict observance of this presentation results in a diagnosis of acute sinusitis for 6% to 7% of children with upper respiratory tract symptoms who are evaluated by primary care providers.[8,9]

The second presentation is characterized as onset with severe symptoms. Severity is described as a combination of high fever (≥38.5°C) and purulent nasal discharge occurring for at least 3 to 4 consecutive days.[7] Two features help distinguish this presentation from an uncomplicated viral URI. In ABS, the fever is higher and lasts longer, and the nasal discharge is purulent from the beginning of the illness.

The third presentation of ABS is worsening symptoms or a biphasic illness (i.e., *double sickening* in the Scandinavian literature).[7,10] Illness begins similar to an uncomplicated viral URI from which the patient seems to be recovering. On the 6th or 7th day of illness, the patient becomes substantially worse. The worsening symptoms can manifest as an increase in respiratory symptoms (i.e., exacerbation of nasal discharge or nasal congestion or daytime cough) or the new onset or recurrence of fever.

Patients with subacute or chronic sinusitis have a history of protracted (i.e., >30 days and not improving) respiratory symptoms. Nasal congestion (i.e., obstruction) and cough (i.e., day and night) are most common. Sore throat is a frequent complaint resulting from mouth breathing due to nasal obstruction. Nasal discharge of any quality and headache are less common, and fever is rare.

On physical examination, the patient with ABS can have mucopurulent discharge in the nose or posterior pharynx. The nasal mucosa usually is erythematous but can occasionally be pale and boggy; the throat can show moderate injection. Examination of the tympanic membranes can show evidence of acute otitis media or otitis media with effusion, which occurs more often in chronic than acute sinusitis. The cervical lymph nodes usually are not enlarged significantly or tender. Occasionally, there is tenderness with palpation or percussion over the paranasal sinuses or appreciable periorbital edema with soft, nontender swelling of the upper and lower eyelid and discoloration of the overlying skin. Facial tenderness, however, is not a sensitive or specific sign of sinusitis. Malodorous breath in the absence of pharyngitis, poor dental hygiene, or a nasal foreign body can suggest bacterial sinusitis. None of these characteristics, however, differentiates rhinitis from sinusitis.

Diagnostic Methods

Imaging

In cases of uncomplicated sinusitis, no confirmatory imaging is recommended.[7] Many studies have documented that when images of any kind (i.e., plain radiograph, computed tomography [CT], or magnetic resonance imaging [MRI]) are obtained in children or adults with uncomplicated viral URIs, most exhibit the same findings that in the past were associated with acute sinusitis (i.e., diffuse opacification, mucosal swelling, or an air-fluid level).[11–15] This is attributable to the continuity of the respiratory mucosa of the upper respiratory tract, which often is diffusely inflamed during a viral URI.

Although normal images can exclude sinusitis in patients with respiratory symptoms, abnormal images cannot confirm a diagnosis and are not indicated for uncomplicated infections. In contrast, when patients have complications of acute sinusitis (e.g., subperiosteal abscess, intracranial disease) or have protracted or nonresponsive symptoms, imaging (usually CT and occasionally MRI) is extremely helpful in clarifying the precise diagnosis and informing the necessity for surgical interventions.[7]

Sinus Aspiration

Although rarely done, maxillary sinus aspiration can be performed safely by a skilled otolaryngologist in the ambulatory setting using a transnasal approach (Fig. 32.2). Sedation or general anesthesia may be required for adequate immobilization of the young child. Current indications for maxillary sinus aspiration are a lack of response of sinusitis to multiple courses of antibiotics, severe facial pain, orbital or intracranial complications, and evaluation of an immunocompromised host.

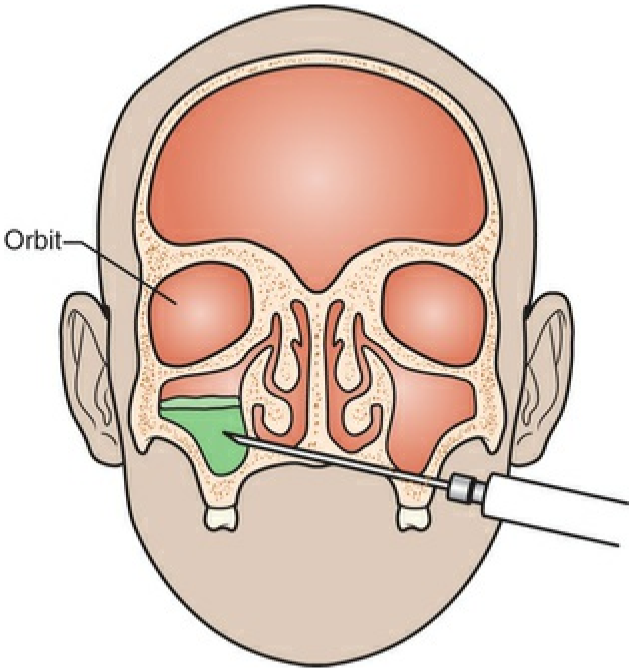

FIGURE 32.2 Coronal section of the nose and paranasal sinuses demonstrates how a maxillary sinus aspiration is performed. After sterilization of the mucosa beneath the inferior turbinate, a trocar is passed across the lateral nasal wall into the maxillary sinus.

There must be careful decontamination and anesthesia of the area beneath the inferior turbinate through which the trocar is passed. Material aspirated from the maxillary sinus should be sent for Gram stain and quantitative aerobic and anaerobic cultures. The recovery of bacteria in a density of at least 10^4 colony-forming units (CFUs) per milliliter represents true infection.[16] The finding of at least one organism per high-power field on Gram stain of sinus secretions correlates with the recovery of bacteria in a density of 10^5 CFU/mL.

Microbiology

Data on the microbiology of sinusitis in pediatric patients are best organized according to the duration of clinical symptoms (Table 32.2). However, the literature review is complicated by various definitions of acute, subacute, and chronic sinusitis.

TABLE 32.2

Bacteriology of Sinusitis

Bacterial Species	Acute (10–29 Days)	Subacute (30–120 Days)	Chronic (>120 Days)
Streptococcus pneumoniae	++	++	+
Haemophilus influenzae	+++	++	+
Moraxella catarrhalis	++	++	+
Staphylococcus aureus	—	—	+
Anaerobic bacteria[a]	—	—	+

[a] Respiratory anaerobic cocci, *Bacteroides* spp., *Prevotella* spp., *Veillonella* spp.

+++, Most common; ++, common; +, less common.

Several studies of ambulatory patients with acute (i.e., 10–30 days' duration) and subacute (i.e., 30–120 days' duration)[17,18] illnesses have found the important bacterial pathogens to be *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis.* Historically, *S. pneumoniae* has been most common in all age groups, accounting for 30% to 40% of isolates. *H. influenzae* and *M. catarrhalis* have similar prevalences, and each accounts for approximately 20% of cases. In the past decade, the prevalence of penicillin-resistant *S. pneumoniae* has depended on the use of conjugate pneumococcal vaccine and emergence of nonvaccine serotypes. Many of the *H. influenzae* (35% to 50%) and *M. catarrhalis* (55% to 100%) organisms produce β-lactamase and are resistant to penicillin.[19,20] Less frequently recovered bacteria are group A streptococci, group C streptococci, viridans streptococci, *Peptostreptococcus* spp., other *Moraxella* spp., and *Eikenella corrodens.*[16] Neither staphylococci nor anaerobic respiratory flora are recovered commonly from patients with acute or subacute sinusitis.

Respiratory viruses, including adenovirus, parainfluenza virus, influenza virus, and rhinovirus, are identified with or without bacterial species in approximately 10% of patients. The percentage would almost certainly be higher if nasal samples were obtained earlier in the course of respiratory symptoms.

No data regarding the microbiology of ABS in children have been generated since 1984.[21] However, because of the similarity of the pathogenesis and microbiology of acute otitis media and ABS, data from cultures of middle ear fluid obtained by tympanocentesis from children with acute otitis media have been used as a surrogate for cultures of the paranasal sinuses.[22] After 2000, heptavalent pneumococcal conjugate vaccine (PCV7) was used in the United States, and several reports in 2004 highlighted a decrease in isolates of *S. pneumoniae* and an increase in isolates of *H. influenzae* recovered from middle ear aspirates.[23,24] The change in microbiology reflects the decrease in recovery of vaccine strains of *S. pneumoniae* from the nasopharynx.[19] However, after several years, the emergence of nonvaccine strains of *S. pneumoniae* restored temporarily the relative proportions of *S. pneumoniae* and *H. influenzae* to those observed before 2000.[20,25]

Licensure of PCV13 in 2010 again decreased the recovery of *S. pneumoniae* from children with acute otitis media and presumably from children with ABS. In a 2014 publication, 36% of middle ear isolates were *H. influenzae*, and 29% were *S. pneumoniae*.[26] Diminishing sources of information regarding the microbiology of acute otitis media and ABS are a challenge.

In patients with very protracted (i.e., years) or severe sinus symptoms (i.e., requiring surgical intervention), *S. aureus* and anaerobic organisms are recovered more frequently. Commonly recovered anaerobic bacteria are gram-positive cocci (e.g., *Peptococcus* spp., *Peptostreptococcus* spp.) and *Bacteroides* or *Prevotella* spp.[27] Viridans streptococci and *H. influenzae* also are recovered frequently.

Medical Management

Acute Sinusitis

Antimicrobial agents are mainstays in the medical management of sinusitis.[7,9] Table 32.3 shows a list of agents potentially useful in patients with ABS. Amoxicillin has been the treatment of choice for many cases of uncomplicated sinusitis in children. It is effective most of the time, has a narrow spectrum, and is inexpensive and safe. Concern about penicillin-resistant *S. pneumoniae* should prompt the use of high-dose amoxicillin (90 mg/kg/day).[7] Resistance due to alteration of the penicillin-binding proteins can be overcome for the most part with high-dose amoxicillin. However, amoxicillin at any dose does not cover β-lactamase–producing *H. influenzae* and *M. catarrhalis*. Amoxicillin, if used at all, should be reserved for children with mild illness early in the respiratory season who have no risk factors for infection with resistant bacterial species.

TABLE 32.3

Antimicrobial Agents and Dosage Schedules for the Treatment of Sinusitis in Children

Antimicrobial Agent	**Dosage**
Amoxicillin	45–90 mg/kg/day in 2 divided doses
Amoxicillin/potassium clavulanate	45/10 mg/kg/day in 2 divided doses
Amoxicillin/potassium clavulanate (high dose)	90/6.4 mg/kg/day in 2 divided doses
Cefpodoxime proxetil	10 mg/kg once daily
Cefuroxime axetil	30 mg/kg/day in 2 divided doses
Cefdinir	14 mg/kg/day in 1 or 2 daily doses
Cefprozil	30 mg/kg/day in 2 divided doses

A broader-spectrum regimen is appropriate in the following clinical situations: lack of symptom improvement with amoxicillin therapy in 48 to 72 hours, any risk factors for resistant bacterial species (e.g., young age, attendance at childcare, recent treatment of the index case or a close contact with an antibiotic), frontal or sphenoidal sinusitis, complicated ethmoidal sinusitis (i.e., with even minimal eye swelling), and protracted (>30 days) symptoms. Antimicrobial agents with the most comprehensive coverage for patients with sinusitis are high-dose amoxicillin with potassium clavulanate (90 mg/kg/day of amoxicillin and 6.4 mg/kg/day of clavulanate in 2 divided doses; maximal dose of 8 g/day of amoxicillin), cefuroxime axetil (30 mg/kg in 2 divided doses), and cefpodoxime proxetil (10 mg/kg once daily). For patients with chronic sinusitis, amoxicillin with potassium clavulanate is an attractive choice, especially because the mode of amoxicillin resistance in the pathogens causing chronic sinusitis is β-lactamase production.

Other antimicrobial agents that are available for the management of respiratory infections but are considerably less potent or adequate in spectrum are cefdinir, cefprozil, clarithromycin, and azithromycin. Clarithromycin and azithromycin should be reserved for children who have lower respiratory tract disease suggesting

Mycoplasma infection or have a type 1 hypersensitivity reaction to β-lactam agents. Neither agent is effective against *H. influenzae*.

Infections due to penicillin-resistant pneumococci are a persistent problem. Organisms are classified as *susceptible* when the minimum inhibitory concentration (MIC) of the drug is less than 0.1 μg/mL, *moderately resistant* when the MIC is between 0.1 and 1.0 μg/mL, and *resistant* when the MIC is more than 1 μg/mL for oral β-lactams. The frequency of penicillin-resistant pneumococci varies geographically, and many isolates of pneumococci are resistant to other commonly used antimicrobial agents, such as trimethoprim-sulfamethoxazole, erythromycin-sulfisoxazole, clindamycin, and the macrolides azithromycin and clarithromycin. Therapeutic options include high-dose amoxicillin, an advanced-generation cephalosporin (for some pneumococci with moderate resistance), linezolid, and rifampin. Selection of an antimicrobial agent should be guided by susceptibility test results when available.

Patients with ABS may require hospitalization because of systemic toxicity or an inability to take antibiotics orally. These patients can be treated with intravenous ceftazidime (150 mg/kg/day in 3 divided doses), intravenous ceftriaxone (100 mg/kg/day given once daily), or intravenous ampicillin-sulbactam (200 mg/kg/day of the ampicillin component in 4 divided doses [not approved for children younger than 12 years]).

Clinical improvement is prompt in almost all children treated with an appropriate antimicrobial agent, with a remarkable reduction in 48 to 72 hours of fever, nasal discharge, and cough. If symptoms do not improve or worsen in 48 to 72 hours, clinical re-evaluation is appropriate. If amoxicillin was prescribed initially, an antimicrobial agent effective against β-lactamase–producing bacterial species and penicillin-resistant pneumococci should be prescribed. If amoxicillin-clavulanate was prescribed originally and the patient has not improved, cefpodoxime, cefuroxime, or a combination of linezolid and cefixime are reasonable second-line therapies. Levofloxacin may be considered for patients with a type I hypersensitivity reaction to amoxicillin. If the patient still has not improved, parenteral therapy and sinus aspiration for precise bacteriologic identification should be considered.

The appropriate duration of antimicrobial therapy for patients with ABS has not been investigated systematically. For patients whose respiratory symptoms improve dramatically within 3 to 4 days of commencement of therapy, 10 days of treatment is adequate. For cases that respond more slowly, it is reasonable to treat until the patient is symptom free plus an additional 7 days.

Adjuvant therapies such as antihistamines, decongestants, and nasal irrigation have received little systematic evaluation. There is no evidence to demonstrate whether the use of these modalities is efficacious in children with acute sinusitis.[28]

Chronic Sinusitis

Some children experience recurrent or chronic episodes of sinusitis. The most common cause of recurrent sinusitis is a recurrent viral URI, which often is a consequence of attendance at out-of-home childcare or the presence of a school-aged child in the household. Other conditions predisposing to sinus ostial obstruction should be considered (see Table 32.1). Evaluation of children with recurrent or chronic sinusitis should include consideration of consultation with an allergist, performance of a sweat test, quantitative measurements of serum immunoglobulin levels, and a mucosal biopsy to assess ciliary structure and function.

If specific allergens are identified or an allergic diathesis is documented, therapy may include desensitization, an antihistamine, or topical intranasal steroid therapy. If a treatable immunodeficiency is identified, specific immunoglobulin therapy is initiated. Antimicrobial prophylaxis has not been studied in patients with recurrent acute sinusitis, although it has proved to be a useful strategy in reducing symptomatic episodes of acute otitis media in patients with frequent recurrences. Recent concerns regarding antibiotic resistance have discouraged the use of antibiotic prophylaxis. If sinusitis does not respond to maximal medical therapy, surgical intervention may be appropriate.

The major complications of acute sinusitis are shown in Box 32.2. Subperiosteal abscess of the orbit and intracranial abscess (i.e., subdural and epidural empyema) are the most common.[29,30] Signs of orbital infection are eyelid swelling, proptosis, and impaired extraocular eye movements. With intracranial spread of infection, there may be signs of increased intracranial pressure, meningeal irritation, and focal neurologic signs. CT or MRI is essential for diagnosis. Antibiotic therapy and surgical drainage usually are required for successful treatment. For small subperiosteal abscesses unaccompanied by visual loss, a trial of antibiotic therapy alone is appropriate.

Box 32.2

Major Complications of Sinusitis

Orbital

Inflammatory edema[a]

Subperiosteal abscess

Orbital abscess

Orbital cellulitis

Optic neuritis

Intracranial

Epidural empyema

Subdural empyema

Cavernous or sagittal sinus thrombosis

Meningitis

Brain abscess

Osteitis

Frontal (Pott puffy tumor)

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[a] Inflammatory edema is not a true orbital complication of sinusitis. Infection is confined to the paranasal sinuses, and periorbital swelling results from impedance of venous blood flow.

Surgical Management

Patients with acute sinusitis rarely require surgical intervention in the absence of orbital or central nervous system complications. An appreciation of allergic rhinitis or other underlying medical problems such as gastroesophageal reflux in chronic sinusitis has led to more aggressive medical management and less enthusiasm for surgical solutions.[31] Occasionally, sinus aspiration is required to ventilate a sinus in a patient with no response to aggressive antimicrobial therapy.

In the rare child who has failed conventional treatment with oral antibiotics and an array of local and systemic adjuvants to therapy, a trial of antibiotic therapy delivered by a percutaneous intravenous catheter may be worthwhile.[32] It can be combined with adenoidectomy, or adenoidectomy can be undertaken as a solo intervention. Adenoidectomy is considered first-line surgical therapy for chronic rhinosinusitis in childhood,[33,34] although the success of the procedure correlates with associated conditions such as adenoiditis and asthma.[35]

When functional endoscopic sinus surgery is performed, the focus is on the ostiomeatal complex (Fig. 32.3). This area between the middle and inferior turbinates represents the confluence of drainage areas of the frontal, ethmoid, and maxillary sinuses, and it is predisposed to local impairment of mucociliary clearance. Using an endoscope, the natural meatus of the maxillary outflow tract is enlarged by excising the uncinate process and the ethmoid bullae and performing an anterior ethmoidectomy.

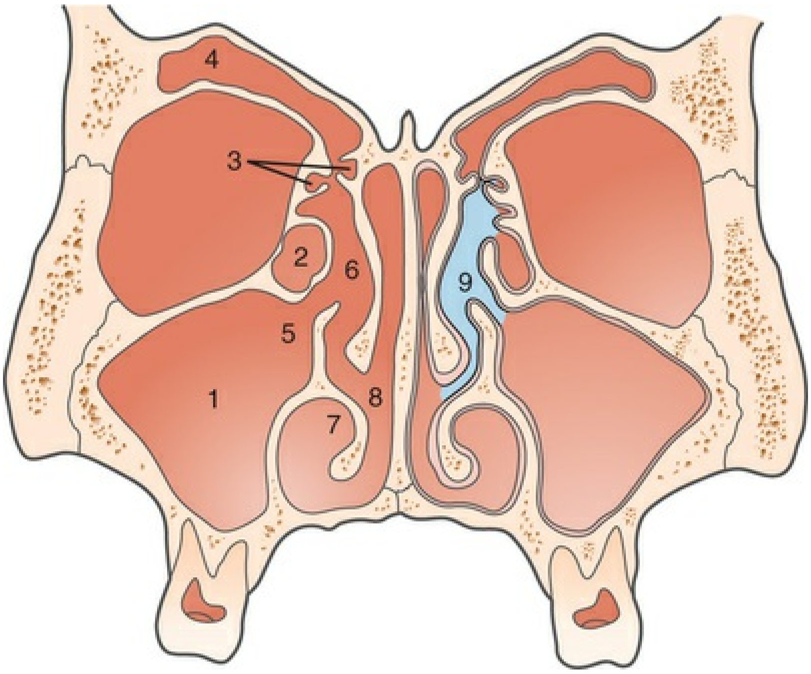

FIGURE 32.3 Coronal section of the nose and paranasal sinuses: *1*, maxillary sinus; *2*, ethmoidal bursa; *3*, ethmoid cells; *4*, frontal sinus; *5*, uncinate process; *6*, middle turbinate; *7*, inferior turbinate; *8*, nasal septum; *9*, ostiomeatal complex *(blue area)*. (From Wald ER. Sinusitis in children. N Engl J Med 1992;326:319–323.)

As understanding of the pathogenetic factors predisposing to sinusitis expands and therapy for these mucosal diseases becomes more effective, the pediatric candidates for surgical management of sinus disease will continue to decrease. Judicious use of surgery in young children with chronic rhinosinusitis is strongly recommended.[36]

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D

Lower Respiratory Tract Infections

OUTLINE

33 Bronchiolitis
34 Acute Pneumonia and Its Complications
35 Persistent and Recurrent Pneumonia
36 Pneumonia in the Immunocompromised Host

33

Bronchiolitis

H. Cody Meissner

Bronchiolitis is a syndrome of inflammation and obstruction of the lower respiratory tract that usually is caused by a viral infection occurring in the first 12 months of life.[1] Between 2% and 3% of infants younger than 1 year of age are hospitalized with bronchiolitis annually, accounting for 57,000 to 175,000 hospitalizations in the United States.[2–4]

Yearly hospital admissions attributable to bronchiolitis increased more than twofold between 1980 and 1996, likely reflecting the increased use of childcare centers and changes in criteria for hospital admission for children with bronchiolitis.[5] However, during the first 16 years of the 21st century, bronchiolitis hospitalization rates have fallen by 20% to approximately 20 to 30 admissions per 1000 children younger than 12 months of age.[6] One explanation for lower rates of bronchiolitis hospitalization is the improved health of neonates at the time of discharge compared with several years earlier. This can be attributed to the use of antenatal glucocorticoids, surfactant replacement, improvements in methods for ventilatory support, corrective cardiac surgery performed earlier in life, and a better understanding of neonatal nutrition.

Etiologic Agents

During seasonal outbreaks of bronchiolitis from November through March in North America, respiratory syncytial virus (RSV) is identified as the etiologic agent in up to 80% of hospitalized children[7] (Table 33.1). Other respiratory viruses that cause a largely indistinguishable syndrome include human rhinoviruses, parainfluenza viruses, human metapneumoviruses, coronaviruses, adenoviruses, influenza viruses, enteroviruses, and human bocaviruses.[8–11] The yearly cycles of respiratory virus circulation are depicted in Fig. 33.1.

TABLE 33.1

Infectious Causes of Bronchiolitis

Infectious Agent	**Occurrence**[a]
Respiratory syncytial virus	++++
Rhinovirus	++
Human metapneumovirus	++
Parainfluenza virus 3	++
Parainfluenza virus 1	+
Parainfluenza virus 2	+
Coronaviruses	+
Adenovirus	+
Influenza virus (A or B)	+
Mycoplasma pneumoniae	+
Enterovirus	+

[a] Relative importance varies with season and epidemic disease.

++++, Most common cause; ++, causes substantial percentage of cases in some studies; +, occasional cause.

Data from references 7, 8, 39–41.

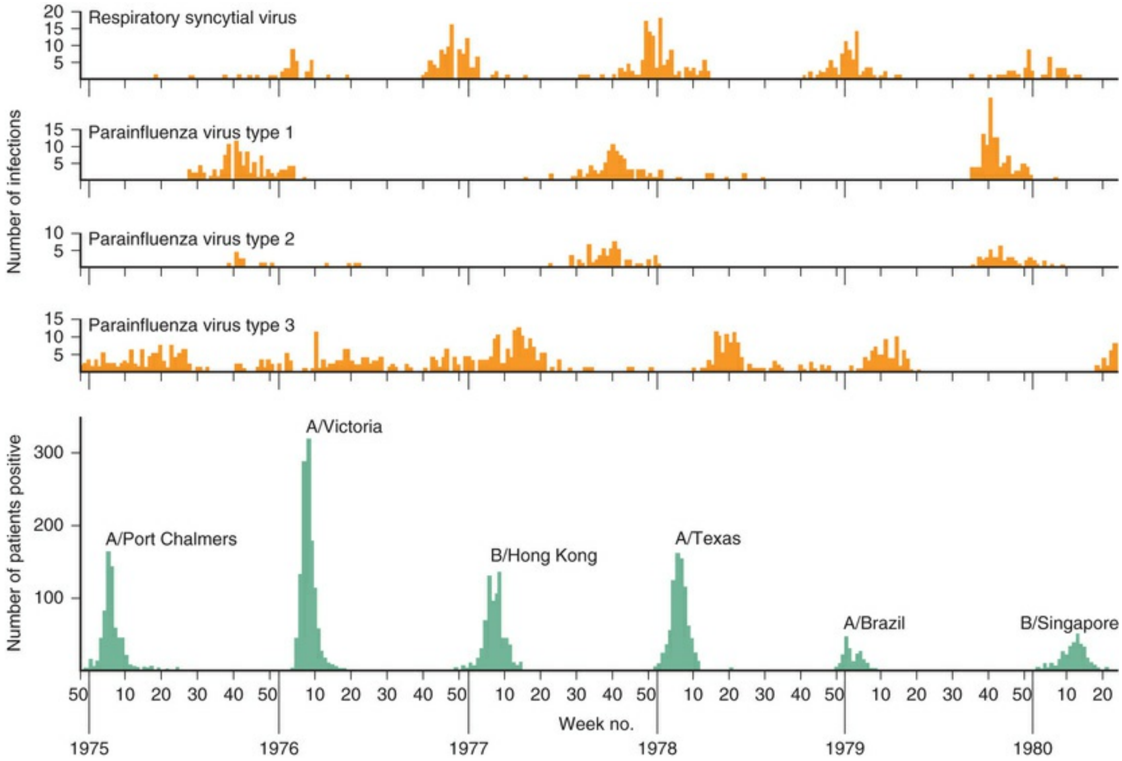

FIGURE 33.1 Patterns of occurrence of respiratory syncytial virus and parainfluenza virus in Houston, Texas. (From Couch RB. Viral respiratory diseases. In: Stringfellow DA [ed]. Virology. Kalamazoo, MI: Scope; 1983, p. 65.)

No evidence has been found for a primary role for bacteria as a cause of bronchiolitis. However, *Bordetella pertussis, Chlamydia trachomatis,* and *Mycoplasma pneumoniae* should be included in the differential diagnosis of a young child with lower respiratory tract infection.

Epidemiology

The peak incidence of severe disease occurs before 6 months of age, and the highest rates of hospitalization occur among infants between 60 and 90 days of age.[1] Most of those hospitalized for bronchiolitis are term infants with no known risk factors. Chronologic age is the single most important determinant for severe bronchiolitis; about two thirds of hospitalizations occur before 6 months of age.[1,2] Several reasons may account for this age distribution. Birth shortly before or soon after the onset of the RSV season results in a longer period of exposure to RSV earlier in life. Maternal antibody concentrations to RSV also show seasonal variation, and infants born early in the RSV season are more likely to be born to mothers with low neutralizing antibody concentrations.[12–14]

Certain comorbidities, including prematurity (<29 weeks' gestation), chronic lung disease of prematurity, and hemodynamically significant congenital heart disease, may result in more severe disease compared with children without these comorbities.[15,16] Worldwide, 65,000 to 200,000 deaths due to bronchiolitis were estimated to occur in 2005 among children younger than 5 years of age.[17,18] Fewer than 100 US pediatric deaths occur annually as a complication of RSV-associated bronchiolitis.[19]

Occurrence of the respiratory virus season is predictable even though the severity of the season, the date of onset, the peak of activity, and the end of the season cannot be predicted with precision.[20] There can be variation in timing of community outbreaks of disease due to RSV from year to year in the same community and among neighboring communities, even in the same season. Southern US communities tend to experience the earliest onset of RSV activity, and those in the Midwest tend to experience the latest onset. The duration of the season in western and northeastern areas is typically between that in the South and the Midwest. Nevertheless, these variations occur within the overall pattern of RSV outbreaks, usually beginning in November or December, peaking in January or February, and ending by the end of March or April.[20–23]

Limited numbers of cases of bronchiolitis may occur during late spring, summer, and early fall, and they often are caused by viruses other than RSV, such as rhinoviruses or parainfluenza viruses. These cases often are milder than RSV-related cases. In tropical countries, the annual epidemic of RSV coincides with the rainy season, although cases can occur throughout the year.

Household crowding is a risk factor for severe viral lower respiratory tract illness due to RSV and other respiratory viruses.[24–27] As the number of household members increases, the likelihood of close exposure to infectious respiratory secretions also increases. Childcare attendance has been correlated with an increased risk of bronchiolitis in some studies.

Unlike other respiratory viral infections, exposure to passive household tobacco smoke has not been associated with an increased risk of RSV hospitalization on a consistent basis. Exposure to secondhand smoke has been associated with an increased risk of respiratory infections due to other viruses. In contrast to the well-documented benefit of breastfeeding against some viral illnesses, existing data are conflicting regarding the specific protective effect of breastfeeding against RSV infection.

Other reported risk factors for bronchiolitis include poverty, malnutrition, maternal smoking during pregnancy, congenital malformation of the airways, neuromuscular impairment, household crowding, childcare attendance, size of the childcare facility, lower level of maternal education, and living at an increased altitude. However, most of these risk factors are inconsistent from study to study, and in most instances, the impact on increased hospitalization is small.[15]

Pathogenesis and Pathologic Findings

Acute bronchiolitis is caused by an infectious agent, usually a respiratory virus with specific tropism for bronchiolar epithelium. Because most infants experience mild illness and recover from bronchiolitis, information regarding the pathologic changes caused by infection is not available.

Largely based on results from animal studies, RSV infection of the epithelial cells of the human respiratory tract mucosa results in a lymphocytic infiltration of the bronchiolar walls and edema of the surrounding tissue. Disease progression is associated with proliferation and necrosis of the bronchiolar epithelium. The sloughed necrotic epithelium and the increased mucus production lead to obstruction of the lumen of the infant's small airways. Air movement is restricted during inspiration and expiration but is more restricted during expiration, when the lumen is further compromised by positive expiratory pressure, resulting in expiratory wheezing. Obstruction results in air trapping and the characteristic appearance of hyperinflation on chest radiographs. As this air is absorbed, the radiographic pattern evolves to show atelectasis.[23,27–29] Chapter 225 discusses the pathophysiology of RSV bronchiolitis.

Clinical Manifestations

Upper respiratory tract symptoms consisting of nasal congestion and discharge and a low-grade fever begin about 3 to 5 days after the onset of infection. Bronchiolitis represents the later stage of a respiratory viral infection that develops after 2 to 4 days of illness. Approximately 30% to 40% of RSV-infected infants experience progression of disease to the lower respiratory tract. Spread to the lower airway occurs by aspiration of sloughed RSV-infected epithelial cells from the upper airway or by cell-to-cell spread of the virus.

Lower airway involvement is marked by an increase in the work of breathing, cough, tachypnea, wheezing, crackles, use of accessory muscles, and nasal flaring.[1] The respiratory rate often exceeds 60 to 70 breaths/min in young infants. Intercostal, supracostal, and subcostal retractions are evident. Initially, wheezing occurs during the expiratory phase only and is audible only through a stethoscope. As wheezing progresses, it can be heard without a stethoscope. The chest becomes hyperexpanded and hyperresonant, respirations become more labored, and retractions become more severe. Mild hypoxemia occurs in most infants with bronchiolitis. Respiratory failure can occur due to progressive hypercapnia and respiratory muscle fatigue.[1]

Disease severity may be recognized by the absence of audible air exchange on auscultation; flaring of the alae nasi; expiratory grunting; severe subcostal, supraclavicular, and intercostal retractions; and hypoxemia. A child with these findings may require intubation and ventilatory support. Apnea can be an early manifestation of RSV infection, sometimes resulting in respiratory failure.[30–32] Because the severity of bronchiolitis often waxes and wanes before consistent improvement, serial assessment of respiratory status should be performed. The ability of a young infant to breastfeed or bottle-feed without distress over time often provides a practical guide to disease severity and management. An infant who has substantial difficulty feeding as a result of respiratory distress has moderate or severe illness and usually requires hospitalization.

Otherwise healthy infants younger than 2 months of age, infants born prematurely (<29 weeks′ gestation), and infants with chronic lung disease of prematurity or infants born with congenital heart disease are most likely to experience severe RSV disease.[1] Infants born with hemodynamically significant congenital heart disease are at increased risk of more severe bronchiolitis.[15,16,33,34] Infants with hemodynamically insignificant heart disease, including secundum atrial septal defect, small ventricular septal defect, pulmonic stenosis, uncomplicated aortic stenosis, mild coarctation of the aorta, and patent ductus arteriosus, and infants with lesions adequately corrected by surgery (unless they continue to require medication for management of congestive heart failure) are not considered to be at increased risk for hospitalization.[35] Severe respiratory distress with bronchiolitis can be the presenting manifestation of previously unrecognized congenital heart disease.

RSV-infected infants have various courses after hospitalization.[22] Among otherwise healthy infants, intensive care unit admission because of respiratory deterioration is uncommon (approximately 2% of patients). The decision to admit to the intensive care unit is based on the possible need for intubation because of progressive hypercapnia, increasing hypoxemia despite supplemental oxygen, or episodes of apnea.

The typical course for a previously healthy infant older than 6 months of age is one of improvement over 2 to 3 days, as evidenced by a lower respiratory rate and fewer retractions. Pulmonary function abnormalities and evidence of mild desaturation may persist for several weeks. The differential diagnosis of bronchiolitis includes airway hypersensitivity to environmental irritants, anatomic abnormality of the airway, cardiac disease with pulmonary edema, cystic fibrosis, foreign-body aspiration, and gastroesophageal reflux.

Diagnosis

A diagnosis of bronchiolitis should be based on the history and physical examination. Serial examinations may reveal fluctuations in disease acuity over a short period, reflecting rapid changes in blockage of the lumens of the small airways.[1] Specific signs and symptoms at the time of presentation have a limited ability to predict disease severity. Assessment of the likelihood of progressive disease should consider the risk factors, including: age younger than 12 weeks, a history of prematurity, underlying cardiopulmonary disease, or immunodeficiency.[1]

Routine radiographic studies are not recommended. Infants with bronchiolitis may have abnormalities (e.g., atelectasis) on chest radiography, but the changes have little correlation with disease severity.[36,37] Radiography should be reserved for infants who require intensive care management and for those who do not improve as expected.

Routine virologic testing is not recommended because the result is unlikely to influence management.[1] Respiratory isolation recommendations are similar for most viral infections and are based largely on the symptoms, not the specific cause. The positive predictive value of an antigen detection assay decreases as disease incidence goes down. Specificity of antigen detection assays is lowest during the off-season and at the onset and the end of the respiratory virus season.

Polymerase chain reaction (PCR) assays have improved sensitivity and specificity compared with antigen detection, but they are expensive, and results are unlikely to influence management. Using PCR assays, coinfections with more than one virus have been identified in as many as one third of hospitalized patients with bronchiolitis. The significance of coinfections is incompletely understood.[38–42] PCR assays should be interpreted with caution because positive results can be found in more than 30% of asymptomatic young children.[43] Whether this reflects prolonged shedding from a previous infection, the incubation period for a pending infection, infection by a strain with limited ability to cause disease, or a low-grade infection producing small amounts of virus is unknown.

Management

General Measures

Most infants with bronchiolitis can be managed at home with supportive care, but concerns regarding increasing respiratory effort, apnea, or inability to feed adequately may precipitate hospitalization of a young child.[1] Disease severity may be estimated by respiratory rate, use of accessory muscles, and degree of hypoxemia. However, the course of bronchiolitis varies, ranging from mild dyspnea to progressive respiratory distress. Certain underlying conditions such as prematurity, immunodeficiency, chronic lung disease of prematurity, and congenital heart disease are associated with an increased risk of progression to severe disease.

Despite the high burden of disease from bronchiolitis, no available treatment shortens the course or hastens the resolution of symptoms. Therapy is supportive, and most children with bronchiolitis do well regardless of management.[1]

Therapies

Bronchodilator Therapy.

Most randomized, controlled trials have failed to demonstrate a consistent benefit from α- or β-adrenergic agents. Although transient improvement in respiratory status has been reported, most infants treated with bronchodilators do not benefit from their use.[44–47] The potential adverse effects (i.e., tachycardia and tremors) and cost of these agents outweigh the potential benefits. Recommendations from the American Academy of Pediatrics state, "Clinicians should not administer albuterol to infants and children with a diagnosis of bronchiolitis."[1]

Epinephrine.

Epinephrine is an adrenergic agent with α- and β-receptor agonist activity. It has been evaluated in children with bronchiolitis after systemic administration and when delivered directly into the respiratory tract. Large, multicenter trials comparing nebulized epinephrine with albuterol or placebo in hospitalized children with bronchiolitis found no improvement in outcomes.[48–50] Available evidence does not support a role for epinephrine use among hospitalized patients or outpatients with bronchiolitis.

Corticosteroid Therapy.

Although corticosteroids may benefit selected patients with asthma or croup, no evidence supports the use of corticosteroid therapy in the general population of children with bronchiolitis. Numerous studies have documented a lack of benefit.[51–53]

Oxygen Therapy.

Various degrees of hypoxia are commonly seen in infants and young children with bronchiolitis. Intermittent periods of hypoxemia (≥90% oxyhemoglobin saturation) as measured by pulse oximetry should not be interpreted as a need for supplemental oxygen. Transient desaturation is common in healthy infants. Oxygen saturation has much less impact on respiratory drive than carbon dioxide concentration in the blood. Oxygen saturation and respiratory distress have poor correlation among infants with lower respiratory tract infections. Continuous monitoring with pulse oximetry of children with mild degrees of oxygen desaturation has been associated with prolonged length of stay compared with children who do undergo continuous monitoring.[54,55]

Chest Physiotherapy.

Suctioning of the nasopharynx to remove secretions and temporarily improve airflow is a common practice for children with bronchiolitis. Chest physiotherapy using vibration or percussion or deep suctioning is not recommended.[56,57]

Hydration.

As many as one third of patients admitted to the hospital with a diagnosis of bronchiolitis require fluid replacement therapy. The ability to swallow may be compromised when the respiratory rate exceeds 60 breaths/min, especially if the child has nasal congestion. For infants who are unable to maintain hydration orally, fluid may be administered intravenously or through a nasogastric tube.[58,59]

Antibiotic Therapy.

Antibacterial therapy should not be administered to an infant or young child with bronchiolitis unless there is a strong suspicion of a concomitant bacterial infection.[1]

Nebulized Hypertonic Saline.

Data suggest that nebulized hypertonic saline may have a modest benefit in infants with RSV bronchiolitis.[60–62] Hypertonic saline may facilitate mucociliary clearance of the bronchioles that results from the inflammatory response to infection. Some evidence suggests that 3% inhaled saline may be safe and may reduce length of hospital stay when a hospitalization lasts longer than 3 days.

Antiviral Therapy.

Ribavirin is a nucleoside analogue with in vitro activity against RSV, adenovirus, influenza A and B viruses, and parainfluenza viruses. Early trials indicated that ribavirin therapy was associated with a modest improvement in clinical scores, oxygenation, and duration of mechanical ventilation for infants with severe bronchiolitis due to RSV infection. These studies were challenged on the basis that control groups received water aerosols, which can produce bronchospasm in individuals with hyperreactive airways. Clinical trials with ribavirin have not demonstrated a consistent decrease in the need for mechanical ventilation, decrease in length of stay in the intensive care unit, or reduction in days of hospitalization. Conflicting results from efficacy trials, concern about the potential toxic effects among exposed healthcare professionals, aerosol route of administration, and high cost have resulted in the limited use of ribavirin.[63]

Chapter 225 discusses ribavirin. Options for the treatment of bronchiolitis if caused by influenza A or B viruses are discussed in Chapter 229.

Prognosis, Complications, and Sequelae

Most infants recover completely from acute bronchiolitis. Severe bronchiolitis early in life is associated with an increased risk of asthma, especially after RSV or rhinovirus bronchiolitis, and the risk can persist into early adulthood. It is not understood whether bronchiolitis injures the lung such that normal lung development does not occur and predisposes to subsequent episodes of wheezing or whether certain infants have a pre-existing aberration of the immune response or airway function that predisposes to severe bronchiolitis and recurrent wheezing.[64–69]

Prevention

Strategies that reduce exposure of vulnerable infants to contagious individuals with respiratory tract infections offer opportunities to reduce bronchiolitis morbidity. Encouraging breastfeeding and avoiding passive exposure to cigarette smoke are critical aspects of proper healthcare for all children. The role of monoclonal antibodies in reducing the risk of RSV infection in certain high-risk infants and young children is discussed in Chapter 225.

No safe and effective vaccine is available to prevent infection with RSV or most other viral causes of bronchiolitis. The influenza vaccine is the only exception, and this vaccine should be administered annually to all infants starting at 6 months of age. Because influenza vaccine is not approved for use in infants younger than 6 months of age, annual influenza vaccination is important for the family members and caregivers of young patients.

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34

Acute Pneumonia and Its Complications

Chitra S. Mani

Pneumonia is a Greek word meaning “inflammation of the lungs.” It is the most common cause of morbidity and mortality in infants and children due to infection worldwide.[1]

Acute Pneumonia

Pneumonia is a lower respiratory tract disease usually caused by an infectious agent resulting in inflammation of the tissues of one or both lungs.[2] Pneumonia in developing countries occurs in >150 million new cases and results in >1.3 million preventable deaths each year.[1,3] Morbidity and mortality rates for community-acquired pneumonia (CAP) among the children in the United States is considerably less. Outpatient pediatric visit rates for CAP in the US ranges from 16.9 to 22.4 per 1000 children, with 32.3 to 49.6 cases per 1000 children 1 to 5 years of age.[4] Rate of hospitalization in the US for acute pneumonia decreased from 12–14 to 8–10 per 10,000 in children <2 years of age following universal conjugate pneumococcal vaccination.[5] In 2007, the overall mortality for acute pneumonia in US children was ≤2%, depending on factors including age, race, socioeconomic status and geographical region.[6]

Epidemiology

In the US, lower respiratory infections (LRIs) occur throughout the year but excessively during the fall and winter when children are confined indoors, resulting in more efficient spread of the infections by contact or droplet transmission.[7] Multiple factors predispose to acquisition of LRI: daycare and school attendance, indoor crowding, passive exposure to smoke, lack of or underimmunization, alcohol abuse in adolescents causing aspiration pneumonia, and underlying medical conditions such as low birth weight, bronchopulmonary dysplasia, asthma, heart disease, seizures, neuromuscular illness, gastroesophageal reflux disease, malnutrition, immunocompromised state, sickle cell disease, and cystic fibrosis.[1,8–10] Additional risk factors associated with pneumonia in children <5 years of age include frequent upper respiratory tract infections (URIs; >3 episodes in 12 months), wheezing at any age, and history of otitis media requiring tympanocentesis before 2 years of age. Risk factors for pneumonia in children >5 years of age include wheezing at any age and ≥3 episodes of URI within 12 months.[11]

Etiologic Agents

Multiple microbes, most predominantly viruses and bacteria, cause LRI in infants and children. The true prevalence of the pathogens causing LRI is uncertain because microbial etiology is ascertained infrequently, owing to difficulty in differentiating infection from colonization and lack of dependable diagnostic laboratory tests.[12] In two studies of immunocompetent children with pneumonia, specific etiologic agents were confirmed in only 43% to 66%.[13,14] Some cases have more than one pathogen identified, making assigning etiology difficult.[15] Confirming etiology of bacterial pneumonia is challenging because of coexistence of bacteria as pathogens as well as normal upper respiratory tract flora, and because of occurrence of bacteremia in only 1% to 10% of hospitalized children with presumed bacterial pneumonia.[2,16,17] Etiologic agents causing pneumonia vary by age, underlying illnesses, maturity, and condition of the immune system.[18] In most cases of acute pneumonia, extensive invasive testing is not warranted. Epidemiologic information frequently is useful in guiding differential diagnosis and management (see Chapter 21). Certain pathogens, particularly respiratory syncytial virus (RSV), rhinoviruses, influenza viruses, and *Mycoplasma,* are seasonal. In other instances, the pattern of family illness provides a clue to the causative nonbacterial agents.

For purposes of management, the relative importance of etiologic agents in a series of patients who have been extensively evaluated is extrapolated to patients with similar clinical syndromes, physical findings, and laboratory results. Table 34.1 lists the common etiologic agents of acute pneumonia in children.

TABLE 34.1

Microbial Causes of Community-Acquired Pneumonia in Childhood

Age	Etiologic Agents[a]	Clinical Features
Birth–3 wk	Group B *Streptococcus*	Part of early-onset septicemia; usually severe
	Gram-negative enteric bacilli	Frequently nosocomial; occurs infrequently within 1 week of birth
	Cytomegalovirus	Part of systemic cytomegalovirus infection
	Listeria monocytogenes	Part of early-onset septicemia
	Herpes simplex virus	Part of disseminated infection
	Treponema pallidum	Part of congenital syndrome
	Genital *Mycoplasma* or *Ureaplasma*	From maternal genital infection; afebrile pneumonia
3 wk–3 mo	*Chlamydia trachomatis*	From maternal genital infection; afebrile, subacute, interstitial pneumonia
	Respiratory syncytial virus (RSV)	Peak incidence at 2–7 months of age; usually wheezing illness (bronchiolitis/pneumonia)
	Parainfluenza viruses (PIV), especially type 3	Similar to RSV, but in slightly older infants and not epidemic in the winter
	Streptococcus pneumoniae	The most common cause of bacterial pneumonia
	Bordetella pertussis	Primarily causes bronchitis; secondary bacterial pneumonia and pulmonary hypertension can complicate severe cases
3 mo–5 yr	RSV, PIV, influenza, hMPV, adenovirus, rhinovirus	Most common causes of pneumonia
	Streptococcus pneumoniae	Most likely cause of lobar pneumonia; incidence may be decreasing after vaccine use
	Haemophilus influenzae	Type b uncommon with vaccine use; nontypable stains cause pneumonia in immunocompromised hosts and in developing countries
	Staphylococcus aureus	Uncommon, although CA-MRSA is becoming more prevalent
	Mycoplasma pneumoniae	Causes pneumonia primarily in children >4 yr

	Mycobacterium tuberculosis	Major concern in areas of high prevalence and in children with HIV
5–15 yr	*Mycoplasma pneumoniae*	Major cause of pneumonia; radiographic appearance variable
	Chlamydophila pneumoniae	Controversial, but probably an important cause in older children in this age group

[a] Ranked roughly in order of frequency. Uncommon causes with no age preference: enteroviruses (echovirus, coxsackievirus), mumps virus, Epstein-Barr virus, Hantavirus, *Neisseria meningitidis* (often group Y), anaerobic bacteria, *Klebsiella pneumoniae, Francisella tularensis, Coxiella burnetii, Chlamydia psittaci. Streptococcus pyogenes* occurs sporadically or especially associated with varicella-zoster virus infection.

CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus;* HIV, human immunodeficiency virus; hMPV, human metapneumovirus.

Agents in Neonates and Young Infants

Pneumonia in neonates can manifest as early-onset disease (within 3 days of life) or late-onset disease (after 3 days of life). Most early-onset infections are caused by organisms acquired from the maternal genital tract through aspiration of contaminated amniotic fluid or genital tract secretions. Group B *Streptococcus* is the most frequent cause of early-onset pneumonia.[2] Early-onset infection due to group B *Streptococcus*, *Listeria monocytogenes, Escherichia coli,* and other gram-negative bacilli can cause severe respiratory distress resembling hyaline membrane disease, usually as a part of a widespread systemic infection. Prenatal and perinatal risk factors, including preterm delivery, maternal chorioamnionitis, and rupture of membranes >18 hours, increase the risk for neonatal pneumonia. Hematogenous dissemination can occur occasionally from an infected mother.

Pneumonia due to *Chlamydia trachomatis* acquired perinatally can become symptomatic 2 to 3 weeks after birth, and characteristically the infant is afebrile.[19] *Bordetella pertussis* infection in very young infants can have severe complications of apnea, bronchopneumonia, or pulmonary hypertension.[20] With wide availability of extended panels for rapid molecular diagnostic tests, viruses are increasingly confirmed as important causes of pneumonia in young infants.[21] Severe, often fatal pneumonia also can be the result of disseminated herpes simplex virus (HSV) infection in noenates.[22] Congenital cytomegalovirus (CMV) and *Treponema pallidum* are less common causes of neonatal pneumonia. Genital *Mycoplasma* and *Ureaplasma* spp. are purported causes of

LRI, especially in very low birth weight infants.[23]

Agents in Infants, Children, and Adolescents

In a recent study determining the etiologic agents for CAP in children <18 years of age, viruses accounted for 66%, bacteria for 8%, and mixed infection for 7% of cases.[7] This study also noted that viral pneumonia was more common in children <2 years of age compared with older children, whereas *Mycoplasma* was more common in children >5 years of age (19%) compared with younger children (3%).

Viruses.

Overall, viruses account for approximately 73% of CAP in childhood.[7] However, when categorized by age, viruses accounted for >80% of CAP in children <2 years compared with 49% in those >2 years of age.[7] RSV is the predominant viral pathogen of childhood pneumonia, accounting for 28%, with highest incidence in children <2 years of age.[7] Other viruses include human metapneumovirus (hMPV), parainfluenza viruses (types 1, 2, and 3), influenza viruses (A and B), adenoviruses, bocavirus, rhinoviruses, and enteroviruses. Rhinoviruses have been recovered from culture in 22% to 27% of cases of childhood pneumonia.[7] Although influenza, RSV, and hMPV are significantly associated with CAP in children, the roles of other viruses such as parainfluenza viruses, enteroviruses, rhinoviruses, coronaviruses and bocavirus are difficult to ascribe owing to dual virus detections in illness, detections in well children, and extended durations of shedding.[23a] In a case-control study, the latter viruses were negatively associated with CAP.[24] Varicella-zoster virus (VZV), CMV, and HSV typically cause LRI in immunocompromised or very young immune-naïve children. Cases of LRI due to human parechoviruses (HPeV types 1–4) have been reported, but a substantial role awaits description. LRI viral infections mirror general seasonality: RSV, hMPV, and influenza (winter), parainfluenza (spring and autumn), and rhinoviruses and adenoviruses (throughout the year).[25]

Mycoplasma pneumoniae and *Chlamydophila pneumoniae*.

LRI due to *Mycoplasma pneumoniae* affects school-aged children predominantly; molecular detection in upper respiratory secretions in younger children has less clear meaning. Coinfections with either *Streptococcus pneumoniae* (30%) or *Chlamydophila pneumoniae* (15%) occurs.[26] Infections due to *M. pneumoniae* occur in 2-to 4-year cycles.[27] Unlike respiratory viruses, transmission of *M. pneumoniae* among family members is slow, with a median interval of 3 weeks between cases.[27] Pneumonia is rarely ascribed to *C. pneumoniae* in children in the US compared with European and Asian countries and is associated with reactive airway disease or asthma in children >5 years of age. Asymptomatic carriage of *C. pneumoniae* is well documented and confounds assessment of pathogenicity.

Bacterial Pathogens.

Bacterial pneumonia is more common in children living in developing countries, related to several factors, including chronic malnutrition, crowding, inadequate vaccinations, and constant exposure to biomass fuels without adequate ventilation.[28] Various tests that determine bacterial products in blood, respiratory tract secretions, and urine have been used in an attempt to assign a causative LRI role of bacteria but are positive in <10% of cases.[7,15,29] Evidence from multiple sources indicates that *S. pneumoniae* is the single most common cause of bacterial pneumonia beyond the first few weeks of life, causing >76% of bacterial pneumonia cases.[15,16,29] Pneumococcal serotypes causing uncomplicated pneumonia in the US generally are similar to those that cause bacteremia and other invasive pneumococcal disease (IPD) or acute otitis media (see Chapter 123). In the PCV13 era, IPD, including pneumonia, occurs increasingly in older children with underlying medical condtions.[29a] Pneumococcal pneumonia occurs in all age groups, but especially in those <2 years of age.[15]

In countries with widespread immunization with the Hib conjugate vaccine, the frequency of *Haemophilus influenzae* type b (Hib) infection, including pneumonia, has plummeted.[30] Pneumonia due to non–type B and nontypable *H. influenzae* is uncommon in otherwise healthy children in the US, except in premature infants and in children with underlying chronic conditions or diseases or with hospital-associated pneumonia.[31] Acute pneumonia and necrotizing pneumonia can be caused by methicillin-susceptible *Staphylococcus aureus* (MSSA), methicillin-resistant *S. aureus* (MRSA) or community-associated MRSA (CA-MRSA), especially carrying virulence factors like Panton-Valentine leukocidin.[32] *Streptococcus pyogenes* (group A *Streptococcus*) is not a frequent cause of acute pneumonia but can cause rapidly progressive and severe pneumonia, frequently leading to hypoxemia and pleural effusion within hours. Other bacteria, especially gram-negative organisms, are rare causes of pneumonia in previously healthy children but can cause LRI in premature babies, neonates, and patients with cystic fibrosis, sickle cell disease, primary or acquired immune deficiency, or immune suppression.

Other Pathogens.

A variety of epidemiologic and host factors prompt consideration of specific organisms (Table 34.2). The most important of these is tuberculosis, which should always be suspected if there is a history of exposure, in the presence of hilar adenopathy, or when pneumonia does not respond to usual therapy. In North America and Europe, primary tuberculosis pneumonia occurs predominantly in children born to or in contact with recent immigrants from countries where tuberculosis is endemic, after contact with infected adults, or in HIV-infected children.

TABLE 34.2

Occasional Causes of Pneumonia in Special Circumstances

Organism	Risk Factors	Diagnostic Methods
Histoplasma capsulatum	Exposure in certain geographic areas (Ohio and Mississippi river valleys, Caribbean)	Culture of respiratory tract secretions; urine antigen; serum immunodiffusion antibody test; and serum *Histoplasma* complement fixation antibody test
Coccidioides immitis	Exposure in certain geographic areas (southwestern United States, Mexico, and Central America)	Culture of respiratory tract secretions; serum immunodiffusion antibody test
Blastomyces dermatitidis	Exposure in certain geographic areas (Ohio, Mississippi, St. Lawrence river valleys)	Culture of respiratory tract secretions; serum immunodiffusion antibody test
Legionella pneumophila	Exposure to contaminated water supply	Culture or direct fluorescent assay of respiratory tract secretions; antigen test on urine
Francisella tularensis	Exposure to infected animals, usually rabbits	Acute and convalescent serology
Pseudomonas	Travel to rural areas of	Culture of respiratory tract secretions; acute and

pseudomallei (melioidosis)	Southeast Asia	convalescent serology
Brucella abortus	Exposure to infected goats, cattle, or their products of conception; ingestion of unpasteurized milk	Acute and convalescent serology
Leptospira spp.	Exposure to urine of infected dogs, rats, or swine, or to water contaminated by their urine	Culture of urine; acute and convalescent serology
Chlamydia psittaci	Exposure to certain infected birds (often parakeets)	Acute and convalescent serology
Coxiella burnetii	Exposure to infected sheep	Acute and convalescent serology
Hantavirus	Exposure to dried mouse dung in a closed structure (opening cabins after winter closure)	Acute and convalescent serology; PCR test on the respiratory tract secretions

PCR, polymerase chain reaction.

Residing in or traveling to certain geographic areas raises concern for special pathogens. *Coccidioides immitis* is endemic in the southwestern US, northern Mexico, and parts of Central and South America. *Histoplasma capsulatum* is endemic in the eastern and central US and Canada. *Chlamydia psittaci* and *Coxiella burnetii* are transmitted from infected birds, animals, or humans. *Pneumocystis jirovecii* causes pneumonia in unrecognized HIV-infected infants at 3 to 6 months of age, in severely malnourished children, and in other immunocompromised or immunosuppressed hosts not receiving prophylaxis. *Legionella pneumophila* is a rare cause of pneumonia in children, affecting older or immunocompromised children after certain water-associated environmental exposures.

Pathogenesis and Pathology

Pneumonia occurs when a host susceptible to a virulent pathogen is exposed to a high-density aerosol inoculum, has a compromised systemic or secretory immunity, or has an impaired clearance mechanism.[33,34] Most patients with pneumonia have initial colonization or infection of the upper respiratory tract. Invasion of the lower respiratory tract usually occurs when normal defense mechanisms are impaired, such as associated with a viral infection, chronic malnutrition, chronic aspiration, impaired cough reflex (e.g., after sedation, neurologic damage, intubation) or after exposure to environmental pollutants. Bacterial pneumonia can occasionally occur by the hematogenous route. In the early stages of lobar or bacterial pneumonia, protein-rich edema fluid containing numerous organisms fill the alveoli, leading to marked capillary congestion and causing neutrophil exudation and intra-alveolar hemorrhage. There is decrease in lung compliance, increase in pulmonary resistance, small airway obstruction, air trapping, and change in ventilation-perfusion ratio, all leading to the clinical signs of respiratory distress.

Defense mechanisms against LRI consist of (1) anatomic and physiologic barriers; (2) humoral and cell-mediated protection; and (3) phagocytic activity. The presence of hairs in the anterior nares (that trap particles >10 μm in size), configuration of the nasal turbinates, and acute branching of airways form protective anatomic barriers. Filtration and humidification capacities of the upper airways, mucus production, and middle airway protection by the epiglottis and cough reflex (eliminating particles 2–10 μm) form physiologic barriers. The mucociliary blanket transports microscopic amounts of normally aspirated oropharyngeal flora and particulate matter up the tracheobronchial tree, minimizing the presence of bacteria below the carina. Particles <1 μm can escape into the lower airways. Immunoglobulin A (IgA) antibody is secreted into the upper airways, and IgG and IgM leach from the local capillaries into the lower airways. Alveolar fluid surfactant, fibronectin, complement, lysozyme, and iron-binding proteins also have antimicrobial activity. The lower respiratory tract has three distinct populations of macrophages: alveolar, interstitial, and intravascular macrophages. Alveolar macrophages are the preeminent phagocytic cells that ingest and kill bacteria. In addition to phagocytic function, interstitial macrophages are antigen-processing cells, whereas the intravascular macrophages clear inflammatory debris through the bloodstream. Viral infection (especially due to influenza virus), high oxygen concentration, uremia, and use of alcohol or drugs can impair function of alveolar macrophages, predisposing to pneumonia. Cell-mediated immunity plays an important role in pulmonary infections caused by viruses and intracellular organisms such as *Mycobacterium tuberculosis* and *Legionella* that survive within pulmonary macrophages.

Viral Pneumonia

Viral pulmonary infections follow three pathologic patterns: bronchiolitis, interstitial pneumonia, and parenchymal infection.

The first two patterns often overlap.[35,36] Viral pneumonia is characterized by neutrophilic infiltration of the lumen of the airway with lymphocytic infiltration of the interstitium and parenchyma of the lungs.[37] Giant cell formation and viral inclusions within the nucleus of the respiratory cells are histologically evident in many viral infections, including those caused by adenovirus, measles, varicella, CMV, and Epstein-Barr virus, especially in children with immune deficiency. Air trapping with disturbances in ventilation-perfusion ratio occur when obstructed or obliterated small airways and thickened septa impede oxygen diffusion. Necrosis of bronchial or bronchiolar epithelium occurs in severe, sometimes fatal, viral infections (e.g., adenovirus infection).

Bacterial Pneumonia

Bacterial pneumonia can follow five pathologic patterns: (1) parenchymal infection, inflammation, and consolidation of a lobe or a segment of a lobe (lobar pneumonia, the classical pattern of *S. pneumoniae*; (2) primary infection of the airways and surrounding interstitium (bronchopneumonia, often due to *S. pyogenes* and *S. aureus*); (3) necrotizing parenchymal pneumonia that occurs after aspiration of anaerobes or with certain *S. aureus* or *S. pneumoniae*; (4) caseating granulomatous disease, as due to *M. tuberculosis*; and (5) peribronchial and interstitial disease with secondary parenchymal infiltration, as can occur when viral pneumonia is complicated by bacterial infection. In bacterial pneumonia, airspaces become filled with transudates and neutrophilic exudates, impairing oxygen diffusion. The proximity of the infected alveoli to the rich pulmonary vascular bed increases the risk for bacteremia, septicemia, or shock.

Clinical Manifestations

The symptoms of pneumonia are varied and nonspecific and may be subtle depending on several factors, including the etiologic agents, age of the host, inoculum size, and individual's immune response (see Chapter 21). Acute onset of fever, rapid breathing (tachypnea), and cough are classical.[38] Fever can be absent in very young infants with *C. trachomatis*, *B. pertussis*, or *Ureaplasma* infection.[39] Infants can manifest only poor feeding and increased fussiness.[40] Children <5 years of age often have a prodrome of low-grade fever and rhinorrhea due to a viral URI before developing lower respiratory tract symptoms. Fever and rapid breathing can precede onset of cough in some children. Older children can complain of pleuritic chest pain or nuchal rigidity (each referable to lobe involvement). Signs of respiratory distress include tachypnea, hypoxemia (oxygen saturation <92%), apnea, increased work of breathing (subcostal, intercostal or suprasternal retractions; nasal flaring; or grunting) or altered mental status.[41] Guidelines developed by the World Health Organization (WHO) for the clinical diagnosis of pneumonia in developing countries highlight tachypnea and retractions as the two best indicators of LRI.[42] Tachypnea is defined as >50 breaths/min in infants <12 months, >40 for those 1 to 5 years, and >30 for children >5 years of age. Among children <5 years of age, tachypnea (as defined by WHO) had the highest sensitivity (74%) and specificity (67%) for radiologically confirmed pneumonia, but was less sensitive and specific in early disease.[38,43] Tachypnea can occur with other conditions, such as fever, asthma, cardiac disease, and metabolic acidosis. The predictive values of clinical findings for pneumonia have been studied repeatedly.[44–47] In one study, the combination of a respiratory rate >50 breaths/min, oxygen saturation <96%, and the presence of nasal flaring in children <12 months of age was highly associated with radiographically confirmed pneumonia.[40] Oxygen saturation is frequently decreased with moderate to severe pneumonia and is an indication for hospital admission.[41,48] A hypoxemic infant or child may not appear cyanotic.[49] Although hypoxemia, use of accessory muscles of respiration, head bobbing, nasal flaring, and grunting are predictive of pneumonia, their absence does not exclude pneumonia.[46,50] Decreased and bronchial breath sounds, egophony (“E” to “A” change), bronchophony, tactile fremitus, and dullness to percussion are specific signs of lung consolidation. Crackles can be absent in a dehydrated patient.[51] Isolated wheezing or prolonged expiration is associated with bronchiolitis and is uncommon in bacterial pneumonia.[44] Almost three fourths of children with radiographically confirmed pneumonia appear ill. Severity of illness correlates with the likelihood of a bacterial cause. Approximately 6% to 25% of children <5 years of age with body temperature >39°C and a white blood cell (WBC) count >20,000/mm^3 without an alternative source of major infection and with no symptoms or signs of lower respiratory tract disease have radiographically confirmed pneumonia.[47]

In one study determining the interobserver agreement of signs of pneumonia, there was more observer agreement with clinical signs (respiratory rate and cyanosis) compared with auscultatory signs (crackles, retractions, and wheezing) of pneumonia.[40] Unfortunately, neither respiratory rate nor cyanosis is a sensitive or specific indicator of hypoxia. Oxygen saturation should be measured in any child with respiratory distress.[52]

Neonates and Young Infants

The neonate with bacterial infection due to group B *Streptococcus*, *L. monocytogenes,* or gram-negative bacilli usually manifests with respiratory distress in the first few hours of life. Septicemia and infection at other sites can dominate the clinical presentation. Pneumonia in children <2 months of age usually is characterized by tachypnea (respiratory rate >60 breaths/min), intercostal retractions, or both.[52] In very young infants, particularly those who are born prematurely, fever can be absent and apneic spells can be the prominent initial finding.[53] *C. trachomatis* pneumonia in infants is insidious, with infants coming to attention at 3 to 12 weeks with staccato cough, tachypnea, and crackles in absence of fever. Wheezing is uncommon.[54] Eosinophilia and elevated total serum IgM concentration can be present.[55,56]

Infants, Children, and Adolescents

Viruses.

Viral pneumonia usually occurs in the context of a preceding upper respiratory tract illness with gradual increase in irritability, respiratory congestion, cough, posttussive emesis, and fever. The patient may not appear toxic, although hypoxia can be marked, particularly in a young infant whose initial presentation can also be apnea. The auscultatory findings are not anatomically confined, but rather there are diffuse, bilateral wheezes and crackles. Although adenovirus usually follows the pattern of other viral infections, adenovirus can cause severe pneumonia with lobar consolidation similar to a bacterial infection and is especially severe in immunocompromised hosts.[58]

Bacterial Pneumonia.

Bacterial pneumonia may follow several days of mild URI, but onset then usually is abrupt. The patient usually is ill and toxic appearing with high fever, rigors, and tachypnea. Respiratory distress and hypoxemia can be absent or mild unless there is widespread disease or a large pleural effusion. Cough occurs later in the course of the illness when alveolar debris is swept into the upper airway. Unilateral pleuritic chest pain, abdominal pain, neck pain, or sepsis in the presence of radiographically demonstrable infiltrate are specific signs of bacterial pneumonia. Unless there is a parapneumonic effusion, auscultatory findings usually are few and are limited to an anatomic lung segment.

Other Pathogens.

The major symptoms of LRI due to *M. pneumoniae, C. pneumoniae,* and *C. burnetii* (Q fever) are fever and cough that persist for more than 7 to 10 days. The onset of pneumonia caused by *M. pneumoniae* usually is not well demarcated; malaise, headache, photophobia, sore throat, fever, and chills occur early and sometimes subside when the gradually worsening, nonproductive cough ensues. Although coryza is unusual, otitis media can occur.[59] Findings on physical examination and auscultation can be minimal with confined rales, wheezing, or both.[60] The presence of Stevens-Johnson syndrome or hemolytic anemia in a patient with pneumonia suggests *M. pneumoniae* infection.[61] *M. pneumoniae* can cause severe disease in persons with sickle cell disease in whom acute chest syndrome is common.[62] Pneumonia due to *C. pneumoniae* usually has an insidious onset with sore throat, hoarseness, and associated sinusitis.[63] Pneumonia due to *C. burnetii* is rare and usually is mild in children. Symptomatic patients can have intractable headache, myalgia, arthralgia, and nonproductive cough. Chest radiograph findings include segmental or lobar consolidation; "round pneumonia" has been described with Q fever.[64]

Differential Diagnosis

Pneumonia is highly probable in children with fever, cough, tachypnea, and shortness of breath in whom chest radiograph demonstrates pulmonary infiltrates. There are many alternative diagnoses, particularly in the absence of fever, or with chronic, relapsing symptoms and signs. These include foreign-body aspiration, asthma, gastroesophageal reflux, cystic fibrosis, congestive cardiac failure, systemic vasculitis, and bronchiolitis obliterans. Children who develop chemical pneumonia after ingestion of volatile hydrocarbons can have severe necrotizing pneumonia with high fever and peripheral neutrophil counts exceeding 15,000/mm^3.[65]

Imaging and Laboratory Findings

Chest radiography often is obtained to determine whether a patient with respiratory symptoms and signs has pneumonia. However, accurate interpretation of a chest radiograph for pneumonia has multiple challenges: insensitivity in differentiating bacterial from nonbacterial cause, falsely negative in children examined early in the course of pneumonia or in dehydrated patients, lag in abnormal findings, substantial inconsistency in reading by radiologists, and influence of radiologist's knowledge of clinical information on accuracy of interpretation.[44,48,66–70] Prescription of an antibiotic has been linked to radiography,[67] but because routine chest radiography does not appear to alter the clinical outcome of acute LRI,[71,72] radiography should be restricted to special circumstances.

Chest radiography is indicated to confirm the presence and determine the location of pneumonia in children who are hospitalized or are severely ill; have recurrent disease or chronic medical conditions, poor response to initial antibiotic therapy, or complicated pneumonia; and in whom the diagnosis is uncertain or alternative causes of respiratory distress must be excluded.

Bilateral diffuse infiltrates are seen with pneumonia caused by viruses, *P. jirovecii*, *L. pneumophila*, and occasionally with *M. pneumoniae*. Both *C. pneumoniae* and *M. pneumoniae* (Fig. 34.1) cause focal radiographic abnormalities, which are out of proportion to clinical findings. Distinctly confined lobar or segmental abnormality or a large pleural effusion suggests bacterial infection

(Fig. 34.2), but rarely, *M. pneumoniae* or adenovirus can manifest with these findings.[73–75] "Round" pneumonia is the circular appearance of a lung infiltrate. It is common in children <8 years of age with bacterial pneumonia and most often is due to *S. pneumoniae,* although in rare cases, *H. influenzae, S. aureus,* or atypical organisms (*C. burnetii*) can be responsible.

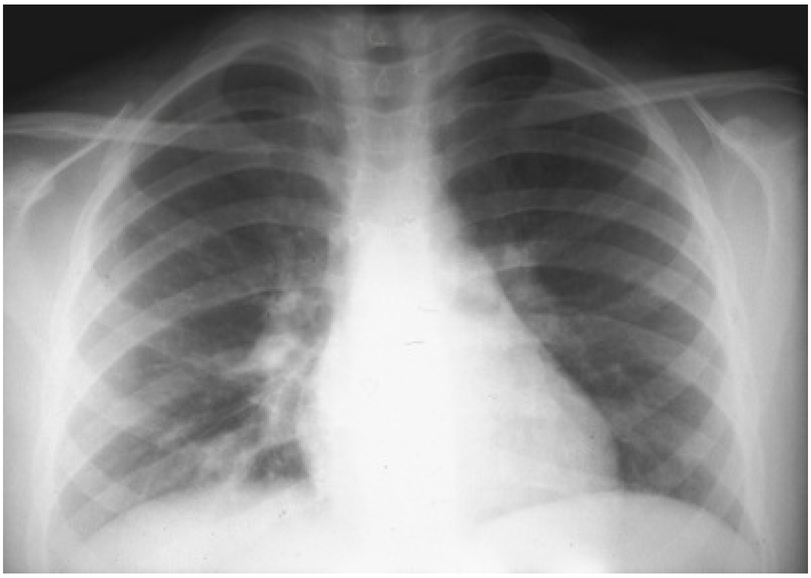

FIGURE 34.1 Plain radiograph showing patchy infiltrates in the right lower lobe, typical of *Mycoplasma* or other "atypical" pneumonias. (Courtesy of S. S. Long, St. Christopher's Hospital for Children, Philadelphia, PA.)

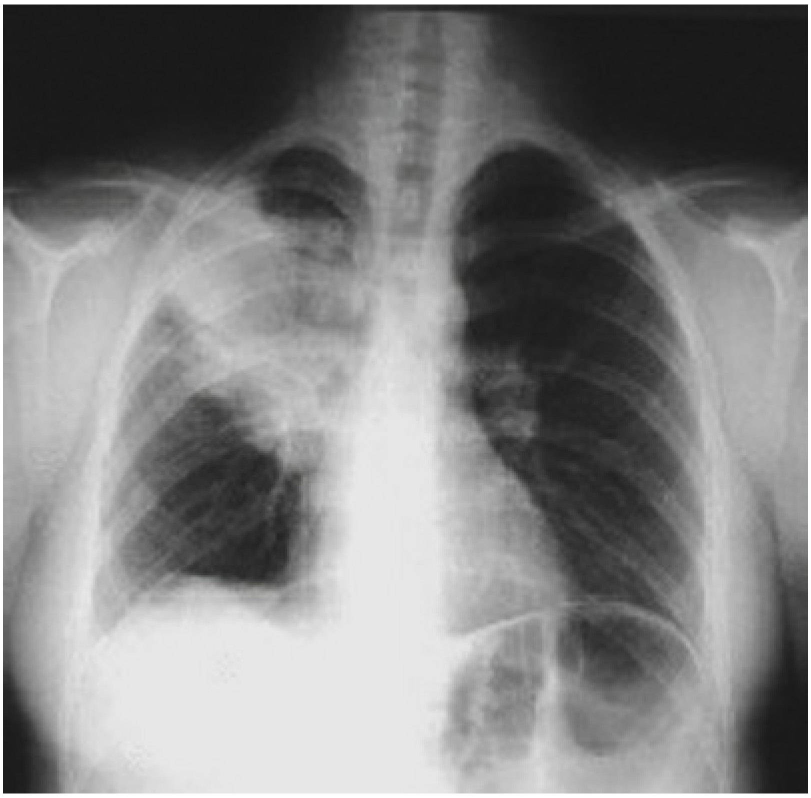

FIGURE 34.2 Plain radiograph showing consolidative pneumonia in the right upper lobe, typical of acute bacterial pneumonia.

Enlarged or calcified hilar lymph nodes suggest tuberculosis or a fungal infection such as *Histoplasma* or *Coccidioides*. *Mycoplasma* and chronic infection in cystic fibrosis can cause hilar lymphadenopathy. Pneumatoceles (thin-walled, air- or fluid-filled cavities) resulting from alveolar rupture usually are associated with infection due to *S. aureus* but can be a necrotizing component of *S. pneumoniae, S. pyogenes, H. influenzae,* gram-negative bacteria, or anaerobe infection. See Chapter 35 for other considerations.

Radiographic improvement of pneumonia lags clinical improvement, and complete resolution of radiologic abnormalities in children may take 4 to 6 weeks. Follow-up radiography is indicated only for persistent atelectasis, complicated pneumonia, recurrent pneumonia, or round pneumonia (to exclude tumor as the cause).[76,77]

A prospective study examining the utility of routine acute-phase reactants in children (WBC count and differential, C-reactive protein, erythrocyte sedimentation rate) with pneumonia concluded that these tests do not differentiate bacterial and viral pneumonia accurately.[78,79] A Cochrane meta-analysis found that patients with bacterial pneumonia usually have C-reactive protein level ≥4 mg/dL.[80]

Diagnosis of Specific Agents

Detecting the causative agent of pneumonia is very important for optimal management but is challenging without use of invasive techniques. Mild to moderately ill ambulatory patients usually can be managed empirically without specific diagnostic tests. Identifying the specific etiologic agent is important for all patients admitted to the hospital, those with underlying conditions, and when there is a community outbreak caused by an apparent emerging agent. A number of investigations may be necessary to confirm an etiologic diagnosis.

Viruses

A viral pathogen is best identified by recovering or detecting the organism in tissue culture or by detecting viral antigens or nucleic acid in respiratory tract secretions using immunofluorescence or polymerase chain reaction (PCR) techniques. Although viral culture is still considered the gold standard to confirm a diagnosis, clinical utility is low because of difficulty and duration of in vitro growth. Real-time PCR test panels rapidly detect common viral and atypical bacterial agents of CAP.[81] Added advantages include the facilitation of appropriate treatment decisions and cohorting of contagious patients. A nasopharyngeal wash or aspirate is the most sensitive specimen because it contains infected epithelial cells. Clinical interpretation of PCR detections is essential. Detection may be related to prolonged shedding.[23a] The presence of a viral agent in the upper respiratory tract does not exclude the presence of secondary bacterial pneumonia. Obtaining acute and convalescent sera to assess rising specific antibodies is usually confined to research settings.

Bacteria

The specific diagnosis of bacterial pneumonia is problematic in infants and children. You do not effectively cough up sputum. In older children, a sputum sample is considered appropriate for microbiologic evaluation when Gram stain reveals <10 squamous epithelial cells and >25 neutrophils per low-power field with a predominant organism. Cultures of nasopharyngeal specimens are not reliable. Tracheal aspiration is useful for culture if performed with direct laryngoscopy. Culture samples obtained through a catheter directly passed through a tracheostomy or an endotracheal or nasotracheal tube have limitations because of frequent contamination with upper respiratory tract organisms; these, however, could be evaluated as for a sputum sample. Quantitative culture performed on a bronchoalveolar lavage (BAL) specimen is useful when the isolate colony count is $>10^4$/mL. BAL is recommended in severely ill, intubated, or immunocompromised individuals not responding to initial antibiotic therapy.[82] The prevalence of bacteremia with pneumonia is reported to be 2.6% to 7%, depending on whether illness is mild or required hospitalization, but increases to 13% to 26% in cases of complicated pneumonia and parapneumonic effusion or empyema.[83–85] *S. pneumoniae* is the most frequent cause of bacteremic pneumonia with or without empyema.[85] Blood culture can confirm etiologic diagnosis, provide susceptibility test results, and alter antibiotic management.[82] Blood cultures are recommended in children who are hospitalized, especially with parapneumonic effusion or empyema.[41] Urine antigen test to detect pneumococcal infection in children in the US is no longer recommended because of low specificity for disease and low sensitivity. *Legionella* urine antigen testing has high sensitivity and specificity and should be performed selectively.[86] Research is ongoing to develop tests to identify pneumonia and characterize etiology (e.g., urine metabolic and exhaled breath condensate tests) that could aid clinical diagnosis in the future.[87–89]

Other Pathogens

M. pneumoniae is detectable by expanded respiratory panels for PCR testing used broadly. *Mycoplasma* culture also is available in some commercial and hospital laboratories but can take 3 weeks to complete. Cold agglutinins (*Mycoplasma*-specific IgM antibodies that agglutinate human red cells) are found in only 30% to 50% of individuals with *M. pneumoniae* pneumonia during the acute phase of the disease.[90] Low titers of cold agglutinins occur in other respiratory viral infections, some collagen vascular diseases, malignancies, and some tropical diseases, making this a less specific diagnostic test as well.[91] Complement fixation (CF) continues to be a widely used serodiagnosis test for *Mycoplasma* pneumonia with sensitivity and specificity of ≥90%.[92] A positive titer is defined as fourfold or higher increase in titer in paired sera or a single titer >1 : 32. The CF test can be negative in young children and in those with mild disease and can be falsely positive in certain inflammatory and autoimmune conditions (including neurologic diseases and bacterial meningitis) or acute pancreatitis because of cross-reactivity between host autoantibodies and the CF antigen.[93,94] Commercially available enzyme immunoassays for anti–*M. pneumoniae* IgM and IgA have unacceptably high false-positive rates.

Comparison of real-time PCR testing with microimmunofluorescence serology shows superiority of PCR for early detection of *C. pneumoniae* infection.[95] Interpretation of detection is required because asymptomatic infection occurs. Specific serology is effective in detecting infections with other agents that cause atypical pneumonia, namely *C. psittaci* and *C. burnetii.*

Screening tests for *M. tuberculosis* includes placing a skin test or obtaining a whole blood specimen for interferon γ release assay (IGRA). Patients and all immediate family members and other significant contacts also should be tested. In children with primary infection and acutely ill patients, IGRA and the skin test can be nonreactive because of general or specific anergy. Additionally, there are data on the utility of IGRA in diagnosis of tuberculosis in children <5 years of age. With suspicion of tuberculosis, multiple specimens should be obtained for smear and culture, including 3 daily samples of sputum (spontaneous or induced) or gastric aspirate, with or without BAL specimen.[96] PCR testing of specimens for *M. tuberculosis* compared with microscopy and culture has higher sensitivity in children with clinical disease.[97]

See also the pathogen-specific chapters in this text.

Treatment

All neonates with pneumonia are best managed, at least initially, in the hospital because of risk for rapid decompensation. Empiric antimicrobial therapy is similar to treatment for neonatal sepsis (see Chapter 92). Therapy is modified based on culture results, clinical response, and severity at presentation.

Outpatient Treatment

Infants 1 to 6 months of age with mild pneumonia can be managed as outpatients with close medical supervision, provided that they do not appear ill or have respiratory distress, hypoxemia (oxygen saturation <92%), feeding intolerance, signs of dehydration, or an underlying chronic medical condition.[98] It is preferable to hospitalize during the peak stage of illness in young infants <4 months of age suspected of having pertussis or viral bronchiolitis because of risk for apnea or hypoxia and, for pertussis, pulmonary hypertension. Infants 1 to 6 months of age should be hospitalized if they have uncertain follow-up, have failed initial oral antibiotic therapy, or have pneumonia that is necrotizing or associated with parapneumonic effusion, empyema, or lung abscess. Most children >6 months of age with mild to moderately severe pneumonia can be managed effectively without hospitalization provided they have reliable follow-up and absence of complication. Diagnostic tests to determine the etiology of pneumonia or radiography are seldom required or useful in most infants and children who are managed as outpatients. In influenza season, suspected influenza should be treated with oseltamivir. Antibiotic therapy is prescribed only when findings suggest bacterial infection. Treatment is empiric, based on likely etiologic agent by age, considering underlying medical conditions, and likely antimicrobial susceptibility, tolerability, and cost. Azithromycin is appropriate for the treatment of infants for infections with pertussis, *C. trachomatis* and *Ureaplasma.* Vigilence for drug-associated infantile hypertrophic pyloric stenosis is prudent, especially in infants <2 weeks of age.[99] Azithromycin dose for pertussis is 10 mg/kg per day once daily for 5 days.

High-dose amoxicillin therapy at 90 mg/kg/day is the preferred outpatient therapy for CAP in infants and children.[41,48,100,101] A pharmacokinetic simulation study predicted excessive failure of treatment of pneumonia due to *S. pneumoniae* with minimal inhibitory concentration (MIC) ≥2 µg/mL using high-dose amoxicillin in 2 divided doses.[102] Dosing in 3 divided doses is preferable in areas where *S. pneumoniae* with MICs ≥2 µg/mL occur.

In antibiotic-experienced children, high-dose amoxicillin-clavulanate (14 : 1 formulation) and ceftriaxone given intravenously are the most active agents for likely gram-positive or gram-negative respiratory pathogens, whereas trimethoprim-sulfamethoxazole, azithromycin, cefaclor, and cefprozil are the least active.[103] Cefuroxime axetil could be used in patients with pneumonia and non–type 1 hypersensitivity reaction to penicillin. Clindamycin could be used in patients with type 1 hypersensitivity reaction to penicillin and in those suspected to have staphylococcal pneumonia or aspiration pneumonia. In one study from the central US, however, 40% of *S. pneumoniae* cases were resistant to clindamycin.[103] Empiric use of cefdinir or azithromycin is an option for mild pneumonia in patients who are allergic or unresponsive to initial therapy with amoxicillin, but these drugs have limited activity against *S. pneumoniae* and nontypable *H. influenzae*.[103]

In children >5 years of age in whom *Mycoplasma* or *C. pneumoniae* are suspected, empiric treatment with a macrolide or doxycycline may be appropriate as single therapy or in combination with amoxicillin if pyogenic bacteria also are suspected. High-dose amoxicillin-clavulanate or clindamycin is effective for children with aspiration pneumonia. Fluoroquinolone therapy or treatment using agents with enhanced gram-positive activity (e.g., levofloxacin, moxifloxacin) can be considered in adolescents with frequent aspiration, as well as in those infected with atypical organisms, because their activity includes *M. pneumoniae* and *C. pneumoniae*.[104]

Duration of antibiotic therapy for pneumonia also is empiric and depends on several factors including patients' age, severity of illness, underlying illnesses, and response to therapy. In most cases the duration of therapy is 7 to 10 days. Oseltamivir therapy for influenza is initiated as soon as possible (i.e., before test results) for children at high risk for complications (e.g., underlying medical conditions including asthma) and for all children hospitalized with influenza. Oral oseltamivir phosphate is approved by the US Food and Drug Administration for children >2 weeks of age. Inhaled zanamavir also is approved as an alternative anti-influenza therapy in children >5 years of age with influenza and no underlying pulmonary disease.

Inpatient Treatment

Hypoxemia (oxygen saturation <92%) is the single most important indication for hospitalization because a hypoxemic child has greater risk for death than an adequately oxygenated child.[51] Other indications include cyanosis, rapid respiratory rate (>70 breaths/min in an infant or >50 breaths/min in a child), apnea, dyspnea, expiratory grunting, dehydration, toxic appearance, poor oral intake, recurrent pneumonia, underlying medical condition, or uncertain observation at home.

Supportive Therapy

Oxygenation is assessed continuously by measuring oxygen saturation or arterial P_{O_2}. Hypoxic infants and children may not appear cyanotic until terminal. Mental agitation, clinically evident as increased irritability, can be an indication of hypoxemia. Supplemental oxygen therapy is indicated in any patient whose oxygen saturation is persistently ≤92%. Sole reliance on pulse oximetry values, without blood gas determination, is hazardous in ill patients because hypercarbia is an important sign of impending respiratory failure.

Rapid breathing, fever, decreased oral intake, and fatigue increase the fluid requirements. Most patients can be hydrated orally if given small volumes of fluids frequently, but intravenous fluids usually are necessary for seriously ill children with rapid breathing because of increased likelihood for pulmonary aspiration. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) can occur in up to one third of patients hospitalized with pneumonia and is associated with more severe disease and with poor outcome.[105] Fluid restriction is required in these cases to improve outcome.

Malnutrition has been associated with a worse prognosis of pneumonia. Infants and small children fare better if fed in small quantities and more frequently to prevent aspiration.[106] Placement of an enteral feeding tube or parenteral nutrition may be necessary in a seriously ill or intubated child to maintain nutritional balance.

Persistent and high fever increases the basal metabolic rate and oxygen consumption. Similarly, pain interferes with the depth of breathing and with the ability to cough effectively. Age-appropriate antipyretic or analgesic agents may be necessary.

Oral antibiotics can be effective in certain hospitalized older infants and children with uncomplicated pneumonia who have good oral intake. Otherwise, initial intravenous therapy with ampicillin is appropriate. Ampicillin-sulbactam or a third-generation cephalosporin should be considered for those who previously received antibiotics or have severe pneumonia. A third-generation cephalosporin should be considered in areas where *S. pneumoniae* with MICs ≥2 μg/mL are prevalent. Intravenous clindamycin may be considered in patients with type-1 hypersensitivity to penicillin, suspected staphylococcal infection or aspiration pneumonia. Intravenous cefepeme, ceftazidime, or piperacillin-tazobactam is used for empiric therapy in immunocompromised patients with pneumonia, especially in those with neutropenia. Empiric antifungal therapy is considered initially or if there is inadequate response to antibiotic therapy. Vancomycin or linezolid usually is given for MRSA-confirmed infection or empirically in children with severe, life-threatening pneumonia. Patients with cystic fibrosis will need adequate antibiotic coverage for *S. aureus* and *Pseudomonas* spp. until sputum cultures guide further choices. Broad antibiotic therapy is reconsidered pending identification of an organism by susceptibility test results or pending the clinical course. Generally, appropriate oral antibiotic is selected to complete therapy for uncomplicated pneumonia when the patient responds to therapy and begins to tolerate oral fluids.

Viral pneumonia is complicated by bacterial superinfection with variable frequency.[107,108] Evidence suggests that withholding antibiotics from hospitalized children with pneumonia clinically compatible or proved to be of viral origin is safe and is preferable to broad use of empiric antibiotic treatment.[109] Use of specific antiviral therapy other than for influenza depends on the pathogen, the severity of the clinical course, and benefit-versus-risk considerations. Use of aerosolized ribavirin for the treatment of RSV and acute LRI is guided by recommendations from the American Academy of Pediatrics,[110] although the value of treatment has been questioned.[111]

Prognosis and Sequelae

Mortality due to CAP is uncommon beyond infancy in Europe and North America because of improved and enhanced immunization rates, early access to medical care, and availability of appropriate antimicrobial therapy. Most healthy children with acute LRIs recover without complications or sequelae. In some patients, especially premature infants, immunocompromised hosts, or children with chronic lung, neuromuscular, or sickle cell disease or cardiovascular disease, acute complications are more common.

Several epidemiologic studies have questioned a linkage of asthma and other respiratory morbidity occurring later in childhood to viral bronchiolitis or atypical pneumonia in infancy, but not to bacterial pneumonia.[112–114] RSV and *C. trachomatis*, in particular, have been implicated,[112–115] and one study linked asthma with *C. pneumoniae* infection.[116] Abnormal pulmonary function in adults has been reported after pneumonia or pertussis in early childhood.[117,118] Other longitudinal studies of pulmonary function in children with bronchiolitis, however, have suggested that abnormalities may have preceded the acute infectious illness.[119,120] Thus it remains unclear whether childhood pneumonia causes chronic pulmonary disease.

Prevention

Most respiratory viral infections are transmitted by direct inoculation from hands contaminated with respiratory secretions on to conjunctival and nasal mucosa. Spread by airborne droplets also occurs occasionally. Adequate hand hygiene by caregivers and medical personnel is the single most important method of preventing hospital-associated infections. Hospitalized patients with respiratory tract infection who are <5 years of age, and older children who are unable to follow proper respiratory etiquette, are cared for under isolation precautions (droplet and contact) to prevent transmissions by large droplets. Spread of infection by small droplets (pertussis) is reduced by use of airborne precautions in a negative-pressure room.

Universal immunization with pneumococcal conjugate vaccines, PCV7 and then PCV13, has reduced dramatically the incidence of invasive pneumococcal disease and pneumonia in children as well as in young adults and elderly people through community (herd) protection.[121–123] Children ≥2 years of age and adolescents at heightened risk for invasive pneumococcal disease should receive

PCV13 followed by pneumococcal polysaccharide vaccine 23 (PPV23).

RSV bronchiolitis and pneumonia can be reduced in high-risk infants by avoidance of multiple environmental risk factors (see Chapter 225). Monthly administration of RSV monoclonal antibody can reduce by 50% hospitalization due to RSV and is recommended for certain high-risk infections.[124] Annual vaccination against influenza is recommended for all individuals ≥6 months of age, with emphasis on strict implementation for those with underlying medical conditions such as chronic lung diseases (including mild asthma), neuromuscular disorders, congenital cardiac conditions, and diabetes who have high risk for severe and complicated lower respiratory tract influenza infection.[125,126] It is anticipated that prevention of influenza (and varicella) by immunization reduces the incidence of bacterial pneumonia in children due to *S. pneumoniae*, *S. aureus*, and *S. pyogenes*.

Acute Complicated Pneumonia

The acute complications of bacterial pneumonia include parapneumonic effusion, empyema, necrotizing pneumonia, pneumatocele formation, and lung abscess.

In the late 1990s, there was a significant increase in the relative incidence of complications from bacterial pneumonia in infants and children living in North America, the exact reason for which is still obscure.[16]

Pleural Effusion, Parapneumonic Effusion, and Empyema

Pleural effusion is the presence of abnormal fluid collection between the visceral and parietal pleurae. Pleural effusions are classified as a *transudate* or an *exudate* based on Light criteria for the biochemical characteristics of the fluid.[127] The relative concentration of pleural fluid protein to serum protein is <0.5 in a transudate versus >0.5 in an exudate (Table 34.3). Transudates are infrequently caused by infection, whereas exudates can have an infectious or noninfectious cause. Noninfectious causes of pleural effusions are listed in Table 34.4. Several drugs, including hydralazine, nitrofurantoin, dantrolene, amiodarone, methysergide, procarbazine, bromocriptine, methotrexate, and agents associated with a lupus-like reaction, are associated with pleural effusion.[128]

TABLE 34.3

Biochemical Characteristics of Parapneumonic Pleural Effusions

Laboratory Value	Uncomplicated Effusion Transudate	Complicated Effusion Exudate
pH	>7.2	<7.1
Glucose level	>40 mg/dL	<40 mg/dL
Lactate dehydrogenase concentration	<1000 IU/mL	>1000 IU/mL
Pleural protein–to–serum protein ratio	<0.5	>0.5

TABLE 34.4

Noninfectious Causes of Pleural Effusion in Children

Transudate	Exudate	
Hypoalbuminemia	Spontaneous chylothorax	Malignancy
Congestive heart failure	Posttrauma or postsurgical	Collagen vascular disease
Cirrhosis with ascites	Postoperative chylothorax	Pancreatitis
Myxedema	Pulmonary lymphangiectasia	Subphrenic or other intra-abdominal abscess
Peritoneal dialysis	Uremic pleuritis	Drug reaction
Central venous catheter leak	Sarcoidosis	Meig syndrome (pelvic tumor)
Fluid mismanagement	Dressler syndrome (postmyocardial infarction)	
Adult respiratory distress syndrome		

Parapneumonic effusion is an inflammatory fluid collection adjacent to a pneumonic process, seen overall in 2% to 12% of children with pneumonia and in up to 28% of hospitalized children.[129] Parapneumonic effusion can be classified as uncomplicated or complicated based on fluid pH, glucose, and lactate dehydrogenase (LDH) concentrations (see Table 34.3).[130] *Empyema* refers to purulent collection (exudate) in the pleural sac[131] and represents a spectrum from uncomplicated to complicated parapneumonic effusion.

Parapneumonic effusion usually occurs as a complication of pyogenic bacterial pneumonia but can occur occasionally, secondary to other etiologic agents (e.g., *Mycoplasma*, adenovirus)[132] or as a consequence of an infection from another contiguous site.[133] The estimated incidence of empyema in hospitalized children in the US was reported to be approximately 3.7 per 100,000 (range, 3.3–4.2) from 1997–2006, which was a 70% increase that occurred while the incidence of bacterial pneumonia, especially that due to *S. pneumoniae,* decreased.[134] The increase in empyema is thought to be related to increase in *S. pneumoniae* serotypes 1, 3, and 19A; *S. pyogenes*; and CA-MRSA.[135,136] Most cases of complicated pneumonia requiring surgical drainage occur in children <5 years of age.[137] Necrotizing pneumonia with pneumatoceles frequently coexists with empyema, predominantly in children <3 years of age.[138] The risk for developing empyema also is increased in children with certain underlying infectious (influenza) and medical conditions, including congenital heart disease, chronic pulmonary conditions, immune deficiencies, and neuromuscular disorders.[139,140] Complicated effusion or empyema is a serious illness often associated with significant morbidity (such as that needed for care in an intensive care unit), surgical drainage, longer hospital stay, and longer antibiotic course, resulting in high healthcare costs; mortality rates, however, have been low except in children <2 years of age.[85,141,142]

Etiologic Agents

S. pneumoniae is the most common cause of culture-confirmed and culture-negative parapneumonic effusions.[132] Although penicillin-nonsusceptible *S. pneumoniae* strains were recognized in the late 1980s to early 1990s, serotype 1, a highly invasive but penicillin-susceptible pneumococcal strain developed. During the late 1990s in Utah, *S. pneumoniae* serotype 1 emerged as a virulent agent of complicated pneumonia.[85] In the mid-2000s, before the introduction of PCV13, serotypes 1, 3, 7F, and 19A were detected in other areas of the US in more than half of cases of empyema in children.[132,143,144] In many cases, *S. pneumoniae* was detected by PCR in fluid or blood and not by culture, especially in patients pretreated with antibiotics. In a recent study from Greece, one third of 15 children with *S. pneumoniae* serotype 3 pneumonia and pleural effusion had been immunized with PCV13 after 12 months of age (with the then recommended 2 doses); no case occurred in children whose immunizations began in infancy and included all 4 recommended

PCV13 doses.[145] Universal childhood immunization against Hib has made Hib a rare cause of parapneumonic effusion. CA-MRSA is an important cause of complicated pneumonia[146,147]; in southeast Asia, *S. aureus* is the most common cause.[148] Less frequently, group A *Streptococcus*, *Pseudomonas aeruginosa,* mixed anaerobic pathogens, *Mycobacterium* spp. and, rarely, fungi and parasites can be the etiologic agents.[149] Although effusion can accompany pneumonia due to *M. pneumoniae* and common viruses, they seldom are large enough to require intervention.[149,150] Parapneumonic fluid, other than in *S. aureus* infection, frequently is sterile, especially if the patient has received antibiotics or when the infection is caused by fastidious organisms.[132,143,146] In such situations, PCR testing often can confirm the etiology.

Pathogenesis and Pathologic Findings

Under normal circumstances, the pleural space contains a small amount (0.1–0.2 mL/ kg) of low protein fluid that forms a lubricant film between the two layers of the pleura.[151] The pleural circulation is maintained by a delicate balance between secretion and absorption of pleural fluid by lymphatic vessels. When this balance is disturbed, fluid accumulates. Transudate occurs when there are changes in the hydrostatic forces with normal capillary permeability, whereas exudate results when there is increased capillary permeability and lymphatic obstruction.[152,153] Pleural mesothelial macrophages contribute to the innate local defense against infection.[154] Pathogens can gain entry into the pleural space by direct extension from the alveoli, by hematogenous spread from the skin surface through a penetrating injury, from rupture of the esophagus, or from an intra-abdominal site through the diaphragm.[155] Direct extension from the alveoli is by far the most common. Certain pathogens such as *S. aureus, S. pneumoniae,* and *S. pyogenes* demonstrate tropism for the pleural surface for reasons that are not well understood but that likely include virulent factors such as exotoxins, endotoxins, or attachment molecules. Exposure of the pleural mesothelial cells to lipopolysaccharide, thrombin, or bacteria can incite an innate and adaptive inflammatory response causing pleural mesothelial macrophage dysfunction.[156,157] Vascular endothelial growth factor is released, which potentiates endothelial injury, increased capillary permeability, and extravasation of pulmonary interstitial fluid into the pleural space.[158] Mesothelial cells recruit neutrophils and monocytes and secrete large amounts of chemokines, including interleukin-8 (IL-8), into the pleural fluid that, when inhibited by bacterial proteins, results in an acidic, purulent fluid (i.e., empyema).[159] Acidic environment of the pleural fluid both suppresses bacterial growth and interferes with antibiotic activity. With disease progression, more inflammatory cytokines are released, and there is activation of coagulation leading to deposition of fibrin.

Three stages in the natural course of empyema are recognized. First, in the *exudative phase*, the fluid has low cellular content, normal glucose, and normal pH. Second, in the *fibrinopurulent phase*, frank pus containing neutrophils and fibrin is formed, and glucose and pH of fluid are low. This fibrinous pus coats the inner surfaces of the pleura, interfering with lung expansion, and leads to loculations. Third, in the *organizational phase* (late stage), fibroblasts migrate into the exudate from visceral and parietal pleurae, producing a nonelastic membrane called the *pleural peel*. Before the availability of antibiotics, spontaneous drainage through the chest wall (empyema necessitans) or into the bronchus (bronchopleural fistula) sometimes followed. Such events now are rare and usually are due to healthcare-associated antibiotic-resistant bacteria or insidiously progressive actinomycosis.

Clinical and Radiographic Manifestations[85,138,141,149]

Effusion should be suspected when the response of a lobar, lobular, or alveolar pneumonia to appropriate antibiotic therapy is slow, or if there is clinical deterioration during treatment. Symptoms of pleural effusion can begin nonspecifically with malaise, lethargy, and fever, followed by cough and rapid breathing, the latter which are expected in >90% of children with complex parapneumonic effusion.[141] Dyspnea, difficulty breathing, and grunting become apparent as the effusion progresses. Pain in the chest or abdomen develops on the involved side and is associated with high fever, chills, and rigors. The child may splint or lie on the involved side to minimize pain. The patient usually is ill, toxic appearing, and febrile, with significant tachypnea and shallow respirations, or can have severe respiratory distress, hypotension, and septic shock. Scoliosis may be noted on the involved side, and the affected side may be tender to palpation. On auscultation of the involved side, breath sounds usually are frankly diminished, crackles from the associated pneumonia may be audible, pleural rub may be audible when the effusion is small, and the percussion note is dull when the effusion is free flowing. By contrast, dullness can decrease as the effusion organizes.

Plain chest radiography is more sensitive than physical examination but less sensitive than ultrasonagraphy in detecting small effusions.[160] A chest radiograph can indicate size and loculation of effusion and whether drainage likely is indicated and can define parenchymal lung consolidation as well as an unexpected underlying cause of the effusion, such as a mass, hilar adenopathy, or cardiomegaly. Blunting of the costophrenic angle, thickening of the normally paper-thin, pleural-shadow, and a subpulmonic density all suggest pleural effusion (Fig. 34.3). Compression of the lung, with shift of the trachea away from the effusion, may be seen when the effusion is large, usually ≥1000 mL.[161] Lateral decubitus films can differentiate free effusion from loculated collections, pulmonary consolidation, and pleural thickening. Chest radiographs, however, cannot differentiate between a parapneumonic effusion and an empyema.[149] Ultrasonography is the imaging modality of choice because it is portable, inexpensive, and involves no radiation exposure; differentiates parenchymal from pleural space disease; helps localize and estimate the size of an effusion precisely; identifies the best site for thoracentesis and chest tube placement; and is superior to computed tomography (CT) in detecting early loculation and septation.[162] Quality of ultrasonography is dependent on level of experience of the operator. Although CT is not necessary routinely to differentiate simple parapneumonic effusion from empyema, CT may be indicated to evaluate parenchymal disease (necrotizing pneumonia or lung abscess), to determine noninfectious causes, or to aid the surgeon before thoracotomy or thoracoscopy.[16]

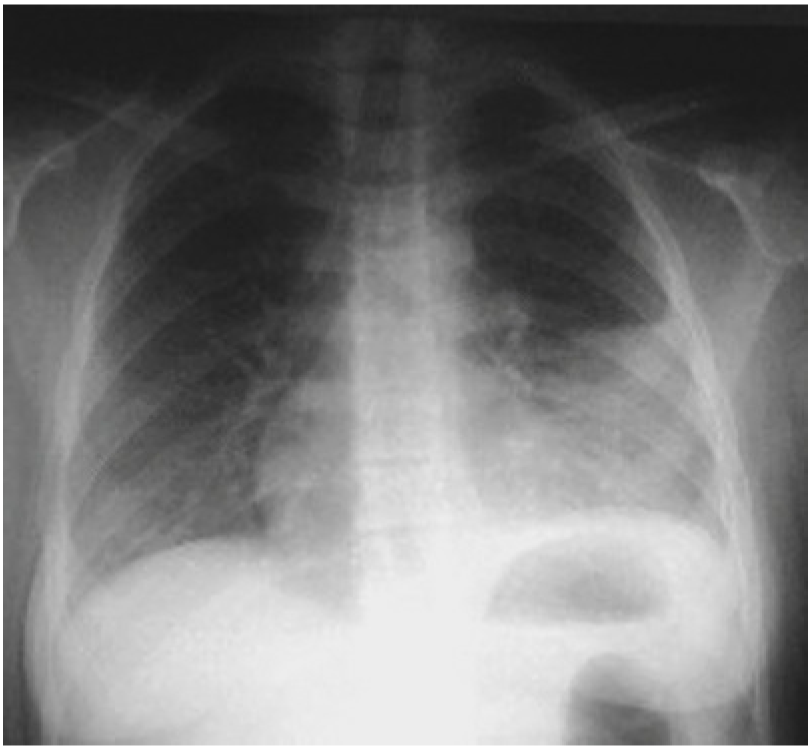

FIGURE 34.3 Plain radiograph showing left lower lobe pneumonia and a parapneumonic effusion, typical of acute bacterial pneumonia.

Laboratory Findings and Diagnosis

Children with parapneumonic effusion or empyema often have an elevated peripheral WBC count, left shift of neutrophils, elevated C-reactive protein, and thrombocytosis (>500,000 platelets/mm^3). Hypoalbuminemia can occur if the effusion is large and proteinaceous and hyponatremia raises consideration of SIADH. Blood cultures are obtained before therapy because a positive result (10%–22%) is useful for management when pleural fluid is sterile.[85,145] Culture of sputum or tracheal aspirate, if possible, may be useful. Gram staining determines whether the quality of the sample is good (>25 neutrophils/low-power field and absent squamous epithelial cells) and if a single organism type is predominant.

Pleural fluid specimen is inspected to determine color, odor (putrid odor being pathognomonic of anaerobic infection), and character (bloody, purulent, seropurulent, or serosanguineous); centrifuged if cloudy (persistent cloudiness is suggestive of a chylothorax); and analyzed for total WBC count with differential and by special stains and culture. Cellular histology and flow cytometry are performed if infectious etiology is uncertain. Empyema is likely when biochemical analysis reveals pleural fluid-to-serum ratio for LDH >0.6, pH <7, glucose <40 mg/dL, and LDH >1000 U/L.[163] Because biochemical analysis rarely influences management, Pediatric Infectious Diseases Society and Infectious Diseases Society of America guidelines do not recommend evaluation unless the patient has an underlying condition (e.g., collagen vascular disease).[41] Cytokine levels in pleural fluid, especially IL-8, are expected to be high in empyema.[156] IL-8 level may be useful to differentiate a complex from simple parapneumonic effusion.

Total and differential WBC count of pleural fluid is helpful in differentiating bacteria, mycobacteria, or fungi infection and malignancy.[149] Presence of >50,000 neutrophils/mm^3 is usual in empyema. Lymphocytic predominance suggests tuberculosis and some fungal or *Mycoplasma* infections but also can indicate a chylothorax. Mixed mononuclear cell types suggest a more chronic process, such as tuberculosis, malignancy, uremia, or collagen vascular disease. Eosinophilic effusion in adults, especially with air or blood in the pleural space, suggests tuberculosis, asbestosis, malignancy, paragonimiasis, drug-related hypersensitivity, pleurisy, collagen vascular disease, other parasitic infections, or an idiopathic case (14%–20%).[164–167]

Bacteriologic examination always includes Gram stain and culture for aerobic and anaerobic bacteria. Acid-fast stain and culture for *M. tuberculosis*, as well as fungal stain and culture, should be obtained from both fluid and sputum when clinically indicated. Rapid non–culture-based diagnostic tests such as PCR, immunoassay, and rapid antigen testing increasingly are performed because their rate of culture positivity is low and the knowledge of etiology aids management.[168]

Tuberculous pleural effusion usually is caused by a delayed hypersensitivity reaction to mycobacterial antigens in the pleural space.[169] Diagnosis often is delayed because of paucity of organisms in pleural fluid, anergy to tuberculin skin test, and IGRA in blood.[170,171] High levels of adenosine deaminase (>40 IU/L) and interferon γ (>75 pg/mL) in pleural fluid are very suggestive of tuberculous effusion.[172] Rapid and accurate diagnosis, as well as prediction of rifampin resistance, is possible using the Xpert

MTB/RIF (Cepheid, Sunnyvale, CA) assay on pleural biopsy and pleural fluid specimens in patients with suspected tuberculous pleural effusion who have a negative sputum smear for acid-fast bacilli.[173] Pleural biopsy is considered to diagnose other granulomatous infections (histoplasmosis, other fungal infections, and *Francisella tularensis)* and malignancies.

Management

The main objectives of therapy are eradication of infection and reestablishment of pleural fluid circulation, thereby reinstating normal lung function.[174] These can be achieved by either medical or surgical interventions depending on the age of the patient, size of the effusion, severity of respiratory distress, loculation, and failure of initial medical therapy. Supportive care using appropriate antipyretics, analgesics, oxygen supplementation, and fluid therapy must be instituted early and patients must be monitored closely to recognize respiratory deterioration, central respiratory depression from excessive analgesics, or fluid overload related to SIADH. Chest physiotherapy is avoided because this causes discomfort and can further compromise the respiratory effort.[149]

Antimicrobial Therapy.

In choosing therapy, consideration is given to probable pathogens (predicted by age), pathogen and geographic resistance patterns, clinical circumstances (community or healthcare onset), host factors (immunocompetent or compromised), radiographic findings, and Gram stain and culture of the pleural fluid. Children with small, uncomplicated effusion can be managed as outpatients with an empiric antibiotic regimen as for CAP. In most hospitalized patients, ceftriaxone or cefotaxime given intravenously is recommended as empiric therapy to adequately treat *S. pneumoniae* and *S. pyogenes*. Vancomycin is added if the patient is very ill appearing or CA-MRSA or hospital-acquired MRSA is considered a potential pathogen. In areas where CA-MRSA is highly clindamycin susceptible, clindamycin could be an adequate addition. Vancomycin has poor pharmacokinetics for infections in the lung. Other agents with good MRSA activity include linezolid, telavancin, ceftaroline, and quinupristin-dalfopristin; these agents are considered second-line treatment for patients who do not respond to vancomycin therapy. Daptomycin should not be used because it is inactivated by surfactant. In patients with suspected pneumonia aspiration, clindamycin can be used instead of vancomycin to cover anaerobic bacteria. In cases in which atypical pathogens are suspected, a macrolide (for children <7 years) or doxycycline (for children >7 years) may be added. When a specific pathogen is detected, or when the clinical course and microbiologic screening cultures make Staphylococcal infection highly unlikely, the antibiotic spectrum should be narrowed. Duration of parenteral therapy and total treatment is individualized on the basis of clinical response and adequacy of drainage. It is common practice to replace parenteral therapy with oral therapy when substantial improvement occurs and the patient has good oral intake, with continuation of antibiotics for a total course of 2 to 4 weeks for empyema.[41] The treatment may be prolonged when drainage is delayed and systemic manifestations are protracted. In circumstances in which the effusion persists and the microbial etiology is unknown, it is important to remember that even with optimal antibiotic therapy, fever, anorexia, and toxicity can be due to a prolonged inflammatory response. Additions or changes in appropriately selected antibiotic therapy should be avoided.

Surgical Intervention.

Thoracentesis is recommended to relieve moderate to large effusions, defined as fluid layering >1 cm on lateral decubitus radiograph or opacifying more than one fourth of the hemithroax.[41,149,162] A therapeutic approach to moderate-sized, nonloculated parapneumonic effusion not associated with respiratory compromise is to slowly drain 10 to 20 mL/kg, send the fluid for microbiologic studies, and begin empiric antibiotic therapy intravenously. It is important not to drain fluid too rapidly because reexpansion pulmonary edema can occur, causing increased morbidity and even mortality.[175] The course is observed over 48 to 72 hours. Many patients improve. If the patient does not improve or worsens, ultrasonography is performed to determine the extent of reaccumulation. If fluid has reaccumulated, continuous drainage is required; if not, an antibiotic regimen is reconsidered. For patients with a large effusion or patients with respiratory compromise, a chest tube is placed as soon as possible for continuous drainage. A small bore chest tube is preferable for patient comfort and was associated with shorter hospital stay and found to be superior to surgical stiff drains in two studies.[176,177] Chest radiography is repeated to verify chest tube placement and to exclude the development of pneumothorax during placement. Complications of chest tube placement include bleeding or infection at the exit site, persistent atelectasis, development of bronchopleural fistula, or (very rarely) laceration of the lung.[178]

Loculated complex parapneumonic effusion or empyema usually requires more aggressive management, but optimal management remains controversial. According to the British Thoracic Society and American Pediatric Surgical Association guidelines,[149,162] medical therapy (chemical debridement with fibrinolysis) should be considered as initial therapy of choice followed by video-assisted thoracic surgery (VATS) in patients who fail medical therapy. Recommendations are based on several studies showing comparable outcomes and complications for procedures, with safety and cost favoring chemical debridement with fibrinolysis.[179,180] However, a 2005 meta-analysis showed that primary operative therapy compared with nonoperative therapy was associated with a lower cumulative in-hospital mortality rate (0% vs. 3.3%) and rate of reintervention (2.5% vs. 23.5%). In addition, primary operative therapy was associated with shorter duration of hospitalization (10.8 vs. 20 days), chest tube days (4.4 vs. 10.6 days), and antibiotic therapy (12.8 vs. 21.3 days), respectively.[181] Most experts agree that either approach is reasonable and that choice of procedure will depend on local expertise, cost considerations, and patient preference.

Available fibrinolytic agents include urokinase, streptokinase, and alteplase. Alteplase is the most commonly used fibrinolytic agent in the US because urokinase is not available and streptokinase has limited efficacy and possible allergic reactions.[182] Common adverse effects of fibrinolytic therapy include fever, discomfort, intrapleural bleeding, and anaphylaxis.[177] Fibrinolysis is contraindicated in patients with bronchopleural fistula or when there is an air leak because this could cause tension pneumothorax.

In VATS surgery, fibrinous material is debrided, loculations are broken, and drainage of purulent material from the pleural space is established. VATS is most effective when performed early in the course of complex effusions or empyema, has good outcomes, and is relatively safe. Compared with open thoracotomy, VATs is less invasive and has a comparable success rate, earlier resolution of the disease, shorter hospital stay, and better cosmetic appeal.[183,184] Partial decortication frequently can be accomplished when necessary. The few contraindications to performing VATS include inability to access the pleural cavity because of thick, purulent fluid and severe fibrosis.

Bronchoscopy may be indicated in anaerobic infections to hasten drainage or the removal of a foreign body. Open pleural decortication is reserved for patients who have come to optimal management late and have entrapment of lung with persistent and severe restrictive lung disease.

Most children improve after surgical drainage, as evidenced by improved activity, appetite, vital signs, and chest physical findings and resolving acute phase reactants. After radiographic examinations related to chest tube removal, follow-up chest radiograph usually is not necessary unless the child has persistent symptoms or has had a previous episode. Follow-up chest radiograph for the latter indication should be delayed 4 to 6 weeks because radiographic resolution lags clinical resolution.[174]

Prognosis

Most children with complex parapneumonic effusion or empyema recover completely despite the severity of their initial presentation. The mortality rate was about 3% in previously healthy children medically managed with antibiotics and chest tube drainage, but no deaths were reported in children who underwent a fibrinolytic procedure, VATS, or open thoracotomy.[181] Historically, mortality was highest in small infants.[185] Increased morbidity can be expected in children with underlying medical conditions (e.g., malnutrition, neuromuscular disorders, or chronic pulmonary disease) or with infection due to MRSA or multidrug-resistant organisms. A long-term prospective follow-up study of children treated for complex effusions or empyema showed no sequelae despite substantial complications within 1 month of illness.[186] A recent study evaluating the long-term effect of parapneumonic effusion, especially in children with prior history of asthma, concluded that there were no long-term important effects despite small changes in lung function and exercise capacity.[187]

Necrotizing Pneumonia and Lung Abscess

Necrotizing pneumonia and lung abscess represent the spectrum of disease. The etiology and course in children differ compared with adults. Lung abscess usually occurs as a consequence of a localized lung infection by particularly virulent, pyogenic bacteria. Necrotizing pneumonia in an otherwise healthy child usually resolves with antimicrobial treatment, but occasionally can progress to formation of pneumatoceles (blebs in the lung parenchyma created by coalescence of alveolar spaces after rupture of septa), lung abscess, or bronchopleural fistula. Lung abscess is usually the outcome of widely variable pathogenic processes; it can be the consequence of (1) necrotizing pneumonia; (2) localized infection after aspiration of heavily infected mouth secretions (sometimes along with a foreign body); (3) focal infection of the lung that occurs during high-grade bacteremia or as a result of infarcting septic emboli from distant sites; or (4) complication of a subacute or chronic airway infection seen as a late result of cystic fibrosis, after prolonged intubation, or after nosocomial pneumonia. In immunocompromised hosts, bacteria or fungi can invade the vessel walls, leading to subsequent lung infarction and necrotizing pneumonia (see Chapter 36).

Etiologic Agents

Community-acquired bacterial pneumonia can result in necrosis of parenchyma, which often is discovered on chest radiography or increasingly because CT is performed in a child with prolonged fever and ill appearance.[188] The causative pathogen is not identified in many cases, but when detected, *S. pneumonia* is most common.[189] Less commonly, *S. aureus* (especially CA-MRSA), *S. pyogenes* (especially after influenza illness), β-hemolytic streptococci (Lancefield groups C and G), and other streptococcal species are causative.[190–192] Pneumatoceles can complicate *S. pneumoniae* or *S. aureus* pneumonia, and the latter can lead to abscess formation.[190,193,194] Rarely, severe *M. pneumoniae* pneumonia is accompanied by abscess formation.[195,196]

When pneumonia follows aspiration of oropharyngeal flora, or regurgitated stomach contents and obstruction, the volatile fatty acids produced by anaerobic bacteria are particularly prone to cause necrosis and abscess. Most aspiration pneumonias, lung abscesses, and empyema are mixed infections.[197,198] The predominant anaerobic bacteria isolated are *Peptostreptococcus*, *Fusobacterium*, *Prevotella melaninogenica,* and *Porphyromonas* spp.[197] *Veillonella* may be more likely isolated in children with prior surgery, malignancy, corticosteroid therapy, aspirated foreign body, or immunodeficiency.

Single or multiple lung abscesses (usually due to *S. aureus* infections) can result from right-sided endocarditis, severe septicemia, or distant osteoarticular or deep muscle infection with thrombosis. Necrotizing pneumonia and lung abscess also can follow endovascular infection or phlebothrombosis of the large veins in the neck (Lemierre syndrome).[199] *Fusobacterium necrophorum* is the most common pathogen, but *S. aureus,* α-hemolytic streptococci, *Streptococcus anginosus* group, *Actinomyces* spp., or molds can be causative.[200]

Lung abscesses in intubated infants and children usually are due to hospital-associated pathogens.[201] Abscesses can develop in the later stages of cystic fibrosis secondary to chronic bronchiectasis. In such cases, *S. aureus, P. aeruginosa,* and atypical mycobacteria should be considered.[202,203]

Pathogenesis

Necrotizing pneumonia is a consequence of severe inflammation confined to a cluster of alveoli or a lobe resulting in significant parenchymal damage and tissue necrosis. Abscess formation can follow even when treatment is adequate but more frequently when treatment is delayed or inadequate.

Aspiration and obstruction of the airways predispose to polymicrobial and anaerobic lung abscess. Risk factors include decreased level of consciousness due to neurologic disease, anesthesia, alcohol, or drugs or during surgical instrumentation; neuromuscular disorders depressing the gag reflex; esophageal abnormalities; gastroesophageal reflux; and prolonged endotracheal intubation. Poor dental hygiene and periodontal infection increase the density of anaerobes and predispose to lung abscess in adolescents. Impaired phagocytic responses as seen in neutropenic patients or after viral infections with influenza, measles, and VZV also can predispose to complicated pneumonia. Aspirated acid contents of the stomach cause chemical injury to lung tissue.[204] Location of abscess favors the middle or right lower lobe in patients who aspirate while erect, and favors the posterior upper or lower lobes in the supine patient. Abnormal drainage as occurs in congenital pulmonary sequestration, lobar emphysema, and pneumatocele formation can predispose to abscess formation. Experimental studies in animals show a timeline from aspiration to pneumonia to lung abscess of at least 1 to 2 weeks.[205]

Heavy seeding of the pulmonary circulation during high-grade bacteremia can lead to lung abscess, as can pulmonary infarction associated with septic embolization. These circumstances usually lead to multiple abscesses, unilaterally or bilaterally. Chronic airway disease, cystic fibrosis, congenital ciliary dysfunction, and bronchiectasis predispose to lung abscess. The inherited abnormalities of humoral or cellular immune responses, such as chronic granulomatous disease or hyper-IgM syndrome, permit persistence of certain pathogens, which can result in abscess formation.

Clinical Manifestations

Clinical manifestations of necrotizing pneumonia are similar to but usually more severe than those of nonnecrotizing pneumonia due to the same bacteria. The evolution from necrotizing pneumonia to abscess frequently is insidious.[206] Lung abscess after aspiration usually manifests 1 to 2 weeks after the event. Prolonged fever and a toxic appearance or persistent hypoxia despite appropriate antimicrobial therapy is characteristic. Fever is the most common sign in patients with lung abscess.[188] Cough, dyspnea, and sputum production are present in approximately one half of patients.[188,206] Cough usually is nonproductive, but with spontaneous rupture of the abscess into the bronchus, it can be massively productive. Hemoptysis can be seen in necrotizing pneumonia. Older children may report chest pain with or without radiation. Other symptoms are nonspecific and include rhinorrhea, sore throat, lymphadenopathy, decreased appetite, irritability, and malaise or lethargy.[188] Physical findings also are nonspecific unless there is accompanying pleural fluid.

The differential diagnosis of lung abscess includes common necrotizing bacterial infections as well as tuberculosis, nocardiosis, fungal infections, melioidosis, paragonimiasis, and amebic abscess. Certain noninfectious diseases, such as malignancy, sarcoidosis, and pulmonary infarction, can produce lesions that mimic abscess on chest radiograph.

Diagnosis

A chest radiograph should be obtained in a child whose symptoms do not respond to appropriate antibiotic treatment (Fig. 34.4). The initial finding usually is an irregular cavitary lesion (with or without a thick wall) with air-fluid level adjacent to a segmental or lobar lung infiltrate, without prominent hilar adenopathy. Multilobar involvement can be seen in patients with underlying immune dysfunction or after septic embolization.[207] Chest radiography may not be diagnostic initially in approximately 20% of cases. In one study of 18 cases, abscess location was the right lower lobe (8), left lower lobe (6), right upper lobe (3), and left upper lobe (1).[206] CT is more sensitive than plain radiography and often is useful to define the extent of disease, underlying anomalies, presence or absence of a foreign body (Fig. 34.5), and endobronchial obstruction and to distinguish parenchymal abscess from air-fluid levels in the pleural space.[208]

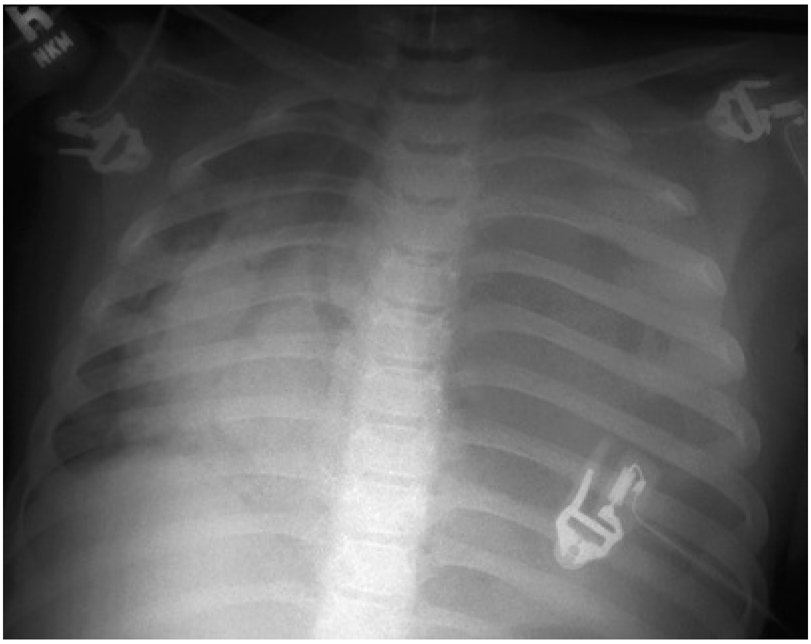

FIGURE 34.4 Anaerobic pleural empyema in a 5-year-old girl who came to medical attention because of a 1-month history of abdominal pain, tiredness, and constipation, but no history of an aspiration event, fever, respiratory distress, or cough. This radiograph was obtained after an acute respiratory event during evaluation for constipation. Note complete opacification of the left hemithorax with severe shift of the heart and trachea to the right. Three liters of putrid pus was drained, revealing a left lower lobe abscess. Gram stain and culture revealed polymicrobial anaerobic and facultative oropharyngeal flora. (Courtesy of E. N. Faerber and S. S. Long, St. Christopher's Hospital for Children, Philadelphia, PA.)

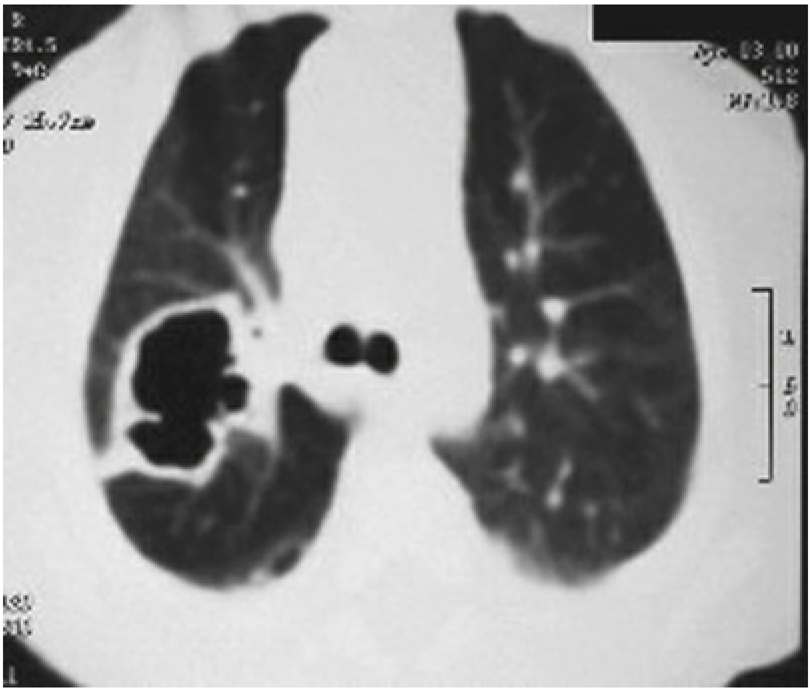

FIGURE 34.5 Lung windows of computed tomography study showing right lower lobe abscess.

Ultrasonography using color Doppler is a powerful diagnostic tool to differentiate fluid-filled lung abscess from empyema and has the advantages of greater convenience, lower cost, and avoidance of radiation.[209]

Bronchoscopy may be a therapeutic means to facilitate the removal of a foreign body or to promote the drainage of purulent fluid, or both.[206] Only 3% of bronchoscopic specimen cultures grew an organism that later was recovered from a lung abscess.[210] Cultures of sputum, BAL, or blood are of limited diagnostic value compared with culture of direct lung aspirate. In one study, 94% of the specimens obtained by transthoracic aspiration yielded a pathogen despite prior receipt of an antibiotic compared with only 11% of sputum cultures and 3% each of blood and BAL cultures.[210] Ultrasound-guided transthoracic aspiration technique was used successfully to obtain specimens for diagnosis to drain lung abscesses in 3 premature infants.[211] There is a potential risk for spillage of contaminated fluid into the pleural space during ultrasound- or CT-guided transthoracic aspiration; procedures are reserved for patients not improving clinically on antibiotic therapy and for those who have a large abscess that must be drained.

Management

Prolonged antibiotic administration is the mainstay of therapy for necrotizing pneumonia and lung abscess. Duration of therapy is based on clinical response and usually is 4 weeks, or at least 2 weeks after the patient becomes afebrile and has clinical improvement. In most cases, parenteral therapy is initiated. Two randomized clinical trials in adults found clindamycin to be superior to penicillin for the treatment of anaerobic lung abscess.[123,212,213] A randomized clinical trial for treatment of children with aspiration pneumonia found no difference between these two drugs. Ampicillin-sulbactam has an excellent spectrum of activity against organisms in aspiration lung abscesses.[214] Parenteral clindamycin is appropriate empiric therapy in children with complicated lung infection possibly due to *S. aureus* or CA-MRSA. Vancomycin is an alternative in patients with allergy or where clindamycin resistance of *S. aureus* is prevalent. Other antistaphylococcal medications, such as linezolid, could be used in case of allergy or poor response to vancomycin or clindamycin.[215] Combination therapy with ticarcillin or piperacillin and a β-lactamase inhibitor (e.g., tazobactam) with or without an aminoglycoside may be considered when necrotizing pneumonia follows aspiration in a hospitalized child or in a child for whom an Enterobacteriaceae (e.g., *E. coli, Klebsiella* spp.) or *P. aeruginosa* infection is suspected or has been identified from a percutaneous lung aspirate. Metronidazole would be effective treatment for β-lactamase–producing anaerobes in lung abscess after aspiration but cannot be used alone without an agent active against aerobic and microaerophilic streptococci.[216]

Necrotizing pneumonia or abscess frequently is complicated by parapneumonic effusion, which benefits from percutaneous drainage or other invasive procedures depending on size and other clinical factors. Previously, percutaneous drainage of the abscess often was complicated with the development of bronchopleural fistula.[217,218] Because of expected good outcome with medical therapy, percutaneous drainage should be considered only in patients with poor response 5 to 7 days after initiating therapy, for an abscess >4 cm in diameter, for presence of mediastinal shift, or for an abscess resulting in ventilator dependency. Surgical wedge resection or lobectomy is rarely required and is reserved for cases in which medical management and drainage fail, or bronchiectasis has occurred.

Prognosis and Complications

Most cases of necrotizing pneumonia in otherwise healthy children resolve with antibiotic treatment alone.[188] Similarly, 80% to 90% of lung abscesses resolve with antibiotic therapy alone provided there is no associated bronchial obstruction or underlying lung disease such as cystic fibrosis. Fever can persist for an average of 4 to 8 days despite appropriate therapy. Complications due to lung abscess are rare in developed countries and in otherwise healthy hosts. These could include intracavitary hemorrhage with hemoptysis, spillage of abscess with spread of infection to other parts of the lung, empyema, bronchopleural fistula, septicemia, cerebral abscess, and SIADH.

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35

Persistent and Recurrent Pneumonia

Robert R. Wittler

Persistent pneumonia has been defined as continuation of symptoms and radiographic findings beyond 4 weeks given that most acute pneumonia improves clinically and radiographically within that time.[1] Persistent or residual abnormalities occur in 10% to 30% of children with radiographically confirmed community-acquired pneumonia (CAP) 3 to 7 weeks after initial imaging.[2,3] In adults with CAP, clinical resolution occurs in more than 85% of cases and radiographic resolution in 67% of cases by 4 weeks after onset.[4] In both adults and children with CAP, radiologic abnormalities lag behind clinical resolution.[4] Although pneumonia due to respiratory syncytial virus (RSV) or parainfluenza virus clears within 2 to 3 weeks,[5] pneumonia due to adenovirus can cause persistent abnormalities for up to 12 months.[6] Thus, in children making an uneventful clinical recovery from a first episode of uncomplicated CAP, a repeat chest radiograph is not recommended routinely.[7]

Recurrent pneumonia has been defined as occurrence of two or more episodes of pneumonia in a 1-year period or three or more episodes in any period, with radiographic resolution between episodes.[1] Using this definition, approximately 8% of children requiring hospitalization for pneumonia would be identified as having recurrent pneumonia.[8] In children with underlying conditions such as cystic fibrosis (CF) or pulmonary sequestration, complete resolution does not occur between exacerbations.

Radiographic documentation of episodes is essential for categorization because precise clinical distinctions are made infrequently and “pneumonia” is the diagnosis sometimes conveyed to the parent (or the parent perceives) for conditions such as bronchiolitis, bronchitis, asthma, or persistent cough.

Although a chest radiograph is not necessarily indicated to confirm the diagnosis of acute pneumonia in previously healthy outpatients, nor indicated routinely at the end of treatment of the first episode of acute pneumonia requiring hospitalization,[7] a history of prior episodes, especially in the same lobe, and persistence or recurrence of symptoms are indications for initial and follow-up radiographic evaluations.[9,10] In a child with a history of “recurrent pneumonia,” documenting a normal radiographic appearance 2 months after an acute episode (the time at which radiographic findings are expected to be normal in more than 90% of cases) is the most useful step in shaping a differential diagnosis. Before investigations are initiated for persistent or recurrent pulmonary infection, radiographs should be obtained and reviewed with a radiologist experienced in disorders of children to define the abnormalities precisely and to consider both infectious and noninfectious processes as well as underlying conditions and anatomic abnormalities.[1]

The differential diagnosis for and clinical approach to recurrent pneumonia in children are distinct from those for persistent pneumonia and also depend on (1) whether the site of parenchymal disease is the same or different with each episode and (2) whether the infiltrate is, on the one hand, dense, focal, and consolidated, or, on the other, atelectatic, patchy, diffuse, nodular, or interstitial. The specific approach to children whose pneumonia is associated with hospitalization, human immunodeficiency virus (HIV) infection, or some other form of immunologic deficiency is addressed in other chapters in this book.

Persistent or Progressive Pneumonia at a Single Site

Pathogen-Related Causes

Unresolved or untreated acute infection usually is responsible for persistent pneumonia (Table 35.1). In a patient receiving empiric antibiotic therapy, the cause is (1) infection by an organism not eliminated by the chosen antibiotic, either because of antimicrobial resistance of a common bacterial pathogen (penicillin-resistant *Streptococcus pneumoniae,* methicillin-resistant *Staphylococcus aureus* [MRSA], β-lactamase-producing *Haemophilus influenzae, Prevotella melaninogenica,* resistant gram-negative bacilli); or (2) more commonly, infection with organisms for which the chosen antimicrobial therapy was ineffective (*Mycobacterium tuberculosis, Mycoplasma pneumoniae, Chlamydophila* spp., *Coxiella burnetii, Francisella tularensis,* fungi, viruses, helminths).[11] Complications of appropriately treated bacterial pneumonia, such as necrotizing pneumonia, pleural effusion, and progression to lung abscess or empyema, or bronchiectasis also must be considered. The clinical, radiographic, and other imaging findings, as well as the context of the patient's illness, help prioritize possible causes (Fig. 35.1).

TABLE 35.1

Diagnostic Considerations for Pneumonia at a Single Site

Persistent or Progressive	Persistent or Recurrent
Untreated common acute infection **Segmental bronchiectasis** **Unresolved common acute infection** **Complication of acute infection** **Tuberculosis** **Uncommon infection**	**Atelectasis**
	Intraluminal obstructing lesions Foreign body Granuloma (infective or foreign body)
	Right middle lobe syndrome
	Bronchial tumor (adenoma, papilloma, lipoma)
	Extrinsic obstructing lesions
	Lymph nodes (infective or malignant)
	Tumor
	Enlarged heart, pulmonary arteries
	Vascular ring, sling
	Congenital abnormalities
	Bronchial anomalies (bronchomalacia, bronchial stenosis or web, tracheal bronchus)
	Tracheobronchial cysts (cyst adenomatoid malformation, lobar emphysema, bronchogenic cyst)
	Pulmonary sequestration

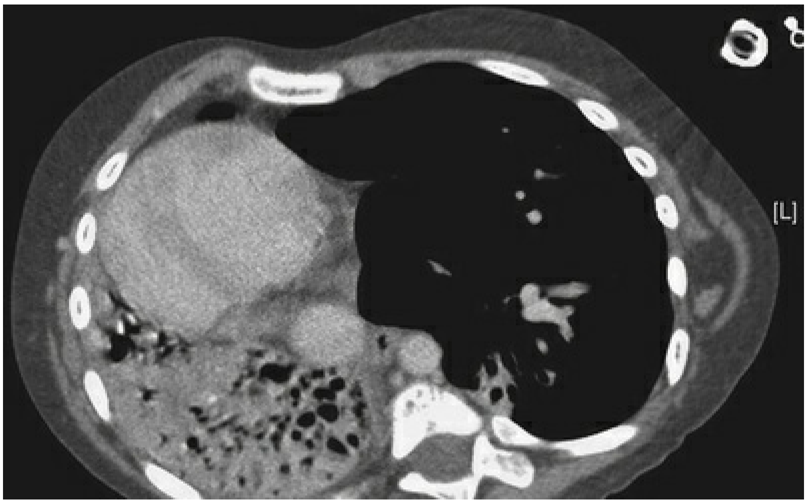

FIGURE 35.1 Computed tomography study of a 9-year-old boy with severe cerebral palsy, seizures, aspiration, and recurrent right lower lobe pneumonia showing severe bronchiectasis. Surgical resection was necessary. (Courtesy of J.H. Brien©.)

Tuberculosis always should be considered in children with persistent pneumonia or subacute presentation even if exposure is not obvious. Immigration from or travel to a region of the world with a endemic tuberculosis (Asia, Middle East, Africa, Latin America, countries of the former Soviet Union) or contact with individuals at high risk for tuberculosis (immigrants from regions in which tuberculosis is endemic; homeless persons; individuals with history of drug abuse or imprisonment; or persons with HIV infection) heightens the likelihood of tuberculosis.[12] A history of weight loss, cough, or fever is not always present. The radiographic abnormality generally is more impressive than the limited clinical findings, although occasional patients can manifest hectic fever, respiratory distress, and toxicity simulating acute pyogenic pneumonia. The presence of enlarged thoracic lymph nodes is a suggestive, but inconsistent, finding.

C. burnetii (Q fever) and *Chlamydia psittaci* infections are considered in patients with persistent fever, malaise, and myalgia, hacking cough, persistent parenchymal infiltrate, and exposure to farm animals or psittacine birds. Systemic illness usually overshadows pulmonary symptoms in young children with Q fever; psittacosis is rare in young children.

The likelihood of fungal pneumonia in a previously healthy child depends on place of residence or unusual environmental exposure.

Nodular or miliary densities are more common than lobar consolidation, but not consistently. *Histoplasma capsulatum* is endemic to the Midwest and to the St. Lawrence River valley in Canada. Subacute presentation with fatigue and a persistent cough is usual, and hilar lymphadenopathy is a clue. *Blastomyces dermatitidis* is a rare cause of persistent pneumonia in children. Endemic areas partially overlap those of histoplasmosis, including parts of the Mississippi, Ohio, Missouri, and St. Lawrence waterways. Older children with *Blastomyces* pneumonia may produce purulent sputum and often fail at least one course of treatment with an antibacterial agent before the etiology is identified correctly. *Coccidioides immitis* is endemic to the southwestern United States, including west Texas, Arizona, New Mexico, California, Utah, and Nevada, as well as northern Mexico and parts of Central and South America. Erythematous rashes and erythema multiforme are frequent early in the course, and erythema nodosum (also seen in *Blastomyces* or *Histoplasma* infection) can accompany pneumonia. Because environmental exposure often is a cause of fungal pneumonia, clusters of cases within the same family or in other persons exposed simultaneously can occur with *Histoplasma, Blastomyces,* and *Coccidioides* spp. infections. Rarely, a previously healthy child with or without undue exposure to dust, pigeon excreta, model terrarium, construction, or home renovation develops pneumonia due to *Cryptococcus* or *Aspergillus* spp. that leads to a protracted infection.

In adolescents at risk for HIV infection, *Pneumocystis jirovecii* should be considered, especially when persistent pneumonia is bilateral, interstitial, and associated with hypoxemia disproportionate to the severity of clinical illness or physical findings. Risk factors for HIV infection (injection drug use, multiple sexual partners, bisexual partner) need to be evaluated. In the infant with HIV infection, *P. jirovecii* pneumonia, especially when not properly treated, is rapidly progressive and has a high mortality.

Diffuse lower respiratory tract inflammation caused by some respiratory viruses can predispose to bacterial superinfection, especially in patients hospitalized with influenza or RSV infection requiring intensive care.[7] For children with laboratory-confirmed viral respiratory infection for whom symptoms persist or progress, a viral-bacterial coinfection deserves consideration. Several viruses, including influenza, can cause a rapidly progressive pneumonia nonresponsive to antibacterial therapy. Hantavirus can act similarly and also can involve other organs. Adenovirus can cause a necrotizing pneumonia (bronchiolitis obliterans).

Host-Related Causes

Multiple congenital or acquired anatomic abnormalities also are considered in children whose pneumonia (1) fails to resolve, (2) responds symptomatically to antimicrobial therapy but does not resolve radiographically, or (3) resolves and then recurs at the same site (see Table 35.1). Atelectasis (parenchymal volume loss) should be differentiated from persistent infiltrate or consolidation (without volume loss). Atelectasis occurs commonly with RSV bronchiolitis, airway hyperreactivity in infants and toddlers, asthma, and complete bronchial obstruction from intrinsic or extrinsic causes. Except with fixed obstructing lesions, atelectasis is expected to be transient or migratory; if atelectasis persists, the affected lung segment can become infected secondarily.

Bronchiectasis, with dilation of the bronchi, arises most commonly from damage to bronchial walls by infection or chronic inflammation. The bronchial wall then is susceptible to further dilation and distortion during breathing. Severe acute viral, bacterial, or fungal infection or recurrent infection related to CF, immunodeficiency, or local obstruction are known causes of bronchiectasis.[13] Adenovirus and measles virus infections, retained foreign body, and tuberculosis are associated most commonly with segmental bronchiectasis in the healthy host. In children with untreated or poorly controlled HIV infection or congenital immunodeficiency, lymphocytic interstitial pneumonia or recurrent bronchitis or pneumonia can progress to bronchiectasis.[14] After bronchiectasis has developed, impaired ciliary function and bronchial mechanics predispose to recurrent pneumonia. Children with extensive bronchiectasis often are fatigued easily, may have slower growth, and commonly have digital clubbing.

Intraluminal Obstructing Lesions

In otherwise healthy children, aspirated foreign body (or granulation tissue resulting from presence of a foreign body) is the most common cause of incompletely resolved or recurrent pneumonia at the same site.[1,15] The diagnosis is apparent if history of an event is elicited or a foreign body is visualized radiographically. Neither finding is present in most cases, but frequently older children remember the event after the object is retrieved at bronchoscopy. Spontaneous hemorrhage from the lower respiratory tract suggests foreign body (or pulmonary sequestration) and can be life-threatening.

Pneumonia at a single anatomic site can be related to particular positional vulnerability in children who are relatively immobile and who aspirate oropharyngeal material because of impaired neuromuscular function or coordination. A dependent segment or segments of lung are involved usually. Other intraluminal bronchial obstructions can cause associated single-site pneumonia, including bronchial adenoma, lipoma, papilloma, foreign body granuloma (e.g., peanut, other vegetable matter), granuloma of *M. tuberculosis* or nontuberculous *Mycobacterium* spp., or segmental bronchomalacia or bronchial stenosis.

The right middle lobe is predisposed to persistent atelectasis and subsequent infection or delayed resolution of pneumonia because of the acute angle and length of its bronchus, the proximity of its bronchus to hilar nodes, and poor to absent collateral ventilation compared with other regions of the lung. The right middle lobe also is a site of aspiration in the upright position. Recurrent right middle lobe pneumonia and atelectasis make up the so-called right middle lobe syndrome. Right middle lobe syndrome in children can have an intraluminal cause secondary to a primary ventilation disorder and chronic inflammation; asthma and foreign body aspiration are two such causes. Extraluminal compression from anatomic abnormalities and compression through lymph nodes from infectious causes, such as fungi and *M. tuberculosis,* also can be responsible. Evaluation of children with recurrent abnormalities of the right middle lobe should include bronchoscopy with direct visualization of the airway and sampling for cultures and cytology.[16]

Extrinsic Obstructing Lesions

Extrinsic airway compression most commonly is due to lymph node enlargement. Tuberculosis is most common, causing hilar, carinal, and other superior mediastinal airway compression, leading to secondary bacterial pneumonia. Pulmonary histoplasmosis, blastomycosis, and coccidioidomycosis also are important causes of hilar adenopathy.[1] Tumors can cause compression of the airway directly or through lymph node involvement. Congenital or acquired heart disease associated with an enlarged heart can cause compression of left lower lobe bronchus especially, leading to pneumonia. Shunting procedures that cause excessive pulmonary blood flow can lead to airway compression or segmental congestion and impaired drainage, predisposing to localized infection.

Congenital Abnormalities of the Respiratory Tract

Congenital abnormalities of airways, pulmonary parenchyma, or the diaphragm can cause localized persistent or recurrent pneumonia (Fig. 35.2). Tracheal bronchus, an abnormal bronchus arising from the trachea, leads to impaired drainage of the right upper lobe and persistent collapse. Congenital cystic anomalies of the tracheobronchial tree include congenital pulmonary airway malformation (CPAM; previously termed *congenital cystic adenomatoid malformation* or CCAM), congenital lobar hyperinflation, and bronchogenic cysts[17] (Fig. 35.3).

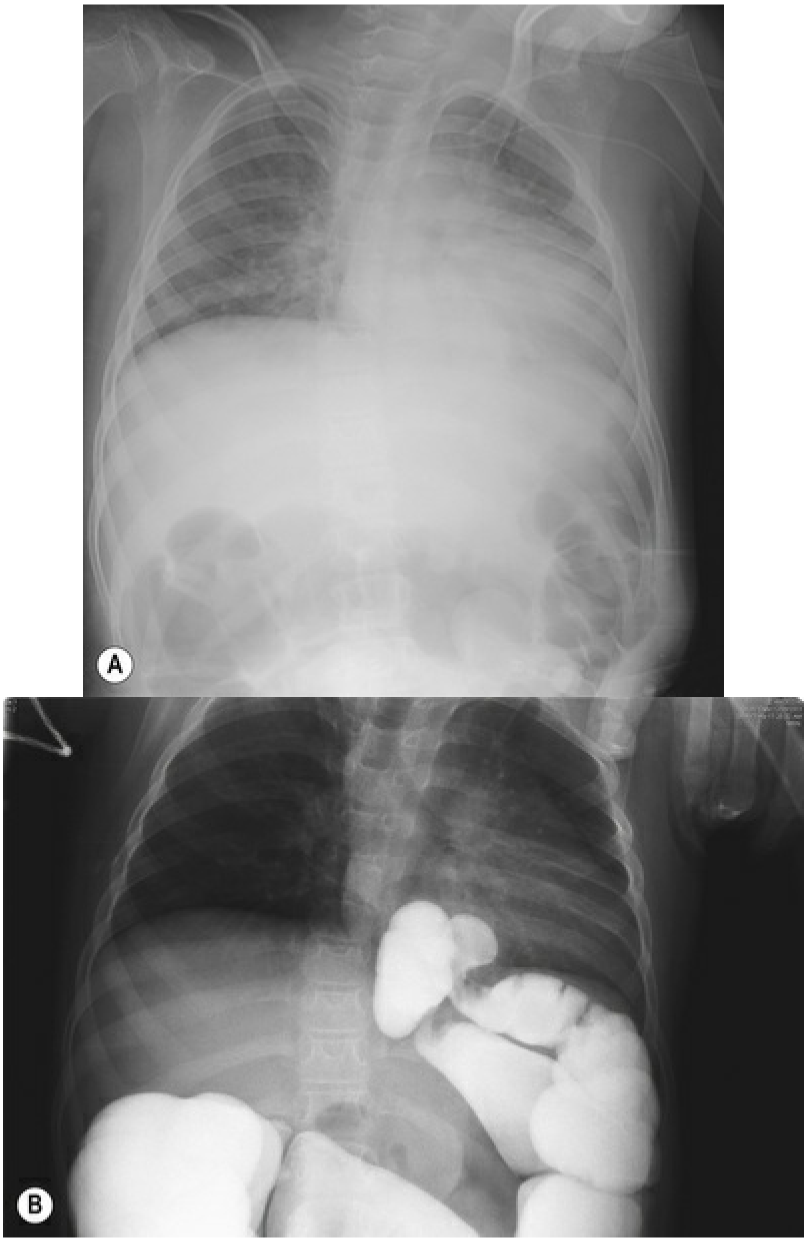

FIGURE 35.2 A 9-year-old girl with microcephaly had multiple episodes over multiple years of left lower lobe pneumonia (A) when barium study revealed congenital diaphragmatic hernia as the cause of persistent "consolidation" (B). (Courtesy of J.H. Brien©.)

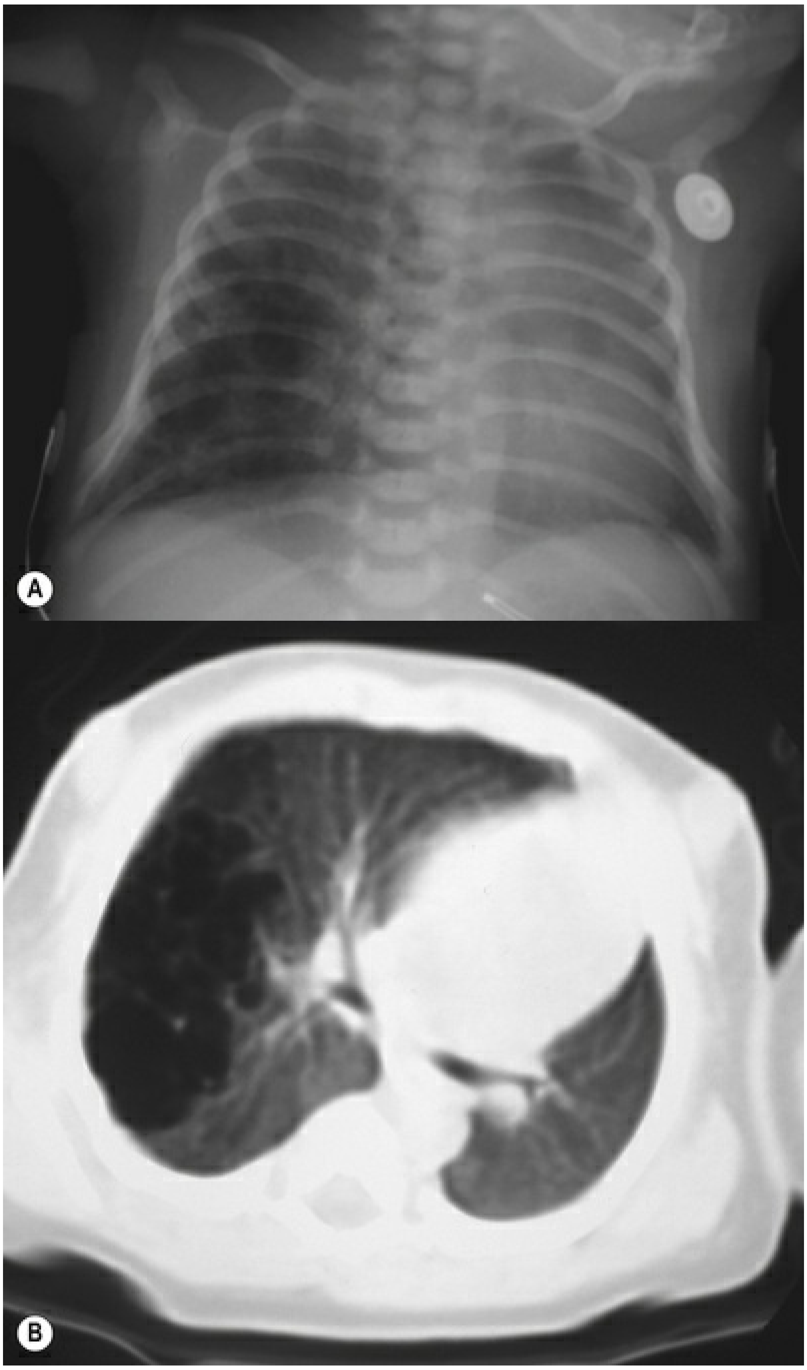

FIGURE 35.3 Congenital pulmonary airway malformation (previously termed *congenital cystic adenomatoid malformation*) in a term neonate who was evaluated because of respiratory distress. Plain radiograph (A) and lung window of axial computed tomography (B) show typical cluster of cysts, varying in size. Note superiority of computed tomography in demonstrating sites and extent of pathology. (Courtesy of E.N. Faerber.)

CPAM is the most common congenital lung anomaly, representing 30% to 40% of cases. CPAM and congenital lobar hyperinflation manifest early in infancy with respiratory distress (and cystic abnormality on radiographs) but can come to attention later as recurrent infection in the same segment of lung. Pulmonary sequestrations are the second most common congenital pulmonary anomaly and are composed of dysplastic pulmonary tissue that contains no connection or an aberrant connection to the tracheobronchial tree and receives a systemic vascular supply. Bronchogenic cysts are a form of foregut duplication cyst resulting from defective foregut budding. Bronchogenic cysts and pulmonary sequestrations, particularly intralobar sequestrations, can manifest as chronic or recurrent pneumonia later in childhood. Radiographically, bronchogenic cysts usually appear as round or oval well-circumscribed lesions typically in the paratracheal, hilar, and subcarinal areas. Pulmonary sequestrations appear as a focal opacity or mass in the lower lobe, usually on the left. With recurrent infection, intralesional necrosis can develop, and a more cystic appearance with or without air-fluid levels can be seen.[17]

Approach to Diagnosis

The history of illness, associated symptoms, environmental or contact exposures, judgment about adherence to prescribed therapy, possibility of partial improvement, and reevaluation of the appropriateness of prescribed therapy usually identify children with incompletely or inadequately treated uncomplicated acute pneumonia. Continued therapy or change in therapy with follow-up to document resolution is appropriate in many situations.

A tuberculin skin test, or for immunocompetent children 5 years and older, an interferon γ release assay (IGRA), should be performed. Because of their higher specificity and lack of cross-reaction with bacille Calmette-Guérin (BCG), IGRAs may be preferred in children 5 years and older who have received BCG.[18] In infants and young children, serial first-morning gastric aspirates are obtained for testing; these specimens may be superior to those obtained by bronchoscopy. Sputum is obtained from older children and adolescents. HIV testing is indicated for all individuals in whom tuberculosis is diagnosed.

Serologic tests for Q fever, psittacosis, mycoplasmal infection, histoplasmosis, coccidioidomycosis, or blastomycosis are useful when the setting and clinical findings are compatible. The diagnosis of histoplasmosis is improved by testing for both antibody and antigen.[19] Molecular-based methods, such as polymerase chain reaction assays, are available for some organisms. Fungal pneumonia due to *Candida, Cryptococcus,* or *Aspergillus* spp. can be difficult to diagnose. Serologic testing for cryptococcal and galactomannan antigen can be helpful. Bronchoalveolar lavage (BAL) usually is the next diagnostic specimen obtained for persistent pneumonia and has been reported to confirm the etiology of persistent pneumonia (including *Blastomyces* and *Histoplasma* spp., viruses, bacteria, and obstructing lesions) in 30% of immunocompetent children,[20] 27% of children with cancer,[21] and in 70% of children with acquired immunodeficiency syndrome (AIDS).[22]

If *P. jirovecii* pneumonia is suspected in an adolescent, diagnosis can be attempted through identification of the organism with methenamine silver staining of an induced sputum specimen. If the result is negative or a specimen cannot be obtained, BAL is performed. If *P. jirovecii* pneumonia pneumonia is confirmed, an underlying immunodeficiency must be sought.

Patients with documented recurrent pneumonia, segmental bronchiectasis, suspected anatomic or obstructing lesions, or pneumonia that persists beyond 8 weeks of appropriate therapy require further evaluation. Poor weight gain, weight loss, digital clubbing, polycythemia, or anemia validates a history of chronicity and the need to proceed aggressively. Bronchoscopy is performed to (1) exclude, or detect and remove, a foreign body; (2) detect extrinsic compression or intraluminal anomaly; (3) obtain a biopsy specimen of a mass; or (4) obtain a specimen for microscopy and culture.

Computed tomography (CT) is useful to evaluate more distal airways (including for bronchiectasis), mass lesions, tracheal bronchus, and congenital cystic anomalies and to define precise relationships of cysts with surrounding structures before surgical excision.[23,24] Additionally, CT is better than chest radiography to detect parenchymal lung complications (cavitary necrosis, abscess, bronchopleural fistula) and can better define pleural versus parenchymal disease.[25] For children with moderate to large parapneumonic effusions, imaging with chest ultrasound or CT is warranted to assess for loculation.[7] Multidetector CT with three-dimensional reconstruction generally is used for confirmation of pulmonary sequestration and presurgical planning.[17]

Persistent or Recurrent Pneumonia Not Confined to a Single Site

Causes of Dense Focal or Multifocal Infiltrates

Primary pulmonary as well as a variety of nonpulmonary disorders can predispose to a diagnosis of recurrent and persistent pneumonia affecting multiple areas of the lungs (Table 35.2). Primary pulmonary disorders include inflammatory diseases (such as asthma), congenital and acquired causes of epithelial dysfunction (ciliary dyskinesia, CF, viral infection), and congenital and acquired structural abnormalities (laryngeal and tracheal anomalies, chronic lung disease in infancy). Nonpulmonary disorders that cause pneumonia are myriad, comprising (1) conditions that impair or overcome normal pulmonary clearance mechanisms, such as impaired cough or gag reflex, neuromuscular disorders, and gastroesophageal reflux; and (2) conditions that increase the risk for infections in the lung, such as congenital and acquired immunodeficiency states and sickle cell hemoglobinopathies.

TABLE 35.2

Diagnostic Considerations for Recurrent or Chronic Pneumonia Not Confined to a Single Site

Dense Focal or Multifocal Infiltrates[a]	Diffuse Interstitial Infiltrates[b]
RESPIRATORY TRACT DISORDERS AND ASPIRATION	**MISCELLANEOUS CONDITIONS**
Asthma Cystic fibrosis Ciliary dyskinesia Bronchiolitis obliterans Recurrent aspiration (drugs, seizures, cricopharyngeal incoordination, neuromuscular disorders) Gastroesophageal reflux Laryngotracheal anomalies (laryngeal or submucosal cleft)	Bronchopulmonary dysplasia Pulmonary lymphangiectasia Hypersensitivity pneumonitis Allergic bronchopulmonary aspergillosis Vasculitis syndromes Desquamative interstitial pneumonitis Lymphocytic interstitial pneumonitis Histiocytosis Metastatic malignancies (neuroblastoma, Kaposi sarcoma)Alveolar proteinosis

Esophageal obstruction or dysmotility (webs, stricture, achalasia) Tracheoesophageal fistula Congenital abnormalities of heart and vessels **IMMUNOLOGIC ABNORMALITIES**[c] Agammaglobulinemia Common variable immunodeficiency Immunoglobulin G subclass deficiency Cellular immunodeficiency Complement deficiency Phagocytic defects Immunodeficiency secondary to disease or drug	Idiopathic pulmonary fibrosis Drug, chemotherapy, radiation, or physical agent (e.g., smoke inhalation, kerosene) injury
OTHER DISEASES	
Sickle cell disease	
Pulmonary hemosiderosis[b]	

[a] Most pneumonitis is infectious.

[b] Most pneumonitis is noninfectious.

[c] Infiltrates can also be diffuse interstitial or nodular, depending on pathogen.

Respiratory Tract Disorders and Aspiration

Asthma.

Many children referred for evaluation of recurrent pneumonia have asthma.[26] Asthma causes recurrent pulmonary atelectasis or infiltrates in children by inducing diffuse inflammation or mucous plugging of airways (Fig. 35.4); common manifestations include recurrent wheezing and cough.[26] Pulmonary densities that clear in hours or in a few days are likely to have been atelectasis rather than infectious pneumonia. Most asthma exacerbations are associated with occurrence of viral infections.[27] Nocturnal cough, protracted coughing after upper respiratory illnesses, and, even if not acutely ill, exercise-induced cough are important historical clues to asthma, especially in older children. Wandering atelectasis, segmental overaeration, and nonconsolidated, perihilar, peribronchial, and interstitial infiltrates are helpful radiographic clues that asthma is the underlying cause. In patients with these features, asthma is far more likely than an underlying cause of presumed recurrent infectious pneumonia in children.[28,29]

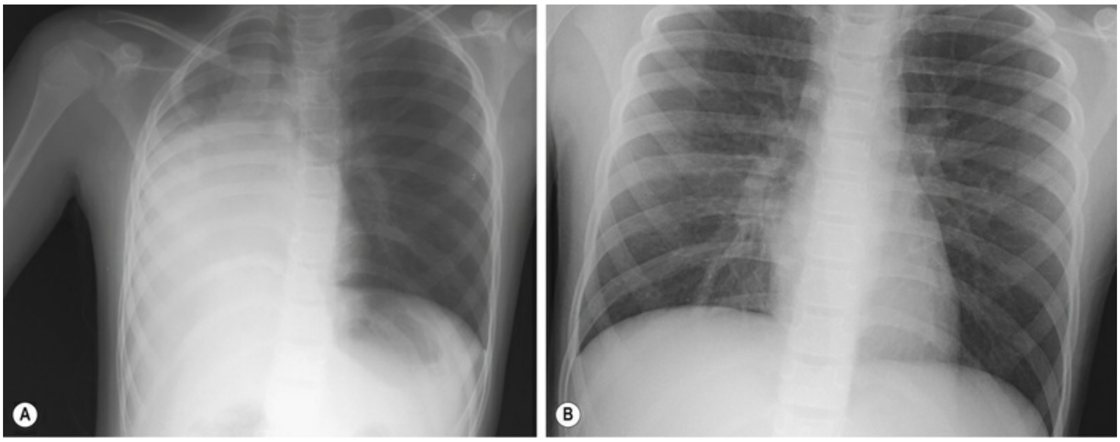

FIGURE 35.4 A 9-year-old girl with asthma was hospitalized for treatment of “pneumonia.” Chest radiograph on admission shows dense right lung consolidation (A). Note decreased volume of right side of chest with deviation of trachea and heart to the right, suggesting atelectasis. Chest radiograph 2 days later, following chest physical therapy and treatment of asthma (B). Course is most compatible with mucus plug. (Courtesy of J.H. Brien©.)

Cystic Fibrosis.

CF is characterized by early colonization and infection of the airways.[30] Functional deficiency of the CF transmembrane conductance regulator causes deficient chloride and bicarbonate secretion into airway secretions. Loss of the critical hydration of the airway surface liquid and mucus layer leads to chronic retention of pathogens in the lower airways and a secondary inflammatory response. Classical pathogens causing chronic suppurative infection are *Pseudomonas aeruginosa*, *Burkholderia cepacia*, and *S. aureus* and, now, MRSA. Emerging pathogens include nontuberculous mycobacteria, *Achromobacter* spp., and *Stenotrophomonas maltophilia*.[31] Chronic cough, poor weight gain, digital clubbing, sinusitis, and nasal polyposis at a preadolescent age are distinctive characteristics. Chest radiographs can be abnormal in infancy and are never normal again, with multiple persistent and new areas of parenchymal consolidation, overinflation, and eventual bronchiectasis. All states in the United States perform newborn screening for CF, and measurement of sweat chloride concentration remains the primary test for the confirmation of the diagnosis of CF.

Primary Ciliary Dyskinesia.

Primary ciliary dyskinesia, also called *immotile cilia syndrome*, is a rare disease characterized by congenital impairment of mucociliary clearance. Originally described as the Kartagener triad, consisting of dextrocardia, sinusitis, and bronchiectasis, ciliary dyskinesia leads to recurrent sinopulmonary infections. Clinical features include neonatal respiratory distress (82%), chronic cough (99%), chronic nasal congestion (97%), and chronic or recurrent otitis media (92%).[32] The chronic cough and nasal congestion begin at a median of 1 month of age. Laterality defects (situs inversus totalis and heterotaxy) occur in 55% of patients, and chest CT reveals prominent bronchiectasis (median of 3 involved lobes) and alveolar consolidation (median of 2 involved lobes).[32] Although limited to specialized centers, measurement of nasal nitric oxide is a useful screening test for patients 5 years and older with a clinical suspicion of primary ciliary dyskinesia.[33] Diagnosis is confirmed by high-speed videomicroscopy and electron microscopy of specimens of respiratory tract columnar cells obtained by nasal brush biopsy. Samples should be obtained when the patient is not infected acutely.

Epithelial Damage.

Damage of epithelium due to infection by viruses, *Bordetella pertussis,* and *M. pneumoniae* can lead to impairment of defense mechanisms and recurrent pneumonia.[34] Additionally, exposure to cigarette smoke and other environmental pollutants impairs ciliary function.

Bronchiolitis Obliterans.

Bronchiolitis obliterans is a chronic lung disease, which in most cases in children follows lower respiratory tract infection, usually caused by adenovirus. The incidence is highest when children are infected between 6 months and 2 years of age. Certain populations of Native Americans and Maoris (New Zealand) have a higher incidence of chronic lung disease after pulmonary adenovirus infection in childhood. Bronchiolitis obliterans also occurs after inhalation of various acids, as a late complication after lung transplantation, and in bone marrow transplant recipients associated with graft-versus-host disease. Bronchiolitis obliterans organizing pneumonia arises from masses of granulation tissue in alveolar ducts that obliterate airspaces. Dyspnea and cough, combined obstructive and restrictive functional abnormalities, radiographic hyperaeration, and airspace consolidation, are typical. In occasional cases, the obliterative process is confined to one lung, which then can result in unilateral hyperlucent lung or Swyer-James syndrome. Patients with bilateral, diffuse obliterative disease often have pulmonary edema. Although the clinical course, chest radiograph, and CT are suggestive, the diagnosis is confirmed by lung biopsy.[35]

Neurologic Dysfunction.

Neurologic dysfunction with associated aspiration is the most common identified cause of recurrent pneumonia.[8,29,36] Dysfunction predisposes to pneumonia as a result of pharyngeal incoordination or muscle weakness, which leads to failure of the gag, cough, or swallow reflex to protect the airway. Lesions of upper motor neurons, seizures, and decreased level of consciousness are common predisposing conditions. Pneumonia tends to occur in dependent lobes (e.g., the middle lobe or lung bases when aspiration occurs in the upright position, and the upper lobes when in the supine position). Fluoroscopic examination during a barium meal can be performed to examine upper pharyngopalatal coordination. Although gastric fundoplication and placement of a gastrostomy tube frequently are performed in such patients for feeding, the aspiration of oropharyngeal secretions (antegrade aspiration) continues. Chronic pulmonary aspiration results in progressive pulmonary disease, bronchiectasis, and respiratory failure eventually. Chronic pulmonary aspiration is the leading cause of death in children with severe neurologic disorders.[37] Radionuclide salivagram is a useful test to detect antegrade pulmonary aspiration.[38,39]

Gastroesophageal Reflux Disease.

Gastroesophageal reflux disease (GERD) can cause pneumonia in infants by spillover of gastric acid, particulate matter, or both into the trachea. A history of postprandial emesis, irritability accompanied by arching of the back (Sandifer syndrome), and stridor are recognized manifestations, and notable is the temporal association between feeding and respiratory symptoms.[8] In a series of hospitalized children, recurrent pneumonia from aspiration in association with GERD came to attention at a mean age of 1.4 years.[8] Esophageal pH monitoring is a valid measure of esophageal acid exposure and may be useful to correlate symptoms (e.g., cough) with acid reflux episodes and to select those patients with wheezing or respiratory symptoms in whom GERD is an aggravating factor.[40] Combined impedence and pH monitoring has the advantage of detecting non–acid reflux (e.g., patients taking proton pump inhibitors) in addition to acid reflux and is superior to pH monitoring alone for evaluation of the temporal relationship between symptoms and GERD.[40,41] A barium swallow study is not useful for the diagnosis of GERD but is useful for the evaluation of anatomic abnormalities.[40] Nuclear scintigraphy (milk scan) may have a role in the diagnosis of pulmonary aspiration in patients with chronic and refractory respiratory symptoms, but a negative test does not rule out possible pulmonary aspiration of refluxed material.[40] Children with recurrent aspiration related to GERD are generally considered most likely to benefit from antireflux surgery when medical therapy fails, but additional study is required to confirm that.[40]

Congenital Anomalies.

H-type tracheoesophageal fistula is a rare developmental abnormality that can escape recognition in the neonatal period and manifest later as recurrent pneumonia. Respiratory distress with feeding is typical. Radiographic demonstration of caudad-to-cephalad fistula to the trachea during retrograde filling of the esophagus with water-soluble contrast is diagnostic. By 1 year after anastomosis in infants with esophageal atresia or tracheoesophageal fistula, 39% developed esophageal stricture and 3.3% recurrent fistula,[42] which predisposes them to recurrent pneumonia from aspiration. Within 2 years of patient discharge after esophageal atresia repair with or without tracheoesophageal fistula, 12.7% were readmitted with pneumonia.[43] Clues to other congenital anomalies of the trachea, great vessels, or esophagus that cause recurrent pneumonia are usually present in associated symptoms or signs (positional respiratory distress, cough, stridor, feeding disorders).

Ventilator-Associated Pneumonia.

Ventilator-associated pneumonia (VAP) is defined as a healthcare-associated pneumonia based on clinical, radiologic, and microbiologic criteria in ventilated patients[44] (see Chapter 99). VAP is the most common infection occurring in mechanically ventilated patients. Bacteria that colonize the oropharynx can evade host defenses more easily in the presence of endotracheal intubation or tracheostomy tube and neuromuscular blockade or dyscoordination. *P. aeruginosa, Staphylococcus aureus* (including MRSA), enteric gram-negative bacilli, and nontypable *H. influenzae* are the most frequently recovered organisms.[45,46] Reported incidences of VAP varied widely and reflect the absence of a diagnostic gold standard and lack of specificity of current diagnostic methods.[46,47] Microbiologic specimens obtained by BAL have greater diagnostic accuracy compared with tracheal aspirate cultures.[46] Tracheal aspirate Gram stains and cultures do not appear to distinguish between infection and colonization.[47] Implementation of a sustainable prevention bundle focusing on prevention of aspiration and bacterial colonization resulted in a reduced rate of suspected VAP.[45] Prevention of pneumonia in children ventilated outside of the hospital continues to be challenging.

Immunologic Abnormalities

Immunologic abnormalities constitute an uncommon cause of recurrent pneumonia. The characteristic pattern of pulmonary involvement is recurrent, dense focal infiltrates at different sites, but diffuse interstitial or alveolar and interstitial infiltrates can occur, depending on the pathogen and defect. Qualitative or quantitative defects in phagocytic function, immunoglobulin synthesis, cellular immune function, or complement activity can lead to recurrent pneumonia.[1,8,26,29,36] The etiologic agents of pneumonia and involvement of the sinopulmonary system exclusively, or in concert with other organ involvement, predict the presence and type of immune defect.

Immunoglobulin and Complement Deficiency.

Recurrent pulmonary infections caused by encapsulated organisms such as *S. pneumoniae* and *H. influenzae* suggest a quantitative or qualitative abnormality in immunoglobulins. Nontypable *H. influenzae, S. aureus,* and *P. aeruginosa* also are pulmonary pathogens associated with X-linked agammaglobulinemia and other antibody deficiency syndromes and chronic obstructive lung disease due to frequent aspiration. Dysfunctional hypergammaglobulinemia of HIV infection is associated with sinopulmonary and invasive infection due to *S. pneumoniae* and other encapsulated organisms. Complement deficiency, although rare, can predispose to recurrent pulmonary pyogenic infection.

Phagocytic Cellular Defects.

Abnormalities in the number or function of phagocytic cells predispose to recurrent pyogenic infection, including pneumonia. Recurrent skin and soft tissue infections, and other invasive infections, also occur commonly. The most common neutrophil disorder resulting in recurrent infections is chronic granulomatous disease (CGD), a genetic immunodeficiency characterized by defective phagocyte respiratory burst and superoxide production. In the national registry of CGD patients, 80% had at least one episode of pneumonia.[48] Infections are caused by catalase-producing organisms and can be a clue to the defect. *Aspergillus* spp., *B. cepacia*, *Nocardia* spp., *Serratia marcescens,* and *S. aureus* are the most common causes of pneumonia in patients with CGD.[48,49] Fungal infection is a major determinant of survival.

Cellular Immune Defects.

Abnormalities of T lymphocytes, such as those due to severe combined immunodeficiency, DiGeorge (22q11.2 deletion) syndrome, HIV infection, or immunodeficiency secondary to disease or therapeutic agents, predispose to recurrent, progressive, and persistent infections, frequently pneumonia. Patients with ataxia-telangiectasia can develop interstitial lung disease, even in the absence of infection. Progressive disseminated viral, fungal, or mycobacterial infection and *P. jirovecii* pneumonia are suggestive of cellular immune defects.

Other Conditions

Acute thoracic, bony infarction or pulmonary infarction in a patient with sickle cell hemoglobinopathy can lead to the “acute chest syndrome,” which can be difficult to distinguish from pneumonia and commonly is precipitated or complicated by pneumonia (see Chapter 106). Idiopathic pulmonary hemosiderosis can masquerade as recurrent pneumonia with diffuse pulmonary infiltrates. Diagnosis is made by clinical features (rapid onset and resolution of symptoms and parenchymal pulmonary infiltrate, usually without fever) and bronchoscopy, with BAL showing hemosiderin-laden macrophages. Cow milk protein allergy, environmental (*Stachybotrys* fungi), genetic, and autoimmune conditions have been postulated as causes of idiopathic pulmonary hemosiderosis. A review of a series of 25 patients supported the role of autoimmunity and genetic factors.[50]

Causes of Diffuse Interstitial Infiltrates

A variety of noninfectious entities cause chronic or recurrent lower respiratory tract symptoms and diffuse interstitial or alveolar infiltrates on chest radiographs that can be difficult to distinguish from pneumonia (see Table 35.2). Childhood interstitial lung disease describes a heterogeneous group of rare chronic respiratory disorders in children, particularly younger than 2 years, which includes growth and developmental abnormalities as well as immunologic problems. These disorders have variable lung pathology associated with poor gas exchange.[51] The term *diffuse lung disease* often has been used interchangeably. Typical features are progressive cough, dyspnea, tachypnea, and crackles in the presence of diffuse infiltrates on radiography or CT. Diagnostic evaluation includes pulmonary function tests, high-resolution chest CT, genetic testing for surfactant disorders, and lung biopsy.

Cardiac abnormalities leading to recurrent pulmonary symptoms and radiographic abnormalities include congestive heart failure, anomalous pulmonary venous return, and congenital or acquired inequality of pulmonary artery blood flow. Congenital lymphangiectasia or pulmonary veno-occlusive disease can be misdiagnosed as recurrent pneumonia or pulmonary edema. Idiopathic or autoimmune disorders that cause infiltrates include hypersensitivity pneumonitis, allergic aspergillosis, sarcoidosis, vasculitis syndromes, granulomatosis with polyangiitis (Wegener granulomatosis), and Goodpasture syndrome. Reticulonodular infiltrates suggest a differential diagnosis that includes *M. pneumoniae* infection, *P. jirovecii* infection, HIV-related lymphoid interstitial pneumonitis, Kaposi sarcoma, histiocytosis, metastatic neuroblastoma, and lymphoma.

Approach to Diagnosis

Clues from history, physical examination, growth and development, radiographic pattern, and confirmed causes of pneumonia or other infections should guide investigation and permit a staged evaluation.[28,52,53] For example, stridor suggests tracheal anomalies; chronic cough productive of purulent sputum suggests bronchiectasis possibly due to disorders of antibody or phagocytic function, CF, or ciliary dyskinesia; severe and complicated sinusitis or otitis media suggests antibody deficiencies or ciliary dyskinesia; wheezing commonly indicates asthma but can be present in a variety of respiratory tract disorders (e.g., foreign body, CF, bronchiolitis obliterans). A history of recurrent problems confined exclusively to the respiratory tract makes cellular immune defects and phagocytic defects unlikely. Infections involving other organ systems, such as recurrent boils or soft tissue abscesses, raise the possibility of phagocytic defects.

Confirmation of specific infectious agents heightens suspicion of certain disorders. Examples of sentinel organisms are catalase-producing agents for CGD; *P. aeruginosa* for CF; *B. cepacia* for CF and CGD; and *P. jirovecii* for cellular defects and HIV infection.

A complete blood count is used to assess anemia or polycythemia; abnormal numbers, appearance, or differential makeup of leukocytes; and thrombocytopenia (associated with immunologic disorders such as Wiskott-Aldrich syndrome, primary hematologic cytopenias, or suppression by disseminated virus infection) or thrombocytosis (associated with an inflammatory response). A tuberculin skin test or an IGRA for children 5 years or older generally should be performed, particularly but not only if there are risk factors for tuberculosis.

An underlying medical condition was identified in 86% to 92% of children with recurrent pneumonia in two series.[8,36] In a third series that excluded children with wheezing, 31% of patients did not have an underlying cause identified.[29] Asthma often is diagnosed in children referred for recurrent “pneumonia.” In many cases the preceding episodes of pneumonia are not true lobar consolidations with fever but rather focal abnormalities on physical examination or chest radiograph that occur with an asthma exacerbation.[53] Clues to the diagnosis of asthma include the presence of atopy in the patient, a family history of asthma or atopy, prior response to a bronchodilator or corticosteroid, predominance of wheezes and rhonchi, and rapid resolution of radiographic abnormality (which usually is atelectasis rather than infiltrate).

In three retrospective series of children with recurrent pneumonia, the most common identified cause was aspiration, particularly in children with underlying neurologic or neuromuscular disorders.[8,29,36] A pattern of pneumonia in dependent pulmonary segments suggests aspiration. For other patients, certainly those with impaired growth or digital clubbing and those with radiographs showing lobar or segmental infiltrates, thoracic adenopathy, or bronchiectasis, a specific diagnosis must be pursued. Testing for CF should be performed routinely. If infections are confined to the respiratory tract in infants, a barium swallow study is a useful early test to assess for anatomic anomalies such as vascular rings, duplication cysts, and tracheoesophageal fistulas. Further diagnostic tests, including combined impedence and pH monitoring, CT, magnetic resonance imaging, and nuclear medicine scans (salivagram, milk scan), are selected according to the likely etiology. Measurement of nasal nitric oxide and evaluation of a nasal or bronchial biopsy to assess ciliary structure and function should be considered if the child has a documented history of recurrent sinusitis, otitis media, and pneumonia, especially when bronchiectasis is present.

Although immunologic defects are not common, when suspected, screening tests should include testing for HIV, quantitative measurement of immunoglobulins (IgG, IgA, IgM, and IgE), complement hemolytic activity assay, and functional white blood cell tests, such as dihydrorhodamine flow cytometric assay for CGD. Measurement of specific antibody responses to proteins (tetanus IgG antibody) and polysaccharide antigens (IgM isohemagglutinins and prepneumococcal and postpneumococcal polysaccharide vaccination IgG antibodies in children 2 years and older) are more reliable measurements for B-lymphocyte function than the quantity of immunoglobulins. Flow cytometry for lymphocyte enumeration and mitogen proliferation assays assess cell-mediated immune function.

Bronchoscopy with BAL (or in older, larger children obtaining a protected brush specimen) can confirm underlying conditions and specific infectious causes of pneumonia. Lung biopsy is the definitive test required to establish the etiology or pathophysiology of many causes of chronic, recurrent pneumonia when specific pathogens are not otherwise confirmed, especially when the pattern of involvement is interstitial and a noninfectious cause is suspected.

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Key Points

Persistent and Recurrent Pneumonia

Definitions and Epidemiology

- Persistent pneumonia is defined as continuation of symptoms and radiographic findings beyond 4 weeks after onset.
- Recurrent pneumonia is the occurrence of ≥2 episodes of pneumonia in a 1-year period or ≥3 episodes in any period, with radiographic resolution between episodes.
- Approximately 8% of patients hospitalized with pneumonia have recurrent pneumonia.

Clinical Features

- Unresolved or untreated acute pneumonia progresses to persistent pneumonia.
- Often patients referred for “recurrent pneumonia” have a history of recurrent wheezing and have asthma, frequently with transient atelectasis.

- Many patients with recurrent pneumonia have a known predisposing condition such as neurologic or neuromuscular disorders leading to aspiration.

Diagnosis

- Pathogen-related causes (e.g., tuberculosis, fungal) and host-related causes (intraluminal or extraluminal obstruction, congenital lung anomalies) must be considered for patients with persistent pneumonia.
- Involvement of one area of the lung (e.g., foreign body aspiration, congenital pulmonary airway malformation, sequestration) versus multiple areas (asthma, aspiration, cystic fibrosis, immunologic disorders) influences the evaluation for both persistent and recurrent pneumonia.
- Specific diagnostic testing should be guided by the following:

▪ Involvement of other organ systems such as sinusitis with cystic fibrosis, immunodeficiencies, or primary ciliary dyskinesia

▪ Gastrointestinal involvement with cystic fibrosis

▪ Feeding difficulties with gastroesophageal reflux disease

▪ Leukopenia with cell-mediated defects

- Isolation of specific or sentinel organisms (e.g., catalase-positive organisms with chronic granulomatous disease, or *Pseudomonas aeruginosa* and *Burkholderia cepacia* with cystic fibrosis) also helps guide diagnostic testing.

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Pneumonia in the Immunocompromised Host

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Pneumonia is a common disease in naturally occurring states of immunologic incompetency, such as congenital immunodeficiencies, malnutrition, and human immunodeficiency virus (HIV) infection, as well as in iatrogenically induced immunodeficiency, as occurs during chemotherapy for cancer, during treatment of rheumatologic diseases, or after tissue transplantation. The clinical findings are diverse, the potential for extended morbidity and mortality is great, and there is a broad range of causative microorganisms.

Etiologic Agents and Epidemiology

The etiologic agents of pneumonia in the immunocompromised host consist not only of the same agents that cause pneumonia in the immunocompetent host but also of a large number of opportunistic agents. The importance of agents in various forms of immunologic incompetence depends on the particular part of the immune system that is deficient and on the part of the immune system that is normally critical in defense against that microorganism (Table 36.1).

TABLE 36.1

Microorganisms Associated With Severe Pneumonia in Immunodeficiency States

Deficiency	Viruses	Pyogenic Bacteria	Mycobacteria	Fungi
B-lymphocyte deficiency	Enteroviruses Adenoviruses	*Streptococcus pneumoniae* *Haemophilus influenzae* Meningococcus	None	None
T-lymphocyte deficiency (including tumor necrosis factor-α deficiency)	Varicella-zoster virus Rubeola virus Herpes simplex virus Cytomegalovirus Adenovirus Respiratory syncytial virus Parainfluenza virus Human metapneumovirus	*Neisseria meningitidis* *Listeria monocytogenes* *Pseudomonas aeruginosa* *Stenotrophomonas* spp. *Burkholderia* spp. *Legionella* spp. Other opportunistic bacteria	*Mycobacterium tuberculosis* *Mycobacterium avium* complex *Mycobacterium fortuitum* Calmette-Guérin bacillus Other opportunistic mycobacteria	*Pneumocystis jirovecii* *Candida albicans* *Cryptococcus neoformans* *Nocardia* spp.
Neutrophil dysfunction	None	*Staphylococcus aureus* *Burkholderia cepacia* *Serratia marcescens*	*Mycobacterium tuberculosis* Calmette-Guérin bacillus Nontuberculous mycobacteria	*Aspergillus* spp. *Nocardia* spp. *Candida* spp.
Neutropenia	None	*Pseudomonas aeruginosa* *Stenotrophomonas* spp. *Burkholderia* spp. Other opportunistic bacteria	None	*Aspergillus* spp. *Pseudallescheria boydii* Agents of mucormycosis

In conditions in which the normal quantities of functional antibody are deficient, such as hypogammaglobulinemia,[1] or in the functional B-lymphocyte deficiency that accompanies HIV infection in infants and children,[2] bacterial pneumonias are common. Pneumonia largely is caused by *Streptococcus pneumoniae,* various species of *Haemophilus,* and other encapsulated bacteria. Pneumonia due to respiratory viruses is not more frequent or more severe in antibody deficiency states.

In conditions of relatively pure deficiency in cell-mediated (lymphocyte) immunity, such as severe malnutrition, the late stages of AIDS, and some congenital immunodeficiencies, certain viral infections are life-threatening and require careful prophylaxis and potent treatments. These viruses include the herpesviruses, especially cytomegalovirus, varicella-zoster virus (VZV), herpes simplex virus (HSV), and, occasionally, human herpesvirus 6 (HHV-6),[3] all of which are unusual causes of clinically significant pneumonia in healthy children. In areas of the world where measles remains endemic, pneumonia is a common complication of infection in the malnourished child and can be severe. Common respiratory viruses, particularly respiratory syncytial virus (RSV), parainfluenza viruses, human metapneumovirus, and adenovirus, can cause prolonged, severe life-threatening infection.[4–6] Lymphocyte deficiencies also predispose to pneumonia due to many bacteria (see Table 36.1) as well as several fungi, including *Pneumocystis jirovecii.*

Epstein-Barr virus (EBV) is a special case. A form of subacute pneumonia characterized by micronodules of proliferating lymphoid tissue, known as *lymphocytic interstitial pneumonitis* (LIP), frequently (although not exclusively) is associated with EBV infection in several states of immunologic dysregulation, particularly in untreated children with HIV infection between 18 months and 6 years of age.[7–9] LIP usually manifests as a slowly developing, afebrile pulmonary disease associated with progressive hypoxia and generalized lymphadenopathy, with characteristic diffuse micronodular infiltrates apparent on chest radiography (see Chapter 112, Fig. 112.3).

In states of neutrophil dysfunction or profound neutropenia, an entirely different spectrum of organisms is commonly implicated in pneumonia. In chronic granulomatous disease and pure neutropenia, pneumonia is frequently caused by *Staphylococcus aureus* (including methicillin-resistant strains) and opportunistic bacteria and fungi such as *Pseudomonas aeruginosa, Burkholderia cepacia, Nocardia* spp., *Mycobacterium tuberculosis* (particularly in areas where it is widespread[10]), nontuberculous mycobacteria, and *Aspergillus* spp.[11] Neutropenia alone does not appear to predispose to either viral or *Pneumocystis* pneumonia (PCP).

Defects in innate immunity, either genetic or drug-induced, add complexity to susceptibilities. IRAK4 and MYD88 deficiencies manifest much like B-lymphocyte defects, with frequent pyogenic pneumonias in childhood.[12] Common genetic polymorphisms in the mannose-binding lectin gene may contribute to susceptibility to opportunistic pneumonias in the posttransplantation period.[13] Innate immunity also can be inhibited pharmacologically, and drugs that block tumor necrosis factor-*α* predispose to mycobacterial and fungal infections as well as other infections for which cellular immunity is important.[14]

Immunodeficiencies that are drug induced, particularly those that occur during cancer chemotherapy or after organ or stem cell transplantation, are complex. These include drug-induced compromise of the oral and intestinal mucosal barriers, neutropenia or neutrophil dysfunction, and defective lymphocyte function. In this setting, pneumonia commonly is due to opportunistic bacteria and fungi, acquired nosocomially or from resident mucosal flora, such as *P. aeruginosa* and *Stenotrophomonas maltophilia;* α-hemolytic streptococci and other oral bacteria; *Nocardia, Candida,* and *Aspergillus* spp.; and other yeast and filamentous fungi.[15–17] Children undergoing cancer chemotherapy or solid organ transplantation may have normal antibody levels (native or infused) but are nonetheless at increased risk for infections due to encapsulated bacteria because the defense against microorganisms is multifaceted and mixtures of drug-induced lymphocyte and neutrophil dysfunction among these children are common.[18,19]

The most common viral infections in these drug-induced immunodeficiency states are those that cause pneumonia in children with pure lymphocyte deficiencies: cytomegalovirus (CMV), VZV, HSV, and, in endemic areas, rubeola.[20,21] Viruses that commonly cause pneumonia in healthy hosts, such as RSV, influenza, parainfluenza viruses, human metapneumovirus, and adenovirus, display greater virulence in both children and adults after solid -organ or human stem cell transplantation, particularly when cellular immunity is profoundly suppressed.[22–29] In the posttransplantation setting, EBV can cause progressive pulmonary disease, but this is usually in the form of posttransplantation lymphoproliferative disease, with enlarging masses of lymphoid tissue in the mediastinum and parenchyma of the lung rather than diffuse LIP, as was described earlier.[30]

Because patients with iatrogenically imposed states of immunodeficiency tend to spend long periods in the hospital, organisms that cause significant pneumonia in such patients often are nosocomially acquired. In addition, they reflect the epidemiology and antimicrobial resistance patterns of healthcare-associated organisms, whether through carriage on the hands of caregivers (e.g., methicillin-resistant *S. aureus* or multidrug-resistant gram-negative enteric organisms), through the hospital's water supply (e.g., *Legionella* species), through the spread of small-particle aerosols (e.g., *Aspergillus* spp.), or because these patients often receive antimicrobial agents that alter normal bacterial flora, creating a void or niche for other more antibiotic-resistant bacteria to flourish.

The frequency and reported cause of pneumonia after solid-organ transplantation vary greatly by transplantation center and the organ transplanted. Nonetheless, certain etiologic patterns emerge. CMV pneumonia occurs in 12% to 45% of renal,[19] liver,[31,32] lung,[33] and allogeneic hematopoietic stem cell transplant recipients.[34,35] Risk is highest among CMV-negative recipients from CMV-positive donors for solid-organ transplantations, whereas risk is highest among CMV-positive recipients from CMV-negative donors for hematopoietic stem cell transplantations. Risk also is increased among patients with graft-versus-host disease who require higher degrees of immunosuppression. Anticipatory strategies[36] or prophylaxis with ganciclovir or valganciclovir have reduced but not eliminated CMV pneumonia.[37,38] Nosocomially acquired viruses and bacteria remain major causes of pneumonia among transplant recipients.[31–35,39,40] *Aspergillus* has been identified as the cause of up to 35% of pneumonia cases after bone marrow or solid-organ transplantation, although its incidence may decrease with increased use of antifungal prophylaxis.[19,31–35,39,40] There is high risk for tuberculosis after renal transplantation in endemic areas.

The causes of pneumonia and of other infections often follow a temporal pattern specific to the chemotherapy used or tissue transplanted. For example, after solid-organ transplantation, nosocomially acquired bacteria predominate as a cause of pneumonia in the first month; later, viruses, especially CMV and adenovirus, and to a lesser extent *Listeria, Nocardia,* and *Aspergillus* spp., may be the cause. More than 6 months after solid-organ transplantation, the agents of community-associated bacterial pneumonia become more common.[41] After hematopoietic stem cell or marrow transplantation, the risk for *Aspergillus* infection is bimodal, with peak incidence at less than 40 days, followed by a second peak occurring more than 100 days after transplantation. The first peak likely is related to neutropenia, and the later peak likely is related to use of high doses of corticosteroids for the treatment of graft-versus-host disease.[42,43]

Pathogenesis and Pathologic Findings

The pathogenesis of pneumonia in the immunocompromised host is similar to that of pneumonia in the healthy host, except that defects in host defense play a critical part in the spread of microorganisms from the upper respiratory tract, where they reside as commensals or have recently been acquired from the environment, to the lower respiratory tract and then within the lung itself. Many states of systemic immunodeficiency are accompanied by mucosal immunodeficiency. In the upper respiratory tract, mucosal immunity is primarily mediated by immunoglobulin A (IgA), but in the lower respiratory tract, IgG is more important. There also is a role in the healthy host for mucosal cellular immunity along the respiratory tract (the bronchus-associated lymphoid tissue, or BALT), analogous to Peyer patches along the gastrointestinal tract.[44] Because the function of macrophages, including alveolar macrophages, depends on interleukins secreted by T lymphocytes, the normal phagocytic and microbicidal activities of these important defenders are impaired when cell-mediated immunity is deficient or when critical interleukins are blocked.[14] Clearly, neutrophils also play an important part in the defense of the airway and lung.

Patients with congenital or acquired immunodeficiencies often develop structural abnormalities that compromise the airways, such as ciliary damage and bronchiectasis due to recurrent bronchitis,[37] or intubation in the hospital setting. These defects lead to more rapid and extensive spread of microbes from the upper to the lower respiratory tract. Often, such patients have been exposed to multiple antimicrobial agents and nosocomial organisms, with resultant colonization and subsequent infection by resistant bacteria, yeast, or fungi.

Clinical Diagnosis and Radiographic Manifestations

The diagnosis and management of pneumonia in the compromised host overlap in time. A flow diagram is shown in Fig. 36.1 to serve as a rough guide for decisions.

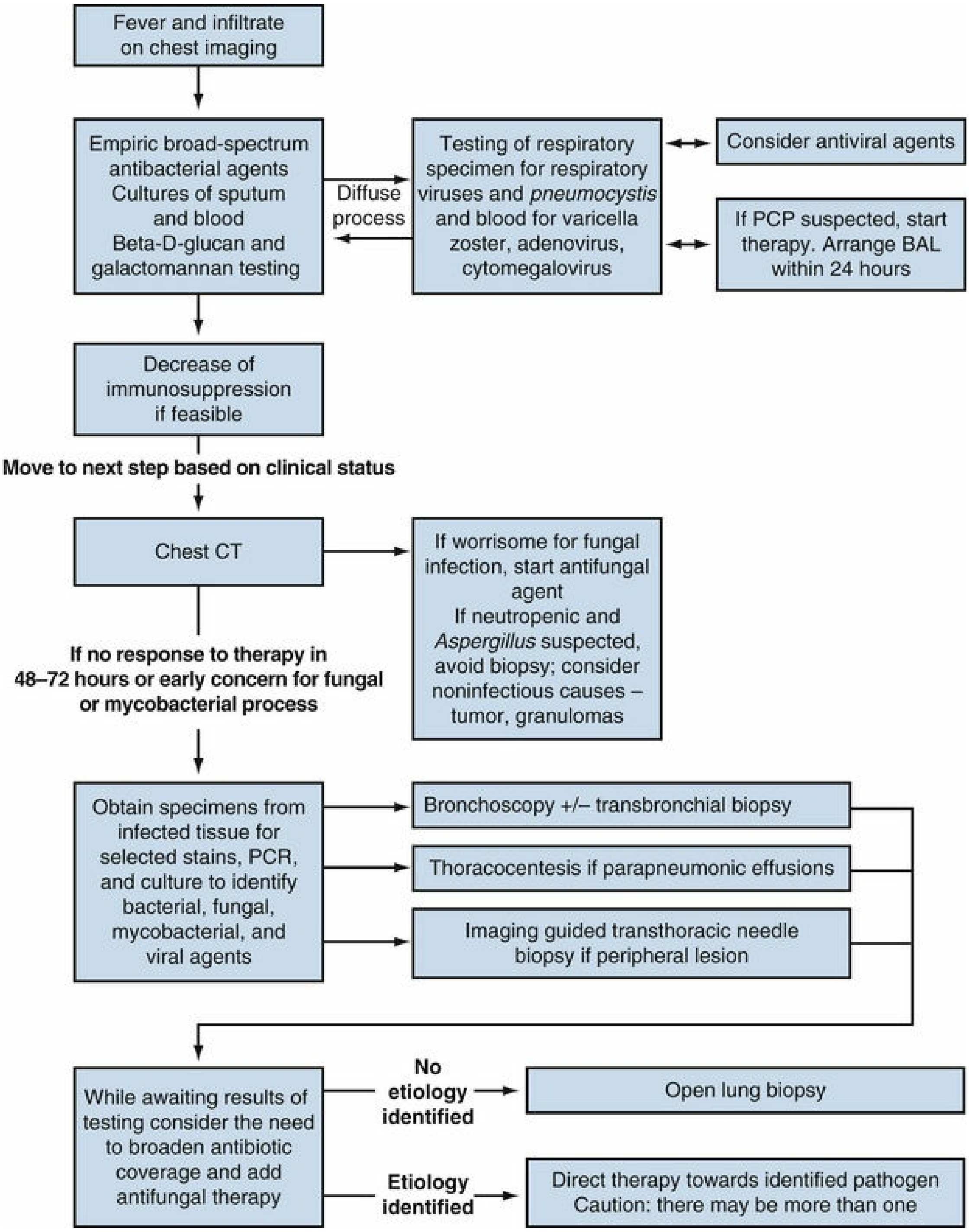
Fever and infiltrate on chest imaging
Empiric broad-spectrum antibacterial agents Cultures of sputum and blood Beta-D-glucan and galactomannan testing
Diffuse process
Testing of respiratory specimen for respiratory viruses and *pneumocystis* and blood for varicella zoster, adenovirus, cytomegalovirus
Consider antiviral agents
If PCP suspected, start therapy. Arrange BAL within 24 hours
Decrease of immunosuppression if feasible
Move to next step based on clinical status
Chest CT
If worrisome for fungal infection, start antifungal agent If neutropenic and *Aspergillus* suspected, avoid biopsy; consider noninfectious causes – tumor, granulomas
If no response to therapy in 48–72 hours or early concern for fungal or mycobacterial process
Obtain specimens from infected tissue for selected stains, PCR, and culture to identify bacterial, fungal, mycobacterial, and viral agents
Bronchoscopy +/– transbronchial biopsy
Thoracocentesis if parapneumonic effusions
Imaging guided transthoracic needle biopsy if peripheral lesion
While awaiting results of testing consider the need to broaden antibiotic coverage and add antifungal therapy
No etiology identified
Open lung biopsy
Etiology identified
Direct therapy towards identified pathogen Caution: there may be more than one

FIGURE 36.1 Approach to evaluation of the immunocompromised patient with pulmonary infiltrates. The pace of working through the algorithm will depend on the overall clinical status of the patient, prior therapy, and likelihood of finding a pathogen at each step. Invasive procedures are likely to carry higher risk in the neutropenic patient, and therefore a longer trial of empiric therapy and a delay before biopsy may be appropriate for these patients. At any step, if the clinical picture, early tests, or imaging points to a specific etiology, the treatment can be tailored and there may be no need to continue the algorithm. BAL, bronchoalveolar lavage; CT, computed tomography; PCP, *Pneumocystis* pneumonia.

Clinical manifestations of pneumonia in the

immunocompromised host are variable. Fever, with or without cough, may be the only sign of a potentially life-threatening disease.[18] Conversely, a chronic cough without fever also can signal significant lower respiratory tract disease. Certain infections, such as PCP, and interstitial viral pneumonia, caused by RSV, parainfluenza viruses, CMV, or other herpesviruses, impair oxygenation and commonly manifest as hypoxia. Pleuritic chest pain indicates localized pneumonia at the periphery of the lung and, in this setting, can be due to either bacterial or fungal infection.

Radiographic imaging is critical to both the diagnosis and management of pneumonia in immunocompromised children. Conventional radiographs, computed tomography (CT), or both should be performed. Although not generally required, magnetic resonance imaging may be more sensitive than CT for the early recognition of necrotizing pneumonia.[45] High-resolution CT has been shown to have high sensitivity and specificity for the characterization of pneumonia after pediatric hematopoietic stem cell transplantation (HSCT).[46] Among iatrogenically immunocompromised patients, the differential diagnosis often includes noninfectious disorders, such as an underlying malignancy, drug-induced pulmonary disease, emboli, or hemorrhage.[18]

The pattern of abnormality on chest radiograph or CT often is helpful in narrowing the differential diagnosis and guiding further investigations and treatment (Table 36.2). If an interstitial pattern is present, viruses and atypical bacteria such as *Mycoplasma pneumoniae* should be sought by sampling of the nasopharynx and the use of rapid identification methods. A positive test result for respiratory viruses or *M. pneumoniae* in nasopharyngeal specimens may be useful evidence of their causative role in pneumonia; such simple tests can sometimes spare the patient an invasive procedure such as bronchoscopy or lung biopsy. Definitive diagnosis of *P. jirovecii* pneumonia depends on finding “cysts” in pulmonary secretions. In older children, these “cysts” sometimes can be identified in a hypertonic saline–induced sputum sample, but the most useful procedure is bronchoscopy with bronchoalveolar lavage (BAL) or brush biopsy. In the proper clinical setting, however, a positive β-D-glucan test or *P. jirovecii* polymerase chain reaction (PCR) can provide sufficient evidence for the presumptive diagnosis of PCP. Diagnosis of CMV pneumonia often is difficult because CMV can colonize the upper respiratory tract asymptomatically, and its isolation from BAL fluid may not be meaningful. The definitive diagnosis can be made by the presence of characteristic inclusion bodies in biopsy tissue. In the proper clinical setting, identification of CMV in circulating white blood cells by fluorescence testing or at high levels in plasma or serum by PCR suggests CMV as the cause of pneumonia.[47]

TABLE 36.2

Radiographic Patterns and Pathogens of Pneumonias in Immunocompromised Hosts

Radiographic Pattern	Likely Pathogens	Diagnostic Approach
Diffuse, interstitial	Viruses (CMV, RSV, parainfluenza, HSV) *Mycoplasma pneumoniae*[a] *Chlamydia* spp.[a] *Pneumocystis jirovecii*	Rapid viral, mycoplasmal, or chlamydial diagnostic tests on upper airway secretions; β-D-glucan for *Pneumocystis;* bronchoscopy with PCR or immunofluorescence for viruses, and methenamine silver stain for *Pneumocystis*
Focal, consolidative	Pyogenic bacteria (*Streptococcus pneumoniae, Haemophilus influenzae,* others) Nosocomial bacteria *Legionella* spp. (Also consider fungi and mycobacteria)	Blood cultures Gram stain and culture of deep respiratory tract secretions *Legionella* antigen in urine *Cryptococcus* antigen (blood) *Histoplasma* antigen (urine) Galactomannan (blood) Acid-fast smears Bronchoscopy Biopsy
Micronodular	Viruses (adenovirus, VZV, EBV [LIP]) Mycobacteria *Histoplasma, Candida, Cryptococcus* spp.	Rapid viral diagnostic tests on upper respiratory tract secretions Acid-fast smears, cultures of lower respiratory tract secretions *Histoplasma* antigen (urine) *Cryptococcus* antigen (blood)
Nodular	*Aspergillus* spp., other fungi, agents of mucormycosis *Nocardia* spp. EBV lymphoproliferative disease	Galactomannan (blood) *Histoplasma* antigen (urine) *Cryptococcus* antigen (blood) EBV PCR (blood) Bronchoscopy Biopsy (transbronchial, fine-needle, VATS, or open)

[a] Can also cause patchy infiltrate in less compromised individuals.

CMV, cytomegalovirus; EBV, Epstein-Barr virus; HSV, herpes simplex virus; LIP, lymphocytic interstitial pneumonitis; PCR, polymerase chain reaction. RSV, respiratory syncytial virus; VATS, video-assisted thoracoscopic surgery; VZV, varicella-zoster virus.

Determining the cause of consolidative or nodular pneumonia can be difficult. Invasive pulmonary aspergillosis can mimic tuberculosis on chest CT.[48] Blood should be obtained for culture and, in the appropriate setting, quantitative tests for EBV and CMV. A positive test for galactomannan in the blood supports a diagnosis of invasive *Aspergillus* infection.[49] β-D-glucan also is a useful marker for *P. jirovecii* infection but also can be elevated in other pulmonary fungal infections, including *Aspergillus*.[50] Pleural fluid, if present, should be sampled; often it is sterile, however, when patients have been receiving antimicrobial treatment. Bronchoscopy can be helpful, but organisms causing consolidative infiltrates can colonize the upper respiratory tract, and results of culture may be misleading. Gram stain of deep tracheal secretions or BAL fluid often is helpful in indicating density of bacteria in the lower respiratory tract and in guiding therapy. Protected brush BAL has limited sensitivity in detecting pathogens (50% to 80% or less for small lesions), with similar specificity. Bronchoscopy is particularly useful for diagnosis of PCP and CMV pneumonia, although identification does not prove the organism as causing pneumonia (biopsy may be required). A positive microbiologic result in bronchoscopic specimens is useful for the diagnosis of *M. tuberculosis* and fungal infections, including pulmonary aspergillosis when PCR and galactomannan assays can be performed on alveolar lavage fluid. Open lung biopsy or biopsy obtained during video-assisted thoracic surgery often is the definitive diagnostic procedure. Neither bronchoscopy nor surgical intervention is an attractive option in the setting of severe thrombocytopenia or respiratory failure with hypoxia. For the intubated patient, blind endotracheal suctioning can be useful, especially if quantitative cultures are performed, but with reduced sensitivity and specificity compared with bronchoscopy for focal pneumonias.

There also is a role for empiric antimicrobial treatment for pneumonia in the immunocompromised patient, particularly if the immunocompromised state is likely to be temporary. However, an aggressive approach to definitive microbiologic diagnosis of pneumonia in highly immunocompromised patients often is indicated because appropriate therapy may be complex, prolonged, and toxic, as well as lifesaving.[51]

Management and Therapy

Empiric treatment should be guided by the risks posed by the type of immunocompromise and the radiologic, clinical, and epidemiologic circumstances. The presence of diffuse pulmonary infiltrates, particularly with hypoxia, should generally prompt early investigation for respiratory viruses and consideration for bronchoscopy to identify *P. jirovecii.* Empiric therapy should include trimethoprim-sulfamethoxazole for PCP because infection is potentially life-threatening. In addition, macrolide therapy for *Mycoplasma* or *Legionella* spp. should be considered. Treatment of CMV pneumonia with ganciclovir or Foscarnet, as well as changes in transplantation practices, have been associated with increased survival after HSCT.[52] Although it is clearly preferable to perform diagnostic tests *before* therapy has been started, *P. jirovecii* usually can be identified for several days after treatment has been started.[53] Decision concerning adjunctive corticosteroid therapy for treatment *of P. jirovecii* pneumonia, however, should generally await definitive diagnosis.

Localized infiltrates are more likely due to bacterial infection, and empiric antibiotic therapy should include agents that are effective against resident flora and nosocomial organisms, including methicillin-resistant *S. aureus*. Nodular infiltrates can suggest fungal infection[35] or, especially if associated with lymphadenopathy, lymphoproliferative disease.

Patients with prolonged neutropenia who fail to improve despite treatment with broad-spectrum antibacterial agents will need extensive diagnostic testing and empiric treatment for *Aspergillus* infection. Voriconazole is the recommended primary therapy for most patients with pulmonary aspergillosis, although liposomal amphotericin B also can be used along with reversal of underlying immune defects. No “rule,” however, is completely reliable, and further clinical and epidemiologic information always should be used to guide decisions. Aggressive diagnostic procedures are indicated more urgently if the illness is severe and the immunosuppressed state is likely to be of longer duration.

Some clinicians serially monitor the biomarkers used to diagnose infections (e.g., quantitative PCR, galactomannan, β-D-glucan) to evaluate response to therapy. Few data exist, however, to guide interpretation or determine the utility of these tests measured serially in managing pulmonary infections.[54]

Colony growth factors can be used to decrease the period of neutropenia among neutropenic patients. Their use, however, has not been demonstrated to be of benefit for the management of pneumonia or other established infections, and there are case reports of pulmonary deterioration among healthy stem cell donors and patients with growth factor–induced neutropenia recovery.[55] There is little published information regarding the use of inhaled antimicrobial agents for the management of respiratory tract pathogens in the immunocompromised host.

Prevention

Preventive strategies depend on the nature of the immunodeficiency, the consequent anticipated threats, and the circumstances under which these threats occur (after organ transplantation, during chemotherapy, or in an evolving immunodeficiency, such as with HIV infection). All preventive modes are important. Pathogens should be avoided whenever possible. Examples of such simple preventive measures are the use of barrier precautions in the hospital environment, influenza immunization of family contacts, avoidance of *Salmonella*-contaminated foods or reptiles at home, and, most important, maintenance of good hand hygiene by family caregivers, medical personnel, and patients. Vaccines should be administered in such a way as to optimize response (e.g., *before* solid-organ transplantation, or early in the life of an infant with HIV infection, when $CD4^+$ lymphocyte counts are likely to be highest). When particular vaccines are contraindicated (e.g., live viral vaccines immediately after stem cell transplantation), ineffective (as in children with many congenital immunodeficiencies), or not available, the use of pooled immune globulin, pathogen-specific immune globulin (such as CMV immune globulin), or monoclonal antibody (such as palivizumab to prevent severe disease due to RSV) can be protective. In selected circumstances, antimicrobial chemoprophylaxis is extremely effective in preventing important and potentially life-threatening pneumonias, such as those due to *P. jirovecii,* HSV, and CMV. In certain diseases, such as chronic granulomatous disease, interferon γ, injected 3 times per week, reduces the occurence of serious infections by as much as two thirds.[56] Recommendations for prevention of infection by specific organisms such as *P. jirovecii*, CMV, and *Aspergillus* depend on clinical circumstances, which are detailed in other chapters.

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E

Cardiac and Vascular Infections

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Endocarditis and Other Intravascular Infections

Stéphanie Levasseur, Lisa Saiman

The American Heart Association (AHA) and the European Society of Cardiology, as well as other national societies, provide updated scientific statements on many of the topics discussed in this chapter.[1–9] Readers are encouraged to review these consensus statements and seek updated documents by these authoritative groups.

Infective Endocarditis

Infective endocarditis is an uncommon infection of the cardiac endothelium. In this disease process, pathogens become enmeshed in fibrin and platelets to form *vegetations,* which are attached to heart valves, mural endocardial surfaces, or the endocardium that forms over prosthetic material such as prosthetic valves, pacemaker leads, or catheters. The historical risk factors of rheumatic heart disease and unrepaired congenital heart disease remain relevant, particularly in developing countries,[10–12] but in developed countries, endocarditis in children and young adults occurs more often after surgery for congenital heart disease, as a result of complications of intravenous drug abuse or use of indwelling central venous catheters, or as healthcare-associated infections (see Chapter 100).[12–20]

Endocarditis was uniformly fatal in the preantibiotic era, but the rate of cure in referral centers is as high as 90% with appropriate treatment.[12,21–25] Mortality rates of 3.5% to 6.8% were reported in two studies from the United States using administrative datasets of children hospitalized with endocarditis.[26,27] However, the crude mortality rate of endocarditis when including endocarditis diagnosed postmortem may be as high as 21% to 24%.[22,28]

Etiologic Agents and Associated Risk Factors

The pathogens causing endocarditis in children from representative case series are shown in Table 37.1. Streptococci, especially viridans streptococci (e.g., *Streptococcus sanguis, S. mitis, S. salivarius, S. mutans,* and *S. oralis*) are frequent causes of endocarditis. These pathogens generally are associated with infection after rheumatic fever and unrepaired congenital heart disease and with late postoperative endocarditis.[29–31] Staphylococci are more common than streptococci in some series.[21,27,32] Coagulase-negative staphylococci (CoNS) can cause endocarditis after cardiac surgery, and *S. aureus,* including community-acquired methicillin-resistant *S. aureus* (CA-MRSA), causes endocarditis in normal hearts as well.[33] *Candida* and *Aspergillus* spp. increasingly are common causes of healthcare-associated endocarditis, particularly among patients in the neonatal intensive care unit (NICU), with central venous catheters, or after prosthetic valve surgery.[31,34,35] Gram-negative bacilli and fastidious gram-negative oropharyngeal flora, the so-called HACEK organisms, an acronym for ***H**aemophilus* spp., ***A**ggregatibacter* spp., ***C**ardiobacterium hominis;* ***E**ikenella corrodens;* and ***K**ingella kingae,* are uncommon causes of endocarditis in children. Among the HACEK group, *K. kingae* and *A. parainfluenzae* are the most common causes of endocarditis in children.[36] In the preantibiotic era, *Streptococcus pneumoniae* caused 15% of cases of endocarditis. Today, pneumococcal endocarditis is rare but is associated with a high rate of mortality.[37]

TABLE 37.1

Trends in Agents of Infective Endocarditis

Period of Data Collection	**1950–1992**[23,28,50,191,192]	**1990–2008**[164,169,193-195]
Number of cases	421	202
Streptococci		
Viridans streptococci	158 (38%)	58 (29%)
Streptococcus pneumoniae	11 (3%)	3 (1%)
Group B streptococci	3 (<1%)	1 (<1%)
Other	2 (<1%)	1 (<1%)
Enterococci	16 (4%)	20 (10%)
Staphylococci		
Staphylococcus aureus	113 (27%)	46 (23%)
Coagulase-negative staphylococci	22 (5%)	25 (12%)
Gram-negative bacilli	26 (6%)	19 (9%)
Fungi	9 (2%)	17 (8%)
Other organisms	5 (1%)	—
Polymicrobial	4 (1%)	12 (6%)
Culture negative	58 (14%)	21 (10%)

Culture-negative endocarditis seems to be less common in children than in adults. Approximately 5% to 10% of children with endocarditis have sterile blood cultures. Previous treatment with antibiotics is a common cause of negative blood cultures, but fastidious HACEK organisms and other rare fastidious pathogens such as *Bartonella, Brucella, Mycoplasma, Legionella,* and *Coxiella burnetii* can be causative. Non-HACEK pathogens are better detected by serologic or polymerase chain reaction (PCR) testing.[38–42] Endocarditis in children is rarely caused by mycobacteria, *Chlamydia psittaci,*[43] and *Tropheryma whipplei.*[43]

Epidemiology

The true incidence of endocarditis in children has been difficult to ascertain because the literature primarily derives data from referral centers. Between 1930 and 1972, 1 per 2000 to 5000 pediatric hospital admissions were due to endocarditis, and during the 1960s to 1980s, incidence was 1 per 500 to 1000 hospitalizations.[44–46] In 2003, 1 in 3500 randomly selected hospital admissions from a national database were attributed to endocarditis,[27] whereas a multicenter study conducted from 2003 to 2010 reported that endocarditis was associated with 0.05 to 0.12 per 1000 pediatric hospital admissions.[47] On the other hand, the risk of endocarditis between birth and the age of 18 years was found to be 6.1 per 1000 children with congenital heart disease (or 4.1 cases in 10,000 person-years) in a recent population-based cohort from Canada.[48] In a cohort of adults with congenital heart disease from the Netherlands, the incidence was significantly higher at 11 cases in 10,000 person-years.[49]

The risk factors for endocarditis in children have changed over the past several decades. As shown in Table 37.2, congenital heart disease is the most common predisposing condition in the US. Although surgical correction of ventricular septal defect or patent ductus arteriosus substantially reduces the risk for endocarditis, other interventions such as palliative shunts, valve replacement, and placement of pacemakers or defibrillators, or both, can increase the risk for endocarditis due to the sustained presence of foreign material in the bloodstream.[50] Advances in surgical techniques and supportive care now permit earlier repairs of certain lesions (e.g., tetralogy of Fallot) as well as neonatal palliation of previously inoperable lesions.[51,52] These changes are associated with increased endocarditis, including early postoperative endocarditis, occurring in younger patients, with a median age of ≤2 years in some series.[26,28,32,48] However, endocarditis can occur years after repair of congenital heart defects. Of note, 18% to 39% of patients with endocarditis in developed countries have no previously known cardiac defect.[12,20,21,23–26,28,32]

TABLE 37.2

Trends in Underlying Cardiac Diseases in Children With Infective Endocarditis

Reference	**Series 1**[45]	**Series 2**[21]	**Series 3**[28]	**Series 4**[26]
Years of study	1930–1972	1977–1992	1992–2004	2004-2010
Number reported	266	62	85	1033
Cardiac defect, *n* (%)				663 (64%)
Congenital cardiac defect, *n* (%)	208 (78%)	40 (64%)	68 (80%)	NA
Acyanotic, *n* (%)	NA	18 (45%)	48 (71%)	517 (78%)
Cyanotic, *n*	NA	22	20	146
Rheumatic heart disease	37 (14%)	3 (5%)	1 (1%)	NA
No cardiac defect	21 (8%)	19 (31%)	13 (18%)	370 (36%)

NA, not available.

Neonatal endocarditis is not rare and usually arises as a complication of extreme prematurity, major surgery, or prolonged use of indwelling central venous catheters (CVCs).[29,31,44,53,54] Fewer than 30% of neonates with endocarditis have congenital heart disease, and most endocarditis is right sided.[32,55] Older children without cardiac defects also can develop right-sided endocarditis, including adolescents with intravenous drug abuse, those with pacemakers, or critically ill patients with CVCs.[27,28,44,56–64]

A significant increase in the hospitalization rates for endocarditis in the American adult population was noted from 2000 to 2011 with an increase of 11 to 15 per 100,000 population.[65] The proposed explanations include an aging population, increases in individuals with high-risk conditions such as diabetes and those requiring hemodialysis, and increased survival of adults with congenital heart disease and prosthetic implants.

Pathogenesis and Pathologic Findings

Native Valve Endocarditis

The most important factor in the pathogenesis of endocarditis is disruption of the endothelium, typically caused by turbulent blood flow or foreign body (e.g., a CVC) in contact with the endocardium, or both. Turbulence generally is from an area of high pressure to an area of low pressure, that is, across a ventricular septal defect or regurgitation through an incompetent valve.[18,29,46,53,66,67] Erosion of endothelium occurs, facilitating deposition of platelet-fibrin thrombi on the mural surface or on an abnormal valve on the down-pressure side.

Important pathogen factors include bacteremia or bloodstream infection (BSI) or fungemia and microbial adhesins. The peptidoglycan surface of oral streptococci facilitates adherence to endothelial cells. Similarly *S. aureus* binds to collagen, fibronectin, laminin, vitronectin, and fibrinogen.[1,68] Microbial surface components that recognize adhesive matrix molecules (MSCRAMMS) likely are virulence factors of *S. aureus.*[15] Patients with *S. aureus* endocarditis have higher serum levels of adhesin molecules than patients with *S. aureus* BSI without endocarditis.[69] The bacterial adhesins of CoNS are less well understood but may be capsular polysaccharides.[70]

The rate of bacteremia associated with common events and medical procedures is shown in Table 37.3.[71] Although dental procedures, such as drainage of an abscess, gingival surgery, and tooth extraction, are particularly likely to cause bacteremia, transient bacteremia after common daily activities such as tooth brushing is far more frequent. Thus an antecedent event clearly responsible for endocarditis rarely is identified.[2]

TABLE 37.3

Rate of Bacteremia After Various Procedures

	Episodes of Bacteremia per Episode[71]	
Procedure	**Mean (%)**	**Range (%)**
Tooth extraction	60	18–85
Periodontal surgery	88	60–90
Tonsillectomy	35	33–38
Rigid bronchoscopy	15	
Tracheal intubation	<10	0–16
Urinary tract catheter insertion or removal	13	0–26
Upper endoscopy	4	0–8
Barium enema	10	5–11
Colonoscopy	5	0–5
Cardiac catheterization	2	0–5

Right-sided endocarditis can be due to a CVC extending into the structurally normal heart. In an experimental model in rabbits, endocarditis only develops when bacteremia is preceded by placement of an intravenous polyethylene catheter across the tricuspid valve into the right ventricle.[59] The catheter acts as a foreign body, abrading endocardial and valvular surfaces and resulting in sterile vegetations that serve as a nidus for infection.

Postoperative Endocarditis

The pathogenesis of endocarditis occurring ≤6 months (early) and >6 months after surgery (late) differ. In the early postoperative period, denuded endothelium and exposed sutures are adjacent to prosthetic material; thrombi can form at these sites with fibrin deposition. Endocarditis can result if bacteremia or fungemia follows contamination of intravenous solutions, the cardiac bypass pump, a surgical site, CVC, or exposed pacemaker wires or intracardiac catheters. In addition, bacterial or fungal contamination of the operative site can be caused by infected homografts or the colonized hands of healthcare personnel.[72–74] Late postoperative endocarditis occurs after re-endothelialization of cardiac and vascular surfaces, with pathophysiology more akin to native valve endocarditis.

Pacemaker and Ventricular Assist Device Infections

Placement of a pacemaker or cardioverter-defibrillator in children and adolescents is increasing.[75,76] Contamination during placement and infection of the pulse-generator pocket are the usual preceding events. Endocarditis is relatively rare and accounts for approximately 10% of implantable device-associated infections,[3] although younger patients may have more frequent lead-wire infections than older patients.[76,77] Complete removal of the device is recommended when a deep pocket infection occurs because of the high risk for relapse and for contaminating the intravascular portion of the device.[57,78]

Ventricular assist devices (VADs) are increasingly being used to support patients awaiting heart transplantation.[79] Although data are limited, the rate of infectious complications is high, occurring in 18% to 59% of patients, and complications include surgical site infections, BSIs, and endocarditis presenting as relapsing BSI.[80–82] Management of VAD-related infections is highly complex owing to the critical need for the device, presence of intravascular and intracardiac foreign material, and high risk for relapse.

Pathologic Lesions

Gross Findings.

Vegetations can be single or multiple and vary in size from 1 to 2 mm to several centimeters (Figs. 37.1 and 37.2).[1] Endocarditis can destroy the underlying valve or perforate valve leaflets; rupture the chordae tendineae, papillary muscle, or interventricular septum; or lead to abscess of the valve ring. Healing can result in fibrosis and calcification. Myocardial abscesses and pericarditis also can be present.

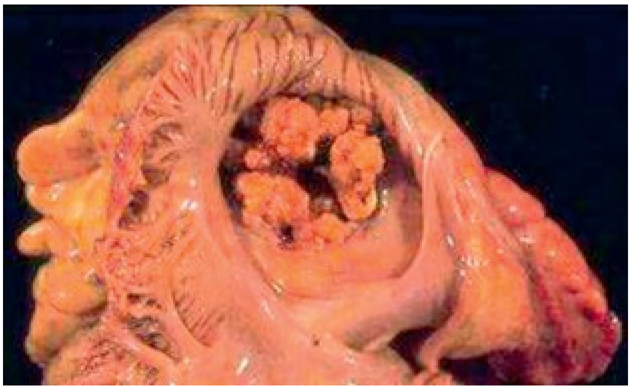

FIGURE 37.1 Infective endocarditis of the surface of the mitral valve. Note the healing masses at 10:00 and 2:00; this is "subacute" endocarditis with healing granulation tissue and fibrosis microscopically. No exophytic acute vegetation is present. (Courtesy of Charles Marboe, MD, Department of Pathology, Columbia University.)

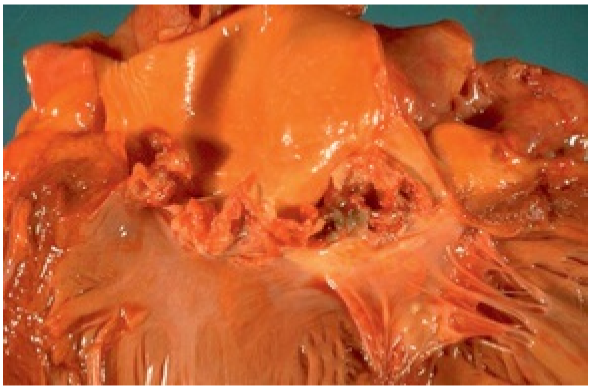

FIGURE 37.2 Infective endocarditis of the aortic valve. The left ventricular outflow tract is below the severely damaged valve, and the aorta is above. The anterior leaflet of the mitral valve is to the right and below the aortic valve. The aortic valve leaflets are almost entirely destroyed by the multiple vegetations of acute endocarditis. (Courtesy of Charles Marboe, MD, Department of Pathology, Columbia University.)

Microscopic Findings.

Vegetations consist of fibrin, platelets, and bacteria. Neutrophils and red blood cells also can be seen (Fig. 37.3).

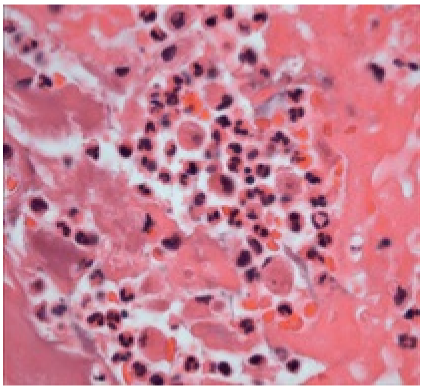

FIGURE 37.3 The histopathology of infective endocarditis. Vegetations are composed of neutrophils, macrophages and fibrin (*red*). Organisms are present in acute, untreated endocarditis. (Courtesy of Charles Marboe, MD, Department of Pathology, Columbia University.)

Embolic Findings.

Pathologic processes after emboli to distal organs consist of abscesses or infarction, or both. In the kidney, the lesions of glomerulonephritis also can occur, characterized by subepithelial deposits containing immunoglobulin G (IgG), IgM, IgA, or complement. Mycotic aneurysms are detected most commonly in the central nervous system and arise from direct bacterial invasion, embolic occlusion, or immune complex deposition within the arterial wall. Intracerebral or subarachnoid hemorrhage can result from emboli. Emboli to the lung can result in pneumonia, lung abscess, empyema, or effusion.

Clinical Manifestations

Symptoms

Classically, the clinical presentations of endocarditis were categorized as either subacute, generally manifesting with a prodrome of moderate illness and nonspecific symptoms for several weeks, or acute, with a short prodrome and a sepsis-like presentation. However, individual cases can have mixed features, and the presentation does not always predict the infecting microorganism.

Common symptoms of endocarditis in children are shown in Table 37.4. The subtle and nonspecific nature of symptoms can delay diagnosis for weeks.[29,53,83,84] Endocarditis should be suspected in patients with (1) congenital heart disease or other risk factors for endocarditis with unexplained fever and fatigue (or anemia) that can remit temporarily when oral antibiotics are prescribed; (2) congenital heart disease with new onset of congestive heart failure or conduction abnormalities, especially if accompanied by fever; (3) abrupt onset of septicemia or appearance of vascular lesions in soft tissues or mucous membranes; and (4) structurally normal hearts in whom CVC has been removed but blood cultures are persistently positive.

TABLE 37.4

Frequency of Findings in Pediatric Infective Endocarditis

Symptom	**Frequency (%)**[21,30,46,53,66,83,164]
Fever	75–100
Malaise	50–75
Anorexia/weight loss	25–50
Heart failure	25–50
Arthralgia	17–50
Chest pain	0–25
Neurologic symptoms (focal neurologic deficit, aseptic meningitis)	0–25
Gastrointestinal symptoms	0–50
Sign	**Frequency (%)**[21,30,46,52,64,81,162]
Fever	75–100
Splenomegaly	50–75
Petechiae	21–50
Embolic phenomenon	25–50
New or changed murmur	21–50
Clubbing	0–10
Osler nodes	0–10
Roth spots	0–10
Janeway lesions	0–10
Splinter hemorrhages	0–10
Conjunctival hemorrhages	0–10
Abnormal Laboratory Finding	**Frequency (%)**[a]
Positive blood culture	75–100
Elevated erythrocyte sedimentation rate	75–100
Anemia	75–90
Presence of rheumatoid factor	25–50
Hematuria	25–50
Low serum complement	5–40

[a] From references 21, 30, 46, 52, 64, 81, 162.

Vegetations, especially those on valve leaflets, can break off into the circulation. Significant morbidity can result from infectious emboli to the lungs (right-sided endocarditis) or to the central nervous system, kidney, spleen and extremities (left-sided endocarditis). Embolic events can be the predominant clinical feature in some patients.[85,86] Thus patients with fever and neurologic symptoms or with pneumonia or pulmonary emboli should be promptly evaluated for endocarditis.

Physical Examination

Table 37.4 shows frequency of physical findings in endocarditis.[4] Subtle changes in an existing murmur or detection of a new murmur in a febrile and tachycardic child may be difficult to appreciate. In patients with rapidly progressing infection, physical examination may not reveal the usual signs of endocarditis, and thus endocarditis is suspected because of underlying heart disease or persistently positive blood cultures or embolic events, including splinter hemorrhages (i.e., dark linear streaks in the nail beds). Signs due to deposition of immune complexes composed of bacterial antigens, antibodies, and complement are rare in children.[1] These include Osler nodes, that is, small (2–15 mm), painful, purplish lesions in the pulp of the fingers or toes that persist for hours or days; Janeway lesions, that is, painless hemorrhagic macular plaques on the palms or soles due to emboli that persist for days; or Roth spots, that is, small hemorrhagic retinal lesions with a pale center, usually near the optic disk.

Differential Diagnosis

When the onset of endocarditis is abrupt, the differential diagnosis includes septicemia, septic shock, and other acute cardiac inflammatory diseases, such as myocarditis, pericarditis, or rheumatic fever. Persistently positive BSI can arise from suppurative thrombophlebitis, as described later. If the onset of endocarditis is insidious, with prolonged or intermittent fever, the differential diagnosis includes fever of unknown origin, prolonged viral illness, and collagen vascular disorders. In patients with systemic lupus erythematosus or the antiphospholipid syndrome, sterile, verrucous vegetations called Libman-Sacks vegetations can be misdiagnosed as infective endocarditis.[87] Other echocardiographic findings that can mimic infective endocarditis include ruptured chordae and flail leaflet, severe myxomatous valvular changes, rheumatic fever valvular damage, and some cardiac tumors.

If the complications of endocarditis are the main clinical presentation, the differential diagnosis includes stroke, vasculitis, or cerebral vascular malformation. Glomerulonephritis can be the predominant presenting sign and endocarditis must be distinguished from other causes.[88,89]

Laboratory Findings and Diagnosis

Ancillary Laboratory Tests

Supporting laboratory test results are presented in Table 37.4. However, with the exception of positive blood cultures, these tests are nonspecific and are not diagnostic. In contrast, immunologic phenomena, including presence of rheumatoid factor, hematuria, nephritis, and low serum complement associated with glomerulonephritis, are considered minor diagnostic criteria.[90] Laboratory evidence of cardiac injury, that is, elevated serum levels of troponin I and B-type natriuretic peptide, is associated with worse outcomes in adults and may play a role in identifying patients who would benefit from surgical intervention.[91,92]

Microbiologic Evaluation

Persistent bacteremia or fungemia is the most helpful laboratory test in endocarditis. In streptococcal endocarditis, 96% and 98% of the first versus second blood cultures were found to be positive.[93] In endocarditis caused by other species, 82% to 94% and 100% of the first versus second blood cultures yielded the diagnosis.[94] Total volume of blood sampled is most important. Nevertheless, collection of 3 to 5 specimens from separate venipuncture sites is recommended to optimize recovery of a pathogen, particularly a fastidious microorganism, and to clarify a possible contaminated culture. Determining the clinical significance of a single positive blood culture, particularly with a possible contaminant (e.g., CoNS or occasionally viridans streptococci) can be difficult. If recent antibiotics have been received and the patient is clinically stable, antimicrobial therapy should be suspended for 24 hours to improve the yield of blood cultures. Ideally, each anaerobic and aerobic bottle is inoculated with 1 to 3 mL of blood for infants, 3 to 5 mL for small children, and 5 mL for larger children to optimize detection of pathogens, particularly in the setting of low-level bacteremia.[95] If limited blood is available for culture, the aerobic bottle should be inoculated.

The clinical microbiology laboratory should be alerted that endocarditis is being considered. Modern blood culture technologies can detect nutritionally variant streptococci and the HACEK organisms. Prolonged incubation or specialized media rarely are required. Additional testing sometimes is required (Table 37.5) and can include serologic tests, urine antigen tests, and molecular technologies, that is, PCR testing for 16S ribosomal DNA (rDNA) performed on excised valves and serum specimens (e.g., *Bartonella*) cases.[1,41,96] With the exception of *C. burnetii* antibodies, these diagnostic assays are performed only at specialized laboratories, are not standardized, and hence are not yet diagnostic criteria in the modified Duke classification.[1,97]

TABLE 37.5

Adjuvant Diagnostic Testing for Culture-Negative Endocarditis[41,42]

Pathogen	Test	Comment
Aspergillus spp.	Serology	Indirect hemagglutination assay
Bartonella henselae, Bartonella quintana	Blood culture Valve culture Serology PCR	Direct inoculation of blood agar, 5% CO_2 and shell vial Indirect immunofluorescent antibody test; titer ≥1:800 Western immunoblot
Brucella melitensis	Serology	IgG ≥1:200[a]
Coxiella burnetii	Blood/valve culture Serology PCR	Routine or heparinized blood inoculated in shell vials to detect bacteria by immunofluorescence[a]
		Anti–phase I IgG antibody titer >1:800 is major criterion
		IgG, IgA, IgM to phase I and phase II[a]
		htpAB-associated repetitive element of *C. burnetii*[a]
Legionella pneumophila	Serology	Indirect immunofluorescent antibodies ≥1:256
	Urine antigen	Available for serogroup 1
Mycoplasma pneumoniae	Serology PCR	IgG ≥1:200[a]
Tropheryma whipplei	See below	Etiologic agent of Whipple disease
Unknown	16S rDNA blood	Universal primer to identify bacteria by amplification and sequencing[a]
	16S rRNA valve	Universal primer for yeast
	18S rDNA blood	

	18S rRNA valve	
	Pathology of valve	Immunoenzymatic assay with polyclonal specific antibodies for *Coxiella, Bartonella, Chlamydia, Tropheryma*[a]

[a]Available in reference laboratories.

Ig, immunoglobulin; PCR, polymerase chain reaction.

Diagnostic Imaging

Echocardiography is the main diagnostic imaging modality to identify the pathology and define the cardiac complications of endocarditis and must be performed early to ensure rapid diagnosis and appropriate treatment, including surgical intervention if indicated.[98,99] Two-dimensional imaging can visualize vegetations as small as 2 mm, intracardiac abscesses, pseudoaneurysms, valve aneurysms, and dehiscence of a prosthetic valve (Fig. 37.4). Color and spectral Doppler imaging can identify flow through cardiac structures, as well as flow in pseudoaneurysms, fistulas, and valve dehiscences, and can identify consequences of pathologic lesions, including valvar insufficiency and perforations. Echocardiography can be falsely negative early in disease because of small vegetations or embolization and should be repeated within 7 to 10 days if there is continuing suspicion for endocarditis.[1,5,100] Echocardiograms remain negative in about 15% of infective endocarditis cases; thus a negative study does not rule out endocarditis.[99]

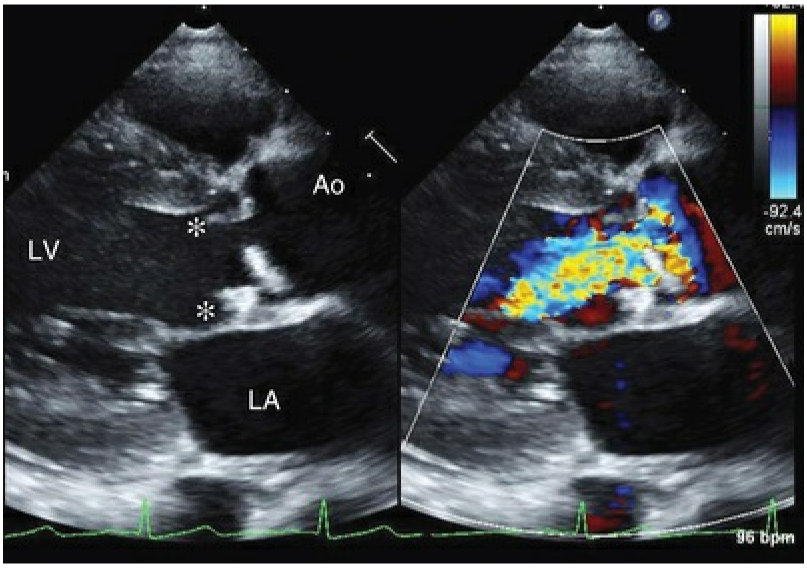

FIGURE 37.4 Valvular vegetations (*asterisk*) and their destructive effect on a bicuspid aortic valve. The color

Doppler image demonstrates severe valvular regurgitation from lack of valve coaptation. Ao, aorta; LA, left atrium, LV, left ventricle.

In adult populations, transthoracic echocardiography (TTE) has significantly lower sensitivity (40% to 63%) compared with transesophageal echocardiography (TEE) (≥90%).[101–105] TEE is used less frequently in pediatrics because of its relative invasiveness, its technical limitations in very small children, and the higher sensitivity of TTE (≥80%).[1,106–111] TEE does have a role in pediatrics to evaluate prosthetic valves, to assess certain complications, particularly aortic root abscesses, and to evaluate patients with complex anatomy from previous cardiac surgery, thoracic cage abnormalities, or weight >60 kg.[4,9,111] Intraoperatively, TEE is invaluable to improve visualization of lesions and to assess surgical results.

Echocardiography plays a central role during the treatment of endocarditis, establishing the need for urgent or emergent surgery in cases of heart failure (e.g., acute severe valvar regurgitation or obstruction) and uncontrolled infection (e.g., abscess, fistula).[98,112] Serial echocardiograms are used to monitor hemodynamic consequences of endocarditis and enlarging vegetations and to detect later complications (e.g., perivalvular extension and abscesses) that may require surgery. Echocardiography can be used to assess heightened risk for important embolization, by vegetation size (>10 mm), location (mitral valve anterior leaflet), and increased mobility of the vegetation. In certain cases of early embolism, urgent surgery may be indicated.[85,98,113,114]

In adult populations, three-dimensional echocardiography improves characterization of the pathology associated with endocarditis although concerns remain regarding inferior resolution for fast moving structures.[1,115–119] Cardiac magnetic resonance imaging (MRI) and computed tomography (CT) offer adjunctive imaging strategies.[120–124] CT may optimally visualize abscess extension (Fig. 37.5) and pseudoaneurysms,[120,121] and MRI may be most useful to investigate extracardiac complications including cerebral and splenic embolic infarcts.[99] Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose combines nuclear and CT technologies and is a promising imaging modality that detects inflammatory leukocytes.[125–129] Reduction in radiation exposure will be necessary before PET is used commonly in children. Finally, intracardiac echocardiography has been found to increase diagnostic yield compared with TEE among adults being evaluated for right-sided vegetations associated with leads of implantable cardiac devices.[130]

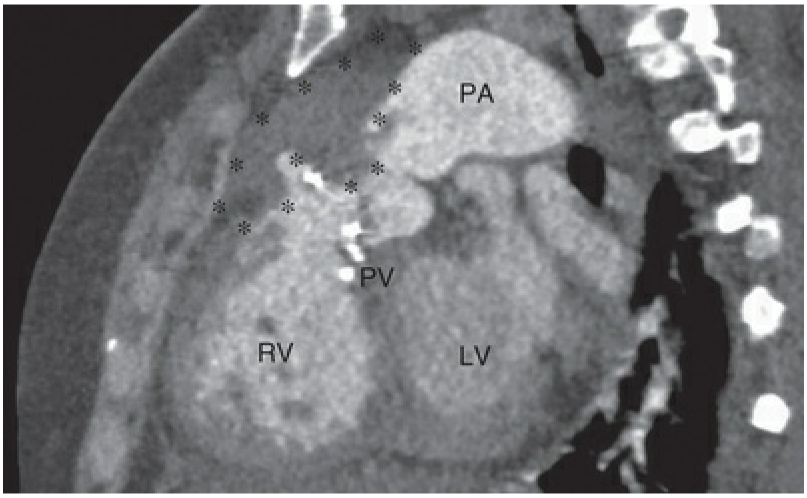

FIGURE 37.5 Computed tomographic sagittal view of the right ventricular outflow tract in a patient with tetralogy of Fallot who had previously undergone pulmonary valve replacement and who presented with prosthetic pulmonary valve endocarditis. Note the extension of abscess anteriorly (*asterisks*) presumably from fistula formation. RV, right ventricle; LV, left ventricle; PA, pulmonary artery; PV, pulmonary valve.
(Courtesy of the 3D imaging laboratory at New York-Presbyterian, New York.)

Diagnostic Criteria

The diagnosis of endocarditis is obvious in the setting of new valvular vegetations and multiple positive blood cultures. Diagnosis can be challenging in high-risk patients with negative blood cultures or echocardiograms, or with blood cultures positive for unusual pathogens. Diagnostic criteria originally were developed as epidemiologic and research tools, but after years of revisions, criteria have an important clinical role in more complex cases.[131] The modified Duke Criteria (Boxes 37.1 and 37.2)[97] now are accepted widely as a guide for diagnosing endocarditis[1,98] and can be used in children.[4,132–134] However, diagnostic criteria cannot replace clinical judgment. Treating patients who do not meet criteria fully may still be indicated. It is likely that further modifications of the Duke Criteria will be made as improvements in microbiologic and imaging tests become validated and available more readily.[1]

Box 37.1

Modified Duke Clinical Criteria for Diagnosis of Infective Endocarditis[a]

Definite Infective Endocarditis

Pathologic Criteria

- Microorganisms demonstrated by culture or histology in a vegetation, embolized vegetation, or intracardiac abscess
- Pathologic lesions (vegetation or intracardiac abscess) with active endocarditis confirmed by histology

Clinical Criteria

- 2 major criteria
- 1 major and 3 minor criteria
- 5 minor criteria

Possible Infective Endocarditis

- 1 major criterion and 1 minor criterion
- 3 minor criteria

Rejected

- Firm alternative diagnosis for manifestations of endocarditis
- Resolution of endocarditis manifestations with antibiotic therapy ≤4 days
- No pathologic evidence of infective endocarditis at surgery or autopsy with antibiotic therapy for ≤4 days

- Does not fulfill criteria above

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[a] Any one of the findings listed above is taken as evidence.

Modified from Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000;30:633–638.

Box 37.2

Definitions of Major and Minor Criteria Used in the Duke Schema for the Diagnosis of Infective Endocarditis

Major Criteria

1. **Positive blood culture for IE**

- Typical microorganism consistent with IE from two separate blood cultures:
  - Viridans streptococci[a]
  - *Streptococcus gallolyticus bovis*
  - HACEK group (see group)
  - *Staphylococcus aureus*
  - Community-acquired enterococci (without a primary focus)
- Microorganism consistent with IE from persistently positive blood cultures if:
  - At least 2 positive blood cultures sampled more than

12 hours apart

- All 3 or a majority of more than 4 blood cultures

- Single positive blood culture for *Coxiella burnetii* or IgG antibody titer >1:800

2. **Evidence of endocardial involvement by positive echocardiogram for IE, defined as:**

- Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material

- Abscess

- New partial dehiscence of prosthetic valve

- New valvular regurgitation (worsening or changing of preexisting murmur not sufficient)

Minor Criteria

1. **Predisposing heart condition or intravenous drug abuse**

2. **Fever: temperature ≥38°C**

3. **Vascular phenomena:** major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions

4. **Immunologic phenomena:** glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor

5. **Microbiologic evidence:** positive blood culture but does not meet major criteria or serologic evidence of active infection with organism consistent with IE

IE, infective endocarditis; IgG, immunoglobulin G.

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[a] Includes nutritionally variant strains (*Abiotrophia* spp).

Modified from Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000;30:633–638.

Management

When endocarditis is suspected, urgent evaluation of hemodynamic status is critical. If signs and symptoms of heart failure are present, an echocardiogram and several blood cultures are obtained quickly, and empiric antibiotic therapy and hemodynamic support are provided without delay. Patients with heart failure often require urgent cardiac surgery, which can be lifesaving.

Empiric Antibiotic Therapy

Presumptive antibiotic therapy is based on patient age, clinical presentation, comorbid conditions, preexisting cardiac status, recent cardiac surgery, prior episodes of BSI or endocarditis, community versus healthcare acquisition, and local antibiogram. Antimicrobial treatment for endocarditis in children is derived from recommendations developed for adults; pediatric infectious disease consultants should help select an empiric antibiotic regimen (Tables 37.6 and 37.7). High doses of bactericidal antibiotics delivered intravenously are needed; penetration of bioactive cells and substances into the infected vegetation can be difficult. Bacteriostatic agents are less effective. Pathogens exist within a biofilm and are not metabolically active, rendering them less susceptible to β-lactam and other cell-wall active agents. Furthermore, heart valves do not have a dedicated blood supply. When combination therapy—generally a β-lactam agent plus an aminoglycoside—is used for synergy, close temporal administration of the two drugs may maximize potential activity.[1]

TABLE 37.6

Antimicrobial Agents for Treatment of Pediatric Infective Endocarditis Caused by Gram-Positive Cocci

Definitive Therapy	Agent	Prosthetic Material or Artificial Valves	
		Duration, if Absent	Duration, if Present
STREPTOCOCCI AND RELATED SPECIES			
(Includes most viridans streptococci and *Streptococcus gallolyticus* [formerly *S. bovis*])			
Highly susceptible to penicillin (MIC ≤0.12 μg/mL)	Penicillin G (or ampicillin) *or*	4 wk	6 wk (with or without 2 wk gentamicin)
	Ceftriaxone *or*	4 wk	6 wk (with or without 2 wk gentamicin)
	Penicillin G *plus* gentamicin *or*	2 wk	Not applicable
	Ceftriaxone *plus* gentamicin *or*	2 wk	Not applicable
	Vancomycin[a]	4 wk	6 wk
Relatively resistant to penicillin (MIC >0.12 to <0.5 μg/mL)	Penicillin G *plus* gentamicin *or*	4 wk + 2 wk gentamicin	6 wk + 6 wk gentamicin
	Ceftriaxone *or*	4 wk	6 wk + 6 wk gentamicin
	Vancomycin[a]	4 wk	6 wk
Resistant to penicillin (MIC ≥0.5 μg/mL) (includes *Streptococcus* spp. and *Abiotrophia, Granucatella, Gemella* spp.)	Penicillin G (or ampicillin) *plus* gentamicin *or*	Duration to be determined in consultation with infectious diseases specialist	6 wk + 6 wk gentamicin
	Ceftriaxone *plus* gentamicin *or*		6 wk + 6 wk gentamicin
	Vancomycin[a]		6 wk
ENTEROCOCCI			
Susceptible to penicillin	Ampicillin (or penicillin) *plus* gentamicin[b] *or*	4–6 wk[d]	6 wk + 6 wk gentamicin[b]
	Ampicillin *plus* ceftriaxone[c]	6 wk	6 wk
Resistant to penicillin, susceptible to vancomycin			
β-lactamase producer	Ampicillin –sulbactam *plus* gentamicin[b]	6 wk	6 wk
Intrinsic resistance	Vancomycin *plus* gentamicin[b]	6 wk	6 wk
Resistant to vancomycin	Linezolid or daptomycin	> 6 wk	> 6 wk
STAPHYLOCOCCI			
(*Staphylococcus aureus* or coagulase-negative staphylococci)			
Susceptible to oxacillin	Oxacillin (or nafcillin) *plus* gentamicin	4–6 wk[e]	≥6 wk + ≥6 wk rifampin + 2 wk

	(optional for 3–5 days[9])		gentamicin
	Cefazolin[f]	≥6 wk	≥6 wk + ≥6 wk rifampin + 2 wk gentamicin
Resistant to oxacillin	Vancomycin *plus* rifampin *plus* gentamicin	≥6 wk	≥6 wk *plus* ≥6 wk rifampin *plus* 2 wk gentamicin

[a] If unable to tolerate β-lactam agent.

[b] If resistant to gentamicin, can use streptomycin.

[c] If resistant to aminoglycosides, can use double β-lactam combination: ampicillin plus ceftriaxone.

[d] Duration of therapy 4 weeks if symptoms <3 months, and 6 weeks if symptoms >3 months.

[e] Recommendation for children is 4−6 weeks[9] and for adults ≥6 weeks.[1]

[f] Nonanaphylactoid penicillin allergy; recommendation for adults.

MIC, minimal inhibitory concentration.

Modified from Baddour LM, Wilson WR, Bayer AS, et al. infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications. A Scientific Statement for Healthcare Professionals From the American Heart Association. Circulation 2015;132:1435−1486; and Baltimore RS, Gewitz M, Baddour LM, et al. Infective endocarditis in childhood: 2015 update. A Scientific Statement From the American Heart Association. Circulation 2015;132:1487−515.

TABLE 37.7

Doses of Commonly Used Antibiomicrobial Agents Recommended to Treat Infective Endocarditis

	Total Daily Dose[a,b]		
Antimicrobial Agent	**Children[c]**	**Adults[c]**	**Interval for Divided Doses[b]**
Ampicillin	200–300 mg/kg	12 g	4 hr
Cefazolin	100 mg/kg	6 g	8 hr
Ceftriaxone	100 mg/kg[b]	2 g[c]	24 hr
Penicillin (PCN) G			
If native valve and PCN-susceptible (MIC ≤0.12 μg/mL)	200,000 U/kg	12–18 million U	4 hr
If native valve and PCN-resistant (MIC >0.12 μg/mL)	300,000 U/kg	24 million U	4 hr
If prosthetic material	300,000 U/kg	24 million U	4 hr
If enterococci PCN-susceptible	300,000	18–30	4 hr

	U/kg	million U	
Gentamicin[d]	3 mg/kg	3 mg/kg	24 hr or 8–12 hr
Oxacillin, nafcillin	200 mg/kg	12 g	4–6 hr
Rifampin	15–20 mg/kg Max: 900 mg	900 mg	24 hr if oxacillin susceptible 8 hr if oxacillin resistant
Vancomycin[e]	40–60 mg/kg	15–20 mg/kg	Children: 6–12 hr
		Max: 2 g/day	Adults: 8–12 hr
Daptomycin	Regimen in consultation with infectious diseases specialist		

[a] Doses are recommended for normal renal function.

[b] Dosage adjustment is necessary when renal insufficiency exists.

[c] Do not exceed maximum dose for large children and adolescents.

[d] Synergy target peak 3−4 μg/mL and target trough <1 μg/mL.

[e] Target trough 10−20 μg/mL.

MIC, minimal inhibitory concentration; PCN, penicillin.

Definitive Antibiotic Therapy: Drug, Dose, Duration

Recommendations for targeted treatment of endocarditis depend on the pathogen, in vitro susceptibility test results, site of endocarditis (right- versus left-sided), presence of a foreign body (e.g., prosthetic valve), need for surgery, and tolerability and toxicity of first-line therapy (see Tables 37.6 and 37.7).[1,135,136] When clinical experience is limited, such as with endocarditis caused by multidrug-resistant organisms, recommendations are based on case reports, expert opinion, or data from animal models.

Endocarditis of native valves caused by viridans streptococci (e.g., *S. sanguis, S. oralis, S. mutans)* or *Streptococcus gallolyticus* (formerly *S. bovis*) that are highly susceptible to penicillin (minimal inhibitory concentration [MIC] ≤0.12 μg/mL) can be treated with penicillin (ampicillin) or ceftriaxone[1] after blood cultures are negative. Short courses (2 weeks) of either penicillin or ceftriaxone with gentamicin can be considered in select patients with uncomplicated endocarditis and normal renal function without extracardiac infection. *S. pneumoniae* endocarditis should be treated according to specific β-lactam MICs (see Tables 37.6 and 37.7). Endocarditis caused by *S. pyogenes* can be treated with penicillin or ceftriaxone, and endocarditis caused by group B, C, or G streptococci can be treated similarly with the addition of gentamicin for the first 2 weeks owing to increased MICs of penicillin and to bactericidal capacity of the combination. Endocarditis of prosthetic valves or other prosthetic material, such as shunts, requires longer courses than endocarditis of native valves.

Endocarditis due to enterococci susceptible to penicillin should be treated with a combination of penicillin (ampicillin) and an aminoglycoside (gentamicin or streptomycin) if susceptible to high concentrations.[1,137,138] Gentamicin dosing should be given in divided doses to achieve a trough concentration <1 μg/mL and a peak of 3 to 4 μg/mL. If the enterococcal isolate is resistant to ampicillin or the patient is allergic to penicillin, vancomycin plus an aminoglycoside is used, and trough levels of vancomycin should be 10 to 20 μg/mL. Vancomycin-resistant enterococcal endocarditis is treated with linezolid[139,140] or daptomycin. Recent clinical experience with daptomycin in Europe demonstrated successful treatment of 10 children with endocarditis.[141]

Patients with native valve endocarditis caused by methicillin-susceptible *S. aureus* (MSSA) should be treated with oxacillin or nafcillin, and those with MRSA or CoNS (e.g., *S. epidermidis* or *S. lugdunensis*) resistant to oxacillin should be treated with vancomycin (see Table 37.6). The addition of a second agent for treatment of staphylococcal endocarditis (generally gentamicin or rifampin) is not recommended for native valve endocarditis in adults.[1]

Recommendations for endocarditis of prosthetic valves or other prosthetic material caused by MSSA, MRSA, or CoNS include the addition of rifampin for the full course (at least 6 weeks) and gentamicin for the initial 2 weeks. Compared with streptococcal endocarditis, the treatment response of children with staphylococcal endocarditis is more protracted, with a mean of 2 days to sterile blood cultures, mean of 7 days to defervescence, and >14 days of fever in 17% of cases.[30] To date, glycopeptide-intermediate *S. aureus* (GISA), heterogeneous GISA, and glycopeptide-resistant *S. aureus* are rarely associated with endocarditis, and evidence-based strategies are limited. Quinupristin-dalfopristin, telavacin, trimethoprim-sulfamethoxadole (potentially with daptomycin), or ceftaroline may be useful.[1]

For endocarditis caused by enteric gram-negative bacilli, two bactericidal agents are chosen on the basis of in vitro susceptibility and generally include an expanded-spectrum β-lactam agent and an aminoglycoside or fluroquinolone.[1] The HACEK organisms frequently express β-lactamases and are slow growing, which makes susceptibility testing more difficult to perform. Thus treatment with a third-generation cephalosporin (ceftriaxone most commonly) is recommended.[1]

Management of endocarditis caused by *Candida* and *Aspergillus* spp. generally includes both medical and surgical approaches (discussed later) to optimize cure. Rare cases of fungal endocarditis have been managed successfully with antifungal therapy alone.[142,143] Traditionally, amphotericin or lipid amphotericin products have been used,[144] but caspofungin[145,146] and voriconazole[147] may be reasonable therapeutic alternatives. Unfortunately, pharmacokinetic studies with these newer agents have not been performed in neonates. “Lifelong” (long-term) fluconazole prophylaxis has been advocated in patients with fungal endocarditis to prevent relapses or as suppressive therapy in patients not deemed to be surgical candidates.[1]

Duration of antimicrobial therapy is based on the pathogen, susceptibility results, presence of prosthetic cardiac material, and clinical course. In children with native valve endocarditis due to viridans streptococci, 4 weeks of penicillin G alone (from the first negative blood culture) is effective and may be preferred because of limited experience with the 2-week regimen in young patients. Treatment for 6 weeks generally is recommended in “high-risk” situations, including infection due to relatively resistant streptococci or to enterococci, staphylococci, gram-negative bacilli, and in patients with intravascular prosthetic material. For the HACEK organisms, 4 weeks (if native valve) or 6 weeks (if prosthetic valve) of treatment is recommended. At least 6 weeks of therapy is recommended for patients with enterococcal endocarditis who had >3 months' duration of symptoms.[1] Even more prolonged courses are recommended for complicated endocarditis (e.g., intracardiac abscess) and in patients who have a slow response to therapy. Regardless of surgical intervention, fungal endocarditis should be treated with prolonged courses (≥6 weeks) of parenteral antifungal agents followed by oral fluconazole as describe previously.

Although no controlled trials document safety of outpatient therapy for endocarditis, clinically stable patients at low risk for complications (heart failure or embolic phenomena) can be selected who will have meticulous catheter care, regular home visits by an infusion nurse, easy access to a hospital if needed, and close follow-up with an experienced clinician.[148]

Antibiotics are almost always administered intravenously. Although there are reports of successful oral treatment of endocarditis, including with linezolid[139,149] and voriconazole,[147] this strategy has not been studied systematically and generally is not recommended. In addition, there are reports of successful management with antibiotics given orally for *S. aureus* endocarditis in intravenous drug abusers who are not candidates for parenteral therapy.[1]

Surgery

Studies in adult populations report lower mortality and fewer complications with surgery compared with medical therapy alone for some patients with endocarditis.[150] Critical review of studies reveals survivor and selection bias, confounding of differing types of endocarditis (e.g., native vs. prosthetic valve, right vs. left-sided) and indications.[1] Prudent surgical decision considers the host, the pathogen, persistent bacteremia, features of endocarditis (vegetation size, local cardiac complications, heart failure), and the occurrence or risk for embolic phenomena. The AHA expert advisory panel and the European Society of Cardiology define guidelines for surgery while emphasizing individualized management[1,8,9] (Table 37.8).[110,151–153]

TABLE 37.8

Considerations for Early Surgical Interventions[a] for Left-Sided Endocarditis[1,9]

Indication	Surgery
Heart failure from valve dysfunction from dehiscence, intracardiac fistula, or prosthetic valve dysfunction	Indicated
Heart block	Indicated
Annular or aortic abscesses or destructive penetrating lesions	Indicated
Endocarditis caused by fungi, mold, or multidrug-resistant organisms, e.g., vancomycin-resistant enterococci or multidrug-	Considered if native valve; indicated if

resistant gram-negative bacilli	prosthetic valve
Persistent infection, i.e., fever and positive blood cultures for more than 5–7 days (when other sites of infections are excluded)	Indicated
Recurrent emboli and persistent or enlarging vegetations	Reasonable
Mobile vegetation >10 mm and severe valve regurgitation	Reasonable
Relapsing prosthetic valve endocarditis	Reasonable
Mobile vegetation >10 mm and involving anterior mitral leaflet	Considered

[a] Defined as during initial hospitalization for endocarditis and before completion of antimicrobial therapy.

Although both guidelines recommend early surgery after a left-sided embolic event if vegetations persist, European guidelines recommend early surgery for silent events, whereas the American guidelines emphasize clinical events. The preservation of the native valve, particularly the mitral valve, is recommended when possible.[154] Although earlier recommendations were endorsed by the American Academy of Pediatrics,[5] collective data in children with endocarditis only recently confirms surgical survival rates similar to those of adults and low rates of recurrence.[155–157] In a review of 25 pediatric patients in Texas, surgery within 3 days of presentation was associated with a low risk for embolization.[156]

After embolic complications, surgical resection of an enlarging mycotic aneurysm in the cerebral vasculature is necessary if neurologic symptoms or bleeding ensue. Increasingly, early cardiac surgery is considered in patients with minor cerebral embolic events if imaging excludes intracranial hemorrhage. However, in patients with major ischemic stroke or intracranial hemorrhage, it is reasonable to delay valve surgery for at least 4 weeks to avoid hypotension and anticoagulation during surgery.

Delayed splenic rupture due to emboli is a potentially fatal complication of endocarditis. Large emboli to major blood vessels can lead to cold, painful, and pulseless extremities and require immediate surgical intervention.

Anticoagulation

There is no evidence that anticoagulation therapy with either aspirin or other agents is beneficial as an adjuvant therapy for endocarditis. However, controversy persists regarding management of patients receiving anticoagulation therapy who develop endocarditis because risk for hemorrhagic stroke is high.[1,5,158,159] It is reasonable to stop all anticoagulation therapy for at least 2 weeks in patients who have experienced a central nervous system event.[1] If cerebral hemorrhage has been excluded, anticoagulation during indicated cardiac surgery is acceptable.[160–163]

Complications

Complications of endocarditis include direct valvular damage, perivalvar extension of infection, and heart failure. Infection can disrupt valvular structure, causing leaflet fenestrations and chordae rupture, secondary valvular incompetence, and heart failure. Heart failure also can be caused by obstructive vegetations or new shunt lesions leading to extensive damage to cardiac structures. Perivalvar extension can result in endocardial abscesses, secondary fistulas, or pseudoaneurysms. Most abscesses in children are associated with native aortic valve and *S. aureus* endocarditis.[112] Clues to possible abscess formation include persistent fever and BSI; conduction abnormalities occur less frequently than is reported in adults with abscesses. Acute renal failure can result from immune complex deposition, renal infarction, hemodynamic instability, adverse effects of antibiotic therapy, or combinations thereof.

The risk for embolization varies from approximately 20% to 50% and may be higher if MRI is performed to detect silent lesions. The greatest risk for emboli is associated with *S. aureus, Candida,* HACEK organism, and *Abiotrophia* endocarditis.[1] Large (>10 mm) left-sided vegetations, particularly of the mitral valve, are associated with a higher risk for significant embolic events.[22,85,106,158,164–167] Most embolic events occur before or within the first 2 weeks of commensing therapy but also can occur after therapy has been completed.[158] Emboli from right-sided endocarditis can cause necrotizing pneumonia and prolonged fever; outcome generally is good with prolonged therapy. Left-sided endocarditis causes systemic emboli to the brain (more than half of embolic events), visceral organs, limbs, and coronary arteries. Brain emboli can result in stroke, mycotic aneurysms, and meningitis. Although the risk for neurologic events is ill-defined in children, 6% of pediatric patients with endocarditis were reported to have a stroke.[168] Visceral septic emboli can result in hemorrhage, infarct, or abscess.

Prognosis

Cure depends on the virulence of the infecting organism, the site of endocarditis, embolic phenomena, and the underlying clinical state of the host. More than 90% of children with native valve endocarditis due to viridans streptococci are cured,[21,83,84,164,169] whereas fungal endocarditis has the poorest prognosis, with overall cure rates <50%.[170]

Features associated with adverse outcome include multidrug-resistant pathogen, heart failure, presence of prosthetic cardiac material (especially artificial valve), cyanotic heart disease, previous episode of endocarditis, infant age, and vegetations >10 mm (especially left-sided). Persistence of fever for ≥2 weeks is associated with increased morbidity (myocardial abscesses, urgent cardiac surgery, healthcare-associated complications) and mortality.[21,30,96,171]

In some pediatric series, the prognosis of endocarditis has not improved in the modern era,[28,172] whereas in others, mortality rates are 4% to 5%.[27,173] In adults with healthcare-associated endocarditis, risk for in-hospital and 1-year mortality was increased compared with community-acquired endocarditis.[174] In an adult study, mortality was reduced from 18.5% to 8.2% when an interdisciplinary team of infectious diseases and microbiology specialists, cardiologists, and cardiac surgeons implemented a therapeutic protocol for endocarditis.[175]

Posttreatment Management

At completion of treatment, an echocardiogram should be performed to establish a new baseline for subsequent comparisons. Patients should be educated on signs and symptoms of relapse and should return for evaluation (including blood cultures) with any febrile illness. Daily dental hygiene and routine dental care are emphasized. Providers should be alert for heart failure and antimicrobial toxicity, including ototoxicity or *Clostridium difficile* infection.

Prevention

In 2007, the AHA modified antibiotic prophylaxis guidelines because existing evidence did not support widespread prophylaxis (see Chapter 7).[176] With targeting only of patients with the highest risk for endocarditis complications, recommended instances of prophylaxis are reduced, and antibiotic regimens are simplified.[5] In fact, the National Institute for Health and Clinical Excellence (NICE) of England and Wales halted recommending prophylaxis in 2008, instead emphasizing excellent dental hygiene and routine dental care.[177–180]

Using administrative pediatric hospitalization data from 2003 to 2010, endocarditis admissions declined without a change in the proportion of streptococcal infections following restricted 2007 guidelines.[47] Adverse consequences have not been noted in adults,[181,182] although one study showed an increase in streptococcal infections after 2007.[65]

Other Endocarditis-Like Intravascular Infections

Other types of infection can manifest as persistent BSI (bacterial or fungal). These include septic (or suppurative) thrombophlebitis, defined as venous thrombosis, inflammation, and bloodstream infection or, more commonly, *central line–associated blood stream infection* (CLABSI), defined as positive blood cultures in a patient with a central line and no other source for bacteremia.[183] Septic thrombophlebitis is a rare cause of hospital admissions (0.12%) in children, likely owing to improvements in catheter insertion and maintenance strategies.[184] In-hospital occurrence may be underrecognized.

Risk factors for septic thrombophlebitis include prolonged use (>96 hours) of intravascular catheters, surgical manipulation of a vessel, extension of infection from adjacent nonvascular structures, or severe burns. Septic thrombophlebitis can result from thrombi, fibrin clots, or biofilms forming on catheters, generally at the distal tip, or at the site of a surgical anastomosis or vascular prosthesis. Phlebitis results from trauma or irritation of the vessel wall. The clot or inflamed vessel becomes infected during bacteremia, from contaminated infusates, or from infected adjacent structures.[185] Suppurative thrombophlebitis develops if the vessel wall becomes infected. Progression of infection and inflammation can occlude the vessel, leading to a painful, enlarged, thickened, and tortuous vessel.

Nonvascular infections at adjacent sites can cause septic thrombophlebitis syndromes. Pharyngitis or peritonsillar abscess can cause Lemierre syndrome, that is, internal jugular vein septic thrombophlebitis.[186] Appendicitis, intra-abdominal infection, or abdominal surgery can cause pylephlebitis, that is, portal vein septic thrombophlebitis.[183] Septic abortions, pelvic surgery, or pelvic abscesses can cause pelvic vein thrombosis and infection.

Symptoms of superficial thrombophlebitis include fever, chills, induration, warmth, erythema, and tenderness of the infected vessel. In contrast, only about half of patients with central thrombophlebitis have signs of inflammation, and symptoms may not occur until several days after catheter removal.[187] Symptoms of portal vein thrombophlebitis include fever, right upper quadrant pain, anorexia, weight loss, and malaise.

Blood cultures usually are positive persistently, but pathogens also can be isolated from pus at the exit site, aspiration of the thrombosed vein, or the surgically resected vessel. *S. aureus* is the most common etiology of suppurative thrombophlebitis, but Enterobacteriaceae or fungi can be causative. Vaginal flora, including *Bacteroides* spp., streptococci, and gram-negative bacilli cause pelvic thrombophlebitis; and intestinal flora, including gram-negative bacilli and enterococci, cause intra-abdominal thrombophlebitis. Lemierre syndrome usually is caused by *Fusobacterium necrophorum* in singular or polymicrobial pathogenesis.

Septic thrombophlebitis can be life-threatening, particularly if diagnosis and treatment are delayed. Lesions are not vascularized, and penetration of antibiotics can be poor. Thus principles of therapy are similar to those for endocarditis. A fluctuant mass along the course of a previously catheterized vein can be aspirated, which frequently eliminates persistent BSI abruptly. Otherwise, treatment of suppurative thrombophlebitis requires antimicrobial therapy, catheter removal, and surgical consideration, including ligation of the infected vessel, excision of the infected segment, and potential anticoagulation if the thrombus extends.[183–185,188]

Complications of septic thrombophlebitis include sepsis, hypotension, and septic embolization. Septic embolization can provide the clue to the diagnosis. Lemierre disease, for example, can present with embolic cavitating pulmonary lesions. Superficial thrombophlebitis (manifesting as tenderness and inflammation) can complicate subperiosteal abscesses of the long bones.[189] Pulmonary emboli or osteomyelitis can complicate deep vein thrombophlebitis.[190] Superior vena cava syndrome can complicate septic thrombophlebitis of the thoracic central veins after catheterization.

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38

Myocarditis

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Myocarditis is an inflammatory disease of the heart muscle that may progress to dilated cardiomyopathy. The condition can manifest with a range of clinical presentations from nonspecific systemic symptoms to fulminant heart failure or sudden death. There is continued debate regarding the appropriate diagnosis, classification, and management of myocarditis.[1,2]

Etiology

Myocarditis can have a variety of infectious and noninfectious etiologies. For most cases in routine clinical practice, a specific cause is not found. Viruses are the most common causes of acute myocarditis in North America and Western Europe. Initial studies using serologic assays implicated enteroviruses, particularly coxsackievirus B serotypes 1 through 5, as important causes.[3,4] More recent studies using polymerase chain reaction (PCR) assays of endomyocardial biopsy specimens have confirmed the importance of enteroviruses in acute myocarditis (10%–20%)[5,6] and dilated cardiomyopathy (10%–30%).[7,8] Other viruses that are commonly identified by PCR in the myocardium include adenovirus,[5,6] parvovirus B19,[9] Epstein-Barr virus, and cytomegalovirus.[5] Myocarditis is also recognized as a complication during outbreaks of influenza, measles, mumps, and polio.[10-13] Human immunodeficiency virus[14] and hepatitis C virus[15] have been implicated in myocarditis, although the exact role each virus plays in causing disease is unclear.

Bacteria cause myocarditis less frequently than viruses. Invasion of the bloodstream by a bacterial pathogen, such as *Staphylococcus aureus, Neisseria meningitidis,* or *Salmonella* spp., can result in myocardial seeding and resultant microabscesses.[16-18] Myocarditis or myocardial dysfunction also can be a toxin-mediated complication of tetanus or diphtheria or can be caused by other bacteria such as *Borrelia burgdorferi* (occurring in up to 16% of children with early disseminated Lyme disease),[19,21] *Rickettsia* spp. (especially scrub typhus),[20] *Mycoplasma pneumoniae,* and toxin-producing staphylococci and streptococci.

Parasites are a major cause of myocarditis worldwide, with *Trypanosoma cruzi* (the causative agent of Chagas disease) being the principal cause in Central and South America.[22] Many additional agents have been reported to cause myocarditis in immunocompromised hosts, most importantly cytomegalovirus, *Toxoplasma gondii, T. cruzi, and Cryptococcus, Candida,* and *Aspergillus* spp.

Epidemiology

Myocarditis is diagnosed in up to 0.05% of pediatric hospitalizations in the United States.[23] Myocarditis has a slight male predominance and a bimodal age distribution that peaks in infancy and adolescence.[24] The incidence of myocarditis can coincide with the occurrence of epidemic enterovirus infections.[25] Enteroviruses cause approximately 10 to 15 million infections annually in the United States and can occur in any demographic population. In the US, enterovirus activity peaks in the summer and fall, although transmission is year-round in the tropics.[26] Chagas disease is endemic in Central and South America and is the most important cause of myocarditis in those regions.[22]

Myocarditis has been implicated in 4% to 20% of sudden cardiac deaths in autopsy series of young previously healthy adults.[27,28] Other studies using PCR techniques highlight the possible role of myocarditis in sudden infant death syndrome (SIDS). Enteroviruses, parvovirus B19, and adenoviruses are the most commonly detected viruses in cases associated with SIDS, although Epstein-Barr virus, cytomegalovirus, and *T. gondii* also have been detected.[29-31]

Pathophysiology

Pathogenesis

The pathogenesis of myocarditis has been gleaned in large part from animal models. These models suggest that both direct myocardial infection and host immune responses are important in the pathogenesis of disease. Viruses often initiate the process through binding to specific surface receptors on cardiac myocytes. A common coxsackievirus-adenovirus receptor has been identified on cardiac myocytes, which may in part explain the tropism of these viruses.[32] Infection and myocardial injury induce innate immune responses, most importantly proinflammatory cytokines tumor necrosis factor-α and interleukin-1β.[33] Mixed inflammatory cells subsequently infiltrate into the myocardium, and adaptive immune responses, including antigen-specific T lymphocytes and antibodies, are activated. At this stage, most patients clear the viral infection and recover from the acute illness with minimal sequelae. However, a subset of patients experience ongoing inflammation, which can lead to cardiac remodeling, fibrosis, myocyte necrosis, and ultimately dilated cardiomyopathy. Persistent viral replication[34] and autoimmune targeting of cardiac autoantigens[35] are postulated mechanisms of ongoing inflammation. Both $CD4^+$ and $CD8^+$ T lymphocytes are key mediators of myocardial damage and chronic inflammation.[36] Autoantibodies directed against a variety of cardiac antigens have also been implicated in this process.

Pathologic Findings

Several standardized criteria have been developed to diagnose myocarditis using histopathology or immunohistochemistry. The Dallas pathologic criteria, initially proposed in 1986, define myocarditis as histopathologic evidence of inflammatory cellular infiltrate with or without myocyte necrosis on conventionally stained heart tissue biopsy specimens.[37] Inflammatory infiltrates are further classified based on severity, distribution, and type as lymphocytic, eosinophilic, or granulomatous. However, more recent studies suggest these criteria lack sensitivity, in part owing to biopsy sampling site error and variability in interobserver interpretation.[38-40] The addition of immunohistochemical stains to characterize inflammatory cell infiltrates can improve diagnostic sensitivity and add prognostic value.[41] The World Health Organization and International Society and Federation of Cardiology Task Force on the Definition and Classification of Cardiomyopathies defines *myocarditis* as immunohistochemical evidence of mononuclear infiltrates ($CD3^+$ T lymphocytes or $CD68^+$ macrophages) with more than 14 cells/mm^2 on endomyocardial biopsy in addition to enhanced expression of HLA class II molecules.[42,43]

Myocarditis from bacterial, parasitic, and fungal causes can show specific findings with histologic staining. Bacterial and fungal infection result in polymorphonuclear cell infiltrates, which can be focal or organized into microabscesses. Trypanosomes can often be visualized in the biopsy specimens from patients with chronic Chagas disease. Giant cell myocarditis is a rare disorder of suspected autoimmune etiology in which multinucleated giant cells are found in the absence of granulomas.

Clinical Manifestations

Clinical manifestations of myocarditis are variable but usually arise in the setting of a systemic infection. The spectrum of cardiac manifestations ranges from subclinical cardiac dysfunction to heart failure, arrhythmia, and sudden death. A viral prodrome consisting of an influenza-like illness with fevers, myalgias, and gastrointestinal complaints often precedes cardiac involvement. This can be followed abruptly by myocarditis with hemodynamic collapse. Sudden death can be a presentation of myocarditis at any age, but particularly in infants and children.[44]

Infants and children frequently present with nonspecific symptoms, such as respiratory distress, feeding difficulties, irritability, and constitutional symptoms. Typical findings of heart failure also can be present, including tachycardia, a new-onset heart murmur or gallop, hepatomegaly, peripheral edema, and decreased peripheral perfusion. Chest pain may be present owing to concomitant pericarditis or, occasionally, to coronary artery spasm. In a retrospective review of 31 children with biopsy-confirmed or probable myocarditis, emergency department findings included preceding “viral illness” (77%), tachypnea or other respiratory difficulty (68%), chest pain (29%), symptoms related to hypoperfusion (23%), Kawasaki-associated symptoms (10%), and gastrointestinal complaints (7%).[45] Chest radiography abnormalities were observed in 55% of cases, and decreased ventricular function was present in 73% of cases. ST-segment or T-wave changes on electrocardiography were also noted in 67% of cases.[45]

Differential Diagnosis

There are many noninfectious causes of acute myocarditis. Most involve systemic inflammatory conditions, toxic or hypersensitivity drug reactions, envenomations, endocrinopathies, radiation, or transplant rejection (Box 38.1). Several cardiac diseases can manifest similarly to or in conjunction with infectious myocarditis. Pericarditis can be distinguished by the findings of precordial chest pain, signs of pericardial fluid, and absence of arrhythmia. Endocarditis can be distinguished by primary valvular abnormalities in the presence of positive blood cultures and echocardiographic evidence of vegetations. Myocardial infarction can have findings similar to myocarditis, whether the infarction is due to coronary artery atherosclerosis or to drug ingestions such as cocaine or methamphetamine. Primary and secondary cardiomyopathies, including genetic abnormalities of cardiac structure and electrical conduction, can also mimic acute myocarditis. The term *idiopathic* (or *lymphocytic* if characteristic lymphocytic infiltrates are seen) *myocarditis* is used to describe cases in which no causative agent is found.

Box 38.1

Noninfectious Causes of Myocarditis in Children

Inflammatory Diseases

Inflammatory bowel disease

Systemic lupus erythematosus

Polymyositis and dermatomyositis

Mixed connective tissue disease

Kawasaki disease

Rheumatic fever

Rheumatoid arthritis

Sarcoidosis

Thyrotoxicosis

Transplant rejection

Giant cell myocarditis

Drug Reactions

Adriamycin

Amitriptyline

Amphetamines and methamphetamines

Arsenic

Catecholamines

Cefaclor

Cocaine

Cyclophosphamide

Daunorubicin

Ethanol

Furosemide

Isoniazid

Lead

Lithium

Methyldopa

Penicillins

Sulfonamides

Tetracyclines

Bites and Stings

Bee

Scorpion

Snake

Spider

Wasp

Idiopathic Causes (Lymphocytic)

PERIPARTUM PERIOD
PHEOCHROMOCYTOMA
RADIATION THERAPY

Laboratory Findings and Diagnosis

A high index of suspicion is required to establish the diagnosis of acute myocarditis in children. If the diagnosis is considered, the initial evaluation should include chest radiography, electrocardiography (ECG), and echocardiography. Nonspecific laboratory findings associated with myocarditis include elevations in erythrocyte sedimentation rate, C-reactive protein, serum transaminases, brain natriuretic protein, and the MB isoform of creatine kinase.[45,46] Cardiospecific troponins are also elevated in most pediatric cases[46] and have higher sensitivity and specificity for detection of myocyte necrosis than other cardiac enzymes.[47]

ECG findings are abnormal in essentially all children with myocarditis, although they are highly variable. Common ECG changes in myocarditis include ST-segment or T-wave abnormalities (67%), axis deviation (40%), ventricular hypertrophy (30%), heart block (23%), infarction pattern (13%), and decreased ventricular voltages (7%).[45] Other related findings include tachycardia out of proportion to fever, conduction disturbances, and arrhythmias. Arrhythmias occur in nearly half of pediatric patients hospitalized with acute myocarditis, the most common of which are ventricular tachyarrhythmias.[46] Most ECG abnormalities resolve with recovery of acute illness over a period of 1 to 2 months.

Echocardiography is the most frequently used noninvasive technique to evaluate for acute myocarditis. Biventricular dysfunction on echocardiogram is the most powerful predictor for death or need for cardiac transplantation. Other echocardiographic findings commonly associated with myocarditis include valvular regurgitation, left ventricular dilation, and abnormalities of wall motion. Echocardiography also can exclude other causes of cardiac dysfunction, such as valvular vegetations or pericardial effusions. Repeated echocardiograms are useful to follow the evolution of disease, with persistent abnormalities suggesting progression to dilated cardiomyopathy.

Other imaging modalities that can be useful for diagnosing myocarditis include cardiac magnetic resonance imaging (MRI) and nuclear imaging techniques. Cardiac MRI has the ability to depict functional, morphologic, and tissue abnormalities such as edema, hyperemia, fibrosis, and necrosis. Because of its high spatial resolution and improved diagnostic accuracy, some have proposed the use of MRI as a noninvasive alternative to endomyocardial biopsy.[48] Consensus criteria have been published to describe the indications for cardiac MRI and to set forth diagnostic criteria based on MRI findings.[49] Nuclear imaging techniques can also detect the extent of myocardial inflammation and myocyte necrosis.[50] However, these techniques are not routinely used in the diagnosis of acute myocarditis because of limited specificity, spatial resolution, and radiation exposure.

Endomyocardial biopsy remains the gold standard for establishing the diagnosis of myocarditis, despite its limited sensitivity and specificity. In a large series of patients with suspected myocarditis, only 38% had positive biopsy results using the Dallas histopathologic criteria.[41] In general, biopsies performed within the first weeks of symptom onset have a higher yield than biopsies performed later in the course. Immunohistochemical stains and molecular techniques can also improve diagnostic sensitivity and enable identification of potential pathogens. However, in many cases the risks of biopsy outweigh the potential clinical and diagnostic benefits. The American Heart Association, American College of Cardiology, and European Society of Cardiology have issued a joint statement on the limited indications for and diagnostic role of endomyocardial biopsy in acute myocarditis.[51]

Specific diagnosis of infectious etiologies can be made in several ways. Pathogens can be isolated directly from myocardial tissue by culture or visualized using specific stains, or nucleic acid can be amplified using molecular techniques. Indirect associations can be made by detection of likely pathogens from other tissues or body fluids, such as the nasopharynx, throat, stool, or blood. In the acute setting, blood can be obtained for PCR analysis for common viruses such as enteroviruses, adenovirus, cytomegalovirus, and Epstein-Barr virus. Serologic assays showing a fourfold or greater rise of titers in paired sera, or a single positive immunoglobulin M assay, can also implicate specific infectious causes. Epidemiologic clues such as the season and geographic location may help narrow the differential diagnosis and focus the diagnostic evaluation.

Management

Supportive care is a key component of the initial management of patients with myocarditis. Although patients with mild myocarditis often recover with minimal intervention, those with heart failure or fulminant disease may require management in an intensive care setting. If congestive heart failure is present, patients should be managed according to established clinical guidelines. The American College of Cardiology Foundation and American Heart Association guidelines recommend routine use of angiotensin-converting enzyme inhibitors and β-blockers for patients with symptomatic heart failure and reduced left ventricular ejection fraction.[52] Diuretics and salt restriction are also indicated for patients with fluid retention and edema. Implantable cardioverter-defibrillators, pacemakers, and pharmacologic therapies may be indicated for patients with arrhythmias. Digoxin should be used with caution in patients with myocarditis owing to its association with increased myocardial injury and mortality in murine models.[53] Retrospective studies and case reports have demonstrated the benefits of ventricular assist devices and extracorporeal membrane oxygenation in pediatric patients for whom they are necessary.[54-56]

Specific infectious agents such as bacteria, fungi, or parasites should be treated with appropriate antimicrobial therapy. Diphtheric myocarditis should be treated with a combination of antitoxin and antibiotics. Clinical trials have not been performed to evaluate the efficacy of specific antiviral agents for viral myocarditis. However, if a treatable viral cause of myocarditis is established, antiviral therapy seems prudent.

Many studies have been performed to evaluate immune-modulating agents, including systemic corticosteroids, immune globulin intravenous (IGIV), interferons, and other immunosuppressive drugs for treatment of myocarditis; however, results remain controversial. The high incidence of spontaneous recovery after myocarditis necessitates that studies include a control group for accurate analysis of efficacy. In one of the largest trials of immunosuppressive agents, the Myocarditis Treatment Trial, 111 adults with biopsy-proven myocarditis were randomized to receive placebo or an immunosuppressive regimen consisting of prednisone plus either cyclosporine or azathioprine. No differences in mortality were found between the groups, and improvement in left ventricular function was identical at 28-week follow-up.[57] Another controlled trial evaluating prednisone (60 mg daily) for the treatment of unexplained dilated cardiomyopathy in adults showed initial improvement in left ventricular ejection fraction at 3 months of follow-up, but the benefit was not sustained at 6 or 9 months.[58] A meta-analysis, performed to review the use of immunosuppressive regimens for acute myocarditis in children, concluded that immunosuppressive therapy does not significantly improve pediatric outcomes.[59] For these reasons, and because of similar findings in other studies, immunosuppression should not be used routinely in the treatment of myocarditis.

The use of IGIV as therapy for myocarditis also has been controversial. A single retrospective cohort study of 21 children demonstrated high-dose IGIV (2 g/kg) was associated with improved left ventricular function and trends toward improved survival compared with historical controls.[60] However, a randomized controlled study in adults,[61] larger noncontrolled studies in children,[62,63] a systematic literature review,[64] and analyses of large national databases[23,24] have not demonstrated a consistent clinical benefit. Thus, the benefits of IGIV have not been fully substantiated, despite its widespread use in patients with pediatric myocarditis.[23,24] Interferon α and interferon β have demonstrated benefit in patients with dilated cardiomyopathy and myocarditis in small, single-center trials. However, larger trials are needed to confirm these findings.[65]

Complications

Complications of myocarditis include congestive heart failure, arrhythmias, cardiac rupture, sudden death, and progression to dilated cardiomyopathy. A large prospective study of 174 patients with biopsy-proven myocarditis demonstrated that biventricular dysfunction on echocardiography was the main predictor of mortality or need for heart transplantation.[66] Echocardiographic evidence of decreased ejection fraction (<30%), shortening fractions (<15%), left ventricular dilation, and moderate to severe mitral regurgitation also predicted progression to unremitting severe cardiac failure in a small pediatric study.[67] Other predictors of mortality include clinical signs and symptoms of heart failure, longer duration of symptoms, and younger age at presentation.[66] In a retrospective analysis of 41 children with myocarditis, 66% made a complete recovery, 10% had incomplete recovery, 12% died, and 12% underwent cardiac transplantation. Although medical management of this cohort varied, therapy was not significantly associated with patient outcomes.[62]

Prevention

Prevention of acute infectious myocarditis relies on prevention of underlying microbial causes. Hand hygiene, avoidance of fomites, and disinfection of surfaces are important measures to prevent transmission of many viral causes of myocarditis. Adherence to the standard immunization schedule, including administration of the seasonal influenza vaccine, can also prevent infections by specific pathogens.

Key Points

Epidemiology, Clinical Features, Diagnosis, and Management of Myocarditis

Epidemiology

- Viruses are the most common causes of myocarditis: enterovirus, adenovirus, parvovirus B19, human immunodeficiency virus, Epstein-Barr virus, cytomegalovirus, and other herpesviruses

- *Trypanosoma cruzi* (Chagas disease) is the most common cause in Central and South America

Clinical Features

- Clinical syndromes include subclinical cardiac dysfunction, heart failure, chest pain mimicking myocardial infarction, arrhythmias, and sudden death

- Symptoms often are nonspecific in children and include respiratory distress, feeding difficulties, chest pain, and fever in the setting of a viral prodrome

- Physical examination can show signs of heart failure such as tachycardia, hypotension, poor peripheral perfusion, hepatomegaly, and edema

Diagnosis

- The initial evaluation should include chest radiography, electrocardiography, and echocardiography

- Endomyocardial biopsy or cardiac magnetic resonance imaging can be useful in certain cases

- Specific diagnosis often is made by polymerase chain reaction, viral culture, and serologic tests

Management

- Supportive care is the mainstay of therapy
- Evidence is lacking to support routine use of immunosuppressants
- Immune globulin intravenous (IGIV) is administered commonly. Although a small retrospective pediatric study demonstrated benefit of IGIV, larger studies to date have not substantiated benefit.

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39

Pericarditis

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Pericarditis is inflammation of the pericardium and proximal great vessels. The etiologies of pericarditis are diverse and include infectious and noninfectious causes. Pericarditis may be acute, subacute, chronic, or recurrent in presentation. It may be the sole manifestation of a disease or part of a multisystem disorder. Pericarditis can manifest as cardiac tamponade with a fulminant, life-threatening process, as constrictive pericarditis from chronic disease, or as the incidental finding of an asymptomatic pericardial effusion. The European Society of Cardiology has published extensive guidelines on the diagnosis and management of pericardial diseases, which were updated in 2013.[1,2]

Etiology

Infectious pericarditis can be classified as benign, purulent, or granulomatous. Benign pericarditis is caused by viral infection, postinfectious, or postpericardiotomy syndromes; purulent pericarditis is caused by bacterial infection; and granulomatous pericarditis is caused by *Mycobacterium tuberculosis* and, occasionally, by fungal infection. Although the etiologic distribution varies among studies, in developed countries, upward of 80% of cases are idiopathic.[3] Noninfectious causes include neoplasia, uremia, hypothyroidism, cardiac injury, radiation, drug hypersensitivity, and autoimmune and autoinflammatory diseases.

Viral pericarditis commonly is associated with concurrent myocarditis, and its presentation ranges from subclinical infection to fulminant disease with severe hemodynamic manifestations. A viral etiology is assumed if a pericardial effusion is nonpurulent and if spontaneous resolution occurs. Enteroviruses, especially the coxsackieviruses, are considered the most common causes of viral pericarditis. Other viruses that are implicated commonly include adenovirus, parvovirus B19, human immunodeficiency virus (HIV), Epstein-Barr virus, cytomegalovirus, and other herpesviruses. Less commonly, influenza A and B, hepatitis B and C, mumps, and lymphocytic choriomeningitis are reported. Cytomegalovirus is an important cause of pericarditis in immunocompromised and HIV-infected people.[4]

Purulent pericarditis occurs when bacteria invade the pericardium as a result of bacteremia, contiguous spread from an intrathoracic infection, or direct inoculation from trauma or surgery. *Staphylococcus aureus* is the most common cause of purulent pericarditis, accounting for up to 44% of cases in children (Table 39.1).[5] Staphylococcal pericarditis often coincides with infection at other sites, including osteomyelitis, septic arthritis, skin infections, and pneumonia.[5–9] Historically, *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, and *Neisseria meningitidis* also have been important causes of purulent pericarditis.[10–12] However, the incidence of invasive disease caused by these pathogens has declined in the postvaccine era. Other bacteria, including group A streptococci,[13] the *Streptococcus milleri* group,[14] *Salmonella* species, *Pseudomonas aeruginosa*, and other gram-negative bacilli, are implicated less commonly.[15] Rarely, anaerobic bacteria can cause pericarditis, either by hematogenous seeding (especially *Bacteroides fragilis*),[16] contiguous spread (especially pulmonary actinomycosis),[17] or as part of a polymicrobial infection.[16] HIV infection is an important predisposing factor worldwide for pericarditis, especially for bacterial and mycobacterial etiologies.[18]

TABLE 39.1

Causes of 163 Cases of Purulent Pericarditis, 1950–1977

Causative Organism	Number of Isolates (%)
Staphylococcus aureus	72 (44)
Haemophilus influenzae	35 (22)
Neisseria meningitidis	14 (9)

Streptococcus pneumoniae	9 (6)
Salmonella species	4 (3)
Escherichia coli	3 (2)
Other[a]	7 (5)
Unknown	17 (10)

[a] Includes isolates of *Klebsiella* spp., *Streptococcus pyogenes*, "Paracolon" spp., *Pseudomonas aeruginosa, Staphylococcus epidermidis, Bacteroides* spp., anaerobic streptococci, singly or in combination.

Data from Feldman WE. Bacterial etiology and mortality of purulent pericarditis in pediatric patients: a review of 162 cases. Am J Dis Child 1979;133:641.

Pericarditis caused by *M. tuberculosis* occurs in approximately 1% of cases of tuberculosis, either from lymphatic or bacteremic seeding or by direct extension from a pulmonary focus. Although an uncommon cause of pericarditis in developed countries, *M. tuberculosis* causes up to 70% of cases of pericarditis in Africa and other endemic regions.[19] Tuberculosis is also the most common cause of pericarditis in HIV-infected patients, accounting for 85% of cases.[20]

Pericarditis is occasionally caused by fungal infection, usually in the setting of surgery, instrumentation, neutropenia, or other immunosuppression. Fungi associated with pericarditis include *Candida, Aspergillus, Cryptococcus, Coccidioides, Histoplasma,* and *Blastomyces* spp. Less common infectious causes of pericarditis include *Mycoplasma* spp., *Ureaplasma urealyticum,* Rickettsiae, *Borrelia burgdorferi, Entamoeba histolytica, Toxoplasma gondii,* and *Toxocara canis.*

Epidemiology

The exact incidence and prevalence of pericarditis are unknown because epidemiologic studies are lacking. However, in a large series of children presenting to an emergency department with chest pain, 0.1% to 0.2% had pericarditis.[21] Approximately one third of pediatric pericarditis cases are classified as idiopathic or viral.[22] Idiopathic pericarditis is more common in adults than in children, and the incidence increases during adolescence.[23] In contrast, purulent pericarditis was once considered a disease of infancy and young childhood. However, with the advent of antibiotics and vaccines, the age distribution has shifted and the incidence has decreased substantially.[15] Bacteria are now rare causes of pericarditis, accounting for 5% or less of all pediatric cases.[22]

Tuberculous pericarditis is the most common cause of pericarditis in regions where *M. tuberculosis* is endemic. In developed countries, tuberculosis accounts for only 4% of cases of pericarditis and is more common among HIV-infected patients and immigrants from high-risk regions.[24]

Pathogenesis

The pericardium is a fibroserous sac that encompasses the heart and consists of an inner layer, the visceral pericardium, and an outer layer, the parietal pericardium. The visceral pericardium covers the surface of the myocardium with mesothelial cells, which reflect onto the parietal pericardium to form an enclosed sac containing pericardial fluid. The parietal pericardium contains a dense fibrous outer membrane that lines the mediastinal structures and attaches to the sternum, diaphragm, and adventitia of the great vessels. Both layers are 1 to 2 mm thick, with a space between them that contains 10 to 15 mL of pericardial fluid in healthy children and 15 to 35 mL in adults. The pericardium has independent blood supply from the internal mammary arteries and innervation from the vagus nerve. Primary functions of the pericardium are to provide the heart with structural support, lubrication by pericardial fluid, and protection from infection at adjacent sites.

In the setting of infection or acute injury, the pericardial response is nonspecific and limited to exudation of inflammatory cells, fluid, or fibrin. This process may result in a spectrum of disease ranging from dry pericarditis, to pericardial effusion with or without hemodynamic compromise, to fibrosis that may progress to constrictive or effusive-constrictive pericarditis. In effusive pericarditis, the accumulation of fluid within the pericardial sac may be tolerated if the effusion is small or if the rate of fluid accumulation is slow. However, large or rapid increases in fluid secretion can exceed the maximal resorptive capacity of the pericardium. When this occurs, compression of the cardiac chambers can acutely impair diastolic filling, leading to tamponade and death. Constrictive pericarditis, in contrast, generally is a late complication of chronic pericardial inflammation. Proliferation of fibrous tissue, neovascularization, and scarring result in a loss of pericardial elasticity and impaired cardiac filling. The combination of pericardial effusion under the pressure of a fibrosed pericardium is known as *effusive-constrictive pericarditis*.

Viral pericarditis typically manifests as dry or effusive pericarditis with a benign, self-limited course. Cardiotropic viruses can spread hematogenously and directly infect the pericardium and myocardium. Pericarditis can be the sole manifestation of viral infection or part of disseminated, multiorgan disease. Although pericarditis typically occurs as a single episode, up to 36% of pediatric patients experience recurrences.[25] The pathogenesis of recurrences is incompletely understood, but immunologic mechanisms are thought to be involved. Patients with recurrent pericarditis have increased rates of circulating antiheart, anti-intercalated disk, and antinuclear antibodies, which support the role of autoimmunity in this process.[26] Autoinflammatory diseases, especially familial Mediterranean fever and tumor necrosis factor receptor−associated periodic syndrome also have known associations with recurrent pericarditis and may underlie the pathogenesis in a minority of patients.

Purulent pericarditis arises from contiguous extension of an adjacent infection, hematogenous seeding, or direct inoculation from trauma or surgery. Contiguous extension of a pulmonary or pleural infection is an important cause of bacterial pericarditis, especially of pneumococcal and staphylococcal etiologies. Less common origins of bacterial pericarditis include suppurative mediastinal, subdiaphragmatic, and intracardiac infections. Bacteria also can be inoculated into the pericardium by hematogenous seeding, which commonly is the pathogenesis of *S. aureus* pericarditis. Additionally, intrathoracic surgical procedures can be complicated by purulent pericarditis, usually in the setting of sternal wound infection with osteomyelitis and mediastinitis. In these cases, *S. aureus, S. epidermidis, Candida* species, and nosocomial gram-negative bacilli usually are responsible.[8]

Tuberculous pericarditis can result from lymphatic spread, hematogenous (miliary) seeding, or rarely by direct extension of pulmonary disease. Granulomas containing *M. tuberculosis* initially develop in the pericardium and are followed by serous or serosanguineous effusion containing lymphocytes and monocytes. Healing of tuberculous pericarditis results in deposition of fibrin and collagen, which often leads to constrictive or effusive-constrictive pericarditis.

Clinical Manifestations

Pericarditis causes a variable spectrum of clinical manifestations. The most common presenting symptom is chest pain, which is reported in nearly all pediatric cases.[25] Pericardial chest pain may be felt over the entire precordium, to the left side over the trapezius ridge, and over the scapula. The pain may radiate down the arm and may be aggravated by movement. Chest pain generally is worse when supine and relieved when sitting forward. It is more common in acute infectious pericarditis than in chronic, indolent forms. Pain may be unrecognized in young children, who are more likely to present with irritability and respiratory distress.

Other symptoms of pericarditis in children include fever, respiratory, and gastrointestinal complaints. Fever is present in most children with pericarditis, although it is more common in those with purulent etiologies.[27] Respiratory symptoms include coughing, dyspnea, and exercise intolerance. Young children may additionally have tachypnea, use of accessory muscles of respiration, and grunting expiratory sounds as they splint the thoracic cavity. Gastrointestinal symptoms of pericarditis include abdominal pain, vomiting, and poor feeding. Because pericarditis frequently follows an upper respiratory tract infection, a preceding febrile or respiratory tract illness should alert clinicians to consider the diagnosis.

Examination of the heart can reveal tachycardia and muffled heart sounds caused by the surrounding pericardial effusion. A pericardial friction rub can be audible, especially when the effusion is small. Friction rubs are best heard during deep inspiration when a patient is kneeling or in the knee-chest position, leaning forward. Friction rub typically is a to-and-fro, high-pitched, loud, rasping sound heard throughout the cardiac cycle or limited to systole.

Clinical manifestations of tamponade include sinus tachycardia, elevated jugular venous pressure, peripheral vasoconstriction, reduced arterial pulse pressure, and pulsus paradoxus. Pulsus paradoxus represents a drop of more than 10 mm Hg in systolic blood pressure during inspiration due to decreased venous return to the heart. Other findings on examination of patients with pericarditis may include the Kussmaul sign (a rise or failure to fall of jugular venous pressure with inspiration) and the Beck triad (hypotension, muffled heart sounds, and elevated jugular venous pressure).

Differential Diagnosis

Chest pain and fever occur with pneumonia, empyema, myocarditis, and pleuritis. Although rare in children, myocardial infarction can also mimic symptoms of pericarditis. The differential diagnosis of pericardial effusion includes many noninfectious causes, most notably neoplasia, metabolic disease, collagen vascular disease, other systemic inflammatory disorders, trauma, irradiation, and drug hypersensitivity. Postpericardiotomy syndrome also is an important cause of pericardial effusion in the 6 weeks after cardiac surgery.[28]

Laboratory Findings and Diagnosis

The diagnosis of pericarditis is made on the basis of history, physical examination, and imaging studies. All patients with suspected pericarditis should undergo chest radiography, electrocardiography (ECG), and echocardiography.[1] The specific cause of pericarditis is best determined by direct examination of the pericardium or pericardial fluid. Analysis of fluid for complete cell count, glucose level, lactate dehydrogenase, and protein concentration is useful to support likely causes. Common laboratory findings include systemic leukocytosis and elevated acute phase reactants. Troponin I also can be elevated in children with pericarditis or myopericarditis.[29,30]

Chest radiography and ECG are important components of the initial evaluation. On chest radiograph, pericardial effusion causes an enlarged cardiac silhouette that is often globular in shape. The effusion can cause an epicardial “fat pad” sign on lateral views, which is a widened space anterior to the heart between the epicardial and the anterior mediastinal fat. Concomitant findings of pneumonia or findings suspicious for tuberculosis can be helpful etiologic clues. Typical ECG features of pericarditis include generalized ST elevation without reciprocal ST depression, except in leads V_1 and aVR. A few days into illness, ST segments return to baseline and T waves may flatten or invert. Low-voltage QRS complexes may be evident as a result of dampening of electrical activity by the pericardial effusion. Most ECG results normalize with resolution of disease, although T-wave abnormalities can persist.

Echocardiography is the most valuable tool for diagnosis and assessment of the severity of pericarditis. Echocardiography can differentiate between pericarditis, myocarditis, and endocarditis and can also assess for tamponade physiology. When pericardial fluid is present, both M-mode and two-dimensional echocardiography demonstrate a sonolucent space between the two layers of pericardium. M-mode is the more sensitive procedure and can reliably estimate the volume of pericardial effusion. Computed tomography (CT) and magnetic resonance imaging (MRI) are second-line imaging techniques that should be considered in scenarios with complex clinical presentation or inconclusive echocardiographic findings. CT and MRI provide superior anatomic resolution and characterization of inflammation, calcification, constriction, and intracardiac and extracardiac masses. The American Society for Echocardiography has published extensive recommendations to guide the use of multimodality cardiac imaging in patients with pericardial diseases.[31]

Microbiologic diagnosis of pericarditis is best established by direct examination of pericardial fluid or tissue. Standard diagnostic evaluation should include Gram, acid-fast, and fungal stains and cultures for bacteria, viruses, mycobacteria, and fungi. Special attention to rapid transport under anaerobic conditions is necessary to optimize recovery of anaerobic bacteria. Blood cultures should also be obtained and are frequently positive in patients with purulent pericarditis. If pericarditis results from extension from a contiguous focus, cultures of sputum, pleural fluid, or other foci may identify the pathogen.

Viral causes of pericarditis may be determined by culture, rapid antigen tests, serologic tests, and molecular genetic techniques. In general, a combination of these techniques is implemented to maximize diagnostic yield. Tissue culture should be inoculated for recovery of viruses from pericardial fluid and other foci of infection. Viruses detected in the respiratory tract, throat, or stool are often considered the likely cause of concomitant pericarditis. Paired serologic testing can also be helpful in the identification of certain viral etiologies. Because HIV remains an important cause of pericarditis, testing with a fourth generation HIV-1/2 antigen/antibody combination immunoassay is often prudent. Unfortunately, traditional diagnostic approaches have relatively low yield for detection of viral pathogens.[3,32] Although molecular techniques can increase sensitivity,[33,34] the clinical impact of viral polymerase chain reaction (PCR) testing is unclear because of the lack of specific antiviral therapeutics and the tendency for idiopathic cases to self-resolve. PCR may be helpful for purulent or constrictive pericarditis when bacterial or mycobacterial etiologies are suspected but cultures remain sterile.[33]

Recovery of mycobacteria or fungi is uncommon, but appropriate cultures for these agents should be performed in cases of granulomatous, constrictive, or effusive-constrictive pericarditis. When these agents are suspected, biopsy of the pericardium for histologic examination and culture has a higher yield than direct stain or culture of pericardial fluid alone. If tuberculous pericarditis is suspected, a tuberculin skin test or an interferon γ release assay also should be performed. PCR for *M. tuberculosis* performed on pericardial fluid can offer the advantage of rapid diagnosis, although sensitivity ranges from 30% to 64%.[35–37] Pericardial adenosine deaminase, interferon γ, and lysozyme are ancillary tests that may aid in the diagnosis.[37,38] Current guidelines recommend incorporating these nonspecific biomarkers into the evaluation when tuberculous pericarditis is suspected.[1]

Management

Patients who have a small pericardial effusion of apparent viral etiology may be conservatively managed with close monitoring, bed rest, and nonsteroidal anti-inflammatory drugs. However, the presence of a large effusion with tamponade or significant hemodynamic compromise requires immediate evacuation of fluid by pericardiocentesis or open drainage. Patients with suspected bacterial or fungal etiologies also should undergo prompt pericardiocentesis. The combination of pericardiocentesis and antimicrobial therapy in purulent pericarditis substantially improves mortality compared with antimicrobial therapy alone.[5] Although not routinely necessary, creation of a pericardial "window" may allow drainage of thick or rapidly accumulating fluid. Case series also suggest that instillation of a fibrinolytic agent may help liquefy pericardial exudate in cases of incomplete evacuation.[39] Pericardiectomy, the definitive procedure to remove the pericardium, is indicated for persistent or hemodynamically unstable restrictive pericarditis.[1] Although pediatric data are limited, case series suggest that pericardiectomy can be successfully performed in children with recalcitrant pericardial disease.[40,41]

Therapy with broad-spectrum antimicrobial agents should be initiated empirically if purulent pericarditis is suspected (Table 39.2). Bacterial pericarditis usually is treated with parenteral antimicrobial agents for 3 to 4 weeks. For areas with high rates of methicillin-resistant *S. aureus*, empiric therapy for purulent pericarditis should include vancomycin. Addition of a third-generation cephalosporin provides coverage for *S. pneumoniae*, *H. influenzae*, and *N. meningitidis*. Fungal pericarditis caused by disseminated candidiasis, aspergillosis, or dimorphic fungi *(Histoplasma*, *Coccidioides*, or *Blastomyces* spp.*)* usually requires prolonged antifungal treatment (see chapters on specific pathogens). Empiric antituberculous therapy using three or four drugs should be initiated if tuberculous pericarditis is suspected. Corticosteroids also should be considered, although the impact on outcomes is unclear; a large multicenter trial to assess corticosteroid effectiveness is underway.[42]

TABLE 39.2

Antimicrobial Therapy of Major Causes of Pericarditis

Causative Agent	**Antimicrobial Agent**	**Dosage (mg/kg/day)**
Enterovirus and other viruses	None[a]	—
Empiric therapy for purulent pericarditis	Vancomycin *or*	60
	Nafcillin[b] *or*	200
	Oxacillin[b] *plus*	200
	Cefotaxime *or*	200
	Ceftriaxone	100 (daily)
Therapy when agent is confirmed		
Staphylococcus aureus or *S. epidermidis*	Oxacillin *or*	200

(susceptible to methicillin)	Nafcillin	200
S. aureus or *S. epidermidis* (resistant to methicillin)	Vancomycin[c]	60
Haemophilus influenzae	Ampicillin (if susceptible) *or*	200–300
	Cefotaxime *or*	150
	Ceftriaxone	75 (daily)
Streptococcus pneumoniae (susceptible to penicillin) or *S. pyogenes*	Penicillin G	200,000–300,000 units
S. pneumoniae (intermediate to penicillin)	Cefotaxime *or* Ceftriaxone	300 mg (cefotaxime), 100 mg (ceftriaxone)
S. pneumoniae (highly resistant to penicillin)	Vancomycin	60
Mycobacterium tuberculosis[d]	Isoniazid	10–15 for 6 mo
	+	
	Rifampin	10–20 for 6 mo
	+	
	Pyrazinamide	30–40 for 2 mo
	+	
	Ethambutol	15–25 until susceptibility studies are available

[a] Cytomegalovirus may respond to ganciclovir or valganciclovir.

[b] Nafcillin or oxacillin should only be used if community rates of methicillin-resistant *Staphylococcus aureus* (MRSA) are low.

[c] Linezolid would be an alternative; some community-associated MRSA are susceptible to clindamycin.

[d] Addition of corticosteroids to antibiotic regimen can be considered (e.g., prednisone 1 mg/kg/day for 6–8 wk with taper). In communities where isoniazid-resistant *Mycobacterium tuberculosis* has been encountered, a four-drug initial treatment is recommended.

Complications

The major long-term complication of pericarditis is thickening and stiffening of the pericardial membrane leading to constrictive pericarditis. Although constriction is a rare complication of viral or idiopathic pericarditis, the incidence is much higher in patients with purulent, tuberculous, or neoplastic etiologies.[24] Pericardiectomy is the only definitive treatment for permanent constrictive pericarditis.[1] The most important negative prognostic factor after pericardiectomy is poor preoperative functional status.[41]

Recurrences complicate up to one third of cases of acute pericarditis. Conventional management in adults consists of nonsteroidal anti-inflammatory drugs for 10 to 14 days, colchicine for 6 months, and low-dose steroids for nonresponsive disease.[2]

Although the efficacy of colchicine in preventing recurrences is well established in adults,[43,44] controlled studies of its use in children are not yet available. Case series have described the benefits of immunomodulators[45–47] and immune globulin intravenous[48] in pediatric cases refractory to conventional therapy.

Prognosis

Historically, mortality rates of untreated purulent pericarditis have approached 100%. However, the combination of antimicrobial therapy and pericardial drainage has substantially improved patient outcomes. Of 162 children with purulent pericarditis reported in 1979,[5] mortality was 22% in children who had both antimicrobial therapy and drainage compared with 82% in those who received antimicrobial therapy alone. Young age and infection with *S. aureus* were independent risk factors for poor prognosis. More recent studies have reported improved patient outcomes with much lower mortality rates in the current era. In a 1994 report, 42 of 43 children with purulent pericarditis treated with both antimicrobial agents and drainage recovered completely.[7]

Key Points

Epidemiology, Clinical Features, Diagnosis, and Management of Pericarditis

Epidemiology

- One third of cases are idiopathic.
- Viruses are the most commonly proven infectious etiologies.
- Purulent pericarditis is rare in the postantibiotic era (≤5% of cases).
- *Staphylococcus aureus* is the most common bacterial etiology.
- Tuberculosis is the most common etiology in endemic regions and in HIV-infected people.

Clinical Features

- Symptoms include fever, chest pain, and shortness of breath.
- Physical examination findings include pericardial friction rub, muffled heart sounds, tachycardia, and respiratory distress.
- Signs of tamponade include tachycardia, hypotension, narrowed pulse pressure, elevated jugular venous pressure, and pulsus paradoxus.

Diagnosis

- The initial evaluation should include chest radiography, electrocardiography, and echocardiography.
- Specific diagnosis can be made by analysis of pericardial fluid or tissue with stains, polymerase chain reaction (PCR) testing, and cultures for viruses, bacteria, mycobacteria, and fungi.
- PCR, serologic, and rapid antigen tests improve diagnostic yield.

Management

- Viral or idiopathic pericarditis is managed by supportive care and nonsteroidal anti-inflammatory drugs.
- Purulent pericarditis requires both pericardial drainage and antimicrobial therapy.
    - Empiric antibiotics should include vancomycin because of the prevalence of methicillin-resistant *Staphylococcus aureus* plus a third-generation IV cephalosporin.
    - Duration of therapy with IV antibiotics usually is 3 to 4 weeks
- Cardiac tamponade requires emergent pericardial drainage to

prevent progression to obstructive shock and death.

- Pericardiectomy is indicated for persistent or hemodynamically unstable restrictive pericarditis.

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F

Central Nervous System Infections

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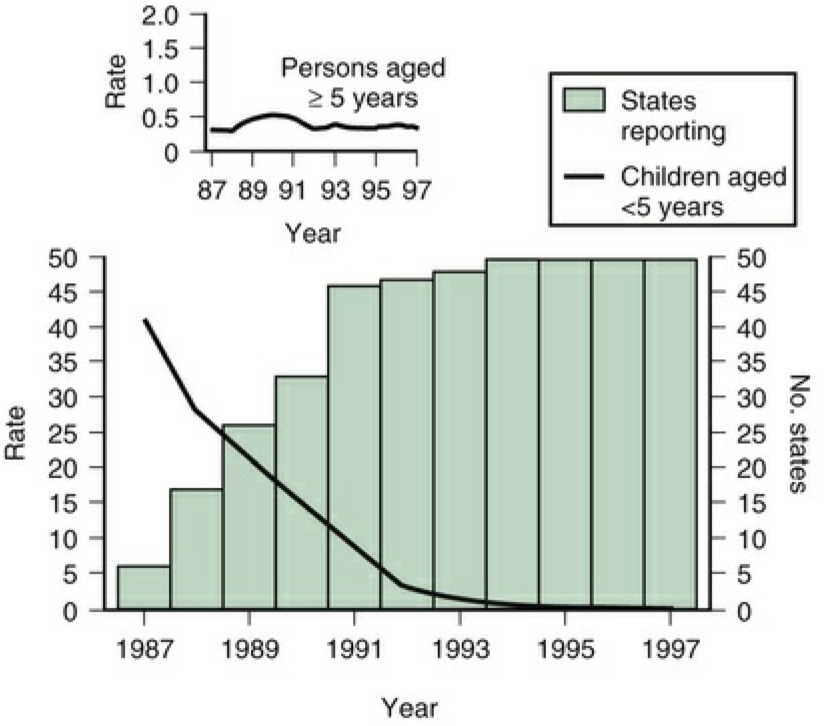
Acute Bacterial Meningitis Beyond the Neonatal Period

Suresh Kumar Panuganti, Simon Nadel

Etiologic Agents and Epidemiology

In otherwise healthy children, the three most common organisms causing hematogenously acquired acute bacterial meningitis worldwide are *Streptococcus pneumoniae, Neisseria meningitidis,* and *Haemophilus influenzae* type b (Hib). Previously, Hib accounted for up to 48% of all bacterial meningitis cases in United States[1]; however, the introduction of the Hib conjugate vaccination program led to a dramatic reduction in the incidence of Hib meningitis. In surveillance studies conducted by the Centers for Disease Control and Prevention (CDC), the incidence of Hib disease declined by 95% from 1987 to 1993 in children younger than 5 years (41 cases per 100,000 in 1987 to 2 per 100,000 in 1993) (Fig. 40.1).[2] Similar data from 1997 indicated a further decline to 1.3 cases per 100,000,[3] and there was a further decline to 0.11 cases per 100,000 in 2008.[4] The incidence also has decreased markedly in other areas of the world where Hib conjugate vaccines have been implemented for universal use in infants.[5,6] Currently, Hib accounts for only 7% of meningitis cases in the US, predominantly in unvaccinated adults[1] and in children who have not completed the primary immunization series.[4,7]



* Per 100,000 children age <5 years

† Per 100,000 persons age ≥5 years

§ Because of the low number of states reporting surveillance data during 1987–1990, rates for those years were race-adjusted using the 1990 U.S. population

FIGURE 40.1 Incidence of invasive *Haemophilus influenzae* disease among children younger than 5 years and the number of states reporting *H. influenzae* surveillance data to the National Notifiable Diseases Surveillance System, 1987–1997, United States. Insert represents the incidence of invasive *H. influenzae* disease among persons 5 years or older. Rate is expressed as cases per 100,000 population. (From Centers for Disease Control and Prevention. Progress toward eliminating *Haemophilus influenzae* type b disease among infants and children—United States, 1987–1997. MMWR 1998;47:993.)

Pneumococcal and meningococcal (and previously *Haemophilus*) meningitis occurred more commonly during the winter. In 1994–1999, the annualized incidence of *S. pneumoniae* meningitis in children aged <2 years in the US was 7.7 per 100,000,[8] and 7 (4, 6B, 9, 14, 18F, 19F, and 23F) of >90 pneumococcal serotypes accounted for >80% of invasive disease in children in the US and other developed countries. Serotypes 5 and 1 also were prevalent in developing countries.[9] The incidence of invasive disease caused by vaccine serotypes of *S. pneumoniae* fell by >95% after the implementation of universal 7-valent pneumococcal conjugate vaccine (PCV7) in US infants in 2000,[10] from 80 cases per 100,000 population to <1 case per 100,000 by 2007.[11] The rate of hospitalizations for pneumococcal meningitis in infants decreased by 66%.[8] Between 2000 and 2010, the incidence of disease caused by nonvaccine serotype 19A increased, with many isolates resistant to β-lactam antibiotics, including penicillin and third-generation cephalosporins.[12,13] Universal implementation of PCV13 (including serotypes 1, 3, 5, 6B, 7F, and 19a) has led to decrease in vaccine serotype invasive disease and only modest further decrease in meningitis cases.[14]

Six serogroups of *N. meningitidis* are responsible for severe disease and meningitis: serogroups A, B, C, X, Y, and W-135.[15] Infection with *N. meningitidis* can be either epidemic or endemic,[16] and although most cases in the US are sporadic,[1] *N. meningitidis* is the only bacterium that can cause meningitis outbreaks in the US.[15] Throughout America and Europe, serogroups B, C, W, and Y account for most cases of meningococcal meningitis, and serogroup B is the leading cause of endemic meningitis in developed countries overall.[1,15,17] The annual incidence of *N. meningitidis* meningitis in children younger than 5 years was approximately 4 to 5 cases per 100,000 in 1980. The overall incidence of meningococcal disease had begun to fall in 2005 when quadrivalent (A/C/Y/W-135) polysaccharide-protein meningococcal conjugate vaccine (MCV4) was licensed and recommended in the US for adolescents beginning at 11 to 12 years of age and for persons 2 through 54 years of age who have an increased risk for invasive meningococcal disease.[18,19] During 2005–2011, an estimated 800 to 1200 cases of meningococcal disease occurred annually (0.3 cases per 100,000), with a further decline to 564 cases in 2013 (0.18 cases per 100,000). Since 2005, declines have occurred among all age groups and in all vaccine-associated serogroups.[20] In addition, incidence of disease attributable to serogroup B, a serogroup not included in the vaccine, declined for reasons that are not known. Although disease incidence is at a historical low, the overall case-fatality rate remains at 10% to 15%, and 11% to 19% of survivors have long-term sequelae.[20] A novel protein and outer membrane vesicle–based vaccine against serogroup B meningococcus has recently been licensed in Europe. This vaccine and a protein-based vaccine have been licensed in the US and recommended for use in specific people and settings (see Chapter 6).[21]

The epidemiology of bacterial meningitis in the United Kingdom has changed dramatically in the past two decades after the introduction of vaccines to control Hib, serogroup C meningococcus, and some types of pneumococcus. After implementation of serogroup C MCV (MenC vaccine) in 1999, there was an approximate 80% reduction in serogroup C disease within 2 years.[22] Serogroup B meningococcus is now the most common cause of bacterial meningitis (and septicemia) in children and young people 3 months or younger.[23] The incidence of invasive meningococcal disease in the UK since 2004–2005 is depicted in Fig. 40.2.[24]

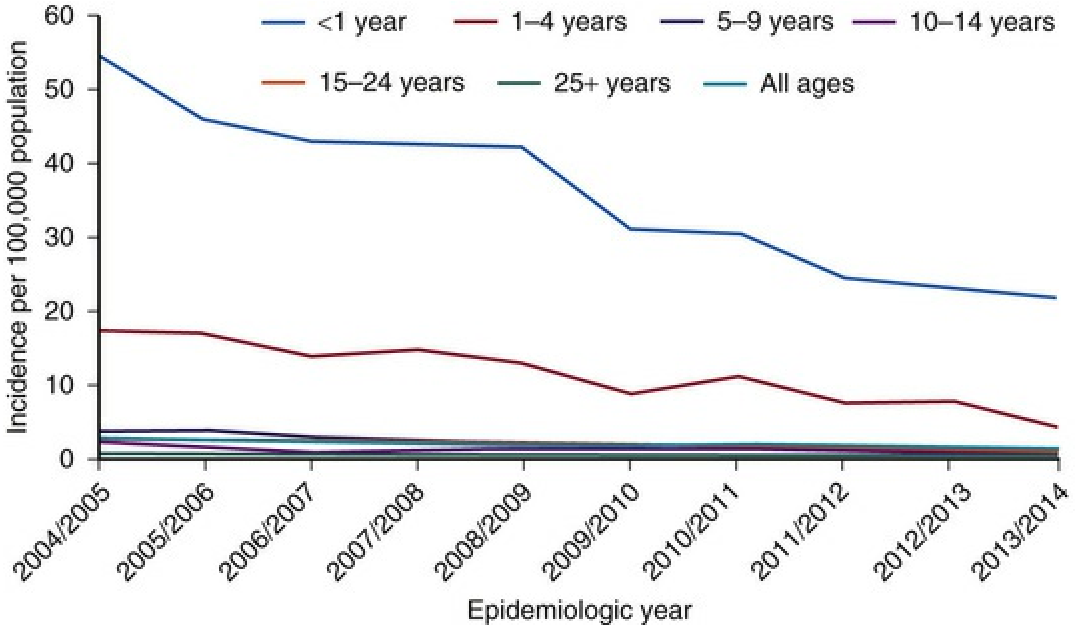


FIGURE 40.2 Incidence of invasive meningococcal infections in England and Wales by age group and epidemiologic year, 2004/05−2013/14.

Underlying conditions can be associated with increased risk for invasive infection, meningitis or infection due to particular pathogens, or both (Table 40.1). Children with a basilar skull or cribriform fracture and a cerebrospinal fluid (CSF) leak have greater risk for pneumococcal meningitis, as do children with asplenia (anatomic or functional) or human immunodeficiency virus (HIV) infection. Deficiencies in terminal components of complement lead to greater risk for meningococcal infection. Common causes of meningitis after penetrating head trauma or neurosurgery are *Staphylococcus aureus* and coagulase-negative staphylococci, streptococci, and gram-negative enteric bacilli, especially *Escherichia coli, Klebsiella* spp., and *Pseudomonas aeruginosa*. These organisms also are associated with meningitis related to a dermal sinus or embryopathy of the neurenteric canal. Nontypable *H. influenzae* meningitis is associated with immunoglobulin deficiencies, and *Listeria* meningitis with cellular immune defects; *Listeria* meningitis occurs occasionally in immunocompetent infants and children as well. *Salmonella* spp. rarely cause meningitis in immunocompetent children beyond early infancy. The presence of a ventriculoperitoneal shunt is a risk factor for meningitis and ventriculitis. Shunt contamination with gram-positive skin organisms at the time of surgery or subsequent tract infections, as well as ultra-abdominal contamination of ventriculoperitoneal shunts with gut organisms, can occur.

TABLE 40.1

Underlying Conditions and Organisms Commonly Associated With Bacterial Meningitis

Condition	Organism
Cerebrospinal fluid leak (otorrhea, rhinorrhea)	*Streptococcus pneumoniae, Haemophilus influenzae*
Dermal sinus tracts meningomyelocele	Staphylococci, gram-negative enteric bacilli, intestinal bacteria (related to site of defect)
Persistent complement deficiency	*Neisseria meningitidis*
Asplenia (anatomic or functional)	*S. pneumoniae, N. meningitidis, Salmonella* spp.
Renal transplantation, T-lymphocyte deficiency	*Listeria monocytogenes*
Otic fistula (stapes footplate, oval window; cochlear implant)	*S. pneumoniae*
Ventriculoperitoneal shunt	Staphylococci (coagulase-negative and *Staphylococcus aureus*), *S. pneumoniae, H. influenzae, N. meningitidis* (hematogenous), diphtheroids (e.g., contaminated shunt)
Antibody deficiency state (including HIV	*S. pneumoniae, N. meningitidis, H. influenzae* type b

infection)	
Penetrating trauma	Varies with nature and site of trauma (e.g., *Pasteurella multocida* after dog or cat bite, skin organisms after skull trauma, nasopharyngeal organisms after orbital or sinus trauma)
Surgery	Skin organisms, nosocomial pathogens

HIV, human immunodeficiency virus.

Isolation of an organism other than pneumococcus, meningococcus, or Hib or isolation of an unusual serotype or a vaccine-preventable organism in a vaccinated individual from the CSF of a child older than 2 months requires an explanation, with evaluation for unusual host susceptibility such as an anatomic abnormality or immunologic disorder.[25] Children with recurrent pneumococcal or meningococcal infections also should undergo thorough investigation, including neuroimaging and immunologic evaluation, with measurement of complement studies. Patients with cochlear implants, especially using a positioner device, have a >30-fold increased incidence of pneumococcal meningitis[26] and an increased risk for Hib meningitis.

Pathophysiology

Bacterial meningitis usually follows stepwise progression: bacterial colonization of the nasopharynx (or skin), mucosal invasion (or breach in skin barrier) leading to bloodstream infection, intravascular multiplication and passage through the blood-brain barrier, generation of inflammation within the subarachnoid space, and induction of neuronal and auditory cell damage.[27]

The three most common meningeal pathogens colonize the nasopharyngeal mucosa in 5% to 40% of children or adolescents at any given time; for Hib and *N. meningitidis,* fimbriae mediate adherence to epithelial cells; for *S. pneumoniae,* specialized surface components, such as surface adhesion proteins, may be important. These encapsulated organisms are able to evade local host defenses and either invade between epithelial cells (Hib) or pass through epithelial cells (*N. meningitidis*) to reach the subepithelial tissues, where the organisms can invade the vascular endothelium.[27] A viral upper respiratory tract infection can facilitate invasion by altering local tissue defenses. Increased hospitalization for invasive pneumococcal and meningococcal disease has been correlated with the viral respiratory season.[28,29] Intravascular replication leads to bacteremia and, with sufficient density of organisms, egress through the endothelium of the choroid plexus and cerebral capillaries into the ventricular fluid. A complex interplay between endothelial cells and microbial gene products appears to orchestrate the traversal of bacteria across the blood-brain barrier—transcellularly, paracellularly, or through infected phagocytes. For organisms that invade transcellularly, including *E. coli,* group B *Streptococcus*, and *S. pneumoniae,* the process is mediated by interactions with host receptors in the brain's microvascular endothelial cells.[30] For *N. meningitidis,* invasion is mediated by the outer membrane protein Opc invasin binding to human fibronectin to attach and invade brain endothelial cells.[31] Organisms multiply quickly and spread throughout the subarachnoid space because of the lack of intrinsic host defenses within the CSF. The host inflammatory response to bacteria leads to many of the alterations in central nervous system (CNS) function and in the CSF that are characteristic of bacterial meningitis.

Communications between mucosal surfaces or skin and CSF that result from trauma or congenital malformations can lead to direct invasion of the CNS by bacteria. A fracture through the cribriform plate (CSF rhinorrhea), paranasal sinuses, or temporal bone (CSF otorrhea) provides entrance for respiratory tract organisms into the CNS. Penetrating injuries of the skull by sharp objects (toys, teeth) in younger infants or children can precede bacterial meningitis. Bacteria also can reach the CNS through congenital defects, such as a dermoid sinus tract, meningomyelocele, or fistula through the stapes footplate, oval window, or cochlear aqueduct. These defects should be sought in patients with recurrent bacterial meningitis or meningitis due to unusual organisms.[32] Bacterial meningitis also can be a complication of neurosurgery, spinal anesthesia, or placement of a ventricular shunt or external ventriculostomy device (see Table 40.1).[33]

The pathologic features of bacterial meningitis have been described in detail.[34,35] Increased brain weight and flattened convolutions are evidence of cerebral edema. Temporal lobe or cerebellar herniation can occur. The brain and spinal cord are covered with a purulent subarachnoid exudate that consists primarily of neutrophils, which also infiltrate the perivascular spaces of blood vessels in the outer layers of the cortex of the brain and connective tissue sheaths of cranial and spinal nerves. Endothelial cells of small subarachnoid arteries and veins are swollen, leading to narrowing of the lumen and microscopic changes within brain parenchyma consistent with ischemia. The interstitial tissue of the choroid plexus is infiltrated with neutrophils. Phlebitis, venous thrombosis, arteritis, and brain necrosis are pathologic changes noted at necropsy in children who had untreated bacterial meningitis for less than 3 weeks. The foramina of Magendie and Luschka can be obstructed by exudate, resulting in obstructive hydrocephalus; however, communicating hydrocephalus is more common. This exudate, rich in bacterial products and proinflammatory substances, also can traverse the cochlear duct to involve the auditory tissue. Complex molecular events are being assessed to better understand the precise mechanisms of brain damage resulting from bacterial meningitis.[27] It is currently believed that neuronal death is caused mainly by apoptosis through caspase-dependent and independent pathways.[36] High levels of tumor necrosis factor-α have been observed in CSF of patients with meningococcal meningitis when sample was obtained within 48 hours of symptom onset.[37] Index of release of cytokines and chemokines per cell was significantly higher in pneumococcal meningitis.[37] Levels of only interferon γ were significantly higher in patients with meningitis due to *S. pneumoniae* compared with *N. meningitidis*. Changes in these mediators and in interleukin-1β (IL-1β) and IL-6 are the best-studied inflammatory responses in patients with bacterial meningitis.[38–40]

The molecular mechanisms responsible for oxidant-induced neuronal injury in experimental pneumococcal meningitis are summarized in Figs. 40.3 and 40.4.[41]

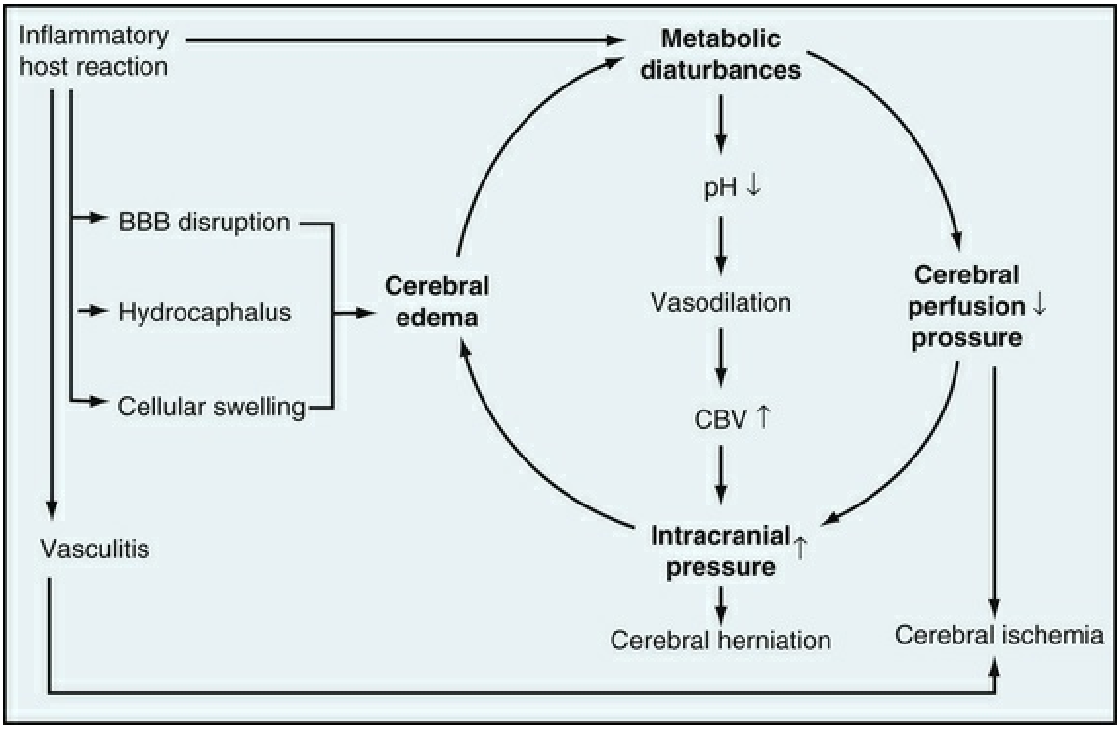


FIGURE 40.3 Pathophysiologic alterations leading to neuronal injury during bacterial meningitis. BBB, blood-brain barrier; CBV, cerebral blood volume. (From Scheld WM, Koedel U, Nathan B, Pfister HW. Pathophysiology of bacterial meningitis: mechanism(s) of neuronal injury. J Infect Dis 2002;186[Suppl 2]:S225–233.)

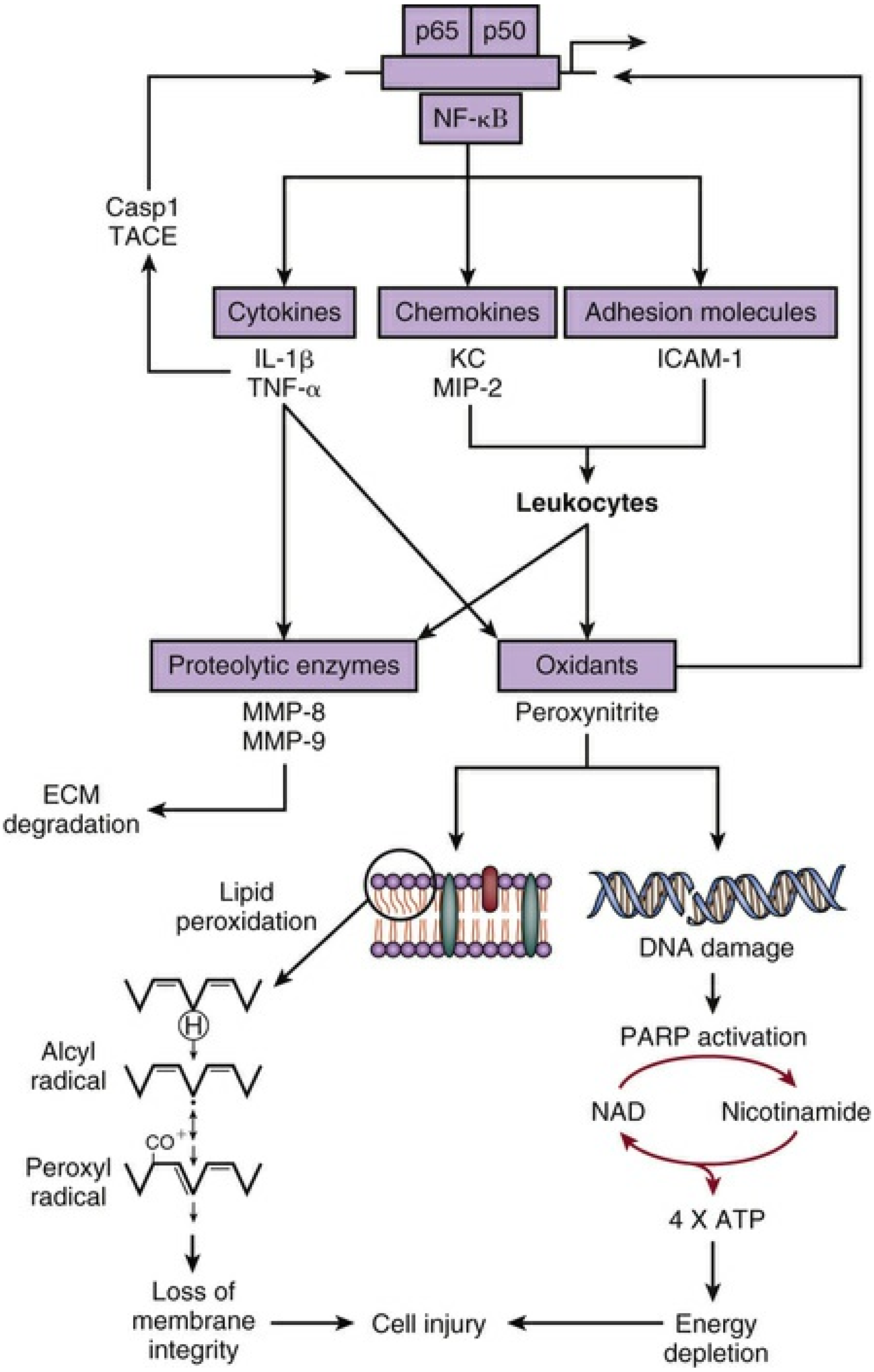


FIGURE 40.4 Mechanisms of brain damage in experimental pneumococcal meningitis. NF-κB, a transcriptional activator of many genes involved in the pathogenesis of bacterial meningitis, encodes host factors including proinflammatory cytokines, chemokines (e.g., interleukin [IL]-8), and adhesion molecules. The proinflammatory cytokines IL-1β and tumor necrosis factor (TNF)-α are synthesized as inactive precursors that are processed to mature active forms by proteases (caspase 1 [Casp1], also known as IL-1β–converting enzyme, and TNF-α–converting

enzyme [TACE]). IL-1β and TNF-α are potent activators of NF-κB. This process can lead to the uncontrolled expression of proinflammatory mediators and the increased expression of adhesion molecules both on the endothelium (e.g., intercellular adhesion molecule [ICAM]-1) and on neutrophils, leading to subsequent massive influx of leukocytes into the subarachnoid space. Once present, activated leukocytes release a complex variety of potentially cytotoxic agents including oxidants and proteolytic enzymes (e.g., matrix metalloproteinase [MMP]), which may contribute to tissue destruction. Also, peroxynitrite may cause brain damage through a variety of independent mechanisms. The best studied are attack of polyunsaturated fatty acids, leading to lipid peroxidation, and an alternative pathway that involves oxidant-induced DNA strand breakage and subsequent poly(adenosine diphosphate ribose) polymerase (PARP) activation, which initiates an energy-consuming intracellular cycle that ultimately results in cellular energy depletion and cell death. Both mechanisms likely contribute to cell injury during pneumococcal meningitis. ATP, adenosine triphosphate; ECM, extracellular matrix; KC, keratinocyte-derived chemokine; MIP, macrophage inflammatory protein; NAD, nicotinamide adenine dinucleotide. (From Scheld WM, Koedel U, Nathan B, Pfister HW. Pathophysiology of bacterial Meningitis: mechanism(s) of neuronal injury. J Infect Dis 2002;186[Suppl 2]:S225–233.)

Clinical Presentation

The clinical symptoms and signs of bacterial meningitis in children vary depending on the age of the child and duration of disease. Nonspecific findings include abnormal vital signs such as tachycardia and fever, poor feeding, irritability, lethargy, and vomiting.[1] An infant may become progressively more irritable and lethargic, refuse feeds, and manifest increasingly less interaction with caregivers. Older children may complain of headache, vomiting, back pain, myalgia, and photophobia; may be confused or disoriented; and may verbalize specifically that the neck is stiff or sore. Seizures are noted in up to 30% of patients before or soon after hospital admission and tend to occur more frequently in pneumococcal or Hib meningitis than in meningococcal disease. Complex seizures at the time of presentation increases the likelihood of meningitis more than twofold.[42] Focal neurologic signs or a reduced level of consciousness may be present. Coma on presentation, compared with irritability or lethargy alone, portends a worse prognosis.

On physical examination, the fontanel of an infant may be bulging, but this sign is neither highly sensitive nor specific for meningitis; the finding requires urgent evaluation. The infant demonstrates diminished activity and may show little interest in the environment. Kernig and Brudzinski signs and neck stiffness are more specific physical findings of meningeal inflammation and occur more commonly in children older than 12 to 18 months. The presence of meningeal signs increases the likelihood of meningitis, and absence decreases the likelihood.[39] No classical symptoms and signs, however, distinguish accurately children with or without meningitis.[16–43]

Cranial nerve VI palsy and, less commonly, cranial nerve III or VII dysfunction suggest increased intracranial pressure (ICP). Papilledema is uncommon in a child with uncomplicated meningitis and, if present, suggests another diagnosis (brain abscess, epidural or subdural empyema, another cause of increased ICP) or a complication of meningitis (venous sinus thrombosis). Unilateral weakness (hemiparesis) often is a result of ischemia or infarction, usually associated with vasculitis or cerebral artery spasm. Occasionally in an older child, ataxia is the major neurologic sign.

A petechial or purpuric rash and shock classically are associated with meningococcal septicemia (frequently coexisting with meningitis) but also can occur occasionally in infection due to Hib or *S. pneumoniae*. A maculopapular rash, which is difficult to distinguish from a common enteroviral exanthem, can occur in up to 15% of children with meningococcemia. Focal infections such as pneumonia, pyogenic arthritis, buccal cellulitis, pericarditis, and endophthalmitis can be present concurrently with bacterial meningitis; their presence should not discourage evaluation of CSF unless the severity of the condition warrants deferral of the lumbar puncture.

Children with bacterial meningitis usually have one of three patterns of illness: (1) nonspecific symptoms that progresses over 2 to 5 days; (2) rapidly progressive symptoms and signs over the course of 1 or 2 days; and (3) fulminant, rapid deterioration and shock early in the course of illness.[44]

Recognizing the uncommon infant or child with meningitis or other invasive bacterial infection among the large numbers of children evaluated for febrile illnesses requires expertise and a high index of suspicion, careful observation, and examination. The differential diagnosis in children with fever and alteration in CNS function includes other infections, such as viral and fungal meningitis, viral and protozoa encephalitis, focal brain or parameningeal abscess, Lyme disease, rickettsial disease, or infection. Noninfectious conditions also are considered, such as Kawasaki disease, collagen vascular disease and other vasculitides, acute disseminated encephalomyelitis, hypersensitivity to drugs (e.g., trimethoprim-sulfamethoxazole, immune globulin intravenous, antithymocyte globulin) and Reye syndrome.

Laboratory Findings and Diagnosis

A lumbar puncture to obtain CSF is necessary when the diagnosis of bacterial meningitis is considered. CSF should be collected from all cases with suspected meningitis before commencement of antimicrobial therapy, unless lumbar puncture is contraindicated or must be delayed (Table 40.2).[22] Antimicrobial therapy should not be delayed if lumbar puncture must be deferred. When considering acute infections, examination of CSF should include macroscopic, cytologic, and Gram stain examination, chemical determinations, culture and antimicrobial susceptibility testing, and testing such as by polymerase chain reaction (PCR) in certain circumstances.[45] By appearance, the CSF is normally clear like water. Hazy, cloudy, turbid CSF indicates the degree of pleocytosis, density of pathogen, or both.

TABLE 40.2

Contraindications for Lumbar Puncture in Children

Signs suggesting raised intracranial pressure	Reduced or fluctuating level of consciousness (Glasgow Coma Scale score <9 or a drop of ≥3 points) Relative bradycardia and hypertension Focal neurologic signs Abnormal posture or posturing Unequal, dilated, or poorly responsive pupils Papilledema Abnormal doll's eye reflex
Shock	Defer until stabilization
Extensive or spreading purpura	Defer until shock and coagulopathy
After convulsions	Defer until airway and breathing are stabilized
Coagulation abnormalities	Defer if results of coagulation studies are outside the normal range, platelet count is <100,000/mm^3, or patient is receiving anticoagulant therapy
Local superficial infection at the lumbar puncture site	Defer
Respiratory insufficiency, severe respiratory distress (nonintubated)	Lumbar puncture is contraindicated because of high risk for precipitating respiratory failure

Cerebrospinal Fluid Cytology, Chemistry, and Gram Stain

Although the typical CSF white blood cell (WBC) count in bacterial meningitis is >1000 cells/mm^3, few or no WBCs can be present in CSF in the early phase (usually of rapidly progressive infection). Bacterial meningitis usually leads to a neutrophil predominance in CSF, typically between 80% and 95%; 10% of patients with acute bacterial meningitis present with a lymphocyte predominance (defined as >50% lymphocytes or monocytes).[46] Presence of immature neutrophils is suggestive of bacterial infection. Viral meningitis (especially due to enterovirus) initially can elicit neutrophilic pleocytosis.

Traumatic lumbar puncture or intracerebral or subarachnoid hemorrhage can result in bloody CSF. Correction to assess actual CSF WBC pleocytosis is calculable, considering peripheral blood WBC count and red blood cell (RBC) mass.[47]

Normally, CSF in children older than 6 months shows <6 WBCs/mm^3 (with no polymorphonuclear leukocytes), glucose >45 mg/dL, and protein <45 mg/dL.[47] Values for 677 infants younger than 90 days with febrile illness but without meningitis have been reported.[48] In months 1, 2, and 3 of life, respectively, mean CSF WBCs were 6, 3, and 3 cells/mm^3 and protein 75, 59, and 40 mg/dL.[48] Effects of traumatic lumbar puncture of CSF values also have been studied, showing presence of approximately 2 WBCs/mm^3 and 1.1 mg/dL protein for every 1000 RBCs.[49] Only 2 of 122 children with proven bacterial meningitis in one study had CSF with <6 WBCs/mm^3.[50] The protein concentration is elevated (mean, 100–200 mg/dL), and the glucose concentration usually is depressed (CSF/serum ratio <0.6), but the degree of abnormalities depends on the offending organism as well as the cadence and duration of infection. Chemical meningitis, as can occur after posterior fossa neurosurgery, can have CSF findings similar to bacterial meningitis. In chemical meningitis, CSF glucose is rarely <10 mg/dL or WBCs >7500 cells/mm^3.[51] Occasionally, patients with rapidly progressive meningitis (especially due to *S. pneumoniae*) or with concurrent septic shock lack CSF pleocytosis, which is a poor prognostic sign.[1]

The CSF Gram stain smear is positive in up to 80% of patients with untreated bacterial meningitis, and when positive, it confirms meningitis and can raise suspicion of etiology. Gram stain is negative in cases of bacterial meningitis with abnormal CSF. Positive Gram stain can be present and growth negative in patients who received antimicrobial therapy before lumbar puncture.[1] Table 40.3 can guide a pathogen-based differential etiologic diagnosis based on characteristic CSF findings.

TABLE 40.3

Usual Cerebrospinal Fluid Findings in Children With Meningitis Caused by Various Microbial Etiologies

CSF Finding	Viral	Bacterial	Partially Treated Bacterial	Lyme	Fungal	TB
Leukocytes/mm^3	<1000	>1000[a]	>1000	<500	<500	<300
Neutrophils	20%–40%[b]	>85%–90%	>80%	<10%	<10%–20%	<10%–20%[b]
Protein (mg/dL)	N or <100	>100–150	60 to >100	<100	>100–200	>200–300
Glucose (mg/dL)	N[c]	UD to <40	<40	N	<40	<40
Blood-to-glucose ratio	N	<0.4	<0.4	N	<0.4	<0.4
Positive smear[d]	—	>85%[e]	≥80%	—	<40%	<30%
Positive culture	Rare	>95%	<90%	—	>30%[f]	<30%
PCR or other methods	Enterovirus, herpesvirus	16S RNA, bacterial DNA	16S RNA, bacterial DNA	*Borrelia burgdorferi* antibodies	*Histoplasma* and *Cryptococcus* antigen, India ink for *Cryptococcus*	*Mycobacterium tuberculosis*

[a] Fewer than 500 leukocytes can be seen in severe/rapid-onset pneumococcal meningitis.

[b] Neutrophil predominance can be observed in early stages of meningitis.

[c] Low glucose concentration can occur in meningitis caused by mumps and herpesviruses.

[d] Gram or acid-fast bacilli staining for bacteria or *Mycobacterium*, respectively.

[e] Fewer positive smears in *Listeria* meningitis because of lower bacterial inoculum.

[f] Better culture isolation rates for *Candida* than for *Histoplasma* or *Cryptococcus* organisms.

CSF, cerebrospinal fluid; N, normal; PCR, polymerase chain reaction; TB, tuberculosis; UD, undetectable.

Additional Tests

Latex Agglutination.

The reported sensitivities of latex agglutination of CSF samples from patients with untreated bacterial meningitis ranged from 78% to 100% for Hib meningitis, 59% to 100% for pneumococcal meningitis, and 22% to 93% for meningococcal meningitis.[1] Because of false-positive and false-negative test results and its limited value in management, latex agglutination testing is rarely used.

Urinary bacterial polysaccharide antigen may be detected readily in children with Hib and pneumococcal meningitis but also can be detected after immunization with the respective polysaccharide and conjugate vaccines. The test is rarely more discriminating than Gram stain and cannot be used to direct specific therapy.

Oral therapy before performing CSF examination rarely affects findings substantially for Hib meningitis[52]; effect is potentially more likely and is less well studied for pneumococcal or meningococcal meningitis. Antigen detection testing, with positive results, is most helpful in pretreated patients in whom CSF is abnormal but results of Gram stain and culture are negative.

Other Tests.

Measurement of serum C-reactive protein concentration may have value for detection of complications or treatment failures after serial measurements. A CSF leukocyte aggregation test has been suggested as a sensitive adjunctive screening tool for diagnosis of bacterial meningitis but has the limitation of low specificity.[53] Two meta-analyses suggest that an elevated CSF lactate level is a good distinguishing marker of bacterial meningitis.[54,55] However, CSF lactate level can be affected by a number of factors, including pretreatment with antibiotics (reducing the level) and seizures or cerebral hypoxia (increasing the level). Potential value awaits prospective evaluation.

Polymerase Chain Reaction Testing.

Primers are available for the simultaneous PCR detection in CSF of *N. meningitidis, S. pneumoniae,* and Hib. PCR testing on CSF can be valuable, especially when culture is negative in a pretreated patient.

In culture-confirmed cases, acute bacterial meningitis sensitivities of CSF detection for *H. influenzae*, *S. pneumoniae,* and *N. meningitidis* were 92%, 100%, and 88% respectively; specificity was 100%.[1] Sensitivity of PCR on CSF may be lower in pretreated compared with untreated patients.[1] PCR carried out on blood also may significantly increase diagnostic yield, especially in pretreated patients when there is a contraindication to lumbar puncture. Quantitative PCR showing high density of bacteria has been associated with unfavorable outcomes of both pneumococcal and meningococcal disease.[1]

Flow Cytometry.

Flow cytometry facilitates the detection of a large spectrum of cellular characteristics on a per-cell basis, determination of absolute cell numbers, and detection of rare events with high sensitivity and specificity.[56] Novel use of flow cytometry with a dedicated bacterial channel has been explored for diagnosis of meningitis.[57] Technical pitfalls include low number of cells in CSF, rapid decline (but variable by cell type) of leukocyte integrity within 30 minutes of sampling, and application after traumatic lumbar puncture.[56] A meta-analysis concluded that neutrophil CD64 expression could be a promising biomarker for diagnosing bacterial infection.[58] Large prospective studies are needed with validation of cutoff points established.

Blood Culture.

Blood culture is valuable in detecting the causative organism and establishing susceptibility patterns, especially when CSF cultures are negative. Reported positivity rates are 50% to 90% for *H. influenza*e, 75% for *S. pneumoniae*, and 40% for *N. meningitidis*.

The yield after commencement of antimicrobial therapy falls rapidly.[1] Culture recovery of *N. meningitidis* is enhanced by inoculation of broth without sodium polyanethole sulfonate. Aspiration of an inflamed joint, cellulitis, purpuric lesion, or purulent middle-ear fluid maximizes identification of the infecting organism and provides a pathogen for susceptibility testing. In children with meningitis after surgery or trauma, culture of a specimen protected from infected wounds is useful. Culture specimens obtained from puncture of sinus, middle-ear cavity, or mastoid bone can be useful when meningitis complicates these infections. Blood PCR assay can increase the diagnostic yield substantially, especially in patients pretreated with antibiotics.

Imaging Studies.

Nonenhanced computed tomography (CT) and magnetic resonance imaging (MRI) of patients with uncomplicated acute bacterial meningitis can be unremarkable.[59] CT often is performed to exclude contraindications for lumbar puncture; usefulness is limited to evidence of mass effect or hemorrhage and does not exclude the presence of raised ICP.[60,61] Raised ICP should be evaluated clinically.

Currently, MRI is the most sensitive imaging modality to assess extent of inflammatory changes in the meninges, brain abnormalities, and complications.[62] Leptomeningeal enhancement and distention of the subarachnoid space with widening of the interhemispheric fissure, small ventricles, and effacement of sulci can be reported to be an early finding in severe meningitis. Meningeal enhancement can be visible on contrast-enhanced CT and MRI but is nonspecific and is also present in carcinomatous meningitis, reactive meningitis (e.g., surgery, shunt, trauma), chemical meningitis (e.g., ruptured dermoid and cysticercoid cysts, intrathecal chemotherapy), and inflammatory conditions (e.g., sarcoidosis, collagen vascular disease).[62]

Neuroimaging can identify conditions that predispose to bacterial meningitis. Thus imaging is indicated in patients who have a history of head trauma, sinus or mastoid infection, and congenital anomalies. In addition, neuroimaging studies typically are used to identify and monitor complications of meningitis, such as hydrocephalus, subdural effusion, empyema, and infarction, and to exclude parenchymal abscess and ventriculitis. Identifying cerebral complications early is important because some complications, such as symptomatic hydrocephalus, subdural empyema, and cerebral abscess, may require prompt neurosurgical intervention.[63]

Management

Empiric antibiotic therapy should be begun urgently and without delay if lumbar puncture cannot be performed expeditiously. The choice of agents is based on the patient's age (an indication of etiologic pathogens) and underlying disease status and with knowledge of local antimicrobial susceptibility patterns and of dosing and pharmacodynamics of antimicrobial agents. When the infecting pathogen is isolated, antimicrobial therapy can be modified for optimal definitive treatment.

Antibiotics and dosages should be selected to produce CSF drug concentrations likely to be at least 8- to 10-fold greater than the minimal inhibitory concentration (MIC) required to inhibit and kill the pathogen in vitro, a level in animal models that predicts successful treatment.[64] For β-lactam antibiotics and vancomycin, the time during which the drug concentration exceeds the MIC appears to determine drug effectiveness (concentration-independent activity). For aminoglycosides and fluoroquinolones, effectiveness is determined by the ratio between the peak concentration or area under the curve of the antibiotic and the MIC of the pathogen (concentration-dependent activity).[65]

Antimicrobial Resistance

H. influenzae with ampicillin resistance due to β-lactamase production increased to 40% in the US by the mid-1990s.[66,67] Occasional additional isolates are ampicillin resistant as a result of alterations in penicillin-binding proteins or are chloramphenicol resistant because of production of chloramphenicol acetyltransferase enzyme.[66] Third-generation cephalosporins such as cefotaxime and ceftriaxone have excellent activity against all Hib strains and are comparable in efficacy but superior in rapidity of CSF sterilization compared with chloramphenicol for treatment of ampicillin-resistant Hib meningitis.[68–70]

The penicillin resistance of *S. pneumoniae* is a growing problem worldwide.[71] Before the mid-1980s, there were only scattered reports of bacterial meningitis due to penicillin-resistant *S. pneumoniae* throughout the world. Penicillin-nonsusceptible isolates had risen up to 40% in the US and as high as 60% in other countries by the 1990s.[72] In January 2008, the Clinical and Laboratory Standards Institute established breakpoints for *S. pneumoniae* depending on clinical site of infection (Table 40.4). For meningitis, strains are defined as nonsusceptible if penicillin MIC is ≥0.12 μg/mL.[73] *S. pneumoniae* infections with relative or high-level resistance to penicillin have alterations in penicillin-binding proteins and also can have reduced susceptibility to other β-lactam antibiotics. *S. pneumoniae* also can demonstrate resistance to multiple other classes of antibiotics (trimethoprim-sulfamethoxazole, chloramphenicol, and macrolides). Prevalence of resistance has fallen in many countries where PCV13 has been implemented.[74] In children's hospitals in the US, up to 20% of pneumococci recovered from children with invasive infections can be expected to show penicillin resistance. Penicillin or ampicillin even at high doses parenterally has been associated with treatment failure of meningitis due to pneumococci that are relatively or highly resistant to penicillin. Treatment failures for ceftriaxone or cefotaxime also can occur, usually with MIC ≥0.5 μg/mL.[75,76] Vancomycin and rifampin are active against cefotaxime- or ceftriaxone-resistant *S. pneumoniae*. Microbiology laboratories should routinely test all pneumococcal isolates from normally sterile sites for penicillin susceptibility. Screening can be accomplished with several methods, including oxacillin disk, Etest (AB Biodisk, Solna, Sweden), and commercial microtiter methods.[77]

TABLE 40.4

Clinical and Laboratory Standards Institute Guidelines for Interpretation of Susceptibility Testing of *Streptococcus pneumoniae* for Meningitis

	Minimal Inhibitory Concentration (μg/mL)					
Interpretation	**Penicillin**	**Cefotaxime/Ceftriaxone**	**Meropenem**	**Vancomycin**[a]	**Rifampin**	**Chl**
Susceptible	≤0.06	≤0.5	≤0.25	≤1	≤1	≤4
Intermediate	—	1.0	0.5	—	2	—
Resistant	≥0.12	≥2.0	≥1	—	≥4	≥8

[a] Absence or rare occurrence of resistant strains precludes defining results categories.

Pneumococcal isolates that are tolerant to β-lactam antibiotics and vancomycin have also been documented.[78] Because of defective autolysis, tolerant bacteria produce fewer cell wall–derived substances that cause meningeal inflammation, so CSF abnormalities can be mild.[79] As a result of tolerance, organisms can persist in CSF and cause relapse after treatment is stopped.

Aqueous penicillin G remains the agent of choice for meningococcal meningitis, although ampicillin and third-generation cephalosporins also are effective and are easier to administer. Clinical isolates of *N. meningitidis* with relative resistance to penicillin (MIC ≥0.125 μg/mL) have been reported.[80] Resistance is not associated with β-lactamase production but with alterations in penicillin-binding proteins. The clinical significance of this type of resistance in the treatment of meningococcal meningitis is unclear. Cephalosporin resistance is extremely rare.

Choice and Mode of Antimicrobial Therapy

Although a recent Cochrane review of preadmission antibiotics for suspected cases of nonsevere meningococcal disease included nonsubstantiated evidence, one randomized controlled trial indicated that a single dose of intramuscular (IM) ceftriaxone or long-acting chloramphenicol was equally effective, safe, and economical in reducing serious outcomes.[81]

The principles of antimicrobial therapy for acute bacterial meningitis include use of agents that penetrate well into CSF and attain appropriate CSF concentration, are active in purulent CSF, and are rapidly bactericidal against the infecting pathogen.[82]

Empiric therapy of suspected bacterial meningitis in the US is urgent administration of antibiotics parenterally: ampicillin *plus* cefotaxime for infants younger than 3 months, and vancomycin *plus* cefotaxime or ceftriaxone for children 3 months or older.[83] Ceftriaxone should not be used in premature infants or in infants with jaundice, hypoalbuminemia, or acidosis as ceftriaxone displaces bilirubin from albumin. Use in neonates with calcium-containing infusions can lead to cardiac precipitation and death.

After an organism has been identified and the antimicrobial susceptibility pattern is known, antibiotic therapy can be simplified or modified (Table 40.5).[46] Penicillin G or ampicillin can be used to complete therapy for pneumococcal or meningococcal meningitis due to susceptible organisms. Cefotaxime or ceftriaxone is continued for penicillin-nonsusceptible pneumococci that are susceptible to these agents (MIC ≤0.5 μg/mL).[83] Although many patients with isolates having third-generation cephalosporin MIC of 0.5 to 1 μg/mL have been treated successfully, treatment with cephalosporin alone usually is not recommended. It is prudent to repeat the CSF examination after 48 to 72 hours of therapy in patients with poor response or when infection is due to β-lactam–nonsusceptible pneumococci to document a negative Gram stain and sterile culture. If results of the second CSF Gram stain or culture are positive, or a pneumococcal isolate has an MIC of ≥1 μg/mL for extended-spectrum cephalosporins, vancomycin (if not begun previously) with or without rifampin should be added.[84] Rifampin should be added if the patient already is receiving vancomycin. Vancomycin penetration into CSF during meningitis can be unpredictable, and thus peak and trough serum values should be in the upper therapeutic range (35–40 and 10–15 μg/mL, respectively).

TABLE 40.5

Recommendations for Specific Antimicrobial Therapy in Bacterial Meningitis Based on Isolated Pathogen and in Vitro Susceptibility Testing

Microorganism	Standard Therapy	Alternative Therapies
Streptococcus pneumoniae		
Penicillin MIC <0.1 μg/mL	Penicillin G or ampicillin	Ceftriaxone or cefotaxime,[a] *or* chloramphenicol
Penicillin MIC 0.1–1 μg/mL[b]	Ceftriaxone or cefotaxime	Cefepime; meropenem
Penicillin MIC ≥2 mg/mL, *or* cefotaxime; *or* ceftriaxone MIC ≥1 mg/mL	Vancomycin + a third-generationcephalosporin[a,c]	Fluoroquinolone[d]
Neisseria meningitides		

Penicillin MIC <0.1 mg/mL	Penicillin G or ampicillin	Third-generation cephalosporin[a]; chloramphenicol
Penicillin MIC 0.1–1 mg/mL	Third-generation cephalosporin[a]	Chloramphenicol; fluoroquinolone; meropenem
Listeria monocytogenes	Ampicillin or penicillin G[e]	Trimethoprim-sulfamethoxazole
Streptococcus agalactiae	Ampicillin or penicillin G[e]	Third-generation cephalosporin[a]
***Escherichia coli* and other Enterobacteriaceae[g]**	Third-generation cephalosporin[a]	Aztreonam; fluoroquinolone; meropenem; trimethoprim-sulfamethoxazole; ampicillin
***Pseudomonas aeruginosa*[g]**	Cefepime[e] or ceftazidime[e]	Aztreonam[e]; ciprofloxacin[e]; meropenem[e]
Haemophilus influenzae		
β-lactamase negative	Ampicillin	Third-generation cephalosporin[a]; cefepime; chloramphenicol, fluoroquinolone
β-lactamase positive	Third-generation cephalosporin[a]	Cefepime; chloramphenicol, fluoroquinolone
Staphylococcus aureus		
Methicillin-susceptible	Nafcillin or oxacillin	Vancomycin; meropenem; linezolid; daptomycin
Methicillin-resistant	Vancomycin[f]	Trimethoprim-sulfamethoxazole; linezolid; daptomycin
Staphylococcus epidermidis	Vancomycin[f]	Linezolid

[a] Ceftriaxone or cefotaxime.

[b] Ceftriaxone/cefotaxime-susceptible isolates.

[c] Consider addition of rifampin if ceftriaxone MIC is >2 mg/mL.

[d] Moxifloxacin. No clinical data available; if used, many authorities would combine with vancomycin or a third-generation cephalosporin (e.g., cefotaxime or ceftriaxone).

[e] Addition of an aminoglycoside should be considered.

[f] Consider addition of rifampin.

[g] Choice of a specific antimicrobial agent must be guided by in vitro susceptibility testing.

Data from Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004;39:1267–1284.

Although rarely used in developed countries, chloramphenicol is an option for treatment of bacterial meningitis caused by ampicillin-resistant Hib or in a child with a history of anaphylaxis associated with penicillin or other β-lactam antibiotics. Because the pharmacokinetics of chloramphenicol are variable, serum concentrations should be monitored to ensure that safe and effective concentrations are achieved.[85] Ideal peak values are 15 to 30 μg/mL at 60 to 120 minutes after the completion of infusion.

Values exceeding 30 μg/mL are associated with bone marrow suppression; concentrations greater than 50 to 80 μg/mL have been associated with grey baby syndrome (which is not confined to infants) and impaired myocardial contractility. Several drugs affect the metabolism of chloramphenicol; concurrent administration of phenobarbital or rifampin lowers the chloramphenicol level, whereas administration of phenytoin raises the level.

Other potentially useful antimicrobial agents for the treatment of bacterial meningitis are cefepime and meropenem, both of which have been shown in limited studies to be equivalent to third-generation cephalosporins in the treatment of children infected with common meningeal pathogens.[86–89] The efficacy of these antibiotics against β-lactam−resistant pneumococci has not been defined, although they appear to be equivalent to the third-generation cephalosporins. Because of increased resistance to β-lactam agents, use of newer fluoroquinolones (gemifloxacin, moxifloxacin) and novel glycopeptides has been described in case reports. Linezolid appears to enter the CNS adequately, based on limited data in children and adults.[90,91]

A meta-analysis of randomized controlled trials involving severe infections mainly outside the CNS showed that fewer clinical failures were seen in infections treated with continuous intravenous infusion of antibiotics that act by time-dependent killing (e.g., β-lactams) and even with aminoglycosides that exhibit concentration-dependent killing.[91,92] Although continuous infusion can permit maintenance above the minimal bactericidal concentration during nearly 100% of the dosing interval, lower peak CSF concentrations are attained.[92,93] Knowledge of the relative importance of these findings and clinical observations in meningitis are lacking.

Monitoring During Therapy

Performance of complete blood counts during therapy is helpful for early detection of neutropenia, which is associated with β-lactam antibiotics and chloramphenicol; neutropenia is readily reversible when antibiotics are discontinued. Anemia is common in children with bacterial meningitis and also can be exacerbated by chloramphenicol. Ceftriaxone has been associated with immune-mediated, rapidly fatal hemolysis in patients with sickle cell disease, HIV infection, and leukemia.[94,95] Thrombocytosis (platelet count >750,000/mm^3) occurs frequently in patients with meningitis and has no apparent adverse clinical effect, and platelet counts need not be monitored. Diarrhea is the most common adverse effect of ampicillin and the extended-spectrum cephalosporins. Rashes, eosinophilia, and mild elevation in serum hepatic transaminase values can occur with any of these agents as well. Ceftriaxone occasionally has been associated with abdominal discomfort and pseudolithiasis ("sludge") in the gallbladder, as seen on ultrasonography[96]; this is reversed with discontinuation of the drug. Routine performance of MRI or CT has no benefit but is useful if the course is complicated, the pathogen is unusual, or reason for occurrence is sought.[97]

Duration of Therapy

The duration of antibiotic therapy for meningitis varies with the organism and the clinical response.[98]

When possible, therapy should be completed in the hospital to permit careful assessment of the response to treatment and to prevent complications of disease or therapy. Parenteral therapy can be completed at home for carefully selected older patients if meningitis is due to a fully susceptible organism and the patient has resumed normal activity. Ceftriaxone is approved for a once-daily dosing schedule, making it more convenient and perhaps less expensive than other agents for treatment of fully susceptible organisms. It is essential, however, to calculate and administer each dose correctly so that the patient is not treated inadequately for 24 hours because of a dosage or administration error.

Usual total duration of parenteral therapy for uncomplicated meningitis is pathogen specific: *H. influenzae* type b, 10 days; *S. pneumoniae*, 14 days; *N. meningitidis*, 7 days. A multicenter randomized trial in children with *H. influenzae, S. pneumoniae,* or *N. meningitidis* meningitis suggested equivalency of 5 days versus 10 days of therapy in selected, clinically well patients with no complications.[99]

Newer β-lactam monotherapies (cefepime, meropenem, ertapenem), fluoroquinolones (garenoxacin, gemifloxacin, gatifloxacin, moxifloxacin), and lipopeptide (daptomycin) antibiotics have been evaluated in the rabbit model of meningitis, with special emphasis on the potential role of combination treatments for synergy for resistant pathogens.[100]

For other organisms and neonates, see other specific chapters. In general, parenteral therapy is given for uncomplicated meningitis due to group B *Streptococcus* for >14 days; *Listeria monocytogenes* for 21 days; and gram-negative bacilli for ≥21 days. For theses pathogens, in neonates and those with complicated courses, neuroimaging and clinical course can aid decisions for more prolonged courses of therapy. Individual decisions are made for patients with suspected bacterial meningitis and negative CSF culture. Pretreatment drug is considered. For children 3 months or older, ceftriaxone or cefotaxime may be given for a total course of 10 days; for infants younger than 3 months, ampicillin plus cefotaxime may be given for ≥14 days.

Meningitis Due to Unusual Organisms

Gram-negative bacillary meningitis beyond the neonatal period occurs almost exclusively in compromised hosts and as a healthcare-associated infection.[101] Management is challenging.[102]

E. coli and *Klebsiella* spp. are the most common gram-negative enteric organisms outside of the neonatal period.[103] Combination therapy using an extended-spectrum cephalosporin or meropenem *plus* an aminoglycoside is usual empiric therapy, with consideration of susceptibility patterns of nosocomial organisms in hospital-associated cases.[104] Modifications are made after antimicrobial susceptibility test results (e.g., cefepime or meropenem *plus* an aminoglycoside for *Pseudomonas* meningitis). For patients with gram-negative bacillary meningitis, a repeat CSF specimen is obtained for culture at 24 to 48 hours after commencement of therapy and approximately every 48 hours thereafter until CSF sterilization is documented. Intrathecal administration of antibiotics is considered for unsuccessful sterilization. Rarely, an aminoglycoside is instilled directly into the ventricles (almost exclusively in postoperative, device-associated, or posttraumatic cases). This is best done through an Ommaya reservoir. Systemic treatment is continued for a minimum of 21 days or for at least 2 weeks beyond the first documented sterile CSF culture, whichever is longer.

Surgical drainage of wound infections after trauma or neurosurgery also is required, as is removal of contaminated devices. Imaging studies are performed in patients with gram-negative bacillary meningitis before the decision to terminate therapy, to assess the nature of cerebral involvement, necrosis, and loculated collections and the need for surgical intervention.

Meningitis caused by *S. aureus* is treated with nafcillin when the organism is susceptible (oxacillin does not adequately penetrate into CSF). Vancomycin is an alternative for patients who are allergic to penicillin or have a methicillin-resistant isolate. Adding rifampin to the antistaphylococcal regimen may be necessary if CSF Gram stain or culture results remain positive despite the use of agents active in vitro. Ampicillin plus an aminoglycoside is recommended for patients with meningitis due to susceptible strains of *Enterococcus* species. Vancomycin (with aminoglycoside) is used for ampicillin-resistant *Enterococcus* spp. Scattered case reports of successful therapy with linezolid and daptomycin in adults with meningitis caused by resistant staphylococci and enterococci have been published.[105–107] Ampicillin is the drug of choice for *L. monocytogenes* infection; data support the possible beneficial role of concurrent aminoglycosides, at least for the first several days of therapy. When infection occurs in a patient with a ventriculoperitoneal shunt, bacterial eradication is best accomplished by removal of the device coupled with antimicrobial therapy.

Supportive Care

Unless the patient is only mildly affected, initial supportive care of the child with bacterial meningitis is best provided in an intensive care setting, where the patient can be observed and monitored continuously.[108] Typically, most life-threatening complications of bacterial meningitis (septic shock, cerebral herniation, cerebral infarction, seizures, and inadequate ventilation) occur early in the course of treatment and require urgent intervention for optimal outcome. Early, protocolized, aggressive care by a consultant supervised pediatric team improves survival and outcomes.[109] Early tracheal intubation and mechanical ventilation should be considered for any child with evidence of respiratory compromise, threatened airway, ongoing shock, refractory seizures, or elevated intracranial pressure.[110]

A recent Cochrane meta-analysis supported use of maintenance, rather than restrictive fluids in the first 48 hours.[111] Fluid restriction is advised only in patients without clinical evidence of dehydration who have hyponatremia (suspicious inappropriate antidiuretic hormone secretion). If the patient is hypovolemic or in shock, additional intravenous fluids must be given accordingly. There is no evidence that fluid restriction reduces cerebral edema in children with bacterial meningitis. Maintenance of blood pressure within the normal range for age may require infusion of a vasoactive agent, such as noradrenaline.

Increased ICP is a major component of the pathophysiologic alterations of meningitis. In addition to elevation of the patient's head, some clinicians administer mannitol (0.5–2 g/kg) if clinical signs (apnea, bradycardia, sluggish pupils, or pupillary dilation) of extremely high intracranial pressure are detected. Immediate tracheal intubation and hyperventilation can be lifesaving if cerebral herniation is imminent. Seizures are controlled with standard anticonvulsants, such as benzodiazepines, phenobarbital, and phenytoin. Most seizures occur early in the illness and are generalized, usually can be controlled easily, and have limited prognostic significance. However, seizures that are focal, occur ≥48 hours after admission, or are difficult to control imply an underlying vascular disturbance (e.g., venous thrombosis, cerebral infarction), brain abscess, or subdural empyema and are associated with development of epilepsy and other neurologic sequelae.[112] Secondary stroke prevention should be considered.[113]

After adequate therapy begins, the duration of fever typically is 4 to 6 days. Recurrence of fever or persistence of fever beyond 8 days can be caused by several conditions (Box 40.1). Fever patterns should be evaluated carefully, although a specific explanation often is not found. It is unlikely that uninfected subdural effusions cause prolonged fever.

Box 40.1

Causes of Prolonged or Recurrent Fever in Children With Bacterial Meningitis

Inadequate treatment

Nosocomial infection

Transient elevation after discontinuing dexamethasone

Phlebitis

Suppurative complication

Pericarditis

Pneumonia

Pyogenic arthritis

Subdural empyema

Immune-mediated arthritis

Drug fever (rare)

Unknown

Adjunctive Therapy

Modulating the host response to infection may be beneficial in decreasing some of the sequelae of bacterial meningitis. In a recent Cochrane meta-analysis, adjunctive corticosteroid therapy in bacterial meningitis was associated with a nonsignificant reduction in mortality (17.8% vs. 19.9%;, risk ratio [RR], 0.90; 95% confidence interval [CI], 0.80–1.01; P = 0.07) but was associated with a reduction of hearing loss and neurologic sequelae.[114] Subgroup analyses for causative organisms showed that adjunctive corticosteroids reduced mortality in pneumococcal meningitis (RR, 0.84; 95% CI, 0.72–0.98), but not in Hib or meningococcal meningitis. Corticosteroids reduced severe hearing loss in children with Hib meningitis, but not in children with meningitis due to non-*Haemophilus* species.[114]

For potential benefit in bacterial meningitis, dexamethasone must be administered before or concomitantly with parenteral antibiotics, or within 4 hours after commencement if earlier administration is not possible.[22] Some clinical reports indicate that dexamethasone does not affect the bactericidal activity of a third-generation cephalosporin combined with vancomycin against highly resistant pneumococci.[115] Careful clinical assessment and second CSF evaluation are warranted in this situation.

Dexamethasone administration is associated with a rapid resolution of fever in treated patients, but a secondary transient rise in body temperature is observed in up to 40% of cases after the drug is discontinued.[114] Its administration has been associated rarely with severe gastrointestinal bleeding. The recommended dose of dexamethasone is 0.6 mg/kg/day in 4 divided doses for 4 days.[22]

In developing countries, novel adjuvant therapies are needed. The use of oral glycerol may be beneficial for children with bacterial meningitis through its action in increasing plasma osmolality, without inducing diuresis, leading to a reduction in cerebral edema and a presumed improvement in cerebral circulation and brain oxygenation.[116] A large randomized trial in Latin America showed a significant reduction in neurologic sequelae in children given adjuvant glycerol, or glycerol in combination with dexamethasone, compared with placebo.[117] Because glycerol is a relatively safe, inexpensive medication that can be administered orally, it may be especially attractive in resource-limited settings. Criticisms of the trial's design, in addition to a recent trial that failed to show benefit of glycerol in adults with meningitis, have led to questions about its use.[118]

Prognosis

With modern management, the mortality rate for bacterial meningitis in children caused by the three most common pathogens generally is <5% to 10%. Case-fatality rate and incidence of neurologic sequelae are greatest with pneumococcal meningitis. The neurologic sequelae of meningitis are listed in Box 40.2. Sensorineural hearing loss is the most common readily identifiable sequela. Hearing loss occurs in approximately 20% to 30% of previously healthy children after meningitis due to *S. pneumoniae* and in 5% to 10% of patients after meningitis caused by Hib or *N.*

meningitidis. Disturbances of balance are common in these children because the vestibular portion of cranial nerve VIII is affected. Hearing loss has been associated with CSF glucose concentration <20 mg/dL. Hearing should be tested before discharge or within 1 month after discharge in all children with bacterial meningitis so that if hearing loss is detected, potentially beneficial interventions are not delayed. Reversible deafness has been documented in some children tested at discharge and 4 to 6 months later.

Box 40.2

Neurologic Sequelae of Bacterial Meningitis

Sensorineural hearing loss

Ataxia

Vascular compromise

Hemiparesis

Quadriparesis

Epilepsy

Spinal cord infarction

Cortical blindness

Diabetes insipidus

Hydrocephalus

Behavioral disorder

Intellectual deficits

Acute hydrocephalus, as well as many sequelae related to cerebral vascular compromise, can improve with time. Hemiparesis can resolve several months to years after the event. Imaging studies demonstrate evidence of infarction in such patients, although these findings usually do not affect or change management.

Behavioral and academic problems are common, and more subtle consequences of bacterial meningitis may not be apparent for several years after infection. Although formal testing generally is not necessary, careful follow-up and assessment over time is essential; any concerns regarding school performance or behavioral disturbance warrant further investigation.

Prevention

Close contacts of patients with meningococcal disease should receive chemoprophylaxis with rifampin (5 mg/kg if <1 month of age, 10 mg/kg if ≥1 month of age; maximal dose 600 mg) twice daily for 2 days, started ideally within 24 hours of the exposure. A single oral dose of ciprofloxacin (20 mg/kg, maximal dose 500 mg) or azithromycin (10 mg/kg, maximal dose 500 mg) or a parenteral dose of ceftriaxone (125 mg IM if <15 years, 250 mg IM if ≥15 years) are suitable alternatives; the last is preferred for pregnant women. Immunization of unvaccinated individuals is also recommended depending on the serogroup and age.

Rifampin prophylaxis is recommended for all household contacts of an index case with Hib disease when at least one household contact is younger than 4 years and is unimmunized or incompletely immunized. Unvaccinated children younger than 5 years also should be given Hib vaccine as soon as possible.[119]

A marked reduction of pneumococcal meningitis in PCV7 vaccinated US children has been documented.[120–122] A trial of PCV9 conducted in African children with or without HIV infection was associated with 65% and 83% reductions, respectively, in invasive pneumococcal disease (IPD) caused by vaccine serotypes.[123] Universal implementation of PCV13 in the US has been associated with further reduction in incidence of IPD.

Epidemiologic studies identifying cases of invasive pneumococcal disease through Active Bacterial Core surveillance (ABCs) of the CDC before and after the implementation of PCV7 showed remarkable decrease in pediatric pneumococcal meningitis[124] and 76% reduction in all IPD cases in the US.[125] A decline in cases of pneumococcal meningitis in children younger than 2 years also was evident in Europe and the US after implementation of PCV7.[8] However, an increase in pneumococcal meningitis cases in children 2 years and older due to nonvaccine serotypes was noted in France.[126] Children younger than 2 years who are at high risk for developing invasive pneumococcal disease, such as patients with specific dysfunction (sickle cell disease, asplenia) and nephrotic syndrome, or who are at increased risk for meningitis, such as children with cochlear implants, also should receive the 23-valent polysaccharide vaccine (PPSV23) at 2 years of age.[127]

Mass campaigns using MCV have led to control of serogroup C meningococcal disease in the UK, Canada, Australia, Spain, Belgium, Ireland, and Iceland. Serogroup B disease, predominant in New Zealand, has been dramatically decreased, partly owing to the introduction of an outer membrane vesicle (OMV) vaccine. Polysaccharide vaccines were used in high-risk people in Saudi Arabia and Syria and in routine immunization in China and Egypt. For serogroup B, vaccine development has included protein vaccines based on meningococcal OMV, whereas more recently a range of conserved proteins, including factor H binding protein (fHBP), *Neisseria* adhesin A (NadA), and *Neisseria* heparin binding antigen (NHBA), have been used as vaccine components.

A 4CMenB vaccine (Bexsero), containing three recombinant proteins, and OMV derived from a serogroup B meningococcal strain (MenB) has been licensed in Europe, Australia, and the US for persons 2 months and older. A serogroup B fHBP vaccine (Trumenba) has been licensed in the US. Although recommendation for use of serogroup B vaccines in the US include certain at-risk populations and use during outbreaks,[128] vaccine has not been recommended for universal use because of current low burden of disease. The UK Joint Committee on Vaccination and Immunisation has taken a position to introduce this vaccine into the routine infant schedule in 2015.[23]

Since the introduction of the meningococcal C (MenC) vaccination program in the UK in November 1999, the vaccine schedule has undergone changes. In 2013, the UK recommended an adolescent booster dose to extend protection into early adulthood. In addition, because of the increase in incidence of serogroup W disease and high carriage among university students of serogroup Y, quadrivalent conjugated meningococcal vaccine (containing serogroups A, C, W, and Y) has been recommended in UK adolescents.[129] Other countries that introduced the vaccine in later years have followed similar schedule changes based on the experience of the vaccine in the UK. The MenC vaccine was introduced in Australia in 2003 as a single dose for all children younger than 12 months. Since 2013, the combined Hib and MenC conjugate vaccine, Menitorix, was added to the National Immunisation Program schedule at 12 months of age.[127]

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41

Chronic Meningitis

Douglas Swanson, Christopher J. Harrison

Chronic meningitis is defined arbitrarily as persistent or progressive signs and symptoms of meningeal irritation and cerebrospinal fluid (CSF) pleocytosis lasting for at least 4 weeks without improvement. The symptoms of chronic meningitis vary, but most patients have a gradual onset of fever, headache, and vomiting. The 4-week timeframe is intended to avoid extensive evaluation for individuals with self-limited processes (e.g., acute or subacute meningoencephalitis, resolving acute meningitis). In most cases of prolonged meningitis, diagnosis and treatment occur before clinical symptoms have continued for 4 weeks; thus chronic meningitis is relatively rare.

Etiology and Epidemiology

There are many infectious (Table 41.1[1–31]) and noninfectious (Box 41.1[32–42]) causes of chronic meningitis. Several parameningeal infections also can manifest as chronic meningitis. The most common entities are shown in Box 41.2. The etiology and epidemiology of chronic meningitis can vary considerably, depending on a patient's geographic locality or underlying medical conditions. Individuals with an impaired immune system are at increased risk for developing chronic meningitis, and potential etiologies also are increased. The overall incidence of chronic meningitis is unknown because of limitations of the medical literature and differs for each etiologic agent. The literature consists primarily of case reports and case series, which contain demographic and diagnostic bias.[43–45] Furthermore, most case reports are of adults. Except for tuberculosis, there is a paucity of information regarding children with chronic meningitis. The history, physical examination findings, and laboratory test results may help identify the cause of chronic meningitis; however, an etiology is not found in about one third of cases.[43,44]

TABLE 41.1

Infectious Causes of Chronic Meningitis

Agent	Reference No.
BACTERIA	
Mycobacterium tuberculosis	1
Treponema pallidum	2
Brucella spp.	3
Borrelia burgdorferi	4
Nocardia spp.	5
Actinomyces (or *Arachnia*) spp.	6
Nontuberculous *Mycobacterium* spp.	7, 8
Leptospira spp.	9
Tropheryma whipplei	10
Mycoplasma or *Ureaplasma* spp.	11
VIRUSES	
Human immunodeficiency virus	12
Lymphocytic choriomeningitis virus	13
Enterovirus[a]	14
Cytomegalovirus[b]	15
FUNGI	
Blastomyces dermatitidis	16
Histoplasma capsulatum	17
Coccidioides immitis	18
Cryptococcus neoformans or *gattii*	19
Candida spp.	20
Aspergillus spp.	21
Pseudallescheria boydii (asexual form, *Scedosporium apiospermum*)	22
Zygomycetes	23
Cladosporium spp.	24
Sporothrix schenkii	25
OTHERS	
Toxoplasma gondii	26
Taenia spp. (cysticercosis)	27
Acanthamoeba spp.	28
Balamuthia spp.	29
Angiostrongylus spp.	30
Baylisascaris spp.	31

[a] In patients with agammaglobulinemia.

[b] In patients infected with the human immunodeficiency virus.

Box 41.1

Noninfectious Causes of Chronic Meningitis

Sarcoidosis[32]

Neoplasm (e.g., non-Hodgkin lymphoma)

Systemic lupus erythematosus

Polyarteritis nodosa

Rheumatoid arthritis

Granulomatous angiitis[33]

Other forms of vasculitis[34]

Behçet syndrome[35]

Sjögren syndrome[36]

Neonatal-onset multisystem inflammatory disease[37]

Uveomeningoencephalitis syndrome[38]

Chronic benign lymphocytic meningitis[39]

Subarachnoid hemorrhage

Subdural hematoma

Drug-induced (e.g., ibuprofen, cyclooxygenase-2 inhibitor, trimethoprim)[40,41]

Wegener granulomatosis[42]

Box 41.2

Parameningeal Infections That Can Manifest as Chronic Meningitis

Encephalitis

Brain abscess

Subdural empyema

Cranial osteomyelitis

Mastoiditis

Sinusitis

Main Features of Agents Causing Chronic Meningitis

Mycobacterium tuberculosis

Epidemiology.

Most tuberculous meningitis occurs in children between 6 months and 4 years of age.[1,46–50] Risk factors include close contact with contagious cases, travel to or residence in tuberculosis (TB) endemic areas, human immunodeficiency virus (HIV) infection, other viral infections (i.e., measles), malnutrition, and immunosuppression. Close contact with an adult with pulmonary TB disease can be established in 45% to 75% of children; however, the exposure history may not be elucidated initially.[1,46–50] African Americans and immigrants and adoptees from countries where tuberculosis is endemic account for a disproportionate number of cases of tuberculous meningitis in the United States.[51] Large epidemiologic studies including children and adults find that about 1% of tuberculosis disease involves the central nervous system (CNS).[52,53] However, children are at a higher risk for developing CNS tuberculosis. A review of pediatric tuberculosis cases in the US from 1993 to 2006 shows that meningeal infection accounted for 3.1% of all cases[54] and depended on age: 7.5% in those younger than 1 year, 3.5% for 1- to 4-year-olds, 1.4% for 5- to 9-year-olds, and 1.8% for 10- to 14-year-olds.[54]

Pathogenesis.

Tubercle bacilli are inhaled, enter the lung alveoli, are filtered into draining lymph nodes, and then are spread lymphohematogenously throughout the body. Meningitis develops when caseous lesions in the brain cortex or leptomeninges rupture into the subarachnoid space.[55,56]

Clinical Manifestations.

The clinical onset of CNS tuberculosis can be acute, but more often there is gradual progression of symptoms. CNS tuberculosis usually manifests as meningitis and less frequently as intracranial tuberculoma or a brain abscess.[1,46–51] Association with disseminated (miliary) tuberculosis is not uncommon. A compilation of 913 children from 6 retrospective case series of CNS tuberculosis identifies common presenting symptoms to be fever (72%), altered mental status (62%), vomiting (61%), seizure (47%), and headache (37%).[1,46–48,50,51] Apathy is common, and about 29% of children develop cranial nerve paresis.[1,46,48–51] In outcome studies totaling 847 children with CNS tuberculosis, 18% died and 46% had neurologic sequelae.[1,46–51]

Laboratory Findings and Diagnosis.

A careful history for tuberculosis risk factors in concert with clinical findings suggests the diagnosis. Abnormalities on chest radiograph consistent with TB are present in about 75% of cases, and tuberculin skin test (TST) is positive in about 50% of children.[1,46–51] Cranial computed tomography (CT) frequently reveals hydrocephalus and basilar enhancement.[1,46–51] CSF abnormalities can be modest initially but become progressively more abnormal with increasing duration of symptoms. The CSF leukocyte count typically ranges from 10 to 500 cells/mm^3 and can briefly show polymorphonuclear cell predominance, but usually there is lymphocytic predominance. The CSF glucose level typically is low (frequently <20 mg/dL), and the protein level often is very elevated (>400 mg/dL). Reported positivity of acid-fast bacilli (AFB) stains of CSF range from 5% to 51%. The likelihood of detecting organisms on AFB stain depends on the volume of CSF sampled and the diligence of microscopic evaluations[57,58]; large volumes (5–10 mL) of centrifuged CSF and ≥30 minutes of microscopic inspection yield better results. Growth of *M. tuberculosis* from CSF occurred in 155 of 374 (41%) children with TB meningitis reported, and yields as high as 70% have been reported when up to 10 mL of CSF is sampled.[1,46–49,51] Gastric aspirate or sputum AFB smear and culture can increase the probability of diagnosis in children. Nucleic acid amplification (NAA) tests, such as polymerase chain reaction (PCR), are commercially available to detect mycobacterial DNA in CSF. A meta-analysis of the accuracy of NAA for diagnosing tuberculous meningitis revealed a sensitivity of 56% (negative predictive value, 44%) and a specificity of 98% (positive predictive value, 35.1%) among commercially available assays.[58] The PCR test can remain positive for several weeks after treatment is initiated.

Treponema pallidum

Epidemiology.

Chronic syphilitic meningitis is rare and occurs in <1% of persons with syphilis; the incidence of meningitis is greatest in the first 2 years after *T. pallidum* infection.[2] Incidence rates of syphilis have increased in the US in recent years, primarily among men who have sex with men.[59] Although neurosyphilis rarely manifests as chronic meningitis, partially treated neurosyphilis can imitate chronic meningitis.

Pathogenesis.

Congenital syphilis usually occurs by transplacental transmission of *T. pallidum* into the fetal circulation.[60] Postnatally acquired syphilis develops by penetration by *T. pallidum* through mucous membranes or abraded skin after direct contact with ulcerative lesions of infected people. The organism disseminates lymphohematogenously and can invade the CNS.

Clinical Manifestations.

In children, syphilis usually is congenitally acquired. Most infants do not have symptoms at birth, although those with syphilitic meningitis are more likely to have symptoms than those without meningitis. Common clinical features of congenital infection include ≥1 of the following: hepatosplenomegaly, mucocutaneous lesions, lymphadenopathy, and osteochondritis.[61] About 50% of infants with symptoms of congenital syphilis and 10% of asymptomatically infected infants have CSF abnormalities: a reactive Venereal Disease Research Laboratory (VDRL) test, elevated white blood cell (WBC) count, and/or elevated protein level. Despite CNS infection and abnormal CSF, neurologic signs or symptoms usually are not detectable.[62] Without treatment, congenitally infected infants can develop acute leptomeningitis between 3 and 6 months of age with ≥1 of the following signs: stiff neck, vomiting, bulging fontanel, or hydrocephalus.[61] If untreated, chronic meningovascular syphilis with progressive hydrocephalus, cranial nerve palsies, and intellectual deterioration develops by 12 months of age.

About one third of patients with the early stage of postnatally acquired syphilis have CNS involvement, which may or may not lead to acute meningovascular neurosyphilis. If untreated, one half of those with CNS infection develop symptomatic or asymptomatic late neurosyphilis. Features of symptomatic late neurosyphilis include dementia, tabes dorsalis, meningovascular disease, seizures, and optic atrophy.

Laboratory Findings and Diagnosis.

The diagnosis of syphilitic meningitis can be difficult. A serum fluorescent treponemal antibody, absorbed (FTA-ABS) test is positive in >95% of patients. If the serum FTA-ABS test result is negative, the probability of syphilitic meningitis is very low (except in patients with poorly controlled HIV infection, who may fail to produce antibodies).

Useful tests for CSF samples include specific treponemal immunoglobulin M antibodies, VDRL test, and FTA-ABS.[63] The specificity of the VDRL test on CSF is high, but sensitivity is low (30%–70%). A nonreactive result does not exclude the diagnosis. False-positive reaction can be due to blood contamination or high CSF protein. In contrast, a negative result of FTA-ABS test on CSF rules out neurosyphilis, but a positive test does not confirm the diagnosis because false-positive results can occur as a result of CSF contamination with blood or small amounts of antibodies from the serum. The best indicator of CNS infection in neonates is an abnormal physical examination, anemia, thrombocytopenia, CSF abnormalities, and abnormal bone radiographs. Detection of *T. pallidum* DNA in the blood or CSF by PCR is highly predictive of neurosyphilis.[62] PCR testing is sensitive for diagnosis of acute neurosyphilis but is less useful in chronic cases.[64] CSF chemokine CXCL13 level is elevated in neurosyphilis but can also be elevated in other conditions, so its diagnostic value remains to be determined.[65]

Brucella Species

Epidemiology.

Brucellosis is a zoonotic disease, associated particularly with sheep, goats, swine, and cattle. Humans become infected by direct contact with infected animals or by ingestion of unpasteurized milk products. There does not appear to be an increased risk for patients with underlying diseases.[66] Brucellosis is uncommon in the US, with about 100 cases annually, and less than 10% occurring in children.[67] Brucellosis is a common disease worldwide. Thus a history of travel and consumption of unpasteurized dairy products is important, especially travel in the Mediterranean region, India, or Latin America. Meningitis occurs in fewer than 5% of patients with brucellosis and is the first manifestation of the disease in about 1%. The incubation period varies from <1 week to several months, with an average of 3 to 4 weeks.

Pathogenesis.

Brucella are facultative intracellular pathogens that can survive and multiply within phagocytes and other cells. It is postulated that infected leukocytes carry organisms into the CNS.[68] Another hypothesis is that bacteria enter the CNS through direct endothelial cell invasion.

Clinical Manifestations.

Meningitis is the most common presentation of neurobrucellosis. Symptoms are nonspecific and include fever, headache, myalgia, sweating, vomiting, and meningeal irritation.[3,69,70] CSF findings include lymphocytic pleocytosis with a low to normal glucose concentration and high protein concentration. Systemic manifestations of brucellosis may be present. If treated, the prognosis usually is good; however, cases with serious neurologic sequelae are reported.[69]

Laboratory Findings and Diagnosis.

Because neurobrucellosis has nonspecific symptoms, it is important to obtain a careful history regarding travel, diet, and animal exposures. CSF lymphocytic pleocytosis with low to normal glucose and elevated protein concentrations is typical. The CSF Gram stain usually is negative. CSF culture is positive in <25% of cases; cultures of blood and, especially, bone marrow increase the diagnostic yield. The laboratory should be advised to maintain the cultures for at least 4 weeks. The diagnosis can be confirmed by detection of specific *Brucella* antibodies in the CSF or serum by agglutination or enzyme immunoassay (EIA) and Western blot.[71,72] PCR detection of *Brucella* DNA in the CSF or serum is a promising tool.[73–75]

Borrelia burgdorferi

Epidemiology.

Borrelia burgdorferi should be considered in endemic areas, which includes the northeast, upper Midwest, and northern Pacific coast of the US. Approximately 2% of children with Lyme disease develop clinical evidence of meningitis.[76] Chronic meningitis with serious neurologic sequelae is rare.[4]

Pathogenesis.

The spirochete enters the host from a bite of an infected tick: *Ixodes scapularis* in the northeast and upper Midwest of the US or the *Ixodes pacificus* in the West. *Borrelia* multiplies locally in the skin at the site of the tick bite. Local inflammation typically results in erythema migrans. In days to weeks, the spirochete can spread lymphohematogenously to other sites, including the CNS.

Clinical Manifestations.

Meningitis usually manifests during the early disseminated phase of disease with acute onset of symptoms similar to viral meningitis: fever, headache, stiff neck, and malaise. However, clinical symptoms with Lyme meningitis usually are prolonged (>7 days) compared with viral meningitis.[77–79] In addition, about one half of patients develop cranial neuropathies, with facial palsy being the most common. The prognosis usually is very good with therapy. If untreated, symptoms may persist for months.

Laboratory Findings and Diagnosis.

Residence in or travel to an endemic area and a history of untreated erythema migrans are important clues to the diagnosis. The CSF typically shows a modest monocytic and lymphocytic pleocytosis with modestly elevated protein concentration. In the absence of a history of erythema migrans, the features of prolonged headache, cranial neuropathy, and predominance of CSF mononuclear cells can help distinguish Lyme meningitis from other forms of aseptic meningitis.[77–79] Spirochetes can only rarely be isolated from CSF using a specific culture medium.[80–82] Intrathecal antibodies specific to *B. burgdorferi* can be measured by EIA, although the sensitivity and specificity of the test is uncertain.[81,82] Simultaneous serum antibodies should be obtained so that the CSF/serum antibody ratio can be determined.[80,82] An elevated CSF/serum antibody ratio might reflect past CNS infection but, in conjunction with a CSF pleocytosis and elevated protein, can be used to support the diagnosis of active infection. DNA PCR detection of *B. burgdorferi* from the CSF has good specificity, but poor sensitivity—ranging from 20% to 50% in acute cases to 0% to 25% in chronic cases.[82,83] Because of limited studies, the advantage of immunoassays over PCR for diagnosing Lyme meningitis has not been demonstrated conclusively. If the result for the immunoassay is negative and there is a high suspicion of Lyme neuroborreliosis, PCR testing may be considered. CSF levels of the chemokine CXCL13 are elevated in neuroborreliosis and decline with treatment. However, other conditions can cause elevated CSF CXCL13, and its diagnostic value for Lyme neuroborreliosis is uncertain.[84]

Other Bacteria

Leptospirosis is a rare cause of chronic meningitis because the clinical signs and symptoms of meningitis generally disappear within 7 to 21 days.[9] Other rare bacterial causes include *Nocardia*,[5] *Actinomyces*,[6] nontuberculous mycobacterdia[7,8] and *Tropheryma whipplei*.[10] Both *Mycoplasma hominis* and *Ureoplasma urealyticum* can cause chronic meningitis in preterm infants associated with development of hydrocephalus.[11]

Cryptococcus Species

Epidemiology.

Cryptococcus neoformans is a yeast-like fungus with worldwide distribution and is probably the most common cause of fungal meningitis in immunocompromised adult patients. Although *Cryptococcus* can infect normal hosts, it more commonly develops in patients with risk factors for primary impaired cellular immunity, high-dose corticosteroid treatment, leukemia, lymphoma, or HIV infection. Cryptococcal meningitis develops in up to 10% of adults with AIDS; it is the most common life-threatening fungal infection in patients with poorly controlled HIV infection, and in 40% of those affected, it is the first AIDS-defining opportunistic infection.[85] However, cryptococcal meningitis is relatively rare in children. Abadi and colleagues retrospectively compiled 30 cases of *C. neoformans* infections in HIV-infected children from 1985 to 1996 and estimated a 1% 10-year point prevalence of cryptococcosis among children with AIDS.[86] *Cryptococcus gattii* historically was found more often in tropical and subtropical geographic regions, but now is reported in temperate areas, mostly on the west coast of California and British Columbia.[87] *C. gattii* meningitis is associated with progressive CNS disease in immunocompetent patients, suggesting that genotypic or phenotypic differences of the fungus, or both, may explain its virulence in immunocompetent hosts.[87]

Pathogenesis.

C. neoformans is found in bird droppings and soil, and *C. gattii* is found in certain trees and soils. Humans become infected by inhaling airborne fungi into the lungs, where organisms can spread lymphohematogenously to the meninges.

Clinical Manifestations.

The most common presenting signs and symptoms are insidious onset of headache, fever, vomiting, nuchal rigidity, changes in mental status, and seizures.[85,86] Focal neurologic signs are not uncommon. The clinical presentation can be very similar to tuberculous meningitis. However, some patients can be completely asymptomatic.[88]

Laboratory Findings and Diagnosis.

CSF typically shows lymphocytic pleocytosis and low glucose concentration; however, infected patients with AIDS can have normal CSF findings.[85] Nevertheless, most patients have confirmatory findings from CSF India ink or calcofluor white fluorescent stains, CSF or serum cryptococcal antigen, and CSF fungal culture. Fungal cultures of the blood, urine, and sputum (if available) should be obtained, even in patients without clinical manifestations of specific organ involvement. Repeated large volumes (5–10 mL) of CSF sampling may be needed to confirm the diagnosis. The possibility of capsule-deficient *Cryptococcus* should be considered in the rare event that the diagnosis is suspected strongly but the staining and antigen detection tests are negative. In such cases, the diagnosis can be established by indirect immunofluorescence staining or reformation of the capsule by inoculation into mice, although the latter is not available readily.[89]

Histoplasma Species

Epidemiology.

Histoplasma capsulatum is a dimorphic fungus found in soil and is endemic in the Mississippi, Ohio, and Missouri River valley regions of the US. CNS infection is rare and usually occurs in immunocompromised or malnourished individuals or infants. Neurologic involvement is reported in 8% to 18% of cases of disseminated disease,[17] but an incidence of 55% has been found in AIDS patients with disseminated histoplasmosis.

Pathogenesis.

Humans become infected by inhaling spores into the lungs, which then spread lymphohematogenously to the meninges or brain.

Clinical Manifestations.

In a report of 18 cases and review of 86 cases from the literature, chronic meningitis was the most common form of CNS *Histoplasma* infection, with about 40% of patients coming to medical attention with accompanying disseminated histoplasmosis and 25% with isolated chronic meningitis.[17] Clinical symptoms are nonspecific among chronic meningitis cases and include headache (24%), depressed level of consciousness (29%), confusion (22%), and cranial neuropathy (19%). Personality changes and seizures occur in 10% to 15% of patients. Fever typically is present. The onset of symptoms is at least 2 months before diagnosis in more than 70% of cases.

Laboratory Findings and Diagnosis.

CSF reveals an elevated protein concentration, modestly low glucose concentration, and 50 to 500 WBCs/mm^3 (predominantly mononuclear cells).[17] CSF culture for *Histoplasma* is positive in 30% to 50% of cases. Culturing a large volume (>10 mL) of CSF is recommended for optimal yield.[90] Blood culture is positive in about 50% of cases. *Histoplasma* antigen can be assayed in blood, urine, and CSF. In earlier reports, the sensitivity of antigen detection in chronic meningitis was 38% in blood, 71% in urine, and 38% in CSF. However, a new assay with improved sensitivity is available commercially, but performance in CSF samples has not been evaluated sufficiently. The antigen test can cross-react in cases of blastomycosis. CSF and serum antibody tests are approximately 90% sensitive but can reflect past infection. In addition, the antibody response can be impaired in immunosuppressed individuals, and the test can have false-positive results because of cross-reactions caused by infection with other fungi, including *C. neoformans*. Current recommendations to evaluate for CNS histoplasmosis are to perform multiple tests, including (1) fungal culture, antigen, and antibody tests on CSF; (2) fungal culture, antigen, and antibody tests on blood; and (3) antigen test on urine.[91] CSF specimens should be obtained repeatedly if there is no diagnosis and suspicion for histoplasmosis remains. Chest radiographs may provide a clue to the diagnosis; one half of cases have abnormalities consistent with histoplasmosis.[90]

Coccidioides Species

Epidemiology.

Coccidioides species are dimorphic fungi found in the soil of southwestern US, northern Mexico, Central America, Venezuela, Argentina, and Paraguay. Primary infection develops from the inhalation of airborne spores and occurs most frequently in the summer and fall. The incidence of coccidioidomycosis appears to increase when rainy summers are followed by dry winters and windstorms.[91] Although respiratory infection with *Coccidioides* is common, disseminated disease develops in only 1% of persons. Approximately one third of patients with disseminated disease develop meningitis. Those at increased risk for disseminated disease and meningitis include immunosuppressed hosts, African American and Filipino people, pregnant women, neonates, and elderly people.[92]

Pathogenesis.

Airborne spores are inhaled into the lungs, where organisms then can spread lymphohematogenously to the meninges or brain.

Clinical Manifestations.

Primary respiratory infection often is asymptomatic, but fever, malaise, cough, myalgia, headache, and chest pain can occur. The most common presenting symptoms of meningitis in adults include headache (75%), nausea and vomiting (52%), and fever (50%). Meningismus and focal neurologic symptoms occur in one third and one fourth of patients, respectively.[18]

Laboratory Findings and Diagnosis.

A history of travel or residence in endemic areas provides an important clue to the diagnosis. Cranial CT or MRI is abnormal in more that one half of cases, with basilar enhancement, hydrocephalus, or infarctions the most common findings.[18] Visualization of *Coccidioides immitis* in CSF samples is rare, and although the organism is not fastidious in growth requirements, only about one third of patients with meningitis have a positive CSF culture. Sampling of large volumes of CSF, followed by sterile filtration and culture of the filter, increases the yield. Detection of antibodies to *Coccidioides* by EIA has a sensitivity of 93% on serum and 75% on CSF specimens.[18] Diagnosis by real-time PCR analysis of CSF may be promising.[93]

Other Fungi

The usual course of *Candida albicans* meningitis is acute. Chronic meningitis is an uncommon manifestation of disseminated candidiasis that can be seen in premature infants and children with congenital immunodeficiencies. CNS *Candida* infection also can occur in children with a ventriculoperitoneal shunt. Chronic meningitis due to *Blastomyces dermatitidis* is uncommon but should be considered in the immunocompetent host from an endemic area (i.e., the Mississippi and Ohio River valley regions and regions along the Great Lakes and the St. Lawrence River of the US). Other fungi, such as *Aspergillus, Sporothrix, Cladosporium,* and *Allescheria* spp., and agents of mucormycosis and phaeohyphomycosis are rare causes of chronic meningitis. Disseminated aspergillosis often involves the CNS, but usually as a focal brain lesion, and not as isolated chronic meningitis. Fungal meningitis can occur rarely from CNS-related procedures, as recently reported in a large multistate outbreak of polymicrobial fungal CNS infections due to contaminated epidural or paraspinal administration of compounded methylprednisolone formulations.[94]

Parasites

Protozoa and parasites can cause chronic meningitis, including *Toxoplasma,*[26] *Taenia,*[27] and rarely *Acanthamoeba,*[28] *Balamuthia,*[29] *Baylisascaris,*[31] and *Angiostrongylus* spp.[30] Reactivation of *Toxoplasma gondii* is a rare cause of CNS infection in immunosuppressed children and usually causes focal brain lesions rather than meningitis. *Taenia* tapeworms endemic to Latin America, Asia, and East Africa can form cysts in the brain (neurocysticercosis) that most commonly result in acute onset of afebrile seizures; neurocysticercosis rarely presents as chronic meningitis.

Viruses

HIV is probably the most common viral cause of chronic meningitis,[12] but patients with poorly controlled HIV infection also can develop chronic cytomegalovirus (CMV) meningitis. In patients with agammaglobulinemia, enteroviruses can cause persistent meningitis.[14] Another rare viral cause of chronic meningitis is lymphocytic choriomeningitis virus.[13] Diagnosis based on viral isolation from the CSF or demonstration of specific antibody responses (in blood or CSF) can require 4 to 6 weeks and is insensitive. PCR assays offer rapid detection (within hours if necessary) for many viruses (e.g., enteroviruses, CMV) with excellent sensitivity and specificity. In chronic meningitis viral replication can be low; PCR especially is valuable.

Evaluation

Before testing for the myriad infectious causes of chronic meningitis (see Table 41.1), noninfectious and parameningeal conditions should be considered (see Boxes 41.1 and 41.2). In addition, cases of recurrent meningitis (i.e., repeated episodes of acute meningitis separated by symptom-free periods) should be distinguished from chronic meningitis (see Chapter 42). Fig. 41.1 is an algorithm to guide differential diagnosis.

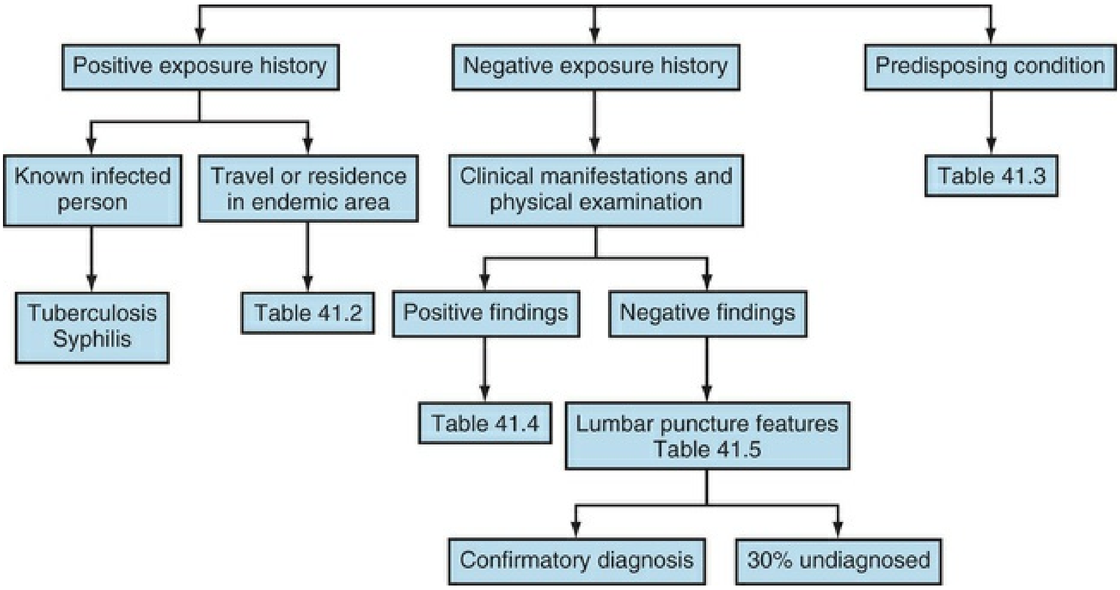
Positive exposure history
Negative exposure history
Predisposing condition
Known infected person
Travel or residence in endemic area
Clinical manifestations and physical examination
Table 41.3
Tuberculosis Syphilis
Table 41.2
Positive findings
Negative findings
Table 41.4
Lumbar puncture features Table 41.5
Confirmatory diagnosis
30% undiagnosed

FIGURE 41.1 Algorithm for evaluation of patients with signs and symptoms of chronic meningitis.

History

Although the exact cause of chronic meningitis may not be found in up to one third of cases,[43,44] close attention to details can provide important clues to the diagnosis, or at least help narrow the differential diagnosis. A history of environmental exposure (e.g., travel, drugs, unusual foods, animals, insects) or exposure to persons infected with pathogens spread by person-to-person contact (e.g., tuberculosis, syphilis, HIV) should be sought (Table 41.2). The travel history should be thorough and include travel or residence in both domestic and international regions. Concomitant symptoms, such as rash or chronic cough, can assist in determining the etiology. Although in most cases signs and symptoms of illness develop within a short time after the exposure (such as in brucellosis, Lyme disease, and blastomycosis), a long incubation period (such as for cysticercosis) or reactivation of a dormant focus several years after exposure (such as in the source adult with tuberculosis, in histoplasmosis, and toxoplasmosis) can occur.

TABLE 41.2

Agent Causing Chronic Meningitis and Likely Exposure History in Patient

Agent	Exposure History
Brucella spp.	Ingestion of unpasteurized dairy products or animal contact, especially in the Mediterranean, India, or Latin America
Leptospira spp.	Occupational (farmer) or recreational (camper, swimmer) exposure to urine of wild and domestic mammals during summer and fall
Borrelia burgdorferi	T/R[a] in northeast United States, Wisconsin, Minnesota, California, and Oregon, especially during late summer and early fall, or in Europe, China, Japan, and Australia, with consequent tick exposure
Blastomyces spp.	T/R in Ohio and Mississippi River valleys or North Carolina
Histoplasma sp.	T/R as for *Blastomyces*, plus Appalachian mountains and Virginia
Coccidioides sp.	T/R in southeastern United States, Mexico, Central America, Venezuela, Argentina, or Paraguay
Sporothrix sp.	T/R in tropical and subtropical Americas, or a prick from a rose thorn
Cysticercosis	T/R in Latin America, Southeast Asia, Africa, eastern Europe, and southwestern United States
Angiostrongylus sp.	T/R in Hawaii, Australia, Southeast Asia, or Philippines
Baylisascaris sp.	Exposure to raccoon feces

[a] T/R, travel or residence.

A careful history also can reveal predisposing conditions that increase the risk for opportunistic infections (Table 41.3). For example, prematurity, prolonged use of corticosteroid therapy, cancer, HIV infection, intravenous drug abuse, or use of indwelling catheters facilitates invasion and dissemination of *Candida* spp. Direct extension of *Aspergillus* spp. infection from an adjacent sinus, ear, or orbit or after head trauma or surgery can lead to infection of the CNS.

TABLE 41.3

Causes of Chronic Meningitis With Predisposing Conditions

	Predisposing Conditions						
Causative Organism	**Indwelling Catheter**	**Trauma or Surgery**	**Illicit IV Drug Use**	**Long-Term Corticosteroid**	**Cancer**	**Transplant**	**HIV Infection**
Candida	●	●	●	●	●	●	●
Aspergillus	●	●	●	●	●	●	●
Cryptococcus				●	●	●	●
Cladosporium		●					
Zygomycetes		●	●				
Histoplasma					●	●	●
Coccidioides				●	●	●	●
Blastomyces					●	●	●
Toxoplasma					●	●	●
Nocardia				●	●	●	
Mycobacterium tuberculosis[a]				●	●	●	●

[a] Also occurs in immunocompetent host.

HIV, human immunodeficiency virus; IV, intravenous.

Physical Examination

A thorough and careful physical examination is important because, occasionally, the physical findings suggest the diagnosis (Table 41.4).

TABLE 41.4

Etiology of Chronic Meningitis Relative to Clinical Manifestations

Skin Lesions	**Erythema Nodosum**	**Lung Involvement**	**Chorioretinitis**	**Endophthalmitis**	**Neuropath**
Blastomyces *Candida* *Coccidioides* *Cryptococcus*	*Mycobacterium tuberculosis*	*Blastomyces*	*Candida* *Histoplasma* *Mycobacterium tuberculosis*	*Candida*	Cranial *Mycobacteri tuberculosis* *Treponema*
	Histoplasma	*Coccidioides*		*Cryptococcus*	

Zygomycetes (e.g., mucormycosis) *Sporothrix* *Treponema pallidum* *Borrelia burgdorferi* *Nocardia* *Taenia*	*Coccidioides*	*Cryptococcus*	*Treponema pallidum* *Toxoplasma* CMV Sarcoidosis	*Coccidioides*	*pallidum*[b] *Borrelia* *Histoplasma* HIV Cancer Sarcoidosis Peripheral *Borrelia* *Brucella* Sarcoidosis Systemic lupus erythematc CMV[c]
	Behçet disease	*Histoplasma*		*Sporothrix*	
	Sarcoidosis	*Paracoccidioides*		*Pseudallescheria*	
	Systemic lupus erythematosus	*Mycobacterium tuberculosis*		*Treponema pallidum*	
		Sarcoidosis		*Actinomyces*	
				Mycobacterium tuberculosis	

[a] Especially cranial nerve VI.

[b] Especially cranial nerves VII and VIII.

[c] In AIDS patients.

AIDS, acquired immunodeficiency syndrome; CMV, cytomegalovirus; HIV, human immunodeficiency virus

Skin.

The skin examination can reveal a typical lesion, such as the erythema migrans of Lyme disease, or provide a source for culture or biopsy to identify an etiology. Erythema nodosum is seen in some diseases, and nonerythematous nodules can be found in patients with systemic candidiasis, blastomycosis, and nocardiosis. Although uncommon, the umbilicated nodules of cryptococcal infection in HIV-infected patients and the characteristic palmar lesions of secondary syphilis can guide investigations.

Lungs.

The lungs are the portal of entry for many of the pathogens that cause chronic meningitis, including *Blastomyces, Cryptococcus, Coccidioides, Histoplasma,* and *M. tuberculosis*. Careful physical examination and selective laboratory evaluations (chest radiography, microscopy, sputum culture, and, occasionally, lung biopsy) can be useful.

Eye.

An examination by an ophthalmologist can sometimes identify important ocular lesions suggestive of an etiology. Findings of endophthalmitis can support the diagnosis of infection with

Candida, *Cryptococcus*, and rarer infections. Chorioretinitis can be indicative of CMV, histoplasmosis, or toxoplasmosis. Uveitis might suggest a possible noninfectious etiology, such as systemic lupus erythematosus (SLE). If mental status changes or papilledema are present, cranial CT should precede performance of the lumbar puncture.

Neurologic Examination.

The neurologic examination is of limited use in identifying a specific etiology, because a variety of neurologic abnormalities can be seen with most causes of chronic meningitis. Cranial neuropathy is more commonly seen with syphilis, tuberculosis, and Lyme disease. Peripheral neuropathy and chronic meningitis may indicate Lyme disease, CMV infection, or SLE.

Liver.

Hepatomegaly, not a common finding in patients with chronic meningitis, should direct the diagnosis toward a relatively few associated pathogens (see Table 41.4).

Imaging Studies

CT or MRI with contrast material should be performed before lumbar puncture to exclude space-occupying lesions, hydrocephalus, or increased intracranial pressure. Imaging also can help to identify a parameningeal infectious site, meningeal inflammation, focal brain lesions, or cerebral infarction. Because the lungs often are the primary site of infection for many organisms that cause chronic meningitis, chest radiograph is obtained routinely.

Cerebrospinal Fluid Analysis

Most infectious causes of chronic meningitis elicit similar CSF abnormalities (i.e., pleocytosis <500 WBCs/mm^3, with lymphocyte predominance, low or normal glucose concentration, and elevated protein concentration), but CSF findings can help to direct the differential diagnosis (Table 41.5). An infectious cause other than early *M. tuberculosis* is rare when CSF has <50 WBCs/mm^3; in such cases, noninfectious causes should be considered.

TABLE 41.5

Predominant Leukocyte Found in Cerebrospinal Fluid for Various Causes of Chronic Meningitis

	Predominant Leukocytes in CSF		
Causative Agent	**Lymphocytes**	**Neutrophils**	**Eosinophils**
Bacteria	*Mycobacterium tuberculosis*	*Nocardia*	*Mycobacterium tuberculosis*
	Treponema pallidum	*Actinomyces*	*Treponema pallidum*
	Borrelia	*Brucella*	
	Brucella	*Leptospira*	
Fungi	All	All	*Coccidioides*
Parasite	*Taenia*	*Entamoeba histolytica*	*Angiostrongylus*
	Toxoplasma		*Taenia solium*
			Baylisascaris
Viruses	LCMV	Mumps	
	CMV	CMV[c]	
Other	Parameningeal focus[a]	Suppurative parameningeal focus[a]	Hodgkin disease
	Sarcoidosis[b]	Systemic lupus erythematosus	Chemical meningitis
	Chronic idiopathic meningitis	Chemical meningitis	Drug hypersensitivity
	Malignant process	Drug hypersensitivity	
	Behçet disease	NOMID/CINCA	

[a] See Box 41.2.

[b] See Box 41.1.

[c] In AIDS patients.

AIDS, acquired immunodeficiency syndrome; CMV, cytomegalovirus; LCMV, lymphocytic choriomeningitis virus; NOMID/CINCA, neonatal-onset multisystem inflammatory disease/chronic infantile neurologic cutaneous articular syndrome.

CSF pleocytosis with predominance of neutrophils is uncommon in chronic meningitis but can be seen in infection due to *Actinomyces, Nocardia, Aspergillus,* or *Candida* spp. and early in tuberculous meningitis. A suppurative parameningeal focus, such as brain abscess, subdural or epidural empyema, cranial osteomyelitis, mastoiditis, or sinusitis, can cause sympathetic inflammation in the CSF, mild pleocytosis, and mild elevation of protein, typically without hypoglycorrhachia. Noninfectious causes of neutrophilic pleocytosis in CSF include SLE, exogenous chemicals (e.g., radiographic contrast material, chemotherapeutic agents, povidone iodine), and drugs (i.e., isoniazid, ibuprofen, or sulfa drugs).

Eosinophilic pleocytosis in chronic meningitis occurs rarely, and possible etiology includes parasites, such as *Angiostrongylus cantonensis, Taenia solium,* and *Baylisascaris procyonis* (ascarid of raccoons). Neurosyphilis, tuberculous meningitis, and coccidioidal meningitis rarely can cause mild CSF eosinophilia (<10% of WBCs). Noninfectious processes, such as Hodgkin disease, chemical meningitis, drug hypersensitivity, and complications of ventriculoperitoneal shunts, also should be considered in the differential diagnosis of CSF eosinophilia.

Stains for bacteria, fungi, and acid-fast organisms should be performed. Special staining (using monoclonal antibodies) of lymphocytes in CSF should be considered if leukemia or lymphoma is suspected. Culture of a CSF sample is important and should include appropriate techniques for isolation of aerobic, facultative anaerobic, and fastidious bacteria (e.g., increased CO_2 to enhance growth *of Actinomyces, Nocardia,* and *Brucella* spp.); fungi; and mycobacteria. Cultures should be incubated for an extended time because growth of some bacteria and fungi is slow.

CSF and serum for cryptococcal antigen should be performed in most instances. When indicated, testing for CSF antibodies to agents, such as *Treponema pallidum, Borrelia burgdorferi, Histoplasma capsulatum, Coccidioides immitis, Sporothrix schenckii, Toxoplasma gondii,* and *Taenia* spp., is performed with concurrent serum specimen testing. (1-3)-β-D-glucan testing of CSF may become useful for suspected fungal meningitis.[95,96] Measurement of antigen in CSF or blood and PCR testing are available for some pathogens (Table 41.6). Lumbar puncture may need to be repeated for cultures and additional studies and to follow the course of meningeal inflammation.

TABLE 41.6

Commercially Available Diagnostic Tests for Causative Agents of Chronic Meningitis[a]

	CSF					Blood	
Agent	Stain	Culture	Antigen	Antibody	PCR	Ab	Ag
Mycobacterium tuberculosis	+	++			++		

Treponema pallidum	+/–			+++	++	+++	
Brucella	+/–	+		++		++	
Borrelia burgdorferi	+/–	+/–		++	+	+++	
Nocardia	+/–	++					
Actinomyces	+/–	++					
Leptospira		+/–				++	
Mycoplasma		++			+++		
Ureaplasma		++			+++		
Blastomyces	+/–	+/–		+		+	
Histoplasma	+/–	+/–	++	+		+	++
Coccidioides	+/–	+	++	+		+	++
Cryptococcus	++	+	+++			++	++
Candida	++	+++	+				
Aspergillus	+/–	+			++		++
Sporothrix	+/–	+		+	++	+	
Toxoplasma	+/–	+/–		++	+++	++	
Angiostrongylus	+		++				
Taenia				++		+++	
Viruses		+		+	+++	+	

[a] +++ Test of choice; ++ modestly useful; + occasionally useful; +/− rarely useful.

Ab, antibody; Ag, antigen; CSF, cerebrospinal fluid; PCR, polymerase chain reaction.

Additional Evaluations

Many patients with chronic meningitis also have disseminated disease; therefore, fungal and mycobacterial blood and urine cultures should be considered. With an appropriate exposure history, serologic tests for some pathogens (see Table 41.6) can be diagnostic. Because immunodeficiency greatly modifies the differential diagnosis, HIV testing should be performed for all patients with chronic meningitis. If immune suppression is considered likely, PCR assays may be more reliable than antibody testing. A Mantoux tuberculin skin test or, in children 5 years or older, an interferon γ release assay (IGRA) on blood is indicated to evaluate for tuberculosis. Repeat testing may be helpful if tuberculosis remains a concern. Brain biopsy should be considered when the diagnosis remains elusive and radiographic imaging identifies a focal lesion or meningeal enhancement.[97]

Empiric Therapy

When the initial evaluation of the patient identifies the cause of chronic meningitis, specific therapy should be instituted. When choosing the antimicrobial agent or agents, the drug's ability to penetrate the blood-brain or CSF barrier to achieve consistent and adequate drug levels is of paramount importance. Chapters on specific pathogens contain specific recommendations.

After the initial evaluation, the cause of chronic meningitis remains unknown in many patients. In these situations, decisions regarding use of empiric treatment and preferred antimicrobial agents are controversial. Because tuberculous meningitis is probably the most common cause of chronic meningitis, an empiric trial with antituberculous drugs is favored by many clinicians. However, such an approach was not found to be beneficial in one study from the Mayo Clinic.[98] If empiric antituberculous therapy is initiated, further studies should be done in patients who are seriously ill or who deteriorate rapidly. Corticosteroid therapy should only be added if the patient continues to deteriorate while receiving antituberculous therapy or if fungal meningitis is reasonably excluded. Several adults with idiopathic chronic meningitis in the Mayo Clinic study were treated with empiric corticosteroid and had a favorable response.[98] The mean length of symptoms before starting corticosteroids was 17 months. Corticosteroid therapy should be considered cautiously because of the potential catastrophic outcome when given to patients with unrecognized and untreated tuberculous or fungal meningitis. If fungal meningitis is a possibility, empiric antifungal treatment should be considered, recognizing the potential adverse drug effects, and that response to therapy may be difficult to determine because patients with fungal meningitis often respond slowly to treatment. Choice of antifungal agent should be made on the basis of activity against the suspected organism and CSF penetration.

In previously healthy patients who have had symptoms of meningitis for several weeks and who are not seriously ill, it is reasonable to investigate the cause of meningitis without initiating treatment. If the cause cannot be found and the patient is not improving, empiric therapy is considered. If antituberculous medications are initiated and the patient does not improve within a few weeks, antifungal therapy should be considered.

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42

Recurrent Meningitis

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Recurrent meningitis typically is defined as two or more separate episodes of meningitis weeks to months apart with full recovery between events. This is in contrast to recrudescence or relapse of meningitis, which represents persistence of the original infection due to treatment failure.[1] Recurrent meningitis is relatively uncommon, and its etiology often is difficult to determine. When the cause is detected, most cases are bacterial in origin, although recurrent episodes can be characterized by negative cerebrospinal fluid (CSF) cultures, and rarely a virus such as herpes simplex virus (HSV) can be causative.

Etiologic Agents

The pathogen in more than 50% of patients with recurrent bacterial meningitis is *Streptococcus pneumoniae*, most often in association with an underlying anatomic abnormality or immunodeficiency. *Neisseria meningitidis* is the second most common bacterial pathogen, accounting for approximately 25% of cases of recurrent bacterial meningitis,[1] most often associated with complement deficiency. Recurrent meningitis due to *Haemophilus influenzae* type b (Hib) has been reported rarely since the introduction of conjugate Hib vaccine. *Staphylococcus aureus* and gram-negative bacilli such as *Escherichia coli* can be associated with recurrent meningitis; the recurrent isolation of any of these organisms suggests a communication between the subarachnoid space and the paranasal sinuses, skin (such as a dermal sinus), or intestine if gram-negative organisms are isolated (such as posterior neurenteric fistula or anterior meningomyelocele). Other bacteria, such as oral streptococci, *Proteus* spp., enterococci, *Klebsiella* spp., and group B *Streptococcus* have been sporadically reported to cause recurrent meningitis. In cases in which bacteria cannot be detected, the differential diagnosis of recurrent aseptic meningitis should be considered (Box 42.1).[2–15]

Box 42.1

Conditions Associated With Recurrent Aseptic Meningitis

Mollaret syndrome[2]

Familial Mediterranean fever (FMF)[3]

Intracranial or intraspinal cyst[4]

Dermoid or epidermoid tumor[5]

Behçet disease[6]

Sarcoidosis[7]

Systemic lupus erythematosus[8]

Intracranial tumor[9]

Drug-induced (e.g., penicillins, cephalosporins, trimethoprim-sulfamethoxazole, nonsteroidal anti-inflammatory drugs, immune globulin intravenous, OKT3)[10,11]

Herpes simplex virus type 1 or 2 infection[12]

Enterovirus infection[13]

Migraine syndrome[14]

Vogt-Koyanagi-Harada syndrome[15]

Epidemiology

Recurrent episodes of meningitis are rare, and the prevalence for each of the predisposing causes varies. A 1999 review of 463 cases of bacterial meningitis in children identified 6 patients with confirmed recurrent episodes, representing 1.3% of bacterial meningitis cases.[16] The most common predisposing condition is a communication between the subarachnoid space and the base of the skull (CSF leak or fistula) resulting from head trauma, surgery, or a congenital defect; immunologic defects are less common. CSF rhinorrhea or otorrhea occurs after approximately 1% to 2% of all head injuries, but either condition is more frequent in selected presentations (i.e., 11% of basilar skull fractures[17] and 25% of fractures involving the paranasal sinuses[18]). Most CSF leaks resolve spontaneously within a few days. Persistent CSF leaks are associated with an increased risk for meningitis.[19]

The risk for development of meningitis at a particular time after injury varies. About one fifth of cases of posttraumatic meningitis occur within 1 to 2 weeks after head trauma,[20] one third within the first month, and half within 6 months. However, almost 50% of patients have the first episode of meningitis ≥7 months after the traumatic event causing a CSF leak, and delay of as long as 34 years has been reported.[21] Procedures such as intracranial surgery, nasal and paranasal sinus surgery, and otologic surgery also can predispose to recurrent meningitis.[18] On average, postneurosurgical meningitis develops within 10 days of the procedure, with an incidence of 0.3% to 8.9%[22]; gram-negative bacteria frequently are isolated.

Various congenital defects in the bony structure of the skull contribute to the development of CSF fistulas and thus predispose to recurrent meningitis (Box 42.2). The incidence of recurrent meningitis in patients with a congenital defect is unknown but probably is low, although the defects themselves are not uncommon. For example, in children with idiopathic sensorineural hearing loss, computed tomography (CT) of the temporal bone revealed that 21% had an inner-ear malformation.[23] Mondini dysplasia (a developmental arrest at the seventh week of gestation characterized by hypoplasia of the cochlear labyrinth resulting in 1 to 1.5 turns instead of the normal 2.5 turns and occasionally associated with intrauterine CMV infection) is commonly cited as contributing to recurrent meningitis (Fig. 42.1).[24] Although deafness frequently is associated with Mondini dysplasia, it is unilateral and therefore often unrecognized. Additionally, trauma can precipitate a fistulous connection in milder defects and lead to meningitis. Epidermoid and dermoid cysts with dermal sinus tract are well-known causes of recurrent meningitis, with many cases coming to attention because of a new-onset neurologic deficit, infection, or both.[25] Lymphangiomatosis of the skull is a rare cause of CSF leak and recurrent meningitis.[26]

Box 42.2

Congenital Anomalies Associated With Recurrent Bacterial Meningitis

Anomalies of the Anterior Fossa

Encephalocele

Meningocele

Defects of the cribriform plate

Enlarged subarachnoid space

Intracranial cyst

Anomalies of the Temporal Bone

Mondini dysplasia

Stapedial anomalies

Klippel-Feil syndrome

Pendred syndrome

Petromastoid fistula

Widened cochlear aqueduct

Hyrtl fissure

Spinal Defects

Dermoid or epidermoid cyst

Neuroenteric fistula

Other

Asplenia

Vein of Galen malformation

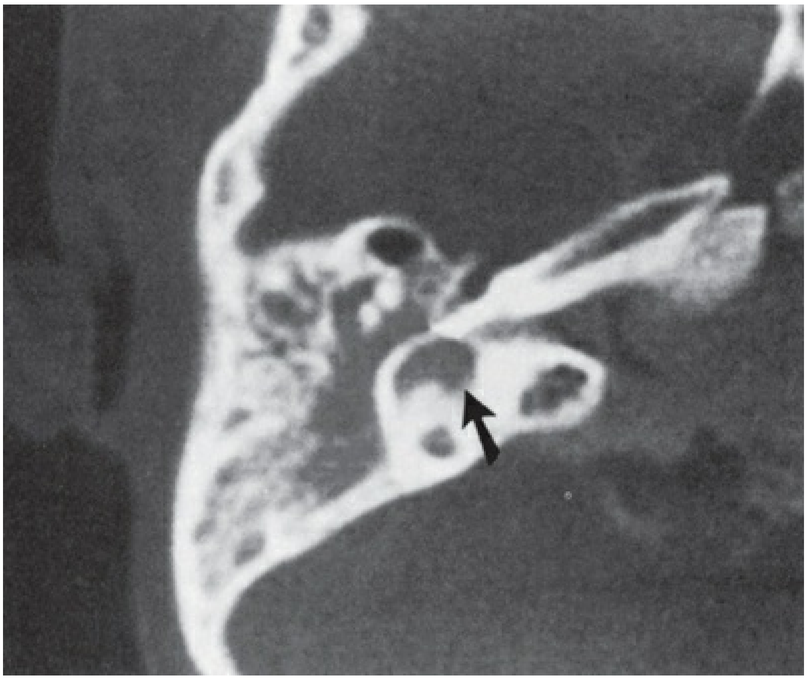


FIGURE 42.1 Computed tomography with intravenous contrast enhancement of the right middle ear showing a dysplastic cochlea *(black arrow)* consistent with Mondini dysplasia. (Courtesy of N. M. Young, MD, Children's Memorial Hospital, Chicago.)

The incidence of recurrent bacterial or culture-negative meningitis after a parameningeal focus of infection (Box 42.3) or related to more distant foci (e.g., endocarditis) is unknown, but these entities should be considered in the differential diagnosis of recurrent meningitis. Vein of Galen malformations have also been implicated as a cause of recurrent meningitis.

Box 42.3

Parameningeal Foci of Infection Associated With Recurrent Meningitis

Sinusitis

Mastoiditis

Brain abscess

Subdural empyema

Central nervous system shunt infection

Infected dermoid sinus

Infected porencephalic cyst

Cranial or vertebral osteomyelitis

Neurenteric fistula

Anterior meningomyelocele

Immunologic Defects

Several disorders of the immune system can predispose to recurrent meningitis, particularly meningitis caused by encapsulated bacteria. These include antibody immunodeficiencies (X-linked agammaglobulinemia, common variable immunodeficiency, immunoglobulin G [IgG] subclass deficiencies), HIV infection, splenic dysfunction (i.e., surgical splenectomy, congenital asplenia, sickle cell disease, or hemoglobinopathies), properdin deficiency, and complement deficiencies (see Chapters 101 to 103).

The frequency of a persistent complement deficiency in the general population is most likely <0.03%.[27] Deficiency of properdin (the molecule that stabilizes the C3bBb complex) and terminal components of complement are associated with recurrent meningococcal infection. Meningitis occurs in approximately 39% of patients with terminal complement deficiencies and 6% of those with properdin deficiency.[28] Recurrent bacterial meningitis (especially due to *N. meningitidis*) occurs in patients with deficiency of one of the terminal complement components (i.e., C5 to C9) and can be mild. In contrast recurrent meningococcal meningitis is rare in individuals with properdin deficiency because the initial infection usually is fatal.[29]

Bacterial infections are less frequent in C4 deficiency, presumably because affected individuals can compensate through the alternative pathway. In general, C5 deficiency is associated with a higher incidence of bacterial meningitis than deficiencies in more terminal components, probably because C5 promotes chemotaxis that localizes infection before invading the meninges. Almost 50% of individuals with C6 deficiency and 40% with C7 deficiency experience bacterial meningitis. Specific defects in the trimeric C8 molecule are associated with race. Deficiency of the C8-α and C8-γ subunits (the portion responsible for membranolytic function) is seen in black and Hispanic populations, whereas deficiency of the C8-β subunit (the portion responsible for attachment of C8 to C5b67) is seen in white populations. Most patients with C9 deficiency are healthy and rarely have meningococcal meningitis. Reported complement deficiencies in blacks involve terminal components almost exclusively.[27]

Persons with a complement deficiency have a 42% lifetime risk for any meningococcal infection compared with 0.0072% in the general population.[27] An estimated 10% to 15% of all patients with single or recurrent systemic infections due to *Neisseria* spp. have a complement deficiency.[27,30] The median age for the first episode of meningococcal infection in the general population is 3 years (peak age, 3 to 8 months), compared with 17 years in individuals with complement deficiency. In addition, recurrent meningococcal infection is rare in the general population, and relapsing infection is uncommon, with a rate of about 0.6%. In contrast, the recurrence rate in patients with complement deficiencies is high, approximately 45%, and the relapse rate is 10 times higher than in the general population, about 6%. The mortality rate for meningococcal infection with meningococcemia was estimated to be 25% in the general population compared with only 6.9% for all complement-deficient patients and 4.5% for those with terminal complement deficiencies.

Deficiency in some immunoglobulin subclasses (such as IgG2 and

IgG3) is associated rarely with recurrent meningitis, as are mutations in mannose-binding lectin (MBL).[31–33]

Pathogenesis

Trauma and Congenital Defects

Recurrent meningitis after head trauma only occurs if, in addition to fracture, there is a tear of the dura. Because the dura is bound more tightly to the base of the skull in children than in adults, a higher incidence of CSF leak occurs after head trauma in children. CSF leak is a portal of entry for bacteria comprising normal flora of the nasopharynx into the central nervous system (CNS). Fracture through the paranasal sinuses can manifest as an apparent CSF leak only transiently or not at all, with recurrent bacterial meningitis perhaps the only indication of the abnormal communication. Fracture of the temporal bone is the most common cause of CSF leak into the middle ear.[34] After fracture of the petrous bone, CSF can leak into the nasopharynx, but the expected rhinorrhea may not be detected externally. Meningitis or recurrence can occur years or even decades after the initial skull fracture occurred. Obtaining a detailed history for previous head trauma is crucial.[35]

Encephalocele is a rare cause of CSF leak that predisposes to recurrent meningitis. The probable etiology is a small congenital defect in the skull bone that allows cerebral tissue to protrude, but trauma, intracranial infections, tumor, or a surgical procedure can be the cause.

In patients with congenital abnormalities of the inner ear, several mechanisms contribute to the communication between the CSF and the middle-ear space.[36] First, the cochlear aqueduct (i.e., the perilymphatic duct), which normally connects the subarachnoid space with the inner ear, can be abnormally wide, allowing CSF to flow freely to the inner ear (a cochlear implant using a spacer can provide the same connection). Second, a Hyrtl fissure (an embryonic cleft connecting the posterior fossa and the middle ear), which usually is obliterated during normal ossification of the petrous bone, can remain patent. Third, there may be an abnormal communication between the internal acoustic canal (traversed by the eighth nerve) and the perilymph of the vestibule. CSF leakage from the vestibule to the middle ear occurs most commonly through the oval window. A hole in the stapes footplate with CSF leakage through the oval window due to increased vestibular perilymph pressure that displaces the stapes footplate has been described.[37,38]

In Pendred syndrome (congenital perceptive hearing loss with thyroid enlargement and abnormal perchlorate test result), a cochlear defect that resembles Mondini dysplasia predisposes to recurrent meningitis.[39] In Mondini dysplasia, the CSF leaks into the middle ear through a defective foramen ovale.[40] In Klippel-Feil syndrome (low hairline with short neck and limitation of neck movement), several anomalies can predispose to recurrent meningitis.[41] The most common are inner-ear abnormalities, including fistulas through the oval window, stapes footplate, or round window or along the facial nerve. Anomalies of vertebral bodies with neurenteric cyst or fistulas or a dermoid cyst, with or without dermal sinus tract, also have been described in children with Klippel-Feil syndrome and can serve as portals for entry of bacteria.

Occult CNS abnormalities should be suspected in any patient who has recurrent meningitis and does not have known predisposing CNS abnormalities or underlying immunologic defects. A dermal sinus tract ending intracranially (Fig. 42.2) or intraspinally (Fig. 42.3) in a dermoid cyst can permit entry of skin flora into the subarachnoid space.[42] Thus meningitis caused by skin organisms (i.e., *Staphylococcus* spp., gram-negative bacilli) should prompt a careful search for such a lesion. Other abnormalities, such as an enteric cyst contained within a meningocele,[43] continuous sequestration of bacteria on a CNS shunt or in paraventricular sites (i.e., brain abscess[44]), or a neurenteric fistula, can serve as the entry points. Rare cases of recurrent meningitis also have been reported secondary to migration of a ventriculoperitoneal shunt through the bowel wall into the gastrointestinal tract, or associated with procedures to dilate the rectum or esophagus or after spinal arthrodesis for scoliosis.[45,46]

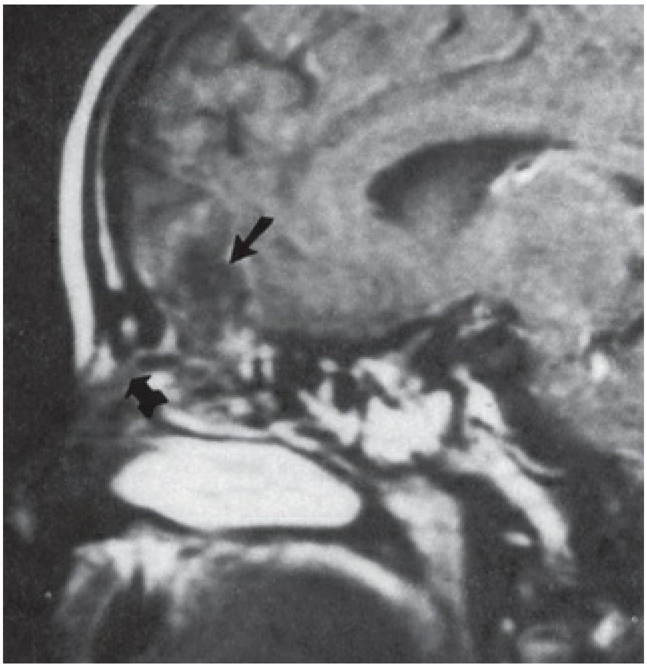


FIGURE 42.2 Sagittal T1-weighted magnetic resonance image showing dermal cyst *(long arrow)* with sinus tract *(short arrow)* extending to the skin surface of the nose. (Courtesy of T. T. Tomita, MD, Children's Memorial Hospital, Chicago.)

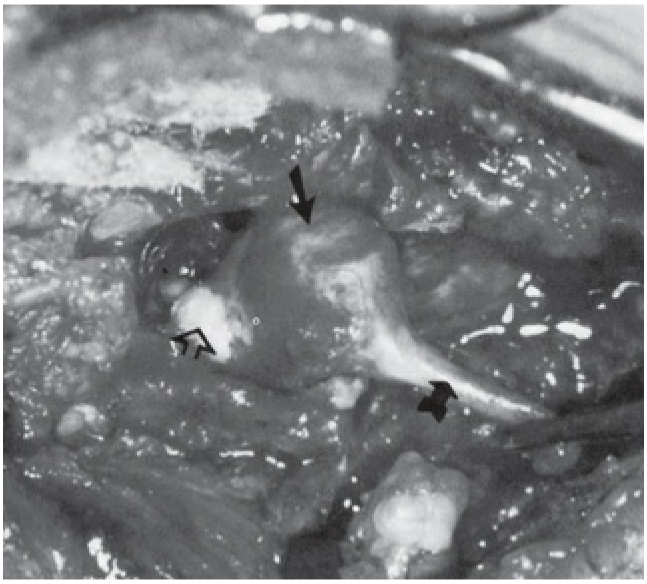


FIGURE 42.3 A lumbosacral dermal sinus tract *(broad black arrow)* leading into a dermal cyst *(thin black arrow).* Note the white material extruding from the cyst, which may cause chemical meningitis *(open arrow).* (Courtesy of J. Grant, MD, Children's Memorial Hospital, Chicago.)

Immunologic Defects

The pathogenesis of bacterial infections in patients with complement deficiencies is not understood fully. In individuals with complement deficiency, as in the general population, specific antibodies against pathogenic bacteria develop after exposure early in life, even without clinical infection. Complement defect, however, precludes full bactericidal activity of antibodies, and affected individuals experience a lifelong susceptibility to these pathogens. Although this process explains recurrent infections, it fails to explain adequately the unique susceptibility to *N. meningitidis* but not to other gram-negative bacteria, such as *H. influenzae* or *E. coli,* or other encapsulated bacteria, such as *S. pneumoniae,* in such people. Additional factors that influence the activation of the complement system (e.g., the presence of sialic acid on the bacterial surface) also may be important in the unique susceptibility of these patients and could explain the excessive occurrence of serogroup Y *N. meningitidis* infections in patients with complement deficiency compared with the general population (44% vs. 11%, respectively).[27] The lower rate of mortality may be the result of lower virulence of infecting organisms or more effective recruitment of other host defense mechanisms, such as the C3b complement pathway, or less disturbance of clotting systems or less activation of systemic cytokine release.

Drug-Induced Meningitis

Drug-induced recurrent meningitis has been reported in connection with several antibiotics (e.g., trimethoprim-sulfamethoxazole, penicillin, and cephalosporins), nonsteroidal anti-inflammatory drugs (e.g., ibuprofen, naproxen), cytotoxic drugs (e.g., azathioprine, cytosine arabinoside), OKT3 monoclonal antibody, and immune globulin intravenous (IGIV).[10,11,47] The likely pathogenesis of meningitis in these situations is either a direct chemical irritation by the drug or a hypersensitivity reaction. In ibuprofen-induced meningitis, immune complexes have been found in the CSF.[48] The onset of drug-induced meningitis varies from a few minutes to several months after drug intake. The onset of IGIV-induced meningitis generally is <24 hours after administration. The CSF findings typically resemble those of bacterial or aseptic meningitis, (hundreds to several thousand white blood cells per cubic millimeter, a polymorphonuclear predominant pleocytosis, normal-to-low glucose concentration, and modestly increased protein level).[10]

Mollaret Meningitis

Mollaret meningitis is characterized by recurrent episodes of aseptic meningitis lasting 3 to 5 days followed by spontaneous recovery.[2] Symptom-free periods vary from weeks to months, and the period of recurrences usually is 3 to 5 years, although longer durations have been reported. Symptoms include fever, headache, and meningismus, with occasional transient neurologic findings. CSF analysis reveals a polymorphonuclear pleocytosis up to several thousand cells per milliliter early in the course of illness followed by a lymphocytic predominance later. Early in the course of illness, large “endothelial” cells (Mollaret cells) with distinct nuclear shapes, often with deep nuclear clefts, are seen commonly in the CSF but can be absent. Further ultrastructural and immunohistochemical studies suggest that these cells are of monocyte-macrophage lineage.[49] The protein level is moderately increased, and glucose concentration is normal or slightly decreased.

Several etiologies have been postulated for Mollaret meningitis. Eosinophilia in a few patients has suggested a possible allergic or hypersensitivity mechanism. Elevated CSF cytokines levels may cause the symptoms. The occurrence of uveitis or transient facial paralysis suggests that Behçet disease or sarcoidosis may be related etiologically. The resemblance of Mollaret meningitis to familial Mediterranean fever (FMF), specifically the pattern of recurrent attacks and the response to colchicine, suggests the possibility that FMF is one possible cause.[3] Intracranial and intraspinal epidermoid cysts can produce chemical meningitis upon release of contents into the subarachnoid space.[4,50] However, since the development of polymerase chain reaction (PCR) technologies, recent studies have shown that the CSF of many patients with benign recurrent lymphocytic meningitis, including Mollaret meningitis, contain HSV DNA.[12] In most cases, HSV-2 DNA was detected, in the absence of cutaneous lesions, suggesting that recurrent lymphocytic meningitis may be a unique presentation of HSV-2 infection of the CNS.[51]

Clinical Manifestations

In most patients the signs and symptoms of recurrent meningitis are suggestive of classic acute bacterial meningitis, although the intensity may be milder, resembling aseptic meningitis. Physical examination otherwise is normal. History of trauma, congenital abnormalities, or recent surgery should prompt a detailed physical examination for a CSF leak, including a detailed examination for skull fracture or congenital bony malformations. Anosmia, hearing loss, otitis media with effusion, and hemotympanum are important clues to the potential presence of congenital or acquired CSF fistula or head trauma. CSF rhinorrhea or otorrhea can be intermittent and can cease when increasing pressure during an acute episode of meningitis occludes fistulas. Certain maneuvers, such as coughing, sneezing, Valsalva maneuver, or bending the head forward, may initiate or exacerbate CSF rhinorrhea. The craniospinal axis (especially the occipital, lumbosacral, and midline face) should be examined carefully for a dimple or bulge, tract, tuft of hair, nevus, or hemangioma. Some patients note recurring fluid discharges from sites of a mucosal or cutaneous lesion (Figs. 42.4 to 42.6). Examination of the nasal cavity may reveal granulation tissue or a meningocele at the site of the leak.

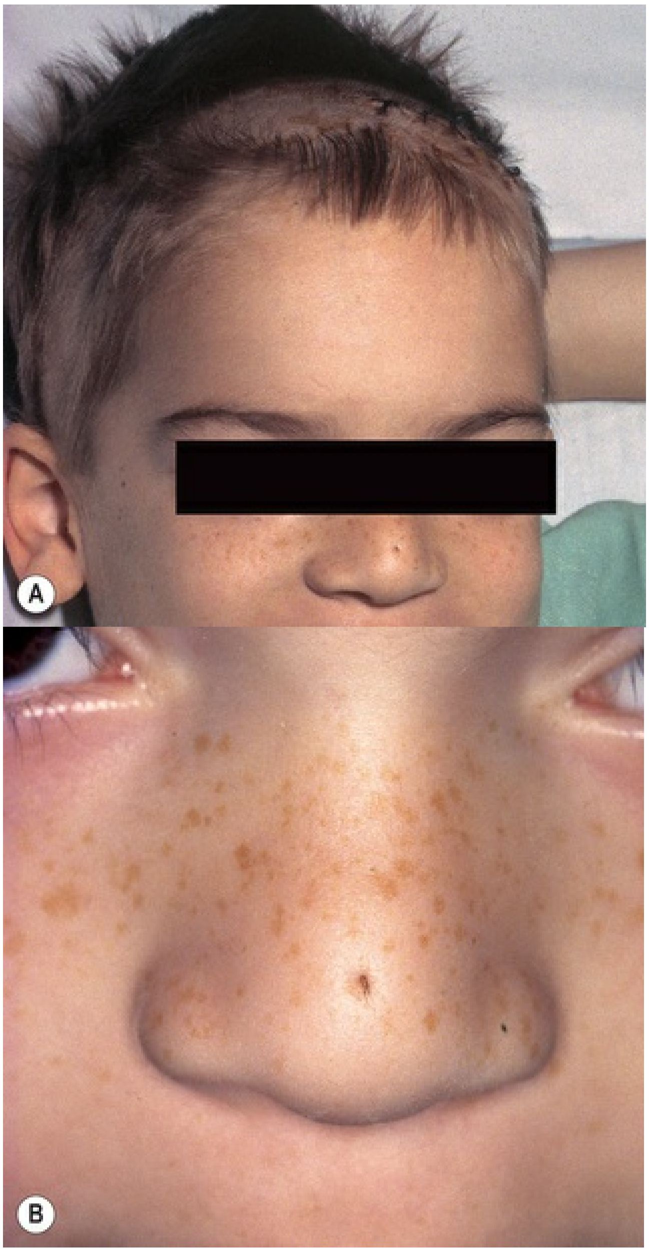


FIGURE 42.4 Dermoid cyst. A 6-year-old boy had a 3-week history of severe headache and then seizure, hemiparesis, and obtundation. *Enterobacter agglomerans* was isolated from a frontal lobe brain abscess and subarachnoid space. Postoperatively, a midline “comedone” was noted (A), which on closer inspection was a pit with a tuft of hair (B) overlying a dermoid cyst and tract to the subarachnoid space. The family recalled that the nose lesion had periodically discharged fluid over the child's lifetime. (Courtesy of E. N. Faerber and S. S. Long, St. Christopher's Hospital for Children, Philadelphia, PA.)

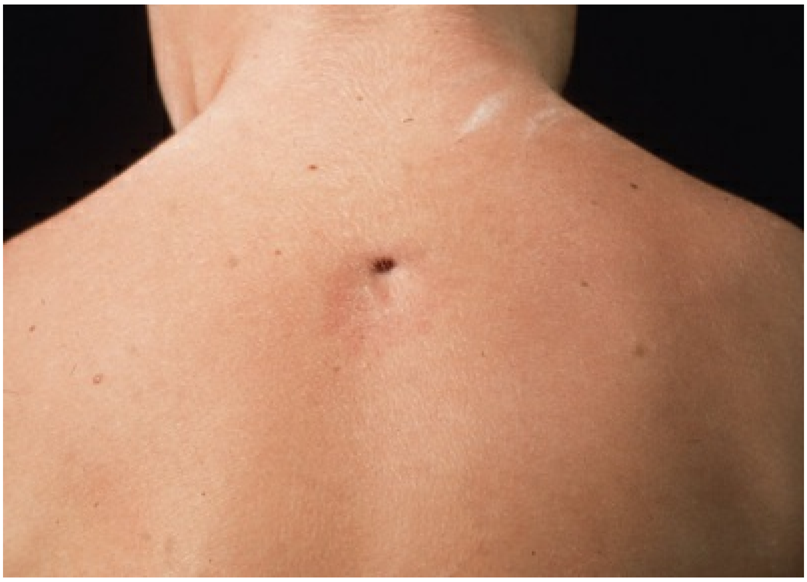
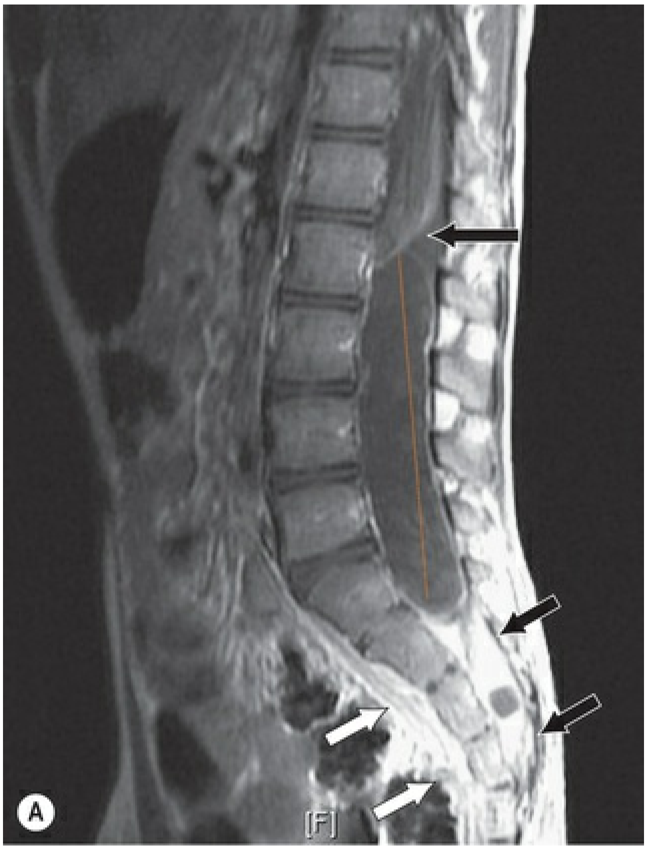


FIGURE 42.5 Dermoid cyst. “Pit and pucker” on the midline of the back of a boy with a dermoid cyst connecting to the subarachnoid space. (Courtesy of J. Bass, through J. H. Brien.)



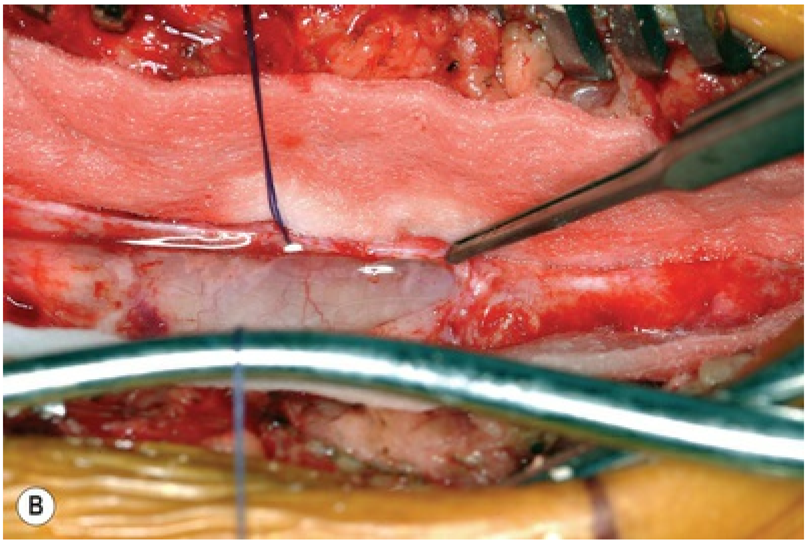


FIGURE 42.6 Arachnoid cyst with sinus tract. A 5-year-old boy came to medical attention for draining sacral osteomyelitis. His parents had throughout his life repeatedly “popped” a pustule over his sacrum. Sagittal magnetic resonance image (A) and operative field (B) show a large sausage-shaped arachnoid cyst *(dotted line within)* occupying the entire bony central canal from L2 to S1. Note the tip of the spinal cord conus at L1–L2 level *(large arrow)* and enhancing soft tissue, bone, and bony canal in the sacral region *(small arrows)*. (Courtesy of J. H. Brien©.)

Diagnosis

If history of recurrent episodes of meningitis is obtained, special attention should be given to any history of head injuries, cranial surgery, multiple serious non-CNS bacterial infections, family history of recurrent infections, splenectomy, fluid leakage from ears or nostrils, and medication use. In addition, any child who experiences meningitis and has known deafness or a family history of anomalies of the ear should be evaluated for anatomic abnormalities, as should individuals whose deafness is discovered in association with meningitis after trauma. Evaluation of children with recurrent meningitis requires coordinated efforts, frequently between neuroradiology and neurosurgery. An algorithm has been proposed for diagnostic tests for children with recurrent meningitis of unknown origin.[16]

The results of tests performed on CSF from episodes of meningitis help differentiate bacterial causes from aseptic causes (see Boxes 42.1 and 42.2). The type of bacteria isolated can lead to suspicion of the site of the predisposing condition. For example, *S. pneumoniae* or *H. influenzae* (or oral streptococci or anaerobic bacteria of oropharyngeal flora) is more common in patients with head trauma or congenital CSF communication to the middle ear, nose, or sinuses, whereas *N. meningitidis* suggests a complement deficiency. Recurrent pneumococcal infection, including meningitis, can occur in individuals with agammaglobulinemia, IgG subclass deficiency, early complement deficiency (C2–C4), HIV infection, or asplenia.[1] If *S. aureus,* coagulase-negative staphylococci, *Corynebacterium* spp., enteric or environmental gram-negative bacteria, anaerobic bacteria, or a combination of such organisms is isolated, a dermal sinus should be suspected. For polymicrobial gram-negative or anaerobic infections, a neurenteric defect or sequestration of bacteria in the CNS should be suspected.

Fluid suspicious for CSF rhinorrhea or otorrhea can be tested for glucose and protein using multireagent strips. However, glucose testing often is unreliable with both false-negative and false-positive results reported. The β_2-transferrin assay has been used for decades as a first-line screening method for CSF leaks. More recently, the β-trace protein (βTP) test has been used to detect CSF leaks. βTP is produced mainly in the leptomeninges and choroid plexus but also serum and is secreted into CSF. The test should not be used in patients with renal insufficiency or bacterial meningitis because these conditions increase serum concentrations and decrease CSF concentrations of βTP.[52] Both β_2-transferrin and βTP are reliable markers for the detection of CSF leak.[53]

Several imaging methods are available for the evaluation of suspected CSF fistulas and other anomalies. Plain radiography can detect large defects or abnormalities. CT and magnetic resonance imaging (MRI) are more precise for localizing smaller lesions; multiple thin-cut coronal views must be obtained because small defects can be missed in axial views. Use of dyes or contrast material (Fig. 42.7) is helpful in visualizing smaller bony defects.[54] Radionuclide cisternography (RC) alone or in combination with pledgets placed in the nostrils or ears is considered by some to be the method of choice for localizing occult CSF fistulas in the skull.[17] RC using diethylenetriamine penta-acetic acid (DTPA), labeled with either technetium-99m or indium-111, allows for up to 72 hours of observation, increasing the detection of slow or intermittent CSF leaks.[55]

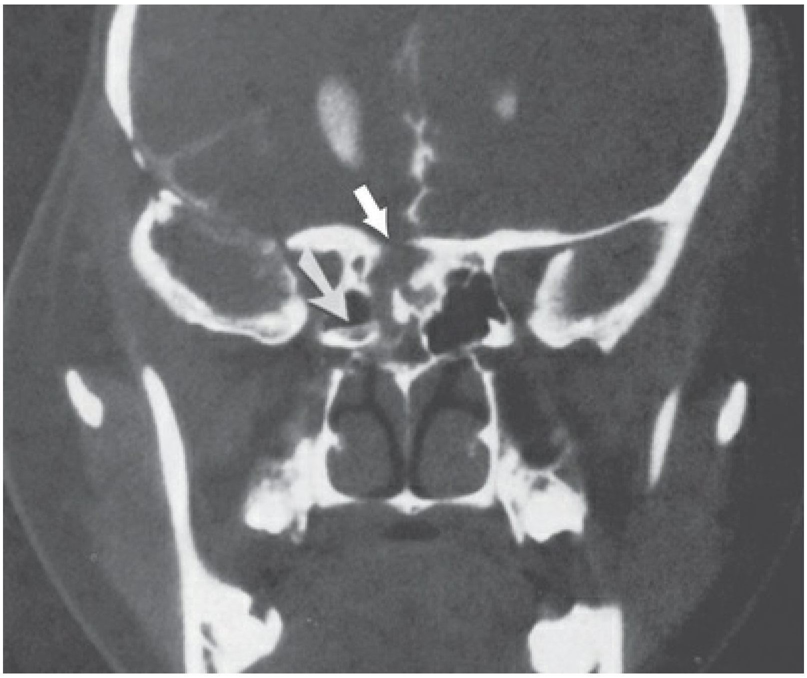


FIGURE 42.7 Coronal computed tomography with intravenous contrast enhancement showing defect in the bone *(gray arrow)* and collection of contrast material with fluid level *(white arrow)* in the sphenoid sinus. (Courtesy of S. E. Byrd, MD, Children's Memorial Hospital, Chicago.)

The initial screening test for complement deficiencies is the total hemolytic complement (CH50) assay. A low CH50 assay value suggests that one or more of the classical or terminal components is missing. CH50 may be within normal range if only C3 or C4 is abnormal. If there is high suspicion for complement deficiency, individual components may need to be tested despite a normal CH50. If the complement cascade is intact, analysis of quantitative serum immunoglobulins and subclasses is warranted. Imaging of the abdomen (e.g., ultrasound or splenic scan) can be performed to rule out hyposplenism or asplenia. If Mollaret meningitis is suspected, CSF PCR for HSV is useful. In addition, the serum/CSF ratio of antibodies for HSV can be done if PCR is negative.[56]

Treatment

For recurrent bacterial meningitis due to head trauma, congenital malformations, or complement deficiency, the choice of empiric antibiotic therapy should be similar to that for single-episode meningitis. For patients with a known dermal sinus or history of meningitis due to staphylococcal or gram-negative bacteria, an antibiotic with a broader spectrum of activity but also targeting the identified pathogens is required. In rare cases when multidrug-resistant infections have not responded to treatment intravenously, antibiotic has been administered intraventricularly,[57] although adverse effects can be related to such installations.

The length of therapy is normally the same as that for sporadic cases; there is no advantage to longer courses of therapy. Time to sterilization may be prolonged in cases of gram-negative bacillary infections associated with dermoid or epidermoid cysts because squamous collections can act like foreign bodies, so sterility of CSF should be documented by repeat lumbar puncture. Meticulous examination and diagnostic evaluation (occasionally including exploratory surgery) to identify and perform primary repair of the site of CSF fistula are most important. In the case of otorrhea, packing of the middle ear with fat is inadequate because it fails to close the fistula permanently. Even packing with muscle or fascia alone seems to be insufficient; additional grafting of the vestibule is needed. For CSF rhinorrhea, extracranial surgery may be the preferred technique, because of lower morbidity; the few disadvantages of this procedure are cranial nerve paralysis and postoperative sinusitis. In patients with Mollaret meningitis, initial anti-HSV therapy followed by long-term suppression (e.g., acyclovir) may be helpful.

Fresh frozen plasma has been given as replacement therapy to patients with complement deficiency. Although this may be reasonable in the few patients who suffer from life-threatening disease, routine administration of plasma can stimulate the production of antibodies against the missing component. Additionally, the short half-life of complement proteins makes this approach impractical. Weekly or monthly immunoglobulin infusions for patients with immunoglobulin subclass deficiency should be individualized according to the severity of the disease (i.e., recurrent bacterial vs. aseptic meningitis).

Prevention and Prophylaxis

Imaging of the temporal bone should be considered in children with idiopathic sensorineural hearing loss to identify those who have an inner-ear anomaly. Parents of children with proven inner-ear anomaly should be educated about the risk for recurrent meningitis from middle-ear infection, contact sports, and activities that may increase the inner- or middle-ear pressure (e.g., diving, prolonged Valsalva maneuver). Suspected middle-ear infections should be treated promptly and aggressively, and in patients with common cavity abnormalities, exploratory tympanotomy should be considered. If cochlear implantation is considered in patients with inner-ear malformation, the type of implant, the risk for meningitis, and preprocedure immunization should be discussed.[58] All efforts should be made to identify and seal CSF leaks because continued leakage increases the risk for postoperative meningitis.[59]

Although prophylactic antibiotics often are given to patients with recurrent meningitis, their efficacy in preventing further episodes is questionable. Antibiotic prophylaxis has been prescribed to prevent meningitis associated with basilar skull fracture. However, a 2006 Cochrane review concluded that prophylactic antibiotics had no effect on the prevention of meningitis in these patients.[60] In addition, one review suggested that antibiotic prophylaxis after basilar skull fracture could be harmful because of increased risk for infection due to antibiotic-resistant organisms.[61] Prophylactic antibiotics have been used in patients with complement or significant immunoglobulin subclass deficiency. In some cases, such treatment markedly reduced the incidence of infection, yet the clinical failure of penicillin prophylaxis against meningococcal disease suggests that long-term prophylaxis may have limited value.[29] The advisability of antibiotic prophylaxis in patients with recurrent meningitis should be made on a case-by-case basis; firm guidelines are not available. Limited data suggest that chronic oral acyclovir (for 1 year or more) may prevent recurrences of Mollaret meningitis.[62]

Vaccination with an age-appropriate meningococcal conjugate vaccine against meninogoccal serogroups A, C, Y, and W 135 is recommended for children aged 2 to 23 months who are at increased risk for meningococcal disease (i.e., those with persistent complement deficiencies such as C3, C5–C9, properidin, factor D, and factor H, and those with functional or anatomic asplenia, including sickle cell disease)[63] Individuals aged 2 to 55 years with high-risk conditions who were not previously vaccinated are also recommended to receive meningococcal vaccine. Booster doses are required (see Chapter 125.) Two serogroup B menigococcal vaccines were recently approved for use in persons 10 to 25 years of age with increased risk for meningococcal disease.[64] A quadrivalent meningococcal polysaccharide vaccine (MPSV4) is approved as a single dose in persons aged ≥2 years but is not currently recommended for children and largely is supplanted by conjugate vaccine.

Pneumococcal conjugate vaccine (PCV13) currently is recommended for prevention of invasive pneumococcal disease (IPD) in all children beginning at 2 months of age.[65] In addition, children 2 years of age or older and adults in high-risk groups for IPD (e.g., patients with CSF leak, functional or anatomic asplenia, or cochlear implant, or who are immunocompromised) also should receive pneumococcal polysaccharide vaccine (PPSV23). Ideally, children should complete age-appropriate pneumococcal vaccines (PCV13 followed by PPSV23) at least 2 weeks before implantation of a cochlear device because these children have a significantly increased risk for pneumococcal meningitis.[66] A second dose of PPSV23 5 years after the first dose is recommended for children with immunocompromising conditions. Children with a cochlear implant are recommended to receive a single dose of PPSV23 (after PCV vaccination). Failure of pneumococcal vaccines to prevent recurrent episodes of meningitis in predisposed individuals can occur.[67] Education of families to seek immediate medical attention for illness is critical.

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43

Aseptic and Viral Meningitis

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The term *acute aseptic meningitis* was introduced in 1925 to describe a self-limited central nervous system (CNS) syndrome characterized by acute onset of fever and meningeal irritation in which the cerebrospinal fluid (CSF) exhibited a mononuclear pleocytosis and was bacteriologically sterile.[1] With advances in diagnostic methodologies it is now recognized that multiple infectious agents, drugs, and localized and systemic inflammatory conditions can cause aseptic meningitis (AM) syndrome (Box 43.1).[2,3]

Box 43.1

Major Causes of Aseptic Meningitis Syndrome

Common

Enteroviruses A–D (echoviruses, coxsackieviruses, numbered enteroviruses)

Human parechoviruses

Arboviruses (Western equine encephalitis virus, St. Louis encephalitis virus, Colorado tick fever, La Crosse encephalitis virus, West Nile virus, tickborne encephalitis virus, Toscana virus)

Borrelia burgdorferi

Partially treated bacterial meningitis

Uncommon

Herpes simplex virus type 2

Mumps virus

Human immunodeficiency virus

Mycobacterium tuberculosis

Parameningeal bacterial infection

Fungi *(Cryptococcus, Coccidioides, Histoplasma, Blastomyces)*

Rare

Respiratory viruses (adenovirus, influenza, parainfluenza)

Lymphocytic choriomeningitis virus

Other herpesviruses (herpes simplex virus type 1, human herpesvirus 6, Epstein-Barr virus, varicella-zoster virus, cytomegalovirus)

Measles virus

Miscellaneous viruses (parvovirus B19, rotavirus)

Bartonella spp. (cat-scratch disease)

Spirochetes

Leptospira spp.

Brucella spp.

Parasites (e.g., *Taenia solium* (cysticercosis), *Toxoplasma gondii, Trichinella spiralis* [trichinosis])

Mycoplasma pneumoniae

Rickettsia spp.

Noninfectious Causes

Drugs (e.g., nonsteroidal anti-inflammatory agents, agents instilled into cerebrospinal fluid)

Biologic products (e.g., immune globulin, OKT3)

Systemic immunologically mediated diseases (e.g., rheumatologic diseases, Behçet disease)

Neoplastic diseases

Viral meningitis can be described as a CNS infection that is associated with signs of meningeal irritation (i.e., neck stiffness, Kernig and Brudzinski signs) but not neurologic dysfunction as a result of brain parenchymal involvement. In contrast, viral encephalitis is a CNS disorder with evidence of brain parenchymal dysfunction as manifest by an altered state of consciousness or other objective signs of neurologic dysfunction (e.g., seizures, cranial nerve palsies, abnormal reflexes, paralysis). Although commonly discussed as separate syndromes, overlap (meningoencephalitis) occurs frequently. This chapter focuses on viral agents more commonly associated with acute aseptic meningitis.

Etiologic Agents and Epidemiology

Because aseptic meningitis is not a reportable disease in the United States, the total annual cases and incidence are unknown. The estimated annual number of aseptic meningitis cases is believed to be at least 75,000. In Olmsted County, Minnesota, the incidence of aseptic meningitis over 32 years was found to be 10.9 per 100,000 person years.[4] The highest rates occurred in infants, toddlers, and children. The Centers for Disease Control and Prevention (CDC) reported that over a 10-year period the incidence of aseptic meningitis ranged from 1.5 to 4 per 100,000.[5] The differences in incidences may be the result of underreporting owing to a passive reporting system used by the CDC. In Finland, a 14-year birth cohort study found the annual incidence of viral meningitis to be 27.8 per 100,000.[6] The highest rates were observed in infants and children <4 years of age.

Before the advent of cell culture, a specific etiology of aseptic meningitis was identifiable in only 25% of cases.[7,8] Cell culture led to a substantial improvement in the identification of viral causes of aseptic meningitis, primarily owing to identification of enterovirus (EV). Using cell culture in addition to animal inoculation and serology, the etiology of aseptic meningitis could be established in ~55% to 70% of cases.[9–11] Cell culture clearly established EV as the dominant etiology of aseptic meningitis, accounting for ~55% to 90% of all identifiable causes.[4,9–12] Use of vaccines for prevention of mumps and polio led to nonpolio EVs becoming the overwhelming dominant cause of aseptic meningitis.[4,9–12] Nucleic acid amplification tests (NAATs) continue to support their significant etiologic role.[13–15]

Enteroviruses and Parechoviruses

EVs are members of the Picornaviridae family of viruses.[16] Four species (enteroviruses A–D), encompassing more than 100 confirmed or putative serotypes, are recognized within the genus.[16]

EVs have a worldwide distribution. Although >100 serotypes comprise the genus, only a few cause disease each year. The dominant serotypes vary geographically and temporally.[17–21] In regions with temperate climates, EV infections exhibit a strong seasonal epidemiology, occurring primarily in the summer and fall.[17–19] In topical and subtropical regions, infections occur year-round with increased incidence during the rainy season.

The use of NAAT has demonstrated that >70% of aseptic meningitis cases in children for which an etiology is identified are attributable to EV.[13–15,22] Given their significant contribution as causes of aseptic meningitis, it is not surprising that the seasonal occurrence of aseptic meningitis parallels activity of these viruses (Fig. 43.1).

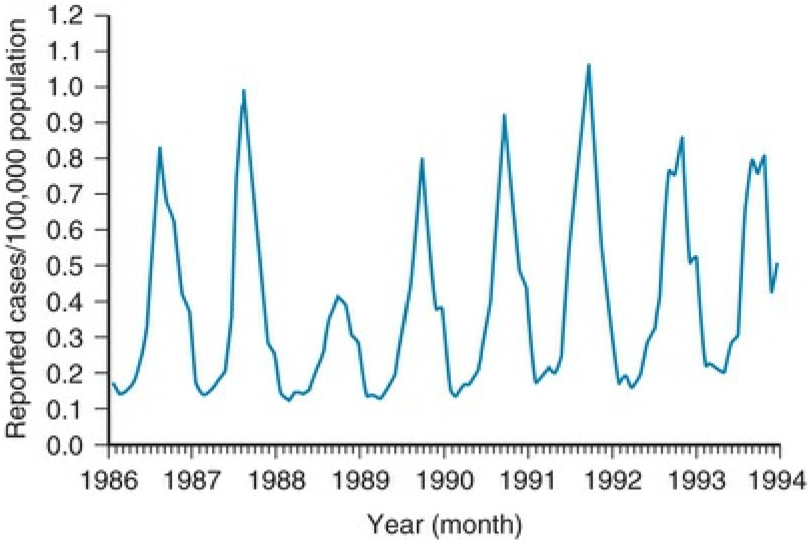

FIGURE 43.1 Seasonal incidence of aseptic meningitis in the United States from 1986 to 1993, as reported to the Centers for Disease Control and Prevention. The summer predominance reflects the role of enteroviruses as the leading cause of the aseptic meningitis syndrome. (Redrawn from Centers for Disease Control and Prevention. Summary of notifiable diseases, United States, 1993, MMWR 1994;42:69.)

Parechoviruses, also in the family Picornaviridae, are recognized causes of aseptic meningitis.[23–25] Initially classified as EVs, biologic, antigenic, and genomic differences led to their reclassification into a novel genus.[16,26] Most human parechovirus (HPeV) infections occur during the summer and fall. HPeV type 3 is the dominant type associated with aseptic meningitis and has been identified in an average of 5% to 7% of EV-negative archival CSF specimens,[23,24] with higher rates in very young infants evaluated because of fever, sepsis-like, or neurologic symptoms.[27–29]

Arboviruses

The arboviruses comprise a group of >500 viruses from multiple viral families transmitted by an arthropod vector.[30] Human-to-human transmission is rare and is the result of blood, organ, or maternal-fetal/infant transmission. Mosquitoes are the vectors for most clinically significant arboviruses endemic to North America. Notable exceptions include Colorado tick fever (CTF) and Powassan virus (POWV), as well as, in Eurasia, tickborne encephalitis virus (TBEV), which are transmitted by ticks.[31,32] TBEV infection also can occur through consumption of infected unpasteurized milk.[32] In the Mediterranean region, sand flies serve as the vectors for Toscana virus (TOSV).[33] The peak incidence of arboviral infections coincides with the periods of maximal activity of their vectors. In North America this is summer and fall.

Most arboviruses associated with aseptic meningitis in North America are members of the Flaviviridae family. Neurotropic Flaviviridae include Japanese encephalitis virus, West Nile virus (WNV), St. Louis encephalitis (SLE) virus, Murray Valley encephalitis virus, and the tickborne encephalitis virus (POWV, CTF, TBEV) complexes.

WNV is the most common cause of arboviral infection in North America. However, <1% of infections in adults and children result in CNS disease. In the United States, children account for 4% of WNV neuroinvasive disease (WNND). Meningitis is the most common manifestation in children, accounting for ~50% of cases.[34] Cases of WNND in children have been reported from most states in the US and multiple countries worldwide.[34,35] The median annual incidence is 0.07 cases per 100,000 children.[34] South Dakota, Wyoming, North Dakota, and Nebraska, in decreasing order, have the highest median annual incidence (0.52 to 1.04 per 100,000 children).

SLE virus was first recognized in 1933 and is widely distributed throughout the American continent.[36,37] Epidemics or sporadic cases have been reported in virtually every state in the US. A mean of 4.25 cases of SLE neuroinvasive disease (SLEND) were reported annually from 2006 to 2008.[38] The reported rate of SLE in 2008 for children aged 1 to 14 years was 0.02 per 100,000.

Three neurologic syndromes have been reported with SLEND: encephalitis, aseptic meningitis, and febrile headache.[39] Aseptic meningitis accounts for ~40% of SLEND cases in children. In Japan and Asia, a related flavivirus, Japanese encephalitis virus, can cause aseptic meningitis in children.[40]

In Europe, TBEV is an important cause of aseptic meningitis.[32] Three subtypes exist: European, Siberian, and Far Eastern. The European and Siberian subtypes can cause meningitis, encephalitis, or myelitis. Aseptic meningitis constitutes ~60% to 70% of pediatric TBEV CNS disease.[41,42] TBE occurs primarily from March to November. The reported incidence in Swiss children is 1 per

100,000.[41] In Slovenia, the annual incidence varies from 3.7 to 24.6 per 100,000; 12% to 27% of cases occur in children <15 years of age.[43] Although not endemic to North America, cases have occurred in persons returning from Europe and China.[44]

In North America, POWV, a related virus, causes occasional cases of aseptic meningitis.[31] The tickborne CTF virus in the Reoviridae family also can cause aseptic meningitis.[44,45]

La Crosse virus (LACV) is in the family Bunyaviridae. In the US, LACV was the most common etiology (55%) for pediatric neuroinvasive arboviral disease from 2003 to 2012, with an annual incidence of 0.09 per 100,000 persons.[34] About 88% of LACV CNS disease occurs in children <18 years of age.[34] Aseptic meningitis accounts for 20% of children with CNS disease caused by LACV.[34]

Toscana virus (TOSV) belongs to the *Phlebovirus* genus within the Bunyaviridae family. It is increasingly recognized as an etiologic agent for aseptic meningitis in the Mediterranean area.[33]

Paramyxoviruses

Multiple Paramyxoviridae, including measles, mumps, and parainfluenza viruses, can cause CNS infection.[46] In mumps, aseptic meningitis occurs as complication in 0.5% to 15% of cases, and CSF pleocytosis is seen in >50% of patients with mumps parotitis.[47,48] In North America, before mumps vaccine, mumps caused 2.5% to 15% of all aseptic meningitis cases and 17.5% to 22% of known causes of meningitis.[4,9–12,49] In countries where mumps remains endemic, meningitis continues to occur.[50,51] During each of two recent US outbreaks, cases of meningitis were reported.[52,53] There are >10 mumps vaccine strains used around the world.[54] Although the Jeryl Lynn and its related vaccine strains (used exclusively in the US) rarely, if ever, cause aseptic meningitis, other vaccine strains have been associated with varying incidences of aseptic meningitis.[54]

Parainfluenza viruses can cause aseptic meningitis.[46] The dominant serotype identified has been type 3. Measles infection can be associated with pleocytosis, usually without signs or symptoms of meningitis.[55]

Arenaviruses

The arenavirus lymphocytic choriomeningitis virus (LCMV) was identified as a cause of aseptic meningitis in 1935.[56,57] Although previously a major cause of aseptic meningitis,[8,9] owing to undefined epidemiologic factors or, perhaps, lack of testing, LCMV meningitis is now uncommon. Rodents, particularly the common house mouse, are its natural reservoirs; hamsters and guinea pigs also are capable hosts.[57] LCMV is shed in rodent excreta and secretions throughout the animal's life. Human infection occurs through contact with LCMV-contaminated fomites or inhalation or ingestion of aerosolized virus. The highest incidence of infections is seen during the late fall and winter.

Herpesviruses

Virtually every member of the human herpesviruses has been associated with aseptic meningitis in children.[58–61] Notable among these are varicella-zoster virus (VZV) and herpes simplex virus 2 (HSV-2). VZV-related meningitis has been reported in immunocompetent children during primary infection and reactivation.[59,60] Cases of aseptic meningitis associated with the vaccine strain of VZV (Oka strain) have been reported.[60,61] The use of NAAT has allowed the identification of VZV-associated meningitis in zoster cases lacking cutaneous lesions.[62,63]

Use of NAATs has documented HSV-2 and, less commonly, HSV-1 as causes of meningitis in children and adolescents.[64–67] HSV-2 infection can cause primary or recurrent aseptic meningitis. The latter occurs more frequently in women.

Other Viruses

Various other viruses, including parvovirus B19,[68] adenovirus aseptic meningitis,[10] rotavirus,[69,70] influenza A and B viruses,[71] and human immunodeficiency virus, occasionally have been identified as causes of aseptic meningitis.[72]

Other Etiologies

Less commonly, certain bacteria not readily visualized in stains of CSF or grown in standard culture systems, such as *Borrelia, Treponema,* and *Rickettsia* spp., mycoplasma, and fungi, can cause aseptic meningitis syndrome) (see Box 43.1). Additionally, various paramenigeal processes, neoplasms, systemic illnesses, drugs, and noninfectious etiologies can result in an aseptic meningitis syndrome.[3,73]

Pathogenesis and Pathology

Most of what is known regarding the pathogenesis of EV infections has been derived from the study of the polioviruses.[74,75] EVs are transmitted primarily by the fecal-oral route and, less commonly, by respiratory droplets and transplacentally. After ingestion, infection and replication occur in the nasopharynx and lower gastrointestinal tract. Replication at these sites results in a minor or primary viremia that seeds multiple organs, including the CNS, liver, lungs, and heart. Further replication at these sites produces a major or secondary viremia. The CNS can be seeded during the initial viremic phase or during the major viremia. Viremia continues until the host develops type-specific antibodies.

The exact means by which polioviruses and other EVs enter the CNS is unclear, and multiple routes have been proposed.[74,75] Infection of endothelial cells expressing specific receptors may facilitate CNS entry. Infection of mononuclear cells may allow CNS access through a “Trojan horse” mechanism. Access to the CNS also can occur by axonal retrograde transport from the peripheral nervous system.

The pathogenesis of arbovirus infections begins with vector-mediated intradermal inoculation of the virus.[32,76] Viral replication occurs at the site of inoculation. For some flaviviruses, replication occurs in Langerhans dendritic cells, which migrate to the regional lymph nodes. Viral replication continues in the regional lymph nodes, followed by a viremia that seeds the entire reticuloendothelial system. Viremia results in infection of multiple organs, including the brain. The mechanism by which arboviruses enter the CNS is not known. For some, infection of cerebral microvascular endothelial cells or transneural spread after infection of the olfactory bulb are modes of entry. Viremia persists until the host develops type-specific antibodies.

Because of the generally favorable outcome of aseptic and viral meningitis, histopathologic data are scarce. The histopathology of

EV aseptic meningitis characteristically shows varying degrees of edema and lymphocytic infiltration of the meninges.[77] Perivascular lymphocytic cuffing may be seen within the cerebral parenchyma as well as the presence of neutrophils. Demyelination near blood vessels (suggesting an autoimmune process) and evidence of acute parenchymal involvement have been observed in the rare fatalities associated with mumps meningitis.[78]

Clinical Manifestations

The clinical manifestations of enteroviral meningitis vary with age of the patient. Regardless of age, clinical findings of meningitis can coexist with clinical findings of other syndromes (e.g., myocarditis, pericarditis, pleurodynia, hand-foot-and-mouth syndrome).

Neonates can come to attention with abrupt onset of fever and irritability. Poor feeding and lethargy can occur. Physical examination can reveal a bulging or full fontanel. Exanthems occasionally are present. Nuchal rigidity is uncommon.[79–81] In severe cases, evidence of involvement of other organ systems can be dominant (i.e., hepatitis, myocarditis, pneumonitis, disseminated intravascular coagulopathy).[81]

In infants and children, fever of abrupt onset is the most common presenting sign.[82–85] In some, the fever pattern and clinical course are biphasic.[82,86] In infants, nonspecific symptoms such as irritability, lethargy, poor feeding, emesis, or diarrhea can be present.[84,87,88] In older children, additional nonspecific findings include generalized malaise, sore throat, abdominal pain, nausea, myalgia, and exanthems. Physical findings may include nuchal rigidity and Brudzinski and Kernig signs. Less than 10% of infants <3 months of age exhibit these findings, which increase in frequency with advancing age.[83,87] In children able to report it, headache is almost always present and may be temporarily relieved by the performance of a lumbar puncture.[88,89] Photophobia is common. Seizures occur in <5%.[87,90] When the presentation exhibits a biphasic course, nonspecific signs and symptoms are followed by a brief period of improvement and then with evidence of neurologic involvement.[82,91]

In adolescents and adults, headache usually is present.[92–95] Fever, photophobia, signs of meningeal irritation, nausea, emesis, and neck stiffness occur in most patients. Myalgia is common. Abdominal pain and exanthems also are reported occasionally.

The clinical presentation of HPeV aseptic meningitis in infants parallels that of the EVs with several notable differences.[24,96] Gastrointestinal (vomiting, diarrhea) or respiratory symptoms (cough, tachypnea, wheezing, apnea) occur in up to half of cases. Neurologic symptoms and a sepsis-like syndrome consisting of fever, tachycardia, poor perfusion, and irritability occur with varying frequency.[27–29]

Typically, in children with mumps parotitis, the onset of meningitis occurs during the first week of illness. However, aseptic meningitis can precede parotitis by a week or follow it by as much as 3 weeks.[46] Fever, headache, emesis, and meningeal signs are common.[8,97,98] Approximately 50% of patients have no evidence of parotitis. Additional symptoms include abdominal pain, diarrhea, and sore throat.

The clinical findings of arbovirus meningitis are not sufficiently unique to distinguish it from other viral meningitides. The signs and symptoms of WNV meningitis in children are similar to those reported in adults.[99] The onset is abrupt with fever, headache, and neck stiffness and Kernig and Brudzinski signs. Photophobia, phonophobia, and weakness can be present. Additional symptoms can include nausea, vomiting, diarrhea, sore throat, cough, rash, and lymphadenopathy.

TBEV meningitis has a biphasic course in approximately two thirds of children.[42,43] Onset is abrupt with fever, headache, malaise, abdominal pain, emesis, and arthralgia lasting 3 to 5 days. The second, symptomatic phase follows a 6- to 10-day period of recovery and is characterized by fever, headache, fatigue, emesis, and signs of meningeal irritation.

Aseptic meningitis due to TOSV has an abrupt onset with fever and headache, in children old enough to describe it. Nuchal rigidity is the most frequent physical finding. The presence of Kernig sign is variable.[100]

A biphasic illness also can be seen with CTF.[45] The initial phase consists of sudden onset of high fever, headache, emesis, and flu-like constitutional symptoms lasting 2 to 3 days. After 1 to 2 days of improvement, fever returns in association with nuchal stiffness and signs of meningeal irritation.

In HSV meningitis and HSV-2 recurrent benign lymphocytic meningitis, the onset of illness is acute with severe headache, neck stiffness, fever, photophobia, and emesis.[64,65,67] Most patients have no history of genital HSV infection.[65] Each episode lasts 1 to 3 days.[67] Multiple recurrences can occur.

The onset of LCMV meningitis is preceded by nonspecific symptoms suggestive of a viral upper respiratory tract illness and, occasionally, a rash. A brief period of improvement precedes the sudden onset of severe headache, nausea, emesis, photophobia, and myalgia. Physical examination reveals nuchal stiffness and signs of meningeal irritation.[2,8,56]

Differential Diagnosis

Borrelia burgdorferi (Lyme) meningitis has a high prevalence in endemic areas.[101,102] Longer duration of headache, predominance of CSF mononuclear cells, and cranial nerve palsy are suggestive of Lyme meningitis.[103,104] Endemicity, time of year, and history of erythema migrans or tick exposure are helpful in considering Lyme disease.

A small proportion (1%–2%) of children with untreated *Mycobacterium tuberculosis* infection develop meningitis.[105] Because symptoms early in the illness are vague and nonspecific, a high index of suspicion is required to make the diagnosis.

Treponema pallidum can cause aseptic meningitis during the secondary or tertiary phases of syphilis. Headache and signs of meningeal irritation can be present, or the patient may be symptom free.[106]

Meningitis associated with leptospirosis occurs during the immunologic phase of illness. In addition to typical signs of meningeal irritation, patients can exhibit rash, uveitis, conjunctival suffusion, and hepatosplenomegaly.[2] Aseptic meningitis complicates brucellosis in ~ 5% of cases.[107] *Mycoplasma pneumoniae, M. hominis, Chlamydophila pneumoniae,* and *Ureaplasma urealyticum* infections have been associated with aseptic meningitis.[108–111]

Parameningeal infectious foci (e.g., sinusitis, mastoiditis, vertebral osteomyelitis, epidural or subdural empyema) can manifest as aseptic meningitis. Rupture of intracranial dermoid or epidermoid cysts results in aseptic meningitis and can be recurrent.[112,113] Endocarditis may result in CSF abnormalities suggestive of aseptic meningitis.[114]

Aseptic meningitis occurs in up to 26% of children with Kawasaki disease and also can occur with Kikuchi disease.[115,116] Urinary tract infections in children have been associated with CSF pleocytosis in the absence of bacteria in the CSF.[117] Pleocytosis also can occur following complex migraines and prolonged seizures.[118,119] Aseptic meningitis has been associated with systemic illnesses such as sarcoidosis, systemic lupus erythematosus, Behçet disease, other connective tissue and vasculitis syndromes, and malignancies.[73]

Multiple medications and biologic agents can cause aseptic meningitis.[3] The major groups of drugs associated with drug-induced aseptic meningitis are nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, immune globulin intravenous (IGIV), antiepileptic drugs, and immunomodulating agents. Aseptic meningitis related to NSAIDs is more commonly seen in women. Trimethoprim alone or in combination with sulfamethoxazole is the most common cause of antibiotic-induced aseptic meningitis. Antiepileptic drugs, most notably lamotrigine, also are associated with aseptic meningitis. Immunomodulating agents, including various monoclonal antibodies, chemotherapeutic agents, and intrathecal agents, are associated with aseptic meningitis.

Laboratory Findings and Diagnosis

The cytochemical analysis of the CSF is key to the diagnosis of aseptic meningitis. Pleocytosis is a prerequisite and typically is lymphocytic in character, ranging from 100 to 1000 cells/mm^3.[8,42,43,46,64,65,79,84,87,90,97] Count can exceed 2000 cells/mm^3 in some cases of LCMV, EV, and mumps meningitis.[46,57] In most cases of HPeV meningitis, detection of virus occurs in the absence of pleocytosis.[24,96] If the CSF is examined early in the illness, particularly with enteroviral meningitis, polymorphonuclear pleocytosis can predominate.[86,87,90,120] Reexamination several hours to days later reveals a shift toward lymphocytic predominance.[86,91,121] Eosinophilic pleocytosis has been reported with EV meningitis.[122]

The CSF protein concentration generally is mildly to moderately elevated, whereas the glucose concentration usually is normal.

Hypoglycorrhachia occurs in up to one fourth of LCMV and mumps meningitis cases as well as sporadic cases of EV and HSV-2 meningitis.[46,57,90,97,120,122]

Traditionally, the diagnosis of EV meningitis has relied on cell culture detection of virus from CSF.[123] NAATs are significantly more sensitive and rapid; they have become the standard for detection of EV in CSF, and timely results can reduce length of hospital stay and antibiotic use.[123–125]

In neonates with suspected EV meningitis, blood, CSF, and rectal swab or stool samples can be submitted for cell culture. Viral shedding from mucosal sites infers recent infection. The same is not true in older patients, who can shed EV from mucosal sites for weeks to months after infection.

Serologic confirmation of EV infection generally is impractical and not useful in acute management.[123]

NAATs are the methodology of choice for the diagnosis of parechovirus meningitis.[24]

Because the sensitivity of CSF culture for HSV is too low to be of clinical utility, NAAT detection should be used.[64,65,67] Detection of HSV antibodies in CSF should not be used to confirm the diagnosis of HSV meningitis.[66] Inflammation of the blood-brain barrier can permit serum HSV antibodies to cross into the CSF, resulting in a false-positive assay. CSF NAAT also should be used to detect other herpesviruses (VZV, EBV, CMV, human herpesvirus 6).

The diagnosis of arbovirus meningitis relies on the detection of virus-specific antibodies.[30,31] Immunoglobulin M (IgM) or IgG capture immunoassay or immunofluorescence typically is used; antibody capture format is more sensitive than other methods for IgM detection. Hemagglutination inhibition and complement fixation tests mainly are used for research.

The approach to the diagnosis of any arbovirus meningitis generally follows that used for WNV.[30,31] Because the presence of arbovirus-specific IgM antibodies in CSF infers intrathecal production, this test should be performed to diagnose WNV meningitis. WNV-specific IgM antibodies usually are present in the CSF by days 3 to 5 of illness.[30] Serum IgM appears 3 days later. Although the finding of specific IgM in CSF is considered diagnostic, detection in serum is not because IgM anti-WNV can be present for >2 years after infection.[126] Prolonged false-positive result of serum IgM anti-WNV also can occur with SLE virus. Because of cross-reactions with related viruses, a positive IgM anti-WNV assay result should be followed by a virus-specific neutralization test.

If only serum is available for testing, an arbovirus-specific cause can be established by documenting rising titers. Although serum NAAT can detect WNV early in infection, by the time CNS symptoms appear, NAATs are less sensitive than antibody tests because of rapid clearance of the virus.[30]

The appearance of antibodies to CTF virus occurs late in the illness (10−14 days after onset of symptoms), limiting the value of serology for diagnosis.[31,127] NAAT permits early (within 5 days of onset) detection of CTF virus. Detection of intraerythrocyte CTF virus using immunofluorescence staining is possible, but interpretation is subjective. Virus isolation using cell culture or animal inoculation is possible. However, the latter is rarely used.

The diagnosis of mumps meningitis can be made by virus isolation, documentation of significant convalescent antibody titers, presence of mumps-specific IgM antibodies, or NAAT detection of mumps genome.[128] Mumps virus can be isolated from saliva, blood, urine, and CSF. The virus may be present in saliva 9 days before and 8 days after the onset of parotitis and in urine for up to 2 weeks after the onset of symptoms. Serum IgM antibodies to mumps virus is present within 3 to 4 days of the onset of symptoms and can persist for up to 3 months.[128] A single serum sample obtained within 10 days of the onset of illness documenting the presence of IgM antimumps virus is sufficient to establish the diagnosis. IgG antibodies are detectable 7 to 10 days after symptom onset and persist for life. Antibodies to other paramyxoviruses can cross-react with mumps serologic assays, leading to false-positive results.

Management and Empiric and Definitive Therapy

When it is not possible to exclude a bacterial etiology, hospitalization and empiric antibiotic therapy are initiated while awaiting results of bacterial cultures of CSF and NAAT. Hospitalization usually is not necessary for patients who appear well and have CSF findings that are not suggestive of a bacterial infection.

Treatment of viral meningitis is supportive. Antipyretics, intravenous fluids, and narcotic analgesic may be indicated. Anticonvulsants may be used to manage seizures should they occur, but a need for prolonged use is uncommon.

No antiviral therapies approved by the US Food and Drug Administration (FDA) are available for most viral causes of meningitis. Reports of the use of immune serum globulin, maternal serum or plasma, or commercial IGIV in severe neonatal enteroviral disease have been published.[81] No definitive conclusions can be derived from these reports.[81]

Pleconaril, an antiviral compound that inhibits EV uncoating and blocks viral attachment to host cell receptors,[129] failed to meet criteria for FDA licensure for uncomplicated aseptic meningitis.[75]

Acyclovir is the drug of choice for the treatment of HSV encephalitis. However, the benefit of acyclovir and its derivatives (valacyclovir and famciclovir) in the therapy of HSV-related meningitis and recurrent meningitis (unlike HSV encephalitis) remains unproved.[67]

Complications, Prognosis, and Sequelae

Complications of EV meningitis are reported in ~10% of infected patients and include coma, increased intracranial pressure, and inappropriate secretion of antidiuretic hormone.[87,121] EVs require antibody-mediated mechanisms for their elimination. EV in individuals with agammaglobulinemia or hypogammaglobulinemia can lead to chronic meningitis or meningoencephalitis that persists and progresses over many years, often with a fatal outcome.[131]

Beyond the neonatal period, EV meningitis rarely has a poor outcome, but recovery can be prolonged.[80,92,95,132] The incidences of morbidity and mortality due to perinatal EV infections may be as high as 73% and 10%, respectively.[81] Death usually is the result of hepatic failure or myocarditis. The long-term prognosis for young children with EV meningitis is good; no differences in neurodevelopmental testing between patients and controls were reported in one large study.[87] In children and infants the duration of illness generally is ≤1 week. In adolescents and adults the time to complete recovery is 2 to 3 weeks.[92,95]

Mumps meningitis is benign with minimal risk for mortality or long-term sequelae. A review of ~200 cases of mumps aseptic meningitis revealed that all recovered without sequelae and none developed deafness.[46] Hydrocephalus complicating mumps meningitis has been reported but occurs rarely.[46] Occasional deaths have occurred in children with mumps meningoencephalitis.

Arboviral meningitis in children generally is associated with an excellent prognosis. The mortality rate for reported cases of WNND in the US over a 10-year period was <1%.[34,35] Recovery from WNV meningitis appears to be complete.[33] Long-term sequelae in Western forms of TBEV are infrequent, and virtually all pediatric patients with meningitis recover fully.[32,41,42] The duration of TOSV meningitis is ~7 days, with almost patients all exhibiting complete recovery.[33,100]

Individuals with HSV-2 primary meningitis or recurrent benign lymphocytic meningitis can exhibit transient neurologic findings that include seizures, hallucinations, diplopia, and cranial nerve palsies.[64,66] Less commonly, patients may be drowsy or have altered mental status. Failure of any of these symptoms to resolve should call into question the diagnosis. Recurrent episodes can occur, but recovery occurs without sequelae.[67]

Meningitis due to LCMV has a benign course lasting 10 to 14 days, with complete recovery in immunocompetent individuals.[67]

Prevention

The use of vaccines for the prevention of poliomyelitis and mumps has dramatically reduced these agents as causes of aseptic meningitis. Several effective vaccines for prevention of TBEV are available in Europe and Russia.[32]

Handwashing prevents the spread of EVs. In patients with inherited antibody deficiency, therapy with IGIV reduces the risk for chronic meningitis.

Use of insect repellents and appropriate clothing and avoidance of areas known to be mosquito-, flea-, or tick-infested help decrease the risk for arbovirus infection. Routine maintenance of screens and house integrity decreases the risk for exposure to mosquito-borne arboviruses and murine LCMV.

Suppressive therapy with acyclovir, valacyclovir, and famciclovir has been used to control HSV-associated recurrent meningitis. Regardless of a history of genital lesions, individuals with HSV-2 meningitis should receive counseling regarding genital herpes and the possibility of transmission of infection; prepubertal children should be evaluated for sexual abuse.[67]

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44

Encephalitis

Carol A. Glaser, Karen C. Bloch

Encephalitis refers to inflammation of the brain parenchyma; typical signs and symptoms include fever, headache, and alteration in consciousness. Alteration in consciousness distinguishes encephalitis from uncomplicated meningitis, which features typically include fever, headache, and nuchal rigidity but lack global or focal neurologic dysfunction. Encephalitis is one of the most challenging conditions for clinicians to diagnose and manage because of the severity of illness, the vast number of potential etiologies, lack of an identifiable etiology in most cases, and ineffective treatment options for many causes. Without the identification of a neurotropic agent or analysis of brain tissue, the diagnosis of encephalitis is presumptive and is based on clinical features.[1] Patients with encephalitis can manifest parenchymal brain findings alone, but most have associated meningeal inflammation, thus representing the overlap syndrome termed *meningoencephalitis*. For the purposes of this chapter, the terms *encephalitis* and *meningoencephalitis* are used interchangeably. Encephalitis is a major healthcare cost. Total charges for encephalitis-associated hospitalizations in the United States in 2010 were estimated to be $2 billion.[2] This chapter focuses predominantly on viral causes of encephalitis in the immunocompetent host, but other pertinent agents and special hosts also are considered.

Etiologic Agents and Epidemiology

Although the term *encephalitis* often is used in conjunction with a viral etiology, bacteria, fungi, and parasites also are causative (Table 44.1), and a number of noninfectious conditions can mimic encephalitis (Box 44.1). Despite the multitude of infectious and noninfectious etiologies of encephalitis, no etiology is identified in more than 50% of cases.[2]

TABLE 44.1

Exposures Associated with Agents Causing Encephalitis and Encephalitis-Like Syndrome

Exposure and/or Reservoir	Agent	Risk Factors and Epidemiology
ARTHROPODS		
Mosquito	**Alphaviruses**	
	Chikungunya virus	Tropical Africa and Southeast Asia, Indian Ocean and parts of Europe, Caribbean countries, South and Central America
	Western equine encephalitis (WEE) virus	Summer and early fall onset; western US and Canada, Central and South America; rare cause of encephalitis, with 640 cases reported in the US from 1964 to 1999. There have been only 4 cases of neuroinvasive disease due to WEE since 1989, with no cases reported in the last 10 years (through 2009)
	Eastern equine encephalitis virus	Eastern and southern coastal states; children and elderly disproportionately affected; rare cause of encephalitis, with 260 cases reported in the US from 1964 to 1999
	Venezuelan equine encephalitis virus	Mexico, Central and South America; rarely in border states of US (Texas, Arizona)
	Semliki Forest virus	Africa
	Flaviviruses	
	West Nile virus	Emerging cause of epidemic encephalitis throughout US, Europe; endemic in Middle East; cases also found in Africa, Caribbean, India, Australia, Russia, and Southeast Asia; peak incidence adults >50 years
	Japanese encephalitis virus	Most common worldwide cause of encephalitis, endemic throughout Asia; vaccine preventable
	St. Louis encephalitis virus	Endemic to western US; with periodic outbreaks in central/eastern US, peak incidence in adults >50 years
	Murray Valley encephalitis virus	Australia and New Guinea
	Bunyaviruses	
	California/La Crosse virus	US with most cases in upper midwestern states (MN, WI, IA, IL, IN, OH) and more recently in mid-Atlantic and southeastern states (WV, VA, KY, NC, and TN); peak incidence in school-aged children
	Phleboviruses	
	Rift Valley Fever virus	Africa and Arabia

Tick	Powassan virus	In the US, endemic in the Upper Midwest, Great Lakes, New England, and New York; endemic in eastern Canada
	Anaplasma phagocytophila	Endemic to New England and north central and western US
	Ehrlichia ewingii	Endemic to southeastern and central US
	Ehrlichia chaffeensis	Endemic to northeastern US and Midwest
	Rickettsia rickettsii	Rocky Mountain spotted fever has been reported throughout the US with the exceptions of Hawaii and Vermont; states with highest incidence are Oklahoma, North Carolina, Arkansas, Tennessee, and Missouri
	Tickborne encephalitis virus	Endemic to Eastern and Central Europe, East and Southeast Asia
	Borrelia burgdorferi	Encephalitis in early disseminated Lyme disease; encephalopathy in late disease
	Kyasanur Forest disease virus	India
Sandflies	*Bartonella bacilliformis*	Colombia, Ecuador, and Peru
	Toscana virus	Italy, Mediterranean
	Chandipura virus	India
Tsetse flies	*Trypanosoma brucei gambiense*	West Africa and India; central nervous system (CNS) illness can occur years after infection
	Trypanosoma brucei rhodesiense	East Africa; CNS illness can occur years after infection
WILD OR DOMESTIC ANIMALS		
Bats	Rabies virus	Vaccine preventable. Between 1995 and 2009, 43 rabies cases were recognized in the US; 10 of these cases were imported (usually from a canine strain), and the remaining cases were acquired in the US mostly related to bat exposures and often with an unknown bite exposure
	Nipah virus	Epidemics in Southeast Asia; also found in Bangladesh and India. Reservoir host is fruit bat, but humans generally acquire disease through direct contact with infected swine
	Histoplasma capsulatum	Eastern and central US; occupational or recreational activities where there is exposure to disturbed soil, such as gardening; playing in barns, hollow trees, bird roosts, or caves; and examination, demolition, or renovation of contaminated buildings
Deer	*Borrelia burgdorferi*	Deer is reservoir host, but infection usually is transmitted to humans via tick vector
Elk	*Anaplasma phagocytophilum* *Brucella abortus*	Deer is reservoir host, but infection usually is transmitted to humans via tick vector Almost total eradication in cattle in the US, but the disease still occurs in some elk herds and wild bison in the western US
Dogs	Rabies virus	Vaccine preventable; dogs important in developing countries; worldwide distribution
	Toxocara canis	Dogs, especially puppies, shed eggs in feces, and organism survives in soil for prolonged period
Cats	*Bartonella henselae*	Typically follows scratch or bite from cat or kitten; highest incidence in children
	Toxoplasma gondii	Cats and other felines are reservoir hosts; they shed oocytes in feces, and the soil becomes contaminated. Sheep, goats, swine, cattle serve as intermediate hosts

	Rabies virus	Vaccine preventable; most common vector in the US is bat, and bites often unrecognized; cats are second to dogs in importance in developing countries; worldwide distribution
	Toxocara cati	Cats, especially kittens, shed eggs in feces, and organism survives in soil for prolonged period
Rodents	Lymphocytic choriomeningitis virus	Peak incidence in fall and winter; chronic infection in laboratory or house mice, hamsters, and guinea pigs; humans infected by inhalation or ingestion of dust or food contaminated by urine, feces, blood, nasopharyngeal secretions of infected rodents
	Leptospira spp.	Rodents (and other animals) excrete organism in urine, and the organism remains viable in soil or water for weeks to months
Raccoon	*Baylisascaris procyonis*	Pica, particularly near raccoon latrine
	Rabies virus	"Raccoon strain" extends along eastern seaboard of the US and has reached as far north as Ontario and New Brunswick in Canada
Sheep, goats	*Brucella melitensis*	Direct contact with infected animals or their secretions (note that *B. melitensis* eradicated in the US since early 1970s)
	Coxiella burnetii	Inhalation; either direct exposure to animal or exposure to contaminated materials (e.g., wool, straw)
Birds	*Cryptococcus neoformans*	Inhalation of soil contaminated with bird feces
	Chlamydophila psittaci	Healthy and sick birds can harbor and transmit organism to humans; usually acquired via inhalation of fecal dust/sections of birds
	West Nile virus	Birds are reservoir host, but infection usually is transmitted to humans via mosquito vector
Old World monkeys	Herpes B virus	Bite of Old World monkey (e.g., macaque)
Horses	Hendra virus	Endemic in Australia; associated with excretions/tissues from horses
Swine	Nipah virus *Brucella suis*	Epidemics in Southeast Asia; close contact with pigs No longer found in domestic swine but present in some wild hog populations
Skunks **Squirrel**	Rabies virus Bornavirus	Skunk populations are widely distributed in the US; cases found in California, Arizona, north central US, eastern coast of US Only 3 human cases described to date, exposure to squirrels in Germany
Parturient animals (especially farm animals)	*Coxiella burnetii*	Humans generally acquire via inhalation; either direct exposure to animal or exposure to contaminated materials (e.g., wool, straw)
INGESTION OR INHALATION		
Fresh water	*Naegleria fowleri*	Swimming or diving in warm, natural bodies of water (rarely poorly chlorinated pools reported)
	Leptospira spp.	Organisms excreted in animal urine or placental tissue and can remain viable for weeks to months in soil or water; recreational exposure associated with wading or swimming in contaminated water (particularly after floods)
Soil	*Balamuthia mandrillaris*	Contact with soil seems to be important risk factor, presumably through inhalation or inoculation
	Acanthamoeba spp.	Contact with soil seems to be important risk factor,

		presumably through inhalation or inoculation
	Baylisascaris procyonis	Pica, particularly near raccoon latrine; raccoons infected with *B. procyonis* appear to be common in many parts of the US; human cases reported in California, Oregon, New York, Pennsylvania, Illinois, Michigan, Georgia, Minnesota, and Missouri
	Coccidioides spp.	Also known as *Valley fever*. Infection is seasonal and is acquired by inhalation of soil or dust or laboratory acquired; endemic in certain areas of Arizona, California, Nevada, New Mexico, Texas, Utah, and northwestern Mexico. Also found in northern Argentina, northwest Brazil, Colombia, Paraguay, Venezuela, and Central America
	Histoplasma capsulatum	Inhalation of airborne spores from soil. Outbreaks have occurred in endemic areas with exposure to bird, chicken, or bat droppings or recently contaminated soil. Globally distributed, with the Ohio and Mississippi River basin, Mexico, and Central and South America being endemic areas in which as many as 80% of children have been infected. Also found in Africa, East Asia, Australia, and rarely in Europe
	Blastomyces dermatitidis	Endemic areas include the midwestern, southwestern, and south central US and the Canadian provinces near the Great Lakes and the St. Lawrence Seaway
	Toxocara canis/*T. cati*	Eggs in sandboxes and playgrounds; organisms survive long periods in soil
Undercooked pork or beef (rarely chicken)	*Toxoplasma gondii*	Consuming raw or undercooked infected meat; worldwide
Undercooked freshwater fish, chicken, or pork	*Gnathostoma* spp.	Southeast Asia and Mexico
Freshwater crayfish or crabs	*Paragonimus westermani*	Mostly in Asia but some reports from Africa and South America
Raw or undercooked meat	*Trichinella* spp.	Mostly associated with pigs but has been found in other mammals (e.g., horses, bear, foxes)
Frogs, snakes	*Gnathostoma spinigerum*	Southeast Asia and some areas in South and Central America
Raw or undercooked freshwater prawns, crabs, or frogs, or unwashed produce (with snails or slugs)	*Angiostrongylus cantonensis*	Reported in Louisiana, Hawaii, the South Pacific, Pacific Islands, Southeast Asia, Asia, Australia, and the Caribbean
Raw vegetables	*Toxoplasma gondii*	Consumption of raw, unwashed vegetables
Unpasteurized milk	*Coxiella burnetii*	Animal exposures (particularly placenta and amniotic fluid)
	Tickborne encephalitis virus	Tick bite or ingestion of unpasteurized milk; endemic to Eastern and Central Europe, East and Southeast Asia
	Listeria monocytogenes	Can be found in about 5% of unpasteurized milk samples and products
	Toxoplasma gondii	Consumption of raw goat milk
SEASON		

Fall	Enteroviruses	Peak incidence in late summer and early fall; enterovirus 71 a cause of large outbreaks in Asia, with children primarily affected
	Arthropod-borne pathogens	Geographically specific agents/risks
Winter	Influenza virus, other respiratory viruses	Sporadic cases in children, with most reports from Japan and Southeast Asia
Spring	Enteroviruses	Peak incidence in late summer and early fall; enterovirus 71 a cause of large outbreaks in Asia, with children primarily affected
	Arthropod-borne pathogens	
Summer	Enteroviruses	Peak incidence in late summer and early fall; enterovirus 71 a cause of large outbreaks in Asia, with children primarily affected
	Naegleria fowleri	Swimming or diving in brackish, freshwater lakes or ponds
	Arthropod-borne pathogens	Geographically specific agents/risks
RECREATION		
Camping or hunting	Arthropod-borne pathogens	Geographically specific agents/risks
Spelunking	Rabies virus	Airborne transmission has been reported rarely in caves inhabited by millions of bats
	Histoplasma capsulatum	Inhalation of spores from soil contaminated with bat guano
Sexual activity	Human immunodeficiency virus	Global risk
	Treponema pallidum	Global risk
	Herpes simplex virus 2 (HSV-2)	HSV-1 also can be transmitted by sexual activity
Water sports	*Naegleria fowleri*	Swimming or diving in brackish, freshwater lakes or ponds
	Leptospira spp.	Exposure to water contaminated with urine of infected animals via swallowing water or skin contact
BLOOD TRANSFUSION OR ORGAN TRANSPLANTATION		
	Toxoplasma gondii	Infection can occur through blood transfusion or organ transplantation
	Rabies virus	Rare case reports of transmission via organ transplantation
	Balamuthia mandrillaris	Rare case reports of transmission via organ transplantation
	Lymphocytic choriomeningitis virus	Rare case reports of transmission via organ transplantation
FOREIGN TRAVEL		
Global	West Nile virus	Geographically specific risks
	Rabies virus	Dog bites are the most common mode of acquisition in developing countries
	HSV-1 and HSV-2	Sporadic
	Influenza	Seasonal by region
	Measles	Measles subacute sclerosing panencephalitis can occur despite history of immunization (child generally had unrecognized infection before measles vaccine)
	Enteroviruses	Seasonal by region

	Human immunodeficiency virus	Sexual activity and bloodborne
	Plasmodium spp.	Tropical and subtropical areas
Africa	Chikungunya virus	Particularly Tanzania
	Poliovirus	Wild poliovirus transmission still occurs in Afghanistan, India, Pakistan, Nigeria
	Histoplasma capsulatum	
	Microfoci throughout Africa	
	Taenia spp.	East Africa, particularly in underdeveloped communities with poor sanitation and where people eat raw or undercooked pork
Asia	Chikungunya virus	Particularly India, Indonesia, Thailand, and Indian Ocean islands
	Japanese encephalitis virus	Including Southeast Asia
	Tickborne encephalitis virus	Central Europe to Japan
	Borrelia burgdorferi	Temperate forested regions throughout northern Asia
	Histoplasma capsulatum	Microfoci throughout eastern Asia
	Gnathostoma spinigerum	Southeast Asia, particularly Thailand, and Japan
	Nipah virus	Southeast Asia, particularly Malaysia
	Taenia spp.	Southeast Asia, particularly in underdeveloped communities with poor sanitation and where people eat raw or undercooked pork
Australia	Murray Valley encephalitis virus	Also in New Guinea
	Japanese encephalitis virus	Northern Australia
	Histoplasma capsulatum	Microfoci throughout Australia
	Hendra virus	Exposure to body fluids and excretions of infected horses is important
Caribbean	Venezuelan equine encephalitis virus	Trinidad
Europe	Tickborne encephalitis virus	Central Europe to Japan
	Chikungunya virus	Italy (northeastern), France (southern)
	Anaplasma phagocytophila	Temperate zones, particularly Germany, Portugal, and Denmark
	Toscana virus	Italy, Mediterranean
	Borrelia burgdorferi	Temperate forested regions throughout Europe, particularly eastern and central Europe
	Taenia spp.	Eastern Europe, particularly in underdeveloped communities with poor sanitation and where people eat raw or undercooked pork
Mediterranean	Toscana virus	Central Italy, France, Spain, Portugal, Greece, Cyprus
North America	Powassan virus	Northeastern and central US, Canada
	California/La Crosse virus	Midwestern and eastern US

	St. Louis encephalitis virus	Geographic range extends from Canada to Argentina, but most human cases in the western US, with periodic outbreaks in central and eastern US
	Ehrlichia chaffeensis	Southern and central US, and mid-Atlantic and coastal states
	Anaplasma phagocytophila	Wooded areas of the north and northeastern US, mid-Atlantic, Midwest, West Coast
	Rickettsia rickettsii	Throughout southern Canada and North America, with peak incidence in southeast and south central US, northern and southwestern Mexico, Costa Rica and Panama
	Eastern equine encephalitis	Highest incidence in Atlantic and Gulf states
	Venezuelan equine encephalitis virus	Florida and southwestern US, rarely in border states (Texas, Arizona); tropical latitudes of Mexico and Central America
	Western equine encephalitis virus	Most cases occur in western US and prairie provinces in Canada, but WEE also occurs in Mexico and Central America; infection associated with residence in rural areas and with agricultural occupations and other outdoor activities that lead to contact with the vector mosquito
	Borrelia burgdorferi	Eastern US, Upper Midwest, and Pacific Northwest; epidemics in summer months when ticks actively seek hosts and human outdoor activity is greatest
	Coccidioides spp.	Semiarid regions of southwestern US and Mexico
	Blastomyces dermatitidis	Southeastern and central states, midwestern states bordering the Great Lakes; thrives in decaying vegetation or wet soil
	Histoplasma capsulatum	Endemic in Mississippi, Ohio and Missouri River valleys in US and other microfoci throughout US, Mexico, and Central America
	Balamuthia mandrillaris	Highest number of cases reported from Arizona, California, and Texas in US; also occurs in Mexico and Central America
	Taenia spp.	Mexico and Central America, especially in underdeveloped communities with poor sanitation and where people eat raw or undercooked pork
	Gnathostoma spinigerum	Mexico and Central America; humans become infected by eating undercooked fish or poultry containing third-stage larvae, or reportedly by drinking water containing infective second-stage larvae
Russia	*Taenia* spp.	More prevalent in underdeveloped communities with poor sanitation and where people eat raw or undercooked pork
	Tickborne encephalitis virus	Eastern Russia
South America	Venezuelan equine encephalitis virus	Tropical latitudes, particularly Colombia, Venezuela, Peru, and Ecuador
	St. Louis encephalitis virus	From Canada to Argentina, but most human cases occur in the US
	Western equine encephalitis virus	Associated with residence in rural areas and with agricultural occupations and other outdoor activities that lead to contact with the vector mosquito
	Rickettsia rickettsii	Brazil and Argentina
	Coccidioides spp.	Semiarid regions

	Histoplasma capsulatum	Microfoci throughout South America
	Gnathostoma spinigerum	Consuming undercooked fish or poultry containing third-stage larvae, or reportedly by drinking water containing infective second-stage larvae
	Bartonella bacilliformis	Middle altitudes of Andes Mountains
	Taenia spp.	More prevalent in underdeveloped communities with poor sanitation and where people eat raw or undercooked pork

Box 44.1

Conditions Mimicking Encephalitis

Immune Mediated

Anti-*N*-methyl-D-aspartate receptor-associated (NMDAR) and other autoimmune encephalitides[a]

Rheumatologic causes (systemic lupus erythematosus, Sjögren syndrome, Behçet disease, sarcoidosis)

Small vessel vasculitis

Corticosteroid-responsive encephalopathy associated with Hashimoto thyroiditis

Acute disseminated encephalomyelitis (ADEM)

Periarteritis nodosa

Toxic Encephalopathy

Bacterial toxins (*Shigella* spp., *Campylobacter jejuni, Salmonella* spp.)

Reye syndrome

Acute toxic ingestion

Lead intoxication

Hyperpyrexic encephalopathy and shock syndrome

Inborn Error of Metabolism

Ornithine transcarbamylase deficiency, heterozygote

Glutaric acidemia type 1

Medium-chain acyl coenzyme A dehydrogenase deficiency

Mitochondrial encephalopathy with lactic acidosis and stroke syndrome

Acute intermittent porphyria

Acquired Metabolic

Electrolyte disturbances

Renal disorder

Liver disorder

Endocrine disorder

Vitamin deficiency

Tumor

Brainstem glioma

Other neoplasms (primary or metastatic; paraneoplastic disease)

Other Central Nervous System Conditions

Stroke

Pseudotumor cerebri

Acute confusional migraine

Brain malformations

Psychosis

Epilepsy

Bacterial meningitis

Brain or parameningeal abscess

Endocarditis complicated by brain embolism

Venous sinus thrombosis

Subdural or epidural hematoma

Head injury

Connective tissue disorder

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[a] Two broad categories of antigens: (1) intracellular paraneoplastic antigens, including Hu, Ma2, CV2 CRMP5; and (2) cell surface antigens, such as voltage-gated potassium channels and others.

The reported incidence of acute encephalitis varies throughout the world and ranges between 1.5 and 7.4 per 100,000 population.[2–4] Most studies find a higher incidence in the pediatric age group than in adults.[3] Data from hospitalizations in England over a 10-year period show an overall population incidence of 1.5 per 100,000, with rates of 2.8 per 100,000 children and 8.7 per 100,000 infants.[5] Similar rates in children were found in Finland, where the incidence was 8.8 per 100,000 from 1973 to 1987, and in Slovenia, where the incidence was 6.7 per 100,000 from 1979 to 1991.[5,6]

Encephalitis due to vaccine-preventable diseases such as measles, mumps, and rubella has decreased dramatically in the past several decades in the US and in other regions where these vaccines are available. The spectrum of causative agents has changed over time, especially as new pathogens have been discovered, including West Nile virus, Nipah virus, enteroviruses (EVs) 71 and D68, *Balamuthia mandrillaris, Baylisascaris procyonis,* and Chandipura virus.[6–8]

Viruses

Enteroviruses

EVs, nonenveloped RNA picornaviruses, cause approximately 10 to 15 million symptomatic infections per year in the US.[9] EVs are common causes of aseptic meningitis. Encephalitis is a rare complication of EV infection, but because EV infections are ubiquitous, they are a leading cause of encephalitis in children and are responsible for 10% to 15% of encephalitis cases for which an etiology is identified.[10] In the late 1990s, outbreaks of EV-71 in Asia associated with hand-foot-and-mouth disease in young children were noted along with neurologic complications.[11,12]

An emerging issue involving EV-D68, an enterovirus typically associated with respiratory symptoms, has been putatively associated with encephalitis and acute flaccid myelitis (AFM).[13] A widespread respiratory outbreak of EV-D68 in the Midwest in 2014 was temporally associated with cases of AFM.[14] Phylogenetic analysis of a subset of cases showed that they all grouped into a clade B1 virus, further strengthening the putative association between EV-D68 and AFM.[15]

Human Parechoviruses

The reclassification of former enteroviruses, echovirus 21 and echovirus 22, was the genesis of the new human parechovirus (HPeV) genus. Echoviruses 21 and 22 now are classified as HPeV-1 and HPeV-2 respectively. At least 16 HPeV serotypes have been described to date; many have been associated with encephalitis, most often in children <2 years of age.[16] The relative frequency of HPeV encephalitis is unknown. Encephalitis due to HPeV would have been missed in the past because polymerase chain reaction (PCR) testing for EVs does not detect HPeVs.

Herpesviruses

Herpesviruses are a large group of enveloped DNA viruses, and at least 8 herpesvirus types are known to infect humans. Similar to EVs, herpesviruses are a frequent cause of human disease. Herpes simplex virus 1 (HSV-1) is the most commonly identified cause of sporadic encephalitis in adults and follows EV as the most commonly identified cause of encephalitis in children.[17,18] The worldwide incidence of HSE is approximately 500,000 persons per year, and 30% to 50% are <20 years of age. Outside of the neonatal period, most cases of herpes simplex encephalitis (HSE) in children are a consequence of primary HSV-1 infection, whereas most HSE cases in adults are the result of HSV-1 reactivation. In a cohort of

322 pediatric encephalitis cases over a 12-year period at a single tertiary care facility in Canada, 5% were due to HSE.[19]

Other herpesviruses can cause encephalitis. Varicella-zoster virus (VZV), previously a significant cause of encephalitis, became uncommon among pediatric patients after the introduction of universal vaccination.[20]

Primary varicella infection can be complicated by pure cerebellar ataxia, meningoencephalitis, or acute disseminated encephalomyelitis (ADEM), with the median time to development of neurologic symptoms 5 days after onset of rash.[21] However, neurologic manifestations may predate the onset of cutaneous findings or, in some cases, can be present in the absence of rash, complicating recognition of this infection.

The diagnosis of Epstein-Barr virus (EBV) encephalitis is challenging because after acute infection, the virus remains latent in lymphocytes and can reactivate in various settings. Detection of EBV in cerebrospinal fluid (CSF) therefore is not necessarily diagnostic of EBV encephalitis and, alternatively, lack of CSF EBV detection does not rule it out. In a cohort of pediatric patients with encephalitis, microbiologic evidence of EBV infection was identified in 6% of cases, but only 1 of 21 children had a clinical presentation suggestive of infectious mononucleosis.[22] Distinctive presentations of EBV CNS infection include pure cerebellar ataxia and “Alice in Wonderland” syndrome, characterized by metamorphopsia.[23,24]

The role of human herpesvirus 6 (HHV-6) in encephalitis in the immunocompetent host is controversial. Interpretation of CSF PCR results is problematic because once infected, the virus results in a lifelong latent infection in humans. Additionally, HHV-6 DNA is covalently integrated into the cell chromosomes in about 1% of the general population. Both situations lead to false-positive HHV-6 PCR results in CSF.[25] Nevertheless, HHV-6 likely is responsible for some portion of encephalitis in immunocompetent hosts, particularly in children <2 years experiencing a primary infection.[26] Other herpesvirus infections are rare in immunocompetent children.

Arboviruses

Arboviruses are viruses transmitted by an arthropod vector and are well-recognized causes of encephalitis. Three arbovirus families are known to cause encephalitis in humans: Togaviridae, Flaviviridae, and Bunyaviridae. Of these families, the viruses responsible for most clinically significant disease in the US include eastern equine encephalitis (EEE) virus and western equine encephalitis (WEE) virus (Togaviridae family); West Nile virus (WNV), St. Louis encephalitis virus, Powassan virus (Flaviviridae family); and La Crosse virus (LACV) from the California serogroup (Bunyaviridae family).

WNV was detected for the first time in the Western hemisphere in 1999 and currently is the leading cause of arboviral encephalitis in the US.[27] From 2003 to 2012, 13,108 cases of WNV were reported in the US, but only 505 (4%) of all reported cases of West Nile neuroinvasive disease (WNND), which includes encephalitis, aseptic meningitis, and acute flaccid paralysis, were in children.[28] The Centers for Disease Control and Prevention (CDC) report a WNND incidence of 0.68 cases per million children compared with 5.35 cases per million adults from 2003 to 2012.[28] Of the pediatric patients, the median age was 12 years.

LACV is the second most common cause of arboviral infections in the US but is the most common cause of neuroinvasive arboviral disease in children.[28] Over a 10-year period from 2003 to 2012, 754 cases of LACV were reported; 665 (88%) were in children <18 years, with median age of 7 years.[28] In contrast to WNV, infection with LACV occurs in specific geographic areas, primarily in the Appalachian and midwestern regions. Powassan virus, an emerging tickborne arbovirus in the northeastern US and Canada, is rarely identified in children, with only 8 pediatric cases identified in the US between 2003 and 2012.[28] A number of arboviruses are important outside the US (see Table 44.1). In hyperendemic areas, Japanese encephalitis virus causes several thousand cases annually, primarily in children in Asia, southern Asia east of Pakistan, and Southeast Asia.[29] Chikungunya virus is an arbovirus first discovered in Tanzania in 1952, with most illnesses characterized by fever, rash, and polyarthralgia. In the past decade, explosive outbreaks of chikungunya have occurred in several areas of the world, including Africa, Asia, Europe, the Indian and Pacific Oceans, the Americas, and the Caribbean. Neurologic illnesses, including encephalitis, have been associated with some cases. Zika virus has also resulted in explosive outbreaks and seems to have particular neurologic virulence. A few case reports of encephalitis have been linked to Zika virus, but more importantly, it has been shown to cause microcephaly in the fetus.

Other Viruses

Other less frequent but important viral causes of encephalitis include lymphocytic choriomeningitis (LCM) virus and rabies virus. LCM is an arenavirus acquired from infected house mice, hamsters, and guinea pigs. Infections occur when feces, saliva, or urine from LCM-infected rodents are inhaled or ingested. Infections are reported more frequently in winter months when rodents typically migrate indoors.[30] The incidence of LCM is unknown, but it is likely that infections go unrecognized.

Rabies is rare in the US, but 25,000 to 61,000 deaths are estimated to occur annually worldwide, primarily from contact with rabid dogs.[31] These cases occur mostly in Asia, Africa, and Latin America, where animal rabies control and postexposure prophylaxis are limited. Rabies is unique among encephalitis viruses; the incubation period generally is between 20 and 60 days but can range from a few days to 6.5 years.[32] In the US, 43 rabies cases were recognized between 1995 and 2009; 10 cases were imported (usually a canine strain), and the remaining cases were acquired in the US. Most US cases were related to bat exposures, and often the bite event was unrecognized. Bats have very small teeth and, therefore, bites may not be noticed and marks not visible (Fig. 44.1).

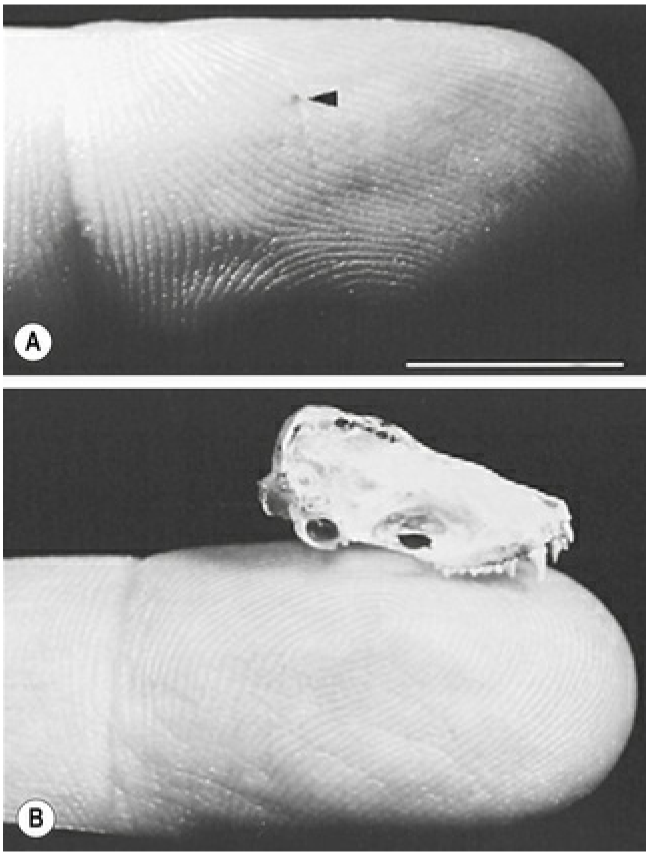

FIGURE 44.1 Puncture wound of a bite from a silver-haired bat (A) and skull of silver-haired bat (B). (Reprinted from Jackson AC, Fenton MB. Human rabies and bat bites. Lancet 2001;357:1714.)

Influenza-associated encephalitis and encephalopathy have been described sporadically in children and follow seasonal influenza patterns during winter months in temperate climates. Most influenza-associated encephalitis cases, especially acute necrotizing encephalopathy (ANE), are reported from Japan,[33] but cases of encephalitis and encephalopathy occur throughout the world, including the US.[34] Neurologic complications may be particularly prominent with specific strains of influenza, such as the 2009 pandemic influenza A virus H1N1.[35]

Other viruses important outside the US include measles, Nipah virus, and arboviruses. There are an estimated 30 million cases of measles worldwide annually, and acute encephalitis occurs in 1 of 1000 cases. Subacute sclerosing panencephalitis (SSPE) is an indolent, progressive, and fatal form of measles encephalitis that typically becomes manifest several years after infection. Because measles vaccination is universal in the US and many other countries, a history of vaccination is common in patients with SSPE.

These SSPE cases likely represent an unrecognized infection acquired before immunization.[36] This is supported by genetic analysis of virus from brain specimens where wild-type measles virus is identified rather than vaccine type virus.[37]

Emerging zoonotic viruses associated with encephalitis include Nipah, Hendra, and bornavirus. Nipah virus is a paramyxovirus first identified as a cause of epidemic encephalitis in pig farmers in Malaysia in 1999,[38] and later in Singapore,[39] Australia,[40] Bangladesh,[41,42] and India.[42] Hendra virus is another paramyxovirus originally reported in Australia among people with contact with horses, although the natural reservoir likely is bats.[43] A newly described bornavirus has been linked to three human encephalitis cases in adults in Germany, all with squirrel contact.[44]

Bacteria

Important bacterial causes of encephalitis include *Rickettsia rickettsii*, *Borrelia* species, *Bartonella henselae* (and other *Bartonella* species), *Anaplasma phagocytophila, Ehrlichia* spp., and *Mycobacterium tuberculosis*. Importantly, meningitis due to *Neisseria meningitidis* and *Streptococcus pneumoniae* can cause clinical manifestations that are indistinguishable from encephalitis.

Bacterial tickborne diseases follow a seasonal pattern. Rocky Mountain spotted fever (RMSF), caused by infection with *R. rickettsii*, occurs during the spring, summer, and fall months when ticks are most active and when there is an increase in human outdoor recreational activity. Although the vector tick for RMSF is widespread throughout the US, the tick associated with Lyme disease is endemic to the eastern and upper midwestern states, and Lyme neuroborreliosis is most commonly found in patients with residence in or travel to these regions. Neuroborreliosis typically follows acute infection with *Borrelia burgdorferi* by 3 to 10 weeks and thus can manifest in cooler months. *B. henselae* (and other *Bartonella* spp.), the agent of cat-scratch disease, is associated with encephalopathy in approximately 15% of cases.[45] Cat-scratch encephalopathy occurs most commonly in children and is characterized by seizures and often status epilepticus.

Fungi

Fungal central nervous system (CNS) disease generally manifests as meningitis and brain abscesses, but some patients have encephalitis-like symptoms. Fungal CNS infection typically is subacute or chronic, in contrast to the more acute presentations of viral or bacterial encephalitis. Important fungal causes in the US include *Coccidioides* spp., *Cryptococcus* spp., *Histoplasma capsulatum,* and *Blastomyces dermatitidis* (see Table 44.1 for endemic areas). *Cryptococcus gattii* has emerged recently in the Pacific Northwest and has a greater propensity to cause illness in immunocompetent hosts than *Cryptococcus neoformans*.[46]

Free-Living Amebas and Parasites

Encephalitis due to free-living amebas can be divided into two clinical entities: (1) primary amebic meningoencephalitis, a fulminant infection occurring in children and young adults due to *Naegleria fowleri* (also known as "the brain-eating ameba") and (2) granulomatous amebic encephalitis, typically caused by infection with *Acanthamoeba* spp. or *Balamuthia mandrillaris.* These three pathogens are widely dispersed in soil and water. *N. fowleri* infects immunocompetent hosts, *Acanthamoeba* spp. chiefly causes infections in immunocompromised hosts, and *B. mandrillaris* infections are described in both host groups. The importance of *Balamuthia* as a causative agent of encephalitis is increasingly recognized.[47]

Significant protozoan parasites associated with encephalitis include *Toxoplasma gondii* and *Plasmodium falciparum*. *T. gondii* typically is acquired through foodborne contact or through direct contact with cat feces containing oocysts.[48] Most cases of *P. falciparum* malaria in the US are imported in people returning from endemic areas in Africa, Asia, and the Americas.[49]

B. procyonis, the common raccoon roundworm, is an important cause of eosinophilic encephalitis, especially in the US.[50] Other important neurotropic helminths include *Gnathostoma spinigerum* and *Angiogstrongylus* spp. *G. spinigerum* is endemic in Southeast Asia and is being recognized increasingly in Central and South America.[51,52] *Angiostrongylus* spp. have been reported in the South Pacific, Asia, Australia, and the Caribbean and in the US in Louisiana and Hawaii. Notably, Hawaii is experiencing an upsurge of cases.[53,54]

Other Causes

Hundreds of additional infectious agents have been associated with encephalitis, but the relevance and frequency of many are unknown. In particular, when a nonneurotropic agent is identified in a patient with encephalitis, particularly when identified only outside the CNS, causality is uncertain. For example, several large case series have identified *Mycoplasma pneumoniae* as one of the most commonly diagnosed infections among children with encephalitis.[54,55] However, *M. pneumoniae* is a ubiquitous pathogen, and up to 80% of the human population have evidence of past exposure. Even when immunoglobulin M antibody to *M. pneumoniae* is identified in a patient, the significance of the finding is unclear given the high background incidence of acute infection and the limitations of serologic testing.[56,57] With similar uncertainty, adenovirus, parvovirus B19, rotavirus, and human metapneumovirus have been implicated in encephalitis.[58–61]

Common noninfectious illnesses can mimic infectious encephalitis, including neoplasms, vasculitis, stroke, drug reactions, paraneoplastic syndromes, and autoimmune disease (see Box 44.1). Immune-mediated encephalitis, anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis, is recognized increasingly as a relatively frequent cause of encephalitis syndrome.[62] Initially, the syndrome was described in young women with ovarian teratomas who came to attention with acute psychosis and personality changes that progressed to decreased level of consciousness, dyskinesia, autonomic instability, and hypoventilation.[62] Movement disorders, seizures, and psychiatric symptoms are described commonly in affected individuals. As awareness increases, there are a striking number of cases of anti-NMDAR encephalitis identified in children and young adults.[63] Unlike adult patients, pediatric patients are less likely to have a tumor identified.[64] Viral encephalitis also may trigger anti-NMDAR and other autoimmune encephalitides.[65]

Pathogenesis

The pathogenesis of acute viral encephalitis is not well understood and is highly variable depending on the causative agent. Enteroviruses, HPeVs, HSV-1, arboviruses, and rabies are examples of neurotropic viruses in which the virus directly infects neuronal tissue. Measles, EBV, and rubella are examples of viruses that can trigger an autoimmune reaction with a resultant postinfectious encephalitis, ADEM, in which the white matter of the brain is involved predominantly (discussed in Chapter 45). Encephalitis symptoms in bacterial meningitis and rickettsial infections, on the other hand, are caused by the vasculitis and inflammation of the surrounding infection. Inflammatory response to bacteria, fungi, and parasites especially can lead to hydrocephalus.

Infectious agents can enter the CNS through diverse pathways. The most common route of invasion is through the bloodstream, as is the case for EVs, HPeVs, and arboviruses as well as for most bacteria, rickettsia, and fungal agents. The bloodborne agent penetrates the blood-brain barrier through the choroid plexus or through vascular endothelium.[66] An intraneuronal route is used by some viruses, such as rabies and HSV-1. HSV-1 can cause encephalitis during the primary infection or reactivation of the latent virus.

When inside the CNS, the offending pathogen may target only certain cells, and, depending on the region involved, variable clinical manifestations develop. Cortical infection or reactive parenchymal swelling can lead to an altered level of consciousness, a ubiquitous clinical sign in encephalitis. Agents with specific predilection to areas such as the brainstem can progress rapidly to coma or respiratory failure. Arboviruses primarily affect the cortical grey matter, brainstem, and thalamic nuclei. HSE is characterized by hemorrhagic and necrotizing lesions characteristically located in the temporal lobes, orbital frontal lobe cortex, and limbic structures.[67]

Typical histology in viral encephalitis includes perivascular mononuclear cell inflammation, phagocytosis of neurons, and microglial nodules. Certain viruses have distinctive histopathologic features, such as intranuclear inclusions with herpesviruses, and Negri bodies pathognomonic for rabies.

For some organisms, such as influenza and *B. henselae*, mechanisms causing neurologic signs and symptoms are not always well understood. In these cases, there is definitive evidence of recent infection, but the pathogen generally is not found in the brain or CSF. In many influenza-associated encephalopathy cases, there is bilateral symmetric edema and apoptosis of neurons in the absence of pleocytosis, suggesting a different pathogenesis, such as that mediated by cytokines.

Rickettsial agents generally cause endovascular infections, with CNS manifestations related to a small vessel vasculitis. Subsequent meningeal irritation with perivascular mononuclear infiltrates develops. Characteristic CNS pathologic lesions include multifocal glial nodules and arteriolar microinfarctions.[68] In tuberculous, fungal, or partially treated bacterial meningitis, subarachnoid exudate from chronic basilar meningeal inflammation leads to obstruction of CSF reabsorption with resultant communicating hydrocephalus and cranial nerve palsies. Vasculitis of intraparenchymal vessels leads to infarcts and focal neurologic deficits.

N. fowleri causes hemorrhagic destruction of grey matter and devastation of the olfactory bulbs.[69] The hallmark of *B. mandrillaris and Acanthamoeba* infections is granulomatous amebic encephalitis characterized by multinucleated giant cells, focal necrosis, and hemorrhage. The pathology of *B. procyonis* is characterized by CNS larval migration with histology demonstrating inflammation and necrosis with track-like spaces, as well as abundant eosinophils.[70]

Clinical Manifestations and Differential Diagnosis

The clinical manifestations of encephalitis are extremely variable and reflect the specific area and degree of brain involvement and inherent pathogenicity of the offending agent (Table 44.2). Clinical criteria for the diagnosis of encephalitis have been established (Box 44.2).[1] The hallmark of encephalitis is altered level of consciousness lasting more than 24 hours, not attributable to an alternative cause. Other clinical findings can include fever, seizures, impaired cognition, behavioral changes, speech disturbances, hemiparesis, cranial neuropathies, and other focal neurologic signs. Physical findings outside the CNS can provide important clues to etiology. For example, a petechial skin eruption is suggestive of RMSF, whereas regional lymphadenopathy may indicate bartonellosis.

TABLE 44.2

Associated Manifestations for Specific Agents in Encephalitis

Clinical Features	**Agents**
Subacute or chronic neurologic symptom	*Acanthamoeba* spp. *Balamuthia mandrillaris* *Coccidioides* spp.
	Cryptococcus neoformans
	Histoplasma capsulatum Measles (subacute sclerosing panencephalitis) *Mycobacterium tuberculosis* *Tropheryma whipplei*
Hepatitis	*Coxiella burnetii*
Hepatosplenomegaly	*Histoplasma capsulatum*
Hydrophobia	Rabies virus
Lymphadenopathy	*Bartonella henselae*
	Cytomegalovirus[a]
	Epstein-Barr virus
	Human immunodeficiency virus
	Mycobacterium tuberculosis
	Toxoplasma gondii[a]
	West Nile virus
Parotitis	Human immunodeficiency virus
	Mumps virus Lymphocytic choriomeningitis virus
	Parainfluenza virus
Respiratory symptoms	Adenovirus
	Histoplasma capsulatum
	Influenza virus
	Mycoplasma pneumoniae
	Mycobacterium tuberculosis
	Parainfluenza virus
Retinitis/chorioretinitis	*Bartonella henselae*
	Cytomegalovirus[a]
	Histoplasma capsulatum *Mycobacterium tuberculosis* *Toxoplasma gondii*[a]
	Treponema pallidum
	West Nile virus
Exanthems	
Hand-foot-and-mouth disease	Enterovirus
Macules/papules on trunk	West Nile virus
Petechiae	*Rickettsia rickettsii* (and other rickettsia)
Recent macular exanthem	Human herpesvirus 6
Salmon-colored macules/papules	Rubella virus
Vesicles	Herpes B virus
	Varicella-zoster virus
Neurologic Features	
Ataxia	Epstein-Barr virus

	Listeria monocytogenes
	Mycoplasma pneumoniae
	Varicella-zoster virus
Change in taste or smell	*Naegleria fowleri* Herpes simple virus type 1 (anosmia)
Cranial nerve palsies	*Balamuthia mandrillaris*
	Borrelia burgdorferi
	Coccidioides spp.
	Epstein-Barr virus
	Histoplasma capsulatum
	Mycobacterium tuberculosis
	Naegleria fowleri
	Toxoplasma gondii[a] Syphilis
Paralysis[b]	Enteroviruses (71, D68)
	Japanese encephalitis virus
	La Crosse virus
	Tickborne encephalitis virus
	West Nile virus
Psychiatric abnormalities	Herpes simplex virus 1 Anti-NMDAR encephalitis Rabies
Myoclonus/jerks	Measles virus (SSPE)
	Nipah virus
Sensorineural hearing loss	Mumps virus
Visual loss	JC virus (progressive multifocal leukoencephalopathy)[a]
	Baylisascaris procyonis
Laboratory Features	
Cerebrospinal fluid (CSF) atypical lymphocytes	Cytomegalovirus[a]
	Epstein-Barr virus
	West Nile virus
CSF eosinophils (can be mistaken for neutrophils in CSF; Wright or Giemsa stain is needed to identify eosinophils)	*Angiostrongylus* spp. *Baylisascaris procyonis* *Coccidioides* spp.
Morulae in white blood cells	*Anaplasma phagocytophila*
	Ehrlichia spp.
CSF lymphocytosis with hypoglycorrhachia	*Mycobacterium tuberculosis* *Balamuthia mandrillaris* *Coccidiodes* spp.
Neuroimaging Abnormality	
Acute necrotizing encephalopathy (ANE)	Influenza virus (and other respiratory viruses)
Arteritis/infarctions	*Rickettsia* spp.
	Treponema pallidum
	Varicella-zoster virus
Basal ganglia	Influenza virus (ANE)
	Enteroviruses
	Epstein-Barr virus West Nile virus and other arboviruses (Japanese encephalitis)
Brainstem	Enteroviruses
	Epstein-Barr virus
	Herpes simplex virus 1

	Influenza virus (ANE)
	Listeria monocytogenes
	Mycobacterium tuberculosis
	West Nile virus
Calcifications (neonate)	Cytomegalovirus
	Lymphocytic choriomeningitis virus
	Toxoplasma gondii
Cerebellar	Epstein-Barr virus
	Mycoplasma pneumoniae
	Varicella-zoster virus
	West Nile virus
Corpus callosum	West Nile virus
Frontal lobe	Enteroviruses
	Herpes simplex virus 1
	Herpes simplex virus 2
	Treponema pallidum
Hydrocephalus	*Balamuthia mandrillaris*
	Coccidioides immitis
	Histoplasma capsulatum
	Mycobacterium tuberculosis
	Toxoplasma gondii (neonate)[a]
Microcephaly	Cytomegalovirus[a]
	Lymphocytic choriomeningitis virus
	Toxoplasma gondii (neonate)[a] Zika virus
Myeloencephalitis	*Gnathostoma* spp.
Parietal lobe	West Nile virus
Space-occupying lesions	*Acanthamoeba* spp. *Balamuthia mandrillaris* *Mycobacterium tuberculosis*
	Toxoplasma gondii[a]
Temporal lobe	Enteroviruses
	Herpes simplex virus 1
	La Crosse virus
	Treponema pallidum
Thalamus	Enteroviruses
	Epstein-Barr virus
	Influenza virus (ANE)
White matter (different from ADEM)	*Balamuthia mandrillaris*
	Baylisascaris procyonis
	HPeV-3 (especially neonate)
	Human immunodeficiency virus
	JC virus[a]
	Measles virus (SSPE)
	West Nile virus
Electroencephalogram Abnormality	
Periodic lateralizing epileptiform discharges	Herpes simplex virus 1
	Epstein-Barr virus
	La Crosse virus
	Measles virus (SSPE)

[a] Causes encephalitis primarily in immunocompromised patients or the neonate or both.

[b] Testing should be performed on serum at acute phase of disease and then later when sera in acute and convalescent phase of disease are available.

SSPE, subacute sclerosing panencephalitis.

Box 44.2

Diagnostic Criteria for Encephalitis and Encephalopathy of Presumed Infectious or Autoimmune Etiology

Major Criterion (Required)

Altered mental status (defined as decreased or altered level of consciousness, lethargy, or personality change) lasting >24 hours with no identifiable alternative cause

Minor Criteria (2 Required for Possible Encephalitis; ≥3 Required for Probable or Confirmed[a] Encephalitis)

Documented fever ≧38°C (≥100.4°F) within the 72 hours before or after presentation

Generalized or partial seizures not fully attributable to a preexisting seizure disorder

New onset of focal neurologic findings

CSF WBC count ≧5/mm

Abnormality of brain parenchyma on neuroimaging suggestive of encephalitis that is either new from prior studies or appears acute in onset

Abnormality on electroencephalography that is consistent with encephalitis and not attributable to another cause

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[a] Confirmed encephalitis requires one of the following: (1) pathologic confirmation of brain inflammation consistent with encephalitis; (2) defined pathologic, microbiologic, or serologic evidence of acute infection with a microorganism strongly associated with encephalitis from an appropriate clinical specimen; or (3) laboratory evidence of an autoimmune condition strongly associated with encephalitis.

Adapted from Venkatesan A, Tunkel AR, Bloch KC, et al. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the International Encephalitis Consortium. Clin Infect Dis 2013;57:1114–1128.

The characteristic presentation of EV encephalitis is a generalized syndrome, with nonspecific alterations in consciousness ranging from lethargy and mild disorientation to coma. Some strains, such as EV-71 and coxsackievirus A16, cause localized inflammation; clinical symptoms correspond to the specific neurologic area involved. In a Taiwanese epidemic of EV-71, nearly 90% of cases had a biphasic illness where either hand-foot-and-mouth disease or herpangina preceded the onset of myoclonus, tremor, or ataxia.[71] Of hospitalized patients, brainstem encephalitis was a common feature and the case fatality rate was 14%.

Focal CNS involvement is typical of HSE. The classical presentation in adults includes fever, altered level of consciousness, dysphasia or aphasia, focal motor seizures, and hemiparesis, with imaging showing involvement of one or both temporal lobes. Children, however, are more likely to have atypical manifestations. In one study, 25% of children with HSE had atypical features of ataxia, decreased visual acuity, or generalized tonic-clonic seizures.[19] In a large cohort study of children with HSE, more than 50% had neuroimaging evidence of infection outside of the temporal lobes.[72]

Several clinical findings may be suggestive of other herpes group encephalitides. Encephalitis associated with primary varicella infection can manifest as either a nonspecific syndrome or as acute or postinfectious CNS disease, or it may be associated with isolated symptoms of cerebellar ataxia acutely or of ischemic stroke within 6 months after chickenpox.[73,74] Recognition of VZV encephalitis is complicated when neurologic symptoms predate or occur in the absence of skin lesions.[75] Symptoms of EBV encephalitis can include distinguishing features such as “Alice in Wonderland” syndrome (micropsia, macropsia, and/or size distortion of other sensory modalities) or, like VZV, isolated cerebellar ataxia or stroke.[76] HHV-6 infection typically causes a limbic encephalitis, or in the immunocompromised host it can present with multifocal areas of demyelination.[77,78]

Most children with WNV infection are asymptomatic or have a mild febrile illness. Clinical manifestations of West Nile encephalitis

(WNE) include fever, headache, seizures, confusion, paralysis, tremors, facial palsy, photophobia, ataxia, and dysphasia. Acute flaccid paralysis causing a polio-like syndrome is a characteristic finding.[79] Additional manifestations can include hepatitis, myocarditis, pancreatitis, cardiac dysrhythmia, rhabdomyolysis, orchitis, uveitis, and vitritis. Brainstem encephalitis, seizures, movement disorders, cranial neuropathies, cerebellitis, and optic neuritis also are described accompanying features of WNE.[80] Clinical manifestations of LACV are typically nonspecific, with seizures, increased intracranial pressure, focal neurologic signs, and cerebral herniation all reported. Rarely, LACV encephalitis can mimic HSE.[81]

Rabies always should be considered in patients with rapidly progressive encephalitis. Paresthesia at or near the site of bite is a unique feature of rabies. A small percentage of patients with rabies come to attention with the "paralytic" form, with ascending paralysis followed by confusion and then coma. The "furious" form of rabies is more common and is characterized by agitation, hydrophobia, delirium, and seizures.

Neurologic findings of influenza-associated encephalitis typically occur several days after the onset of upper respiratory tract symptoms.[82] One of most serious presentations is ANE.[83–85] Diagnostic criteria for ANE include acute-onset encephalopathy with seizures, absence of CSF pleocytosis, normal blood ammonia levels, and exclusion of an alternative etiology (Box 44.3). Neuroimaging is characterized by symmetric multifocal brain lesions involving the thalamus, internal capsule, cerebellum, and sometimes brainstem (Fig. 44.2).[85] Most cases of ANE occur in previously healthy children <5 years of age, many of whom are of Asian descent, and mortality approaches 30%.[85]

Box 44.3

Clinical Characteristics of Acute Necrotizing Encephalopathy

Clinical

Typical age <5 years, rarely >10 years

Neurologic symptoms onset *during* the peak of febrile illness

Rapid development of encephalopathy, often with seizures

Variable elevation of serum aminotransferases, normal blood ammonia

Normal CSF (increased pressure, or mildly elevated protein level)

Exclusion of other causes (e.g., hypoxia, intoxication, HUS, metabolic disorder)

Cranial Mri

Diffuse, bilateral, symmetric high-intensity signal on T2-weighted images

Unremarkable T1-weighted images

Involvement of periventricular and deep white matter (thalamus, brainstem tegmentum, cerebellum, medulla)

No enhancement with gadolinium

Associated Conditions

Disseminated intravascular coagulopathy/SIRS that *follows* CNS signs

Multiorgan failure that *follows* CNS signs

Autopsy Findings

Edema, apoptosis/necrosis of neurons

No vasculitis

No inflammation

CSF, cerebrospinal fluid; HUS, hemolytic uremic syndrome, MRI, magnetic resonance imaging; SIRS, systemic inflammatory response syndrome.

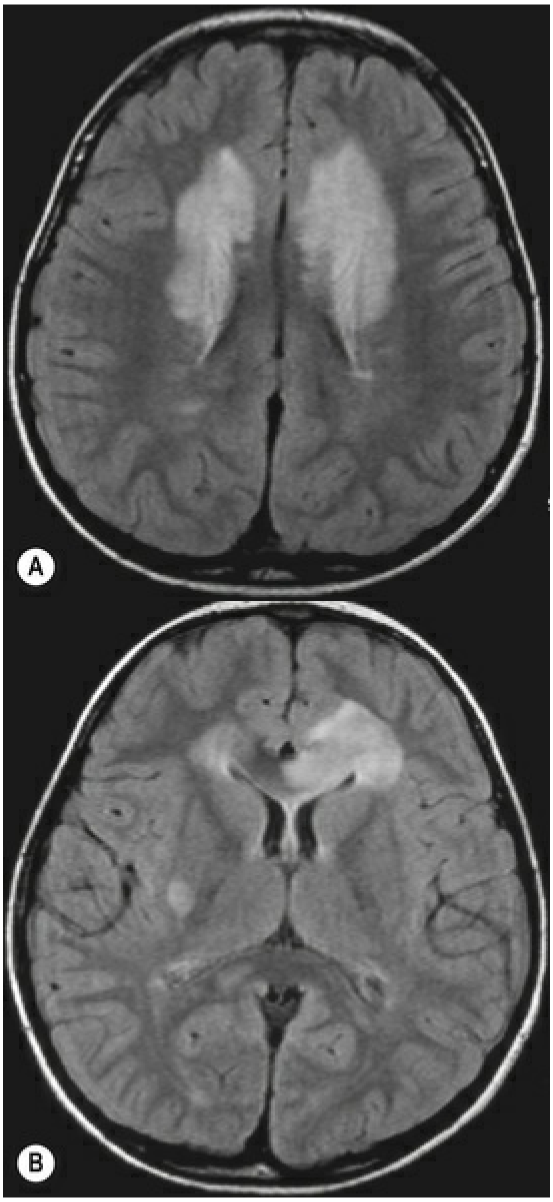

FIGURE 44.2 Acute necrotizing encephalopathy in a 3-year-old with influenza B Sichuan group/Shanghai-like. On the third day of fever and flu-like symptoms, he had acute onset of diminished arousal and recognition, mutism, ataxia, and left-sided increase in tone and reflexes. Axial fluid-attenuated inversion recovery magnetic resonance imaging shows bilateral symmetric, extensive hyperintense lesions in the centrum semiovale with periventricular involvement (A) and in the white matter anterior to the frontal horns, in the corpus callosum, and right globus pallidus (B). (Courtesy of E. N. Faerber and S. S. Long, St. Christopher's Hospital for Children, Philadelphia.)

The clinical descriptions of *M. pneumoniae*–associated encephalitis include a wide variety of neurologic (e.g., lethargy, seizures, hallucinations, and focal neurologic findings) and extraneurologic (e.g., respiratory and gastrointestinal) symptoms. Severity of illness is extremely variable.[56,86] Fungal and *M. tuberculosis* infections of the CNS generally manifest with subacute meningitis. However, acute fulminant presentations with encephalitis-like features have been described.[87]

The clinical manifestations of parasitic infections are highly variable depending on the etiologic agent. For *N. fowleri*, patients typically have headache, nausea, vomiting, and nuchal rigidity, which rapidly progresses to irreversible coma. Individuals also may experience a change in taste or smell. *B. mandrillaris* and *Acanthamoeba* spp. have a less fulminant course characterized by fever, headache, vomiting, ataxia, hemiparesis, tonic-clonic seizures, cranial nerve palsies (particularly third and sixth cranial nerves), and diplopia.[47,88,89] Neuroimaging in patients with *B. mandrillaris* is invariably abnormal, with meningeal enhancement, edema, hydrocephalus, or ring-enhancing lesions[47,90] (Fig. 44.3). Patients with CNS complications of *B. procyonis* have clinical manifestations similar to other encephalitides but also can have ocular disease and CSF eosinophilic pleocytosis; neuroimaging often shows diffuse periventricular white matter changes[91] (Fig. 44.4).

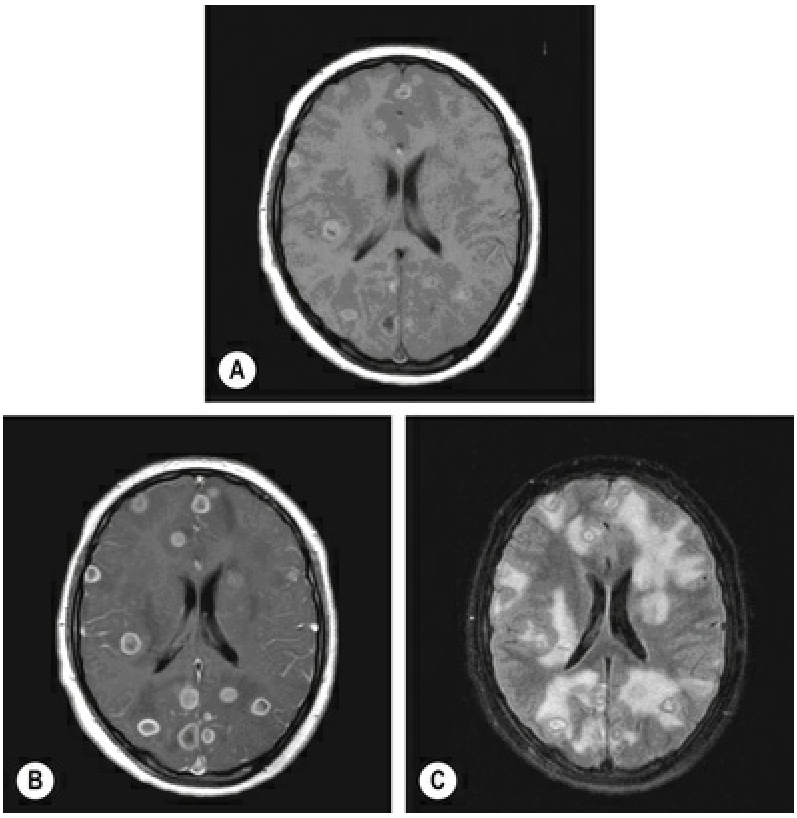

FIGURE 44.3 Magnetic resonance imaging of a patient with widely disseminated amebic encephalitis from *Balamuthia mandrillaris* (1.5-Tesla scanner) using axial T1 (precontrast [A] and postcontrast [B]) and fluid-attenuated inversion recovery (FLAIR) sequences (C). Images demonstrate numerous ring-enhancing lesions seen within the cerebral cortex, subcortical white matter, and deep grey matter, including the thalami and basal ganglia. The T2 hyperintensity seen on the FLAIR images is consistent with perilesional edema and contributes to the lesions having mild local mass effect. (Courtesy of D. Michelson, Loma Linda University School of Medicine, Loma Linda, CA.)

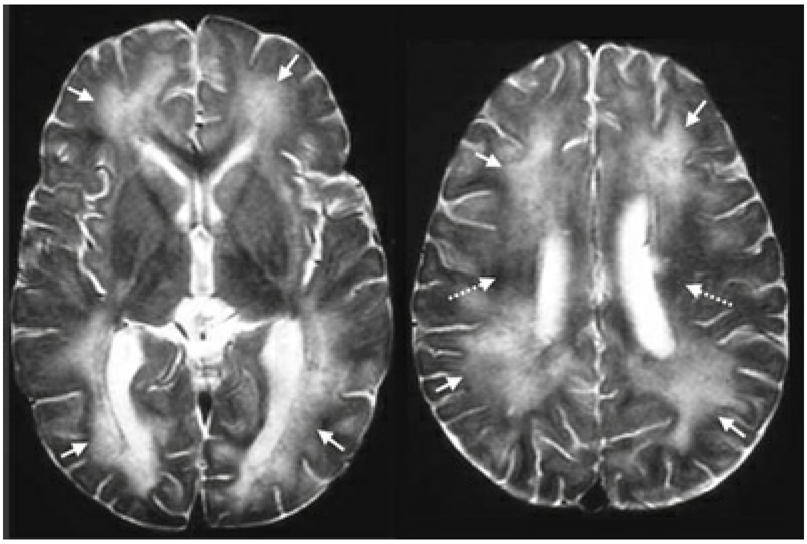

FIGURE 44.4 Magnetic resonance images of a 13-month-old boy with *Baylisascaris procyonis* encephalitis, showing abnormally high signal throughout the central white matter compared with darker signal expected for age. (Courtesy of Sorvillo F, Ash LR, Berlin OGW, et al. *Baylisascaris procyonis:* an emerging helminthic zoonosis. Emerg Infect Dis 2002;8:355–359.)

Noninfectious entities that can mimic encephalitis may have suggestive clinical features. Early symptoms of anti-NMDAR encephalitis, for example, include behavioral changes or psychosis, seizures, and involuntary movements. Recognition of this syndrome is important because, despite the severity, improvement can occur with immunosuppressive therapy and removal of tumor if present.[62] Several other disease processes must be considered in the differential diagnosis of acute encephalopathy, including immune-mediated diseases, toxic ingestions, inborn errors of metabolism, acquired metabolic disorders, mass lesions (tumor or abscess), and other CNS conditions (see Box 44.1).

Special Hosts

Neonates

The epidemiology and clinical presentation of agents causing congenital or neonatal encephalitis differ from those of older children (Table 44.3). Identifying infants with CNS infections can be particularly problematic because the clinical features are extremely vague during the early phase of illness. Congenital infection with cytomegalovirus (CMV), VZV, rubella virus, LCM virus, and *T. gondii* can include CNS infection with structural brain damage and neurologic symptoms present at birth. If infection occurs during the first trimester, there is an increased risk for spontaneous abortion.[92] Later in gestation, congenital infection can lead to chorioretinitis, intracranial calcifications, hydrocephalus, microcephaly or macrocephaly, mental retardation, and seizures.

TABLE 44.3

Differential Diagnosis of Encephalitis in the Neonate

Infection or Disorder	Frequency
PERINATAL INFECTION	
Herpes simplex virus	++
Enterovirus[a]	+++
Adenovirus	+++
Group B *Streptococcus*[b]	+
Listeria monocytogenes[b]	+
Citrobacter spp.[b]	+
CONGENITAL INFECTIONS	
Cytomegalovirus	+++
Lymphocytic choriomeningitis virus	+
Toxoplasmosis	+
Rubella virus	+
Syphilis	+
GENETIC AND INBORN ERRORS OF METABOLISM	+[c]
Aicardi-Goutières syndrome	
Leigh disease (subacute necrotizing encephalomyelitis)	
Maple syrup urine disease	
Organic acidopathies (methylmalonic acidemia, propionic acidemia)	
Urea cycle defects	
PRIMARY CENTRAL NERVOUS SYSTEM DISORDER	
Nonconvulsive status epilepticus	+
Hemorrhage	+
Hypoxic ischemic encephalopathy	++

[a] Includes aseptic meningitis.

[b] Cerebritis.

[c] Combined incidence.

+++, most frequent; ++, frequent; +, occasional.

HSV-1 and HSV-2, EV, HPeV, and HIV are acquired primarily in the perinatal period. Meningoencephalitis may be the sole manifestation of HSV infection or can be associated with skin-eye-and-mouth disease or disseminated disease. Neuroimaging can show diffuse (multilobar) involvement rather than temporal lobe predominance; of 29 infants with HSE, bilateral multilobar (8), thalamic (6), internal capsule and corticospinal tract (5), and pontine involvement was seen.[93] Recognition of HSV is particularly important because of beneficial treatment with acyclovir. Before the availability of antiviral therapy, the infant mortality rates associated with disseminated and HSV CNS disease were 85% and 50%, respectively. Presentation of neonatal HSV CNS disease constitutes a spectrum including nonspecific signs and symptoms,[94,95] apnea, lethargy, focal or generalized seizures, and paralysis.

In neonates, a variety of EVs and HPeVs have been associated with serious complications, including encephalitis and death.[96,97] HPeV-3 is noteworthy in the neonatal period because it appears to be a major cause of neonatal encephalitis, possibly 3 times more common than EV.[98] The typical presentation is fever, rash, irritability, seizures, and occasionally hepatitis. Notably, the CSF is normal in most cases (90%), which suggests that the diagnosis of encephalitis could be overlooked easily.[16,98] Further, neuroimaging in HPeV-3 cases often demonstrates distinctive white matter involvement that may be thought erroneously to be hypoxic ischemia injury or periventricular leukomalacia. Unlike periventricular leukomalacia, however, white matter abnormalities in neonatal HPeV-3 involve the subcortical white matter, entire fiber tracts including the corpus callosum, optic radiation, and grey matter regions such as the posterior thalamus.[98]

As outlined in Table 44.3, evaluation of neonates is somewhat unique. Acyclovir should be administered empirically to ill infants with signs compatible with HSV CNS infection and no other likely diagnosis.

Immunocompromised Hosts

In addition to agents that can cause encephalitis in the immunocompetent host, many additional agents must be considered in the immunocompromised host.

Several herpesviruses (CMV, EBV, HHV-6, VZV) can reactivate to cause encephalitis. CMV is particularly problematic in organ transplant recipients and HIV-infected individuals. CMV encephalitis can manifest as diffuse encephalopathy with confusion, disorientation, psychomotor slowing, and cranial nerve palsies and also can cause periventricular encephalitis.[99] HHV-6 encephalitis occurs predominantly in patients after hematopoietic stem cell transplantation.[100] Although HPeV encephalitis is described most commonly in young children, the report of severe myocarditis and encephalitis in an adolescent with hypogammaglobulinemia highlights its role in patients with humoral immunodeficiencies.[101] JC virus typically causes multifocal demyelinating disease, progressing to multifocal leukoencephalopathy, and is seen almost exclusively in patients with AIDS. Although fungal CNS infections are relatively rare, they are recognized increasingly as the immunocompromised population grows. Similarly, the free-living amebas, *Acanthamoeba* spp. and *B. mandrillaris*, also can cause encephalitis in the immunocompromised host.

Clinical Approach

Despite a thorough diagnostic evaluation, a pathogen is identified in less than half of all cases of encephalitis.[102] Even when an infectious etiology is identified, there may be no specific treatment. However, diagnostic testing has an important role in prognosis, potential postexposure prophylaxis of contacts, counseling of patients and families, and public health interventions. Additionally, the identification of a specific agent can lead to discontinuation of unnecessary antimicrobial and antiviral therapies.[1] There are many important caveats to laboratory testing in patients with encephalitis (Table 44.4).

TABLE 44.4

Laboratory Testing with Focus on Pathogens Found in the United States

Agent	Recommended Diagnostic Studies	Caveats
VIRUS		
Adenovirus	• Cerebrospinal fluid (CSF), respiratory, brain tissue for polymerase chain reaction (PCR) or culture	• Pathogen of unknown neurologic potential
Arboviruses	• Serology is the most useful assay for most arboviruses: CSF immunoglobulin M (IgM), serum IgM and	• Acute viremia stage often over by the time of clinical presentation; however, PCR is sometimes positive in very acute specimens • PCR can be helpful in immunocompromised host because of prolonged viremia and

	IgG (paired sera if possible) for specific viruses as suggested by geography: – West Nile virus (WNV) – St. Louis encephalitis (SLE) virus – California serogroup viruses (e.g., La Crosse virus [LACV]) – Eastern equine encephalitis virus (EEE) – Powassan virus (POW) – Western equine encephalitis (WEE) virus	delayed antibody response • Knowledge of geographic and seasonal variation of arboviruses important and can limit unnecessary testing • CSF IgG for specific arbovirus usually not helpful because of blood-brain barrier integrity; CSF blood contamination can cause false-positive results for both IgM and IgG • High rate of serologic cross-reactivity among arbovirus (WNV, SLE, and POW; individual with prior dengue infection will test positive for WNV IgG) • Antibody typically positive early in presentation, but if negative, repeat on later specimen • WNV: predominance of polymorphonuclear cells in CSF can persist beyond the first 24 hr in contrast to other viral encephalitides • WNV: abnormal-appearing reactive lymphocytes including plasma cell-like and Mollaret-like cells • EEE: CSF WBC counts can be very high, with counts up to 4000/mm^3 • POW: testing only available at Centers for Disease Control and Prevention (CDC) and a few state laboratories
Cytomegalovirus (CMV)	• CSF for PCR • Shell vial on urine, saliva (neonate)	• Serology can be problematic especially because of false-positive results • Rare causes of encephalitis in immunocompetent host • Atypical lymphocytes in CSF
Enteroviruses (EV)	• CSF for PCR • Respiratory swab for PCR • Stool for PCR or culture	• PCR on CSF alone can be negative because EV is present only transiently in CSF; test non–central nervous system (CNS) site (respiratory sample PCR, viral stool culture) to increase yield
Epstein-Barr virus (EBV)	• CSF for PCR • Serum for anti-VCA IgM/IgG, anti-EBNA • Serum heterophile antibody	• Both serology (serum) and PCR (CSF) are recommended • False-negative and false-positive results can occur with EBV PCR. False-positive results occur because EBV DNA is found in peripheral blood mononuclear cells • Atypical lymphocytes in CSF or peripheral blood are consistent but not always present
Herpes simplex virus 1 (HSV-1)	• CSF for PCR • CSF for antibody if >1 wk of symptoms • Neonate: – CSF for culture and/or PCR – Nasopharyngeal (NP) swab for culture and/or PCR – Conjunctival swab for culture and/or PCR – Rectal swab for culture and PCR – Skin lesion swab for	• Outside neonatal period, HSV-1 causes most cases of herpes simplex encephalitis (HSE). In neonatal period, most infections are due to HSV-2 • Approximately 5%–10% of HSE patients have a normal CSF in first lumbar puncture (LP), particularly in children. HSV PCR can be negative in first LP. For cases in which HSE is highly suspected (e.g., temporal lobe involvement), a second LP should be performed for CSF PCR and intrathecal HSV antibody testing • Presence of either HSV IgG or IgM antibody can indicate CNS infection; however,

	culture and/or PCR	diminished blood-brain barrier and possible CSF contamination with blood should be considered when interpreting results
Herpes simplex virus 2 (HSV-2)	• CSF for PCR • CSF for antibody if >1 wk of symptoms • Neonate: – CSF culture and/or PCR – NP, conjunctival, rectal swabs for culture and/or PCR – Skin lesion swabs for PCR and culture	• Neonatal period, HSV-2 important cause of HSE. Beyond neonatal period, HSV-2 causes primarily meningitis syndrome but has been associated with encephalitis • Presence of either HSV IgG or IgM antibody can indicate CNS infection; however, blood-brain barrier issues and possible CSF contamination of blood need to be considered when interpreting results
Human herpesvirus 6 (HHV-6)	• CSF for PCR	• Pathogen of unknown neurologic potential • Not all HHV-6 CSF PCR–positive results correlate with disease; when positive, important to consider chromosomal integration or latent infection
Human immunodeficiency virus (HIV)	• p24 antigen and HIV antibody • Plasma and CSF for PCR	
Human metapneumovirus	• Respiratory tract (NP or throat swab) for PCR	• Pathogen of unknown neurologic potential • CSF PCR rarely positive
Influenza A/B virus	• Respiratory secretions for viral culture • Respiratory secretions for viral antigen test • Respiratory secretions for PCR	• Most cases are encephalopathy (vs. encephalitis) • CSF PCR rarely is positive
JC polyomavirus	• CSF for PCR	• A positive result correlates with diagnosis; negative result does not rule it out
Lymphocytic choriomeningitis virus (LCM)	• CSF for LCM IgM/IgG antibody • Serum for LCM IgM/IgG antibody • Neonate: – Serology on both infant and mother	• One of the few viruses that can cause low glucose in CSF
Measles virus—acute	• CSF for measles virus antibodies • CSF for measles virus PCR • Serum IgG/IgM (paired serum samples if possible) • Brain tissue (if available) for measles virus PCR	• Measles PCR and antibody testing (both serum and CSF)
Measles virus—SSPE	• CSF IgG antibodies • Serum IgG antibodies • Brain tissue (if available) PCR	• Because SSPE is result of longstanding infection, measles IgM is negative; IgG levels in CSF and serum very high
Mumps virus	• CSF for culture or PCR • CSF for IgM/IgM antibodies • Serum for IgM/IgG antibodies (paired	• One of few viruses that can cause low glucose in CSF

	serum samples if possible) • Throat swab for PCR	
Parvovirus B19	• Serum for IgM antibody • CSF for PCR	• Pathogen of unknown neurologic potential
Rabies virus	• Antemortem: serum for antibodies – Saliva and CSF for PCR – Nuchal biopsy for PCR and DFA – Brain tissue (if available) for DFA • Postmortem: – Brain tissue for culture; or antigen detection	• Antemortem testing is challenging but possible • Multiple samples and different assays should be performed. Negative tests antemortem do not rule out rabies • Coordinate testing with local and state health department
Respiratory syncytial virus (RSV)	• Respiratory secretions or PCR antigen	• Pathogen of unknown neurologic potential • CSF PCR rarely positive
Rotavirus	• Stool for antigen detection • CSF PCR (CDC)	• Pathogen of unknown neurologic potential • Typically young child with history of diarrhea; mechanism of CNS illness unclear
Rubella virus	• Serum for antibody • CSF for antibodies	• One of few viruses that can cause low glucose in CSF
Varicella-zoster virus (VZV)	• CSF for PCR • CSF for antibody if >1 week of symptoms • Serum for IgM/IgG • Skin lesions for direct fluorescent antibody (DFA) or PCR	• Because some CNS VZV infections are reactivation, IgM not always positive • Positive test on VZV skin lesions does not prove CNS etiology but may be suggestive
West Nile virus	• See earlier entry "Arboviruses"	
FUNGUS		
Coccidioides spp.	• CSF culture (large volume) • CSF for antigen • CSF for antibody • Serum for antigen • Serum for antibody	• Warn laboratory that coccidioidomycosis is being considered if culture ordered • Eosinophils sometimes present in CSF • "EDTA-heat"–treated antigen test reported to increase sensitivity for CSF and serum samples
Histoplasma capsulatum	• CSF for culture (large volume) • CSF, serum, and urine for antigen detection • CSF for antibody • Serum for antibody	• May need to do multiple tests • Isolated CNS disease can be difficult to diagnose because of insensitive assays • "EDTA-heat"–treated antigen test reported to increase sensitivity for CSF and serum samples
Blastomyces dermatitidis	• CSF for culture (large volume) • CSF, serum, urine for antigen detection • CSF for antibody • Serum for antibody	• May need to do multiple tests • "EDTA-heat"–treated antigen test reported to increase sensitivity for CSF and serum samples
FREE-LIVING AMEBAS AND PARASITES		
Naegleria fowleri	• Wet mount of warm CSF • Brain (if available) histopathology	• Demonstration of motile ameba on wet mount • CSF often demonstrates very high WBC (often with neutrophil predominance), high protein (>100 mg/dL), and low glucose (<50

		mg/dL)
Balamuthia mandrillaris	• Serum for antibody • CSF and/or brain for PCR • Brain (if available) histopathology (special stains)	• Serology and PCR available at specialized laboratories • Brain tissue can show necrotic and hemorrhagic meningoencephalitis • CSF often shows high WBC (lymphocyte or neutrophil predominance), high protein (>100 mg/dL), resembling tuberculous meningitis
Acanthamoeba spp.	• Serum for antibody • CSF and/or brain for PCR • Brain (if available) histopathology (special stains)	• Serology and PCR available at specialized laboratories
Baylisascaris procyonis	• CSF for antibody • Serum for antibody	• Serology available in specialized laboratories (Parasitic Disease Branch, CDC) • Eosinophils almost always present in CSF and peripheral blood
Toxoplasma gondii	• Neonatal: serum for IgG, IgM, IgA, IgE antibodies. Older child: serum for IgG, IgM; CSF for PCR	• Serology can be falsely negative; important to test mother and infant • Often reactivation of disease, so IgM may not be positive, IgG titers persistently high
BACTERIA		
Bartonella henselae	• Serum for indirect fluorescent antibody • Lymph node for PCR	• CSF PCR often negative
Borrelia burgdorferi	• Serum for antibodies sequential (enzyme immunosorbent assay and Western blot) • CSF for serum/CSF antibody index	• CSF for *Borrelia;* may be delay in CNS intrathecal synthesis • CSF PCR rarely positive (in contrast to synovial fluid) but may be useful in some cases
Brucella spp.	• CSF for IgG and IgM • CSF for culture • Serum for IgG and IgM	• Perform serology on both CSF and serum; culture increases sensitivity • PCR available in some research settings; unknown sensitivity
Leptospira spp.	• Serum IgM and IgG • Urine culture	• If serology negative on acute serum, important to repeat on convalescent serum
Listeria monocytogenes	• Routine bacterial culture	• May also be helpful to test CSF for *Listeria* antibody because detection of CSF antibody can indicate CNS infection
Mycobacterium tuberculosis	• CSF for acid-fast bacilli smear, culture, PCR, direct examination • Respiratory secretions for culture highly suggestive	• CSF PCR is insensitive; important to test multiple samples • Should be considered in patients with lymphocytic pleocytosis (but neutrophilic predominance can occur), with CSF protein >100 mg/dL or CSF glucose <50 mg/dL
Mycoplasma pneumoniae	• Nasopharyngeal swab or respiratory secretions for culture or PCR • Serum for IgM • Serum for IgG paired	• Pathogen of unknown neurologic potential • Perform PCR on respiratory samples, serology on acute/convalescent serum • CSF PCR rarely positive • Single IgG titer is not helpful • Single IgM test can have false-positive results
Treponema pallidum	• CSF for Venereal Disease Research	• Multiple tests as well as clinical findings are important for definitive diagnosis

	Laboratory (VDRL) test • CSF for fluorescent treponemal antibody (FTA) • CSF for PCR • Serum for VDRL and FTA	• CSF VDRL test is specific but CSF FTA is more sensitive • FTA does not distinguish between syphilis and other treponematoses such as pinta and yaws • Nontreponemal tests can have a prozone phenomenon resulting in false-negative FTA • Infection with *Borrelia burgdorferi* can cause false-positive FTA
RICKETTSIA		
Anaplasma phagocytophila	• Peripheral blood for morulae in neutrophils • Whole blood for PCR • Serum IgG/IgM (paired sera if possible)	• If serology negative on acute serum, important to repeat on convalescent serum
Coxiella burnetii	• Serum for acute and convalescent antibody	• Utility of PCR for *Coxiella burnetii* PCR for Q fever encephalitis unknown
Ehrlichia chaffeensis	• Morulae in peripheral blood monocytes • Whole blood for PCR • Serum for IgG/IgM (paired sera if possible	• If serology negative on acute serum, important to repeat on convalescent serum
Ehrlichia ewingii	• Morulae in peripheral blood granulocytes • Whole blood for PCR • Serum for IgG/IgM antibodies	• If serology negative on acute serum, important to repeat on convalescent serum
Rickettsia spp.	• Serum for indirect fluorescent antibody • Skin biopsy of rash for PCR or immunohistochemical staining	• If serology negative on acute serum, important to repeat on convalescent serum

A thorough history is crucial and should include an assessment of epidemiologic and clinical exposures as outlined in Table 44.1, with an emphasis on ill contacts, vector and animal exposures, outdoor activities, ingestions, and travel history. Any current or recent antecedent respiratory illness, gastrointestinal illness, or rash should be obtained because this may narrow the differential diagnosis or suggest a postinfectious syndrome such as ADEM.

Initial evaluation should include a complete blood count and tests of renal function and hepatic enzyme levels (Box 44.4). A baseline chest radiograph also should be obtained because focal infiltrates might be suggestive of certain pathogens (e.g., fungi or mycobacteria) and might prompt other diagnostic studies (e.g., bronchoscopy). An ophthalmologic examination also is suggested if there are supporting signs or symptoms because chorioretinitis may be identified in the newborn infant, or a migratory nematode in an older individual. Chorioretinitis also can be associated with WNE, bartonellosis, syphilis, histoplasmosis, tuberculosis, and noninfectious conditions such as sarcoidosis.[103]

Box 44.4

Initial Diagnostic Evaluation for Patients with Encephalitis

General Studies

CBC with differential

Renal function tests

Serum hepatic enzymes

Blood cultures

Chest radiograph

Ophthalmologic examination

Lumbar Puncture

Opening pressure

CSF WBC and RBC counts and differentials, protein, and glucose

Gram stain and culture for bacteria

PCR for herpes simplex virus and enterovirus

PCR for human parechovirus (<3 years of age)

Other tests as indicated based on specific host factors, exposures, clinical features

Serum for Antibody

Mycoplasma pneumoniae IgM/IgG

Epstein-Barr virus panel

Human immunodeficiency virus

Other tests as indicated based on specific host factors or exposures

Respiratory Secretions/Stool Specimen

PCR on respiratory tract specimen for enterovirus and *Mycoplasma pneumoniae*

PCR or culture on stool specimen for enterovirus

If respiratory symptoms: rapid tests, PCR panel, culture for influenza (during appropriate season) and other respiratory viruses

Neuroimaging

MRI (preferred; CT if not available)

Electroencephalogram

CBC, complete blood count; CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; RBC, red blood cell; WBC, white blood cell.

Neuroimaging is critical in evaluating encephalitis. Cranial computed tomography is helpful to identify abnormalities, such as ventriculomegaly, abscess, or tumor, and can help determine whether it is safe to perform a lumbar puncture (LP). However, magnetic resonance imaging is more sensitive for detecting changes of encephalitis.[104,105] Electroencephalography is an informative early test to assess for subclinical seizure activity and can help localize the region of affected brain.

An LP with measurement of the opening pressure and sampling for CSF analysis (cell count with differential analysis, glucose and protein concentrations), Gram stain, and culture should be performed unless there is a specific contraindication.[102,106] Results from the LP offer important clues as to whether the patient has an infectious or noninfectious etiology and whether an infectious cause is viral, bacterial, fungal, or parasitic. Fungal and mycobacterial testing should be performed selectively in suggestive cases. CSF viral culture is not recommended because its sensitivity is extremely low and may unnecessarily deplete the CSF sample.[107] PCR testing for viruses is more sensitive and rapid, including for herpesvirus, HPeV, and EV.[108,109] There are, however, important limitations of sensitivity and specificity for CSF PCR testing, as outlined in Table 44.4. The diagnostic test for HSE is CSF PCR testing for HSV DNA. If initial testing is negative and HSE is strongly suspected, the test should be repeated on a CSF specimen obtained a few days after the first LP.[1] For HSE and VZV encephalitis, intrathecal antibody assays can be performed to supplement nucleic acid testing.[110] For many of the arboviruses, antibody testing of serum or CSF is preferred to PCR testing because peak viremia generally occurs before symptom onset.

In patients with respiratory symptoms, respiratory specimens should be tested for common viral pathogens early in hospitalization to optimize detection. Molecular and antigen detection testing is more sensitive than culture. If diarrhea is present, a stool specimen should be obtained for viral pathogens. In a young child, a stool viral culture or enterovirus PCR should be performed to optimize enterovirus detection, regardless of presence of diarrhea, and in the appropriate setting, rotavirus antigen testing performed.[111]

An extra red-topped serum tube should be collected in the acute phase of illness and held for later serologic studies. A convalescent serum should be collected 10 to 21 days later. Although immediate management is not altered, documentation of seroconversion or a fourfold rise in titer can determine the diagnosis (see Box 44.4).

Brain biopsy is rarely performed but has value in selected cases because of limitations in both molecular and serologic methods. The utility of targeted brain biopsy was illustrated in a series of 16 patients with unknown CNS illnesses, detecting bacterial abscess (6), toxoplasmosis (3), HSV (1), *Aspergillus* infection (2), and *M. tuberculosis* infection (2) that were not detected by other methods.[112] Biopsy also is helpful for diagnosis of noninfectious entities such as small vessel vasculitis and intravascular lymphoma.[113] In the event of the death of a patient with undiagnosed encephalitis, an autopsy should be sought to determine the cause of death.

Laboratory Findings

Routine laboratory studies (see Box 44.4) infrequently help to identify specific etiologies but can suggest particular etiologies. For instance, finding leukopenia, thrombocytopenia, and elevated serum transaminase levels during summer months would be suggestive of CNS *Ehrlichia* disease.[114] Additionally, test results guide appropriate dosing regimens for antimicrobial therapy.

Most patients with viral encephalitis have CSF mononuclear cell pleocytosis, with cell counts ranging from 10 to 200 mg/dL.[3] However, early in the course, pleocytosis can be absent or show neutrophil predominance. Repeat LP in 1 to 2 days may be useful.[115] The CSF protein level generally is elevated (usually <100 mg/dL), whereas the glucose level is normal or minimally low, with a few important exceptions (LCM and mumps).

Neutrophilic pleocytosis (particularly with CSF WBC count >1000 cells/mm^3, protein >200 mg/dL, or CSF glucose less than two thirds of blood concentration) is suggestive of a bacterial entity. In fungal infections moderate lymphocytic pleocytosis usually is found. *Naegleria* infection generally elicits extreme CSF neutrophilic pleocytosis. Eosinophils in the CSF suggest infection due to a parasite (e.g., *B. procyonis, Angiostrongylus* spp., or *G. spinigerum*), *M. tuberculosis,* or *Coccidioides* spp. As noted in Table 44.4, there are important considerations if eosinophils are detected in spinal fluid.

Management

Management should focus on treatable and common causes of encephalitis.[102] Empiric treatment for bacterial meningitis (vancomycin plus a third-generation cephalosporin) should be started because the clinical presentation can overlap with encephalitis. Therapy with ampicillin is considered additionally when rhomboencephalitis is present or there is significant cellular immunocompromise (e.g., chronic corticosteroid use). HSE is one of the few treatable causes of viral encephalitis; therapy with high-dose parenteral acyclovir should be started and continued until HSV-1 has been reasonably excluded as a diagnosis, which can require serial CSF samples. Antiviral therapy considerations generally are restricted to treatment of herpesviruses (HSV-1 and

VZV) and the unusual instance of HIV infection.[102] Therapy for tuberculous or fungal meningitis should be initiated empirically when clinical and laboratory testing is compatible. If rickettsial or *Ehrlichia* infections are suspected, doxycycline should be initiated empirically. For influenza-associated encephalitis, oseltamivir, although not proved to be efficacious, is given and may be beneficial.[116] Corticosteroids and immune globulin intravenous also may be helpful in some influenza-associated encephalitis cases because a mechanism of hyperintense cytokine response is suggested.[116] There is no evidence that treatment of CNS *Mycoplasma* infection alters outcome.

In addition to directed therapy, aggressive supportive care is critical, and minimizing secondary brain injury is a high priority.[117] Cerebral edema should be considered in patients who are not improving with empiric antimicrobial and supportive therapy. Physicians frequently neglect to measure CSF opening pressure, which may be a helpful clue to impending complications. Repeat neuroimaging to monitor for cerebral edema is particularly important in comatose patients. Typical indicators of elevated intracranial pressure, such as poorly reactive dilated pupils, decorticate or decerebrate posture, or Cushing triad (systolic hypertension, bradycardia, and shallow respirations) are late findings. Subclinical seizures are common; continuous electroencephalographic monitoring is considered in patients with persistent alteration in mentation.[118] Patients should be monitored for the syndrome of inappropriate secretion of antidiuretic hormone. If hyponatremia is present, it is important to correct sodium levels slowly to avoid the complication of extrapontine osmotic myelinolysis.[119]

Conditions that mimic infectious encephalitis should be considered, and metabolic and toxic disorders causing encephalopathy and seizures should be excluded. Anti-NMDAR encephalitis is of particular importance given its high incidence and therapeutic considerations.[62,120] As outlined in Chapter 45, in patients suspected to have postinfectious encephalitis or ADEM, often with a characteristic magnetic resonance image showing prominent white matter inflammation, corticosteroid or other immunotherapy often is recommended.

Complications and Prognosis

In a large cohort of pediatric patients with encephalitis due to a variety of causes, one third of patients had incomplete recovery, and 6.8% of patients died.[121] Prognosis is highly dependent on the specific infectious cause. Rabies and *N. fowleri*, for instance, have an almost 100% fatality rate. Even with effective antiviral therapy, >35% of patients with HSE suffer severe sequelae or death.[122,123] Relapse of HSV-1 encephalitis, both early (within weeks of disease onset) and late (within months to years), is described in up to 26% of children.[124] In addition, the anti-NMDAR autoimmune form of encephalitis can be triggered by HSE, in which case immunosuppressive therapy is indicated.[125]

WNND has a much better prognosis in children than in adults. From 2003 to 2012, of 505 pediatric WNND disease cases, most (88%) were hospitalized, but the case-fatality rate was <1%[28]; this contrasts with WNV case-fatality rates of 9% overall (all ages) and 17% for individuals ≥60 years.[126] LACV and EEE cause more severe neurologic disease in children than WNV.[127] In a study of 127 children with LACV, 12% had neurologic deficits at discharge.[127] EEE also is known to have a higher mortality rate (almost 30%) and potentially severe neurologic complications.

Other viral etiologies are less well studied, with information limited to case reports and small series. Persistent neurologic deficits after EBV encephalitis are reported to be rare.[123] ANE associated with influenza has a high mortality rate, with most fatalities reported in Japan and Taiwan.[128,129] In the US, ANE cases are less common and appear to have better outcome.[130]

Bacterial infections causing meningoencephalitis are associated with significant morbidity despite the availability of effective antibiotic therapies. In a French study, *L. monocytogenes* and *M. tuberculosis* meningoencephalitis accounted for 46% of fatalities due to encephalitis.[131] *L. monocytogenes* infections are less common in the US.[132] Tuberculous meningoencephalitis was associated with a 30% mortality, with 40% of survivors suffering moderate or severe disabilities.[133] On the other hand, encephalopathy due to *Bartonella* spp. is associated with an excellent outcome, with >90% of patients recovering completely without sequelae.[134]

Although studies are limited, one study reported significant sequelae in up to 53% of survivors hospitalized for encephalitis ultimately of unknown cause.[135]

Progress in Treatment and Prevention

Progress is being made toward treatment of some infections once considered to be universally fatal. In 2004, an unvaccinated adolescent survived rabies encephalitis after a novel therapy was used.[136] Good outcomes have been achieved with various combination drug regimens for *B. mandrillaris* and *B. procyonis*.[137–139] In 2015, a third well-documented survivor of *N. fowleri* was reported after miltefosine therapy.[140] Pleconaril-like compounds are being tested against some enteroviruses.[141]

Routine immunizations decrease dramatically encephalitis related to diseases such as measles, mumps, rubella, varicella, and influenza, and postexposure rabies immune globulin plus vaccine prevents rabies. For the immunocompromised host, passive postexposure prophylaxis for varicella and measles also is available. Avoidance of exposure to arthropod vectors is an effective means of preventing arboviral and tickborne encephalitis. EV-71 vaccine candidates are in clinical trials.[142]

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45

Parainfectious and Postinfectious Neurologic Syndromes

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Inflammation of the central or peripheral nervous system can produce a myriad of symptoms depending on site. The inflammation often arises during, or in response to, an infection. However, the same syndrome can be seen when there have been no signs of a preceding illness, and occasionally the syndrome can develop after vaccination. The presentation can be localized to one structure, such as in optic neuritis (ON), or affect multiple structures, such as in acute disseminated (or demyelinating) encephalomyelitis (ADEM). Inflammation typically causes temporary demyelination, although it can cause injury to the underlying parenchyma or axons, leading to more permanent injury. The focus of this chapter is the more common syndromes seen in the pediatric population, their various etiologies, diagnostic evaluation, and management (Tables 45.1 and 45.2).

TABLE 45.1

Etiologies of Parainfectious and Postinfectious Syndromes of the

Central Nervous System

ACUTE DISSEMINATED ENCEPHALOMYELITIS	**Viruses**	**Bacteria**	**Noninfectious Associations**
	Enteroviruses	*Bartonella henselae*	Adrenoleukodystrophy
	Epstein-Barr virus	*Borrelia burgdorferi*	Behçet syndrome
	Herpes simplex virus 1 and 2	*Streptococcus pyogenes*	CNS lymphoma
	Influenza A and B	*Leptospira* sp.	Langerhans cell histiocytosis
	Measles virus	*Mycoplasma pneumoniae*	Metachromatic leukodystrophy
	Mumps virus	**Parasites**	Mitochondrial disorders
	Parainfluenza viruses	*Plasmodium falciparum*	Multiple sclerosis
	Rubella virus		Primary CNS vasculitis
	Varicella-zoster virus		Systemic lupus erythematosus
	Variola virus		Sjögren syndrome
			Sarcoidosis
			Vaccines
ACUTE FLACCID MYELITIS	**Viruses**		
	Poliovirus		
	Enteroviruses		
	West Nile virus		
	Japanese encephalitis virus		
TRANSVERSE MYELITIS	**Viruses**	**Bacteria**	**Noninfectious Associations**
	Enterovirus	*Bartonella henselae*	Antiphospholipid antibody syndrome
	Epstein-Barr virus	*Borrelia burgdorferi*	Ischemic myopathy
	Herpes simplex virus 1 and 2	*Streptococcus pyogenes*	Neuromyelitis optica (Devic disease)
	Influenza A and B	*Leptospira* sp.	Spinal cord tumor
	Measles virus	*Mycoplasma pneumoniae*	Sjögren syndrome
	Mumps virus	**Parasites**	Systemic lupus erythematosus
	Parainfluenza viruses	*Plasmodium falciparum*	
	Rubella virus	*Schistosoma* spp.	
	Varicella-zoster virus	*Toxocara canis*	
	Variola virus		
CEREBELLITIS	**Viruses**	**Bacteria**	**Noninfectious Associations**
	Adenovirus	*Borrelia* spp.	Antineuronal antibodies (e.g., anti-Hu)
	Cytomegalovirus	*Coxiella burnetii*	Methadone ingestion

	Enteroviruses	*Rickettsia* spp.	Systemic lupus erythematosus
	Herpes simplex virus 1 and 2	*Salmonella typhi*	Tick paralysis
	Human herpes virus 6		Vaccines
	Human immunodeficiency virus		
	Influenza virus		
	Mumps virus		
	Rotavirus		
	Varicella-zoster virus		
	West Nile virus		

CNS, central nervous system.

TABLE 45.2

Etiologies of Parainfectious and Postinfectious Syndromes of the Peripheral Nervous System

GUILLAIN-BARRÉ SYNDROME	**Viruses**	**Bacteria**	**Noninfectious Associations**
	Cytomegalovirus	*Campylobacter* spp.	Chronic progressive external ophthalmoplegia
	Epstein-Barr virus	**Mimicking**	Heavy metal poisoning
	Herpes simplex virus 1 and 2	Infant botulism	Myasthenia gravis
	Varicella-zoster virus	Poliovirus	Tick paralysis
		West Nile virus	Vaccines
FACIAL NERVE PALSY (BELL)	**Viruses**	**Bacteria**	**Noninfectious**
	Herpes simplex virus 1	*Borrelia* spp.	Aneurysm of vertebral, basilar or carotid arteries
	Epstein-Barr virus	*Mycobacterium tuberculosis*	Cholesteatoma of the middle ear
	Human herpesvirus 6	*Mycobacterium leprae*	Drugs (e.g., linezolid)
	Human immunodeficiency virus Parvovirus B19 Varicella-zoster virus	**Mimicking**Acute otitis media Intraparotid lymphadenitis Necrotizing otitis externa Osteomyelitis of the skull base Parotid gland abscess	Kawasaki disease Leukemic meningitis
			Parotid tumors
			Sarcoidosis
			Fracture of base of the skull
			Fracture of the temporal bone
			Trauma
OPTIC NEURITIS	**Viruses**	**Bacteria**	**Noninfectious Associations**
	Chikungunya virus	*Bartonella henselae*	ADEM
	Varicella-zoster virus	**Parasites**	Autoimmune (IBD, SLE)
	West Nile virus	*Angiostrongylus cantonensis*	Copper deficiency

		Baylisascaris procyonis	Diabetes mellitus
		Toxocara canis/cati	Drugs (e.g., ethambutol)
		Treponema pallidum	Neuromyelitis optica (Devic disease)
			Multiple sclerosis
			Vasculitis
OCULOMOTOR NEUROPATHY	**Viruses**	**Infectious**	**Noninfectious Associations**
	Varicella-zoster virus	Brain abscess	Aneurysm
		Meningitis	Congenital palsy
			Diabetes mellitus
			Myasthenia gravis
			Sarcoidosis
			CNS tumor
			Trauma

ADEM, acute disseminated encephalomyelitis; CNS, central nervous system; IBD, Inflammatory bowel disease; SLE, systemic lupus erythematosus.

Cranial Nerve Palsies

Facial Nerve Palsy (Bell Palsy)

The most common parainfectious neurologic syndrome is inflammation of the peripheral facial nerve (cranial nerve [CN] VII). When no etiology is identified, the condition often is referred to as *Bell palsy*. One study reported an incidence of 4.2 per 100,000 children <10 years of age, increasing to 15.3 per 100,000 in children aged 10 to 20 years.[1] There are no seasonal or sex differences. Palsy typically is unilateral, is acute in onset, and often develops after a preceding illness. Facial nerve palsy also can occur in conjunction with peripheral nervous system involvement.

There are two proposed pathologic mechanisms, both leading to edema and entrapment of the nerve in the facial canal. The most likely explanation is direct inflammation of the nerve. Magnetic resonance imaging (MRI) can show gadolinium enhancement of the nerve,[2] and pathologic studies describe lymphocytic infiltration and associated demyelination or axonal degeneration.[3] Another possibility is that increased capillary permeability, as occurs in diabetes, leads to edema and compression of the nerve's microcirculation. This mechanism is supported by the finding that diabetic people are 2.5 times more likely to develop Bell palsy than people without diabetes.[4]

Herpes simplex virus (HSV) has been the most frequent virus associated with Bell palsy,[5] although other viruses, including Epstein-Barr virus (EBV) and hepatitis B virus, have been implicated. Ramsay Hunt syndrome, a rare complication of latent varicella-zoster virus (VZV) infection, is defined as an acute peripheral facial neuropathy associated with an erythematous vesicular rash of the skin of the ear canal, auricle (also termed *herpes zoster oticus*), or mucous membrane of the oropharynx. *Borrelia burgdorferi* infection also can cause facial palsy, which can develop without a history of tick bite or erythema migrans.[6] In one study in a Lyme disease endemic area, 34% of people ≤20 years of age who were evaluated in the emergency department because of facial palsy were found to have Lyme disease.[7] Facial palsy due to Lyme disease often is bilateral, associated with accompanied headache and fever, and typically occurs from June through October.

Treatment is aimed at the underlying etiology, but good eye care is important to protect the cornea. Bacterial causes should be treated with appropriate antibiotics. Cases due to Lyme disease should be treated with doxycycline or amoxicillin for 14 to 21 days to prevent late disease; treatment has no effect on resolution of the facial nerve palsy.[8] Most palsies resolve without treatment. A meta-analysis of adults and children with Bell palsy demonstrated a 17% improvement with corticosteroid treatment compared with no treatment.[9] There is controversy regarding whether acyclovir should be used to treat acute Bell palsy because many cases are associated with HSV infection. The addition of an antiviral agent to corticosteroid therapy, even when used in the first 72 hours of onset of illness, does not appear to improve outcome.[10] The extent of facial nerve recovery does not necessarily relate to the severity of the initial nerve involvement.[11]

Optic Neuritis

The second most common cranial nerve to be affected by parainfectious demyelination is the optic nerve. ON has been reported to have an incidence of 0.2 per 100,000 in Canadian children,[12] similar to that of ADEM and transverse myelitis (TM). ON typically manifests with reduced vision (e.g., blurred or “foggy” vision) and pain with eye movement. ON can be accompanied by other neurologic signs or symptoms, as is seen in ADEM, or can be the heralding manifestation of multiple sclerosis (MS) or neuromyelitis optica (NMO; Devic disease). Therefore brain MRI is recommended for patients with isolated ON. Up to 85% of cases are preceded by an infection or vaccination, and most patients regain at least 20/40 vision.[13]

Females are more commonly affected than males[12,14,15]; however, female sex does not necessarily increase the risk for subsequently developing MS. ON often is unilateral but can be bilateral.[15] On funduscopic examination, the head of the optic nerve may be swollen but can appear normal even to an experienced ophthalmologist. The presence of white matter lesions on MRI disseminated in space and time (more than one episode) is the strongest predictor for developing MS[14,15]; a normal MRI at first-episode ON does not preclude the development of MS.[16] The presence of NMO antibodies is highly specific for the diagnosis of Devic disease; their sensitivity is approximately 80%.[17] Brain MRI often is normal in this condition.

Bartonellosis is one of the most common infectious causes of isolated ON as well as when accompanied by lymphadenopathy and fever. Arboviruses, including West Nile virus[18] and chikungunya,[19,20] also have been associated with ON. Animal roundworms, e.g., *Toxocara canis* and *Baylisascaris procyonis,* are rare causes of ON. When these nematodes invade the eye, a neuroretinitis also can occur and the worm itself is sometimes visualized in the retina. *Angiostrongylus cantonensis* (a cause of eosinophilic meningitis) is found in Southeast Asia, the South Pacific, Australia, the Caribbean, and some areas of the United States (Louisiana and with increasing frequency in Hawaii) and also can cause ON.

The typical treatment for ON is a 3-day course of high-dose corticosteroid administered intravenously followed by a short oral taper, regardless of underlying cause. Additional treatment with specific antimicrobial therapy may be needed depending on the cause. In 1992, the Optic Neuritis Treatment Group found that treatment with intravenous (IV) corticosteroid hastened recovery over placebo, but did not change long-term outcome.[21] Treatment with oral corticosteroids did not seem to affect outcome, although patients receiving oral therapy relapsed more frequently than those receiving IV therapy. Prognosis is good, with visual acuity at or near baseline in at least 70% of patients.

Ocular Motor Nerve Palsies

Isolated neuropathies affecting one of the three nerves that move the eye, the oculomotor nerve (CN III), trochlear nerve (CN IV), and abducens nerve (CN VI) have been reported to occur as a postinfectious entity.[22] These are rare conditions that often do not require treatment. However, more common causes of these neuropathies, such as trauma, increased intracranial pressure, tumor, and vascular causes, should be excluded. Ocular motor palsies also are associated with the Miller-Fisher variant of Guillain-Barré syndrome (GBS).

Cerebellitis

Apart from affecting individual nerves in the central nervous system (CNS), the cerebellum can become inflamed because of an infectious or postinfectious process, commonly known as *cerebellitis* or *acute cerebellar ataxia*. Acute-onset ataxia is typical and often is self-limited with complete recovery. It is estimated to occur in approximately 1 per 100,000 to 500,000 children,[23] although it is difficult to determine an accurate incidence because many children with mild disease may not come to medical attention or may be evaluated only by their primary care physician.

Cerebellitis often presents concurrently with a viral illness, with VZV having the best recognized association. Cerebellitis also has been reported in association with EBV, *Mycoplasma pneumoniae*, *Listeria*, mumps, and enterovirus, as well as vaccinations.[23,24] Pathologic studies have shown inflammation, primarily composed of T lymphocytes, of the leptomeninges and molecular layer of the cerebellum. Imaging typically demonstrates enhancement of the cerebellum, localized mostly to the leptomeninges (Fig. 45.1).[24] Cerebrospinal fluid (CSF) analysis can be normal or show mild mononuclear pleocytosis and elevated protein concentration.

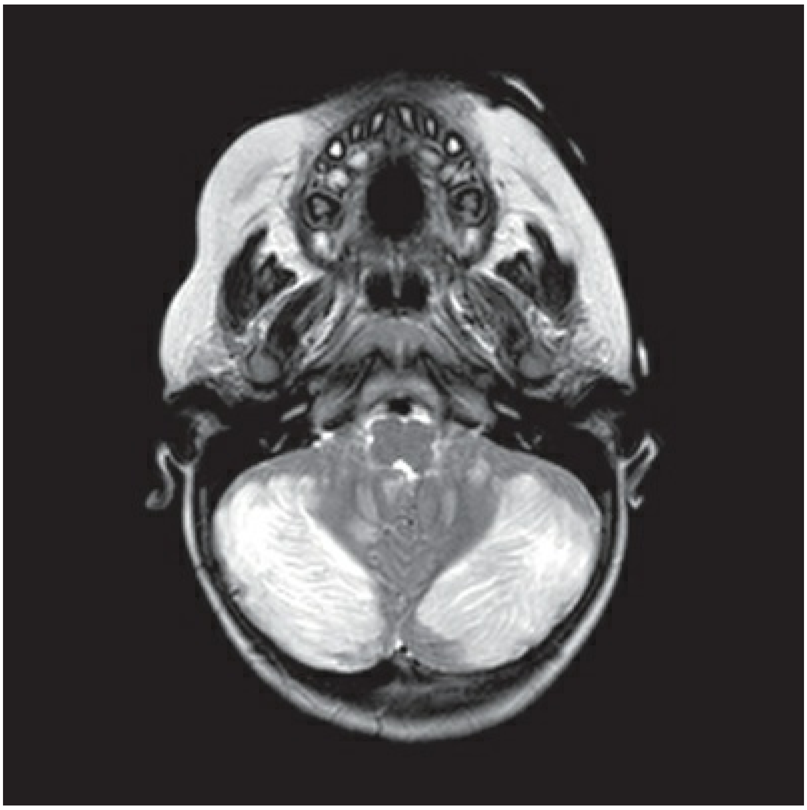


FIGURE 45.1 Brain magnetic resonance image from a patient with cerebellitis and diffusely increased fluid-attenuated inversion recovery T2 signal. (Courtesy of Brian Lee, MD, Children's Hospital & Research Center, Oakland, CA.)

Management is supportive; however, owing to its location, cerebellar swelling can lead to acute and severe hydrocephalus, eventually causing herniation and brainstem compression. In severe cases, corticosteroid therapy is indicated to help minimize swelling and prevent complications.[25]

Acute Disseminated Encephalomyelitis

ADEM usually is a monophasic polysymptomatic disorder that can affect any part of the brain and spinal cord. ADEM has an estimated incidence of 0.4 to 0.8 per 100,000, accounting for about 10% to 15% of cases of encephalitis in the US.[12,26,27] Neurologic symptoms often develop 2 to 4 weeks after an infection or vaccination and typically progress quickly, often over hours to days.[27] Up to 75% of cases of ADEM have an identifiable trigger. Historically, vaccine-preventable diseases such as measles and mumps were common precedents of ADEM. Measles virus can cause direct viral encephalitis and also is considered one of the most important triggers of ADEM. In countries where vaccines are widely used to prevent measles, mumps, rubella, and varicella infections, upper respiratory infections are the most common illnesses preceding ADEM. Vaccines also can trigger ADEM. The incidence of measles vaccination−associated ADEM is reported to be 0.1 per 100,000, compared with 0.2 to 0.3 per 100,000 after wild-type measles infection.[28] ADEM also has been reported temporally associated with human papillomavirus vaccination.[29]

Clinical manifestations of ADEM include altered mental status in 50% to 75% of cases and seizures in 10% to 35% of cases.[27] The presenting symptoms vary according to the regions of the CNS that are affected, which differ substantially from patient to patient. Motor weakness (e.g., acute hemiparesis), ataxia, decreased verbal output or mutism, cranial neuropathies, and urinary disorders are common.[30]

Less than one third of patients with ADEM have a recurrent or multiphasic course, which can be difficult to distinguish from MS in some instances.[27] Recurrent ADEM is defined as a new event with recurrence of initial symptoms ≥3 months after the first event and ≥1 month after discontinuing corticosteroid therapy; MRI does not show new lesions in ADEM, although original lesions may have enlarged.[31] Involvement of the deep grey structures such as basal ganglia and thalamus can occur in ADEM, whereas these structures rarely are involved in MS.

Many disorders can have MRI appearance similar to ADEM. These include systemic immunologic and inflammatory disorders such as systemic lupus erythematosus, sarcoidosis, Behçet syndrome, and Langerhans cell histiocytosis, which often have multisystem involvement. Meningitis, meningoencephalitis, and brain abscesses or tumors usually are easily distinguishable from ADEM. However, some infectious agents, such as *Balamuthia mandrillaris* and *Baylisascaris procyonis,* can have MRI changes that can be confused with ADEM due to T2 signal changes in the white matter. Metabolic disorders, such as adrenoleukodystrophy and metachromatic leukodystrophy, tend to manifest more insidiously, whereas mitochondrial disorders can cause acute T2 signal lesions on neuroimaging but tend to have more of a relapsing and remitting course.

The diagnosis of ADEM is based primarily on the clinical course and MRI findings (Fig. 45.2). Lumbar puncture should be performed to exclude infectious etiologies. The most common CSF abnormalities are a mild pleocytosis (usually with lymphocytic predominance) and elevation in protein concentration. Evaluation for the presence of oligoclonal bands should be performed when MS is considered. However, the presence of oliogoclonal bands does not confirm a diagnosis of MS because they can be found in up to almost 30% of patients with ADEM.[32]

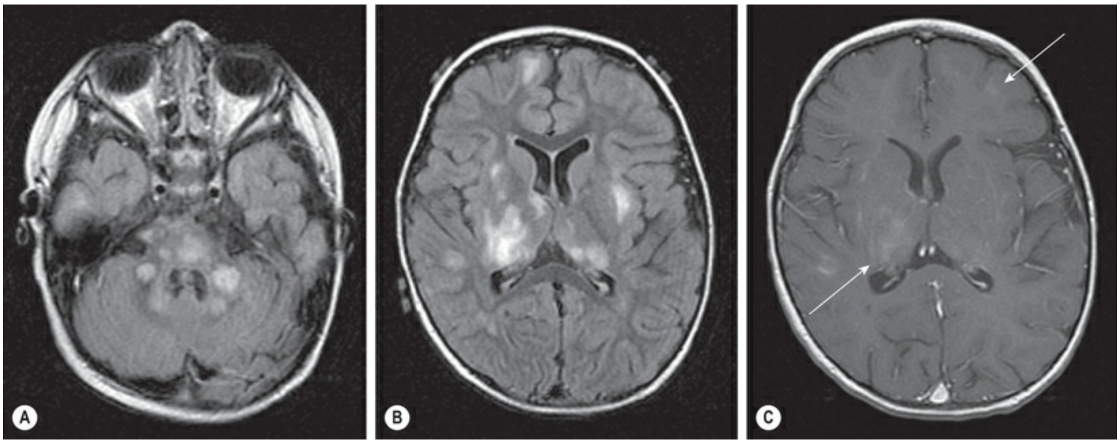


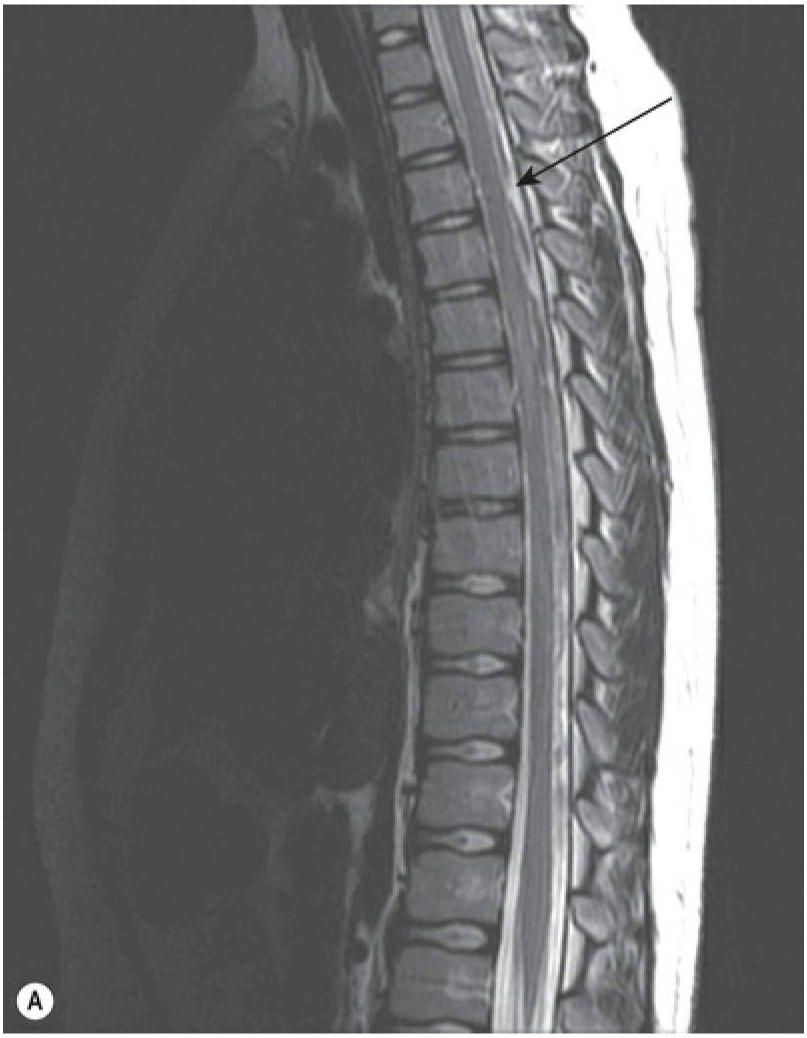
FIGURE 45.2 Brain magnetic resonance images from patient with acute disseminated encephalomyelitis showing multiple hyperintense lesions in the cerebellum and brainstem (A) as well as deep and superficial white matter and deep grey matter (B) with subtle patchy enhancement (*arrows* in C).

High-dose corticosteroid therapy is first-line therapy for ADEM.[33] Immune globulin intravenous (IGIV) or plasmapheresis often is used if there is no response to corticosteroid. Immunomodulating agents, such as cyclophosphamide, sometimes are used in refractory cases. Recovery often is complete, although residual deficits can occur in up to 30% of patients.

Transverse Myelitis

TM can occur in association with ON, neuromyelitis optica, or cerebral lesions (ADEM) or in isolation. Approximately 1400 new cases of isolated TM occur each year in the US, 20% in children <18 years of age.[34] In a Canadian cohort, the incidence was reported as 0.2 per 100,000, which is similar to the incidence of ADEM and ON.[12] Incidence is approximately equal in males and females. TM has been reported in infants as young as 6 months of age. Approximately 50% to 75% of cases have a history of a preceding illness, often a presumed respiratory tract infection, or vaccination.[34,35]

Diagnosis of TM is based on evidence of spinal cord inflammation, such as CSF pleocytosis, increased CSF immunoglobulin G index, or gadolinium enhancement on MRI (Fig. 45.3), and lack of an alternative etiology. Presenting symptoms depend on the affected area but often begin with back pain with progression to loss of bowel and bladder function as a result of autonomic dysfunction and lower extremity weakness and sensory loss. MRI is abnormal in 80% to 95% of patients, typically showing involvement of >3 vertebral bodies in length.[35] CSF is abnormal in up to 70% of patients, often showing elevated protein and less often an increased white blood cell count.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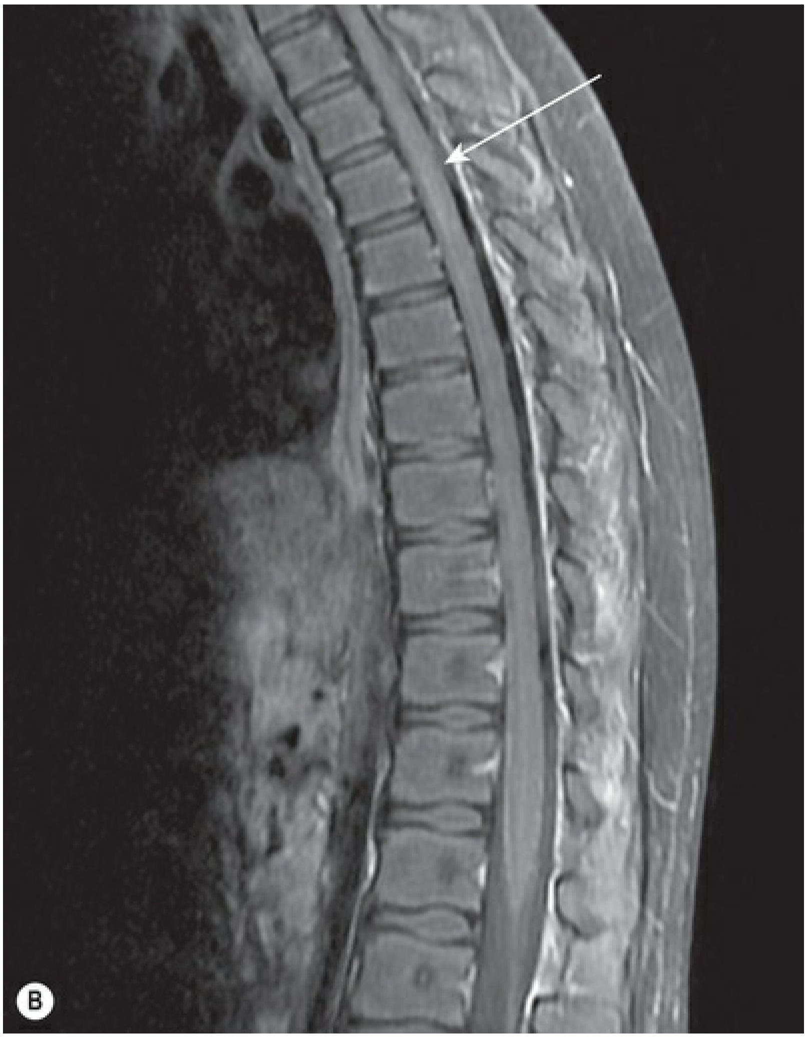


FIGURE 45.3 Thoracic spine magnetic resonance images from patient with transverse myelitis showing increased T2 signal (*arrow* in A) and patchy gadolinium enhancement (*arrow* in B).

A number of different infections, similar to those associated with ADEM, have been implicated as causes of TM (see Table 45.1). Enteroviruses are one of the most frequently implicated causes.[36]

The mainstay of treatment of TM is corticosteroids. Plasma exchange or IGIV also sometimes is used. Recovery often is not complete, and treatment has not been associated with improved outcome. The most common neurologic deficit is impaired bladder control,[34] but >25% of children with TM require ongoing assistance with self-care activities. Younger age, longer time to diagnosis, and larger extent of lesions are associated with poorer prognosis.

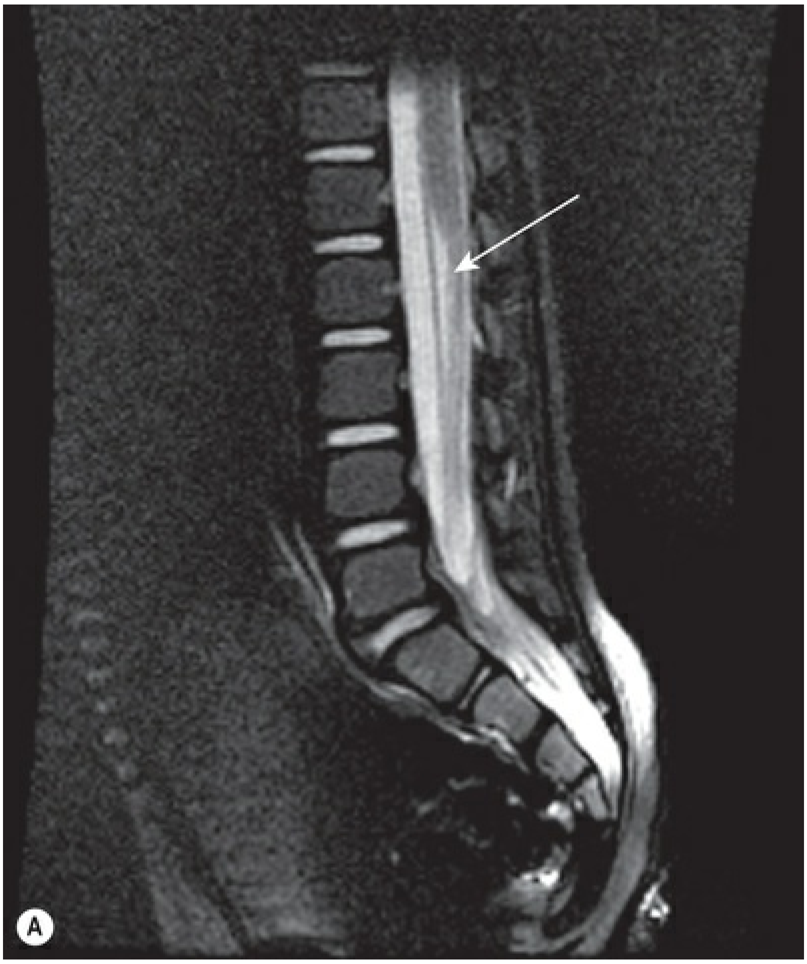
Acute Inflammatory Demyelinating

Polyradiculoneuropathy (Guillain–Barré Syndrome)

Acute inflammatory demyelinating polyradiculoneuropathy, better known as GBS, is an acute to subacute disorder often associated with ascending paralysis, but there are several variants. In the postpolio era, GBS is the most common cause of acute motor paralysis in children, with an estimated incidence of 0.5 to 1.5 per 100,000 people <18 years of age,[37] and with a slight male predominance.

In the classical form of GBS, extremity weakness is accompanied by areflexia and occurs in an ascending pattern. Sensory and autonomic symptoms, including urinary retention, cardiac arrhythmias, and autonomic instability, are common. Radicular back pain is a frequent initial complaint. Symptoms often are preceded by a gastrointestinal or upper respiratory tract illness. *Campylobacter jejuni* infection[38] and influenza vaccine are the most commonly identified specific precipitants of GBS.[39] In the US, 95% of cases are the classical demyelinating sensorimotor neuropathy form.[40] Other forms include axonal forms (both acute motor and sensorimotor), which account for up to 30% of cases in China and Latin America, and the Miller-Fisher variant, characterized by ataxia and ophthalmoplegia. Cranial nerve involvement also can occur in the classical form.

Electromyography and nerve conduction studies (EMG/NCS) can be helpful in diagnosing GBS, with findings consistent in almost 70% of cases in one pediatric series.[40] However, electrophysiology can be normal for up to a week into the illness, with the initial abnormality often being prolongation of the F wave, a measure of proximal nerve conduction. EMG/NCS can be helpful in excluding other conditions, such as infant botulism and myasthenia gravis, if ophthalmoparesis is present, as well as other neuropathies, such as heavy metal poisoning. The most typical CSF finding is albuminocytologic dissociation, that is, elevated protein without pleocytosis; however, CSF with white blood cell counts $>50/\text{mm}^3$ has been observed.[40] MRI can be helpful diagnostically, occasionally showing hyperintensity of the anterior nerve roots (Fig. 45.4).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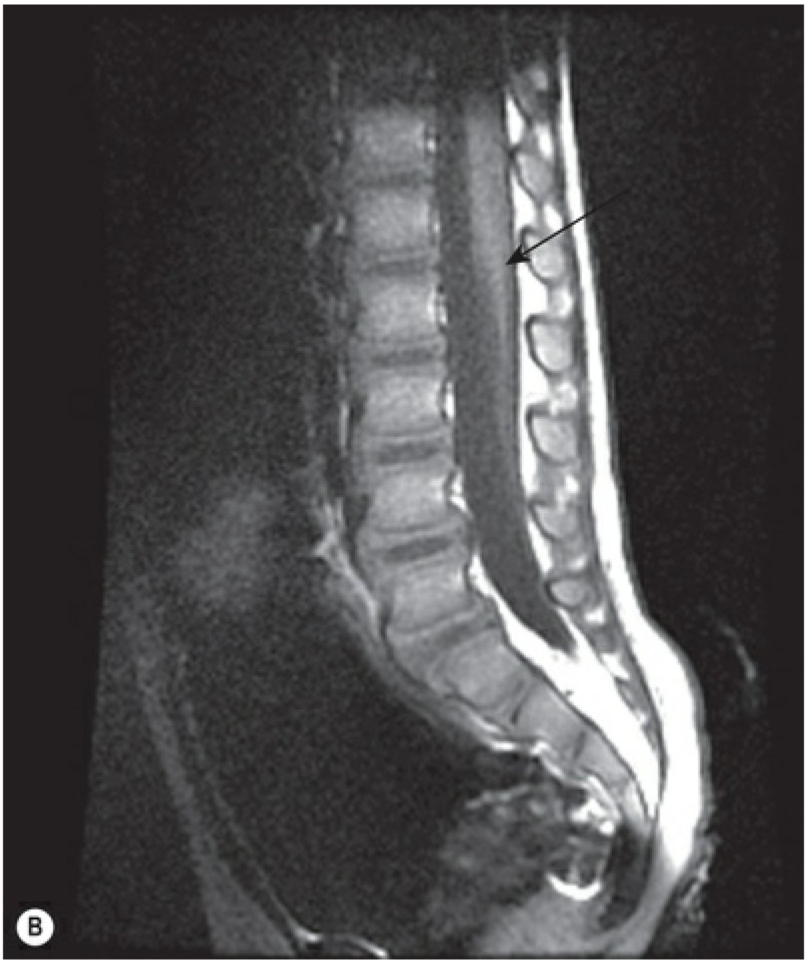

FIGURE 45.4 Magnetic resonance images of lumbar spine from patient with Guillain-Barré syndrome showing increased T2 signal in the cauda equina (*arrow* in A) with smooth enhancement (*arrow* in B).

Clinically, GBS symptoms plateau eventually, and then recovery begins. Respiratory support may be necessary during the nadir of the illness. Expert guidance, published in 2003, recommends plasma exchange for nonambulatory patients within 4 weeks of symptoms.[41] Plasma exchange also should be considered in ambulant patients who present within 2 weeks from symptom onset. IGIV is considered equivalent to plasma exchange in patients who require aid to walk and is associated with less frequent complications. Therefore IGIV is used more often as first-line therapy. Unlike a number of the other parainfectious conditions, corticosteroids are not recommended for treatment of GBS.

Overall, children with GBS have a good prognosis. Up to 95% of children are symptom free or only minimally affected 2 years after onset.[42,43] Mortality in GBS is low, occurring in <10% of patients,[42] mostly from respiratory failure and often in association with cardiac arrhythmia or autonomic dysfunction.

Acute Flaccid Myelitis

Acute flaccid myelitis (AFM) is a syndrome defined by rapid onset of weakness in one or more limbs, shortly after an upper respiratory tract infection or gastrointestinal illness, with absent deep tendon reflexes and normal sensory examination, mimicking that seen decades ago before the eradication of poliovirus in all but 3 countries.[44] AFM has been reported in association with other viruses over the years, most significantly West Nile virus and enterovirus 71.[45,46] During an outbreak in the US of enterovirus D68 during 2014, 107 children in 34 states developed this condition,[47] raising the potential connection between the virus and the condition. Enterovirus D68 was detected in respiratory samples in two thirds of patients from a cluster of patients who presented during the outbreak in Colorado and California and grouped into clade B1, which emerged in 2010.[48]

MRI often shows lesions predominantly in the anterior horn, which can be longitudinally extensive (Fig. 45.5). Acute enhanced T2 signal lesions involving the brainstem also were seen frequently in the recent enterovirus D68–associated outbreak.[49] Nerve conduction studies often are normal early on, and electromyography shows decreased recruitment of motor units with eventual development of fibrillation potentials (personal experience). CSF characteristically shows a pleocytosis with normal to mildly elevated protein and normal glucose concentrations.[47,48]

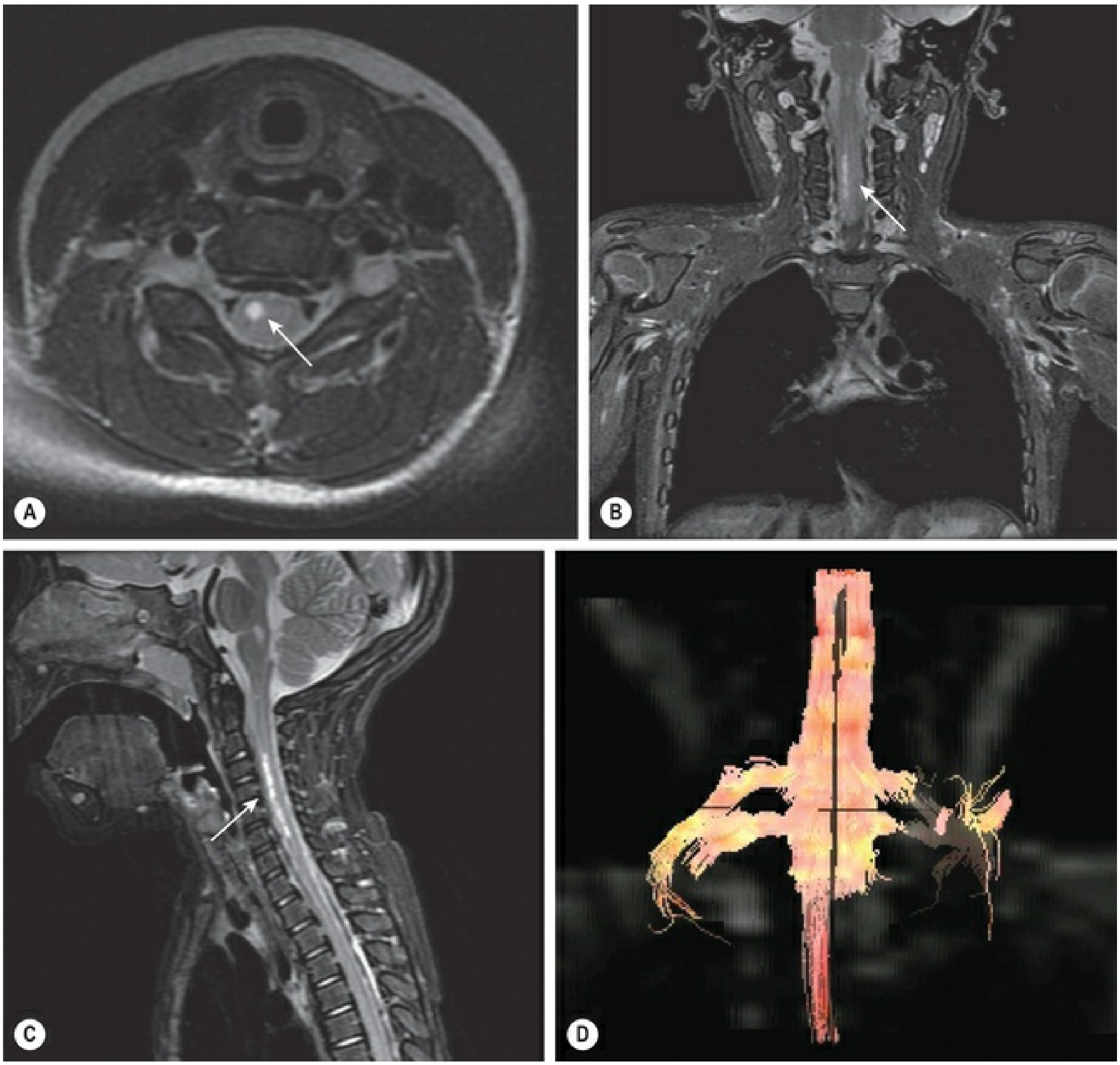

FIGURE 45.5 Magnetic resonance images of the brain and spinal cord from a patient with acute flaccid myelitis showing increased T2 signal in the anterior horn on axial (*arrow* in A), coronal (*arrow* in B) and sagittal (*dashed arrow* in C) images and in the brainstem (*solid arrow* in C). Diffusion tensor imaging shows absence of C5 and C6 nerve roots after exiting the spinal cord (D).

Treatments such as IGIV, corticosteroids, and plasma exchange have not been helpful for most patients.[47] Most patients have long-term persistent motor deficient (personal experience) requiring ongoing physical and occupational therapy. Nerve transfer and grafting have been performed in many children, but long-term follow up is not yet available to assess value.

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46

Focal Suppurative Infections of the Nervous System

Christopher J. Harrison

Diverse microorganisms cause focal suppurative nervous system infections; however, most are due to a few, mostly gram-positive species. The causative pathogen and anatomic site are usually linked to the original portal of entry.

Risk factors include cyanotic congenital heart disease (CCHD), hematogenous dissemination from distant persistently infected sites, regional penetrating trauma or instrumentation, and contiguous sinus, middle-ear, or mastoid infection.

Fungal specific risk factors include altered immune capabilities, broad-spectrum antibacterial therapy, and long-term indwelling foreign material. As more children experience iatrogenic prolonged neutropenia or cell-mediated suppression, more invasive fungal nervous system infections are likely.

Etiology

Gram-positive cocci dominate as brain abscess pathogens. The *Streptococcus milleri* group (*S. constellatus, S. intermedius,* and *S. anginosus)* comprise 50% to 70%, and staphylococci account for 10%

to 30%. Although *Streptococcus pneumoniae* causes meningitis, it rarely causes brain abscess.[1] Up to 30% of brain abscesses are polymicrobial, often including nutritionally variant streptococci (e.g., *Abiotrophia* species[2]) or anaerobes (e.g., *Bacteroides, Prevotella,* or *Peptostreptococcus* spp.). Detection of anaerobes often requires anaerobic culture methods.[3]

Gram-negative bacteria comprise 10% to 25% of brain abscesses or subdural empyemas (Table 46.1), mostly in young infants.[4,5] *Citrobacter,*[6,7] *Salmonella,*[8] *Serratia,*[9] *Proteus,*[10] and *Cronobacter* species (previously *Enterobacter sakazakii*)[11] and *Bacteroides fragilis*[12] are most frequent. *C. sakazakii* (associated with powdered formula) and *Citrobacter koseri* cause multifocal brain abscesses.

TABLE 46.1

Likelihood (Percentage of Cases) of Bacterial Pathogen in Focal Suppurative Nervous System Infections

Bacteria	Brain Abscess	Subdural Empyema	Epidural Abscess	
			Cranial	Spinal
Mixed	20–40	5–10	5–10	5–10
Alpha streptococci, not pneumococcus[a]	50–70	20–30	40–60	5–10
Anaerobic bacteria[b]	20–30[b]	5–10[b]	10–20	5–10
Staphylococci	10–30	10–20	10–20	60–80
Enterobacteriaceae	10–25	5–10	5–15	5–20
Pathogens of meningitis[c]	5–10	30–50	5–10	<1
Sterile[d]	10–25	20–30	20–30	5–10

[a] Aerobic, anaerobic, or microaerophilic (e.g., *Streptococcus anginosus* group).

[b] Mostly anaerobic streptococci.

[c] *Streptococcus pneumoniae, Haemophilus influenzae* type b, or *Neisseria meningitidis.* Much less common in countries with routine use of pediatric conjugate vaccines.

[d] More common with antibiotic pretreatment or in children

Chronic middle-ear infections, uncontrolled diabetes mellitus, and chemotherapy-induced neutropenia are risks for *Pseudomonas aeruginosa*.[13] Impaired cell-mediated immune function, such as, macrophage- or T-lymphocyte–related defects, or neutrophil phagocytic defects predispose to *Listeria monocytogenes*[14] or *Nocardia* spp.[15]

Fungal brain abscesses occur with congenital or acquired neutrophil abnormalities, stem cell[16] or solid organ transplantation,[17] or poorly controlled AIDS, particularly after broad-spectrum antibacterial treatment. More than 90% of brain abscesses after bone marrow or stem cell transplantation are due to fungi, usually *Candida* or *Aspergillus* spp.[18] In premature infants, *Candida* spp. increasingly cause multiple small brain abscesses.[19]

Although *Cryptococcus* usually manifests as meningitis, it can cause brain abscess. Other fungi rarely causing brain abscess include *Blastomyces,*[20] *Histoplasma,*[21] *Pseudallescheria,*[22] Zygomycetes,[23] *Coccidioides,*[24] *Dactylaria, Fonsecaea, Ramichloridium, Bipolaris, Exophiala, Curvularia,* and *Xylohypha (Cladosporium)* spp.

Protozoa causing brain abscess include *Acanthamoeba, Schistosoma,* or *Paragonimus* spp. With poorly controlled HIV, *Toxoplasma gondii* rarely causes brain abscess in children[25] but is more common in adults. *Entamoeba histolytica* brain abscess is rare even with amebiasis. Helminthic migration (*Strongyloides stercoralis, Trichinella* or *Taenia* spp.) can cause brain abscesses or masses.[26] Neurocysticercosis relatively frequently causes single or multiple, often ring-enhancing, central nervous system (CNS) masses among people from endemic areas (e.g., Mexico) and can be misconstrued as bacterial brain abscesses.

Table 46.2 includes additional uncommon pathogens.[27–30] Rarely, *Mycoplasma* or *Ureaplasma* spp. are causal.[31] *Mycobacterium tuberculosis* brain abscess[32] differs from tuberculoma, a granulomatous mass containing epithelioid and giant cells. Tuberculous abscesses are purulent collections containing acid-fast bacilli. Magnetic resonance imaging (MRI) differentiates these two conditions.

TABLE 46.2

Uncommon Pathogens in Brain Abscesses or Focal Ring Enhancing Lesions

Bacteria		Fungi	Parasites
Aerobic	**Anaerobic**		
Aggregatibacter aphrophilus	*Propionibacterium*	*Mucormycosis*	*Taenia solium*
Streptococcus pneumoniae	*Fusobacterium*	*Pseudallescheria boydii*	*Toxoplasma*
Eikenella	*Peptostreptococcus*	*Scedosporium*	*Entamoeba*
Enterococcus	*Bacteroides*	*Curvularia*	*Schistosoma*
Moraxella	*Clostridium*	*Histoplasma*	*Trichinella*
Pasteurella	*Actinomyces*	*Blastomyces*	*Strongyloides*
Bacillus cereus		*Coccidioides*	*Paragonimus*

Nocardia		*Cladosporium*	*Acanthamoeba*
Streptococcus pyogenes[a]			
Listeria			
Brucella[b]			

[a] *Streptococcus pyogenes* usually concurrent with acute mastoiditis.

[b] *Brucella melitensis* occurs mostly in the Middle East and Mediterranean areas.

Lesion location or distribution can suggest the pathogen. Frontal lobe abscess (usually a complication of sinusitis) suggests oral flora, that is, *Streptococcus* spp. (aerobic, microaerophilic, anaerobic), staphylococci, or anaerobic bacteria[33] (Table 46.3). Penetrating trauma increases the risk for *Staphylococcus aureus* (often methicillin-resistant *S. aureus* [MRSA]), but *Streptococcus* spp. remain more common. Temporal lobe or cerebellar abscesses suggest middle-ear or external-ear pathogens in addition to oral flora (mostly anaerobic or microaerophilic streptococci plus other anaerobes, and less often Enterobacteriaceae or *Pseudomonas* spp.).

TABLE 46.3

Relative Importance of Organisms by Site of Focal Lesion

Site	Most Common Pathogens
SOLITARY LESION	
Frontal lobe with sinusitis or oral/dental infection	Oral and/or nasopharyngeal aerobic and/or anaerobic flora, e.g., streptococci, *S. aureus*
Temporal lobe area, posterior fossa, or cerebellum contiguous with middle-ear/mastoid infection	Streptococci (aerobic and anaerobic), anaerobic oral flora, Enterobacteriaceae
Posttrauma	*S. aureus,* nonpneumococcal alpha streptococci, *Propionibacterium,* Enterobacteriaceae
MULTIPLE LESIONS	
Underlying congenital heart disease	Nonpneumococcal α-streptococci (aerobic and/or anaerobic), *Haemophilus* spp.
With endocarditis	Nonpneumococcal α-streptococci, *S. aureus*
With lung infection	Oral flora including anaerobes, *Nocardia* spp.
No known risk	*Staphylococcus aureus*
Immunocompromised host	*Toxoplasma,* fungi, *Nocardia* spp., Enterobacteriaceae

Hematogenous spread due to endocarditis, septic thrombophlebitis, lung abscess, pleural empyema, bronchiectasis (in cystic fibrosis), osteomyelitis, or skin infections classically produces multiple lesions in the distribution of the middle cerebral artery. However, hematogenous abscesses can produce any pattern.

Common hematogenous pathogens are *S. aureus,* aerobic or anaerobic streptococci, and rarely, *Candida, Nocardia,* or *Actinomyces* spp. With CCHD, *Aggregatibacter* (formerly *Haemophilus*) *aphrophilus* (an AACEK, formerly HACEK organism) is relatively common[34]; in contrast, *S. aureus* is more frequent with prosthetic valve endocarditis or prolonged bloodstream infection (de novo or associated with intravascular catheter).

Clues to pathogens in subdural empyemas relate to the pathogenesis. In young children, subdural empyema usually accompanies bacterial meningitis, a less frequent condition in countries with universal use of conjugate vaccines for the three major pathogens, that is, *Haemophilus influenzae* type b, pneumococcus, or meningococcus[35,36] (see Table 46.2).

Subdural empyemas not accompanying meningitis result from the same pathogens as brain abscesses. Aerobic and anaerobic streptococci (e.g., *S. intermedius* and *S. anginosus* group) predominate when associated with sinusitis. *S. aureus* is more common postoperatively or after trauma but can occur when associated with sinus or middle-ear infection. Cultures are sterile in 20% to 30%, likely owing to antibacterial pretreatment, nonviability of fastidious or anaerobic bacteria, or nonoptimal collection, transportation, and isolation procedures.[37]

Rare subdural pathogens include nontyphoidal *Salmonella,*[38] *S. pyogenes,*[39] *Burkholderia,*[40] *Brucella melitensis,*[41] *Propionibacterium,*[42] *Prevotella,*[43] fungi (e.g., *Candida albicans,*[44] *Pseudallescheria boydii*),[45] or *Mycobacterium tuberculosis*.[46] Gram-negative organisms are increasingly detected in both subdural empyema and epidural abscess.[47]

S. aureus is the most common pathogen causing both cranial and spinal epidural abscess.[48,49] However, *S. pneumoniae*[50] or *S. agalactiae*[51] also cause cranial epidural abscesses. *Pseudallescheria,*[45] *Aspergillus,*[52,53] or *Candida* spp.,[54] Zygomycetes, or *M. tuberculosis* can cause cranial epidural abscess in immunocompromised hosts.[55] Spinal epidural abscess rarely is due to *Brucella melitensis* (Middle Eastern and Mediterranean area),[56] *Nocardia asteroides* group,[57] *Actinomyces israelii,*[58] *Cryptococcus neoformans,*[59] or *Aspergillus* spp.[60] Epidural and other paravertebral abscess can complicate *Bartonella henselae* vertebral osteomyelitis.[61,62]

Septic intracranial thrombophlebitis most often is associated with sinusitis, mastoiditis, or facial infections (*S. pneumoniae,*[63,64] *S.*

pyogenes, or *S. aureus)*. Other otopathogens or non−group A streptococci also are reported.[61] Anaerobes (e.g., *Fusobacterium* spp.[65]) are infrequent causes, especially associated with Lemierre disease, which appears to have increased in frequency since 2005 and can have severe complications. Polymicrobial infections can occur.[66,67]

Epidemiology

Brain abscess is uncommon in developed countries but remains relatively common among socioeconomically disadvantaged people in developing countries. Risks vary geographically; for example, chronic otitis media is the primary risk in 60% of brain abscesses in China,[68] but only 30% in Europe.[69] Overall, nearly 25% of brain abscesses occur before 15 years of age, peaking between 4 and 7 years of age. Neonatal brain abscesses are associated most often with gram-negative bacterial meningitis. In immunocompetent hosts, most brain abscesses are solitary. Multiple brain abscesses are more frequent from hematogenous spread and occur in neonates or in immune-compromised patients.[70] Brain abscesses are multiloculated in 10% to 20% of immunocompetent hosts.

For intracranial subdural empyema, males predominate (3:1) among older children. The incidence by sex is neutral in young children.[71] In older children, the source is paranasal sinuses or middle ear or mastoid in about 85% and is hematogenous in 5% to 10%. Intracranial subdural empyema after neurosurgical procedures (e.g., craniotomy) is infrequent (0.04%).[47]

Spinal subdural abscess is rare in children,[72] with obesity as a possible risk factor.

Intracranial epidural abscess is the most common CNS suppurative complication of middle-ear, mastoid, or temporal bone infection. Posterior fossa epidural abscesses are extensions from the middle-ear or mastoid infection after osseous erosion of the petrous pyramid or over the sigmoid sinus plate.[73] Intracranial epidural abscesses also result from orbital abscesses or frontal sinusitis via valveless emissary veins or are concurrent with subdural empyema or cavernous sinus thrombosis.[74] Intracranial epidural abscess is 10 to 40 times more frequent than intracranial subdural empyema after neurosurgical procedures but still is uncommon (0.43%−1.8% of procedures).[47]

Spinal epidural abscess accounts for 6 out of 100,000 hospital admissions,[75] with fewer than 100 reported pediatric cases,[76] the largest series being 58 cases.[50]

Suppurative intracranial thrombophlebitis usually accompanies another intracranial infection, usually extradural, as a complication of mastoiditis or paranasal sinusitis. However, 10% to 20% of cases originate from facial (typically the middle third), dental, or neck infections.

Pathogenesis

Brain Abscess

A hematogenous source was traditionally most common, usually related to CCHD (Box 46.1). Among patients with unrepaired CCHD, 6% develop brain abscess. Brain infarction or emboli lead to infection, the risk increasing with time until repair. Right-to-left shunting, including through patent foramen ovale,[77] allows transiently circulating pathogens to bypass the reticuloendothelial filter in the lung. Classically, uncorrected tetralogy of Fallot or transposition of the great vessels was the most common anomaly predisposing to brain abscesses, but fewer now occur (about 28% overall),[78] owing to routine early surgical repair.

Box 46.1

Risk Factors for Brain Abscess[a]

Hematogenous (Approximately 30%)

Uncorrected cyanotic congenital heart disease

Septic thrombophlebitis

Lung infections, bronchiectasis

Cystic fibrosis[75]

Esophageal/rectal dilation or endoscopy[b,77]

Hereditary hemorrhagic telangiectasia

Pulmonary arteriovenous malformation[77]

Hepatopulmonary syndrome[78]

Septic abortion[80]

Contiguous Spread (Approximately 40%)

Middle-ear and/or mastoid infection

Sinusitis

Meningitis

Other focal infections (e.g., teeth, orbit, bone)

Penetrating head trauma

Ventriculoperitoneal shunt infection[89]

Postoperative intracranial surgery

Halo device to immobilize cervical spine[8]

UNKNOWN SOURCE (approximately 30%)

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[a] Under "Hematogenous" and "Contiguous Spread," conditions are listed in order by relative frequency.

[b] It is unclear whether some infections result from direct spread from mucosal site via local drainage through the Batson plexus.

Endocarditis (especially acute left-sided) predisposes to brain abscess because septic embolization is more common. Increased magnitude and duration of bacteremias increase the risk for CNS infection. Septic embolization from deep neck phlebitis associated with parapharyngeal infection (Lemierre disease) produces brain abscess, often polymicrobial, with oral and anaerobic flora, especially *Fusobacterium* spp.[79] Brain abscesses also occur by hematogenous seeding from distant pyogenic infections, including bone, teeth, skin, and abdomen infections, chronic lung abscess, empyema, and bronchiectasis.[80]

Chronic pyogenic lung disease, such as associated with immunoglobulin deficiency or bronchiectasis from longstanding cystic fibrosis, increases the risk for brain abscess.[81] Rarely, brain abscess occurs with pulmonary arteriovenous malformations,[82] aspirated foreign body, or hepatopulmonary syndrome.[83] Endoscopy-associated brain abscess results from intestinal bacteria translocating to paravertebral veins and from there into the cavernous sinus.[84] Septic abortion and in situ intrauterine devices are associated with brain abscess.[85]

Extension from nearby infection (middle-ear, mastoid, sinus, orbit, face, or scalp) is now the most common cause of brain abscess (about 36%).[78] Extension from middle ear predominates in young children and from paranasal sinuses in male adolescents.[86–88] In teenagers, frontal, ethmoid, and sphenoid sinuses have thin bony or cartilaginous walls abutting the dura, allowing erosion (osteomyelitis) and ingress into the CNS. Other portals include preexisting or posttraumatic anatomic cranial openings or diploic or emissary veins.

Bacterial meningitis rarely causes brain abscess except in neonates. Thrombophlebitis, venous stasis, or ischemia likely contributes to the pathogenesis. Focal deep cerebritis, deep infarcts, and pathogen virulence (e.g., *S. aureus* or *Cronobacter*) appear important for brain abscess formation. Rarely, pyogenic infection between the lateral ventricles occurs because of anatomic communication with the ventricular system.[89]

Postoperative or posttraumatic brain abscess is uncommon (about 9%.).[78] However, reimplantation of bone flaps,[90] penetrating skull injuries (e.g., dog bite,[91] pencil,[92] or lawn dart puncture[93]), or open skull fracture increase the risk. Oral flora can penetrate through intraoral punctures (e.g., chopstick, umbrella).[94] Gut-associated ascending infection along a ventriculoperitoneal shunt or an untreated shunt infection can lead to brain abscess.[95] Other rare causes are orthopedic halo-pin device[96] or intracranial migration of foreign body (e.g., cervical spinal sublaminar or interspinous wire).[97] Preexisting intracerebral hematoma, necrosis, or neoplasm rarely can serve as the nidus of infection.

Subdural Empyema

In young children, subdural empyema can follow meningitis. In older children subdural empyema usually results from extracranial infection (e.g., middle ear, sinus, or calvarium).[35] Risk increases with postmastoidectomy bone defects, prior craniotomy,[37] skull trauma,[37] septic phlebitis of emissary veins,[87] ventriculoperitoneal shunt,[95,98] preexisting hematoma,[99] halo-pin traction,[100] bloodstream infection from lung abscess, or endoscopic procedures.[101]

Epidural Abscess

Intracranial epidural abscesses usually extend from infected sinuses,[102] middle ear, or orbit, but rarely result from penetrating head injuries, fetal monitoring,[103] or wrestling injury.[104] Tightly adhering dura usually impedes expansion of epidural abscesses, causing insidious clinical presentations. Epidural abscesses can extend (e.g., to the subdural space, brain), causing coexistent intracranial infections. MRSA is observed in epidural abscesses associated with deep lower extremity or pelvic septic venous thrombosis.[105]

Spinal epidural abscesses usually are hematogenous (e.g., from infected skin, soft tissue, bone, respiratory or urinary tract infection). Other sources are nearby infections (bacterial meningitis, osteomyelitis or retropharyngeal, retroperitoneal, or abdominal abscess); iatrogenic introductions (after spinal fracture,[106] penetrating injury, spinal surgery, spinal fusion, spinal rod placement, lumbar puncture, steroid injection,[107] or epidural analgesia[108]); fistulas (Crohn disease),[109] midline neuroectodermal defect, dermal sinus; or intradural tumor (e.g., lipoma). Almost one third of epidural abscesses have no identified source.

Intracranial Septic Venous Thrombosis

Intracranial septic thrombosis also follows bacterial meningitis (especially superior sagittal sinus) or arises from contiguous infections (sinuses, ear, face, or oropharynx) through emissary veins.[110] Lateral venous sinus involvement usually is otogenic, but cavernous sinus thromboses originate from teeth, paranasal or sphenoid sinuses, or face.[111] Septic venous sinus thrombosis can occur near an epidural abscess or by hematogenous spread.

Increased risk for nonseptic thrombosis occurs with sickle cell disease, dehydration, or malignancies.

Clinical Manifestations

Brain Abscess

Abscess location affects presenting signs and symptoms (Box 46.2). Frontal lobe abscesses may have prolonged asymptomatic periods, producing symptoms and signs only when mass effect increases intracranial pressure (ICP). Parietal lobe abscesses often remain silent until extending to the sensorimotor cerebral cortex. Pathogen virulence and host immune status also affect the clinical acuity. Although the mean duration of bacterial brain abscess symptoms before diagnosis is 2 weeks, range is up to 4 months.[4]

Box 46.2

Signs and Symptoms in Relation to Site of Brain Abscess

Any Site

Signs of increased intracranial pressure (often late signs)

- Headache, nausea, emesis, papilledema
- Depressed consciousness

Behavioral changes

- Confusion, decreased attentiveness

Frontal Lobe

Behavioral changes

- Personality changes, emotional lability, impulsive behavior

Motor abnormalities

- Motor speech disorder (apraxia), forced grasping and sucking
- Focal weakness, hemiparesis

Temporal Lobe

General

- Ipsilateral headache

Cranial nerve dysfunction

- Upper homonymous hemianopia, ipsilateral third cranial nerve palsy

Motor abnormalities

- Speech dyspraxia, aphasia[a]
- Motor dysfunction of face and arm

Parietal Lobe

Visual abnormalities

- Homonymous hemianopia, visual field defects in inferior quadrant

Motor abnormalities

- Dysphasia,[a] speech dyspraxia[b]

Perceptive abnormalities

- Contralateral spatial neglect[b]

Intrasellar

Visual field defects

Endocrine imbalance via altered pituitary function

Cerebellar

Balance/perception abnormalities

- Lateral nystagmus (fast component toward lesion)
- Dizziness or central vertigo, ipsilateral ataxia, tremor
- Vomiting aggravated by motion

Cranial nerve dysfunction

- Sixth cranial nerve palsy

Brainstem

Dysphasia

Facial and multiple cranial nerve palsies

Hemiparesis

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[a] If abscess is in dominant hemisphere.

[b] If abscess is in nondominant hemisphere.

The initial presentation of brain abscess in about 50% of cases includes headache, fever, and vomiting (Table 46.4). Mental status changes or generalized seizures occur in fewer than 50% of cases of brain abscess. Lateralized headache in children increases risk for organic intracranial pathology. Focal neurologic abnormalities occur in 35% to 40%. Papilledema and meningismus occur in 30% of affected children. Coma, a late sign, occurs in 15% to 20%.

TABLE 46.4

Clinical Manifestations of Focal Suppurative Infections of the Central Nervous System by Percentage of Cases

Signs or Symptoms	Brain Abscess (%)	Subdural Empyema (%)	Cranial Epidural Abscess (%)	Septic Venous Thrombosis		
				Superior (%)	Lateral (%)	Cavernous (%)
Headache	60–70	60–80	100	70–90	80–90	75–90
Emesis	50–60	60–70	20–30	50–80	60–80	30–50
Fever	40–60	80–90	80–90	60–70	75–90	70–85
Focal neurologic deficit	35–50	30–40	10–20	40–60	60–75	75–90
Mental status change	30–40	60–80	50–60	55–75	20–45	15–30
Papilledema (usually late)	30–40	35–50	<5	40–60	25–40	65–80
Seizures	25–40	50–60	20–30	50–60	15–25	15–25
Meningeal signs	25–35	50–60	10–20	60–70	30–40	25–40
Hemiparesis	20–30	60–70	15–30	45–55	<5	<5
Coma	15–20	20–30	<5	60–80	25–45	10–15

The classic triad (fever, headache, and focal neurologic deficit) suggesting brain abscess occurs in fewer than 30%. Most pediatric brain abscesses have nonspecific clinical presentations that must be distinguished from other CNS processes (Table 46.5). Sudden clinical deterioration with meningismus suggests rupture of abscess into the ventricles or subarachnoid space.[112]

TABLE 46.5

Differential Diagnosis of Brain Abscess

Infectious Etiologies	Noninfectious Etiologies	
	Vascular	**Other**
Meningitis	Hemorrhage	Primary tumor
Encephalitis[a]	Parenchymal	Metastatic tumor
Meningoencephalitis	Intracerebral	Multiple sclerosis
Subdural empyema	Subarachnoid	Acute disseminated encephalomyelitis (ADEM)
Mycotic aneurysm[b]	Subdural (chronic)	
Epidural abscess	Venous sinus thrombosis[d]	

Cranial osteomyelitis Suppurative thrombosis Cysticercosis Tuberculoma[c] Cryptococcosis	Cerebral infarction	
	Migraine	
	Central nervous system vasculitis	

[a] Especially when the etiologic agent is herpes simplex virus.

[b] As a result of septic embolus (e.g., endocarditis).

[c] Or tuberculous abscess.

[d] Nonseptic.

Intracranial Subdural Empyema

In infants, subdural empyema can evolve during appropriate antimicrobial meningitis therapy as bulging fontanel, persistent fever beyond 5 days of treatment, or new onset of neurologic findings (e.g., depressed responsiveness, seizures). Persistent febrile meningismus also suggests subdural empyema.[37,113] Signs of increased ICP (vomiting, depressed responsiveness, enlarging head circumference, or papilledema) warrant investigation for subdural empyema.[114]

In older children, subdural empyema mimics brain abscess, with fever or vomiting, or both, but often occurs without headache. Diagnosis can be delayed until onset of hemiparesis or hemiplegia. After surgery or trauma, an overlying wound infection with occurrence of focal neurologic signs suggests subdural empyema.

Intracranial Epidural Abscess

Onset is insidious, with nonspecific symptoms (fever, headache, and mental status changes, sometimes with localized pain or tenderness,). Additional signs that are common in other intracranial suppurative processes (vomiting, seizures, focal neurologic deficits, papilledema, or meningeal signs) are relatively rare, developing only if mass effect or increased ICP occurs.

Unilateral facial pain with weakness of the ipsilateral ocular rectus muscle (Gradenigo syndrome) indicates an epidural abscess near the petrous bone. Confusion progressing rapidly to coma with focal or generalized seizures (symptoms of obstructed superior sagittal sinus) suggests an occipital epidural abscess.

S. aureus, particularly MRSA, is the most common pathogen in epidural abscesses accompanying orbital cellulitis and acute sinusitis.[115]

Spinal Epidural or Subdural Abscess

Initially, spinal epidural abscess[116] manifests as localized or generalized back or flank pain exaggerated by movement, particularly spinal rotation. Local edema or tenderness to percussion can develop, followed by nerve root pain, which assist in abscess localization. Focal neurologic deficits (usually sensory and motor) develop early, progressing to weakness and impaired sensation. Signs then progress to paraparesis, bladder or bowel dysfunction, or altered consciousness. Early intervention prevents paralysis or paraplegia, which can occur in as few as 4 days from onset of nerve root pain or one week from initial back pain.[117]

Spinal subdural abscess manifests similarly to epidural abscess but can be differentiated by meningismus without focal spine tenderness to percussion.

Septic Venous Thrombosis

Clinical presentations vary based on the involved venous sinus. Complete thrombosis plus obstruction of blood flow in superior sagittal sinuses commonly presents as severe generalized or frontal headache. Soon nausea, vomiting, and meningismus develop, sometimes progressing rapidly to coma. Focal or generalized seizures or hemiparesis can occur. If venous obstruction is incomplete, symptoms are less severe and progress more slowly.

Cavernous sinus thrombosis is more frequent in teenage males, manifesting as cranial nerve deficits (usually III and VI) plus prominent headache often localizing to the orbit or second branch of the trigeminal nerve. Unilateral periorbital edema quickly becomes bilateral.[111] Ptosis with ophthalmoplegia can cause impaired vision or blindness. Papilledema or retinal venous dilation occurs in 50% and meningismus in up to 33% of cases.

Septic thrombosis of lateral sinuses manifests subacutely, usually with temporal or occipital headache, followed by nausea, vomiting, or vertigo. The otogenic source often is detected by middle-ear examination (e.g., ruptured tympanic membrane, cholesteatoma). Meningismus is less frequent than with cavernous sinus thrombosis, but altered mental status is more common. Gradenigo syndrome or any soft tissue swelling behind the auricle (Griesinger sign) raises suspicion for lateral sinus thrombosis.

Caveat With Extracranial Infections

Despite obvious extracranial infections, concurrent occult intracranial foci also can be present, such as with orbital suppurative complications of sinusitis.[33,118] Multifocal intracranial or parameningeal CNS infections are not uncommon (e.g., subdural empyema or brain abscess accompanying meningitis). Rapidly progressing symptoms, change in neurologic status, or poor response after antimicrobial therapy or surgical drainage of an orbital abscess suggests concurrent intracranial focus. Pott puffy tumor (with frontal sinusitis) (Fig. 46.1) requires imaging to assess for intracranial suppurative foci.[119]

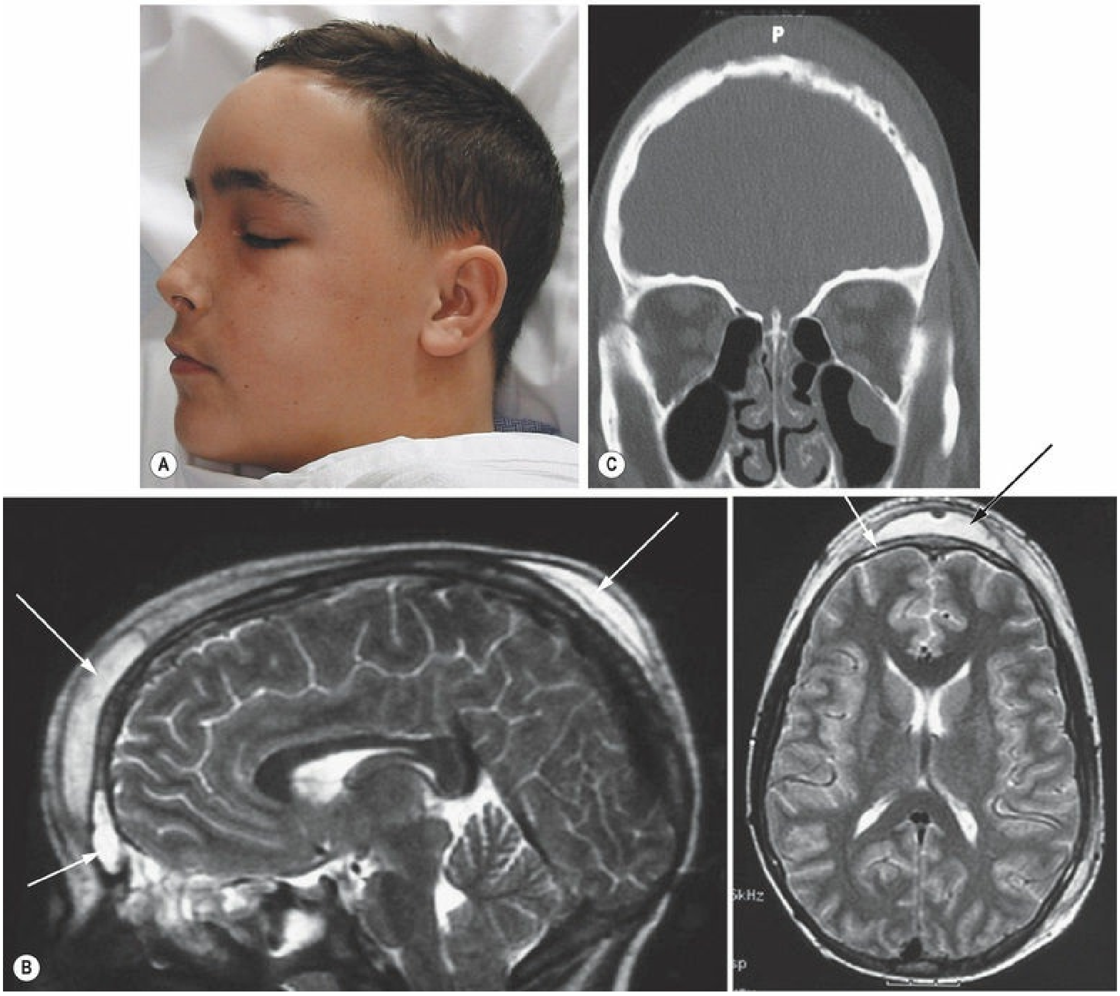

FIGURE 46.1 A 14-year-old presents with 1 week of high fever and chills, followed by facial and forehead pain and swelling. There is an edematous, tender, fluctuant mass over the forehead and occiput (A). Computed tomography (CT) showed pansinusitis. Sagittal and axial, T_2-weighted magnetic resonance imaging (B) revealed increased signal in extracranial frontal and occipital masses *(long arrows),* the frontal sinus *(medium arrow),* and frontal bone *(short arrow).* Blood culture yielded *Fusobacterium necrophorum.* Coronal CT after drainage confirmed osteomyelitis of the frontal bone (C). Prolonged antibiotics yielded complete recovery. (Courtesy of E. D. Thompson and S. S. Long, St. Christopher's Hospital for Children, Philadelphia, PA.)

Differential Diagnosis

Brain Abscess

The differential diagnosis of brain abscess includes infectious and noninfectious conditions (see Table 46.5). Vascular and oncologic diagnoses are the most common noninfectious causes. Altered consciousness, seizures, headache, nausea, and emesis should raise suspicion for postinfectious acute disseminated encephalomyelitis.

Focal suppurative CNS infection should be considered when any three of the following are present: fever, headache, nausea or emesis, increased ICP, altered consciousness, seizures (focal or generalized), or cranial nerve abnormality. However, these CNS symptoms and signs also can reflect nonpurulent conditions, infectious or otherwise, that mimic purulent brain abscess.

Extracerebral Intracranial Infections

Differentiating among various extracerebral intracranial infections is difficult because signs and symptoms overlap and usually are nonspecific. The differential diagnosis of suppurative intracranial extracerebral infection resembles that of brain abscess; however, some signs may be more specific. Focal neurologic signs during confirmed bacterial meningitis warrant brain imaging for focal complications. Meningismus persisting more than 3 days into antibiotic therapy or an initial cerebrospinal fluid (CSF) not fully compatible with bacterial meningitis warrant search for a parameningeal suppurative focus. Persisting meningismus rarely indicates parenchymal brain abscess, except with rapid clinical deterioration due to abscess rupture into ventricles or parameningeal spaces.

Cranial epidural abscess can complicate infections outside the CNS (orbital abscess or phlegmon) or with the CNS (meningitis, brain abscess, venous thrombophlebitis, or subdural empyema). Thus delineating all foci requires neuroimaging.

The differential diagnosis of septic thrombosis of dural venous sinuses includes any cause of spontaneous, inflammatory, or posttraumatic thrombosis. These include disseminated intravascular coagulopathy, hypercoagulopathy (e.g., protein S and antithrombin III deficiency), polycythemia, sickle cell anemia, dehydration, congenital heart disease, malformation of the vein of Galen, nephrotic syndrome, use of oral contraceptives, pregnancy, trauma, neoplasm, asphyxia, brain infarction, and pseudotumor syndrome. Other intracranial infections, such as brain abscess, subdural empyema, and meningitis, also are possible causes of thrombosis. Cavernous sinus septic thrombosis can mimic orbital cellulitis or ophthalmoplegic migraine and often is accompanied by cranial nerve abnormalities.

Spinal Infections

Spinal epidural abscess or subdural empyema can mimic diskitis or syphilis (tabes dorsalis), or can complicate vertebral or spinal tuberculosis or vertebral osteomyelitis. Acute transverse myelitis, spinal cord tumor, lymphoma, hematoma in the epidural or subdural space or spine, and vascular malformation must be considered. Larger differential diagnoses can be found in two literature reviews.[120,121]

Laboratory Findings and Diagnosis

Routine Tests

Blood tests are generally nonspecific. Peripheral white blood cell counts are more than 10,000 cells/mm^3 in nearly 50% of children with brain abscess, but only 30% exceed 20,000/mm^3 and only 25% exhibit a left shift (band forms, >10%). The erythrocyte sedimentation rate (ESR) is insensitive, being normal in up to 40% of brain abscesses, particularly when associated with CCHD.[122] C-reactive protein (CRP) is more sensitive but is not specific.[123] Both ESR and CRP appear to be elevated more often when intracranial suppurative foci complicate sinusitis.[124] In spinal infection neither the ESR nor CRP is reliably abnormal.[125] Procalcitonin is not useful.

Blood cultures yield a pathogen in approximately 10% of cases of brain abscess.[3] Low-frequency delta waves on electroencephalogram are compatible with brain abscess.[4,126]

To prevent notable morbidity, brainstem herniation, or even death, increased ICP must be excluded by computed tomography (CT) or MRI before lumbar puncture when suspecting focal intracranial suppuration.[3]

Normal CSF occurs in up to 20% of brain abscesses. Elevated CSF protein (>40 mg/dL) occurs in 70% to 85%; mild to moderate pleocytosis (<500/mm^3) occurs in 60% to 80%, with neutrophil predominance in 40% to 60%. Hypoglycorrhachia (<40 mg/dL) occurs in fewer than one third. Positive CSF culture is uncommon (<10%) except with coexisting meningitis or rupture of brain abscess into subarachnoid spaces. Polymerase chain reaction testing of brain abscess material can provide rapid pathogen identification,[127] but is not widely available, and sensitivity and specificity are not defined fully. Testing for 16S recombinant RNA detects more species than are cultivatable in polymicrobial brain abscesses but is not standardized or available universally.[128]

CSF findings associated with spinal epidural abscess or subdural empyema are nonspecific, with normal to moderately elevated neutrophil and protein values. Lumbar puncture through infected lumbar tissue (e.g., spinal epidural abscess) can inadvertently inoculate CSF. Partially or completely obstructed CSF flow around the spinal cord from infection or tumor can elevate CSF protein concentration (>100 mg/dL), but usually CSF shows 100 to 300 white blood cells/mm^3 (mostly lymphocytes) and normal glucose concentrations.

Imaging Studies

Imaging of brain, sinuses, middle ears, and orbits is critical to identify intracranial infections, potential sources, and to formulate management.

Specific Considerations

Brain Abscess.

Use of contrast-enhanced CT or MRI reduces mortality rates from brain abscess by 90% because lesions are diagnosed earlier, localized more accurately, and surgically drained more safely and completely.

Contrast-enhanced CT shows enhanced vascularity related to inflammation.[129] Typically, a hypodense signal from brain tissue edema surrounds a bright ring of signal enhancement, which in turn surrounds a central hypodense signal of the abscess core (Fig. 46.2). Cerebritis can appear similarly but is not as well demarcated. CT findings can lag clinical manifestations by several days; an initially normal CT (particularly non−contrast-enhanced) does not exclude brain abscess. Further, neutropenia and corticosteroid therapy can diminish ring enhancement.[130] Tumor, granuloma, resolving hematoma, or infarct can produce ring enhancement.

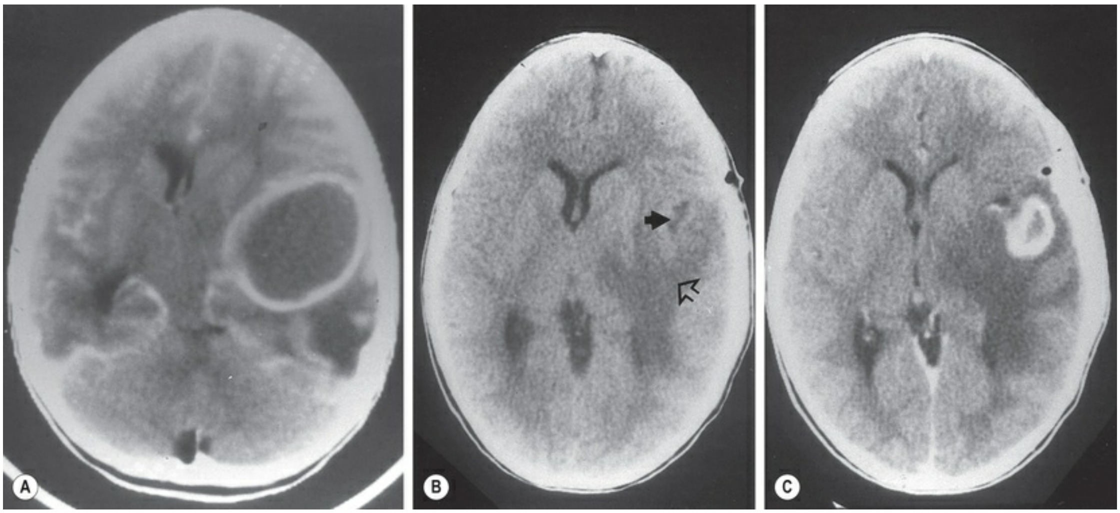

FIGURE 46.2 Computed tomography (CT) in a child with headache for 6 weeks and temporal lobe brain abscess. (A) CT with contrast at diagnosis shows intense ring enhancement and edema. (B) CT without contrast following surgical drainage shows a much smaller abscess cavity *(solid arrow).* Marked edema persists *(open arrow).* (C) Postsurgical contrasted CT reveals an abscess cavity with air, enhanced abscess wall, and marked edema. (Courtesy of M. A. Radkowski, MD, Children's Memorial Hospital, Chicago.)

Gadolinium-enhanced MRI may be superior to CT, revealing a peripherally enhancing lesion with enhanced signal on diffusion-weighted imaging (DWI). Experienced radiologists often can differentiate infectious from noninfectious lesions in the brain.[131,132]

Subdural Empyema.

Open fontanels may permit use of high-resolution ultrasonography to detect and differentiate subdural empyema from subdural effusion.[133] Intralesional particulate or shifting material suggest an empyema. CT is more specific and does not require an open fontanel. Non−contrast-enhanced CTs can demonstrate hypodense pus collections, but contrast-enhanced CT is superior at delineating the inflamed meninges or cerebral cortex (Fig. 46.3). Higher resolution of MRI makes MRI superior to CT for detecting smaller lesions, extra-axial fluid near bones, and rim enhancement.[134] Neither CT nor routine MRI always definitively distinguishes subdural empyema from reactive subdural effusion (the more common meningitis complication). DWI can improve characterization of subdural fluid.[135]

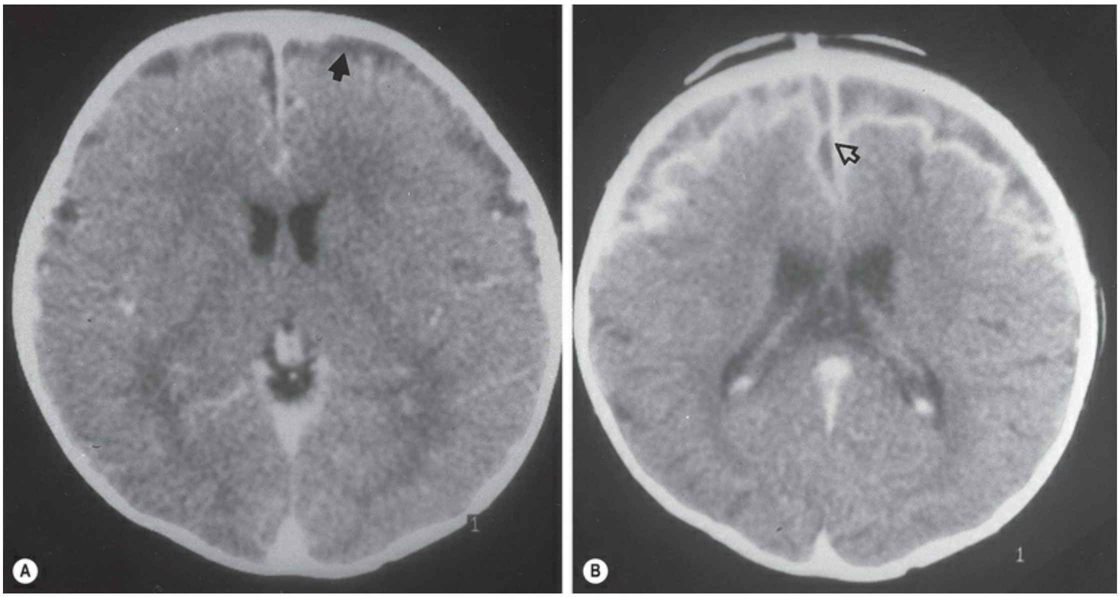

FIGURE 46.3 Computed tomography in an 8-month-old with meningitis and seizures during therapy (A) shows bilateral extra-axial fluid collections in the frontal region *(solid arrow),* suggesting early subdural empyema. (B) One week later, there is increased extra-axial fluid extending to the anterior interhemispheric fissure *(open arrow)* and enhanced membrane consistent with subdural empyema. (Courtesy of M. A. Radkowski, MD, Children's Memorial Hospital, Chicago.)

Epidural Abscess.

Cranial epidural abscesses show focal hypodense pus collections between dura and calvarium by CT. Contrast-enhanced CT shows enhanced rims around abscesses, displacing dura (Fig. 46.4). MRI reveals subdural abscesses in more detail and otherwise undetected concomitant epidural abscesses.

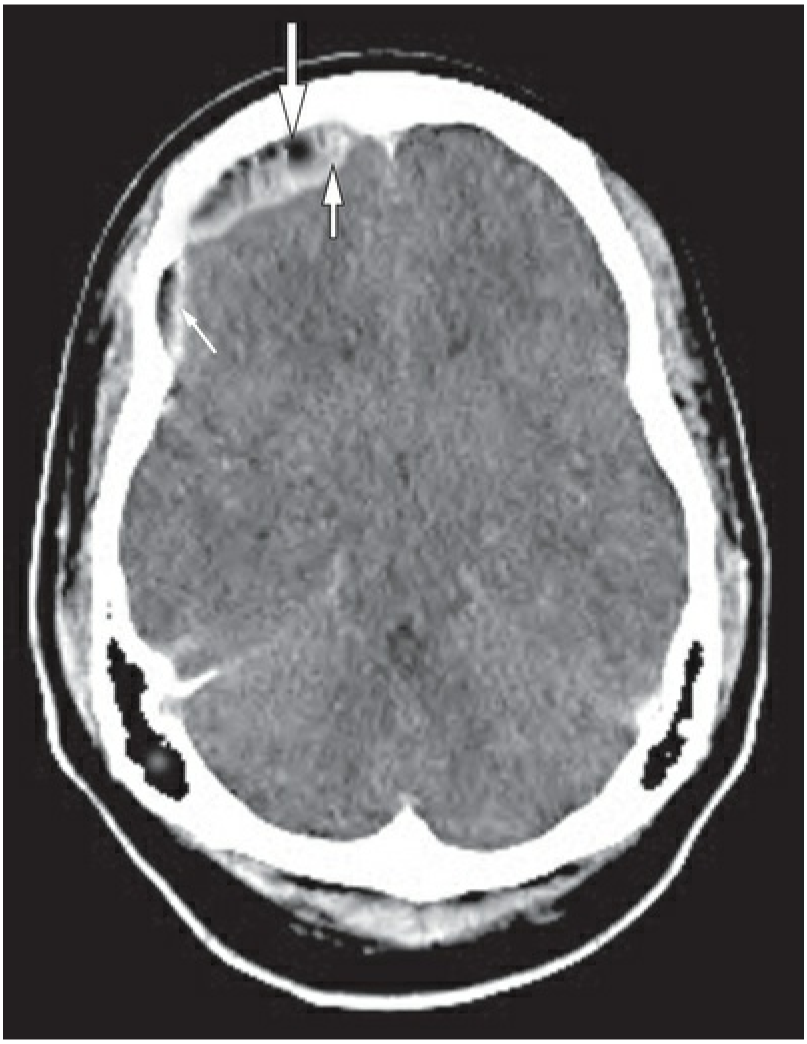

FIGURE 46.4 Contrast-enhanced computed tomography of a 16-year-old with sinusitis and persistent fever despite therapy shows collections in the frontal region *(large arrow),* which is relatively large and has epidural abscess, and subdural extension *(medium arrow).* There is an additional small extra-axial collection consistent with epidural abscess *(small arrow)* in the parietal area. (Courtesy of Lisa Lowe, MD, Children's Mercy Hospitals and Clinics, Kansas City, MO.)

Venous Sinus Thrombosis.

Sagittal venous sinus thromboses in infants can be detected by ultrasonography.[136] Filling defects in thrombosed sinuses are visible on contrast-enhanced CT. Superior sagittal sinus thrombosis appears as hypodense triangular areas surrounded by a hyperintense ring (the delta sign).[61] MRI is superior for detecting diminished venous flow (Fig. 46.5).

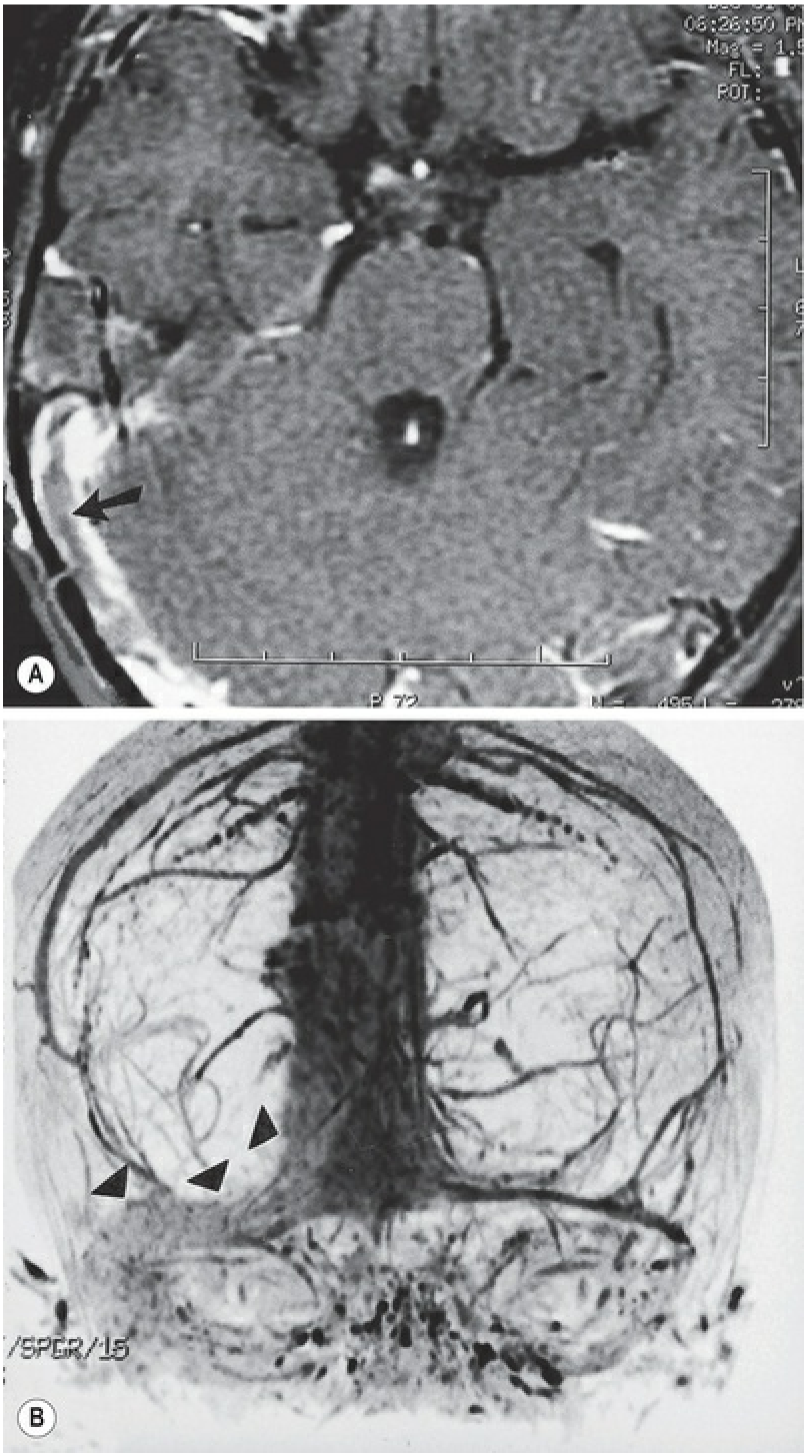

FIGURE 46.5 (A) T_1-weighted magnetic resonance imaging with contrast shows thrombosis of the transverse (lateral) sinus. The greyish area *(arrow)* represents the thrombus itself. (B) Three-dimensional, time-of-flight magnetic resonance angiography in the same patient shows complete blockage of the sinus, with extension of thrombus into the superior sagittal sinus *(arrowheads).* (A, Courtesy of C. Darling, MD, Children's Memorial Hospital, Chicago.)

General Considerations

MRI is the most sensitive routine diagnostic test currently available for intracranial suppurative infections because of superior soft tissue detail compared with CT.[137] Lesions are detected earlier, and smaller lesions undetectable by CT can be apparent. Contrast-enhanced CT with reconstructed coronal and sagittal planes extending through frontal bone and sella turcica can avoid missing suppurative processes (e.g., epidural or interhemispheric abscess) not seen with standard maxillofacial or orbital CT.

Contrast-enhanced MRI differentiates abscess fluid from CSF and is more accurate for detecting ruptured abscess.[138] If conventional and diffusion MRI does not differentiate abscess from cystic tumor, perfusion-weighted images may be useful. Because abscess capsules are hypovascular compared with tumor capsules, relative blood signal is different.[139] Although MRI is superior to CT for venous thrombosis and surrounding inflammation, magnetic resonance angiography can demonstrate diminished flow in occluded veins. Contrast-enhanced magnetic resonance venography can be helpful to discern dural venous thrombosis from artifact due to sluggish venous flow. Magnetic resonance spectroscopy also may distinguish bacterial brain abscess from necrotic brain tumor.[140]

MRI is superior to CT for epidural or subdural spinal abscesses, which typically are isointense on T_1-weighted images but hyperintense on T_2-weighted images. Concomitant diskitis, osteomyelitis, or paraspinal abscess is identified easily. Further, MRI differentiates active inflammation from chronic granulation. MRI also is superior in differentiating more common reactive subdural effusions from empyema, and subdural from epidural abscess. Because of intense radiation exposure from CT, MRI is preferred for follow-up, particularly if MRI was used initially.

Management

Medical-Surgical Management Versus Medical Therapy Alone

CT- or MRI-guided stereotactic techniques revolutionized management of intracranial suppurative infections,[141] being minimally invasive and performed using local anesthesia with minimal risk for hemorrhage or complications. Pathogen detection in aspirates using Gram, acid-fast, India ink, or specialized immunohistochemical stains as well as by aerobic or anaerobic, fungal, and mycobacterial culture allows specific antimicrobial therapy. New molecular methodologies allow detection of nucleic acids from nonviable organisms.[142]

Brain Abscess

Antibiotic therapy plus open surgical drainage has been standard management. However, antimicrobial therapy without aspiration or surgery is preferred (1) when concomitant bacterial meningitis is due to a confirmed pathogen; (2) when abscess is deep seated or in critical or high-risk anatomic sites; or (3) for poor surgical candidates. Medical-only therapy, even in ideal candidates, can fail. Follow-up is necessary, with repeated imaging if signs and symptoms do not resolve as expected or if deterioration occurs. Reduced ring enhancement, less edema, and less mass effect generally occur within 1 to 2 weeks of initiating therapy when patients respond favorably to medical-only management. Reduced abscess size usually occurs within 2 to 4 weeks.

Antibiotics plus lesion aspiration are successful with small (<3 cm), well-encapsulated brain abscesses in alert, clinically stable patients without signs of increased ICP.[143] It may not be possible to sample each of multiple abscesses, but culture of aspirated material from at least one abscess by CT- or MRI-directed stereotactic technique should be helpful.

Antibiotic susceptibilities of pathogens from blood (10% or less of patients), CSF culture (<10% of patients), or imaging-guided aspiration of abscess material (65%) improve likelihood of treatment success in the absence of open surgery.

Patients with large abscesses and those who are failing medical-only management require either closed stereotactic aspirational drainage or craniotomy (hopefully with excision). Disadvantages of stereotactic aspiration can be the need in some cases for repeated aspirations (leading possibly to more tissue damage or bleeding) and the relative inaccessibility of posterior fossa lesions. Excision is preferred for (1) fungal or helminthic abscesses not responding to medical therapy; (2) posterior fossa abscesses, especially with coma or brainstem compression[144]; (3) failure to improve clinically or by imaging despite aspiration of multiloculated abscesses; or (4) reaccumulation after repeated aspirations.[145]

Cure rates of more than 90% result from combining (1) surgical aspiration or removal of all abscesses greater than 2.5 cm in diameter; (2) 6 weeks or longer of effective antibiotic therapy; and (3) repeat neuroimaging to ensure abscess cavity resolution before cessation of antibiotics.[144,146]

Decision on duration of therapy, as well as intravenous versus oral formulations, is individualized. Antibiotics are continued for 3 to 6 weeks with the expectation of improvement of clinical and imaging findings. The shorter 3- to 4-week course is reasonable if complete surgical excision of the brain abscess is possible.[147] The mean time to normalization of CRP values if elevated is about 3 weeks.[146] Follow-up imaging studies near the end of the proposed treatment duration should provide evidence of lesion improvement before stopping therapy and provide a baseline in the case of later symptoms and signs suggesting relapse. The end point of therapy should be resolution of the abscess cavity, not absence of enhanced signal. Repeat imaging in asymptomatic patients beyond this is not necessary and can be misleading because enhanced signal persists beyond resolution of infection.

Corticosteroid treatment for brain abscess is controversial and is used infrequently because of potential disadvantages, including reduced antibiotic penetration through the steroid-stabilized blood-brain barrier. However, small series have not shown increased mortality, or significant outcome differences, related to corticosteroid use.[148] Corticosteroids directly decrease ring enhancement out of proportion to improvement in infection, and "rebound" of enhancement can occur on discontinuation, compromising interpretation of repeated imaging. Corticosteroids should be reserved for cases of severe or progressively increased ICP or neurologic deterioration, when reduction of edema may be lifesaving. A short course (3 to 6 days) of high-dose dexamethasone (0.4 to 2 mg/kg/day divided every 6 hours) generally is considered safe.

Extracerebral Abscesses

Antibiotics alone are sufficient for treatment of a small subdural empyema (<3 cm in diameter) or in neurologically stable patients rapidly responding to empiric therapy.[37,149] Management with appropriate antibiotic therapy plus aspiration of subdural empyema accompanying bacterial meningitis usually is sufficient as antimicrobial susceptibility of the pathogen is documented. Subdural empyema from other causes (e.g., contiguous site infection or after penetrating trauma) may not be aspirated easily, necessitating a bur hole or craniotomy. The empyema's location and extent dictate the type of drainage procedure. Although craniotomy provides better evacuation of pus from a larger empyema, bur hole plus irrigation can be effective.[150] Irrigating empyema cavities with antibiotics is not recommended or supported by current data. As little as 2 weeks of intravenous antibiotics can be sufficient in patients with subdural empyema completely drained by craniotomy.[151]

Unless cranial epidural abscess is less than 1 cm in diameter or close to critical structures making intervention dangerous, drainage and debridement plus appropriate antibiotic given systemically usually is performed, although there is increasing use of medical management with (or sometimes without) aspiration. For example, medical management appears adequate for isolated epidural abscesses with minimal mass effect, such as complicating sinusitis.[152–154] Repeat MRI should show reduced abscess size and absence of subdural extension. Decreased abscess size may not occur until after more than 2 weeks of therapy. Total antibiotic therapy for 3 to 4 weeks is adequate, except with concomitant osteomyelitis (when total therapy usually is 4 to 6 weeks).

In most cases of infection with suppurative complete venous thrombosis, appropriate antibiotic therapy plus surgical drainage of the suppurative source is performed.[111] Anticoagulant therapy is somewhat controversial because of the risk for hemorrhage[155] but is becoming standard, particularly with incompletely thrombosed obstruction of a lateral sinus. The risk for hemorrhage appears to be low in patients with no evidence of hemorrhagic complications by CT or MRI, and early anticoagulant treatment appears to be beneficial.[156] Internal jugular vein ligation is not necessary, but repeated MRI or CT monitoring for progression of thrombosis is important.

For spinal epidural or subdural abscess, urgent drainage and appropriate antibiotic therapy are critical to halting progressive permanent neurologic deficits. Endoscopic surgery is preferred to open laminectomy.[157] Antibiotics alone can be successful in patients with localized pain but without progression of root pain or evidence of spinal cord compression, or in patients who are stable for more than 3 days without radiculopathy or signs of partial cord compression.[158] Frequent MRI studies are important to document regression.

Antibiotic regimen for spinal epidural or subdural abscess should be designed to adequately penetrate to the site, and antibiotic generally is given for 3 to 4 weeks, unless osteomyelitis is present, in which case therapy may be as long as 8 weeks. The duration of intravenous antibiotics depends on the extent of the epidural or subdural abscess, accompanying foci of infection (e.g., myositis or osteomyelitis), and drug susceptibility of identified pathogens and bioavailability of oral forms of drug. Adequate CSF penetration is important with subdural abscesses, but is not as critical with epidural abscesses without a concomitant intradural or brain focus. Intravenous therapy for as few as 5 to 7 days can be effective if the pathogen and antimicrobial susceptibility are known; therapy can be completed using oral agents having sufficient bioavailability (e.g., fluoroquinolones, linezolid, clindamycin, rifampin).

Specific Antimicrobial Regimens

Recommended empiric antibiotics (Table 46.6) are based on likely pathogens, predisposing conditions, expected susceptibility patterns, and concentration of antibiotic at infected sites.[159] Recommendations are based on clinical experience or case series (mostly in adults) because there are no well-controlled pediatric trials.

TABLE 46.6

Empiric Therapy for Brain Abscess Based on Predisposing Factors

Predisposing Factor	Antibiotic (Dose)
Congenital heart disease	Vancomycin (60 mg/kg/day) *plus* ceftriaxone (100 mg/kg/day)[a] *plus* metronidazole (30 mg/kg/day)[b]

Dental pathology	Penicillin (300,000 U/kg/day) *plus* metronidazole[b] (as above); *or* Ampicillin-sulbactam (300–400 mg/kg/day)[c]
Sinusitis, mastoiditis, and/or otitis media[d,e]	Vancomycin (as above) *plus* ceftriaxone (as above)[a] *plus* metronidazole (as above)[b]
Penetrating trauma or postsurgery	Vancomycin (60 mg/kg/day) *plus* ceftriaxone (100 mg/kg/day)[a] or cefepime (150 mg/kg/day)
Meningitis	
Neonates	Cefotaxime (50 mg/kg/dose) *plus* ampicillin (100 mg/kg/dose) with dosing interval for each drug being q12h in first week of life, q8h from 8 to 28 days of life and q6h >28 days of life)
Infants and children	Ceftriaxone (as above)[a] *plus* vancomycin[b] (60 mg/kg/day)
Endocarditis	
Natural valve	Ampicillin[f] (as above) *plus* aminoglycoside (maximal doses); *or* Ceftriaxone (as above)[a] *plus* vancomycin (as above)
Prosthetic valve	Vancomycin (as above) *plus* gentamicin
Unknown or immunocompromised[g]	Vancomycin (as above) *plus* ceftazidime (see below) *plus* metronidazole

[a] Cefotaxime (300 mg/kg/day) can be substituted.

[b] If anaerobic bacteria are resistant to metronidazole and β-lactam, change to meropenem (120 mg/kg/day), or in countries where still available, use chloramphenicol (80–100 mg/kg/day).

[c] Ampicillin-sulbactam (≥300–400 mg/kg/day of ampicillin) acceptable only if methicillin-resistant *Staphylococcus aureus* or penicillin-resistant pneumococcus is not a risk.

[d] When staphylococci or penicillin-resistant *Streptococcus pneumoniae* is suspected, add vancomycin. See Infectious Diseases Society of America guidleines[176] for specifics.

[e] With chronic otitis media or sinusitis, substitute ceftazidime (150–200 mg/kg/day) or cefepime (100 mg/kg/day) as third-generation cephalosporin.

[f] Penicillin (300,000–400,000 U/kg/day) can be substituted.

[g] If no response within 1 week and organism is unknown, consider amphotericin B.

Ceftriaxone (or cefotaxime) plus metronidazole were appropriate empiric therapy for brain abscess and subdural empyema accompanying otitis media, mastoiditis, sinusitis, or CCHD before multidrug-resistant serotype 19A pneumococci (resistant to third-generation cephalosporins). Vancomycin was added to empiric regimens for coverage of resistant pneumococci and MRSA. Small numbers of patients with brain abscess have been treated successfully with alternative antibiotics, such as imipenem,[160] meropenem,[161] and ciprofloxacin,[162] but these agents have no activity against MRSA. Approximately 25% of *S. pneumoniae* 19A strains are carbapenem resistant, so carbapenem use requires confirmed susceptibility. *S. pneumoniae* 19A rarely (<3% in the

United States) is resistant to fluoroquinolones, but only anecdotal data exist for their use in intracranial abscesses. Despite the decreased prevalence of 19A strains and attendant penicillin resistance since use of 13-valent pneumococcal conjugate vaccine (PCV13), vancomycin should be included in empiric therapy for abscesses associated with otic or sinus origin and likely is needed empirically (because of a role of MRSA) in complicated sinusitis and orbital infections and (because of a role of coagulase-negative staphylococci) in focal CNS infections, such as associated with penetrating head trauma, ventriculoperitoneal shunts, or prosthetic valve endocarditis.

Vancomycin plus a third-generation cephalosporin plus an agent with anaerobic coverage is the recommended empiric regimen for CNS infections because of their polymicrobial nature. Some experts choose cefepime as the third-generation cephalosporin when *Pseudomonas* spp. is considered—that is, with chronic otitis media or sinusitis, after neurosurgery, or in immunocompromised patients.

In neonates, cefotaxime plus ampicillin is preferred because *S. pneumoniae* is rare, whereas *L. monocytogenes* and enterococci remain potential pathogens.

For brain abscess associated with α-streptococcal endocarditis on a natural valve, high-dose combination therapy recommended for endocarditis (e.g., penicillin plus aminoglycoside) is useful, although aminoglycosides in purulent collections can be relatively ineffective (low pH and low oxygen content reduce binding to ribosome). Therapy with a third-generation cephalosporin appears to be a reasonable alternative.

The rare *Nocardia* brain abscess is treated with trimethoprim-sulfamethoxazole (15 to 30 mg/kg/day divided every 6 or 8 hours). If local trimethoprim-sulfamethoxazole resistance is present or response is inadequate, a carbapenem or a third-generation cephalosporin plus amikacin or minocycline may be effective. Linezolid has been reported to be effective against multiple *Nocardia* brain abscesses.[163,164] CSF and CNS penetration of linezolid is 44% to 69% in adults.[165,166]

Prevalence of fungal species in brain abscesses parallels prevalence in other invasive fungal disease. In one review[167] including all ages, *Candida* spp. were most common (42%), followed by *Aspergillus* (29%), other molds (14%), and *Cryptococcus* (4% and mostly in adults). Endemic fungi (*Histoplasma, Blastomyces, Coccidioides*, 3%) occur mostly in defined endemic geographic areas. *Scedosporium* spp. is seen increasingly, particularly in stem cell transplant recipients.

Antifungal therapy for focal CNS infection is challenging and is based on knowledge of expected fungicidal activity against pathogens such as that confirmed, and pharmacodynamics of the drug (Table 46.7). Data from double-blind well-controlled treatment trials of CNS fungal infections are scant even for single antifungal drugs. Possible combinations of drugs are myriad given four classes of antifungal agents (polyenes, pyrimidine analogues, imidazoles, and echinocandins) and multiple class members (see pathogen-specific chapters and Chapter 293).

TABLE 46.7

Antifungal Therapy for Central Nervous System Focal Infections[177,178]

Pathogen	Therapy	Alternative Therapy
Candida spp.	Initial: AmB[a] *with or without* flucytosine[b] Step-down: fluconazole	Fluconazole
Aspergillus spp.	Voriconazole[b]	LFAmB *or* itraconazole[b] *or* posaconazole[b]
Agents of mucormycosis, e.g., *Rhizopus* spp.	L-AmB[c,d]	Other AmB or posaconazole[b,e,f]
Coccidioides immitis	Fluconazole[g]	Itraconazole[b,g] or AmB *plus* intrathecal AmB-d
Cryptococcus neoformans	Induction: AmB-d *plus* flucytosine[b] Consolidation: fluconazole, high-dose Maintenance: fluconazole	L-AmB or ABLC may substitute for AmB-d
Blastomyces dermatitidis	Initial: AmB[a] Step-down: fluconazole[e] *or* itraconazole[b,e] *or* voriconazole[b,e]	Initial therapy with an azole alone is not recommended.
Histoplasma capsulatum	Initial: L-AmB Step-down: itraconazole	AmB-d or another LFAmB may substitute for L-AmB
Scedosporium/Pseudallescheria spp.	Voriconazole[b,e,f]	Not well defined

[a] LFAmB formulations often are favored because of decreased risk for nephrotoxicity; in general, children tolerate AmB-d better than adults. L-AmB formulations attain the highest levels in the brain, whereas both L-AmB and AmB-d had the greatest antifungal efficacy in a rabbit candidiasis model that compared AmB-d, ABCD, ABLC, and L-AmB.

[b] Therapeutic drug monitoring may be beneficial.

[c] Although hyperbaric oxygen has been used as adjunct therapy, results have been controversial.

[d] Higher doses of L-AmB should be used: 5−10 mg/kg/day.

[e] Experience is limited.

[f] Susceptibility varies by species.

[g] For meningitis, some clinicians also initiate intrathecal AmB deoxycholate in addition to an azole. Patients nonresponsive to an azole would be candidates for intrathecal AmB deoxycholate with or without azole continuation.

ABCD, amphotericin B colloidal dispersion; ABLC, amphotericin B lipid complex; AmB, amphotericin B product; AmB-d, amphotericin B deoxycholate; L-AmB, liposomal amphotericin B; LFAmB, lipid formulation of amphotericin B.

Usual doses: AmB-d, 1.0–1.5 mg/kg/day; LFAmB, 3−6 mg/kg per day (varies by product and organism); fluconazole, 12 mg/kg per day; itraconazole oral suspension, 7.5−15 mg/kg/day in 3 divided doses for 3 days, then 5−10 mg/kg/day in 1 or 2 divided doses; flucytosine, 100–150 mg/kg/day in 4 divided doses; posaconazole oral suspension, age 2−12 years: 18−24 mg/kg/day in 4 divided doses, age ≥13 years: 800 mg/day in 4 divided doses (optimal pediatric dose unknown); voriconazole intravenous, age 2−11 years: 18 mg/kg/day in 2 divided doses for 1 day, then 16−18 mg/kg/day in 2 divided doses, age ≥12 years: 12 mg/kg/day in 2 divided doses for 1 day, then 8 mg/kg/day in 2 divided doses. (Dosage information courtesy of Dwight E. Yin, MD.)

Complications and Prognosis

About two thirds of patients with brain abscess recover without sequelae. Pediatric mortality fell from more than 30% in the preimaging era to 3% to 15% after use of CT.[168] Higher mortality is associated with rapid onset (<4 days), severe mental status changes at diagnosis, or rapidly progressing neurologic impairment.[148] Higher mortality also is associated with multiple abscesses[4] and with rupture of abscess into ventricles (40% mortality despite aggressive management).[169] Seizures develop in 10% to 30% of patients after treatment of brain abscess, with onset sometimes several years after treatment.[170] Frontal or temporal lobe abscess, or any large abscess, is associated with a higher incidence of seizures. Other sequelae include hemiparesis (10% to 15%), cranial nerve palsy (5% to 10%), hydrocephalus (5% to 10%), and behavioral and intellectual disorders (more serious in children <5 years of age[171]). Less common sequelae include spasticity, ataxia, optic atrophy, and visual deficits.

Outcomes for patients with subdural empyema also improved with use of CT, MRI, and improved surgical techniques[37]; mortality is less than 2%.[172] Mortality is lowest (<10%) if the patient at presentation is alert and highest (>50%) if comatose. The 5% to 10% of patients with venous sinus thrombosis accompanying subdural empyema have increased morbidity and mortality. Patients with subdural empyema have more persistent neurologic problems (15%–40%), such as seizures or hemiparesis, than patients with brain abscess.[37]

Patients with uncomplicated intracranial epidural abscess (i.e., no accompanying subdural empyema or brain abscess) have an excellent prognosis. However, delay in diagnosis can produce long-term neurologic sequelae similar to those after subdural empyema or brain abscess.

Suppurative septic sinus thrombosis with complete occlusion is associated with 25% to 35% mortality despite improved diagnostic tools and antibiotic therapy.[63] With superior sagittal sinus thrombosis, complete occlusion has the highest mortality, whereas anterior segment thrombosis commonly is associated with complete recovery.[63] Lateral sinus thrombosis has sequelae in up to 20%, such as hearing loss, decreased visual activity, brain abscess, or rarely meningitis.[111] Cavernous sinus thrombosis has sequelae in up to 33%, such as blindness, oculomotor paralysis, hemiparesis, or pituitary insufficiency.[173]

The prognosis with spinal epidural or subdural abscess is excellent if therapy begins before radicular symptoms appear. The overall mortality is less than 10%.[174] Long-term sequelae correlate with the duration of paralysis before surgery, the degree of thecal sac compression, and younger age.[76,175] Common neurologic sequelae include sphincter disturbance, spasticity, and paraparesis.

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47

Eosinophilic Meningitis

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The finding of even a few eosinophils in human cerebrospinal fluid (CSF) raises suspicion of certain pathologic states. Helminthic infestation of the central nervous system (CNS), particularly with the rat lungworm *Angiostrongylus cantonensis,* is the most common cause of eosinophilic meningitis worldwide.[1–9] The differential diagnosis of CSF eosinophilia, however, is broad and includes infestation by other parasites, such as the raccoon ascarid *Baylisascaris procyonis*[10–19]; reaction to placement, malfunction or infection of a ventriculoperitoneal shunt[20–22]; medications[23–26]; malignancies[27,28]; hypereosinophilic syndrome[29]; and an unusual manifestation of a more common parasitic, fungal, bacterial, or viral infection of the CNS.[30–35] Table 47.1 lists the causes of eosinophilic meningitis to be considered.

TABLE 47.1

Causes of Eosinophilic Meningitis

Cause	Association With EM	Possible Transmission	Country	Comments
NEMATODES (ROUNDWORMS)	Most common causes			
Angiostrongylus cantonensis		Contact with rat lungworm; consumption	South Pacific, Africa, Australia,	Neurotropic Usually self-limited

		of snail, slug, crustacean, mollusk, crab; frogs, fish, lizards; lettuce and vegetable	Caribbean, Hawaii, US port cities	
Baylisascaris procyonis		Contact with raccoon or feces; rarely dogs, rodents, small mammals, birds	US	Neurotropic Prolonged, profound encephalitis Young children with pica are typical patients
Gnathostoma spinigerum		Contact with dog, cat; consumption of raw fish, poultry, crustaceans, amphibians	Southeast Asia, Japan, China, Mexico, Central and South America, Africa, and the Middle East	Peripheral eosinophilia common
Ascaris lumbricoides		Exposure to embryonated eggs in human feces	Worldwide	Rarely associated with EM
Trichinella spiralis		Consumption of raw or undercooked meat	Worldwide; endemic in Japan and China	Larvae usually found in skeletal muscle Rarely associated with EM
Toxocara canis, catis		Exposure to eggs in feces dogs, cats	Worldwide	Rarely associated with EM
CESTODES (TAPEWORMS)	Occasional causes			
Taenia solium		Exposure to eggs in human feces	Worldwide	Neurocysticercosis is a rare cause of EM
Echinococcus granulosus		Exposure to eggs in feces sheep; wolves, dogs, moose, reindeer	Europe; northern North America and Eurasia	Rarely infects CNS and associated with EM
OTHER PARASITES	Rare			
Toxoplasma gondii		Consumption of undercooked meat; exposure to oocyst in cat feces	Worldwide	Anecdotal report
Schistosoma japonicum		Contaminated water	Worldwide, tropical and subtropical; most cases Africa	

Paragonimus westermani		Contaminated water	Far East	Lung fluke but can invade CNS and other sites
Fasciola hepatica		Contaminated water	Worldwide; southeast Asia	
FUNGI	Occasional			
Coccidioides immitis		Exposure to aerosolized arthroconidia	Southwestern US, Mexico, South America	Low level of CSF eosinophils common; true EM also reported
Cryptococcus neoformans		Environmental exposure		Diabetes is a risk factor
BACTERIA AND VIRUSES	Case reports			
Treponema pallidum		Exposure to infected person	Worldwide	EM rarely associated with neurosyphilis
Mycobacterium tuberculosis		Exposure to infected person	Worldwide	Questionable association with direct CNS infection versus treatment
Rickettsia rickettsii		Tick bite	North, Central, and South America	Rare
Lymphocytic choriomeningitis virus		Exposure to rodents	Worldwide	Association made through serologic studies
Ventricular shunt bacterial infections				Same pathogens as in shunt infections without eosinophils
NONINFECTIOUS ETIOLOGIES	Occasional or case reports	Not applicable	All or not applicable	
Ventricular shunt complications/reaction to shunt material Bovine dural graft				No infection and improvement with removal of shunt
Systemic drugs				Reported with fluoroquinolones, nonsteroidal anti-inflammatory drugs and illicit drugs intravenously
CNS neoplasms				Reported with Hodgkin lymphoma, acute lymphoblastic leukemia, and primary CNS tumors
Hypereosinophilic syndrome				Reported in patients without other cause

Immunologic/hypersensitivity reaction				Reported with sarcoidosis or rabies vaccine

CNS, central nervous system; CSF, cerebrospinal fluid; EM, eosinophilic meningitis.

Eosinophilic meningitis is defined as (1) at least 10 eosinophils/mm^3 in CSF or (2) eosinophils making up at least 10% of the white blood cells (WBCs) in CSF, but the presence of eosinophils in the CSF should always be considered as an abnormal finding.[5] Diagnostic examination of CSF should always include Giemsa, Wright, or other stain of a cytocentrifuged specimen to delineate the exact composition of pleocytosis, as well as routine CSF examination, including Gram stain, quantitative cell count, and biochemical tests.[5]

Infectious Causes

Helminths

Angiostrongylus cantonensis

The rat lungworm, *A. cantonensis,* is the most common cause of eosinophilic meningitis worldwide. Although no cause is predominant in the United States, it is important that clinicians still consider parasitic infections in cases of eosinophilic meningitis. Travelers to endemic areas should be warned about the risks of dietary indiscretions as well. *Angiostrongylus* infestation has been the subject of several reviews.[1–4,7,9,36,37] CNS migration is characteristic of the lungworm's normal life cycle in the rat as well as in the accidental human host. Adult worms live in the rat pulmonary arteries and lay eggs in the lung. After hatching, larvae make their way through the alveolar spaces and up the trachea, from which they are swallowed and then excreted in rat feces.

Many species of slugs and snails serve as intermediate hosts, in which the larvae develop into infectious third-stage larvae. When third-stage larvae are ingested by rats, the definitive host, larvae migrate across the intestinal wall and are carried by the circulatory system to the brain. Juvenile worms have been found in the eyes, brain, and spinal cord in human infections.[38] In the CNS, larvae undergo two more moltings and mature into adult worms; the worms return to the pulmonary arteries to renew the cycle. Human infection occurs after consumption of raw snails, shrimp, or fish that have fed on infected snails. Likewise, infectious larvae can be ingested accidentally on raw vegetables, raw vegetable juice, or fomites contaminated with snail slime.[3,4,9,36,39,40] CNS tropism is retained in human infection; however, the life cycle is disrupted, and generally, the disease is self-limited, with larvae dying in the CNS.

Human infection by *A. cantonensis* probably is more widespread than believed and has been found in Asia, notably in Thailand, Malaysia, and China; the South Pacific, including Taiwan, Hawaii, American Samoa, New Guinea, Indonesia, and Australia; India, Egypt, Brazil, and the Caribbean.[1–4,8,41–43] Worms can migrate on ships within their natural hosts (the rat) to distant countries, including mainland United States.[40] The first published, nonimported case in the US was a child from New Orleans who reported eating a raw snail "on a dare."[43] The child had meningitis that abated with supportive care.

In adults, symptoms classically begin 2 to 35 days after infection, with acute onset of headaches.[1–4] Other common complaints are nausea and vomiting, weakness, paresthesias or hyperesthesias, pruritus, somnolence, and cranial nerve palsies, especially optic nerve and cranial nerves VII and VIII.[1–4,40,44] About 20% of patients also have a stiff neck.[38] Fever, if present, usually is of low grade. Hearing loss has been reported, as has retinal detachment or hemorrhage.[18,45] Periorbital cellulitis can be associated. Most patients recover completely, with symptoms beginning to abate within several weeks of the initial neurologic manifestations. Headaches and paresthesias can be more persistent.[3,44] Neurologic symptoms may be due to mechanical damage caused by worm migration in the brain as well as the neurotoxicity of eosinophil-derived basic proteins.

Infected children may not complain of headache. Clinical manifestations in younger patients can be more insidious, with upper respiratory symptoms, cough, and fever preceding mental status changes, seizures, or focal neurologic abnormalities.[2,6,39] Psychiatric changes also have been reported.[46] One series of 16 young adults consuming raw infected great African *Achatina fulica* snails in American Samoa was notable for the absence of headache as a major complaint.[47] All of the patients experienced severe radiculomyeloencephalitis; one died. Unlike other intermediate hosts or contaminated vegetables, *A. fulica* snails can harbor thousands of parasites, possibly accounting for the more fulminant course in patients who acquire parasites from consuming these snails. Other reported fatalities or sequelae are observed primarily in young children, who are at risk for acquiring a relatively higher infectious load.[2,39,48]

CSF examination reveals pleocytosis typically between 150 and 2000 WBCs/mm^3.[1,2,47] Peak eosinophilia occurs between 2 and 4 weeks of illness, with CSF eosinophils representing a median of 49% of the total WBCs (range, 15%–97%).[1–4,6,39,48] The CSF protein value often is elevated, and the glucose value is normal or mildly decreased.[1,2] Peripheral blood eosinophilia is common but does not correlate with the extent of CNS eosinophilia.[1,2,4] Coincident infections with other parasites may contribute to peripheral eosinophilia.

A diagnosis of eosinophilic meningitis usually is made on the basis of clinical presentation in patients who are from or are traveling from an area enzootic for *A. cantonensis* and have a consistent dietary history. The history of eating raw seafood can be absent in young children who have a propensity for pica.[6,39,48] On occasion, worms are found in the CSF, especially if a large-bore cannula is used for removal of CSF or if CSF is aspirated rather than allowed to flow by gravity.[2] Enzyme immunosorbent assays to detect antibody in serum or CSF have been developed and are available in enzootic areas and can be facilitated by contact with the Centers for Disease Control and Prevention, Disease Surveillance Division of Parasitic Infections (770-488-7775).[3,4]

Baylisascaris procyonis

The ascarid parasite of the raccoon, *Baylisascaris procyonis,* is found in 20% to 90% of both rural and urban raccoons in the US.[11,49–51] Evidence of raccoon latrines near human habitation[50] increases the concern for this emerging infection, which has been highlighted in several reviews.[15,52] Like *A. cantonensis,* this ascarid migrates through the CNS during its normal life cycle and is neurotropic in humans.[10,11,15,52] The ascarid causes little disease in the raccoon, but ingestion of eggs by aberrant hosts, such as foxes, rabbits, birds, and humans, can result in migration of larvae, causing severe CNS damage. Experimental disease in nonhuman primates consists of eosinophilic meningitis, neurologic deterioration, coma, and death (discussed in references 11, 15, and 52). Despite the high prevalence of this parasite in raccoons, *B. procyonis* is rarely documented in humans. In the US, just more than a dozen clinical cases have been reported, most commonly in young children, resulting in eosinophilic meningoencephalitis with dramatic eosinophilic CSF pleocytosis, severe neurologic devastation, and death in 6 patients.[10,11,15,52–55] Ocular larva migrans and visceral larva migrans also can occur.[15,56] Exposure to raccoon droppings near nesting sites is the expected mode of acquisition. Behavior related to substance abuse has been identified as a possible risk factor.[57] Because clinician awareness of this parasite is limited, and diagnosis is not straightforward, it is possible that the disease is more widespread and that less severe symptoms remain undiagnosed.[58] Asymptomatic infection has been suspected by finding a low level of seropositivity in otherwise healthy children (reviewed in references 15 and 52). As improved serodiagnostic assays become more readily available, the true incidence and clinical array will become more apparent. Currently serologic testing of serum and CSF is only available from the Department for Veterinary Pathobiology at Purdue University, West Lafayette, IN (765-494-7558).

Gnathostoma spinigerum

The nematode of dogs and cats, *Gnathostoma spinigerum,* is found commonly in Thailand and other parts of Southeast Asia, but its prevalence is increasing in Mexico and Central and South America.[44] *Gnathostoma* can cause visceral larva migrans when it infects humans who consume raw or undercooked fish, frogs, pigs, snakes, fowl, eels, or poultry containing third-stage larvae or, rarely, have direct larval penetration of the skin.[22,36,44] Gnathostomiasis typically presents as cutaneous, visceral, or CNS forms. Gnathostomiasis most often is characterized by migratory subcutaneous nodules, but larvae can wander to organs and cause local symptoms[59] or enter the CNS through the nerve root, causing a myeloencephalitis.[18,59,60] Patients can manifest disease over a period of a year, with intermittent intense nerve root pain followed by paralysis or sudden deterioration in mental status.[18,59] The CSF shows a striking eosinophilia but often also can have many red blood cells or xanthochromia. Frequently, *G. spinigerum* infection is associated with concurrent peripheral blood eosinophilia, which is pronounced.[36,59,60] Infection can be severe and results in death more often than infection with *A. cantonensis*.[1,5] Diagnosis is challenging; blood eosinophilia may be lacking, or head computed tomography can show nodular lesions, area of hemorrhage, or hydrocephalus.[44]

Other Infectious Causes

Other parasites can invade the CNS, including *Taenia solium, Toxocara canis, Taenia cati, Toxoplasma gondii, Paragonimus westermani, Fasciola hepatica, Trichinella spiralis, Ascaris lumbricoides, Echinococcus granulosus, Schistosoma japonicum,* and *Onchocerca volvulus.* Associated CSF eosinophilic pleocytosis characteristically is mild.[3,5,13,35,36,61]

Bacterial meningitis occasionally can be associated with mild degrees of CSF eosinophilic pleocytosis. The first descriptions of eosinophilic meningitis were in patients with neurosyphilis.[5] Other implicated agents are *Mycobacterium tuberculosis*, group B *Streptococcus*, and *Rickettsia rickettsii*.[32,33,62,63]

A retrospective review of 27 adults in the southwestern US with *Coccidioides immitis* meningitis noted eosinophils in the CSF of 70% of patients; 30% of instances met the definition of eosinophilic meningitis.[34] Other fungal infections of the CNS, such as those due to *Histoplasma capsulatum* or *Cryptococcus neoformans,* and *Aspergillus* species are occasionally associated with CSF eosinophilia.[64,65] Rarely, viral infections of the CNS (lymphocytic choriomeningitis virus, coxsackieviruses B3 and B4, measles virus, echovirus 6, and varicella-zoster virus) have been associated with eosinophilic pleocytosis of CSF.[30,31,63] In some of these cases, diagnosis was suggested by results of serologic testing or by isolation of the virus from sites other than the CNS.[30,31]

Noninfectious Causes

Review of series of children with complications of ventriculoperitoneal shunts have shown varying rates of eosinophilic pleocytosis associated with bacterial infection,[22,63] intraventricular administration of antibiotics,[24] or antibiotic-impregnated ventriculostomy catheters,[25] or without any risk factor other than the shunt itself.[20] In one series evaluating 558 shunt insertions, 36 (6.5%) were found to have more than 8% eosinophils in the CSF.[20] Affected children characteristically had experienced excessive numbers of shunt revisions and shunt infections. Another study demonstrated activation of eosinophils in CSF related to shunt obstruction.[21] This study found that 6.4% of 404 children with ventriculoperitoneal shunts had transient CSF eosinophilia.[21] However, in most of these children, the eosinophilia value was no more than 3%, or eosinophils were present before placement of the shunt. Vinchon and associates[22] reported finding eosinophilic meningitis associated with 27 of 81 presumed bacterial shunt infections; CSF culture results were positive in 63% of cases, and the microbes found did not differ from the types of organisms found in patients with noneosinophilic shunt infections. Persistent eosinophilic pleocytosis, failure to isolate infectious agents in many cases, and an association with eventual extrusion of subcutaneous tubing in some populations suggest that hypersensitivity to shunt material occasionally occurs. Replacement of the shunt with one of a different material sometimes is undertaken and sometimes is curative. One report associated the use of a minocycline- and rifampin-impregnated ventricular drain in a child with a shunt malfunction and the development of eosinophilic pleocytosis; eosinophilia resolved coincident with corticosteroid administration and removal of the tubing.[25]

Several other noninfectious possibilities are included in the differential diagnosis of eosinophilic meningitis. Systemic drug administration has been associated on occasion with aseptic meningitis, and, more rarely, fluoroquinolone and nonsteroidal anti-inflammatory agents have been associated with eosinophilic meningitis.[23,36] In addition, CNS involvement with Hodgkin primary lymphoma[27] or acute lymphoblastic leukemia[28] has caused eosinophilic meningitis. Other primary CNS tumors (as well as aseptic meningitis after resection of tumors) can be associated with mild eosinophilic pleocytosis.[63] Patients with sarcoidosis and hypereosinophilia syndrome have been reported to have accompanying eosinophilic meningitis.[29,63] Eosinophilic meningitis also has been described in two intravenous drug users who were negative for human immunodeficiency virus or other identifiable infections.[66] The authors postulate that this might represent an eosinophilic response to systemically injected drug adulterants that were used as cut substances for street drugs.

Diagnosis and Treatment

Careful attention to the clinical setting (i.e., occurrence, history of exposure or travel) and findings on physical examination almost invariably narrow possible causes of eosinophilic meningitis to one or two categories. Careful examination of large amounts of CSF for parasites and malignant cells and culture of CSF for fungus can yield a diagnosis.

Examination of stool for ova and parasites often is unrewarding because most human neurotropic parasites do not complete the life cycle in humans. However, (1) parasitic infestations often occur concurrently and (2) on occasion, *A. lumbricoides, S. japonicum, T. solium,* and *F. hepatica* have been associated with eosinophilic meningitis. Therefore stool evaluation is justified. Serologic tests of the CSF and serum for *C. neoformans* (CSF antigen test), *A. cantonensis,* or *B. procyonis,* when epidemiologically indicated, are appropriate. However, for angiostrongyliasis, the sensitivity and specificity of serologic assays vary greatly, rarely exceed 80%, and may present cross-reactivity with other microorganisms, such as *Gnasthostoma* spp.[38,44] Reliable antigen-specific immunoassays are still needed. CSF often is cloudy, with increased opening pressure and protein concentration but normal glucose concentration. Neuroimaging can be of benefit and can guide biopsy of the meninges or brain if other tests do not confirm a diagnosis. Approximately half of the patients have abnormal magnetic resonance imaging results, with leptomeningeal enhancement and lesions in the brain parenchyma or hydrocephalus.[44,67]

The treatment and prognosis of parasitic and infectious causes of eosinophilic meningitis or meningoencephalitis depend on the cause, underlying conditions, and extent of involvement at time of diagnosis. Recommendations for specific therapies can be found in chapters addressing individual pathogens.

No systematic study of treatment with antiparasitic agents has been undertaken for *A. cantonensis,* and treatment is primarily supportive. A multicenter study prospectively evaluated patients between 2 and 65 years of age with eosinophilic meningitis; 19% of patients were younger than 20 years. Treatment was not dictated by the study; however, no difference was noted in course or outcome among patients who received 5 days of corticosteroid therapy, antibiotics, or analgesics alone.[1] Uncontrolled studies have reported the use of corticosteroids to be beneficial.[68,69] A randomized controlled trial in adults in Thailand showed no benefit of prednisolone plus albendazole compared with prednisolone alone.[25,68] Another group reported in a placebo-controlled trial that albendazole decreased the duration of headache in adult patients. The revised Cochrane review showed that only a single randomized controlled trial demonstrated that corticosteroids decrease headache, making the evidence of usefulness of moderate quality.[70] In mice, anti-CCR3 monoclonal antibodies decreased significantly the eosinophil infiltration of the brain and may offer new possibilities for future treatment in human. Observations that clinical improvement occurs after (repeated) lumbar puncture or is temporally related to use of corticosteroid and mannitol suggest that some symptoms may be a consequence of the inflammatory response, raised intracranial pressure, or both.[1,2,29]

Children with severe eosinophilic meningitis due to *Baylisascaris* have not been shown to benefit from treatment; however, experimentally infected mice were protected from neurologic disease if treated with albendazole or diethylcarbazine before larvae entering the brain (reviewed in reference 15). In some cases, antipsychotic drugs have been used as well in specific cases.[46] Because of the potential for severe, even fatal, outcome, particularly in young children, some experts recommend treatment of children exposed to raccoon excrement with albendazole to prevent disease.[15,50,52]

Educating the public about potential dangers from exposures to raccoons and their feces is the most important component of prevention. Raccoons have adapted readily to human habitats and are attracted to areas with sources of water and food. Therefore their presence should be discouraged by cleaning up areas and ensuring that food is not left out unwittingly. Parents of toddlers in particular should be mindful of potentially contaminated play areas, encourage good handwashing after playing outside, and discourage pica.

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Genitourinary Tract Infections

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Urinary Tract Infections, Renal Abscess, and Other Complex Renal Infections

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Infections of the genitourinary tract in children remain a significant health concern, with more than 1.1 million US physician visits annually.[1] Of all infectious agents, bacteria are the most common cause of urinary tract infection (UTI). In infants, UTI is a common cause of fever and may result in renal parenchymal damage and functional loss. As such, rapid diagnosis, proper treatment, and prevention of recurrent UTI are key to reducing renal damage.

Etiologic Agents

The most common bacteria that cause UTI are gram-negative Enterobacteriaceae, primarily *Escherichia coli* and then *Klebsiella*, *Proteus*, *Pseudomonas,* and *Enterobacter* spp. Some serotypes of *E.*

coli, including uropathogenic *E. coli* (UPEC) and extraintestinal *E. coli,* contain specific cell wall O-antigens that facilitate infection.[2–4] Gram-positive organisms other than *Enterococcus* spp. are less common causes of UTI, and isolates such as *Staphylococcus saprophyticus* account for only 15% of pediatric UTIs. *Staphylococcus aureus,* including methicillin-resistant strains, rarely cause symptomatic UTI, and isolation in the urine should suggest primary infection elsewhere. Infections caused by *Pseudomonas* spp. should be considered in children who have been hospitalized recently, had prior episodes of UTI, or had prior antibiotic treatment.[5]

Viral cystitis can occur in immunocompromised hosts. In children with a history of bone marrow transplantation, BK virus can cause a severe hemorrhagic cystitis that improves only with immunologic recovery.[6,7] Levofloxacin has failed to show prophylactic benefit for managing BK virus infection in patients after transplantation, despite in vitro activity of the drug.[8]

Epidemiology

UTI accounts for 2.4% to 2.8% of pediatric physician visits, 51 hospitalizations per 100,000 children, and 174 hospitalizations per 100,000 infants each year.[1] Girls are hospitalized 2.5 times more often than boys.[9,10] During the first year of life boys have more UTIs than girls.[4,11] For uncircumcised boys the risk for UTI is 10 times greater than for circumcised boys during the first year.[12]

Definitions

Using routine culture techniques, normal urine shows no bacterial growth (i.e., <100 colony-forming units [CFUs]/mL for catheter-obtained specimen and <1000 CFUs/mL for clean-catch specimen). There is, however, controversy about whether urinary tract colonization (“benign bacteriuria”) occurs. UTI is diagnosed when an appropriately collected urinary specimen shows growth of defined density for UTI diagnosis.

Because the anatomic level of UTI is difficult to determine without specific invasive techniques or excessive imaging, *UTI*—in this chapter and unless otherwise specified—refers to urinary tract bacteriuria with accompanying symptoms and signs—a spectrum from cystitis with lower tract bladder symptoms to pyelonephritis with systemic and abdominal symptoms.

Pathogenesis

UTI begins with bacterial adherence to host epithelial cells along a fecal-perineal-urethral route, with potential retrograde ascent of bacteria along the urinary tract.[13] Aspects of bacterial virulence and patient risk factors influence this course but do not predict pyelonephritis, renal scarring, or parenchymal and functional loss. Of the 3% of girls and 1% of boys who have UTI prepubertally, about 17% will have infection-related renal scarring.[4] Of children with scarring, 10% to 20% may develop renal-related hypertension. A child only rarely progresses to end-stage renal disease requiring transplantation because of UTI.

Bacteria must overcome urethral defenses to cause UTI. These defenses include (1) urethral washout, (2) epithelial shedding, and (3) paraurethral glandular secretion.[14] Also, host defenses such as toll-like receptors triggered by bacterial lipopolysaccharide and urinary Tamm-Horsfall protein may adhere to uropathogenic *E. coli* and assist urethral washout.[15]

Two important markers of *E. coli* virulence are mannose-resistant hemagglutination and P blood group–specific adhesion (P-fimbriae or P-pili).[16–18] Attachment between the uroepithelial cell and bacteria through type 1 pili and fimbriae initiates a molecular interaction that allows for bacterial uptake into the umbrella cells on the bladder surface.[19] Intracellular bacteria then transform into biofilms that allow for microbial adaption and systemic infection, antimicrobial resistance through plasmid exchange, endotoxin production, and increased resistance to host systems.[20] When in the bladder, retrograde ascent from the bladder to kidney is affected by host immunity, impaired ureteral peristalsis, vesicoureteral reflux (VUR), and organism-specific uropathogenicity.

Risk Factors for Bacteruria and Renal

Damage

Age.

The prevalence of UTI in both males and females younger than 1 year of age is higher than at any other time during childhood. This may be due to a number of factors including density of periurethral colonization, lack of breastfeeding, immature immune status, and, in boys, circumcision status.

Race and Ethnicity.

Epidemiologic studies show racial variance in the prevalence and complications, with Asian, Hispanic/Latino, and white children having higher rates of UTI than black children.[2,21] Black children also have less VUR and renal scarring compared with other races.[1,21,22]

Genetic Predisposition.

Genetic factors that may predispose to UTI include blood group phenotypes, such as P1 blood group, ABO, Lewis secretor phenotypes, host genetic polymorphisms of adhesion molecules (ICAM-1), transforming growth factor-β, toll-like receptor, and vascular endothelial growth factor.[23–25] Being younger than 15 years of age at first UTI (odd ratio, 3.9) and having a history of maternal UTI (odds ratio, 2.3) are risk factors for recurrent UTI in girls.[26] Predisposition for pyelonephritis correlates with decreased expression of interleukin-8 receptors (CXCR1) on peripheral neutrophils regardless of VUR status.[24,27]

Colonization.

The incidence of UTI is higher during the first few months of life than at any subsequent time in a healthy childhood. During this time the periurethral area of healthy infants is extensively colonized with aerobic bacteria, such as *E. coli*, enterococci, and staphylococci.[28] Periurethral colonization decreases to low density during the first year of life, and after the age of 5 years, colonization is associated with recurrent UTI. For the first 6 months of life, uncircumcised infant boys have greater periurethral colonization than circumcised boys[12,29–32]; during this time, uncircumcised boys have more UTIs than circumcised boys.

Immune Status.

After birth, levels of serum immunoglobulin G (IgG) and IgA fall to a nadir at 3 months and periurethral colonization high.[33,34] During this period breastfeeding may protect against UTI and other infections because immunoglobulins, particularly secretory IgA, and oligosaccharides in maternal milk may inhibit adherence of *E. coli* to uroepithelium.[35,36]

Sexual Activity.

Sexual activity is a risk factor for UTI. The upsurge of UTI in adolescents may signal the onset of sexual activity in teenagers[37]; the prevalence of *Chlamydia* is 13% to 26% and *Neisseria gonorrhoeae* is 2% to 10% in this population. Male and female teenagers who have dysuria, urinary frequency, or urgency should be evaluated for both UTI and sexually transmitted infections.

Obesity.

Obesity can be associated with chronic indolent inflammation that increases susceptibility to infections. Compared with lean children, obese children have an 80% increased risk for developing cystitis and an almost 100% increased risk for developing pyelonephritis.[38] These findings mirror those in adults.

Genitourinary Anatomic and Functional Abnormalities.

Studied after a first UTI, 40% to 56% of children have imaging abnormalities,[39,40] the most common abnormalities being hydronephrosis found in 34% and VUR in 30%.

The presence of VUR does not correlate with increased susceptibility to UTI[4] but does correlate with an increased likelihood of developing pyelonephritis after bacteriuria. VUR is a congenital abnormality that results from immature or inadequate muscular support at the ureteral orifice, facilitating retrograde urinary flow from the bladder into the ureter and pelvicaliceal system. Thus, infected retrograde urinary flow can lead to pyelonephritis. Children with high-grade reflux appear to be at greater risk for renal damage compared with children with low-grade reflux.[41,42] Uropathogenic virulence may be more likely to predict development of pyelonephritis and subsequent nephropathy than the degree of reflux.[43]

Whether related to neuropathic bladder dysfunction, ineffective spontaneous bladder emptying,[44] or more subtle increased postvoid residual bladder urine with or without VUR,[45] dysfunctional voiding is associated with increased UTIs.

Identifying anatomic or functional urinary tract abnormalities in the setting of UTI is important because correction can reduce the risk for persistent or recurrent infection. A nidus of bacterial persistence, such as struvite stones, papillary necrosis, or sites of poor antimicrobial penetration (poorly functioning duplicated segments) may be removed, or VUR causing recurrent pyelonephritis can be repaired.

Clinical Manifestations

UTI should be considered in infants and young children who have fever or other signs of infection. Children may present with flank pain accompanied by fever, chills, nausea, or vomiting. Other symptoms can include dysuria, frequency, incontinence, and urgency. Although parents may mention the presence of malodorous urine, this has not been correlated with UTI.[46]

Adolescents with lower urinary tract symptoms should be evaluated for both UTI and sexually transmitted infection. Because UTI is relatively uncommon in adolescent males, they should be evaluated for structural abnormalities, such as previously undiagnosed obstruction, ectopic collecting systems, or voiding dysfunction. Older children are more likely to localize tenderness on palpation and may report pain in the suprapubic and flank region. A palpable flank mass can be caused by hydronephrosis, pyonephrosis, or xanthogranulomatous pyelonephritis.

Laboratory Findings

Urinary Specimens

Obtaining an uncontaminated urine specimen to diagnose infection accurately can be difficult, particularly in young children. Of the various methods for urine collection, suprapubic aspirate is the most reliable because it bypasses potential urethral and periurethral contamination. Although the presence of bacteria in a suprapubic aspirate is diagnostic of a UTI, practitioners avoid this technique because of its perceived invasive nature.

In most cases, urethral catheterization can be performed in a sterile fashion, providing adequate sampling for urinalysis and culture; risks for catheterization include urethral trauma and the introduction of bacteria into the bladder. Voided urinary specimens generally are reliable in circumcised boys, older girls who can retract labial tissue while urinating, or older uncircumcised boys who can retract the foreskin reliably to reduce contamination by resident flora. Bagged urinary specimens are the least reliable method of collecting urine and are useful only when the culture result is negative.[47–49] Even with extensive cleansing of the surrounding skin, the bagged urine specimen typically contains perineal and rectal flora.

Urinalysis

Findings of urinalysis that support a diagnosis of UTI include (1) pyuria, defined as more than 5 white blood cells (WBCs) per high-power field (HPF) in a centrifuged specimen; (2) any bacteria visualized under high power in an unstained centrifuged urinary sediment (×40); (3) presence of urinary leukocyte esterase; and (4) positive test for urinary nitrite. Urinary leukocyte esterase is a byproduct of the degradation of WBCs in the urine. The urinary nitrite test measures dietary nitrates reduced to nitrates by gram-negative Enterobacteriaceae. Gram-positive bacteria, yeasts, and organism such as *Pseudomonas* spp. do not reduce dietary nitrates. Assuming a urine specimen has been collected appropriately, the combination of a result of positive leukocyte esterase and nitrite tests and microscopic visualization of bacteria approaches positive predictive value of nearly 100% for UTI and allows presumptive treatment.[49,50] When all components (or leukocyte esterase and nitrite tests) are negative, the negative predictive value approaches 100%.

In children younger than 2 years, the sensitivity of routine urinalysis for UTI is only about 80%.[51,52] In a multicenter analyses of infants younger than 3 months with bacteremic UTI (identical organism in the blood and urine), investigators found that the sensitivity of leukocyte esterase and pyuria (>3 WBCs/HPF 96%) each exceeded 95%.[53]

Urine Culture

Quantitative urine culture is the gold standard for the diagnosis of UTI. Traditionally, a UTI has been defined as growth of 100,000 CFUs/mL from a voided urine sample.[54] Guidelines from 2011 suggest that the presence of pyuria plus bacterial growth of 50,000 CFUs/mL or more is sufficient for UTI diagnosis.[55] Under some circumstances (e.g., suprapubic aspiration) the presence of less than 10,000 CFUs/mL can be consistent with infection.

Serum Tests

Although urinary culture is the standard for diagnosing UTI, other tests to predict the severity of infection have been examined. For example, elevated erythrocyte sedimentation rate and C-reactive protein have been associated with severity of bacterial infection.[56] Procalcitonin is a hormonally inactive precursor of calcitonin and is elevated in sepsis. Two meta-analyses correlated elevated procalcitonin with both pyelonephritis and high-grade VUR.[57–59]

Urinary Tract Infection Imaging Evaluation

Radiologic imaging often is used in the evaluation of children with febrile UTI. Imaging studies can demonstrate the extent and location of an acute UTI, detect renal damage from infection, identify underlying genitourinary abnormalities that may predispose to future infection, and follow the development of the renal/urinary system over time. Issues of timing of imaging after UTI, optimal modalities, and importance and significance of diagnosing VUR are controversial.

Prior recommendations for performance of renal and bladder ultrasonography and voiding cystourethrogram (VCUG) resulted in high rates of normal findings in children with upper and lower urinary tract infections, respectively. These findings have resulted in attempts to limit UTI imaging, in particular VCUG, given high cost, exposure to ionizing radiation, and invasive catheterization. Current guidelines limit UTI imaging to be more efficient and less invasive UTI evaluation (Royal College Physicians, National Institute for Health and Care Excellence [NICE], American Academy of Pediatrics [AAP], and others).

NICE published guidelines in 2007 that recommend the selective use of ultrasonography for children with atypical UTI, infants younger than 6 months of age, and children with recurrent UTI.[60] Dimercaptosuccinic acid scintigraphy (DMSA) is recommended 4 to 6 months after an atypical UTI in children younger than 3 years and for all children with recurrent UTI. VCUG is not recommended as part of evaluation after a typical first UTI.

Guidelines published by the AAP in 2011 recommend the performance of VCUG in children who have abnormal ultrasonography with hydronephrosis, a second febrile UTI, renal scarring, or atypical or complicating factors that might be associated with high-grade VUR.[55]

Multiple investigators are examining the health implications of these latest recommendations from NICE and AAP. There is lack of agreement on the relevance of diagnosing all grades of VUR, especially when considering the patient discomfort, costs, and radiation exposure resulting from VCUG.

Retrospective analyses using these guidelines observe that most “missed” abnormalities are VUR.[61–64] When kidney-bladder ultrasonography is used in the evaluation of children with UTI, “missed” abnormalities appear to be both uncommon and clinically insignificant.[65–68] Although most analyses concluded that following newer guidelines decreases use of imaging, one study concluded that the 2007 NICE guidelines increase the numbers of DMSA studies performed.[69]

Several groups have proposed further refinements to the guidelines based on these data. Kidney Health Australia guidelines recommend the use of renal ultrasonography in children with UTI who are bacteremic, younger than 3 months, or infected with atypical organisms (e.g., *Staphylococcus* and *Pseudomonas* spp.) or have poor clinical response after 48 hours, renal impairment, significant electrolyte imbalance, abdominal mass, or poor urinary stream. Other groups recommend using high serum procalcitonin concentrations and the presence of dilated ureters as imaging criteria to enhance the detection of high-grade VUR.[68,70] The European Association of Urology/European Society of Pediatric Urology recommends the use of ultrasonography after the first UTI and more widespread use of VCUG in children with UTI.[71]

In all cases when appropriate UTI management is not followed by expected improvement, more extensive imaging such as magnetic resonance urography or DMSA scan should be considered. Current controversies and concerns emphasize a need for improved risk analyses and diagnostic imaging stratification for children with UTI.

Other Imaging Findings

In addition to structural anomalies, such as congenital obstruction or VUR, findings such as hydronephrosis or perinephric stranding may be seen with acute pyelonephritis. Renal ultrasonography may show areas of focal hypoechogenicity or hyperechogenicity that represent localized, severe, and nonliquefactive infection of the renal lobules seen in focal pyelonephritis, or lobar nephronia.[72,73] Previously diagnosed hydronephrosis or pelviectasis may reveal transient increase on imaging during acute UTI, secondary to increased collecting system pressure caused by infection.[74,75] Renal damage also can be seen on functional studies such as DMSA scans and magnetic resonance urography.

Management

Antimicrobial Treatment

Children younger than 3 months of age can have rapid progression of infection, and as many as 30% are bacteremic.[76–78] As a result, these children are usually hospitalized for treatment with intravenous antibiotics. In this age group, gram-negative bacteria are the most common cause of UTI. Infection also can be caused by *Listeria monocytogenes* and *Enterococcus* species, which can be acquired perinatally and postnatally, respectively.[79] Considering etiology, treatment with ampicillin and gentamicin typically is recommended in this age group.

Children older than 1 month who do not have major genitourinary abnormalities and can take fluids and oral medications can be treated effectively with either a complete course of oral antibiotics, or 2 to 4 days of parenteral therapy followed by oral therapy for a total duration of 10 to 14 days.[80] Studies comparing the effectiveness of oral and parenteral therapy typically excluded children with impaired renal function, severe urinary tract abnormalities including VUR grades 3 to 5, immune compromise, signs of shock, and recurrent UTI. In these patient groups, more intensive therapy should be considered.

Oral medications that have been studied and found to be effective include cefixime, ceftibuten, and amoxicillin-clavulanic acid.[80] Resistance of more than 30% of *E. coli* to amoxicillin-clavulanate makes it a poor choice for empiric therapy.

Presumed lower urinary tract infections in children can be treated effectively with relatively short courses of an oral antibiotic. Whereas 10 days of therapy are more likely to eradicate bacteriuria than 1 day of therapy, no differences in cure rates have been observed in simple cases in older children for those treated for 2 to 4 days compared with 7 to 10 days.[81]

Antibiotic Resistance and Selection of Antimicrobial Agents

For children with UTI requiring parental antibiotic treatment, third-generation cephalosporins, such as ceftriaxone, provide broad-spectrum coverage and effectively treat most Enterobacteriaceae but are not active against enterococci.[71]

Aminoglycosides provide excellent coverage against gram-negative pathogens.[82] Once-daily dosing of aminoglycosides is safe and effective and facilitates outpatient treatment. To limit bacterial resistance and alterations of the microbiome, one should consider the drug with the narrowest spectrum and shortest course that will be efficacious.

Nitrofurantoin is active against most uropathogens. Although it has low serum concentration, it is concentrated in the urine and therefore works well for the treatment of cystitis, except for those with poor renal concentrating ability. Because of low serum concentrations, it is a poor choice for the treatment of pyelonephritis or systemic infection.[83] Despite many years of use, bacterial resistance to nitrofurantoin is low.

Fluoroquinolones are commonly used for the treatment of UTI in adults, but experience in children is limited. Ciprofloxacin and levofloxacin are approved for the treatment of children with complicated UTI and pyelonephritis, are orally bioavailable, and have activity against *Pseudomonas aeruginosa*.[5] Oxytetracycline is an alternative agent that can be considered for the oral therapy of UTI caused by *Pseudomonas* spp.[84]

Many uropathogens now are resistant to commonly used antibiotics, including ampicillin and trimethoprim-sulfamethoxazole, and, in some institutions, they are also resistant to quinolones.[78,85–87] Risk factors for resistance include recent hospitalization, recent receipt of antibiotics, urethral catheter, and a complicating urologic condition, such as urologic anatomic malformation and renal segments with poor function.[88,89]

Ambulatory medical settings may provide rates of bacterial resistance based on practitioner antibiotic usage; patients from ambulatory urology clinics have been found to have higher rates of *E. coli* resistance compared with other general and hospital medical settings within the same institution.[86] These factors portend potential antimicrobial resistance and should prompt consideration of alternative drugs.[90]

Antibiotic Prophylaxis

The daily administration of antibiotics to prevent recurrent UTI in children would be useful if future morbidities and renal damage could be avoided without undue risk.[91,92] A Cochrane systematic review demonstrated only small decreases in recurrent symptomatic UTI.[93]

Two large placebo-controlled trials, PREVENT (Prevention of Recurrent Urinary Tract Infection in Children with Vesicoureteric Reflux and Normal Renal Tracts)[94] and RIVUR (Randomized Intervention for Children with Vesicoureteral Reflux),[95] concluded that long-term low-dose trimethoprim-sulfamethoxazole (TMP-SMX) decreased recurrent symptomatic UTIs. PREVENT enrolled children from birth to 18 years who had at least one symptomatic UTI with or without VUR. Based on their results, the PREVENT authors concluded that antibiotic prophylaxis for children who had a single symptomatic UTI was not recommended.

RIVUR included children from 2 to 71 months of age with grades 1 to 4 VUR. Children received randomized double-blind therapy (TMP-SMX versus placebo) and were followed for 2 years. Investigators found recurrent UTI in 39 of 302 children receiving antimicrobial prophylaxis and 72 of 305 children on placebo (relative risk, 0.55). Prophylaxis was more effective in those with index febrile UTI and bladder and bowel dysfunction. There was no significant difference in renal scarring outcome.

Antibiotics used for UTI prophylaxis should attain high urinary concentrations, to maximally inhibit uropathogens, and low serum concentrations, to minimally affect other flora. Additionally, the agent should be inexpensive, easily administered, and well tolerated. Parental compliance with prophylaxis has been estimated to be 40% to 69%.[96] Prophylaxis decreases the frequency of recurrent UTI but the effect on eventual renal function is not clear.

Complications and Sequelae

Children at increased risk for renal scarring include those with infections associated with high temperatures (>39° C), those who have abnormal ultrasonography, and those with infections caused by organisms other than *E. coli*.[97]

Recurrent UTIs in children who have renal scars is more likely to be associated with the development of hypertension and progressive renal dysfunction. Data from a large cohort of children with more than 11 mean years of follow-up noted that 15% had unilateral renal parenchymal defects, primarily occurring among those with reflux. Blood pressure and renal function were normal in all children.[42] However, these findings differ from an older investigation by Smellie and associates, who examined long-term consequences of UTI and found hypertension and abnormal renal function in 8%; these latter children had frequent *recurrent* UTI.[98] This study also emphasized that those with normal kidneys at baseline rarely developed new scars. Population-based data from developed countries support that childhood UTI rarely is associated with long-term renal function deterioration.[99]

Craig and others reported that end-stage renal failure attributable to UTI is low (about 2%–3%) in developed countries. In contrast, reflux nephropathy is a significant cause of end-stage renal disease (about 7%–17%) in under resourced countries.[100] There are no data associating childhood or recurrent UTI with renal failure in children with normal urologic anatomy and normal kidneys on imaging.[101]

Focal Bacterial Nephritis (Acute Lobar Nephronia) and Perinephric Abscess

Severe pyelonephritis may evolve into an inflammatory mass without drainable pus known as *acute focal bacterial nephritis* (AFBN). This is an intermediate stage between pyelonephritis and intrarenal abscess. Similar to renal abscess, AFBN results from hematogenous or ascending infection and is more commonly observed in patients with genitourinary malformations such as VUR. AFBN can be distinguished from renal abscess by imaging that shows a lobar or wedge-shaped distribution of hypodense or hyperdense lesions without a clear abscess wall.[102,103]

Although differentiating between AFBN and abscess was important when open renal drainage was the main treatment for abscesses, this differentiation is difficult, and current management is based on other factors. Improvements in imaging of the genitourinary tract and use of broad-spectrum antimicrobial agents have changed the evaluation and natural history of perinephric and renal abscesses.[104] The high mortality rates associated with perinephric abscess associated with diagnostic delays now are rare because of widespread availability of computed tomography (CT) and magnetic resonance imaging (MRI).

Although childhood perinephric and renal abscesses were common 50 years ago,[105] they now are infrequent in developed countries. Renal abscesses arise from either hematogenous seeding from extragenital sites of infection or renal extension of ascending urinary infections. Although hematogenous seeding of *S. aureus* from skin and soft tissue sites was a common cause of past renal abscesses in children and adults, any resulting renal abscess is uncommon when skin infections are treated promptly.

Currently, gram-negative organisms (e.g., *E. coli*) from retrograde extension of ascending bacteriuria are the most common cause of renal and perirenal abscesses.[106–109] Anaerobic bacteria can cause perinephric or renal abscesses in association with previous abdominal surgery, renal transplantation, malignancy, and oral or dental infection[110]; other fastidious organisms,, such as *Ureaplasma* spp., have been reported to cause abscesses in immunocompromised patients.[111]

Children with renal and perirenal abscesses have symptoms of severe pyelonephritis, including fever, flank pain, leukocytosis, and occasionally sepsis. Because abscesses have a fluid component, perinephric collections usually appear lucent (hypoechoic) on ultrasonography, and guided diagnostic aspiration for culture usually carries minimal morbidity. Although most children with renal abscess have a urinary culture growing gram-negative organisms (commonly *E. coli*), *S. aureus* can be causative. A negative urinary culture does not eliminate the possibility of renal abscess.[112]

When UTI does not respond to appropriate management, advanced imaging is required to evaluate for a more complicated infection. CT and MRI can assess abscess extent and can show perirenal fluid or gas, renal distortion, and involvement of the retroperitoneum.[113–115]

Retrospective reviews conclude that modern imaging assessment may permit the management of most renal abscesses with antibiotics alone.[116,117] When there is poor response or obstructive uropathy, however, percutaneous or surgical drainage combined with appropriate antibiotic therapy may be required.[116,118]

Pyonephrosis

Pyonephrosis is characterized by accumulation of purulent debris and sediment in the renal pelvis and urinary collecting system. Children with pyonephrosis have symptoms similar to acute pyelonephritis but have additional structural obstructive hydronephrosis. This situation usually implies bacterial infection and obstruction (pus under elevated pressure), so rapid diagnosis and treatment are essential to avoid extravasation, sepsis, and parenchymal loss. Most partially obstructed kidneys with pyonephrosis are either nonfunctioning or poorly functioning.

Renal ultrasonography may show shifting fluid-debris levels with changes in the patient's position, persistent echoes from the lower collecting system, air in the collecting system, or weak echoes secondary to pus in a dilated poorly transonic renal collecting system.[119] When pyonephrosis and obstruction are present together, antimicrobial agent penetration and efficacy can be impaired because of edema and poor blood flow into the area. The treatment for pyonephrosis is combination of optimal antimicrobial therapy and prompt drainage to deflate the infected pelvis by either retrograde catheterization or nephrostomy placement.

Xanthogranulomatous Pyelonephritis

Under certain circumstances, chronic bacterial pyelonephritis and obstruction are associated with a distinct severe inflammatory process known as *xanthogranulomatous pyelonephritis* (XGP). Although XGP occurs in only about 1% of cases and is now diagnosed more frequently with imaging,[120,121] the diagnosis is important because XGP can be confused with childhood renal tumors (Wilms tumor, multilocular cystic nephroma, congenital mesoblastic nephroma, malignant rhabdoid, and clear cell sarcoma). Although the cause is unknown, the process usually is associated with both infection and obstruction.

XGP is less common in children than adults. Symptoms include flank pain, fever, chills, and chronic bacteriuria. Vague symptoms of malaise, malnutrition, weight loss, and failure to thrive often are present. Lower tract irritative symptoms are uncommon. Most patients with XGP have had symptoms for longer than a month.[121,122]

The most common infecting organisms are *Proteus* spp. and *E. coli*. Urine contains white blood cells and protein; anemia, reflecting the chronic nature of the disease, is common. The process usually is unilateral and can involve pericalyceal tissue alone (focal) or the kidney diffusely (diffuse), with extension into the perinephric fat, and even the retroperitoneum with encasement of the great vessels.[120,123]

In children, XGP often affects those younger than 8 years and is of the focal rather than diffuse form (17%–25% of cases). Boys are affected more frequently, and contralateral renal hypertrophy can be present.[122,124] Although obstructive calculi occur in both children and adults, obstruction may involve congenital genitourinary abnormalities in children.

Radiologic findings include renal calculi in 38% to 70% of patients; nonfunctioning renal segments in 27% to 80%, and a mass in as many as 62%.[120,125] Ultrasonography can show an enlarged kidney with hypoechoic areas that represent areas of necrosis and pus-filled calyces. CT with contrast shows areas of low attenuation that do not enhance and may show extension of the mass into the perinephric fat. Grossly the kidney shows yellow-white nodules and evidence of pyonephrosis. The histologic diagnostic feature is the xanthoma cell—a foamy lipid-laden histiocyte that can simulate the renal carcinoma cell. These xanthoma cells also can appear in other tissues and conditions of chronic inflammation and obstruction such as obstructive pneumonia.

Complex Urinary Tract Infections: Imaging Evaluation

Computed Tomography and Magnetic Resonance Imaging

More complicated renal abnormalities and UTIs with a spectrum of pyonephrosis, abscess, calculi, and infection require more extensive three-dimensional imaging. Although seldom used to evaluate acute renal inflammatory processes unless unusual or complicating anatomic configurations are seen on ultrasonography, CT or MRI can reveal detailed and sensitive signs of acute renal inflammation. These modalities often are able to differentiate and distinguish between inflammatory, neoplastic, and other renal masses seen using other imaging modalities.

Acute inflammatory changes of the kidney can be described as (1) unilateral or bilateral, (2) focal or diffuse, (3) with or without focal swelling, and (4) with or without renal enlargement. Other features that can be seen during the various phases are cortical hypoattenuation, wedge defects, poor corticomedullary differentiation during the nephrogram phases, and linear bands of alternating hyperattenuation and hypoattenuation parallel to the tubules and collecting ducts, creating a striated effect during the excretory phase. Scans delayed 3 hours or longer may help to differentiate renal abscess from hypofunctioning parenchyma in severe pyelonephritis.[126] It is notable that acute focal pyelonephritis (or lobar nephronia) has been misinterpreted as renal abscess by CT because of an appearance of acutely decreased central lobar perfusion, and at times guided needle aspiration may be needed to clarify the clinical situation.

Risks of Ionizing Radiation and Responsible Imaging

There is evidence for a linear increase in excess lifetime solid cancer and leukemia risk for radiation exposure from 1 to 150 mSv and highest for those exposed as children.[127,128] Concern specifically relates to childhood radiation exposure because (1) childhood radiation has a longer time span during which effects may become manifest, (2) developing cells have greater potential for developing direct damage from radiation exposure, and (3) medical and diagnostic procedure radiation appropriate for adults is often unadjusted for children, causing disproportionately high radiation exposure.

CT scan with and without contrast in a child using pediatric settings will give an effective radiation dose of 6 to 10 mSv, almost 3.5 years of equivalent background radiation,[129] and the estimated lifetime cancer mortality rate from an abdominal pediatric CT in a 1-year old is 0.18%.[130]

Radiation exposure risks to young developing infants and children must be considered carefully as practitioners consider individualized evaluation of UTI. Radiation risk to children may be limited in two ways: (1) decreased exposure through technologic imaging advances and (2) practitioner decision analysis in which imaging studies with risk for ionizing radiation exposure are selected only when information obtained likely would alter management. Although there are few data indicating that MRI is better than CT, there are data indicating that, except when renal calculi are suspected, MRI is as good as CT and confers advantages in pediatric urinary tract imaging.[114,115,131]

Special Considerations

Urinary Tract Infection and Circumcision

The 2012 recommendations of the AAP state that "health benefits of newborn male circumcision out-weigh the risks, and the benefits of newborn male circumcision justify access to this procedure for those families who choose it."[132] The AAP literature review concludes that circumcision may reduce risk for UTI and sexually transmitted infections such as HIV, herpes simplex virus type 2, human papillomavirus, and invasive penile cancer. The AAP recommends that that clinicians give educational material to parents and that parents determine what is in the best interest of their child.

Covert or Asymptomatic Bacteriuria

Covert and asymptomatic bacteriuria usually are defined as genitourinary tract colonization by bacteria that do not activate a local or systemic response—therefore causing few symptoms. Bacteriuria ("UTI") is found on incidental testing or screening. Whether bacteriuria truly is asymptomatic sometimes is not clear because children may exhibit nocturnal or diurnal enuresis, urinary urgency, and squatting. At least 20% of children with asymptomatic bacteriuria have a history of UTI, and only 50% have normal imaging of the genitourinary tract; this led some experts previously to consider bacteruria on par with symptomatic UTI.[10,133]

Most children with asymptomatic bacteriuria clear the bacteria without intervention.[134,135] A study from Sweden found that the median time to clearance was 2 months in girls and 1.5 months in boys.[136]

Although evidence for and against treatment of covert or asymptomatic bacteriuria is sparse and inconclusive, reviews and Cochrane analysis of available studies do not demonstrate that antibiotic treatment confers benefit.[137,138] Children with asymptomatic bacteriuria and a known normal urinary tract need no follow-up UTI screening or imaging. Antibiotic treatment should be avoided, unless surgery involving the urinary tract is planned or the patient becomes pregnant.[71,139]

Recurrent Urinary Tract Infection and a

Normal Genitourinary System

In evaluating children for recurrent infection, it is important to differentiate between bacterial reinfection and bacterial persistence. The former involves reinfection with the same or new organism after the initial UTI was cleared[4]; the latter indicates that the original infection was never properly cleared because an infected nidus persists (e.g., struvite infection stone, bacterial prostatitis, urethral diverticulum).[140]

About 20% of those who develop a UTI have a recurrent infection.[141] For a girl who has a UTI, the risk for developing another UTI within 1 year is directly proportional to the number of previous infections, regardless of the severity of prior infections. In a child with frequently recurrent UTI, defined as two or more infections in a 6-month period, prophylactic antibiotics may provide benefit.[4,142] After the antibiotics are stopped, however, the child typically reverts to repeated UTIs; sometimes recurrent UTI can be related to bowel and bladder dysfunction, and management of voiding habits and constipation may decrease UTI frequency.[143]

Healthcare-Associated Urinary Tract Infection

The urinary tract is the most common site of nosocomial infection, and prevention of catheter associated urinary tract infections is a critical measure in reducing healthcare-associated morbidity and improving healthcare quality.[21,144] There is no evidence to support the use of antimicrobial prophylaxis before routine urethral catheterization.

Positive culture of a bladder urinary specimen from an indwelling urethral catheter in place for longer than 3 to 4 days should be considered as a sign of infection.[145,146] Because the catheter surface becomes covered with a biofilm, persistent bacteriuria is inevitable with long-term catheter drainage, and these hospital-acquired UTIs often are resistant to routine antimicrobial treatment.[147] There is no evidence that cultures of urethral catheter tips correlate with routine urinary cultures; thus there is no need to culture the catheter tip.[148] Infectious complications associated with urethral catheterization include acute epididymo-orchitis, pyelonephritis, periurethral abscess, and infectious calculi such as struvite stones. Replacement or obstruction of the urinary catheter can cause transient or acute bacteremia or sepsis, especially if bacteriuria is present. To decrease these complications, culture and treatment of bacteriuria before catheter removal or presumptive treatment at the time of removal is prudent.

Cardiovascular Abnormalities or Prophylaxis for Genitourinary Manipulation

Most often, children who have indwelling catheters, nephrostomy tubes, other foreign bodies within the urinary tract, or open drainage systems such as ileal conduits or catheterizable stomas are at high risk for bacteriuria; presumptive or definitive treatment should be given before urinary tract procedures.

In the past, antimicrobial prophylaxis was recommended before catheter placement or urinary tract manipulation for children with cardiac abnormalities; however, the American Heart Association no longer recommends antibiotic prophylaxis "solely to prevent infective endocarditis" for genitourinary tract procedures.[149] Antimicrobial prophylaxis against enterococcal infective endocarditis is appropriate in those with heart defects at highest risk for infective endocarditis (prosthetic cardiac valves, previous infective endocarditis, congenital heart disease—unrepaired cyanotic heart disease, for 6 months after heart defect repair with prosthetic materials, heart defects with residual defects near the prosthesis, and cardiac transplantation).[149,150] For patients who undergo elective urinary tract surgery, UTI should be treated before the procedure. For those in whom the procedure is not elective, antimicrobial prophylaxis with a drug active against enterococcus should be considered.

A survey of US pediatric cardiologists noted that many continue to recommend preprocedure antimicrobial prophylaxis "even when not recommended to do so per the 2007 AHA guidelines."[151] Using a decision-based cost-effectiveness analysis of retrospective data, others calculate that infective endocarditis prophylaxis before urinary catheterization of children (0–24 months of age) evaluated in emergency departments for fever is not cost-effective.[152] A child with an indwelling urinary collecting device should be considered to have bacteriuria.

Fungal Urinary Tract Infection

Fungal UTI has become an increasingly prevalent healthcare-associated infection, particularly in patients who recently received antimicrobial agents or recently were catheterized.[153,154] Predisposing factors include recent antimicrobial therapy, prematurity, intravenous or umbilical artery catheterization, parenteral nutrition, and immunocompromised state.[155] Differentiating between fungal contamination, colonization, and infection is important but often is challenging.[156]

A carefully collected second specimen frequently can verify contamination. Symptoms and signs may be inadequate to distinguish between colonization and infection. Although children can have bladder irritative symptoms as found with bacterial UTI, young children and those with other impairments may be unable to appreciate or communicate symptoms. In these children, further imaging to examine for fungal upper tract infection or obstructing fungus balls may be needed.

Prophylactic administration of oral nystatin or fluconazole in very low birth weight infants (<1000−1500 g) is useful in the prevention of fungal colonization and invasive infection.[157,158] *Candida albicans* is the most commonly isolated species and is responsible for half of all infections. *Candida glabrata* is the next most common isolate. It is important to recognize this because *C. glabrata* frequently is resistant to fluconazole.[154]

Renal ultrasonography can be useful in evaluating the extent of fungal infection. Fungal bezoars can form in the renal pelvis, causing obstruction and potentially anuria in infants with bilateral involvement.[155,159–161] Urinary alkalization or oral and intravenous antifungal chemotherapy may "dissolve" some of these fungal balls. In small infants, fungal mass can cause obstruction; percutaneous or open removal of the bezoars may be required. Therapy can then proceed with local irrigation and systemic antifungal treatment to clear the infection.

The decision to treat asymptomatic funguria in the setting of an indwelling urethral catheter is controversial; the progression to disseminated candidemia is uncommon.[154] Therefore treatment is recommended when cultures repeatedly yield more than 10,000–15,000 CFUs/mL.[162] Treatment measures include (1) stopping all unnecessary antimicrobial agents, (2) changing or removing the indwelling catheter, (3) urinary alkalization, and for persistent colonization (4) irrigation of the bladder with amphotericin B, administration of oral fluconazole, or both. Recurrence of fungal colonization is common.[163,164]

Key Points

Diagnosis and Management of Urinary Tract Infections

Epidemiology

- Girls are hospitalized 2.5 times more often than boys.
- In the first year of life, boys have more UTIs than girls; in uncircumcised boys, risk for UTI is 10 times more than in circumcised.
- Risk factors: age, race/ethnicity, genetics, periurethral colonization, immune status, sexual activity, obesity, genitourinary abnormalities, voiding dysfunction, constipation

Imaging Evaluation

- Perform ultrasonography with selective voiding cystourethrography
- Consider using imaging evaluations that do not use ionizing radiation

Treatment and Management

- Children without major genitourinary abnormalities older than 1 month who are otherwise healthy may be treated with oral antibiotics for 10–14 days.
- Bacterial antimicrobial resistance is affected by regional and local factors and antibiotic exposures.

- Low-dose antimicrobial prophylaxis decreases recurrent UTI but increases antimicrobial resistance.

- Focus should be to identify UTI risk factors that may be modified to prevent future infections.

UTI, urinary tract infection.

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49

Sexually Transmitted Infection Syndromes

Margaret J. Blythe

Recent surveys of high school students indicate that almost one half of them are sexually active, including almost two thirds of senior students. Reported percentages for males and females do not vary.[1] Sexually transmitted infections (STIs) are common and have the potential for significant health and economic consequences for youth in the United States. The US Centers for Disease Control and Prevention (CDC) estimate 19.7 million new sexually transmitted infections occurred in 2013, with one half occurring among people between the ages of 15 and 24 years and an almost equal distribution between boys (51%) and girls (49%).[2]

Confidentiality is extremely important for adolescents and young adults seeking reproductive healthcare. Providers must feel comfortable taking a comprehensive history and discussing behaviors that place teens and young adults at risk for STIs. Confidential testing, appropriate treatment, and counseling on partner notification are important parts of care.[3]

Genitourinary Syndromes

STI manifestations in adolescents and young adults can be divided into six clinical syndromes: (1) discharge and dysuria, (2) anal discharge and proctitis, (3) genital ulcer and lymphadenopathy, (4) pelvic or scrotal pain, (5) pharyngeal infection, and (6) dermatologic syndromes.

Discharge and Dysuria Syndrome

Presentation

Male urethritis is characterized by acute or chronic inflammation defined microscopically by visualization of leukocytes. Signs of urethritis may be seen with or without symptoms and include mucoid or purulent urethral discharge, dysuria, urethral pruritus, and meatal erythema. Female urethritis due to STIs may be asymptomatic but manifests clinically as dysuria, which is suspected when white blood cells (WBCs) are documented in urine with a negative urine culture (i.e., sterile pyuria). Urethral syndrome in women (i.e., dysuria, frequency, and sterile pyuria) can accompany cervicovaginal infection due to meatal irritation or urethral infection. Clinical features of vaginal discharge include altered color, odor, quantity, and accompanying pruritus, but none is a reliable predictor of the cause of genital discharge and dysuria. Vaginal discharge and dysuria may be accompanied by abnormal vaginal bleeding, dyspareunia, and mild pelvic pain. Sterile pyuria and vaginal discharge suggest cervicitis, which may be accompanied by a normal-appearing cervix on examination with a purulent or mucopurulent discharge at the cervical os or sustained endocervical bleeding referred to as *cervical friability*.[3]

Etiologic Agents

Genital discharge or dysuria syndrome usually is caused by one of four primary infectious agents: *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, or *Mycoplasma genitalium* (Table 49.1). Most published studies include populations from sexually transmitted disease clinics where Gram stain is used for diagnostic evaluations of male patients (Table 49.2). Demographics, region of the country, sexual practices, and diagnostic testing may suggest or confirm the cause. For example, urethritis can be acquired by fellatio, and it sometimes results from transmitted chlamydial or gonorrheal infections or pathogens found in the pharynx (e.g., adenovirus).[4,5]

TABLE 49.1

Sexually Transmitted Infection Syndromes in Adolescents and Young Adults

STI Syndrome	Primary Organisms	Other Causal Organisms
GENITOURINARY SYNDROMES		
Discharge and dysuria	*Chlamydia trachomatis* *Neisseria gonorrhoeae* *Trichomonas vaginalis* *Mycoplasma genitalium*	*Ureaplasma urealyticum* *Mycoplasma hominis* Herpes simplex virus 1, 2
Proctitis, proctocolitis, and enteritis	*Chlamydia trachomatis* *Neisseria gonorrhoeae* *Treponema pallidum* Herpes simplex virus 1, 2	*Campylobacter* species *Entamoeba histolytica* *Giardia lamblia* *Salmonella* species *Shigella* species
Genital ulcer and lymphadenopathy	Herpes simplex virus 1, 2 *Treponema pallidum*	*Calymmatobacterium granulomatis* *Haemophilus ducreyi* *Chlamydia trachomatis* lymphogranuloma venereum
Pelvic pain (e.g., pelvic inflammatory disease)	*Chlamydia trachomatis* *Neisseria gonorrhoeae* *Mycoplasma genitalium*	*Mycoplasma hominis* Mixed aerobic and anaerobic bacteria
Scrotal pain (e.g., epididymitis)	*Chlamydia trachomatis* *Neisseria gonorrhoeae*	*Mycoplasma genitalium* *Ureaplasma urealyticum*
PHARYNGEAL SYNDROMES		
Infections of pharyngeal mucosa	*Neisseria gonorrhoeae* Herpes simplex virus 1, 2	*Treponema pallidum* Human papillomaviruses
DERMATOLOGIC SYNDROMES		
Genital warts	Human papillomaviruses	—
Molluscum contagiosum	Molluscum contagiosum virus	—
Rash, alopecia	*Treponema pallidum*	—
Arthritis and dermatitis syndrome	*Neisseria gonorrhoeae* *Chlamydia trachomatis*	—
Jaundice, hepatitis	Hepatitis A, B, C viruses	—
Scabies	*Sarcoptes scabiei*	—
Pubic lice	*Phthirus pubis*	—

TABLE 49.2

Tests Used to Determine the Cause of Sexually Transmitted Infection Syndromes in Adolescents and Young Adults

STI Syndrome	Office Tests Available	Preferred Laboratory Tests
GENITOURINARY SYNDROMES		
Discharge and dysuria	Females: microscopic wet prep vaginal secretions, pH paper, whiff test, KOH; LET; rapid tests for GC, CT, TV, BV, and	Females, males: NAATs for GC, CT, and TV; HIV test

	HIV; UPT Males: Gram stain smear of urethral discharge looking for ≥5 WBCs per oil immersion field and intracellular gram-negative diplococci; LET; microscopic examination of first-void spun urine sediment with ≥10 WBCs per high-power field; rapid tests for GC, CT, and HIV	
Proctitis, proctocolitis, and enteritis	Females, males: Gram stain smear of anorectal exudate; rapid test for HIV Females: UPT	NAATs for GC and CT; see HSV and syphilis under genital ulcer; cultures for other gram-negative pathogens and ameba; HIV test
Genital ulcer and lymphadenopathy	Females, males: darkfield examination for syphilis; rapid test for HIV Females: UPT	Cultures for HSV-1 and HSV-2 or PCR for HSV; serology for type-specific glycoprotein G to discern HSV-1 or HSV-2 RPR or VDRL and confirmatory tests for syphilis if positive or treponemal EIA or CIA chemiluminescence immunoassays and confirmatory nontreponemal test (RPR or VDRL) if positive NAATs for *C. trachomatis;* PCR genotyping or serology for LGV (complement fixation or microimmunofluorescence) Gram stain and culture for chancroid; staining for Donovan bodies on tissue biopsy; HIV test
Pelvic pain (e.g., pelvic inflammatory disease)	Microscopic wet prep vaginal secretions, pH paper, whiff test, KOH; LET; rapid tests for GC, CT, TV, BV, and HIV; UPT	NAATs for GC, CT, and TV; HIV test
Scrotal pain (e.g., epididymitis)	Gram stain smear of urethral discharge looking for ≥5 WBCs per oil immersion field and intracellular gram-negative diplococci; LET; microscopic examination of first-void spun urine sediment with ≥10 WBCs per high-power field on first-void urine; rapid tests for GC, CT, and HIV	NAATs for GC and CT; HIV test
PHARYNGEAL SYNDROMES		
Infections of pharyngeal mucosa	Rapid strep test	NAATs or culture for GC and CT; culture or PCR for HSV-1 and HSV-2, serology for type-specific glycoprotein G to discern HSV-1 and HSV-2; RPR or VDRL and confirmatory tests if positive; HIV test
DERMATOLOGIC SYNDROMES		
Genital warts	Characteristic lesions	
Molluscum contagiosum	Characteristic lesions	Wright or Giemsa staining for intracytoplasmic inclusions
Rash, alopecia	—	RPR or VDRL and confirmatory tests if positive

Arthritis, dermatitis	Males: Gram stain smear urethral discharge looking for ≥5 WBCs per oil immersion field and intracellular gram-negative diplococci; LET Females: Microscopic wet prep vaginal secretions for WBCs; LET; rapid tests for GC, CT; and UPT	Females, males: NAATs or culture for GC and CT from rectum or pharynx Females: NAATs of vaginal swab Males: NAATs of first-void urine
Jaundice, hepatitis	—	Appropriate laboratory tests for hepatitis
Scabies	Microscopic examination of skin and hair	—
Pubic lice	Identification of eggs, nymphs, and lice with naked eye or microscopy	—

BV, Bacterial vaginosis; CIA, chemiluminescence immunoassay; CT, *Chlamydia trachomatis*; EIA, enzyme immunoassay; GC, *Neisseria gonorrhoeae*; HIV, human immunodeficiency virus; HSV-1, herpes simplex type 1; HSV-2, herpes simplex type 2; KOH, potassium hydroxide; LET, leukocyte esterase test of urine; LGV, lymphogranuloma venereum; NAATs, nucleic acid amplification tests; RPR, rapid plasma reagin; STI, Sexually Transmitted Infection; TV, *Trichomonas vaginalis*; UPT, urine pregnancy test, VDRL, Venereal Disease Research Laboratory; WBCs, white blood cells.

Where US testing is available for male patents, *M. genitalium* has been reported as the cause of 15% to 25% of symptomatic nongonoccocal urethritis (NGU) cases. Presenting symptoms and physical findings for the different pathogens are similar. For women, the role *M. genitalium* plays in urethral syndrome compared with cervicitis is less clear.[6,7]

Management

Point-of-care office tests should be performed to determine the cause and guide therapy to prevent complications, reinfection, and transmission (see Table 49.2).[3,8,9] Nucleic acid amplification tests (NAATs) are preferred for the detection of *C. trachomatis* and *N. gonorrhoeae*; optimal specimens are vaginal swabs from women and first-catch urine from men.[3,9] If an infection is identified, appropriate treatment should be given and sex partners referred for evaluation and treatment.

Empiric treatment for chlamydial and gonorrheal infections is recommended for symptomatic men at high risk for infection or who are unlikely to return for follow-up.

The prevalence of *T. vaginalis* is 2% to 3% among adolescents, with higher prevalences documented in selected populations.[10–12] The most common method of detection in female patients is microscopic evaluation of a wet preparation of vaginal secretions, which has a sensitivity in at-risk populations of 50% to 65%.[12,13] Although commercial reference laboratories have validated NAAT for *T. vaginalis*, none of the assays is cleared by the US Food and Drug Administration (FDA).[9,14] In-office tests are FDA cleared to detect *T. vaginalis* in vaginal secretions but are not approved for use on urine samples.[15,16] There is no FDA-approved test available for *M. genitalium*.[6]

Anal Discharge, Proctitis, Proctocolitis, and Enteritis Syndrome

Presentation

Sexually transmitted gastrointestinal syndromes include proctitis, proctocolitis, and enteritis. Different organisms should be considered based on sexual behaviors, history of symptoms, exposure to similar illnesses, and physical examination findings (see Table 49.1). Predominantly associated with receptive anal intercourse, proctitis is inflammation of the rectum resulting in rectal discharge, anorectal pain, and tenesmus. Rectal infections without a history of anal sex can occur in females but not males.[3]

Etiologic Agents

The most common sexually transmitted pathogens reported include *N. gonorrhoeae, C. trachomatis* (including serovars L1, L2, and L3), *Treponema pallidum*, and herpes simplex virus (HSV) (see Table 49.1).[17,18] In one large, multicenter, case-control study, symptomatic proctitis due to *C. trachomatis* lymphogranuloma venereum (LGV) serovars was more likely associated with tenesmus, constipation, anal discharge, and weight loss compared with those with other causes.[19]

Depending on the pathogen, proctocolitis extending up to 12 cm above the anus can be acquired through receptive anal intercourse or by oral-anal contact. Symptoms are similar to proctitis but include diarrhea or abdominal cramps. LGV proctocolitis can lead to chronic colorectal fistulas and strictures with secondary bacterial infections.[3] Other opportunistic agents as cytomegalovirus (CMV) can be involved in immunosuppressed patients infected with human immunodeficiency virus (HIV). Enteritis usually results in diarrhea and abdominal cramping without signs of proctitis or proctocolitis and occurs among persons whose sexual practices include oral-anal contact. In otherwise healthy persons, *Giardia lamblia* is most frequently implicated, whereas those with HIV may have a variety of pathogens that may not be sexually transmitted.[3]

Management

Evaluation should include an anoscopic examination with th anorectal exudate evaluated by Gram stain for WBCs and intracellular gram-negative diplococci. All persons should be evaluated for gonococcus, chlamydia, syphilis, and HSV infection (see Table 49.2). If the chlamydia test result is positive for a rectal swab, testing for LGV should be performed. NAAT is more sensitive than culture and is the preferred method for detection of *N. gonorrhoeae* and *C. trachomatis* anorectal infections.[9]

Empiric treatment should be initiated based on clinical presentation. It should then be adjusted according to diagnostic test results.

Genital Ulcer and Lymphadenopathy Syndrome

Presentation and Etiologic Agents

In the United States, most young, sexually active patients with genital, anal, or perianal ulcers have genital herpes or syphilis. Less common infectious causes of genital, anal, or perianal ulcers include chancroid, LGV, and donovanosis (see Table 49.1).

Herpes Simplex Virus.

Approximately 776,000 new cases of genital herpes are diagnosed annually, with 45% of cases occurring in patients 15 to 24 years of age.[2] Genital herpes may be caused by type 1 or 2 HSV(HSV-1 or HSV-2). Based on data from the National Health and Nutrition Examination Survey (NHANES), HSV-1–positive serologic results for children between the ages of 14 and 19 years decreased from 39% during the 1999–2004 period to 30% during 2005–2010 period. HSV-2–positive serologic results decreased from 1.6% to 1.2% over the same timeframe. The declines in childhood acquisition of HSV-1 along with the increase in oral-genital sexual behaviors that occur during adolescence make teenagers more vulnerable to acquisition of genital HSV-1 infections.[20]

Initial symptoms can be limited to pain, burning, or pruritus in the area where lesions eventually appear. Development of single vesicle or small groups of vesicles typically follows within a few hours. Vesicles often are quite painful, and they progress to ulcers over a period of a few days. Tender, usually bilateral, inguinal lymphadenopathy can appear at this time.

The length of viral shedding and time required to heal depend on whether the infection is primary (i.e., seronegative for HSV-1 and HSV-2 antibodies), nonprimary (i.e., HSV-2 infection with pre-existing HSV-1 antibodies), or recurrent (i.e., HSV genital outbreak with the same HSV type). For primary infections, viral shedding continues for 10 to 12 days, and healing requires up to 3 weeks. For recurrent infections, shedding occurs for up to 4 days, with healing in 5 to 7 days.[21]

Syphilis.

Primary syphilis is an important cause of genital ulcer and lymphadenopathy syndrome, although it is relatively uncommon among US adolescents. If untreated, infection facilitates the transmission of HIV acquisition. During 2013 to 2014, the rates of primary and secondary syphilis increased 14.4% for men (from 10.3 to 11.8 cases per 100,000 men) and 22.7% for women (from 0.9 to 1.2 cases per 100,000 women).[22]

The classic primary syphilis lesion is a single, deep, indurated, painless ulcer associated with unilateral, nonfluctuant, ipsilateral inguinal lymphadenopathy. Multiple chancres occur in approximately 25% of cases. These lesions occur about 3 weeks (range, 10 to 90 days) after sexual contact with an infected person. Untreated infections heal spontaneously without treatment in 1 to 6 weeks. Lesions can occur almost anywhere in the genital and rectal area. Perianal and rectal chancres usually are the result of rectal intercourse for men.

Other Causes.

Other causes of genital ulcer disease are rare in the United States, with sporadic outbreaks of LGV occurring primarily among HIV-infected men who have sex with men (MSM). LGV is caused by *C. trachomatis* serovars L1 through L3 after an incubation period of 3 to 12 days.

Most infections begin as an asymptomatic, self-limited ulcer, papule, or erosion at the site of infection and can be associated with nonspecific urethritis. Lesions typically progress to tender, unilateral femoral or inguinal lymphadenopathy. By the time patients seek care, the lesions have often disappeared. Most reported infections in MSM were found in the anorectal canal and not the urogenital area.[23]

A rare cause of genital ulcer and lymphadenopathy syndrome in the United States is *Haemophilus ducreyi* (i.e., chancroid), a gram-negative anaerobic bacillus. Since 2001, the number of US cases has fluctuated, with only 6 cases reported in 2014.[22] The incubation period usually is 4 to 7 days, and there are no prodromal symptoms. Lesions are tender papules surrounded by erythema that become pustular, erode, and then form painful ulcerations over 14 to 48 hours, progressing to painful, suppurative lymphadenopathy.

Granuloma inguinale (i.e., donovanosis), caused by *Klebsiella* (*Calymmatobacterium*) *granulomatis*, can be considered as a possible case of genital ulcerative disease if the infection was acquired in a developing country or by sexual contact with someone traveling from a developing country. Lesions typically are painless, highly vascular, and beefy red, and they gradually progress to ulcerations without regional lymphadenopathy. Subcutaneous nodules also can be associated with infection.[3]

Management

Most persons infected with HSV-2 have not received a diagnosis.[22,24] Subclinical shedding of HSV-2 occurs whether the disease is symptomatic or not, and it accounts for disease transmission.[25] All patients who have genital, anal, or perianal ulcers should be evaluated for genital herpes and syphilis (see Table 49.2). In areas where chancroid is prevalent, a test for *H. ducreyi* should be performed.

Genital and lymph node specimens (i.e., lesion swab or bubo aspirate) also can be tested for *C. trachomatis* by NAAT. Chlamydial NAATs are not FDA cleared for testing these specimens, but some laboratories have validated the assays.[9] Additional serologic tests are used to differentiate LGV from non-LGV *C. trachomatis*. In the absence of specific testing, patients with a clinical syndrome consistent with LGV, including proctocolitis or genital ulcer disease with lymphadenopathy, should be presumptively treated for LGV.[3]

Pelvic or Scrotal Pain Syndrome

Presentation and Etiologic Agents

Pelvic or scrotal pain often is associated with an STI in adolescents and young adults. Pelvic pain is common in female patients with pelvic inflammatory disease (PID). PID comprises a spectrum of inflammatory disorders of the upper female genital tract, including any combination of endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis. PID symptoms can be mild or severe; mild cases often are unrecognized.

The clinical diagnosis of PID is imprecise and relies on historical and clinical indicators. Due to the significance of disease sequelae, empiric therapy for PID should be initiated in sexually active teenagers and young adults experiencing pelvic or lower abdominal pain without an identifiable cause who meet the minimal criteria of cervical motion tenderness, uterine tenderness, or adnexal tenderness on physical examination.[3] Specificity can be increased with evidence of associated lower genital tract infection and inflammation. Additional supportive criteria include a temperature greater than 38.3°C, an elevated erythrocyte sedimentation rate or C-reactive protein level, or laboratory documentation of *N. gonorrhoeae* or *C. trachomatis* infection. Microorganisms that comprise the vaginal flora and *M. genitalium* also have been associated with PID.[7] Empiric therapy should be initiated based on appropriate clinical symptoms even if further supporting evidence is not available.

Scrotal pain in young men at risk for STIs most often represents epididymitis. Presentation usually is insidious, with onset of unilateral scrotal pain, tenderness, and swelling in the affected area. Torsion of the testicle first must be excluded with an imaging evaluation. Patients often have a history of dysuria and urethral discharge. Fever or bilateral involvement is uncommon. Alleviation of pain with gentle manual elevation of the affected side (i.e., Prehn sign) supports the diagnosis.[3]

Management

Infection is indicated by a positive leukocyte esterase result on a first void urine specimen from males or females or at least 10 WBCs per high-power field on a first-void urine sediment from males. A urine pregnancy test, urine dipstick for nitrites, and culture always should be performed for female patient because ectopic pregnancy, urinary tract infection, and pyelonephritis can cause pelvic pain.[3] All women who have acute PID should be screened for HIV infection and tested for *N. gonorrhoeae* and *C. trachomatis* using NAATs, and presumptive treatment should be initiated.

Among young men, gonorrhea and chlamydia are the most commonly identified causes, and NAATs used for male urine are preferred (see Table 49.2). Presumptive treatment for both organisms is indicated. The role of *M. genitalium* in PID and epididymitis is not known, and testing for the organism is not currently available.[3,7]

Pharyngeal Syndromes

Gonococcal and chlamydial infections occur on mucosal surfaces lined with columnar epithelium, including the pharynx, and most infections are asymptomatic. Routine screening of clinics serving MSM detected prevalence rates 1% to 2% for chlamydial infections and 3% to 7% for gonorrhea.[26]

The clinical significance of asymptomatic pharyngeal chlamydia infection is unknown except for sexual transmission.[7] Gonococcal pharyngeal infection may be asymptomatic or manifest as mild infection with pharyngeal erythema. Undetected gonococcal infection of the pharynx can result in sexual transmission to a partner, may rarely result in disseminated gonorrhea infection, and may also contribute to development of gonococcal antimicrobial resistance.[7,26]

HSV-1 and HSV-2 can infect the pharynx and manifest as fever, malaise, myalgia, headache, tender anterior cervical lymphadenopathy, and sore throat with mild ulcerations and diffuse erythema. Oral syphilis can cause painless chancres on the lips, buccal mucosa, tonsils, and pharynx; lesions on the tonsils and pharynx may be painful. Oral and laryngeal papillomas due to human papillomavirus (HPV) can appear after oral-genital contact. Nononcogenic, low-risk HPV types 6 and 11 are the cause of recurrent respiratory papillomatosis, whereas persistent infection with oncogenic HPV type 16 is the strongest risk factor for development of HPV-associated oropharyngeal cancer.[3,27]

Dermatologic Syndromes

HPV subtypes 6 and 11 are responsible for 90% of genital warts.[27] Oncogenic subtypes 16, 18, 31, 33, and 35 can be associated with genital warts but usually are coinfections with types 6 and 11.[3] Common squamous epithelial sites of warts are the glans, prepuce, urethral meatus, shaft of the penis, and perianal area for young men. In young women, warts are found on almost any area of the vulva, perianal area, vagina, and cervix. HPV types 6 and 11 also have been associated with warts in nasal, conjunctival, oral, and laryngeal regions. The quadrivalent and nanovalent HPV vaccines each protect against the HPV types that cause 90% of genital warts (i.e., HPV types 6 and 11).[27]

Molluscum contagiosum can be acquired during sexual contact and confused with genital warts. Lesions typically are asymptomatic, 1 to 2 mm, smooth, skin-colored papules. Infections can be transmitted by any skin-to-skin contact, and lesions on nongenital skin are common. The dermatologic lesions of secondary syphilis occur 2 to 6 weeks after initial infection when the primary lesion not diagnosed and treated. Secondary syphilis typically manifests as a diffuse maculopapular rash of the trunk, arms, and legs with a papulosquamous rash involving the palms and soles. Wart-like growths (i.e., condyloma lata) typically appear in the perianal or posterior vulvar area and can be confused with genital warts.

The arthritis and dermatitis syndrome of disseminated gonococcal infection classically includes dermatitis, tenosynovitis, and migratory polyarthritis. Knee, ankle, wrist, and metacarpophalangeal joints are involved most commonly. Dermatitis usually is a painless, maculopapular rash that typically occurs on the trunk and limbs. Tenosynovitis usually involves the hands and fingers and can be asymmetric. More common in young women than men, disseminated gonococcal infection can result from any *N. gonorrhoeae* infection of the genitalia, anus, or pharynx.

For many adolescents, jaundice associated with acute viral hepatitis can be the result of sexually acquired hepatitis A or B virus, cytomegalovirus, or Epstein-Barr virus. Vaccines make hepatitis A and B preventable diseases. Hepatitis C virus is mainly transmitted parentally (i.e., shared needles or paraphernalia) and not efficiently transmitted sexually except for sexually active men with HIV infection.

Scabies is caused by the mite *Sarcoptes scabiei.* Genital infestations can result from sexual contact and may be more difficult to treat in HIV patients. It manifests with rash and pruritus, and clinical symptoms often occur weeks after the initial exposure.

Infestation with pubic lice (*Phthirus pubis*) manifests with itching and lice or nits on pubic hair. Transmission usually occurs through sexual contact.[3]

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Skin and Mucous Membrane Infections and Inguinal Lymphadenopathy

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In children and adolescents, inguinal lymphadenopathy often occurs as part of generalized lymphadenopathy caused by systemic disease. In contrast, isolated inguinal lymphadenopathy commonly results from localized infections of the groin, buttocks, lower abdominal wall, or lower extremities. Firm or fixed nodes should always raise suspicion for malignancy.

Inguinal Lymphadenopathy With Genital Ulcers

Genital ulcer disease (GUD) frequently manifests as unilateral or bilateral inguinal lymphadenopathy, even when ulcers are not identified clinically. Although GUD can have infectious or noninfectious origins, most cases are caused by sexually transmitted infections (STIs).[1] Prompt diagnosis and treatment of GUD is important to minimize sequelae and decrease transmission of STIs. For example, GUD increases the risk of human immunodeficiency virus (HIV) acquisition and transmission.[2–6] The diagnosis and management of GUD can be challenging because of many possible causes, diverse clinical presentations, and various diagnostic requirements and treatments.[1,7,8]

Etiologic Agents

The most common infectious causes of GUD are herpes simplex viruses (i.e., HSV-2 and HSV-1) and *Treponema pallidum* (i.e., syphilis). Although both are STIs, HSV-1 and HSV-2 also can be spread by nonsexual transmission by caregivers or from autoinoculation.[1,8] Other STIs that cause GUD include *Haemophilus ducreyi* (i.e., chancroid); *Chlamydia trachomatis* serovars L1, L2, and L3 (i.e., lymphogranuloma venereum [LGV]); and *Klebsiella granulomatis* (i.e., donovanosis or granuloma inguinale). With any GUD, regional lymph nodes can become involved and lead to femoral or inguinal adenopathy or ulceration. Infrequently, scabies and pubic lice can cause GUD.

Non-STI infectious GUD causes include varicella-zoster and Epstein-Barr virus infections, tuberculosis, HIV/AIDS, leishmaniasis, secondary bacterial infections, pyoderma, and infections with *Candida* species, *Capnocytophaga* species, *Histoplasma capsulatum, Francisella tularensis*, *Yersinia enterocolitica,* or *Entamoeba histolytica*.[9–13] GUD also can be associated with noninfectious conditions, including fixed drug eruptions, pyoderma gangrenosum, psoriasis, Behçet syndrome, lichen planus, malignancies, aphthae, Lipschütz vulvar ulcers, and Crohn disease.[10,14,15]

Epidemiology of Genital Ulcer Disease Caused by Sexually Transmitted Infections

In the United States, most young, sexually active people with genital, anal, or perianal ulcers have genital herpes or syphilis.[16] Their frequencies vary by geographic area and population. However, genital herpes is more prevalent and is the leading cause of GUD worldwide.[17,18]

HSV infections are lifelong, often asymptomatic, and cause intermittent viral shedding in the genital tract. Most HSV infections are transmitted by people unaware that they are infected.[1] In 2008, an estimated 2.4 million HSV-2 infections occurred among US people between the ages of 15 and 24 years.[19] HSV-1, which typically causes orolabial herpes, is increasingly the cause of genital herpes. The growing numbers of adolescents who lack HSV-1 antibodies at sexual debut likely contributes to the percentage of genital herpes (50%–80%) due to HSV-1 in some populations of young women.[20–22]

Syphilis remains a major US health problem, particularly among men who have sex with men (MSM).[23] Primary and secondary syphilis rates have increased over the past decade, with 75% of all cases occurring among MSM in 2013.[16] Of the 4500 primary and secondary syphilis cases among US persons between the ages of 15 and 24 years in 2013, 86% occurred in males.

The US prevalence of chancroid has declined, with only 10 cases reported in 2013, and it has declined in countries where it was previously endemic.[16,24,25] However, due to the difficulty in detecting *H. ducreyi* in the laboratory, chancroid may be underreported. chancroid infections in the United States are usually associated with sporadic outbreaks.

LGV is endemic in parts of Africa, Southeast Asia, Latin America, and the Caribbean. Since 2003, LGV has also been reported among MSM in the United States, Europe, and Australia. Most men with LGV have had HIV infection associated with high-risk sexual behaviors.[26] Granuloma inguinale occurs rarely in the United States but is endemic in parts of India, the Caribbean, Brazil, Australia, and South Africa.[25]

Clinical Manifestations and Differential Diagnosis

Determining the cause of GUD is challenging based solely on clinical presentation.[1] GUD in children and adolescents requires a thorough history and physical examination to exclude underlying systemic conditions, recent illnesses, or medications and to identify associated factors such as sexual activity or abuse. Frequently, specialized testing is required to establish the cause.

Classic features of GUD are described in Table 50.1. In practice, the causes may be indistinguishable because of coexisting infections, atypical presentations, medication effects, or immunocompromising conditions. Careful examination of the entire genital region, including the perineum and anus, and areas of lymphadenopathy which is facilitated by a good light source and magnifying lens, may improve clinical assessments and guide the choice of diagnostic tests. Anoscopic examinations can identify asymptomatic anorectal manifestations potentially overlooked by the patient and clinician and improve GUD diagnosis and treatment.

TABLE 50.1

Clinical Features of Sexually Transmitted Genital Ulcer Disease Syndromes

Feature	**Herpes Simplex (Herpes)**	***Treponema pallidum* (Syphilis)**	***Haemophilus ducreyi* (Chancroid)**	***Chlamydia trachomatis* (Lymphogranuloma Venereum)**
Estimated incubation period	2–7 days	10–90 days	1–14 days	3–42 days
Site				
Male	Glans, prepuce, penis, anus, rectum	At site of inoculation	At site of inoculation	At site of inoculation (urethral or rectal)
Female	Cervix, vulva, perineum, buttocks, legs, anus, rectum	At site of inoculation	At site of inoculation	At site of inoculation (urethral or rectal)
Typical primary lesion presentation	Vesicle (depends on lesion duration, host immune status)	Papule (ulcerates)	Papule or pustule	Papule, vesicle, vesiculopustular lesion
Number of lesions	Usually multiple; can coalesce, especially in immunocompromised host	Usually single, can be multiple	Often multiple; can coalesce	Usually single
Ulcer appearance	Small, superficial, smooth; with erythematous edge, circular	Superficial, medium size, well demarcated with elevated edge, circular/oval	Deep, small to large; undermined, with ragged edge, irregular shape	Variable depth, small to medium size; elevated edge, round or oval
Induration	None	Firm	Soft	Occasionally firm
Pain	Exquisitely painful	Typically painless	Varies	Varies
Lymphadenopathy characteristic	Firm, tender, often bilateral	Firm, nontender,	Tender, unilateral; can	Large, tender, unilateral; can

		bilateral	suppurate; superinfection	suppurate
Treatment	Acyclovir, valacyclovir, famciclovir, or other acyclovir analogues	Penicillin (dose and duration depend on clinical stage)	Azithromycin, ceftriaxone, ciprofloxacin, or erythromycin	Doxycycline (alternative: erythromycin)

Laboratory Diagnosis and Management

Clinical GUD diagnoses should be confirmed by laboratory testing. A cause is usually identifiable with appropriate specimen collection and testing (Table 50.2), although up to 25% of patients with GUD may not have the cause ascertained.[27] Discussions with laboratory staff can facilitate optimal testing because collection materials, equipment, or appropriate personnel may not available in every laboratory.

TABLE 50.2

Specimen Selection and Laboratory Tests for Diagnosis of Genital Ulcer with Lymphadenopathy Syndrome

Condition	Specimen Type	Test
Herpes	Scraping from ulcer base	Tissue cell culture, PCR
	Serology	HSV-1 and HSV-2 antibodies
Syphilis	Exudate from ulcer	Darkfield microscopy
	Serology	Nontreponemal (with titer quantification); if positive, confirm with treponemal test
Chancroid	Swab from ulcer base or aspirate from bubo	Semiselective media, PCR
Lymphogranuloma venereum	Aspirate from bubo	Tissue culture
	Lesion or swab from ulcer base approved	Direct immunofluorescence, nucleic acid detection for *C. trachomatis*
Donovanosis (granuloma inguinale)	Crush preparation from lesion	Giemsa or Wright stain for Donovan bodies

HSV, herpes simplex virus; PCR, polymerase chain reaction.

All patients with genital, anal, or perianal ulcers should be tested for syphilis and herpes; *H. ducreyi* testing should be performed in settings where chancroid is prevalent.[1] Biopsy can help identify ulcers that do not respond to therapy or are unusual. Because concurrent infections may exist, testing for other STIs is recommended. Thorough risk assessments, counseling, and testing for HIV are important for all people diagnosed with STIs and for those at ongoing risk for infection. Partner counseling and treatment (if indicated) are also recommended as part of comprehensive care. STI diagnoses for children should trigger thorough evaluations for sexual abuse.[1]

The preferred HSV tests for patients with active genital ulcers include viral culture or detection of HSV DNA by polymerase chain reaction (PCR) methods. However, culture sensitivity is low, especially for recurrent lesions, and it declines as lesions heal. PCR is used increasingly because it is more sensitive. Because viral shedding is intermittent, failure to detect HSV by culture or PCR does not indicate an absence of HSV infection. Tzanck preparations are insensitive and nonspecific and should not be used.[1]

Because HSV antibodies develop several weeks after infection and persist indefinitely, type-specific glycoprotein G (gG)–based serologic tests are useful for asymptomatic patients and for patients with negative culture or PCR test results.[1] Determining HSV type influences prognosis and counseling because recurrences and subclinical shedding are less common for genital HSV-1 than genital HSV-2. Repeat testing may be indicated, particularly if recent acquisition of herpes is suspected. Immunoglobulin M (IgM) testing is not useful because IgM tests are not type specific and can be positive during recurrent genital or orolabial HSV infection.

Definitive methods for diagnosing early syphilis include darkfield examinations and tests to detect *T. pallidum* in lesion exudate or tissue.[1] A presumptive syphilis diagnosis is possible with the use of two types of serologic tests: nontreponemal tests (e.g., venereal disease research laboratory [VDRL], rapid plasma reagin [RPR]), and treponemal tests (e.g., fluorescent treponemal antibody, absorbed [FTA-ABS], *T. pallidum* passive particle agglutination [TP-PA], enzyme immunoassays [EIAs]). Using only one type of serologic test is insufficient for diagnosis and can result in false-negative treponemal test results in the primary stages of disease or false-positive nontreponemal test results for persons with certain medical conditions, including HIV infection, autoimmune conditions, pregnancy, and injection drug use.[1]

Optimal GUD management includes empiric treatment for the most likely diagnosis based on clinical presentation and epidemiology (see Table 50.1).[1] Suspected syphilis cases should be treated at the initial visit, even before test results are available, because early treatment decreases transmission. First episodes of genital HSV should be treated presumptively because patients with mild clinical manifestations can develop severe symptoms. The course of HSV can be modified if treatment is started during the prodrome or within 24 hours of symptom onset.[1] Patients should abstain from sexual activity while lesions are present and throughout treatment. If no clinical improvement occurs after treatment, providers should consider other infectious and noninfectious causes or confounding factors, including concurrent STI or HIV infections, reinfection, adequacy of partner treatment, and antimicrobial resistance.[1]

Special Considerations: HIV

HSV-2, syphilis, and chancroid are associated with an increased risk of HIV acquisition and transmission.[2–6] However, GUD treatment has not been effective in preventing HIV acquisition or transmission.[5,28,29] Rates of coinfection with HIV and syphilis or HSV are high, particularly among MSM. In 2013, 35% of US MSM between the ages of 15 and 24 years with primary and secondary syphilis were coinfected with HIV.[23,30,31] Immunocompromised persons with GUD can have prolonged or more severe episodes, have increased transmission, and may require repeated or longer courses of therapy.

Prevention

Prompt diagnosis and treatment of GUDs and other STIs in patients and sexual partners can prevent recurrences and decrease transmission. HSV-2 transmission can be reduced with daily suppressive therapy. Persons should remain abstinent from sexual activity when ulcers are present. Consistent and correct condom use can reduce the risk of GUD and other STIs.[32–34] Male circumcision reduces the risk of GUD.[35]

Inguinal Lymphadenopathy Without

Genital Ulcers

Any infection or inflammation in the groin, lower abdominal wall, or lower extremities can cause inguinal lymphadenopathy without ulcers (Table 50.3), including urinary tract infections, fungal infections, skin infections, appendicitis, and abdominal trauma.

TABLE 50.3

Differential Diagnosis of Inguinal Lymphadenopathy

Condition	Organism	Pattern of Lymphadenopathy	Associations
WITHOUT ULCERS			
Pyogenic bacteria	*Staphylococcus aureus*, group A *Streptococcus*	Suppurative, unilateral, and tender; can progress to abscess	Retrocecal appendicitis, osteomyelitis, pyogenic arthritis, infection of skin or abdominal wall
Cat-scratch disease	*Bartonella henselae*	Unilateral, tender, slowly progressive	Scratch lesion on lower limb
Tuberculosis	*Mycobacterium tuberculosis*	Caseating; can be unilateral, nontender	Miliary tuberculosis, osteomyelitis
Plague	*Yersinia pestis*	Large cluster, very tender nodes	Exposure to fleas, rodents, or rabbits
Tularemia	*Francisella tularensis*	Unilateral, very tender, inflamed	Exposure to rabbits, prairie dogs, rats, sheep, cattle, cats, hamsters, ticks, deerflies, contaminated water or soil
WITH ULCERS			
Herpes	Herpes simplex virus	Bilateral nodes	Sexually transmitted
Syphilis	*Treponema pallidum*	Bilateral nodes	Sexually transmitted
Chancroid	*Haemophilus ducreyi*	Bilateral nodes	Sexually transmitted
Lymphogranuloma venereum	*Chlamydia trachomatis* (L1, L2, L3)	Bilateral nodes	Sexually transmitted
Granuloma inguinale (donovanosis)	*Klebsiella granulomatis*	Bilateral nodes	Sexually transmitted
Tularemia	*Francisella tularensis*	Large, very tender lymph nodes with ulcerated skin lesions	Exposure to rabbit, squirrel, coyote
Mononucleosis	Epstein-Barr virus	Vulvar ulcers with regional adenopathy	—
Yersiniosis	*Yersinia enterocolitica*	Inguinal (unilateral or bilateral)	Fecal-oral route; consumption of pork chitterlings

Other infections can cause acute onset of unilateral inguinal lymphadenitis with occasional progression to abscess formation. *Staphylococcus aureus* and group A *Streptococcus* are the most common causes of suppurative lymphadenitis among children. Patients whose lymphadenitis progresses to abscess formation can come to attention for unexplained limp, inability to extend the leg, and fever, which can mimic septic arthritis or osteomyelitis; right-sided symptoms can suggest retrocecal appendicitis.[36]

Other lymphadenitis causes include anaerobic bacteria, cat-scratch disease (see Chapter 160), and mycobacterial infections (see Chapters 134 and 135).[37–39] Inguinal or femoral buboes can occur in bubonic plague if flea bites occur on the leg (see Chapter 148). Rarely, *Yersinia enterocolitica* infections manifest as inguinal lymphadenitis. Tularemia typically manifests with ulceroglandular syndrome but can manifest as inguinal lymphadenitis (see Chapter 171).

Management of isolated inguinal lymphadenopathy depends on the suspected cause. Lymph node aspiration with smear examination and culture is useful for pyogenic infections. Specific antimicrobial therapy is directed against the inciting pathogen. Further diagnostic investigations, such as ultrasonography or computed tomography, are helpful if osteomyelitis or retrocecal appendicitis is suspected.

Genital Dermatosis

Yeast Infections

Candida albicans or *C. glabrata* (see Chapter 243) commonly cause diaper dermatitis and perineal skin infections. In infants, eruption often starts in the perianal area and spreads to the perineum and upper thighs. Onset can be acute, with scaly macules or papules that coalesce to form well-demarcated, erythematous lesions with irregular borders and satellite lesions. Treatment consists of keeping the area dry and applying topical antifungal cream.

In older children and adolescents, genital candidal infection can involve the vagina or penis. Vulvovaginitis symptoms include pruritus, pain, erythema, and a white discharge (see Chapter 51). Treatment with topical azoles is effective for uncomplicated infections. Balanitis or balanoposthitis can manifest with pruritus, discharge, dysuria, and erythematous lesions with whitish patches on the glans, prepuce, and shaft of the penis. Topical antifungal therapy is effective, but relapses can occur.[40]

Dermatophyte Infections

Excessive perspiration and friction in intertriginous areas such as the groin predispose to superficial infections with dermatophytes, including *Trichophyton rubrum, T. mentagrophytes,* or *Epidermophyton floccosum* (see Chapter 254). These infections are more common in hot weather and occur more often in males. The infection, although often symmetric, can be asymmetric with extension from crural areas to the upper thigh. Erythematous, scaly patches with papular or vesicular margins are typically pruritic, and scratching can lead to lichenification.

Treatment consists of topical antifungals. Systemic therapy (e.g., fluconazole) is occasionally used for widespread or recalcitrant lesions that are common manifestations of candidiasis in immunocompromised patients.

Genital Warts

Genital warts (i.e., condyloma acuminatum) are caused by human papillomavirus (HPV) infection of the epidermis, especially types 6 and 11 (see Chapter 54) (Fig. 50.1). Among adolescents and adults, anogenital warts most often are transmitted sexually. In children, the mode of acquisition is more difficult to assess (see Chapter 56).[1] Pre-exposure vaccination is the most effective method for preventing HPV infection.[41,42]

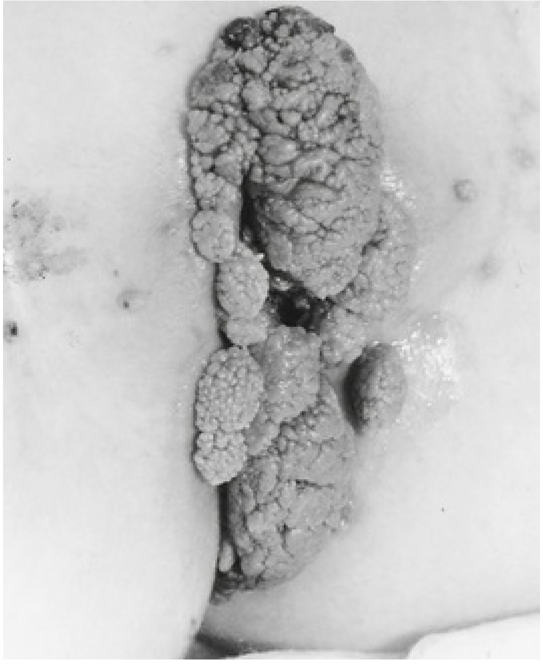

FIGURE 50.1 A 3-year-old girl has large, cauliflower-like genital warts with satellite lesions caused by human papillomavirus infection.

Molluscum Contagiosum Infection

Molluscum contagiosum is caused by parapoxvirus and can be transmitted sexually or nonsexually (see Chapter 202). The incubation period is 2 weeks to 3 months.[40]

Lesions are dome shaped with central umbilication, and the diagnosis is based on the clinical appearance. Although lesions are typically on the face, trunk, and extremities, genital lesions also occur. Unlike genital warts, which occur predominantly on external genitalia, molluscum contagiosum lesions occur most often on the thighs, inguinal region, buttocks, and lower abdominal wall. Lesions can be removed mechanically with curettage or by induction of local inflammation, as with podophyllin application. HIV infection can cause atypical and extensive lesions and should be considered in children and adolescents with multiple lesions, particularly if they occur on the face. Patients should be referred to dermatologic specialists for treatment of extensive infections.

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51

Urethritis, Vulvovaginitis, and Cervicitis

Paula K. Braverman

Urethritis

Urethritis is inflammation of the urethra. The clinical presentation includes dysuria, urinary frequency, and urethral discharge or itching. Neutrophils usually are found in urethral secretions.[1] According to the Centers for Disease Control and Prevention (CDC), urethritis is documented by one of the following: visibly abnormal urethral discharge, a positive leukocyte esterase (LE) test result for a man younger than 60 years of age without other urinary tract disease that could cause pyuria, Gram stain of a urethral smear showing at least 2 white blood cells per high-power field (WBCs/HPF), and a positive LE test result for the first-void urine or 10 or more WBCs/HPF in the first-void urine sediment.[2,3] However, studies have demonstrated that symptoms of urethritis can occur without microscopic evidence of pyuria on the Gram stain of urethral swab specimens or in the first-void urine samples.[4,5]

It may be difficult to establish the diagnosis of urethritis in women because they may not have localized symptoms and some pathogens simultaneously infect multiple genital areas.[6] In the absence of a documented urinary tract infection, female dysuria can represent vulvar inflammation from vaginitis or vulvar dermatoses, interstitial cystitis, or urethral infection with a sexually transmitted infection (STI).[6,7]

Etiologic Agents

Infectious Causes

Organisms associated with STIs are the most significant etiologic agents in urethritis. Newer, more sensitive molecular diagnostic testing modalities for STIs have advanced the understanding of specific pathogens that cause urethritis.

Male Patients.

Chlamydia trachomatis and *Neisseria gonorrhoeae* are common causes of urethritis in men.[1] *N. gonorrhoeae* is estimated to cause one third of acute urethritis cases and is differentiated from other agents, which cause nongonococcal urethritis (NGU).[8] NGU is the most common clinical STI syndrome in men. Rates of specific etiologic agents vary by geography, socioeconomic factors, age, race, and sexual orientation or practices.[1,5,8–14] Coinfection with multiple pathogens can occur, and in 25% to 40% of cases, no pathogen is identified.[15] Approximately 15% to 40% of NGU in men is caused by *C. trachomatis*, 15% to 25% by *Mycoplasma genitalium*, 10% to 20% by *Trichomonas vaginalis,* and 10% to 20% by *Ureaplasma urealyticum*.[15,16]

There has been confusion in the literature regarding the role of *U. urealyticum* as a cause of nongonococcal, nonchlamydial infection in men.[2,5,11,15,17–23] The genus *Ureaplasma* has two types: biovar 1 *(U. parvum)* and biovar 2 *(U. urealyticum)*. Biovar 2 is the biotype most likely associated with urethritis.[15,17–24] Further analysis has revealed that within biovar 2, only specific subtypes may be independently associated with NGU.[18]

T. vaginalis traditionally was considered a less common cause of urethritis in men. However, a nucleic acid amplification testing (NAAT) such as polymerase chain reaction (PCR) and transcription-mediated amplification (TMA) demonstrate that *T. vaginalis* is associated with 10% to 20% of cases of urethritis.[10,15,25–27] *T. vaginalis* can be demonstrated in males without clinical signs of urethritis and commonly is associated with other STIs.[15,28–30]

Herpes simplex virus (HSV) is a less common cause of urethritis in men.[5,11,31] Urethritis develops in 30% of men with primary HSV infection and is found in 2% to 3% of cases of NGU.[15] Studies reported in 2006 found that HSV-1 was responsible for more cases of NGU than HSV-2 and that HSV-1 was more likely to be associated with men engaging in oral-genital sex and men with male partners.[5,11] Infrequent causes of urethritis in men include adenoviruses, *Haemophilus* species, and *Neisseria meningitidis;* coliforms can be an etiologic agent in men who have sex with men (MSM).[1,5,11,15] Identification of some pathogens associated with urethritis suggests that infection with oropharyngeal flora, which are normal nonpathogenic organisms in monogamous partners, is possible.[11]

Nonsexually transmitted NGU is associated with urinary tract infection (UTI), bacterial prostatitis, urethral stricture, phimosis, and urethral catheterization.[1] In 25% to 40% of cases, the cause of NGU in male patients remains unknown.[15]

Female Patients.

Urethritis in female patients can be caused by *N. gonorrhoeae, C. trachomatis,* HSV, and *M. genitalium. T. vaginalis* typically causes vaginitis in women but is known to infect the urethra and is associated with pyuria.[6,7,10,29,32–36]

Noninfectious Causes

In men and women, urethritis can accompany noninfectious systemic diseases such as Stevens-Johnson syndrome, or it can result from chemical irritation.[1,6]

Epidemiology

One half of new STIs occur in adolescents and young adults between the ages of 15 and 24 years.[37] Population-based data for this age group derived from the National Health and Nutrition Examination Survey (NHANES) showed the prevalence of *C. trachomatis* was 1.7% among males and 3.2% among females (2005–2008 data); prevalence of *N. gonorrhoeae* was 0.3% among males and 0.6% among females (1999–2008 data); and prevalence of *T. vaginalis* was 0.9% among males and 1.5% among females (2001–2004 data).[37]

Other studies have demonstrated that prevalence rates of *T. vaginalis* infection increase with age; they are highest among black women, lower among black men, and lowest among whites.[38,39] Similar ethnic or racial differences have been found for *C. trachomatis* and *N. gonorrhoeae*.[40] Data from several studies, including the CDC's 2013 sexually transmitted disease (STD) surveillance report, illustrate that the STI rates vary by specific populations.[25,38,40,41] Youth in correctional facilities and the National Job Training Program have among the highest STI rates.[2,40,41]

Sexual practices and behavior can influence the epidemiology of urethritis. Urethritis due to *C. trachomatis, N. gonorrhoeae,* or HSV among adolescent women correlates with having new sex partners.[6] Adenovirus and HSV-1 have been associated with oral-genital contact and having a male partner, whereas *M. genitalium* and *C. trachomatis* have been associated with vaginal sex.[5] In one study, *N. gonorrhoeae* and *U. urealyticum* urethritis were found in heterosexual men, *C. trachomatis* urethritis was associated with MSM, and *T. vaginalis* was more common in men older than 30 years of age.[42]

Urethritis due to STI pathogens also can occur in prepubertal boys and, less frequently, in prepubertal girls. In this age group, transmission commonly results from sexual abuse with genital-to-genital contact (see Chapter 54).

Clinical Manifestations and Differential Diagnosis

Symptomatic urethritis in adolescent males is characterized by dysuria, urethral discharge, or urethral pruritus. Discharge can be mucoid, mucopurulent, or purulent. Gonococcal urethritis compared with NGU usually has a shorter incubation period, more acute onset, and more profuse discharge (Table 51.1).[1] Discharge in patients with NGU can be so scant that it is only noticed in the morning or is apparent as crusting on the meatus or as stains in underwear.[1] Urethral infection with *N. gonorrhoeae* and the various organisms causing NGU also can be asymptomatic.[43]

TABLE 51.1

Clinical Manifestations of Nongonococcal and Gonococcal Urethritis

Characteristic	Nongonococcal Urethritis	Gonococcal Urethritis
Incubation period	2–3 weeks	2–6 days
Onset	Insidious	Abrupt
Dysuria	+, may wax and wane	++, continuous
Discharge	Scant to moderate, may be absent	Profuse, absent in <10%

+, modest discomfort; ++, more severe discomfort.

Urethritis must be differentiated from UTI, particularly in adolescent boys with dysuria but no discharge. In contrast to UTI, frequency, hematuria, and urgency are uncommon in urethritis. However, if the male adolescent is sexually active, pyuria is more likely to be caused by urethritis than UTI because UTI is uncommon in this age group. A focused STI history (see Chapter 49) and thorough medical history can help establish relative risks of urethritis and UTI.

In adolescent girls, dysuria is the cardinal feature of urethritis, which must be differentiated from acute bacterial cystitis and vulvovaginitis (Table 51.2). The literature differentiates *internal* and *external* dysuria. Internal dysuria is pain that is felt internally during voiding. External dysuria is discomfort that is felt as urine passes over the labia.[7] Internal dysuria, urinary frequency, and isolation of more than 10^2 uropathogens per milliliter of voided urine suggest acute bacterial cystitis; isolation of 10^2 or fewer uropathogens per milliliter suggests acute urethritis due to STI pathogens.[6] Pain that is felt internally only at the end of urination is consistent with bacterial cystitis.[7] External dysuria can occur with vulvovaginitis. Female adolescents can have vaginitis alone or a concurrent UTI and may not be able to adequately distinguish between internal and external dysuria.[7,44] Any female patient suspected of having urethritis requires an STI-directed history and physical examination to identify other STIs or STI syndromes (e.g., pelvic inflammatory disease [PID]).

TABLE 51.2

Distinguishing Features of Urethritis, Acute Bacterial Cystitis, and Vulvovaginitis in Adolescent Females

Feature	Urethritis	Acute Bacterial Cystitis	Vulvovaginitis
Symptoms	Internal dysuria	Internal dysuria, frequency, urgency, hematuria	External dysuria, vaginal discharge, vulvar burning, itching
Duration of symptoms	Often ≥7 days	Usually ≤4 days	Varies with cause

Signs	Mucopurulent cervicitis Vulvar lesions	Suprapubic tenderness	Vulvar lesions and inflammation, vaginal discharge
Epidemiologic associations	New sex partner Previous STI Sexual partner with STI	Previous cystitis Onset of symptoms within 24 hours of intercourse Use of diaphragm Use of a spermicide	History of genital herpes Sex partner with genital herpes Antibiotic use Previous vulvovaginitis Candidiasis

STI, sexually transmitted infection.

Modified from Holmes KK, Stamm WE, Sobel JD. Lower genital tract infection syndromes in women. In: Holmes KK, Sparling PF, Mardh P-A, et al. (eds). Sexually Transmitted Diseases, 4th ed. New York, McGraw-Hill, 2008, pp. 987–1016.

In prepubertal boys and girls, urethritis due to STI pathogens can manifest with dysuria and urethral or vaginal discharge. There may be vague lower abdominal pain, unwillingness to void, and in boys, irritation in the distal urethra or meatus. Dysuria in a prepubertal child is much more likely to be caused by UTI than urethritis associated with STI. Urethritis is more probable in the setting of a discharge or a history of sexual abuse, especially if genital-to-genital contact has occurred.

Laboratory Findings and Diagnosis

Male Patients.

For male patients, specimens are obtained to document urethritis and to detect common causes such as *N. gonorrhoeae* and *C. trachomatis*. The definitive diagnosis is enhanced if the patient has not voided recently; examination in the morning before voiding is ideal.[1] A meatal swab specimen of a discharge can be taken for Gram stain; the finding of gram-negative intracellular diplococci of the typical kidney bean morphology pattern (Fig. 51.1) or at least 2 neutrophils per oil immersion field (×1000) is diagnostic of urethritis.[1,2] A Gram stain smear is sensitive and specific in diagnosing gonococcal urethritis if intracellular diplococci are detected. If the Gram stain is equivocal, negative, or unavailable and the criteria for urethritis are met, NAAT for *N. gonorrhoeae* and *C. trachomatis* is indicated.[2]

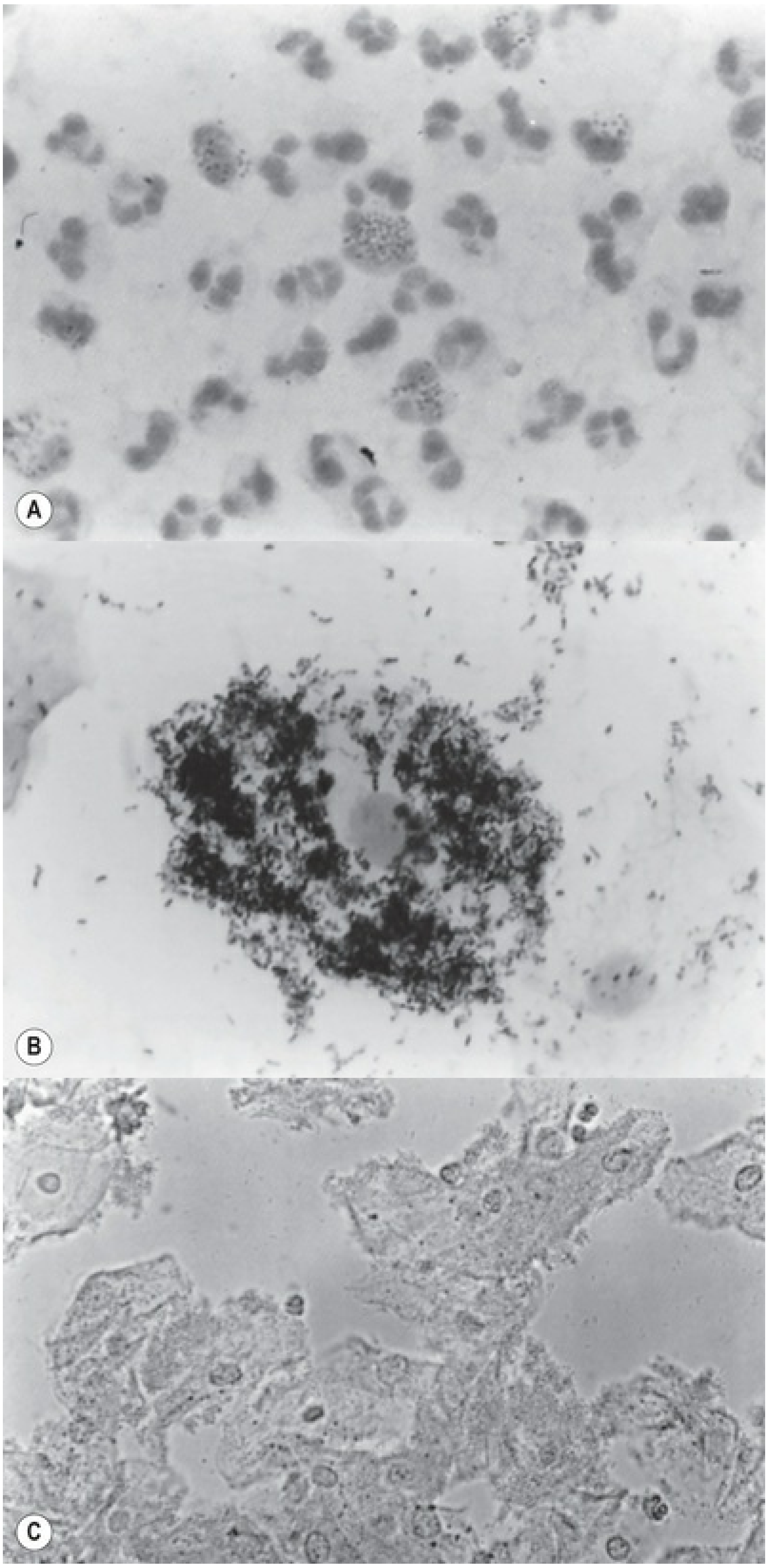

FIGURE 51.1 (A) Gram stain of urethral discharge from an male adolescent with urethritis shows multiple neutrophils and intracellular diplococci with the kidney-bean morphology typical of *Neisseria gonorrhoeae* (magnification ×1000). (B) Gram stain of vaginal fluid from an adolescent with bacterial vaginosis shows clue

cells and squamous vaginal epithelial cells covered with coccobacilli, which gives them a stippled or granular appearance. Notice the absence of rods with blunt ends (i.e., lactobacilli) (magnification ×2000). (C) Wet mount of vaginal secretions from a female adolescent with bacterial vaginosis shows clue cells. Notice the stippled epithelial cells with ragged (i.e., bacteria-covered), ill-defined borders (magnification ×200).

In all patients, regardless of whether *N. gonorrhoeae* is suspected by Gram stain, a first-voided urine or urethral specimen should be obtained for detection of *C. trachomatis* by NAAT. The optimal specimen from male patients is a first-voided urine.[2,45] NAAT for *N. gonorrhoeae* and *C. trachomatis* may detect infection in male patients with symptoms of urethritis but no objective evidence of urethral inflammation.[2]

The diagnosis of *T. vaginalis* in men is more challenging than in women. Wet mount preparation of a urethral smear detects only 30% of *T. vaginalis* infections in men.[28] Culture can be performed on urine, semen, or urethral specimens and appears to yield better results if multiple sites are tested.[2,29,46] The InPouch culture system (BioMed Diagnostics, San Jose, CA) is equivalent to the gold standard Diamond media, and urethral or urine sediment specimens can be inoculated.[25] However, studies have shown that NAAT is superior to a wet mount preparation or culture to detect *T. vaginalis* in male patients.[10,26,28,29,47–49] Although the TMA test is approved only in the United States for female specimens, it may be used in laboratories that have conducted validation procedures on male specimens.[2,46,50] *T. vaginalis* PCR is not commercially available. Specific testing of men for *T. vaginalis* should be considered for cases of nongonococcal urethritis in high-prevalence areas or populations.[2]

Cultures for *U. urealyticum* are not available readily, and *M. genitalium* is difficult to isolate.[1,32,51] In research studies, both are diagnosed and evaluated using NAAT. However, these tests are not cleared for use by the US Food and Drug Administration (FDA), and management relies on the clinical presentation and exclusion of other causes.[2]

Female Patients.

Endocervical or vaginal and urethral specimens should be obtained for NAAT for *N. gonorrhoeae* and *C. trachomatis* in adolescent girls with urethritis because concurrent infection is common.[2,6] Urinalysis and urine culture also are indicated because simultaneous UTI and STI can occur in sexually active females.[7] Urine testing using NAAT for *C. trachomatis* and *N. gonorrhoeae* is not as sensitive as endocervical specimen testing.[2,45] Studies using NAAT for vaginal specimens have shown good correlation with cervical specimens, and the vaginal specimens can be collected by the healthcare personnel or the patient.[2,45]

T. vaginalis can be diagnosed by a variety of methods, including wet mount preparation, culture, nucleic acid probe, immunochromatographic capillary flow dipstick technology, and NAAT.[2,25,48,49,52,53] As for male patients, wet mount microscopy has poor sensitivity compared with other methods.[2] NAAT for *T. vaginalis* (e.g., strand displacement amplification [SDA]), and TMA are FDA cleared for use in women for endocervical, vaginal, or urine specimens.[2,48,52]

Treatment

Initial treatment for male patients can be based on Gram stain results (Table 51.3).[2] Patients with evidence of *N. gonorrhoeae* by Gram stain should be treated with dual single-dose therapy, including intramuscular ceftriaxone and oral azithromycin to reduce the development of antimicrobial-resistant *N. gonorrhoeae.* Although oral cefixime can be substituted for ceftriaxone, it is not the first-line drug due to resistance patterns and poor efficacy if there is a concomitant pharyngeal infection.[2]

TABLE 51.3

Recommended Treatment of Urethritis in Postpubertal Children and Adolescents

	Gram Stain	Suggested Treatment
RESULTS AVAILABLE		
Increased Neutrophils	Gram-Negative Intracellular Diplococci	

Present	Present[a]	Treat for gonococcal and chlamydial urethritis. For *Neisseria gonorrhoeae:* for postpubertal children >45 kg and adolescents, ceftriaxone (250 mg IM once) or cefixime (400 mg PO once) *and* azithromycin (1 g PO once) For *Chlamydia trachomatis:* for postpubertal children ≥8 years and adolescents, azithromycin (1 g PO once) *or* doxycycline (100 mg bid PO for 7 days)
Present	Absent	Treat for nongonococcal urethritis. Azithromycin (1 g PO once) *or* doxycycline (for 7 days) *or* ofloxacin (300 mg PO bid for 7 days) *or* levofloxacin (500 mg PO once daily for 7 days) *or* erythromycin base (500 mg PO qid for 7 days) *or* erythromycin ethylsuccinate (800 mg PO qid for 7 days)
Absent	Absent	Defer treatment until microbiologic results are available, or if patient is high risk by history and follow-up cannot be ensured, treat for gonococcal and chlamydial urethritis
RESULTS NOT AVAILABLE		
Urethral discharge	—	Treat for gonococcal and chlamydial urethritis
No urethral discharge	—	Defer treatment until microbiologic results are available, or if patient is high risk and follow-up cannot be ensured, treat for gonococcal and chlamydial urethritis
RECURRENT OR PERSISTENT URETHRITIS		
—	—	Azithromycin (1 g PO once) if not used for initial episode; for failure, moxifloxacin (400 mg PO qd for 7 days) to cover *Mycoplasma genitalium*; metronidazole (2 g PO once) or tinidazole (2 g PO once) to cover *Trichomonas vaginalis*

[a] Gram stains are considered inadequate to evaluate prepubertal children for *N. gonorrhoeae*.

IM, intramuscularly; IV, intravenously; PO, orally.

Data from Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep 2015;64(RR- 3):1–137.

All patients with negative Gram stain results should be tested for *C. trachomatis* and treated if positive. For NGU, a single dose of azithromycin may be preferred over a 1-week course of doxycycline in adolescents because of adherence.[2] Single-dose azithromycin is also preferred because it is most effective in treating *M. genitalium*, which is the most common cause of persistent and recurrent NGU.[2] Confirmed cases of *N. gonorrhoeae* or *C. trachomatis* must be reported to the local health authorities, and sexual partners should be contacted for assessment and treatment.

Immediate follow-up and repeat testing for *N. gonorrhoeae* or *C. trachomatis* urethritis in adolescents are not recommended routinely if appropriate treatment is completed, signs and symptoms disappear, and no re-exposure to an untreated partner occurs. However, because of the high rate of reinfection after initial treatment, repeat testing for *N. gonorrhoeae* and *C. trachomatis* is recommended in 3 months.[2] If symptoms persist despite good adherence and no re-exposure and the person meets diagnostic criteria for persistent or recurrent NGU, further management is indicated. Treatment without signs for urethral inflammation has not been demonstrated to be effective.[2,54,55]

M. genitalium is the most common cause of persistent or recurrent NGU.[2] If doxycycline was used initially, single-dose azithromycin should be tried because it is more effective than multidose doxycycline for this organism.[2] However, resistance has developed to azithromycin, and studies have demonstrated treatment failure in men treated with both single-dose and extended-dosing regimens of azithromycin, possibly related to the selection of resistant organisms with the common use of single-dose azithromycin for treatment of *N. gonorrhoeae* and *C. trachomatis*. Seven days of moxifloxacin (400 mg daily) is effective for treatment failures for *M. genitalium*.[2,16,51,54–57] Fluoroquinolone resistance has also been demonstrated.[57,58]

For male patients with persistent urethritis, culture of a urethral specimen or first-void urine for *T. vaginalis* should be performed because of the high prevalence of *T. vaginalis* infection among men with nongonococcal, nonchlamydial urethritis and coinfection with these organisms. If there has been laboratory validation, testing of urethral or urine specimens with NAAT is preferred.[2] If *T. vaginalis* is diagnosed, metronidazole or tinidazole is prescribed (see Chapter 274). Current CDC guidelines recommend presumptive treatment with metronidazole or tinidazole in cases of persistent urethritis in areas of high prevalence for men who have sex with women.[2] *U. urealyticum* can be difficult to eradicate, and resistance to tetracyclines has been demonstrated.[1,51] Patients who do not respond to therapy should be referred to a urologist.

Female patients with findings suggesting bacterial cystitis can be treated presumptively for UTI. However, if urethritis is suspected, a single dose of azithromycin (1 g) or a 7-day course of doxycycline (100 mg twice per day) is indicated pending results of urine culture and STI testing.[2] If symptoms of dysuria due to vulvovaginitis are found, treatment should be directed at the cause. Although the CDC's 2015 STD treatment guidelines do not specifically discuss persistent urethritis in females, treatment of *M. genitalium* should be considered when other causes have been ruled out, and ideally, testing for this organism should be done.[35]

Complications

Complications of urethritis include disseminated gonococcal infection (0.5% to 3%) and reactive arthritis syndrome (i.e., Reiter syndrome). In male patients, epididymitis (1% to 2%) and, rarely, prostatitis and balanoposthitis also occur.[1,16] Female patients with *N. gonorrhoeae*, *C. trachomatis*, and *M. genitalium* infection also are at risk for PID and infertility.[7,16,36,59] *M. genitalium* has been associated with preterm birth and spontaneous abortion.[2,59] In male and female patients, STIs associated with urethritis increase susceptibility to infection with, viral shedding, and transmission of HIV.[2,60,61]

Prevention

Correct and consistent use of condoms is the most effective means of preventing and reducing transmission of the STIs associated with urethritis.

Vulvovaginitis

Vulvovaginitis (i.e., inflammation of the vagina or vulva) is a common gynecologic problem in prepubertal and adolescent girls. The cause, pathogenesis, and management are substantially different for the two age groups.[7] Vaginitis and vulvitis are a continuum in young children, whereas they are distinct clinical entities in adolescents.

Vulvovaginitis in Prepubertal Girls

Etiologic Agents and Epidemiology

Prepubertal girls can have specific or nonspecific vaginal infections.[7] Several factors predispose young girls to vulvovaginal irritation, including proximity of the vagina to the rectum, poor hygienic practices, lack of protective labial fat pads and pubic hair, and lack of an estrogen effect on vaginal mucosa.[7,62] Prepubertal girls are more likely than postpubertal girls to experience vulvar irritation and trauma from soaps, bubble baths, and clothing.[7] The lack of estrogen effect in prepubertal girls promotes an environment with a neutral pH, predisposing to overgrowth with a variety of potential pathogens.[6,62] Vaginal microbial infections that are not STIs usually are caused by respiratory tract and enteric pathogens.

T. vaginalis is rare in prepubertal children because lack of estrogen makes the vagina resistant to this infection.[7] Isolation of *Gardnerella vaginalis* in prepubertal vaginitis is not diagnostic of bacterial vaginosis (BV) but has been reported in prepubertal girls after sexual assault.[7] *Candida* vulvovaginitis is not common in prepubertal girls unless there are other risk factors, such as antibiotic use, diabetes mellitus, immunosuppression, or use of diapers; 3% to 4% of prepubertal girls have *Candida* spp. as part of normal vaginal flora.[7,62]

Although prepubertal vulvovaginitis is not often sexually transmitted, sexual abuse must be considered if pathogens such as *C. trachomatis, N. gonorrhoeae, T. vaginalis,* human papillomavirus (HPV), or HSV are identified.[7,62] Attributing HPV to sexual abuse rather than vertical transmission or inoculation from caregivers and autoinoculation is challenging because of the lack of studies in this age group regarding incubation, latency to clinical presentation, and cutoff ages for vertical transmission.[62] Similar to the cervical epithelium of postpubertal girls, the cuboidal vaginal epithelium of prepubertal girls is susceptible to *N. gonorrhoeae* and *C. trachomatis.*[6] Other causes of vulvovaginitis include foreign body, vulvar skin disorders, and allergic reactions (Box 51.1).

Box 51.1

Etiologic Factors in Prepubertal Vulvovaginitis

Nonspecific Causes

Contact or Allergic Reactions (Common)

- Bubble-bath preparations
- Shampoos, soaps
- Laundry detergents
- Clothing (e.g., nylon undergarments)

Physical Factors (Common)

- Foreign body
- Sand (e.g., sandbox)
- Poor hygiene (e.g., wet diapers)

Specific Microbiologic Causes

Not STI Related

- *Shigella* spp.
- *Yersinia enterocolitica*
- Enteric bacilli
- *Staphylococcus aureus*
- Group A *Streptococcus*
- *Haemophilus influenzae*
- *Enterobius vermicularis*
- *Moraxella catarrhalis*
- *Streptococcus pneumoniae*
- *Neisseria meningitidis*
- *Candida* spp.

Possibly STI Related (Less Common)

- *Neisseria gonorrhoeae*
- *Chlamydia trachomatis*
- *Trichomonas vaginalis*
- Herpes simplex virus

Vulvar Skin Disorders

- Eczema
- Psoriasis

STI, sexually transmitted infection.

Clinical Manifestations, Differential Diagnosis, and Clinical Approach

The clinical features of vulvovaginitis in children include vaginal discharge, vulvar irritation, pruritus, dysuria, bleeding, genital inflammation, and foul smell.[7,62] When associated with a foreign body, the discharge can be profuse, foul smelling, and blood tinged.[7] Parents often are unaware that the child has inserted something into the vagina. In *Enterobius vermicularis*–associated vulvovaginitis, recurrent symptoms and vulvar or anal pruritus are common. Discharge can be bloody in cases of vulvovaginitis caused by *Shigella* spp. or *Streptococcus pyogenes* infection.[6,7,62] Bleeding also should raise concern about trauma. Diffusely hyperemic vulvar mucosa suggests streptococcal vulvovaginitis. Discharge associated with gonococcal infection is commonly green and purulent, whereas discharge is less common with chlamydial infection.

All prepubertal children with vulvovaginitis require a careful history and physical examination. Vaginitis due to *S. pyogenes* can occur after a pharyngeal or skin infection in the patient or family members. Finding a sibling with an STI raises concern about sexual abuse by someone associated with the family.[7,62] Gynecologic examination includes abdominal inspection and palpation. In a gentle and supportive manner, inspection of the perineal skin, vulva, and perirectal and genital areas is performed to detect excoriation, erythema, ulcers, or structural abnormalities. Visualization of the vagina and cervix without instrumentation usually is possible with the patient in the knee-chest position.[7] This facilitates detection of a foreign body, especially if a magnifying lens or otoscope head is used. Examination with the patient under anesthesia may be necessary in some cases.

Laboratory Findings and Diagnosis

Samples of a vaginal discharge are obtained (Box 51.2) using a sterile, saline-moistened swab for potassium hydroxide (KOH) preparation, Gram stain, and culture.[62] A vaginal wash using nonbacteriostatic saline or vaginal aspiration using an eyedropper are alternative methods of specimen collection.[7,62] However, the latter specimens may not be as sensitive for identification of *C. trachomatis* if few epithelial cells are collected, which are necessary because the organism is an obligate intracellular pathogen. Culture confirmation of *N. gonorrhoeae* and *C. trachomatis* is the most admissible legal evidence for cases of suspected sexual abuse.

Box 51.2

Testing Vaginal Discharge or Aspirate Specimens From Prepubertal Girls With Vulvovaginitis

Gram stain for bacteria and white blood cells[a]

Culture for aerobic and anaerobic bacteria

Culture for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*[b]

Wet mount to detect clue cells[c] or trichomonads[d]

Potassium hydroxide preparation to detect fungal elements[d] and note odor

Scotch tape specimen from perianal area in early morning if pinworms are suspected

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[a] Gram stain should not be used to diagnose or exclude *N. gonorrhoeae* in prepubertal children.

[b] Nonculture tests usually are not recommended in cases of abuse due to the risk of false-positive results, but nucleic acid amplification testing (NAAT) of vaginal or urine specimens may be an acceptable alternative particularly in other circumstances.

[c] Clue cells are stippled epithelial cells whose borders are obscured by adherent bacteria.

[d] Culture also can be performed for *Trichomonas vaginalis* and yeast. NAAT for *Trichomonas vaginalis* has not been adequately studied in prepubertal children.

NAAT for vaginal or urine specimens may be an alternative to culture for testing of vaginal secretions in girls.[2] *T. vaginalis* can be detected in vaginal wash specimens or by culture.[7,53] If *Enterobius* infestation is suspected, the parent is instructed to examine the perianal region at night for the small, white pinworms, and a Scotch tape swab or paddle specimen is collected from the perianal area immediately on the child's awakening. Samples for culture for yeast should be considered if itching persists or the history suggests risk factors for candidal infection.[7,62]

Treatment

The mainstay of treatment for nonspecific vulvovaginitis is education, attention to personal hygiene, and avoidance of agents such as bubble baths and tight nylon undergarments that provoke the problem.[62] Sitz baths in warm water without soap may be helpful. Vitamin A and D ointment or petroleum jelly can protect the vulva, and a short course of 1% hydrocortisone cream can alleviate acute exacerbations of irritant vulvitis.[7,62] In severe cases, an estrogen cream may be applied for several weeks to ameliorate symptoms.[7,62] If a foreign body is detected, removal usually resolves the problem.

Treatment of vulvovaginitis due to specific pathogens is initiated on the basis of the Gram stain, wet mount preparation, culture, or NAAT results. Recommended treatments for *N. gonorrhoeae* are ceftriaxone alone for patients who weigh 45 kg or less and ceftriaxone along with azithromycin for those who weigh more than 45 kg. For *C. trachomatis*, erythromycin is given to patients who weigh less than 45 kg, azithromycin for those younger than 8 years of age and who weigh 45 kg or more, and azithromycin or doxycycline for older girls. For *Candida*, an antifungal agent, such as clotrimazole, is used, or oral fluconazole is used if topical therapy is not effective. Treatment for *S. pyogenes* is penicillin or amoxicillin. Other antimicrobial agents are chosen on the basis of vaginal bacterial culture results.[2,7,62]

Complications

The follow-up of children with vulvovaginitis depends on the cause. Fortunately, gonococcal and chlamydial vulvovaginitis rarely are associated with upper tract disease, and impairment of fertility is unlikely if the infection is treated adequately.[7] For recurrences due to *S. pyogenes,* pharyngeal colonization in the patient and carriage in family members are considered.[62]

Vaginitis in Pubertal Girls

Etiologic Agents and Epidemiology

Under the influence of estrogen at puberty, the vaginal epithelium shifts from cuboidal to a glycogen-containing stratified squamous epithelium, and there is an associated increased growth of lactobacilli that produce lactic acid and hydrogen peroxide.[6,7,63] This results in a decrease in vaginal fluid pH from a prepubertal level of about 7.0 to about 4.0. Changes in the epithelium, colonizing flora, and pH render the vaginal environment relatively resistant to infection caused by *C. trachomatis* and *N. gonorrhoeae.* In adolescents, these two organisms cause cervicitis rather than vulvovaginitis.

Leukorrhea, the normal white mucous vaginal discharge that represents the effect of estrogen on the vaginal mucosa in adolescents, must be distinguished from pathologic discharge. Saline wet mount examination of vaginal secretions reveals sheets of epithelial cells without inflammatory cells, yeast, clue cells, or trichomonads. Leukorrhea sometimes is considered excessive by patients, and they need reassurance.[7,63]

The major causes of vaginitis in adolescents are BV, candidiasis, and *T. vaginalis* infection. BV has replaced the term *nonspecific vaginitis* because the condition usually is not inflammatory but arises from a change in the vaginal flora.[7,64] Less common causes of vaginitis in adolescents include ulceration and infection associated with tampons, cervical caps, vaginal contraceptive ring, and other foreign bodies; chemical agents such as those found in douches and spermicides; and toxin-producing *Staphylococcus aureus.*[6,7,65]

Bacterial Vaginosis.

BV is the most common cause of vaginitis in postpubertal women, affecting approximately one third of women.[63,66–68] BV represents a disruption in the normal vaginal flora, with a decrease in lactobacilli and overgrowth of a variety of primarily anaerobic organisms. BV-associated organisms include *G. vaginalis,* genital mycoplasmas *(M. hominis), U. urealyticum, Bacteroides, Prevotella, Porphyromonas, Peptostreptococcus, Fusobacterium,* and *Mobiluncus* species.[63,64,69–71] Although many patients with BV have moderate to heavy concentrations of vaginal *Gardnerella* species, detection of this organism is not diagnostic because vaginal colonization is common in patients without BV and not specific for the diagnosis.[63,64,71]

New technologies employing amplification of ribosomal RNA are being used to characterize bacterial species that are not identified by culture [64,70–72] They include three clostridial bacteria, *Leptotrichia* and *Megasphaera* species, and Eggerthella-like bacteria.[70–72] In one study, detection of these noncultivatable bacteria had excellent sensitivity and specificity for diagnosing BV compared with standard diagnostic criteria.[71]

In a multivariate analysis of NHANES data from 2001 through 2004, risk factors for BV included a higher number of lifetime sex partners, douching, low educational achievement, and being non-Hispanic black.[68] BV has also been associated with poverty, smoking, having a female sex partner, high body mass index, and previous pregnancy.[68,73,74] The prevalence of BV among women attending STI clinics is higher (30% to 37%) than among college students (4% to 15%)[7] and the prevalence of BV in a nationally representative sample of 14-19 year old women was 18.5%.[68]

BV is more common among adolescents and young adults who are sexually active and have multiple sexual partners. However, designating BV as an STI has been controversial because some studies have found BV in sexually inexperienced females.[64,66,68,75,76] One study of women entering the military found that 19% of subjects denying a history of vaginal intercourse met criteria for BV compared with 28% who had been active sexually.[75] Another study questioned the accuracy of sexual histories having failed to find BV in truly sexually inexperienced college students.[77] Studies have shown a concordance between the presence of *G. vaginalis* in the urethra of male sex partners of women diagnosed with BV but did not find this organism in male controls.[64] Sexual activity, multiple sexual partners, receptive oral sex, and vaginal insertion of sex toys that were not cleaned are associated with BV, whereas the use of condoms appears to be protective.[64,73,74,77–80] Treatment of sex partners does not appear to prevent recurrence.[64] However, a systematic review of randomized, controlled trials of male partner treatment for BV criticized these studies for having methodologic flaws.[81]

Up to one third of women experience recurrent episodes of BV within 3 months of treatment.[66] In one study, factors associated with recurrence over a 12-month period included a history of BV and having a female sex partner or a regular sex partner.[82] Recurrence may be related to reinfection from an infected partner or to failure to re-establish lactobacilli dominance with persistence of pathogenic bacteria.[63,67,72] Some investigators have postulated that the recurrence of BV is related to persistence of a biofilm containing *G. vaginalis* and other organisms that adheres to the epithelial cells and provides protection from systemic and topical antibiotics.[72,83–85]

Candidiasis.

Vulvovaginal candidiasis has an estimated lifetime incidence of up to 75%.[86] Candidal colonization of the vagina usually originates from the gastrointestinal tract, and sexual transmission is not an important mode of acquisition.[2,63,86] As many as 30% of healthy asymptomatic women are colonized with yeast, and *Candida albicans* is the organism found in most uncomplicated cases.[63,66] Risk factors include pregnancy, poorly controlled diabetes, immunosuppression, receptive oral sex, use of estrogen, and use of various contraceptives, including intrauterine devices, diaphragms, vaginal rings, and possibly spermicides.[63,65,66,86] Antibiotic use is mentioned frequently, but it is not a major cause of infection in most women. Rather, colonization by species of *Candida* may place a subpopulation of women at higher risk for symptomatic infection.[66,86–88] For approximately one half of girls and women, no risk factors are identified.[63,66]

Most women experience uncomplicated vulvovaginal candidiasis, with infrequent mild to moderate episodes caused by *C. albicans*.[86] However, 10% to 20% of women have complicated vulvovaginal candidiasis that is more severe, recurrent, or caused by other *Candida* species. These women are more likely to have underlying medical risk factors such as diabetes or immunocompromise.[2,86] Approximately 5% of women have recurrent disease (i.e., ≥4 episodes in a 12-month period), which is more likely to be associated with *C. glabrata* and other non-*albicans Candida* species.[2,66,86,89] Most women with recurrent vulvovaginal candidiasis do not have diabetes mellitus or immunosuppression, but these conditions increase the risk. It is postulated that some patients may have a genetic predisposition to recurrent vulvovaginal candidiasis, suppression of local immunity due to virulence factors produced by the *Candida* species, or an alteration in local innate response leading to an aggressive inflammatory leukocytic response to yeast colonization.[63,66,86,90,91]

Trichomonas vaginalis.

T. vaginalis is the third most common cause of infectious vaginitis and has a worldwide distribution, with prevalence in community-based studies ranging from 2% to 46% of women.[10,63] It is the most prevalent curable STI worldwide, with most cases found in women.[27] In the United States, an estimated 3.7 million people are infected.[37]

Studies using PCR testing of urine or vaginal swabs from girls and women between the ages of 14 and 26 years have shown *T. vaginalis* prevalence rates of approximately 2% to 3%, which was higher than the rate for gonorrhea among the same people.[52] Certain populations may have a higher prevalence, including 26% of symptomatic and 7% of asymptomatic women at STI clinics, up to 18% of patients at adolescent clinics, 10% of women in college health programs, and up to 47% of incarcerated women.[2,10,52] Other risk factors include being African American, smoking, using alcohol and drugs, having multiple partners, and adolescents having an older sexual partner.[2,10] *T. vaginalis* facilitates transmission and acquisition of HIV and commonly is associated with other STIs.

Clinical Manifestations and Differential Diagnosis

Clinical presentations that help differentiate BV from candidal vulvovaginitis and trichomonal vaginitis are shown in Table 51.4. In the sexually active adolescent, cervicitis also must be excluded because it can occur as a coinfection or as the sole cause of the vaginal discharge.[92]

TABLE 51.4

Characteristics and Recommendations for Treatment of Vaginitis in Adolescents

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	Bacterial Vaginosis	Candidal Vaginitis	Trichomonal Vaginitis
SYMPTOMS			
Odor of vaginal discharge	Malodorous	Usually not malodorous	May be malodorous
Vulvar itch	Sometimes	Yes or discomfort	Yes
Dysuria	Sometimes	Yes	Yes
Dyspareunia	Sometimes	Yes	Yes
Other symptoms	No	Symptoms often exacerbated before menses	No
SIGNS			
Appearance of vaginal discharge	Thin, homogeneous, white, clings to vaginal wall, ± frothy	Thick, curd-like	Heavy, grey or yellow-green, frothy
Other signs	No	Vulvar and vaginal erythema, vulvar edema	Vulvar and vaginal erythema
LABORATORY FINDINGS			
pH	>4.5	<4.5	>4.5
KOH preparation	Fishy, amine odor when mixed with 10% KOH (positive whiff test)	Hyphae or pseudohyphae	Occasionally positive whiff test
Saline preparation	Clue cells, few neutrophils	Neutrophils and epithelial cells in equal numbers	Motile trichomonads, neutrophils
Gram stain	Few gram-positive bacilli; abundant mixed flora	Hyphae or pseudohyphae or blastospores	Trichomonads visualized rarely
Culture	Not useful	Can be useful if KOH negative	Culture more sensitive than wet mount
TREATMENT			
	Oral Metronidazole (500 mg bid for 7 days) *or* clindamycin (300 mg bid for 7 days) *or* tinidazole (2 g qd for 2 days) *or* tinidazole (1 g qd for 5 days) **Topical intravaginal** Clindamycin cream 2% (one full applicator amount per vagina at bedtime for 7 days) *or* clindamycin ovules (100 mg per vagina at bedtime for 3 days) Metronidazole 0.75% gel (one full applicator amount per vagina qd for 5 days)	**Topical intravaginal**[a] Butoconazole cream Clotrimazole cream Miconazole cream or vaginal suppository Terconazole cream or vagina suppository Tioconazole ointment **Oral** Fluconazole (150 mg once)	**Oral** Metronidazole (2 g for 1 dose *or* 500 mg bid for 7 days) *or* tinidazole (2 g in a single dose)

[a] Intravaginal therapies are available in 1- to 14-day regimens.

KOH, potassium hydroxide.

Symptomatic BV manifests with a thin, white-grey, homogeneous vaginal discharge that adheres to the vaginal walls and has a fishy odor.[64,66] Women with symptomatic candidal infection commonly complain of vaginal pruritus and burning, dysuria, and dyspareunia. Discharge can be thick and white with a cottage cheese appearance or can be watery and homogeneous. Discharge usually is not malodorous, and in many cases, women do not notice a change in vaginal discharge.[66,86] Patients with symptomatic trichomoniasis often have pruritus and a malodorous, frothy, yellow or greenish discharge and can have dysuria, abdominal pain, vulvar erythema and edema, and bloody vaginal discharge. Cervicitis can occur, with punctuate hemorrhages (i.e., strawberry cervix) and friability. Asymptomatic *T. vaginalis* infection occurs commonly.[10]

Laboratory Findings and Diagnosis

Laboratory features that help distinguish BV from candidal vulvovaginitis and trichomonal vaginitis are shown in Table 51.4.

Bacterial Vaginosis.

The diagnosis of BV is commonly established in the clinical setting by the finding of three or more of the following Amsel criteria: (1) thin, homogeneous vaginal discharge; (2) vaginal pH >4.5; (3) characteristic fishy or amine odor released when 10% KOH is added to the vaginal fluid specimen (i.e., positive whiff test); and (4) 20% or more of epithelial cells having the appearance of clue cells, which are stippled epithelial cells whose borders are obscured by adherent bacteria (see Fig. 51.1).[64] Diagnostic accuracy increases with use of the Amsel criteria.[25] Alternative tests include the use of Gram stain to group bacteria into morphologic types (i.e., Nugent scoring). Amsel criteria and Nugent scores show good correlation.[2,93]

Alternative testing includes nonmicroscopic point-of-care testing. Some tests detect the metabolic products of BV-related organisms such as sialidase and prolineaminopeptidase.[2,64] A DNA probe for *G. vaginalis* ribosomal RNA is available but is not useful if rapid results are needed. This test is most helpful as a supplemental marker to detect high concentrations of *G. vaginalis*.[22,93]

Routine aerobic and anaerobic vaginal cultures are not helpful, and molecular diagnostic techniques are primarily a research tool.[2,67] BV usually does not produce an inflammatory response, and the finding of WBCs on a vaginal smear indicates concurrent vaginitis or cervicitis due to another cause.[92,93]

Candida species.

Candida vaginitis is diagnosed by demonstrating budding, hyphae, pseudohyphae, or blastospores on microscopic examination of a saline or 10% KOH preparation.[2,63] This technique has a sensitivity of about 50% because organisms such as *C. glabrata*, which does not form hyphae or pseudohyphae, are easily missed on microscopy.[2] If the KOH preparation is negative, culture can confirm the diagnosis in symptomatic people.[67,86] Culture may be particularly helpful for patients with ongoing nonspecific symptoms in whom BV and trichomoniasis have been excluded.[86] In cases of complicated vulvovaginal candidiasis, culture is important in identifying the species of the organism because therapy may be different or longer.[63,94] Culture can also demonstrate eradication of the organism, and for patients with persistent symptoms, an alternative cause should be investigated.[63,94] It is useful to measure vaginal pH because the vaginal pH remains low (<4.5) in vaginal candidiasis, unlike BV or trichomoniasis.[86]

Trichomonas vaginalis.

Diagnosis of trichomoniasis can be made by visualizing the motile protozoa on a wet mount preparation; however, the test result is negative in 30% to 50% of cases.[2,67] Culture using Diamond media or the InPouch *T. vaginalis* culture system is more sensitive.[2,25,67] Culture can be performed on vaginal specimens, including patient self-collected specimens.

Conventional and liquid Papanicolaou (Pap) tests are not considered diagnostic because of high false-positive and false-negative rates.[2,95] A DNA probe test has a sensitivity of 63% and specificity of 99% compared with culture and TMA. It usually is best performed in the laboratory rather than the office setting because the test is moderately complex and requires about 45 minutes to complete.[2]

One point-of-care test that uses an immunochromatographic capillary flow assay with monoclonal antibodies takes 10 minutes to complete and has 82% to 95% sensitivity and 97% to 100% specificity.[2] PCR has excellent sensitivity and specificity (85% to 100%) but is not available commercially.[10] TMA has 95% to 100% sensitivity and 95% to 100% specificity and is approved for endocervical, urine, and vaginal swab specimens in women.[2,47,48] NAAT using SDA is approved for use with female endocervical, vaginal, and urine specimens.[2]

Because urine or vaginal specimens collected without use of a speculum can be used to detect trichomoniasis, vulvovaginal candidiasis, *N. gonorrhoeae*, and *C. trachomatis*, it is possible to avoid the more invasive speculum examination to determine the cause of vaginitis in adolescents.

Management

Bacterial Vaginosis.

Metronidazole administered orally for 7 days is the recommended therapy for women with symptomatic BV,[2] and it is preferred over single-dose therapy because of superior efficacy.[2,25,64,69] Alternative regimens with intravaginal metronidazole or clindamycin, which are outlined in Table 51.4, have fewer gastrointestinal side effects and cure rates similar to those for oral metronidazole at 1 month after treatment.[2,25,67,69] Clindamycin cream should not be used when condoms are used because the oil base weakens the latex.[2] Alternate therapeutic regimens have included the use of tinidazole, which has fewer side effects than metronidazole but is more expensive, and oral clindamycin.[2,66,96]

A Cochrane review found insufficient evidence to recommend for or against probiotics. The 2015 STD treatment guidelines do not recommend this therapy or currently available lactobacillus formulations as adjunctive or replacement therapy to restore normal vaginal flora.[2,97]

There are no current standard recommendations for treatment of recurrent BV infection, which occurs within 3 months in approximately one third of women.[69] Treatment may only suppress biofilm-embedded infection and allow organisms to evade host defense responses. Recurrences may be due to relapse rather than reinfection.[67,69,85] A large, multicenter study demonstrated the 70% efficacy of twice-weekly maintenance therapy using metronidazole vaginal gel, but it only suppressed BV in many subjects and led to vaginal candidiasis as a complication.[98,99] One uncontrolled study showed promising results with nitroimidazole and boric acid used to disrupt the biofilm and allow penetration of the antibiotic.[100] Other regimens that have been evaluated include oral nitroimidazole and intravaginal boric acid followed by suppressive metronidazole gel and a combination of monthly oral metronidazole and fluconazole.[100,101] The latter regimen was associated with decreased BV episodes and increased colonization with normal flora.

Long-term treatment with vaginal metronidazole is well tolerated, unlike oral treatment, which can be associated with neutropenia or peripheral neuropathy. Prolonged treatment with clindamycin increases the risk of *C. difficile* colitis.[69] Resistance to metronidazole and clindamycin has been seen in cases of recurrent BV.[68] The 2015 STDs treatment guidelines do not recommend treating asymptomatic nonpregnant women.[2]

Candidiasis.

Topical therapy with azoles, such as clotrimazole, terconazole, miconazole, butoconazole, and tioconazole, is effective for vulvovaginal candidiasis in 1- to 7-day regimens. Many of these topical formulations are available over the counter. Single-dose fluconazole (150 mg) therapy has efficacy that is comparable to topical therapy.[2,63,66,102] Symptomatic relief and negative fungal cultures are achieved in up to 90% of patients with uncomplicated vulvovaginal candidiasis. Sexual partners usually do not require therapy unless they have candidal balanitis.[2]

Recurrent or chronic candidal vulvovaginitis merits investigation for predisposing conditions, which includes obtaining cultures to confirm the diagnosis and identify the pathogen.[63] These infections may require a longer duration of topical (7 to 14 days) or oral therapy including nonfluconazole imidazole drugs.[2,66,67,86] Topical boric acid in the form of suppositories (600 mg in a gelatin capsule) and topical flucytosine have been useful in patients with non-*albicans Candida* species and imidazole-resistant species. Alternative therapies are useful, especially in cases of non-*albicans Candida* species.[66,86,94] When using fluconazole, patients with recurrent vulvovaginal candidiasis can be treated initially with a single dose every 3 days for a total of three doses, followed by 100 mg, 150 mg, or 200 mg once each week for 6 months.[2] For women who cannot take fluconazole, repeated topical imidazole therapy has been effective.[2,66,67]

Suppressive therapy usually is continued for 6 months, but recurrence is common after therapy is discontinued because organisms are suppressed rather than eradicated. Prophylaxis can be reinstituted.[2,63,86] Fluconazole resistance and clinical failure is uncommon but increasing, and although not usually warranted, in patients with breakthrough *Candida* infection, susceptibility testing may be helpful.[2,103] Only topical azole medications are recommended in pregnancy.[2]

Trichomonas vaginalis.

Systemic therapy with oral metronidazole or tinidazole is indicated for treatment of trichomoniasis.[2] Metronidazole has an 84% to 98% cure rate with a 7-day course (500 mg twice daily) or a large single dose (2 g taken orally). Most recurrent infections are from reinfection, and although uncommon, metronidazole resistance has been reported in approximately 4% to 10% of cases.[2,49,67,69] Topical therapy with metronidazole gel is not effective because the gel does not penetrate the urethral and perivaginal glands adequately.[2,10,49]

Single-dose tinidazole (2 g taken orally) has a 92% to 100% cure rate and reports of 1% resistance.[2] Studies show tinidazole to be equivalent or superior to single-dose metronidazole for cure and symptom resolution.[2] One study found a 92% cure rate using a combination of oral and vaginal tinidazole in patients unresponsive to metronidazole.[104] Tinidazole appears to be better tolerated than metronidazole and has fewer gastrointestinal tract and central nervous system side effects.

Sexual partners should be evaluated for STIs and treated for trichomoniasis. For treatment failures, susceptibility testing is recommended for metronidazole and tinidazole.[2,49] Women with HIV infections should be treated with metronidazole for 7 days rather than single-dose therapy because the latter is less effective in these patients due to concurrent BV, impaired immunity, and concurrent antiretroviral therapy, which may impact clearance and reduce the efficacy of metronidazole.[2,105] There are no contraindications to using metronidazole during pregnancy, but tinidazole should not be used because of concerns about moderate adverse risks.[2]

Complications

Bacterial Vaginosis.

BV has been associated with chorioamnionitis, postpartum endometritis, posthysterectomy vaginal cuff cellulitis, postabortion PID, premature rupture of membranes, preterm labor and delivery, low birth weight, spontaneous abortion, and intra-amniotic infection.[25,64,76,106] The risk of preterm delivery is restricted to a small subset of women; risk may be related to the genetic host response to inflammation and cytokine production.[25,64,76] Vaginal microorganisms can ascend to the upper tract, causing infection and inflammation in the decidua, chorioamnion, or amniotic fluid.[64]

Data are conflicting about whether the treatment of pregnant women for BV prevents complications.[2,25,64,76,107–110] Two systematic reviews found little evidence that screening and treating all pregnant women prevents preterm birth.[108,109] The evidence for screening asymptomatic women at low risk for preterm delivery were poor, and evidence for women at high risk for preterm delivery were conflicting. The 2015 STD treatment guidelines state that the evidence is insufficient to recommend screening of asymptomatic pregnant women at low or high risk for preterm delivery, but they do recommend treatment for all symptomatic pregnant women using any oral or vaginal regimen.[2]

BV has been associated with an elevated risk of acquiring *T. vaginalis*, *N. gonorrhoeae*, *C. trachomatis*, and HSV-2.[2,109,111] Studies also have shown an association between BV and cervicitis and PID, but a causal relationship remains unproved.[64,66] Organisms associated with BV have been found in the upper genital tracts of women with PID. Studies using endometrial biopsies have found an association between BV and endometritis, which may be silent clinically or manifest as intermenstrual or increased bleeding.[64]

Women with BV are more likely to have PID, and women with PID are more likely to have BV.[25,64,76] Treatment of BV has been associated with decreased PID in women undergoing abortion and decreased postoperative cuff cellulitis.[64,76] Intravaginal treatment of BV has been associated with improved rates of resolution of cervicitis.[64] However, the relationship between BV and PID for women not undergoing abortion or uterine instrumentation is not clear.[25,76,112] There is no current recommendation for treatment of nonpregnant, asymptomatic women as a standard clinical practice.[2,64]

Trichomonas vaginalis.

Trichomoniasis has been associated with premature rupture of membranes, preterm delivery, and low-birth-weight infants,.[2,25,113] *T. vaginalis* has also been associated with an increased risk of PID in women who are HIV positive.[2,113] Although treatment of *T. vaginalis* during pregnancy does not appear to reduce complications, the 2015 CDC STD treatment guidelines recommend that all symptomatic pregnant women should be tested and considered for treatment at any stage of pregnancy.[2,107,114] Although a single dose of metronidazole has been demonstrated to be safe at all stages of pregnancy, more studies are needed regarding use of tinidazole, and current recommendations recommend avoiding use in pregnancy.[2]

Human Immunodeficiency Virus.

BV and *T. vaginalis* enhance acquisition of HIV and transmission to a partner.[2,25,29,64,76,105,115] Vulvovaginal candidiasis has been associated with increased HIV seroconversion in HIV-negative women and higher levels of cervicovaginal HIV shedding in HIV-positive women. Treatment of *T. vaginalis* reduces HIV viral shedding in vaginal secretions.[105] However, no studies have demonstrated similar effects on viral shedding in subjects with BV or vulvovaginal candidiasis.[2,25]

Vulvitis in Adolescents

Inflammation of the vulva in adolescents most commonly is caused by HSV and yeasts (see Table 51.4). HSV often causes painful genital ulcers, along with vulvar inflammation and inguinal lymphadenopathy (see Chapter 50).[7] Occasionally, inflammation can be associated with *T. vaginalis* infection.

Prevention

Correct and consistent use of condoms is the most effective means of preventing and reducing transmission of the STIs associated with vulvovaginitis.

Cervicitis

Cervicitis is inflammation of the endocervix or ectocervix. Both are common problems among adolescents, but neither is common in prepubertal girls. Under the influence of estrogens after puberty, the vaginal epithelium and ectocervix become cornified and relatively resistant to infection with a number of pathogens, including *N. gonorrhoeae* and *C. trachomatis*.[7] In contrast, the endocervix continues to be lined with columnar epithelium and remains susceptible to infection with these organisms. In adolescents and adult women, these organisms usually cause endocervicitis in the absence of vaginitis.

A normal developmental finding in adolescents is the ectropion, an erythematous area surrounding the os at the junction between columnar and stratified squamous epithelium. During adolescence, the ectropion recedes as the result of squamous metaplasia. Although some adolescents with a large ectropion may have significant vaginal discharge, this is not a pathologic or infectious process. The ectropion usually is not friable, and edema or friability suggests infection.[6]

Ectocervicitis

Ectocervicitis represents infection of the stratified squamous epithelium of the ectocervix. Ectocervicitis can occur in conjunction with trichomonal vaginitis and HSV infection. HSV causes ectocervicitis and endocervicitis.[6]

Endocervicitis

Etiologic Agents and Epidemiology

Endocervicitis represents infection of the endocervical columnar epithelium and can produce mucopurulent cervicitis. Common pathogens that cause endocervicitis are *N. gonorrhoeae*, *C. trachomatis*, *M. genitalium*, and HSV.[6,116–119] Multiple studies have demonstrated an association between *M. genitalium* and mucopurulent cervicitis.[16,33,36,59,116–118,120–123] There also is a possible association with BV because cervicitis is more likely to resolve when patients also are treated for BV.[25,116–118,120] Theories about this relationship include proinflammatory vaginal cytokines in patients with BV and the glycosidases and proteinases produced by BV-associated organisms that may degrade cervicovaginal mucus.[116,117]

The prevalence of cervicitis varies from 22% to 41% depending on the definition used, which is inconsistent among the various studies in the literature.[116] A randomized, multicenter study that ruled out *C. trachomatis*, *N. gonorrhoeae*, *T. vaginalis*, and *M. genitalium* by NAAT found that 61% of subjects had mucopurulent cervicitis of unknown origin.[124]

Clinically apparent cervicitis is not caused solely by sexually transmitted agents. Other entities include tuberculosis, noninfectious causes such as sarcoidosis and Behçet disease, and local insults due to chemical douches, spermicides, and foreign bodies.[116–119]

Clinical Manifestations and Differential Diagnosis

Endocervicitis often is overlooked and underdiagnosed because signs and symptoms can be mild or absent. PID is one consequence of untreated mucopurulent cervicitis.[6] Sexually active adolescents with vaginal discharge, lower abdominal pain, abnormal vaginal bleeding, or deep dyspareunia should be evaluated for endocervicitis.[6] Evaluation also is indicated if a sexual partner has an STI.

Cervical abnormalities associated with endocervicitis range from subtle changes to a yellow endocervical discharge and an edematous, erythematous, and easily friable appearance to the cervix.[6] There is no consensus definition for mucopurulent cervicitis, which makes evaluation of the research literature difficult.[116,117] Definitions include inflammation of the endocervix with possible edema, yellow-green endocervical discharge, increased numbers of neutrophils on microscopic examination of cervical secretions, and inducible endocervical bleeding.

The 2015 CDC STD treatment guidelines outline the two major diagnostic criteria as purulent or mucopurulent endocervical discharge and sustained endocervical bleeding.[2] Mucopurulence is characterized by a yellow or green color on a cotton-tipped applicator obtained from the endocervix. The number of neutrophils considered significant varies in different studies from at least 30 cells per 400× magnified microscopic field to more than 10 cells per 1000× magnified microscopic field. Although the use of a 30-cell cut point provides greater specificity, detection of yellow endocervical mucopus is more accurate than the number of WBCs.[2,6,117–119]

Laboratory Findings and Diagnosis

Specific microbiologic diagnosis informs appropriate treatment. Patients should be tested for *N. gonorrhoeae, C. trachomatis, T. vaginalis*, and BV. Gram-negative intracellular diplococci are seen on Gram stain in about one half of cases of gonococcal endocervicitis.[6] Given the poor sensitivity of the Gram stain and the possibility of infection in the absence of any abnormality, evaluation for gonococcal endocervicitis must include NAAT.[2] Inflammatory changes can be even less remarkable with endocervicitis caused by *C. trachomatis*. NAAT is recommended in all cases of suspected *C. trachomatis* infection.[2] A saline wet mount preparation can be used to diagnose *T. vaginalis* and to help establish the diagnosis of BV.[2,6,7,117] Because of the poor sensitivity of wet mounts, further testing for *T. vaginalis* by culture, antigen-based tests, or NAAT should be conducted if the wet mount result is negative.

If HSV is suspected, a culture or PCR test should be obtained, although the utility of HSV testing remains unknown.[2] NAAT for *M. genitalium* is not available commercially but may be available in laboratories where validation testing has been completed.[2]

Treatment

The initial management of endocervicitis depends on the clinical findings and risk of the adolescent for certain STIs (Table 51.5). A positive laboratory test result for *N. gonorrhoeae, C. trachomatis, T.*

vaginalis, or HSV defines treatment. However, empiric treatment can be considered if there is a strong suspicion of *N. gonorrhoeae* or *C. trachomatis* based on a high prevalence of either microbe in the community or a concern that the patient may be at risk for loss to follow-up.[2,120]

TABLE 51.5

Treatment of Cervicitis in Adolescents

Results	Suggested Treatment
Mucopurulent or purulent endocervical discharge and/or sustained easily induced endocervical bleeding	Treat for *Chlamydia trachomatis or Neisseria gonorrhoeae* with positive test results *or* consider presumptive treatment for *C. trachomatis* and *N. gonorrhoeae* if prevalence is high in patient population or community (e.g., known contact, new and/or multiple sex partners, age ≤25, unprotected sex) and testing not possible and/or follow-up cannot be ensured; if at low risk for STIs, treatment can be deferred pending microbial results
Trichomonas seen on wet mount or identified on rapid test, culture, NAAT	Treat with oral metronidazole or tinidazole
Bacterial vaginosis diagnosed	Treat with oral metronidazole *or* tinidazole *or* intravaginal metronidazole *or* clindamycin
Clinical presentation suggesting herpes simplex virus infection	Consider oral acyclovir *or* famciclovir *or* valacyclovir
Persistent or recurrent cervicitis	Rule out re-exposure or treatment failure for *N. gonorrhoeae* and *C. trachomatis* or other identified STIs and exclude BV. Testing for *Mycoplasma genitalium* in settings with validated assays can be conducted. Moxifloxacin can be used if NAAT results are positive and initial treatment with azithromycin (1 g PO once) failed. CDC recommends deferring therapy until further microbial results are available[a]

[a] Data from Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep 2015;64(RR-3):1–137.

BV, bacterial vaginosis; CDC, Centers for Disease Control and Prevention; NAAT, nucleic acid amplification test, STIs, sexually transmitted infections.

BV should be treated because some studies have shown higher rates of resolution of endocervicitis with treatment of BV.[117] For women at lower risk for STIs, treatment can await the results of diagnostic testing.[2]

More data are needed about the treatment of *M. genitalium* cervicitis. The antibiotics directed at treating *N. gonorrhoeae* and *C. trachomatis* are not adequate to treat cervicitis caused by other organisms, and the standard treatment regimen for PID with cefoxitin and doxycycline is ineffective for women with *M. genitalium* associated with PID.[120,125,126] Testing for *M. genitalium* is recommended for women with persistent cervicitis or persistent PID for whom re-exposure to an infected partner or nonadherence has been ruled out.[2,35,116] If the initial treatment did not include azithromycin, the antibiotic should be given. According to CDC guidelines, moxifloxacin can be given based on having positive *M. genitalium* test results.[2] Other investigators have suggested considering this treatment for recurrent or persistent cervicitis when testing is not available,[35] but some have questioned the treatment of cervicitis of unknown origin because the clinical cure described is not related to antibiotic therapy.[127]

The need to consider *M. genitalium* in the adolescent population was demonstrated in several studies. One showed a cumulative rate over a 27-month period among 14- to 17-year-old girls to be 14%, which was concordant with their male partners.[128] Another study of girls and women 14 to 21 years old found a rate of 22%.[129]

Follow-up after completion of therapy is recommended for adolescents with persistent symptoms.[2] The management of mucopurulent cervicitis also requires evaluation and treatment of all sexual partners for STIs, and it provides an opportunity to reinforce STI prevention measures.[2]

Complications

Complications of untreated mucopurulent cervicitis include PID and the possible long-term sequelae of ectopic pregnancy and infertility. The relationship between *N. gonorrhoeae* or *C. trachomatis* and PID is well established, and there is increasing evidence that *M. genitalium* also is associated with PID.[6,59,118,130–132] Cervicitis also increases the risk of transmission and acquisition of HIV infection. Viral shedding of HIV decreases with effective treatment for cervicitis.[2,6,118]

Prevention

Consistent use of condoms can reduce transmission of STI pathogens associated with cervicitis.

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52

Pelvic Inflammatory Disease

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Pelvic inflammatory disease (PID) is an ascending, polymicrobial genital tract infection that is considered to be the sequela of a sexually transmitted disease (STD) due to *Chlamydia trachomatis* or *Neisseria gonorrhoeae* and endogenous microorganisms from the lower genital tract (i.e., vagina and cervix). PID can include endometritis, salpingitis, tubo-ovarian abscess, or pelvic peritonitis. Morbidity from PID includes chronic pelvic pain, ectopic pregnancy, and tubal-factor infertility.

Over the past several decades, rates of PID have declined in hospital and ambulatory settings in the United States.[1,2] Although no single factor explains this trend, increases in chlamydia screening, use of more sensitive diagnostic technologies, and availability of single-dose therapies for uncomplicated lower genital tract infections may be responsible.[1–3] Despite declining trends, sexually active adolescents have among the highest age-specific rates of PID, potentially impacting future fertility.[1,4] Risk factors, including biologic and behavioral predispositions, barriers to healthcare, poor compliance, and issues surrounding confidentiality, make this age group especially vulnerable.[5]

Epidemiology

The US incidence estimates provided by the Centers for Disease Control and Prevention (CDC) in 2001 indicate that approximately 750,000 cases of PID are diagnosed annually, with 20% occurring among sexually active girls younger than 19 years.[4] High-risk sexual behavior among adolescents, including engaging in unprotected sex, having multiple sex partners, age discrepancy of partners, early sexual debut, drug or alcohol abuse, and having serially monogamous relationships of short duration and high frequency, have been identified as risk factors.[6–8] Young adolescent women have a cervical transitional zone of columnar epithelium (i.e., ectropion) that is the targeted attachment site of *C. trachomatis* and *N. gonorrhoeae*.[9]

Contraceptives play an important role in modulating the risk of PID. Nonuse of contraception is a risk factor for PID, whereas barrier methods decrease the risk of STD acquisition and subsequent development of PID.[10,11] Most studies that evaluate the role of oral contraceptive pills demonstrate a protective role, which may result from thickening of the cervical mucus, shorter duration of menses, or a decreased receptivity of the endometrium to infection.[9,12–14]

Intrauterine devices (IUDs) have had limited use among the adolescent population due to concerns about the increased risk of PID and STDs. Modern IUDs do not increase the risk of PID beyond the risk associated with insertion of the device, nor do they increase the risk of STD acquisition.[15,16] The American Congress of Obstetricians and Gynecologists supports the use of the IUD as a first-line agent in adolescents and women who have never been pregnant.[17] Douching also has been implicated, and although the elevated risk may be caused by an alteration of the vaginal flora or mechanical flushing of organisms into the upper genital tract, the exact mechanism is unknown.

A prior history of PID or another STD is a recognized risk factor for PID. The increased risk observed may reflect reinfection from untreated partners, relapse from inadequate therapy for the first infection, increased vulnerability to subsequent gram-negative or anaerobic bacterial infection, or continued presence of other risk factors. Estimates that almost one third of female adolescents diagnosed with PID return with a subsequent STD or PID within 6 months of their original treatment highlights that reinfection is likely to be extremely common in this group.[18]

Etiologic Agents

C. trachomatis and *N. gonorrhoeae* have been isolated from the lower and upper genital tracts in women with PID and are accepted universally as etiologic agents of PID. Estimates from the PID Evaluation and Clinical Health (PEACH) study found that approximately 40% of women diagnosed with PID had cervical *C. trachomatis* or *N. gonorrhoeae* infection.[19] *Chlamydia* is the most commonly reported STD in the United States, with more than 1 million reported female cases in 2014.[20] Women between the ages of 20 and 24 years had the highest incidence of reported *Chlamydia* infection (3651 per 100,000), and girls between the ages of 15 and 19 years had the second highest incidence (2941 per 100,000).[20]

Data from prospective studies suggest that about 15% of untreated chlamydial infections progress to clinically diagnosed PID.[21,22] *Chlamydia* infection has been associated with tubal scarring, obstruction, and peritubal adhesions.[23–25] Evidence demonstrates that *C. trachomatis* infection is particularly important in *subclinical or silent PID*, a term used to describe women with lower genital tract infections and concurrent endometritis or salpingitis but with mild or no symptoms. Subclinical PID is estimated to account for 50% or more of all PID cases.[9]

N. gonorrhoeae is the second most commonly reported bacterial STD, with incidence reaching 569 cases per 100,000 US girls between the ages of 15 and 19 years in 2014.[20] Women younger than 25 years of age are at the highest risk for acquiring gonorrhea, and between 10% and 20% of women with inadequately treated gonococcal cervicitis will develop PID.[26]

Endogenous microorganisms associated with bacterial vaginosis (BV), a disruption of the normal vaginal microflora leading to an overgrowth of anaerobic and facultative bacteria, have been recovered from the upper genital tract in women with acute PID. Many investigations have demonstrated an association between BV and acute PID,[19,27–34] concluding that BV facilitates the ascending spread of vaginal microorganisms and provides an inoculum of potentially pathogenic microorganisms. Sexually transmitted *Mycoplasma genitalium* also has emerged as a likely cause of cervicitis, endometritis, salpingitis, and infertility, but research is needed to further investigate the importance of this organism.[35,36]

Pathogenesis and Pathologic Findings

The ascent of *C. trachomatis* and *N. gonorrhoeae* from the cervix through the endometrium to the fallopian tubes is the most common antecedent to PID. After infection-induced inflammation reaches the fallopian tube, a complex interaction of epithelial degeneration, edema, and other inflammatory responses occurs, leading to scarring of the fallopian tube (Fig. 52.1).[37] The presence of other bacteria may be explained by priming of tissue by the STD organisms (i.e., monomicrobial phase) for opportunistic invasion by facultative and anaerobic bacteria from the lower genital tract (i.e., polymicrobial phase).[38] Priming can result from alteration of local mucosal defenses or anatomic interference with mechanical host defenses that drain secretions from the upper genital tract mucosa.

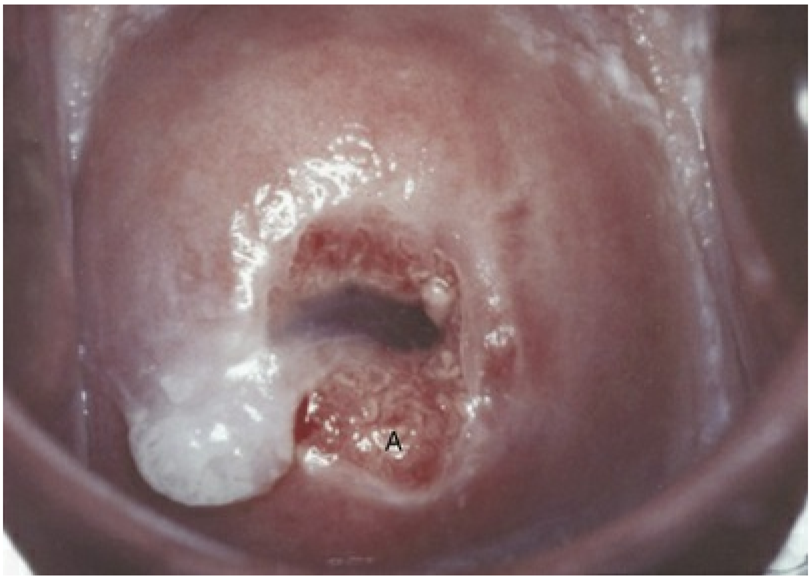

FIGURE 52.1 Examination of an adolescent girl shows an area of cervical ectopy (*A*), where the columnar cells that line the inner area of the cervix extend to the outer area.

Diagnosis

Despite published guidelines (Box 52.1), the clinical diagnosis of PID is challenging because of variations in clinical presentation. Studies have documented suboptimal healthcare personnel adherence to recommended guidelines for the diagnosis of PID.[39,40] Diagnosing PID in female adolescents can pose unique challenges because they may be unable to recognize their symptoms, may be reluctant to reveal their sexual activity, or may forgo the use of medical care because of the stigma of having an STD. Clinicians need to recognize the implication of mild or nonspecific findings, particularly in a girl giving a challenging history and undergoing her first pelvic examination.[41]

Box 52.1

CDC Guidelines for the Clinical Diagnosis of Pelvic Inflammatory Disease

Minimum Criteria

Cervical motion tenderness *or* uterine tenderness *or* adnexal tenderness

Empiric treatment of PID should be initiated in sexually active young women and others at risk for STIs if ≥1 of the minimum criteria exist and no other causes for the illness can be identified.

Additional Criteria

Oral temperature >38.3°C (>101°F)

Abnormal cervical or vaginal mucopurulent discharge

Abundant numbers of WBCs on saline microscopy of vaginal secretions

Elevated erythrocyte sedimentation rate

Elevated C-reactive protein level

Laboratory documentation of cervical infection due to *Chlamydia trachomatis* or *Neisseria gonorrhoeae*

Definitive Criteria

Endometrial biopsy with histopathologic evidence of endometritis

Transvaginal sonography or magnetic resonance imaging techniques showing thickened, fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex, or Doppler studies suggesting pelvic infection (e.g., tubal hyperemia)

Laparoscopic abnormalities consistent with PID

CDC, Centers for Disease Control and Prevention; PID, pelvic inflammatory disease; STIs, sexually transmitted infections; WBCs, white blood cells.

Pelvic pain is the most common symptom of PID, although it may be mild in some women. Other symptoms are listed in Box 52.2, although the absence of these findings does not exclude PID. A through history, including an assessment of symptoms, risk factors, sexual and menstrual history, and prior STD, is essential in making an accurate diagnosis. A pelvic examination should be performed to assess for signs of cervical inflammation (i.e., cervicitis), including mucopurulent discharge and cervical friability (i.e., easy bleeding to touch). After the speculum examination and collection of the appropriate microbiologic samples, a bimanual examination should be performed to assess for cervical, uterine, or adnexal tenderness or masses. Microscopy of the vaginal secretions can be performed to evaluate leukorrhea (>1 leukocyte per epithelial cell).

Box 52.2

Symptoms Associated With Clinically Suspected Pelvic Inflammatory Disease

Abdominal pain

Abnormal purulent discharge

Metrorrhagia (i.e., uterine bleeding at irregular intervals)

Postcoital bleeding

Fever

Dysuria

Nausea and vomiting

When there is concern about a tubo-ovarian abscess or the patient is not responding to conventional therapy for PID, further diagnostic evaluation using imaging studies can be helpful. Although other causes of pelvic or abdominal pain should be explored, the rarity of some of these conditions in adolescence helps to narrow the diagnosis (Box 52.3 and Table 52.1). Healthcare personnel should maintain a low threshold for treating PID in at-risk populations (e.g., sexually active adolescents), and empiric therapy should be initiated unless another cause is discovered.

Box 52.3

Differential Diagnosis of Pelvic Inflammatory Disease

Gynecologic Causes

Pregnancy (i.e., ectopic or a septic or threatened abortion)

Ovarian cyst (i.e., intact, ruptured, or torsed)

Endometriosis

Mittelschmerz (i.e., pain associated with ovulation)

Dysmenorrhea

Gastrointestinal Causes

Appendicitis

Constipation

Diarrhea

Gastroenteritis

Inflammatory bowel disease

Irritable bowel syndrome

Urinary Tract Causes

Cystitis

Urethritis

Urinary calculus

Pyelonephritis

Modified from Shrier LA. Bacterial sexually transmitted infections: gonorrhea, chlamydia, pelvic inflammatory disease, and syphilis. In: Emans SJH, Laufer MR, Goldstein DP (eds). Pediatric and Adolescent Gynecology, 5th ed. Philadelphia, Lippincott-Raven, 2005, p. 591.

TABLE 52.1

Characteristics of Pelvic Inflammatory Disease, Ectopic Pregnancy, and Acute Appendicitis

Characteristic	Pelvic Inflammatory Disease	Ectopic Pregnancy	Acute Appendicitis
HISTORY			
Age	Any after puberty	Risk increases with age	Any
Onset of symptoms	75% within 7 days of menses	At 4 weeks' gestation or later; rupture at 6–10 weeks' gestation	Any
Abdominal pain	Dull, crampy, localized to lower abdomen; possible right upper quadrant pain (perihepatitis)	Before rupture: localized or diffuse, dull abdominal pain After rupture: severe, poorly localized pain, rectal pressure	Poorly localized periumbilical or epigastric pain with shift to right lower quadrant after 4–6 hours; increasing severity
Vaginal discharge	55%	Not associated	Not associated
Menstrual pattern	Metrorrhagia; missed menstruation not associated	Intermittent bleeding or spotting; often missed or late menstruation	No change in usual pattern
Fever	>38°C in up to 35%	>38°C in up to 20%	Usually <38°C; >38°C after perforation
Nausea and	Uncommon	Uncommon	50%–60%

vomiting			
SIGNS			
Cervicitis	Purulent exudate in 80%	Not associated	Not associated
Cervical motion tenderness	>95%	Can be elicited; not as pronounced as in salpingitis	Usually none; can occur with perforation if appendix adjacent to adnexa
Adnexal mass	5%–50%	35%–50%	Not associated
LABORATORY EVALUATION			
Anemia	Not associated	Significant (hematocrit <25%) after rupture	Not associated
Leukocyte count	Normal or elevated	Usually elevated	Mildly elevated
Pregnancy test	Usually negative	Positive 1–2 weeks after conception	Usually negative but pregnant patients can have appendicitis
Ultrasonography	Common findings: cul-de-sac fluid, adnexal enlargement, complex adnexal mass	Intrauterine gestational sac absent	Can detect inflamed appendix
Laparoscopy	Inflammation of fallopian tubes	Fallopian tube pregnancy with or without rupture	Normal fallopian tubes; inflamed appendix

Modified from Paradise JE, Grant L. Pelvic inflammatory disease in adolescents. Pediatr Rev 1992;13:216–223.

Laboratory Findings and Diagnosis

A cervical or vaginal nucleic acid amplification test for *C. trachomatis* and *N. gonorrhoeae* should be obtained for all patients with suspected PID.[42] Laboratory confirmation of an STD is helpful but is not necessary to justify initiation of therapy for PID. Treatment should not be delayed if PID is suspected on clinical evaluation. Patients can be assessed for other vaginal infections such as BV and *Trichomonas vaginalis*. Molecular tests for *M. genitalium* are becoming available commercially.

All women diagnosed with acute PID should have a pregnancy test to exclude ectopic pregnancy, and they should be screened for human immunodeficiency virus (HIV) infection.[42] Pregnancy always should be excluded in sexually active women evaluated for pelvic pain.

An elevated white blood cell count discovered by serum testing is a nonspecific marker of PID. An elevated erythrocyte sedimentation rate or C-reactive protein level can increase the specificity, but the clinical usefulness is limited.[43] Although an endometrial biopsy offers an acceptable approach to documenting inflammation of the upper genital tract, a biopsy usually is not performed for adolescents, and the delay between the biopsy and final histopathologic report makes this test most appropriate for cases in which there is diagnostic uncertainty. Although laparoscopy is considered the gold standard for the diagnosis of PID, costs and surgical risks preclude the universal use of laparoscopy for the diagnosis of PID. HIV and syphilis testing should be offered.

Management

The principles of management and criteria for hospitalization are outlined in Box 52.4. The severity of disease usually dictates whether a patient is treated on an outpatient or inpatient basis. Most women with uncomplicated PID are treated on an outpatient basis with oral therapy because long-term outcomes are not improved with parenteral antibiotics.[19]

Box 52.4

Principles of Management of Pelvic Inflammatory Disease

- Exclude pregnancy and appendicitis
- Use minimum criteria to guide diagnosis[a]
- Err on the side of overdiagnosis
- Perform testing for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*
- Consider screening and treating for lower genital tract infections, including bacterial vaginosis and *Trichomonas vaginalis*
- Offer HIV testing to all women diagnosed with acute PID
- Treat early and with broad-spectrum antibiotics
- Reassess patient 48–72 hours after initiating therapy
- Criteria for hospitalization

- Surgical emergency (e.g., appendicitis cannot be excluded)
- Patient is pregnant
- Patient does not respond clinically to oral antimicrobial therapy
- Patient is unable to follow or tolerate an outpatient oral regimen
- Patient has severe illness, nausea and vomiting, or high fever
- Patient has a tubo-ovarian abscess

- Identify, evaluate, and treat sex partners. In settings where only women are treated, male sex partners should be referred for appropriate treatment.
- Educate patient about STI prevention (see Chapter 49), including abstinence, encouraging the use of barrier methods of protection, and regular assessment for STIs

HIV, Human immunodeficiency virus; *PID*, pelvic inflammatory disease; *STI*, sexually transmitted infection.

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[a] See Box 52.1.

A critical component of outpatient management is short-term follow-up, especially in the adolescent population. Adolescent patients should be reassessed 2 to 3 days after oral antibiotics are prescribed to ensure satisfactory improvement. It is important to consider that adolescents may be reluctant to disclose their diagnosis of PID or have greater dependence on adults for financial and logistical support, and they may not be able to obtain prescriptions or keep follow-up appointments.

PID treatment regimens provide broad-spectrum coverage of likely pathogens. Current guidelines recommend that empiric treatment for PID be initiated in sexually active young women and other women at risk for STDs if they are experiencing pelvic or lower abdominal pain, if no cause for the illness other than PID can be identified, and if cervical motion, uterine, or adnexal tenderness are identified on cervical examination (see Table 52.1).[42] Additional supportive criteria are intended to help clinicians recognize when PID should be suspected and when additional information is needed to increase diagnostic certainty.

Recommended treatment regimens for PID are outlined in Table 52.2. The need to cover anaerobes has not been definitively established, but because BV is commonly found in women with PID, some experts recommend an agent with activity against β-lactamase–producing anaerobes. Increased gonococcal resistance to quinolones has led to the discontinuation of recommending a quinolone agent for the treatment of acute PID. Concerns about compliance and tolerability issues, especially among adolescents, have prompted a search for alternative regimens that demonstrate efficacy equal to currently recommended regimens. Although most patients are successfully treated as outpatients, there is a poor correlation between short-term responses and long-term sequelae such as infertility.[44]

TABLE 52.2

Centers for Disease Control and Prevention Treatment Guidelines for Acute Pelvic Inflammatory Disease

Parenteral Regimens	Oral Regimens
RECOMMENDED REGIMENS	RECOMMENDED REGIMENS
Cefotetan, 2 g IV every 12 hr *Or* Cefoxitin, 2 g IV every 6 hr *Plus* Doxycycline, 100 mg PO or IV every 12 hr. Clindamycin, 900 mg IV every 8 hr *Plus* Gentamicin, loading dose IV or IM (2 mg/kg of body weight) followed by a maintenance dose (1.5 mg/kg) every 8 hr. Single daily dosing (3–5 mg/kg) can be substituted.	Ceftriaxone, 250 mg IM in a single dose *Plus* Doxycycline, 100 mg orally bid for 14 days *With or without* Metronidazole, 500 mg orally bid for 14 days. Cefoxitin, 2 g IM in a single dose, and probenecid, 1 g PO administered concurrently in a

ALTERNATIVE REGIMENS	
Ampicillin-sulbactam, 3 g IV every 6 hr *Plus* Doxycycline, 100 mg PO or IV every 12 hr.	single dose *Plus* Doxycycline, 100 mg PO bid for 14 days *With or without* Metronidazole, 500 mg PO bid day for 14 days. Other parenteral third-generation cephalosporin (e.g., ceftizoxime, cefotaxime) *Plus* Doxycycline, 100 mg PO bid for 14 days *With or without* Metronidazole, 500 mg PO bid for 14 days.

Modified from Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep 2015;64(RR-3):1–137.

Complications and Sequelae

Several factors, including the number of PID episodes, severity of infection, and delayed diagnosis or treatment, can influence a woman's risk of developing adverse reproductive long-term outcomes. At least one fourth of women with PID experience one or more serious sequelae, including increased risk of ectopic pregnancy (6- to 10-fold increased rate), tubal factor infertility, or chronic abdominal pain (3-fold increased rate).[45–47] Women treated within 3 days of the onset of illness have improved fertility compared with women whose treatment is delayed, reinforcing the importance of early and often empiric treatment.

Prevention

Adolescents should be queried about their sexual activity and risk factors, and they should be educated about the symptoms and signs of STD and PID. They should be screened routinely for STDs and offered treatment according to accepted guidelines. The U.S. Preventive Services Task Force recommends annual chlamydia and gonorrhea screening for all sexually active females 24 years of age or younger and for older women at increased risk for infection.[48] There is evidence that screening for and treating *C. trachomatis* reduces the incidence of PID and its sequelae.[49–51] The rate of PID among an asymptomatic study population undergoing risk-based enhanced screening for *C. trachomatis* was reduced by 66% compared with controls.[47]

Because STDs play a major role in PID, diagnosis and treatment of male sexual partners is critical to prevent reinfection and improve the long-term health of young women.[19,39] Repeat testing for gonorrhea or chlamydia in 3 to 6 months is recommended if initial testing is positive for either infection. Unprotected intercourse should be avoided until both partners have completed their course of antibiotics to avoid reinfection. The diagnosis of PID gives healthcare personnel an opportunity to perform counseling about safer sex practices and risk reduction.

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53

Epididymitis, Orchitis, and Prostatitis

Noni E. MacDonald, William R. Bowie

Epididymitis

Epididymitis is an inflammatory reaction or infection of the epididymis, the coiled tubular structure attached to the upper posterior part of each testicle that collects, stores, and matures sperm.

Etiology, Epidemiology, and Pathogenesis

Accurate epidemiologic data on epididymitis are lacking, but this disorder is common in sexually active older adolescents and young adult men; epididymitis is rare in prepubertal boys, however, with a reported incidence of only 1.2 in 1000 boys and peak hospital admissions in summer and winter.[1–3] The age distribution in boys is bimodal, with peaks at <5 years of age and then again in early puberty.[4] Acute epididymitis in boys is more common than testicular torsion.[5,6]

Epididymitis can occur as an inflammatory postinfectious reaction to several bacterial and viral pathogens,[1,3,7] or it can be a complication of urethral infections caused by sexually transmitted pathogens,[1,8] by genitourinary tract pathogens (especially if predisposing obstructive anatomic conditions, neurologic genitourinary abnormalities, or anorectal malformations exist),[6,9–12] or, more rarely, through hematogenous spread to the epididymis from a primary focus of infection (e.g., *Haemophilus influenzae* type b, *Salmonella* spp., *Streptococcus pneumoniae, Brucella* spp. or *Mycobacterium tuberculosis*).[13] The microbial cause and predisposing factors in acute bacterial epididymitis in children and adolescents vary with age (Table 53.1). Occasionally, epididymitis is not caused by inflammation or infection but is related to trauma, systemic diseases (e.g., Henoch-Schönlein purpura or Kawasaki disease), or medications (e.g., amiodarone).[2,3,12,14,15] Recurrent epididymitis in a prepubertal boy suggests an underlying genitourinary disorder.[16]

TABLE 53.1

Microbial Etiology and Predisposing Factors in Acute Epididymitis in Children and Adolescents

Predisposing Factors	Etiology	Incidence
PREPUBERTAL CHILDREN		
Underlying structural or neurologic abnormalities of the genitourinary tract	Enterobacteriaceae *Pseudomonas aeruginosa*	Uncommon
Hematogenous spread from primary focus	*Haemophilus influenzae* type b *Streptococcus pneumoniae* *Neisseria meningitidis* *Salmonella* spp.	Uncommon
Postinfectious factors	Adenovirus, enterovirus *Mycoplasma pneumoniae*	Uncommon
ADOLESCENTS		
Urethritis	*Chlamydia trachomatis*	Related to frequency of sexual activity
	Neisseria gonorrhoeae	
Underlying genitourinary tract disorder	Enterobacteriaceae *Pseudomonas aeruginosa*	Uncommon
Hematogenous spread from primary focus	*Streptococcus pneumoniae* *Neisseria meningitidis* *Mycobacterium tuberculosis*	Rare

Clinical Manifestations and Differential Diagnosis

Epididymitis, whether inflammatory or infectious in origin, typically has an acute onset, with unilateral scrotal pain and swelling that increases over 1 or 2 days. Commonly associated symptoms include dysuria and other lower urinary tract symptoms. Sexually transmitted epididymitis usually is accompanied by urethritis, which frequently is asymptomatic. Differentiation of epididymitis from testicular torsion, which requires immediate surgical intervention, is critical.[17,18] Bacterial orchitis, an extension of epididymitis, is another important consideration in the differential diagnosis, especially in prepubertal children. Table 53.2 compares the clinical and laboratory differences among these disorders. The presence of Prehn sign (i.e., relief of pain with testicular elevation) supports the diagnosis of epididymitis but is not definitive.[19] The cremasteric reflex usually is present in epididymitis but is absent in testicular torsion. The presence of urethral discharge is suggestive but not diagnostic of epididymitis. In prepubertal boys with acute scrotal pain, urinalysis and urine culture frequently are performed; but a positive yield is low in epididymitis.[7,20,21] Ultrasonography, radionuclide scan, and, occasionally, magnetic resonance imaging[13,18–25] are helpful in differentiating among these entities (see Table 53.2). For the diagnosis of acute epididymitis, although radionuclide scan was recommended in the past as most accurate, it is not routinely available, and color duplex Doppler ultrasonography is now more often recommended.[25]

TABLE 53.2

Comparison of Clinical Manifestations and Laboratory Findings in Acute Epididymitis, Acute Orchitis, and Testicular Torsion in Children and Adolescents

		Acute Orchitis		
	Acute Epididymitis	**Bacterial**	**Viral**	**Testicular Torsion**
CLINICAL FEATURES				
Most common age	Adolescence	Rare in childhood	Adolescence	Peripubertal
Predisposing factors	After puberty: urethritis	Epididymitis	Failure to be immunized against	None

	(sexually transmitted infection)		mumps	
	Before puberty: structural abnormality			
PAIN				
Onset	Gradual	Gradual	Acute; occasionally gradual	Acute
Severity	Mild to severe	Moderate to severe	Mild to severe	Severe
Fever	Moderate	Moderate to high	Low to high	Uncommon
SYSTEMIC SYMPTOMS				
Anorexia, vomiting, malaise	Can occur with severe infection, uncommon	Common	Can occur	Uncommon
Dysuria	Common	Common	Can occur	Uncommon
SCROTAL FINDINGS				
Testicular lie	Vertical (normal)	Vertical	Vertical	Possibly horizontal
Swelling	++; usually unilateral	++	++ to +++	+
Prehn sign	Pain ↓	Pain ↓	No change in pain	Pain unchanged or ↓
Cremasteric reflex	Usually present	Usually present	Usually present	Usually absent
Tenderness				
Testes	± epididymis tenderness	++	+ to ++ (can be unilateral)	++
Spermatic cord	++	++	++	−
Presence of hydrocele	Common	Common	−	−
Skin inflammation	++	+	−	± (~30%)
Urethral discharge	Possible	Possible	−	−
LABORATORY FINDINGS				
Peripheral blood leukocytosis	++	++	±	±
C-reactive protein	++	+	++	Normal
Pyuria (>10 WBCs/hpf)	++	±	Usually −	Usually −
IMAGING FINDINGS				
Epididymis				
Doppler blood flow	↑ or normal vascularity	↑ vascularity	↑ vascularity	↓ vascularity or avascular
Sonogram	Enlarged and thickened	↑ perfusion	↑ perfusion	Enlarged with ↑ echotexture versus opposite side
Testis				
Doppler	↑ or normal	↑ vascularity	↑ vascularity	↓ vascularity

blood flow	vascularity			or avascular
Sonogram	Enlarged, hypervascular; ↑ perfusion	Testicular masses or swollen testicles with hypoechoic and hypervascular areas	Testicular masses or swollen testicles with hypoechoic and hypervascular areas	No change in echotexture unless late

+, mild to moderate; ++, moderate to severe; ±, variably present; −, absent; ↑, increased; ↓, decreased; WBCs, white blood cells.

Laboratory Findings and Diagnosis

Organisms responsible for infectious epididymitis usually can be isolated from urine and urethral specimens, especially when a sexually transmitted infection (STI) is suspected. A Gram stain of urethral exudate or an intraurethral swab specimen and a culture of intraurethral exudate or a nucleic acid amplification test (NAAT) (either on an intraurethral swab or first-void urine) for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are indicated.[1] As with any STI syndrome, testing for other STIs, including human immunodeficiency virus (HIV) infection, should be considered based on the patient's sexual history and risk factors (see Chapter 49). For prepubertal cases, culture of urine is recommended but may not reveal a pathogen.[19,20]

Management and Complications

Early empiric treatment of suspected STI epididymitis cures the infection, improves the symptoms and signs, prevents transmission of these STI microbes to others, and decreases potential complications.[1,26] For epididymitis most likely caused by gonococcal or chlamydial infection, the recommended treatment regimen is ceftriaxone (single 250-mg intramuscular dose) in addition to doxycycline (100 mg orally twice a day for 10 days) while awaiting laboratory test results.[1,26] For acute epididymitis most likely caused by enteric organisms such as *Escherichia coli* or *Pseudomonas,* levofloxacin or ofloxacin is recommended.[26] Bearing in mind the low rate of positive urine culture results in prepubertal boys with epididymitis, antibiotic therapy is reserved for young infants and for boys with pyuria or positive urine culture results.[27] In addition to antimicrobial therapy, bed rest, scrotal elevation, and administration of analgesics are recommended until fever and local inflammation resolve. Failure of symptoms to improve within 3 days requires reevaluation of the diagnosis and therapy, and it can require hospitalization. If an STI is identified, any sexual partners are contacted for assessment and treatment.

Patients with isolated gram-negative organisms also may need investigation for underlying anatomic or neurologic abnormalities that may be causing urinary tract obstruction. Direct aspiration of the epididymis for specimen collection can be done if other testing does not provide the answer or if evidence of an abscess is present.

In patients with inflammatory postinfectious reactive epididymitis, treatment includes analgesics and supportive care; antimicrobial therapy is not indicated.[27] Complications of epididymitis include testicular abscess, chronic epididymitis, testicular infarction, and infertility. Drainage of scrotal abscesses or orchiectomy is seldom needed if the condition is diagnosed and treated promptly and close follow-up is performed.

Orchitis

Orchitis, inflammation of the testis, rarely occurs in prepubertal patients. Although bacterial epididymo-orchitis does occur, usually infection has spread from the epididymis to include the testicle.[28] Primary orchitis is uncommon except with certain viral diseases, especially mumps.[29–31] Less frequently, enterovirus[32] or, rarely, adenovirus,[33] varicella-zoster virus,[34] or West Nile virus[35] is responsible.

When associated with mumps, orchitis usually follows parotitis by 4 to 8 days, but it can develop up to 6 weeks after parotid gland involvement or in the absence of parotitis. The onset of viral orchitis can be gradual but usually is abrupt with mumps[29] and is heralded by fever, chills, nausea, and lower abdominal pain (see Table 53.2). When the right testis is involved, appendicitis can be suspected erroneously if the scrotum has not been examined carefully. The affected testis is warm, swollen and tender, and the adjacent skin is edematous and red. Patients with mumps orchitis appear to have high levels of interleukin-6 and interferon γ but not as high as in acute mumps meningitis or mumps encephalitis.[30] The mumps virus can be detected in the semen for 14 days, and mumps RNA can be detected for up to 40 days.[36] Mumps orchitis is associated with a transient but significant reduction in sperm count and abnormal sperm morphology, which can account for the long-term adverse effect on fertility in some patients.[37] Although antisperm antibodies can be detected, they do not seem to play a role in mumps orchitis or in subsequent infertility.[37]

Bacterial epididymo-orchitis usually occurs as a consequence of contiguous spread from bacterial epididymitis and is caused by organisms such as *E. coli, Pseudomonas aeruginosa,* and *Klebsiella* or from hematogenous seeding from another source such with *Brucella.*[13] Signs and symptoms are similar to those of epididymitis (see Table 53.2).

Management of viral orchitis is supportive and symptomatic, and it consists of bed rest and analgesia. Corticosteroid therapy is not recommended because no evidence indicates that therapy speeds resolution, and corticosteroids may contribute to testicular atrophy.[37] Early treatment of mumps orchitis with interferon α_{2B} can lead to earlier symptom resolution.[38] Bacterial epididymo-orchitis is treated with antimicrobial therapy (see the earlier section on epididymitis). Surgical treatment may be necessary if testicular abscess or pyocele of the scrotum occurs. Infertility can result from viral or bacterial orchitis, but it is uncommon even after bilateral mumps.[27,37]

Prostatitis

Prostatitis, inflammation of the prostate, encompasses a group of poorly defined clinical entities associated with pelvic and genital pain or discomfort and variable voiding and sexual complaints[39,40]

Etiology, Pathogenesis and Epidemiology

The National Institutes of Health consensus classification of prostatitis includes 4 syndrome categories: (1) acute bacterial prostatitis, (2) chronic bacterial prostatitis, (3) chronic prostatitis or chronic pelvic pain syndrome, and (4) asymptomatic inflammatory prostatitis.[41] Prostatitis does not occur in prepubertal boys and is unusual in adolescents and young adults.[40] Suggested risk factors for bacterial prostatitis include urinary tract instrumentation, urethral strictures, and urethritis.[39] Pathogens reach the prostate by reflux of infected urine, hematogenous spread, or lymphatic spread.

The most commonly associated pathogen is *E. coli,* which is found in 65% to 80% of cases; *P. aeruginosa, Klebsiella* spp., *Serratia* spp., and *Enterobacter aerogenes* account for 10% to 15% of cases.[39,40] In adolescents, sexually transmitted pathogens are not a cause of bacterial prostatitis except when prostatitis accompanies Reiter syndrome precipitated by *C. trachomatis.* Reflux of sterile urine, which incites an inflammatory reaction, can contribute to noninfectious prostatitis.

Clinical Manifestations and Differential Diagnosis

Acute bacterial prostatitis typically manifests abruptly, although occasionally insidiously, with voiding symptoms, poorly localized pain, and often fever and malaise. In adolescents, the sudden onset of chills, fever, and malaise with voiding difficulties is much more likely to be caused by urinary tract infection, epididymitis, or urethritis than by acute bacterial prostatitis. With acute bacterial prostatitis, rectal examination usually is painful, and the prostate is warm, tense, and swollen. Prostatic massage is not recommended because this can precipitate bacteremia.

In adolescents, scrotal or pelvic pain variant also is a possibility. These patients have a history of vague scrotal pain with or without voiding symptoms but no fever and, on examination, no objective physical findings. Adults with chronic bacterial prostatitis have symptoms of recurring episodes of pain or discomfort in the perineum, groin, lower back, or scrotum, as well as voiding dysfunction, and they usually have a history of recurrent urinary tract infection. Often, prostatic examination is not helpful because findings are variable.

Nonbacterial (inflammatory) prostatitis and chronic pelvic pain syndrome are also seen in adults with a presentation similar to that of chronic bacterial prostatitis but without the history of preceding urinary tract infection. On examination, the prostate is either boggy, with nodular areas caused by inflammation, or is fibrous and difficult to massage. Whether chronic prostatitis occurs in adolescents is unclear, but 2 studies suggest it does, albeit at a low rate.[42,43]

Laboratory Findings and Diagnosis

When acute bacterial prostatitis is suspected based on clinical findings, urinalysis, urine culture, and STI screening are indicated, as well as blood cultures and a complete blood count.[39] In patients with suspected chronic prostatitis or nonbacterial prostatitis, prostate fluid is cultured and examined for leukocytes. Examination of expressed prostate secretions has been the definitive test for differentiating the prostatitis syndromes since introduction of the prostate localization 4-cup urine collection test.[40] This method is cumbersome, time-consuming, and expensive, however, and it has not been well validated.[37] A study of a simpler 2-cup screening test using urine collected before and after prostatic massage reported accuracy similar to that of the traditional 4-cup test.[44] The specimens are sent for quantitative bacterial culture, and Gram stain of the urinary sediment is performed to examine for leukocytes.

Management

Treatment of bacterial prostatitis can be difficult because of limited penetration and activity of antibiotics in acidic prostatic fluid.[39] Parenteral antibiotics, usually a broad-spectrum β-lactam agent with or without an aminoglycoside, are recommended for acute bacterial prostatitis if the patient is systemically ill; the duration of therapy is 2 to 4 weeks.[39] Therapy for less acute cases includes trimethoprim-sulfamethoxazole, a macrolide, doxycycline, or a fluoroquinolone for 2 weeks. If mechanical obstruction is contributing to the problem, correction is required.

No formal guidelines are available for treatment of nonbacterial chronic prostatitis or chronic pelvic pain syndrome, and no proven therapies exist.[40] Antibiotic therapy is not indicated. A report from China on pubertal chronic prostatitis suggested a role for pelvic floor biofeedback training.[43]

Complications

Abscess of the prostate and stone formation are rare complications of acute bacterial prostatitis.[45]

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54

Infectious Diseases Associated With Child Abuse

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Sexual abuse is the persuasion or coercion of a child to engage in sexually explicit conduct.[1] In 2013, of the 679,000 children in the United States found to be abused or neglected, sexual abuse accounted for 9%.[2] Among child victims of sexual abuse in 2012, 26.3% were 12 to 14 years old, and 33.8% were younger than 9 years of age.[3] Most perpetrators of child sexual abuse are adult male caregivers.[2] Federally mandated reporting laws require that all healthcare workers report cases of suspected sexual abuse to child protective service agencies.[4]

Medical Evaluation

In most cases of sexual abuse, the diagnosis is based on the child's statements; rarely are physical residual present from the abuse.[5–7] The following also can be used to confirm the diagnosis: sexually reactive behaviors; penetrating genital trauma without a history of unintentional genital trauma; presence of seminal products in a child; pregnancy; presence of a sexually transmitted infection (STI) beyond the incubation period of vertical transmission (*Neisseria* *gonorrhoeae, Chlamydia trachomatis, Treponema pallidum, Trichomonas vaginalis*).

The decision to perform screening tests for STIs in pediatric victims of sexual abuse depends on the type of abusive exposure, the regional prevalence of STIs in the adult population, previous consensual sexual activity (in adolescents), and most importantly for prepubertal children, the presence of genital symptoms or an abnormal genital examination. Among children evaluated for abuse, the prevalence of STIs is low, and this can affect the positive predictive value of the tests used.[8] Girardet and colleagues[9] found an overall prevalence of STIs of 8.2% in girls (24.5% of girls with vaginal discharge and 6.3% of those without) and 0% in boys with a history of sexual abuse. The presence of 1 STI in any child or adolescent should prompt an evaluation to exclude other STIs. Beyond the perinatal period, during which vertical transmission can occur, these infections usually are acquired from abusive contact.[10]

Infectious Agents

Neisseria gonorrhoeae and *Chlamydia trachomatis*

The prevalence rates for *N. gonorrhoeae* and *C. trachomatis* range from 0.7 to 3.7% in prepubertal children who have been sexually abused.[9,11–14] Most children with such infections are girls with genital complaints (e.g., vaginal discharge) or with abnormal genital examinations.[9,11,13–15] Therefore, the use of routine screening tests for *N. gonorrhoeae* and *C. trachomatis* in otherwise asymptomatic prepubertal girls after sexual abuse is not recommended.[14,16] Up to 14% of adolescent female victims of sexual abuse have an STI.[12,13] This prevalence is higher than in a nonabused, sexually active, adolescent population.[17]

The use of nucleic acid amplification tests (NAATs) in children and adolescents who have been sexually abused has not been extensively studied. Using NAATs can be beneficial in young children because less biologic sample is required, the specimen is less susceptible to environmental changes, and a urine specimen can be used.[18] However, caveats to using NAATs exist.[18–22] Even with their high sensitivity (97%) and specificity (99%), NAATs may have low positive predictive values in prepubertal children because of the low prevalence of *N. gonorrhoeae* and *C. trachomatis* in this population.[18–22] Falsely positive NAATs in prepubertal children could erroneously lead to a diagnosis of sexual abuse.[20,22] Thus, it is our practice to use cultures for *N. gonorrhoeae* and *C. trachomatis* in this population when feasible. If NAATs are used, specimens from tests with positive results should be maintained for additional confirmatory testing (Fig. 54.1).[9,23–25] No data support the use of NAATs for the diagnosis of extragenital infections.[8]

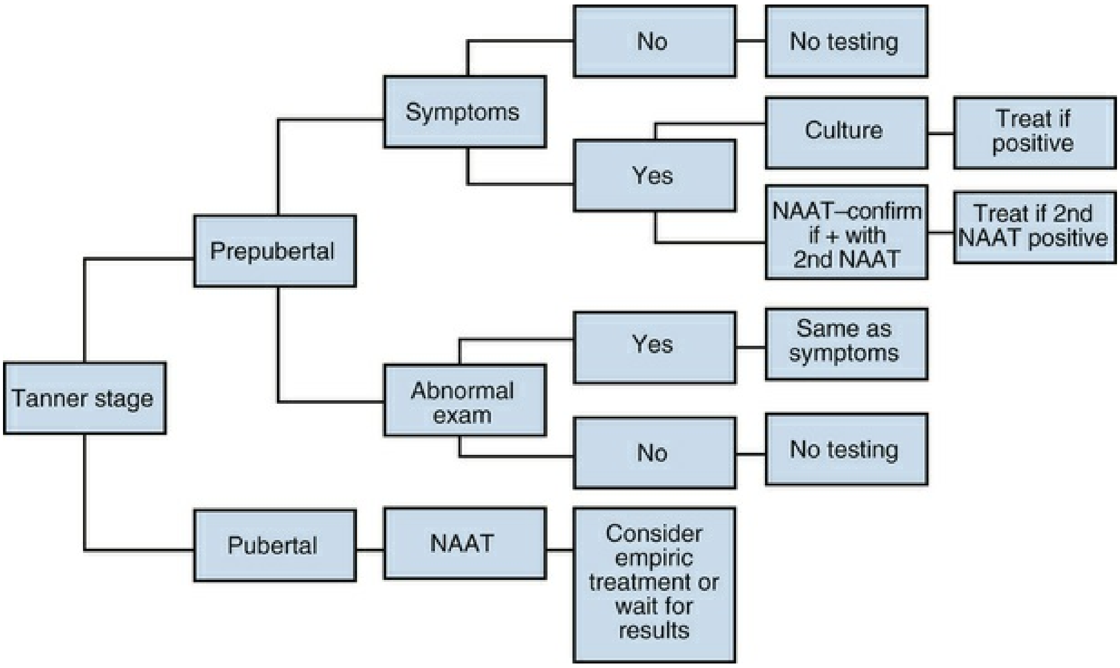

FIGURE 54.1 Algorithm for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* testing in prepubertal and pubertal children. NAAT, nucleic acid amplification test.

Several studies have evaluated NAATs in children who have been sexually abused. Matthews-Greer and colleagues[26] found that polymerase chain reaction (PCR) and culture were equivalent in the detection of *C. trachomatis*. Kellogg and associates[27] found that although agreement among ligase chain reaction (LCR), PCR, and culture for *N. gonorrhoeae* was poor, 84% agreement for urine and vaginal PCR for *C. trachomatis* was noted. These investigators concluded that urine PCR can be substituted for vaginal PCR for the detection of *C. trachomatis* in children and adolescents evaluated for sexual abuse. Neither of these studies confirmed a positive test result by using a second NAAT targeting a different genomic sequence.

Black and colleagues[23] compared urine and genital swabs for *N. gonorrhoeae* and *C. trachomatis* by using PCR confirmed by a second PCR test using an alternate target. The sensitivity of urine NAATs relative to vaginal culture was 100% and resulted in a 33% increase in detection of infection. These results suggest that NAATs performed on urine, with confirmation, may replace culture diagnosis of *N. gonorrhoeae* and *C. trachomatis* in children who have been sexually abused.

Empiric antibiotic treatment for *N. gonorrhoeae* or *C. trachomatis* generally is not indicated for asymptomatic prepubertal girls who have been sexually abused.[28–33] If NAATs are used, any positive test result should be confirmed by a culture or a second NAAT that targets a different genomic sequence.[24] Empiric antibiotics should be prescribed only if the confirmatory test result is positive. One could consider empirically treating sexually abused adolescents after cultures or NAATs have been obtained because the prevalence of infection is higher and false-positive test results are less common.

Azithromycin and doxycycline are the antibiotics of choice for adolescents warranting postexposure prophylaxis (PEP) against *C. trachomatis*. Ceftriaxone or cefixime are indicated for prophylaxis against *N. gonorrhoeae*.[25,34]

Treponema pallidum

Syphilis is an uncommon infectious complication of child abuse.[35,36] Girardet and colleagues[9] found a prevalence of 0.3% among children referred for evaluation after sexual abuse. Sexual transmission should be assumed in children who contract syphilis.[37] Determining the mode of acquisition of syphilis in preverbal children can be difficult. Horowitz and Chadwick[35] and Christian and associates[38] described 5 such children who presented with signs of secondary syphilis, including condylomata lata (3 children), syphilitic nephropathy (1 child), and corymbiform rash (1 child). The child with syphilitic nephropathy had a history of genital rashes consistent with a primary chancre and condylomata lata that were missed by medical providers.[30] None of these cases had a history from the child or caregivers of sexual abuse. When the mode of transmission of an STI is likely to be sexual abuse, a comprehensive investigation is needed to ensure that the child has no other STI and that no other children in the home have a history of sexual abuse or an STI.[35,38]

Human Papillomavirus

The most common human papillomavirus (HPV) subtypes that cause genital warts are 6, 11, 16, and 18. Although the methods by which children acquire genital warts are unclear, sexual abuse is the most worrisome form of transmission.[39] Vertical acquisition at delivery may not become clinically apparent for years and may not be the sole source of nonabusive HPV infection in infants and young children. Horizontal mother-to-child transmission can occur during childhood. Marais and colleagues[40] evaluated the likelihood of vertical maternal-to-child transmission by measuring serum antibodies to HPV-16 and HPV-18. The prevalence of antibodies was higher in children of seropositive mothers compared with seronegative mothers, but these differences were not statistically significant. Castellsague and associates[41] found that at a mean age of 14 months, 19.7% of infants born to mothers with cervical HPV and 16.9% of infants born to HPV-negative mothers tested positive for HPV. Dunne and colleagues[42] evaluated the prevalence of antibodies to HPV-16 in a sample of children 6 to 11 years of age. Overall, 2.4% of 1316 children were seropositive. Seroprevalence was higher in boys than in girls (3.5% vs. 1.2%), and in children >7 years of age than in younger children (3.3% vs. 0.4%). Unger and associates[43] reported an association of HPV positivity with sexual abuse in a sample of patients aged 6 months to 13 years.

Several investigators have evaluated the mode of acquisition of genital warts in children. Marcoux and colleagues[44] concluded that the modes of acquisition in children cannot be identified either by the clinical appearance of the lesions or by HPV typing. Sinclair and associates[45] evaluated the likelihood of sexual abuse in 55 children with HPV anogenital infection; 31% of the children provided a history of sexual abuse. The risk of sexual abuse increased with the child's age at presentation with genital warts (odds ratio of 12.1 in children 8 years of age and older). The positive predictive value of HPV for possible sexual abuse was 36% for children 4 to 8 years of age at diagnosis and 70% for children >8 years of age. No differences were noted in history of parental genital or hand warts in HPV-infected children with and without a history of sexual abuse. An evaluation for sexual abuse is recommended for patients with anogenital warts outside the age range at which exposure during caretaking activities is expected.[46]

Herpes Simplex Virus

Infection with herpes simplex virus (HSV) in children can indicate sexual abuse. This infection also it can result from nonabusive hand-to-genital contact (autoinoculation in a child with primary oral HSV or transmission from caregivers during bathing and toileting).[25] The potential value of typing HSV to determine whether sexual abuse was the mode of transmission is limited by the knowledge that an increasing proportion of genital HSV infections in adults are caused by HSV-1.[47] The prevalence of antibodies to HSV-2 in children and adolescents who have a history of sexual abuse is low, and thus routine screening for HSV-2 antibodies is not useful.[48]

It is more helpful to conduct a careful clinical history in children with genital HSV to determine whether sexual abuse has occurred. A review of several case series in children found that more than one half of reported cases of genital HSV had a sexual mode of transmission; this was reported more commonly in children ≥5 years of age, children with genital lesions only, and those whose infection was caused by HSV-2.[49] A careful assessment for sexual abuse should be performed in any child with genital HSV.

Human Immunodeficiency Virus

Human immunodeficiency virus (HIV) seroconversion after sexual abuse is rare. Gellert and associates[50] found that only 28 (0.4%) of 5622 children who had been sexually abused were HIV seropositive. The mean age of children at the time of diagnosis was 9 years, and 75% provided a clear history of sexual abuse, with 50% describing genital-genital contact. Of the perpetrators, 67% were HIV seropositive, 42% were a parent, 25% were a relative, and 33% had another STI at the time of the child's evaluation.[50] Girardet and colleagues[51] found that of 1750 children screened for HIV at the time of evaluation for sexual abuse, only 1 patient (0.06%) contracted HIV after the abusive contact. In children who have been sexually abused, HIV testing and PEP should be considered in those with a concurrent STI or with mucosal injury resulting in bleeding, those with a perpetrator who either is HIV positive or has high risk for HIV seropositivity, those living in an area with high regional disease prevalence in adults, those whose sexual abuse involved multiple perpetrators, and adolescents with a history of sexual assault by an unknown perpetrator.[52,53]

The rationale for HIV PEP is the possibility of a window during which the viral load can be controlled by the immune system; the commencement of antiretroviral agents during this window potentially would end viral replication. HIV PEP ideally should be initiated within 72 hours of exposure; within 1 hour is optimal.[54] Within this time frame, PEP would be beneficial for children who have been sexually abused.[55] PEP should be given only to patients without a suspicion of current HIV infection, when they and their guardians clearly understand the risks and benefits of PEP and agree to adhere to a follow-up program including serologic testing.[56] However, given that many cases of child and adolescent sexual abuse come to attention after 72 hours, PEP usually is not indicated.

Even if a child or adolescent presents at a time when PEP may be beneficial, no consensus exists on the number or type of antiretroviral agents that should be used. Some investigators recommend 3 drugs only with exposures most likely to transmit HIV infection and to use zidovudine-lamivudine as the base regimen,[57] whereas other investigators suggest that it is important to consider local resistance patterns and to consider a regimen containing zidovudine or stavudine.[58] Centers for Disease Control and Prevention guidelines, as of 2005, for prophylaxis include both non-nucleoside reverse transcriptase inhibitor–based and protease inhibitor–based options.[53] PEP efficacy after sexual exposure has not been evaluated formally. Reports documenting seroconversion after PEP in adults suggest that PEP may not be completely effective, perhaps because of ongoing exposure.[59]

Even when children are provided PEP, often drugs are not administered in a timely fashion or the drugs provided are not appropriate.[54] Other difficulties are compliance and follow-up.[60–63] Even with outpatient support teams and provision of the full course, very few adolescents finish their entire course of PEP drugs.[52,53] Uncertainty about exposure, low follow-up rates, intolerance of side effects, and psychiatric comorbidity also can limit adherence.[60,62]

Trichomonas vaginalis

Trichomonas infection can indicate sexual assault among pediatric patients, but in children younger than 1 year of age, this infection can represent vertical transmission.[64] Among pediatric victims of sexual assault, it is estimated that *Trichomonas vaginalis* infects 4% to 5.9%.[9,65] Between 42% and 90% of these patients can be asymptomatic.[65,66] Several options for testing exist, including wet mount, culture, and NAAT. The sensitivity of wet mount ranges from 36% to 70%; the sensitivity of culture is 81% to 95%.[65–68] The use of NAAT testing and nested PCR analysis has not been approved for prepubertal patients.[8,24,69] Testing of urine samples collected by bag is discouraged because contamination with the gastrointestinal organism *Pentatrichomonas hominis* can cause false-positive results.[8] A single dose of metronidazole is effective treatment.[66]

Vaccine-Preventable Diseases

Sexual assault can include exposures to certain vaccine-preventable diseases. Hepatitis B vaccine should be administered to patients who have not been completely immunized, especially if the patient had genital injuries that resulted in bleeding.[52,53,70] Tetanus booster should be administered if the patient has not received a dose within 5 years and lacerations or abrasions are present.[71]

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Gastrointestinal Tract Infections and Intoxications

OUTLINE

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Approach to the Diagnosis and Management of Gastrointestinal Tract Infections

Jumi Yi, Andi L. Shane

Most infections of the gastrointestinal tract manifest as diarrhea, a clinical syndrome of diverse origin associated with frequent loose or watery stools often accompanied by emesis, fever, abdominal bloating or pain, and occasional extraintestinal manifestations. Infectious diarrhea can have a bacterial, viral, or parasitic origin (Table 55.1), and most cases are associated with specific epidemiologic factors or clinical manifestations.[1] Establishing an etiologic diagnosis for a specific episode sometimes is difficult because of the wide array and complexity of potential agents. Therapy is directed at fluid and electrolyte replacement and maintenance, nutrition, and specific antimicrobial therapy in some cases. The mainstay of prevention is hand hygiene; licensed vaccines are available in the United States for the prevention of typhoid and rotavirus infections.[2,3]

TABLE 55.1

Causative Agents of Gastroenteritis

Bacteria	Parasites	Viruses
Aeromonas species *Bacillus cereus* *Campylobacter jejuni* *Clostridium difficile* *Clostridium perfringens* *Escherichia coli* *Listeria monocytogenes* *Plesiomonas shigelloides* *Salmonella* species *Shigella* species *Staphylococcus aureus* *Vibrio cholerae* *Vibrio parahaemolyticus* *Vibrio vulnificus* *Yersinia enterocolitica*	*Cryptosporidium parvum* *Cyclospora cayetanensis* *Entamoeba histolytica* *Giardia intestinalis* *Cystoisospora belli* Microsporidia (including *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis*)	Astrovirus Enteric adenovirus Norovirus Rotavirus Sapovirus

Epidemiology

Enteropathogens are acquired through the fecal-oral route from person-to-person contact or via contaminated food or water. People with certain host defects may be more susceptible to infection with various enteric pathogens and may experience greater mortality or morbidity.

According to a 2011 estimate, approximately 179 million cases of acute gastroenteritis, defined as acute vomiting or diarrhea, result in 475,000 hospitalizations and 5000 deaths annually in the US.[4] Children at higher risk of death from diarrhea include young infants who were born prematurely, infants residing in crowded settings where dehydration may not be recognized, infants born to mothers who have had little or no prenatal care, and children with underlying immunodeficiencies. In the US, the incidence of diarrhea in children <3 years of age is estimated to be 1 to 3 episodes per child per year, with higher rates in children attending group childcare. Worldwide, diarrheal diseases are leading causes of pediatric morbidity and mortality, with 1.5 billion episodes and 1.5 to 2.5 million deaths estimated annually among children <5 years of age.[5–7] Repeated early-childhood enteric infections can result in long-term disability, including stunted growth.

Most episodes of severe diarrhea worldwide in children <5 years of age are attributed to rotavirus infections[7]; however, hospitalizations attributed to rotavirus infections decreased 60% to 94% in the US since licensure of 2 rotavirus vaccines.[8–11] In 2009, the World Health Organization (WHO) recommended inclusion of a rotavirus vaccine series in all national immunization programs to lower the global disease burden of rotavirus.[5,6,12,13]

Pathogenesis

The gastrointestinal tract is barraged constantly by foreign material, including bacteria, viruses, parasites, and toxins. Numerous protective host factors include gastric acidity, intestinal motility, enteric microflora, glycoconjugates, and specific immune components (cells and humoral compounds). Host age, personal hygiene, intestinal receptors, past exposures, and food intake influence these protective factors and are major determinants of colonization and disease.

The effect of microbial factors is influenced by the size of the inoculum and specific virulence traits of the enteropathogen. For example, *Escherichia coli* can cause gastrointestinal tract disease through the transmission of plasmids or phages that encode for virulence traits, by producing secretory heat-stable or heat-labile enterotoxins and cytotoxins, by promoting invasiveness, or by increasing aggregability. In addition, some bacteria (e.g., *Clostridium botulinum, Staphylococcus aureus,* and *Bacillus cereus*) produce neurotoxins, whereas other bacteria have variations in toxin genes that enhance virulence. Generally, all bacteria that cause gastrointestinal tract disease possess one or more of these virulence traits.

Enteric viruses can cause diarrhea through selective destruction of absorptive cells (villus tip cells) in the mucosa, thus leaving secretory cells (crypt cells) intact, affecting absorptive fluid balance, and also reducing brush-border digestive enzymes.[2,14] *E. coli* pathotypes and many parasitic infections induce similar changes.[14–17]

Clinical Manifestations

Clinical manifestations usually consist of primary gastrointestinal tract manifestations including diarrhea, vomiting, and extraintestinal complications. The WHO defines diarrhea as 3 or more loose or liquid stools per 24 hours, or more frequently than is normal for an individual person. Stools that are formed, regardless of the frequency, or loose, "pasty" stools in infants are not considered diarrheal. Diarrhea can be classified by exposure and by the duration of symptoms, which may provide clues to the implicated pathogen (Fig. 55.1). Clinical manifestations localized to the gastrointestinal tract can be categorized by likely organisms and their pathogenesis for diagnostic and therapeutic considerations (Fig. 55.2 and Table 55.2).

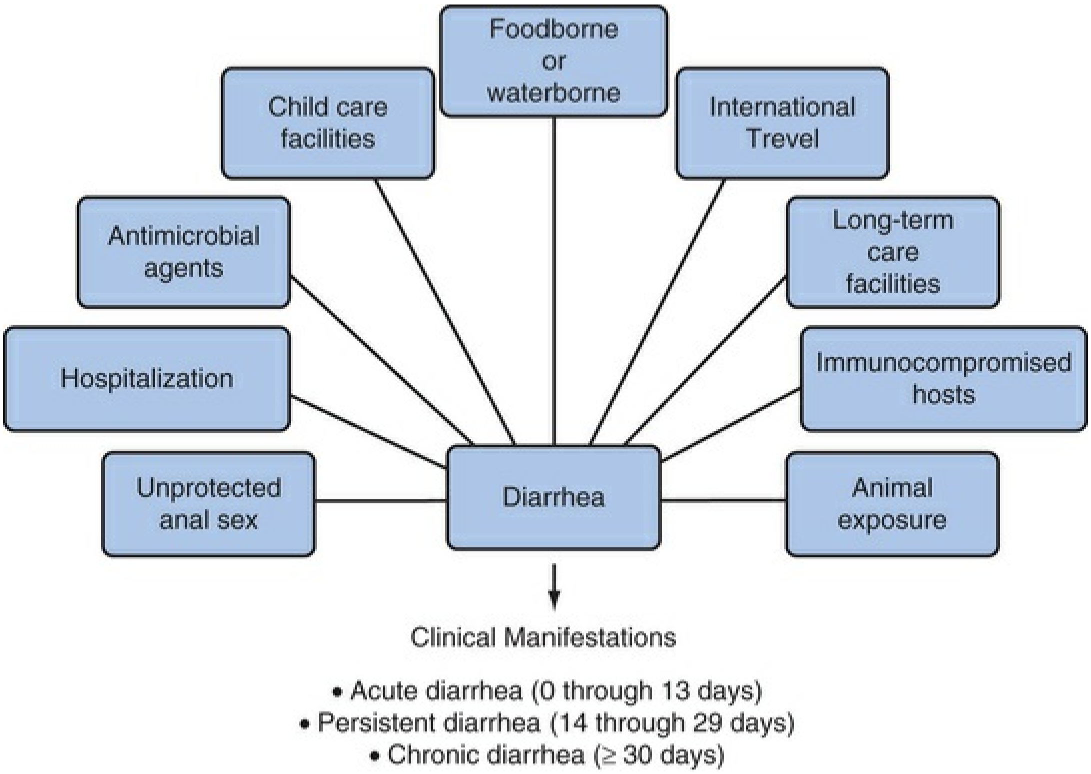
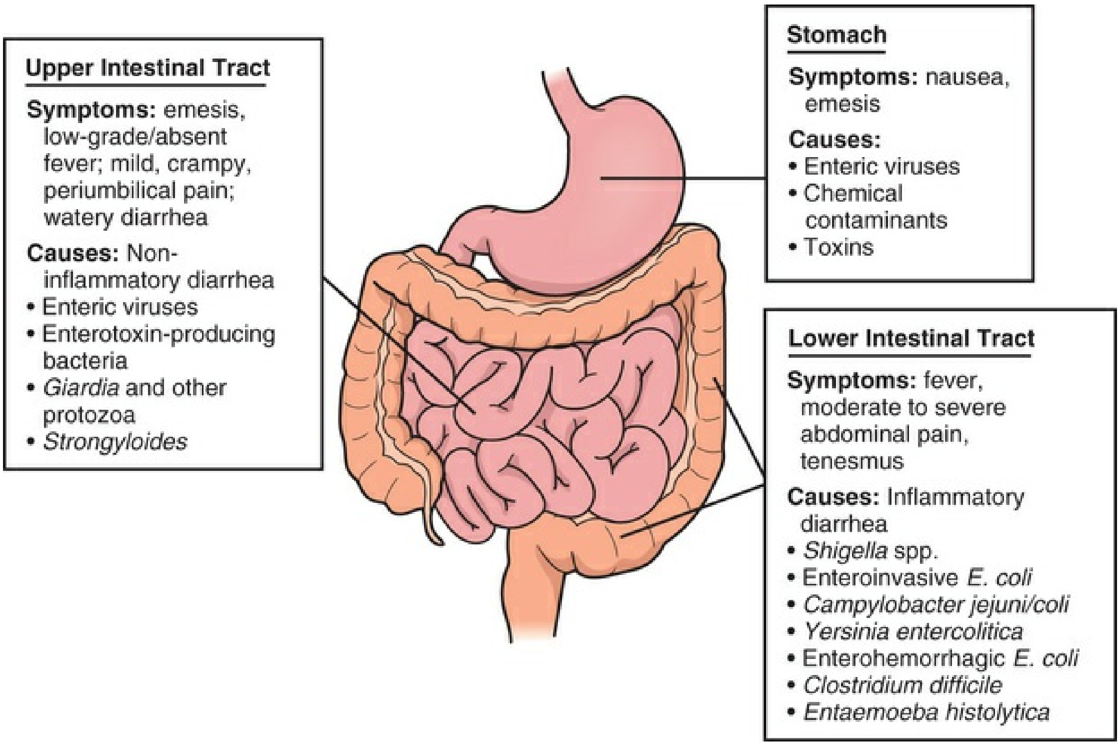


FIGURE 55.1 **Exposures to consider when evaluating people with possible infectious diarrhea.**



Upper Intestinal Tract

Symptoms: emesis, low-grade/absent fever; mild, crampy, periumbilical pain; watery diarrhea

Causes: Non-inflammatory diarrhea

- Enteric viruses
- Enterotoxin-producing bacteria
- *Giardia* and other protozoa
- *Strongyloides*

Stomach

Symptoms: nausea, emesis

Causes:

- Enteric viruses
- Chemical contaminants
- Toxins

Lower Intestinal Tract

Symptoms: fever, moderate to severe abdominal pain, tenesmus

Causes: Inflammatory diarrhea

- *Shigella* spp.
- Enteroinvasive *E. coli*
- *Campylobacter jejuni/coli*
- *Yersinia entercolitica*
- Enterohemorrhagic *E. coli*
- *Clostridium difficile*
- *Entaemoeba histolytica*

FIGURE 55.2 Localizing gastrointestinal tract signs and symptoms and possible causes of illness.

TABLE 55.2
Clinical Manifestations of Diarrhea and Corresponding Pathogens

Clinical Manifestations	Corresponding Pathogens
Watery diarrhea	Enteric viruses, enterotoxin-producing bacteria, and protozoa that infect the small intestine
Dysentery with scant stools that contain blood and mucus	Pathogens that invade the large intestine such as *Shigella* and *Campylobacter*
Persistent diarrhea that lasts for ≤14 days	Select viruses and bacteria, *Cryptosporidium* spp., *Giardia intestinalis, Cyclospora* spp., *Cystoisospora belli*
Vomiting with minimal or no diarrhea	Chemical contaminants and toxins associated with foodborne and waterborne outbreaks, viral enteropathogens
Bloody stool	STEC, *Shigella* spp., *Salmonella* spp., *Campylobacter* spp., *Entamoeba histolytica,* noncholera *Vibrio* species, *Clostridium difficile*
Abdominal pain	STEC, *Salmonella* spp., *Shigella* spp., *Campylobacter* spp., *Yersinia* spp., noncholera *Vibrio* species, *Clostridium difficile*
Persistent abdominal pain and fever	*Yersinia enterocolitica* (can mimic appendicitis)
Severe abdominal pain, grossly bloody stool (occasionally nonbloody), minimal or no fever	STEC
Nausea and vomiting lasting ≤24 hr	Food poisoning from *Staphylococcus aureus* enterotoxin or *Bacillus cereus*
Diarrhea and abdominal cramping lasting 1–2 days	Food poisoning from *Clostridium perfringens* or *Bacillus cereus*
Vomiting and diarrhea lasting 2–3 days	Norovirus

Chronic, watery diarrhea, often lasting ≤1 yr	Diarrhea of unidentified origin (Brainerd diarrhea), postinfectious irritable bowel syndrome

STEC, Shiga toxin–producing *Escherichia coli.*

Extraintestinal manifestations result from spread of the enteropathogen and immune-mediated mechanisms (Table 55.3), and they usually occur after diarrhea has resolved. In a population-based cohort study, an increased risk of inflammatory bowel disease was demonstrated in people with a preceding episode of gastroenteritis caused by *Salmonella* or *Campylobacter* spp.[18] Functional gastrointestinal disorder, which is defined as the presence of chronic or recurrent gastrointestinal symptoms without a clear cause, may occur in 50% of children with acute gastroenteritis for up to 6 months after the initial infection.[19] This disorder is not well understood but may be explained by multiple etiologic factors including ongoing intestinal inflammation, altered motility, increased intestinal permeability, smooth muscle hyperreactivity, genetic disposition, continuous antigenic exposure, or molecular mimicry.[19]

TABLE 55.3

Extraintestinal Manifestations of Enteric Pathogens

Manifestation	Related Enteric Pathogens
Erythema nodosum[a]	*Yersinia* spp., *Campylobacter* spp., *Salmonella* spp.
Glomerulonephritis[a]	*Shigella* spp., *Campylobacter* spp., *Yersinia* spp.
Guillain-Barré syndrome[a]	*Campylobacter* spp.
Hemolytic anemia[a]	*Campylobacter* spp., *Yersinia* spp.
Hemolytic uremic syndrome[a]	STEC
Immunoglobulin A nephropathy[a]	*Campylobacter* spp.
Reactive arthritis[a]	*Salmonella* spp., *Shigella* spp., *Yersinia* spp., *Campylobacter* spp., *Cryptosporidium* spp.
Reiter syndrome[a]	*Shigella* spp., *Salmonella* spp., *Campylobacter* spp., *Yersinia* spp.
Postinfectious irritable bowel syndrome	*Campylobacter* spp., *Salmonella* spp., *Shigella* spp., STEC, *Giardia intestinalis*
Meningitis	*Listeria monocytogenes, Salmonella* spp. (infants ≤3 mo at high risk)
Intestinal perforation	*Salmonella* spp. (including Typhi), *Shigella* spp., *Campylobacter* spp., *Yersinia* spp.
Encephalopathy, seizure	*Shigella* spp.
Toxic megacolon	*Shigella* spp., *Clostridium difficile*
Aortitis, osteomyelitis	*Salmonella* spp.

[a] Immune-mediated extraintestinal manifestations.

STEC, Shiga toxin–producing *Escherichia coli.*

Considerations of The Host and Exposures

Consideration of possible exposures assists in evaluation of the cause of diarrhea. Etiologic factors may overlap, but specific agents are responsible for most episodes of gastroenteritis following an exposure. Evidence-based recommendations, reviews, and meta-analyses that provide guidance for management of people with diarrhea are available and include information about the following: (1) administration of fluid and electrolyte solutions, (2) clinical and epidemiologic evaluation in immunocompetent and immunocompromised hosts, (3) selection of diagnostic tests, (4) use and avoidance of antimotility agents; (5) institution of selective antimicrobial therapy, (6) immunization recommendations, and (7) prevention of traveler's diarrhea.[1–3,20–27]

Foodborne and Waterborne Disease

Foodborne and waterborne diseases, including infections and intoxications, are acquired by consumption of contaminated food[23–33] at a variety of locations including at home and in restaurants.[34] Major causes of foodborne disease are listed in Table 55.4 (see also Chapter 59). Viruses are the most common causes of foodborne illness, of which 42% to 60% of cases are attributed to norovirus.[23,24,35,36] From 1971 to 2006, cryptosporidiosis was the most common gastrointestinal tract illness reported to the US Waterborne Disease and Outbreak Surveillance System (WBDOSS, http://www.cdc.gov/healthywater/surveillance/).[25]

TABLE 55.4

Causes of Foodborne Illness

Category	Cause
Chemical contaminants	Heavy metals, organic compounds
Bacteria	*Salmonella* spp., *Shigella* spp., *Escherichia coli*, *Brucella* spp., *Yersinia* spp., *Campylobacter* spp., *Vibrio* spp., and *Listeria monocytogenes*
Bacterial toxins	Enterotoxins of *Bacillus cereus*, *Staphylococcus aureus*, *Clostridium perfringens*, *Clostridium botulinum*, *Escherichia coli*
Viruses	Norovirus, rotavirus, and hepatitis A virus
Parasites	*Giardia intestinalis*, *Cyclospora cayetanensis*, *Cryptosporidium* spp., *Taenia* spp., *Toxoplasma gondii*, and *Trichinella* spp.

Products accumulated in the food chain of fish and shellfish	Scombroid, ciguatera, mycotoxins, neurotoxic and paralytic shellfish poisoning, pufferfish tetrodotoxin, domoic acid

An outbreak of foodborne disease is defined as the occurrence in ≥2 people of a similar illness, usually involving the gastrointestinal tract, following consumption of a common food.[23,24] Prompt and thorough laboratory evaluation of involved people and implicated food or water is critical for a definitive diagnosis. Individual cases may be difficult to identify unless a distinct clinical syndrome exists, such as occurs with foodborne botulism.

Most foodborne infections are self-limited and require only supportive care. Exceptions include foodborne and infant botulism (that results in constipation rather than diarrhea), paralytic shellfish poisoning, long-acting mushroom poisoning, and typhoid fever, all of which can result in significant morbidity and death in previously healthy people. Antitoxins or antibiotics may be indicated in the management of these infections, and prevention and control of these diseases are based on avoidance of food contamination or on destruction or denaturation and prevention of further spread or multiplication of contaminants. A suspected case of foodborne illness should be reported to public health officials because it could represent the sentinel case of a widespread outbreak. Detailed information on food safety issues and practices, including steps consumers can take to protect themselves, can be obtained online at the following sites: http://www.foodsafetyworkinggroup.gov, www.foodsafety.gov, www.fightbac.org, and http://www.cdc.gov/foodsafety/outbreaks/index.html. A list of nationally notifiable enteric diseases can be found at http://www.cdc.gov/foodborneburden/surveillance-systems.html.

Waterborne outbreaks occur in the US despite improvements in water management and sanitation. From 2009 to 2010, 33 outbreaks associated with drinking water were reported to the WBDOSS. *Legionella* was most commonly reported, but *Campylobacter* was associated with 12% of the outbreaks resulting in 78% of 1040 illnesses.[37] Recreational water-associated outbreaks may occur through fecal or soil contamination of treated water (e.g., pools and hot tubs) or untreated water (e.g., oceans and lakes) and most commonly manifest as diarrhea. From 2009 to 2010, 27 (33%) of 81 outbreaks were attributed to *Cryptosporidium*, and 24 (30%) were associated with treated recreational water. Enteric bacteria and viruses (*Campylobacter jejuni, E. coli* O157:H7, *Shigella sonnei*, norovirus) were associated with 8 (10%) outbreaks.[38] In addition to maintaining appropriate chlorine and disinfectant levels in pools and hot tubs, the Centers for Disease Control and Prevention (CDC) recommend showering before swimming, checking children with diapers every hour, and taking regular bathroom breaks to prevent contamination of water.[39] Resources for prevention of recreational water illnesses can be found at http://www.cdc.gov/healthywater/swimming/protection/steps-healthy-swimming.html. Recommendations for responding to fecal accidents in swimming venues can be found at http://www.cdc.gov/healthywater/swimming/pdf/fecal-incident-response-guidelines.pdf.

Antimicrobial-Associated Diarrhea

Antimicrobial-associated diarrhea occurs commonly in children and can result from changes in small bowel peristalsis or from alterations in the intestinal microflora. A subset of antimicrobial-associated diarrhea has been associated with *Clostridium difficile* overgrowth and toxin production.[40,41] Risk factors for pediatric *C. difficile* infection include antibiotic exposure within the past 4 to 12 weeks, previous or prolonged (>3 days) hospitalization, and an underlying diagnosis of cancer or inflammatory bowel disease.[41] The increasing trend is toward *C. difficile* detection in hospitalized children,[42–45] but interpretation of the role of *C. difficile* toxin and detection by molecular methods in young children is difficult. Studies have shown that *C. difficile* toxin detection rates are similar in children with and without diarrhea in both the inpatient and outpatient settings.[46–51] Furthermore, *C. difficile* toxin has been isolated in one fourth to two thirds of asymptomatic infants <1 year of age,[46,52] as well as in pediatric gastrointestinal pathology specimens that did not show evidence of the organism on tissue immunohistochemistry or polymerase chain reaction (PCR).[53] Other causes such as concomitant infection, dysbiosis resulting from antibiotics, or alteration in gastrointestinal flora as a consequence of enteral nutrition should be considered as contributing factors when *C. difficile* toxin production is detected.[54]

The American Academy of Pediatrics recommends against testing for *C. difficile* in children <1 year of age (unless they have a severe dysmotility syndrome or in an outbreak situation), recommends considering other causes (especially viral) before *C. difficile* testing, and recommends testing children >3 years of age judiciously. Children who are taking proton pump inhibitors or who have underlying bowel disease, renal insufficiency, or impaired humoral immunity are at greater risk for a *C. difficile* infection.[55] Discontinuation of antibiotics is the first step in the management of a *C. difficile* infection. Metronidazole or vancomycin can be used in children with moderate and severe disease.[55] Diagnostic tests are unlikely to be beneficial in an asymptomatic child unless the child has ileus. Complications of pediatric *C. difficile* infection are rare, and rates of colectomy and morbidity have not increased in affected children as they have among adults.[41,44] The Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America have published clinical practice guidelines for the management of *C. difficile* infections.[56]

Healthcare-Associated Diarrhea

Diarrhea can develop in children as a result of infections acquired before or during healthcare encounters. Episodes that meet the CDC National Healthcare Safety Network definition of a gastrointestinal infection with respect to clinical presentation and timing are considered to be healthcare-associated infections.

Several important factors affect transmission of enteric organisms in hospitals: (1) patient-to-patient transmission through the hands of hospital personnel, generally after contact with a child who has diarrhea; (2) asymptomatic carriers; (3) hospital personnel with gastroenteritis; (4) contaminated food, medications, or medical instruments; (5) hospital crowding; and (6) improper cleaning procedures. Host risk factors include immunocompromised states, prolonged hospitalization, young age, and antibiotic use. Prevention of healthcare-associated gastrointestinal tract infection is best accomplished by prevention and control. Contact isolation is recommended for children with diarrhea or vomiting to prevent transmission of infectious organisms among staff members and children.[57,58] Guidelines for isolation precautions in healthcare settings are available at http://www.cdc.gov/HAI/surveillance/index.html.

Diarrhea in Immunosuppressed Children

Diarrhea may be a presenting symptom of primary immunodeficiency (common variable immunodeficiency, X-linked agammaglobulinemia, and hyper–immunoglobulin M [hyper-IgM] syndrome) or secondary immunodeficiency (human immunodeficiency virus [HIV] infection), it may be a result of transplantation or immunosuppressive drugs, or it may have infectious causes.[59,60] Both enteropathogens of healthy hosts and enteropathogens unique to immunosuppressed children may be implicated. Clinical manifestations and ease of eradication depend on the location of involvement in the gastrointestinal tract, the immune status of the host, the severity of intestinal tract injury, and the availability and effectiveness of therapy. Guidelines have been published for prevention of opportunistic infections, including gastrointestinal tract infections, in HIV-infected people and recipients of hematopoietic stem cell transplants.[61,62]

Gastrointestinal tract disease in children with HIV stage 3, or acquired immunodeficiency syndrome (AIDS), can be caused by enteric infection (e.g., chronic cryptosporidiosis or cystoisosporiasis), malignant disease, wasting syndrome, or invasion by HIV.[62] Organisms and diseases of the gastrointestinal tract that fulfill the surveillance case definition of HIV stage 3 (AIDS) have been published.[63] Before the use of highly active antiretroviral therapy, both acute and persistent episodes of diarrhea and death from opportunistic gastrointestinal pathogens were frequent among HIV-infected infants. The overall incidence of opportunistic infections (including cryptosporidiosis) declined from 14.4 cases per 100 patient-years before the introduction of highly active antiretroviral therapy to 1.1 cases per 100 patient-years after the use of this therapy.[64]

Diarrhea in patients who have undergone allogeneic hematopoietic stem cell transplantation is most commonly caused by to graft-versus-host disease, whereas diarrhea in solid-organ transplant recipients most commonly is the result of infections and immunosuppressive drugs. The most common cause of infectious diarrhea after hematopoietic stem cell transplantation is *C. difficile* infection, and after solid-organ transplantation it is cytomegalovirus, followed by *C. difficile* infection.[59] Gastrointestinal cytomegalovirus infection also occurs in patients with HIV and those with immunosuppression secondary to medications including corticosteroids, chemotherapy, and immunomodulators. Certain immunodeficiencies increase the risk of infection with specific enteropathogens. For example, patients with selective IgA deficiency and common variable immunodeficiency are at increased risk for infection with *Giardia intestinalis*, and patients with hyper-IgM are at increased risk for infections with *Cryptosporidium* species.[60]

Diarrhea in Out-of-Home Childcare Settings

The greater use of out-of-home childcare has had a significant impact on the epidemiology of diarrheal disease in the US (see Chapter 3). After respiratory tract illness, diarrhea is the most common disease among children in childcare facilities, and it occurs at a rate of approximately 3 cases per year among children <3 years of age.[65] Norovirus, rotavirus, enteric adenoviruses, astroviruses, *Shigella* species, *Cryptosporidium* species, *E. coli* O157:H7, and *G. intestinalis* are the most frequently identified organisms associated with outbreaks in these settings. The major route of transmission is from person to person. Risk factors include gathering of children (specifically <3 years of age), new enrollment in a center, centers that house large numbers of children, and inadequate hand hygiene facilities and practice. The single most important procedure for minimizing fecal or oral transmission of enteric pathogens is frequent hand hygiene combined with education, training, and monitoring of staff regarding infection control procedures.[66,67]

Traveler's Diarrhea

Traveler's diarrhea affects 10% to 40% of people visiting resource-limited areas during the first 2 weeks of travel.[68–70] Diverse enteric pathogens are associated with traveler's diarrhea and can be identified in 50% to 94% of persons with symptoms.[69] Bacteria (e.g., enterotoxigenic and enteroaggregative *E. coli, Campylobacter jejuni, Salmonella* spp., and *Shigella* spp.) are implicated most frequently, followed by viruses (e.g., norovirus and rotavirus)[14,69,71,72]; parasites account for a smaller percentage of infections.

Risk factors for traveler's diarrhea are young age, season of travel, eating in restaurants, and duration of stay in a resource-limited country. Children, especially those <4 years of age, are at higher risk of severe presentations of travel-related illness, including dehydration requiring hospitalization.[73–75] Travelers should use alcohol-based hand sanitizers and carefully select adequately prepared food and beverages. Children traveling to high-risk countries should be up to date on age-appropriate vaccinations including rotavirus and typhoid vaccines, if age eligible.[76] Oral, live typhoid vaccine is available for children 6 years old and older, and an inactivated, intramuscular typhoid vaccine is available for those 2 years old and older. Immunization, however, is not a substitute for careful selection of foods and beverages and adherence to hand hygiene. Destination-specific vaccine and illness prevention recommendations are available at http://wwwnc.cdc.gov/travel/destinations/list.

Travelers to resource-limited settings should be prepared to manage a potential bacterial enteric infection empirically. Azithromycin for treatment of traveler's diarrhea generally is recommended for children traveling from low-risk to such high-risk settings.[69] However, self-administered antibiotics for diarrhea have been associated with higher rates of colonization with extended-spectrum β-lactamase–producing Enterobacteriaceae, especially in travelers to South Asia and Southeast Asia.[77] Judicious use of antimicrobial agents for prevention or for treatment of mild diarrhea is recommended. Laboratory evaluation for a treatable cause should be performed on patients with the following: body temperature >101.3°F; dysentery; large-volume, watery diarrhea with any degree of dehydration; or diarrhea lasting ≥14 days.[69]

Travelers should be informed about the following: (1) the ubiquitous exposure to pathogens during travel; (2) safe foods and beverages and unsafe items, which may depend on the travel destination; (3) the need to follow appropriate rules of hygiene, including proper preparation of food, and use of hand hygiene; and (4) the importance of fluid replacement if diarrhea occurs. Travelers should also seek evaluation by a travel medicine specialist before an international trip to receive region-specific advice, vaccinations, and illness prevention recommendations (see Chapter 8).

Diagnosis

Diagnostic testing may be beneficial in guiding therapy and contributing to surveillance, but often tests are not required because most episodes of diarrhea are self-limited. The approach to a child with acute diarrhea aims to (1) assess the degree of dehydration and provide fluid and electrolyte replacement and nutrition, (2) determine whether the episode is part of an outbreak, (3) prevent spread, and (4) determine the etiologic agent, and (5) provide specific therapy if indicated. In some children, additional laboratory tests on stool specimens may be indicated.

Clinical History

A detailed clinical history is important in determining the likely cause of diarrhea, selecting appropriate testing, interpreting results, and administering anti-infective agents if necessary (Table 55.5; see Fig. 55.1).

TABLE 55.5

Clinical History Considerations When Assessing a Child With Diarrhea

Host Factors	Exposures	Characteristics of Presentation
Presence of immunodeficiency Presence of chronic disease	Childcare center attendance Travel to diarrhea-endemic area Visit to farm or petting zoo Contact with reptiles or other animals Use of antimicrobial agents Contacts with similar symptoms Food exposures: seafood, unwashed produce, unpasteurized milk or dairy products, or incompletely cooked meats	Symptom onset Duration Stool frequency and consistency Presence of mucus and blood Other associated signs and symptoms: fever, vomiting, abdominal pain, headache, and seizures

The immune status of the symptomatic child should be assessed because underlying primary or secondary immunodeficiency or chronic disease leads to consideration of special pathogens. Persistent diarrhea, defined as diarrhea lasting more than 14 days, can occur with both viral and bacterial pathogens, but infections with parasitic pathogens should also be considered. A postinfectious manifestation should be considered in children with persistent or recurrent symptoms.

Examination of Stool

Fecal leukocyte examination and stool lactoferrin detection are no longer recommended in the evaluation of infectious diarrhea. Accurate interpretation and quantification of fecal leukocytes may be difficult because of degradation during processing and uneven distribution throughout stool. Detection of fecal lactoferrin has been used in place of fecal leukocyte examination as a result of its stability during processing, but lactoferrin also is present in noninfectious inflammatory diarrhea. Furthermore, lactoferrin is present in human milk, and interpreting results of fecal lactoferrin testing can be difficult in an infant who has received human milk.

Diagnostic tests should be performed when hemolytic uremic syndrome (HUS) is suspected, when stools contain blood, during outbreaks, in children who are immunosuppressed, and for public health surveillance. When children with acute diarrhea require performance of a stool diagnostic study, the specimen should be obtained as early in the course of disease as possible.[1] All stools submitted for routine testing from patients with acute community-acquired diarrhea should be assessed for *E. coli* O157:H7 and assayed for Shiga toxin to identify non-O157 Shiga toxin–producing *E. coli* (STEC).[78] Fecal specimens that cannot be inoculated immediately can be transported to the laboratory in a non–nutrient-holding medium such as Cary-Blair transport medium to prevent drying or overgrowth of specific organisms. If a stool culture is obtained, the clinician should be aware that *Yersinia enterocolitica,* diarrhea-causing *E. coli* organisms, *Vibrio cholerae, Vibrio parahaemolyticus, Aeromonas* spp., *C. difficile,* and *Campylobacter* spp. may require special requests to ensure that the laboratory modifies its routine procedures to evaluate the sample for these organisms.

The increasing availability of nonculture diagnostic tests (e.g., enzyme immunoassay, PCR, and mass spectrometry) that are highly sensitive for bacterial, viral, and parasitic enteropathogens can dramatically decrease time to organism detection and therefore optimize management. For example, multiplex PCR testing, capable of detecting many diarrheal pathogens simultaneously, has been increasingly used in clinical laboratories.[79–81] One study showed that 3 different multiplex PCR platforms were more sensitive in detecting enteropathogens in diarrheal specimens when compared with stool culture, enzyme immunoassay, and PCR detecting a single pathogen.[80] However, multiplex PCR also increased simultaneous detection of more than one organism and organisms in nondiarrheal specimens, thus increasing the need for clinical interpretation. Disadvantages of nonculture diagnostic tests include the inability to generate susceptibility data and information needed for public health investigations including serotyping and subtyping. Studies evaluating new methods of enteropathogen detection are ongoing.

Other modalities including endoscopy, proctosigmoidoscopy, and abdominal imaging may be helpful in establishing a diagnosis in children with severe colitis, those who are immunocompromised, or those with an inflammatory enteritis syndrome of unknown origin.

Treatment

All patients with diarrhea require some level of fluid and electrolyte therapy and attention to diet. A few patients need other nonspecific support, and some may benefit from specific antimicrobial therapy.

Fluid and Electrolyte Therapy

Oral rehydration therapy (ORT) is the preferred treatment for fluid and electrolyte losses resulting from diarrhea in children with mild to moderate dehydration,[20,82] but this recommendation is not always followed when alternative forms of rehydration are available. Stool losses of water, sodium, potassium, chloride, and base must be restored in children with dehydration to ensure effective rehydration.

Since the early 1980s, studies have proven the effectiveness of glucose-electrolyte ORT solutions compared with rapidly administered intravenous therapy in children with diarrhea from causes other than cholera. Compared with children who received intravenous fluid, children who received ORT had a reduction in subsequent unscheduled follow-up visits, lower rates of complications, and comparable rates of frequency and volume of stools, duration of diarrhea, and rate of weight gain. Additional benefits of ORT include decreased cost and ease of administration in many settings, thereby reducing the need for hospitalization.[83] The WHO and the United Nations International Children's Emergency Fund (UNICEF) recommend a reduced-osmolarity formulation of ORT to avoid the risk of hypernatremia and 10 to 14 days of zinc supplementation for treatment of children with diarrhea.[84,85]

Intravenous fluid administration provides rapid resuscitation for severely dehydrated children, those who are unable to tolerate oral fluids, and those whose condition is worsening while they are receiving ORT. Isotonic solutions as maintenance fluids are preferable to hypotonic solutions. A meta-analysis of rehydration fluids used in the first 24 hours among hospitalized children showed that isotonic fluid was protective against hyponatremia in multiple settings when adjusting for age, severity of illness, and admission to a medical or surgical service.[86]

Dietary Intake

Early feeding, within 12 hours of initiating rehydration, of age-appropriate foods to children with diarrhea should be an integral component of management and is safe and effective.[87] When used with glucose-electrolyte ORT, early feeding can reduce stool output as much as cereal-based ORT. Studies of early-feeding regimens have shown that unrestricted diets do not worsen the course of symptoms of mild diarrhea and can decrease stool output compared with rehydration therapy alone. Studies of early refeeding indicate a reduction in duration of diarrhea by 0.4 days (95% confidence interval [CI], 0.1–0.7).[20] Although these beneficial effects are modest, the added benefit of improved nutrition with early feeding has major importance. During the refeeding period, certain foods, including complex carbohydrates (rice, wheat, potatoes, bread, and cereals), lean meats, yogurt, fruits, and vegetables, are better tolerated than other foods. Fatty foods and foods high in simple sugars (including juices and soft drinks) should be avoided.[20]

Antimicrobial Therapy

Antimicrobial agents are of no benefit and may have deleterious effects in children infected with enteric viruses, including rotavirus, enteric adenovirus, astrovirus, and norovirus. Children with diarrhea associated with certain bacterial and protozoal agents may benefit from therapy. Limited benefit can be achieved with therapy in people infected with *Aeromonas* species (trimethoprim-sulfamethoxazole), *Blastocystis hominis* (metronidazole or iodoquinol), *Campylobacter jejuni* (erythromycin or azithromycin, if given early in the course of therapy), *Cryptosporidium* (nitazoxanide), or intestinal microsporidia (albendazole).[21] Antimicrobial therapy of immunocompetent children with intestinal salmonellosis or *Y. enterocolitica* infection is of no known benefit, except possibly for infants <3 months of age. A matched case-control study of patients <20 years of age in Minnesota with *E. coli* O157:H7 gastroenteritis showed that those who developed HUS were more likely to have received a β-lactam antibiotic (penicillin or cephalosporin) compared with those who received other classes of antibiotics or no antibiotics (odds ratio = 17.1; 95% CI, 2.2–135.0).[88] A larger prospective cohort study of 259 children with *E. coli* O157:H7 infection showed that exposure to any antibiotic was associated with greater HUS rates (36% vs. 12%; P = 0.001) and greater oligoanuric HUS rates (12% vs. 3%; P = 0.005).[89] The evidence accumulated to date suggests that certain classes of antibiotics in children with *E. coli* O157:H7 infection should be avoided.

Adjunctive Therapy

Various pharmacologic agents have been used as nonspecific therapy for people with acute infectious diarrhea (Table 55.6). These compounds can be classified according to the following mechanisms of action: (1) alteration of intestinal motility, (2) alteration of secretion, (3) adsorption of toxins or fluid, and (4) alteration of intestinal microflora. Many of these compounds, especially agents that alter motility, have systemic toxic effects that are augmented in infants and children. Most of these agents are not approved for children <3 years of age. Few published data are available to support use of most antidiarrheal agents to treat acute diarrhea, especially in children.[20,90,91]

TABLE 55.6

Adjunctive Therapies for Reduction of Diarrheal Symptoms in Children

Mechanism	Example	Recommended Age
Alteration of intestinal motility	Loperamide	≥6 yr
	Difenoxin and atropine	≥2 yr; requires prescription
	Diphenoxylate and atropine	≥2 yr; requires prescription
	Ondansetron (for nausea and vomiting)	≥4 yr
Alteration of secretion	Bismuth subsalicylate	≥12 yr
Alteration of intestinal microflora	Probiotics (e.g., *Lactobacillus, Saccharomyces, Bifidobacterium*), fecal biotherapy or transplant	Any age
Bowel nutritional support	Zinc	Any age

Zinc has been shown to decrease the duration of acute diarrhea by 20%,[92] improve intestinal permeability, and improve short-term recovery from intestinal injury[93] when consumed by children residing in low-resource countries.

Use of probiotics has been shown to be effective in randomized clinical trials for treating acute viral gastroenteritis in previously healthy children and modestly effective in preventing antibiotic-associated diarrhea in healthy children. Despite heterogeneity among studies, children receiving *Lactobacillus* GG in an emergency department had a median duration of diarrhea of 51 hours (interquartile range, 45–120 hours) versus 74 hours (interquartile range, 32–78 hours) compared with children who received placebo (P = 0.02).[94] Length of hospitalization was decreased by 1.1 days (95% CI, 0.4–1.2) among children who consumed a probiotic in 10 studies comprising a systematic review involving 1932 children.[95] The consumption of human milk by infants during episodes of diarrhea is recommended for its complete nutritional source, for delivery of prebiotics and probiotics, and for optimizing anti-inflammatory effects on intestinal epithelia. Continued evaluation of specific probiotic products, in well-designed clinical trials involving infants and children, will be needed to develop definitive recommendations for the use of prebiotics and probiotics.[96,97]

Fecal biotherapy, or stool transplantation, has been used in patients with refractory or relapsing *C. difficile* infections. Various delivery methods, including duodenal or colonic instillation, nasogastric tube, and capsules containing fecal flora, have been used. Donors are screened before stool donation and have included healthy volunteers, intimate partners, household members, and relatives. Adverse events are uncommonly reported and are mild. Studies have shown that fecal biotherapy was curative for 90% of adults and for 70% to 90% of children with refractory or recurrent *C. difficile* infection.[98–100] Optimal dosing, donor selection, and method of delivery are areas of active investigation.

Prevention

The most important aspect in the prevention and control of diarrheal disease is hygiene, both public and personal. These measures include meticulous hygiene, food preparation techniques,[66] and limited use of antacids, antimotility drugs, and antimicrobial agents. Ergonomically conducive diaper-changing facilities and reinforcement of hygienic diaper-changing techniques should be available and implemented in childcare centers. Written infection control policies must be in place and adhered to in all healthcare and childcare facilities. Guidelines for preventing opportunistic gastrointestinal infections in children with HIV infection and recipients of hematopoietic stem cell and organ transplants are published,[61,62] as are guidelines to prevent disease associated with pets in the home and exposure to animals in public settings.[101]

Human milk consumption provides young infants with significant protection against morbidity and death from diarrheal disease.[102] Immunologic components such as secretory IgA, oligosaccharides, glycoconjugates, and lactoferrin in human milk protect infants against disease after exposure to an infectious agent.[103]

Currently, vaccines to prevent typhoid, rotavirus infection, and hepatitis A are recommended for administration to children and adults meeting certain age and exposure parameters in the US that can be found at http://www.cdc.gov/vaccines/hcp/acip-recs/index.html. Candidate vaccines against enteric pathogens, agents that may interfere with microbial adherence or virulence mechanisms, and compounds that serve as competitors for binding of organisms or toxins to intestinal receptors are being studied.[104–106] Applications of glycoconjugates, probiotics, and fecal biotherapy in diarrheal disease prevention are active areas of investigation.[107,108]

Key Points

Gastrointestinal Tract Infections

Epidemiology

- Diarrhea is an important cause of childhood morbidity and mortality.

- Children are at risk of morbidity and death as a consequence of infectious diarrhea.

- Premature infants, infants living in crowded settings, and children with underlying immune deficiencies are at greater risk of disease.

Diagnosis

- Obtaining a thorough history is important in determining the cause, appropriate diagnostic testing, and treatment.

- Diagnostic testing should be considered if stools contain blood, during outbreaks, in people who are immunosuppressed, when hemolytic uremic syndrome is suspected, and for public health surveillance.

Treatment

- Low-osmolarity oral rehydration therapy is recommended for management of children with mild to moderate dehydration associated with diarrhea.

- Early refeeding of age-appropriate foods is recommended.

- Antibiotics are unlikely to be effective in the management of the most common causes of viral and bacterial diarrhea and may contribute to antibiotic-associated diarrhea.

Prevention

- Hygiene, both public and personal, is the most important aspect in the prevention and control of diarrheal disease.
- Vaccines to prevent rotavirus and hepatitis A infections are recommended for age-eligible children.
- Vaccine to prevent typhoid is recommended for age-eligible children who travel to a typhoid-endemic area.

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56

Viral Gastroenteritis

Eyal Leshem, Ben A. Lopman

Viral agents are the most common causes of acute gastroenteritis, a syndrome of acute vomiting and diarrhea associated with inflammation of the stomach, small intestines, or large intestines. Among children, viral gastroenteritis remains a leading cause of pediatric morbidity and mortality worldwide.[1,2] With the discovery of norovirus[3] and rotavirus[4] in the early 1970s, and subsequent development of improved diagnostic strategies for these and other enteric viruses,[5,6] the importance of viral agents as causes of diarrheal disease has been increasingly appreciated. The global introduction of highly effective rotavirus vaccines has resulted in substantial reductions in the burden of rotavirus gastroenteritis and recognition of norovirus as a major cause of acute gastroenteritis.[7–12]

Etiologic Agents

A small group of viruses accounts for most cases of acute gastroenteritis among children. These include group A rotaviruses, human caliciviruses (including noroviruses and sapoviruses), enteric adenoviruses (types 40 and 41), and human astroviruses.[7] Other viruses frequently are detected in children suffering from diarrheal illnesses; however, the prevalence of many of these other viruses in healthy children has not been determined, and therefore a causal association with diarrhea has not been established.

Rotaviruses (family Reoviridae) are 100-nm particles consisting of an outer capsid, an inner capsid, and a core.[13] The double-stranded

RNA genome is composed of 11 segments that code for 6 structural proteins and 6 nonstructural proteins. The outer capsid is composed of 2 proteins: VP7 (G protein, for glycoprotein) and VP4 (P protein, for protease-cleaved protein). These proteins are the principal antigens to which neutralizing antibodies are directed and account for the classification scheme for rotavirus strains.[14]

Caliciviruses are nonenveloped, 27- to 40-nm, single-stranded RNA viruses in the family Caliciviridae.[15] Human caliciviruses are divided into 2 genera: norovirus and sapovirus. Noroviruses include numerous genetically related viruses, further divided into 6 genogroups (I–VI), 3 of which (I, II, and, rarely, IV) are associated with human disease. At least 9 and 22 genotypes, respectively, have been identified for genogroups I and II.[16] Despite this extensive genetic diversity among noroviruses, genogroup II genotype 4 (GII.4) viruses are the most common causes of norovirus outbreaks worldwide[17]; the emergence of new GII.4 strains occurs every 2 to 4 years and can be associated with a global increase in gastroenteritis outbreaks.[18–20] Efforts to cultivate noroviruses in available cell culture systems or to develop an animal model have been unsuccessful, and this failure has hampered the development of simple diagnostic tests and the evaluation of disinfectants.[21] Important progress has been made by using B cells, but this system is not widely available.[22]

Astroviruses are nonenveloped, 28-nm, single-stranded RNA viruses in the family Astroviridae. Until 2008, human astroviruses were thought to be limited to 8 closely related genotypes (serotypes), now referred to as the “classic” human astroviruses (HAstV 1–8). HAstV genotype 1 is most commonly detected, followed by types 2 to 5; however, more than a single serotype usually circulates in communities during each season.[23] Non–type 1 viruses can predominate in a season, and greater serotype diversity can be found in developing countries.[23–25]

Adenoviruses are 70- to 100-nm, nonenveloped, double-stranded DNA viruses in the family Adenoviridae.[26] Although 7 species of adenoviruses (classified as HAdV A–G) containing at least 51 different genotypes can cause human infection, species F (genotypes 40 and 41) adenoviruses typically cause gastroenteritis.[27]

Many studies report the detection of viruses in stool samples from children with diarrheal illness. A key method to establish a causal association between a virus and a disease is to observe a higher prevalence among children with gastroenteritis compared with asymptomatic children (Table 56.1).

TABLE 56.1

Positivity Rates of Viral Pathogens Among Children <5 Years of Age With Acute Gastroenteritis and Healthy Controls: United States, 2008 to 2009[7]

Agent	Acute Gastroenteritis (N = 1564) No. (%)	Healthy Controls (N = 1000) No. (%)
Group A rotaviruses	282 (18)	2 (<1)
Noroviruses	334 (21)	40 (4)
Adenoviruses 40/41	186 (12)	18 (2)
Sapoviruses	80 (5)	42 (4)
Parechoviruses	76 (5)	44 (4)
Astroviruses	75 (5)	30 (3)
Bocaviruses	22 (1)	24 (2)
Aichiviruses	4 (<1)	0 (0)

Many other viruses have been found in fecal specimens, but the data are inconclusive regarding the pathogenicity for many of these viruses. Reports of the clinical characteristics of patients infected with the severe acute respiratory syndrome (SARS) coronavirus and with the more recently described Middle East respiratory syndrome (MERS) coronavirus have noted diarrhea in approximately one fourth of cases.[28,29]

Epidemiology

All the major enteric viruses are transmitted primarily through close person-to-person contact by the fecal-oral route.[30] Noroviruses, in addition, are easily spread through contaminated food and water and therefore are major causes of foodborne disease.[31–33] Noroviruses are present in the vomitus of ill people, and droplet spread through exposure to vomitus has been demonstrated to be a mechanism of spread in both healthcare and public settings.[34–36] Contact with a symptomatic child is a major determinant of norovirus infection. Children <5 years of age seem to be more contagious than older children and adults and therefore play key roles in norovirus transmission to all age groups.[37] The modes of transmission of adenoviruses are less well understood, but transmission is presumed to occur primarily through close contact by fecal-oral spread. Spread through fomites is possible for each of the agents, and it can play an important role in disease acquired in institutional and group childcare settings.[38]

Common viral gastroenteritis viruses are globally distributed. Although traditionally temperate climates are associated with a strong winter peak of rotavirus, a meta-analysis showed that the level of country development was a stronger predictor of seasonality than was geographic location or climate.[39] Since the introduction of routine vaccination in the United States, the rotavirus season has diminished substantially in magnitude, and it has also been delayed in some years.[12,40] A biennial pattern of lower, delayed rotavirus seasons followed by slightly higher peaks has emerged in the US. (Fig. 56.1).[12,40,41] In low-income and tropical settings, rotaviruses typically circulate year-round.[39,42,43] Noroviruses circulate year-round in most areas, but a clear wintertime seasonality to outbreaks is present, particularly in healthcare settings.[31,44,45] Astroviruses typically peak during winter and sapoviruses peak during early spring months in temperate countries.[7,46] The seasonality of adenoviruses is less distinct, and transmission has been described year-round, with summertime epidemics.[7,47]

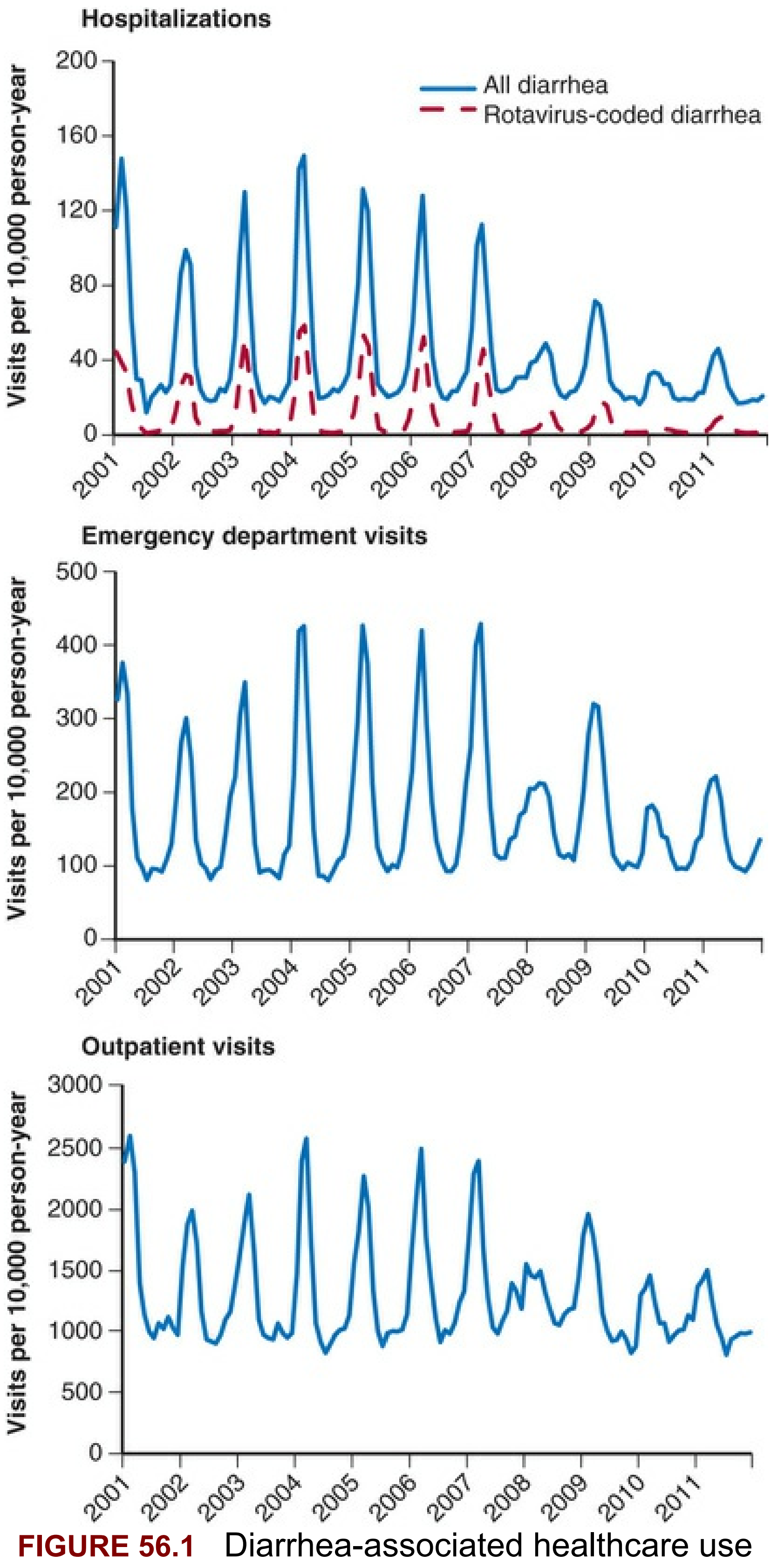

FIGURE 56.1 Diarrhea-associated healthcare use rates among United States children <5 years of age, 2001 to 2011. (From Leshem E, Moritz RE, Curns AT, et al. Rotavirus vaccines and health care utilization for diarrhea in the United States (2007–2011). Pediatrics 2014;134(1):15–23.)

The highest rates of severe rotavirus infections occur in the first 2 years of life; most hospitalizations and severe dehydrating disease occur between 4 and 23 months of age.[48–50] Infections in the first 3 months are less common and are often asymptomatic, probably because of protection from maternally acquired antibodies.[48,51] Rotaviruses can infect children more than once, with each subsequent infection less severe as a result of immunity that develops following infection.[48] Severe rotavirus disease among older children and adults is less common, but infection can occur in people exposed to younger children in childcare settings and schools. Outbreaks also occur in long-term care facilities.[52]

Before the introduction of rotavirus vaccines, rotaviruses accounted for 25% to 50% of hospitalizations for gastroenteritis among children <5 years of age and for 5% to 20% of milder cases in people who sought care in clinics.[49,53] Following vaccine introduction, the rates of rotavirus-associated healthcare use substantially decreased (see Fig. 56.1).[11,12] Population-based surveillance in the US detected rotavirus in 13% of children hospitalized for gastroenteritis and in 6% of pediatric outpatient visits for gastroenteritis.[11] Globally, rotavirus causes approximately 500,000 deaths/year in children less than 5 years of age, and deaths among children in the poorest countries account for more than 85% of the total.[1,54] In middle-income countries (Mexico and Brazil) where rotavirus vaccines were introduced in 2006, sustained reductions were documented in diarrhea-associated pediatric mortality rates (Fig. 56.2).[9,10] Rotavirus-associated death is rare in developed countries.[55,56]

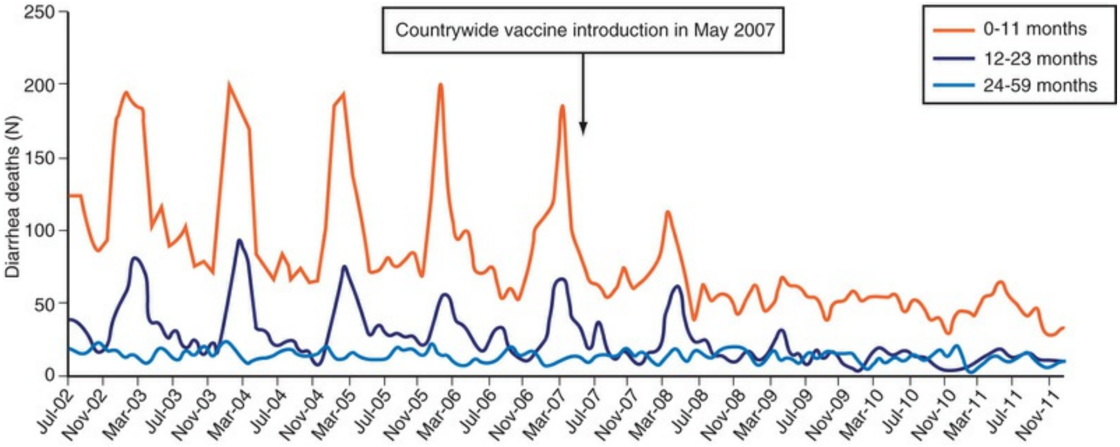

FIGURE 56.2 **Number of diarrhea-related deaths among children aged**

<5 years from July 2002 through December 2011 in Mexico according to age group. (From Gastanaduy PA, Sanchez-Uribe E, Esparza-Aguilar M, et al. Effect of rotavirus vaccine on diarrhea mortality in different socioeconomic regions of Mexico. Pediatrics 2013;131(4): e1115–1120.)

Noroviruses now are recognized as the most common causes of both endemic disease and outbreaks of gastroenteritis.[11,32,57] Noroviruses are estimated to cause 19 to 21 million illnesses a year in the US that result in 1.7 to 1.9 million outpatient visits, 400,000 emergency department visits, 56,000 to 71,000 hospitalizations, and 570 to 800 deaths.[32] Globally, norovirus is estimated to cause 18% of the cases of severe diarrheal disease in children <5 years old (17% of inpatient cases and 24% of community episodes).[58] Following the introduction of rotavirus vaccines and the subsequent decline in rotavirus disease burden, noroviruses have overtaken rotavirus to become the predominant causes of severe gastroenteritis in the pediatric population.[11,59,60] Among children <5 years old who were studied in an active surveillance network in the US, norovirus accounted for 21% of gastroenteritis cases requiring medical attention, including 17% of children admitted to the hospital and 28% of outpatients (see Table 56.1).[11]

All age groups are affected by noroviruses, but the disease incidence is highest in children <5 years of age.[61] Noroviruses are the most commonly reported causes of foodborne disease in the US, whereas internationally, estimates vary widely.[32,62] Common foods associated with outbreaks include those that are uncooked or handled after cooking (which can be contaminated by ill food handlers), as well as shellfish harvested from contaminated water. Healthcare facilities, including nursing homes and hospitals, are the most common settings of norovirus outbreaks; other environments such as childcare facilities and cruise ships are frequently affected.

Sapoviruses are most commonly associated with sporadic gastroenteritis, usually among young children.[63,64] Outbreaks caused by sapoviruses are less common and tend to occur in older adults.[65] Sapoviruses were detected in approximately 10% of all gastroenteritis episodes in England and Finland and in 4% of hospitalized cases in Finland among children <2 years of age.[66,67] In the US, sapoviruses were detected in 5% of pediatric diarrhea cases compared with 4% among healthy controls ($P < 0.01$) (see Table 56.1).[7] Sapovirus infections tend to be less severe than norovirus infections; vomiting is common, and diarrhea may not be present.[7,67]

Although astroviruses have been detected in all age groups, most infections are in children <2 years of age and tend to be less severe than rotavirus infections.[68] Serosurveys in the US have shown that >90% of children have antibodies to human astroviruses by 6 to 9 years of age.[69] Disease in adults is uncommon, but it can occur in outbreak settings.[70] Astroviruses are usually detected in <10% of young children treated for gastroenteritis in outpatient clinics or in hospitals, but these viruses are occasionally found at higher frequencies.[7,47,71] Although astroviruses primarily cause sporadic disease, outbreaks have been reported in a range of settings, and astroviruses can be common causes of nosocomial gastroenteritis in children's hospitals.[72]

Most enteric adenovirus infections occur in children <2 years of age, and these viruses appear to be less important causes of gastroenteritis among adults.[7,73,74] Enteric adenoviruses were shown to account for 5% to 12% of hospitalizations for acute gastroenteritis in children and can be common causes of healthcare-associated diarrhea.[7,75] Enteric adenoviruses are detected in 1% to 12% of children with community-associated diarrhea.[7,76,77]

Pathogenesis

After oral inoculation, viruses infect cells of the small intestinal villi.[78] Infection of the mature villous enterocytes, which have both digestive and absorptive functions, leads to cell death and sloughing of the villus cells. In a normal host, infection resolves as the number of susceptible mature enterocytes decreases secondary to cell death and as the host generates an immune response. Viruses are shed in the stool during the acute illness in large quantities. Rotaviruses, noroviruses, and astroviruses can also be shed for 1 to 2 days before illness and for several days following resolution of symptoms.[30,38] Although viral gastrointestinal infections are generally confined to the intestine, rotavirus and norovirus infections can result in antigenemia and the presence of nucleic acid in blood of ill patients, but extraintestinal disease is rare.[79,80] Asymptomatic infection is common, especially for norovirus,[66] and is thought to play a role in disease transmission.[81]

Immunity to rotavirus is acquired, and multiple infections typically are required until the child is fully protected against disease.[48,82,83] After a primary infection, homotypic immunity is stronger, but immunity seems to broaden to other serotypes with subsequent infections.[48] Wide estimates of the duration of immunity to norovirus range from 6 months to 4 to 9 years after natural infection occurs; however, heterotypic immunity may be limited.[37,84] Because diarrheal disease caused by astrovirus, adenovirus, and sapovirus is largely restricted to children, immunity is believed to be long-lasting.

A correlation exists between the expression of histo–blood group antigens (HBGAs) and susceptibility to norovirus and possibly rotavirus infections.[85–92] HBGAs comprise a diverse family of carbohydrates expressed on the mucosal epithelia of the respiratory, genitourinary, and digestive tracts; HBGAs are recognized as receptors allowing norovirus attachment and cellular entry. The expression of HBGAs is determined by 3 gene families expressing the *ABO* (A/B enzymes), secretor *(FUT2)* gene, and Lewis-type *(FUT3)* gene. Single nucleotide gene polymorphisms can inactivate the expression of these gene products, thereby breaking a link in the norovirus binding and infection process. Mutations in the *FUT2* gene leading to the absence of HBGA expression (nonsecretor phenotype) have been associated with resistance to infection, in particular to GII.4 noroviruses, which are the predominant global genotype.[85,86,88,89,93–96] HGBA expression appears to vary by ethnicity; 20% to 25% of the US. white population consists of nonsecretors compared with 2% of persons of Meso-American or Hispanic ancestry. In East Asia, different secretor mutations (*A385T* and *FUT3*) observed in Chinese and Vietnamese children confer lower risk of norovirus infections.[91,97] Evidence points to lower susceptibility of nonsecretors to rotavirus infections in various populations.[90–92]

Clinical Manifestations

Although these viruses differ genetically and structurally, the clinical presentations of acute gastroenteritis caused by these agents are indistinguishable. After a short incubation period, infections with any of the viruses lead to an acute onset of gastroenteritis

(Table 56.2). Vomiting is often an early sign, common in rotavirus infection, and particularly pronounced in norovirus and sapovirus infections.[7,98] Typically diarrhea is watery, and without blood, mucus, or fecal leukocytes. Fever occurs in approximately half of children with rotavirus infection and in approximately one fourth of children with nonrotavirus viral gastroenteritis, and it is often an early sign. Vomiting and fever frequently cease within 1 to 3 days, whereas diarrhea can persist longer, especially in rotavirus infections. Other symptoms include abdominal cramps, malaise, and seizures.[7,99]

TABLE 56.2

Epidemiologic Features of Viral Causes of Gastroenteritis

Feature	Rotavirus	Noroviruses	Sapoviruses	Astroviruses	Adenoviruses
Predominant age of illness	<5 yr	All ages	<5 yr	<2 yr	<2 yr
Mode of transmission	Person-to-person through fecal-oral route, fomites	Person-to- person through fecal-oral and vomitus-oral, fomites, food or water	Person-to-person through fecal-oral route	Person-to-person through fecal-oral route	Person-to-person through fecal-oral route
Incubation period	1–3 days	12–48 hr	12–48 hr	1–4 days	3–10 days
Symptoms					
Diarrhea	Explosive, watery	Watery with acute onset	Watery; milder than rotavirus	Watery; milder than rotavirus	Watery; milder than rotavirus; can be prolonged
Vomiting	80%–90%	>50%; often dominant symptom	Less common than rotavirus	Less common than rotavirus	Less common than rotavirus
Fever	Frequent	Less common, usually mild	Less common, usually mild	Less common, usually mild	Less common, usually mild
Illness duration	2–8 days	1–5 days	1–4 days	1–5 days	3–10 days
Clinical diagnosis	Stool EIA or LPA	RT-PCR	RT-PCR	Stool EIA (not available in United States)	Stool EIA

EIA, enzyme immunoassay; LPA, latex particle agglutination; RT-PCR, reverse transcriptase–polymerase chain reaction.

Modified from Peck AJ, Bresee JS. Viral gastroenteritis. In: McMillan JA, Feigin RD, De Angelis CD, Jones MD Jr (eds). Oski's Pediatrics, 4th ed. Philadelphia, Lippincott Williams & Wilkins, 2006, pp. 1288–1294.

The most important and common complication of viral gastroenteritis is dehydration, often associated with electrolyte abnormalities. Malabsorption can occur during the illness and persist for weeks following infection. Extraintestinal complications are rare, but encephalitis, seizures, acute myositis, hemophagocytic lymphohistiocytosis, acute flaccid paralysis, and sudden infant death syndrome have been described in children with rotavirus infections.[13,99,100] The association of these complications with rotavirus infection remains unclear. Severe and prolonged diarrhea associated with each agent has been reported among children with malnutrition and among children with congenital or acquired immunodeficiencies.[101–105]

Although viral causes of gastroenteritis are not distinguishable by clinical signs and symptoms, clinical characteristics of cases in outbreak settings have been helpful in predicting the presence of noroviruses. Kaplan and colleagues[98] found that outbreaks that met simple epidemiologic and clinical criteria were likely to have been caused by noroviruses. These criteria included (1) failure to detect a bacterial or parasitic pathogen in stool specimens, (2) the occurrence of vomiting in >50% of patients, (3) mean duration of illness of 12 to 60 hours, and (4) mean incubation period of 24 to 48 hours. The "Kaplan criteria" have been validated and are used by local health departments for the diagnosis of outbreaks in the absence of laboratory testing for norovirus.[106]

Diagnosis

Laboratory diagnosis of viral gastroenteritis is made by detection of viral antigen or nucleic acid in fresh, whole stool samples obtained during the acute illness. Commercially available assays to detect rotavirus antigen in stools offer easy and inexpensive methods to diagnose infection in children. These tests are available as either enzyme immunoassay (EIA) or a latex particle agglutination test for group A rotaviruses, designed to detect the VP6 protein.[13] Antigen detection tests generally have high (90% to 95%) sensitivity and specificity.[93] Other methods of rotavirus detection include electron microscopy, viral isolation, and RNA polyacrylamide gel electrophoresis. Reverse transcription–polymerase chain reaction (RT-PCR) is rarely used in clinical practice because of the test's high sensitivity; it may detect virus when that virus is not causing disease.[107] Serologic testing for rotavirus infection is possible but impractical and thus is not widely available in clinical care settings.

Real-time RT-PCR is the preferred laboratory method for detecting noroviruses. This assay is highly sensitive and can detect as few as 10 norovirus copies per reaction and provide a semiquantitative estimate of viral load. The assay is generally used to detect norovirus in stool, but it can also be used for vomitus, foods, water, and environmental specimens for outbreak investigations, although with reduced sensitivity. Conventional PCR followed by sequence analysis of the PCR products is used for norovirus genotyping.[108] Given the exquisite sensitivity of RT-PCR for norovirus and the high frequency that the virus can be found in healthy persons,[11,66,109] diagnostic results should be interpreted in light of clinical characteristics and, if available, the background level of detection in a control population. A commercial EIA for norovirus was approved in the US in 2011; however, this assay has low sensitivity and is not recommended for diagnosing norovirus infection in sporadic cases. Norovirus EIA can be useful in outbreak investigations.[110–112]

Commercial EIAs for detection of astrovirus viral antigen in stool are available in Europe, but not in the US. RT-PCR is a sensitive and specific method for detection of astroviruses.[113] RT-PCR, serologic assays, and electron microscopy are used primarily in research settings. Similarly, RT-PCR, EIA, and latex particle agglutination kits are available commercially and provide highly sensitive and specific antigen detection of enteric adenoviruses.[26] All viral agents of gastroenteritis are detectable by electron microscopy and immune electron microscopy, but these tests are seldom used because of their relatively low sensitivity and specificity, expense, and required expertise.

Treatment

No specific therapies are available for viral gastroenteritis. Case management depends on accurate and rapid assessment of the severity of dehydration, correction of fluid loss and electrolyte disturbances, and maintenance of adequate hydration and nutrition.[113] Treatment with oral rehydration solution (ORS) containing appropriate glucose-electrolyte solutions is sufficient for most patients. ORS use a protein sodium-glucose cotransporter 1 (SGALT1) that facilitates solute absorption across the luminal membrane. Water passively follows the osmotic gradient generated by transcellular transport of electrolytes and nutrients. In 2004, the World Health Organization recommended use of low-osmolarity ORS (245 mOsm/L), which has been shown to decrease stool output and vomiting in comparison with children treated with traditional ORS (311 mOsm/L). Intravenous rehydration can be required for children with severe dehydration (≥10% fluid deficit, shock, or near shock), intractable vomiting, or ORS treatment failure. Factors such as young age, unusual irritability or drowsiness, progressive course of symptoms, or uncertainty of diagnosis can indicate a need for close observation.

Breastfed infants should continue to nurse on demand. In children who are not breastfed, change to a lactose-free diet may result in earlier resolution of acute diarrhea and reduce treatment failure.[114] Children taking solid foods should continue to receive their usual diet during episodes of diarrhea, although substantial amounts of foods high in simple sugars should be avoided because the osmotic content may worsen diarrhea. Evidence on the use of oral probiotics (e.g., *Lactobacillus* spp.) to reduce the duration of diarrhea caused by rotavirus is conflicting.[115–117] Zinc, used both as supplement and treatment, reduces the severity, duration, and incidence of diarrhea in low- to middle-income settings and is considered one of the mainstays of treatment in developing countries[118,119]; however, the role of zinc supplementation in high-income settings has not been extensively studied. Because viral agents account for most cases of infectious gastroenteritis in children, antimicrobial therapy is not usually indicated for children (see Chapter 55).[120]

Prevention

The best public health intervention to reduce the incidence of severe viral gastroenteritis is the implementation of live, oral rotavirus vaccines in routine immunization programs. Rotavirus vaccines are attenuated strains given in multiple doses designed to replace a child's first exposure to wild-type rotavirus with strains that will not cause disease but will generate an adequate immune response to confer protection. Currently, 2 rotavirus vaccines are licensed in the US.[121] A third vaccine has been evaluated in India.[122] Additional vaccines are in development and may be available within several years.

As of 2015, rotavirus vaccines have been added to routine immunization programs in more than 75 countries, and these vaccines exert a dramatic impact with rapid and sustainable reductions in diarrhea-associated healthcare use and acute gastroenteritis–associated mortality rates.[9,10,12,40,123] Vaccine efficacy was shown to be very high in high- and middle-income settings and moderate in low-income populations[124–128]; however, vaccines may have their greatest impact in these low-income settings because of the higher burden of disease. The World Health Organization issued a global recommendation for the use of rotavirus vaccines.[129] Vaccine effectiveness in real-life routine use across various demographic and geographic settings has been good.[130,131]

Except for rotavirus, prevention of viral gastroenteritis is limited to nonspecific strategies. Breastfeeding confers some protection against rotavirus infection, and probably other viral infections, in young infants. Good hygiene, including meticulous handwashing practices, is an effective prevention strategy and should be encouraged, particularly in institutional settings, such as childcare centers and hospitals.[132] Significantly reducing transmission of viral agents of gastroenteritis requires strict adherence to recommendations because of the low infectious dose and the high quantity of viruses excreted in stool (and often vomitus) from infected persons and because these viral agents are quite stable in the environment. Noroviruses are relatively resistant to environmental disinfection; cleaning contaminated surfaces and food preparation areas with Environmental Protection Agency–approved cleaners is effective in settings where viral gastroenteritis outbreaks occur.[132,133]

Although experimental vaccines against noroviruses are in development, proof that these vaccines could protect against natural infection remains to be established.[134,135] These vaccines are based on virus-like particles and showed promise in volunteer challenge studies when they were administered both intranasally and intramuscularly. No vaccines against other viral gastroenteritis agents are yet in human trials.

Key Points

Epidemiology, Clinical Features, Diagnosis, Treatment, and Prevention of Viral Gastroenteritis

Epidemiology

- Viruses account for most cases of acute gastroenteritis among children. These include rotaviruses, noroviruses, enteric adenoviruses (types 40 and 41), astroviruses, and sapoviruses.

- Viral gastroenteritis occurs in endemic and epidemic forms. Rotaviruses and noroviruses are the major causes of endemic disease, with seasonal peaks during the winter months in temperate climates. Noroviruses are the main causes of epidemic disease.

- Following introduction of rotavirus vaccine, rates of rotavirus gastroenteritis have decreased substantially, and currently noroviruses are the major causes of acute gastroenteritis in the United States.

Clinical Features

- The clinical characteristics of illnesses caused by different viruses generally are indistinguishable. These include watery diarrhea and, in some cases, vomiting and fever.

- The most common severe complication of viral gastroenteritis is dehydration, often with electrolyte abnormalities.

- Prolonged diarrhea has been reported among children with malnutrition and among immunocompromised patients.

Diagnosis

- Laboratory diagnosis of viral gastroenteritis is best made by detection of viral antigen or nucleic acid in fresh, whole stool samples obtained during the acute illness.

- Commercially available assays to detect rotavirus antigen in stools offer an easy and inexpensive method to diagnose infection in children.

Treatment

- No specific therapies are available for viral gastroenteritis.
- The mainstays of therapy include assessment of dehydration severity, correction of fluid loss and electrolyte disturbances, and maintenance of adequate nutrition.
- Oral rehydration using oral rehydration solution with appropriate glucose-electrolyte solutions is sufficient for most patients.
- Zinc is used for treatment in low-income countries.

Prevention

- Rotavirus vaccines have been added to routine immunization programs in more than 75 countries and have substantially reduced diarrhea-associated healthcare use and acute gastroenteritis-associated mortality rates.
- Except for rotavirus, prevention of viral gastroenteritis is limited to nonspecific strategies including breastfeeding, hand hygiene, and strict adherence to hygiene guidelines including use of Environmental Protection Agency–approved cleaners for food preparation areas and contaminated surfaces.

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57

Inflammatory Enteritis

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Inflammatory enteritis is a pathologic diagnosis characterized by ileal or colonic inflammation, or both, which can range from small, superficial patches of leukocyte infiltration amid relatively normal mucosa to deep, exudative ulcerations with involvement of the entire intestinal wall.[1] The large number of infectious and noninfectious causes of inflammation results in a wide range of manifestations. Inflammatory enteritis should be considered in the differential diagnosis of patients with abdominal pain, dysentery, or watery diarrhea, particularly when patients come to attention with fever and blood or mucus in stool.

Classification

Inflammatory enteritides can be classified into several distinct clinical entities. Recognition of these entities facilitates suspicion of etiologic agents (Table 57.1), as well as diagnosis and management. However, many patients with inflammatory enteritis do not fit easily into any of these categories, thereby broadening the differential diagnosis.

TABLE 57.1

Differential Diagnoses of Inflammatory Enteritis

Acute Inflammatory Enteritis	Chronic Inflammatory Enteritis (≥2 Wk)	Proctitis
BACTERIAL	**BACTERIAL**	**MULTIPLE CLASSES**
Aeromonas hydrophila *Campylobacter jejuni or coli* Enteroaggregative *Escherichia coli* Enterohemorrhagic *E. coli* Enteroinvasive *E. coli* *Plesiomonas shigelloides* *Salmonella* spp. *Shigella* spp. *Vibrio parahaemolyticus* *Yersinia enterocolitica*	*Campylobacter jejuni or coli* Enteroaggregative *Escherichia coli* *Mycobacterium tuberculosis* *Salmonella* spp. *Shigella* spp. **FUNGAL** *Candida* spp. *Histoplasma capsulatum* *Paracoccidioides brasiliensis* Phycomycosis agents[a]	*Chlamydia trachomatis* *Entamoeba histolytica* Herpes simplex virus *Neisseria gonorrhoeae* *Shigella* spp. *Treponema pallidum* Other enteric pathogens[a]
PARASITIC		
Balantidium coli		
Cryptosporidium parvum[a]		
Entamoeba histolytica		
Schistosoma species		
Strongyloides stercoralis		
Trichinella spiralis		
VIRAL		
Cytomegalovirus[a]		
Enteroviruses[a]		

[a] Primarily in immunocompromised patients.

Acute dysentery is defined by the presence of fecal blood and mucus associated with frequent, small loose bowel movements. Fever often is present. Dysentery is the result of microbial invasion of the colonic mucosa, with mucosal and submucosal inflammation and destruction. Shigellosis is a prototype of acute dysentery.

Chronic inflammatory enteritis typically is an indolent and slowly progressive illness. The patient can have fever, abdominal pain, and weight loss over several weeks. Recurring, relapsing symptoms commonly occur. *Mycobacterium tuberculosis* is a classic cause of chronic inflammatory enteritis; children in the United States with chronic inflammatory enteritis are more likely to have inflammatory bowel disease.

Ulcerative proctitis is characterized by severe anorectal pain, purulent discharge, tenesmus, hematochezia, constipation, and fever. Erythematous, friable mucosa is visualized in the rectal vault.[2–4] Severe disease can lead to rectal abscesses or fistulas. This condition, which occurs primarily in men who have sex with men and in immunocompromised patients, can be caused by a variety of sexually transmitted and other infectious agents[4] (see Table 57.1).

Necrotizing enterocolitis of the newborn is characterized by varying degrees of mucosal necrosis.[5–8] This disorder occurs almost exclusively in premature infants, who typically demonstrate a sepsis-like illness with abdominal distention and, commonly, grossly bloody stools. Although many factors contribute to development of intestinal necrosis, a common pathway features ischemia, followed by disruption of the mucosal barrier, bacterial invasion, proliferation, and gas formation within the bowel wall.[5,6] Gram-negative bacteria of the normal flora may be important factors in triggering the injury process in a setting of a paucity of bacterial species and possible lack of protective gram-positive organisms.[7] Although outbreaks of necrotizing enterocolitis ascribed to single pathogens are described, prospective studies have failed to implicate a specific infectious cause in most cases (see Chapter 58).[8]

Antimicrobial-associated colitis is characterized by the presence of multiple yellow, plaque-like ulcerative lesions (1 to 5 mm) overlying erythematous, friable, colonic mucosa. In severe cases, lesions become confluent, resulting in sloughing of necrotic tissue and formation of the characteristic pseudomembrane.[9–11] Clinical manifestations of antimicrobial-associated colitis range from mild, watery diarrhea (with or without crampy abdominal pain) to fulminant colitis that can progress to toxic megacolon, colonic perforation, shock, and death. Overgrowth of toxigenic *Clostridium difficile* with release of potent cytotoxins is responsible for almost all cases.[9,10] *C. difficile*-associated colitis in the absence of antibiotic therapy is unusual; however, the use of both proton pump inhibitor and histamine H_2-receptor agonist drugs is associated with increased risk of community-associated *C. difficile*–associated disease.[11] The role of acid suppression in *C. difficile* infection is unclear.[12] Another high-risk group consists of patients who have inflammatory bowel disease.[13–16] It is unclear which risk factors play a major role, although it is hypothesized that the overall inflammatory state, immunosuppressive medications, poor nutritional status, and altered gastrointestinal flora are contributing factors.[17,18] Data suggest that the incidence and severity of *C. difficile*–associated disease are increasing in the US.[11,19] These increases may be associated with the emergence of newer strains with heightened virulence, antimicrobial resistance, or both. These "hypervirulent" strains, which carry variations in toxin genes and also are more resistant to the fluoroquinolones, erythromycin, and tetracycline, have emerged as a cause of *C. difficile*–associated disease outbreaks.[19–21] *C. difficile*-associated colitis is common in patients with human immunodeficiency virus (HIV) infection, in whom *C. difficile* can account for up to 54% of cases of bacterial diarrhea.[22] Even in the age of combination antiretroviral therapy, large bowel infections frequently are caused by opportunistic pathogens, such as cytomegalovirus (CMV), cryptosporidiosis, *Mycobacterium avium* complex, and spirochetosis.[23]

Noninfectious causes of inflammatory enteritis include ulcerative colitis, Crohn disease, Henoch-Schönlein purpura, eosinophilic gastroenteritis, enterocolitis complicating Hirschsprung disease, Behçet disease, and allergic colitis.[24,25] Intussusception can cause the onset of bloody, diarrheal stools, but inflammatory exudate is not expected.

Principal Etiologic Agents

Various infectious agents classically are considered causes of acute inflammatory enteritis (see Table 57.1). Patients come to medical attention with fever, abdominal pain, blood or mucus in stool, or a combination of these findings. However, many of these pathogens can cause clinical illnesses without overt characteristics of inflammation. The absence of clinical signs of inflammation therefore does not rule out these agents. In the US, most cases of inflammatory enteritis in children are caused by bacterial pathogens, whereas parasites are common among travelers to or indigenous populations of developing areas. Generally, differentiation among bacterial enteropathogens on clinical grounds alone is not possible; pathogenesis and potential complications associated with these agents are shown in Table 57.2. Detailed description can be found in pathogen-specific chapters.

TABLE 57.2

Pathogenesis and Complications of Principal Infectious Causes of Inflammatory Enteritis

Agent	Pathogenesis	Intestinal Complications	Extraintestinal Complications
Shigella spp. and enteroinvasive	Invasion of colonic enterocytes with lateral spread through	Colonic perforation,	Seizures, septicemia, HUS, immune-

Escherichia coli	mucosa and submucosa[110]; enterotoxins possibly involved[56]	protein-losing enteropathy	mediated disease (reactive arthritis, Reiter syndrome)
***Salmonella* spp.**	Invasion of distal ileal mucosa; can spread to reticuloendothelial system[111]	Colonic perforation (enteric fever), chronic carriage	Septicemia, meningitis, disseminated foci
Campylobacter jejuni* or *coli	Invasion of colonic enterocytes[112]	Chronic disease	Dissemination, immune-mediated disease (Guillain-Barré syndrome, reactive arthritis)
Yersinia enterocolitica	Invasion of ileal mucosa with inflammatory response; enterotoxins possibly involved[33,58]	Mesenteric adenitis	Dissemination with septicemia, suppurative foci
Enterohemorrhagic *E. coli*	Attaching and effacing lesions of colonic mucosa; production of Shiga-like toxins linked to HUS[46]	Toxic megacolon, colonic perforation	HUS, seizures
Clostridium difficile	Cytotoxin production	Toxic megacolon, colonic perforation	Septicemia
Entamoeba histolytica	Contact-dependent and contact-independent cytotoxicity; proteases; secretory factors possibly involved[43]	Chronic disease, toxic megacolon, colonic perforation	Ameboma, liver abscess, disseminated foci

HUS, hemolytic uremic syndrome.

Shigella Species.

All *Shigella* species can elicit prototypic acute bacillary dysentery, but *Shigella sonnei* most often causes uncomplicated watery diarrhea and is most prevalent in developed countries.[26,27] *Shigella* spp. have no known animal reservoir. Organisms are highly contagious and have a low infectious dose (as low as 10^2 colony-forming units), a feature hypothesized to be related to the organism's acid resistance.[28,29] Person-to-person and foodborne transmissions are most common in childhood shigellosis[27]; environmental contamination also can be a source of transmission.

Salmonella Species.

Nontyphoidal *Salmonella* serotypes cause a spectrum of illness that includes mild diarrhea, dysentery-like inflammatory enteritis, and disseminated disease, including septicemia and focal seeding (especially in immunocompromised hosts).[30] Most infections with

Salmonella in the US are foodborne,[31] most commonly through contaminated animal products such as unpasteurized milk, eggs, and improperly cooked meat. Enteric fever, caused by *Salmonella enterica* serovars Typhi, Paratyphi A, Paratyphi B, and Paratyphi C, can manifest with diarrhea or constipation.

Escherichia coli.

Diarrheagenic *Escherichia coli* organisms are divided into 5 major pathogenic categories on the basis of mechanism of pathogenesis.[32] Categories are (1) enterotoxigenic (watery diarrhea in infants and travelers), (2) enteroinvasive (dysentery identical to that caused by *S. sonnei*), (3) enteropathogenic (acute and chronic watery diarrhea in infants and children), (4) enterohemorrhagic or Shiga toxin–producing E. coli (hemorrhagic colitis associated with the hemolytic uremic syndrome), and (5) enteroaggregative (acute or persistent watery diarrhea prevalent in developing countries and in the immunocompromised host). Each type of *E. coli* except enterotoxigenic strains can cause inflammatory enteritis. Both enterohemorrhagic and enteroaggregative *E. coli* pathotypes occur commonly in the US.

Yersinia enterocolitica.

Yersinia enterocolitica typically causes acute diarrhea, fever, and abdominal pain.[33] Other manifestations include septicemia in infants and immunocompromised hosts, mesenteric lymphadenitis (mimicking appendicitis) in older children and young adults, dysentery, and postinfectious syndromes, including reactive arthritis, Reiter syndrome, glomerulonephritis, and erythema nodosum.[34,35] In the US, most *Y. enterocolitica* transmissions are foodborne, with outbreaks often caused by unpasteurized milk and contaminated pork or chitterlings.[36]

Campylobacter jejuni.

Campylobacter jejuni is one of the most commonly documented bacterial causes of diarrhea among people of all ages in the US and Canada.[37] Inflammatory enteritis and acute dysentery with severe abdominal pain and fever are common manifestations.[37] Bacteremia or dissemination is rare. The reservoir for *C. jejuni* is the gastrointestinal tract of wild and domestic birds and, to a lesser extent, other animals, thus allowing for foodborne outbreaks by ingestion of contaminated water, raw milk, or undercooked meat and poultry. Person-to-person spread has been documented; however, *C. jejuni* has a considerably higher ($10^{4–6}$ organisms) infectious dose and is less transmissible than *Shigella* spp.[37]

Aeromonas hydrophila.

Aeromonas species are found in soil and in fresh and brackish waters worldwide. *Aeromonas hydrophila* is associated with acute gastroenteritis, soft tissue infection, and bacteremia, especially in immunocompromised hosts. *A. hydrophila* is a significant cause of infection in the wake of natural disasters (hurricanes, tsunamis, and earthquakes) and has been linked to emerging illnesses, including prostatitis and hemolytic uremic syndrome.[38] Diarrhea caused by *A. hydrophila* also is associated with the consumption of seafood.[39] The mechanism of intestinal disease is unknown.

Vibrio parahaemolyticus.

Vibrio spp. other than *Vibrio cholerae* can elicit acute inflammatory enteritis with explosive, watery diarrhea. Illness usually is caused by *Vibrio parahaemolyticus* acquired through consumption of undercooked seafood.[40] Some non-O1 *V. cholerae* organisms also have been implicated in inflammatory enteritis.[41,42]

Entamoeba histolytica.

The classic clinical manifestation of *Entamoeba histolytica* enteritis is amebic dysentery, which can be acute and fulminant, especially in children, or mild and insidious with only abdominal pain, tenesmus, and small, frequent bowel movements.[43,44] Illness often follows an intermittent or waxing and waning course over weeks to months. Long incubation periods (1 week to 1 month) allow the onset of symptoms long after return from travel to a developing country where infection was acquired. Dissemination, most frequently to the liver, can occur after resolution of untreated amebic dysentery. Examination of the colonic mucosa of people with dysentery often reveals shallow, flask-like ulcers.[43] Trophozoites characteristically are found in stools of patients with dysentery or diarrhea; cysts more commonly are found in asymptomatic people.

Epidemiology

The epidemiology of infectious inflammatory enteritis is determined by the specific causative agent and the susceptibility of the host. Predictive epidemiologic associations should be explored in the patient's history, including foreign travel, childcare or institutional exposure, swimming and other exposure to water sources, receipt of antibiotics, diet, animal exposure, and underlying conditions. Risk factors and associated agents are shown in Table 57.3.

TABLE 57.3

Epidemiologic Risk Factors Associated With Infectious Agents of Inflammatory Enteritis

Risk Factor	Infectious Agents
Travel	Enterotoxigenic and enteroaggregative *Escherichia coli, Shigella, Salmonella, Campylobacter* spp., *Entamoeba histolytica*
Beef consumption	Enterohemorrhagic *E. coli, Salmonella*
Poultry consumption	*Salmonella, Campylobacter*
Pork consumption	*Yersinia enterocolitica, Salmonella* spp.
Seafood consumption	*Vibrio parahaemolyticus, Aeromonas hydrophila*
Water contamination	*Shigella, Salmonella, Campylobacter, Cryptosporidium* spp.
Institutional exposure or childcare	*Shigella, Cryptosporidium, Giardia lamblia,* enterohemorrhagic *E. coli*
Sexual transmission	*Treponema pallidum,* herpes simplex virus, *Neisseria gonorrhoeae, Chlamydia trachomatis, Shigella, E. histolytica*
Unpasteurized milk consumption	*Salmonella, Campylobacter, Y. enterocolitica, Mycobacterium* spp.
Antimicrobial therapy	*Clostridium difficile*

Infectious inflammatory enteritis often occurs in outbreaks related to person-to-person, foodborne, or waterborne transmission. The cause of outbreaks of enteric disease often can be predicted from the incubation period.[45] Cases with an onset between 1 and 16 hours of the source event usually are not inflammatory and are toxin mediated; those with an onset between 16 and 72 hours can be caused by infection, such as with *Salmonella* or *Shigella* spp., *C. jejuni,* enteroinvasive *E. coli, V. parahaemolyticus,* and *Y. enterocolitica;* an incubation period >72 hours suggests enterohemorrhagic *E. coli* O157:H7.[45,46] The implicated vehicle of transmission also can be helpful in predicting the cause. Cysts of parasites, including *Cryptosporidium parvum, Balantidium coli,* and *E. histolytica,* resist chlorination and thus contaminate municipal water supplies. Some pathogens are associated with specific foods, such as *Salmonella* spp. (undercooked poultry, produce, and eggs), *C. jejuni* (undercooked poultry), *V. parahaemolyticus* (raw and undercooked seafood), and *Y. enterocolitica* (pork, chitterlings, milk). *Neisseria gonorrhoeae,* herpes simplex virus, *Chlamydia trachomatis,* and *Treponema pallidum* are sexually transmitted agents of ulcerative proctitis in men who have sex with men, who also have an increased risk for colitis caused by typical enteric pathogens.

Pathogenesis

All inflammatory enteritides share common features of mucosal damage and accompanying release of inflammatory mediators. The mechanism of such damage elicited by infectious agents follows 1 of 2 general paradigms—cytotoxin elaboration or mucosal invasion, although some organisms are able to execute both mechanisms. The cytotoxic mechanism is exemplified by *C. difficile* colitis. Two *C. difficile* exotoxins (toxin A, a 308-kd enterotoxin, and toxin B, a 250- to 270-kd cytotoxin) damage enterocytes, thus leading to mucosal necrosis, and also may be responsible for secretion of fluid into the intestinal lumen.[47–49] Both toxins act by catalyzing glycosylation of Rho proteins (guanosine triphosphate-binding proteins) in target eukaryotic cells, thereby inducing derangement of the cytoskeleton and altering multiple cellular processes.

In addition, *C. difficile* toxins induce release of cytokines from epithelial cells, monocytes, macrophages, and neuronal cells of the lamina propria; these cytokines contribute to the toxin-mediated inflammation, apoptosis of colonocytes, and damage of colonic mucosa with formation of colonic ulcers and pseudomembranes.[10,50,51] A third potent toxin has also been described: a binary toxin named *C. difficile* transfer (CDT). CDT is not produced by all strains of *C. difficile*; disease caused by CDT-producing strains is associated with increased mortality. CDT is thought to disrupt the cellular cytoskeleton and increase adherence to the host cell.[52]

The invasive mechanism of bacterial enteritis is exemplified in shigellosis, yersiniosis, and salmonellosis. Pathogens penetrate the mucosa of the ileum and colon. The role of inflammation in these infections is not entirely clear, but apparently it is complex and may benefit both host and pathogen.[53] For example, experimental evidence suggests that migration of neutrophils into the intestinal lumen can exacerbate both *Shigella*- and *Salmonella*-associated diarrhea.[54,55] Moreover, mice deficient in the apoptotic (and proinflammatory) enzyme caspase 1 are resistant to *Salmonella* infection. However, mice deficient in certain cytokine responses also are unable to limit *Salmonella* infection to the intestine and are more likely to die of systemic disease. Much is known about the molecular events underlying *Salmonella* pathogenesis.[56] The clinical manifestations of inflammatory enteritis may be the result of a finely tuned coevolution between host and parasite, the result of which favors the survival of both. In addition, invasive pathogens can secrete enterotoxins.[56–59] A summary of pathogenic mechanisms for principal pathogens is shown in Table 57.2.

Diagnostic Evaluation

Before embarking on a diagnostic evaluation of a patient with enteric disease, one should consider whether determining the causative agent will affect management. Most gastrointestinal tract infections in the US are caused by viruses, for which no specific therapy exists. Most viral infections do not elicit an inflammatory syndrome, and therefore the presence of acute inflammatory enteritis suggests a bacterial or parasitic origin. Some bacterial agents of inflammatory enteritis can be treated to benefit the patient, potential contacts, or both, whereas others (e.g., nontyphoid *Salmonella* confined to the gut) are not responsive to antimicrobial therapy. A practical, selective diagnostic approach to the patient with enteritis should be cost-effective and likely to yield information helpful for management.

By far the most common infectious causes of acute inflammatory enteritis in US children are the bacterial enteropathogens. Relevant epidemiologic factors (see Table 57.3), disease patterns in the community, and patient-related characteristics are useful in assessing the likelihood of a bacterial cause.[60–62] Suggestive signs and symptoms include fever, abrupt onset of diarrhea, >4 stools per day, absence of vomiting before the onset of diarrhea, and presence of blood or mucus in stool. The patient with none of these features is unlikely to have a bacterial pathogen. A scoring system for predicting bacterial enteritis has been proposed, in which risk is weighted for each feature.[61] However, such a quantitative approach is unlikely to determine the precise risk of inflammatory enteritis in all locales.

The leukocyte assay of stool mucus is a practical, inexpensive screening test that can be used to predict probable inflammatory enteritis, thereby helping to limit performance of stool culture.[60,63,64] The sensitivity and specificity of this test in predicting bacterial enteritis have been reported to be >80% (for ≥5 white blood cells/high-power field)[60]; however, the reported values vary widely among studies, in part reflecting differences in the definition of a positive result. Moreover, the predictive value of the assay depends on the likelihood of bacterial inflammatory enteritis as indicated by historical factors and clinical signs. Most leukocytes detected in stool are neutrophils (mononuclear cells also can be associated with *Salmonella* infection).[64] The presence of leukocytes is not always indicative of bacterial inflammatory enteritis (Table 57.4), given that leukocytes can be present in inflammatory bowel diseases such as ulcerative colitis and Crohn disease, and fecal neutrophils occasionally can be present in cases of viral enteritis.[65]

TABLE 57.4

Association of Fecal Leukocytes With Intestinal Pathogens

Present	Variable	Absent
Campylobacter Enteroinvasive *Escherichia coli* *Shigella*	*Clostridium difficile*	*Bacillus cereus*
	Salmonella	*Clostridium perfringens*
	Schistosoma	*Entamoeba histolytica*
	Vibrio parahaemolyticus	Enteric viruses
	Yersinia enterocolitica	Enteropathogenic *E. coli*
		Enterotoxigenic *E. coli*
		Giardia intestinalis
		Vibrio cholerae

Fecal lactoferrin, detected with a commercially available rapid agglutination test, correlates closely with the presence of fecal leukocytes.[66] In one study, 94% (16 of 17) of patients whose smears of fecal mucus had >1 neutrophil/high-power field also had a positive lactoferrin test result, whereas 16% (3 of 19) of patients with diarrhea without neutrophils in smears and none of 7 healthy controls had positive test results. In another study, the fecal lactoferrin test had a better positive predictive value than did the fecal leukocyte smear or occult fecal blood detection for the detection of bacterial pathogens.[67] Lactoferrin is stable in fecal specimens and can be detected even when leukocytes disintegrate during transport or storage. Fecal lactoferrin tests can have false-positive results in infants who are breastfed. Fecal calprotectin, an early predictor of acute bacterial versus viral gastroenteritis, is another valuable noninvasive marker in young children, with a diagnostic accuracy of 92%. In one study, combined fecal calprotectin and serum C-reactive protein tests improved diagnostic accuracy to 94% for acute bacterial gastroenteritis.[68]

Selection of Tests to Confirm Cause

When performance of stool culture is indicated on the basis of history, physical examination, or fecal leukocyte assay, specimens should be inoculated into culture medium adequate for recovery of *Shigella, Salmonella, Y. enterocolitica,* and *C. jejuni.* In the US, the Centers for Disease Control and Prevention recommends that detection of Shiga toxin–-producing *E. coli* should be attempted regardless of age, seasonality, and the presence or absence of blood in stool.[69] If a history of seafood ingestion or exposure to brackish water is elicited, specialized media should be requested for isolation of *Vibrio, Aeromonas,* and *Plesiomonas* spp. Other specialized tests are sometimes indicated in the evaluation of patients with diarrhea. Preferred diagnostic methods for etiologic agents of inflammatory enteritis are shown in Table 57.5 (see Chapter 286).

TABLE 57.5

Diagnostic Studies for Enteropathogens

Organism	Diagnostic Studies
ACUTE DISEASE	
Balantidium coli	Examination of stool or mucosal scrapings (sigmoidoscopy) for trophozoites or cysts
Campylobacter	Stool culture (selective media and incubation conditions); antigen detection by EIAs for *C. jejuni* and *Escherichia coli* (variable performance); multiplex PCR-based assays[a]
Cryptosporidium	Modified acid-fast or auramine or fluorescein-labeled monoclonal antibody stain of stool, duodenal aspirate, or small bowel biopsy specimen; antigen detection by EIA or immune chromatographic tests

Entamoeba histolytica	Examination of stool, biopsy or mucosal scrapings (proctosigmoidoscopy) for trophozoites or cysts; antibody detection by EIA on serum in invasive disease
Escherichia coli	Stool culture on sorbitol-MacConkey agar for detection of O157 STEC strains for further testing; immunoassay to detect non-O157 STEC; multiplex PCR assays that can detect STEC, enterotoxigenic *E. coli*, enteropathogenic *E. coli* enteroaggregative *E. coli* and enteroinvasive *E. coli*[a]
Salmonella	Stool culture (enteritis; see Chapter 146 for diagnostic testing in enteric fever and invasive infections); multiplex PCR assays[a]
Schistosoma	Detection of eggs on microscopic examination of stool and rectal mucosal biopsy
Shigella	Stool culture; multiplex PCR assays[a]
Yersinia enterocolitica	Stool culture, blood culture, culture of specimen from other body sites (e.g., mesenteric lymph nodes, peritoneal fluid, synovial fluid); see Chapter 148)
Cytomegalovirus	Endoscopic mucosal biopsy for microscopy (viral inclusions), immunochemical staining, shell-viral culture, pp65 antigen
CHRONIC DISEASE	
Candida	Potassium hydroxide stain; stool culture
Enteroaggregative *E. coli*	Stool culture; DNA probe; adherence to human laryngeal cell line (HEp-2)
Mycobacterium	Acid-fast examination and mycobacterial culture of biopsy specimens
PROCTITIS	
Chlamydia trachomatis	Culture; NAAT (limited data in this setting)
Herpes simplex	Culture; enzyme immunoassay or direct fluorescent antibody test
Neisseria gonorrhoeae	Culture; NAAT
Treponema pallidum	Dark-field microscopy examination of mucosal scrapings; serology
Entamoeba histolytica	Microscopic examination of stool or intestinal biopsy tissue; serology
OTHER	
Antimicrobial-associated colitis	Toxin assays, sigmoidoscopy with rectal biopsy
Necrotizing enterocolitis	Abdominal radiograph

[a] Several commercially available multiplex PCR assays that are licensed by the Food and Drug Administration provide simultaneous detection of multiple enteropathogens. Although data on test performance are available, these tests need clarification of significance of multiple enteropathogen detections before wide implementation.[113]

EIA, enzyme immunoassay; NAAT, nucleic acid amplification test; PCR, polymerase chain reaction; STEC, Shiga toxin–producing *Escherichia coli.*

Direct microscopic examination of stool specimens can reveal the following: protozoal trophozoites, cysts, or oocysts; fungal spores; or helminthic larvae. Although parasitic diseases are not as common in the US as elsewhere and rarely cause inflammatory enteritis, their presence should be suspected, and direct examination for parasites should be performed, in the following high-risk situations: (1) recent travel to a developing country, (2) persistent diarrhea (>14 days), (3) immunocompromised status, (4) contact with a person with intestinal parasitic disease, and (5) occurrence of diarrhea in the presence of an outbreak of undetermined cause. Eosinophilia in a patient with inflammatory enteritis may indicate strongyloidiasis.[70] If amebic dysentery is suspected on the basis of risk factors, at least 3 fresh stool specimens should be examined using the iodine-trichrome method. Yield can be increased by examining stool concentrates stained with iron-hematoxylin.[43] The diagnosis is made visually by detection of hematophagous trophozoites or characteristic cysts in stools. Serum antibody to *E. histolytica* is present in 85% to 95% of patients with invasive disease but is likely to be absent in asymptomatic cyst excreters and persons with mild diarrhea.[43]

Intestinal biopsy (for histologic examination, special staining for microscopic identification of pathogen, and culture) should be considered in patients with persistent inflammatory enteritis or in an immunocompromised host when the diagnosis cannot be made by noninvasive methods. Specimens obtained at biopsy generally have better yield for parasites such as *E. histolytica.* Certain entities, such as enteropathogenic *E. coli,* exhibit characteristic histopathologic features on electron microscopy.

Several tests are available for diagnosis of *C. difficile* disease using targets for toxin (enzyme immunoassay [EIA]), toxin gene (nucleic acid amplification test), glutamate dehydrogenase or organism dehydrogenase (GDH-EIA), and isolation (culture). The optimal testing method remains an area of controversy.[71] Culture-based methods are resource intensive and not widely used. Toxin EIA has suboptimal sensitivity and specifically, and Infectious Diseases Society of America and Society for Healthcare Epidemiology of America guidelines for adults discourage use as a single test.[72] Nucleic acid amplification tests have higher sensitivity but are more costly, and tests detect the gene that encodes toxin and not the toxin itself; thus, a positive test result may represent colonization.[73] Algorithmic approaches have gained popularity. A common 2-step approach consists of GDH and toxin EIA testing, followed by confirmatory testing with nucleic acid amplification testing for specimens with discrepant findings.[74]

Inflammatory Enteritis in the

Immunocompromised Host

Clinical Approach

Diarrhea is a symptom in up to 50% to 60% of patients with the acquired immunodeficiency syndrome (AIDS) in the US.[22,75] Although hospital admissions attributable to diarrhea have declined, diarrhea still is a debilitating symptom in patients infected with HIV, even in the era of combination antiretroviral therapy.[22,23,76,77] Digestive tract disease in children with AIDS and other immunodeficiencies can be produced by a variety of infectious agents, including HIV.[22,23,75,78–80] Depending on the specific pathogen and the immunologic status of the patient, clinical manifestations can be acute or chronic. Patients with $CD4^+$ T-lymphocyte counts <50 cells/mm^3 and low serum albumin levels are more likely to have an infectious cause of digestive tract disease.[81] Signs and symptoms include diarrhea, vomiting, anorexia, failure to thrive, weight loss, and malabsorption. Histopathologic abnormalities in immunocompromised patients usually are similar to changes in healthy patients, although the changes often are more severe. In addition to typical enteric pathogens, opportunistic agents cause acute and chronic inflammatory enteritis in immunocompromised patients; disease caused by the following agents fulfills the AIDS-defining criteria of the Centers for Disease Control and Prevention: *Candida, Cryptosporidium, Histoplasma, Cystisospora* (formerly *Isospora*) spp., *M. avium* complex, *Salmonella* infection with septicemia, CMV, and herpes simplex virus.[22,75,76]

In early studies, no infectious cause of enteric disease was found in a large proportion of patients with AIDS. Subsequent studies demonstrated that aggressive evaluation, including endoscopy with biopsy, substantially improved diagnostic yield.[79,80] These data, coupled with the broad range of pathogens seen in the HIV-infected population (even in the era of combination antiretroviral therapy), support an intensive diagnostic approach when reasonable empiric therapy fails.[82]

Typhlitis (necrotizing enterocolitis of the cecum and surrounding tissues) is a life-threatening condition that occurs in profoundly neutropenic patients, usually people undergoing aggressive chemotherapy (with or without radiation) for malignant disease.[83]

Typhlitis also can occur in people with AIDS.[76] Typhlitis manifests as fever, abdominal pain, tenderness (especially right-sided, lower-quadrant tenderness mimicking that of acute appendicitis), and diarrhea. Evidence of right-sided colonic inflammation can be obtained using computed tomography, ultrasonography, and plain radiography.[83]

An approach to evaluation of the immunocompromised host with inflammatory enteritis is summarized in Box 57.1.

Box 57.1

Diagnostic Evaluation of Immunocompromised Patients With Inflammatory Enteritis

1. Routine stool culture for *Shigella, Salmonella,* and *Campylobacter jejuni* or *coli*
2. Specialized stool culture for *Mycobacterium avium* complex, other *Campylobacter* spp., *Yersinia enterocolitica, Escherichia coli*
3. Assay for *Clostridium difficile* toxin
4. Microscopic stool examination:
    a. Fecal leukocytes or fecal lactoferrin test for assessment of invasive bacterial cause
    b. Ova, cysts, and parasites such as *Giardia intestinalis, Strongyloides, Entamoeba histolytica* (see Table 57.1)
    c. Acid-fast stain for *Mycobacterium, Cryptosporidium, Cyclospora, Isospora*
5. Blood culture for bacteria, mycobacteria, detection of cytomegalovirus
6. If symptoms persist, if results of the preceding workup are negative, or if the patient is severely ill:

a. Obtain abdominal radiographs to detect pneumatosis intestinalis (present in severe cytomegalovirus colitis).

b. Consider esophagogastroduodenoscopy or colonoscopy with intestinal biopsy for histologic examination, culture, special stains, and molecular diagnosis.

Specific Agents

Cytomegalovirus.

Gastrointestinal tract disease caused by CMV occurs almost exclusively in the setting of immunodeficiency (including AIDS), organ transplantation, cancer chemotherapy, and corticosteroid therapy.[84–87] Colitis, the most common manifestation of enteric CMV disease, is characterized by fever, diarrhea, abdominal pain, and hematochezia. Abdominal radiographs can reveal pneumatosis intestinalis or free peritoneal air.[78] Endoscopic findings in patients with CMV-associated inflammatory colitis range from localized hyperemia to deep ulceration with overlying exudate and necrosis; the most common finding is mild, patchy colitis. If CMV is suspected, biopsy should be performed even if the mucosa appears normal grossly. Pp65 antigen detection and CMV DNA detection with polymerase chain reaction technology aid the diagnosis.[87,88] Complications of CMV-associated colitis include intestinal perforation, severe hemorrhage, peritonitis, small bowel obstruction, and toxic megacolon. Ganciclovir therapy has been shown to be beneficial for CMV-associated colitis when treatment is initiated early in the disease.[84,87] Ganciclovir induction therapy should be administered for 3 to 6 weeks, depending on the degree of involvement and immunologic state of the patient; maintenance therapy may be required thereafter.[88]

Cryptosporidium.

Cryptosporidial infection, one of the most common causes of enteric disease in patients with AIDS, occurs in 10% to 20% of adults with AIDS in the US.[89,90] This infection may be less common in children and has been decreasing in frequency in the age of antiretroviral therapy.[91] Typical AIDS-related diarrheal syndromes consist of profuse, watery, and often bloody diarrhea associated with anorexia and weight loss; death is common.

Mycobacterium avium Complex.

M. avium complex infections are common in patients with AIDS and low CD4$^+$ T-lymphocyte counts.[92] Signs and symptoms usually are nonspecific and include fever, night sweats, malaise, and diarrhea. The small intestine appears to be involved more commonly than the colon. Mucosal changes include erythema, edema, friability, and, occasionally, small erosions and fine white nodules.

Fungi.

Local or systemic fungal infections can cause chronic inflammatory enteritis.[93,94] Fungal pathogens include the following: *Candida* spp., which can cause chronic, bloody, or nonbloody diarrhea; *Paracoccidioides brasiliensis* (South American blastomycosis), which causes a granulomatous or ulcerative lesion in the gastrointestinal tract; *Histoplasma capsulatum,* which can manifest with ulceration, bleeding, or obstruction; and the phycomycoses, which can cause abdominal pain, diarrhea, gastrointestinal tract bleeding, and peritonitis.

Management

Fluid loss is the most important consequence of acute gastroenteritis. The primary aims of management are aggressive rehydration and replacement of electrolytes by oral or intravenous routes, maintenance of blood volume and acid-base balance, and replacement of ongoing diarrheal losses. Nutritional support also is important, especially in immunocompromised and malnourished patients, who are prone to persistent illness. Early feeding minimizes caloric deficit and stimulates repair of the intestinal brush border.[95] Breastfeeding of infants should be continued, especially in developing countries, thus adding the benefit of passively acquired protective factors. In severe persistent inflammatory enteritis in which absorption is compromised, parenteral nutrition is considered.

Antimicrobial therapy is reserved for the small proportion of patients with suspected or proven bacterial causes of diarrhea in whom benefit is likely.[45] Empiric antibiotic therapy is appropriate in the following patients with inflammatory enteritis: (1) severely ill patients with strongly suspected bacterial dysentery; (2) immunocompromised people, including patients with AIDS and recipients of immunosuppressive drugs; (3) infants <3 months of age with *Salmonella* infection (who are at high risk of bloodstream infection [BSI]); (4) patients with hemoglobinopathy or asplenia; and (5) people with a high likelihood of a treatable cause according to history, physical findings, or epidemiologic factors. Antibiotics are not recommended in patients with suspected Shiga toxin–producing *E. coli* infection (these patients typically present afebrile with bloody diarrhea) because such therapy may increase the risk of hemolytic-uremic syndrome,[96] although this is controversial.[97]

Antibiotics hasten clinical improvement in people with shigellosis and severe *Campylobacter*-associated enteritis if treatment is given early in the course.[97] Therapy also shortens the duration of fecal shedding of these organisms and of *Y. enterocolitica* infection. In developed countries, trimethoprim-sulfamethoxazole has long been effective empiric treatment for suspected shigellosis in children. However, increasing antibiotic resistance renders this agent ineffective in many cases. Antibiotic susceptibility testing should be performed on patient isolates, and clinicians should be aware of susceptibility patterns in their area. Cefixime has in vitro activity against most strains of *Shigella* that are resistant to ampicillin or trimethoprim-sulfamethoxazole and is safe for use in children.[98] One dose of ciprofloxacin usually is adequate for treatment of all *Shigella* species except *Shigella dysenteriae* 1; however, use of fluoroquinolones in children should be restricted. Additionally, fluoroquinolones are a risk for *C. difficile* infection. A Scientific Working Group of the World Health Organization raised the possibility that the efficacy of fluoroquinolones for shigellosis may outweigh the small risk of adverse effects in selected children.[99] The role of antibiotics in treating people with specific causes of bacterial gastroenteritis is summarized in Table 57.6.

TABLE 57.6

Use of Antimicrobial Therapy in Inflammatory Enteritis

Antimicrobial Therapy	Enteropathogens
Effective clinically	*Shigella,* enteroinvasive *Escherichia coli*
Decreased excretion	*Shigella,* enteroinvasive *E. coli, Yersinia enterocolitica, Campylobacter jejuni*
Indicated in certain hosts[a]	*Salmonella, Campylobacter,* enteropathogenic *E. coli,* enterotoxigenic *E. coli, Clostridium difficile, Yersinia enterocolitica*
Unclear effect	Enteroaggregative *E. coli, Aeromonas,* noncholera *Vibrio* spp.
Controversial[b]	Enterohemorrhagic *E. coli*

[a] Antimicrobial agents warranted for patients with severe colitis or with increased risk of disseminated disease: infants <3 months of age, persons with immunodeficiency disorders (including acquired immunodeficiency syndrome, hemoglobinopathy, and asplenia), and recipients of immunosuppressive drugs.

[b] See Chapter 137 and text.

Nonspecific therapies other than antimicrobial agents are available for symptomatic treatment of patients with diarrhea. Bismuth subsalicylate has some effect in decreasing stool volume and illness in traveler's diarrhea.[100] One study showed a decrease in frequency and volume of diarrhea in children.[101] Antiperistaltic agents (loperamide and diphenoxylate hydrochloride) and antiemetic agents can be effective in the management of diarrhea in adults; however, their use is not recommended in infants and young children because safety and efficacy data are lacking.[102] Antiperistaltic agents have been demonstrated to worsen the clinical course of disease caused by *Shigella* spp., *C. difficile,* and *E. coli* O157:H7. Fecal microbiota transplantation has demonstrated promising results in adults for treatment of relapsing *C. difficile* infections. Patients appear to have immediate improvement of diarrhea after a fecal microbiota transplantation procedure and usually are symptom-free for several months. The ideal protocol for screening potential donors and the optimal mode of transplantation remain unclear. Methods of transplantation have advantages and disadvantages. Transplantation by nasogastric tube, upper endoscopy, nasoduodenal or nasojejunal tube, colonoscopy, and enema has shown similar results. The opinion of some experts is that transplantation directly into the colon is most physiologic; however, active infection also carries a risk of perforation.[103,104] Transplantation in the proximal gastrointestinal tract carries less risk for perforation, although concern exists regarding aspiration or potential degradation from gastric and pancreaticobiliary secretions.[105,106]

Infants With Inflammatory Enteritis

An infant <3 months of age with inflammatory enteritis should be managed cautiously because of the propensity of *Salmonella* strains to cause BSI with disseminated suppurative foci in this age group.[107,108] Although the precise frequency of BSI is not known, a prospective study of children with gastroenteritis caused by *Salmonella* spp. reported BSI in 6 of 91 patients (2 of the 6 infants were ≤3 months of age).[108] Infants whose condition appears toxic and who have diarrhea as the prominent feature of illness should be hospitalized, cultures of blood and cerebrospinal fluid should be obtained, and intravenous antibiotics with a spectrum of activity against enteric pathogens, as well as common invasive pathogens, should be given. In the infant ≤3 months of age whose condition does not appear toxic, one panel of experts recommended obtaining blood and stool cultures if the stool contains blood or leukocytes.[108] Cefotaxime or ceftriaxone is effective for treatment of invasive focal *Salmonella* infections.[109] If stools contain blood or leukocytes, empiric antimicrobial therapy may be initiated. The value of antimicrobial therapy for *Salmonella* gastroenteritis without BSI has not been established. No evidence of clinical benefit of antimicrobial therapy exists in otherwise healthy children and adults with nonsevere *Salmonella* diarrhea.

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58

Necrotizing Enterocolitis

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Necrotizing enterocolitis (NEC) is the most common neonatal gastrointestinal emergency. NEC results in substantial morbidity and mortality, particularly in premature infants. Although no significant improvements in morbidity and mortality rates have been made in recent years, our understanding of the pathogenesis of NEC continues to improve. Incomplete gastrointestinal development, underlying gastrointestinal pathologic features, and bacterial translocation likely all have roles in the development of NEC. Further advancement of knowledge about the interaction of these factors in the development of NEC may lead to more effective prevention and management, thereby improving the duration and quality of life for many premature infants.

Epidemiology

NEC affects predominantly premature infants, and its incidence has not significantly changed in recent years. According to studies conducted by the Canadian Neonatal Network and the National Institute of Child Health and Human Development Neonatal Research Network, NEC affects approximately 5% of infants <33 weeks of gestation and 11% of infants ≤28 weeks of gestation.[1,2] NEC has no seasonal, geographic, or sex predilection.[3,4] Among infants with less than 1000 g birth weight, NEC usually develops after the first 2 weeks of life; among more mature and full-term infants, NEC may occur as early as the first week of life.[1,5–7]

Risk factors for NEC in full-term infants suggest that mucosal injury and ischemia are important (Table 58.1).[5–7] In a multicenter review of 30 term and near-term infants, these infants were more likely to develop NEC if they had congenital heart disease, polycythemia, or documented early-onset sepsis.[8] Although cyanotic congenital heart disease is a risk factor for NEC among full-term infants, the overall incidence in this population is low. In an analysis of nearly 7000 full-term infants with ductal-dependent congenital heart disease, NEC occurred in 21 (0.3%); only 12 of these infants were less than 37 weeks of gestational age.[9]

TABLE 58.1

Factors and Conditions Associated With Necrotizing Enterocolitis

Premature Infant	Full-Term Infant
Lower gestational age	Cyanotic congenital heart disease
Feeding	Polycythemia
Histamine H_2-blocking agents	Exchange transfusion
Empiric antibiotics	Perinatal asphyxia
	Small for gestational age or intrauterine growth restriction
	Umbilical catheter
	Maternal pre-eclampsia
	Antenatal cocaine
	Premature rupture of membranes
	Milk allergy
	Gestational diabetes

Pathologic Findings and Pathogenesis

Pathologic lesions of NEC occur throughout the intestine, but the most common sites in preterm infants are the watershed areas of the intestine including the distal ileum and proximal colon.[10] Initial lesions manifest as superficial mucosal ulceration, submucosal hemorrhage, and edema.[11] Apoptosis or necrosis of intestinal epithelia contribute to loss of intestinal epithelia, and this loss of mucosal barrier function may allow passage of bacteria and undigested food antigens into the submucosa and initiation of inflammatory processes.[12,13] In severe cases, coagulative transmural necrosis and perforation occur. If the disease does not progress to this stage, healing can occur by epithelialization and proliferation of fibroblasts and granulation tissue. Strictures can follow, and their occurrence can be independent of NEC severity.[14–16]

Although the pathologic findings in NEC provide some insight into its pathogenesis, the physiologic processes associated with the disease are not completely understood. Clinical NEC is likely the "final common pathway" of multiple interactions of immaturity, injury, bacteria, and substrate (Box 58.1).[10,11,17] Intestinal immaturity is characterized functionally by poor motility, weak barrier function, incomplete immune defenses, and limitations in digestion and absorption.[13,18,19] The high incidence of NEC after initiation of enteral feedings (90% of NEC cases) suggests an interaction between substrate and intestinal immaturity that contributes to the development of the disease.[20]

Box 58.1

Limitations of the Preterm Infant's Intestine That May Contribute to Risk of Necrotizing Enterocolitis

Immunologic Factors

Decreased secretory immunoglobulin A

Decreased intestinal lymphocytes

Poor antibody response

Innate immune system immaturity

Luminal Factors

Lower hydrogen ion output in stomach

Lower proteolytic enzyme activity

Immature Intestinal Barrier

Less protective mucin barrier

Less protective microvillous membrane

Higher permeability

Lower or Less Organized Motility

Most investigators believe that intestinal injury caused by major perinatal hypoxic-ischemic events is not likely to contribute directly to NEC pathogenesis in preterm infants. However, hypoxia and ischemia lead to increased production of nitric oxide and endothelin. These molecules help regulate vascular tone and likely have a downstream role in NEC pathogenesis.[19,21]

Unlike hypoxic-ischemic events, processes that allow microbial invasion of the intestinal epithelia and submucosa likely have direct effects on the pathogenesis of NEC. The immature epithelium of a newborn infant is unable to adapt its immune function in response to the increased microbial exposure that occurs during intestinal colonization. Ideally, innate immunity factors balance proinflammatory functions that prevent bacterial overgrowth and invasion, with anti-inflammatory functions. The inability of the immature epithelium to balance these opposing factors leads to weakening of barrier function and intestinal cell apoptosis.[13,22]

The premature infant's increased expression of the proinflammatory mediator toll-like receptor 4 (TLR4) and decreased expression of the inflammatory regulator IκB, compared with adults, may provide some basis for the excessive inflammatory response that leads to NEC.[19,23,24] TLR4 is located on intestinal cell surfaces and signals synthesis of proinflammatory mediators in response to the bacterial cell wall component lipopolysaccharide. IκB regulates the proinflammatory transcription factor nuclear factor κB (NF-κB).

The inflammatory processes that lead to NEC suggest that the existence of microbial colonization is an important inciting event. However, epidemiologic observations suggest that the composition of microbial colonization may also be important. NEC has been associated with prolonged exposure to antibiotics and antacids, 2 therapeutic drug classes that are likely to modify the extent and composition of microbial colonization.[25,26] Moreover, multiple bacteria known to colonize the intestines have been associated with

NEC: bacteria with known toxins (e.g., hemolysins of staphylococci, enterotoxins of *Escherichia coli,* and clostridia toxins), and other gram-negative bacteria. These bacteria are thought to be responsible for the pathognomonic hepatobiliary gas or intramural gas (pneumatosis intestinalis; Fig. 58.1) produced during invasion of the intestinal submucosa.[27–29]

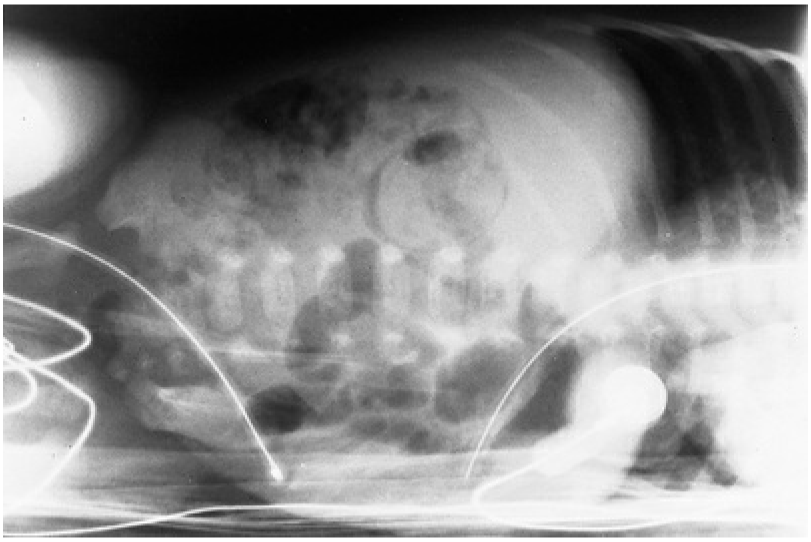

FIGURE 58.1 Abdominal radiograph of an infant with necrotizing enterocolitis and pneumatosis intestinalis. (From Willoughby RE Jr, Pickering LK. Necrotizing enterocolitis and infection. Clin Perinatol 1994;21:307–315.)

Notably, molecular methods to characterize intestinal flora in preterm babies with and without NEC have failed to identify consistent bacterial pathogens.[30–32] This finding and the observation that organisms implicated in NEC are found in symptomatic and asymptomatic infants further support the complexity of NEC pathogenesis and the low likelihood that infectious etiologic agents are solely responsible. However, infectious causes may be the final defining factor in some cases; NEC outbreaks have been associated with illness in caregivers, and viruses (e.g., rotavirus and cytomegalovirus) have been implicated in clusters of NEC cases.[33–38]

Clinical Manifestations, Differential Diagnosis, and Clinical Approach

Although progress has been made in understanding the mechanisms of the pathogenesis of NEC, diagnostic and therapeutic approaches have not advanced. The clinical course of NEC can vary from a slow, indolent process to one that is fulminant with lethal progression over hours. Classic signs include abdominal distention with discoloration or erythema of the overlying skin and bloody stools. NEC also may occur in the absence of these signs, especially in the most premature infants.[36] Many infants have less specific signs indicative of generalized sepsis (Box 58.2). Thrombocytopenia and low or high white blood cell counts are common. The combination of systemic hypotension, falling leukocyte and platelet counts, and worsening metabolic acidosis suggests worsening disease.[19] These signs may reflect the bloodstream or peritoneal infection that occurs in approximately 30% of preterm infants with advanced NEC. Intestinal bacterial flora organisms, specifically including gram-negative organisms, are most often isolated.[39,40]

Box 58.2

Initial Signs of Necrotizing Enterocolitis

Feeding intolerance (decreased oral intake, vomiting, increased gastric residual fluid)

Lethargy

Temperature instability

Apnea

Metabolic acidosis

Shock

Disseminated intravascular coagulation

Ileus

Clinitest[a]-positive stools

Heme-positive stools or heme-positive vomitus

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[a] Proprietary (Bayer) alkaline copper sulfate reagent test.

Differential diagnoses include medical conditions associated with decreased intestinal motility: bacterial or viral infections, metabolic disorders such as hypothyroidism, and congenital heart disease. NEC is suspected when gastrointestinal signs predominate. Infectious enterocolitis, small bowel volvulus, colonic aganglionosis with enterocolitis, focal intestinal perforation (FIP), and other surgical diseases of the intestinal tract also should be considered.[19,36]

Of all possible differential diagnoses, FIP is potentially most difficult to distinguish from NEC. NEC and FIP have similar predilection for the distal ileum and may have similar outcomes. The age of disease onset is different. FIP usually occurs in the first few postnatal days in extremely low–birth weight (<1000 g at birth) infants, whereas NEC in the most premature infants occurs beyond the first 2 postnatal weeks.[41,42] FIP is more commonly associated with *Candida* and staphylococcal peritonitis, whereas positive peritoneal cultures in NEC are more likely the result of Enterobacteriaceae.[40]

Once the diagnosis of NEC is suspected, confirmation of the disease depends on radiographic findings (see Fig. 58.1). Pneumatosis intestinalis can be subtle, but it is pathognomonic. Thickened and dilated loops of small bowel are common but nonspecific. Pneumoperitoneum (best assessed on a cross-table or left lateral decubitus radiograph) or intra-abdominal fluid suggests the need for surgical intervention. Diagnostic criteria for NEC were originally developed by Bell and Conorkers. Modified criteria provide uniformity for therapeutic decision making (Table 58.2).[43]

TABLE 58.2

Modified Bell Staging for Necrotizing Enterocolitis

Stage	Classification	Systemic Signs	Intestinal Signs	Radiograph
IA	Suspected NEC	Temperature instability, apnea, bradycardia, lethargy	Increased pregavage residuals, midabdominal distention, emesis, heme-positive stool	Normal or intestinal dilation, ileus
IB	Suspected NEC	Same as above	Bright red blood from rectum	Same as above
IIA	Proven NEC: mildly ill	Same as above	Same as above, plus absent bowel sounds, with or without abdominal wall tenderness	Intestinal dilation, ileus, pneumatosis intestinalis

IIB	Proven NEC: moderately ill	Same as above, plus mild metabolic acidosis and mild thrombocytopenia	Same as above plus absent bowel sounds, definite tenderness, with or without abdominal cellulitis or right lower quadrant mass	Same as stage IIA plus definite ascites
IIIA	Advanced NEC: severely ill, bowel intact	Same as stage IIB, plus hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis, disseminated intravascular coagulation, and neutropenia	Same as above plus signs of generalized peritonitis, marked tenderness, and distention of the abdomen	Same as stage IIA plus definite ascites
IIIB	Advanced NEC: severely ill, bowel perforated	Same as stage IIIA	Same as stage IIIA	Same as stage IIB plus pneumoperitoneum

Some researchers have investigated early indicators of NEC that may prompt early intervention and potentially decrease morbidity and mortality. Among these indicators, increases in the following biomarkers have been associated with NEC: exhaled breath hydrogen, serum levels of interleukin-6, endotoxin, α_1-antitrypsin, stool-reducing substances and specific short-chain fatty acid profiles, neutrophil CD64, and C-reactive protein (CRP). Investigators also have evaluated the utility of ultrasound examination to diagnose early NEC. When compared with plain radiographs, ultrasound examination may be able to identify a wider array of pathologic findings in the early stages of NEC. Neither ultrasound study nor biomarker determination has been introduced into clinical practice.[44–48]

Management

Management of NEC is largely supportive and is directed at preventing progression, restoring homeostasis, and minimizing complications. Providers should withhold oral feedings and decompress the stomach through placement of a large-bore nasogastric tube and application of intermittent suction. Intravenous access is required to provide fluid, electrolytes, nutrition, and antimicrobial agents. The duration of enteral feeding restriction depends on radiographic findings, clinical status, and local practice. Many patients whose signs resolve and whose NEC does not progress beyond stage I (Table 58.2) are fed after 48 to 72 hours. If the period of enteral restriction is longer (e.g., >7 days, common if ≥stage II), total parenteral nutrition should be considered. Infants are initially fed low volumes of elemental formula or breast milk. This strategy allows optimal nutrient absorption and avoids osmolar challenge and further injury to the intestinal mucosa.[49]

Few randomized clinical trials have been performed to guide feeding strategies after NEC.[49] Among such studies, however, serial CRP levels in the days following NEC diagnosis appeared to be useful. When less severe disease was observed, and radiographs normalized, CRP was persistently low. These infants were safely fed earlier and antibiotics were stopped sooner (48 hours if cultures were negative) than in infants whose CRP levels remained elevated. Abnormal CRP values in infants with stage II NEC returned to normal at a mean of 9 days from onset, except in 7 infants, all of whom required exploratory operations (4 identifying strictures and 3 for intra-abdominal abscesses and peritonitis).[50]

Providers should consider the role of microbes in the pathogenesis and as a complication of NEC when microbes invade the intestinal epithelium and enter the bloodstream. Because NEC can clinically resemble sepsis, providers should obtain blood, stool, urine, and cerebrospinal fluid cultures and administer intravenous antibiotics.

Recommendations for initial antimicrobial therapy vary among experts. Some experts advocate the routine use of ampicillin and gentamicin. When perforation is diagnosed or necrosis is suspected, providers should add an agent with activity against anaerobes (e.g., clindamycin or metronidazole). Providers should add vancomycin if resistant *Staphylococcus* species are documented.[19,51] Some experts recommend immediate empiric use of vancomycin in addition to broad-spectrum gram-negative bacillus coverage.[52] However, the empiric use of vancomycin for possible coagulase-negative staphylococci must be balanced against the risk of selecting vancomycin-resistant enterococci. Reinforcement of strict handwashing is essential. Infection control measures such as barrier isolation and cohorting of affected infants and personnel may abort epidemics.

Routine inclusion of antimicrobial agents active against anaerobic bacteria does not seem to be indicated in NEC without perforation, but few well-controlled studies have been conducted. Clindamycin use was associated with increased strictures following stage II NEC in a small randomized study, as well as in a multicenter observational study using propensity matching of 1390 infants exposed to anaerobic therapy. However, mortality rates were decreased in infants with surgical NEC who received anaerobic therapy compared with infants who did not receive this therapy.[53,54]

Despite conservative management, including withholding of feedings, abdominal decompression, and antimicrobial therapy, some infants require more invasive therapy with surgical management. Indications for surgical intervention include pneumoperitoneum on abdominal radiography or cellulitis of the anterior abdominal wall. Both pneumoperitoneum and cellulitis are signs of perforation or gangrenous bowel. Abdominal radiography is repeated every 6 hours to assess the progression of NEC. Third-spacing of fluid may indicate intestinal inflammation and edema. Progressive neutropenia, thrombocytopenia, and metabolic acidosis are potential signs of progression and may indicate the need for exploratory operation.

The classic operative strategies have been relatively conservative, including resection of grossly gangrenous bowel and creation of a proximal enterostomy or, conversely, placement of a drain. In a prospective, randomized, multicenter study comparing laparotomy with drain placement in 117 preterm infants with birth weights <1500 g, no difference was reported between the 2 groups in mortality rates at 28 days after procedure, mortality rates at 90 days after procedure, or prolonged duration of total parenteral nutrition.[55] In another multicenter observational trial that followed 156 infants with surgical NEC or isolated intestinal perforation, mortality rates were not different for laparotomy compared with drain placement, but neurodevelopmental outcome at 18 to 22 months of adjusted age was better among infants with laparotomy.[56] Randomized clinical trials are ongoing to determine the effect of laparotomy compared with drain placement on longterm patient outcomes.

Prognosis and Complications

NEC is associated with significant mortality. In a multicenter cohort study of 1722 extremely low–birth weight infants, the incidence of death among those with NEC was twice that of infants who did not develop NEC ($P < 0.01$). The death rate did not change substantially over the 12-year period (1998–2009).

Epidemiologic studies indicate that the requirement for surgical treatment or bloodstream infection associated with NEC increases the risk for death. Of 208 infants who developed NEC, 53 of 87 (61%) with medical NEC and 50 of 121 (41%) with surgical NEC survived until hospital discharge.[57] The incidence of death among all infants with surgical NEC is approximately 50%.[39,58,59] Among 410 infants with NEC, an NEC-associated bloodstream infection nearly quadrupled the odds of requiring surgical intervention (odds ratio: 3.5; 95% confidence interval [CI] 1.98, 6.24), and tripled the odds of death (odds ratio: 2.9; 95% CI, 1.39, 5.97) when compared with infants who did not have bloodstream infection.[60]

Substantial morbidity also accompanies NEC. Preterm infants with NEC, particularly surgical NEC, have much higher risk for developmental delay than infants who do not have NEC.[61,62] Other acute and chronic complications of NEC often result in prolonged hospitalizations for affected infants (Box 58.3).[58,63]

Box 58.3

Complications of Necrotizing Enterocolitis

Intestinal or colonic strictures

Enterocolonic fistulas

Fluid and electrolyte imbalance

Malabsorption

Cholestasis

Anastomotic leaks and stenosis after surgical treatment

Short gut syndrome after surgical treatment

Morbidity related to the longterm effects of NEC on the gastrointestinal tract is seen in 10% to 30% of affected infants and is highest among infants with NEC who require surgical treatment. One of the most serious complications of NEC is short bowel syndrome. This condition occurs when more than 70% of the intestine is removed and is particularly difficult to manage if the terminal ileum and ileocecal valve cannot be preserved because of the tendency to injury of this area in NEC. The potential consequences of short bowel syndrome include malabsorption, extensive parenteral nutrition requiring prolonged venous access, bacterial overgrowth, and bowel transplantation.[64]

Advances in Understanding of Pathophysiology

The understanding of NEC pathophysiology continues to advance. Awareness of the following is increasing: (1) factors that influence the integrity of the neonatal epithelial barrier[65,66]; (2) the intricacies of innate immunity, particularly the influence of TLR4 on innate immunity[67]; and (3) the contribution of the gut microbiota of premature infants to the development of NEC.[32,68] The transformation of this information into clinically useful data for new therapies, early identification of infants with NEC, and prevention, is ongoing.

Prevention

Multiple strategies to prevent NEC have been proposed. Most common among these is the use of human milk as the primary nutrition source. In a meta-analysis of 9 randomized (or quasirandomized) controlled trials in 1070 infants who received infant formula or donor breast milk, feeding with formula significantly increased the risk of NEC (risk ratio: 2.77; 95% CI, 1.40–5.46).[69] An analysis of 1272 infants suggested that the benefits of human milk administration in the prevention of NEC are dose related. The incidence of NEC or death decreased for every 10% increase in the proportion of total intake that was human milk.[70] In a single multicenter, randomized clinical trial, a human milk–derived human milk fortifier was compared with a bovine milk–derived fortifier, the incidence of NEC was significantly reduced among those infants receiving an exclusively human milk–derived diet.[71]

Human milk may influence physiologic pathways that lead to NEC in several ways. Human milk may cause intestinal maturation and healing against insults through the presence of immune and growth factors, including platelet activating factor acetyl hydrolase, immunoglobulin A, cytokines, and epidermal growth factor, among others.[72] Human milk may also promote the growth of commensal bacteria.

Investigators also have evaluated the relationships among timing of feeding initiation, rate of feeding advancement, and the incidence of NEC. A meta-analysis of 9 randomized controlled trials of 1106 infants found no statistically significant difference in risk of NEC for infants who had feedings introduced at ≤4 days of life compared with infants who received first feedings >4 to 7 days after birth.[73] In a meta-analysis of 6 randomized controlled trials, including 618 infants, no difference was noted in the incidence of NEC between groups fed 15 to 20 mL/kg and those fed 30 to 35 mL/kg. However, infants fed at the slower rates took longer to regain birth weight and reach full enteral feedings.[74] Long periods of not feeding can cause gut atrophy and worsened inflammatory responses, which predispose infants to NEC.[13]

Administration of prophylactic probiotics or prebiotics is thought to prevent bacterial migration, replenish nonpathogenic bacteria, and enhance the host immune response, thereby preventing NEC. In a meta-analysis, administration of *Lactobacillus,* alone or in combination with *Bifidobacterium,* was associated with reduction of severe NEC (stage II or worse; risk ratio: 0.43; 95% CI, 0.33–0.56). The authors of this meta-analysis suggested that the evidence for probiotic use is robust enough to support practice change; however, the available data include little information about the safety, feasibility of product consistency, most effective dosing, and ideal timing of probiotic administration.[75] In a multicenter, randomized controlled trial of 400 infants, those infants who received probiotics alone (2%) or in combination with prebiotics (4%), had a lower incidence of NEC compared with infants receiving prebiotics or placebo alone (12%) ($P < 0.001$).[76]

As the understanding of NEC continues to advance, it is hoped that new therapies to decrease the incidence of NEC among low–

birth weight infants will be developed. Studies to investigate the benefits of increasing intestinal nitric oxide synthesis, modulating the immune system, improving surgical techniques, and altering the intestinal biota will be informative.

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Enteric Diseases Transmitted Through Food, Water, and Zoonotic Exposures

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More than 200 known pathogens and noninfectious agents can be transmitted through ingestion of food or water contaminated with viruses, bacteria, parasites, microbial or chemical toxins, metals, and prions or through contact with animals or their environments.[1] Enteric disease is one of the most common illness types resulting from foodborne, waterborne, or zoonotic transmission. Symptoms of enteric illness range from mild gastroenteritis to life-threatening sepsis and neurologic, hepatic, ocular, and renal syndromes. Children <5 years of age, pregnant women, older adults, and immunocompromised persons are at higher risk for serious illness. Despite improvements in water, sanitation, and hygiene, foodborne, waterborne, and zoonotic enteric diseases remain major public health problems in developed and developing countries.

Epidemiology

Foodborne Disease

The Centers for Disease Control and Prevention (CDC) estimates that 48 million domestically acquired foodborne illnesses occur in the United States each year, resulting in approximately 128,000 hospitalizations and 3000 deaths.[2,3] Among known pathogens, norovirus is the leading cause of foodborne illness in the US, followed by nontyphoidal *Salmonella*, *Clostridium perfringens*, and *Campylobacter*.[3] The highest incidence rates for nontyphoidal *Salmonella*, *Campylobacter*, *Shigella*, *Escherichia coli* O157, and *Yersinia enterocolitica* occur in children <5 years of age, and the highest rate of invasive *Cronobacter* spp. (formerly *Enterobacter sakazakii*) infections is among infants.[4,5] These 6 bacterial pathogens are estimated to cause >290,000 illnesses annually among children <5 years of age and to result in nearly 8000 hospitalizations and 64 deaths.[4,5] Nontyphoidal *Salmonella* is estimated to cause the most hospitalizations and deaths each year in this age group. Although norovirus causes approximately 50% of recognized foodborne illnesses associated with outbreaks in the US, the highest rates of hospitalizations and deaths associated with norovirus occur in adults ≥65 years old and older.[6] With widespread administration of antimicrobial agents to humans and feed animals, antimicrobial resistance has become increasingly prevalent among strains of *Salmonella*, *Campylobacter*, and *Shigella*.[7]

Most foodborne illnesses are not linked to outbreaks. However, data from foodborne illness outbreaks provide useful insights into important pathogens, new and high-risk food vehicles, and settings associated with illness. From 1998 to 2012, more than 16,500 foodborne disease outbreaks affecting more than 330,000 people in the US were reported to the CDC, with an annual average of >1000 outbreaks and >22,000 ill persons.[8–11] Norovirus continues to be the leading cause of confirmed, single-agent foodborne disease outbreaks in the US, followed by *Salmonella* species.[8]

Many different foods have been linked to foodborne illness outbreaks; poultry, fish, beef, unpasteurized dairy products, fruits, and vegetable row crops have been commonly implicated in recent foodborne outbreaks.[8–10] Contaminated produce (particularly leafy green vegetables) increasingly has been linked to foodborne outbreaks caused by norovirus, *Salmonella*, *E. coli* O157:H7 and other Shiga toxin producing–*E. coli* (STEC), *Listeria monocytogenes*, *Shigella* spp., *Cryptosporidium*, and *Cyclospora cayetanensis*.[11–29] Imported fresh raspberries, basil, cilantro, and snow peas have been linked to outbreaks of *Cyclospora* infection.[13,21,30] Despite its risk, unpasteurized (raw) milk continues to be sold legally in many states and sometimes is given to school groups who visit farms; more than 130 outbreaks linked to unpasteurized milk or cheese have been reported in the US since 1993,[8–10,31] and etiologic agents include norovirus, *Salmonella*, *Campylobacter*, *Staphylococcus aureus*, *Listeria monocytogenes*, and STEC.[31–34] During 2007 to 2012, most outbreaks associated with unpasteurized milk were caused by *Campylobacter* spp.[35] Formula-fed infants have a heightened risk of salmonellosis compared with breastfed infants, perhaps because they are not receiving immunologic protection from human milk or because of contamination of formula in the bottle.[36] Powdered infant formula is also associated with *Cronobacter* spp. (formerly *Enterobacter sakazakii*) infection in infants, which can result in sepsis and meningitis.[37] Commercial processed foods and ready-to-eat foods have also been implicated in outbreaks of *Salmonella*, *E. coli* O157, and *L. monocytogenes*, including prepackaged cookie dough, salami made with contaminated pepper, snack foods, and frozen microwaveable meals.[38–42] Ready-to-eat foods, such as salads and sandwiches, as well as self-service food items, often are implicated in norovirus and shigellosis outbreaks.[43,44] Additional information about vehicles associated with enteric disease etiologic agents is shown in Table 59.1.

TABLE 59.1

Characteristics and Diagnosis of Enteric Illnesses Caused by Microbes or Toxins

Etiology	Incubation Period	Signs and Symptoms	Duration of Illness	Selected Vehicles	Labo
BACTERIAL					
Bacillus anthracis	2 days to weeks	Nausea, vomiting, malaise, bloody diarrhea, abdominal pain	Weeks	Insufficiently cooked contaminated meat	Blood
Bacillus cereus (diarrheal toxin)	10–16 hr	Abdominal cramps, nausea, watery diarrhea	24–48 hr	Meats, stews, gravies, milk products, vegetable dishes	Durir consi quant testin stool

Bacillus cereus (preformed enterotoxin)	1–6 hr	Sudden onset of severe nausea and vomiting; possibly with diarrhea	24 hr	Improperly refrigerated cooked rice, meats	Durir consi quant testin emesi
Brucella abortus, Brucella melitensis, Brucella suis	7–21 days	Fever, chills, sweating, weakness, headache, myalgias, arthralgias, bloody diarrhea	Weeks	Raw milk, unpasteurized goat cheese, meats	Blood serol
Campylobacter jejuni	2–5 days	Fever, cramps, vomiting, diarrhea (can be bloody)	2–10 days	Raw and undercooked poultry, unpasteurized milk, contaminated water, animal contact	Stool media incub
Clostridium botulinum (preformed toxin)	12–72 hr	Vomiting, diarrhea, diplopia, dysphagia, descending muscle weakness, respiratory paralysis	Variable (days to months)	Home-canned foods with low acid content, improperly canned commercial foods, fermented fish, herb-infused oils, potatoes baked in foil, bottled garlic, foods held warm for extended periods	Stool, food for to food
Clostridium botulinum (infant)	3–30 days	Lethargy, weakness, hypotonia, poor head control, poor feeding, poor gag reflex, constipation	Variable	Honey, corn syrup	Stool, food for to food
Clostridium perfringens (toxin)	8–16 hr	Nausea, cramps, watery diarrhea; fever rare	24–48 hr	Meats, poultry, fish, gravy, dried or precooked foods, time- or temperature-abused foods	Stool be tes enter quant cultu organ CFU/ $>10^5$ C
Cronobacter spp.	Unknown	Diarrhea possible, sometimes bloody;	Variable; meningitis	Powdered infant formula	Blood cereb

		sepsis; meningitis	associated with brain abscesses and prolonged illness		cultu infan be tes and s healt
Enterotoxigenic *Escherichia coli* (ETEC)	24–72 hr	Cramps, possible vomiting, watery diarrhea	3 to >7 d	Contaminated water or food (often during international travel)	Stool (requ testin
Shiga toxin–producing *Escherichia coli* (STEC)	1–8 days	Abdominal pain, vomiting, diarrhea that becomes bloody; usually no fever	5–10 days	Undercooked beef (especially ground beef), unpasteurized dairy and juice, leafy green vegetables, sprouts, contaminated water, petting zoos or farms featuring ruminant animals	Stool O157 speci toxin done comm
Listeria monocytogenes	9–48 hr for gastrointestinal symptoms; 2—6 wk for invasive disease	Fever, myalgias, nausea, diarrhea; pregnant women may have a flu-like illness, and infection can cause premature delivery or fetal loss; infants born to infected mothers and immunocompromised patients can have bacteremia or meningitis	Variable	Soft cheeses, raw fruits and vegetables, hot dogs, delicatessen meats (especially turkey) and delicatessen salads	Blood cultu asym carria stool helpf
Salmonella spp.	24–72 hr	Fever, cramps, vomiting, diarrhea; S. *enteritidis* serotype Typhi and *S. enteritidis* serotype Paratyphi cause typhoid, characterized by fever, headache, constipation, myalgias, and abdominal pain	4–7 days	Poultry, eggs, beef, pork, unpasteurized milk or juice, raw fruits and vegetables (especially sprouts, melons, tomatoes), nuts; reptiles, amphibians, rodents, live poultry; typhoid is associated with international travel	Stool

Shigella spp.	12–72 hr	Fever, cramps, tenesmus, diarrhea that can be bloody and mucoid	4–7 days	Low infectious dose leading to person-to-person spread, particularly in childcare settings and within households, foods contaminated by ill food handlers, contaminated swimming venues (especially freshwater)	Stool
Staphylococcus aureus (preformed enterotoxin)	1–6 hr	Sudden onset of severe nausea and vomiting; possibly with diarrhea and fever	24–48 hr	Improperly refrigerated meats, potato and egg salads, cream pastries	Stool, food for to cultu indica
Vibrio cholerae (toxin)	24–72 hr	Profuse watery diarrhea, vomiting; severe dehydration and death possible within hours	3–7 days	Contaminated water or food during international travel	Stool (requ testin
Vibrio parahaemolyticus	2–48 hr	Cramps, nausea, vomiting, watery diarrhea	2–5 days	Undercooked or raw seafood	Stool (requ testin
Vibrio vulnificus	1–7 days	Vomiting, abdominal pain, diarrhea, bacteremia, wound infections; more common in immunocompromised persons and in those with chronic liver disease	2–8 days	Undercooked or raw shellfish, especially oysters; wounds exposed to seawater	Stool, blood (requ testin
Yersinia enterocolitica and *Yersinia pseudotuberculosis*	24–48 hr	Appendicitis-like symptoms (fever, abdominal pain, diarrhea, vomiting), typically in older children and young adults. *Y. pseudotuberculosis* may cause scarlatiniform rash	1–3 wk	Undercooked pork, unpasteurized milk, tofu, water; infant infections have been associated with caregivers who handled	Stool, blood (requ testin serolo possil and r labora

				chitterlings	
VIRAL					
Hepatitis A	28 days (15–50 days possible)	Diarrhea, jaundice, flu-like symptoms	Variable; 2 wk–3 mo	Shellfish, raw produce, frozen berries, drinking water, foods contaminated by infected food worker	Increa biliru testin
Norovirus	12–48 hr	Nausea, vomiting, watery, large-volume diarrhea; fever rare	1–3 days	Shellfish, salads, sandwiches, ready-to-eat foods handled by infected food worker, person-to-person spread	Rever transc stool; analy genot
Rotavirus	1–3 days	Low-grade fever, vomiting, watery diarrhea; temporary lactose intolerance possible	4–8 days	Foods contaminated by ill food handlers	Stool
Other viral agents (astroviruses, caliciviruses, adenoviruses, parvoviruses)	12–72 hr	Headache, fever possible, nausea, vomiting, diarrhea, malaise	2–9 days	Foods contaminated by ill food handlers; shellfish	Antig PCR, testin
PARASITIC					
Angiostrongylus cantonensis	1 wk to >1 mo	Severe headache, neck stiffness, nausea, vomiting, paresthesias, seizures, other neurologic symptoms	Weeks to months	Raw or undercooked snails or slugs, infected crabs or freshwater shrimp, contaminated raw produce	CSF p prote and e serolo
Cryptosporidium	7 days (2–28 days possible)	Low-grade fever, cramps, nausea, diarrhea (usually watery)	May remit and relapse over weeks to months	Recreational or drinking water; food or water contaminated by ill food handler; raw milk; camping or backpacking; petting zoos; person-to-person spread	Antig
Cyclospora cayetanensis	7 days (1–14 days possible)	Cramps, nausea, vomiting, anorexia, weight loss, diarrhea (usually watery), fatigue	May remit and relapse over weeks to months	Imported fresh produce (berries, lettuce); international travel	Requ testin stool
Entamoeba	2 days–4 wk	Lower abdominal	May last	Food or water	Serial

histolytica		pain, bloody diarrhea	weeks to months	contaminated by ill person; international travel	exam cysts serol
Giardia	1–4 wk	Cramps, diarrhea, flatulence	Days to weeks	Food or water contaminated by ill person; recreational fresh water; camping/back-packing; international travel; person-to-person spread	Serial exam
Toxoplasma gondii (enteric exposure)	6–10 days	Generally asymptomatic; 20% may develop cervical lymphadenopathy or flu-like symptoms; Immunocompromised patients can have CNS disease, myocarditis, or pneumonitis	Months	Soil contaminated with cat feces, raw or partially cooked meat	Isolat obser paras or oth PCR
Toxoplasma gondii (prenatal exposure)		Few symptoms at birth; later, mental retardation, cerebral palsy, impaired vision, seizures	Months to years	Vertically transmitted, when mother is acutely infected during pregnancy	Isolat umbi placen blood blood fluid, serol
Trichinella spiralis	1 day–8 wk	Acute: fever, nausea, vomiting, abdominal pain, diarrhea, muscle soreness, weakness; later, occasionally cardiac and neurologic complications	Months	Raw or undercooked meat (usually pork or wild game)	Serol larva biops
NONINFECTIOUS					
Aflatoxin	Variable and dose dependent	Vomiting, jaundice, hemorrhagic liver necrosis, liver cancer, death	Variable and dose dependent; usually days to weeks	Fungal contamination of improperly dried and stored grains, nuts, spices, particularly in Africa and Asia	Ident aflato or afl deriv or bl
Algal toxins	Variable and dose dependent	Skin irritation, stomach cramps, vomiting, nausea, diarrhea, fever, sore throat, headache, muscle and joint pain, blisters of the mouth, liver damage	Variable and dose dependent	Exposure by physical contact, inhalation, or ingestion to water, or dietary supplements	Labor detec cyano other toxin- algae cyano toxins

				contaminated by harmful algae or toxins (e.g., cyanobacteria, red tide)	speci body, drink suppl dieta
Antimony	Variable and dose dependent; usually minutes to hours	Vomiting, metallic taste	Variable and dose dependent	Metal food containers; intentional or unintentional contamination of foods	Ident metal food,
Arsenic	Variable and dose dependent; usually minutes to hours	Vomiting, cramps, diarrhea, encephalopathy and peripheral neuropathy with high-dose exposure; lower-dose, longterm exposure may not produce GI symptoms	Variable and dose dependent; usually several days	Contaminated food or water	Urine
Cadmium	Variable and dose dependent; usually minutes to hours	Abdominal pain, salivation, nausea, vomiting, myalgia	Variable and dose dependent	Seafood, oysters, clams, lobster, grains, peanuts; intentional or unintentional contamination of foods	Blood levels of me
Ciguatera toxin	2–6 hr	GI: abdominal pain, nausea, vomiting, diarrhea	Variable and dose dependent; usually days to weeks	Reef fish (e.g., grouper, red snapper, amberjack, barracuda)	Radi in fis
	3 hr	Neurologic: paresthesias, reversal of hot or cold, pain, weakness	Variable and dose dependent		
	2–5 days	Cardiovascular: bradycardia, hypotension, T-wave abnormalities	Variable and dose dependent		
Copper	Variable and dose dependent; usually minutes to hours	Nausea, vomiting with blue or green vomitus	Variable and dose dependent	Copper food or beverage container; intentional or unintentional contamination of foods	Ident metal food
Lead	Chronic or acute	Irritability, anorexia, abdominal pain, cerebral edema, encephalopathy, seizures, death	Weeks to months	Drinking water; foods from lead-containing cans or grown in lead-contaminated soil; lead-	Veno levels

				containing kitchen ware (nonfood or nonbeverage sources, e.g., batteries, jewelry, and paint more common)	
Mushroom toxins, short-acting (museinol, muscarine, psilocybin, coprius artemetaris, ibotenic acid)	<2 hr	Dependent on mushroom species: confusion, diaphoresis, visual disturbance, salivation, vomiting, diarrhea, disulfiram-like reaction	Hours to few days	Wild mushrooms (cooking may not destroy toxins)	Mush identi toxin speci
Mushroom toxins, long-acting (amanitin)	6–24 hr (diarrhea); 2–4 days (liver failure)	Cramps, diarrhea, hepatic and renal failure, coagulopathy, seizures, death	2–8 days	Wild mushrooms	Mush identi toxin speci
Nitrite	1–2 hr	Headache, dizziness, loss of consciousness, nausea, vomiting, cyanosis (blue baby syndrome)	Hours to days	Well water; cured meats; spinach, beets, and other vegetables exposed to excessive nitrification	Ident eleva levels or uri meth
Pesticides (organophosphates or carbamates)	Variable and dose dependent; usually minutes to a few hours	Headache, nervousness, twitching, convulsions, miosis, cramps, nausea, vomiting, diarrhea	Weakness or neuropathy may last weeks	Pesticide-contaminated foods	Analy blood
Puffer fish (tetrodotoxin)	<30 min	Paresthesias, ascending paralysis, respiratory failure, abdominal pain, vomiting, diarrhea, death	Death in 4–6 hr	Puffer fish	Detec tetroc
Scrombroid (histamine)	1 min–3 hr	Dizziness, paresthesias (burning sensation of mouth, throat and skin), flushing, urticaria	3–6 hr	Fish: bluefin, tuna, skipjack, mackerel, marlin, escolar, mahi mahi	Detec hista
Shellfish toxins (diarrheic, neurotoxic, amnesic, paralytic)	30 min–2 hr (diarrheic)	Fever, headache, nausea, vomiting, abdominal pain, diarrhea	Hours to 2–3 days	Shellfish from Gulf of Mexico and Florida coast: mussels, oysters, scallops	Detec toxin
	Minutes to a few hours (neurotoxic)	Dizziness; reversal of sensations of hot and cold; tingling or numbness of lips,	Variable and dose dependent		

		tongue and throat; vomiting; diarrhea; myalgias			
	24–48 hr (amnesic)	Confusion, memory loss, disorientation, seizures, coma, abdominal pain, vomiting, diarrhea	Variable and dose dependent		
	30 min–3 hr (paralytic)	Diarrhea, nausea, vomiting, paresthesias of mouth and lips, weakness, dysphagia, dysphonia, respiratory paralysis	Variable and dose dependent; usually days		
Sodium fluoride	Minutes to 2 hr	Salty or soapy taste, numbness in mouth, vomiting, diarrhea, dilated pupils, spasms, pallor, shock; severe hypocalcemia, hyperkalemia	Variable and dose dependent	Dry foods (e.g., powdered milk, flour, baking powder, cake mixes) contaminated with sodium fluoride–containing pesticides	Detec vomit wash
Thallium	Variable and dose dependent; usually minutes to hours	Acute: nausea, vomiting, diarrhea; delayed: painful paresthesias, motor polyneuropathy, hair loss	Variable and dose dependent; usually days	Contaminated food	Detec blood
Tin	Variable and dose dependent; usually minutes to hours	Nausea, vomiting, diarrhea	Variable and dose dependent	Metallic container; intentional or unintentional contamination of foods	Serun levels toxin
Vomitoxin	Minutes to a few hours	Nausea, headache, abdominal pain, vomiting	Variable and dose dependent	Grains (e.g., wheat, corn, barley)	Detec food
Zinc	Variable and dose dependent; usually minutes to hours	Stomach cramps, nausea, vomiting, diarrhea, myalgias	Variable and dose dependent; usually hours to days	Metallic container; intentional or unintentional contamination of foods	Detec food, saliva

ALT, alanine aminotransferase; CDC, Centers for Disease Control and Prevention; CFU, colony-forming unit; CNS, central nervous system; CSF, cerebrospinal fluid; GI, gastrointestinal; IV, intravenous; PCR, polymerase chain reaction; TMP-SMX, trimethoprim-sulfamethoxazole.

Adapted from Centers for Disease Control and Prevention. Diagnosis and management of foodborne illnesses: a primer for physicians and other health care professionals. MMWR Morb Mortal Wkly Rep 2004;53(RR-04):1–33.

Toxin-mediated enteric illnesses caused by *C. perfringens*, *Bacillus cereus*, and *S. aureus* are estimated to cause 1.3 million illnesses annually in the US.[45] Illness outbreaks are most commonly linked to errors in food handling, such as holding foods at room or outdoor temperatures for several hours, improper reheating practices, and slow cooling of foods.[45] *C. perfringens* spores are ubiquitous in the environment; illness occurs after ingestion of contaminated food with resulting sporulation and toxin production in the gastrointestinal tract.[46] Meat and poultry are most commonly implicated in outbreaks.[45,47] *B. cereus* has been isolated from a wide variety of foods, including rice, spices, dried foods, vegetables, and dairy products.[48] Outbreaks of the short-incubation "emetic syndrome" of *B. cereus* food poisoning most commonly are associated with rice, particularly fried rice.[45] Outbreaks of longer-incubation "diarrheal syndrome" have been linked to a variety of foods, including vegetables, milk products, sauces, and pudding, in addition to meat products.[45,48] Staphylococcal food poisoning has been linked many different foods, including cooked meats and poultry, custard or cream-filled baked goods, dairy products, sandwiches, and salads.[45,49]

Foodborne botulism is caused by ingestion of foods contaminated with preformed botulinum toxin. In the US, foodborne botulism is typically associated with consumption of home-canned, low-acid foods, such as vegetables and fish.[50] However, commercially produced products such as carrot juice and canned chili have been linked to past outbreaks.[51,52] Infant botulism occurs after swallowed spores of *Clostridium botulinum* (and rarely, other neurotoxigenic *Clostridium* spp.) germinate, temporarily colonize the large intestine, and produce botulinum toxin.[53] Honey has been implicated as the source of *C. botulinum* spores in some cases of infant botulism.[54]

Histamine fish poisoning is commonly associated with scombroid fish (e.g., tuna, mackerel, skipjack), although other fish have been implicated in illness.[55] Ciguatera fish poisoning has been associated with more than 400 species of fish, including barracuda, snapper, amberjack, and grouper.[56] Shellfish, especially bivalve mollusks, are important vehicles of foodborne illness, particularly because they are often consumed raw. Shellfish can be colonized naturally with pathogenic *Vibrio* organisms, including *Vibrio* *vulnificus*, *Vibrio cholerae* non-O1, *Vibrio parahaemolyticus*, and *Vibrio mimicus*. As filter feeders, shellfish concentrate pathogens from contaminated water, including hepatitis A virus, norovirus, toxigenic *V. cholerae* O1, *Shigella*, and *Plesiomonas*.[57]

Foodborne outbreaks of heavy-metal poisoning are most often associated with acidic beverages such as lemonade, fruit punch, and carbonated drinks that have been stored in corroded metallic containers.[58] Mushroom poisoning occurs most often in the spring, late summer, and fall and is associated with species-specific syndromes (see Table 59.1).[59,60]

Waterborne Disease

Enteric waterborne disease resembles disease resulting from contamination of food and can be caused by many of the same pathogens. Large waterborne disease outbreaks resulting in enteric illness have been caused by *Cryptosporidium*, *Campylobacter*, *E. coli*, *Salmonella*, *Shigella*, chemical agents, hepatitis A virus, norovirus, *Giardia*, and other agents.[61–73] *Cryptosporidium*, a chlorine-tolerant protozoa, has been associated with 16 drinking-water outbreaks from between 1971 and 2013; a single outbreak in Milwaukee accounted for an estimated 403,000 cases.[61]

An estimated 16.4 million cases of acute gastroenteritis are associated with public drinking water systems annually.[74] However, drinking water–associated outbreaks in the US have been decreasing, particularly outbreaks associated with public water systems.[75] This change corresponds with the implementation of federal regulations designed to reduce illnesses associated with public water systems. Privately owned systems tend to serve fewer people and do not fall under the drinking water regulations established by the US Environmental Protection Agency (EPA) to protect water quality in public drinking water systems. Increased illnesses among children have been associated with the use of water from private wells.[76] Water system contamination resulting in drinking water–associated outbreaks can occur at a variety of points, including the water source, treatment processing, storage, distribution system, premise plumbing, and point of use. In studies of public systems using ground water, human enteric viruses, such as enteroviruses and norovirus, have been isolated from aquifers that may have been contaminated from surface water intrusion or sewage discharges.[77,78] The broader public health impact of such contaminated ground water could be substantial because approximately 45% of the US population is supplied by ground water, either through public or individual water systems.[79]

In contrast, the number of enteric disease outbreaks associated with recreational water has dramatically increased.[73] Recreational water illnesses are caused by pathogens transmitted by ingesting, inhaling aerosols or by having contact with contaminated water in pools, hot tubs, interactive fountains, lakes, rivers, oceans, and so forth. Recreational water illnesses also can be caused by chemicals in the water or by chemicals that volatilize from the water and cause indoor air quality problems. *Cryptosporidium* has become the leading cause of enteric illness outbreaks associated with treated recreational water (e.g., pools and interactive fountains). *Cryptosporidium* accounted for >75% of the outbreaks associated with treated recreational water reported to CDC during 2001 to 2010.[73]

Water used for recreational purposes may be treated or untreated. *Cryptosporidium* is most commonly implicated in outbreaks associated with treated recreational water. Because *Cryptosporidium* is extremely tolerant to chlorine levels used in treated water, these outbreaks can occur even in well-maintained facilities and have the potential to expand community wide, starting in recreational water transmission and moving by person-to-person transmission into childcare programs and other settings.[80–82] Outbreaks of gastrointestinal illness associated with untreated water primarily are caused by bacteria and viruses (e.g., *E. coli*, norovirus, *Shigella*) and usually are linked to swimming in lakes or ponds.[73] This finding suggests that swimmers themselves can be important sources of water contamination.

Zoonotic Disease

Zoonotic transmission of enteric pathogens can occur through direct or indirect exposure to pets, livestock, and other animals. A 2012 study estimated that 14% of all illnesses caused by *Campylobacter* spp., *Cryptosporidium*, *E. coli* O157:H7 and other STEC, *L. monoctyogenes*, nontyphoidal *Salmonella*, and *Yersinia* *enterocolitica* are attributable to animal contact.[83] This estimate translates to a total of almost 450,000 illnesses each year for these pathogens combined. Children <5 years of age are at higher risk for serious infections, as are pregnant women, people >65 years of age, and people with immunodeficiencies.[84]

Animal exposure can occur in many venues, including homes, farms, zoos, fairs, petting zoos, camps, childcare centers, and schools. The primary mode of transmission is the fecal-oral route. Because animal fur, hair, skin, and saliva can become contaminated with fecal organisms, transmission can occur when persons pet, touch, or are licked by animals.[85] Enteric pathogens also can contaminate the environment (e.g., water sources, soil, bedding) and persist in animal housing areas for long periods. The following have been cited as reasons for zoonotic infection: direct contact with animals, particularly young animals; indirect exposure through contamination of food, water, or the environment; and inadequate hand hygiene.[85,86]

Contact with animals in public settings provides opportunities for pathogen transmission to visitors. From 1996 to 2012, approximately 200 human infectious disease outbreaks linked to interacting with animals in public settings were reported to the CDC.[85] Multiple *E. coli* O157 outbreaks have been linked to petting zoos.[85,87–89] Turtles and other reptiles, amphibians, rodents, and live poultry are well-known sources for zoonotic transmission of human *Salmonella* infections. Multiple large, multistate salmonellosis outbreaks in recent years were linked to small turtles, chicks, ducklings, and other live poultry purchased from mail-order hatcheries for backyard poultry flocks.[90–95] Outbreaks also have been linked to contaminated dry dog and cat foods, pet treats, frozen rodents used to feed pet reptiles, and products used for educational activities in schools.[96–102] Cattle are the major source of zoonotic transmission of human cryptosporidiosis, although other mammals can be infected.[103–105] Zoonotic transmission of *Giardia* to humans and the relative importance of animal contamination of food and water are being reexamined because of advances in molecular epidemiology. *Giardia* infects nearly all classes of vertebrates, including domestic animals and wildlife; however, molecular characterization has identified relatively species-specific genetic *Giardia* assemblages.[106]

Pathogenesis and Clinical Syndromes

Enteric diseases are often classified according to the mechanism of pathogenesis: ingestion of various classes of chemicals or preformed toxins, in vivo production of bacterial toxins, direct pathogen attachment and local invasion, or disseminated infection. Considering the clinical syndrome is more useful for the diagnosis of enteric illness. The cause of an enteric illness is suggested by clinical symptoms, the incubation period, and epidemiologic clues. Laboratory testing is required to confirm the identity of specific pathogens. An outbreak should be suspected when ≥2 people who have shared a common exposure (e.g., food, water, or animal) develop the same acute illness, most often characterized by nausea, vomiting, diarrhea, systemic, or neurologic symptoms. For additional information, refer to Table 59.1 and pathogen-specific chapters.

Enteric Disease Surveillance and Outbreak Detection

Medical care providers play essential roles in public health surveillance and the timely detection of enteric disease outbreaks because they are frequently the first persons to be contacted by persons with foodborne, waterborne, or zoonotic illness. Prompt diagnosis and reporting of enteric infections to state and local public health jurisdictions as required by law can aid recognition and mitigation of illness outbreaks. Currently, many outbreaks of enteric illnesses go undetected because they are misinterpreted as illnesses caused by person-to-person spread. Stool examinations and cultures may not be performed because these tests are not considered cost-effective for an individual patient or may not lead to specific therapy, despite providing a public health benefit. Culture-independent diagnostic tests are becoming more widely available for the clinical diagnosis of bacterial enteric infections, and results are not always confirmed by isolating bacteria from culture.[107] However, detailed characterization of bacterial isolates obtained from patients' cultures is necessary to distinguish among strains of pathogens and detect foodborne outbreaks. In addition, timely reporting, public health investigation, and use of rapid subtyping methods can help identify outbreaks, detect emerging pathogens, identify new vehicles and modes of transmission, and prevent additional illness. If an enteric disease outbreak is suspected, appropriate clinical specimens, including cultures, should be collected for laboratory testing if possible, and clinicians should notify local public health officials.

As the food production system has become more centralized, contaminated food can be distributed widely throughout the US and cause illnesses across multiple jurisdictions.[7] This situation can result in a few illnesses within each local or state public health jurisdiction, thereby making it difficult for local public health officials to recognize that illnesses in their jurisdiction are part of a more widely disseminated outbreak. PulseNet USA is a national network of public health and food regulatory laboratories started in 1996 with the aim of enhancing bacterial enteric disease outbreak detection and investigation.[108] Clinical laboratories send bacterial isolates obtained from culture of persons ill with enteric pathogens to PulseNet laboratories for further characterization. PulseNet performs molecular subtyping of these isolates to distinguish among strains of bacterial enteric pathogens, including *Campylobacter jejuni*, STEC, *Shigella*, *L. monocytogenes*, and *Salmonella*. The resulting molecular fingerprints are shared electronically and are uploaded into national databases at the CDC. These databases are routinely monitored to identify clusters of isolates that are indistinguishable or very highly similar by molecular subtyping, which may indicate an outbreak. PulseNet refers identified clusters to the CDC and state epidemiologists for investigation. By quickly compiling and comparing molecular subtyping data from enteric bacteria isolated from ill persons nationwide, PulseNet has aided in the detection of widely dispersed foodborne disease outbreaks. The main subtyping method used by PulseNet is pulsed-field gel electrophoresis, but other advanced methods such as next-generation whole genome sequencing are beginning to be used for outbreak detection and response.

A limitation of this surveillance system is that the current methods used by PulseNet require a bacterial isolate obtained from culture for public health laboratories to be able to characterize the bacterial strain further by serotyping and molecular subtyping. Although culture-independent diagnostic tests have several advantages, their increased use could have a substantial impact on public health surveillance and the ability of PulseNet to detect outbreaks.

Because water, with the exception of bottled water, is normally not a widely distributed product, most detected waterborne disease outbreaks are confined geographically to the service area, and multistate outbreaks are rare.[62,75] Illnesses associated with recreational water that does not attract patrons from a large geographic area (e.g., a local community pool) tend to be confined to a single community; conversely, illnesses associated with recreational water that attracts patrons from more geographically dispersed area (e.g., waterparks and oceans) can involve residents of a wide area. Dispersion of affected people may decrease the likelihood that the outbreak will be detected.[73]

Recognition of an outbreak can lead to removal of contaminated food items from the marketplace or correction of contaminated drinking water systems or recreational water venues and enhance industry and regulatory control measures to prevent contamination in the future. A list of nationally notifiable infectious conditions in the US can be found at: http://wwwn.cdc.gov/nndss/conditions/. State health departments can provide additional information about reporting infectious diseases within their jurisdictions.

Diagnosis

Epidemiologic Clues

The incubation period, clinical syndrome, and exposure history (including foods consumed and how they were prepared, as well as water and animal exposures) provide clues to the pathogenic etiologic agents of enteric disease, but a definitive diagnosis requires laboratory confirmation. The incubation period often is underestimated or unknown. Patients and clinicians may focus incorrectly on the most recent meals and fail to consider water or animals as potential sources of disease transmission. Most bacterial, viral, and parasitic enteric infections are transmitted by the fecal-oral route through ingestion of contaminated food or water.

Persons, especially young children, can become infected through person-to-person transmission or transmission by fomites without eating the implicated food, ingesting the implicated water, or directly handling animals. Toxin-mediated illnesses from organisms such as *S. aureus*, *B. cereus*, and *C. perfringens* are often linked to foods held at improper temperatures after cooking. A history of eating home-canned foods or feeding an infant honey should raise the index of suspicion of foodborne botulism or infant botulism, respectively, in a clinically compatible illness. Recent exposure to animals or animal environments can indicate a zoonotic route of transmission. A careful exposure history should include animal contact (both in and outside the household), drinking water source, recreational water use, and food and beverages consumed during at least the previous 7 days.

Laboratory Diagnosis

Appropriate collection and processing of clinical specimens and environmental samples are essential for confirming the cause of foodborne, waterborne, and zoonotic diseases. Because of the large number of different specimens, techniques, and culture media needed to evaluate all potential causes, it is most efficient to plan the laboratory investigation based on clinical or epidemiologic suspicion. Where culture-independent diagnostic tests are used, stool specimens should be routinely collected and cultured if evidence indicates bacterial infection.[107] Stool specimens and sera can be obtained early in the investigation and stored for later studies. Table 59.1 summarizes the principal laboratory tests recommended for diagnosis.[109]

All *Salmonella* spp., *Shigella* spp., STEC, *Vibrio* spp., and *L. monocytogenes* isolates should be forwarded to the state public health laboratory for full characterization for surveillance and outbreak detection purposes.[107] Laboratory diagnosis of norovirus infection relies primarily on polymerase chain reaction–based assays in public health and research laboratories. Ideally, whole stool samples to be tested for norovirus should be collected within 10 days after illness onset and kept refrigerated but not frozen.[110] Molecular subtyping through sequence analysis is facilitated in the US through CaliciNet, a national network of public health and regulatory laboratories that contribute to a database of norovirus genetic sequences obtained during investigations of disease clusters.[111] For both *Cryptosporidium* and *Giardia,* molecular testing can be reliably performed on non–formalin-preserved stool specimens that are refrigerated or frozen. Molecular testing is used increasingly in reference diagnostic laboratories to determine species and genotypes of these parasites and thus enhance outbreak investigations.[112] *Cyclospora* testing must be specifically requested of the laboratory and is best diagnosed with examination of at least 3 stool specimens.

Water testing, both in the context of drinking water and of recreational water outbreaks, also is useful during outbreak investigations. Ultrafiltration methods have been developed by which large volumes of water can be filtered in a relatively short time, and the filtrate and filter can then be shipped to reference diagnostic laboratories for analysis.[113] Other water-related media, such as filter cartridges and filter backwash from swimming pools, also can be tested.

Additional information on the collection of specimens for diagnosis and the investigation of enteric disease outbreaks is available at https://www.cdc.gov/foodsafety/outbreaks/investigating-outbreaks/specimen-collection.html and https://www.cdc.gov/healthywater/emergency/preparedness-resources/outbreak-response.html.

Management

Supportive care is central to the management of acute foodborne, waterborne, or zoonotic infectious diarrheal illness. Careful replacement of fluid and electrolyte losses is crucial, particularly in infants. For patients with mild to moderate dehydration, even with some vomiting, oral replacement with appropriate electrolyte solutions is the preferred treatment.[114] Antiemetic agents may be useful for patients with severe or prolonged vomiting, if toxins are not suspected as the cause. Antiperistaltic agents are not recommended for young children or patients with signs of enteroinvasive disease, such as fever or bloody diarrhea.[114] Bismuth subsalicylate provides symptomatic relief and has in vitro activity against norovirus, *E. coli* O157:H7, *Salmonella*, and *Shigella*[115,116]; however, theoretical concerns remain about its use in children, including the potential for excess salicylate absorption and the possibility of precipitating Reye syndrome.[117–119] Certain strains of probiotics have been found useful in hastening the recovery of children from acute diarrheal episodes.[120,121]

For severe illnesses caused by certain confirmed infections, notably listeriosis, shigellosis, enterotoxigenic and enteroinvasive *E. coli* infections, typhoid fever, cholera, cyclosporiasis, giardiasis, and cryptosporidiosis, antimicrobial therapy is indicated. Antimicrobial agents usually are not indicated for salmonellosis, except in very young children, persons with immunodeficiency, or patients with invasive salmonellosis. Outbreaks of salmonellosis and shigellosis have been caused by bacterial strains resistant to multiple antimicrobial agents; antimicrobial therapy for these patients should thus be used only when needed and tailored to the specific susceptibility profile of the pathogen. The role of antimicrobial therapy is less clear for treatment of diarrheal illness caused by *Y. enterocolitica, Campylobacter, V. parahaemolyticus, Aeromonas,* and *Plesiomonas,* but therapy may have a role in severe or prolonged gastrointestinal tract illness caused by these pathogens. The association between antimicrobial agents and increased risk of hemolytic uremic syndrome is not clear.[122–128] Therefore, antimicrobial agents are not recommended for children with *E. coli* O157:H7 and other STEC infections. No specific antiviral agents are available for the treatment of norovirus infections. Additional information about antimicrobial therapy is available in the pathogen-specific chapters.

Medical care providers who suspect botulism should immediately contact their state health departments. Most pediatric botulism cases are infant botulism. The California Infant Botulism Treatment and Prevention Program provides consultation and human botulism immune globulin intravenous (BIG-IV or BabyBIG) for suspected cases of infant botulism (telephone: 510-231-7600). For cases of suspected botulism among older children, the state health department contacts the CDC to arrange for clinical consultation by telephone and, if indicated, release of botulinum antitoxin. The CDC's 24-hour telephone number for state health departments to report possible botulism cases, obtain emergency consultation, and request botulinum antitoxin is 770-488-7100.

Patients with ciguatera or paralytic shellfish poisoning must be observed closely for evidence of respiratory compromise. Preliminary data suggest that intravenously administered mannitol may ameliorate the acute neurologic symptoms of severe ciguatera, and tocainide may improve the dysesthesias, but definitive data are lacking.[129–131] Symptoms of histamine fish poisoning may respond to antihistamines and histamine H_2-receptor antagonists. In patients with bronchospasm, epinephrine may be required.

For most patients with mushroom poisoning and symptom onset <6 hours after exposure, supportive care is adequate.[59,132] Uneaten mushrooms should be saved, and mycologists or experts in poison control (American Association of Poison Control Centers' Poison Help Line: 800-222-1222) should be consulted for species identification and possible use of specific antidotes. Onset of symptoms ≥6 hours after ingestion suggests *Amanita* poisoning, which can be lethal; a poison control center should be consulted for management advice. Liver transplantation may be required in patients with severe *Amanita* poisoning. Pyridoxine hydrochloride may be useful in cases of *Gyromitra* ingestion manifesting with seizures refractory to benzodiazepine therapy.[133]

Therapy for acute heavy-metal poisoning is supportive, although chelation can be helpful in some circumstances.[134] Antiemetic agents are contraindicated. Very severe cases of toxicity may require use of specific antidotes, and a medical toxicologist or poison control center should be consulted. The American Association of Poison Control Centers' toll-free Poison Help Line (800-222-1222) is available 24 hours/day to assist with cases of suspected intoxication.

Complications

The most common complications of foodborne, waterborne, and zoonotic diarrheal illnesses are dehydration, electrolyte abnormalities, and hypoglycemia. Children and older people are more susceptible to these complications. Severe vomiting can result in subconjunctival hemorrhage, syncope, or Mallory-Weiss esophageal tears. Enteric infection with *Salmonella* spp., *Y. enterocolitica, Vibrio* species other than *V. cholerae, Campylobacter* spp., *Cronobacter* spp., and *Shigella* spp. other than *S. sonnei* can be complicated by bloodstream infection or focal extraintestinal infections, such as osteomyelitis, endocarditis, endarteritis, or meningitis. Infants also are at increased risk for bloodstream infection and disseminated infections caused by common bacterial pathogens, particularly *Salmonella* spp. People with defects of cellular immunity (e.g., human immunodeficiency virus infection, leukemia, lymphoma), reticuloendothelial function (e.g., sickle-cell disease, malaria), and iron overload syndromes also have increased risk of bloodstream infection with *Salmonella* and *Campylobacter*.[135–137] People with immunosuppressing conditions are also at risk for disseminated disease, malabsorption, or death caused by *Cryptosporidium*.[138] *Listeria* infection during pregnancy can result in miscarriage, stillbirth, or neonatal sepsis.[139] Postinfectious syndromes have been recognized as important consequences of enteric infections, including the following: hemolytic uremic syndrome after infections with *E. coli* O157:H7[140]; reactive arthritis after salmonellosis, shigellosis, campylobacteriosis, and giardiasis[141–143]; and Guillain-Barré syndrome after campylobacteriosis.[144] Norovirus infections have been associated with necrotizing enterocolitis in neonates, chronic diarrhea in immunosuppressed patients, and postinfectious irritable bowel syndrome.[145–147]

Prevention

Food and Water

Clinicians should counsel patients and their families about ways to minimize their risk of foodborne illness. General food safety measures include the following: thorough handwashing before preparing and eating food and after handling raw meat, poultry, or eggs; cleaning surfaces and equipment used for preparation of raw foods to avoid cross-contamination; separating raw meat, poultry, and eggs from cooked or ready-to-eat foods; cooking food to the recommended minimum safe internal temperature; storing foods at temperatures too low (<4°C) or too high (>60°C) to support bacterial growth; and avoiding preparing or serving food for others during and immediately after a gastrointestinal illness.[148] Exclusion of ill workers from food preparation settings, frequent handwashing with soap and water, and eliminating bare-hand contact with ready-to-eat foods are can help minimize the risk of contamination with human pathogens, such as norovirus and *Shigella*. Raw foods of animal origin require particular attention, including poultry, beef, pork, unpasteurized (raw) milk, uncooked eggs, and uncooked shellfish. Cross-contamination of cooked foods from raw foods through contaminated surfaces and food preparation equipment is a common but avoidable error. Widespread use of hepatitis A vaccine will reduce foodborne transmission of hepatitis A virus. Routine typhoid vaccination is not recommended in the US, but typhoid vaccination is recommended for travelers to areas where typhoid fever is a recognized risk.[149] Updated educational information and materials about preventing foodborne illness are available at several websites (www.cdc.gov/foodsafety/, www.foodsafety.gov, www.nal.usda.gov/food-safety, and https://www.nal.usda.gov/fsrio/food-safety-topics).

People at greatest risk of severe disease (i.e., young children and persons with chronic liver disease, decreased gastric acidity, and acquired or congenital immunodeficiency), as well as people who seek to minimize their risk of illness, should avoid foods such as raw or undercooked shellfish, raw sprouts, unpasteurized milk products, unpasteurized juices, and raw or incompletely cooked eggs, poultry, or meat. To reduce the risk of listeriosis, persons at higher risk for infection (including pregnant women, adults >65 years old, and people with weakened immune systems) should avoid consuming the following: unpasteurized milk; hot dogs, luncheon meats, cold cuts, other delicatessen meats, or fermented or dry sausages unless they are heated to an internal temperature of 165°F or until steaming hot just before serving; soft cheese unless it is labeled as made with pasteurized milk; refrigerated smoked seafood; and, refrigerated pâtés or meat spreads.[150] Persons should also be aware that Mexican-style cheeses made from pasteurized milk (e.g., queso fresco) likely contaminated during cheese making have caused *Listeria* infections.[150] Honey should not be fed to infants younger than 1 year of age because of the risk of infant botulism.

The risk of waterborne disease can be minimized by appropriate drinking water treatment, routine inspections of private wells, and proper hygiene, particularly at childcare facilities and recreational water venues such as pools and beaches. The risk of enteric illnesses caused by recreational water exposures can be reduced by the following means: adequate training of pool operators and enforcement of pool codes through pool inspections; provision of appropriate hygiene infrastructure, such as conveniently placed, well-stocked, and well-maintained showers, toilets, diapering stations, and handwashing facilities at recreational water venues; and public education. Persons with diarrhea, including aquatics staff members, should not swim or participate in water play; all others should shower with soap immediately before entering the water and should wash hands thoroughly after using the toilet or changing diapers. The CDC also recommends checking diapers every 30 to 60 minutes while children are swimming to help prevent fecal contamination of the water. Diapered children should be changed at a diapering station (not at the poolside). Children should be taught not to swallow water while swimming or playing at splash parks. Limiting water play in childcare facilities may also reduce the risk of enteric disease.[151] Additional information is available at www.cdc.gov/healthywater/swimming/.

Much of foodborne and waterborne illness prevention lies in reducing contamination of food and water before it reaches the consumer. Major revision of meat and poultry inspection regulations and procedures and revised requirements for drinking water treatment began in the US in the 1990s. For food and water that still may be contaminated with dangerous pathogens, a systematic disinfection or pathogen reduction step, such as pasteurization of milk and chlorination of water, is required. Meats, seeds for sprouting, spices, shell eggs, and some produce items may also be irradiated before sale in commercial markets in the US. Such regulatory and industry efforts have been successful in decreasing the incidence of infection with several foodborne pathogens. For example, the incidence of *E. coli* O157 and *Salmonella enteritidis* serotype Typhimurium infections was significantly lower in 2014 than during 2006 to 2008.[152] Similarly, Environmental Protection Agency regulations that protect public water supplies, such as the Surface Water Treatment Rule, coincide with a decrease in the proportion of drinking water outbreaks associated with public water systems and surface water supplies.[75] However, foodborne and waterborne illnesses remain important public health concerns.

Clinicians have the important role of providing education and appropriate counseling to high-risk patients, including parents of infants and young children and persons with immunocompromising conditions, about the health hazards of food and waterborne pathogens, vehicles of transmission, and prevention measures.

Zoonotic Exposures

Clinicians should educate individual patients and families about the potential for animals to serve as a source of enteric illness in humans. Many animals carry enteric pathogens but appear healthy. Zoonotic enteric infections can be prevented through careful hand and environmental hygiene and by limiting interaction of some populations with animals and their environments. Children <5 years of age, older adults, and persons with immunocompromising conditions should avoid contact with turtles and other reptiles, amphibians, baby poultry, rodents, farm animals, and animal-derived pet treats and pet foods.[84,85,153] Children should not be allowed to kiss animals or to put their hands or other objects into their mouths while interacting with animals. Pets and other animals should be kept outside areas where food is prepared, stored, or served. Animal habitats and equipment used to care for animals should be cleaned outside the home to reduce the risk of cross-contamination. Careful handwashing with soap and water as soon as possible after contact with animals, their feces, their cages or pens, and their food can help prevent infection. Additional information is available at www.cdc.gov/healthypets/.

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I

Intra-Abdominal Infections

OUTLINE

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60

Acute Hepatitis

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Acute hepatic inflammation in children can have many infectious and noninfectious causes (Table 60.1). Acute liver injury of various causes results in a limited number of clinical manifestations and findings. This chapter covers the evaluation and diagnosis of acute liver injury in immunocompetent children. The pathogenesis of many infectious causes is covered more fully in pathogen-specific chapters.

TABLE 60.1

Age of Onset of Infectious and Noninfectious Causes of Acute Hepatitis

Etiology	Age of Presentation		
	Neonates and Infants	**Children**	**Adolescents**
INFECTIOUS			
Primarily Hepatotropic			
Hepatitis A	−	+	+
Hepatitis B	+	+	+
Hepatitis C	+	+	+
Hepatitis D	+	+	+
Hepatitis E	−	+	+
Generalized Infection			
Adenovirus	+	−	−
Arbovirus	+	−	−
Coxsackievirus	+	−	−
Cytomegalovirus	+	+	+
Enterovirus	+	−	−
Epstein-Barr virus	+	+	+
Herpes simplex virus	+	−	−

Human immunodeficiency virus	+	+	+
Rubella	+	−	−
Varicella	+	+	+
ANATOMIC			
Biliary atresia	+	−	−
Choledochal cyst	+	+	+
Congenital hepatic fibrosis	+	+	+
AUTOIMMUNE			
Autoimmune hepatitis	−	+	+
Sclerosing cholangitis	+	+	+
METABOLIC			
α_1-Antitrypsin Deficiency	+	+	+
Cystic Fibrosis	+	+	+
Disorders of Carbohydrate Metabolism			
Galactosemia	+	−	−
Glycogen storage diseases	+	+	−
Hereditary fructose intolerance	+	−	−
Disorders of Protein Metabolism			
Urea cycle deficiencies	+	−	−
Organic acidemias	+	−	−
Tyrosinemia	+	−	−
Disorders of Metal Metabolism			
Neonatal hemochromatosis	+	−	−
Indian childhood cirrhosis	−	+	−
Wilson disease	−	+	+
Lipid Storage Diseases			
Gaucher disease	+	+	+
Niemann-Pick disease	+	+	+
Wolman disease	+	−	−
Errors of Bile Acid Metabolism	+	−	−
TOXINS OR DRUGS			
Acetaminophen, α-methyldopa, alcohol, amiodarone, chlorpromazine, phenytoin (Dilantin), oral contraceptives, halothane, isoniazid, total parenteral nutrition, and *Amanita* toxin	+	+	+
TUMORS	+	+	+
IDIOPATHIC CONDITIONS			
Byler syndrome	+	−	−
Neonatal hepatitis	+	−	−
Reye syndrome	+	+	+

+, recognized or usual age of occurrence; −, unexpected or not an age of occurrence.

Approach to Evaluation and Diagnosis

Signs and symptoms associated with acute hepatic injury usually include jaundice, vomiting, poor feeding, lethargy, hepatomegaly, and right upper quadrant pain. Assessment of the multiple possible causes begins with the patient's age and a detailed history and physical examination, with special emphasis on potential exposures, evolution of symptoms, concomitant health problems, and family history. The physical examination must include a careful evaluation for extrahepatic manifestations of disease, as well as a thorough assessment of the abdomen.

Elevated serum hepatic enzyme levels, and often elevated bilirubin levels, are present in people with acute hepatitis, but the pattern of elevations rarely is diagnostic.[1–3] In most cases, an initial core set of tests, common to all age groups, is ordered simultaneously to provide a complete initial assessment of the disease process (Box 60.1). Hepatitis virus infection should be suspected in patients with predominant or severe hepatocellular dysfunction and in fulminant hepatitis. The evaluation for infectious causes of hepatitis in children relies on serologic tests to identify antibodies (usually immunoglobulin M) or antigens or the use of molecular diagnostic techniques, especially polymerase chain reaction, to diagnose infection.[1–6] Additional tests are considered individually, depending on the child's age and exposures (Table 60.2). For example, neonates are not evaluated for hepatitis A, D, E, or G except in unusual circumstances. Rubella testing rarely is required because maternal testing is included in routine prenatal care. The TORCH (*Toxoplasma*, other, rubella, cytomegalovirus (CMV), and herpes simplex virus [HSV]) serologic screen is inappropriate because certain agents (*Toxoplasma* and rubella virus) are unlikely to cause hepatitis as a cardinal feature and CMV and HSV infection are optimally diagnosed by other techniques.[3,6] Liver biopsy rarely is required to make the diagnosis of infectious hepatitis. The severity of the child's illness can influence the pace and extent of testing. For example, in a mildly affected child, results of tests for infectious diseases often are evaluated before metabolic disorders are pursued.

Box 60.1

Initial Diagnostic Evaluation for Suspected Hepatitis in All Age Groups

Blood

Tests of hepatic cell injury and function

Bilirubin, total and direct

Alanine aminotransferase

Aspartate aminotransferase

γ-Glutamyltranspeptidase

Albumin

Prothrombin time

Ammonia

Fasting glucose

Tests for infectious causes

Serologic tests for hepatotropic viruses (see Table 60.2)

Serologic tests for Epstein-Barr virus

Serologic, antigen, or molecular tests for cytomegalovirus

Serologic or molecular tests for human immunodeficiency virus

Metabolic screening lists

α_1-Antitrypsin level and protease inhibitor type

Urine

Shell vial culture for cytomegalovirus

Radiology

Liver and biliary ultrasound examination

TABLE 60.2

Additional Age-Specific Evaluation for Patients With Suspected Hepatitis

	Age Group		
	Neonates	**Children**	**Adolescents**
BLOOD TESTS			
Infectious	HBsAg Anti-HBc IgM Anti-HCV, HCV PCR Toxoplasmosis titer: mother and child Plasma HSV PCR, virus culture mucosal strips Plasma enterovirus PCR, virus culture mucosal samples	HBsAg	HBsAg
		Anti-HBc IgM	Anti-HBc IgM
		Anti-HAV IgM	Anti-HAV IgM
		Anti-HCV, HCV PCR	Anti-HCV, HCV PCR
		Anti-HCV	Anti-HCV
		Anti-HDV	Anti-HDV
		Anti-HEV (if travel history)	Anti-HEV (if travel history)
Metabolic	Cystic fibrosis screen or sweat test, serum amino acids	Same as for neonates	Same as for neonates
		Ceruloplasmin	Ceruloplasmin
		24-hr urine copper	24-hr urine copper
Autoimmune		ESR, quantification of serum immunoglobulins; antinuclear antibody; LKM and smooth-muscle antibodies	Same as for children
URINE TESTS			
Metabolic	Reducing substances; organic acid screen	Same as for infants	

anti-HBc IgM, hepatitis B core immunoglobulin M antibodies; ESR, erythrocyte sedimentation rate; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus; HSV, herpes simplex virus; LKM, liver-kidney-microsomal; PCR, polymerase chain reaction.

The diagnosis of most anatomic lesions is made by ultrasound examination (e.g., choledochal cyst) or liver biopsy (e.g., intrahepatic cholestasis, congenital hepatic fibrosis, and sclerosing cholangitis).[1–3] Endoscopic retrograde cholangiopancreatography and magnetic resonance cholangiopancreatography may be helpful in diagnosing biliary tract lesions, especially in older children.[1–3]

Infectious Causes

Neonatal Hepatitis

Hepatitis in neonates caused by specific agents usually is distinguished from the category of neonatal hepatitis, which has been used to designate hepatic inflammation of no known cause.

The 6 hepatotropic viruses (i.e., hepatitis A, B, C, D, E, and G viruses [HAV, HBV, HCV, HDV, HEV, and HGV, respectively]) play a limited role in symptomatic hepatitis in neonates. However, various other infectious agents have been implicated in hepatic inflammation in neonates.[3–6] HSV and enterovirus can cause liver necrosis, coagulopathy, and a fulminant sepsis–like syndrome.[9–11] Congenital viral infections cause milder hepatitis and often are associated with prematurity and growth retardation; rubella virus is associated with congenital malformations.[3,6] Other causes of disseminated infection and associated hepatitis in neonates include congenital syphilis, disseminated candidiasis, and toxoplasmosis.[3,5] Infection caused by the agents of these disorders can involve skin, central nervous, cardiorespiratory, and musculoskeletal systems.[3,5]

Disseminated Infections

Disseminated systemic and extrahepatic infections must be considered when jaundice is present, especially in the newborn infant.[5,6] Gram-negative bacterial infections, disseminated HSV infections, and enterovirus infections are important causes in neonates that require immediate, appropriate therapy.[7,8] The pathogenesis of hepatic dysfunction in sepsis is not understood completely, but the cholestatic effects of endotoxins and endotoxin-induced mediators appear to be important.[7,8] Jaundice also can occur in the absence of severe illness, as in gram-negative bacillary urinary tract infection.[7] Disseminated infection caused by gram-positive organisms and viruses also can be associated with cholestasis.[8] The diagnosis usually is made because infected children appear severely ill. A clue to diagnosis is an elevation of serum levels of conjugated bilirubin greatly out of proportion to elevation of aminotransferases or alkaline phosphatase.[4] In the absence of hemolysis associated with mild liver disease, this pattern suggests septicemia.

Other viruses that can cause hepatic injury as part of a disseminated, multisystem illness include Epstein-Barr virus, cytomegalovirus, adenoviruses, rubella, and human immunodeficiency virus (HIV)[3,5,6] The resulting hepatic dysfunction ranges from mild to fulminant disease. Fulminant hepatitis is characterized by rapid progression to high hepatic enzyme levels, decreased production of coagulation proteins, elevated ammonia, hypoglycemia from loss of glycogen reserves, shock, coma, or death.

Hepatitis Viruses

Hepatitis a Virus.

HAV infection continues to be the most common cause of acute hepatitis reported in the United States.[12,13] Infection primarily is spread through direct human fecal-oral contamination or by contaminated food and water.[13,14] HAV is common in early childhood, especially in developing countries with poor conditions of sanitation and hygiene. Almost all children in these countries become seropositive before 5 years of age.[12,14] In the US, transmission often occurs in childcare facilities, but with inclusion of hepatitis A vaccine in the childhood immunization schedule in the US, a significant decrease in rates of disease has occurred.[6,13,14] Illness usually is mild in young children and often manifests with symptoms of an influenza-like illness.[6,12,14] Outbreaks in childcare facilities are recognized usually by illnesses with jaundice in staff members or parents of attendees (see Chapter 3).

Hepatitis B Virus.

HBV is the only hepatotropic virus that is not directly cytopathic; it causes disease through the host's immune response against virus-infected hepatocytes. The severity of infection is inversely related to the effectiveness of the immune system to diminish viral replication.[15] Two main patterns of transmission occur. In endemic areas such as China, Southeast Asia, and sub-Saharan Africa, transmission usually occurs by vertical transmission at birth or through horizontal transmission among children <5 years of age.[15,16] In the US, the most common routes of transmission are injection drug use, sexual contact, and nosocomial infection; no risk factor is found in approximately 30% of cases.[13,15–17] The incidence of HBV infections in neonates is declining in countries with neonatal immunization programs.[15–17] Most neonatal infections are not associated with clinically evident disease, but chronic infection develops in infants not treated immediately after birth with hepatitis B immune globulin and vaccine.[15–17] Children and adolescents are more likely to develop clinical illness if they are infected with HBV, usually acquired by close contact with an infected adult, sexual contact, or use of intravenous drugs.[15–17] Viral genotypes are important predictors of clinical outcome, drug responses, and mutations.[15] Implementation of a national vaccination strategy to eliminate HBV transmission has greatly reduced the disease burden in the US, but elimination will require an effective vaccination program for several generations, including vaccination of at-risk adults.[13,15–19] In the US, interferon α and oral agents including lamivudine (3 years and older), adefovir and tenofovir (12 years and older) and entecavir and telbivudine (16 years and older) have been approved by the Food and Drug Administration (FDA) for use in children with chronic HBV.[20,21]

Hepatitis C Virus.

HCV infection in young children is acquired primarily by perinatal transmission in the US, but unsafe injections and unsafe medical procedures are important causes in resource-poor countries.[22] In older people, most cases are caused by injection drug use or sexual contact with an infected partner.[22] Because of major improvements in serologic diagnosis, HCV infection now is rarely caused by blood transfusion or organ transplantation. In contrast to HAV and HBV, no effective HCV vaccine is available.[22] The efficiency of perinatal transmission appears to be low in the general population but greatly increases if the mother is coinfected with HIV or has a high titer of HCV RNA.[22,23] HCV infections usually are mild or asymptomatic in children, but in many infected children, disease progresses, and fibrosis, cirrhosis, and hepatocellular cancer develop.[22,23]

Until recently, the standard HCV treatment in adults was a combination regimen of pegylated interferon α with ribavirin.[23] This combination was shown to be effective in randomized trials in children and is approved by the FDA for use in children ≥3 years of age.[23] The emergence of interferon-free, all-oral regimens involving direct-acting antiviral agents (e.g., sofosbuvir, simeprevir, and ledipasvir) revolutionized the therapy of chronic HCV, with a greater than 90% sustained viral response rate and an excellent safety profile.[24] Multicenter clinical trials using combinations of these agents in children with chronic HCV are under way.[24]

Hepatitis D Virus (Delta Virus).

HDV infection, which can occur only in conjunction with HBV infection, has been described rarely in neonates; the importance of perinatal transmission appears to be minimal.[25] In older infants and children, the disease is uncommon and usually occurs in people with chronic HBV infection.[25]

Hepatitis E Virus.

HEV is common in endemic areas of developing countries and in travelers to those areas, especially the Middle East and Asia. However, autochthonous (locally acquired) HEV infection also is emerging in industrialized countries, where HEV is thought to be a zoonosis transmitted by pigs.[26] HEV has not been reported as a cause of neonatal hepatitis.[27] However, pregnant women with jaundice and acute viral hepatitis caused by HEV infection have a higher mortality rate and worse obstetric and fetal outcomes than do pregnant women with other types of viral hepatitis.[28] HEV disease is similar to HAV infection, except that HEV primarily affects older children and adults and has been associated with neurologic disorders.[26,29] An HEV vaccine has been shown to be safe and effective in phase III trials.[30]

Hepatitis G Virus.

HGV, the most recently identified hepatitis virus, appears to produce the mildest illness of the hepatotropic viruses.[31] Although most infected people have evidence of persistent viremia, histologic evidence of HGV infection is rare, and serum aminotransferase values usually are normal. Currently, no conclusive evidence indicates that HGV causes fulminant or chronic disease, and it appears that HGV may not be a pathogen.[31]

Anatomic Causes

Biliary Atresia.

Biliary atresia is the most common cause of neonatal cholestasis and usually is manifest by 1 month of life.[32] Biliary atresia is a process affecting both intrahepatic and extrahepatic ducts that leads to ongoing fibrosis and eventual obliteration of the biliary tract. Even in children who are treated surgically, this process eventually progresses to cirrhosis.[32] Although no clinical or laboratory findings are diagnostic of biliary atresia, most infants are healthy and well grown at birth and are asymptomatic for the first several weeks of life.[1–3,32] Bilirubin levels then rise, along with mild to moderate increases of alanine aminotransferase and aspartate aminotransferase, and a disproportional increase of γ-glutamyltranspeptidase.[32] By contrast, infants with neonatal infections are more likely to be born prematurely, small for gestational age, and ill-appearing at birth.[1–3] The finding of acholic stools, hepatosplenomegaly, situs inversus, splenic abnormalities, and congenital cardiac defects associated with cholestasis should suggest the possibility of biliary atresia.[33]

Paucity of Bile Ducts.

Paucity of bile ducts is a histologic diagnosis made when the ratio of ducts to portal tracts is less than 1.[34] Paucity of bile ducts can be grouped into syndromic or nonsyndromic varieties; both usually are manifest in infancy with jaundice and hepatomegaly. Children with the syndromic type (Alagille syndrome) have a variety of associated anomalies including peculiar facies (broad forehead, hypertelorism, small chin) and cardiac (most commonly peripheral pulmonic stenosis), ocular (posterior embryotoxon), and vertebral arch (butterfly vertebrae) abnormalities.[34] The nonsyndromic form of paucity of bile ducts does not include such anomalies.[34]

Choledochal Cysts.

Choledochal cysts often manifest in infancy but can become symptomatic in any age group.[35] The spectrum of disease ranges from solitary lesions involving the extrahepatic biliary tree to diffuse intrahepatic involvement (Caroli disease).[35] Infants present with jaundice, elevated liver enzymes, and an abdominal mass.

Congenital Hepatic Fibrosis.

Congenital hepatic fibrosis, a syndrome that includes hepatomegaly, cholestasis, cystic disease of the kidneys, and portal hypertension, varies in clinical manifestation depending on the age of the child.[36] The renal form of disease (autosomal recessive polycystic disease) usually predominates in infancy, whereas the hepatic-related form is more common in older children and adults.[36]

Genetic Intrahepatic Cholestasis.

Several forms of genetic intrahepatic cholestasis have been identified in which molecular defects can lead to abnormalities in bile synthesis, transport, and excretion.[37] The most common presentation is jaundice in neonates; pruritus is often reported in older children.[37] Some diseases, such as bile salt export pump abnormalities and multidrug resistance protein 3 (MDR3) deficiency, are liver-specific disorders. Others, such as progressive familial intrahepatic cholestasis, are systemic disorders with multisystem involvement.[38]

Autoimmune Causes

Autoimmune Hepatitis.

Autoimmune hepatitis is a progressive, immune-mediated inflammatory disorder of the liver that may mimic acute viral hepatitis.[39–41] Autoimmune hepatitis usually manifests with the insidious onset of malaise, anorexia, headache, fatigue, and jaundice in adolescents, with a striking female predominance (see Chapter 61). However, the disease can occur in younger children, in both sexes, and with acute manifestations precipitated by another event, such as an intercurrent viral illness.[39–41] The diagnosis of autoimmune hepatitis is made using the clinical and serologic criteria included in a scoring system developed by a group of experts.[41] The constellation of findings in autoimmune hepatitis includes elevated aminotransferases, hypergammaglobulinemia, elevated serum autoantibodies, (smooth muscle antibody [SMA] in type 1 autoimmune hepatitis, anti-LKM [liver-kidney-microsomal]–

1 in type 2 autoimmune hepatitis, and antinuclear antibody [ANA] in both types), and evidence of other disorders known to be associated with disturbances in immunoregulation.[39–41]

Primary Sclerosing Cholangitis.

Primary sclerosing cholangitis is a chronic immune-mediated inflammation of bile ducts that results in progressive fibrosis of the intrahepatic and extrahepatic bile ducts, cholestasis, cirrhosis, and portal hypertension.[42,43] It is rare in young children and usually manifests in adolescence or adult life.[43] Many patients may be asymptomatic at the time of diagnosis and have incidental findings of abnormal serum liver enzymes or intrahepatic bile duct dilatation on cross-sectional imaging.[42,43] In symptomatic patients, jaundice, pruritus, right upper quadrant pain, and fatigue are the most common signs. The disease often is associated with inflammatory bowel disease, especially ulcerative colitis or Crohn colitis.[44] Patients with primary sclerosing cholangitis are at risk for developing associated cholangiocarcinoma.[42,43]

Metabolic Causes

Metabolic conditions include a large group of disorders that must be considered in every infant with hepatitis, especially children in whom usual infectious causes have been excluded.[1–3,45] Initial manifestations including jaundice, lethargy, vomiting, hepatomegaly, and failure to thrive, mimicking many other causes of hepatic dysfunction. Developmental delay can be an important clue to metabolic disease. Many of the metabolic diseases occur in early childhood, so extensive testing for these disorders usually is not required when previously healthy children and adolescents present with hepatic dysfunction.

α_1-Antitrypsin Deficiency.

α_1-Antitrypsin deficiency can cause a hepatitis-like illness in children of any age group, including neonates.[46] Approximately 10% to 20% of people with α_1-antitrypsin deficiency develop signs and symptoms of liver dysfunction at some time.[46,47] Neonatal liver disease usually is limited to infants with homozygous protease inhibitor phenotype ZZ.[46,47] The clinical presentation is not distinctive; infants may present with cholestatic jaundice, poor feeding, poor weight gain, hepatomegaly, elevated aminotransferases, hypoalbuminemia, or coagulopathy.[46,47] Disease should be considered in any infant, child, or adolescent with jaundice or abnormal liver function test results. The condition frequently is unmasked by an intercurrent infection or a hepatic insult.[46,47]

Cystic Fibrosis.

Cystic fibrosis is associated with a wide range of hepatobiliary tract diseases, including steatosis, focal biliary cirrhosis, cholelithiasis, and intrahepatic duct stones or sludge.[48,49] Clinically significant hepatobiliary tract disease occurs in approximately one third of children with cystic fibrosis, but it accounts for only approximately 2% to 3% of deaths.[48,49] In the neonatal period, severe cholestatic disease can occur in the absence of pulmonary involvement. The gold standard test for diagnosis remains the sweat test.[48,49] However, serologic genetic screening can be helpful in suspected patients of European descent because they often have the most common mutations, including δ-F508.[48,49] If the genetic screening result is negative, a sweat test still is required to rule out the diagnosis. Genetic screening can be especially valuable in neonates, in whom a sweat test often is unreliable because of difficulties in obtaining an adequate sample. Given the lack of phenotypic association between the incidence of liver disease and specific mutations, genetic testing cannot be used to predict the development of liver disease.[49]

Carbohydrate Metabolism Disorders.

Several disorders of carbohydrate metabolism can cause hepatic dysfunction in infants and children.[50] A family history of liver disease should be sought because disorders of carbohydrate metabolism are inherited, and the pattern of symptom onset can help to guide the diagnosis. For example, the onset of diarrhea and liver dysfunction occurring after ingestion of fructose (e.g., in fruit juices) raises the likelihood of fructosemia. Galactosemia must be screened for by testing the urine for reducing substances in any neonate with liver dysfunction who receives lactose.[50] In addition, fasting hypoglycemia, in the absence of liver failure or end-stage hepatic disease, is an important clue to the possibility of disorders of carbohydrate metabolism, including 6 of the 8 forms of glycogen storage disease.[51] Splenomegaly is not common in these disorders and usually occurs only in amylopectinosis disease (type IV glycogen storage disease).[50]

Protein Metabolism Disorders.

Disorders of protein metabolism often manifest in infancy, but some diseases, such as the chronic form of tyrosinemia, can occur later in life.[52] Developmental delay and seizures often are associated with these disorders, but they may not be manifest initially; laboratory evaluation or biopsy may be required to establish the diagnosis.[53] Hyperammonemia can be an important clue to disorders involving protein metabolism, including disorders of the urea cycle and organic acidemias.[52,53] Many of these disorders are apparent at birth or shortly thereafter.

Metal Metabolism Disorders.

Consideration of disorders of metal metabolism is influenced by the age of the child. For example, Wilson disease, which can cause acute, chronic, or fulminant liver dysfunction, rarely manifests in children <4 years of age.[54,55] By contrast, Indian childhood cirrhosis typically occurs in children <3 years of age, and hepatic insufficiency develops in the first week of life in neonatal hemochromatosis.[55]

Lipid Storage Diseases.

The lipid storage diseases usually are associated with hepatosplenomegaly and progressive central nervous system deterioration. Signs and symptoms can be apparent early in the first year and can progress quickly to death (Wolman disease), or the onset can occur throughout childhood and even into adulthood (Niemann-Pick and Gaucher diseases).[56]

Disorders of Mitochondrial Fatty Acid Oxidation.

Growing numbers of disorders of fatty acid oxidation are being discovered. Children with these disorders can present in infancy but often do not develop symptoms until later in life, when prolonged fasting, often in conjunction with an acute infection, causes a Reye-like syndrome.[57] Cardinal features include hypoglycemia, acidosis, and hepatic injury, often with little elevation in bilirubin levels.

Disorders of Bile Acid Metabolism.

Increasing numbers of disorders that cause errors in metabolism of bile acids are being discovered; these disorders routinely cause cholestasis and hepatitis in neonates.[58] These rare disorders previously were placed in the category of neonatal or idiopathic hepatitis. Clinical manifestations usually are not diagnostic, but infants often have low serum bile acids, low γ-glutamyltranspeptidase levels, and no pruritus, findings that are otherwise rare in conditions of hepatic dysfunction and chronic cholestasis.[58,59]

Toxins and Medications

Various hepatotoxins, including medications and chemicals, can be associated with a hepatitis-like picture.[60,61] The clinician should obtain a history of exposure to medications including acetaminophen, valproic acid, tegretol, isoniazid, sulfonamides, phenytoin, carbamazine, and phenobarbital. Drug-related hepatitis in neonates is rare, but exposure to these compounds must be considered in older infants and children because the diagnosis usually is made on clinical grounds.[60,61] Children receiving total parenteral nutrition, especially prematurely born infants, are at risk of developing hepatic injury.[61] Given that no diagnostic test is available for this disorder, it must be considered as a diagnosis of exclusion following rigorous evaluation. A rare but important toxic cause of severe hepatic injury in children is ingestion of *Amanita* mushrooms.

Tumors

Hepatic tumors can manifest with hepatomegaly and abnormal serum hepatic tests but usually are identified by initial imaging studies. The liver usually feels hard on palpation.

Idiopathic Causes

Age helps in differentiating disorders in the idiopathic category. Neonatal hepatitis (also called giant cell hepatitis) is defined as a group of disorders of unknown origin that are associated with cholestasis in the neonate and young infant.[62] The presentation can be similar to that of biliary atresia but usually is distinct from neonatal infectious hepatitis, which is characteristically part of an illness affecting multiple organ systems.

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61

Chronic Hepatitis

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Chronic hepatitis is a clinical and pathologic syndrome associated with a wide variety of diseases and conditions (Table 61.1).[1,2] Chronic hepatitis typically is defined as ongoing injury with inflammation lasting ≥6 months. However, the impact of inflammation can vary greatly, so a combination of clinical, laboratory, and histologic findings now is sought that can establish the diagnosis sooner and enable earlier treatment.[1–3]

TABLE 61.1

Causes of Chronic Hepatitis by Age of Onset

Causative Factor	Age of Onset		
	Neonates, Infants	**Children**	**Adolescents**
HEPATOTROPIC INFECTION			
Hepatitis B virus	+	+	+
Hepatitis C virus	+	+	+
Hepatitis D virus	+	+	+
GENERALIZED INFECTION			
Cytomegalovirus	+	+	+
Epstein-Barr virus	+	+	+
Human immunodeficiency virus	+	+	+
Rubella virus	+	−	−
Varicella virus	+	+	+
ANATOMIC ABNORMALITIES			
Biliary atresia	+	−	−
Congenital hepatic fibrosis	+	+	−
Sclerosing cholangitis	−	+	+
Primary biliary cirrhosis	−	−	+
AUTOIMMUNE DISORDERS	−	+	+
METABOLIC DISEASES			
α_1-Antitrypsin deficiency	+	+	+

Cystic fibrosis	+	+	+
Carbohydrate, protein, and lipid disorders	+	+	+
Obesity	−	+	+
Wilson disease	−	+	+
Errors of bile acid metabolism	+	−	−
TOXINS AND DRUGS	+	+	+
IDIOPATHIC CONDITIONS			
Cryptogenic	+	+	+
Neonatal hepatitis	+	−	−

+, recognized or usual age of occurrence; −, unexpected age or never an age of occurrence.

Approach to Evaluation

A careful history and physical examination are important and can be challenging because the onset often is insidious and many patients are asymptomatic.[3] Signs and symptoms, when present, are variable and can include hepatitis, fatigue, abdominal pain, anorexia, weight loss, dark urine, clay-colored stools, and fever.[1–3] Some patients may receive a diagnosis after months or years of puzzling symptoms such as relapsing jaundice. Alternatively, variceal bleeding or organomegaly can be the presenting sign. A history of exposure to blood products, use of intravenous drugs, and maternal infection are important clues to viral hepatitides.[1–3] The presence of thyroiditis, Sjögren syndrome, or idiopathic colitis, especially in a female patient, raises the possibility of autoimmune hepatitis (AIH).[3,4] A history of exposure to drugs and toxins also must be sought.

The pattern of biochemical abnormalities usually is not diagnostic for a specific cause. Serum levels of serum aminotransferases often are elevated but can be intermittently normal in hepatitis C virus (HCV) infection.[5] Levels of serum aminotransferases often do not reflect the severity of disease identified by liver biopsy, and patients can progress to cirrhosis with normal aminotransferase levels.[1–3,5] Bilirubin elevations and levels of other serum enzymes, such as alkaline phosphatase and γ-glutamyltranspeptidase, can be variable.

In contrast to acute hepatitis, liver biopsy often is an essential tool in the diagnosis and management of patients with chronic hepatitis. Liver biopsy also is used to assess prognosis by grading the severity of disease and its progression. The terms *chronic active hepatitis,* *chronic persistent hepatitis*, and *chronic lobular hepatitis* have been replaced by newer terminology that grades the severity of liver inflammation and fibrosis from minimal to severe.[1–3]

Infectious causes are most common and should be included in the initial evaluation (Box 61.1; see Table 61.1). If results of initial testing are negative, further evaluation is warranted.[2,3]

Box 61.1

Laboratory Evaluation of Children With Chronic Hepatitis

Initial Tests

Blood

Tests of hepatic injury and function

- Bilirubin, total and direct
- Alanine aminotransferase
- Aspartate aminotransferase
- Alkaline phosphatase or γ-glutamyltranspeptidase
- Total protein and albumin
- Prothrombin time
- Fibrinogen
- Ammonia
- Fasting glucose
- Platelet count
- Serum iron and ferritin

Tests for infectious agents

- Hepatitis B virus surface antigen and core antibody
- Hepatitis C virus antibody
- Hepatitis D virus antibody
- Epstein-Barr virus antibody
- Cytomegalovirus antibody
- Human immunodeficiency virus antibody

Urine

Shell vial culture for cytomegalovirus for neonates

Imaging

Ultrasonography of the liver

Further Evaluations if Test Results for Infectious Causes Are Negative

Blood

Erythrocyte sedimentation rate

Quantitative serum immunoglobulin levels

Antitissue transglutaminase and serum immunoglobulin A level

Autoantibody tests

- Antinuclear antibody
- Liver-kidney-microsomal antibody

- Anti–smooth muscle antibody
- P-antinuclear cytoplasmic antibody

Metabolic tests

- α_1-Antitrypsin level with protease inhibitor type
- Ceruloplasmin level

Sweat test

Urine

Quantification of copper in 24-hour specimen

Radiology

Magnetic resonance imaging

Liver Biopsy

Etiologic Factors

Infectious Causes

Hepatitis B virus (HBV) infection is one of the most common causes of chronic hepatitis in children worldwide, but the incidence has decreased substantially in the United States as a result of universal vaccination and blood donor screening.[6] Chronic HBV infection still is encountered in US children infected perinatally or adoptees from endemic areas.[2,6] The risk of developing chronic HBV infection is related directly to the age of acquisition. Perinatal infection is associated with a 90% to 95% risk of chronic hepatitis in infants born to mothers who are hepatitis B e antigen (HBeAg) positive, whereas infection in adults results in a <10% incidence of chronic hepatitis.[2,6] Exposure to infected blood products, intravenous drug use, and institutionalized settings increase the risk of HBV infection and subsequent chronic hepatitis.[6,7] Hepatitis D virus (HDV) is an incomplete virus that occurs only in conjunction with HBV infections. Perinatal transmission is rare, and most cases of HDV infection occur as superinfections in patients who are longterm carriers of HBV, thus leading to more severe hepatitis.[8] The signs and symptoms of chronic HBV infection are variable; many children are asymptomatic or have mild disease.[6,7] The diagnosis usually is made based on serologic criteria; a liver biopsy is performed primarily for prognosis or evaluation of therapy.[3,7] Most children remain immune tolerant until late childhood or adolescence, and they do not respond well to currently available treatment. Spontaneous HBeAg clearance occurs in only 1% to 5% of children infected in utero (vertical transmission) but in 70% to 80% of children infected after birth (horizontal transmission).[9] The US Food and Drug Administration has approved interferon α and oral agents for use in children with chronic HBV; approved oral agents include lamivudine (for children ≥3 years of age), adefovir and tenofovir (≥12 years), and entecavir and telbivudine (≥16 years).[9,10] The rate of viral clearance is still low with these therapies, and interferon is associated with significant adverse effects, whereas viral resistance and relapse are commonly seen with the oral agents; therefore, routine treatment of immune tolerant children or carriers is not warranted.[9]

HCV has emerged as a leading cause of chronic hepatitis in adults in the US, but the estimated seroprevalence of HCV antibodies in children is approximately 0.6%.[5] Before the advent of effective screening techniques in the early 1990s, children who had received blood products were at greatest risk for infection. Now most new pediatric cases are caused by vertical transmission, with a 5% to 7% risk of infection in infants born to seropositive mothers.[5,11] Risk factors for transmission include maternal coinfection with human immunodeficiency virus, high maternal HCV viral load, prolonged rupture of membranes, and fetal anoxia. Breastfeeding is not contraindicated, except in the presence of bleeding from the nipple or mastitis.[5] The diagnosis usually is made by detection of antibodies to core and nonstructural antigens, but detection of active infection is best established by polymerase chain reaction. Confirmatory testing should be performed after the first year of life because transient viremia has been observed in neonates.[5,11] Serum aminotransferase values can fluctuate in chronic HCV infection, and liver biopsy often is performed to assess the severity of liver disease or evaluate the efficacy of antiviral therapies.[5,11] The natural history of chronic HCV may be affected by several factors such as genotype, comorbidity with other viral infections, cancer, intravenous drug use, and obesity.[5] Infants infected at birth may clear the infection spontaneously, usually within the first 2 years but occasionally as late as 7 years.[5] Progression of the disease appears to be slower in children than in adults, although advanced fibrosis, cirrhosis, and hepatocellular carcinoma can be encountered in chronically infected children.[11] Treatment of chronic HCV infection has been revolutionized with the emergence of interferon-free, all-oral regimens using direct-acting antiviral agents such as sofosbuvir, simeprevir, and ledipasvir.[12–14] These regimens have been highly successful against all genotypes and have demonstrated excellent sustained viral response and safety profiles.[13,14] Multicenter clinical trials using combinations of these agents in children are just starting.

Cytomegalovirus, Epstein-Barr virus, and other viruses can cause chronic hepatitis, although progression of these infections to cirrhosis and liver failure is rare (see Table 61.1).[2]

Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) refers to a spectrum of conditions associated with fatty infiltration of the liver. Findings range from simple fatty infiltration to nonalcoholic steatohepatitis, which can progress to advanced liver disease and cirrhosis.[15,16] NAFLD is the most common cause of chronic liver disease in pediatrics, with an estimated prevalence of 3% to 10% in all children and as high as 70% to 80% in obese children.[15,16] Patients often are asymptomatic and come to attention when elevated aminotransferase levels are noted incidentally. Physical examination usually is remarkable only for excess weight (body mass index >85% for age) and hepatomegaly.[15,16] Acanthosis nigricans also may be present as a sign of associated insulin resistance. Several factors are implicated in development of NAFLD, including hyperinsulinemia, insulin resistance, associated free fatty acid hepatotoxicity, genetic predisposition, the intestinal microbiota, gut-derived inflammatory mediators, and oxidant stress.[16] Sonography demonstrates a homogeneous pattern of increased liver echogenicity; magnetic resonance imaging is considered to be a more specific diagnostic modality.[16] An extensive workup, often including liver biopsy, may be required to confirm the diagnosis and exclude other causes of liver disease.[15,16] Hepatic dysfunction usually normalizes if the body mass index is improved with a low-glycemic diet and exercise. Pharmacologic agents have been studied, and the use of vitamin E has been associated with improvements in histopathologic features but not in aminotransferase levels.[17] Insulin-sensitizing agents, such as metformin, have not been shown to be effective.[17]

Autoimmune and Autoinflammatory Disorders

Autoimmune liver disease is a heterogeneous group of diseases consisting of AIH, primary sclerosing cholangitis, and primary biliary cirrhosis.[18,19] AIH causes a diffuse pattern of hepatocellular injury. Primary sclerosing cholangitis and primary biliary cirrhosis involve injury to the biliary tract with secondary cholestasis and hepatocyte injury leading to acute liver failure or cirrhosis, if untreated.

AIH mostly occurs in children <18 years of age; the mean age of onset is 6 to 10 years, but the disease has been diagnosed in children as young as 6 months of age.[1,18] AIH should be considered in patients with the following findings: female sex, coexistent autoimmune disease, low ratio of albumin to total protein, elevated immunoglobulins, and relative elevation of serum aminotransferases compared with alkaline phosphatase.[19] In addition, elevated titers of non–organ-specific autoantibodies are characteristic of AIH and are used to identify subgroups of disease. In type 1 AIH, antinuclear antibodies, anti–smooth muscle antibodies, or antiactin antibodies usually are present; in type 2 AIH, anti–liver-kidney-microsomal antibodies or anticytosol antibodies are usually seen.[1,3,18] Although clinical, laboratory, and histologic findings are helpful in suggesting the diagnosis, no single diagnostic test exists for AIH, and exclusion of infectious, toxic, and metabolic causes is critical. Autoantibody-negative AIH also has been reported.[18,19] Liver biopsy may be diagnostic. Treatment usually involves the use of corticosteroids initially, followed by longterm immunomodulator therapy, such as with azathioprine. More recently, budesonide has been used to try to induce disease remission.[20] In some cases, immunosuppressive agents such as cyclosporine, mycophenolate, or tacrolimus have been used.[18,19] Liver transplantation may be required but can be complicated by recurrence of AIH in the transplanted liver.[18,19]

Primary sclerosing cholangitis is a rare cause of chronic liver disease in children and adolescents and often is associated with inflammatory bowel disease.[21,22] It is characterized by progressive fibrosis obliterating the intrahepatic and extrahepatic bile ducts.[21] The presence of jaundice, fatigue, and right upper quadrant pain is the most common presentation.[21,22] The diagnosis often requires endoscopic retrograde cholangiopancreatography and liver biopsy. However, continuing improvements in magnetic resonance cholangiopancreatography may allow this technique to supplant the use of more invasive procedures.[21,22] Treatment with ursodeoxycholic acid and immunosuppressive agents can improve laboratory test results, but it usually does not improve symptoms or affect longterm survival.[21,22] Many patients ultimately require liver transplantation but transplantation is associated with increased risk of rejection, biliary stricture formation, or disease recurrence in the transplanted liver[21] Initial studies of vancomycin therapy have shown normalization of liver function test results in patients with primary sclerosing cholangitis, but longterm results are not yet available.[21,22]

Primary biliary cirrhosis mostly occurs in middle-aged women but has been identified in adolescents. This disease is characterized by the presence of antimitochondrial antibodies.[23]

Metabolic Disorders

Metabolic disorders are uncommon causes of chronic hepatitis but should be considered, especially when initial testing for infectious causes does not yield a diagnosis.[2,3] The clinical presentation of these disorders usually is not distinctive enough to permit diagnosis without laboratory testing, including liver biopsy.

Although α_1-antitrypsin deficiency most commonly affects the lungs, it can cause chronic liver disease in all age groups, including neonates, who usually present with cholestatic jaundice.[24,25] Liver involvement in some infants progresses to cirrhosis and early death, but many patients do not develop signs of chronic liver failure until late adolescence.[24,25] Liver disease developing later in childhood or in adolescence can be associated with a wide spectrum of histologic findings ranging from mild portal fibrosis to cirrhosis or hepatoma. The diagnosis is established by measuring the serum α_1-antitrypsin level and protease inhibitor type of the affected person.[24,25] Severe disease occurs most often in people with homozygous protease inhibitor type ZZ but can occur in heterozygotes having MZ, SZ, and Z null phenotypes.[24,25] Although the current treatment for severe liver disease from α_1-antitrypsin deficiency is liver transplantation, various newer therapies to stimulate the production of α_1-antitrypsin are being studied. These trials include the use of carbamazepine, fluphenazine, and pimozide.[24] Hepatocyte transplantation and gene therapy are other strategies being studied.[24]

Chronic hepatic dysfunction occurs in up to 50% of children with cystic fibrosis and can include steatosis, cholelithiasis, focal biliary cirrhosis, and portal hypertension.[26,27] Except in the first year of life, liver disease rarely is the initial manifestation of cystic fibrosis, so diagnostic difficulties usually are not encountered. The diagnosis of cystic fibrosis can be made by newborn screening, sweat testing, or genetic screening for the most common mutations.[26,27]

Disorders of carbohydrate (e.g., glycogen storage disease), protein (e.g., chronic form of tyrosinemia), and lipid (e.g., Niemann-Pick and Gaucher disease) metabolism rarely manifest after the neonatal period as chronic hepatitis.[2] These diseases often require liver biopsy, as well as laboratory evaluation for diagnosis. They usually are not included in the initial evaluation unless the patient has signs and symptoms such as hypoglycemia, seizures, or developmental delay.

Wilson disease can manifest as acute, chronic, or fulminant hepatitis, and because it is potentially treatable, it must be part of the differential diagnosis of chronic hepatitis in children and adolescents.[28,29] Wilson disease rarely is reported in children <3 years of age but should be considered in older children when liver disease is associated with hemolytic anemia, renal disease, or neuropsychological deterioration.[28] Kayser-Fleischer ring, a brownish-yellow ring around the corneoscleral junction, is the most distinctive finding on physical examination but may not be present in younger children or children with liver involvement alone.[28,29] The diagnosis is suggested by low serum ceruloplasmin levels and elevated urinary copper levels (especially after penicillamine treatment) and is confirmed by elevated levels of copper in the liver biopsy specimen.[28,29] A Wilson disease gene has been identified, and mutation analysis by gene sequencing for *ATP7*B can be a valuable tool in the diagnosis of cases that are indeterminate or difficult to diagnose.[28,29] Treatment requires the lifelong use of chelating agents such as D-penicillamine, trientine, or zinc.[29] Patients also need to be maintained on a low-copper diet. The use of tetrathiomolybdate is being evaluated as a potential therapy.[28] Liver transplantation is often required for patients with decompensated disease or acute liver failure.

Liver disease, although seldom severe, has been observed in association with celiac disease. The diagnosis should be considered in all patients with hepatitis when no other cause can be found.[30]

Toxins and Drugs

Patients with chronic hepatitis should be questioned for a history of exposures to toxins or drugs, including α-methyldopa, nitrofurantoin, isoniazid, dantrolene, propylthiouracil, valproic acid, and sulfonamide.[31,32] Affected people often have markers of autoimmune diseases, including positive lupus erythematosus slide preparation test results and elevated antinuclear antibodies.[32] Discontinuation of the drug usually results in improvement or resolution of the clinical and biochemical abnormalities. The timing of toxic drug reactions is unpredictable, and these reactions can occur after years of regular use of a medication. Longterm total parenteral nutrition also can be an important cause of chronic hepatitis in children, particularly in children with short bowel syndrome.[33]

Idiopathic and Anatomic Causes

Cryptogenic hepatitis (hepatitis of unknown cause) is a diagnosis of exclusion when all the previously described causes have been excluded. Depending on the location and age of the population studied, cryptogenic hepatitis accounts for approximately 25% of cases of chronic hepatitis.[2,3] Analysis of risk factors in adults suggests that silently progressive fatty liver may be an underrecognized cause of cryptogenic cirrhosis.[34]

Neonatal hepatitis, which comprises a group of disorders of unknown origin that cause cholestasis in neonates, also is a diagnosis of exclusion. This diagnosis usually is made early in the neonatal period; patients rarely go unrecognized until later infancy. The number of cases of neonatal hepatitis is decreasing as more sophisticated methods of diagnosis identify new diseases, especially errors in bile salt metabolism and progressive familial intrahepatic cholestasis.[35,36]

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62

Granulomatous Hepatitis

Beverly L. Connelly

Histologically evident granulomas in the liver are referred to as *granulomatous hepatitis*. Granulomas can be an incidental finding, as in biopsies performed in prospective organ donors[1] or can be a manifestation of a disorder primarily of the liver, but they more often are a part of an underlying systemic process.[2] Levels of serum hepatic enzymes are normal or only minimally elevated.[2]

Granulomas are reported in 2% to 15% of liver biopsy specimens from adults and 4% to 7% of specimens from children.[3,4] Increased use of computed tomography (CT) and magnetic resonance imaging (MRI) for patient evaluations has led to increasing recognition of granulomatous hepatitis and spurred the search for causes.

Pathogenesis and Pathologic Findings

The hallmark of hepatic granulomas is epithelioid cells, which are activated macrophages transformed to resemble epithelial cells. Granuloma formation is initiated when monocytes and macrophages migrate into an area of inflammation in response to triggering by intracellular microbial antigens, foreign body reactions, and host immunologic hypersensitivity responses.[5] A Th1 or Th2 pathway can be active in granuloma formation. The Th1 immune response is classically involved in tuberculosis and sarcoidosis, and the Th2 response occurs with parasitic infections. T-lymphocyte–derived tumor necrosis factor (TNF) plays a key role in granuloma formation, a finding supported by the enhanced risk of granulomatous infections by patients receiving TNF-inhibitor agents.[6,7]

Hepatic granulomas are 50 to 300 mm in diameter, and their morphology varies from clusters of epithelioid cells to well-developed granulomas rimmed by lymphocytes.[5,8] Epithelioid cells can merge to form multinucleated giant cells. Central caseation or abscess formation can occur. Distribution of epithelioid cells often is patchy, and the small granulomas may be identified only with serial tissue section analysis.[2,5]

Histologic features can suggest specific diagnoses.[5] Central caseation with epithelioid cells in a radial array at the periphery is typical of tuberculosis, and Langhans giant cells can be seen. Granulomas are large and loose in sarcoidosis, without pattern or caseation, although there can be central eosinophilic necrosis and multinucleated giant cells.[5,9] In chronic granulomatous disease of childhood, pigmented macrophages are found in architecturally normal liver, and necrotizing granulomas are found in areas of active inflammation.[5,10] *Bartonella henselae* causes granulomas with stellate microabscess.[5,11] Eosinophilic infiltrates help to distinguish hepatic granulomas caused by parasitic infestations, and a portion of the larva may seen within the granulomas of visceral larva migrans or the ova in schistosomiasis.[5,12] Eosinophilic granules also can be seen with histoplasmosis.

Special histologic stains and techniques should be used when an infectious cause is suspected. Acid-fast bacilli (AFB) are demonstrated infrequently in granulomas caused by *Mycobacterium tuberculosis*, whereas large numbers of AFB usually are found in patients with the acquired immunodeficiency syndrome (AIDS) who are infected with nontuberculous mycobacteria.[13] Immunohistochemistry techniques can aid in identifying viruses, especially cytomegalovirus (CMV) and Epstein-Barr virus (EBV). Nucleic acid amplification techniques can be useful for identifying various pathogens in tissues.[14]

Clinical Manifestations and Differential Diagnosis

Hepatic granulomas usually reflect a systemic disease.[8] When granulomas are limited to the liver, primary biliary cirrhosis is an important diagnosis for adults.[3]

Clinical manifestations vary with the underlying disease. Fever and chills often are primary symptoms and may be a manifestation in fever of unknown origin.[15] Mild right upper quadrant abdominal pain and tenderness may be found, but serum hepatic enzyme levels usually are normal or mildly elevated.

Although noninfectious causes are more common in adults in case series from western countries,[14,16] infectious causes predominate in children[4,17] and in series from the Middle East and India.[4,18] The principal infectious and noninfectious causes of granulomatous hepatitis are listed in Table 62.1.

TABLE 62.1

Agents and Conditions Associated With Granulomatous Hepatitis

Infectious Agents	Noninfectious Agents or Conditions
BACTERIA	**IMMUNE DYSREGULATION**
Bartonella henselae	Autoimmune hepatitis
Brucella spp.	Biliary cirrhosis, primary
Coxiella burnetii	Chronic granulomatous disease
Francisella tularensis	Common variable immunodeficiency
Listeria monocytogenes	Inflammatory bowel disease
Mycobacterium tuberculosis	Juvenile idiopathic arthritis
Nontuberculous mycobacteria	Sarcoidosis
Nocardia spp.	Systemic lupus erythematosus
Pasteurella multocida	Wegener granulomatosis
Treponema pallidum	**DRUGS AND CHEMICALS**
Yersinia enterocolitica	Allopurinol
VIRUSES	Barium
Hepatitis C virus	Carbamazepine
Epstein-Barr virus	Mebendazole
Cytomegalovirus	Methyldopa
FUNGI	Antimicrobial agents: norfloxacin, penicillin
Blastomyces dermatitidis	Chemotherapeutic agents
Candida spp.	Phenytoin
Coccidioides immitis	Pyrazinamides
Cryptococcus neoformans	Sulfasalazine
Histoplasma capsulatum	Talc
PARASITES AND PROTOZOA	Quinine
Leishmania spp.	**NEOPLASMS**
Schistosoma spp.	Hodgkin disease
Strongyloides spp.	Lymphoma
Toxocara spp.	**IDIOPATHIC CONDITIONS**

Toxoplasma gondii	

Infectious Causes

The prevalence of causative infectious agents of granulomatous hepatitis reflects geography, socioeconomic factors, and host immunocompetence. Worldwide, mycobacteria are the most frequent bacterial cause of granulomatous hepatitis.[8,18] In case series from the Iran and India, more than one half of the cases were tuberculosis, typically as a part of systemic disease.[4,18] In one review of 63 patients with granulomatous hepatitis, 9 of 11 patients younger than 20 years had tuberculosis.[15] Nontuberculous mycobacteria are offenders in immunocompromised patients and those with AIDS and are part of disseminated infection.[13] Bacille Calmette-Guérin (BCG) can disseminate and cause granulomatous hepatitis in children with severe combined immunodeficiency and in adults who receive BCG instillation into the bladder as therapy for bladder carcinoma.[19,20]

Bartonella henselae infection is likely an underdiagnosed cause of granulomatous hepatitis in healthy and immunosuppressed children, who come to medical attention with abdominal pain and prolonged, undiagnosed fever.[11,21] Granulomatous hepatitis should be suspected in patients with atypical *B. henselae* infections.

With improved diagnostics, hepatitis C virus has emerged as a significant cause of granulomatous hepatitis, surpassing tuberculosis in western societies.[22,23] Chronic infection with other viral causes of hepatitis occasionally have been implicated in granuloma formation.[14]

Zoonotic infections, including brucellosis and Q fever (i.e., *Coxiella burnetii* infection), should be suspected in persons with liver lesions and exposure to sheep, goats, or other herded ungulates.[24] Isolated liver disease is unusual, however. Several tickborne infections, including ehrlichiosis, tularemia, and Lyme disease, rarely have been associated with granulomatous hepatitis.[25]

Among conditions caused by parasites and protozoa, schistosomiasis is a leading cause of hepatobiliary disease where the pathogens are prevalent in tropical and subtropical regions of Asia, the Caribbean, South America, and Africa.[5,26] Migrating larvae of *Toxocara canis* can lead to hepatic or splenic granulomatous disease associated with visceral larva migrans.[27] Peripheral eosinophilia often is significant, and organ enlargement can be severe in patients with parasitic granulomatous hepatitis.

Histoplasmosis is the most commonly reported fungal infection associated with granulomatous hepatitis in immunocompetent and immunocompromised patients.[4,17,28] Infections with other endemic dimorphic fungi also can involve the liver. Hepatic and splenic granulomas and abscesses due to *Candida* species are well-recognized complications in neutropenic and otherwise immunocompromised populations. Cryptococcal infections usually seen in immune compromising conditions, including AIDS, can be associated with granulomatous hepatitis.[28]

Noninfectious Causes

Autoimmune and immune dysregulation disorders account for most noninfectious granulomatous hepatitis cases.[5,8,14] Primary biliary cirrhosis is the most common cause of noninfectious granulomas isolated to the liver alone,[3,23] and sarcoidosis is the most common cause of hepatic granulomas seen as a part of a multisystem disease.[29] Hepatic granulomas can be part of the clinical manifestations of other conditions of immune dysregulation, such as chronic granulomatous disease,[30] common variable immunodeficiency, inflammatory bowel disease (e.g., Crohn disease), juvenile idiopathic arthritis,[5,8] and a variety of lymphoreticular disorders (e.g., Hodgkin disease).[31] In each of these conditions, it is important to exclude infectious causes.

Drugs, toxins, inert materials, and chemicals can lead to noncaseating granulomatous inflammation of the liver. Chemotherapeutic agents, biologic agents, antibiotics, anticonvulsants, and anti-inflammatory agents are most frequently associated.[32–34] Many of the idiopathic cases of granulomatous hepatitis may be drug related.[33]

Diagnosis

Granulomatous hepatitis should be suspected in any patient with fever of unknown origin or with a systemic disorder in which right upper quadrant abdominal pain or tenderness, hepatomegaly, or a mild elevation of serum hepatic enzymes is seen. Liver lesions may be visualized on imaging studies as part of the evaluation of symptoms.

CT, MRI, and, less often, ultrasonography provide sensitive screening diagnostic modalities for granulomatous hepatitis. MRI can differentiate caseating from noncaseating granulomas.[35] The role of fluorodeoxyglucose position-emission tomography (FDG-PET) with CT in detection of liver granulomas is growing but requires clinical development.[36]

As depicted in Fig. 62.1, testing guided by a careful history to capture epidemiologic clues and attention on physical examination to clues for underlying systemic disease often can lead to the diagnosis and guide treatment without having to perform a liver biopsy. Because of the prevalence of viral infections such as EBV, CMV, and hepatitis C, testing for these pathogens in the absence of tissue examination may not be adequately specific.

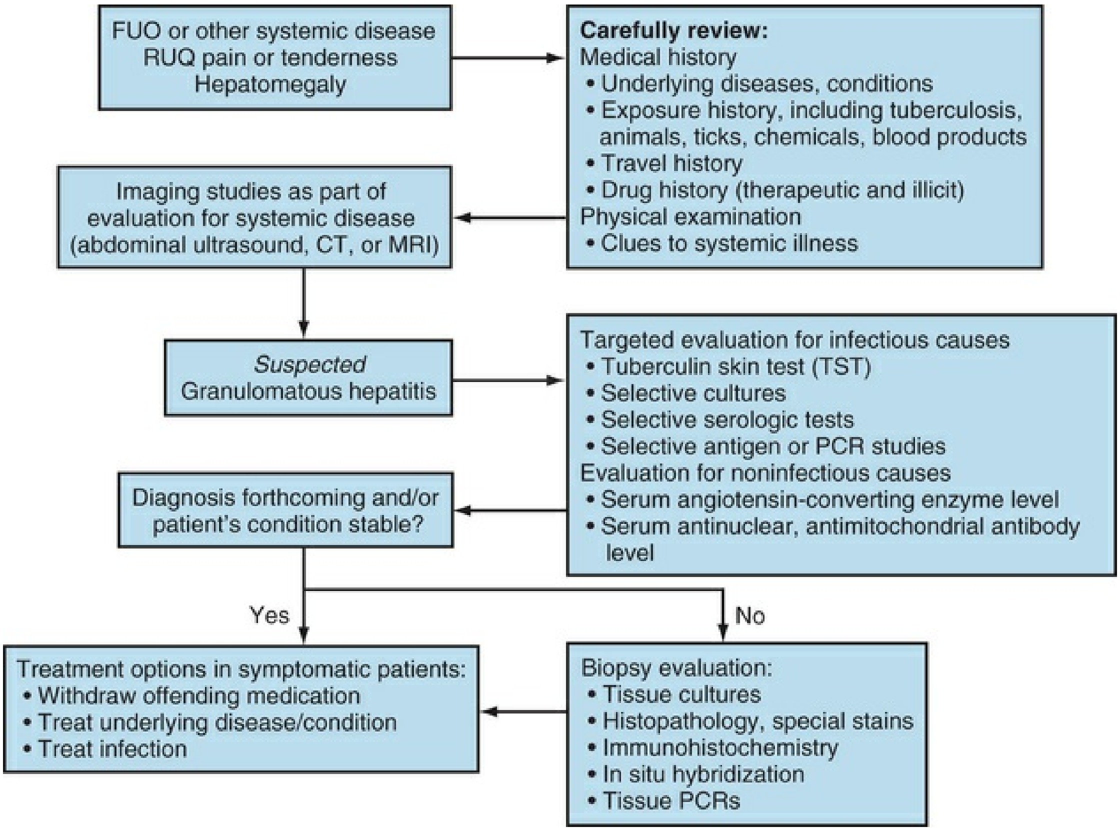
FUO or other systemic disease
RUQ pain or tenderness
Hepatomegaly
Carefully review:
Medical history
• Underlying diseases, conditions
• Exposure history, including tuberculosis, animals, ticks, chemicals, blood products
• Travel history
• Drug history (therapeutic and illicit)
Physical examination
• Clues to systemic illness
Imaging studies as part of evaluation for systemic disease (abdominal ultrasound, CT, or MRI)
Suspected
Granulomatous hepatitis
Targeted evaluation for infectious causes
• Tuberculin skin test (TST)
• Selective cultures
• Selective serologic tests
• Selective antigen or PCR studies
Evaluation for noninfectious causes
• Serum angiotensin-converting enzyme level
• Serum antinuclear, antimitochondrial antibody level
Diagnosis forthcoming and/or patient's condition stable?
Yes
No
Treatment options in symptomatic patients:
• Withdraw offending medication
• Treat underlying disease/condition
• Treat infection
Biopsy evaluation:
• Tissue cultures
• Histopathology, special stains
• Immunohistochemistry
• In situ hybridization
• Tissue PCRs

FIGURE 62.1 An approach to the diagnosis of granulomatous hepatitis. CT, computed tomography; FUO, fever of unknown origin; MRI, magnetic resonance imaging; PCR, polymerase chain reaction;

RUQ, right upper quadrant.

In immunocompromised people and those with progressive symptoms without a compelling diagnosis, a tissue diagnosis should be sought. Tissue from a lymph node or skin lesion in a patient with systemic disease may provide the diagnosis, avoiding the more invasive liver biopsy. Tissue cultures may yield the pathogen. Histopathologic clues from routine and special stains can guide immunohistochemistry (i.e., in situ hybridization) and nucleic acid amplification testing (i.e., PCR) of tissue specimens and substantially increase detection of most infectious agents.[14] Further serologic studies and serum PCR studies then may be indicated. Thorough investigation for all possible causative diseases should be performed before the condition is labeled idiopathic.

Management and Outcome

Granulomatous hepatitis of infectious origin regresses with appropriate targeted therapy. Treatment of the underlying disease, however, is the cornerstone of management. Empiric therapy with corticosteroids has been advocated in idiopathic adult cases, although illness can resolve without therapy in these patients.[37]

There are no collective data regarding the outcome of children with idiopathic granulomatous hepatitis. Empiric therapy with corticosteroids is rarely indicated in children in view of the predominance of infectious causes of pediatric cases.

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63

Acute Pancreatitis

Beverly L. Connelly

Although it is a rare disorder in children, pediatric hospital admissions for pancreatitis have increased over the past decade.[1–3] A possible reason for the rising incidence is an increased awareness by pediatricians of pancreatitis as a cause of abdominal pain in children.[3] In its mild form, pediatric pancreatitis likely is underdiagnosed, and it resolves spontaneously with no sequelae.

Etiologic factors leading to pancreatitis include a wide variety of disorders that vary in incidence by age. Among adults, alcohol and gallstones are the major causes of acute pancreatitis,[2] whereas in children, the causes are more diverse. In children, pancreatitis most often results from systemic illness, biliary disease, trauma, or the side effects of certain medications.[2–7] Infection or infestation accounts for about 10% of cases of acute pancreatitis in children.[3,8]

Pathogenesis

Inflammation of the pancreas in response to a variety of insults is caused by autodigestion of the organ by pancreatic enzymes. The precise circumstances and chronology of events leading to enzyme activation vary by cause.[2,9] The end result is that enzymes are activated within the pancreatic parenchyma, producing local inflammation and damage.

The inflammatory cascade that follows pancreatic injury results in the systemic inflammatory response syndrome (SIRS). Interleukin-1 (IL-1) and tumor necrosis factor (TNF) mediate this response. These agents increase production of platelet-activating factor (PAF), nitric oxide, IL-6, and IL-8. Inflammatory mediators are responsible for the clinical findings of severe acute pancreatitis such as acute respiratory distress syndrome (ARDS), vascular leakage, renal dysfunction, hypovolemia, and shock. Other factors such as activated complement (C5) and IL-10 may act to dampen the inflammatory response.[9,10]

Clinical Manifestations

Abdominal pain is the predominant symptom, occurring in 87% of pediatric patients.[8] Continuous, dull pain typically occurs in the epigastric area. Pain begins abruptly, increases in severity, and peaks in a few hours. Sometimes the pain is mild, is localized elsewhere in the abdomen, or radiates to the middle of the back.[4] Nausea and vomiting occur in 64% of pediatric patients.[8] The child's position of comfort usually is with the knees flexed on the abdomen.

Compared with older children with pancreatitis, infants and toddlers can have significantly fewer signs and symptoms of abdominal pain, epigastric tenderness, or nausea.[11] Epigastric or midabdominal tenderness with guarding often is found on physical examination. Bowel sounds disappear as ileus develops. An abdominal mass can develop as a manifestation of a pancreatic pseudocyst. Rigid abdomen and periumbilical discoloration suggesting intra-abdominal hemorrhage are rare and represent signs of severe pancreatitis.[4,11] In pediatrics, most cases of pancreatitis are mild and have a spontaneous resolution.

Diagnosis

The diagnosis of acute pancreatitis relies on clinical symptoms and should be considered for any child manifesting upper or diffuse abdominal pain or shock.[4,8] No single definitive diagnostic test is available. A comprehensive history highlighting potential causes should be elicited.

The diagnosis usually is confirmed by the finding of elevated serum pancreatic enzymes. An elevated total serum amylase level has a sensitivity of 95% to 100% if tested within the first 24 hours after onset of symptoms. The serum amylase level tends to fall within 48 hours of onset. However, specificity and positive predictive value of an elevated serum amylase level are low.[12] Serum lipase is more specific for pancreatic inflammation and is more sensitive in later stages of the disease.[4,12] When used together, elevated serum amylase and serum lipase values yield a specificity of 90% to 95%.[13] Persistence of elevated amylase levels beyond 48 hours after the onset of symptoms raises the possibility of a pancreatic pseudocyst.

Abdominal ultrasonography is the best initial imaging study when pancreatitis is suspected. Ultrasonography can show swelling of the pancreas, but most importantly, it helps to exclude surgically treatable causes of pancreatitis such as gallstones and extrapancreatic masses. A plain film of the abdomen is useful to exclude other causes of abdominal pain. Pancreatic calcification can occur in patients with acute recurrent or chronic pancreatitis.

Intravenous contrast-enhanced abdominal computed tomography is the most useful modality for the diagnosis of significant abdominal trauma, necrotizing pancreatitis, and pseudocyst,[14] and it should be performed in all cases of severe pancreatitis to guide therapy. Endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP) can be useful in selected cases, particularly when therapeutic intervention is needed.

Differential Diagnosis

The differential diagnosis of acute pancreatitis varies with the severity of the pancreatitis attack. In its mild forms (i.e., most common presentation in children), pancreatitis can mimic acute gastroenteritis. Vomiting often is the principal symptom of very young children.[11] Mild acute pancreatitis also can occur during acute viral gastroenteritis. Biliary tract disease (e.g., cholelithiasis, choledocholithiasis, choledochal cyst), peptic ulcer disease (i.e., penetrating or perforated peptic ulcer), intestinal obstruction, and factitious pancreatitis should be excluded. Renal failure and diabetic ketoacidosis can be responsible for falsely elevated serum amylase levels and should be excluded.

Infectious Causes

Infectious agents are responsible for a few cases of acute pancreatitis. Although many infectious agents have been implicated (Box 63.1), evidence supporting their causality usually is indirect and based on results of serologic assays or epidemiologic association. It is likely that undiagnosed but self-limited viral illnesses account for many idiopathic cases of acute pancreatitis.

Box 63.1

Common Infectious Causes of Acute Pancreatitis in Children

Viruses

Mumps virus

Coxsackie B viruses

Hepatitis viruses: A, B, C, and E

Herpesviruses: cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus (HSV), varicella-zoster virus (VZV)

Human immunodeficiency virus (HIV)

Influenza A virus

Rotavirus

Parasites

Ascaris lumbricoides

Clonorchis sinensis

Cryptosporidium parvum

Echinococcus granulosus

Bacteria

Mycoplasma pneumoniae

Salmonella spp.

Leptospira spp.

The most recognized viral cause of pancreatitis is the mumps virus.[5] Mild pancreatitis occurs in up to 15% of patients with mumps. Parotitis usually precedes abdominal pain and vomiting by 4 to 5 days; pancreatitis rarely occurs alone. Enteroviruses, especially group B coxsackieviruses, also are implicated and have been studied in the context of diabetes.[15,16] Human herpesvirus infections, including cytomegalovirus, Epstein-Barr virus (EBV), herpes simplex virus, and varicella-zoster virus, have been rarely reported to induce pancreatitis.[17–19]

Hepatitis B viral antigens have been demonstrated in the acinar cells of the pancreas and are associated with inflammation.[20] Acute pancreatitis associated with nonfulminant hepatitis A and E is being recognized more frequently and is more common in boys and young men during the second and third weeks of illness. Hepatitis E appears to be associated with more severe pancreatitis.[21]

Pancreatitis in patients with human immunodeficiency virus (HIV) infection can be a direct effect of the disease,[22] but it often results from an opportunistic copathogen or to antiretroviral therapy.[23,24] Pancreatitis unrelated to antiretroviral therapy is an indicator of poor prognosis in HIV-infected children.

Ascaris lumbricoides, *Clonorchis sinensis*, and *Cryptosporidium parvum* cause pancreatitis by physical obstruction of the pancreatic duct by migration from the intestinal lumen into the biliary or pancreatic ducts, or both.[25,26] Bacteria are unusual causes of acute pancreatitis, but enteric organisms complicate necrotizing pancreatitis and worsen the prognosis. Fungal pathogens have not been reported as causes of pancreatitis, but they can infect a necrotic pancreas.

Noninfectious Causes

The leading noninfectious causes of pancreatitis in all ages are shown in Box 63.2. Traumatic pancreatitis associated with blunt abdominal trauma from motor vehicle accidents, sports injuries, or nonaccidental trauma account for up to 40% of pediatric cases.[2]

Systemic inflammatory disorders such as Kawasaki disease, juvenile idiopathic arthritis, systemic lupus erythematosus, inflammatory bowel disease, and hemolytic uremic syndrome account for one third of cases.[2,3]

Box 63.2

Common Noninfectious Causes of Acute Pancreatitis in Children

Trauma

Motor vehicle accidents

Sports injuries

Child abuse

Anatomic Obstructions

Congenital duct anomalies

Annular pancreas

Tumor (blocking pancreatic duct)

Drugs

Corticosteroids

Valproic acid

Chemotherapeutics: L-asparaginase, 6-mercaptopurine, cyclophosphamide

Diuretics: thiazides, furosemide

Antiretrovirals: dideoxyinosine

Azathioprine

Inflammatory Diseases

Kawasaki syndrome

Juvenile idiopathic arthritis

Inflammatory bowel disease

Systemic lupus erythematosus

Henoch-Schönlein purpura

Stevens-Johnson syndrome

Major burns

Hereditary and Metabolic Disorders

Gene mutations: *PRSS1*, *SPINK1*, *CFTR* (cystic fibrosis)

Hyperlipidemia (types I, IV, and V)

Type 1 diabetes

Glycogen storage disease

Mitochondrial disorders

IDIOPATHIC CAUSES

Prescription medications and accidental ingestion of the drugs listed in Box 63.2 can be causal.[3,5,24,26–28] Valproic acid, L-asparaginase, 6-mercaptopurine, and prednisone are the leading drug causes of pancreatitis in children.[3,5] Corticosteroids may be the most commonly implicated drugs causing pancreatitis in children. Pancreatitis after bone marrow transplantation can occur during graft-versus-host disease,[29] possibly as a consequence of corticosteroid treatment. For many other conditions, it is unclear whether corticosteroid therapy or the underlying inflammatory condition is causative.

In infants and toddlers, acute pancreatitis most often is associated with multisystem infection or disease, especially hemolytic uremic syndrome.[6] Acute pancreatitis after liver transplantation likely is caused by a combination of trauma, inflammation, and drugs.[30]

Hereditary pancreatitis, which manifests first in infancy or adolescence, is increasingly recognized.[31] Individuals with mutations in the protease serine 1 *(PRSS1)* gene (which encodes cationic trypsinogen),[32,33] the serine peptidase inhibitor Kazal type 1 *(SPINK1)* gene (which encodes a trypsin inhibitor),[32,34,35] or the cystic fibrosis transmembrane conductance regulator *(CFTR)* gene (which encodes the CFTR protein)[32,36] are at increased risk for acute or chronic pancreatitis.

Treatment

Therapy for acute pancreatitis primarily is supportive and is dictated by the severity of the multiorgan dysfunction that can complicate pancreatitis. Withdrawing an offending agent or treatment of an underlying systemic inflammatory disorder is a critical component of care. Nasogastric suction is used only for symptomatic relief in patients with ileus or severe vomiting. Early aggressive fluid resuscitation has been associated with a reduction in the inflammatory response syndrome and multiple organ failure.

Early enteral feeding (within 24–72 hours) is superior to the traditional approach of bowel rest. Enteral nutrition is thought to maintain the integrity of the intestinal mucosa, reducing the potential for translocation of enteric flora.[2] Bowel rest is indicated only if pain continues or a complication arises.

Meperidine hydrochloride is usually selected for pain control because it has a less constrictive effect on the sphincter of Oddi than does morphine. The administration of broad-spectrum antibiotics to patients with severe, necrotizing pancreatitis (rare in pediatric cases) results in improved mortality and morbidity rates.[37]

Clinical Course

Most children recover completely from acute pancreatitis. Mortality rates for children are not defined clearly but most often reflect the severity of the underlying cause. Death or complications are more likely in those with pancreatic or peripancreatic hemorrhage or necrosis, which presages a complicated acute course that can include hemodynamic instability, serious biochemical abnormalities, and multiorgan failure. Local complications include the formation of an abscess or pseudocyst. Development of a secondary fever indicates a possible complication; abdominal ultrasonography or computed tomography is indicated. Surgical consultation should be sought for complicated cases.

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Cholecystitis and Cholangitis

Beverly L. Connelly

Cholecystitis and cholangitis refer to inflammation of the gallbladder and extrahepatic bile ducts, respectively. Both occur much more commonly in adults than in children but are encountered often enough to be important to clinicians caring for children with acute abdominal illnesses.

Pathogenesis

Cholecystitis is inflammation of the gallbladder, and 90% to 95% of cases are attributed to obstruction of the neck of the gallbladder or the cystic duct by biliary stones (i.e., cholelithiasis).[1] Gallstones frequently are found in asymptomatic individuals; only an estimated 1% to 3% of people with gallstones develop acute cholecystitis.[2] Anatomic abnormalities, stricture of the bile duct after surgery, and stenosis associated with malignancy also can cause obstruction.

The degree and duration of obstruction influence the type of symptoms. If obstruction is partial and brief, symptoms of biliary colic can occur. If the obstruction is complete and prolonged, acute cholecystitis results. The increased intraluminal pressure in combination with bile supersaturated with cholesterol triggers an acute inflammatory response. Secondary bacterial infection can occur in 7 to 10 days if the obstruction is not relieved.[1] Although stones are the most common causes of obstruction, any anatomic or physiologic obstruction can begin the cycle.

Biliary stones are classified as pigment (bilirubin) stones or cholesterol stones. Pigment stones are black or brown. Black pigment stones are not thought to be associated with infection but are associated with hemoglobinopathies (e.g., spherocytosis, thalassemia, sickle cell anemia), advancing age, and cirrhosis.[2] Brown pigment stones are bacteria laden; bacterial β-glucuronidase deconjugates bile acids that then precipitate, forming a stone. Brown stones also can form with nonbacterial pathogens. Cholesterol stones are the most common type of stones and generally are thought not to be infectious in origin. Cholesterol stones form when bile is supersaturated with cholesterol excreted by the liver that forms a precipitate.[2]

Total parenteral nutrition and use of diuretics are predisposing conditions for the formation of biliary sludge and stones in children. Treatment with third-generation cephalosporins can result in biliary sludge (i.e., pseudolithiasis) in children, but it does not lead to cholecystitis.[3]

Acute cholangitis is a systemic process that results from obstruction of bile flow in combination with bacterial growth in the bile. Biliary infection alone is insufficient; progressive obstruction leads to increased intraductal pressure with cholangiovenous and cholangiolymphatic reflux. Bacteria translocate into the bloodstream, causing septicemia.[4]

The incidence of acute cholangitis as a consequence of sclerosing cholangitis and endoscopic manipulation of the biliary tract is increasing.[1] Portoenterostomy (i.e., Kasai procedure), the classic surgical procedure performed for biliary atresia, predisposes children to recurrent cholangitis. Use of the intestinal conduit to restore bile flow from the liver to the small intestine can allow the ascent of intestinal flora and cholangitis.[5,6] Most episodes of cholangitis after the Kasai procedure occur during the first 3 postoperative months; only a few children experience cholangitis after 1 year of age.[7] Because of this well-recognized risk, patients usually are given antibiotic prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) for 6 to 12 months. Similarly, cholangitis occurs, although less frequently, in children who have undergone orthotopic liver transplantation using a Roux-en-Y procedure for a biliary conduit.

Other rare causes of impaired biliary drainage predisposing to cholangitis include choledochal cyst, Caroli disease, primary sclerosing cholangitis, biliary stricture after abdominal trauma, prior duct surgery, cystic fibrosis, and tumors of the extrahepatic ducts (e.g., rhabdomyosarcoma, neuroblastoma).[1] Immunoglobulin G subclass 4–related sclerosing cholangitis is associated with autoimmune pancreatitis and involvement of many other organs.[8]

In areas of high endemicity, biliary obstruction can result from parasites migrating into the biliary tract. Most commonly, the round worm *Ascaris lumbricoides* can migrate into the bile ducts as a part of an intestinal infestation. The larvae of the liver fluke *Clonorchis sinensis*, acquired from infested, undercooked freshwater fish, migrate from the duodenum to the common bile duct and upward, where they develop into adult flukes that can inhabit the biliary tract for several years.[9] Another liver fluke, *Fasciola hepatica,* which is acquired by ingesting cercarial-contaminated aquatic plants, gains access to the biliary tract by the peritoneum and, through the liver capsule. The metacercaria lodge in the biliary tract and develop into mature adult flukes.[9]

Ductal obstruction from any cause results in increased intraductal pressure or distention of the gallbladder, or both. Superinfection of the stagnant bile with organisms of gut flora follows, along with edema and congestion, further compromising the blood supply and lymphatic drainage. Tissue necrosis follows, favoring further bacterial proliferation. In cholangitis, the risk of bacteremia and septicemia is high, and mortality is 2.7% to 10%.[1]

Although obstruction to biliary drainage remains the most frequent cause for cholecystis, cholecystitis occasionally occurs without obstruction. This condition, known as acalculous cholecystitis, occurs in critically ill patients after trauma, burns, and major operations.[10] Acalculous cholecystitis also has been reported in children with infections caused by *Mycoplasma pneumoniae, Salmonella enterica* serovar Typhi and nontyphoidal species, *Shigella* species, and *Giardia lamblia*.[11] Acute acalculous distention (i.e., hydrops) of the gallbladder can occur acutely in infants and children and is associated with a variety of infections and inflammatory conditions (e.g., Kawasaki disease, streptococcal pharyngitis, septicemia, toxic shock syndromes, Henoch-Schönlein purpura), and during prolonged fasting and total parenteral nutrition. A markedly distended, thick-walled gallbladder without distention containing echo-free fluid can be seen by ultrasonography. The course usually is self-resolving.

Etiology

Normally, bile is sterile, but it can become colonized with intestinal bacteria that gain access from the duodenum through the sphincter of Oddi. In the absence of obstruction, colonization rarely progresses to cholangitis.[4]

Commonly isolated organisms from biliary tract infections include gram-negative enteric bacilli such as *Escherichia coli* (31% to 44% of cases), *Klebsiella* spp. (9% to 20%), *Pseudomonas* spp. (0.5% to 9%), and *Enterobacter* spp. (5% to 9%). Identified gram-positive organisms are *Enterococcus* spp. (3% to 34%) and *Streptococcus* spp. (2% to 10%). Anaerobes are *Bacteroides* spp. and *Clostridia* spp.) (4% to 20%).[12] Anaerobic infections are more common in patients who have had biliary tract surgery, biliary-intestinal anastomosis, or chronic biliary tract infections. *Candida* species predominantly are associated with intestinal disease (e.g., necrotizing enterocolitis), surgery, prolonged antibiotic therapy, total parenteral nutrition, proton pump inhibitor therapy, and immune suppression.

Positive blood cultures are reported for 21% to 70% of adults with acute cholangitis and approximately 50% of children.[13] Polymicrobial infections are common (26.9%), and in one third of cases, different organisms may be isolated from bile than are found in the bloodstream.[14] Discordance is particularly evident for anaerobes in bile that are uncommonly isolated from blood. Concordance usually is reported when liver and bile are sampled in patients with acute cholangitis.[13]

Clinical and Laboratory Features

The clinical triad of fever, right upper quadrant pain, and jaundice is a classic alert for biliary tract disease. Clinical manifestations of cholecystitis typically are milder than those of cholangitis, but there can be substantial overlap. Cholecystitis usually is heralded by mild epigastric pain with nausea and vomiting, followed by the pain shifting to the right upper quadrant, sometimes with radiation to the right shoulder or scapula. Pain usually is aggravated by movement or deep breathing. The gallbladder is palpable in less than 50% of cases.

Moderate temperature elevation and mild icterus can be evident, but high spiking fevers, chills, prominent jaundice, circulatory collapse, and other findings of gram-negative bacillary septicemia suggest cholangitis. There also can be signs of localized peritonitis, including guarding, rigidity, and rebound tenderness.[4]

The white blood cell count is normal or slightly elevated in cholecystitis and typically is substantially increased with a shift to immature forms with cholangitis. In patients with cholecystitis, serum levels of bilirubin and aspartate aminotransferase (AST) are elevated in about 50%, and the alkaline phosphatase level is elevated in about 25%. In contrast, most patients with cholangitis have elevated bilirubin, AST, and alkaline phosphatase levels. The degree of abnormality is greater in those with cholangitis than in those with cholecystitis. Serum amylase concentrations can be elevated in both disorders. Disseminated intravascular coagulopathy can occur with cholangitis.

Diagnosis

The differential diagnosis of acute cholecystitis and cholangitis includes appendicitis, pancreatitis, perforating ulcer, acute pyelonephritis, biliary colic without cholecystitis, hepatitis, perihepatitis (i.e., Fitz-Hugh–Curtis syndrome), and right lower lobe pneumonia. A definitive diagnosis is aided by imaging studies, the main goal of which is the detection of biliary obstruction and the likely cause.[4] Modalities commonly used include transabdominal ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasound (EUS), endoscopic retrograde cholangiopancreatography (ERCP), and percutaneous transhepatic cholangiography (PTC), depending on availability, physician expertise, and preference.[4] Since the advent of these testing modalities, use of cholecystography has declined in the diagnostic evaluation of suspected cholecystitis or cholangitis.

For patients with mild symptoms, US is the usual noninvasive way to establish the diagnosis and guide further management. US is expected to demonstrate thickening and edema of the gallbladder wall and surrounding tissue in cholecystitis and dilation of bile ducts in cholangitis. US also can uncover the underlying cause of biliary tract disease by demonstrating stones, a choledochal cyst, or other obstruction to bile flow. MRCP is emerging as another nonradiation, noninvasive diagnostic modality for evaluating the biliary tract. PCT and ERCP are useful diagnostic tools that also can relieve obstruction and provide biliary drainage.[4]

A bile culture should be obtained at the time of any intervention. Positive cultures of bile specimens are reported for 59% to 93% of patients with acute cholangitis, and positive cultures of bile or gallbladder specimens are reported for 29% to 54% of patients with acute cholecystitis. Although no data confirm the value of routine blood cultures for patients with acute biliary disease, they are recommended for all severely ill patients.[12] Recovery of organisms from a liver biopsy provides the most definitive proof of cholangitis. However, a negative culture result for the liver specimen does not exclude the diagnosis of cholangitis in the seriously ill patient with confirmed bacteremia and other compelling features of the disease.

Management

The initial treatment of cholecystitis and cholangitis in children consists of supportive therapy and use of broad-spectrum antibiotic therapy effective against enteric gram-negative bacilli and anaerobic bacteria if there is a biliary-enteric anastomosis.[12] Drainage of the obstructed biliary tract is the mainstay of treatment for patients with cholangitis who are severely ill. Percutaneous or endoscopic drainage has replaced surgical intervention as the method of choice for emergent re-establishment of bile flow.[15]

Antibiotics are complementary to biliary drainage and should be initiated as soon as the diagnosis of biliary infection is suspected. Prompt antimicrobial treatment of the mildly or moderately ill patient may circumvent the need for an invasive procedure. Although guidelines for antimicrobial therapy in acute biliary infections have been published,[12,16] it is important to consider the local prevalence of extended-spectrum β-lactamase (ESBL)–producing *E. coli* and *Klebsiella* spp.

Ampicillin-sulbactam in combination with an aminoglycoside; cefazolin, cefuroxime, or ceftriaxone with or without metronidazole; and ciprofloxacin or levofloxacin with or without metronidazole are advocated regimens for less severe community-onset disease. An ampicillin- or piperacillin-containing regimen offers the advantage of enterococcal coverage. For more severe disease or in patients at risk for multidrug-resistant pathogens, treatment is provided by piperacillin-tazobactam or meropenem alone or by ceftriaxone, ceftazidime, or cefepime with or without metronidazole in combination with vancomycin for enterococcal coverage. These agents and combinations are expected to achieve excellent biliary levels of drug.

Coverage for anaerobic bacteria is essential in patients with biliary-enteric anastomoses. Therapy should be tailored further for isolated organisms and is continued for 7 to 10 days. Antibiotic prophylaxis with piperacillin, cefazolin, cefuroxime, ceftriaxone, or ciprofloxacin before therapeutic ERCP can reduce the risk of bacteremia and cholangitis.[17]

Medical management alone is expected to resolve the signs and symptoms in most cases of cholecystitis and cholangitis. Transition to oral agents (e.g., amoxicillin-clavulanate, cephalexin with or without metronidazole, ciprofloxacin or levofloxacin with or without metronidazole)[12] can be considered when the patient is afebrile, oral feeding is tolerated, and pain is adequately controlled.

Drainage is indicated for patients who fail to respond to medical management and in whom obstruction is demonstrated by ultrasound. Consultation with a gastroenterologist, interventional radiologist, or surgeon is recommended when drainage is indicated. Local expertise in endoscopic cholangiography to establish biliary drainage should be sought. Nonemergent laparoscopic cholecystectomy can be pursued after the active inflammatory process has subsided.[18] Cholecystectomy with exploration and drainage of the common bile duct or percutaneous transhepatic drainage now are performed infrequently.

Complications

Perforation occurs in up to 15% of cases of cholecystitis; sometimes peritonitis results, but more often, the perforation is spontaneously localized by surrounding omentum and serosa of contiguous viscera. When localized, perforation results in persistent fever, a palpable mass, and occasionally, a friction rub over the liver.

Pancreatitis and cholangitis can complicate cholecystitis. Cholangitis is a medical-surgical emergency and should be managed aggressively. Complications include perforation, macroscopic hepatic abscesses, pancreatitis, and septicemia.

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Peritonitis

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Peritonitis is an inflammatory process involving the peritoneum, a specialized lining of the abdominal cavity that lubricates the abdominal organs and clears the cavity of infectious particles and other debris.

Infectious peritonitis classically has been described as primary or secondary, depending on the continuity of the gastrointestinal tract. Primary (i.e., spontaneous) bacterial peritonitis is an uncommon infection that develops in the setting of an intact gastrointestinal tract without an apparent source of inoculation. Secondary bacterial peritonitis is more common and arises from the inoculation with bacteria and other inflammatory debris after intestinal perforation or a postoperative anastomotic leak. Catheter-related infections comprise a third category, in which infections arise after contamination of the indwelling foreign body (e.g., peritoneal dialysis catheters, ventriculoperitoneal shunts).

Epidemiology

The overall incidence of infectious peritonitis among children is difficult to estimate due to the heterogeneity in diagnostic criteria and multiple underlying disease processes associated with the infection. Spontaneous bacterial peritonitis plus catheter-related peritonitis account for approximately 10% of cases of peritonitis in children.[1,2] The decreasing incidence of catheter-related peritonitis has resulted from improvements in catheter and connecting hardware technology used for continuous ambulatory peritoneal dialysis (CAPD) and the reduced frequency of touch contamination.[3–5]

The pediatric incidence of spontaneous bacterial peritonitis peaks between the ages of 5 and 9 years and affects boys and girls equally. Immunocompromised children are at greater risk for primary and catheter-related peritonitis compared with healthy children. Children with ascites due to portal hypertension are at particularly high risk for spontaneous peritonitis, with incidence rates exceeding 20% in some series.[6]

Spontaneous bacterial peritonitis has been associated with nephrotic syndrome. The reported incidence of peritonitis has been as high as 16% among children admitted with serious infectious complications attributable to nephrotic syndrome.[7] The first episode typically occurs during the first 2 years after diagnosis, and the overall incidence may be as high as 5%.[8–10] Risk factors for spontaneous bacterial peritonitis in patients with nephrotic syndrome include severe ascites, more advanced forms of the disease, and elevated serum cholesterol levels. Severe ascites, hypoalbuminemia, gastrointestinal bleeding, and recent endoscopic examinations have been identified as risk factors for children with cirrhosis.[7,11]

Catheter-related peritonitis remains a major concern for children receiving CAPD. Data from the US Renal Data System indicate that infectious complications remain the most frequent cause for hospitalization among children receiving CAPD, and up to two thirds of children receiving peritoneal dialysis experience at least one episode of peritonitis.[12] CAPD-associated peritonitis is especially common in children younger than 6 years of age, with the highest incidence reported for children younger than 1 year of age.[13] This high rate of infection may reflect the proximity of the catheter exit site to a gastrostomy tube and diaper or the frequent use of single-cuffed catheters in children and their shorter tunnel lengths.

The overall incidence of CAPD-associated peritonitis in the United States has decreased over the past several decades from one episode per 3 to 6 patient-months of dialysis to one episode per 14 to 24 patient-months.[13–15] Similar decreases in CAPD-associated peritonitis have been reported in Europe, and the lowest incidence of peritonitis has been observed among Japanese children.[16] These results have been attributed to an intensive CAPD training program and the rigorous attention to hygiene practiced in the Japanese culture.

Pathophysiology

Peritonitis can be caused by a variety of infectious and noninfectious insults that produce an inflammatory response involving the visceral and parietal peritoneum. The initial inflammatory response of the peritoneum to bacterial infection is characterized by vasodilation, tissue edema, transudation of fluid, and the influx of inflammatory macrophages and leukocytes. Lymphatic channels located in the undersurface of the diaphragm facilitate the clearance of bacteria, endotoxin, and other infectious particles from the peritoneal cavity. This drainage system provides an important adjunctive defense mechanism to the local cellular immune response. Impairment of this process by fibrin and inflammatory debris can result in accumulation of peritoneal fluid and dilution of immunoglobulins and opsonins. This may be particularly relevant to the pathophysiology of peritonitis in children with pre-existing ascites, in which serum and peritoneal concentrations of these immunoreactive molecules are lower than that seen in healthy children.[17]

Portal hypertension in patients with cirrhosis increases susceptibility to bacteremia and spontaneous peritonitis, likely due to the translocation of bacteria from the intestine and immune deficiencies related to neutropenia, impaired complement fixation, and decreased Kupffer cell function.[6,18] In patients undergoing CAPD, selective immunoglobulin (IgG) subgroup deficiencies may be an additional factor contributing to more severe peritonitis.[19]

Etiology

Primary Bacterial Peritonitis

Hematogenous seeding is the predominant source of primary bacterial peritonitis. Other sources of infection include lymphatic seeding, retrograde inoculation from a genitourinary source, and translocation of intestinal flora (Table 65.1). The bacteriologic profile of peritoneal infections largely depends on the mechanism of inoculation and underlying comorbidities (Table 65.2).

TABLE 65.1

Proposed Mechanisms and Associated Conditions for Peritonitis in Children

Primary Bacterial Peritonitis	Catheter-Associated Peritonitis	Secondary Bacterial Peritonitis
Hematogenous seeding (sepsis) Direct extension of localized process • Ascending urinary tract infection • Genital or pelvic infection • Mesenteric adenitis (TB) • Omphalitis Lymphogenous seeding Translocation of intestinal flora	Poor sterile technique during dialysis Migration of skin flora along catheter Direct extension of local infection • Exit-site infection (with CAPD) • CNS infection (with VP shunts) Hematogenous seeding of dialysate/CSF	Neonatal period • Necrotizing enterocolitis • Spontaneous gastric perforation • Feeding tube perforation (iatrogenic) • Intestinal volvulus • Hirschsprung disease Postneonatal period and childhood • Acute appendicitis • Intestinal volvulus • Intussusception • Incarcerated hernia

CAPD, continuous abdominal peritoneal dialysis; CNS, central nervous system; CSF, cerebrospinal fluid; TB, tuberculosis; VP, ventriculoperitoneal.

TABLE 65.2

Organisms Commonly Associated With Peritonitis in Children[a]

Primary Bacterial Peritonitis	Catheter-Associated Peritonitis	Secondary Bacterial Peritonitis
Previously healthy children • *Streptococcus pneumoniae* • Group A *Streptococcus* • *Staphylococcus aureus* • Gram-negative bacilli **Neonatal idiopathic primary peritonitis** • Group B *Streptococcus* • *Streptococcus pneumoniae* • *Staphylococcus aureus* • Enteric gram-negative bacilli **Nephrotic syndrome** • Coagulase-negative staphylococci • *Streptococcus* spp. • *Staphylococcus aureus* • Enteric gram-negative bacilli **Cirrhosis**	**CAPD associated** • Coagulase-negative staphylococci • *Staphylococcus aureus* • *Pseudomonas* spp. • Other enteric gram-negative bacilli • Fungi **VP shunt associated** • Coagulase-negative staphylococci • *Staphylococcus aureus* • *Escherichia coli* (late) • Other gram-negative bacilli (late)	**Proximal GI perforations** • Facultative organisms • *Escherichia coli* • *Klebsiella* spp. • *Enterobacter* spp. • *Pseudomonas* spp. • Gram-positive cocci **Anaerobic organisms** • *Bacteroides* spp. • *Clostridium* spp. • *Peptostreptococcus* spp. **Colonic perforations** • *Bacteroides fragilis* • Gram-negative bacilli (*Escherichia coli*) • Other anaerobic organisms • *Enterobacter* spp. (NEC)

• *Streptococcus pneumoniae*[b] • *Escherichia coli* • *Klebsiella* spp.	

[a] Organisms are listed in the order of relative incidence by category, although there may be substantial variation in microbiologic data over time and between different published series.

[b] The use of pneumococcal vaccines have decreased the rate of streptococcal peritonitis, although they are still more prevalent than gram-negative infections in most reported series.

CAPD, continuous abdominal peritoneal dialysis; GI, gastrointestinal; NEC, necrotizing enterocolitis; VPS, ventriculoperitoneal.

Primary peritoneal infections in healthy children often are monomicrobial, and *Streptococcus pneumoniae* is the most common cause.[7,2,21] In the past few decades, the rate of peritoneal infections caused by gram-negative organisms (especially *Escherichia coli*) has been increasing. This trend may reflect a decrease pneumococcal peritonitis related to universal use of pneumococcal conjugate vaccines.[20,22] Gram-positive organisms, particularly group B *Streptococcus,* predominate as the cause of primary peritoneal infections in neonates. These infections, also known as *neonatal idiopathic primary peritonitis*, are likely caused by hematogenous seeding in most cases, although infection also has been associated with omphalitis.[23] Group A *Streptococcus* can cause spontaneous peritonitis in otherwise healthy children.[24]

Mycobacterium tuberculosis is a rare cause of peritonitis but should be considered if the patient has been exposed to a known infected individual. Abdominal tuberculosis accounts for almost 12% of extrapulmonary disease and approximately 1% to 3% of all tuberculosis-associated infections.[25,26] The widespread practice of dairy pasteurization in the United States and other developed countries has effectively eliminated infection caused by *Mycobacterium bovis*.[27]

Peritoneal infection with *S. pneumoniae, Haemophilus influenzae, Neisseria gonorrhoeae,* and other encapsulated organisms should be considered in children with anatomic and functional asplenia. Gonococcal peritonitis can occur from ascending genital or pelvic infection. Infection can lead to inflammation of the liver capsule, resulting in gonococcal perihepatitis (i.e., Fitz-Hugh–Curtis syndrome).

Catheter-Associated Peritonitis

Cultures of peritoneal fluid are positive for approximately 75% of children with clinically apparent peritonitis occurring during peritoneal dialysis.[5] Between one half and two thirds of all episodes are caused by gram-positive organisms.[28,29] Coagulase-negative staphylococci (CoNS) and *Staphylococcus aureus* each account for about 15% of US cases.

The relative importance of gram-negative bacteria is increasing due to improved catheter connection technology, exit-site care, and antibiotic prophylaxis that reduces gram-positive bacterial contamination.[5,30] Gram-negative infections usually are associated with touch contamination and can be caused by a variety of organisms, including *Pseudomonas, Enterobacter, E. coli,* and *Klebsiella*.[28,31] In the United States, the most frequently isolated gram-negative organism is *Pseudomonas.*[32] *Pseudomonas* species are isolated from approximately 10% to 20% of catheter exit-site infections, suggesting a mechanism for bacterial migration along the catheter tunnel. Although gram-negative peritonitis in patients receiving CAPD can be caused by a secondary source (e.g., ruptured appendicitis), isolation of a single organism strongly suggests a catheter-associated cause.

Fungal peritonitis is a rare but serious complication of CAPD and is associated with substantial morbidity and mortality.[33–35] Although fungal pathogens account for only 3% to 6% of CAPD-associated pediatric cases, the incidence appears to be increasing.[34] Many patients with fungal peritonitis have had catheter-related infections treated with antibiotics, suggesting that these infections might be opportunistic. Compared with bacterial peritonitis, fungal peritonitis can be particularly difficult to treat, resulting in a greater likelihood of catheter loss and the need to convert to hemodialysis.[33,35] *Candida* species are the most commonly isolated fungus.[13]

Infectious peritonitis is a rare complication in children with indwelling ventriculoperitoneal shunts, affecting less than 1% of all patients.[36] Peritonitis can arise from contamination of intra-abdominal cerebrospinal fluid (CSF) by hematogenous seeding or bacterial translocation or from contamination of the peritoneal cavity by an infection originating in the central nervous system. In a patient with a ventriculoperitoneal shunt and abdominal pain, bacterial peritonitis must be differentiated from the more common CSF-containing pseudocyst. Ventriculoperitoneal shunt–associated peritoneal infections in the first several months after shunt placement usually are caused by gram-positive cocci (i.e., CoNS and *S. aureus*), whereas late infections are more likely to be caused by gram-negative organisms.[37,38] Secondary peritonitis after spontaneous erosion of the ventriculoperitoneal catheter into the colon has been reported.[39]

Secondary Bacterial Peritonitis

Secondary peritonitis can arise from any condition that results in the loss of gastrointestinal tract continuity (see Table 65.1). In the neonatal period, secondary peritonitis most often results from conditions that lead to intestinal ischemia and perforation, such as necrotizing enterocolitis, gastric perforation, meconium ileus, intestinal atresia, and Hirschsprung disease.[40–42] Acute appendicitis is the most common condition resulting in secondary peritonitis in older children. Intra-abdominal typhoid infections are common causes in poor and developing countries.[43]

In contrast to primary and catheter-related peritonitis, secondary infections tend to be polymicrobial, and the bacteriology depends most on the location of perforation. Aerobic and facultative gram-negative enteric organisms, including *E. coli, Klebsiella, Pseudomonas* spp., and *Candida* spp., are frequently isolated after perforation of the proximal gastrointestinal tract.[44] The colon contains predominately anaerobic and facultative organisms. *Bacteroides* species are the most commonly isolated organisms after colonic perforations.[44] In neonates with distal intestinal perforations, facultative enteric gram-negative bacilli are more commonly isolated than anaerobes, although *Bacteroides* and clostridia often are present.[45] In a large review of neonates with necrotizing enterocolitis, *Enterobacter* was the most common organism isolated, with anaerobes isolated in only 6% of cases.[45]

Clinical Presentation

The clinical presentation of patients with peritonitis depends on many factors, including age, underlying cause of infection, associated comorbidities, and immunologic status. The clinical presentation of the neonate frequently is nonspecific due to a paucity of localizing signs. The neonate usually appears ill, with marked abdominal distention, hypothermia, emesis, and respiratory distress.[46] The abdominal wall can appear erythematous or edematous if peritoneal inflammation is severe. Fever is not a common sign of peritonitis in the neonate.[46]

The clinical presentation of older children with peritonitis can include abdominal pain and tenderness, distention, vomiting, hypoactive bowel sounds, and various degrees of systemic toxicity. Neutropenic children and those receiving high doses of corticosteroids can have relatively benign presentations. These children often are afebrile and have minimal abdominal tenderness, leading to a misdiagnosis of gastroenteritis or another less serious ailment.

Fever or abdominal pain in any child undergoing CAPD should alert the clinician to the possibility of catheter-associated peritonitis, especially in the context of cloudy dialysis effluent. However, other noninfectious conditions, such as chemical peritonitis, eosinophilic peritonitis, hemoperitoneum, chylous ascites, and malignancy, also are associated with a cloudy appearance of the peritoneal effluent.[29] The clinical presentation of patients with ventriculoperitoneal shunt–associated peritonitis can be subtle, with the only symptoms being mild abdominal pain and low-grade fever. The specific organism causing infection can affect the clinical presentation and course. Gram-negative peritonitis often causes intense abdominal pain and is associated with dramatic alterations in the transport capacity of the peritoneal membrane.[13,47]

Peritonitis associated with tuberculosis often is insidious in onset and characterized by weight loss, chronic weakness, fever, night sweats, and anorexia.[26] Approximately 40% of patients with tuberculous peritonitis have symptoms and signs of active pulmonary infection.[26]

Diagnosis

Laboratory Evaluation

Laboratory findings in a child with peritonitis usually are nonspecific, often suggesting a systemic inflammatory process rather than a specific diagnosis. Blood cultures are positive for approximately 50% of children with nephrotic syndrome.[20] Elevated C-reactive protein (CRP) may be helpful in the early diagnosis of peritonitis in children with cirrhosis, but the diagnostic utility of CRP in patients with nephrotic syndrome and other underlying conditions is not known.[48]

Analysis of peritoneal fluid aspirates should be performed and can aid in differentiating primary from secondary peritonitis. Stool, amylase, or bile in aspirates indicates intestinal perforation, whereas blood can be associated with both primary and secondary peritonitis. For children undergoing CAPD, cloudy effluent with a white blood cell (WBC) count greater than 100 cells/mm^3 and a neutrophil predominance is adequate for the diagnosis of peritonitis and an indication to begin antibiotics empirically.[5]

Imaging

The primary utility of imaging in patients with suspected peritonitis is to help determine the cause (i.e., primary vs. secondary causes) and the necessity of urgent laparotomy. Although plain radiography and ultrasound may provide useful information (e.g., free air), computed tomography (CT) is the preferred test for evaluation of the child with an acute abdomen.

The finding of complex ascites, with or without visualization of the appendix, strongly suggests perforated appendicitis in older children. In the case of primary or catheter-related peritonitis, typical imaging findings include ascites, high-attenuation characteristics of peritoneal fluid, and nodular irregularity of the peritoneal lining.[49,50] CT findings for patients with abdominal tuberculosis can include thickening of the intestinal wall, lymphadenopathy, splenomegaly, ascites, and focal mesenteric calcifications.[51]

Management

Primary Peritonitis

In a child with an anatomically normal peritoneal cavity who develops primary bacterial peritonitis, antibiotic treatment should be directed at the most likely organisms, which include gram-positive cocci and gram-negative bacilli in children with nephrotic syndrome or cirrhosis and ascites (see Table 65.2).[20–22] Empiric therapy with cefotaxime or another third-generation cephalosporin is recommended.[11] Antibiotic therapy is tailored based on culture results from blood and peritoneal aspirates. Removal of infected peritoneal fluid has not been shown to improve outcomes and therefore is not recommended. Therapy generally is given for 14 days.

Catheter-Associated Peritonitis

Empiric antibiotics should be initiated when the diagnosis of bacterial peritonitis is suspected (Fig. 65.1). The wide variation in organisms associated with peritonitis in children treated with CAPD warrants the use of broad-spectrum agents until culture results are available. The combined intraperitoneal administration of a third-generation cephalosporin such as ceftazidime (or an aminoglycoside) and a first-generation cephalosporin is recommended as initial therapy. When available, intraperitoneal cefepime is acceptable as monotherapy (Table 65.3).[5,13,52] In a systematic review of antibiotic treatment, intermittent- or continuous-administration regimens were equivalent, but failures of intermittently administered ceftazidime for gram-negative bacillary peritonitis were relatively frequent.[12,53,54]

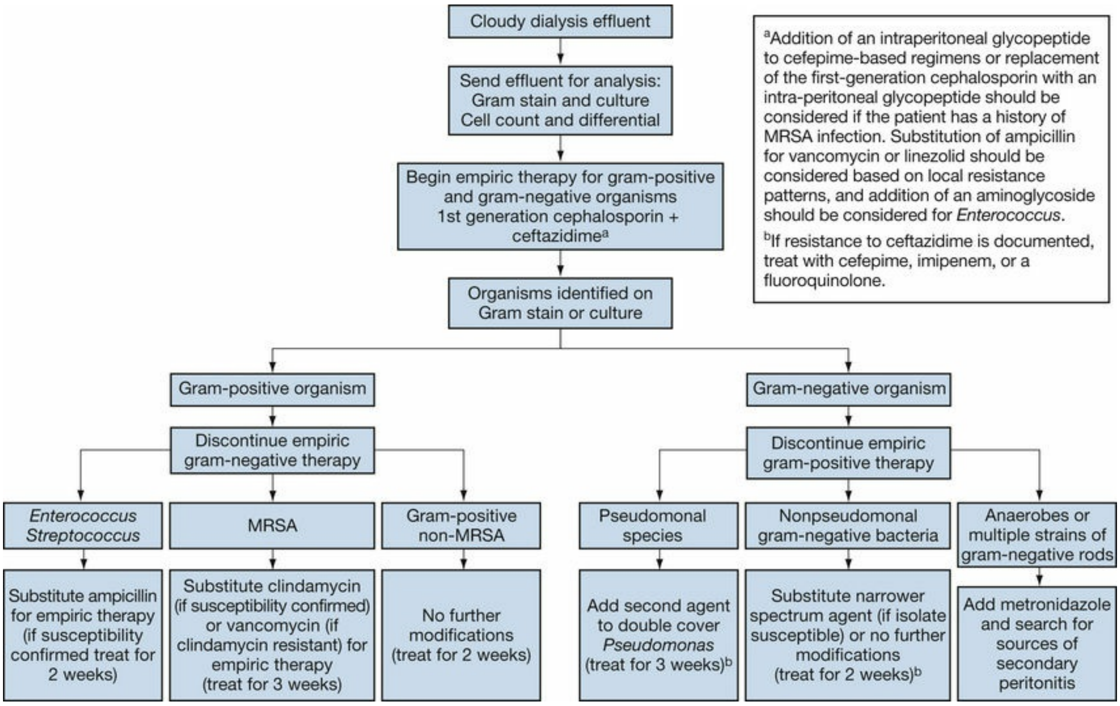
Cloudy dialysis effluent
Send effluent for analysis: Gram stain and culture Cell count and differential
Begin empiric therapy for gram-positive and gram-negative organisms 1st generation cephalosporin + ceftazidime[a]
Organisms identified on Gram stain or culture
Gram-positive organism
Discontinue empiric gram-negative therapy
Enterococcus Streptococcus
MRSA
Gram-positive non-MRSA
Substitute ampicillin for empiric therapy (if susceptibility confirmed treat for 2 weeks)
Substitute clindamycin (if susceptibility confirmed) or vancomycin (if clindamycin resistant) for empiric therapy (treat for 3 weeks)
No further modifications (treat for 2 weeks)
Gram-negative organism
Discontinue empiric gram-positive therapy
Pseudomonal species
Nonpseudomonal gram-negative bacteria
Anaerobes or multiple strains of gram-negative rods
Add second agent to double cover Pseudomonas (treat for 3 weeks)[b]
Substitute narrower spectrum agent (if isolate susceptible) or no further modifications (treat for 2 weeks)[b]
Add metronidazole and search for sources of secondary peritonitis
[a]Addition of an intraperitoneal glycopeptide to cefepime-based regimens or replacement of the first-generation cephalosporin with an intra-peritoneal glycopeptide should be considered if the patient has a history of MRSA infection. Substitution of ampicillin for vancomycin or linezolid should be considered based on local resistance patterns, and addition of an aminoglycoside should be considered for Enterococcus.
[b]If resistance to ceftazidime is documented, treat with cefepime, imipenem, or a fluoroquinolone.

FIGURE 65.1 Algorithm for the management of CAPD-associated peritonitis. CAPD, continuous ambulatory peritoneal dialysis; MRSA, methicillin-resistant *Staphylococcus aureus*.

TABLE 65.3

Recommended Intraperitoneal Antibiotic Dosing for Catheter-Associated Peritonitis

Antibiotic	Continuous Therapy[a]		Intermittent Therapy[b]
	Loading Dose[c]	Maintenance Dose	
Cefazolin	500 mg/L	125 mg/L	15 mg/kg every 24 hr
Ceftazidime	500 mg/L	125 mg/L	15 mg/kg every 24 hr
Vancomycin	1000 mg/L	25 mg/L	30 mg/kg every 5–7 days[d]
Gentamicin	8 mg/L	4 mg/L	—
Ampicillin	—	125 mg/L	—
Clindamycin	300 mg/L	150 mg/L	—
Metronidazole	—	—	35–50 mg/kg/day PO in 3 doses

[a] Concentration dosing assumes approximately 1100 mL/m^2 or usual patient specific fill volume. The administration route is intraperitoneal unless otherwise specified.

[b] Intermittent administration should occur over ≥6 hours using one bag per day for continuous ambulatory peritoneal dialysis patients or over a full fill-volume daytime dwell for automated peritoneal dialysis.

[c] Loading dose should be administered during a 3- to 6-hour dwell period.

[d] Redosing should occur when the blood level is <12 mg/L.

Data from Warady BA, Bakkaloglu S, Newland J, et al. Consensus guidelines for the prevention and treatment of catheter-related infections and peritonitis in pediatric patients receiving peritoneal dialysis: 2012 update. Perit Dial Int 2012;32(Suppl 2):S32–S86; Chadha V, Schaefer FS, Warady BA. Dialysis-associated peritonitis in children. Pediatr Nephrol 2010;25:425–440.

Substitution of an intraperitoneal glycopeptide for the first-generation cephalosporin should be considered in patients at high risk for resistant organisms (e.g., young age, history of *S. aureus* infection, recent catheter-related infection), when local resistance of *S. aureus* to methicillin-oxacillin exceeds 10%, or the patient has a history of MRSA infection.[5,13] Double coverage using agents with different mechanisms of action is recommended if *P. aeruginosa* is suspected or isolated.[5]

Antibiotics are adjusted when culture results are available (see Fig. 65.1). If initial culture results reveal only gram-positive organisms, the third-generation cephalosporin (e.g., ceftazidime) should be discontinued. A first-generation cephalosporin should be used for methicillin-susceptible *S. aureus*, and vancomycin should be used for resistant strains. Rifampin can be considered as an additional agent in the case of documented infection with *S. aureus* or CoNS if there is a delayed response to treatment.[5] Clindamycin can be used as an alternative to vancomycin, in the absence of inducible resistance. Ampicillin is sufficient to treat most strains of *Enterococcus* and *Streptococcus* spp. Antibiotic treatment for gram-positive organisms should continue for 2 to 3 weeks.[5]

If culture and susceptibility test results identify only gram-negative organisms susceptible to ceftazidime, gram-positive coverage should be discontinued. When *Pseudomonas* or *Stenotrophomonas* is isolated, addition of a second agent is recommended.[5,54] If cultures identify anaerobic organisms or multiple gram-negative bacilli, metronidazole should be added, and an intra-abdominal source for secondary peritonitis should be sought. Antibiotic treatment should be continued for a total of 2 to 3 weeks. If the patient improves on empiric therapy and the initial cultures remain negative, the initial combination of antibiotics usually is continued for a total of 2 weeks.

Fungal peritonitis historically has been treated with intravenous amphotericin B or a combination of an imidazole-triazole (e.g., fluconazole) and flucytosine.[55] Fluconazole is considered the preferred agent (when isolated *Candida* species has proven susceptibility) over amphotericin due to superior peritoneal penetration and bioavailability.[13,56] Early removal of the peritoneal dialysis catheter is recommended due to catheter colonization, unlikely success of eradication in situ, and delayed resolution of infection.[5,3,56] If clinical improvement is observed and the dialysis catheter is not removed, antifungal treatment should be continued for an additional 4 to 6 weeks. With removal of the catheter, treatment should be continued for at least 2 weeks after resolution of clinical symptoms.[5,57] Temporary hemodialysis should be used while therapy is completed and until a new peritoneal dialysis catheter can be placed.[5,33]

With appropriate antibiotic coverage, clinical improvement (i.e., reduction in fever, abdominal pain, and cloudiness of the peritoneal effluent) should be observed within 72 hours of initiating therapy, and the dialysate aspirate should reveal a decrease in WBCs by at least 50%. Other potential sources of infection should be sought if no clinical improvement is seen with empiric treatment. In patients with excessively cloudy effluent, use of low-dose heparin (500–1000 U/L) into the dialysate can be beneficial because it decreases fibrin occlusion of the catheter.[13]

Relapsing peritonitis is defined as the recurrence of peritonitis with the same organism within 4 weeks after cessation of treatment. Empiric treatment is the same as for the initial infection, with further modifications guided by culture results. Relapsing peritonitis occurs in up to 20% of gram-positive infections initially responsive to antibiotic therapy.[58] CoNS in a biofilm secreted on the catheter surface can survive antibacterial treatment. *P. aeruginosa* produces a biofilm and can form microabscesses within the catheter tunnel. Catheter removal is not recommended universally after the first recurrence, but removal should be considered strongly with the second recurrence and in all cases associated with *Pseudomonas* species.[5] Catheter removal also is suggested when the source of reinfection is thought to originate within the catheter tunnel.[5,59] Relapsing peritonitis should be treated with intraperitoneal antibiotics for a total of 3 weeks.[59]

The recommendations for the treatment of catheter-associated peritonitis are based largely on expert opinion and convention rather than randomized, controlled trials (RCTs). Wiggins and colleagues examined 36 RCTs (i.e., 2089 adults and children) to assess the evidence for current recommendations and concluded from the available data only that intraperitoneal administration of antibiotics was superior to intravenous dosing and that use of routine peritoneal lavage or urokinase was not supported.[53] Moreover, there is considerable regional variation in the antibiotic susceptibility of pathogens, and a plan of therapy always should take into account institutional patterns of antibiotic resistance.[5,60,61]

Secondary Peritonitis

Management of peritonitis related to a ventriculoperitoneal shunt entails immediate externalization of the distal shunt, Gram stain of peritoneal fluid aspirate, and interrogation of proximal CSF. Empiric therapy is based on these findings and the time since the shunt procedure. Subsequent management of the infection and site and timing of a replacement shunt are collaborative decisions made with the neurosurgeon. Gram-negative polymicrobial infection is managed with immediate externalization of the shunt and as secondary peritonitis.

Patients with secondary peritonitis require urgent laparotomy to identify and control the source of peritoneal contamination. All infectious debris should be removed and necrotic tissue debrided. An indwelling foreign body or device should be removed. Intraoperative peritoneal irrigation may decrease the bacterial burden and reduce postoperative infectious complications, although a randomized trial suggested no benefit for routine irrigation in children with perforated appendicitis.[62] Irrigation with antibiotic solutions does not confer benefit and should be avoided.[63]

Inadequate control of the source of infection at initial laparotomy can lead to recurrent peritonitis and is associated with increased mortality and morbidity rates. Early recognition of tertiary peritonitis and having a low threshold for prompt re-exploration are critical when the possibility of continued contamination is high. This includes situations in which there is massive contamination (e.g., fecal peritonitis) or when intestinal viability is questionable at the time of abdominal closure (e.g., necrotizing enterocolitis). Mandatory re-exploration 24 to 48 hours after the initial laparotomy (i.e., second-look operation) is practiced by many surgeons and has been shown to decrease morbidity and mortality rates compared with selective re-exploration.[63]

Empiric antibiotic treatment for secondary peritonitis should cover enteric pathogens, including anaerobes and gram-negative bacilli. Treatment of secondary peritonitis with ampicillin, gentamicin, and metronidazole has long been the gold standard but usually does not confer benefit over broad-spectrum monotherapy options (e.g., piperacillin-tazobactam). Clindamycin and second-generation cephalosporins were used in the past as first-line therapy, but they should no longer be used because of the increasing resistance of *Bacteroides fragilis*.

There are no consensus guidelines for the length of antibiotic treatment after the source of infection has been controlled with operative management. However, most favor continuing therapy for 7 to 10 days after complete resolution of clinical and laboratory indicators of infection.

Complications and Prognosis

Infectious peritonitis has many life-threatening complications, including mesenteric vein thrombosis, adult respiratory distress syndrome, progressive multiorgan failure, and death. Severe complications are associated more often with secondary peritonitis, although immunocompromised children have an increased risk regardless of the source of peritonitis. Other complications include prolonged ileus, surgical wound infection, intra-abdominal abscess, enteric fistula, and inflammatory adhesions. Inflammatory thickening of peritoneal surfaces and compartmentalization of the peritoneal cavity can limit the subsequent effectiveness of peritoneal dialysis and ventriculoperitoneal shunting.

The prognosis for peritonitis largely depends on the cause of infection, associated comorbidities, and the host response to the inflammatory process. Mortality rates for healthy children who develop perforated appendicitis are very low. Mortality rates associated with peritonitis from necrotizing enterocolitis in low-birth-weight neonates remain in excess of 30% to 50%.[64] Contemporary estimates of case-fatality rates for patients receiving chronic peritoneal dialysis are approximately 6%, with peritoneal infections accounting for more than 15% of the all-cause mortality rate and 69% of the infection-related mortality rate for this cohort. Fungal peritonitis carries a particularly poor prognosis, with some series reporting case-mortality rates exceeding 25% for children.[65]

Mortality rates for primary peritonitis in children can approach 10%. They vary by cause and associated comorbidities, with an approximate rate of 9% for children with nephrotic syndrome.[66] Spontaneous peritonitis in a child with cirrhosis and portal hypertension carries a much worse prognosis, with 1-month mortality rates exceeding 30% to 40%.[67] The overall survival rate at 6 months after the first episode in these children is less than 30%, suggesting that peritonitis may be a marker of rapidly progressing hepatic dysfunction. Some experts consider the first episode of spontaneous peritonitis a relative indication for liver transplantation.

Prevention

Strategies to prevent bacterial peritonitis in children largely have focused on patients undergoing CAPD. The use of strict sterile technique during the dialysis process is crucial to prevent contamination-associated peritonitis.[5,68] Double-bag disconnect systems, which take away the need for spiking dialysis bags, have been associated with a significant reduction in peritonitis caused by touch contamination.[5,68] The competency of CAPD training appears to be critical in this regard, and studies suggest a strong correlation between the duration and quality of training and low incidence of peritonitis.[69–71]

Observational studies conducted from registry data and a few controlled trials have associated decreased rates of peritonitis and exit-site infections with specific techniques during catheter placement,[5] including the use of a double-cuffed Dacron catheter (vs. a single-cuffed model) and directing the peritoneal opening inferiorly (vs. cephalad).[5] However, a systematic review of the data by the Cochrane Collaboration failed to demonstrate a significant benefit with any specific catheter design or insertion technique on the incidence of peritonitis, tunnel-site infections, or need for catheter removal.[68]

Nasal carriers of *S. aureus* have been identified in up to 45% of families of children treated with CAPD.[72] Mupirocin applied to the nares or catheter exit site in patients and family members who are known carriers has decreased the incidence of exit-site infections and peritonitis in several studies.[73] Not all community-associated MRSA infections are susceptible to mupirocin or carried solely in the nose. Topical aminoglycoside has been used with promising results to decrease *Pseudomonas*-related infections, although resistance is a problem.[74]

Prophylactic antibiotic therapy with a first-generation cephalosporin at the time of catheter insertion significantly decreases the incidence of postoperative peritonitis.[75] Chlorhexidine scrubs decrease the density of microorganisms, including MRSA (see Chapters 2 and 100). Children with a history of MRSA colonization should receive vancomycin. A short course (i.e., 24 to 48 hours) of a first-generation cephalosporin is recommended when there is suspected contamination of the dialysate or connecting hardware and before procedures involving the gastrointestinal or genitourinary tract.[5] Prophylactic, systemic, long-term antibiotics are not indicated for patients receiving CAPD. After placement of a catheter, initiation of peritoneal dialysis should be delayed for a minimum of 2 weeks to allow wound healing, and dressing changes should be conducted by trained dialysis staff ideally no more than once per week.[76]

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66

Appendicitis

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Appendicitis is the most common reason for emergent abdominal surgery in children, accounting for more than one third of the hospital days for abdominal pain each year among people younger than 18 years of age in the United States.[1] Although this disease no longer is responsible for appreciable mortality, the morbidity surrounding appendicitis, particularly complicated appendicitis, can be substantial. Efforts to decrease morbidity have focused on improving methods of diagnosis, optimizing surgical management, and improving postoperative care.

Epidemiology

Approximately 80,000 US children younger than 18 years of age have appendicitis each year. Appendicitis can affect children of all ages, including infants younger than 1 year of age, but the peak incidence is among those 12 to 18 years old. There is a slight male predominance, with an 8.7% lifetime risk for boys compared with 6.7% for girls.[2] The incidence increases from 1 to 2 cases per 10,000 children younger than 4 years of age to 25 cases per 10,000 older children.[2]

There may be a modest seasonal peak in acute appendicitis during summer months, with a higher incidence of perforation in fall and winter. This pattern may reflect problems with access to care in colder months.[3] Epidemiologic factors that may increase the risk of appendicitis include a low-fiber intake and possibly the family history.[4] Approximately one third of patients with proven appendicitis have a family history of appendicitis, compared with 14% of children with right lower quadrant pain from other causes.[5]

The rate of perforation at the time of operation ranges from 20% to 95%.[6,7] The incidence of perforation decreases with increasing age, from 70% to 95% among 1- to 4-year-old children to 10% to 20% among adolescents.[4,7,8] Perforation rates are highest among minority and economically disadvantaged children and therefore in the hospitals serving these groups.[3,9–11]

Appendicitis that has advanced to perforation is associated with more severe clinical illness, higher morbidity rates, and longer hospital stays. An elapsed time of more than 36 hours from first reported symptoms to the time of surgery correlates with an increased rate of perforation.[4,12,13] Major factors contributing to a delay in surgical intervention are lack of access to care and diagnostic uncertainty.[14,15] The diagnosis of appendicitis in younger children can be particularly difficult due to the problems of recognizing the signs and symptoms in nonverbal children.

Pathogenesis

Understanding of the pathophysiology of appendicitis depends on histologic examination of surgically removed specimens.[16,17] The initiating event typically is occlusion of the lumen of the appendix between the cecal base and the tip. Occlusion can result from a foreign body such as an appendicolith, inflamed mucosa due to an infectious process, or hyperplasia of intramural lymphoid tissue. Increased intraluminal pressure then leads to swelling, congestion, and distention of the mucosa and the appendiceal wall.

Overgrowth and translocation of bowel flora leads to an acute inflammatory infiltrate in the appendiceal wall. Progressive cellulitis of the luminal wall increases intraluminal pressure. When full-thickness inflammation occurs, localized peritonitis ensues. Untreated, necrosis and frank gangrene of the appendiceal wall follows. Rupture of the appendix can then lead to expanding peritonitis and the development of an inflammatory phlegmon (i.e., intra-abdominal abscess) or generalized peritonitis. Systemic manifestations of sepsis ensue.

Etiology

The organisms responsible for appendicitis and subsequent intra-abdominal infections are those that colonize the bowel. The most commonly documented pathogens associated with appendicitis are listed in Box 66.1. In the past, a culture of the peritoneal fluid was obtained routinely at the time of operation. Studies performed 2 decades ago suggested that this practice was not cost-effective because results infrequently altered patient management.[18,19] With growing rates of antibiotic resistance, however, peritoneal cultures and susceptibility testing can have a substantial impact.[20] Rates of positive peritoneal cultures vary considerably, which can reflect differences in culture techniques or the effect of administration of antibiotics before surgical intervention.

Box 66.1

Common Organisms in Perforated Appendicitis

Escherichia coli

α-Hemolytic streptococci

Bacteroides fragilis

Bilophila wadsworthia

Peptostreptococcus species

Across case series, the most commonly isolated organisms are anaerobes: *Bacteroides fragilis, Clostridium* and *Peptostreptococcus* species, and gram-negative bacilli, including *Escherichia coli and Pseudomonas, Enterobacter,* and *Klebsiella* species. Studies have examined the microbiota of the appendix during an episode of acute appendicitis and have shown an abundance of *Fusobacterium* species in cases of appendicitis, with a corresponding absence of *Fusobacterium* species in normal appendices. Conversely, there was a reduced abundance of *Bacteroides* species. Many additional organisms found commonly in the oral cavity (e.g., *Porphyromonas* spp.) were identified in greater quantities in the specimens from patients with appendicitis.[21,22]

Clinical Manifestations, Differential Diagnosis, and Laboratory Testing

Classically, symptoms of appendicitis are periumbilical pain that migrates to the right lower quadrant, followed by nausea, occasional vomiting, and low-grade fever. The clinical presentation varies greatly, depending on the sequence of pathophysiologic events, location of the appendix in the abdomen, age of the patient, and host response to infection.

In toddlers younger than 2 years, the most common symptoms are vomiting, abdominal pain, fever, abdominal distention, diarrhea, irritability, right hip pain, and limp.[15] In children between the ages of 2 and 5 years, abdominal pain precedes vomiting and usually is associated with fever and anorexia. Tenesmus, which can be perceived as diarrhea, is common in infants and toddlers and can lead to misdiagnosis.[7] School-age children describe abdominal pain that is constant and worse with movement or coughing.[15] Nausea, vomiting, anorexia, tenesmus, and dysuria also can occur in this age group.[15] Older children sometimes report that they are hungry,[1] although anorexia is more common.

Two retrospective studies of children[23,24] and one prospective study of children and adults[25,26] determined the sensitivities and specificities of symptoms. They are, respectively, vomiting, 43% and 64%; fever, 75% and 78%; anorexia 64% and 43%; and migration of pain, 41% and 54%. In older children, the most sensitive symptom (80%) is increased pain with coughing and movement, but the specificity (52%) is low.[26]

Physical findings also vary by age. In toddlers younger than 2 years of age, nonspecific signs such as fever and diffuse abdominal tenderness are most common. Preschool children 2 to 5 years of age demonstrate right lower quadrant tenderness, fever, and involuntary guarding. School-age children are more likely to have localized right lower quadrant tenderness or diffuse guarding and rebound tenderness in cases of perforated appendicitis.[26] Two studies[27,28] found rebound tenderness in children to have low diagnostic accuracy (43%), with a sensitivity of 50% and specificity of 60%. Signs commonly equated with appendicitis such as Rovsing sign, obturator sign, and psoas sign have not been studied in detail for frequency and precision in children[26] (Table 66.1).

TABLE 66.1

Clinical Signs or Symptoms in Appendicitis by Age of Patient

Clinical Sign or Symptom	Percentage of Children with Finding by Age		
	≤2 yr	2–5 yr	6–12 yr
Abdominal pain	35–77	89–100	100
Right lower quadrant pain	<50	58–85	>90
Diffuse tenderness	55–97	19–28	15,[a] 83[b]
Vomiting	85–90	66–100	68–95
Fever	40–60	80–87	64
Anorexia	NR	53–60	47–75

[a] Without perforation.

[b] With perforation.

NR, not reported.

From Neilson IR, Laberge JM, Nguyen LT, et al. Appendicitis in children: current therapeutic recommendations. J Pediatr Surg 1990;25:1113–1116; O'Shea JS, Bishop M, Alario A, et al. Diagnosing appendicitis in children with acute abdominal pain. Pediatr Emerg Care 1988;4:172–176.

Other inflammatory disease, most commonly gastroenteritis, can produce signs and symptoms similar to those of appendicitis[1,29] (Box 66.2). In girls, ovarian pathology such as ruptured ovarian cyst and ovarian torsion can cause right lower quadrant pain and peritoneal irritation. In neutropenic patients, differentiating appendicitis from typhlitis or neutropenic enterocolitis can be difficult, and imaging studies often are necessary.[1,30]

Box 66.2

Differential Diagnosis of Acute Abdominal Pain

Blunt abdominal trauma

Hernia

Infectious gastroenteritis

Inflammatory bowel disease

Intussusception

Meckel diverticulum

Mesenteric adenitis

Orchitis

Ovarian cyst

Pneumonia

Primary peritonitis

Testicular torsion

Urinary tract infection

Laboratory tests often are used in conjunction with the history and physical examination to help clarify a diagnosis in children with abdominal pain. In appendicitis, the white blood cell (WBC) count typically is mildly elevated in the range of 11,000 to 16,000 cells/mm^3, but the count can be normal or elevated markedly. A markedly elevated WBC count suggests perforation or a different diagnosis. In a review of studies examining the utility of the WBC count, a wide range of sensitivity (19%–88%) and specificity (53%–100%) was found.[26]

Studies of elevated serum C-reactive protein levels show sensitivity ranging from 48% to 75% and specificity from 57% to 82% for appendicitis.[26,31] Although for adults the combination of a normal WBC count and normal CRP level makes the diagnosis of appendicitis unlikely, this is not true for children.[32] CRP levels also must be interpreted with caution for obese children because resting levels are significantly higher and the value of testing is lower in obese children.[33] In a study of serum procalcitonin levels in 212 children with appendicitis, a procalcitonin value greater than 0.5 ng/mL had a sensitivity for gangrene or perforation of 73% and a specificity of 95%.[34] However, in most children with simple acute appendicitis, the procalcitonin level was less than 0.5 ng/mL.[34]

Urinalysis results can be abnormal for children with appendicitis; pyuria and hematuria are reported in up to 30%.[35–37] Abnormal urinalysis results especially occur when the inflamed appendix is adjacent to the ureter or bladder. There are inadequate data for children to test the usefulness of urinalysis.

Diagnostic Imaging and Scoring Systems

Imaging Modalities

Plain Radiographs

In the past, plain abdominal radiographs were the most common imaging study performed for patients with suspected appendicitis. However, plain abdominal radiographs have little value, and in one study. they were normal or misleading for 82% of children with appendicitis.[15] Plain films can demonstrate a fecalith in about 5% of cases of perforated appendicitis.[1] The finding of a fecalith in a patient with abdominal pain suggests appendicitis.[38]

Ultrasonography

Ultrasonography (US) has been studied extensively as a tool for diagnosing appendicitis. Diagnostic findings include an appendiceal diameter of 6 to 7 mm, a target sign with five concentric layers, distention or obstruction of the appendiceal lumen, high echogenicity surrounding the appendix, an appendicolith, fluid surrounding the appendix, and enlarged and thickened bowel wall, and lack of peristalsis.[26] Sensitivity of US is 71% to 92%, and specificity is 96% to 98%.[39–42]

US is operator and subject dependent. Its value is enhanced by the skill and experience of the ultrasonographer and is diminished when used for patients with obesity[43] or gaseous distention of bowel loops. Even in nonobese patients, the appendix cannot be visualized in up to 30% of patients.[26]

US can be used to confirm but not rule out appendicitis.[26] In many centers, US is a first-line study due to its low cost, freedom from ionizing radiation, and superiority to clinical judgment alone in equivocal cases.[44–47] A protocol with a sequential three-step positioning algorithm can help increase sensitivity and overall accuracy.[48]

Computed Tomography

Computed tomography (CT) is considered positive for appendicitis if there is an enlarged appendiceal diameter, appendiceal wall thickening, or periappendiceal inflammatory changes, including fat streaking, phlegmon, fluid collection, and extra-luminal gas.[26] CT has a higher specificity and sensitivity than US in adults evaluated for appendicitis.[49] US studies of children have high sensitivity (94%–99%) and specificity (87%–99%).[41,49,50] Several of these studies were prospective, although not blinded, and they used a variety of techniques for administration of contrast. In many studies, many patients had clinically apparent appendicitis and an operation was already planned.

Despite high sensitivity and specificity, CT has several limitations: requirement to drink contrast and potentially to administer triple contrast, possible sedation, and exposure to contrast media and ionizing radiation. Radiation exposure from a single CT scan can subject a child to an estimated lifetime risk of 1 death from radiation-induced cancer per 1000 patients,[51] and the use of CT is increasing.[52]

There is a sustained effort to decrease radiation exposure for children. Image Gently, the Alliance for Radiation Safety in children, is a coalition of healthcare organizations dedicated to reducing radiation exposure for children, especially at dedicated pediatric facilities.[53] The CT radiation dose can be decreased without a significant impact on visualization of the appendix.[54]

Several studies have shown that CT offers no increased accuracy over history, physical examination, and laboratory analysis.[55,56] Diagnostic accuracy of clinical examination alone can be improved by repeated examinations and laboratory testing in 12 to 24 hours. Observation with serial examinations can be a cost-effective method of diagnosing appendicitis. Less than 2% of patients have perforation during such observations.[57] Some practitioners obtain an imaging study for all children with abdominal pain to reduce the rate of negative laparotomy or laparoscopy results. In addition to cost and delay, imaging has a substantial false-negative risk for a child with a high clinical suspicion of disease and false-positive risk for a child with a low clinical suspicion of appendicitis.[58] Imaging studies are most useful when restricted to children with clinically equivocal presentations.

CT may be indicated to evaluate a child with suspected complicated appendicitis because findings may influence the management strategy, directing the surgeon toward initial nonoperative therapy.[59] CT use patterns at 30 pediatric hospitals ranged from 18% to 89% in cases of suspected appendicitis.[6] One study of a selective imaging approach for equivocal cases that started with US and then used CT for inconclusive US studies showed high accuracy (97%) and cost-effectiveness,[58,60] with a sensitivity of 99% and specificity of 92%.[61] Standardized pathways and algorithms for the evaluation and diagnosis of appendicitis may decrease the use of CT and the attendant risk of ionizing radiation.[62,63]

Magnetic Resonance Imaging

Used in conjunction with US, magnetic resonance imaging (MRI) has a high sensitivity and specificity for diagnosing acute appendicitis, and it avoids ionizing radiation. Compared with other modalities, MRI has been shown to be feasible in children older than 6 years without increasing rates of perforation or negative appendectomies (i.e., removal of normal appendixes).[64–67] Using ultrafast, limited sequences, the study can be completed in 17 to 30 minutes, and children older than 5 years who can lie still tolerate the study well.

Scoring Systems

A scoring system for appendicitis was developed from a large cohort of mainly adult patients. The Alvarado scoring system was given the acronym MANTRELS based on its components (Table 66.2). Its use has been tested in children, and its name was changed to the Pediatric Appendicitis Score (PAS).

TABLE 66.2

MANTRELS Score

Feature	Description	Points
Symptoms	Migration of abdominal pain from the epigastrium to the right lower quadrant	1
	Anorexia	1
	Nausea/vomiting	1

Signs	**T**enderness of the right lower quadrant	2
	Rebound tenderness	1
	Elevated temperature	1
Investigation	**L**eukocytosis	2
	Shift to the left	1
Significance of total score	Appendicitis unlikely	<5
	Appendicitis possible	5–6
	Appendicitis likely	>6

Although some physicians found the PAS to be highly accurate,[68] most studies showed a score of ≥7 to be only moderately sensitive (76%–90%) and specific (50%–81%) for children. For adolescents older than 16 years, a score of ≥7 yields high sensitivity (100%) and specificity (93%).[26,69] Another study found PAS most useful to rule out appendicitis when the score was ≤4 and to confirm appendicitis when the score was ≥8 (both score categories negated need for imaging), with scores of 5 through 7 suggesting the need for imaging.[70] The Alvarado scoring system appears to be more useful for risk-stratifying children than for guiding clinical management.

Management

During the past 25 years, the management of appendicitis has improved. Although some aspects of care have become standardized, great variation remains.[6,71] Even within a single state, there are major regional variations in the care and outcomes of children with appendicitis.[72]

Operative Management

For cases of acute, uncomplicated appendicitis, prompt appendectomy continues to be the mainstay of treatment. Studies have suggested that appendectomy after 12 hours of preoperative antibiotic treatment does not result in increased perforation rates or clinical morbidity compared with immediate appendectomy.[73,74]

Laparoscopic and open techniques for appendectomy are used widely, with no clear outcome advantage for either. Some studies have suggested that laparoscopic procedures produce a shorter hospital course, less pain, and a better cosmetic result. A randomized trial in Europe compared differential outcomes and found only a marginal decrease in cost but a quicker return to activities for children who underwent laparoscopic appendectomy.[75] A randomized trial of the approaches in children found that compared with open appendectomy, laparoscopy was associated with less pain, shorter hospitalization, longer operating times, higher operating costs, and overall cost savings.[76]

In cases of perforated appendicitis, some studies have suggested an increased rate of intra-abdominal abscess after laparoscopy compared with open surgery.[77–82] However, a large study of four centers treating children with perforated appendicitis found no effect of surgical modality on abscess formation.[83]

Preoperative antibiotics have long been considered important in the prevention of postoperative infections. Although several studies have challenged the use of routine preoperative antibiotics, the studies were limited by small numbers of patients.[84–87] One prospective, randomized study found no difference in complication rates between patients with simple appendicitis who received antibiotics and those who did not. However, there was a significantly higher rate of infection in the one third of patients who were discovered to have gangrenous appendicitis at operation if they had not received preoperative antibiotics.[85]

A Cochrane review suggests that routine antibiotic prophylaxis for any type of appendicitis helps prevent infectious complications.[88] The Surgical Infection Society guidelines suggest that children with appendicitis routinely should be given prophylactic antibiotics preoperatively, consisting of a single agent or combination of agents that provide adequate gram-negative bacillary and anaerobic coverage.[89] In simple appendicitis, postoperative antibiotics are given for 24 hours or are not used at all. The continuation of antibiotics postoperatively in patients with perforated appendicitis is of unproven efficacy.

Many institutions have adopted clinical algorithms for the management of appendicitis. Most data used to support these algorithms are derived from retrospective reviews of pediatric populations. Examination of the benefits of using guidelines has shown a reduction in cost and length of hospital stay.[90] Some studies also reported lower readmission rates, despite an increase in disease severity, after a care pathway was initiated.[91] It is difficult to conclude what effect standardization of care has in decreasing complication rates.[92]

Nonoperative Management

Nonoperative management of appendicitis has emerged as an alternative treatment for adults with appendicitis. Several randomized, controlled studies and a meta-analysis of these studies showed a success rate of 63% with 1 year of follow-up. The risk of complications was very low, and there was no difference in the risk of developing complicated appendicitis.[93–96]

Many facilities in Europe subsequently adopted medical management as first-line management for uncomplicated appendicitis. A trial of 530 adults with uncomplicated acute appendicitis confirmed by CT who were assigned randomly to early appendectomy or antibiotic treatment found that about 25% of patients randomized to antibiotic treatment required appendectomy during a 1-year follow-up period, which was performed without significant complications.[97]

Few studies have evaluated nonoperative management of appendicitis in children. One initial retrospective[98] and one prospective, nonrandomized study[99] showed early success rates of ≥ 90% for limited numbers of children. Patients (and their parents) treated medically had fewer disability days, fewer missed days of school, and a more rapid return to their normal activities.[99] A meta-analysis of 6 randomized trials (only one performed exclusively in children) showed a pooled estimate of appendectomy rate in 550 medically managed patients to be 8.2% at 1 month and 22.6% by 12 months.[100] Further investigation is necessary to address the success, safety, and efficacy of nonoperative management beyond the first month.

Complicated Appendicitis

Most controversy and variation in the care of children with appendicitis involves complicated appendicitis. There is controversy regarding the definition of complicated appendicitis; which affects comparisons of outcomes. Some surgeons argue that gangrenous and perforated appendicitis cannot be differentiated, and there is inconsistency among surgeons in describing the severity of appendicitis.[101] The distinction is important because gangrenous appendicitis is associated with outcomes and morbidity more aligned with simple appendicitis than perforated appendicitis. The definition of perforation was developed from a prospective, randomized study.[102] Perforation was defined as a visible hole in the appendix or a free fecalith in the abdomen. Universal adoption of this evidence-based definition would enhance investigations of outcomes for cases of complicated appendicitis.

The use of nonoperative management for perforated appendicitis is controversial. In cases of peritonitis, many surgeons advocate immediate appendectomy. However, some have advocated for a treatment interval for these patients using intravenous antibiotics, followed by appendectomy.[103,104] Surgeons in favor of the latter approach cite the high rate of complications when operating during a period of intense inflammation and peritonitis. However, high failure rates for the initial nonoperative approach have been reported. If a child does not respond favorably to antibiotic therapy within 24 to 72 hours, an appendectomy is prudent. Persistence of fever for 24 hours or longer has been associated with failure of nonoperative management.[105] The nonoperative failure rate was 84% among patients whose WBC count had more than 15% bands in one study[104] and 100% with more than 10% bands in another study.[105] When the clinical course is reported in detail, patients who do not respond favorably to initial nonoperative treatment can experience high complication rates and long hospitalizations.[103,106]

The nonoperative approach may decrease morbidity for patients who come to attention with a long duration of pain or missed appendicitis.[106] A prospective, randomized trial of initial nonoperative management versus early appendectomy for children with a well-defined abscess found no difference in total length of hospitalization, recurrent abscess, dose of narcotics, or total charges.[107]

As nonoperative management of perforated appendicitis becomes more prevalent, distinguishing preoperatively between perforated and acute appendicitis becomes more critical. A scoring system has been proposed to aid preoperative differentiation of perforated from nonperforated appendicitis (Table 66.3). A cutoff score of 9 has an improved likelihood ratio and posttest probability of perforated appendicitis compared with the surgeon's diagnosis alone.[108] However, a key feature of this scoring system is the CT findings, resulting in the exposure of many patients to the adverse effects of ionizing radiation.

TABLE 66.3

Scoring System to Differentiate Ruptured Appendicitis

Finding	Points
Generalized tenderness	4
Abscess on CT	3
Symptom duration >48 hr	3
WBC count >19,400 cells/μL	2
Fecalith on CT	1

CT, computed tomography; WBC, white blood cell.

From Williams RF, Blakely ML, Fischer PE, et al. Diagnosing ruptured appendicitis preoperatively in pediatric patients. J Am Coll Surg 2009;208:819–828.

Some proponents of nonoperative management have begun to question the necessity of performing an interval appendectomy because of the insignificant rate of recurrence,[109] positing that the lumen of the appendix is obliterated after perforation. A small histopathologic analysis of interval appendectomy specimens, however, found that all specimens had a patent lumen and an appendiceal tip.[17] One randomized, controlled trial enrolling 60 patients showed a 10% recurrence rate among patients managed nonoperatively.[110] Other cohort studies have reported a similar recurrence rate.[109,111–113] In one study with an average of 7.5 follow-up years, 80% of cases recurred within 6 months, and there were no recurrences after 3 years.[113] A major limitation of these studies is the length of follow-up; the longest is 13 years. The prognosis for children into adulthood is therefore unknown. A survey of members of the American Pediatric Surgical Association found that 86% of surgeons perform an interval appendectomy for perforated appendicitis.[71]

Many surgeons have abandoned the practice of sampling pus or free fluid found during the operation for culture because results infrequently effected a change in therapy.[71] Contemporary bacteriology is not available, and emerging trends in antibiotic resistance may not be appreciated. A study from Hong Kong found that up to one fourth of bacterial species isolated from children with complicated appendicitis were not susceptible to the antibiotics selected.[20] Intra-operative peritoneal cultures will likely increasingly impact optimal antibiotic management.

In a survey of pediatric surgeons, postoperative antibiotics were used routinely,[71] but there was variation in the type and duration of antibiotics. Standard antibiotic regimens have included multidrug therapy, most frequently ampicillin plus gentamicin plus clindamycin or metronidazole. Broad-spectrum monotherapy such as with piperacillin-tazobactam likely is equally effective.[114]

Duration of therapy sometimes follows institutional protocols or is based on specific clinical factors.[71] In one randomized trial, there was no difference in infectious complications between patients given a set course of a minimum 5 days of antibiotics and those whose course was based on clinical factors with no set minimum.[115] Other studies have shown that children can be given outpatient parenteral antibiotics safely and cost-effectively[116] or can be given oral antibiotics after a course of intravenous therapy.[117,118] In one large review, there was no difference in infectious complication rates for those treated with only 3 days of antibiotics compared with those treated longer.[119]

In a prospective study, the strategy of treating with antibiotics until the child was afebrile for 24 hours and had a normal WBC count was effective.[120] A randomized trial found that completing the antibiotic course with oral antibiotics after a child was afebrile for 12 hours and tolerating a regular diet decreased the length of hospitalization without increasing the risk of postoperative abscess.[121] These clinical milestones form the basis for the duration of antibiotic therapy as proposed by the Surgical Infection Society guidelines.[89]

Traditionally, it was thought that progression of appendicitis to appendiceal rupture was within the control of the physician and that a high rupture rate reflected a failure of care. To decrease the rupture rate, early surgical intervention has been the gold standard, and high rates of negative exploration have been acceptable to decrease the likelihood of rupture. Despite many efforts to decrease the rates of complicated appendicitis, rates for children remain high and range from 30% to 74%.[10]

Later studies suggest that high rupture rates more likely reflect a delay in diagnosis and treatment because of inadequate access to medical care. In review of a national pediatric discharge database, the likelihood of perforation differed by race, even while controlling for age and health insurance status.[11] Review of a large pediatric health systems database revealed that the rate of rupture among school-aged children was associated with race and insurance status and not with the negative appendectomy rate.[10,122,123] Examination of a statewide database also revealed that children with Medicaid or no insurance were more likely to develop appendiceal perforation than those with private insurance.[122] These findings suggest a shift to focus on improved access to health care. In a large, retrospective cohort study, a low hospital volume was associated with an increased risk of misdiagnosis but not with a risk of appendiceal perforation.[11]

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67

Intra-Abdominal, Visceral, and Retroperitoneal Abscesses

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Intra-abdominal abscesses that occur in children are sometimes difficult to diagnose and more difficult to treat. Even when managed appropriately, morbidity still can be high. If not managed appropriately, the results can be catastrophic. Abdominal abscesses are categorized as intra-abdominal (i.e., intraperitoneal), visceral, and retroperitoneal. Intra-abdominal abscesses are the most common type.

Bacteria from the original site of colonization or infection can travel hematogenously, pass through regional lymphatics, or spread by direct extension from a local infection to form an abscess. Intra-abdominal abscesses frequently contain mixed flora of facultative and anaerobic bacteria. In visceral and retroperitoneal abscesses, single organisms are more common. The types of bacteria isolated can indicate the origin of the infection. The most common facultative bacteria isolated in intra-abdominal abscesses are *Escherichia coli, Staphylococcus aureus,* and *Enterococcus* spp.[1,2] Anaerobic bacteria include the *Bacteroides fragilis* group, *Peptostreptococcus* spp., *Clostridium* spp., and *Fusobacterium* spp.[1,2] Enteric organisms also can cause visceral abscesses, but gram-positive bacteria of a systemic infection or fungi in immune-compromised hosts can be responsible. Retroperitoneal abscesses contain organisms specific to the site of the primary infection.[3] For example, a perinephric abscess usually is caused by organisms that cause pyelonephritis, whereas an iliopsoas abscess usually is caused by bacteremic *S. aureus*.[3–5]

The tenets of management of an abscess include drainage, appropriate antibiotic therapy, and correction, if possible, of any underlying pathology that can cause a recurrence. Drainage can be accomplished in a variety of ways, including open surgical exploration, laparoscopic surgical exploration, and percutaneous, image-guided drainage. Empiric antibiotic therapy should be initiated immediately on diagnosis considering likely abscesses by site (Table 67.1), and if necessary, it should be changed to definitive therapy when culture and susceptibility test results become available. Coordinated management by the surgical, interventional radiology, and infectious diseases specialists and by the child's primary care physician optimizes care.

TABLE 67.1

Common Organisms Found in Abscesses by Site

Site	Organisms
Intra-abdominal	*Escherichia coli, Enterococcus* spp., *Klebsiella* spp., *Bacteroides* spp., *Peptostreptococcus* spp., *Clostridium* spp., *Fusobacterium* spp., *Staphylococcus aureus,* and *Pseudomonas* spp.
Visceral (liver, spleen, pancreas)	*Staphylococcus aureus, Escherichia coli, Enterococcus faecalis, Klebsiella* spp., *Enterobacter* spp., *Pseudomonas* spp., *Streptococcus* spp., *Salmonella, Bartonella,* and *Candida* spp.
Retroperitoneal (iliopsoas, other)	*Staphylococcus aureus, Streptococcus* spp., *Escherichia coli, Klebsiella* spp., and *Candida* spp.

Data from references 1–3, 8, 29–33, 35, 38, and 41

Intra-Abdominal Abscesses

Etiology and Clinical Manifestations

Complicated appendicitis is the most common cause of intra-abdominal abscesses in children. Patients can come to medical attention with an abscess after perforation of the appendix or can develop an abscess postoperatively.

Other intra-abdominal abscesses originate from the gastrointestinal tract, as in patients who are immunocompromised or have a chronic illness such as Crohn disease. Any operation on the gastrointestinal tract has the potential for causing a postoperative abscess. Elective operation on the bowel carries the risk of contamination of the peritoneum at the time of surgery or later from a complication such as an anastomotic leak. Emergent surgery for perforation is performed in the setting of contamination and has a higher risk of abscess formation. Other emergent causes of a perforated viscus and resultant abscess include necrotizing enterocolitis, inflammatory bowel disease, peptic ulcer, Meckel diverticulum, and trauma.[1]

Location of an abscess within the abdominal cavity, such as subphrenic and pelvic sites, can predict an underlying condition and certain pathogens. The bacteria most frequently isolated in abscesses after bowel disease or surgery include *E. coli, Bacteroides* species, and *Enterococcus* species, but any enteric organism can be present.[2] Brook studied the microbiology of intra-abdominal abscesses in children and found that 8% of cultures yielded only facultative bacteria, 17% only anaerobic bacteria, and 75% mixed flora.[1,6]

Persistence of fever and abdominal pain for 5 or more days after abdominal surgery should prompt evaluation for an abscess.[7] Early imaging may be falsely positive because of fluid collections, leading to unnecessary interventions.[7] Symptoms from compression of the abscess on adjacent structures, such as early satiety for abscesses near the stomach, urinary frequency or urgency for those near the bladder, or diarrhea or tenesmus for abscesses near the colon or rectum, associated with anorexia and weight loss are common findings in patients with abscesses.

Although uncommon, the incidence of biliary tract disease among children is increasing. Children with hemolytic disorders such as sickle cell anemia and hereditary spherocytosis are at increased risk for cholelithiasis and biliary tract disease. Although most cases of cholelithiasis in children are managed electively, some patients have complicated disease and associated cholecystitis. These patients are at risk for postoperative abscess, which should be suspected with persistence of fever and right upper quadrant pain after cholecystectomy.

Additional symptoms can include nausea, vomiting, and back or shoulder pain. The white blood cell count can be elevated, and serum hepatic enzyme levels often are abnormal. The bilirubin level usually is normal, but if elevated, it should prompt an evaluation for ascending cholangitis. Hyperbilirubinemia in children can result from obstruction of the common bile duct by a retained stone, after a Kasai procedure or liver transplantation, or from a congenital anomaly or malignancy. If identified, urgent decompression of the biliary tree is required. The serum bilirubin level also can be elevated by a bile leak postoperatively. This usually occurs at the raw surface of transplanted partial liver in the gallbladder fossa. The resulting collection of bile can become infected and require drainage. A retained gallstone or appendicolith in the peritoneal cavity after cholecystectomy or appendectomy, respectively, is another source of intra-abdominal abscess.[8] The most common pathogens associated with cholecystitis (i.e., *E. coli, Klebsiella* spp., *Pseudomonas* spp., and *Bacteroides* spp.) are considered for empiric antibiotic therapy for a postoperative abscess.

When an intra-abdominal abscess from any cause is suspected, imaging is indicated. Plain radiographs of the abdomen can show indirect evidence of abscess such as a pleural or peritoneal effusion or ileus. The diagnosis is confirmed by cross-sectional imaging. Ultrasonography (US) is preferred and can identify the location and size of an abscess in most cases, and it avoids exposure to ionizing radiation. Computed tomography (CT) should be used when US is nondiagnostic (Fig. 67.1). These studies also provide guidance for aspiration and placement of drainage catheters.

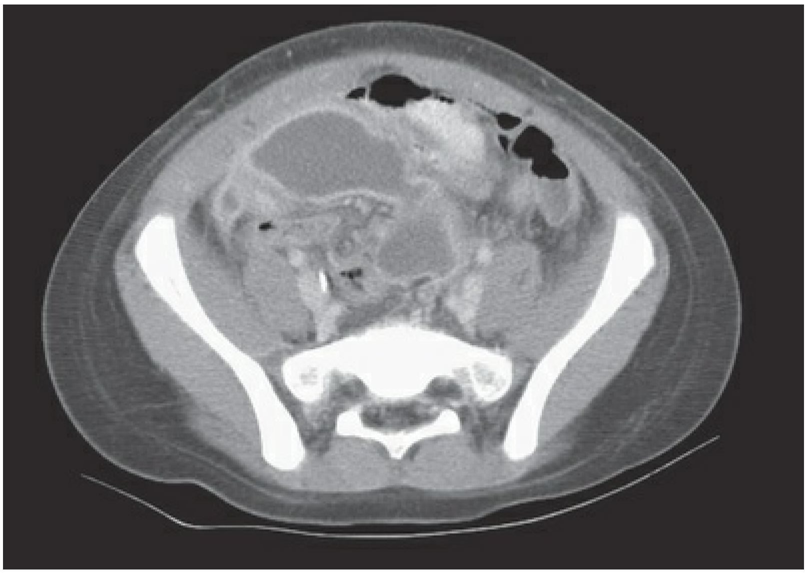

FIGURE 67.1 A postoperative abscess is visualized by computed tomography. This rim-enhancing fluid collection has the typical appearance of an abscess.

Management

Broad-spectrum antibiotics directed against facultative and anaerobic bacteria should be initiated empirically.[1,6] Therapy should be based on the location and presumed cause. Continued therapy should be guided by culture and susceptibility test results, remembering that recovery of enteric organisms also presumes an anaerobic infection. Guidelines from the Surgical Infection Society[9] recommend limiting the duration of intravenous antibiotics to 7 days if there is adequate control of the source and drainage of abscess; otherwise, parenteral antibiotic therapy may be required for an extended period.

The manner in which an intra-abdominal abscess is managed should be individualized. Antibiotics alone can be effective for fluid collections less than 5 cm in diameter or less than 20 cm^2.[10,11] Patients with a large inflammatory mass of fibrinous material with small fluid pockets are considered to have a phlegmon and usually are treated with antibiotics alone. When imaging reveals a larger fluid collection or when a smaller collection has failed to respond to antibiotics, drainage is indicated.

Percutaneous drainage under imaging guidance is standard therapy for children with abscesses (Fig. 67.2). Different modalities have been used to optimize drainage, including US or CT guidance for placement of the drain and US, fluoroscopy, or CT to reevaluate and confirm collapse of the abscess cavity.[2,12] Percutaneous drainage is desirable because it is well tolerated, is less invasive than laparotomy, and provides accurate confirmation of response to therapy[2,9–14] (Fig. 67.3). Although percutaneous drainage frequently requires general anesthesia, the risks of bowel manipulation, visceral injury, and the probability of an adhesive small-bowel obstruction are reduced.

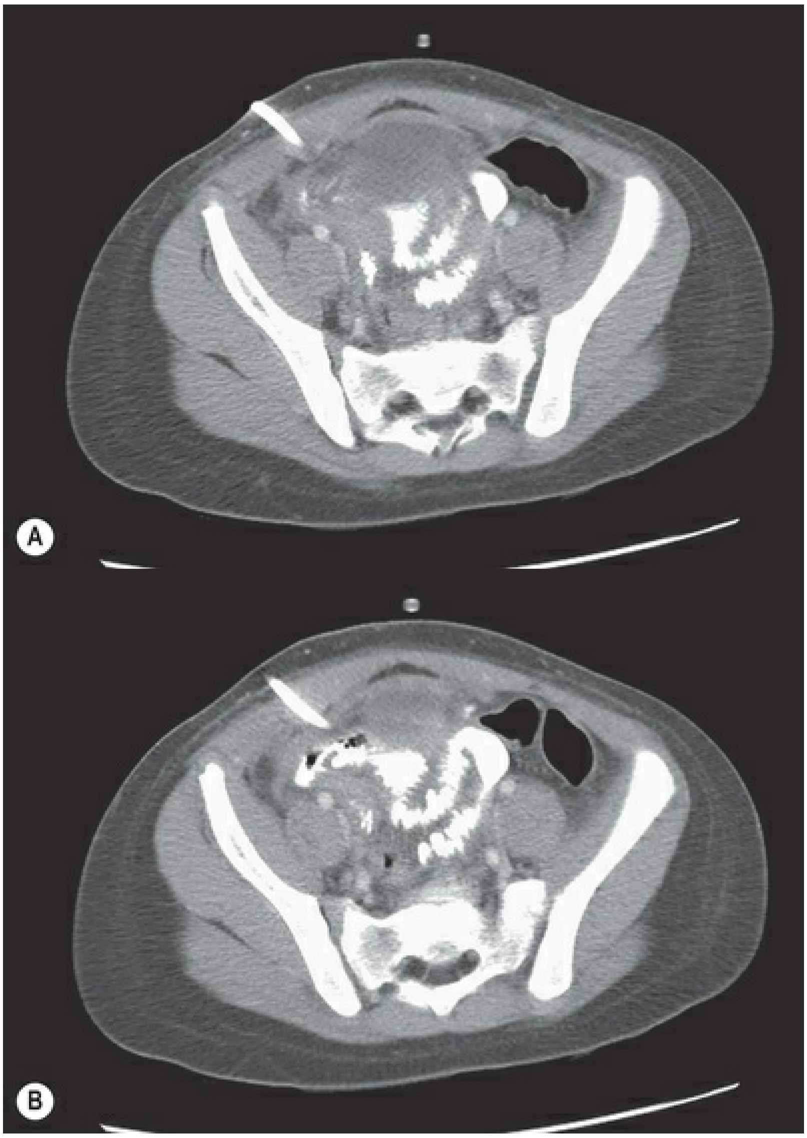

FIGURE 67.2 (A and B) Computed tomography–guided placement of a drainage catheter into the abscess.

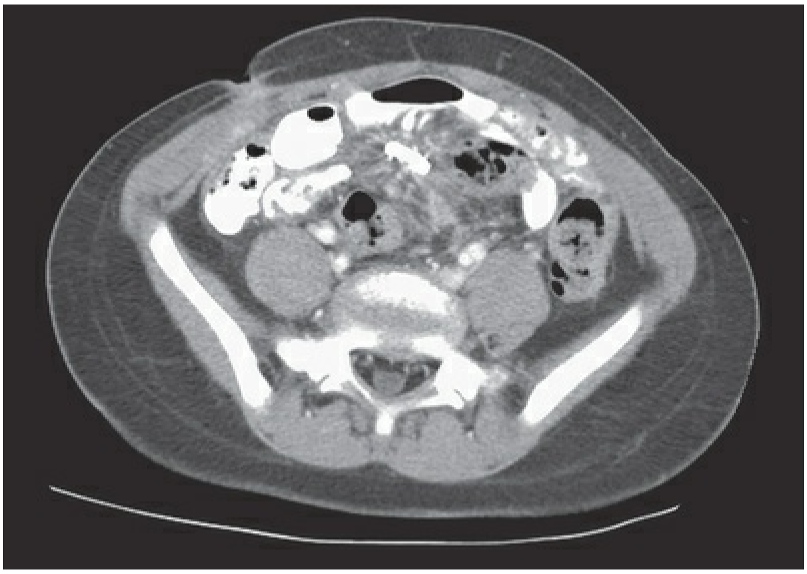

FIGURE 67.3 Resolution of the fluid collection, with the catheter visualized next to the small bowel.

The clinical setting and the location, size, organization, and number of abscesses are factored into advisability of percutaneous drainage.[12,13] Factors associated with reduced success of percutaneous drainage include complex abscesses, loculated or poorly organized abscesses, and those with multiple or extensive collections.[1,12] In one small study, abscesses with less viscous contents, as indicated by the air-fluid levels or peripheral air bubbles, were drained successfully by percutaneous methods in 95% of cases. With thicker fluid collections as evidenced by deep air bubbles, the rate of successful percutaneous drainage was 66%.[13]

Some intra-abdominal abscesses are best managed by operative or reoperative laparotomy. Indications for surgical intervention include uncontrolled septicemia, a cause of the abscess that requires surgical correction (i.e., anastomotic leak), an abscess not amenable to percutaneous drainage, and unsuccessful percutaneous drainage. Surgical drainage can be performed by open or laparoscopic technique, with no clear evidence favoring one method.[15] Several case series have demonstrated the adequacy of laparoscopy for draining abscesses.[15–18] Proponents cite better visualization of the entire abdominal contents and ability to irrigate the area adequately. In other cases, the need for a concomitant surgical procedure (e.g., to form a stoma, revise an anastomosis) is an indication for an open procedure.

Visceral Abscesses

Etiology and Clinical Manifestations

Hepatic Abscess

Before the availability of antibiotics, abscesses in the liver were often found in otherwise healthy children. Currently, most liver abscesses are seen in underdeveloped countries, in immunocompromised patients such as those receiving chemotherapy, or in children with chronic granulomatous disease or acquired immunodeficiency syndrome (AIDS).[1,19] Immunologically normal children who develop pyogenic liver abscesses usually have had a recent episode of appendicitis or cholecystitis.[20]

Pyogenic liver abscesses in children are caused by aerobic, facultative, or anaerobic bacteria, or they are polymicrobial.[1,3,21,22] Bacterial causes include *S. aureus, E. coli, Enterococcus faecalis,* and *Klebsiella, Enterobacter, Pseudomonas,* or *Salmonella* species. Cat-scratch disease also has been associated with multiple microabscesses of the liver and spleen in otherwise healthy children and in immunocompromised children with cancer or human immunodeficiency virus (HIV) infection.[1,23]

Abscesses in the liver can be single or multiple and simple or complex. They can occur as a result of direct extension from a local infection such as cholecystitis or cholangitis. They also can result from hematogenous spread through the hepatic artery or through the portal vein from sources within the abdominal cavity (e.g., associated with appendicitis). Pyelophlebitis, for example, occurs when enteric organisms access the liver through the portal system.

Amebiasis frequently is discussed as a cause of liver abscess, although some argue that the "anchovy paste" collection is not a true abscess.[1] Amebas reach the liver through the portal venous system and usually cause a single, large abscess. Other parasitic infections, including ascariasis, have been associated with hepatic abscesses. The granulomas induced by these infections are recognized predisposing factors for pyogenic liver abscesses in children in endemic areas.[20]

Traumatic injury to the liver has been associated with liver abscess in about 1% of cases.[24] Abscess associated with trauma is most common in patients managed operatively and in those with concurrent injury to a hollow viscus.

Symptoms of hepatic abscesses include fever, abdominal pain that can be diffuse or localized in the right upper quadrant, nausea, vomiting, and anorexia.[25] Jaundice is less common but can occur when the abscess compresses the biliary tract or parasitic infections (e.g., ascariasis) obstruct a bile duct lumen. The white blood cell count and serum hepatic enzyme levels can be elevated. A detailed history is important, including kitten exposure, travel in endemic areas of parasitic infestation, recent trauma, infection, and surgery.

US or CT can be used to identify abscesses. Specific antibody tests can be helpful if a parasitic infection is suspected. The hemagglutination test result usually is positive in cases of amebic abscesses, and serum antibodies for *Bartonella henselae* are detected in cases of hepatosplenic cat-scratch disease.

Splenic Abscess

The incidence of splenic abscesses appears to be increasing, although it is unclear whether this is a true increase in the number of cases or a higher index of suspicion coupled with better diagnostic tools.[26–28] Some reports indicate that the increasing number of immunocompromised patients is contributing to the changing pattern of splenic abscesses.[28] Aggressive cancer chemotherapy, the numbers of patients with HIV/AIDS, and immunosuppression for organ transplantation may be responsible.[28] Other populations at risk are patients with hemolytic disorders such as sickle cell anemia and those with a history of splenic trauma.

Splenic abscesses can be large or small and solitary or multiple. Infections can be caused by single organisms or can be polymicrobial. Organisms frequently identified include *S. aureus, E. coli,* and *Salmonella, Streptococcus, Candida,* and *Klebsiella* species.[28–31]

The triad of fever, leukocytosis, and left upper quadrant pain is common. Patients can have nausea, vomiting, and tender splenomegaly. The diagnosis can be suspected when the chest radiograph shows an elevated left hemidiaphragm or a left pleural effusion.. US, which is the preferred first study, or CT confirms the diagnosis.

Renal and Perinephric Abscess

Renal and perinephric abscesses are visceral abscesses that occur in the retroperitoneal space as a result of urogenital pathology such as pyelonephritis, urinary obstruction from a ureteral stone, or seeding from systemic infections causing bacteremia or fungemia. Renal and perinephric abscesses are discussed elsewhere (see Chapter 48).

Pancreatic Abscess

Pancreatic abscesses in children are rare and can be the result of acute pancreatitis or trauma. Injury of the pancreas due to blunt or penetrating trauma can precipitate an abscess in the setting of devitalized, necrotic tissue or a leak of the pancreatic duct. If not diagnosed preoperatively or identified at the time of exploration, the resulting fluid collection can be infected secondarily. The most common etiologic agents include *E. coli* and *Klebsiella; Enterococcus, Staphylococcus, Streptococcus,* and *Pseudomonas* species; and fungi.[32,33] The mortality rate associated with pancreatic abscesses is 15% to 50%, with morbidity rates as high as 75% to 80%.[32,33]

Symptoms include fever, epigastric or left upper quadrant pain, and hemodynamic instability. Laboratory tests show an elevated white blood cell count with some degree of serum amylase and lipase level elevation. CT with rapid contrast injection is a sensitive test that can show a nonenhancing portion of the pancreas or a fluid collection in or near the pancreas.[32]

Management

Therapy should be broad-spectrum antibiotics with activity against the most common organisms associated with the type of abscess identified. In immunocompromised patients, the addition of antifungal therapy should be considered. Decisions regarding drainage are made based on the clinical presentation, condition of the patient, and need for microbiologic confirmation.

Multiple microabscesses of the liver are treated successfully with antibiotics alone, especially in cases of cat-scratch disease.[23,25] Abscesses smaller than 4 cm in diameter can be successfully treated by aspiration, with antibiotic therapy continued until the patient's clinical status improves and CT shows resolution of the abscess.

However, in patients with abscesses larger than 4 cm or recurrence after aspiration, continuous drainage using a CT- or US-guided percutaneous catheter is indicated in addition to antibiotic therapy.[25] Surgical drainage is recommended for patients with liver abscesses that do not resolve with percutaneous drainage, those with rupture of the abscess into the peritoneal cavity, and in patients with chronic granulomatous disease who have persistent or recurrent liver abscesses.[19,25]

The management of splenic abscesses is similar to that of liver abscesses. Although salvage of the spleen is preferable and usually is possible, the primary goal is eradication of infection. Splenectomy should be considered for patients who do not respond to drainage and antibiotics. Splenectomy also should be considered for patients who are immunocompromised and have ongoing septicemia, patients with sickle cell disease or other hemoglobinopathies, those with rupture of the abscess into the peritoneal cavity, and those who have an abscess after a traumatic splenic injury.[28–31,34]

Pancreatic abscesses should be managed with drainage. In cases of pancreatic fluid collections that may not be infected or in cases of pancreatic phlegmon, CT-guided aspiration of pancreatic or peripancreatic fluid can provide specimens for culture to guide antibiotic therapy. Percutaneous drainage catheters can be left in place if the fluid appears purulent or the Gram stain is positive for organisms. Percutaneous drainage has reported success rates ranging from 69% to 86%.[33,35]

For patients who have ongoing septicemia or whose fluid collections are not amenable to percutaneous drainage, open operative exploration is required.[33,35,36] For patients who ultimately require surgery, percutaneous drainage often is a good temporizing measure for those who are too unstable to undergo surgery due to severe sepsis.

Retroperitoneal Abscesses

Etiology and Clinical Manifestations

In addition to abscesses of the kidney and pancreas, other causes of abscesses in the retroperitoneum include traumatic duodenal injury and iliopsoas abscess. Traumatic duodenal injury can be a result of penetrating trauma or blunt trauma associated with handlebar injuries of bicycles or motorcycles. Several cases of penetrating trauma to the duodenum have been reported in which retroperitoneal abscess followed the ingestion of a sharp foreign body such as a needle, toothpick, or fish bone.[37]

Abscesses associated with duodenal injuries or perforations are difficult to manage and have high morbidity and mortality rates.[38–40] Evacuation of the abscess cavity is difficult, and the underlying problem, a disruption of the duodenal wall, must be addressed to prevent further complications such as duodenal fistula.

Retroperitoneal abscess should be suspected in a patient with right upper quadrant or epigastric pain, fever, nausea and vomiting, an elevated white blood cell count, and in many cases, an elevated serum amylase level after trauma. Findings on physical examination indicating duodenal injury include a contusion of the upper abdomen with signs of peritonitis. Plain radiographs of the abdomen may not be diagnostic unless free air is detected. An upper intestinal contrast study or CT usually is diagnostic.[38,39] Organisms reported in these abscesses include *Staphylococcus* spp., *Streptococcus* spp., *E. coli, Klebsiella* spp., and *Candida* spp.[3,38,41]

Iliopsoas abscess can be primary or secondary.[42] Primary psoas abscess has no detectable source, and it is the most common type in children. Secondary abscess is associated with a known source of infection. Because the psoas muscle is intimately related to the ureter, renal pelvis, spine, appendix, terminal ileum, pancreas, jejunum, and sigmoid colon, an infectious process deriving from any of these structures can cause a secondary psoas abscess.[18,43,44] Examples include pyelonephritis, appendicitis, osteomyelitis, pancreatitis, and inflammatory bowel disease. The most common organism in primary abscess is *S. aureus,* indicating that an unidentified, mucocutaneous source leading to bacteremia is most likely.[15,43,45] Other causes include *Streptococcus pneumoniae* (the most common causative organism in patients with a history of recent respiratory tract infection) and gram-negative organisms such as *E. coli* (in patients with a history of appendicitis or other gastrointestinal infection or surgery). Underlying illness such as diabetes mellitus, HIV infection, or a connective tissue disorder increases risk in adults; case reports of psoas abscess in neonates suggest a predisposing event of femoral venous catheterization or omphalitis.[5,43,44] The most common organism is *S. aureus*, especially methicillin-resistant *S. aureus*.

Symptoms of psoas abscess include fever, leg pain or swelling, and decreased range of motion in the ipsilateral hip.[42] The degree of dysfunction of the hip joint varies from no apparent dysfunction to complete pseudoparalysis. A positive psoas sign, inguinal swelling, or lymphadenopathy can be identified on physical examination.

Septic arthritis of the hip must be differentiated from a psoas abscess. Laboratory tests often demonstrate an elevated white blood cell count and erythrocyte sedimentation rate in both conditions. Plain radiographs may reveal obscuring of the sacroiliac joint or an effusion of the hip in iliopsoas abscess, which is a sympathetic effusion due to the surrounding inflammatory process. Because a delay in treatment of pyogenic arthritis must be avoided, aspiration of the joint is the safest approach to exclude this diagnosis.[42] US is the best initial diagnostic test. It can characterize the abscess, assist in obtaining samples for culture and placement of drains, and be used to monitor resolution. CT is appropriate when US is inconclusive.

Management

Factors influencing the management of retroperitoneal abscesses resulting from duodenal pathology include time since injury, clinical presentation, hemodynamic stability, and concurrent injuries or illnesses. Any approach should accomplish drainage of the retroperitoneal abscess and address the primary pathology of the duodenum.[38–40] Possible surgical approaches include primary repair and drainage with or without pyloric exclusion and the more aggressive pancreaticoduodenectomy. Successful percutaneous drainage also has been reported.[39] Nutritional support is important because enteral feeding is precluded in the postoperative period.[38,40]

Psoas abscesses are managed by drainage and antibiotic therapy. Except in the case of a known prior infection, empiric antibiotic therapy should cover *S. aureus*, the most common etiologic agent. Drainage has been accomplished by percutaneous US-guided aspiration or catheter drainage.[46,47] Retroperitoneoscopy and open operative approaches have been used when percutaneous drainage is not successful.

Key Points

Evaluation and Management of Intra-Abdominal, Visceral, and Retroperitoneal Abscesses

- In postoperative patients, early imaging of fluid collections can lead to a false-positive interpretation as an abscess.
- To avoid radiation, ultrasonography is the preferred imaging modality for the diagnosis and therapeutic interventions.
- Although percutaneous drainage with image guidance has become a mainstay of therapy for children with abscesses, smaller abscesses (<5 cm) probably can be managed with antibiotics alone.

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Skin and Soft Tissue Infections

OUTLINE

68 Superficial Bacterial Skin Infections and Cellulitis
69 Erythematous Macules and Papules
70 Vesicles and Bullae
71 Purpura
72 Urticaria and Erythema Multiforme
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Superficial Bacterial Skin Infections and Cellulitis

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The skin has a primary protective function. It provides a permeability barrier that prevents the loss of water and electrolytes and protects against the invasion of pathogens. Intact skin is resistant to colonization and invasion of bacteria by several mechanisms.[1–3]

The outermost layer of the epidermis, the stratum corneum, constitutes the principal barrier against infection. The stratum corneum consists of corneocytes (i.e., anucleated keratinocytes or skin cells) and an outer lipid matrix. Corneocytes fit together in an overlapping fashion, making penetration by organisms difficult. Because they are shed from the skin after approximately 14 days, pathogenic organisms have a limited time to invade further into the epidermis. The lipid matrix surrounding corneocytes is acidic, providing antimicrobial activity against pathogenic organisms, including *Staphylococcus aureus* and *Streptococcus* species.[1,2]

Keratinocytes also participate in innate immunity by secretion of antimicrobial peptides (AMPs) such as human β-defensins, cathelicidin, psoriasin, and dermcidin. AMPs are small peptides with broad-spectrum antimicrobial activity against bacteria, viruses, and yeast.[2,4–6] Production of AMPs by keratinocytes is stimulated by inflammatory cytokines produced in the skin as a result of injury or inflammation and by invasive organisms through pathogen-associated molecular patterns (PAMPs).[6] Resident bacteria on the skin provide additional protection against infection by preventing colonization with pathogenic organisms through competitive binding to cell surface receptors and by the production of toxic substances called *bacteriocins* that inhibit the growth of similar bacteria.[1,3,7]

Skin microflora can be categorized as two groups: resident flora and transient flora. Resident flora establish secure attachments to the skin, are present in stable numbers, and can tolerate an acidic environment. Transient flora are introduced from the environment and attach only if the skin is disrupted.[1,8] Group A streptococci (GAS) (e.g., *Streptococcus pyogenes*) and *S. aureus* are the most common transient bacteria on the skin that cause infection.[1,3]

Many different bacteria are considered to be normal resident flora, and each organism has a predilection for specific anatomic locations and for hosts of a particular age.[1,3,7] The skin becomes colonized with microorganisms during the birth process and through contact with the environment. Infants born vaginally acquire *Staphylococcus epidermidis* during passage through the vaginal canal, and within hours, coryneform bacteria are found on neonatal skin.[1] The dry surface of the stratum corneum is colonized by micrococci and coagulase-negative staphylococci (CoNS),[1,7] whereas coryneform organisms and gram-negative bacilli prefer moist, intertriginous areas.[1,3,7,9] *Propionibacterium* spp. grow in hair follicles and sebaceous glands and are mainly found after puberty, when sebaceous activity increases.[1–3,7,9] Hair follicles are colonized by micrococci and CoNS superficially[8]; *Corynebacterium* and *Propionibacterium* spp. are found deep in follicular canals.[10]

Transient colonization of the skin by pathogens is facilitated by factors that harm the resident flora, including elevated temperature, humidity, and antibiotic therapy.[1–3,8] When a pathogen achieves successful colonization of the skin, the other cutaneous defense mechanisms must be overcome before infection commences. The main determinant of cutaneous infection is the balance between the virulence of the organism and the defense mechanisms of the host.[11] Compromised cutaneous barrier function occurs in patients with chronic dermatitis or injury and in premature infants, making their skin more susceptible to pathogenic colonization and cutaneous infection.[1]

Primary bacterial infection of the skin can involve the epidermis, dermis, or subcutaneous tissue, whereas soft tissue infections extend deeper to the fascia or muscle. Superficial skin infections are mainly limited to the epidermis and dermis; although secondary inflammation can involve the subcutis.[11] Several types of lesions can form in the skin as the result of a primary infectious process (Table 68.1), but a pathogen usually produces a characteristic primary lesion with a characteristic pattern of spread. When cutaneous bacterial infection occurs, recognition of the type and depth of lesion produced are helpful in determining the likely causative agent.

TABLE 68.1

Primary Skin Lesions

Lesion	Description
Macule	Flat lesion <1 cm
Patch	Flat lesion >1 cm
Papule	Elevated lesion <1 cm
Plaque	Elevated, broad, flat lesion >1 cm
Nodule	Dome-shaped or rounded lesion >1 cm Arises from the dermis or subcutis
Pustule	Pus-filled lesion
Vesicle	Elevated lesion <1 cm Filled with serous fluid
Bulla	Elevated lesion >1 cm Filled with serous fluid

Primary, superficial bacterial infections of the skin and cellulitis are the focus of this chapter (Table 68.2). Other infectious agents (e.g., viruses, fungi) that sometimes resemble these bacterial infections are discussed briefly.

TABLE 68.2

Primary Superficial Cutaneous Bacterial Infections

Disease	Skin Lesions	Infectious Agents
Anthrax	Papule, vesicle, bulla	*Bacillus anthracis*
Blistering distal dactylitis	Vesicle	*Streptococcus pyogenes* (group A *Streptococcus*), *Streptococcus agalactiae* (group B *Streptococcus*), *Staphylococcus aureus*
Cellulitis	Plaque	*S. pyogenes*, *S. aureus*

Diphtheria	Papule, pustule, ulcer	*Corynebacterium diphtheriae*
Ecthyma	Pustule, ulcer	*S. pyogenes*
Ecthyma gangrenosum	Papule, vesicle, ulcer, black eschar	*Pseudomonas aeruginosa*
Erysipelas	Plaque, sometimes vesicles or bullae	*S. pyogenes*, groups B, C, and G streptococci
Erysipeloid	Patch, plaque	*Erysipelothrix rhusiopathiae*
Folliculitis	Pustule, papule	*S. aureus, Malassezia* spp.
Sycosis barbae	Pustule, papule	*S. aureus*
Gram-negative folliculitis	Pustule, papule	*Klebsiella* spp., *Enterobacter* spp., *Escherichia coli, P. aeruginosa*
	Pustule, nodule	*Proteus* spp.
Hot-tub folliculitis	Pustule, papule	*P. aeruginosa*
Erythrasma	Patch	*Corynebacterium minutissimum*
Furuncles, carbuncles	Nodule	*S. aureus*
Impetigo	Vesicle, bulla, pustule, plaque, erosion	*S. aureus, S. pyogenes*
Intertrigo	Patch, plaque, erosion	*Streptococcus* spp., *S. aureus, Candida albicans, S. pyogenes*
Paronychia	Patch	Mixed flora
Perianal dermatitis	Patch	*S. aureus, S. pyogenes*
Pitted keratolysis	Erosion	*Kytococcus sedentarius, Dermatophilus congolensis, Corynebacterium* spp.
Tularemia	Papule, vesicle, ulcer	*Francisella tularensis*

Superficial Infections

Impetigo

Impetigo is a common skin infection caused by *S. aureus* and GAS. Impetigo occurs in two forms, bullous and nonbullous, and it is highly contagious. Children between 2 and 5 years of age are affected most often,[12,13] and infection rates peak in the summer and late fall.[14] Impetigo can be a primary infection or a secondary infection involving skin compromised by dermatitis or trauma.[15] Factors that predispose to infection include poor hygiene, crowded living conditions, humidity, pre-existing dermatitis, and minor skin trauma.[10,14,16]

Nonbullous impetigo is the most common form of the infection, accounting for more than 70% of cases of impetigo.[10,15] Lesions of nonbullous impetigo typically form on traumatized skin and are most often located on the exposed skin of the face and extremities.[10,12] Lesions initially begin as small vesicles or pustules that rupture, forming an adherent, honey-colored crust.[10,12,14,16,17] Impetigo is associated with minimal pain or erythema, and constitutional symptoms usually are absent. Pruritus, regional adenopathy, and leukocytosis are commonly associated with nonbullous impetigo. The differential diagnosis of nonbullous impetigo includes contact dermatitis and viral, fungal, and parasitic (e.g., scabies, pediculosis) infections, all of which can be complicated by secondary infection with impetigo. If left untreated, most cases of nonbullous impetigo resolve in approximately 2 weeks without scarring.[15]

The bacterial cause of lesions of nonbullous impetigo cannot be predicted clinically.[15] The predominant cause of nonbullous impetigo in the United States is *S. aureus,* although infection can also be attributed to GAS[10,12–14,16,18] or mixed pathogens.[14,16,18] Anaerobic bacteria have been isolated from lesions of nonbullous impetigo, although their pathogenic role is unclear.[18] *S. aureus* causes impetigo in children of all ages, and the organism usually is present in the nose, perineum, axillae, or underneath the fingernails before causing cutaneous infection. In contrast, infections due to GAS are unusual before 2 years of age, except in highly endemic areas[10]; and GAS colonizes the skin an average of 10 days before development of impetigo by inoculation of organisms into a break in the skin.[10,12] Several types of GAS can cause nonbullous impetigo, and they usually are different from strains implicated in streptococcal pharyngitis.[10]

Bullous impetigo occurs mainly in infants and young children. It is caused by strains of *S. aureus,* usually from phage group 2,[10,16] capable of producing an exfoliative toxin that disrupts cell-to-cell adhesion in the superficial epidermis, leading to superficial blister formation.[12,13,17] Because the lesions of bullous impetigo are a manifestation of localized toxin production, they develop on intact skin.[10] The flaccid bullae and pustules of this form of impetigo occur beneath the stratum corneum and are easily ruptured, leaving shallow erosions with a collarette of scale (Fig. 68.1).[10,15–17] Bullae can be single or clustered; regional adenopathy and systemic symptoms are unusual. The differential diagnosis of bullous impetigo in the neonate includes transient neonatal pustular melanosis, epidermolysis bullosa, bullous mastocytosis, and herpetic infection. Insect bites, contact dermatitis, burns, erythema multiforme, and autoimmune bullous dermatoses must be considered in older children, particularly if the lesions are unresponsive to therapy.

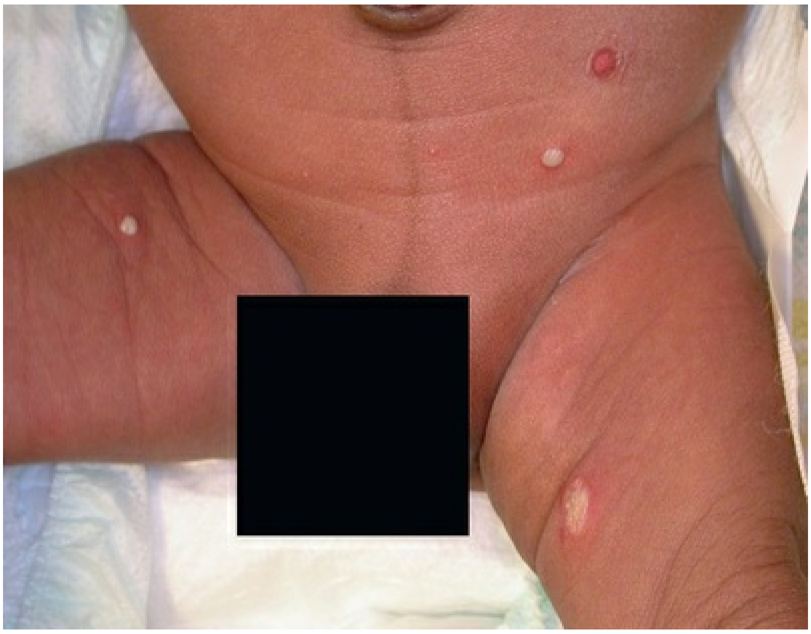

FIGURE 68.1 Scattered pustules on the abdomen and thighs of an infant with bullous impetigo caused by *Staphylococcus aureus*. One lesion has ruptured, leaving an erosion with a collarette of scale.

Complications of impetigo are rare and include invasive infections such as pneumonia, osteomyelitis, pyogenic arthritis, and septicemia. Cellulitis can complicate nonbullous impetigo but rarely is associated with the bullous form. Streptococcal impetigo can be followed by lymphangitis, suppurative lymphadenitis, scarlet fever, and acute glomerulonephritis. Acute poststreptococcal glomerulonephritis occurs after skin and pharyngeal infections with nephritogenic strains of *S. pyogenes* (i.e., M groups 2, 49, 53, 55, 56, 57, and 60 for epidemics associated with impetigo). Symptoms develop an average of 18 to 21 days after skin infection, and children between the ages of 3 and 7 years are most commonly affected.[10] The anti-DNAase B titer is the best serologic test for detecting preceding streptococcal impetigo as the cause of acute glomerulonephritis.[10,12] Strains of *S. pyogenes* associated with endemic impetigo in the United States have little to no nephritogenic potential, and acute rheumatic fever does not occur as a result of impetigo.[10]

Localized impetigo should be treated with topical antimicrobial agents. Topical mupirocin is as effective as oral erythromycin for the treatment of impetigo, and it may be associated with fewer side effects.[19,20] Retapamulin is an effective topical agent for the treatment of impetigo caused by methicillin-susceptible *S. aureus* (MSSA) and GAS. [13,21] Retapamulin applied to lesions twice daily for 5 days was found to be as effective as oral cephalexin twice daily for 10 days in treating secondarily infected skin lesions.[22] Systemic therapy is recommended for patients with widespread lesions and for lesions associated with fever or evidence of deeper involvement (e.g., cellulitis, furunculosis, abscess formation, suppurative lymphadenitis).[10] An agent effective against both *S. aureus* and GAS, such as a first-generation cephalosporin, penicillinase-resistant penicillin, or clindamycin, typically is used when systemic antimicrobial therapy is indicated.[10,12,14,17]

Antibiotic selection is based on local resistance patterns of *S. aureus*. In communities with a high prevalence of methicillin-resistant *S. aureus* (MRSA), clindamycin, trimethoprim-sulfamethoxazole, tetracyclines and fluoroquinolones are appropriate choices for systemic therapy.[15] Antibiotic therapy does not prevent acute glomerulonephritis resulting from GAS impetigo, but it does help to prevent the spread of nephritogenic strains to others.[10,12]

Patients with recurrent impetigo sometimes are evaluated for carriage of *S. aureus*. Focus on controlling density of the organism on skin and in the environment and aggressively managing skin conditions may be more beneficial than attempted decolonization.[10,23] Frequent handwashing and attention to personal hygiene should be emphasized to patients to prevent spread of infection.[14]

Perianal Bacterial Dermatitis

Perianal bacterial dermatitis usually occurs in children between the ages of 6 months and 10 years,[24] and it peaks between the ages of 3 and 5 years.[25] The infection is most commonly caused by GAS, but

S. aureus also can cause infection.[26] Physical examination characteristically reveals superficial, well-demarcated, circumferential erythema extending around the anus and surrounding skin (Fig. 68.2).[24,27,28] Vulvovaginitis with vaginal discharge and vulvar redness is common in girls, as is penile involvement in boys.[24,27] *S. aureus* is the likely pathogen when small papules and pustules on the buttocks and inguinal area are seen in addition to the characteristic findings or when there is extension of erythema onto the buttocks.[26] Additional manifestations include irritability,[28] pruritus, painful defecation (sometimes associated with refusal to defecate), blood-streaked stools, fissures, mucoid discharge, and yellow crust.[24,25,29] Familial spread of perianal dermatitis is common.[24,27] Perianal streptococcal dermatitis is reported to be an infectious trigger for guttate psoriasis, and patients with guttate psoriasis should be examined for asymptomatic GAS infection.[29]

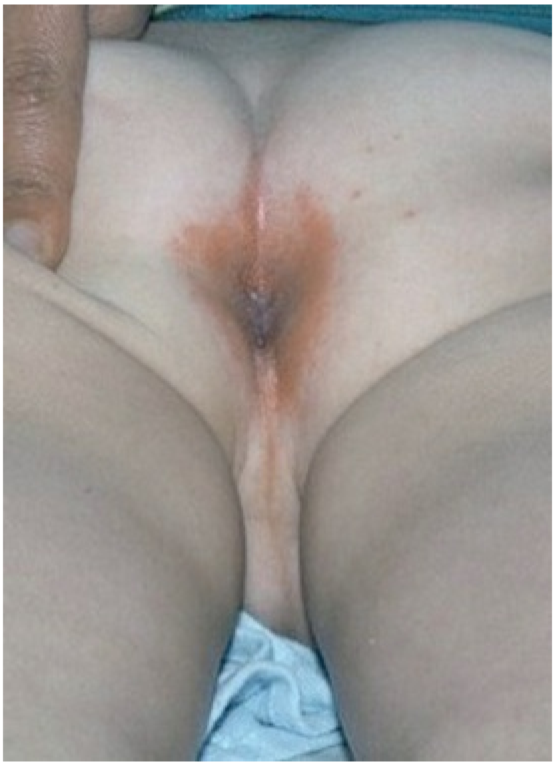

FIGURE 68.2 Brilliant erythematous perianal dermatitis due to group A *Streptococcus*.

The differential diagnosis of perianal bacterial dermatitis includes psoriasis, irritant contact dermatitis, candidiasis, and pinworm infestation. Diagnosis of perianal bacterial dermatitis often is delayed due to misdiagnosis and lack of awareness of the condition,[25] with patients frequently undergoing treatment with topical antifungal agents or topical corticosteroids before the correct diagnosis is made.[24,25] Isolation of *S. pyogenes* or *S. aureus* from culture of perianal swab specimens confirms the diagnosis.[24]

Therapy should be guided by culture results and susceptibility test results. Penicillin is recommended for cases due to GAS; recurrence rates of up to 39% were reported previously,[30] but the rate was only 12% in a recent study.[31] Clindamycin, a β-lactamase resistant penicillin, or a cephalosporin may be useful in cases due to *S. aureus.* A topical antibiotic or erythromycin and mupirocin may be effective as solitary treatment but typically are used as an adjunct to systemic therapy.[32]

Intertrigo

Intertrigo is a disorder of the skinfolds resulting from the friction created by opposing skin surfaces combined with a moist environment. Infants are particularly susceptible to intertrigo because they have deep skinfolds, a flexed posture, chubbiness, and a tendency to drool.[33] Secondary infections with *Candida albicans,* GAS, *S. aureus,* and mixed organisms can occur. Bright red, well-demarcated, weeping patches and plaques are seen in the folds of the neck, axillae, antecubital fossa, inguinal area, or popliteal fossae (Fig. 68.3). Satellite lesions suggest *Candida* infection, whereas streptococcal intertrigo commonly is associated with a foul odor. Affected infants usually appear well but can have associated fever, fussiness, or malaise.[33,34]

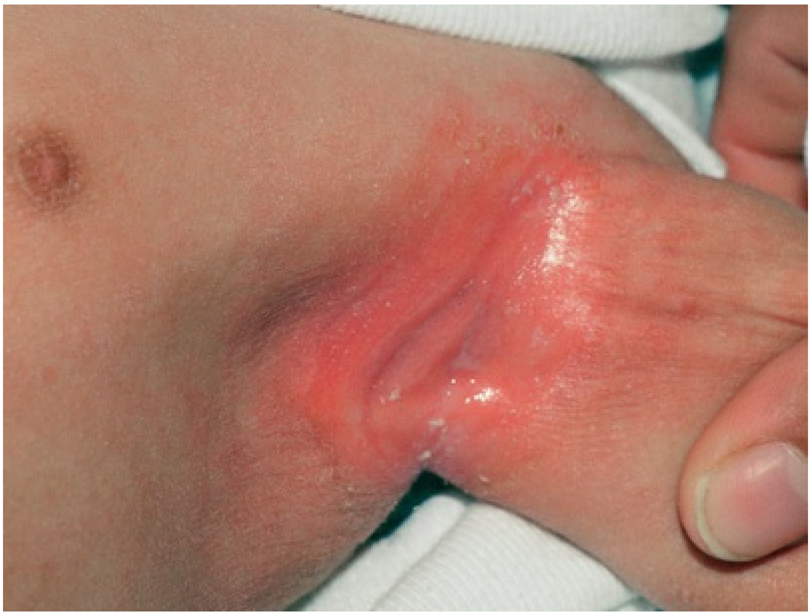

FIGURE 68.3 Erythematous weeping patch of intertrigo in the axillae of a 2-month-old girl, who had similar lesions on the fold of her neck and inguinal creases. Bacterial culture of the lesion grew group A *Streptococcus* and *Staphylococcus aureus*.

The differential diagnosis of intertriginous dermatitis includes seborrheic dermatitis, atopic dermatitis, irritant or allergic contact dermatitis, erythrasma, inverse psoriasis, scabies, and Langerhans cell histiocytosis. The diagnosis is confirmed by culture of a lesion.

Treatment of candidal intertrigo consists of topical antifungal agents such as nystatin, econazole, or ketoconazole, whereas streptococcal intertrigo can be treated with a 10-day course of penicillin or cephalexin in combination with topical mupirocin. Anti-inflammatory agents (e.g., topical 1% hydrocortisone) can be used for associated erythema. Using barrier ointments and ensuring that skinfolds are completely dry reduces the friction and moisture of intertriginous areas, helping to prevent intertrigo.[33]

Erythrasma

Corynebacterium minutissimum is the causative agent of erythrasma. This cutaneous infection manifests as well-demarcated, reddish brown patches and plaques located in moist intertriginous zones. Infections usually occur after puberty. The condition may be asymptomatic or associated with pruritus, and involved skin may be thin with a “cigarette paper” quality.[35] Commonly affected sites include the groin, axillae, intergluteal folds, submammary region, and interdigital spaces of the toes. Heat, humidity, obesity, diabetes mellitus, hyperhidrosis, and poor hygiene are predisposing factors.[35,36]

Erythrasma can be confirmed with a Wood lamp examination. *C. minutissimum* produces porphyrins that fluoresce a brilliant coral-red color under ultraviolet light. However, bathing within 20 hours before the Wood lamp examination can remove the water-soluble porphyrins. When the Wood lamp examination result is negative, a potassium hydroxide examination is useful to exclude dermatophyte infection. Skin scrapings can be stained with periodic acid–Schiff, methenamine silver, or Gram stain to assess for coccobacilli.[35]

The treatment of choice is erythromycin (250 mg four times daily for 2 weeks). Topical clindamycin twice daily also can be used.[36] A single dose of clarithromycin (1g) is reportedly effective for erythrasma in adults.[37]

Pitted Keratolysis

Pitted keratolysis is a skin infection affecting the thick stratum corneum of the plantar surface of the feet and less commonly the palms. Characteristic findings include white, hyperkeratotic areas studded with multiple. 1- to 7-mm, pitted or erosive lesions on the soles, particularly over pressure-bearing sites (Fig. 68.4).[35,38] Ringed erythematous lesions that coalesce can be seen on nonhyperkeratotic areas.[35] The condition can be asymptomatic or associated with hyperhidrosis, foul odor due to production of sulfur compounds, pain, and sliminess of the skin. People whose feet are moist for prolonged periods due to hyperhidrosis, immersion in water, or use of occlusive shoes are affected most frequently. Males are affected more often than females.[35,38,39]

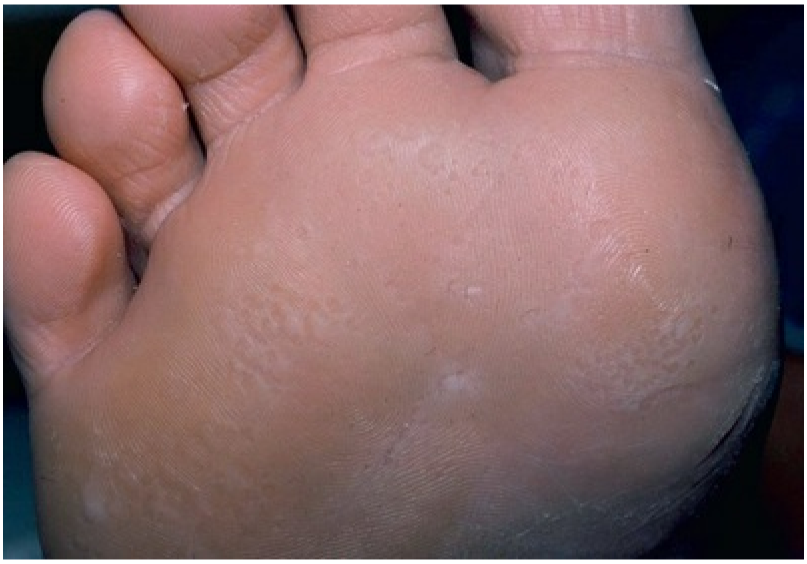

FIGURE 68.4 White plaques with numerous shallow pits on the plantar surface of the foot of a patient with pitted keratolysis.

Kytococcus sedentarius (formerly *Micrococcus* spp.), the suspected causative agent of pitted keratolysis, produces serum proteases capable of degrading keratin in calloused skin.[40] *Dermatophilus congolensis* and *Corynebacterium* spp. also have been implicated as pathogens.[35,38] The diagnosis is based on characteristic clinical findings.

Effective therapeutic regimens include topical therapy for 2 to 3 weeks with erythromycin, clindamycin, mupirocin, benzoyl peroxide, or fusidic acid. Control of hyperhidrosis with topical aluminum chloride or botulinum toxin, improved hygiene, and use of adequately fitting shoes may also help.[35,39]

Trichobacteriosis

Trichobacteriosis (formerly trichomycosis) is an asymptomatic infection of the axillary and less commonly the pubic hair shafts caused by *Corynebacterium flavescens* and other coryneform species.[35,41,42] A bacterial biofilm encases the hair, creating yellow or white concretions distributed along the length of the hair shaft. Hyperhidrosis and a foul odor can be associated with the condition.

The diagnosis is clinical, although a pale yellow fluorescence may be seen with a Wood light examination. Treatment consists of shaving the affected area, applying topical antibiotics (e.g., clindamycin, erythromycin) and use of antiperspirants to control hyperhidrosis.[31,42]

Adnexal and Follicular Infections

Folliculitis

Bacterial folliculitis is a superficial infection of the hair follicle that manifests as discrete, 2- to 5-mm papules and pustules on an erythematous base. The lesions can be single or grouped, and a hair shaft often is seen in the center of the lesion (Fig. 68.5).[17] Lesions usually are located on the scalp, buttocks, or extremities,[15,17] but they can occur on any hair-bearing area.[15]

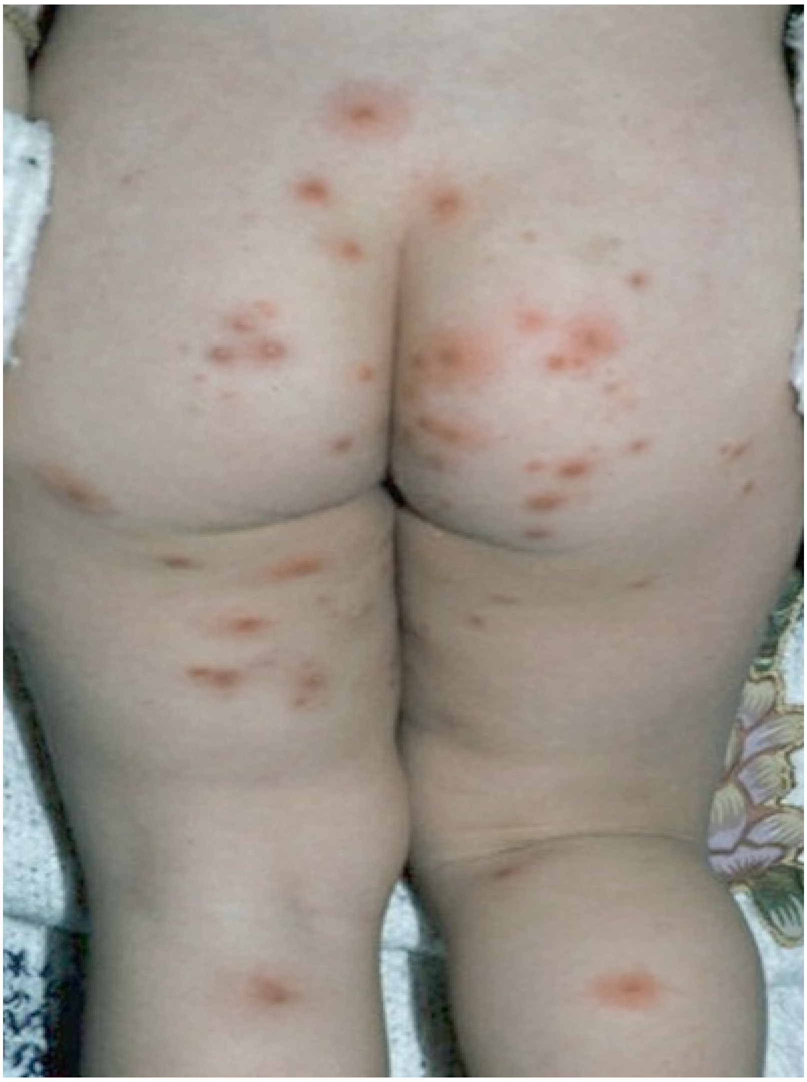

FIGURE 68.5 Erythematous follicular papules and pustules on the buttocks and posterior legs of a young child with folliculitis due to *Staphylococcus aureus*.

Folliculitis can be asymptomatic or accompanied by pruritus; systemic symptoms usually are absent.[17] Gram stain and culture of purulent material from the follicular orifice can identify the causative organism of folliculitis. *S. aureus* is the predominant pathogen,[15,17,43] and affected patients often are chronic carriers of *S. aureus* in the nares, perineum, or axillae.[43] However, gram-negative bacteria also can cause folliculitis (discussed later). The differential diagnosis of bacterial folliculitis includes inflammation of the hair follicle due to physical injury or chemical irritation, eosinophilic folliculitis, insect bites, scabies, pseudofolliculitis barbae, and infection due to *Malassezia* species.

Simple bacterial folliculitis often resolves spontaneously without scarring.[17] When treatment is desired for mild infection, topical antibiotic cleansers such as chlorhexidine, topical antibacterial agents (e.g., mupirocin, clindamycin), and benzoyl peroxide usually are effective.[17,43] In severe or refractory cases, systemic antibiotic therapy (e.g., first-generation cephalosporin, penicillinase-resistant penicillin, clindamycin, tetracycline, fluoroquinolone) is used.[17]

Less common forms of bacterial folliculitis include sycosis barbae, gram-negative folliculitis, and hot tub folliculitis. Sycosis barbae is a severe, recurrent form of facial folliculitis due to *S. aureus*. Painful, erythematous follicular papules and pustules involving the entire depth of the follicle develop on the chin, upper lip, and angle of the jaw, primarily in young black males. Papules can coalesce into plaques, and healing may occur with scarring. Treatment includes warm saline compresses and a topical antibiotic such as mupirocin. Extensive or recalcitrant cases may require therapy with a systemic antistaphylococcal antibiotic with attempted eradication of *S. aureus* carriage.[43]

Gram-negative folliculitis primarily occurs in patients with treatment-resistant acne vulgaris who have received long-term therapy with broad-spectrum systemic antibiotics.[44,45] Prolonged use of antibiotics likely alters normal nasal flora, allowing colonization with gram-negative organisms.[44] However, gram-negative folliculitis also can occur in patients without a history of prolonged antibiotic use.[45] In most patients, lesions consist of perioral and perinasal papules and pustules most often due to *Klebsiella* spp., *Enterobacter* spp., or *Escherichia coli*. A deeper form consisting of inflamed, painful nodules on the face and trunk caused by *Proteus* spp. occurs less commonly. Culture of infected follicles is necessary to establish the diagnosis. Treatment consists of an oral antibiotic selected by susceptibility test results.[44] Isotretinoin is an effective treatment option for severe, recalcitrant cases, but because of the potential for severe side effects, use should be limited to experienced providers.[17]

Hot tub folliculitis is caused by *Pseudomonas aeruginosa*. This infection is seen in patients who bathe in contaminated water or use objects contaminated with *P. aeruginosa,* and it occurs when the bacterium gains entry into the skin through hair follicles or breaks in the skin.[46] Outbreaks of *Pseudomonas* folliculitis have been associated with exposure to underchlorinated swimming pools, whirlpools, hot tubs, and saunas.[46,47] Follicular erythematous macules, papules, and pustules develop in areas of skin exposed to water and abrasive garments (e.g., bathing suits, diving suits). Onset usually occurs 6 to 48 hours after exposure. Fever, malaise, and lymphadenopathy develop occasionally. The eruption usually resolves spontaneously within 1 to 2 weeks,[46,48] often leaving postinflammatory hyperpigmentation.[48]

The diagnosis of hot tub folliculitis is based on history and isolating the organism from culture of purulent lesions. Aa topical agent with antipseudomonal activity (e.g., 0.1% gentamicin cream or ointment) sometimes is used. A systemic antibiotic such as ciprofloxacin is considered for patients with constitutional symptoms.

Pseudomonas hand-foot syndrome, which manifests as painful, red nodules on the palms and/or soles, may be seen in conjunction with hot tub folliculitis or as an isolated infection. The disease course and treatment are similar to those of *Pseudomonas* folliculitis.[46] *Aeromonas hydrophila* folliculitis is an eruption that mimics *Pseudomonas* folliculitis and has been reported in children exposed to contaminated water while swimming.[49]

Malassezia (*Pityrosporum*) folliculitis is a follicular infection caused by the fungus *Malassezia furfur* and is included in the differential diagnosis of infectious folliculitis and truncal acne vulgaris. *Malassezia* folliculitis manifests as pruritic, 2- to 3-mm, monomorphic, erythematous, perifollicular papules and papulopustules on the back, chest, and upper arms.[50–52]

Predisposing factors include diabetes mellitus, malignancy, HIV/AIDS, organ transplantation, and prolonged oral antibiotic therapy.[50,51,53]

The diagnosis of *Malassezia* folliculitis is made by microscopic examination of a potassium hydroxide–treated scraping from a lesion, which reveals budding yeast and spores.[50–52] The skin biopsy also shows dilated follicular ostia with budding yeast and spores, but it rarely is necessary for diagnosis.[50,51,53] Isolation of the organism in culture requires use of a special lipid-containing medium.[51,52]

Mild cases of *Malassezia* folliculitis can be treated with topical imidazoles or selenium sulfide. Systemic antifungal agents (i.e., fluconazole or itraconazole) are indicated for immunosuppressed patients or those with extensive lesions.[50,53] Because recurrence of *Malassezia* folliculitis is common, maintenance regimens of oral or topical antifungal agents often are prescribed after effective treatment.[51,52]

Furuncles and Carbuncles

A furuncle (i.e., boil) is an infection of the hair follicle, but unlike folliculitis in which the infection remains in the epidermis, the inflammation in furuncles extends deep into the dermis.[12,43] Furuncles can originate from a preceding folliculitis and manifest as tender, deep-seated, erythematous, perifollicular nodules with an overlying pustule (Fig. 68.6). With time, the inflammatory mass becomes fluctuant and often opens to the skin surface, draining purulent material.[17] Lesions are found on hair-bearing areas, with the face, neck, axillae, buttocks, and groin commonly affected.

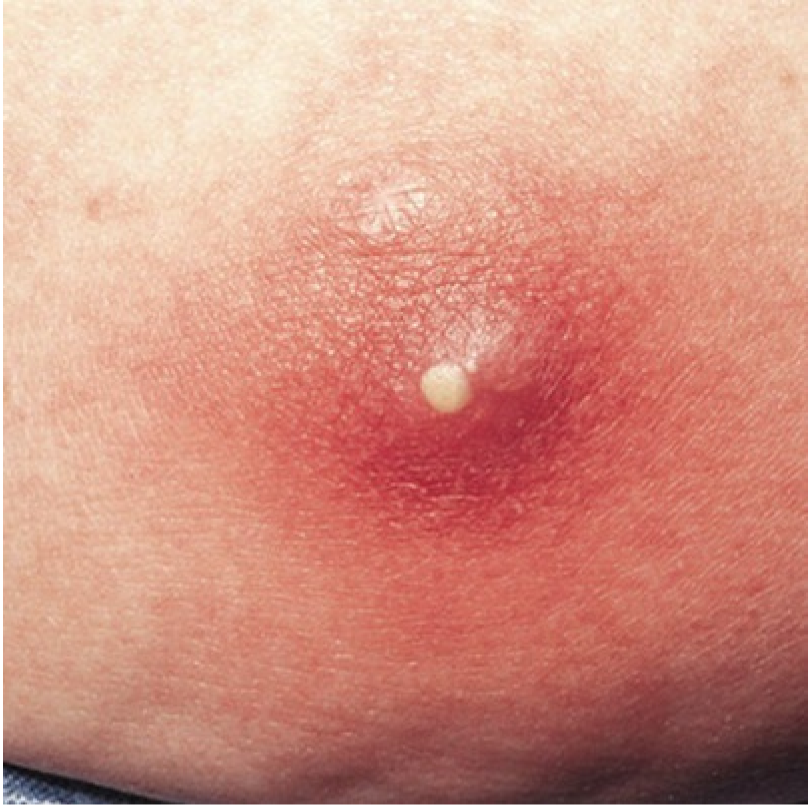

FIGURE 68.6 Furuncle due to *Staphylococcus aureus*.

(Courtesy of J.H. Brien, ©.)

A carbuncle is a painful infection involving an aggregate of contiguous follicles, with multiple drainage points and inflammatory changes in the surrounding connective tissue. Carbuncles commonly are found on the posterior neck and in persons with diabetes mellitus.[12] Although individuals with furuncles usually have no constitutional symptoms, carbuncles can be associated with fever, leukocytosis, and bacteremia. Both furuncles and carbuncles tend to heal with scarring.

The causative agent of furuncles and carbuncles is almost always *S. aureus*. The staphylococcal isolates (i.e., MSSA and MRSA) associated with furunculosis often possess the virulence factor Panton-Valentine leukocidin, a pore-forming toxin that targets neutrophils.[13,43,54] Conditions that predispose to furuncle formation include obesity, immunosuppression, diabetes mellitus, hyperhidrosis, maceration, friction, and pre-existing dermatitis.[43] Outbreaks of furunculosis have been reported in sports teams, families, and other settings with close contact.[12,55]

Recurrent furunculosis frequently is associated with carriage of *S. aureus* at multiple sites (e.g., nares, axillae, perineum) or with sustained close contact with someone who is a carrier. Rarely, children with recurrent furunculosis have an underlying immunodeficiency.[12] Other bacteria or fungi occasionally cause furuncles or carbuncles, and Gram stain and culture of the purulent exudate is indicated. The differential diagnosis of furuncles includes epidermal cysts, cystic acne, and hidradenitis suppurativa.

Treatment consists of frequent application of a hot, moist compress to promote drainage. Large furuncles and most carbuncles require surgical drainage, with disruption of any existing loculations and wound packing as appropriate.[12,13,43] When lesions are large, multiple, or associated with extensive cellulitis or fever, treatment with an oral antistaphylococcal agent is indicated. For recurrent furunculosis, eradication of staphylococcal carriage can be attempted. Attention to personal hygiene, bleach baths, or use of chlorhexidine soap may be beneficial.

Hand and Nail Infections

Paronychia

Acute paronychia is an infection of the soft tissue folds surrounding a fingernail or toenail. Infection occurs when minor trauma allows bacteria to enter the cuticle or nail fold. Paronychia is seen most commonly in children who suck their fingers, bite their nails or cuticles, or have poor hygiene. It also is associated with dishwashing, manicures, and use of artificial nails.

The lateral nail fold becomes warm, erythematous, edematous, and painful, and purulent fluid can accumulate underneath the nail plate. Usually only one nail is affected. In most cases, the infection is caused by *S. aureus* or mixed aerobic (i.e., *S. aureus*, S. *pyogenes*, and *Eikenella corrodens*) and anaerobic flora (i.e., *Bacteroides* spp., *Fusobacterium* spp., and gram-positive cocci).[56–58]

The diagnosis is based on clinical examination. Aerobic and anaerobic culture of purulent material is recommended to recover the pathogens and perform susceptibility testing of *S. aureus*. When exposure to oral flora is suspected (e.g., nail biting), a broad-spectrum oral antibiotic effective against anaerobes (i.e., clindamycin or amoxicillin-clavulanate) is indicated.[56] Warm compresses usually are curative for superficial lesions. In addition to oral antibiotic therapy, incision and drainage is needed for the treatment of deeper lesions with abscesses.

The differential diagnosis of acute paronychia includes chronic paronychia, psoriasis, and herpetic whitlow. Chronic paronychia is distinguished by the duration of symptoms and often is associated with *C. albicans*, usually in people whose hands are frequently exposed to water (e.g., finger sucking, dishwashers, house cleaners, bartenders, food handlers, nurses).[56,57] Herpes simplex virus infection of the fingers can occur after sucking or parental nail trimming by biting. Herpetic whitlow can resemble staphylococcal infection. Multiple coalescing vesicles of the digit associated with edema and a dusky appearance are typical of whitlow. Herpetic lesions should *not* be incised or debrided; instead, oral antiviral therapy should be given.[56,59] Reactivation recurrence is common.

Blistering Distal Dactylitis

Blistering distal dactylitis is an acral infection caused by *S. pyogenes* and less commonly by *S. aureus* or CoNS.[60,61] It usually is seen in children 2 to 16 years of age, but it has been reported in infants and adults.

The infection manifests as a tense nontender bulla with an erythematous base involving the distal volar fat pad of the phalanges.[60–63] Dark discoloration of the surrounding skin may be associated.[60] One or more digits can be affected, as can the nail fold, the volar surfaces of the proximal phalanges, the toes, and the palm.[61–63] Systemic symptoms usually are absent.[60–63] The blisters are filled with a thin, purulent fluid containing neutrophils and the infecting organisms.[60,61] Infections caused by *S. aureus* may be more likely to be associated with pain and involvement of more than one digit.[62]

The diagnosis is based on examination and culture. Treatment consists of incision and drainage or a 10-day course of systemic therapy, or both, using an agent with antistaphylococcal and antistreptococcal activity.[60,62,63]

Ulcerative Infections

Anthrax

Bacillus anthracis causes inhalational, gastrointestinal, meningeal, and cutaneous infections. Cutaneous anthrax in the United States is limited mainly to individuals who work with contaminated animals or animal products, including carcasses, hair, and wool. However, cases due to acts of bioterrorism have been reported.

Cutaneous infection occurs 1 to 7 days after exposure or inoculation of an endospore into the skin, usually at the site of a cut or abrasion.[64] Exposed sites such as the face, neck and arms are the most common locations.[65] The primary lesion is a small, painless, pruritic papule that transforms over a few days into a 1- to 2-cm bulla, which can be associated with satellite vesicles. Characteristic brawny, nonpitting edema surrounds the lesion. The bulla ruptures, forming an ulcer with a central black eschar[64,66] (Fig. 68.7). Malaise, low-grade fever, and regional lymphadenopathy are common.[64]

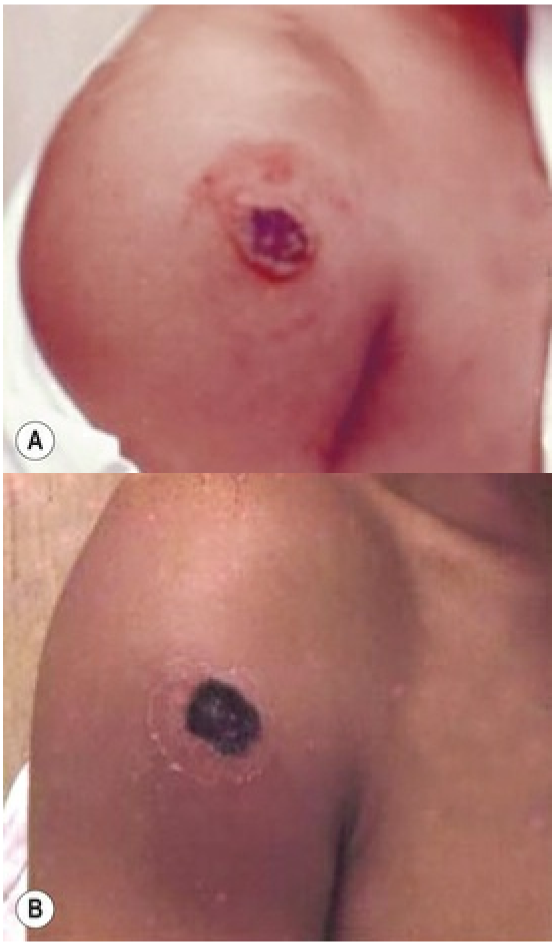

FIGURE 68.7 Cutaneous anthrax. (A) The ulcer has a vesicular ring, induration, and erythema. (B) As an eschar forms, induration lessens; surrounding

desquamation occurs, but erythema persists. (From Centers for Disease Control and Prevention.)

The differential diagnosis includes ecthyma, ecthyma gangrenosum, a furuncle, and necrotic arachnidism. Diagnosis is based on a Gram-stained smear, culture, or polymerase chain reaction (PCR) analysis of vesicular fluid, eschar, or tissue.[64,67] Incision and drainage of the lesion can precipitate bacteremia, but a skin biopsy of a lesion while administering antibiotic therapy likely confers minimal risk.[64,68] Recommendations for obtaining specimens are available from the Centers for Disease Control and Prevention (www.cdc.gov/anthrax/labs/recommended_specimen.html).

Treatment of mild, naturally occurring, cutaneous anthrax consists of penicillin or ciprofloxacin for 7 to 10 days. Cutaneous anthrax in children without systemic involvement associated with bioterrorism is treated with ciprofloxacin or doxycycline for 60 days due to the risk of inhalational exposure to the spores. Therapy can be modified based on antimicrobial susceptibility test results.[64,67]

Diphtheria

Cutaneous infection with *Corynebacterium diphtheriae* is rare in developed countries. It is seen mainly in travelers to endemic tropical areas,[41,69–71] the immunosuppressed, and those living in crowded, unsanitary conditions.[41,69] Infection can occur despite adequate immunization.[41,70]

Cutaneous diphtheria occurs in three forms: primary infection, which consists of a tender pustule that evolves into a punched-out ulcer with an adherent membrane and erythematous, edematous rim; secondary infection of a pre-existing ulcer or wound; and superinfection of eczematous skin lesions.[69,71] Lesional skin sheds bacteria for 2 to 6 weeks without treatment and is an important reservoir for person-to-person transmission and environmental contamination of pathogenic organisms, which can cause cutaneous and respiratory disease.[41,70,71] Systemic complications, including neurologic symptoms and myocarditis, are rare in immunized patients[70,71] and more often are associated with respiratory tract infection than cutaneous diphtheria.[41]

Culture of a lesion or its overlying membrane confirms the diagnosis, and laboratory personnel must be notified when *C.*

diphtheriae is suspected. Treatment consists of cleansing the affected skin and administering systemic antibiotic therapy with penicillin or erythromycin for 10 to 14 days.[41,71] The use of antitoxin in addition to systemic antibiotics is controversial[41,69] because cutaneous lesions are nontoxigenic or produce only small amounts of toxin.[71] To document eradication of the organism, two negative culture results should be obtained after treatment concludes.[41]

Ecthyma

Ecthyma is a rare, deep ulcerative infection of the skin that penetrates down to the dermis and is most commonly caused by *S. pyogenes*. Initially, a vesicle or vesicopustule with surrounding erythema develops; over time, the lesion evolves into a crusted ulcer with an elevated rim and heals with scarring. Lesions usually are located on the legs and frequently are associated with pruritic conditions such as insect bites or scabies. Lymphangitis, cellulitis, and poststreptococcal glomerulonephritis are potential complications of ecthyma.

Systemic antibiotic therapy with an agent effective against streptococci is recommended.[11] Noninfectious causes of ulcerative skin lesions such as pyoderma gangrenosum, vasculitis, cutaneous findings associated with Behçet disease, lymphomatoid papulosis, and factitial dermatitis should be considered if lesions do not improve with appropriate antibiotic therapy.

Ecthyma Gangrenosum

Ecthyma gangrenosum is the characteristic skin lesion associated with gram-negative organisms, especially *Pseudomonas aeruginosa*. *Pseudomonas* septicemia usually occurs in the setting of neutropenia or congenital neutrophil dysfunction, but it also has been described in healthy children, often younger than 1 year of age.[72]

Cutaneous findings are the result of a necrotizing bacterial vasculitis affecting small veins in the skin. Lesions begin as erythematous, indurated papules, vesicles, and nodules that progress over hours to days into a necrotic ulcer with a black eschar and an erythematous rim (Figs. 68.8 and 68.9). Lesions are most common on the gluteal and perineal areas, but they can occur anywhere.[73,74] Ecthyma gangrenosum also can manifest in a localized form, usually on the buttocks and legs, after inoculation of the organism into the skin. The localized form of ecthyma gangrenosum usually is not associated with bacteremia[11,74,75] and can occur in healthy children or those with occult immunodeficiency.[75]

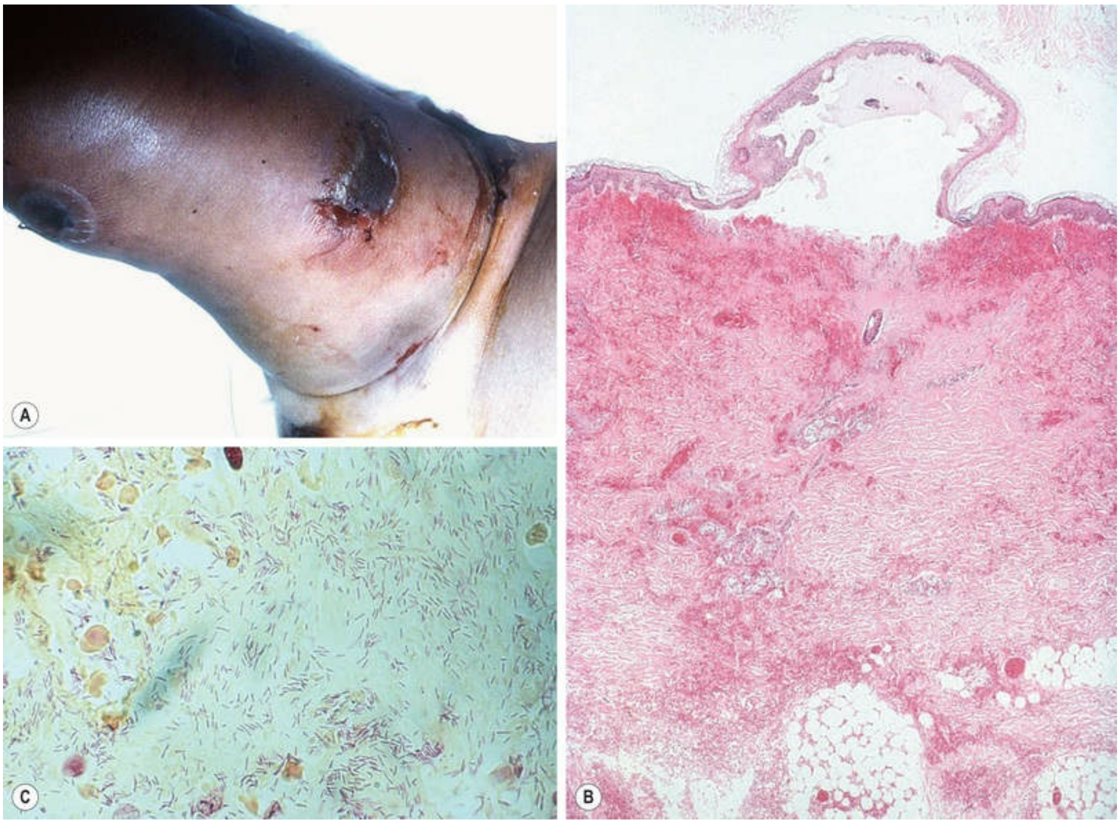

FIGURE 68.8 (A) *Pseudomonas aeruginosa* septicemia and ecthyma gangrenosum in a young boy with severe neutropenia. (B) Microscopic appearance of ecthyma gangrenosum in a fatal case of *P. aeruginosa* septicemia in an infant with leukemia. Haematoxylon and eosin stain shows superficial necrosis and elevation along with bland ischemic necrosis beneath. Gram stain of fluid from the bullous lesion (B) shows dense gram-negative bacilli with rare inflammatory cells (C). (Courtesy of J.H. Brien, ©.)

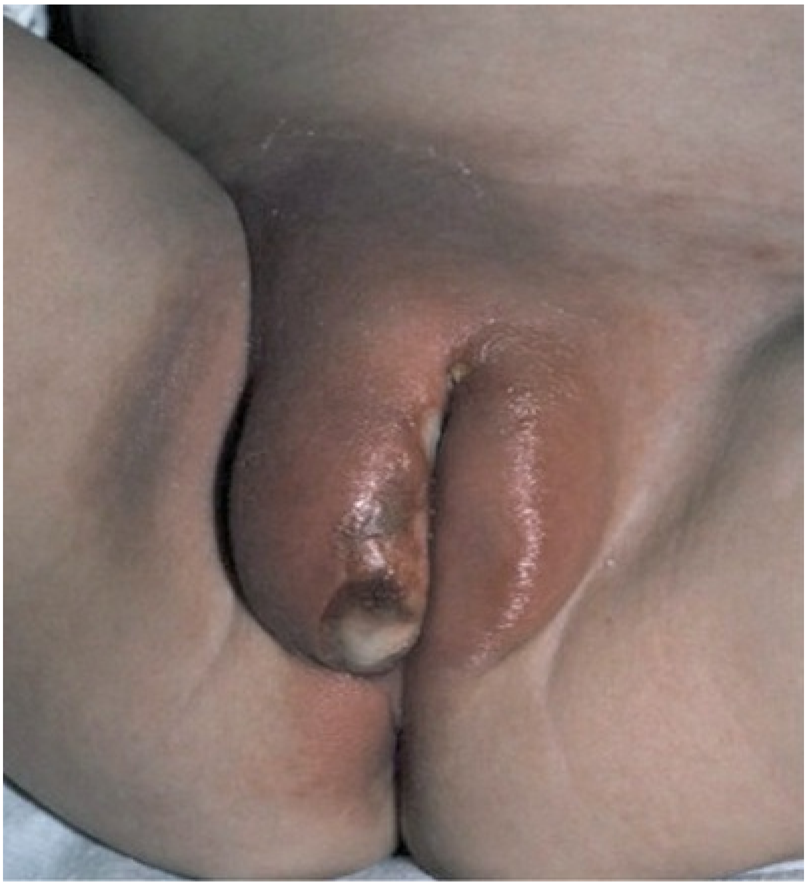

FIGURE 68.9 Ecthyma gangrenosum due to *Pseudomonas aeruginosa.* Necrotic ulcers with surrounding erythema and edema formed on the labium majus of a young girl with neutropenia and leukemia.

Culture of the lesions and blood cultures confirm the diagnosis. Ecthyma gangrenosum–like lesions can develop as a result of infection with other agents, usually in the setting of immunosuppression. Etiologic agents include gram-negative bacteria other than *P. aeruginosa,*[12,74] MSSA, MRSA[74] *Streptococcus* species,[75] *Candida* species, fungi (i.e., *Aspergillus, Mucor,* and *Fusarium* species),[12] and herpesviruses.[74] Effective treatment requires prompt initiation of an antibiotic effective against *P. aeruginosa* or other likely causative organisms.

Tularemia

Francisella tularensis can cause an ulcerative lesion associated with the bite of a tick or deer fly or direct contact with infected animals, most often rabbits or squirrels. Infection manifests in several different forms. The ulceroglandular form of tularemia is associated with cutaneous findings.

Lesions occur an average of 1 to 9 days after exposure[76] and begin as an erythematous, indurated papule or vesicle that may evolve into a punched-out ulcer with regional lymphadenopathy. Lesions can be accompanied by fever and malaise and can last for several weeks.[77] Papular eruptions, erythema nodosum, and erythema multiforme also can occur.[78]

The differential diagnosis includes anthrax, ecthyma, and other ulceroglandular infections, including glanders, bubonic plaque, and cat-scratch disease. If infection with *F. tularensis* is suspected, culture of the lesion is not recommended because of transmission to laboratory staff. Serologic testing is the primary method for confirming the diagnosis.[77,78]

Treatment with gentamicin or streptomycin for 10 days is preferred. Doxycycline or ciprofloxacin are alternatives.[76,77]

Soft Tissue Infections

Erysipelas

Erysipelas is a superficial skin infection affecting the upper dermis and the lymphatic system. In most cases, GAS is causative,[12,13,17,79] but group B, C, and G streptococci occasionally cause the infection,[12,79] and rarely, *S. aureus, Streptococcus pneumoniae, Klebsiella pneumoniae, Yersinia enterocolitica,* and *Haemophilus influenzae* are implicated as pathogens.[79]

Erysipelas has a bimodal age distribution; it is seen most often in young children and older adults.[12,79] Infection occurs when disruption of the skin barrier allows entry of organisms into the skin, and it often is associated with abrasions, leg ulcers, intertriginous or pedal fungal infections, insect bites, venous or lymphatic obstruction, and chronic edema.[12,13,79,80] In neonates, infection can originate at the umbilical stump and spread to the abdominal wall.[79]

The onset of erysipelas is abrupt and is characterized by a painful, bright red, shiny, edematous plaque with well-demarcated and slightly raised borders. In severe cases, necrosis and bullae can occur. Infection occurs on a lower extremity most often or the face, and it can be associated with regional lymphadenitis.[12,13,17,79] Fever, chills, and malaise can precede the onset of cutaneous manifestations. Potential systemic complications of erysipelas include septicemia, streptococcal toxic shock syndrome, endocarditis, and meningitis; however, complications are rare with prompt diagnosis and appropriate treatment.

The differential diagnosis includes contact dermatitis, burns, cellulitis, ecthyma gangrenosum, cutaneous findings associated with familial Mediterranean fever, and urticaria.[79] Diagnosis of erysipelas is made primarily on clinical grounds.[13,79] Blood culture, skin biopsy and needle aspiration have low yields.[12]

Treatment of erysipelas in immunocompetent patients consists of oral penicillin for 10 to 14 days, with follow-up after 48 to 72 hours to ensure the infection is improving. Patients with severe infections, young infants, and immunosuppressed patients may require hospitalization for parenteral therapy.[79] For penicillin-allergic patients, macrolide (depending on regional rates of resistance), clindamycin, or linezolid therapy is considered.[12,79] An antistaphylococcal antibiotic should be used.[12] Local wound care and attention to predisposing factors (e.g., treating tinea pedis, elevating edematous legs) are important aspects of care. Prophylactic therapy is considered infrequently for patients with recurrent disease.[12,79]

Cellulitis

Cellulitis is an acute infection of the skin involving the dermis and subcutaneous tissues that manifests as edema, warmth, erythema, and tenderness of the skin. The lateral margins of cellulitis tend to be indistinct, unlike the well-demarcated borders of erysipelas (Fig. 68.10). Vesicles, bullae, and petechiae can occur on involved skin. The lower legs are affected most commonly, but infection can occur at any site. Associated findings include lymphangitis, regional lymphadenopathy, fever, chills, and malaise. Predisposing factors for cellulitis include pre-existing skin infections (e.g., ecthyma, impetigo), breaks in the skin due to trauma or insect bites, lymphatic obstruction or other causes of edema, leg ulcers, and obesity.[12,13] When cellulitis occurs in a periorbital distribution, especially in the absence of a break in the skin, orbital cellulitis should be considered.

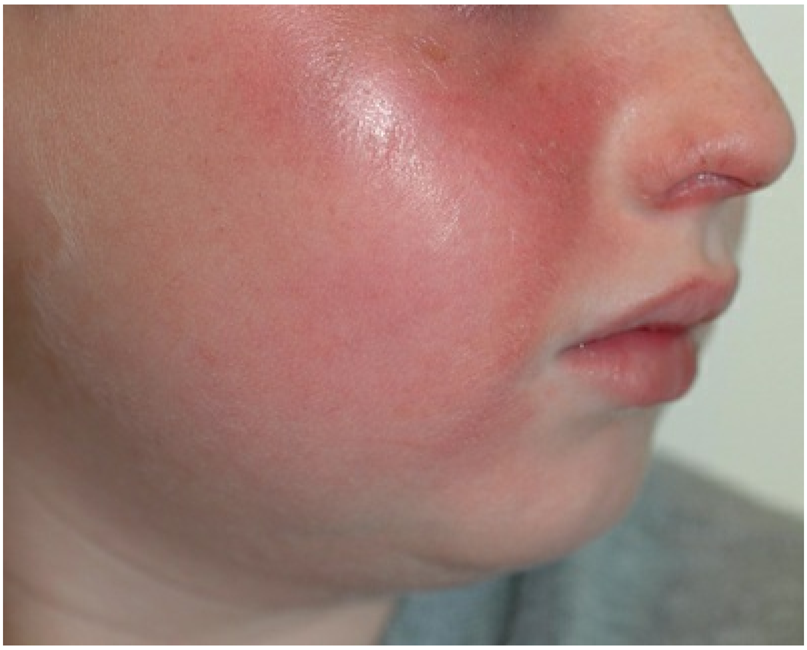

FIGURE 68.10 Ill-defined erythema and edema on the cheek of a boy with cellulitis. (Courtesy of Brandon Newell, MD, Kansas City, Missouri.)

The most common etiologic agents are *S. pyogenes* and *S. aureus*.[12,43] When facial cellulitis in children is associated with a portal of entry such as a tooth abscess, bite wound, or cutaneous trauma, oral anaerobic bacteria can be causative.[81] *H. influenzae* type b (Hib) was an important cause of periorbital[13] and facial cellulitis without a skin site of injury or infection in children 3 months to 3 years of age before the introduction of the conjugate vaccine. Hib cellulitis has a characteristic bluish discoloration resembling a bruise and often is associated with bacteremia.[82] Bacteremic *S. pneumoniae* can cause facial cellulitis in children resembling that due to *H. influenzae*.[83] In patients who are immunocompromised or have been exposed to animals or special conditions, other bacterial or fungal agents must be considered (Table 68.3).

TABLE 68.3
Special Causes of Cellulitis

Setting or Exposure	Causes of Cellulitis
Cat or dog bites	*Pasteurella* species, *Capnocytophaga canimorsus*
Penetrating trauma	*Staphylococcus aureus*
Freshwater immersion	*Aeromonas hydrophila*
Saltwater immersion	*Vibrio* species
Freshwater, saltwater fish	*Streptococcus iniae*
Swine, poultry, fish	*Erysipelothrix rhusiopathiae*

Periorbital or facial cellulitis	*Haemophilus influenzae, Streptococcus pneumoniae*
Neutropenia	*Pseudomonas aeruginosa,* other gram-negative bacilli
Human immunodeficiency virus infection	*Helicobacter cinaedi*
Acute varicella	*Streptococcus pyogenes*
Immunosuppression	*Cryptococcus neoformans*

Diagnosis is based on physical examination and a detailed history to elicit factors predisposing to cellulitis due to a less common pathogen. Blood culture should be performed in the setting of young age or systemic illness; otherwise, the yield is low.[84] Culture of an aspirate from the site of inflammation yields a pathogen in 10% of patients,[85] with an aspirate taken from the point of maximum inflammation yielding the causal organism more often than does a leading-edge aspirate.[86] Tissue culture is positive for 18% to 20% of patients, and the density of organisms is low,[85,87] although a higher density of organisms has been found in specimens taken from a site near an ulcer.[87] Culture of a primary lesion (e.g., ulcer, abrasion) corresponds to that of a tissue culture and can avoid a more invasive procedure.[85] Due to low yield, aspirates and tissue cultures usually are reserved for cases of severe or atypical cellulitis or for patients who are immunocompromised or are not responding to empiric therapy.

Uncomplicated cellulitis in immunocompetent patients should resolve with antimicrobial therapy targeting streptococci and staphylococci. If fever and lymphadenopathy are absent, outpatient treatment using a penicillinase-resistant penicillin, first-generation cephalosporin, or clindamycin is appropriate.[12,13] The need for an agent providing coverage for community-associated MRSA should be guided by local prevalence and antibiotic susceptibilities. Parenteral therapy is instituted for fever, rapid progression, lymphangitis, or lymphadenitis. When erythema, warmth, edema, and fever have decreased substantially in uncomplicated cases, a 10-day course of treatment can be completed with oral therapy. Adjunctive care includes elevation of the affected extremity, analgesic for pain, and tetanus immunization when appropriate.[17]

Erysipeloid

Erysipeloid is a rare, acute cutaneous infection resulting from traumatic inoculation of *Erysipelothrix rhusiopathiae* into the skin. Infection usually occurs in patients with occupational exposure to raw fish, poultry, and meat products[88,89] or to contaminated animals, especially swine.[88]

Localized cutaneous infection manifests as a well-demarcated, erythematous-to-purple inflammatory plaque with raised borders on the dorsal aspect of one hand or fingers, and it typically occurs 2 to 7 days after inoculation. The lesion spreads peripherally and can display central clearing.[88,89] Vesicles, bullae, and edema of the fingers sometimes are seen. Lesions can be asymptomatic or associated with pain, pruritus, or fever.[88]

Untreated, limited cutaneous infection can resolve spontaneously after 2 to 3 weeks, but it can recur weeks to months later.[89] Rarely, a diffuse cutaneous form of infection occurs, manifesting as lesions over several areas of the body,[88,89] and it may be associated with fever, lymphadenopathy, myalgia, and arthralgia. Rare systemic complications of erysipeloid include encephalitis, meningitis, endocarditis, pyogenic arthritis, and sepsis.[88]

E. rhusiopathiae is difficult to isolate, although tissue culture of the advancing edge of the lesion can identify the organism.[89] Diagnosis is based mainly on the patient's occupation or exposure history, clinical findings, and rapid improvement with antibiotic therapy. The recommended treatment for localized cutaneous infection is penicillin or a cephalosporin for 7 days, with improvement usually seen after 2 to 3 days.[88]

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69

Erythematous Macules and Papules

Brittany S. Barros, Andrea L. Zaenglein

Approach

Differentiating rashes due to infection from other common cutaneous eruptions, particularly adverse drug eruptions, can be difficult. Recognizing the differences in presentation and using proper terminology for erythematous exanthems are the initial steps.

The commonly used (and often overused) term *maculopapular* describes a rash that has both macular and papular components at some time during the course of the disease. *Morbilliform* (i.e., measles-like) is used to describe uniform lesions that have coalesced. *Scarlatiniform* is used when the exanthem resembles scarlet fever (i.e., has a sandpaper feel and is confluent in the flexural areas). If lesions are generalized but remain discrete, the term *rubelliform* may be used.

Secondary characteristics should be added to further describe the exanthem; *annular, lacy, reticulated, evanescent, urticarial, petechial,* and *purpuric* are useful descriptors. Color is described in shades, and erythema can range from faint pink to violaceous red.

Many of the classic exanthems, such as measles, rubella, and erythema infectiosum, are associated with macules or papules on the skin. Differentiating common and uncommon causes of infectious rashes often is difficult because the patterns are not always unique to a specific infectious agent. Detailed and accurate history taking is vital to making a correct diagnosis (Box 69.1). The patient's age and pre-existing conditions are important because many infectious rashes occur predominantly within a specific age range or in the context of another illness.

Box 69.1

Questions Used to Elucidate the Causes of Exanthems

- What time of year did the rash start?
- Where on the body did the rash start, and how has it evolved?
- Is the eruption localized or generalized?
- Does the rash come and go? Over what timeframe?
- Is the rash worse at a specific time of day? Is the rash made worse by the sun?
- Is there an associated enanthem?
- Is the rash pruritic, painful, or asymptomatic?
- Are there other symptoms, such as joint swelling, fever, adenopathy, vomiting, cough, headache, or photophobia?
- Is there a recent history of use of any medications, including over-the-counter medications?
- Has there been a recent illness?
- Has there been recent exposure to another person with a similar illness? Is the child in group childcare or school?
- Are immunizations up to date?
- Is there an immunocompromising condition or drug?
- Where was the child born? Has there been recent travel?
- Has there been recent exposure to pets, wildlife, or biting insects?

- What evaluations, including laboratory studies and cultures, have been done already?

- Has treatment been given? Was the treatment effective?

Etiologic Agents, Epidemiology, and Pathogenesis

Macular and papular exanthems can result from numerous infectious causes. An extensive list of viral and nonviral causes is shown in Box 69.2. In children, enteroviruses are by far the most common cause of morbilliform rash with febrile illness, especially for those younger than 1 year of age[1] (Fig. 69.1). Enteroviruses have a marked seasonality, with an increase in prevalence in the summer and a large peak in August and autumn. Parvovirus B19, the etiologic agent of erythema infectiosum, is the maculopapular rash most commonly identified in children 4 through 10 years of age.[2] The exanthem is typified by bright red macules on the cheeks that spare the nasolabial folds (Fig. 69.2), followed by the development of reticulated lacy pink macules and thin papules on the extremities that can persist for up to 3 weeks. Measles occurs as sporadic imported cases or in high-profile outbreaks in the United States and is still prevalent worldwide. Measles is characterized by the classic morbilliform rash accompanied by fever and the three Cs: cough, conjunctivitis, and coryza.[3]

Box 69.2

Infectious Conditions That Cause Macular and Papular Exanthems

Viruses

Human Herpesviruses

Erythema multiforme

Varicella

Shingles

Mononucleosis

Pityriasis rosea

Roseola infantum

Poxviruses

Smallpox

Vaccina

Orf disease

Milker nodules

Cowpox

Molluscum contagiosum

Polyomaviruses

Trichodysplasia spinulosa

Picornaviruses (Coxsackievirus and Echovirus)

Nonspecific exanthems

Hand-foot-and-mouth disease

Boston exanthem

Eruptive pseudoangiomatosis

Paramyxoviruses

Measles

Rubella

Parvoviruses

Erythema infectiosum

Papular-purpuric gloves and socks syndrome

Arboviruses

West Nile fever

Dengue

Alphavirus

Human Papillomaviruses

Warts

Retroviruses

Human T-lymphotropic virus 1 infection

Conditions With Likely Viral Causes

Gianotti-Crosti syndrome

Unilateral laterothoracic exanthem

Bacteria

Impetigo

Folliculitis

Paronychia

Staphylococcal scalded skin syndrome

Toxic shock syndromes

Scarlet fever

Erysipelas

Cellulitis

Perineal dermatitis

Rheumatic fever

Erythrasma

Actinomycosis

Ecthyma

Hot tub folliculitis

Meningococcemia

Gonococcemia

Salmonellosis

Glanders

Cat-scratch disease

Bacillary angiomatosis

Rat-bite fever

Tularemia

Brucellosis

Ehrlichiosis

Anaplasmosis

Leptospirosis

Lyme disease

Secondary syphilis

Yaws

Pinta

Rickettsia

Epidemic typhus

Endemic typhus

Rocky

Mountain spotted fever

Mediterranean spotted fever

African tick bite fever

Yucatan spotted fever

Japanese spotted fever

North Asian tick-bite fever

Queensland tick typhus

Scrub typhus

Rickettsialpox

Q fever

Protozoa

Amebiasis cutis

Leishmaniasis

Trypanosomiasis

Toxoplasmosis

Helminths

Trematodes

Freshwater swimmers' itch

Saltwater marine dermatitis

Nematodes

Pinworms (can cause generalized papules)

Hookworms

Larva migrans

Onchocerciasis

Fungi

Dermatophytes

Tinea capitis

Tinea corporis

Tinea faciei

Tinea cruris

Majocchi granuloma

Early Cutaneous or Deep Fungal Infections

Blastomycosis

Histoplasmosis

Coccidioidomycosis

Phaeohyphomycosis

Chromomycosis

Sporotrichosis

Fusariosis

Aspergillosis

Alternaria infection

Yeast

Candidiasis

Tinea versicolor

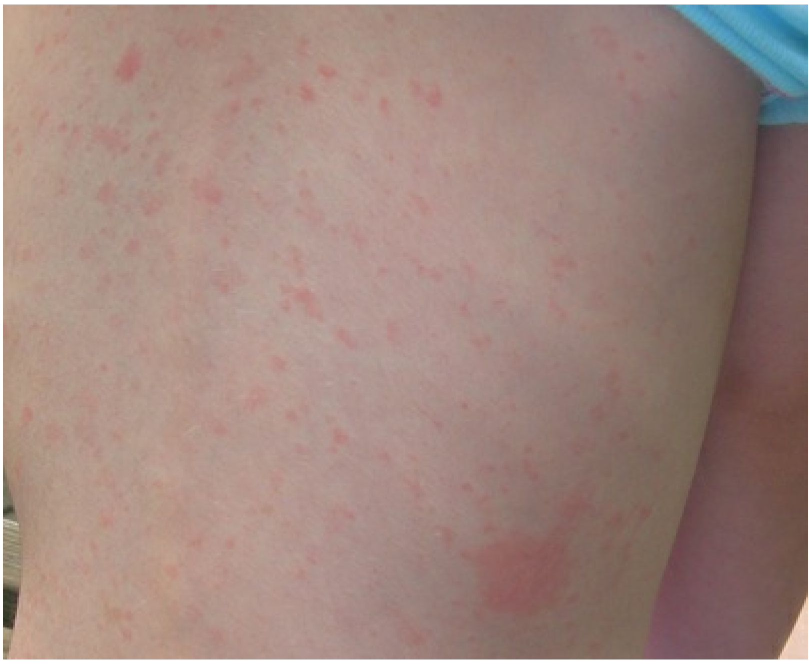

FIGURE 69.1 Discrete, confluent, erythematous, pink, blanchable papules are associated with enterovirus infection.

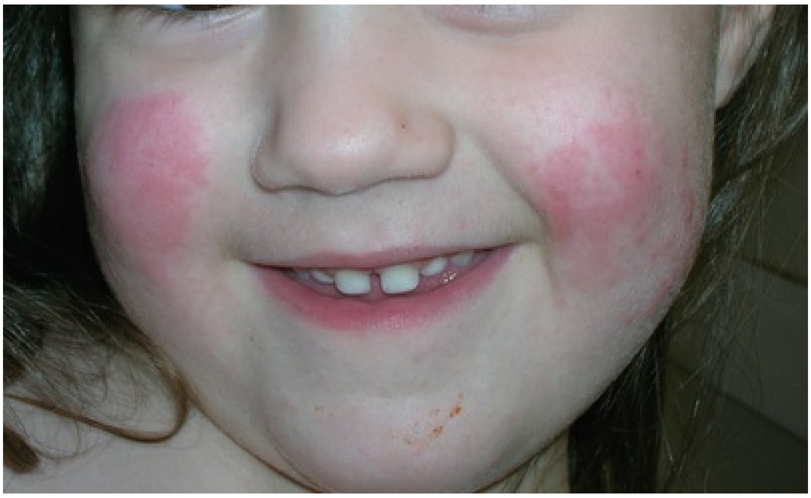

FIGURE 69.2 Bilateral, bright red, macular erythema of the cheeks is typical of parvovirus infection.

Maculopapular rashes in children also can be indirectly related to an infectious agent. An estimated 1.2% to 12% of children develop cutaneous adverse reactions to medications, especially antibiotics.[4] Many cutaneous adverse drug eruptions (CADEs) are indistinguishable from viral exanthems because they have a similar morphology and course (Fig. 69.3). In the case of mononucleosis caused by Epstein-Barr virus, the administration of an antibiotic (classically ampicillin) can lead to a florid maculopapular rash in about 3% of children.[5] More severe CADEs, including Stevens-Johnson syndrome and toxic epidermal necrolysis, can manifest with macules and papules before progressing to blistering. Mucosal involvement in this setting should alert the clinician to this possibility.

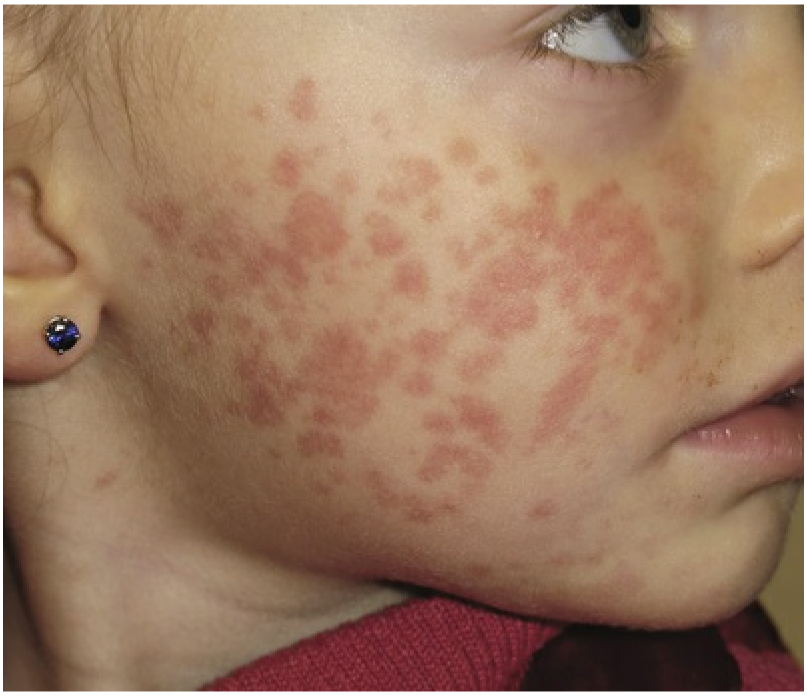

FIGURE 69.3 Many cutaneous adverse drug eruptions are indistinguishable from viral exanthems. The generalized, pink, erythematous macules occurred on a 2-year-old child with an upper respiratory infection that was treated with amoxicillin.

A drug reaction with eosinophilia and systemic symptoms (DRESS) is another severe CADE manifesting with a widespread morbilliform eruption and often with pronounced facial swelling associated with variable systemic involvement, including liver, renal, and pulmonary dysfunction. Type 4 delayed hypersensitivity and reactivation of human herpesvirus 6 have been postulated in the etiopathogenesis of this CADE.[6]

Common noninfectious causes of macular and papular exanthems are listed in Table 69.1. These disorders should be considered in the differential diagnosis.

TABLE 69.1

Common Noninfectious Causes of Macular and Papular Exanthems

Predominantly Papules	Predominantly Macules	Macules and Papules
Insect bites Acne Keratosis pilaris Miliaria	Sunburn Dermatomyositis Systemic lupus erythematosus	Adverse drug eruptions • Urticarial drug reaction • Morbilliform drug reaction • Early Stevens-Johnson syndrome or toxic

Granuloma annulare Cnidarian stings		epidermal necrolysis • Drug reaction with eosinophilia and systemic symptoms (DRESS) Atopic dermatitis Seborrheic dermatitis Guttate psoriasis Contact dermatitis Polymorphous light eruption

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70

Vesicles and Bullae

James Treat

Vesicles and bullae (i.e., blisters) result from a disturbance of epidermal or basement membrane connections, creating spaces that allow fluid collection. Blisters can be caused directly by bacterial, viral, and fungal infections or be a reactive phenomenon to an infection. Diagnosis of vesiculobullous eruptions must be made promptly because although some conditions are benign, others are rapidly progressive and rarely life-threatening.

The skin consists of epidermis, composed primarily of keratinocytes, and an underlying dermis of connective tissue (Fig. 70.1). The basement membrane zone anchors the epidermis to the dermis. Cohesion between layers of the skin is weakest in the epidermis at the stratum corneum–spinous cell transition zone and within the least electron-dense region of the basement membrane zone, called the *lamina lucida*. A plane of cleavage (i.e., blister) is most likely to develop at these levels (see Fig. 70.1). The Nikolsky sign results when application of a lateral, sliding force to nonblistered skin (usually at a site of erythema or adjacent to a bullous lesion) produces a plane of cleavage. This maneuver can be useful in the clinical recognition of a blistering disorder but cannot be used to judge the depth of the blister in the skin.

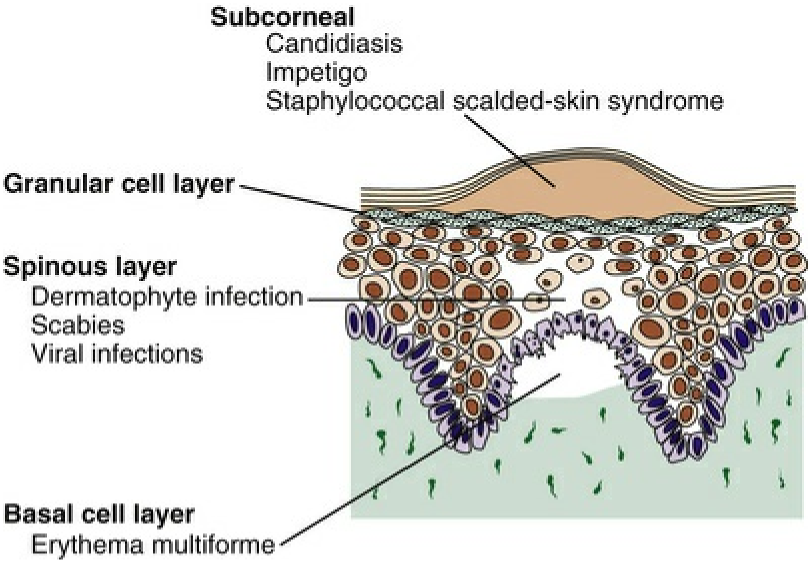


FIGURE 70.1 Sites of vesiculobullous diseases in the skin.

Vesicles and bullae are circumscribed, elevated lesions filled with clear fluid. Depending on the mechanisms responsible for their formation, blisters can contain a combination of serous or lymphatic fluid, serum proteins, antigen-antibody complexes, and soluble inflammatory mediators. Cellular elements can include inflammatory cells, erythrocytes, detached epidermal cells, and infectious agents. Vesicles measure less than 1 cm in diameter, and bullae are 1 cm or larger. Vesicles and bullae associated with infection can be solitary, such as the lesion of streptococcal blistering dactylitis; localized, as in staphylococcal bullous impetigo; grouped or clustered, as in herpes simplex virus (HSV) infection; arranged in a dermatome, as in herpes zoster; or generalized, as in chickenpox.

A vesicle or bulla that is located in the epidermis tends to be *flaccid* and to rupture easily. When located subepidermally, bullae typically are *tense,* have greater structural integrity, and rupture less easily. As a vesicle or bulla matures, an influx of leukocytes and accumulation of cellular debris can occur, leading to development of a *pustule*. Depending on the cause of the inflammatory response, a pustule can be infected or sterile.

Rupture and detachment of the roof of a subcorneal or intraepidermal blister leads to a moist, slightly depressed *erosion*. Erosions do not extend below the epidermal-dermal junction and heal without scarring. Postinflammatory pigmentary changes, however, can exist for weeks to months. When an unroofed blister extends into the dermis or subcutaneous tissue, it forms an *ulcer*. Scarring or postinflammatory pigmentary changes can follow healing of a wound that involves the dermis. Erosion or ulceration is accelerated in areas of friction or maceration, such as in the axillae or perineum, and on the mucous membranes of the oropharynx and vagina. *Crusts* or *scabs* are the dried remnants of serum, blood, and cellular debris. They form quickly over denuded areas.

It is not unusual for several types of lesions to occur at the same time in an individual. For example, the eruptions caused by varicella can comprise a variety of lesions in various stages of evolution, including macules, papules, vesicles, and pustules, mixed with erosions, ulcers, crusts, and self-induced linear excoriations. Bullae can form if staphylococcal superinfection occurs (Fig. 70.2).

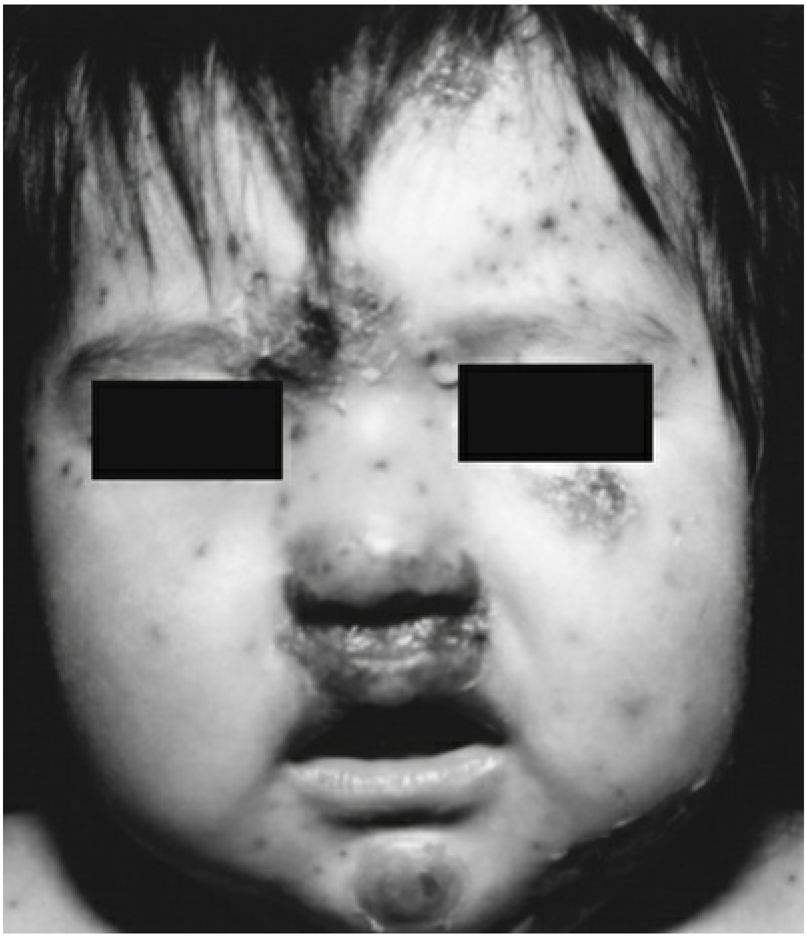


FIGURE 70.2 Chickenpox lesions that are infected secondarily with *Staphylococcus aureus* form crusted plaques and bullae on the face of an infant.

Etiology and Clinical Manifestations

Although the list of infectious agents capable of causing vesiculobullous rashes is lengthy, the most common agents are enteroviruses, varicella-zoster virus (VZV), HSV, *Staphylococcus aureus,* and *Streptococcus pyogenes*. The list of noninfectious conditions that closely mimic the eruption caused by these organisms also is lengthy, often leading to a difficult or delayed diagnosis.[1–3]

The cause of a vesiculobullous infection frequently can be established by consideration of the epidemiologic context. Differentiating the morphology, distribution, and evolution of the eruption is key to diagnosis. The season, patient age, history of recent exposure to infectious agents or medications, previous disease, and concurrent symptoms are factors to be considered. Categorization based on depth (i.e., tense or flaccid) and the predominant size (i.e., vesicles or bullae) also can aid the diagnosis (Table 70.1).

TABLE 70.1

Clinical Features of Blistering Skin Disorders by Etiologic Agent

Infection or Reaction Pattern	Type of Blister	Size	Usual Locations	Other Clinical Signs and Symptoms
Herpes simplex virus	Tense	Vesicles	Most often mucosal or perimucosal	Clustered and painful
Zoster (varicella-zoster virus reactivation)	Tense	Vesicles	Any dermatome	Clustered in a dermatome or disseminated in immunocompromised
Hand-foot-and-mouth disease (enterovirus infection)	Tense	Vesicles	Palms, soles, oral mucosa, and buttocks	Vesicles tend to be oval and on the hands and feet, following dermatoglyphics
Bullous impetigo	Flaccid	Vesicles or bullae	Perioral or perineal	Honey-colored crusting
Staphylococcal scalded skin syndrome	Flaccid, superficial epidermis only	Large bullae	First manifests in intertriginous areas, then can be widespread	Age <5 yr
Dactylitis	Tense	Bullae	Digits	Painful and red
***Vibrio vulnificus* infection**	Tense	Bullae	Feet	Purple edematous (typically on extremity) with tense bullae

Necrotizing fasciitis	Tense	Bullae	Any site	Hyperesthetic or anesthetic purpuric skin
Bullous tinea	Tense	Vesicles or bullae	Feet	Annular or interdigital scaling
Stevens-Johnson syndrome	Flaccid, full thickness of epidermis	Vesicles or bullae	Face and orofacial, any site	Exuberant mucosal involvement (lips, oral mucosa, eyes, perineum)

Infections Associated With Vesicles

Cutaneous HSV infection typically manifests as 1- to 4-mm vesicles that appear in clusters corresponding to the distribution of the infected nerve or primary inoculation site. Mucosa and periorificial areas tend to have microabrasions and are more susceptible to infection. Primary HSV infections can be exuberant and lead to extensive vesiculation especially in the mouth (i.e., primary herpetic gingivostomatitis). Recurrences of HSV usually are localized, and unless the patient is immunocompromised, they may lead only to edematous, crusted papules (Fig. 70.3). HSV infecting digits (i.e., whitlow) usually causes a tense, larger bulla made of many individual vesicles that are held together by the thick acral skin. This often produces a honeycomb pattern of loculated vesicles. Recurrent, clustered vesicles, crusts, or pustules in a fixed spot, even if not mucosal, should alert the clinician to the possibility of HSV infection. Longstanding, crusted ulcerations are a common presentation in immunocompromised patients when the HSV infection cannot be cleared adequately.

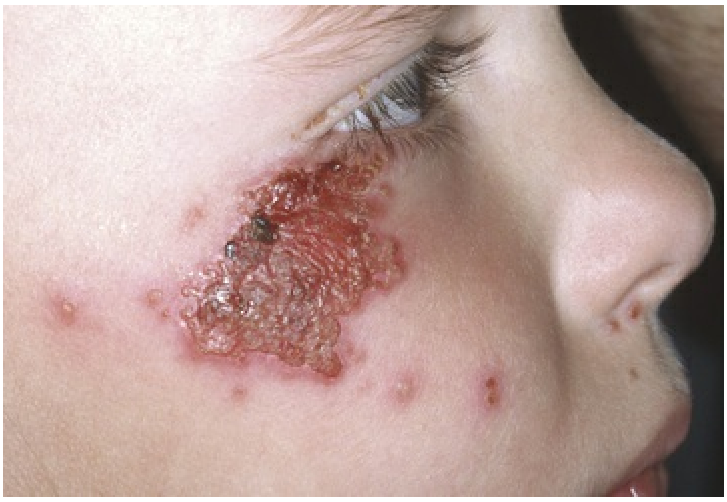
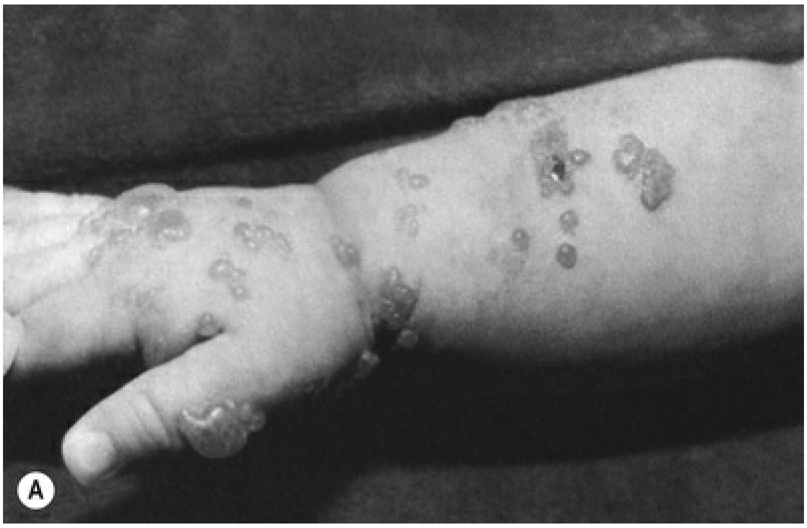


FIGURE 70.3 A young girl hospitalized for febrile

pneumonia had reactivation herpes simplex virus 1 in a dermatomal distribution on her face. (Courtesy of J.H. Brien, ©.)

Zoster is cutaneous reactivation of the VZV virus that corresponds to the sensory nerve in which VZV had been dormant. The initial manifestation may be painful, red papules clustered in a plaque that then vesiculate over a few days and finally crust and leave erosions. The key to diagnosis is the dermatomal distribution (Fig. 70.4). Children may have one to three adjacent dermatomes involved in uncomplicated zoster, which can occur after vaccination but is more common in children who had chickenpox and especially when chickenpox occurred at less than 1 year of age. Most children with zoster are otherwise healthy. Dissemination from an initial dermatomal cluster, involvement of multiple noncontiguous dermatomes, or a concerning review of systems should alert the clinician to the possibility of underlying immunocompromising conditions.



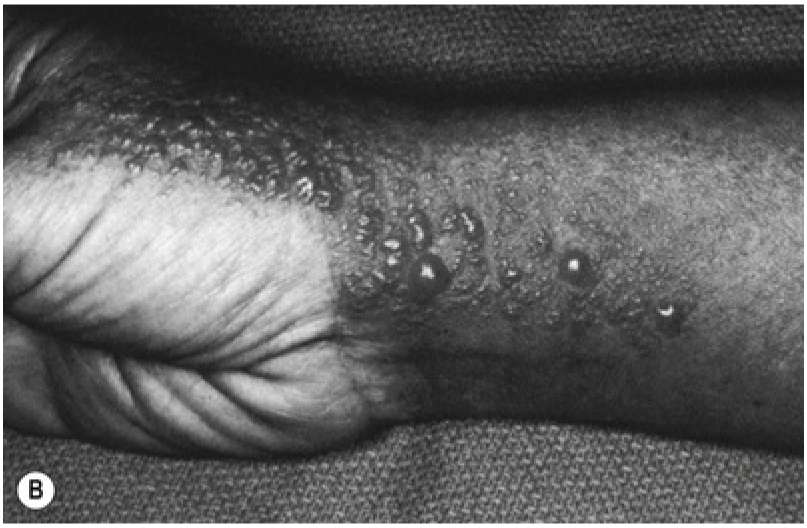


FIGURE 70.4 (A) Bullae on the dorsal hand and forearm of an infant resulted from reactivation of varicella-zoster virus without superinfection. (B) Vesicles and bullae on the hand and wrist of a girl with contact dermatitis were caused by poison oak.

Primary varicella (i.e., chickenpox) and disseminated VZV in immunocompromised patients manifest as widely distributed, crusted papules and vesicles on a red base ("dew drops on a rose petal")

Hand-foot-and-mouth disease (HFMD) is caused by enteroviruses, including coxsackievirus A16, enterovirus 71, and enterovirus A6. HFMD manifests with vesicles anywhere in the mouth (including the tongue) and on the palms, soles, and buttocks. The oral mucosa, which has thin epithelium without stratum corneum, allows vesicles to rupture easily, and it is more common to see only erosions. Conversely, the palms and soles have a thick epidermis, and the vesicles may appear as red macules; it can be difficult to detect the fluid inside. Vesicles on the palms and soles tend to be oval and follow the dermatoglyphics (i.e., fingerprint markings).

Enterovirus A6 has become more prevalent in the United States.[4] Enterovirus A6 infection often manifests with more exuberant HFMD, with larger and more widespread vesicles and bullae that also can occur on acral surfaces such as on the dorsum of feet, hands, and knees. Enterovirus A6 occurring in conjunction with atopic dermatitis can lead to eczema coxsackium.

Infections Associated With Flaccid Bullae

Bullous impetigo is an acute blistering infection caused by *Staphylococcus aureus* group II, typically phage 71 infection. This strain of *S. aureus* carries exfoliative toxin A, which specifically targets and disrupts the intraepidermal keratinocyte connection desmoglein 1 (DSG1).[5] Because DSG1 is most important for intracellular keratinocyte adhesion in the top layers of the epidermis, lesions in bullous impetigo tend to be flaccid and rupture easily. Drying of the ruptured blister and serous fluid results in honey-colored crusting. The function of DSG1 is duplicated in the mucosa by coexpression of DSG3. Because DSG3 is not targeted by the exfoliative toxin, there is no mucosal blistering in bullous impetigo or in staphylococcal scalded skin syndrome (SSSS) (discussed later).

Dissemination of the exfoliative toxin A can cause cleavage of DSG1 distant from the initial infection, resulting in SSSS. Clinically, the cleavage manifests as bright red patches of painful skin that easily shear off with friction because the bullae are superficial. The most common sites for bullae include the neck, axillae, inguinal folds, and periorificial areas (Fig. 70.5). SSSS is more common in children younger than 5 years of age.

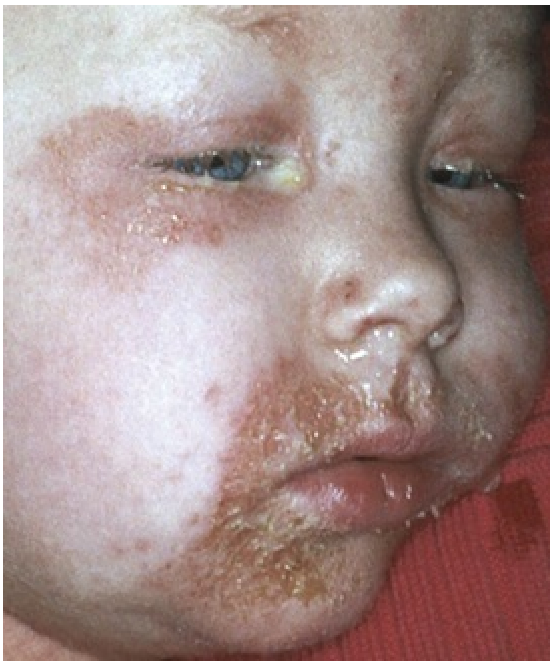


FIGURE 70.5 Staphylococcal scalded skin syndrome in a toddler. (Courtesy of J.H. Brien, ©.)

Infections Associated With Tense Bullae

Blistering distal dactylitis classically is caused by *S. pyogenes* infection. It manifests as tense, firm, single or multiple vesicles and bullae that typically occur on the volar surface of the fingers.

Gram-negative septicemia can lead to *purpura fulminans*. The clinical phenotype is characterized by large, purpuric patches with hemorrhagic, sometimes tense bullae due to vascular damage and epidermal necrosis.

Necrotizing fasciitis also comes to medical attention with large, tense bullae (often hemorrhagic) due to underlying dermal necrosis.

Dermatophyte infections typically cause round, scaling plaques, but if the burden of fungus and inflammation is large enough, a split can occur, typically deep in the epidermis or at the dermoepidermal junction, that leads to tense bullae. This occurs most commonly on the feet but also can occur on the trunk or extremities.

Vesiculobullous Disease Induced by Infection

Stevens-Johnson syndrome (SJS) is a severe, life-threatening, necrotic mucocutaneous reaction. The hallmark is severe mucosal involvement that typically involves the lips, oral mucosa, and conjunctivae and sometimes involves the urethra, anus, and vagina (Fig. 70.6).

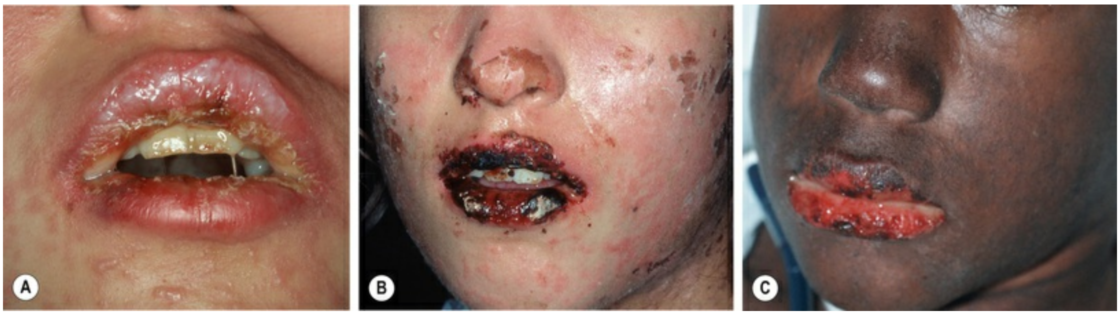


FIGURE 70.6 Adolescents with Stevens-Johnson syndrome in stages of development (A) and resolution (B and C). (Courtesy of J.H. Brien, ©.)

The classic cutaneous lesion has a target appearance characterized by a red-purple macule or patch with central duskiness, which can vesiculate or form large bullae. Traumatized areas can shear off and leave only deep erosions. Medications are the most common cause of SJS. *Mycoplasma pneumoniae* also can induce typical SJS or SJS with a predominant mucosal involvement and few or no cutaneous lesions.[6] SJS is differentiated from SSSS by the predominance of mucosal involvement and the full-thickness epidermal necrosis that typically leads to tense bullae and deeper wounds in SJS.

Diagnosis

To diagnose an infectious cause of a blister, an intact blister can be cleansed with alcohol, the edge incised, and the fluid collected for Gram stain and culture. If there are no intact blisters, the base of an erosion can be swabbed for culture; growth of normal skin flora must be interpreted in context. A potassium hydroxide preparation or fungal culture from the unroofed blister specimen can be used if dermatophyte infection is suspected. Viral causes of blisters can be diagnosed by culture, polymerase chain reaction (PCR), or direct fluorescent antibody testing. A Tzanck smear showing multinucleated giant cells with nuclear molding can rapidly diagnose HSV and VZV infection but is less sensitive than other tests. The flaccid bulla in SSSS typically is sterile because the blister is caused by the toxin distant from the primary infection. A primary site of infection or colonization can be investigated.

The diagnosis of SJS can be made rapidly by evaluation of a frozen section skin biopsy for histologic evidence of full-thickness epidermal necrosis. If there is no inciting medication, *Mycoplasma* serology or PCR can be used to investigate possible causality. The differential diagnosis of noninfectious vesiculobullous eruptions in children includes autoimmune blistering disorders such as linear IgA deposition (i.e., chronic bullous disease of childhood), epidermolysis bullosa, thermal or friction injury, contact dermatitis, bullous mastocytoma, and incontinentia pigmenti. In addition, the so-called salt and ice challenge, which is commonly done intentionally by adolescents as a dare, causes a type of thermal injury that can mimic severe cellulitis or necrotizing fasciitis. When salt is applied to the skin followed by ice, the ice can rapidly freeze the skin, leading to hemorrhagic bullae and crusting. The pattern often is geometric and is seen in areas that are easily accessible (e.g., arms, legs, chest).

After discontinuing an offending drug, the management of SJS is controversial, especially the use of corticosteroids and intravenous immune globulin. It has been reviewed by Wolf and Davidovici.[7]

When the cause of vesicular lesions remains in doubt, culture, biopsy for histopathologic evaluation, and immunofluorescence staining are helpful, particularly to exclude noninfectious bullous disorders.[1]

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71

Purpura

Melissa A. Reyes, Lawrence F. Eichenfield

Purpura is a significant finding, especially because it has been associated with multiple infectious causes, some of which are life-threatening. Purpura results from trauma to blood vessels in the skin, causing hemorrhage into the surrounding tissue. Lesions are not blanched with pressure. Vessel damage can be the result of direct trauma, endothelial infection (e.g., rickettsial infection, meningococcemia), vessel occlusion, immune complex deposition, platelet depletion or dysfunction, or other conditions that cause vascular leakage of erythrocytes into the skin, mucous membranes, conjunctivae, or retina.

The clinical appearance of purpuric lesions depends on the size of the affected vessels, location of the vessels, extent of hemorrhage, and the coagulation status of the patient. Many noninfectious conditions can cause purpura. The morphology and other clinical findings may be useful in discriminating among likely causes. Purpuric lesions can be divided into six subtypes based on the size and morphology of the lesions: petechiae, macular purpura, ecchymoses, palpable purpura, noninflammatory retiform purpura, and inflammatory retiform purpura.[1]

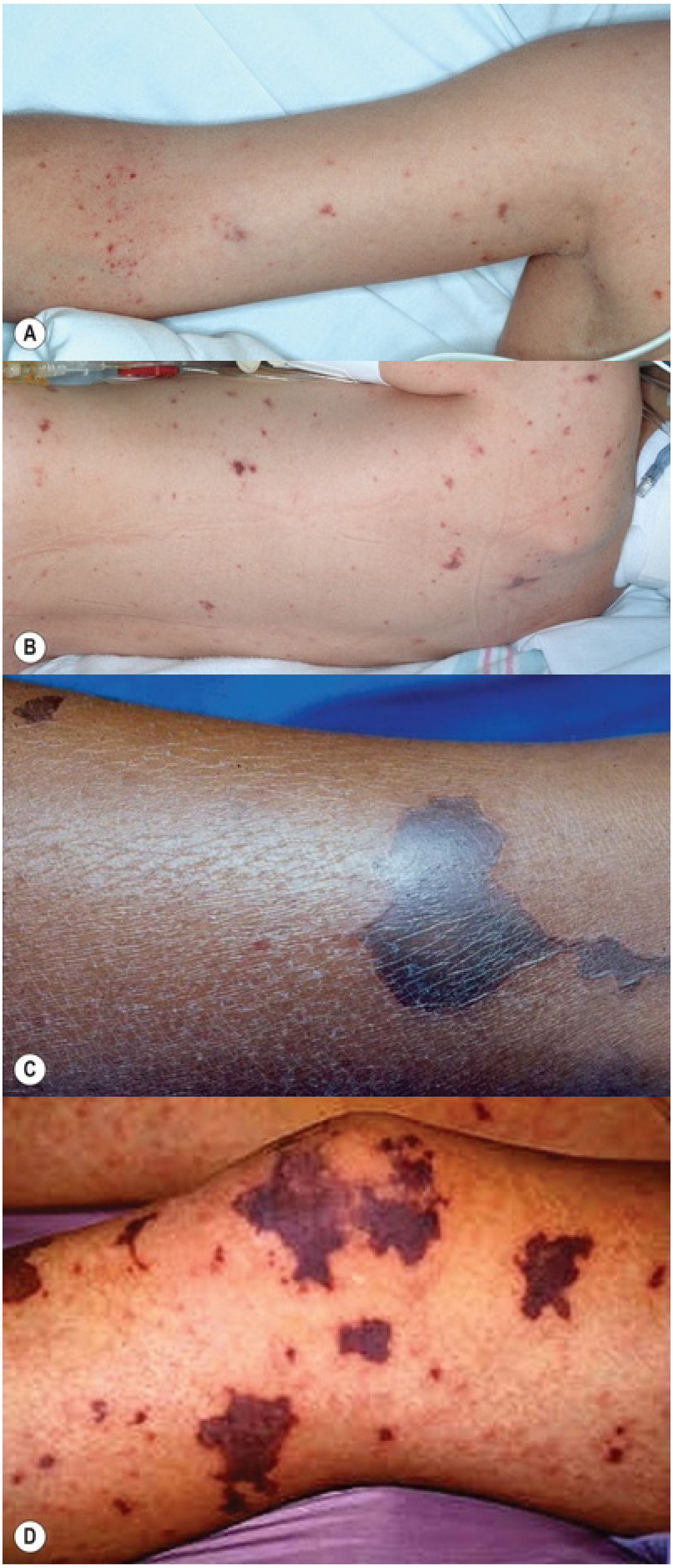
Types of Purpuric Lesions and Pathogenesis

Petechiae, *macular purpura*, and *ecchymoses* are superficial, flat, cutaneous lesions that are 4 mm or smaller, 5 to 9 mm, and 1 cm or larger, respectively. *Palpable purpura* consists of raised, partially blanching, and erythematous to purple lesions, which typically are round. *Retiform purpura* has a lace-like pattern because the affected vessels are larger in the dermis and subcutis. *Inflammatory retiform purpura* initially is erythematous before evolving into purpura.

All purpuric lesions share similar changes in color based on the age of the lesion. They are initially bright red or deep red and become purple as the heme pigments break down and progress to green and yellow-brown before fading. The amount of time to fading depends on the amount of extravasated blood.

Petechiae, macular purpura, and ecchymoses are considered macular or flat purpura and result from simple extravasation of blood into the skin. Histologically, there is minimal inflammation, in contrast to the inflammatory hemorrhage seen in microvascular occlusion or cutaneous small-vessel vasculitis, which results in palpable purpura.[1] Inflammatory purpura results from occlusion by a clot with resulting ischemia and necrosis of the vessel. Vasculitis usually is caused by immune complexes deposited on the vessel lumen, which attracts neutrophils that destroy the complexes and injure the vessel wall. Retiform purpura and inflammatory retiform purpura result from occlusion and vasculitis, respectively, of larger, slow-flow vessels.

In patients with septicemia, purpura can arise from five main mechanisms: disseminated intravascular coagulation (DIC) and coagulopathy, direct vascular invasion and occlusion by organisms, infective vasculitis, emboli (e.g., in endocarditis), and vascular changes due to toxins.[2] Many infections are associated with thrombocytopenia with development of petechiae or ecchymoses, with or without DIC. Invasion of microorganisms into capillaries can occur especially with a bloodstream infection (BSI) due to *Neisseria meningitidis, Neisseria gonorrhoeae,* and *Pseudomonas aeruginosa* (Fig. 71.1). Diffuse vasculitis with pathologic evidence of rickettsiae in vascular endothelial cells is seen with Rocky Mountain spotted fever (RMSF) and epidemic typhus.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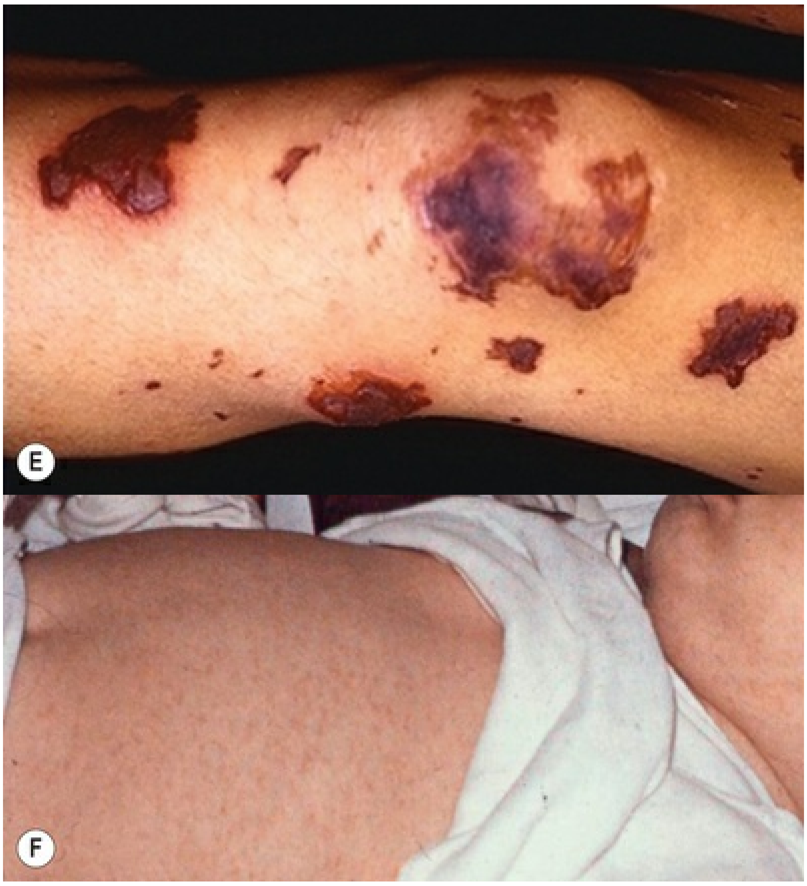

FIGURE 71.1 Skin manifestations of meningococcemia. The examination of one patient with this rapidly progressive disease found petechiae on the arm with exaggeration distal to the site of a tourniquet (A) and petechiae and purpura on the back (B). Another patient had a purpuric plaque on the distal leg (C), and purpuric lesions were seen around the knee in a patient at the time of admission (D) and 4 days later (E). Early manifestations of rapidly progressive, fatal meningococcemia include predominantly nonpetechial, macular lesions (F). (A, B, D, and E, courtesy of J.H. Brien, © C and F, courtesy of S.S. Long.)

Immune-mediated vasculitis is associated with a broad set of petechial rashes associated with atypical measles, hepatitis B, and chronic meningococcemia. Intravascular catheter–associated infections and acute and subacute endocarditis can manifest as infectious embolization complicated by infarction, tissue hemorrhage, and necrosis. Endocarditis also can be associated with immune-mediated vasculitis and petechiae. The scarlatiniform, sometimes petechial, eruptions of *Streptococcus pyogenes* (group A *Streptococcus* [GAS]) are an example of toxin-mediated rashes.

Causes of Purpura

Petechiae and Macular Purpura

Petechiae are small (≤4mm in diameter), nonblanching, purpuric macules that can appear on the skin, conjunctiva, retina, and mucous membranes. Lesions of macular purpura are larger than petechiae but smaller than ecchymoses. Both result from extravasation of blood from capillaries. In this chapter, the term *petechiae* is used to include all macular purpuric lesions smaller than 1 cm in diameter.

Petechiae typically resolve in 2 to 3 days but can evolve into ecchymoses, palpable purpura, vesicles, pustules, or necrotic ulcers, depending on the cause and clinical course. When petechiae occur on the nail bed, they appear as red-brown, longitudinal discolorations under the nail plate and are called *splinter hemorrhages*. In certain cases, they may be difficult to differentiate from telangiectases and angiomas. Because the latter lesions are not the result of extravasated blood, applying pressure with a glass slide to blanch the vessels (i.e., diascopy) can help differentiate petechiae from other vascular lesions.

The occurrence of petechiae in a febrile patient raises the concern for an infectious cause (Table 71.1). Petechiae can occur in crops, are commonly seen in BSIs, and usually occur with fever and as an early clinical sign of a BSI.[3] In contrast, petechiae can be seen in 10% to 32% of otherwise well-appearing infants receiving routine care in outpatient clinics.[4,5]

TABLE 71.1

Major Infectious Causes of Purpura in Children and Neonates

Children	Neonates
BACTERIA	
Aeromonas hydrophila	Gram-positive and gram-negative bacteria associated with septicemia[a] Enterococci *Haemophilus influenzae* type b[a] *Klebsiella* spp. *Listeria monocytogenes* Staphylococci *Streptococcus agalactiae* (group B *Streptococcus*)[a] *Streptococcus pyogenes*
Arcanobacterium haemolyticum	
Bacteroides fragilis	
Bartonella henselae	
Borrelia spp.	
Brucella spp.	
Campylobacter jejuni	
Capnocytophaga canimorsus[a]	
Enterococcus spp.	
Escherichia coli	

Klebsiella pneumoniae	*Treponema pallidum*
Leptospira spp.	
Listeria monocytogenes	
Moraxella spp.	
Mycobacterium leprae	
Morganella morganii	
Mycobacterium tuberculosis	
Neisseria meningitidis[a]	
Neisseria gonorrhoeae[a]	
Pseudomonas aeruginosa[a]	
Salmonella typhimurium	
Serratia marcescens	
Staphylococcus aureus	
Streptobacillus moniliformis	
Streptococcus pneumoniae	
Streptococcus pyogenes[a]	
Viridans streptococci	
Yersinia enterocolitica	
FUNGI	
Agents of mucormycosis	Agents of mucormycosis[a]
Aspergillus spp.	*Aspergillus* spp.[a]
Candida spp.	*Candida* spp.[a]
Fusarium spp.	*Fusarium* spp.[a]
Rhizopus spp.	*Rhizopus* spp.[a]
Scytalidium dimidiatum	*Scytalidium dimidiatum*
VIRUSES	
Adenovirus	Cytomegalovirus[a]
Colorado tick fever virus	Enteroviruses
Coxsackievirus A4, A9, B3–B5	Herpes simplex virus types1 and 2
Cytomegalovirus[a]	Rubella virus
Echovirus 3, 4, 7, 9, 18	
Dengue fever virus	
Epstein-Barr virus	
Hantavirus	
Hepatitis A virus	
Hepatitis B virus[a]	
Hepatitis C virus[a]	
Human immunodeficiency virus	
Parvovirus B19	
Respiratory syncytial virus	
Rotavirus	
Rubella virus	
Rubeola virus	
Varicella-zoster virus	
Yellow fever and other hemorrhagic fever viruses (e.g., Ebola, Chikungunya, Marburg, Lassa)	
HELMINTHS	
Ascaris spp.	
Strongyloides stercoralis (hyperinfection syndrome)	
Trichinella spiralis	
MYCOPLASMA	
Mycoplasma pneumoniae	
PROTOZOA	
Plasmodium falciparum	*Toxoplasma gondii*
RICKETTSIAE	

Anaplasma phagocytophilum	
Ehrlichia canis	
Ehrlichia chaffeensis	
Ehrlichia equi	
Rickettsia akari	
Rickettsia prowazekii (epidemic typhus)[a]	
Rickettsia rickettsii (Rocky Mountain spotted fever)[a]	
Rickettsia typhi	

[a] Greater propensity of agent to cause purpura compared with other agents listed.

Historically, fever and petechiae in a child required evaluation for meningococcal infection. Early studies that focused on hospitalized children reported an incidence of meningococcal disease of 7% to 11% among children with fever and petechiae and a case-fatality rate of 10%.[6] In the past few decades in North America, bacterial causes of fever and petechiae have been relatively uncommon.[7,8] In a retrospective review of 129 hospitalized children with fever and petechiae, 20% had culture-proven bacterial infection, with 11% due to *N. meningitidis* and 6% due to *Haemophilus influenzae* type b.[9] Almost 60% of cases were attributed to viral causes.

A prospective study that included 190 children hospitalized with fever and petechiae documented 7% with meningococcal and 10% with GAS infection.[10] Children with invasive bacterial infections were more likely to appear ill, to have meningeal irritation, and to have petechiae below the nipple line.

Another prospective study attempted to capture a broader cohort of patients by evaluating 411 consecutive pediatric patients with fever and petechiae who were seeking care in a hospital emergency department.[3] Of the 53 ill-appearing patients (i.e., toxic appearance, inconsolable crying or screaming, or lethargy), 6 had invasive bacteremic infections, whereas none of the 357 well-appearing children had a positive blood culture or cerebrospinal fluid bacterial culture. In this study, only 2 patients had *N. meningitidis* (0.5%), 2 had *Streptococcus pneumoniae*, and 1 had GAS invasive infection. The study also found that a white blood cell count of 15,000 cells/mm^3 or higher was predictive of severe BSI.

A febrile patient with petechiae who appears well, has normal simple laboratory test results, has petechiae only above the nipple line, and has no nuchal rigidity has a low risk of invasive bacterial disease.[7] Petechiae in febrile patients most commonly is associated with viral infection because of the prevalence of viral infections and because viruses tend to damage small cutaneous vessels.[11]

Petechiae on the palate are characteristic of streptococcal pharyngitis[12] but also can be seen in Epstein-Barr virus infection, *Arcanobacterium haemolyticum* pharyngitis, rubella, roseola and viral hemorrhagic fevers, with thrombocytopenia, and following palatal trauma.[12] Oral hemorrhagic necrotic lesions have been attributed to *Actinomyces* infection.[13] Palmar and plantar petechiae can be seen in gloves and socks syndrome caused by parvovirus B19. In this condition, there is confluent erythema of the distal extremities with pinpoint macules evolving into petechiae on the palms and soles along with concurrent fever and leukopenia.[14]

Parvovirus also has been reported to cause a generalized petechial eruption[15] and petechiae in a bathing suit distribution.[16] Clusters of patients with generalized petechial eruptions are reported during community outbreaks of erythema infectiosum, and eruptions apparently are associated with the viremic phase of infection.[17]

Other infectious causes of generalized petechiae include scarlet fever, RMSF, parainfluenza, influenza, respiratory syncytial virus, enterovirus, rotavirus, atypical measles, rubella, dengue, and adenovirus.[8] For a patient with petechiae, fever, and recent travel to an endemic area, the clinician should consider epidemic and emerging infections such as Ebola and Chikungunya virus infections[18] and rare causes such as Brazilian purpuric fever,[19] Zika virus,[20] and severe fever with thrombocytopenia syndrome.[21]

Petechiae or purpura can have noninfectious causes such as drug reactions, acute leukemia,[8] low platelet counts, and mechanical causes (Table 71.2). Severe coughing or vomiting can increase intrathoracic pressure, causing petechiae in areas perfused by the superior vena cava and approximately corresponding to skin areas above the nipple line. This distribution of petechiae is not always benign; 25% of patients with fever and petechiae confined to the upper torso had bacterial infection in one study.[9] Petechiae can form distal to placement of a tourniquet and have no clinical significance without other findings. In contrast, the tourniquet test can cause distal petechiae in patients with dengue fever and is positive in most patients with dengue hemorrhagic fever.[22]

TABLE 71.2

Major Noninfectious Causes of True Purpura and Purpura Mimics

True Purpura	Purpura Mimics
PLATELET DISORDERS	**NEONATES**
Thrombocytopenia Decreased production of platelets	**Extramedullary Hematopoiesis (“Blueberry Muffin” Lesions)**
• Drug induced	Congenital infections
• Bone marrow infiltration or aplasia	Aicardi-Goutières syndrome
• Toxin induced	Rh hemolytic disease of the newborn
Decreased survival of platelets	Spherocytosis
• Disseminated intravascular coagulation	Twin-twin transfusion
• Drug induced	Myofibromatosis
• Hemolytic-uremic syndrome	Self-healing reticulohistiocytosis
• Idiopathic and autoimmune thrombocytopenic purpura	Metastatic malignant tumors • Langerhans cell histiocytosis
• Prosthetic heart valve	• Congenital leukemia
• Hypersplenism	• Neuroblastoma
• Sequestration	• Rhabdomyosarcoma • Rhabdomyosarcoma
Platelet Dysfunction	**Neonatal Lupus**
Thrombocytosis	**Phototherapy-Induced Purpura**
VASCULAR DISORDERS	**Subcutaneous Fat Necrosis**
Noninflammatory Purpura	**Vascular Lesions**
Cushing disease	Congenital hemangioma
Corticosteroid therapy	Congenital glomuvenous malformation
Ehlers-Danlos syndrome	Venous malformation
Fat embolism	Tufted angioma
Increased capillary pressure (e.g., vomiting, posttussive)	**CHILDREN** Angiokeratoma corporis diffusum
Scurvy	Arthropod bites
Trauma or child abuse	Blue rubber bleb nevus syndrome
Vasculitis and Inflammatory Purpura	Diffuse reticulate purpura in anorexia nervosa
• Brown recluse spider bite	Erythema multiforme
• Churg-Strauss syndrome	Hemorrhagic urticaria multiforme
• Dermatomyositis	Multifocal lymphangiomatosis with thrombocytopenia
• Drug- or toxin-induced hypersensitivity	
• Dysproteinemias	Pityriasis lichenoides
• Graft-versus-host disease	Pityriasis rosea
• Henoch-Schönlein purpura	After EMLA cream (i.e., lidocaine and prilocaine) application
• Inflammatory bowel disease	
• Malignant atrophic papulosis	Psychogenic purpura
• Pernio (i.e., chilblains)	Sarcoidosis
• Polyarteritis nodosa	
• Pyoderma gangrenosum	
• Pigmented purpura	
• Rheumatoid arthritis	
• Scleroderma	
• Serum sickness syndrome	
• Sjögren syndrome	
• Sweet syndrome (i.e., acute febrile neutrophilic dermatosis)	
• Systemic lupus erythematosus	
• Urticarial vasculitis	
• Wegener granulomatosis	
COAGULATION DISORDERS	
Clotting Factor Deficiencies	

Increased use or proteolysis	
Inadequate production	
Presence of inhibitor of coagulation	
Synthesis of abnormal clotting factor	
Thrombotic Disorders	
Antiphospholipid syndrome	
Antithrombin III deficiency	
Plasminogen deficiency	
Protein C deficiency	
Protein S deficiency	

In newborns, petechiae can occur at sites of pressure during delivery through the birth canal, but petechiae also can result from acquired infection or maternal antiplatelet antibodies, and appropriate evaluation should be performed. Older children with petechiae without fever should be evaluated for blood dyscrasias. Petechial eruptions can occur in the setting of thrombocytopenia due to hematologic malignancy or chemotherapeutic agents, and exanthems can be associated with viral infections or drug eruptions. Careful evaluation of the history, symptom complex, and laboratory evaluation is required, and a skin biopsy may be necessary.

Ecchymoses

Ecchymoses (i.e., bruises) are purpuric, flat patches on the skin. Typically, ecchymoses are 1 cm or larger in diameter and are caused by a greater volume of extravasated blood than occurs with petechiae. Ecchymoses tend to take longer to resolve (1–3 weeks). Petechiae in a patient with an underlying coagulopathy can quickly evolve into ecchymoses.

Ecchymoses resulting from infection are uncommon in children. When ecchymoses occur, they are most frequently caused by *N. meningitidis* septicemia with coagulopathy.[23] Other causes include other gram-negative bacteria, gram-positive bacteria (e.g., *Staphylococcus aureus*, GAS, and *S. pneumoniae*), viruses (e.g., viral hemorrhagic fevers), and *Rickettsia rickettsii* (RMSF).[23–26]

In the neonate, ecchymoses at sites of cutaneous trauma (e.g., medical tape, intravenous catheter, arm board, monitor lead) can be caused by inoculation of molds and other opportunistic pathogens into the skin. Urgent evaluation and empiric treatment are critical as hematogenous spread can occur rapidly.[27]

Ecchymosis occurring acutely and in an ill-appearing patient is called *purpura fulminans*. In this setting, ecchymoses evolve rapidly, usually are symmetric in distribution, and evolve into necrotic patches with eschars.[3] Purpura fulminans is caused by abnormalities in coagulation due to infection. Most commonly, this occurs in the setting of acute infection such as caused by *N. meningitidis*, gram-negative bacilli, or overwhelming infection due to a variety of organisms in a compromised host, especially neutropenic or asplenic patients.[23] Purpura can occur 7 to 10 days after an otherwise benign infection (i.e., idiopathic purpura fulminans). Idiopathic purpura fulminans has been associated with varicella, scarlet fever, streptococcal tonsillopharyngitis, viral exanthems, rubella, measles, upper respiratory tract infections, and gastroenteritis.[23]

A variant of purpura fulminans called *symmetric peripheral gangrene* results in ischemic necrosis of the distal parts of two or more extremities without large-vessel obstruction. This variant is associated with higher mortality and morbidity (e.g., amputation) rates.[28] Purpura fulminans and symmetric peripheral gangrene occur more frequently in infants and children than in older individuals.[2] In neonates, purpura fulminans can be a manifestation of inherited homozygous protein C deficiency or rarely of protein S deficiency. BSIs in older children with these underlying deficiencies (and properdin deficiency, splenic dysfunction, or neutropenia) can lead to purpura fulminans.

Palpable Purpura

Unlike petechiae and ecchymoses, palpable purpura is a condition in which raised, purpuric papules and plaques can range from a few millimeters to a few centimeters in diameter. Palpable purpura favors dependent areas such as the lower extremities, but in the supine patient, lesions can occur on the back, buttocks, and distal arms. Palpable purpura can evolve into nodular, vesicular, pustular, necrotic, or ulcerative lesions.

Palpable purpura classically is associated with leukocytoclastic vasculitis, an inflammatory process that injures the vessel.[29] Histopathologically, fibrin deposition in vessel walls, neutrophilic debris, and perivascular lymphocytes are seen. Palpable purpura also can occur with *S. aureus* BSI or in bacterial endocarditis as the result of infectious microemboli occluding the vascular lumen. Osler nodes and Janeway lesions found in bacterial endocarditis are types of microembolism-induced palpable purpura. Osler nodes are tender nodules that are seen on the palms, soles, and pads of the fingers and toes. Janeway lesions are nontender, purpuric macules, papules, or nodules usually found on the palms and soles. Lesions similar to Osler nodes have been reported in typhoid fever, polyarteritis nodosa, systemic lupus erythematosus, Churg-Strauss syndrome, mixed cryoglobulinemia, and Wegener granulomatosis.[1,2]

Palpable purpura has a variety of causes, including infection (10%–15%), drug reactions, immunization, and autoimmune disease. The most common infectious causes include *N. meningitidis*, *S. aureus*, and *N. gonorrhoeae,* but it also has been caused by *Mycobacterium*, *Rickettsiae*, and *Mycoplasma* spp., and rarely by *Bartonella*, *Salmonella*, *Campylobacter*, *Yersinia*, *Brucella* spp, and *Treponema pallidum*. Viral causes include hepatitis viruses (i.e., hepatitis C is more common than hepatitis B, and hepatitis B is more common than hepatitis A), hepatitis virus vaccine, and infection due to human immunodeficiency virus (HIV), parvovirus, and rarely by cytomegalovirus, varicella, and influenza.[1]

Noninfectious causes of palpable purpura in the pediatric population include Henoch-Schönlein purpura (HSP), which is the most common vasculitis seen in childhood, and acute hemorrhagic edema of infancy (AHEI). Palpable purpura is the presenting sign in almost 50% of cases with HSP. Diagnostic criteria for HSP include palpable purpura (with lower limb predominance), a mandatory criterion, along with at least one of the following: diffuse abdominal pain, tissue biopsy showing predominant IgA deposition, acute arthritis or arthralgia of any joint, and renal involvement.[30] If the distribution of cutaneous lesions is atypical, biopsy confirming IgA deposition is required. Hemorrhagic bullae also have been reported in HSP, and their presence does not appear to affect prognosis.[31]

HSP is most common between the ages of 5 and 10 years, and AHEI usually manifests in children younger than 2 years of age.[32] Some consider AHEI a distinct entity, whereas others consider it infantile HSP. AHEI typically manifests with fever, edema, and rosette-shaped, purpuric cutaneous lesions favoring the face, ears, and limbs. AHEI has a benign course, resolving over 3 weeks without sequelae, and it lacks visceral involvement.[33]

Retiform Purpura

Retiform purpura results from occlusion of dermal and subcutaneous vessels, which causes a lace-like pattern of purpura. A complete reticulate pattern is not usually seen, but rather a puzzle piece–like or branching pattern occurs because of the angulated or sometimes serpentine pattern of the purpura. Vascular invasion by fungi (e.g., *Mucor*, *Aspergillus* in immunocompromised patients), gram-negative organisms (e.g., *Pseudomonas*) that multiply in arterioles, and *Strongyloides* can cause noninflammatory retiform purpura, whereas vasculitis during BSI can cause inflammatory retiform purpura.[1]

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72

Urticaria and Erythema Multiforme

Kara N. Shah

Urticaria and erythema multiforme (EM) are common cutaneous hypersensitivity reactions seen in children. They can be triggered by infection, although noninfectious causes also are prevalent. Although they are distinctly different entities, acute urticaria often is misdiagnosed as EM. Although urticaria usually is an isolated finding, urticaria and urticarial dermatoses can be seen in several syndromes and disorders such as papular urticaria, urticarial vasculitis, and the cryopyrin-associated periodic syndromes (CAPSs).

Some terminology has changed. The use of the historical and confusing terms, such as EM minor to refer to classic EM and EM major to refer to Stevens-Johnson syndrome, has been abandoned.

Urticaria

Etiologic Agents

Acute and chronic forms of urticaria have been attributed to numerous bacterial, viral, fungal, and other infectious agents (Box 72.1). Noninfectious causes and associations include foods, medications, physical stimuli, aeroallergens, and systemic diseases (Box 72.2).[1] In infants younger than 6 months, urticaria largely is caused by a cow's milk allergy, and in older infants, food allergy, infection (particularly viral), and medications predominate.[2–4]

Box 72.1

Infectious Agents Associated With Urticaria

Bacteria

Borrelia burgdorferi (erythema chronicum migrans)

Chlamydophila pneumoniae

Escherichia coli

Helicobacter pylori

Neisseria gonorrhoeae

Neisseria meningitidis

Pseudomonas aeruginosa

Shigella sonnei

Streptococcus pyogenes[a]

Yersinia enterocolitica

Fungi

Candida albicans

Cladosporium spp.

Coccidioides immitis

Histoplasma capsulatum

Candida glabrata

Trichophyton spp.

Helminths

Ancylostoma duodenale

Anisakis simplex

Ascaris lumbricoides

Echinococcus spp.

Enterobius vermicularis

Fasciola hepatica

Necator americanus

Onchocerca volvulus

Schistosoma spp.

Strongyloides stercoralis

Toxocara canis

Trichinella spiralis

Trichobilharzia spp. (avian blood flukes)

Wuchereria bancrofti

Mycoplasma

Mycoplasma pneumoniae

Protozoa

Blastocystis hominis

Entamoeba histolytica

Giardia lamblia

Plasmodium spp.

Trichomonas vaginalis

Rickettsia

Coxiella burnetii

Treponemes

Treponema pallidum

Viruses

Adenovirus[a]

coxsackieviruses A9, A16, B4, B5[a]

Cytomegalovirus

Echovirus 11[a]

Epstein-Barr virus[a]

Hepatitis viruses A, B, C

Influenza B virus[a]

Human immunodeficiency virus

Measles virus, attenuated

Mumps virus

Parvovirus B19

Respiratory syncytial virus[a]

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[a] Most common.

Box 72.2

Noninfectious Causes and Associations of Urticaria and Urticarial Eruptions in Infants

and Children

Arthropod Bites (Papular Urticaria)

Ants *(Solenopsis saevissima)*

Bedbugs *(Cimex lectularius)*

Bees[a]

Body lice *(Pediculus humanus)*[a]

Caterpillars

Fleas *(Pulex irritans)*[a]

Chiggers *(Trombicula irritans)*

Flies

Gypsy moths

Kissing bugs *(Triatoma sanguisuga)*

Mosquitoes

Scabies mites *(Sarcoptes scabiei)*[a]

Scorpions

Spiders

Wasps

Annular Erythemas

Erythema multiforme

Annular erythema of infancy

Acute hemorrhagic edema of infancy

Erythema annulare centrifugum or gyrate erythema

Autoimmune or Contact

Animal dander

Caterpillars and moths *(Lepidoptera)*

Chemicals

Cosmetics

Epoxy resins

Fish

Coral

Jellyfish

Hedgehog

Foods

Medications

Nickel

Parabens

Saliva

Wood dust

Dermal Hypersensitivity Reactions

Eosinophilic cellulitis

Exanthematous drug eruptions

Drugs

Acetylsalicylic acid[a,b]

Allopurinol

Amoxicillin[a]

Barbiturates

Cephalosporin antibiotics

Codeine

Curare

Meperidine

Morphine[a]

Nonsteroidal anti-inflammatory agents (e.g., indomethacin)[a],[b]

Penicillin[a]

Phenytoin

Polymyxin B

Procainamide

Quinidine

Iodinated radiocontrast media[b]

Sulfa-derived antibiotics[a]

Sulfonylureas

Tetracycline

Thiamine

Thiazides

Vancomycin

Zidovudine

Food Additives, Preservatives, and Dyes (Pseudoallergic Reaction)

Azo dyes (e.g., sunset yellow, tartrazine[a])

Butylhydroxyanisole

Butylhydroxytoluene

4-Hydroxybenzoic acid[a]

Sodium benzoate[a]

Sodium metabisulfite

Food Allergy

Chocolate

Eggs[a]

Fish[a]

Fresh berries

Milk[a]

Nuts[a]

Peanuts[a]

Shellfish[a]

Tomatoes

Autoinflammatory Syndromes

Schnitzler syndrome

Cryopyrin-associated periodic syndromes (CAPSs)

Familial cold autoinflammatory syndrome

Neonatal-onset multisystem inflammatory disease (NOMID)

Muckle-Wells syndrome

Inhalant Allergens

Animal danders

Mold spores

Pollens

Physical and Emotional Causes

Aquagenic reaction

Cholinergic stimuli, including emotional stress (psychogenic), exercise, heat

Cold[a]

Dermatographism[a]

Pressure

Sunlight

Sweating

Vibration

Systemic Disease

Autoimmune thyroid disease

Celiac disease

Bullous pemphigoid

Juvenile idiopathic arthritis

Kawasaki disease

Acute rheumatic fever (i.e., erythema marginatum)

Hypocomplementemic urticarial vasculitis (associated with systemic lupus erythematosus and other connective tissue diseases)

Serum sickness

Serum sickness–like reactions

Common variable immunodeficiency

Other

Cutaneous mastocytosis (e.g., urticaria pigmentosa, solitary mastocytoma)

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[a] Most common.

[b] Can cause a pseudoallergic reaction.

In acute urticaria in children, an infectious cause can be demonstrated in up to 60% of cases.[3,5,6] Viral upper respiratory tract and gastrointestinal tract infections are the primary infectious triggers of acute urticaria in children, with rhinovirus, adenovirus, rotavirus, and *Streptococcus pyogenes* the most commonly associated infectious agents.[6,7]

Most cases of chronic urticaria in children have idiopathic, autoimmune, or physical causes.[8–13] Physical urticaria is the most commonly identified cause. Triggers include cold exposure, pressure, heat, exercise, vibration, and water.[11] Chronic urticaria can be associated with a variety of infections.[3,9,12–15] The relevance of occult dental, sinus, or ear infections remains controversial.[16] In one study of adults and children with chronic urticaria evaluated at an academic medical center in Turkey, 10 (31.2%) of 32 of children with chronic urticaria tested positive for *Helicobacter pylori* antigen in their stool, and urticaria resolved after eradication of *H. pylori*.[17] However, based on the lack of resolution of most cases of chronic urticaria after treatment of the purported infectious trigger, some experts argue that there is no relationship between chronic infection and chronic urticaria.[18] Some evidence suggests that patients with chronic autoimmune urticaria may manifest an infection-associated autoreactive response.[19] There is no demonstrated association between chronic urticaria and malignancy.[20]

Epidemiology

Urticaria is a common problem over a lifetime, occurring in 20% to 25% of the population.[21,22] For children and adolescents, prevalence estimates range from 2% to 20%.[3,23–25] There is no known sex, ethnic, or racial predisposition. Most pediatric cases of urticaria are acute and self-limited. In children, chronic urticaria is uncommon, with a prevalence of only 0.1% to 0.3%.[26] Controversy exists about whether there is an increased prevalence of urticaria among people with a personal or family history of atopic disease, although a prospective birth cohort study from Germany demonstrated a significant association between the cumulative prevalence of urticaria at age 10 years and allergic sensitization with peanut, soy, and wheat but not with aeroallergens. A personal history of asthma, eczema, and seasonal allergies and parental history of atopy or urticaria also were strongly associated.[25] A history of atopy has been associated with increased severity and duration of acute urticaria in children.[27,28]

Pathogenesis and Pathologic Findings

Urticaria results from degranulation of mast cells and basophils, which release of histamine and other vasoactive mediators.[29] Histamine acts through H_1 and H_2 receptors to produce vasodilation and altered vascular permeability that result in fluid extravasation and dermal edema, forming urticarial lesions. Together with the axonal reflex, which produces the associated cutaneous flare, these features comprise the triple response of Lewis. Intense pruritus also can result from histamine released into the dermis. Other mediators of urticaria include kinins, prostaglandins, leukotrienes, cytokines, chemokines, and neuropeptides.

Urticaria can be immunologic or nonimmunologic. Immune-mediated urticaria results from an immunoglobulin E (IgE)–mediated type I hypersensitivity reaction; from the development of IgG autoantibodies against IgE or the high-affinity IgE FceRI or FceRII receptor (i.e., type II hypersensitivity reaction); from the binding of circulating immune complexes to mast cells expressing Fc receptors for IgG and IgM (i.e., type III hypersensitivity reaction); and rarely from T-lymphocyte–mediated activation of mast cells (i.e., type IV hypersensitivity reaction).[29]

In nonimmunologic (pseudoallergic) urticaria, direct degranulation of mast cells and basophils occurs in response to exogenous factors such as pressure and cold; from activation of membrane receptors involved in innate immunity (e.g., by opioids); through direct mast cell toxicity, as occurs with iodinated radiographic contrast agents, drugs (e.g., aspirin, nonsteroidal anti-inflammatory drugs [NSAIDs]), and foods; or through inhibition of kinin breakdown by inhibitors of angiotensin-converting enzymes.

Urticaria due to infectious agents is postulated to involve the formation of immune complexes with activation of complement and release of anaphylatoxins or development of IgE antibodies to microbial antigens.[30,31] There is no reported difference in total serum IgE level, peripheral blood eosinophil count, or IgE-mediated sensitization to aeroallergens in children with acute or chronic urticaria, although aeroallergen sensitization is high in both groups.[32]

Clinical Manifestations, Differential Diagnosis, and Approach

Commonly referred to as *hives* or *welts*, urticaria is characterized by the appearance of wheals with or without angioedema. Almost all cases of urticaria in infants and most cases in children are acute and resolve within 6 weeks. Chronic urticaria is diagnosed when urticaria occurs daily or almost daily, with or without angioedema, for more than 6 weeks.

Hallmark clinical features of urticaria include the acute onset of edematous papules and plaques, which often manifest with central clearing; are surrounded by erythema; pruritus, or a burning sensation; and have an evanescent duration of 1 to 24 hours.[14] The size of individual wheals can vary from a few millimeters to several centimeters in diameter. Although classically annular or circular, wheals can assume a bizarre, serpiginous morphology (Fig. 72.1). Occasionally, wheals can have a transient, dusky, violaceous center, which can be confused with EM; this variant of acute urticaria has been referred to as *urticaria multiforme* or *acute annular urticaria*.[33,34] Associated dermatographism, a form of pressure-induced urticaria, often is seen.

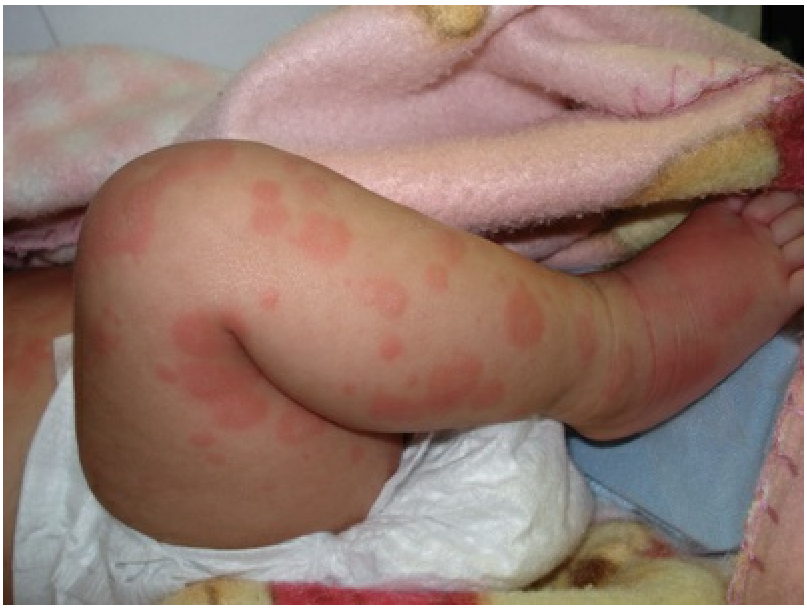

FIGURE 72.1 Acute urticaria. Migratory, edematous, erythematous plaques with central clearing are associated with edema of the hands and feet.

Angioedema, defined by edema of the deep dermis and subcutis that classically involves the mucous membranes and acral areas (i.e., hands, feet, and face), occurs in about 5% to 10% of children with urticaria. Angioedema usually resolves more slowly that urticaria and can last for up to 72 hours. Patients can have a burning or stinging sensation, but pruritus usually is not prominent.

When urticaria is associated with anaphylaxis, systemic symptoms develop as a result of the release of vasoactive mediators, and swelling of viscera can occur. Systemic symptoms and signs include hoarseness, respiratory distress, emesis, diarrhea, abdominal pain, arthralgia, flushing, syncope, hypotension, and cardiovascular collapse.

The clinical approach to urticaria in children involves establishing a definitive diagnosis of spontaneous urticaria and identifying a plausible trigger, both of which in most cases is established by a thorough and pertinent history and physical examination. The history should focus on the frequency and duration of wheals; associated symptoms such as pruritus or burning; systemic symptoms such as fever, arthralgia, or respiratory or gastrointestinal symptoms; and recent medication exposures.

The physical examination should focus on the morphology, distribution, and progression of wheals, and their transient nature can be documented through serial examinations, with marking of individual wheals if necessary. Angioedema, mucous membrane abnormalities, and specific findings such as lymphadenopathy, hepatosplenomegaly, and arthritis should be identified. The differential diagnosis of urticaria includes other annular erythemas, such as EM; autoinflammatory syndromes, particularly CAPSs; exanthematous drug eruptions; and urticarial eruptions associated with systemic disease, such as systemic lupus erythematosus and juvenile idiopathic arthritis[35] (see Box 72.2).

Laboratory Findings and Diagnosis

Skin biopsy can be helpful in equivocal cases or when a diagnosis other than urticaria (e.g., urticarial vasculitis) is suspected. Histologically, urticaria demonstrates dermal edema, dilation of postcapillary venules and lymphatic vessels, and a sparse, mixed perivascular infiltrate with various numbers of eosinophils and neutrophils. An increase in mast cells also may be seen.[36] In some cases, the histology of urticaria can be nonspecific or appear as normal skin.

Diagnostic tests are recommended when the history and physical examination suggest a specific, treatable cause (e.g., streptococcal pharyngitis, bacterial enteritis, food allergy) or when the diagnosis is uncertain or unlikely to be urticaria. For mild, chronic urticaria under pharmacologic control and in the absence of corroborating physical examination findings or a suggestive history, extensive laboratory evaluations usually are not indicated.[37]

Skin prick testing combined with ImmunoCAP testing as clinically indicated can be performed if food or environmental allergy is suspected to be the cause. Oral food challenges and elimination diets, if clinically indicated, should be performed under the guidance of an experienced allergist. Provocation testing may be performed to validate a diagnosis of physical urticaria.

If a specific infectious cause is suspected, directed serologic or microbiologic testing should be performed, if indicated. Additional laboratory evaluations considered in selected cases of urticaria in which the history and physical examination suggest systemic disease include a complete blood cell count with a differential leukocyte count, erythrocyte sedimentation rate (ESR), thyroid function tests, and levels of C-reactive protein, serum hepatic enzymes, antinuclear antibodies, tryptase, immunoglobulins, and complement (e.g., C3, C4, CH50). The basophil histamine release assay is a specialized diagnostic test that can be used to confirm a diagnosis of chronic autoimmune urticaria by detecting IgG antibodies to FcεRI, FcεRII, or IgE or an alternate histamine releasing factor. Imaging studies such as chest or sinus radiography are considered for selected patients.

Management

Primary management focuses on providing symptomatic relief and eliminating or avoiding the known causes or triggers.[38] Factors that can aggravate urticaria include heat, exercise, emotional stress, and medications such as aspirin and NSAIDs.[39] Infection should be treated if indicated, although treatment of the associated infection results in improvement of urticaria in only a minority of patients.

The most successful approach to treating the symptoms of urticaria is with medications that block the effect of histamine at the level of its receptor on cutaneous blood vessels. Antihistamines that block H_1 receptors are considered as first-line therapy for urticaria.[38] Hydroxyzine hydrochloride is the most effective of the classic H_1 antihistamines for suppression of the wheal-and-flare response, pruritus, and dermatographism.[40–42]

Because of significant sedative and anticholinergic effects of the first-generation antihistamines, newer nonsedating H_1 antihistamines such as fexofenadine, loratadine, and cetirizine are recommended as first-line therapeutic agents. These agents are as efficacious as first-generation antihistamines and have a longer duration of action. Levocetirizine is safe and effective in reducing the duration of acute urticaria in infants as young as 12 months of age.[43]

Antihistamine therapy should be initiated at the upper end of the recommended dosage range and then gradually increased as needed until symptoms are relieved or until side effects, particularly sedation, become prohibitive. Use of antihistamines at two to four times the recommended dosage by the manufacturer may be required.[44] Administering most of the daily dose just before bedtime can minimize daytime sedation. Alternative or adjunctive therapies should be considered in patients who do not respond to H_1 antihistamines.[38] The therapeutic response to the H_1 antihistamines can be improved with the addition of an H_2 receptor antagonist such as cimetidine or ranitidine.[45] H_2 receptor antagonists should not be used as monotherapy because of their insufficient H_1 blockade.

Topical corticosteroids are of limited utility in the treatment of urticaria. Use of systemic corticosteroids rarely is indicated in children and discouraged for prolonged use in cases of chronic urticaria due to concerns about significant adverse effects. A short course of oral corticosteroids usually is reserved for children with severe, unremitting symptoms, especially asthma, laryngeal edema, or anaphylaxis, or when angioedema on the face is particularly severe.

Rarely, chronic urticaria is severe enough that despite the use of oral antihistamines, additional systemic therapy is warranted. Alternative or adjunctive therapies include mast cell stabilizers, leukotriene antagonists, tricyclic antidepressants (especially doxepin), dapsone, cyclosporine, mycophenolate mofetil, and omalizumab.[44,46]

Complications and Prognosis

Complications are rare but can result from associated angioedema or anaphylaxis. Most cases of acute urticaria resolve within 1 to 2 weeks, with or without therapy. Approximately one half of cases of chronic urticaria resolve within 6 months, and one half resolve within 1 to 3 years.[3,9,47] Patients with associated angioedema are more likely to have persistent urticaria.[48]

Erythema Multiforme

Etiologic Agents and Epidemiology

Although numerous infections have been reported in association with EM, herpes simplex virus (HSV) is by far the most common and best documented (Box 72.3)[49,50] Recurrent EM is significantly associated with HSV infection.[51,52] Unusual presentations of EM include neonatal disease due to congenital cytomegalovirus infection and recent hepatitis B and bacille Calmette-Guérin (BCG) vaccination; idiopathic neonatal EM also has been reported.[53–55] EM is associated rarely with Kawasaki disease.[56–58] Persistent EM has been associated with Epstein-Barr virus (EBV) infection, inflammatory bowel disease, and malignancy.[59]

Box 72.3

Infectious Agents Associated With Erythema Multiforme

Bacteria

Bartonella henselae

Corynebacterium diphtheriae

Francisella tularensis[a]

Legionella pneumophila

Mycobacterium leprae

Mycobacterium tuberculosis[a]

Neisseria gonorrhoeae

Proteus mirabilis[a]

Pseudomonas aeruginosa

Salmonella spp.[a]

Staphylococcus aureus[a]

Streptococcus pneumoniae

Streptococcus pyogenes[a]

Vibrio parahaemolyticus[a]

Yersinia spp.[a]

Chlamydia

Chlamydophila psittaci

Chlamydia trachomatis (i.e., lymphogranuloma venereum)

Fungi

Coccidioides immitis

Histoplasma capsulatum[a]

Immunizations

Bacille Calmette-Guérin

Diphtheria and tetanus toxoid

Hepatitis B

Measles

Mumps

Rubella

Poliomyelitis

Mycoplasma

Mycoplasma pneumoniae

Parasites

Trichomonas vaginalis

Treponemes

Treponema pallidum

Viruses

Adenovirus 7[a]

Coxsackieviruses A10, A16, B5

Echovirus 6

Epstein-Barr virus[a]

Hepatitis viruses A and B

Herpes simplex viruses 1 and 2[a]

Human immunodeficiency virus

Influenza A virus

Measles virus

Mumps virus

Orf virus

Paravaccinia virus[a]

Parvovirus B19

Varicella-zoster virus

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[a] Most clearly established.

Epidemiologic data on EM in children are lacking. Typically, a disease of adults 20 to 40 years of age, an estimated 20% of cases are seen in children and adolescents.[60–62] There is no clear sex, ethnic, or racial predisposition. Recurrent EM occurs more commonly in the spring.[62] Human leukocyte antigens B62, B35, and DR53 have been associated with a higher risk of HSV-induced EM, particularly recurrent EM.[63]

Pathogenesis and Pathologic Findings

The pathogenesis of EM is incompletely understood, but evidence increasingly implicates a host-specific, cell-mediated immune response to an antigenic stimulus that targets keratinocytes at the dermal-epidermal junction.[61,62] Cytokines released by activated mononuclear cells and keratinocytes contribute to necrosis of keratinocytes. Although circulating and tissue-bound immune complexes can be demonstrated, they do not appear to play a central role in pathogenesis. HSV antigens and DNA have been documented in skin lesions from patients with EM and are absent in unaffected skin of patients.[50,64–66]

Histologically, EM demonstrates mild spongiosis, lymphocytic exocytosis, variable papillary dermal edema, a perivascular and interstitial mononuclear infiltrate, and basal vacuolization with liquefactive degeneration of the basal layer of the epidermis; the feature of satellite cell necrosis is a hallmark of EM.[36] An increased number of eosinophils or nuclear dust, or both, can be seen. Subepidermal blisters and necrosis of the entire epidermis can be seen in more severe cases.

Clinical Manifestations, Differential Diagnosis, and Clinical Approach

EM has various cutaneous manifestations. EM is characterized by the acute onset of a symmetric, fixed cutaneous eruption of erythematous macules, papules, vesicles, and bullae, which most commonly are distributed on the palms, dorsal surfaces of the hands and feet, and extensor surfaces of the arms and legs, with relative sparing of the face, trunk, and mucous membranes.[61]

Lesions can expand and evolve over several days to assume the classic annular target appearance with a dusky, necrotic center surrounded by a ring of edema and pallor and an erythematous border (Fig. 72.2). The development of new lesions 72 hours after onset is unusual. The isomorphic phenomenon, which refers to the development of lesions at sites of prior skin trauma, is common. Lesions usually are asymptomatic, although patients can have a burning sensation or pruritus. Photoaccentuation is common.

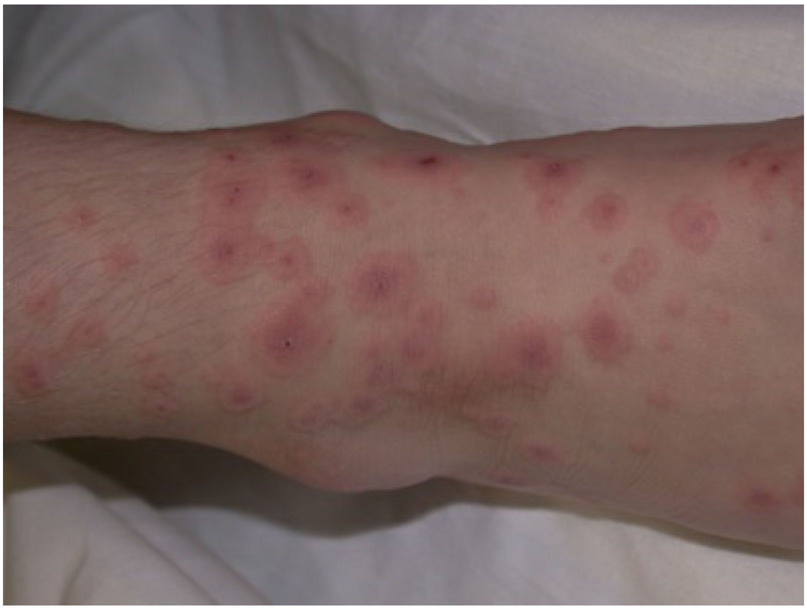

FIGURE 72.2 Erythema multiforme. Target lesions manifest as edematous papules with dusky, necrotic centers and erythematous, annular borders.

Prodromal symptoms usually are absent, although low-grade fever, malaise, and upper respiratory tract symptoms can occur. Cervical lymphadenopathy can be associated with oral involvement, which occurs in about 25% of cases and usually includes localized erosions involving the gingival, tongue, or buccal mucosa (Fig. 72.3). Rarely, more extensive involvement can be seen, but extensive hemorrhagic erosions and crusting such as is seen with Stevens-Johnson syndrome does not occur.[61,62] Ocular or other mucous membrane involvement does not occur and, if present, should raise the possibility of Stevens-Johnson syndrome (see Chapter 70).

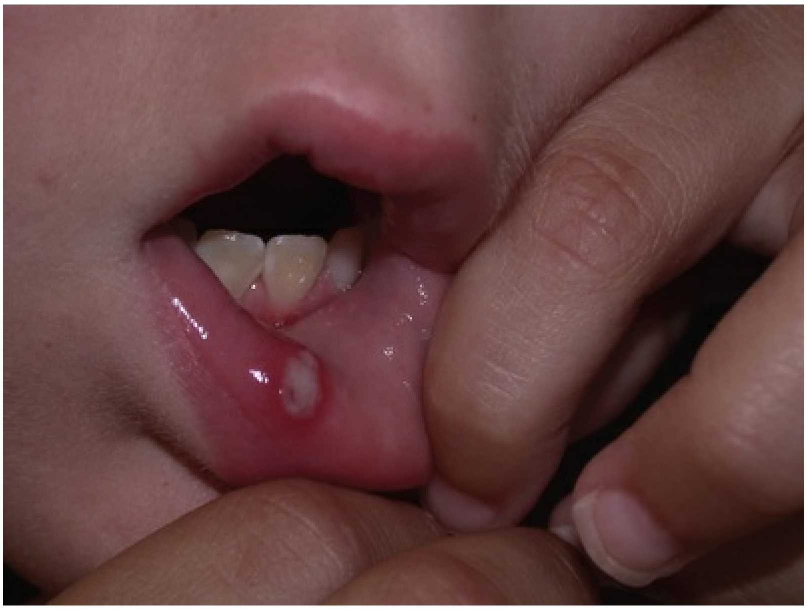

FIGURE 72.3 Oral aphthae in a child with herpes simplex virus (HSV)–associated recurrent erythema multiforme.

Lesions of HSV-induced recurrent EM typically develop 10 to 14 days after the onset of recurrent mucocutaneous lesions (usually oral mucosa) or occur after asymptomatic reactivation of HSV.[67] EM has a similar morphology and distribution from episode to episode, but it can vary considerably in frequency and duration in a given patient.

The differential diagnosis includes acute urticaria, vasculitis, viral exanthem, exanthematous drug eruption, fixed drug eruption, Stevens-Johnson syndrome, acute hemorrhagic edema of infancy, neutrophilic dermatosis, and polymorphous light eruption. An EM-like allergic contact dermatitis can be seen after exposure to agents such as *p*-phenylenediamine in hair dyes and topical triamcinolone.[68–71]

Laboratory Findings and Diagnosis

Although typically a clinical diagnosis, skin biopsy can help to confirm the diagnosis. There are no typical laboratory abnormalities, although elevated an ESR, moderate leukocytosis, and mildly elevated levels of serum hepatic transaminases can be seen in some patients. In cases when HSV infection is suspected, polymerase chain reaction (PCR) or direct fluorescent antigen (DFA) testing can be performed on specimens from primary or recurrent cutaneous lesions.[72]

Management

Supportive treatment is all that is necessary in most cases. Use of antihistamines (orally) and analgesics (orally and topically for oral mucosal involvement) may be helpful in addressing associated pruritus and pain, respectively. Debridement of necrotic skin is not recommended, and blisters should be left intact when possible. Areas that have eroded, blistered, or crusted should be monitored for infection. Re-epithelialization of denuded areas is facilitated by application of bland emollients, antibiotic ointments, or use of petrolatum-impregnated gauze or hydrocolloid or foam dressings. No controlled, prospective study supports the use of corticosteroids.[62,73] Oral acyclovir given early for episodes of primary or recurrent EM may lessen the severity of the clinical course.[67,74] Use of famciclovir for the management of recurrent herpes-associated EM has been reported in a few adults.[75]

Complications, Prognosis, Sequelae, and Prevention

Complications are unusual, but secondary bacterial skin infections can occur. EM typically resolves within 2 to 4 weeks. Significant postinflammatory hyperpigmentation can result, but scarring is unusual unless secondary bacterial infection of the skin has occurred. Recurrent EM usually remits after several years.

Preventive measures for recurrent EM include sun-protective measures such as routine use of sunscreen, use of protective clothing, and avoidance of excess exposure. Use of acyclovir or valacyclovir (in adolescents older than 12 years) for 6 to 12 months can be considered at suppressive doses for children and adolescents with more than three to four recurrences per year (see Chapter 204).

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73

Papules, Nodules, and Ulcers

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Papules, nodules, and ulcers are primary lesions of the skin with a variety of infectious and noninfectious causes (Tables 73.1 and 73.2). A *papule* is a raised superficial lesion that is less than 1 cm in diameter whose surface may be smooth, scaly, or hyperkeratotic. A larger (>1 cm), raised, and often flatter-topped lesion is called a *plaque.* A *nodule* is a solid, palpable lesion that is larger than 1 cm in diameter. An *ulcer* is a loss of skin to the level of the dermis or deeper. An *erosion* is shallower, and the loss of skin is limited to the epidermis.

TABLE 73.1

Primary Infectious Causes of Papules, Nodules, and Ulcers

Disease Entity	Skin Lesions	Infectious Agent
ARTHROPODS		
Cutaneous myiasis	P, N	*Dermatobia hominis*
Scabies	P	*Sarcoptes scabiei*
Tungiasis	P	*Tunga penetrans*
BACTERIA		
Actinomycosis	P, N, U	*Actinomyces israelii*
Anthrax	P, U	*Bacillus anthracis*
Bartonellosis	P, N	*Bartonella bacilliformis*
Brucellosis	P, N	*Brucella* spp.
Cat scratch disease	P, N	*Bartonella henselae*
Chancroid	P, U	*Haemophilus ducreyi*
Diphtheria	P, U	*Corynebacterium diphtheriae*
Ecthyma	U	*Streptococcus pyogenes*

Ecthyma gangrenosum	P, U	*Pseudomonas aeruginosa*
Folliculitis	P	*Enterobacter* spp.
	P	*Escherichia coli*
	P	*Klebsiella* spp.
	P, N	*Proteus* spp.
	P	*Pseudomonas aeruginosa*
	P	*Staphylococcus aureus*
Furunculosis, carbunculosis	N	*Staphylococcus aureus*
Granuloma inguinale	P, N, U	*Calymmatobacterium granulomatis*
Hidradenitis suppurativa	N	Mixed skin flora
Impetigo	P, U	*Staphylococcus aureus*
	P, U	*Streptococcus pyogenes*
Lyme disease	P, U	*Borrelia burgdorferi*
Lymphogranuloma venereum	P, U	*Chlamydia trachomatis*
Malakoplakia	P, N, U	Multiple organisms
Melioidosis	N, U	*Pseudomonas pseudomallei*
Meningococcemia, chronic	P	*Neisseria meningitidis*
Nocardiosis	P, N	*Nocardia brasiliensis*
	P, N	*Nocardia asteroides*
Pyomyositis	N	Multiple organisms
Rhinoscleroma	N, U	*Klebsiella rhinoscleromatis*
Sycosis barbae	P	*Staphylococcus aureus*
Septic emboli	P, U	Multiple organisms
Tularemia	U	*Francisella tularensis*
FUNGI		
Blastomycosis	P, N, U	*Blastomyces dermatitidis*
Candidiasis	P, N, U	*Candida albicans*
	P, N, U	*Candida tropicalis*
Coccidiomycosis	P, N, U	*Coccidioides immitis*
Cryptococcosis	P, N, U	*Cryptococcus neoformans*
Folliculitis	P	*Candida albicans*
	P	*Malassezia furfur*
Histoplasmosis	P, N, U	*Histoplasmosis capsulatum*
Hyalohyphomycosis	N	Multiple organisms
Mycetoma	P, N, U	Multiple organisms
Phaeohyphomycosis	N	Multiple organisms
Sporotrichosis	P, N, U	*Sporothrix schenckii*
Tinea barbae, tinea capitis	P, N	*Trichophyton* spp.
	P, N	*Microsporum* spp.
Tinea corporis	P	*Trichophyton* spp.
	P	*Microsporum canis*
Zygomycosis	U	*Absidia, Rhizopus, Mucor*
HELMINTHS		
Dracunculosis (guinea worm)	U	*Dracunculus medinensis*
Larva currens	P	*Strongyloides stercoralis*
Cutaneous larva migrans	P	*Ancylostoma braziliense*
	P	*Ancylostoma caninum*
Cysticercosis	N	*Taenia solium*
Ground itch	P	*Necator americanus*
Loiasis	N	*Loa loa*
Ancylostoma duodenale		
Onchocerciasis	P, N	
Onchocerca volvulus		
Cercarial dermatitis	P	
Trichobilharzia spp.		

Schistosomiasis	P	
Schistosoma spp.		
MYCOBACTERIA		
Nontuberculous mycobacteriosis	P, N, U	*Mycobacterium marinum*
	N, U	*Mycobacterium kansasii*
	N, U	*Mycobacterium scrofulaceum*
	N, U	*Mycobacterium ulcerans*
	P, N, U	*Mycobacterium avium* complex
	P, N, U	*Mycobacterium fortuitum, M. chelonae*
	P, N, U	*Mycobacterium leprae*
Cutaneous tuberculosis	P, N, U	*Mycobacterium tuberculosis*
	P, N, U	*Mycobacterium bovis*
	P, N, U	Bacille Calmette-Guérin
PROTOZOA		
Amebiasis	N, U	*Entamoeba histolytica*
Leishmaniasis	P, N, U	*Leishmania* spp.
TREPONEMES		
Pinta	P	*Treponema carateum*
Syphilis	P, N, U	*Treponema pallidum*
Yaws	P, N, U	*Treponema pertenue*
VIRUSES		
Epidermodysplasia verruciformis	P	Human papillomaviruses
Herpes simplex	N, U	Human herpes virus types 1 and 2
Herpes zoster	N, U	Varicella-zoster virus (HHV-3)
Milker nodule	P, N	Paravaccinia virus
Molluscum contagiosum	P, N	Molluscum contagiosum virus
Orf	P, N	Orf virus
Parvovirus	P	Parvovirus B19
Warts	P, N	Human papillomaviruses

N, nodule; P, papule; U, ulcer.

TABLE 73.2

Major Noninfectious Causes of Papules, Nodules, and Ulcers

Disease Entity	Skin Lesions
Acne vulgaris	P, N
Amyloidosis	P, N
Arthropod bite hypersensitivity reaction	P, N
Autoimmune disease (SLE, dermatomyositis, Behçet)	P, N, U
Calcinosis cutis	P, N, U
Dermatofibroma	P, N
Dermoid cyst	P, N
Drug hypersensitivity reaction	P
Eczema, follicular	P
Elastosis perforans serpiginosa	P
Epidermal cyst	P, N
Eruptive vellus hair cyst	P
Erythema induratum	N, U
Erythema multiforme	P, U
Erythema nodosum leprosum	N
Factitial panniculitis	N
Foreign-body reaction	P, N

Fox–Fordyce disease	P
Gout	P, N, U
Granuloma annulare	P, N
Juvenile xanthogranuloma	P, N
Kawasaki disease	P
Keloid/hypertrophic scar	P, N
Keratosis follicularis (Darier disease)	P
Keratosis pilaris	P
Langerhans cell histiocytosis	P, N, U
Leukemia	P, N
Lichen nitidus	P
Lichen planus	P, U
Lipoma	N
Lupus erythematosus	P, U
Lupus panniculitis	N
Lymphoma	P, N
Lymphomatoid granulomatosis	N, U
Mastocytoma	P, N
Melanoma	P, N, U
Metastasis, cutaneous	P, N, U
Miliaria rubra	P
Milium	P
Necrobiosis lipoidica diabeticorum	N, U
Neuroblastoma	N
Neurofibroma	P
Neutrophilic dermatosis (Sweet syndrome)	P, N, U
Nevus	P
Panniculitis	N, U
Pilar cyst (trichilemmal cyst)	P, N
Pilomatricoma	P, N
Pityriasis rubra pilaris	P
Polyarteritis nodosa	N, U
Polymorphous light eruption	P
Prurigo nodularis	P, N
Pseudoxanthoma elasticum	P
Psoriasis	P
Pyoderma gangrenosum	N, U
Pyogenic granuloma	P
Rheumatoid nodule	N
Sarcoidosis	P, U
Spitz nevus	P, N
Steatocystoma multiplex	P, N
Subcutaneous fat necrosis	N
Superficial thrombophlebitis	N
Trichoepithelioma	P, N
Tuberous sclerosis	P
Urticaria	P
Urticaria pigmentosa	P, N
Vascular malformation	P, N
Vasculitis	P, U
Xanthoma	P, N

N, nodule; P, papule; SLE, systemic lupus erythematosus; U, ulcer.

Particular cutaneous lesions can be associated with a specific organism (e.g., umbilicated papule with molluscum contagiosum [MC], hyperkeratotic papule with human papillomavirus [HPV]), or multiple morphologic lesions can occur through the course of infection due to a single organism. For example, in tuberculosis or sporotrichosis, an initial papule can enlarge to form a nodule and then break down to an ulcer. The papular or nodular lesions can consist of a proportionately large volume of the infectious agent (e.g., poxvirus of MC), almost exclusively of inflammatory cells (e.g., histiocytes within well-controlled primary cutaneous tuberculosis), or frequently a combination of the inciting agent and inflammatory reaction.

Nodular lymphangitis, often referred to as *sporotrichoid spread* in dermatology, is a distinctive, underrecognized pattern resulting from cutaneous inoculation of a relatively limited number of agents characterized by a linear pattern of lymphadenopathy often proximal to the site of the primary inoculation (e.g., *Sporothrix schenckii, Francisella tularensis, Alternaria, Nocardia brasiliensis, Mycobacterium marinum,* other *Mycobacterium* species, *Leishmania, Yersinia* and *Francisella*).[1–6] Chronic nodular lymphangitis due to any cause can become ulcerative.[3,4]

A variety of nonspecific reactive lesions can manifest in the skin as a result of an infectious process elsewhere (e.g., erythema nodosum as a sign of streptococcal pharyngitis). The eruptions result from a disordered immune response after infection. At the time of lesion development, organisms usually are not recoverable (Box 73.1 and Table 73.3). Drug reactions in children also can manifest as papules or rarely as nodules, often in the setting of a concurrent viral infection, which can be confused with a response to the infection.

Box 73.1

Infectious Agents Associated With Erythema Nodosum

Bacteria

Bartonella henselae[a]

Brucella spp.

Campylobacter jejuni

Corynebacterium diphtheriae

Francisella tularensis

Haemophilus ducreyi

Leptospira interrogans

Neisseria gonorrhoeae

Neisseria meningitidis

Salmonella spp.

Streptococcus mutans

Streptococcus pyogenes[a]

Yersinia enterocolitica[a]

Yersinia pseudotuberculosis

Chlamydia

Chlamydophila psittaci

Chlamydia trachomatis (i.e., lymphogranuloma venereum)

Chlamydophila (Chlamydia) pneumoniae

Fungi

Blastomyces dermatitidis

Coccidioides immitis[a] dermatophytoses (e.g., tinea capitis)

Histoplasma capsulatum

Sporothrix schenckii

Helminths

Ancylostoma duodenale

Necator americanus

Mycobacteria

Mycobacterium bovis

M. leprae

M. marinum

M. tuberculosis[a]

Mycoplasma

Mycoplasma pneumoniae

Protozoa

Toxoplasma gondii

Treponemes

Treponema pallidum

Viruses

Crimean-Congo hemorrhagic fever virus

Epstein-Barr virus

Hepatitis virus B and C

Herpes simplex virus

Mumps virus

Paravaccinia virus

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[a] Most common.

Data from references 40–44.

TABLE 73.3

Conditions With Sterile Papular, Nodular, or Ulcerative Skin Lesions After Infection

Disease Entity	Skin Lesions	Infectious Agent
Autosensitization	P, N	See Box 73.3
Erythema elevatum diutinum	P, N	*Streptococcus pyogenes*
Erythema multiforme	P	See Chapter 72
Erythema nodosum	N	See Box 73.1
Gianotti-Crosti syndrome	P	See Box 73.2
Guttate psoriasis	P	*Streptococcus pyogenes,* EBV, Chikungunya virus
Henoch-Schönlein purpura	P, N	*Brucella* sp, HBV, HEV, HIV, *Helicobacter pylori, Mycobacterium tuberculosis, Mycoplasma pneumonia, Pneumocystis jirovecii, Staphylococcus* sp, *Streptococcus pyogenes* coxsackievirus
Polyarteritis nodosa	P, N, U	Cytomegalovirus, HBV, HCV, HIV, *M. tuberculosis, S. pyogenes, Toxoplasma gondii*
Postscabitic nodule	P, N	*Sarcoptes scabiei*
Reactive arthritis		Multiple causes[a]
• Circinate balanitis	U	
• Keratoderma blennorrhagicum	P, N	
Rheumatic fever	N	*S. pyogenes*
Unilateral laterothoracic exanthema	P	Multiple viral causes[b]
Urticaria	P	See Chapter 72
Common exanthema	P	Multiple viral causes[c]

[a] Sexually transmitted form follows infection with *Chlamydia trachomatis*. The postdysenteric form follows infection with *Salmonella* and *Shigella* species, *Yersinia enterocolitica*, *Yersinia pseudotuberculosis*, *Campylobacter fetus*, and *Clostridium difficile*.

[b] Implicated agents are EBV, PIV, and adenovirus.

[c] Associated viruses include enteroviruses, EBV, human herpesviruses 6 and 7, and respiratory viruses such as RSV, PIV, and adenovirus.

EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HIV, human immunodeficiency virus; N, nodule; P, papule; PIV, parainfluenza virus; U, ulcer.

Data from references 49–65.

This chapter focuses on diseases that can cause papules, nodules, or ulcers. Infections in which skin lesions do not develop primarily but are manifestations of systemic disease (e.g., bartonellosis, tularemia, trypanosomiasis) are discussed elsewhere.

Molluscum Contagiosum

MC is one of the most common cutaneous infections arising in childhood, and it produces a papule in the skin in which viral particles can be identified easily.[7,8] Molluscipoxvirus is as a rule found in abundance within MC lesions, whereas HPV is found in various quantities within the cutaneous lesions of common warts. Papular lesions in MC develop largely from hyperproliferation of basal cells and retention of upper epidermal keratinocytes.

Molluscipoxvirus that causes MC is a double-stranded DNA virus that replicates in the cytoplasm of host epithelial cells (see Chapter 202). Infection is acquired through direct contact with an infected person or from fomites, and it is spread by autoinoculation. School-aged children who are otherwise well and people with impaired cellular immune function are affected most commonly.[9] Children with a history of atopic dermatitis and impaired skin barrier function appear to be at greater risk for the development and spread of lesions. The pruritic nature of the underlying dermatitis makes children more likely to scratch affected areas and autoinoculate through breaks in the skin. The estimated incubation period is 2 to 8 weeks, but it can be longer.

One mechanism the virus uses to evade host mechanisms for killing virus-infected cells is its viral FLICE-like inhibitory protein (FLIP). Viral FLIPs inhibit apoptosis-mediated cell death.[10,11]

Lesions of MC are discrete, pearly pink, or skin-colored, dome-shaped papules 1 to 5 mm in the greatest dimension (Fig. 73.1), which on close inspection have central umbilication. Lesions can coalesce into larger papules or become erythematous and inflamed. In some cases, a plug of cheesy, whitish material can extrude from the center and can be mistaken for purulence. Papules can occur anywhere on the body, but there is predilection for the face, trunk, and sites where skin is in contact with other skin surfaces, such as the thighs and axillae. When the lesions are found in clusters on the genitalia or in the groin of a sexually active adolescent, other sexually transmitted infections should be sought because these lesions can result from sexual contact. Lesions commonly involve the genital area in children and frequently are not acquired by sexual transmission, but an interview and examination for other signs that may suggest sexual abuse should be performed.

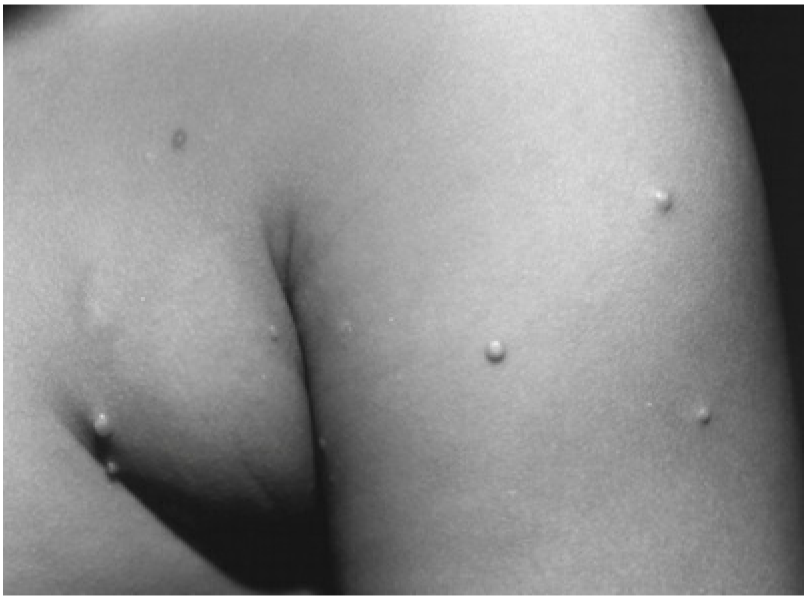

FIGURE 73.1 Umbilicated papules on the upper arm and chest of a child with molluscum contagiosum.

Mild surrounding erythema often heralds resolution of molluscum. An eczematous dermatitis can accompany the papules, especially in children with a history of atopic dermatitis or eczema.[12] Lesions in children with the acquired immunodeficiency syndrome (AIDS) tend to be large and numerous, particularly on the face, and they can have an atypical appearance, which includes coalescent crusted lesions and large, separate lesions on an erythematous base.[13] Exuberant lesions also occur in children with leukemia or other immunodeficiencies.[13]

The diagnosis of MC often is made by the typical appearance of umbilicated papules, but if lesions are clinically atypical, histologic confirmation may be warranted. On microscopic examination, the papule of MC consists of a lobulated mass of virus-infected epidermal cells. These eosinophilic viral inclusion bodies (i.e., Henderson-Patterson or molluscum bodies) become more prominent as infected keratinocytes move upward from the basal layer to the stratum corneum. The central plug of material, which is composed of virus-laden cells, can be shelled out from a lesion and examined under the microscope with 10% potassium hydroxide or with Wright or Giemsa stain. The rounded, cup-shaped mass of homogeneous cells, often with identifiable lobules, is diagnostic.

The differential diagnosis for an immunocompetent child includes noninfectious papules such as pilomatricoma, trichoepithelioma, ectopic sebaceous glands, syringoma, hidrocystoma, and an atypical melanocytic proliferation or Spitz nevus. In immunosuppressed individuals such as those with HIV infection, disseminated deep fungal infections such as cryptococcosis and histoplasmosis can be indistinguishable clinically from MC.[14,15]

MC is a self-limited, epidermal disease. The average duration is 6 to 12 months, although lesions can persist for years,[16] can spread to distant sites, can become secondarily infected with bacteria, and can be transmitted to others. Affected persons should be advised to avoid sharing baths and towels until the infection has cleared. Infection can spread rapidly and produce hundreds of lesions in children with atopic dermatitis or immunodeficiency.[9] Treatment should be considered to eliminate symptoms of pruritus or discomfort, to eliminate visible lesions, and to prevent scarring, superinfection, acquisition of additional lesions, and spread to contacts.

There are few randomized, controlled studies to assess the effectiveness of various treatment modalities in children; most reports are anecdotal. Common therapies include destructive, immunomodulatory, and antiviral measures. Spontaneous resolution or active management can result in postinflammatory pigment changes or a residual shallow atrophic scar.

Cantharidin is considered by many physicians to be very effective therapy for lesions in certain locations after its usually painless in-office application by a trained physician or other healthcare personnel.[17,18] After application, treated lesions develop a superficial blister or inflammation significant enough to result in the loss of the infectious molluscum body. Additional in-office destructive treatments include cryotherapy and curettage before which application of topical anesthetic is indicated to reduce discomfort. A brief, 6- to 9-second topical application of liquid nitrogen is effective. The molluscum body also can be expressed with a needle, a sharp curette, or a comedo extractor.

Once-daily topical application of a retinoic acid product can incite an inflammatory response, which may lead to resolution of lesions, and it is the treatment of choice for MC on the face and genital skin. Cidofovir (i.e., intravenous and topical) has been beneficial for the treatment of immunocompromised adults with severe, recalcitrant MC and in several pediatric cases.[19,20] Due to significant adverse events and toxicity, cidofovir is not indicated for healthy children with self-limited infections.[20]

The role of topical application of imiquimod in children is controversial.[21,22] A retrospective analysis of 170 children with MC demonstrated resolution of approximately 50% of molluscum lesions within 12 months with or without treatment. Although limited by methodology and sample size, the study findings challenge the trend toward treatment.[23]

Erythema Nodosum

Erythema nodosum (EN) is a form of panniculitis that typically manifests as the sudden appearance of tender, erythematous, 1- to 10-cm nodules that are usually located symmetrically on the extensor surfaces of the legs[24] (see Fig. 160.1K). Less commonly, lesions can arise at other sites, including the trunk, upper extremities, head, and neck. Rare in children younger than 2 years of age, EN is most common in adolescents. Nodules typically enlarge over a few days, remain stable for 1 to 2 weeks, and then resolve gradually over 3 to 6 weeks, with color changes that mimic a bruise. Ulceration, suppuration, and scarring do not occur, but residual hyperpigmentation can persist for weeks to months. Patients often have fever, chills, malaise, leukocytosis, and an elevated erythrocyte sedimentation rate.

EN is a hypersensitivity reaction to many triggers, but in US children, it most commonly is associated with group A streptococcal pharyngitis (see Box 73.1). Infection precedes the onset of EN by approximately 3 weeks. A variety of other infectious agents have been associated with EN, most notably tuberculosis (worldwide),[25] coccidioidomycosis (southwestern United States), *Yersinia enterocolitica* (Europe), *Bartonella henselae* (cat-scratch disease), and tularemia. EN also is associated with the use of drugs (e.g., sulfonamides, oral contraceptives), sarcoidosis, and occasionally with malignancies such as leukemia and lymphoma and systemic diseases such as Behçet disease, reactive arthritis, systemic lupus erythematosus, and inflammatory bowel disease.

The differential diagnosis includes insect bite hypersensitivity reaction, lupus panniculitis, factitial panniculitis, superficial thrombophlebitis, polyarteritis nodosa, necrobiosis lipoidica diabeticorum, erythema induratum, erythema nodosum leprosum, and sarcoidosis. Sweet syndrome (i.e., painful, indurated cutaneous plaques accompanied by fever and leukocytosis) also should be considered. Sweet syndrome can be associated with hematologic malignancies or chronic, recurrent, multifocal osteomyelitis.[26,27]

The pathogenesis of EN is poorly understood. EN is classified as a septal panniculitis without vasculitis and is regarded as an immunologic reaction to etiologic antigenic stimuli.

Diagnosis usually is made clinically, but skin biopsy can be useful to confirm the diagnosis and exclude other conditions. Histopathologic analysis reveals septal panniculitis without vasculitis, with inflammation and thickening of the fibrous septa of the subcutaneous fat. In early lesions, the inflammatory infiltrate is predominantly composed of neutrophils. Lesions in a later stage show an infiltrate composed of lymphocytes, giant cells, and granulation tissue,[28] but the changes of leukocytoclastic and lymphocytic angiitis are not seen. Foreign body–type giant cells are typical.

EN is self-limited and usually resolves within 3 to 6 weeks. Recurrent EN, such as that due to repeated streptococcal infections, can occur in children. Potential triggers should be identified and treated. Nonsteroidal anti-inflammatory agents may provide symptomatic relief. Leg elevation and bed rest can minimize lower extremity edema and decrease discomfort. Potassium iodide treatment may hasten resolution of the nodules.[29]

Gianotti-Crosti Syndrome

Gianotti-Crosti syndrome, also known as *papular acrodermatitis of childhood* (PAC), is characterized by erythematous papules that are distributed symmetrically on the extremities, buttocks, and face of children. The syndrome initially was reported in association with hepatitis B virus (HBV) infection. However, a variety of viral infections (frequently infections of the upper respiratory tract) and immunizations have been associated with the syndrome (Box 73.2).[30] Cutaneous viral infections due to poxviruses, such as molluscum contagiosum and milkers' nodules also have been associated with a Gianotti-Crosti–like reaction.[12,31] Since universal HBV immunization in the United States, Epstein-Barr virus infection has become the most common association with Gianotti-Crosti syndrome.[32]

Box 73.2

Infectious Agents Associated With Gianotti-Crosti Syndrome

Immunizations

Bacille Calmette-Guérin

Diphtheria

Tetanus

Pertussis

Measles, mumps, and rubella (MMR)

Haemophilus influenzae type b (Hib)

Hepatitis A and B

Oral poliomyelitis

Japanese B encephalitis

Influenza

Varicella

Viruses

Adenoviruses[a]

Coxsackievirus A16, B4, and B5[a]

Cytomegalovirus

Echovirus 7 and 9[a]

Epstein-Barr virus[a]

Hepatitis virus A, B,[a] and C

Herpes simplex virus type 1 (HSV-1)

Human herpesvirus 6 (HHV-6)

Human immunodeficiency virus (HIV)

Parainfluenza viruses[a]

Parvovirus B19

Poliovirus

Respiratory syncytial virus[a]

Rotavirus

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[a] Most common.

Data from references 30, 45, and 46.

The disorder classically has a sudden eruption of symmetric, flat-topped, discrete, erythematous, 2- to 10-mm papules on the face, upper and lower extremities, and buttocks. The trunk and antecubital and popliteal fossae usually are spared or less involved. Patients can have pruritus and the Koebner phenomenon (i.e., accentuation of lesions at sites of trauma). Peak incidence is between 1 and 4 years of age. The differential diagnosis includes drug eruption, papular forms of urticaria, erythema multiforme, viral eruption, pityriasis lichenoides, and Langerhans cell histiocytosis.

The pathogenesis of the syndrome has been suggested to be an immunoreactive process, perhaps mediated by immune complexes or due to delayed hypersensitivity.[33] When associated with HBV infection, lesions have not yielded evidence of immune complex vasculitis, and the HBV surface antigen has not been demonstrated in skin lesions.

The syndrome usually is self-limited, resolving within 3 to 6 weeks. Lesions occasionally can persist for a few months, and relapses, although rare, have been reported. Treatment is supportive and does not shorten the course of the skin lesions. Orally administered antihistamines may provide symptomatic relief. The response to topical corticosteroids is debatable.

Other Exanthematous Infections

Numerous infections can manifest as papular, or less commonly, ulcerative eruptions on the skin. The bilaterally symmetric exanthem or morbilliform eruption classically progresses cephalocaudad and often is caused by a variety of viruses[34] (see Chapter 69). A careful history and review of systems often can elicit the necessary signs and symptoms to determine the underlying infectious cause.

Morphologically unique eruptions such as unilateral laterothoracic exanthem (i.e., asymmetric periflexural exanthem) deserve recognition to identify possible underlying infectious causes. Exanthems can have an atypical appearance such as ulcerative lesions (e.g., bacterial superinfection of primary vesicular herpes simplex virus [HSV] or varicella-zoster virus [VZV] lesions). Certain strains of bacteria (e.g., group A streptococci) can be associated with exanthems, such as the papular eruption of scarlet fever.

Autosensitization Reaction

A symmetric papular or papulovesicular cutaneous eruption can arise at a site distant to the primary dermatitis and is known as *autosensitization* or an *id reaction*. Id reaction likely is caused by hematogenously circulating products or the resultant host immune response, or both. Most commonly triggered by noninfectious causes such as a contact dermatitis, the id reaction frequently follows dermatophyte or bacterial infections (Box 73.3).[34,35]

Box 73.3

Infectious Agents Associated With a Papular or Nodular Autosensitization (Id) Reaction

Ectoparasites

Pediculus humanus capitis

Fungi

Blastomyces dermatitidis

Candida albicans

Coccidioides immitis

Epidermophyton floccosum

Histoplasma capsulatum

Sporothrix schenckii

Trichophyton mentagrophytes[a]

T. rubrum[a]

T. tonsurans[a]

T. verrucosum

Mycobacteria

Mycobacterium bovis

M. leprae

M. tuberculosis

Protozoa

Leishmania spp.

Treponemes

Treponema carateum

Viruses

Molluscum contagiosum

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[a] Most common.

Data from references 47 and 48.

Epidermal cytokines released from sites of skin infection can cause the heightened sensitivity of skin at sites distant from the site of infection to a variety of stimuli that usually are innocuous. Culture and potassium hydroxide examination of id lesions do not reveal the organism, but the test result for *Trichophyton* skin reactivity is positive. The most common dermatophyte infection triggering a dermatophytid reaction is tinea pedis, although id lesions also can occur in the setting of tinea capitis and tinea corporis. Although less commonly reported, the id reaction to tinea capitis manifesting as an eczematous eruption has been seen in children before or after initiation of systemic antifungal therapy. Antifungal therapy should be continued, and patients can be treated symptomatically with mild topical corticosteroids and oral antihistamines.[36]

Tuberculid reactions are another example of autosensitization.[25] Their genesis appears to be different from that of dermatophytid reactions. Skin lesions are rare, usually appearing in a host who has moderate to strong tuberculin reactivity, has a history of tuberculous infection of other organs, and usually has shown a therapeutic response to antituberculous therapy. Lesions exhibit tuberculoid features histologically but do not contain detectable mycobacteria, although organisms may be detected with methods such as polymerase chain reaction. Tuberculid reactions represent the paucibacillary pole of disease.[25] Rapid local destruction may account for the absence of bacilli in lesions.

The most commonly observed tuberculid in children is lichen scrofulosorum, which is characterized by asymptomatic, grouped, pinhead-sized, often follicular, pink or red papules that form plaques, mainly on the trunk.[37] Healing occurs without scarring. On histopathologic examination, granulomas are seen in the superficial dermis, often surrounding follicles and the ducts of sweat glands. The inflammatory infiltrate contains epithelioid cells, giant cells, and a rim of lymphocytes. Caseation usually is absent. These lesions can be difficult to distinguish clinically and histopathologically from lichenoid sarcoidosis.

Erythema induratum, another form of tuberculid, is a panniculitis associated with tuberculosis infection. Unlike EN, erythema induratum has a tendency to affect the posterior aspect of the lower extremities, although both have a predilection for female patients. Both erythema induratum and the papulonecrotic tuberculid form (i.e., vesicular eczema) often are associated with pulmonary tuberculosis.

In papulonecrotic tuberculid cases, recurrent crops of symmetrically distributed, asymptomatic, firm, sterile, dusky red papules appear on the extensor aspects of the limbs, the dorsum of the hands and feet, and the buttocks. They also may represent the paucibacillary form of intravascular dissemination. Papules can undergo central ulceration and eventually heal, leaving sharply delineated, circular, depressed scars. Lesions are characterized histopathologically by a wedge-shaped area of upper dermal necrosis, with the broad base toward the epidermis, surrounded by a tuberculoid inflammatory infiltrate. Obliterative vasculitis is found in the deep dermis. The duration of the eruption varies, but lesions usually disappear promptly after treatment of the primary infection. Similar tuberculid-like reactions have been seen after bacille Calmette-Guérin (BCG) vaccination.[38]

In addition to dermatophytids and tuberculids, autosensitization has been reported with bacterial (e.g., pharyngitis), spirochetal (e.g., syphilis), and viral (e.g., molluscum contagiosum) infections.[39] These reactions also can occur in response to noninfectious stimuli. A common pediatric example is an id reaction occurring with severe contact dermatitis to nickel. In this example, an eczematous dermatitis can occur at sites distant from the affected area of contact dermatitis.

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74

Subcutaneous Tissue Infections and Abscesses

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Infection of soft tissues can involve the skin, subcutaneous tissues, fascia, and skeletal muscle or a combination of these structures. The *subcutaneous compartment* is continuous over the entire body and consists of fat and loose connective tissue containing blood and lymphatic vessels underlying the dermis.[1] The *fascia* is subdivided into superficial and deep components. The *superficial fascia,* between the dermis and the deep fascia, is further subdivided into two layers. The outer layer, which is closest to the dermis, has various thicknesses and contains loose collagenous tissue and fat. The inner layer of the superficial fascia is a thin membrane that has relatively little fat but is rich in elastic tissue. Superficial arteries, veins, nerves, and lymphatics lie within the superficial fascia. The *deep fascia* is a membranous sheet surrounding muscles and separating them into functioning units, and it forms the deepest boundary of the subcutaneous tissue compartment.

Infections of the skin and subcutaneous tissues can be classified by site of involvement (Box 74.1) and as primary, secondary, or tertiary, depending on the mechanism of infection. *Primary infections* originate directly in skin that grossly appears to be clinically normal, although minor breaks in the integrity of the barrier function may be required (see Chapter 68). Some infections, such as folliculitis, furunculosis, carbunculosis, and paronychia, evolve into abscesses and occasionally extend from the epidermis or dermis to involve deeper subcutaneous tissues

Box 74.1

Subcutaneous Tissue Infections and Abscesses

Cutaneous and Subcutaneous Abscesses

Breast abscess

Carbuncle (see Chapter 68)

Furuncle (see Chapter 68)

Paronychia (see Chapter 68)

Periporitis (i.e., sweat gland abscess)

Perirectal abscess

Scalp Abscess

NONNECROTIZING SUBCUTANEOUS TISSUE INFECTIONS

Cellulitis

Erysipelas

Secondarily infected ulcers: decubitus, diabetic

Folliculitis

Necrotizing Soft Tissue Infections

Anaerobic cellulitis

Clostridial

Nonclostridial

Bacterial synergistic gangrene

Meleney ulcer

Gangrenous cellulitis

Necrotizing fasciitis

Type I: mixed flora (85% polymicrobial)

Type II: *Streptococcus pyogenes* and *Staphylococcus aureus*

Other monomicrobial infections

Fournier gangrene

Noma

Tropical ulcer

Synergistic necrotizing cellulitis

Myositis (see Chapter 75)

Pyomyositis (see Chapter 75)

Secondary infections, which occur in previously diseased or wounded skin, include infection of cysts (e.g., epidermal inclusion, pilar cyst), ulcers (e.g., decubitus ulcer), wounds (e.g., surgical or traumatic wound; burns; scalp electrode sites; arthropod, animal, or human bites, burrows due to scabies, flies, or fleas), and those occurring in areas of dermatitis (e.g., atopic dermatitis, psoriasis). These infections also can spread contiguously to deeper subcutaneous tissue.

Tertiary infections develop when pathogens are spread hematogenously or through lymphatics to soft tissues from a distant focus (e.g., *Clostridium septicum* necrotizing fasciitis or myonecrosis, *Staphylococcus aureus* abscess). These infections can involve any of the deeper soft tissues, but they usually spare direct involvement of the epidermis. Compromise of blood flow of nutrient vessels or extension of an infectious and inflammatory nidus to the epidermis and dermis can result in cutaneous disease.

Many conditions predispose patients to subcutaneous tissue infections and abscesses (Box 74.2). The infections also can be classified as nonpurulent (i.e., erysipelas, cellulitis, and necrotizing fasciitis) or purulent (i.e., furuncles, carbuncles, and abscesses).[2]

Box 74.2

Predisposing Factors for Subcutaneous Tissue Infections and Abscesses

- Alteration of normal skin flora
- Burn wound
- Chronic dermatoses
- Corticosteroid therapy
- Foreign body
- Immunodeficiency diseases
  - Chédiak-Higashi syndrome[a]
  - Chronic granulomatous disease[a]
  - Congenital neutropenia[a]
  - Cyclic neutropenia[a]
  - Griscelli syndrome
  - Hyperimmunoglobulin E and immunodeficiency syndrome[a]

Leukocyte adhesion deficiency[a]

Leukocyte alkaline phosphatase deficiency[a]

Neutrophil-specific granule deficiency[a]

Transient hypogammaglobulinemia of infancy[a]

Wiskott-Aldrich syndrome[a]

X-linked hypogammaglobulinemia[a]

Multiple innate immune defects

Intravenous drug abuse

Malnutrition

Peripheral vascular disease

Obstruction of drainage

Ischemia

Skin trauma

Surgical wound

Circumcision

Umbilical cord stump

Systemic disease

Cachexia

Cirrhosis

Diabetes mellitus

Neoplasia

Leukemia, lymphoma

Solid tumor

Organ transplantation

Renal tubular acidosis

Renal failure

---

[a] Associated with abscess formation.

Etiology

The cause of abscesses and subcutaneous infections in children is not always clear. A study of 246 patients between 4 days and 17 years of age who were seen in an emergency department for skin and soft tissue infections found an increase in the proportion of abscesses from 14% (in 2003) to 65% (in 2008) that most commonly occurred in the buttock area. The most commonly identified abscess pathogen in this study was community-associated, methicillin-resistant *S. aureus* (CA-MRSA).[3]

Identification of the pathogens causing a particular subcutaneous soft tissue infection or, in some cases, exclusion of a variety of noninfectious conditions in the differential diagnosis of subcutaneous tissue infections (Box 74.3) requires proper use of diagnostic tests and interpretation of results. If the surface of a wound or site of infection is sampled with a swab, several organisms can be isolated that are colonizing the area but may not be contributing to the disease process. If an organism is suggested by Gram stain (or special stains in the case of fungi) and identified by culture, the likelihood of its pathogenicity is increased. Chances of identifying the true pathogen are improved further if culture specimens are obtained by decontaminating the skin and then using a no. 11 blade to express material, by swabbing the exudate from a site of suppuration or using fine-needle aspiration, or by performing a punch or excisional biopsy.[4]

Box 74.3

Noninfectious Diseases in the Differential Diagnosis of Subcutaneous Tissue Infections in Infants and Children

Acne conglobate

Acne fulminans

Hidradenitis suppurativa

Majocchi granuloma

Jellyfish, scorpion, snake, and spider (e.g., brown recluse) bites

Factitial disease

Panniculitis

Polyarteritis nodosa

Purpura fulminans

Pyoderma gangrenosum

Sweet syndrome (i.e., acute febrile neutrophilic dermatosis)

Cultures should be obtained for routine and fastidious, aerobic and anaerobic organisms when appropriate. Sampling to identify fungi and viruses, including herpes simplex virus (HSV) and cytomegalovirus (CMV), particularly in immunocompromised patients, usually is appropriate. Susceptibility testing should be performed to guide antibiotic therapy except for anaerobes and *S. pyogenes*, unless therapy other than with a β-lactam agent is contemplated. Remember that sulfonamides are not appropriate for treatment of streptococcal infections.

This chapter describes infections that lead to abscess formation and tissue necrosis involving subcutaneous tissues as deep as the inner layer of the superficial fascia. Infections that commonly extend into the deep fascia and muscle are discussed elsewhere (see Chapter 75).

Abscesses

An abscess is a localized, usually inflamed, walled-off collection of purulent exudate formed by a collection of white blood cells (WBCs), bacteria, and disintegration or necrosis of tissue. An abscess is recognized clinically as a firm, tender, erythematous nodule that is fluctuant. The initial skin lesion commonly can be mistaken for a spider bite.

A subcutaneous abscess most commonly evolves by local extension of a primary infectious process in the epidermis or dermis, such as a cutaneous abscess originating from a skin appendage such as a pilosebaceous unit (e.g., furuncle, carbuncle, infundibular cyst, periporitis) or secondarily from a site of skin disease or injury. A subcutaneous abscess also can arise by direct traumatic implantation or invasion of pathogens into subcutaneous tissue or occasionally by hematogenous spread.

In the patient with an abscess, constitutional symptoms usually are initially absent, unless the process has extended into deeper tissues or the bloodstream. Often, no predisposing factor can be identified, although several processes that disrupt the integrity of the barrier function of the skin or the integrity of local immunologic processes, particularly neutrophil function, are associated with abscess formation. Patients with hyperimmunogobulin E syndrome and chronic granulomatous disease are subject to abscess formation. Despite the extensive list of immunodeficiency diseases associated with abscess formation, most people with recurrent abscesses lack evidence of immunodeficiency.

Pathogenesis

The principal pathogens of subcutaneous abscesses in children are shown in Box 74.4, and they vary with body site. The single most common pathogen is *S. aureus*.[5] CA-MRSA is responsible for more than 60% of the cases of abscesses in children in certain centers in the United States.[6,7]

Box 74.4

Agents of Subcutaneous Abscesses and Decubitus Ulcers in Infants and Children

Bacteria

Common

Staphylococcus aureus (i.e., CA-MRSA and CA-MSSA)

Streptococcus pyogenes, streptococci (e.g., α-hemolytic, nonhemolytic), group B *Streptococcus*

Infrequent or Rare

Aeromonas hydrophilia

Actinomyces

Bacteroides fragilis

Brucella

Clostridium

Eikenella corrodens

Enterococcus

Fusobacterium

Haemophilus parainfluenzae

Mycobacterium

Neisseria gonorrhoeae

Nocardia

Peptococcus

Peptostreptococcus

Porphyromonas

Prevotella

Propionibacterium acnes

Pseudomonas aeruginosa

P. mallei

P. pseudomallei

Fungi

Aspergillus

Candida

Histoplasma capsulatum

Hyalohyphomycoses

Penicillium marneffei

Phaeohyphomycoses

Pseudallescheria boydii

Rhizopus

Mycoplasma

Mycoplasma hominis

Protozoa

Entamoeba histolytica

CA, community-associated; MRSA, methicillin-resistant *Staphylococcus aureus;* MSSA, methicillin-susceptible *Staphylococcus* *aureus.*

CA-MRSA possesses the staphylococcal cassette chromosome mec (SCCmec) (types IV–V), which contains the *mecA* gene complex responsible for antibiotic resistance. The USA300 clone most commonly causes skin and soft tissue infections in the United States.[8] CA-MRSA abscess formation is thought to be associated with Panton-Valentine leukocidin, which causes leukocyte destruction and tissue necrosis, and with α-type phenol-soluble modulins (PSMs). The type I arginine catabolic mobile element (ACME) promotes growth and survival of clone USA300 in the cutaneous surface and enables the bacteria to colonize human skin.[9,10]

Table 74.1 shows groups at risk for CA-MRSA skin and soft tissue infections. As the epidemic of CA-MRSA spread, however, it became clear that many affected children had no risk factors.

TABLE 74.1

Antibiotic Therapy for Cutaneous Abscesses in an Era of Community-Associated, Methicillin-Resistant *Staphylococcus aureus* Infections

Treatment Groups	Antibiotic	Clinical Remarks
Empiric therapy	Clindamycin	If geographic *S. aureus* resistance rate ≤10%
	Trimethoprim-sulfamethoxazole (TMP-SMX)	TMP-SMX alone is inadequate for group A *Streptococcus*. TMP-SMX could be used in combination with a β-lactam agent
	Doxycycline	For children ≥8 years of age
	Minocycline	For children ≥8 years of age
	Linezolid	
Hospitalized patients	Vancomycin	Gold standard for hospitalized patients
	Linezolid, IV or PO	
	Daptomycin	For patients intolerant of vancomycin (not approved for use in children)
	Clindamycin, IV or PO	Depending on low rate of resistance (≤10%)

Occasionally, anaerobic bacteria appear to act alone to cause abscesses. Encapsulated anaerobic bacteria usually are most important.[11] This finding contrasts markedly with observations of pediatric superficial skin infections, in which anaerobic bacteria rarely play a pathogenic role.[12] Anaerobic bacteria also do not act alone to cause necrotizing soft tissue infections in immunocompetent people.[13] Cultures from perineal or perioral abscesses and ulcers in children and adults usually contain organisms that reside normally on adjacent mucous membranes rather than skin, whereas lesions remote from the rectum or mouth primarily contain organisms that reside normally on skin at that site.[5,14–20]

Overall, the most common aerobic and facultative bacteria isolated from cutaneous and subcutaneous abscesses and decubitus ulcers in children are CA-MRSA followed by community-associated, methicillin-susceptible *S. aureus* (CA-MSSA) and less often by *Proteus Mirabilis* and *S. pyogenes*.[7,15] Streptococci (i.e., α-hemolytic and nonhemolytic), *Enterococcus* spp., enteric gram-negative bacilli, *Pseudomonas aeruginosa,* and anaerobes are associated especially with decubitus ulcers.[5,20] Immunocompromised hosts are at risk for abscess formation due to a broader spectrum of pathogenic microbes, including fungi (see Box 74.4).[21]

Management

Incision and drainage of abscesses in a healthy host may be the only therapeutic approach necessary.[15,22,23] The addition of systemic antibiotic therapy is recommended if the patient has signs and symptoms of illness, rapid progression, failure to respond to incision and drainage alone, associated comorbidities or immunosuppression, abscess in an area difficult to drain (e.g., face, hand, genitalia), or associated phlebitis.[15,23] Because of the prevalence of CA-MRSA, clindamycin or trimethoprim-sulfamethoxazole (TMP-SMX) are acceptable first-line treatment options for uncomplicated abscesses in geographic areas where CA-MRSA usually is susceptible to clindamycin.[24] TMP-SMX should not be considered if associated streptococcal infection is suspected.

Guidelines for treatment of CA-MRSA skin and soft tissue infections from the Infectious Diseases Society of America (IDSA) are shown in Table 74.1.[23] A US multicenter prospective, randomized superiority trial enrolling 524 patients (155 children) with uncomplicated cellulitis or an abscess larger than 5 cm demonstrated no difference in efficacy between clindamycin and TMP-SMX (all abscesses were drained).[24] More aggressive therapy for skin abscesses is recommended for immunocompromised patients, patients with recurrent furunculosis, very young patients, or patients who appear ill. Intravenous therapy is reserved for those with moderate to severe, localized or systemic disease and those unable to tolerate oral medications.

Considerations by Clinical Site

Breast Abscess

Breast abscess is an uncommon infection of neonates that is usually caused by *S. aureus* and occasionally caused by group A or B *Streptococcus, Escherichia coli, Klebsiella, Salmonella* spp., *Proteus mirabilis,* or *P. aeruginosa.* Although anaerobic organisms can be isolated from up to 40% of infections, their exclusive pathogenic role in neonates is questionable, and therapy directed specifically against anaerobes usually is unnecessary.[25,26] Breast abscess develops in term neonates during the first 6 weeks of life, most commonly during the second to fourth week.[25–30]

Incidence of breast abscess is twofold higher in girls overall, but it is approximately equal in boys and girls during the first 2 weeks of life.[27] Physiologic breast enlargement, which is more common in infant girls than in boys older than (but not younger than) 2 weeks of age,[31] probably is a factor in the pathogenesis, as also evidenced by the absence of breast enlargement and breast abscess in premature infants.[27] Other factors are involved, and a relatively large, retrospective review of neonates with breast abscess found that only about one half had breast enlargement before development of an abscess.[27] It is likely that organisms from the nasopharynx or umbilicus colonize the skin of the nipple and move retrograde through the glandular ducts of physiologically enlarged breasts.[32]

Breast enlargement accompanied by various degrees of erythema, induration, and tenderness occurs initially and can progress to fluctuation, depending in part on how promptly antibiotic therapy is initiated. Bilateral infection is rare. Fever or constitutional symptoms such as irritability and toxicity affect approximately one third of cases, although leukocytosis (WBC >15,000 cells/mm^3) is found in approximately one half to two thirds of patients.[25] Breast abscess due to *S. aureus* is accompanied by cutaneous pustules or bullae on the trunk, particularly in the periumbilical or perineal region, in 25% to 50% of patients.[27] The symptoms, age at presentation, and clinical findings for infections due to gram-negative bacilli or anaerobes are similar to those for staphylococcal abscesses, except that infants infected with *Salmonella* spp. also can have gastrointestinal symptoms.[29]

The most common complication of breast abscess is cellulitis, which develops in approximately 5% to 10% of affected infants.[27] Cellulitis usually is localized but rarely can extend rapidly over the shoulder or abdomen.[28] Other complications, such as bloodstream infection (BSI), pneumonia, and osteomyelitis, are unusual. Scar formation leading to decreased breast size after puberty can be a late sequela.[27]

Results of Gram stain and culture of material expressed from the nipple or obtained by needle aspiration or incision and drainage help guide antibiotic therapy. If the lesion is fluctuant, the abscess must be drained; antibiotic therapy is adjunctive. If fluctuation is absent, antibiotic therapy alone may be curative. Warm compresses also may be beneficial. In areas with a high incidence of MRSA infections, systemic vancomycin or clindamycin is given; otherwise, nafcillin (or cefazolin if there is no concern about BSI or meningitis) is an option for MSSA. If gram-negative bacilli or no organisms are seen on Gram stain or the infant appears ill, initial therapy also should include an aminoglycoside agent or other antibiotic with gram-negative bacillary coverage. In most instances, a 5- to 7-day course of therapy is sufficient, although the total course of therapy sometimes is 10 to 14 days. The duration of parenteral therapy depends on the isolate, occurrence of BSI, and the clinical course.

Sweat Gland Abscess

Sweat gland abscesses (i.e., periporitis) develop rarely in neonates, most often in association with malnutrition or debilitation.[33] The infection also has been called *periporitis staphylogenes* because of the almost uniform presence of *S. aureus* in the lesions. It appears that lesions of miliaria become infected secondarily, followed by extension of the infection into the sweat gland apparatus and occasionally into the adjacent subcutaneous tissue. Miliaria-like lesions, however, are not a constant feature. The 1- to 2-cm, round to oval nodular abscesses occur most commonly on the neck, occiput, back, and buttocks, and unlike furuncles and carbuncles of follicular origin, they are nontender, nonpointing, and cold. Constitutional symptoms can accompany numerous large abscesses, and lymphangitis or cellulitis occurs rarely.

Therapy consists of controlling factors such as skin occlusion or fever that predispose to miliaria, correction of malnutrition, local care of abscesses, and use of antistaphylococcal antibiotics. Healing occurs over several weeks, usually without scarring.

Axillary abscesses occur predominantly in adolescents, accounting for 6.7% of 564 culture-positive abscesses in patients evaluated in one urban emergency department.[34] In this report, 76% were female. Although 46% of axillary abscesses were caused by CA-MRSA and 24% by MSSA, a surprising 22% were caused by *Proteus mirabilis*.[34] Patients with multiple, recurrent, bilateral axillary abscesses should be evaluated for possible hidradenitis suppurativa, especially when lesions also develop in the groin, scalp, or buttocks.

Perineal Abscess

Most abscesses of the perineal (e.g., inguinal, buttock, perirectal, vulvovaginal) region contain multiple species of facultative and anaerobic fecal organisms, particularly *Bacteroides* spp. Recently, CA-MRSA has become a prevalent cause of superficial genitourinary abscesses in children.

Perineal abscesses usually require surgical debridement. Cure rates are high, and the morbidity rate is low.[35] Antibiotic therapy is adjunctive.

Perirectal Abscess

Perirectal abscesses most commonly affect children younger than 2 years of age, with an incidence that can reach 4%, and a notable predilection for boys. The abscesses are thought to occur because of a congenital anomaly of the anal crypts and an imbalance of the androgen to estrogen ratio or an androgen excess. Others have postulated that perirectal abscesses are caused by local infection of a crypt after trauma to the area.[36]

There may be no apparent predisposing factor, or the abscess can develop after minor abrasions or fissures, particularly in association with diarrhea or constipation. Older children who experience perirectal abscess more frequently have a predisposing condition such as Crohn disease, neutropenia (in association with cancer, autoimmunity, or chemotherapy), neutrophil dysfunction due to immunodeficiency, acquired immunodeficiency syndrome (AIDS), diabetes mellitus, corticosteroid therapy, ulcerative colitis, hidradenitis suppurativa, or prior rectal surgery. In those with neutropenia, the risk of perirectal abscess or cellulitis increases with perirectal mucositis, hemorrhoids, rectal fissure, or manipulation. A break in the mucosal barrier or occlusion of anal crypts usually initiates infection.

The predominant organisms in perirectal abscesses are mixed anaerobic and aerobic flora of the intestine and skin of the anal verge. The most common agent identified is *E. coli* alone or in combination with streptococci, enterococci, or anaerobes, followed by *S. aureus*. Other implicated organisms include *S. pyogenes, P. aeruginosa, Klebsiella* spp., and *Proteus* spp. Anaerobic bacteria include *Bacteroides, Peptococcus, Peptostreptococcus, Porphyromonas, Fusobacterium,* and *Clostridium* species.[37–41] Perirectal abscess rarely can be caused by *Entamoeba histolytica, Mycobacterium* spp., *Nocardia* spp., and *Actinomyces* spp. Buttock abscesses most commonly result from *S. aureus* infection, even in neonates.[37]

Superficial buttock abscess in the infant usually manifests as pain on defecation, sitting, or walking and as redness, swelling, and tenderness in the perianal region. A superficial abscess in the epithelium can extend in any of the following directions: inferiorly along the anal sphincter to exit next to the anus on the buttock (i.e., fistula-in-ano), laterally through the external sphincter to the ischiorectal fossa to form a deep abscess or superiorly to the deep space between the internal sphincter and the levator ani muscles.[42–44] An abscess in deeper tissues can be accompanied by poorly localized, deep pain and constitutional symptoms. An anorectal abscess may not be apparent externally, but pain usually is elicited on rectal examination.

In immunocompetent infants, a superficial perianal abscess can drain spontaneously (and can be self-limited) or may need to be drained surgically. Exploration of the abscess for a fistula depends on the clinical circumstances and isolation of organisms other than *S. aureus.* Empiric therapy with antibiotics to cover anaerobic and aerobic gram-negative bacilli and *S. aureus* may prevent regional spread of the infection and decrease the incidence of complications.[38] A 7- to 10-day course of therapy is recommended.

Children with granulocytopenia may have delayed development of erythema, induration, and fluctuation. In the absence of fluctuation, extensive soft tissue disease, or BSI, a trial of parenteral antimicrobial therapy alone may be initiated. Perirectal abscess in young children is less likely associated with underlying anatomic anomalies and more amenable to complete resolution with conservative nonoperative therapies. However, if progression of disease or fluctuation becomes apparent, surgery should be undertaken.

Complications, which occur more commonly in children with underlying disease, include anorectal fistula, recurrence of abscess, BSI, and necrotizing fasciitis. There is some evidence that conservative treatment with systemic antibiotics rather than drainage may be associated with a decreased risk of fistula formation in infants younger than 12 months of age.[45] A chronic fistula may require a fistulotomy.[43]

Scalp Abscess

Scalp abscess appears as a localized, erythematous area of induration that is 0.5 to 2 cm in diameter, usually at the insertion site of a fetal scalp-monitoring electrode. The site can become fluctuant, pustular, or suppurative. The abscess manifests most commonly on the third or fourth day of life (range, 1 day to 3 weeks).[46] Regional lymphadenopathy can occur, but other, more serious complications, such as cranial osteomyelitis, subgaleal abscess, and necrotizing fasciitis of the scalp, are uncommon. Death associated with a complication of fetal scalp electrode placement has been described in a premature infant who had *E. coli* scalp abscess and BSI.[47]

The incidence of scalp abscess after placement of a spiral fetal scalp electrode (i.e., the type used since the early 1970s) ranged from 0.1% to 1.0% in retrospective studies of approximately 18,000 neonates.[46] Prospective studies have reported incidences between 0.6%[48] and 4.5%.[49]

Reports of predisposing factors are conflicting. Okada and associates[49] found a significant association with longer duration of placental membrane rupture and of monitoring; monitoring for high-risk indications, particularly prematurity; and nulliparous birth, possibly because of a higher risk of infection of an edematous, hypoxic caput succedaneum. Scalp trauma and compression, however, are questionable factors in the pathogenesis of scalp abscess because most reports have not found abscess formation at sites of scalp trauma and abrasion due to forceps or vacuum extraction, at sites of fetal blood sampling, or in association with hematomas.[46,50] There are exceptions because cephalohematomas can become infected,[51] and similar rates of scalp abscess have been reported among infants who were monitored with scalp electrodes and those who were not monitored but were delivered by forceps or vacuum extraction.[52] A threefold greater but not statistically significant rate of scalp abscess has been found for infants delivered by vacuum extraction compared with those born by spontaneous vaginal delivery.[49] In one study[53] but not another,[48] an association with prolonged rupture of membranes and development of scalp abscess was found. Risk factors in the latter study included number of vaginal examinations, concurrent monitoring with an intrauterine pressure catheter, use of more than one spiral electrode, fetal scalp blood sampling, maternal diabetes, and endomyometritis.[48]

Scalp abscess typically is a polymicrobial infection. Cultures from abscesses reveal aerobic or facultative organisms alone in approximately one third, anaerobic isolates alone in 10% to 25%, and mixed aerobic or facultative and anaerobic bacteria in 40% to 60% of cases.[46,49,54] The most common aerobic isolates are *S. aureus;* groups A, B, or D streptococci; *S. epidermidis;* and occasionally *Haemophilus influenzae, E. coli, K. pneumoniae, Enterobacter* spp., *P. aeruginosa,* and *Neisseria gonorrhoeae.* The role of *S. epidermidis* as a pathogen is questionable. Common anaerobic isolates are *Peptococcus, Peptostreptococcus,* and *Bacteroides* species, *Propionibacterium acnes,* and *Clostridium* spp. The anaerobic flora in the abscesses reflects that found in cervical flora during labor. Neonatal necrotizing fasciitis of the scalp has been associated with intrapartum fetal scalp electrode monitoring.[55]

The primary differential diagnostic concern for fetal scalp abscess is HSV infection.[46] The time of appearance of herpetic lesions (peak incidence, 4 to 10 days) overlaps with that for scalp abscess, and the lesions occasionally can be indistinguishable clinically. Mucocutaneous HSV can be associated with central nervous system or disseminated disease, or both.[56] If suspicion of HSV exists, complete evaluation is indicated, and therapy with acyclovir should be initiated while awaiting results of diagnostic tests.

Infants who are subjected to scalp electrode monitoring during birth should be followed closely during the first weeks of life for evidence of infection. Parents should be instructed in surveillance. If weeping, vesiculopustular lesions or an abscess is detected, specimens should be obtained by needle aspiration or swabbing of the exudates from the puncture site for direct testing and culture of aerobic and anaerobic organisms and HSV. Many bacterial infections of the fetal scalp resolve spontaneously, but if fluctuance develops without spontaneous suppuration, incision and drainage may be necessary. Extensive debridement, however, should not be performed. For surrounding cellulitis, a 5- to 7-day course of parenteral antibiotic therapy usually is sufficient, with culture results guiding the antibiotic choice. HSV scalp lesions also can heal spontaneously, but because reactivation and dissemination can occur with serious consequences, full evaluation and polymerase chain reaction (PCR) testing of blood and cerebrospinal fluid are performed. Parenteral acyclovir therapy always should be administered for neonatal HSV scalp infection.

Necrotizing Soft Tissue Infections

Necrotizing soft tissue infections (NSTIs) are uncommon in children but are potentially life-threatening conditions characterized by rapidly advancing local tissue destruction and systemic toxicity. Tissue necrosis distinguishes them from cellulitis (see Chapter 68), in which an inflammatory infectious process involves but does not destroy subcutaneous tissues. Unlike an abscess, NSTIs involve diffuse tissue necrosis and lack localized purulence, although a subcutaneous abscess occasionally forms. These infections can occur anywhere on the body, and the most common locations are the extremities, abdomen, and perineal region. Risk factors for NSTIs in pediatric patients include trauma, surgery, chronic illness, and recent varicella infection[57]

Since the mid-1980s, there has been a resurgence of fulminant necrotizing soft tissue infections due to *S. pyogenes* and recently due to Panton-Valentine leukocidin-positive *S. aureus,* often in healthy people with little or no apparent immunologic deficiency or compromise of skin integrity (e.g., varicella-zoster virus infection). Bacterial virulence factors and absence of specific host resistance factors appear to be important in the pathogenesis.[58]

Classification of NSTIs has undergone several revisions over the years, often using more than one name for the same condition (e.g., clostridial and nonclostridial anaerobic cellulitis, bacterial synergistic gangrene, Meleney ulcer; necrotizing fasciitis, myonecrosis, gangrene) and resulting in a confusing body of literature. Most recent reviews advocate use of the term *necrotizing soft tissue infection* to include all forms of the disease process, regardless of the level of the soft tissue affected, because the approach to diagnosis and management is the same.[59]

Relatively few organisms possess sufficient virulence to cause NSTIs when acting alone (Box 74.5). Fulminating infections are caused by *S. pyogenes,* although a clinically indistinguishable NSTI can be caused by *S. aureus* (including MRSA), *Clostridium perfringens, C. septicum, P. aeruginosa, Vibrio* spp. (particularly *Vibrio vulnificus*), and fungi of the order Mucorales, particularly *Rhizopus, Mucor,* and *Absidia* spp.[58,60–63]

Box 74.5

Agents of Necrotizing Soft Tissue Infections in Infants and Children

Monomicrobial

Bacteria

Streptococcus pyogenes

Staphylococcus aureus

Clostridium perfringens

Clostridium septicum

Haemophilus influenzae type b

Mycobacterium chelonae

Mycobacterium kansasii

Pseudomonas aeruginosa

Streptococcus agalactiae

Streptococci groups C, G, and F

Streptococcus pneumoniae

Vibrio alginolyticus

Vibrio cholerae (i.e., nonserogroup 01)

V. parahaemolyticus

V. vulnificus

Fungi

Absidia spp.

Aspergillus spp.

Fusarium spp.

Mucor spp.

Rhizopus spp.

Saksenaea spp.

Protozoa

Entamoeba histolytica

Polymicrobial

Anaerobic Bacteria

Bacteroides

Clostridium

Fusobacterium

Peptococcus

Peptostreptococcus

Porphyromonas

Prevotella

Aerobic or Facultative Bacteria

Aeromonas

Enterobacter

Escherichia coli

Klebsiella

Proteus

Pseudomonas

Streptococcus aureus

Streptococci (e.g., hemolytic, nonhemolytic nongroup A)

Although NSTIs can be monomicrobial, they more often are polymicrobial. In most cases, a mixture of anaerobic, aerobic, and facultative anaerobic bacteria appears to act together to cause tissue necrosis.[14] Anaerobic isolates are similar to those found in subcutaneous abscesses, consisting of *Bacteroides, Peptostreptococcus, Peptococcus, Prevotella, Porphyromonas, Clostridium,* and *Fusobacterium* species.[14,64] The most common aerobic or facultative bacteria are several species of hemolytic or nonhemolytic nongroup A streptococci, MRSA, *E. coli, Enterobacter* spp., and a variety of other Enterobacteriaceae and *Pseudomonas* spp.[65,66] In corticosteroid-treated patients, *Entamoeba histolytica* and nontuberculous mycobacteria (particularly *Mycobacterium kansasii* and *M. chelonae*) can cause an identical clinical syndrome.[65,67] No particular combination of organisms, however, is diagnostic for any given clinical entity that involves an NSTI. Identification of gas in infected tissue is thought to be a hallmark of clostridial infection, but most soft tissue infections with gas production are caused by facultative gram-negative bacilli, such as *E. coli, Klebsiella* spp., *Proteus* spp., and *Aeromonas* spp.[68]

Tertiary or hematogenous infections of the subcutaneous tissues occur most commonly in immunocompromised hosts and can lead to abscess or NSTI. Although a wide range of organisms, including bacteria and fungi, can be involved, the most common are *S. aureus* and *P. aeruginosa.*

Pathogenesis

Some of the same organisms that cause cellulitis can cause NSTI, with involvement of fascia or tissue necrosis. Responsible factors are poorly understood but involve a complex interaction among predisposing tissue factors such as local trauma, anaerobic wound environment, systemic and local host defense, bacterial virulence factors, and synergy of microorganisms.

Compromise of immune defense is a primary predisposing factor for development of subcutaneous infections. This process can occur locally, result from trauma or surgery that compromises the barrier function of the skin, or involve systemic immunodeficiency, especially in individuals with defective neutrophil function. Systemic immunodeficiency is especially important for the development of necrotizing infections due to *P. aeruginosa* or fungi. Innate cutaneous defenses, including the physical barrier afforded by the lipids and the cross-linked cornified envelope in the stratum corneum, appear to be sufficient most often to prevent infection. Through trauma to skin or mucosal surfaces, however, a pathogen may be able to adhere to a previously unexposed receptor or a receptor that is newly synthesized in the injured skin.

In some infections, such as those due to *Clostridium* spp., the depth of the initial injury is the most important determinant of depth of infection.[34,68] Other infections, such as necrotizing fasciitis due to *S. pyogenes,* can spread rapidly from superficial layers of the skin to deeper subcutaneous tissues, aided by poorly understood virulence factors. In infections that follow varicella, access to tissue beneath the stratum corneum at sites of chickenpox lesions may allow initiation of local infection.[69–73]

In diabetes, compromised blood flow to the skin due to small-vessel vasculopathy and impaired function of neutrophils may predispose to necrotizing infection. The relatively high incidence of subcutaneous infections in those with peripheral vascular disease due to other causes, such arthrosclerosis, supports this concept of pathogenesis, as does the fact that thrombosis of vessels is a major histologic feature of many necrotizing infections in adults.[74,75] A higher degree of vascular thrombosis has been correlated with more acute presentations of necrotizing fasciitis.[74] The cause of vascular thrombosis is not understood completely, but it probably involves direct cytolytic or thrombogenic factors released from bacterial pathogens, immune-mediated vascular damage due to the inflammatory infiltrate surrounding the blood vessels, or noninflammatory intravascular coagulation.[75] Disease in the dermis and epidermis occurs secondarily after thrombosis of deeper vessels.

Synergy of microorganisms does not appear to be necessary for abscess formation, but it does appear to be operative in many NSTIs because anaerobic or facultative organisms rarely are found alone in these infections.[14] The concept of bacterial synergy in the pathogenesis of soft tissue infection as advanced in the 1920s by Brewer and Meleney[76] involved microaerophilic (likely anaerobic) streptococci and *S. aureus*, which caused a progressive, chronic subcutaneous tissue infection called *bacterial synergistic gangrene*. Since then, numerous combinations of organisms have been found to act synergistically in subcutaneous infections.[77]

Synergistic pathogenesis of anaerobic, aerobic, and facultative bacteria is supported by clinical data and animal models, including studies of tropical ulcer showing synergistic associations of *Fusobacterium* spp., other anaerobic bacteria, and spirochetes.[78,79] In an animal model of necrotizing fasciitis, *S. aureus* or crude staphylococcal α-lysin potentiated the pathogenesis of *S. pyogenes.*[80] The mechanism of synergy appears to vary according to the organisms present, but it may result from mutual protection from phagocytosis and intracellular killing, promotion of bacterial capsule formation, production of essential growth factors or energy sources, and use of oxygen by facultative bacteria, lowering the tissue oxidation-reduction potential to facilitate growth of anaerobic organisms.[77,81,82]

Extracellular bacterial toxins and enzymes are important factors in the destruction of subcutaneous tissue.[83] In NSTI due to *Clostridium* spp. or *S. pyogenes* in children, few acute inflammatory cells can be identified in necrotic fascia and subcutaneous tissue. Necrotizing tissue infections appear to be related to the production of a variety of potent toxins and enzymes.[84]

Initiation of an NSTI appears to require a break in the skin or mucous membrane, although the injury often is blunt, trivial, or inapparent.[58] Adherence of *S. pyogenes* to respiratory tract epithelium has been postulated to involve a two-step mechanism: a relatively weak, nonspecific hydrophobic binding followed by high-affinity, specific attachment.[85] The mechanism of adherence of the bacterium to the skin is not well understood.[86–88] Keratinocyte differentiation promotes adherence of *S. pyogenes,*[86] whereas the primary epidermal cytokines tumor necrosis factor-α (TNF-α) and interleukin-1α (IL-1α) decrease adherence.[87] The hyaluronic acid capsule of *S. pyogenes* impedes adherence, and modulation of capsule expression may be important in the pathogenesis of skin infections.[88] The molecular interactions (i.e., bacterial adhesin and keratinocyte receptor) involved in initial attachment to the skin remain unknown. After attachment, invasion of *S. pyogenes* is related to numerous extracellular enzymes and toxins and membrane-bound proteins that function as virulence factors.[89,90]

Patients with streptococcal NSTIs can experience toxic shock-like syndrome that is associated with the streptococcal pyrogenic exotoxins A, B, and C.[91] These toxins and certain M-protein fragments appear to have the ability to interact simultaneously with the major histocompatibility complex (MHC) class II antigen on antigen-presenting cells and with specific Vβ regions of T-lymphocyte receptors, inducing massive synthesis and release of monokines, including TNF-α, IL-1β, IL-6, and the lymphokines TNF-β, IL-2, and interferon-γ.[73] These cytokines, particularly TNF, may in part mediate the rapid, massive tissue destruction seen in necrotizing fasciitis.[55]

Protease activity and production of Panton-Valentine leukocidin are postulated to correlate better with the ability of *S. aureus* to cause invasive disease and may be a mechanism for invasion of pyogenic bacteria from a cutaneous site.[62,63,92,93] A central feature of NSTI is vascular injury and thrombosis of the arteries and veins passing through the fascia.[56,74] A possible mechanism for the vascular injury leading to tissue ischemia and necrosis is greater adherence of neutrophils to vascular endothelium as a result of streptolysin O–induced upregulation of receptors.[94]

Clinical Presentation

NSTIs form a continuum, with some developing primarily in the more superficial layers of the subcutaneous tissues and others typically extending to the deep fascia and muscle. Although the rapidity and extent of tissue destruction and the causative agent vary, patients characteristically manifest few early cutaneous signs relative to the rapidity and extent of destruction of the subcutaneous tissues. Early clinical findings include ill-defined cutaneous erythema and edema that extends beyond the area of erythema. In some circumstances, the contiguous surface may be insensitive to pain or develop bullae. In contrast to the clinical findings of cellulitis, which may have a more distinct border, the patient with an NSTI has pain, tenderness, and constitutional signs that often are out of proportion to the cutaneous findings. This is particularly true with involvement of the deeper tissues, such as deep fascia and muscle.

Patients with involvement of the superficial or deep fascia or muscle tend to be more acutely and systemically ill and have more rapidly advancing disease than those with infection confined to subcutaneous tissues above the fascia. Other cutaneous signs, such as vesiculation, bullae formation, ecchymoses, crepitus, anesthesia, and necrosis, are ominous indications of advanced disease.[85] As reported by Keeley and colleagues, predictors of mortality for patients with NSTIs include bandemia; elevated creatinine, low bicarbonate, and elevated lactate levels; a lower admission temperature; and a shorter duration of presenting symptoms.[86]

Diagnosis and Management

A strong clinical suspicion and careful attention to the presentation and history of progression are important for making an accurate diagnosis and instituting appropriate and timely therapy. Failure to recognize differences among these infections can lead to suboptimal therapy because the need for aggressive surgical intervention and optimal antibiotic therapy varies. The most important question is whether the soft tissue infection is necrotizing or nonnecrotizing; the former requires prompt surgical removal of all devitalized tissue in addition to antimicrobial therapy, whereas the latter responds to antibiotic therapy alone. A study of 334 pediatric patients with NSTIs reported that nonsurvivors had a longer time from admission to their first debridement. Similar to that reported in the adult literature, prompt surgical debridement is the most important intervention for necrotizing disease in children.[87]

If the distinction is in doubt, imaging studies can aid in the diagnosis. Plain radiographs can detect subcutaneous gas, but this tends to be a late finding and is not present in earlier stages of the disease. Computed tomography and magnetic resonance imaging, with or without enhancement, may help to identify increased thickness of the fascial layer that can be associated with NSTI. Although these studies tend to have a high sensitivity, their main limitation is that they lack specificity, and for this reason, they may not be adequate to confirm a diagnosis of NSTI.[88]

Incisional biopsy can help to diagnose early NSTI when the clinical picture is not diagnostic. These procedures, however, should not delay surgical exploration and intervention in the course of destructive or potentially fulminant infection. Ultimately, precise determination of the planes of tissue involved in the infection cannot be based on clinical palpation and must be made definitively in the operating room. NSTI is considered a surgical emergency that requires prompt recognition, hemodynamic support and fluid resuscitation, surgical debridement, and appropriate antibiotic coverage.[89]

The IDSA suggests antibiotic therapy (with pediatric dosing) according to the suspected type of infection (Table 74.2).[2] Antibiotic management should be continued until the patient no longer needs repeated surgical interventions, there is clinical improvement, and the patient has been afebrile for 48 to 72 hours.[59]

TABLE 74.2

Antibiotic Treatment of Necrotizing Infections of the Skin, Fascia, and Muscle

First-Line Antibiotic Agents	Agents for Patients With Severe Penicillin Hypersensitivity
MIXED INFECTION	
Piperacillin/tazobactam *plus* Vancomycin	Clindamycin *or* Metronidazole; *plus* Aminoglycoside *or* Fluoroquinolone
Imipenem-cilastatin	
Meropenem	
Ertapenem	
Cefotaxime *plus* Metronidazole *or* Clindamycin	
***STREPTOCOCCUS* SPP. INFECTION**	
Penicillin *plus* Clindamycin	Vancomycin *or* Linezolid *or* Quinupristin-dalfopristin *or* Daptomycin
***STAPHYLOCOCCUS AUREUS* INFECTION**	
Nafcillin *or* Oxacillin *or* Cefazolin *or* Vancomycin (for resistant strains) *or* Clindamycin	Vancomycin *or* Linezolid *or* Quinupristin-dalfopristin *or* Daptomycin
***CLOSTRIDIUM* INFECTION**	
Clindamycin *plus* Penicillin	

Modified from Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis 2014;59:e10–e52.

Some investigators advocate the use of hyperbaric oxygen as an adjuvant therapy for patients with NSTI. Unfortunately, the lack of adequate studies of hyperbaric oxygen in pediatric patients makes this recommendation less reliable.

Intravenous immunoglobulin (IVIG) has been used as adjuvant therapy in patients with NSTIs, predominantly in those caused by streptococci. IVIG is thought to halt the infectious and systemic inflammatory response by neutralizing destructive toxins.[90] Lack of prospective pediatric studies preclude recommending the use of IVIG in children, and few adult studies demonstrate a potential benefit for IVIG in NSTIs.

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75

Myositis, Pyomyositis, and Necrotizing Fasciitis

C. Buddy Creech

Skin and soft tissue infections (SSTIs) are common in children. They usually are recognized easily and treated with few residual long-term problems. However, myositis, pyomyositis, and necrotizing fasciitis are soft tissue infections that can be difficult to diagnose in their early stages, and despite appropriate antibiotic therapy, they can be associated with substantial morbidity and mortality.

The epidemiology of SSTIs is evolving, and the incidence among children is increasing. Community-associated, methicillin-resistant *S. aureus* (CA-MRSA) first emerged among children in the 1990s. Since then, CA-MRSA has become the predominant cause of purulent SSTIs in the United States. Coincident with this epidemic, the incidence of pediatric ambulatory visits for SSTIs has almost tripled.[1] SSTIs can be atypical and more severe in immunocompromised children.[2]

Myositis

Myositis is inflammation of a muscle, typically a voluntary muscle, characterized by pain, tenderness, swelling, and weakness. Causes of myositis include infection, autoimmune conditions, genetic disorders, medications, electrolyte disturbances, and diseases of the endocrine system.[3] Infectious myositis can be caused by bacteria, fungi, parasites, and viruses (Table 75.1).[3]

TABLE 75.1

Common Infectious Causes of Myositis

Organism Group	Organisms
Gram-positive bacteria	*Staphylococcus aureus*
	Streptococcus pyogenes (group A streptococcus)
	Streptococcus (groups B, C, and G; *S. pneumoniae; S. anginosus*)
Gram-negative bacteria	*Aeromonas hydrophila*
	Citrobacter freundii
	Enterobacter spp.
	Escherichia coli
	Proteus spp.
	Pseudomonas spp.
	Salmonella spp.
	Vibrio vulnificus
Anaerobic bacteria	*Bacteroides* spp.
	Clostridium spp.
	Streptococcus spp. (anaerobic, e.g., *Peptostreptococcus*)
Mycobacterium spp.	*Mycobacterium tuberculosis*
Fungi	*Candida* spp.
Parasites	*Trachipleistophora*
	Plasmodium spp.
	Sarcocystis spp.
	Taenia solium
	Trichinella spp.
Viruses	Enteroviruses (coxsackievirus B and echovirus)
	Human immunodeficiency virus (HIV)
	Human T-lymphotropic virus type 1(HTLV-1)
	Influenza A and B viruses

Modified from Crum-Cianflone NF. Bacterial, fungal, parasitic, and viral myositis. Clin Microbiol Rev 2008;21:473–494.

The clinical course can be acute, subacute, or chronic. Although identification of the causative microbe requires specific diagnostic testing (e.g., cultures), some clinical findings suggest the general category of the agent. For example, bacterial myositis usually causes focal muscle infection, whereas viruses and parasites often cause generalized myalgias or multifocal myositis. Bacterial myositis often occurs in the setting of muscular injury, surgery, ischemia, or a foreign body.

Bacterial Myositis

Acute bacterial myositis, defined as a diffuse muscle infection without an intramuscular abscess, occurs less commonly than pyomyositis and psoas abscess formation. Compared with pyomyositis, myositis is more often seen in adults than children.

Staphylococcus aureus.

Although *S. aureus* myositis is uncommon, the incidence has increased among adults and children in recent years, largely due to the emergence of CA-MRSA.[4,5] In the United States, the USA300 clone of CA-MRSA accounts for most infections. It appears that virulence has evolved in this strain through the increased expression of core genome-encoded virulence determinants, such as the two-component exotoxins (e.g., LukAB, LukDE, α-hemolysin, phenol-soluble modulins) and acquisition of the phage-encoded Panton-Valentine leukocidin (PVL) genes. Each of these toxins impact disease progression in animal models of USA300 infection. The basis of virulence in other CA-MRSA epidemics is less well understood.[5–7]

Streptococcus pyogenes.

S. pyogenes (i.e., group A *Streptococcus* [GAS]) can cause myositis. The most severe form is necrotizing myositis (i.e., streptococcal myonecrosis or spontaneous streptococcal gangrenous myositis).

Cases typically occur among men and young adults. The disease usually occurs spontaneously without a history of penetrating trauma or underlying immunosuppression. The portal of entry often is unknown. Some cases begin with a sore throat, suggesting that pharyngitis might have led to bacteremia and seeding of the muscle, but most cases occur without an antecedent illness.

The clinical presentation includes an initial prodromal stage with flu-like symptoms, which may include rash and myalgia. This evolves to intense local muscle pain that is disproportionate to clinical findings and to local tense swelling and fever.[8] The course can evolve rapidly over several hours (Fig. 75.1).

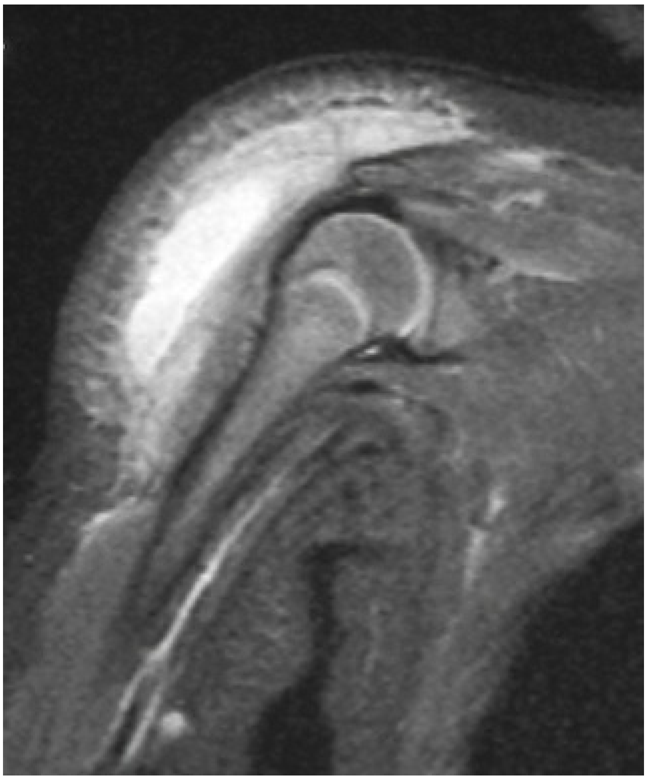

FIGURE 75.1 Necrotizing pyomyositis due to *Streptococcus pyogenes* in a 6-month-old infant with acute onset of fever, erythema, swelling, and pain of her right shoulder and decreased use of her arm. There was no break in the skin. Coronal fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging shows diffuse hyperintensity of the deltoid muscle with associated subcutaneous inflammatory stranding and edema. Osseous and fascial structures are normal. (Courtesy of E.N. Faerber and S.S. Long, St. Christopher's Hospital for Children, Philadelphia, PA.)

Clostridium Species.

Clostridial gas gangrene (i.e., myonecrosis) most commonly is caused by *Clostridium perfringens, C. novyi, C. histolyticum,* and *C. septicum*. *C. perfringens* is the most frequent cause of trauma-associated gas gangrene.[9] Infection occurs in a variety of settings: traumatic wounds with soil contamination, surgery involving the bowel or biliary system, septic abortions, vascular disease with arterial insufficiency, and injection of medications (e.g., epinephrine) or illicit drugs (e.g., heroin). Common inciting events include contamination of the site with *Clostridium* spp. (which exist in the soil and as part of the gastrointestinal flora of humans) and devitalized tissue. A foreign body is also a risk factor. In contrast to traumatic gas gangrene, spontaneous gangrene is principally associated with the more aerotolerant *C. septicum* and occurs predominantly in patients with underlying gastrointestinal conditions, including occult colon cancer, bowel infarction, or neutropenic enterocolitis.

C. septicum infections occur in children with three major predispositions: neutrophil dysfunction (e.g., malignancies, congenital or cyclic neutropenia, aplastic anemia), bowel ischemia (e.g., hemolytic uremic syndrome, intussusception), and trauma.[9] Malignancy underlies more than 50% of cases; acute myelocytic and lymphocytic leukemias are the most common. Cyclic and congenital neutropenia is identified in 20% of the published pediatric cases.

Clinical features associated with *C. septicum* infections in children include fever, vomiting, diarrhea, hematochezia, anorexia, and acute abdomen or distention. Despite treatment with surgery and parenteral antibiotics, mortality rates for children with *C. septicum* infections remain higher than 50%.[9]

Presenting symptoms of clostridial myonecrosis include intense pain, edema, and a sweet-smelling discharge that occur several hours to a few days after injury. The wound is initially pale but can evolve to a bronze color with hemorrhagic bullae. Classic findings include gas in the tissues detected by gas bubbles emitted from the wound or seen on radiographic films. Although gas often is considered to be essential for a diagnosis of gas gangrene, the absence of crepitus or gas on examination should not deter consideration of this diagnosis. Failure of the muscle to contract on stimulation and lack of bleeding of the wound during operation are characteristic findings.

Typical laboratory findings include leukocytosis and a hemolytic anemia due to clostridial α-toxin. Bacteremia occurs in 15% of cases. Gram stain evaluation of the wound exudate usually shows a lack of neutrophils and an abundance of gram-positive bacilli with blunt ends.

Nonclostridial Myositis.

Anaerobic streptococcal myositis has clinical characteristics similar to those of clostridial myonecrosis, including a foul, copious exudate, gas in infected tissues, and extensive necrosis of the involved muscles. Causes include anaerobic streptococci (e.g., *Peptostreptococcus* spp.), GAS, and *S. aureus*.

Synergistic nonclostridial myonecrosis is an infection of the subcutaneous tissues and fascia that can extend into the muscle. The infection often is polymicrobial, consisting of aerobic and anaerobic organisms such as streptococci (including *Peptostreptococcus* spp.), *Bacteroides* spp., *E. coli, Enterobacter* spp., and *Klebsiella* spp. *Aeromonas hydrophila* myonecrosis usually occurs after penetrating trauma in a freshwater environment or tissue injury associated with contact with aquatic animals. Progression can be rapid, and gas may form in the tissues.

Vibrio vulnificus is an opportunistic human pathogen that is lethal.[10] The bacterium is a part of the natural flora of coastal marine environments worldwide and has been isolated from water, sediments, and a variety of seafood. Of all *Vibrio* infections reported in the United States annually, 25% to 30% are nonfoodborne *Vibrio* infections (NFVIs).[11] *V. vulnificus* infections are the most common, accounting for 35% of NFVIs, and 72% of *V. vulnificus* infections are reported for residents of Gulf Coast states. SSTIs due to *V. vulnificus* result in amputation and death in 10% and 17% of cases, respectively.[11] Clinicians should consider *Vibrio* species as an etiologic agent in infections occurring in persons with recent seawater exposure, even if the individual was exposed only during recreational activities.

Other Forms of Bacterial Myositis.

Lyme disease can cause localized myositis of the orbit and other sites, often near areas of erythema migrans or joint involvement.[12] *Mycobacterium* spp. cause myositis by direct extension from a contiguous source such as an infected joint, bone, or abscess or, less commonly, from bacteremia. The most common site is a tuberculous psoas muscle abscess that forms by extension from vertebral osteomyelitis (i.e., Pott disease). Other examples include involvement of the intercostal muscles through extension from the lung or striated muscles of the leg through extension from the knee.

Fungal Myositis

Fungal myositis is uncommon. Most cases occur in immunocompromised patients. Fungal myositis can be caused by *Candida* spp. (most common), *Cryptococcus neoformans, Histoplasma capsulatum, Coccidioides* spp., *Aspergillus* spp., *Pneumocystis jirovecii,* and *Fusarium* spp. Biopsy with culture usually is required to confirm the diagnosis. The diagnosis often is not considered initially and is confirmed by histopathology or culture of muscle tissue.

Parasitic Myositis

A variety of parasites can encyst in muscle. The most common are *Trichinella* spp. (i.e., trichinosis), *Taenia solium* (i.e., cysticercosis), and *Toxoplasma gondii* (i.e., toxoplasmosis). The finding of eosinophilia and a history of travel to an endemic area suggest a possible parasitic cause of myositis.

Infection with *Trichinella spiralis* occurs after ingestion of larval cysts in undercooked pork or the meat of certain wild carnivores. The adult worm develops in the gastrointestinal tract and releases larvae that circulate through lymphatics and the bloodstream to striated muscle, where they become encysted and survive for several years. Most infections are subclinical. Autopsies reveal *Trichinella* cysts in more than 4% of randomly selected diaphragms.[13] Typical manifestations of symptomatic disease include fever, extreme malaise, muscle pain, weakness, and periorbital edema.[14] Serum muscle enzyme levels are elevated, and the patient has eosinophilia. Serodiagnostic testing is available and can preclude the need for biopsy. Most mild cases respond to analgesic therapy. In severe cases, anthelmintic therapy with thiabendazole or mebendazole is effective.[15]

After ingestion of eggs of the pork tapeworm *Taenia solium,* larvae migrate to excyst in skeletal muscle, leading to granulomatous nodules and calcific densities. Although fever, myalgia, and eosinophilia can occur, most cases of muscular cysticercosis, except those involving extraocular muscles, are asymptomatic. For infections that involve extraocular muscles, treatment with albendazole plus a corticosteroid or surgical removal of the encysted parasites may be necessary to preserve vision.[16–18]

During acute *Toxoplasma gondii* infection, tachyzoites can be widely disseminated, and skeletal muscle frequently is infected. Most cases of acquired toxoplasmosis are asymptomatic, although some patients experience a mononucleosis-like syndrome with nonspecific myalgia. Chronic inflammatory myositis associated with *T. gondii* has been reported in human immunodeficiency virus type 1 (HIV-1)–infected and other immunocompromised people.[19] Weakness, muscle wasting, and high serum levels of creatine kinase are characteristic features. Infection in the acute phase may be responsive to pyrimethamine plus sulfadiazine, whereas in the chronic phase, corticosteroid therapy may be beneficial.[20]

Viral Myositis

Many viruses can cause myalgias, polymyositis, or virus-associated rhabdomyolysis. The symptoms of myositis often are diffuse in nature, and patients have other symptoms and signs attributable to the causative viral pathogen. Influenza A and B viruses are the most commonly reported causes of viral myositis. Enteroviruses, human immunodeficiency virus (HIV), human T-cell leukemia-lymphoma virus type 1 (HTLV-1), and hepatitis viruses B and C also can cause myositis.

Influenza-associated myositis (IAM) has been reported only sporadically since its first description in 1957. IAM appears to be more common among children than adults, but its age-specific incidence during influenza epidemics is unknown.[21] IAM in children is characterized by severe lower extremity myalgia and a reluctance to walk.

Because IAM is associated with the influenza B virus, incidence may depend on circulating strains during an epidemic. During one European influenza B season, 219 children with IAM were studied; the median age was 7 years, and 74% were male.[22] IAM typically occurs with a 2 : 1 male predominance among children younger than 14 years and is characterized by an abrupt onset of severe myalgia in calf muscles, inability to walk, and elevated serum creatine kinase levels, usually within 1 week of influenza onset, when respiratory symptoms are improving.

Although the link between influenza and IAM is clearly established, its pathogenesis is not well understood. Two proposed mechanisms are viral invasion of muscle tissue and immune-mediated muscle damage triggered by the respiratory tract infection. Treatment is symptomatic because myositis is self-limited and usually resolves within a mean of 3 days (range, 1 to 30 days).

Influenza virus–associated rhabdomyolysis has been described in children and adults. Rhabdomyolysis is associated more frequently with influenza type A than type B and occurs more frequently in girls. The 2009 pandemic triple-reassortant influenza A (H1N1) virus was associated with neurologic and muscular syndromes that affected primarily children and included myositis.[23] Rhabdomyolysis can be complicated by renal failure and development of a compartment syndrome.

Enteroviruses, including coxsackieviruses (i.e., group A and B) and enteric cytopathogenic human orphan viruses (i.e., echoviruses), also cause myositis. Coxsackievirus B infection manifesting as pleurodynia is most common. Children typically are infected in the summer or fall and come to medical attention with paroxysms of severe, sharp chest pain. The costochondral muscles may be tender on palpation. In addition to pleurodynia, cases of rhabdomyolysis due to coxsackieviruses and echoviruses have been reported. The pathogenesis of myositis is uncertain, but muscle biopsies have shown degenerative necrosis of the muscle fibers and picornavirus-like structures. Therapy is symptomatic, and the disease usually resolves in several days. Recurrences of pleurodynia have been described in up to one fourth of cases.

HIV infection can cause a wide range of skeletal disorders, including myopathy, polymyositis, and rhabdomyolysis. Generalized myalgia, proximal muscle weakness, and elevated serum creatine kinase levels are common.[24] Muscle biopsy shows lymphocytic infiltration and necrosis of muscle fibers. These histologic findings are distinct from the mitochondrial myopathy associated with extended zidovudine therapy.[25] Although one study showed that proviral DNA could be detected in myocytes and muscle macrophages by polymerase chain reaction,[26] other researchers concluded that the disease probably represented a dysfunctional T lymphocyte–mediated process.[27] Corticosteroid therapy may be beneficial.[28]

Chronic Inflammatory Myositis

Several parasites and other pathogens can cause a chronic inflammatory reaction in skeletal muscle. In these disorders, persistence of the infectious agent appears necessary to cause chronic myopathy by direct tissue damage or as a consequence of the normal immunologic response to the infected tissue. In other disorders, such as juvenile dermatomyositis (JDM) and polymyositis, immunologic dysregulation is the hypothesized mechanism of disease.[29]

JDM is the most common form of pediatric idiopathic inflammatory myopathy, with an incidence ranging from 1.9 to 3.2 cases per million children.[30,31] The two major clinical features of JDM are a characteristic rash and symmetric proximal muscle weakness.[32] The gastrointestinal tract and lung often are involved.[32] Compared with the adult form of the disease, JDM more frequently has vasculitis features, skin ulceration, and calcinosis.[33] Patients with JDM often have a flu-like illness approximately 3 months before onset of the disease.

Coxsackievirus B and other enteroviruses are the most frequent infectious agents temporally associated with the onset of JDM.[34–37] Coxsackievirus B1 can induce chronic myositis of the proximal hind limbs in a murine model.[38] Serologic responses consistent with acute coxsackievirus B infection were found in patients in some studies[34] but not in others.[39] Although picornavirus-like particles have been observed on electron-microscopic examination of muscle biopsy samples from some children with JDM, immunofluorescence, polymerase chain reaction,[40] in situ nucleotide hybridization,[41] and tissue culture[36] have failed to identify a virus.

If an infectious agent precipitates JDM, it is hypothesized that immunologically mediated injury (possibly through molecular mimicry) rather than direct infection is the mechanism of injury. This pathogenic mechanism is supported by gene expression profile analyses of untreated JDM muscle biopsies, demonstrating an intense interferon α/β-induced response typical of that seen during an immune response to a viral antigen.[42]

Several reports have demonstrated an association between the human leukocyte antigen (HLA)-DQA1*0501 and JDM.[42–44] This association has been linked to an enhanced cytokine response partly contributed to by the tumor necrosis factor-α (TNF-α)-308A allele,[42,45] which is known to promote TNF-α synthesis. Enhanced TNF-α production was demonstrable in the circulation[45] and in muscle biopsies[46] from untreated JDM patients positive for the TNF-α-308A allele. This allele has been shown to be associated with pathologic calcifications and disease chronicity.[45,47] The pathogenesis of JDM after group A streptococcal infection may involve cytotoxic and cytokine responses elicited by specific epitopes of the streptococcal M-protein homologues of human skeletal myosin.[48]

Pyomyositis

Pyomyositis is an acute intramuscular infection due to hematogenous spread of the microorganism into the body of a skeletal muscle. By definition, it is not caused by a contiguous infection of the soft tissue or bone or by penetrating trauma. Pyomyositis has a predilection for large-muscle groups and often results in localized abscess formation.

Pyomyositis often is called *tropical myositis* because of its prevalence in tropical areas, where pyomyositis accounts for 3% to 5% of hospital admissions.[49–51] The first case of tropical pyomyositis from a temperate region was reported in 1971.[52] Since then, many cases have been reported from various parts of the world.[53–55] In North America, the highest incidence of pyomyositis is in southern regions.[56] Pyomyositis occurs most often in children and young adults,[57,58] exhibits a 2 : 1 male preponderance, and has occurred in the neonatal period.[59]

Methicillin-susceptible *S. aureus* (MSSA) was isolated from the purulent material in approximately 90% of cases in tropical areas and 75% of cases from temperate countries before the 1990s.[53] CA-MRSA (particularly the USA300 clone) has since emerged as a dominant cause in temperate climates.[60] Group A *Streptococcus* accounts for 1% to 5% of cases. Other causes include streptococci (i.e., groups B, C, and G), *E. coli, Citrobacter freundii, Serratia marcescens, Yersinia enterocolitica, Klebsiella* spp., and *Salmonella* spp. Individuals infected with HIV-1 are at increased risk for bacterial pyomyositis, sometimes with multifocal involvement.[61]

Staphylococcal pyomyositis most frequently affects the quadriceps, hamstring, or gluteal muscles but also can affect the paraspinous, shoulder girdle, psoas, and other muscles.[55] Symptoms usually begin insidiously, with low-grade fever, muscle aches, and cramping evolving over several days. Abscesses are multiple in about 25% of patients. In the early stages, examination may reveal only a rubbery firmness to the muscle belly, with no other superficial signs of inflammation. Within days to weeks, boggy swelling, erythema, tenderness, and warmth appear, and the lesion becomes fluctuant. Although substantial muscle destruction can develop with delayed treatment, serum levels of muscle enzymes usually are normal. Pyomyositis occasionally is complicated by metastatic infection such as empyema, pericarditis, or lung abscess. In rare cases, fulminant septicemia or toxic shock syndrome occurs.[62]

Pyogenic abscess in the psoas muscle produces a distinct clinical syndrome with lower abdominal or back pain radiating to the hip.[63] The febrile child may limp or hold the hip in fixed flexion because of muscle spasm. Confusion with pyogenic arthritis is common. Pain on hyperextension or abduction of the hip is elicited on examination. *S. aureus* is the most common cause, but psoas abscesses occasionally can develop as an extension of an abdominal process such as a ruptured appendix.[63] In such cases, a mixed infection with anaerobic and facultative bowel flora is likely.

Group A streptococci are an increasingly important cause of pyomyositis.[64,65] GAS infection of skeletal muscle can manifest as a localized phlegmon, an abscess, or more fulminant necrotizing myositis.[66,67] Intense pain is the most common presenting symptom, often out of proportion to clinical signs of inflammation. The child may refuse to bear weight or to move an extremity. Ultimately, high fever, localized swelling, and overlying erythema are observed. Tachycardia, hypotension, oliguria, confusion, lethargy, and scarlatiniform eruptions are early signs of associated streptococcal toxic shock syndrome. Mild to moderate leukocytosis with immature neutrophils (often >50%) and elevation of blood urea nitrogen, creatinine, and creatine kinase levels are common.[8]

Although a portal of entry is not always evident, the exanthem of primary varicella and various forms of minor skin trauma are important predisposing factors for GAS deep tissue infection in children. A prospective, population-based active surveillance for pediatric invasive GAS disease in Ontario revealed that varicella-zoster virus infection was associated with a 58-fold increased risk of invasive GAS disease among children.[64] Although the attack rate of invasive GAS was relatively low (5.2 cases/100,000 children), 15% of all pediatric invasive GAS infections, including 50% of cases of necrotizing fasciitis, followed varicella infection.

Necrotizing Fasciitis

Necrotizing fasciitis (i.e., hospital gangrene or hemolytic streptococcal gangrene) was described as early as the fifth century BC by Hippocrates.[68] Necrotizing fasciitis is a rapidly progressive, deep-seated bacterial infection of the subcutaneous soft tissue that can involve any area of the body. The course often is fulminant, with mortality rates ranging from 25% to 75%.[69,70] Many terms have been used to describe necrotizing soft tissue infections. A simplified classification is provided in Table 75.2.

TABLE 75.2

Necrotizing Infections of the Soft Tissues

Type	Usual Etiologic Agent	Predisposing Causes	Clinical Manifestations
Meleney synergistic gangrene	*Staphylococcus aureus,* microaerophilic streptococci	Surgery	Slowly expanding ulceration confined to superficial fascia
Clostridial cellulitis	*Clostridium perfringens*	Local trauma or surgery	Gas in skin, fascial sparing, little systemic toxicity
Nonclostridial anaerobic cellulitis	Mixed aerobes and anaerobes	Diabetes mellitus	Gas in tissues
Gas gangrene	Clostridial species (*C. perfringens, C. histolyticum,* or *C. septicum*)	Trauma, crush injuries, epinephrine injections; spontaneous cases related to cancer, neutropenia, cancer chemotherapy	Myonecrosis, gas in tissues, systemic toxicity, shock
Necrotizing fasciitis type 1	Mixed anaerobes, gram-negative aerobic bacilli, enterococci	Surgery, diabetes mellitus, peripheral vascular disease	Destruction of fat and fascia; skin may be spared; involvement of perineal area in Fournier gangrene
Necrotizing fasciitis type 2	Group A *Streptococcus*	Penetrating injuries, surgical procedures, varicella, burns, minor cuts, trauma	Systemic toxicity, severe local pain, rapidly extending necrosis of subcutaneous tissues and skin; gangrene, shock, multiorgan failure

Modified from Bisno AL, Stevens DL. Streptococcal infections of skin and soft tissues. N Engl J Med 1996;334:240–245.

Although more than 500 cases of necrotizing fasciitis have been reported in North America, it is an uncommon disease, and the true incidence is not known.[71,72] Males are affected slightly more commonly than females.[69,70,73] An increased frequency is associated with diabetes mellitus, intravenous drug use, chronic alcohol consumption, immunosuppression, and peripheral vascular disease.[70,71,73] Necrotizing fasciitis also occurs in young, previously healthy children and adults, for whom mortality rates are lower than among the elderly and those with underlying disease.[71]

Patients may report a history of recent surgery, trauma, eczema, or varicella infection.[69,74,75] Other precipitating factors include insect bites, perirectal abscess, incarcerated hernia, and subcutaneous insulin injection. Necrotizing fasciitis commonly is reported as a complication of varicella infection.[71,74,76] Necrotizing fasciitis also can occur after GAS pharyngitis or without any previous evidence of trauma or infection. The purported association between the use of nonsteroidal anti-inflammatory drugs and necrotizing fasciitis was not supported definitively by a prospective, multicenter, case-control study carried out among children hospitalized with primary varicella complicated by invasive GAS infection or necrotizing soft tissue infection.[74,77–79] In neonates, necrotizing fasciitis can complicate omphalitis or circumcision.

Necrotizing fasciitis often is classified as three types. The polymicrobial form of the disease is described as necrotizing fasciitis type 1, and it often occurs postoperatively or in patients with diabetes mellitus or peripheral vascular disease.[69,70,80] Pathogens include gram-negative bacilli, enterococci, streptococci, *S. aureus*, and anaerobes include *Bacteroides* spp., *Peptostreptococcus* spp., and *Clostridium* spp. (see Table 75.2). Necrotizing fasciitis type 2 is caused by GAS infection that can occur postoperatively or as a result of penetrating trauma, varicella infection, burns, or minor cuts; and it is characterized by rapidly extending necrosis and severe systemic toxicity. Type 2 disease is the most common form of necrotizing fasciitis in children.[71,73,81] Necrotizing fasciitis type 3 is rare and is caused by marine *Vibrio* spp., which enter through skin lesions that have been exposed to seawater or marine animals.

In children, necrotizing fasciitis often occurs 1 to 4 days after trauma, with soft tissue swelling and pain over the affected area.

Patients may appear well at initial presentation. When associated with varicella, the findings typically begin 3 to 4 days after onset of the exanthem.[75] Infants and toddlers may be fussy or irritable. Toddlers and young children may limp or refuse to bear weight. Initially, pain with manipulation of the affected extremity often is out of proportion to the cutaneous signs of infection.

Induration and edema usually are apparent within the first 24 hours and are followed rapidly by blistering and bleb formation.[65,76,82] Infection spreads in the plane between the subcutaneous tissue and the superficial muscle fascia, which results in progressive destruction of fascia and fat (Fig. 75.2). Pain and tenderness in the subcutaneous space are exquisite, but destruction of the nerves that innervate the skin eventually can lead to anesthesia of the overlying skin. The rapidly progressing infection can lead to toxic shock syndrome and severe systemic toxicity, including renal and hepatic failure, acute respiratory distress syndrome, and decreased myocardial contractility.

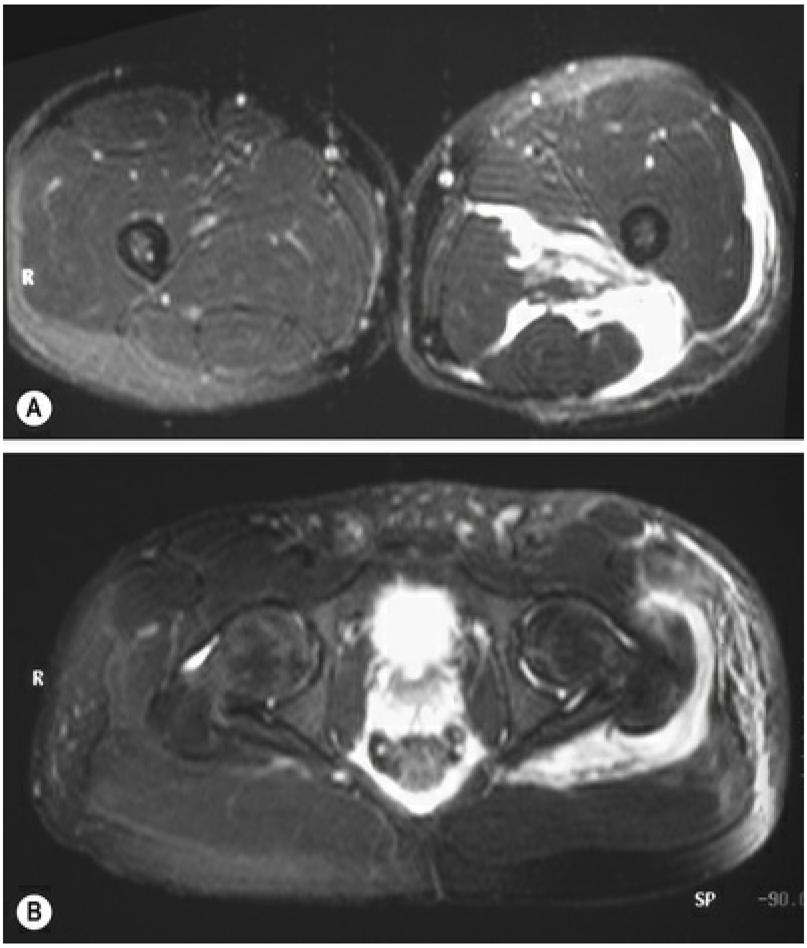

FIGURE 75.2 Pyomyositis and necrotizing fasciitis due to methicillin-resistant *Staphylococcus aureus* in a 17-year-old boy with a 1-day history of fever, poor appetite, and left hip pain, precluding ambulation. Physical examination showed fullness and exquisite tenderness of the buttock and posterior thigh without a break in the skin or erythema. (A and B) Axial T2-weighted magnetic resonance imaging shows hyperintensity of the fascia surrounding the tensor fascia lata and biceps femoris muscles from midthigh to the pelvic girdle. Surgery revealed necrotizing fasciitis. (Courtesy of E.N. Faerber and S.S. Long, St. Christopher's Hospital for Children, Philadelphia, PA.)

Extension of the infection along fascial planes leads to necrosis of the superficial fascia and the deeper layers of the dermis. Destruction and thrombosis of the small blood vessels in the area lead to necrosis of the surrounding tissues. The extensive tissue damage often leads to systemic symptoms, including multiorgan failure and shock.

Although white blood cell counts can be normal or elevated, there often is a pronounced shift to immature neutrophils. Thrombocytopenia and coagulopathy can occur. Attempts to identify causative organisms should be made through collection of anaerobic and aerobic blood cultures.[70,76] Cultures of the wound and surgically debrided tissue should be obtained. Frozen section biopsies can be helpful in making a timely diagnosis.

Pathogenesis

Skeletal muscle tissue is intrinsically resistant to bacterial infections, likely due to sequestration by myoglobin of iron that is required for proliferating bacteria. Staphylococcal muscle infections appear to be a complication of transient bacteremia and typically develop without penetrating injury or another clear portal of entry. Blood cultures frequently are negative.[83] Muscular trauma, strain, or vigorous exercise may be predisposing factors.[56,84] The high prevalence of the disease in the tropics has led to speculation that in patients with migrating parasitic infections, such as toxocariasis, microscopic foci of necrotic muscle develop that predispose to bacterial seeding.[85] Alternatively, a viral infection can be the precipitant; ultrastructural studies of nonsuppurating lesions in some patients with tropical pyomyositis reveal intracellular particles and a lymphocytic infiltrate.[86]

Group A streptococcal infection of skeletal muscle can take the form of a localized phlegmon, an abscess, or more fulminant necrotizing myositis or fasciitis,[66,67] associated with septicemia and toxic shock syndrome. The association of invasive GAS with primary varicella infection may result from the full-thickness skin lesion of chickenpox serving as a portal of entry for the organism (Fig. 75.3).[76,87,88] Varicella also produces a transient immunologic derangement, predisposing to secondary bacterial infection. A potential mechanism underlying the association of blunt trauma and streptococcal myonecrosis was provided by Bryant and colleagues,[89] who reported that muscle injury resulted in increased cellular vimentin expression, which enhanced colonization of GAS at the site of injury.

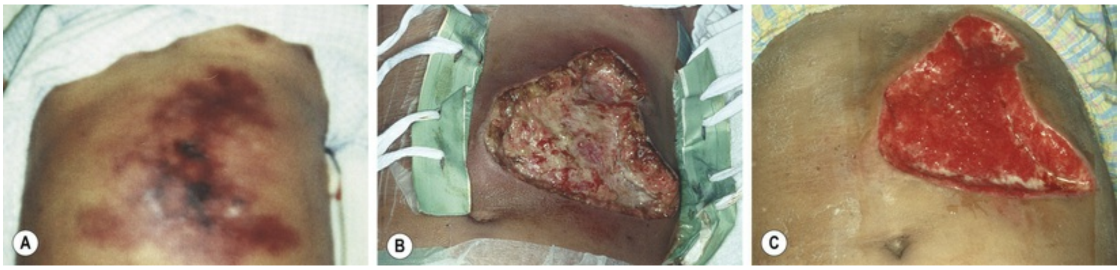

FIGURE 75.3 Necrotizing fasciitis of the abdominal wall due to *Streptococcus pyogenes* as a complication of chickenpox in a 7-year-old girl. (A) Notice the duskiness, ecchymosis, purpura, and edema of the abdominal wall. (B) There was full-thickness necrosis of skin, subcutaneous tissue, and fascia. (C) After multiple surgical debridements, the patient is ready for grafting. (Courtesy of J.H. Brien, ©.)

S. aureus and GAS express virulence factors, including adhesins, cytotoxins, superantigens, and immunomodulatory proteins, that contribute to the pathogenesis of infection. Although specific virulence factors are implicated in certain disease manifestations, such as superantigens as mediators of systemic toxicity and tissue injury,[90–92] no single virulence factor is sufficient to provoke a severe staphylococcal or streptococcal infection. Rather, a coordinated action of virulence factors is required for the bacteria to colonize successfully and spread within the host.[93–95] Tissue injury and systemic toxicity largely result from excessive inflammatory responses. A direct relationship between the magnitude of the inflammatory response and severity of invasive GAS infections has been demonstrated. Although GAS usually is considered an extracellular organism, macrophages can be a reservoir for GAS during acute deep tissue infections.[96] This may partially explain the persistent massive bacterial load despite adequate intravenous antibiotic therapy for a prolonged time in many patients.

Clostridium perfringens elaborates at least two exotoxins (i.e., α-toxin and perfringolysin O) that are cytolytic in host tissues and are lethal when purified and injected into animals.[97] *C. septicum* also expresses a pore-forming cytolysin, α-toxin, which triggers fulminant myonecrosis and inhibition of leukocyte influx into the lesion.[98] Exotoxin-induced microvascular dysfunction is an important factor producing the anaerobic environment that favors *C. perfringens* replication and ischemic necrosis.[39] In contrast, *C. septicum* is relatively aerotolerant, a feature that may partially explain its ability to spread through the bloodstream and establish infection in otherwise healthy muscle.[99]

Diagnosis

Early in the course, myositis, pyomyositis, or necrotizing fasciitis can be difficult to distinguish from a number of noninfectious disorders. Plain radiographs usually are normal, but other imaging techniques can be useful in defining the extent of muscle involvement. Although computed tomography (CT) may be useful in defining the extent of soft tissue involvement, magnetic resonance imaging (MRI) is the preferred imaging modality. MRI can reveal extension of inflammation along the fascial plains and distinguish the compartments and structures (e.g., bone, muscle, fascia, fat) involved (see Fig. 75.2).[100–102] Ultrasonography (US) is helpful in the suppurative phase.[100,103,104]

CT or US may delineate a low-density (or hypoechoic) fluid collection, facilitating diagnostic aspiration or percutaneous drainage.[105,106] Diagnostic MRI findings include hyperintense signal within the muscle with edema in pyomyositis and a hyperintense rim on unenhanced T1-weighted images and peripheral enhancement after intravenous infusion of gadolinium if an abscess has formed[101] (see Fig. 75.1). CT or MRI also can detect marked skeletal muscle abnormalities in GAS necrotizing myositis (Fig. 75.4).[106,107] Infrared thermography may help reveal the extent of tissue viability in clostridial myonecrosis.[108]

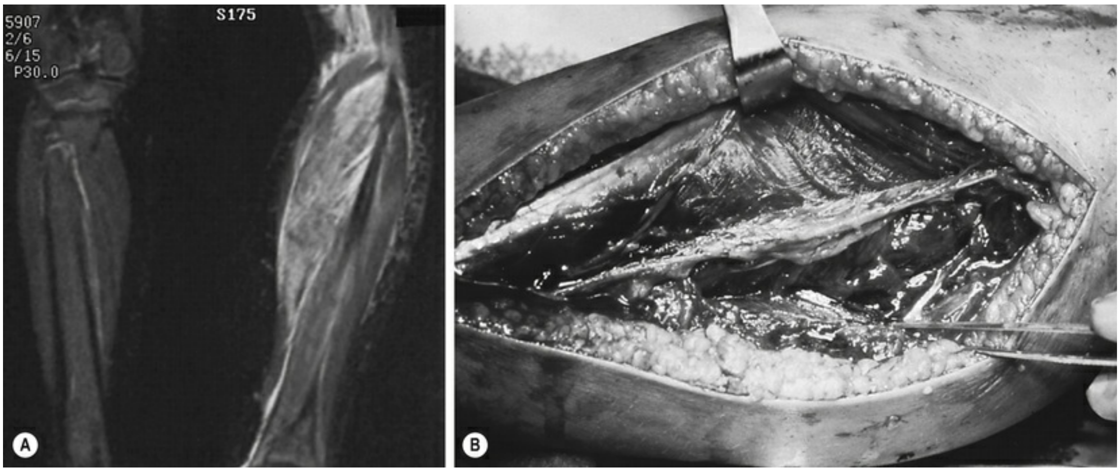

FIGURE 75.4 A 5-year-old girl had severe left posterior calf pain, tenderness, and swelling 1 week after onset of primary varicella. (A) With a magnetic resonance imaging technique in which the fat signal intensity is suppressed, marked signal enhancement is seen diffusely in the calf musculature, indicative of a widespread inflammatory process. (B) Operative exploration of the calf revealed liquefaction necrosis of the soleus muscle and the lateral head of the gastrocnemius muscle, which were radically debrided. Group A *Streptococcus* was isolated from the culture of tissue and blood. (Courtesy of J.H.T. Waldhausen, MD.)

Treatment

Therapeutic interventions for SSTIs include incision and drainage, debridement, compartment release, and antibiotic therapy. Recommendations from the Centers for Disease Control and Prevention[109] and the American Academy of Pediatrics[110] emphasize performing incision and drainage as the primary treatment of abscesses, submitting purulent material for culture, and targeting CA-MRSA when empiric antibiotics are prescribed (Table 75.3). Effective surgical drainage of fluid collections or abscesses often can be accomplished percutaneously with US or CT guidance,[111] but an open surgical procedure may be required.

TABLE 75.3

Antimicrobials for Treatment of Community-Acquired, Methicillin-Resistant *Staphylococcus aureus* Infections in Children

Antimicrobial	Daily Dosage
Daptomycin[a]	4–6 mg/kg/day q24hr
Linezolid	30 mg/kg/day divided q8hr (> or = 12 yr, 20 mg/kg/day divided q 12 hr, max 1.2 g/day divided q 12)
Vancomycin	40–60 mg/kg/day divided q6–8hr
Clindamycin	30 mg/kg/day divided q6–8 hr IV (max 4.8 g/day); 40–60 mg/kg/day divided q6–8hr PO (max 1.8 g/day)
Trimethoprim-sulfamethoxazole	20 mg/kg/day TMP divided q12hr

[a] Daptomycin should not be used to treat pneumonia. It is not approved by the US Food and Drug Administration for the treatment of children.

Surgical debridement usually is necessary for GAS necrotizing pyomyositis after the patient has been stabilized medically.[112] Fasciotomies are performed if there is evidence of increased compartment pressures. GAS uniformly is susceptible to penicillin and other β-lactam antibiotics, and penicillin remains an appropriate antibiotic treatment of GAS infections. However, in patients with aggressive GAS infections such as myositis and necrotizing fasciitis, a β-lactam antibiotic should be combined with clindamycin (40 mg/kg/day) because of its favorable pharmacodynamic properties and activity at the ribosomal level, inhibiting of toxin production.

Treatment of clostridial gas gangrene consists of prompt and radical debridement of involved muscles; amputation may be required. Because 5% of strains of *C. perfringens* are clindamycin resistant, the recommended antibiotic treatment is penicillin plus clindamycin.[113] Although the role of hyperbaric oxygen is controversial, therapy may serve an adjunctive role by retarding growth of *C. perfringens,* inhibiting α-toxin production, and increasing oxidative killing by host neutrophils.[114] Patients who survive may require amputation, skin grafting, or reconstructive surgery.

In severe GAS infections, the use of high-dose immune globulin intravenous (IGIV) has been proposed as adjunctive therapy. The mechanism of action of IGIV in this setting is thought to include inhibition of the superantigen activity through neutralizing antibodies, opsonization through M-specific antibodies, and a general anti-inflammatory effect.[115] Large controlled studies of IGIV therapy in patients with severe invasive GAS infections have not been conducted, but case reports and small controlled studies have reported on the uncontrolled outcomes of IGIV use in GAS toxic shock syndrome, necrotizing fasciitis, and necrotizing myositis (Table 75.4). Favorable results were reported for invasive GAS infections in an observational cohort study of Canadian patients identified through active surveillance[116] and in one European multicenter, placebo-controlled trial.[117]

TABLE 75.4

Intravenous Polyspecific Immunoglobulin as Adjunctive Therapy in Severe Invasive Group A Streptococcal Infections

Study Design	No. of Patients[a]	Case-Fatality Rate (%)
NF and myonecrosis, case series identified through active surveillance[118]	IGIV: 10	19
	No IGIV: 4	25
NF, case series identified through active surveillance[117]	IGIV: 10	10
	No IGIV: 67	37
Severe soft-tissue infections, observational cohort study[111]	7	0
STSS + NM, case report[119]	1	0
STSS + NF, case report[120]	1	0
STSS + NF, case report[121]	1	0
STSS + NF, case report[122]	1	0
STSS, case report[123]	1	0
STSS, case report[124]	1	0
STSS, case report[125]	1	0
STSS, case report[126]	1	0
STSS, case series[127]	5	20
STSS, multicenter placebo RCT[116,b]	IGIV: 10	10
	Placebo: 11	36
STSS, case-control study[115]	IGIV: 21	33
	No IGIV: 32	66

[a] All received IGIV unless otherwise specified.

[b] Trial prematurely terminated due to slow patient recruitment.[116]

IVIG, intravenous immunoglobulin; NF, necrotizing fasciitis; NM, necrotizing myositis; STSS, streptococcal toxic shock syndrome; RCT, randomized, controlled trial.

Data on the efficacy of IGIV for necrotizing fasciitis are limited (see Table 75.4).[112,118,119] In one study, the mortality rate was 10% for IGIV-treated patients, compared with 37% for untreated control subjects.[118] In an observational case study, the use of an aggressive medical regimen that included high-dose IGIV appeared to mitigate the need for aggressive surgical intervention.[82] Seven patients with severe GAS soft tissue infection (6 patients with toxic shock syndrome) were treated with antibiotics parenterally and high-dose IGIV; surgery was not performed or limited to exploration, and all patients survived. This limited study suggests that an initial conservative surgical approach combined with the use of immune modulators such as IGIV may reduce the morbidity associated with extensive surgical exploration in hemodynamically unstable patients.

Guidelines available online from the Infectious Diseases Society of America provide empiric therapeutic options for specific clinical scenarios (e.g., animal bites) and specific pathogens of SSTIs.[113]

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K

Bone and Joint Infections

OUTLINE

76 Osteomyelitis
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78 Diskitis
79 Transient Synovitis

76

Osteomyelitis

David K. Hong, Kathleen Gutierrez

Osteomyelitis is inflammation of bone. It usually is caused by bacteria but occasionally by fungi. Osteomyelitis in children has a mainly hematogenous origin; less commonly, it occurs as a result of trauma, surgery, or spread from infected contiguous soft tissue. Osteomyelitis due to vascular insufficiency is rare in children.

Acute Hematogenous Osteomyelitis

Pathogenesis

Acute hematogenous osteomyelitis (AHO) is primarily a disease of young children, presumably because of the rich vascular supply of their rapidly growing bones.[1–3] Infecting organisms enter the bone through the nutrient artery and then travel to the metaphyseal capillary loops, where they are deposited, replicate, and initiate an inflammatory response (Fig. 76.1). Metaphyseal localization results from sluggish blood flow, endothelial gaps in the tips of growing metaphyseal vessels, and lack of phagocytic cells lining the capillaries.[1–6] Bacteria proliferate, spread through vascular tunnels, and are anchored to areas of exposed cartilaginous matrix. Large colonies of bacteria surrounded by glycocalyx obstruct capillary lumens, impairing phagocytosis and antibiotic penetration.[7]

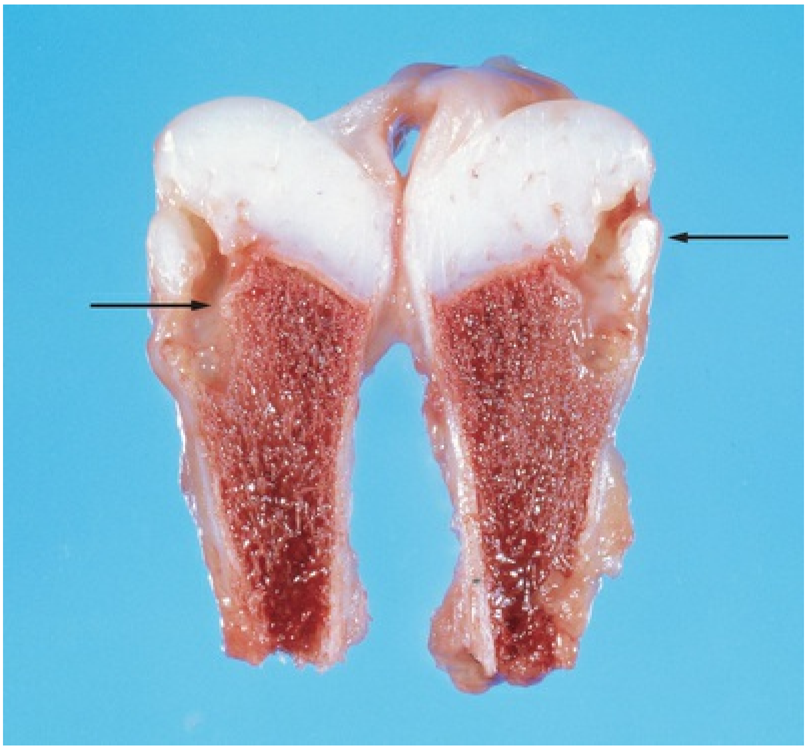

FIGURE 76.1 Gross specimen shows osteomyelitis of the proximal humerus in a 6-week-old infant. Notice the metaphyseal location and bony destruction *(arrows)*. (Courtesy of S.S. Long, St. Christopher's Hospital for Children, Philadelphia, PA.)

Age-related differences in the anatomy of the bone and its blood supply influence the clinical manifestations of osteomyelitis.[1,2] The transphyseal vessels, found in most children younger than 18 months, provide a vascular connection between the metaphysis and the epiphysis[1] (Fig. 76.2A). In infants, infection originating in the metaphysis can spread to the epiphysis and joint space. The risk of ischemic damage to the growth plate is greater in the young infant with osteomyelitis.[8] Before puberty, the periosteum is not firmly anchored to underlying bone. Infection in the metaphysis of a bone can spread to perforate the bony cortex, causing subperiosteal elevation and extension into surrounding soft tissue. Bony destruction also can spread to the diaphysis. By 2 years of age, the cartilaginous growth plate usually prevents extension of infection to the epiphysis and into the joint space. When the metaphysis of the proximal femur or humerus is involved, however, infection can extend into the hip or shoulder joint at any age, because the metaphysis is intracapsular at these sites (see Fig. 76.2B).

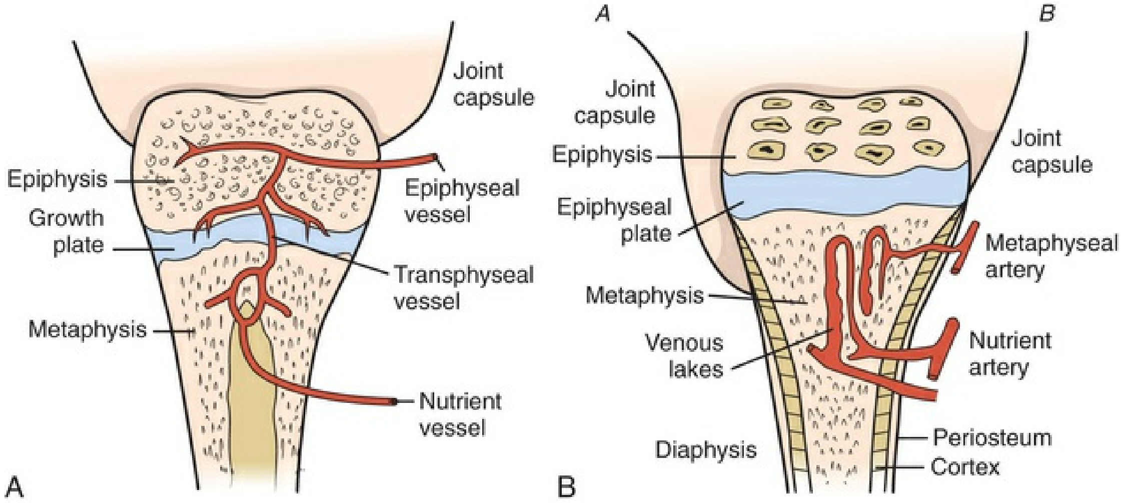

FIGURE 76.2 (A). Major structures of the bone of an infant before maturation of the epiphyseal growth plate. The transphyseal vessel connects the vascular supply of the epiphysis and metaphysis, facilitating the spread of infection between these two areas. (B) Major structures of the bone of a child. The joint capsule *A* inserts below the epiphyseal growth plate, as in the hip, elbow, ankle, and shoulder. Rupture of a metaphyseal abscess in these bones is likely to produce pyogenic arthritis. The joint capsule *B* inserts at the epiphyseal growth plate, as in other tubular bones. Rupture of a metaphyseal abscess in these bones is likely to lead to a subperiosteal abscess but seldom to an associated joint. (Modified from Gutman LT. Acute, subacute, and chronic osteomyelitis and pyogenic arthritis in children. Curr Probl Pediatr 1985;15:1–72.)

Histologic features of acute osteomyelitis include localized suppuration and abscess formation, with subsequent infarction and necrosis of bone. Segments of bone that lose blood supply and become separated from viable bone are called *sequestra.* An *involucrum* is a layer of living bone surrounding dead bone. A *Brodie abscess* is a subacute, well-demarcated focal infection, usually in the metaphysis but sometimes in the diaphysis of bone.[9]

Epidemiology

Approximately one half of AHO cases occur in the first 5 years of life.[10] Boys are affected twice as frequently as girls, except in the first year of life.[10,11] One third of patients have minor trauma to the affected extremity antecedent to infection, but the specific importance of this history is unclear, because virtually all young children experience frequent mild trauma.[12]

The relative risk of developing osteomyelitis appears to be higher in some populations. In one study, Polynesian and Maori children were more likely to develop complicated osteomyelitis with *Staphylococcus aureus* than other children in the same New Zealand community.[13] It is unclear whether genetic, socioeconomic, or environmental factors accounted for this difference.

Microbiology

S. aureus is the most common cause of AHO.[3,12,14–20] *Kingella kingae, Streptococcus pneumoniae,*[21] and *S. pyogenes*[22] are the organisms isolated in most other pediatric cases. *K. kingae* and *S. pneumoniae* infections are most common in children younger than 3 years of age. *S. pneumoniae* accounts for a relatively small proportion of infections, especially in the context of widespread immunization with the pneumococcal conjugate vaccine.[23,24] *K. kingae* can be associated with small outbreaks of bone and joint infections in childcare centers.[16,25] Coagulase-negative staphylococci (CoNS) (almost exclusively as a complication of medical intervention), enteric gram-negative bacilli, and anaerobic bacteria are uncommon etiologic agents.

Bartonella henselae can cause granulomatous infection of bone.[26–28] *Actinomyces* spp. cause facial and cervical osteomyelitis.[29] Infection with *Serratia* spp. and *Aspergillus* spp. should be considered in children with underlying chronic granulomatous disease.[30]

Before widespread use of *Haemophilus influenzae* type b (Hib) conjugate vaccine, Hib was the cause of 10% to 15% of cases of osteomyelitis in children younger than 3 years.[15,17] Hib is a rare cause in immunized children.[31]

Acute osteomyelitis due to community-acquired, methicillin-resistant *Staphylococcus aureus* (CA-MRSA) has become common.[32–34] Some CA-MRSA isolates causing osteoarticular infection carry the genes for Panton-Valentine leukocidin (PVL), a virulence factor or marker for complicated infections.[35,36]

Clinical Characteristics and Differential

Diagnosis

Most patients with AHO have symptoms for less than 2 weeks when they are brought to medical attention, although a small proportion have low-grade fever and intermittent bone pain for several weeks.[12,19] The most common manifestations are fever, pain at the site of infection, and reluctance to use an affected extremity.[15,37] Less common complaints are anorexia, malaise, and vomiting. Physical findings consist of focal swelling, tenderness, warmth, and erythema (usually over the metaphysis of a long bone). Rarely, a draining fistulous tract develops over the affected bone.[12]

Persistent tenderness during treatment of presumed soft tissue infection or cellulitis can be a clue to osteomyelitis. Exaggerated immobility of the joint and lack of point tenderness over the bony metaphysis suggest pyogenic arthritis. Other causes of bone pain are fracture, bone infarction due to hemoglobinopathy, leukemia, vitamin deficiency, and bony neoplasms such as metastatic neuroblastoma and Ewing sarcoma.

Osteomyelitis most frequently occurs in the long bones (Fig. 76.3), although in some series, 10% to 25% of cases involve short or nontubular flat bones, including the pelvis, vertebrae, clavicle, calcaneus, skull, ribs, and scapula.[15,19,38] Multiple bones are involved in about 5% of cases.

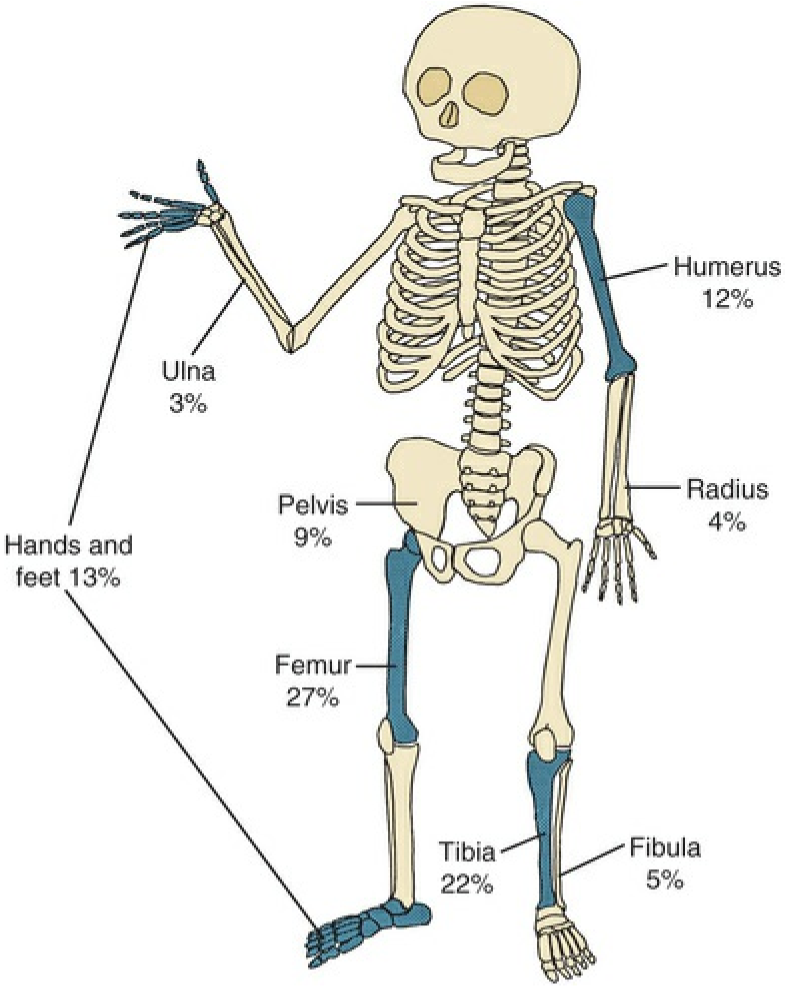

FIGURE 76.3 Sites of acute osteomyelitis in 657 children in whom a single bone was involved. *Shaded areas* constitute sites of approximately 75% of cases. Miscellaneous sites accounting for 5% are not shown.

(Data from references 11, 15, 19, and 37.)

Compared with methicillin-sensitive *S. aureus* (MSSA), patients with MRSA infections can have more protracted courses of fever, prolonged hospitalization, multiple foci of infection, pyomyositis, and subperiosteal and intraosseous abscesses.[35,39–41] Patients with PVL-positive CA-MRSA are at increased risk for deep vein thrombosis and septic emboli to the lungs.[36,40,42] PVL-positive isolates have not been associated with an increased likelihood of causing bone and joint infections.[43] However, compared with infection due to PVL-negative organisms, osteoarticular infections with PVL-positive *S. aureus*, whether MRSA or MSSA, appear to be associated with greater morbidity and are more likely to result in chronic osteomyelitis.[32,43,44]

Laboratory Diagnosis

Bacteriologic diagnosis can be confirmed in 50% to 80% of cases of AHO; bacteriologic confirmation is optimized when multiple specimens, including blood, bone, and joint fluid, are sampled.[2,11,12,15,19,37] Cultures obtained by imaging-guided bone biopsy are more likely to be positive if larger volumes (>2 mL) of purulent material are aspirated.[45] Diagnosis of *K. kingae* infection is enhanced with intraoperative inoculation of culture material directly into liquid media or onto agar plates.[46] The use of real-time polymerase chain reaction (PCR) testing has greatly enhanced the ability to detect *K. kingae*.[47]

The erythrocyte sedimentation rate (ESR) is elevated in up to 90% of cases of osteomyelitis, and the C-reactive protein (CRP) level is increased in 98%.[15,19,35,48] The mean ESR is 40 to 60 mm/hr, but levels greater than 100 mm/hr can occur. The ESR usually peaks 3 to 5 days after initiation of therapy and returns to normal in approximately 3 weeks. The CRP level peaks by the second day (mean, 8.3 mg/dL) of effective therapy and returns to normal (<2.0 mg/dL) after approximately 1 week of therapy.[48] Patients infected with PVL-positive instead of PVL-negative *S. aureus* are more likely to have positive blood culture results and higher ESR and CRP levels at presentation.[35] Higher levels of CRP at diagnosis may predict greater risk of sequelae.[49,50] The peripheral white blood cell count can be elevated or normal. Thrombocytosis can be remarkable, especially when symptoms exist for more than 1 week and persist during treatment.

Imaging Diagnosis

Plain Radiography

Radiographic abnormalities in osteomyelitis reflect inflammation of soft tissue and destruction and new formation of bone.[2,50,51] The earliest abnormalities, seen within the first 3 days of onset of symptoms, are deep soft tissue swelling and loss of the normally visible tissue planes around the affected bone. Osteopenia or osteolytic lesions from destruction of bone usually are not visible until approximately 50% of bone has been demineralized. Lytic lesions, periosteal elevation due to subcortical purulence, and periosteal new bone formation appear approximately 10 to 20 days after onset of symptoms. Sclerosis of bone is seen when infection has been present for longer than a month. If deep soft tissue swelling is seen on the plain radiograph of a patient with a short history of symptoms and with point tenderness over the affected metaphysis, no further imaging studies are necessary to support the diagnosis of osteomyelitis.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is the most accurate way of diagnosing osteomyelitis and offers enhanced sensitivity compared with plain radiography and radionuclide scanning.[52,53] The reported sensitivity of MRI for detection of osteomyelitis is 92% to 100%.

Normal red and fatty portions of the bone marrow have a characteristic appearance on MRI. Fatty marrow produces a bright signal on T1-weighted images.[54] Changes in marrow caused by infection and inflammation produce an area of low signal intensity within the bright fatty marrow. Areas of low signal intensity in infected marrow seen on a T1-weighted image are expected to show bright signal intensity on T2-weighted image. These changes are not specific for osteomyelitis and can be seen in cases of malignancy, fracture, and bone infarction. Major infection confined to the deep soft tissue can result in minor abnormality in adjacent bone.

MRI can detect signal alterations in soft tissue and is particularly useful in differentiating cellulitis from osteomyelitis. MRI also can aid differentiation of acute from chronic osteomyelitis.[55] Gadolinium-enhanced MRI can be particularly useful in the diagnosis of soft tissue, muscle, or bone abscesses.[41] The use of a contrast agent can increase confidence in the diagnosis of osteomyelitis in cases in which bone and soft tissue edema are seen on unenhanced images.[56] MRI has been used to identify bone marrow infection in cases of *B. henselae* infection, particularly when plain radiographs and computed tomography (CT) scans of the affected bones are normal.[27]

Radionuclide Scanning

Radionuclide scanning is useful in the early diagnosis of osteomyelitis, when plain radiographs are normal. A scan can be useful for patients who cannot undergo MRI due to medical devices (e.g., pacemakers) or braces. Radionuclide scans can be valuable when multifocal bone involvement is suspected[57] or when the site of infection cannot be localized, as in a toddler who refuses to bear weight. A technetium-labeled methylene diphosphonate isotope is most frequently used because its uptake by infected bone is enhanced when osteoblastic activity is increased.

The reported sensitivity of technetium-99 bone scanning is between 80% and 100% for patients studied from less than 6 weeks to 15 years of age.[58–62] The bone scan can be normal for 5% to 20% of children with osteomyelitis in the first few days of illness.[61,63–65]

Treatment

Antibiotic Choice

The choice of a specific antimicrobial regimen considers the age of the child, underlying medical conditions, suspected pathogens and their susceptibility pattern, antibiotic pharmacodynamics, and evidence of safety and efficacy.

Most β-lactam antibiotics achieve therapeutic concentrations in bone.[66,67] Clindamycin has particularly good bone penetration, attaining a high bone-to-serum ratio.[66,68,69] Vancomycin has excellent penetration into the bones of experimental animals. Aminoglycoside agents theoretically have poor bactericidal activity in bone because of local tissue hypoxia and acidosis. Although ciprofloxacin penetrates well into bone, fluoroquinolones are not recommended for use in young children.[70]

Most cases of AHO in any age group are caused by *S. aureus.* Empiric therapy should include coverage for MSSA with an agent such as parenterally administered nafcillin, clindamycin, or a first-generation cephalosporin, and in most cases, CA-MRSA. Clindamycin remains a good choice for empiric therapy in communities where less than 10% of MRSA isolates are resistant.[41] In communities where CA-MRSA resistance to clindamycin is greater than 10% to 15%, vancomycin should be considered in empiric therapy.[71] Clindamycin and vancomycin are active against most isolates of *S. pyogenes* and *S. pneumoniae.* Neither offers adequate coverage for *K. kingae* infection, which is susceptible to most β-lactam antibiotics. In children younger than 4 years of age, empiric antibiotic regimens should include coverage against *K. kingae*, as should definitive therapy if initial cultures are negative.[72] Ampicillin-sulbactam or a third-generation cephalosporin should be considered in addition to clindamycin or vancomycin in young children. Hib need not be covered in the fully immunized and immunocompetent child.

Neonates with osteomyelitis should be treated with antibiotics active against MSSA, MRSA, group B *Streptococcus* (GBS), and gram-negative enteric organisms. Suggested initial empiric parenteral antibiotic therapy for neonates and children with AHO is outlined in Table 76.1.

TABLE 76.1

Antibiotic Selection for Initial Treatment of Osteomyelitis

Patient	Likely Pathogen	Antibiotic	Dosage[d]	
			mg/kg per day	Divided Doses/Day
Neonates[a]	*Staphylococcus aureus*	Nafcillin	100	4
	Group B *Streptococcus*	*or*		
	Enteric gram-negative bacteria	Vancomycin	30	2
		plus		
		Gentamicin	4	1
		or		
		Cefotaxime	150	3
Infants and children	*Staphylococcus aureus*	Clindamycin[c]	30–40	3
	Streptococcus pyogenes	*or*		
	Kingella kingae[b]	Vancomycin (if ill-appearing)	45	3
		or		
		Cefazolin	100	3

[a] Dosing may need to be adjusted based on gestational age, postnatal age, and current weight.

[b] If the patient is treated with clindamycin or vancomycin, consider adding ampicillin, ampicillin-sulbactam, or cephalosporin for *Kingella kingae* in children younger than 4 years of age.

[c] If clindamycin resistance locally is >10%, use vancomycin for serious infections, and add cefazolin.

[d] Not to exceed adult dosing.

Antibiotic therapy should be modified according to the results of culture and susceptibility testing. Nafcillin, oxacillin, a first-generation cephalosporin, or clindamycin (if susceptible) are the drugs of choice for infections caused by MSSA. Clindamycin is a good definitive choice for susceptible MRSA without inducible resistance in vitro.[73–75]

There are few antibiotic choices for clindamycin-resistant CA-MRSA infection in children. Guidelines by the Infectious Disease Society of America (IDSA) recommend vancomycin with or without rifampin for the treatment of MRSA osteomyelitis in children. Linezolid is suggested as an alternative.[71] Limited data on the use of linezolid for osteoarticular infections in children suggest that it is safe and effective.[76,77] Linezolid has excellent oral bioavailability and offers an alternative to prolonged intravenous therapy. However, it is expensive, and many children object to the taste of the oral suspension. Long-term use has been associated with neutropenia, thrombocytopenia, and elevated serum transaminase levels.[78] Rare reports of lactic acidosis and optic neuropathy have been associated with linezolid therapy.[79,80]

Most CA-MRSA isolates are susceptible to trimethoprim-sulfamethoxazole, tetracyclines, and rifampin. Clinical experience with these drugs for osteoarticular infections is limited.[81,82] Rifampin should not be used as a single agent because of rapid development of resistance. Although daptomycin and tigecycline have activity against MRSA, neither is approved for use in children. The IDSA guideline suggests daptomycin use in children in selected circumstances.[71] If no organism is isolated, and the symptoms are resolving, initial empiric therapy should be continued. Most cases of culture-negative osteomyelitis respond to therapy with antistaphylococcal antibiotics, with the addition of therapy against *K. kingae* in younger children.

Management of children with osteomyelitis should include concurrent care by an orthopedic surgeon. Indications for surgery include unremitting fever, erythema, pain, and swelling; persistent bacteremia despite optimal antibiotic therapy; soft tissue or periosteal abscess; formation of a sinus tract; and necrotic, nonviable bone.[83]

Duration of Therapy and Transition to Oral Therapy

Duration of antibiotic therapy depends on the cause and extent of infection, adequacy of surgical debridement if required, and the clinical course and laboratory evidence of resolution. The usual duration ranges from 3 to 6 weeks, and treatment should be individualized on the basis of severity of illness and clinical response. Historical evidence suggests that less than 3 weeks of treatment is associated with higher rates of relapse or recurrence than longer duration of therapy.[12,84,85]

Most patients can be managed successfully with early transition from parenteral to oral antibiotics. Oral antibiotics appear to be equally effective as parenteral antibiotics in the posthospital discharge treatment of osteomyelitis.[86] Prolonged intravenous therapy through a peripherally inserted or tunneled central venous catheter (i.e., PICC or CVC) has been associated with substantial risk (15% in one study) of catheter-related complications, including catheter malfunction, thrombosis, and catheter-associated bloodstream infections.[86–88]

The change to oral antibiotics usually is made when fever, pain, and signs of local inflammation have resolved and laboratory values, especially the CRP level, are normalizing. The willingness of the child to take oral medication and the likelihood of adherence to the regimen also must be assessed. Bacteriologic confirmation greatly aids the choice of antibiotic. For unconfirmed bacteriology, the oral antibiotic should have the same spectrum of coverage as the parenteral drug. If a β-lactam agent is used, the usual dosage required is two to three times the usual oral dose (Table 76.2).

TABLE 76.2

Dosage of Antibiotics Commonly Used in the Oral Phase of Treatment of Osteomyelitis

Antibiotic[a]	Dosage[d]	
	mg/kg per day	Divided Doses/Day
Dicloxacillin	75–100	4
Cephalexin	100	3–4
Clindamycin	30–40[b]	3–4
Linezolid	20[c]	2

[a] The dose of β-lactam antibiotics used for osteomyelitis usually is two or three times the dose for skin and soft tissue infection.

[b] Clindamycin (40 mg/kg/day) is recommended for the treatment of susceptible

methicillin-resistant *Staphylococcus aureus* (MRSA) osteomyelitis.[71]

[c] Linezolid dosing for children younger than 12 years of age is 30 mg/kg/day (10 mg/kg/dose every 8 hours). The maximum dose is 600 mg.

[d] Not to exceed adult dosing.

When the change to oral therapy is made, the child should be monitored to ensure continued clinical improvement. The CRP level is expected to return to normal 7 to 10 days after initiation of appropriate therapy, and the ESR returns to normal within 3 to 4 weeks.[48,89]

Special Clinical Situations

Neonatal Osteomyelitis

Osteomyelitis is uncommon in the neonatal period. The incidence of hospital-associated osteomyelitis is approximately 1 to 3 cases for every 1000 admissions to the neonatal intensive care unit.[90]

Associated risk factors include prematurity, low birth weight, preceding infection, bacteremia, exchange transfusion, and an intravenous or umbilical catheter.[91–93] Osteomyelitis of the skull due to contiguous spread of infection has occurred as a complication of fetal scalp electrode monitoring[94] and in association with infected cephalohematoma.[95] Osteomyelitis of the calcaneus has complicated heel lancet puncture.[96]

The diagnosis of osteomyelitis in neonates often is delayed because of nonspecific symptoms and signs, which can include fever, irritability, swelling or decreased movement of a limb (i.e., pseudoparalysis), or erythema, or tenderness over the affected bone.[97] Preterm infants are more likely than term infants to have symptoms of septicemia.[98] Approximately 20% to 50% of neonates with osteomyelitis have infection of multiple bones,[90,99,100] and about 75% have suppurative arthritis of contiguous joints[100] (Fig. 76.4).

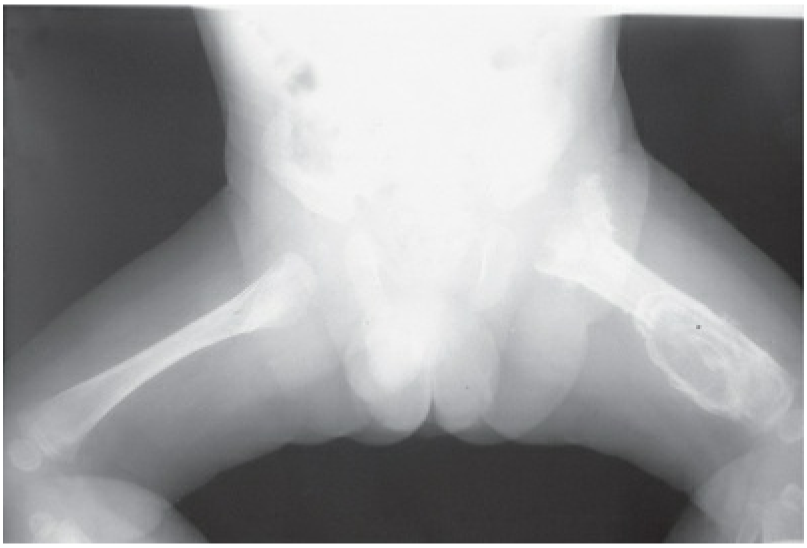

FIGURE 76.4 Plain radiograph of an infant at 2 months of age who had a *Staphylococcus aureus* bloodstream infection during a stay in the neonatal intensive care unit during the first month of life. He had multiple sites of infection, including the proximal and distal femur and hip joint. Notice the widespread destruction of the femur, acetabulum, and joint. (Courtesy of S.S. Long, St. Christopher's Hospital for Children, Philadelphia, PA.)

S. aureus (including CA-MRSA[101]) is the predominant etiologic agent, followed by GBS and enteric gram-negative bacilli, with increased relative importance of gram-negative bacilli and *Candida* species in nosocomial cases. Fungi,[102] *Ureaplasma urealyticum,*[103] CoNS,[104] *Neisseria gonorrhoeae,*[97] and anaerobic bacteria[105] are unusual causes.

Infants with bone infection caused by GBS usually have had an uncomplicated neonatal course and have infection of a single bone. There is a predilection for involvement of long bones on the right, particularly the right proximal humerus, which may be related to trauma during vaginal delivery.[104,106] Misdiagnosis of bone infection as trauma in these mildly ill infants is common.

The white blood cell count commonly is normal; ESR and CRP levels often are elevated.[107] In most infants, an osteolytic lesion is visible on plain radiographs 10 to 12 days after onset of symptoms (sometimes at the time of recognition).[108,109] The radionuclide bone scan result can be positive,[90] but it sometimes is less sensitive than a plain radiograph.

Neonatal osteomyelitis can cause permanent joint abnormalities or disturbance in skeletal growth due to damage to the cartilaginous growth plate, leading to chronic arthritis, decreased range of motion, limb length discrepancy, and gait abnormalities.[110] The reported incidence of permanent sequelae varies from 6% to 50%.[98,104]

Vertebral Osteomyelitis

Vertebral osteomyelitis accounts for approximately 1% to 3% of cases of osteomyelitis in children.[111,112] Boys are affected twice as often as girls.[113] Infection usually occurs as a result of hematogenous seeding of the vertebral bodies. Osteomyelitis also can result from extension of soft tissue infection or as a complication of a surgical procedure.[114]

Clinical manifestations can be indolent and nonspecific, leading to delayed diagnosis.[115] Young infants can have nonspecific signs of septicemia.[116] Symptoms in older children include back, chest, abdominal, or leg pain and loss of normal curvatures.[111,117] Rarely, children have dysphagia due to a paravertebral or retropharyngeal abscess or acute spinal cord paresis or paralysis from paraspinal compression. Fever is common, and there can be tenderness over the involved vertebrae. Neurologic deficits are found in 15% to 20% of cases.[111,113,115,118]

S. aureus is isolated in most cases.[111,113,119] In one review, *Salmonella* spp. caused 12% of cases of childhood vertebral osteomyelitis.[111] Gram-negative bacilli such as *Escherichia coli* cause vertebral osteomyelitis in adults, particularly those with a history of recent urinary tract infection or instrumentation. Vertebral osteomyelitis in intravenous drug users is commonly caused by *Pseudomonas aeruginosa* and less commonly by *S. aureus, Serratia* spp., *Klebsiella* spp., *Enterobacter* spp., or *Candida* spp.[113,120] Tuberculosis and brucellosis should be considered if symptoms and radiographs suggest chronic infection.[121,122]

Characteristic findings on plain radiographs consist of narrowing of the involved disk space, lucency of the adjacent vertebral bodies, and, eventually, reactive sclerosis of the bone with fusion of vertebral bodies.[20,111,119] Vertebral osteomyelitis is differentiated from diskitis radiographically by the minimal vertebral end plate involvement associated with diskitis. MRI is highly sensitive (96%) and specific (92%) for the diagnosis of vertebral osteomyelitis and paravertebral soft tissue extension[123,124] (Fig. 76.5).

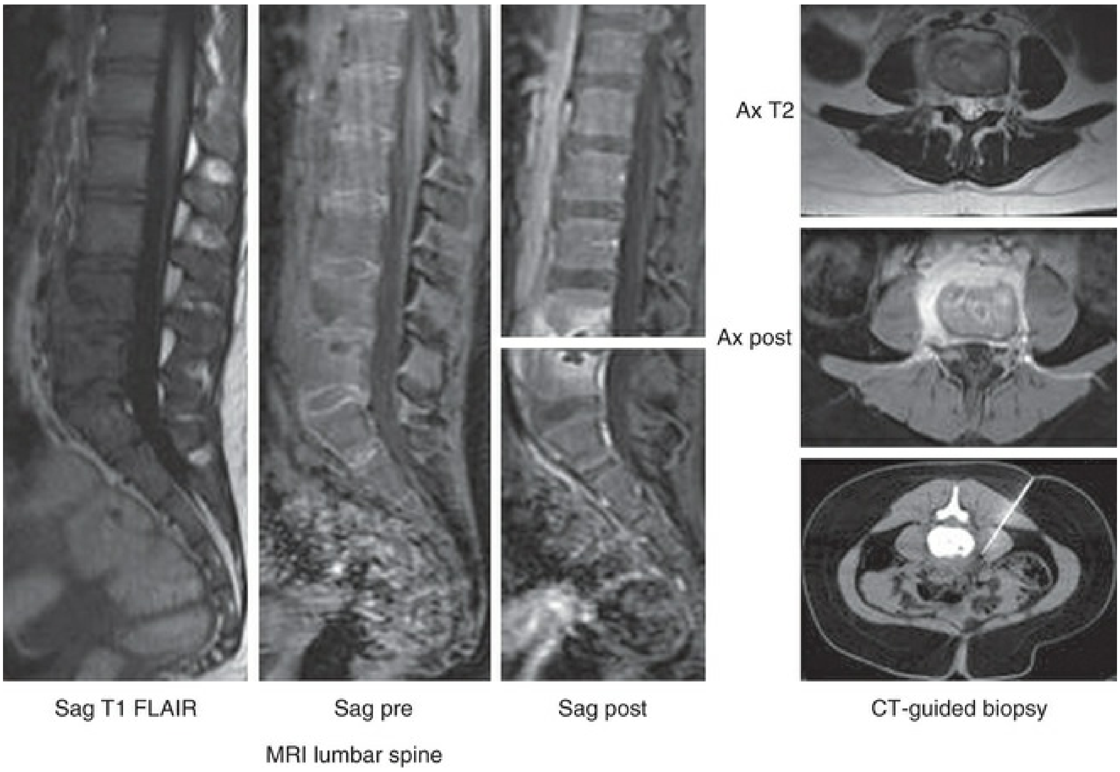

FIGURE 76.5 Sagittal and corresponding axial magnetic resonance imaging *(MRI)* of an adolescent girl who developed subacute, progressive back pain after returning from the Dominican Republic. Fluid attenuated inversion recovery *(FLAIR)* and the precontrast and postcontrast sequences show osteomyelitis of vertebral bodies lumbar 4 and 5 and a paraspinal abscess. The *lower right* image shows the computed tomography *(CT)*-guided site of aspiration, which yielded *Salmonella enterica* serotype Typhi. (Courtesy of S.S. Long and M. Mallon, St. Christopher's Hospital for Children, Philadelphia, PA.)

Blood culture results are positive in only about 30% of acute cases. When blood culture results are negative, obtaining an image-guided biopsy specimen or aspirate of bone or soft tissue phlegmon or abscess must be considered.[124]

Urgent drainage or surgical decompression and debridement are indicated for spinal epidural or paraspinal abscess, signs of spinal cord compression, or extensive bony destruction. Children with uncomplicated vertebral osteomyelitis and no evidence of abscess formation should be treated with at least 4 weeks of antibiotics.[111] In a randomized, controlled noninferiority trial enrolling 359 adults, therapy for 6 weeks was noninferior to that for 12 weeks.[125] Complications of vertebral osteomyelitis include neurologic deficits due to epidural or paravertebral abscess and infected aneurysms of the aorta.[126,128]

Pelvic Osteomyelitis

Approximately 6% to 9% of hematogenous osteomyelitis cases involve the bones of the pelvis.[38,129,130] The ilium and ischium are involved most commonly[129]; infection of the sacrum, acetabulum, or pubic symphysis is rare.[129–132] Risk factors can include a history of pelvic trauma, intravenous drug use, or a genitourinary procedure.[129,131]

Most patients with pelvic osteomyelitis have fever, gait abnormalities, and pain that is often localized to the hip, groin, or buttock.[132–135] Pain with hip movement and point tenderness over the affected bone often is observed. Clinical features can mimic those of pyogenic arthritis of the hip[129]; however, in pelvic osteomyelitis, there is more likely to be near-normal range of motion of the hip, absence of referred pain to the knee, specific point tenderness over the affected bone (or pain on rocking of the pelvic girdle), and abnormal rectal findings.[133] Responsible pathogens are similar to those that cause osteomyelitis of long bones.

Plain radiographs of the pelvis often are normal. MRI is the preferred imaging modality, and it has the additional advantage of differentiating osteomyelitis from infections of the muscles of the pelvic girdle. MRI also can identify abscesses associated with pelvic osteomyelitis, and CT can direct aspiration.[136] Aspiration, surgical drainage, or debridement should be considered in cases of extraosseous abscess formation or for patients whose symptoms do not respond to intravenous antibiotic therapy.

Patients should be treated for at least 4 weeks with antibiotics. Early transition to oral antibiotics can achieve resolution rates similar to those of prolonged intravenous antibiotics.[86,133]

Children With Sickle Hemoglobinopathies

Children with sickle cell disease have increased susceptibility to bacterial infections, including osteomyelitis.[137] The suspected pathogenesis is a primary microscopic infarction in the intestinal mucosa and bone, resulting in bacteremia and focal bone infection. Splenic hypofunction, impaired opsonization, impaired macrophage function, altered expression of proinflammatory and anti-inflammatory cytokines, microembolism, and tissue infarction are likely contributing factors in the development of osteomyelitis.[138,139]

Salmonella spp. and other gram-negative enteric bacilli were the cause of more than 70% of cases of osteomyelitis in children with hemoglobinopathies in past decades.[140–143] *S. aureus* currently is the dominant cause. Other organisms causing osteomyelitis in children with sickle hemoglobinopathies are listed in Box 76.1.

Box 76.1

Bacterial Causes of Osteomyelitis in Children With Sickle Cell Disease

Common

Staphylococcus aureus

Salmonella spp.

Less Common

Escherichia coli

Haemophilus influenzae

Shigella spp.

Streptococcus pneumoniae

Distinctive features of osteomyelitis in children with sickle cell disease are frequent involvement of the diaphyses of long bones, flat bones, and small bones of the hands and feet and multifocal, symmetric bone involvement.[144,145] Manifestations of osteomyelitis are difficult to differentiate from those of acute vaso-occlusive crisis. Fever, bone pain, and leukocytosis are common in both conditions. A temperature above 39°C, a toxic appearance, and an absolute band count greater than 500 cells/mm^3 are more consistent with infection, but there is considerable overlap in clinical and laboratory findings.[143]

Plain radiography, technetium scanning, CT, and MRI cannot differentiate infarction from infection.[145,146] If fever and bone pain have not improved after supportive care has been given for vaso-occlusive crisis, imaging-guided aspiration of the affected area of bone for Gram stain and culture should be performed.

Six to eight weeks of antibiotic therapy may be necessary for treatment of osteomyelitis in patients with sickle hemoglobinopathy because of the usual mixed infarction and infection. Oral therapy can be substituted for parenteral treatment when a pathogen has been confirmed, an appropriate oral agent is identified, and there is clinical improvement. Relapses, especially when due to *Salmonella*, can occur.[143,144]

Osteomyelitis Due to Unusual Organisms

Fungal Osteomyelitis

Fungal osteomyelitis, most frequently is caused by *Candida* spp. and is unusual in healthy children, but it does occur in prematurely born neonates (usually is a complication of device-associated infection), immunocompromised patients, and intravenous drug users.[102,47,148] *Aspergillus* spp. cause osteomyelitis in children with chronic granulomatous disease, often resulting from contiguous spread of pulmonary infection.[149] *Blastomyces dermatitidis, Coccidioides immitis, Histoplasma capsulatum,* and *Cryptococcus neoformans* cause osteomyelitis in indigenous geographic regions and in immunosuppressed hosts.[150–152]

Tuberculous Osteomyelitis

Skeletal lesions occur in approximately 1% of children with tuberculosis.[121,153] Bones and joints are infected through hematogenous or lymphatic dissemination of *Mycobacterium tuberculosis.* Infection can smolder for years before clinical signs are apparent. The most commonly involved bones are the vertebrae (i.e., tuberculous spondylitis), femur, long bones around knees and ankles, and small bones of the hands and feet.[154] Less frequently infected sites are the ribs, mandible, sternum, clavicle, and other long bones. Multifocal osteomyelitis is reported in 10% to 15% of cases.[155,156]

Clinical signs and symptoms of skeletal tuberculosis include low-grade fever, weight loss, pain, and soft tissue swelling at the site of infection. Vertebral involvement begins in the anterior vertebral body, eventually causing disk space collapse and anterior wedging of vertebral bodies, sometimes causing a gibbus deformity. The lower thoracic spine is the usual site of involvement (i.e., Pott disease), followed by the lumbar spine.

The Mantoux tuberculin skin reaction usually is positive. The role of interferon γ release assays in the diagnosis of Pott disease is being evaluated. Plain radiographic findings include periarticular osteopenia, lytic lesions in the body of the vertebra, joint space narrowing, and soft tissue swelling.[157] The chest radiograph often is normal. CT is useful for the evaluation of bone destruction, adjacent soft tissue abscess formation, and calcification and in guiding percutaneous biopsy.[158] MRI is helpful in determining the extent of bone and soft tissue disease.[159] Biopsy specimens should be obtained to demonstrate the organism with stains and culture.

Antituberculous therapy includes 2 months of therapy with four drugs, followed by 7 to 10 months of isoniazid and rifampin (for susceptible organisms) daily or twice weekly (see Chapter 134).[160] Surgical intervention is indicated in cases of spinal instability and neurologic impairment due to paravertebral abscess formation and for drainage of soft tissue abscesses. Nontuberculous *Mycobacterium* spp. infrequently cause osteomyelitis in immunocompromised individuals.

Anaerobic Bacterial Osteomyelitis

Anaerobic bacteria are associated with chronic and nonhematogenously acquired osteomyelitis.[161–163] Risk factors include surgery, trauma, diabetes mellitus, human bites, chronic otitis media or sinusitis, dental infection, fibrous dysplasia of bone, a prosthesis, and decubitus ulcers (Fig. 76.6). Children are more likely than adults to experience anaerobic osteomyelitis of the skull and facial bones.[161] Osteomyelitis of ribs follows contiguous spread from aspiration lung infection; *Actinomyces* spp. are the primary pathogens. Soft tissue swelling or abscess can be the presenting abnormality. Similarly, *Actinomyces* spp. can cause osteomyelitis of the maxilla or mandible, frequently without dental pathology.

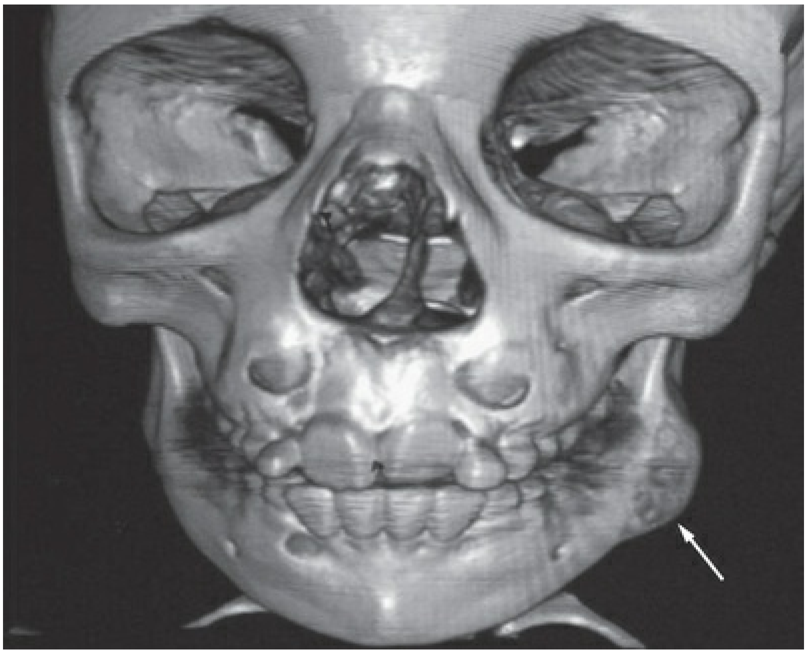

FIGURE 76.6 Actinomycosis of the mandible in a 9-year-old girl with history of painless expansion of the jaw over several months. Reconstructed spiral computed tomography shows expansion of bone with complex lytic and sclerotic mass *(arrow)*. Surgical biopsy confirmed *Actinomyces* osteomyelitis and fibrous dysplasia of bone. (Courtesy of L. Kaban and M. Pasternack, Massachusetts General Hospital, Boston, MA, and S.S. Long, St. Christopher's Hospital for Children, Philadelphia, PA.)

Infection usually is polymicrobial. Gram-positive cocci, *Bacteroides* spp., *Prevotella* spp., and *Fusobacterium* spp. are the most common anaerobes, and *S. aureus* is the most commonly associated aerobic isolate.[162]

Therapy consists of treatment of underlying conditions, surgical debridement of necrotic bone, and appropriate antibiotic therapy. Examples of effective antibiotics are clindamycin, metronidazole, imipenem, and amoxicillin-clavulanate. Many anaerobic isolates, including *Actinomyces*, are susceptible to penicillin. The choice of antibiotic depends on the specific organisms isolated and their potential for β-lactamase production. Therapy is protracted, frequently exceeding 1 year of oral penicillin or amoxicillin plus probenecid for actinomycosis.

Nonhematogenous Osteomyelitis

Contiguous Infection

Factors associated with the development of nonhematogenous osteomyelitis include open fractures requiring surgical reduction,[154,164] implanted orthopedic devices, decubitus ulcers, and neuropathic ulcers.[165,166] Facial osteomyelitis usually is caused by untreated mastoiditis, sinusitis, or periodontal abscess.[161,167] Osteomyelitis can occur after local soft tissue infection or direct inoculation of bone from human and animal bites.[168,169] Puncture wounds can lead to osteomyelitis of the foot (e.g., stepping on a nail or toothpick[170]) or the patella (e.g., kneeling on a needle).

Indolent presentation is common among children with nonhematogenous osteomyelitis. Fever occurs in less than one half of patients.[171] Persistent drainage or ulceration of the soft tissue over the affected bone is typical. A plain radiograph shows bony destruction. The peripheral white blood cell count often is normal, and ESR and CRP levels also can be normal.

Nonhematogenous osteomyelitis often is caused by *S. aureus,* although coinfection with gram-negative and anaerobic organisms occurs.[162] Examination of specimens from an associated sinus tract is unreliable in defining the cause of osteomyelitis.[172] Biopsy with culture of the affected bone is the best method of determining appropriate antibiotic therapy. Therapy should be prolonged if infection is chronic, sometimes with parenteral therapy followed by oral therapy for a total of 4 to 6 months.

The rate of recurrence of nonhematogenous osteomyelitis is as high as 40%, even with prolonged courses of antibiotic therapy.[171] Aggressive surgical debridement or other interventions are required in addition to antibiotic therapy. Implanted devices commonly must be removed for cure. Debridement followed by a muscle flap procedure to re-establish the blood supply in decubitus ulcer–associated osteomyelitis frequently is beneficial.[173]

Puncture Wound Osteochondritis of the Foot

Bacterial osteochondritis is a complication of puncture wounds of the foot, occurring in approximately 1.5% of these injuries.[174–176] Symptoms of osteochondritis, which appear several days to weeks after the initial injury, include increasing tenderness, erythema, and swelling at the site of the puncture.

Infection usually is caused by *Pseudomonas aeruginosa*,[177] often as a result of inoculation from the colonized moist soles of tennis shoes.[127] *S. aureus* is the usual pathogen if symptoms began within 3 to 5 days of injury. Obtaining specimens from bone for microbiologic diagnosis is desirable.

Empiric antibiotic therapy should cover *P. aeruginosa* and *S. aureus.* Ticarcillin-clavulanate, piperacillin-tazobactam, ceftazidime, or cefepime, with or without an aminoglycoside, is appropriate empiric therapy if MRSA is unlikely. Treatment with oral ciprofloxacin in conjunction with surgical debridement also is effective.[178] With appropriate surgical debridement, short-duration (7 to 10 days) antibiotic therapy has been effective for *P. aeruginosa*, as has 3 to 4 weeks of antibiotic therapy without debridement.[174–178]

Chronic Recurrent Multifocal Osteomyelitis

Chronic, recurrent, multifocal osteomyelitis (CRMO) is an inflammatory disease of children and young adults characterized by recurring episodes of low-grade fever, swelling, and pain over affected bones and with radiologic abnormalities suggesting osteomyelitis[179–181] Females are more frequently affected than males.[182] The median age of onset of illness is 10 years. CRMO sometimes is associated with palmoplantar pustulosis,[183] psoriasis, arthritis, sacroiliitis, inflammatory bowel disease,[184] and Sweet syndrome.

Radiographic abnormalities occur most commonly in the metaphysis of long bones (characterized by radiolucent bone lesions with reactive sclerosis) and show soft tissue swelling.[182,185,186] The sternal end of the clavicle, the vertebral bodies, and the smaller bones of the hands and feet often are involved. Radiographic changes are similar to those seen in acute osteomyelitis, but multiple, often symmetric lesions occur in CRMO. Bone scans and MRI are useful in determining the extent and evolution of disease.[185,187,188] An infectious cause of CRMO has not been determined; the condition may be an autoinflammatory condition.

The course of CRMO consists of prolonged bone pain with remissions and relapses over several years; the mean duration of disease is 6 years.[189] In a long-term follow-up study of 23 patients with CRMO, 26% had active disease at a median of 13 years after diagnosis.[184] Although the clinical outcome for most patients is good, approximately 20% of patients have a prolonged and severe course. Young age at onset and multiple sites of involvement predict a less favorable outcome.[190] Treatment with a variety of antibiotics has had no apparent effect on the course or outcome. Some experts have advocated the use of corticosteroids or nonsteroidal anti-inflammatory agents for relief of symptoms.[182,186] Other therapies have included colchicine, interferon γ, interferon α, and infliximab.[184,190,191]

Because multifocal bone lesions in childhood can occur with neuroblastoma, histiocytosis, leukemia, and staphylococcal osteomyelitis, histologic examination and culture of bone specimens should be performed. Histologic findings in CRMO cases show nonspecific acute and chronic inflammatory changes. In the chronic phase of the disease, granulomatous changes can be seen.[192]

Chronic Osteomyelitis

Chronic osteomyelitis develops in less than 5% of cases of AHO.[193] More often, it complicates nonhematogenous osteomyelitis.[171]

Chronic osteomyelitis is characterized by alternating periods of quiescence and recurrence of pain, swelling, and sinus tract drainage. It can persist for years despite prolonged antibiotic therapy. Infections often are polymicrobial, and with skeletal growth, the original metaphyseal infection moves to become a lytic lesion in the diaphysis.[163,173]

Surgical debridement of necrotic bone is the primary management. Alternative therapeutic approaches include the use of antibiotic-impregnated polymethyl methacrylate beads,[194,195] local antibiotic delivery by implantable pumps,[196] and suction vacuum devices or bone grafts, skin grafts, and muscle flaps to eliminate dead space and improve vascularity.[197]

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77

Infectious and Inflammatory Arthritis

David K. Hong, Kathleen Gutierrez

Infectious arthritis in children can be caused by bacteria, viruses, or fungi. Pyogenic arthritis is characterized by a purulent inflammatory response, usually caused by a bacterial infection. Reactive (inflammatory) arthritis is inflammation of one or more joints that can result from a response to infection elsewhere in the body or from a systemic inflammatory or autoimmune disorder.

Infectious Arthritis

Pyogenic Arthritis

Epidemiology

The incidence of pyogenic (bacterial) arthritis is less than that of transient synovitis and varies substantially (i.e., 1 to 37 cases per 100,000 children) depending on the population studied.[1,2] Although pyogenic arthritis occurs in all age groups, the peak incidence of disease is in children younger than 3 years of age.[3–5]

A history of trauma temporally related to the onset of arthritis caused by *Staphylococcus aureus* is common.[6,7] Upper respiratory tract infection frequently precedes pyogenic arthritis caused by *Haemophilus influenzae* type b (Hib) and *Kingella kingae.*[6,8,9] Gastroenteritis and aphthous stomatitis also can precede arthritis caused by *K. kingae.*[10] Although most children have no underlying disorder, risk factors for pyogenic arthritis include immunodeficiency, hemoglobinopathy, diabetes, intravenous drug abuse, and rheumatoid arthritis.[11–13]

Pathophysiology

Most cases of pyogenic arthritis in childhood follow the hematogenous spread of organisms to the vascular synovium of the joint space.[14] Animal models of Hib bacterial arthritis illustrate possible mechanisms of articular damage.[15] Bacterial endotoxin in the joint space stimulates release of tumor necrosis factor and interleukin-1.[16,17] These cytokines stimulate production of proteinases by synovial cells and chondrocytes, enhancing leukocyte migration. Neutrophil elastases augment destruction of cartilage matrix in the joint.[16–19]

Bacteria can spread to joints from contiguous osteomyelitis.[20] The transphyseal blood vessels in the child younger than 18 months facilitates spread of infection from the metaphysis across the growth plate to the epiphysis and adjacent joint space.[21] The joint capsule of the hip and shoulder overlies the bony metaphysis of the femur and humerus, allowing direct extension of bone infection into these joint spaces. Primary pyogenic arthritis infrequently extends into the bone to cause a secondary osteomyelitis except from hip and shoulder joints, in the neonate, or associated with *Kingella* infection. Joints also can be infected from penetrating wounds, intra-articular injections of medications, arthroscopy, and prosthetic joint surgery.[22]

Etiology

Age is the most important predictor of the cause of pyogenic arthritis.[5,6,23–26] *S. aureus,* enteric gram-negative organisms, and group B *Streptococcus* (GBS) are the most frequent causes of pyogenic arthritis among neonates. Methicillin-susceptible *S. aureus* (MSSA), community-associated methicillin-resistant *S. aureus* (CA-MRSA), *K. kingae, Streptococcus pyogenes,* and *Streptococcus* *pneumoniae* cause pyogenic arthritis in children younger than 5 years of age. In one series, *K. kingae* was the most common cause of pyogenic arthritis in children younger than 36 months.[23] *K. kingae* is being reported with increasing frequency as a cause of pyogenic arthritis in the United States.[27–30] Hib infection has become rare among immunized immunocompetent children.[31–33]

Although *S. pneumoniae* caused approximately 6% of cases of pyogenic arthritis before universal pneumococcal conjugate vaccination,[34] cases of invasive disease due to vaccine serotypes have decreased dramatically.[35,36] *S. aureus* and *S. pyogenes* are the most common causes of pyogenic arthritis in children older than 5 years. CA-MRSA osteoarticular infections are common,[37] are more aggressive than MSSA infections involving multiple bones and joints[38] and sometimes are associated with venous thrombosis and pulmonary disease.[37,39]

Other organisms reported to cause pyogenic arthritis in children after *K. kingae*,[40] include *Salmonella* spp.,[41,42] β-hemolytic streptococci other than serogroups A or B,[43] and rarely, anaerobic bacteria.[44,45]

Joint infections caused by *Pseudomonas aeruginosa* and *Candida* spp. are reported for intravenous drug abusers.[12] *Brucella* spp. infection should be considered if a history of travel to endemic areas, contact with livestock, or consumption of unpasteurized dairy products is elicted.[46,47] Arthritis related to *Bartonella henselae* infection has been reported.[48]

Clinical Manifestations

Fever, malaise, poor appetite, and irritability are heralding systemic symptoms. Pain in the affected joint usually occurs early in the course of the illness. As infection progresses, the joint becomes swollen and the overlying skin red. Limp or refusal to walk occurs with infection of a lower extremity. If the affected joint is in the upper extremity, pseudoparalysis or refusal to use the affected joint is seen, and manipulation causes pain. The infected joint is swollen, red, warm, and tender on palpation. The range of joint motion is decreased.

The joints of the lower extremities, especially the knees, are the most common sites of pyogenic arthritis[5,8] (Table 77.1). More than 90% of cases of pyogenic arthritis are monoarticular.[5,25] However, multiple joints can be involved, particularly with infections caused by *Neisseria gonorrhoeae, N. meningitidis,* and *Salmonella* spp.

TABLE 77.1

Frequency of Joint Involvement in 1050 Children With Pyogenic Arthritis

Anatomic Site	No. of Patients	Percentage (%) of Patients
Knee	467	41
Hip	287	25
Ankle	143	13
Elbow	116	10
Shoulder	53	5
Other[a]	70	6
Total[b]	1136	100

[a] Includes the sacroiliac joint, joints of hands and feet, and the sternoclavicular joint.

[b] Some children had more than one joint affected.

Data from references 4, 5, 7, 8, 96, and 98.

The diagnosis of pyogenic arthritis of the hip can be difficult because there is often no obvious joint swelling, and signs and symptoms are nonspecific, especially in infants and young children. Infants with pyogenic arthritis of the hip are irritable when the hip is moved (e.g., during diaper changes). Soft tissue swelling around the hip joint occasionally occurs and can extend to involve the entire leg.[49] The affected hip often is held in a flexed, externally rotated and abducted position.[50] Older children with pyogenic arthritis of the hip limp or refuse to walk and complain of pain, which sometimes is referred to the knee.[51] Range of motion of the hip joint is decreased markedly.

Diagnosis

The erythrocyte sedimentation rate (ESR) is more than 20 mm/hr (mean, 44 to 65 mm/hr) for most patients with pyogenic arthritis.[52,53] Similarly, the level of C-reactive protein (CRP) often is increased (mean, 8.5 mg/dL).[53,54] A normal CRP level is a good negative predictor for pyogenic arthritis. In one study, the probability that the patient did not have pyogenic arthritis was 87% if the CRP was less than 1.0 mg/dL.[55]

Excellent sensitivity for the diagnosis of osteoarticular infections is obtained by using both the ESR and CRP.[54] However, children with pyogenic arthritis caused by *K. kingae* can lack fever or elevation of inflammatory markers, or both.[56]

Analysis of joint fluid helps to differentiate bacterial from other causes of arthritis (Table 77.2). Joint fluid in bacterial arthritis typically has a cloudy appearance. A leukocyte count of >50,000 cells/mm^3 with a predominance of neutrophils strongly suggests bacterial infection, even if the culture result for the joint fluid is negative.[57,58] However, synovial fluid white blood cell (WBC) counts of <50,000/mm^3 can occur in cases of bacterial arthritis, particularly when infection is caused by *K. kingae*.[10,25,40,50,56] Fluid WBC counts of >50,000/mm^3 with neutrophil predominance can occur in children with juvenile idiopathic arthritis or Lyme disease.[59,60] Synovial fluid glucose and protein levels do not differentiate reliably among most infectious and inflammatory processes and therefore have limited value.[61]

TABLE 77.2

Characteristic Synovial Fluid Findings

Diagnosis	WBCs/mm^3 (Typical)	WBCs/mm^3 (Range)	% PMNs (Typical)
Normal	<150	—	<25
Bacterial arthritis	>50,000	2000–300,000	>90
Tuberculous arthritis	10,000–20,000	40–136,000	>50 (range, 10–99)
Lyme arthritis	40,000–80,000	180–140,000	>75
Candidal arthritis	—	7500–150,000	>90
Viral arthritis	15,000	3000–50,000	<50 (variable)
Reiter syndrome	15,000	10,000–22,000	>70 (range, 37–98)
Rheumatoid arthritis	—	2000–50,000	>70
Rheumatic fever	25,000	2000–50,000	>70

PMNs, polymorphonuclear cells; WBCs, white blood cells.

Data from references 57, 59, 60, 144, 148, and 176.

Blood culture should be obtained and synovial fluid sent for Gram stain, culture, and WBC count. Isolation of *K. kingae* is enhanced when synovial fluid is inoculated directly into fluid blood culture medium.[28] Use of real-time polymerase chain reaction (rt-PCR) testing increases the identification of *K. kingae* in culture-negative joint fluid.[62] Similarly, serologic testing and occasional detection of *Borrelia burgdorferi* by PCR in joint fluid aid diagnosis of Lyme arthritis.[63]

For adolescents, specimens should be obtained from the cervix or urethra, throat, skin lesions, and rectum for isolation of *N. gonorrhoeae.* Alternatively, nucleic acid testing of urine is performed.

When appropriate cultures are obtained, the bacterial cause is confirmed in 60% to 70% of cases of pyogenic arthritis.[5,25] Blood cultures are positive in 40%[4,22] of cases, and joint fluid culture is positive in 50% to 60%.[4,5,8,25]

Imaging Studies

Children with suspected pyogenic arthritis should have plain radiographic studies to exclude osteomyelitis or other osseous abnormalities. Soft tissue swelling and widening of the joint can be observed in children with pyogenic arthritis. Erosion of subchondral bone may be evident 2 to 4 weeks after onset of infection.[64]

Swelling of the hip capsule and lateral displacement or obliteration of the gluteal fat planes are early radiographic findings for pyogenic arthritis of the hip.[64] With continued swelling of the hip capsule, the femoral head is displaced upward and outward, and lateral subluxation can occur. Concomitant osteomyelitis of the femur may occur.[50] These findings are particularly common in infants, although in this age group, radiographic findings are difficult to interpret because of minimal ossification of the proximal femur. A plain radiograph sometimes is normal for children with proven pyogenic arthritis of the hip.[65]

Ultrasonography (US) should be performed in suspected pyogenic arthritis of the hip. If fluid is detected in the joint, a diagnostic aspiration should be performed under US guidance.[66,67] False-negative US results reported for children subsequently diagnosed with pyogenic arthritis are related to inadequate imaging or imaging performed very early (<24 hours) after the onset of symptoms.[68]

Although technetium phosphate radionuclide scanning typically is not used in the diagnosis of pyogenic arthritis, a scan can be valuable in evaluating involvement of deep joints such as the hip or sacroiliac joint. A characteristic finding is increased activity in the early (blood pool) phase and increased bony uptake on both sides of the joint (which is uncharacteristic in osteomyelitis). Similarly, computed tomography (CT) may be helpful in the diagnosis of arthritis in areas of complex anatomy, such as the shoulder, hip, and sacroiliac joint.

Magnetic resonance imaging (MRI) is highly sensitive for the early detection of inflamed or infected joints.[69] Abnormal MRI findings in pyogenic arthritis include periarticular high-intensity signal and periarticular abscesses in some cases.[70] MRI can delineate abnormalities of adjacent bone and soft tissue and the extent of cartilage destruction. Compared with patients with transient synovitis, those with pyogenic arthritis are more likely to have MRI findings of high-intensity signals in the bone marrow[71] and decreased signal in the femoral epiphysis on fat-suppressed, gadolinium-enhanced, T1-weighted images.[72]

Treatment

Children with pyogenic arthritis should be managed in conjunction with an orthopedic surgeon experienced in treating children. Goals of therapy include decompression, sterilization of the joint space, and removal of inflammatory debris.

All children with pyogenic arthritis of the hip require prompt surgical drainage and irrigation of the joint space.[73–75] Delay in drainage increases the likelihood of permanent damage because increased intra-articular pressure can compromise blood supply, resulting in avascular necrosis of the femoral head. Muscle spasms also can occur, predisposing the patient to dislocation. Open surgical drainage of joints other than the hip usually is not required. However, aspiration must be performed promptly to decompress the joint and obtain synovial fluid for analysis. Repeated aspirations often are necessary when fluid reaccumulates. Concurrent osteomyelitis can be associated with the need for repeated debridement of the joint.[76] Debridement by arthroscopy has been undertaken in some cases of pyogenic arthritis of the knee and hip.[77,78]

The initial choice of antibiotics is based on age, clinical history, and physical examination of the patient. Adequate penetration into the joint is essential. Penicillin, ampicillin, nafcillin, methicillin, dicloxacillin, some first- and third-generation cephalosporins, clindamycin, vancomycin, and aminoglycosides attain acceptable concentrations in joints after intravenous or intramuscular administration. Agents that are well absorbed from the gastrointestinal tract attain adequate joint space concentrations after oral administration.[24,79–83] Because antibiotics achieve high synovial fluid-to-serum ratios, there is no role for intra-articular instillation of antibiotics, which can produce chemical irritation and inflammation.

Parenterally administered therapy is used initially (Table 77.3). Antistaphylococcal therapy should be given for a child of any age. Infants younger than 3 months of age should be treated with antibiotics active against *S. aureus*, gram-negative enteric organisms, and GBS. Children 3 months to 5 years of age should receive empiric therapy for *S. aureus, K. kingae, S. pneumoniae,* and *S. pyogenes.* Although Hib infection is uncommon in immunized children, other serotypes of *Haemophilus* occasionally cause pyogenic arthritis.[84] Children older than 5 years are treated for the most likely pathogens, *S. aureus* and streptococci. Empiric therapy for *N. gonorrhoeae* is indicated for the sexually active adolescent.[85]

TABLE 77.3

Empiric Antibiotic Therapy for Pyogenic Arthritis in Children

Age	Likely Pathogens	Antibiotic	Dosage[g]	
			mg/kg per day	Divided Doses/Day
Neonate (doses are for infants >2000 g and >7 days old with normal serum creatinine levels)	*Staphylococcus aureus*[a] Group B *Streptococcus* Gram-negative bacilli	Nafcillin	100	4
		or		
		Vancomycin	30	2
		or		
		Clindamycin	20	4
		plus		
		Cefotaxime	150	3
		or		
		Gentamicin	4	1
Child ≤5 yr	*S. aureus*[a] *Haemophilus influenzae*[b] *Kingella kingae*[c] *Streptococcus pyogenes* *Streptococcus pneumoniae*	Nafcillin	150	4
		or		
		Vancomycin	45–60	3
		or		
		Clindamycin[d]	30–40	3
		plus		
		Cefotaxime	150	3
		or		
		Cefuroxime	150	3
		or		
Child >5 yr	*S. aureus*[a] *Streptococcus pyogenes*	Nafcillin	150	4
		or		
		Vancomycin	45–60	3
		or		
		Clindamycin[d]	30–40	3
Adolescent (sexually active)	*Neisseria*	Ceftriaxone[e,f]	50	1

	gonorrhoeae (consider)			

[a] If more than 10% of community-acquired isolates are methicillin-resistant *Staphylococcus aureus*, consider empiric therapy with vancomycin or clindamycin until culture and susceptibility results are available. If infection is confirmed to be caused by MRSA, see Clinical Practice Guidelines by the Infectious Diseases Society of America for treatment of MRSA infections in adults and children for specific dosing recommendations.[87]

[b] Children who have been completely immunized are less likely to have *Haemophilus influenzae* type b infection.

[c] If empiric therapy with vancomycin or clindamycin is used, consider adding ampicillin-sulbactam, a second- or third-generation cephalosporin for *Kingella kingae* coverage in patients younger than 36 months of age.

[d] Maximum oral dose of clindamycin is 1.8 g/day; the adult dose is 600 mg/dose PO or IV given every 8 hours.

[e] The maximum dose of ceftriaxone 1 g/day, given in a single dose.

[f] The addition of azithromycin (1 g) is recommended for adults with gonococcal arthritis. No data exist for children.

[g] Not to exceed adult dosing.

Empiric therapy with vancomycin or clindamycin is indicated when CA-MRSA isolates exceed 10%.[86] Resistance to clindamycin may preclude its use as empiric therapy in many communities. Most *S. pyogenes* and *S. pneumoniae* isolates are susceptible to vancomycin and clindamycin, although susceptibility testing should be performed for both organisms. Neither drug is effective in treating infection caused by *K. kingae.* Most β-lactam antibiotics, including ampicillin, ampicillin-sulbactam, and second- and third-generation cephalosporins, have activity against *K. kingae.*[26]

Nafcillin, oxacillin, and a first-generation cephalosporin remain the drugs of choice if MSSA is isolated. Choices of antibiotics for MRSA infections in children are limited. Vancomycin is effective, but no absorbable oral formulation exists. If MRSA is susceptible to clindamycin (including no inducible resistance), clindamycin is an excellent choice as an oral agent. Linezolid and daptomycin have been used in some patients with serious MRSA infection, although data regarding daptomycin use in children are limited. Linezolid has excellent oral bioavailability, but thrombocytopenia, anemia, and leukopenia can occur after 2 or 3 weeks; and lactic acidosis has been reported. Longer-term use is associated with peripheral and optic neuropathy. Linezolid is a weak, reversible monoamine oxidase inhibitor, and serotonin syndrome has occurred in children who also are receiving a serotonin-receptor inhibitor. The Infectious Diseases Society of America has published guidelines for the management of MRSA infections.[87]

Specific therapy based on culture results and susceptibility testing is continued parenterally until the child is afebrile; joint pain, swelling, and erythema have decreased; and joint mobility has increased. Markers of the acute phase response should decrease. Because the CRP level normalizes more quickly when infection is controlled than the ESR (which typically is elevated for up to 2 weeks), CRP is used to monitor the early response to therapy.[54] Open drainage of any joint (with lysis and irrigation of loculated collections) should be undertaken when aspirations yield samples that are persistently positive on culture.

Orally administered antibiotic therapy can be substituted for parenteral treatment after adequate control of infection and inflammation has been achieved if an oral antibiotic with appropriate coverage is available and if adherence and careful monitoring can be ensured[83,88–91] (Table 77.4). Use of clinical practice guidelines have been successful in decreasing the number of days of parenteral antibiotics and duration of hospitalization without increasing complications or sequelae.[92]

TABLE 77.4

Oral Antibiotic Therapy for Pyogenic Arthritis[a]

Agent	Dosage[b]	
	mg/kg per day	Divided Doses/Day
Dicloxacillin	75–100	4
Cephalexin	100	3–4
Clindamycin	30–40	3

[a] Doses can be modified depending on results of serum bactericidal levels. The oral dose of β-lactam antibiotics used for osteoarticular infections is two to three times the usual dose.

[b] Not to exceed adult dosing.

For children in whom oral therapy is not feasible, outpatient parenteral antibiotic therapy administered through a tunneled central venous catheter or a peripherally inserted central catheter has been successful. Catheter-related mechanical and infectious complications can occur with prolonged intravenous administration of antibiotics, and the risk versus benefit of prolonged central venous access should be considered carefully.[93]

Duration of antimicrobial therapy remains a subject of considerable debate. Duration usually is determined by the specific pathogen, clinical and laboratory response, and whether adjacent osteomyelitis exists. Joint infections caused by *S. aureus* and gram-negative enteric organisms usually are treated for at least 3 to 4 weeks. Arthritis caused by *H. influenzae, S. pneumoniae, S. pyogenes,* and *K. kingae* is treated for 2 to 3 weeks, depending on the clinical response. Therapy for less than 2 weeks for children in Finland with culture-positive arthritis was successful in most cases.[90] None of the children in this study had MRSA infection, and several children with hip infections required longer courses of treatment. A larger, controlled, prospective study is necessary to better evaluate the adequacy of short-course antibiotic therapy.[94]

Prognosis

Sequelae of pyogenic arthritis in children include abnormalities of bone growth, limitation of joint mobility, unstable articulation, and chronic dislocation of the joint. Joint dysfunction may not become apparent for months to years after infection.[95] An estimated 10% to 25% of children with pyogenic arthritis have residual dysfunction.[5,95]

Several risk factors for the development of sequelae have been identified, including age younger than 6 months[3–8]; infection of the adjacent bone, which is evident in 10% to 16% of children with pyogenic arthritis and increases the likelihood of sequelae to approximately 50%[5,39,74,96,97]; infection of the hip or shoulder[5,95,98]; a delay of 4 days or more before decompression and antibiotic therapy[13,50,99–101]; and prolonged time to sterilization of synovial fluid.[102] Staphylococcal and gram-negative bacillary infections carry a high risk of sequelae, whereas meningococcal and gonococcal infections carry a low risk.

Special Situations and Pathogens

Neonatal Arthritis

Risk factors for pyogenic arthritis in the neonate include umbilical vessel catheterization, insertion of a central venous catheter,[103] femoral vessel blood sampling,[49,104,105] and possibly fetal breech presentation.[106] Pyogenic arthritis often is a complication of osteomyelitis, and the onset may be insidious (see Chapter 92). The hip and knee are the most frequently involved joints.[104]

S. aureus, N. gonorrhoeae, and *Candida* spp. frequently cause polyarticular infection. If infection is contracted in the hospital, MRSA and MSSA, enteric gram-negative organisms, and *Candida* spp. are common causes. GBS, *S. aureus,* and *N. gonorrhoeae* are the pathogens most commonly isolated from neonates who develop joint infections after hospital discharge.[107]

Gonococcal Arthritis

Arthritis caused by *N. gonorrhoeae* must be considered in sexually active adolescents.[85] The incidence of disseminated gonococcal infection in people with urethritis or cervicitis is approximately 1%.[108] Disseminated gonococcal infection is characterized by mild fever, polyarthralgia, rash, tenosynovitis, and suppurative arthritis, and it is more common in girls, often during menstruation. Suppurative arthritis most often involves the knee. The hand, wrist, ankle, elbow, and foot are involved less often, and infection of the shoulder or hip is uncommon.[109] Skin lesions occur in approximately 40% of patients. Lesions typically are few in number and represent vasculitis. Lesions occur most frequently on extremities or over affected joints, are papular with a hemorrhagic component, and evolve into vesiculopustular lesions on an erythematous base.[110] Other skin lesions, including bullae and purpura, have been described.[13]

Culture of joint fluid is positive in only 25% to 35% of cases. Cultures of skin lesions and blood, cervical, urethral, rectal, vaginal, or throat specimens may be positive when culture of the joint fluid is negative. Cultures obtained from normally sterile sites should be inoculated onto chocolate agar. Cultures from nonsterile sites should be inoculated immediately onto Thayer-Martin agar and incubated in carbon dioxide. *N. gonorrhoeae* also can be detected by PCR or other DNA amplification tests on first-voided urine specimens and urethral and cervicovaginal swab samples.

Because of the increasing prevalence of penicillin-resistant *N. gonorrhoeae,* 7 days of treatment with a parenterally administered third-generation cephalosporin, such as ceftriaxone or cefotaxime, is recommended.[108,109,111] The addition of azithromycin is recommended for adults with gonococcal arthritis, but there are no data on dual therapy for children.[111] Marked improvement in fever and joint pain usually occurs 1 to 2 days after beginning therapy. Sequelae are rare.

Polyarthritis, Fever, and Rash

Bacterial causes of the clinical syndrome of fever, polyarthritis, and rash include infection with *N. meningitidis* and *N. gonorrhoeae,* rat-bite fever (i.e., *Streptobacillus moniliformis* or *Spirillum minus),* bacterial endocarditis, and rheumatic fever[112]; multiple viruses also are considered (discussed later). Noninfectious causes include Kawasaki disease, serum sickness, erythema multiforme, and other autoinflammatory and autoimmune diseases.

Lyme Arthritis

Arthralgia occurs early in the course of Lyme disease and is recurrent in 18% of individuals. Approximately one half of patients with Lyme disease have arthritis,[113] with a typical onset 1 to 2 months after erythema migrans with sudden onset of monoarticular or oligoarticular joint pain. Joints involved, in descending order of frequency, include the knee, shoulder, elbow, temporomandibular joint, ankle, and wrist. Involvement of the hip or small joints is unusual.[60] In a Lyme endemic area, however, 5.2% of children evaluated in an emergency department because of acute hip pain who had serology performed had Lyme arthritis; symptoms and test results frequently were similar to transient synovitis.[114]

Patients characteristically are not ill, although about half have fever. Affected joints are warm and swollen and have large effusions, but motion typically is not severely limited. The peripheral white blood cell count often is normal, but the ESR and CRP levels usually are modestly elevated.[115] Synovial fluid leukocyte counts range from 180 to 140,000 cells/mm^3, and polymorphonuclear cells predominate.[60] *B. burgdorferi* DNA has been detected by PCR of synovial fluid of patients with Lyme arthritis. Testing of serum for antibodies usually can confirm the diagnosis.[63] Patients with Lyme arthritis are more likely to have MRI findings of myositis, lymphadenopathy, and lack of subcutaneous edema compared with children with pyogenic arthritis.[116]

Lyme arthritis is treated with amoxicillin or doxycycline, depending on age (see Chapter 185). Duration of therapy usually is 4 weeks. Children with multiple recurrences or persistent arthritis sometimes require intravenous or intramuscular ceftriaxone or intravenous penicillin for 14 to 28 days. The prognosis for children is excellent.[117] Rupture of fluid from knee joint into the popliteal space (e.g., popliteal cyst, Baker cyst) with a brisk local inflammatory response has been described.[118]

If untreated, recurrences of arthritis are common. They usually are separated by months to years. Frequency and duration of attacks decrease over time. Chronic synovitis develops in approximately 11% of untreated individuals.

Viral Arthritis

Arthritis as a result of viral infection can occur by direct viral invasion of the synovium or through immune complex deposition (Box 77.1). The viruses most commonly associated with the development of arthritis include rubella, parvovirus B19, certain arboviruses (e.g., chikungunya), and hepatitis B.

Box 77.1

Viruses That Cause Arthritis

Togaviridae

Rubella virus

Chikungunya virus

Ross River virus

O'nyong-nyong virus

Mayaro virus

Sindbis virus

Barmah Forest virus

Parvoviridae

Parvovirus B19

Paramyxoviridae

Mumps virus

Picornaviridae

Echovirus

Coxsackievirus B

Retroviridae

Human immunodeficiency virus type 1

Human T-lymphotropic virus type 1

Herpesviridae

Herpes simplex virus 1

Varicella-zoster virus

Cytomegalovirus

Epstein-Barr virus

Flaviviridae

Hepatitis C virus

Hepadnaviridae

Hepatitis B virus

Rubella Virus

Arthritis after rubella infection is uncommon in childhood, but it occurs in 30% of women and 15% of men. Arthritis usually develops 1 to 2 days after the onset of rash, although arthritis has preceded the rash in a few cases. Symmetric involvement of small joints of the hands is most common. Wrists and knees are sometimes affected.

Analysis of joint fluid shows a predominance of mononuclear cells. Rubella virus has been isolated from synovial fluid. Symptoms resolve after several days, and long-term sequelae do not occur. Arthralgia and arthritis occur in approximately 25% of postpubertal females who receive live attenuated rubella vaccine. Joint symptoms begin 7 to 21 days after vaccination and usually are mild and self-limited.[119,120]

Parvovirus

Symptoms of arthritis or arthralgia were reported by 80% of adults and 8% of children during an outbreak of erythema infectiosum,[121] and arthritis can occur in the absence of rash. Infection often is symmetric and polyarticular, and the joints of the hands, wrists, and knees are involved most commonly. Children are more likely to have asymmetric involvement of a few joints.

Levels of total hemolytic complement are low in some people with parvovirus B19 arthritis, suggesting an immune complex–mediated pathogenesis. Arthritis associated with parvovirus B19 infection usually is self-limited. Resolution of symptoms occurs within 1 to 2 months.

Hepatitis Viruses

Arthralgia can occur as a prodromal symptom of infection with hepatitis A or B viruses, but arthritis occurs only with hepatitis B infection.[122,123] Joint symptoms precede the onset of icterus by 1 or 2 weeks. Multiple small joints of the hands usually are involved. Asymmetric involvement of the knees, elbows, ankles, and shoulders sometimes is seen.

An urticarial or maculopapular rash, usually involving the lower extremities, appears simultaneously with the joint findings in 30% to 40% of patients with arthritis. Hepatitis C viral infection has been associated with development of polyarthralgia and polyarthritis in a few patients.[124]

Arboviruses

Several arboviruses in the family Togaviridae, genus alphavirus, found in Australia, Africa, Asia, and South America cause systemic illness in which arthritis is a predominant manifestation. All are transmitted by bites of mosquitoes or ticks.

Chikungunya virus infection is endemic in Africa, India, and Southeast Asia and recently has expanded into the Western Hemisphere, primarily in the Caribbean and Central and South America.[125] Illness is biphasic, heralded by abrupt onset of fever, nausea, vomiting, and intense pain in one or more joints. The first phase of illness lasts 1 to 6 days, the patient becomes afebrile for 3 days, and then fever recurs. The second phase of illness is characterized by pharyngitis, rash, lymphadenopathy, and persistent arthritis. Children sometimes have febrile seizures and severe hemorrhagic manifestations.

Epidemic polyarthritis caused by Ross River virus occurs most frequently in Australia.[126] Clinical manifestations include fever, papular, petechial or morbilliform rash, adenopathy, and polyarthritis. Small joints of the hands and feet are affected most commonly. Most patients recover spontaneously within 2 weeks. Barmah Forest virus, also endemic to Australia, causes fever, polyarthritis, and rash.[127]

O'nyong-nyong virus (East Africa), Sindbis virus (Africa, Australia, Asia, Europe, and the Middle East), and Mayaro virus (Central and South America) infections cause febrile illnesses that are characterized by rash, adenopathy, arthralgia, and arthritis.

Other Viruses

Other viruses less commonly associated with arthralgia or arthritis include Epstein-Barr virus,[128] enteroviruses (i.e., echovirus and coxsackievirus B),[129] mumps virus,[130] varicella-zoster virus,[131] cytomegalovirus, and herpes simplex virus.[132]

Persistent or intermittent arthralgia involving the knee or shoulder has been reported in 35% to 45% of adults with human immunodeficiency virus (HIV) infection[133,134] but in only 15% of children with this infection.[135]

Mycoplasma Species

Mycoplasma pneumoniae, M. hominis, M. salivarium, and *Ureaplasma urealyticum* have been identified in joint fluid of patients with arthritis.[136–141] Most patients are immunocompromised or have suffered trauma to the joint. Characteristically, onset is insidious, with minimal systemic signs and a mildly affected, boggy joint with relative preservation of movement.

Mycobacterium Species

Skeletal tuberculosis occurs in 1% to 6% of tuberculosis cases. Isolated tuberculosis of the joint is uncommon.[142] Articular infection can represent reactivated or primary infection. The knees and hips are affected most commonly, but infection of other joints can occur. Chronic swelling or pain of the affected joint without systemic symptoms is common.

The tuberculin skin test (TST) is expected to be positive.[143] The synovial fluid WBC count typically ranges between 10,000 and 20,000 cells/mm^3, and neutrophils predominate. Synovial fluid cultures are positive in 79% of cases, and synovial biopsy is diagnostic in more than 90%.[144] MRI shows joint effusion with a high-intensity signal on T2-weighted images and postcontrast enhancement on T1-weighted images. Hypointense internal debris, synovial thickening, and cartilage destruction also may be seen.[145]

Nontuberculous mycobacteria can cause osteoarticular infections in immunocompromised hosts.[146,147]

Fungi

Fungal arthritis is unusual in healthy children, except in areas endemic for specific fungi. Chronic monoarticular arthritis is typical of most fungal joint infections. The diagnosis of arthritis usually requires microscopic evaluation of synovial biopsy specimens and culture of synovial tissue and fluid.

Candida species

Arthritis caused by *Candida* spp. occurs by hematogenous spread or rarely by direct inoculation of the organism into the joint space.[148] Risk factors in neonates include prematurity, use of broad-spectrum antibiotics, intravenous alimentation, and insertion of an intravascular catheter.[103,107] Risk factors in older children include immunosuppression and intravenous drug use.

Clinical manifestations vary. Children with disseminated disease have an acute onset of fever, systemic illness, and joint symptoms. In other cases, systemic symptoms are mild or absent. Joint symptoms may persist for months to years before a diagnosis is established. Neonates often have polyarticular involvement, but monoarticular infection is typical in older children. The knee is most frequently affected. Arthritis caused by *Candida* spp. in intravenous drug users often occurs in fibrocartilaginous joints, such as the sacroiliac joint, costochondral joints, and intervertebral disks.[149]

Synovial fluid WBC counts range from 7500 to 150,000 WBCs/mm^3, with neutrophil predominance. Diagnosis of fungal arthritis is confirmed by culture of synovial fluid or tissue. Culture of blood, urine, or cerebrospinal fluid may be positive in cases of systemic disease and especially in neonates.[148]

Fluconazole for 6 weeks or an echinocandin for 2 weeks followed by fluconazole for 4 weeks is the recommended treatment for *Candida* arthritis.[151] *Candida* spp. should be tested for susceptibility to fluconazole if this drug is considered. Adequate debridement of the joint is necessary for successful therapy.

Sporothrix schenckii

Sporothrix schenckii is a dimorphic fungus found worldwide in soil and decayed plant material. Individuals at risk for infection include those whose occupations place them in frequent contact with plant debris and moist soil. Infection in children is rare.

S. schenckii causes cutaneous and extracutaneous infection. Osteoarticular sporotrichosis is the most common manifestation of extracutaneous infection.[152] Joints most frequently involved include the knee, ankle, wrist, and elbows. Itraconazole is the treatment of choice, with amphotericin B recommended as alternative therapy.[153]

Aspergillus species

Aspergillus infection of the joint is uncommon and usually results from extension of infection from an adjacent bone. Children at risk include those with chronic granulomatous disease, chronic neutropenia, underlying cancer, and prolonged immunosuppression.[154]

Coccidioides immitis

Coccidioides immitis is found in soil in the southwestern United States and northern Mexico. Infection usually is asymptomatic or associated with localized pulmonary disease. Extrapulmonary manifestations include cutaneous lesions, lymphadenopathy, central nervous system infection, and osteoarticular infection. Joint involvement usually is unifocal and often adjacent to sites of osteomyelitis.[155]

Cryptococcus neoformans

Cryptococcus neoformans is found in soil contaminated by bird droppings. Infection typically involves the lungs, skin, or the central nervous system. Although bone lesions are found in 5% to 10% of cases, joint involvement is rare and usually results from infection in an adjacent bone.[156]

Histoplasma capsulatum

Histoplasma capsulatum is endemic to the central and southeastern United States, where large quantities of fungus are found in soil contaminated by bat or bird droppings. Infection usually is asymptomatic. Symptomatic infection is characterized by fever, chills, headache, cough, and chest pain. Approximately 10% of symptomatic patients have arthritis or severe arthralgia accompanied by erythema nodosum. Arthritis and arthralgia can be prolonged.

Antifungal therapy is not always indicated for the immunocompetent host (see Chapter 250).[157,158] Nonsteroidal anti-inflammatory drugs are recommended for relief of joint pain.[158]

Blastomyces dermatitidis

Blastomyces dermatitidis is found commonly in warm, moist soil containing decayed vegetation east of the Mississippi River.

Blastomycosis typically involves the lungs, skin, and genitourinary system. Skeletal disease occurs in 10% to 15% of cases.[159] Arthritis usually results from extension of osteomyelitis from an adjacent bone and usually is monoarticular but can be oligoarticular.[160]

Fungi are identifiable on a wet preparation of synovial fluid.[161] Itraconazole or other imidazoles have been used to treat blastomycoses.[162] Other fungal organisms, such as *Scedosporium* spp., are rare causes of arthritis.[163]

Reactive Arthritis

Reactive arthritis is inflammation in one or more joints related to an infection at a site distant from the joint.[164] Infections of the gastrointestinal, genitourinary, and respiratory tract are associated with reactive arthritis and an increasing number of pathogens are implicated.[165–170] Children are less likely than adults to develop reactive arthritis after enteric infection. Organisms most commonly associated with reactive arthritis are listed in Box 77.2.[164–167,169,171,172] Immune complex–associated arthritis occurs in 2% to 16% of cases of meningococcal disease.[173]

Box 77.2

Bacteria Associated With Reactive Arthritis

Gastrointestinal Pathogens

Shigella spp.

Salmonella spp.

Yersinia enterocolitica

Campylobacter spp.

Clostridium difficile

Sexually Transmitted Pathogens

Chlamydia trachomatis

Pyogenic and Reactive Arthritis–Causing Organisms

Streptococcus pyogenes

Neisseria gonorrhoeae

Neisseria meningitidis

A genetic susceptibility exists for development of reactive arthritis due to distant infection. Individuals who are HLA-B27 antigen positive have an increased incidence of disease.[174] About 80% of people with reactive arthritis associated with Reiter syndrome have the HLA-B27 gene. Reiter syndrome consists of arthritis, urethritis, and bilateral conjunctivitis. In children, symptoms usually follow a diarrheal illness.[175] In adults, Reiter syndrome also can follow an episode of nongonococcal urethritis. Although Reiter syndrome and reactive arthritis are sometimes used interchangeably, reactive arthritis is diagnosed in many children who do not have the triad of symptoms.

Reactive arthritis usually is polyarticular and involves the large joints of the lower extremities. Small joints, wrists, and elbows are involved less frequently. Sacroiliitis is more common among adults than children. Urethritis manifests with dysuria and pyuria. Mucous membrane ulcers in the mouth, rectum, or vagina or on the glans penis sometimes occur. Abnormalities of the eye include keratitis, uveitis, and corneal ulcerations.

The WBC count and ESR usually are elevated. The synovial fluid WBC count is less than 50,000 cells/mm^3 and has a predominance of neutrophils.[176] The ESR ranges from 20 to more than 100 mm/hr. Responsible pathogens are sometimes identified in stool or urethral specimens.

Nonsteroidal anti-inflammatory agents are useful in controlling symptoms. Antibiotic treatment of the predisposing bacterial organism may be appropriate when cultures are positive at the time of onset of joint symptoms.[173,177] In children, joint symptoms persist for 1 to 12 months, and recurrences are rare. The long-term prognosis of the disease is unknown.

Some bacteria cause direct infection of the joint and reactive arthritis. For example, *S. pyogenes* causes infective pyogenic arthritis and is associated with postinfectious reactive arthritis and rheumatic fever.[178] Poststreptococcal reactive arthritis typically occurs 3 to 14 days after streptococcal infection. Arthritis usually is symmetric, can involve large and small joints, and is nonmigratory, characteristics that differentiate it from the arthritis of acute rheumatic fever.[179] Similarly, *N. meningitidis, N. gonorrhoeae,* and *Salmonella* spp. sometimes are isolated from synovial fluid, but in other cases, infection at another site is associated with reactive arthritis.

Reactive arthritis also can be associated with a more generalized autoinflammatory or immunologic disorder, such as Crohn disease, ulcerative colitis, rheumatoid and rheumatic disorders, Kawasaki disease, hereditary autoinflammatory disorders, serum sickness, or Henoch-Schönlein purpura.

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78

Diskitis

David K. Hong, Kathleen Gutierrez

Diskitis is an inflammatory process involving the intervertebral disks and the end plates of the vertebral bodies. It is associated with characteristic clinical and radiologic findings, but information about diskitis is derived primarily from case reports and retrospective studies of small numbers of patients.

Diskitis has been reported under a variety of other names, including spondylodiskitis, pyogenic infectious spondylitis, spondylarthritis, acute osteitis of the spine, intervertebral disk space infection, and benign osteomyelitis of the spine.[1–6] The definition of diskitis varies among studies, and it is often difficult to differentiate disk space inflammation alone from vertebral osteomyelitis. Disk space inflammation likely is part of a spectrum of disease that includes vertebral osteomyelitis, but diskitis appears to have a more benign clinical course.[7,8]

There has been no consistent approach to the diagnosis, treatment, and long-term follow-up of patients with diskitis. Knowledge about the incidence, causes, and optimal treatment of this infection therefore remains limited.

Epidemiology and Etiology

Although the incidence of diskitis is unknown, it appears to be uncommon. In one center, diskitis occurred at a rate of approximately 1 or 2 cases per 30,000 clinic visits per year.[1] Most cases occur among children 6 years of age or younger,[1,9–13] although cases have been reported for older children and adolescents. Disk space infection in adults most commonly occurs in the postoperative setting. Spontaneous diskitis is uncommon in adults,[14,15] but when reported, it has been associated with older age, diabetes mellitus, and systemic infection.[16]

Diskitis is probably the result of low-grade bacterial infection of the disk space.[3,5,6,17,18] Some investigators think that intervertebral disk inflammation is noninfectious and the result of antecedent trauma to the spine.[19]

Most blood culture results obtained from patients with diskitis are negative. If positive, *Staphylococcus aureus* is the most common isolate (Table 78.1). Other organisms isolated from blood cultures or disk aspirates from affected children have included *S. epidermidis*,[20] *Kingella kingae*,[2,15,21–25] anaerobes,[26] gram-negative enteric organisms,[20,26–28] *Streptococcus pneumoniae*,[5] and *Brucella* species.[29] In most cases, cultures of intervertebral disk specimens are sterile (Table 78.2).

TABLE 78.1

Results of Blood Cultures for Children With Diskitis

Study	No. of Patients	Blood Cultures	
		No. of Cultures	No. of Positive Results
Smith and Taylor (1967)[13]	20	24	0
Wenger et al. (1978)[6]	41	22	10[a]
Scoles and Quinn (1982)[28]	29	9	0
Crawford et al. (1991)[47]	36	28	2[b]
Ryoppy et al. (1993)[12]	18	0	0
Brown et al. (2001)[48]	11	11	0

[a] *Staphylococcus* aureus (9 results); diphtheroids (1 result).

[b] *Staphylococcus aureus* (2 results).

TABLE 78.2

Results of Disk Space Aspirates for Children With Diskitis

Study	No. of Patients	No. of Biopsies or Aspirates	No. of Positive Culture Results
Smith and Taylor (1967)[13]	20	3	1/3[a]
Spiegel et al. (1972)[5]	48	15	5/15[b]
Wenger et al. (1978)[6]	41	9	6/9[c]
Scoles and Quinn	29	6	2/6[d]

(1982)[28]			
du Lac et al. (1990)[9]	12	8	6/8[e]
Crawford et al. (1991)[47]	36	3	0/3
Ryoppy et al. (1993)[12]	18	17	0/17
Brown et al. (2001)[48]	11	3	0/3
Garron et al. (2002)[2]	42	35	22/35[f]

[a] *Staphylococcus aureus* (1 result).

[b] *Moraxella* spp., *Staphylococcus aureus*, *Streptococcus pneumoniae*, diphtheroids, and micrococcus (1 result each).

[c] *Staphylococcus aureus* (6 results; 1 also showed α-hemolytic *Streptococcus*).

[d] *Klebsiella* spp. and *Staphylococcus aureus* (1 result each).

[e] *Moraxella* spp. (1 result) and *Staphylococcus aureus* (5 results).

[f] *Staphylococcus aureus* (12 results), *Kingella kingae* (6 results), *Staphylococcus epidermidis* (1 result), *Clostridium clostridiiforme* (1 result), *Streptococcus* spp. (1 result), and *Coxiella burnetii* (1 result).

Viruses have not been isolated from disk space cultures. *Mycobacterium* species and *Candida* species have been isolated by disk space aspiration from older adults.[30]

Pathogenesis and Pathologic Findings

The lumbar or lower thoracic spine is involved in most cases.[31] There are rare reports of diskitis involving the cervical spine.[28,32] Usually only one disk space is involved, although patients with involvement of two intervertebral disk spaces have been reported.[13]

The difference in blood supply to the vertebral bodies and disk spaces in children compared with adults may explain the age-related incidence of diskitis.[33–35] In the young child, there are widespread anastomoses between intraosseous arteries supplying the vertebrae. These vessels begin to involute at about 8 months of age and are few in number by the age of 7 years. By the third decade of life, the anastomoses have atrophied fully, and peripheral periosteal arteries develop. As a result of this rich blood supply to the vertebral end plates, a septic embolus in a child leads only to small areas of vertebral end plate infarction or infection, with disproportionate involvement of the intervertebral disk. A septic embolus in an adult results in a much larger area of vertebral body infarction and subsequent infection, which causes vertebral osteomyelitis.[1,33]

The intervertebral disk is composed of the cartilaginous plate, the annulus fibrosus, and the nucleus pulposus.[36] Examinations of cadavers have demonstrated that blood vessels exist in the cartilaginous end plates until 7 years of age and in the annulus fibrosus until 20 years of age.[34] This may explain the finding of disk space inflammation or infection with relative sparing of the vertebral body that is seen in children. An ovine animal model of diskitis demonstrates that infection of the disk impedes disk development but does not seem to affect vertebral body growth.[37]

Magnetic resonance imaging (MRI) findings in children with diskitis suggest a pathophysiologic sequence in which infection or inflammation begins in the metaphyseal bone near the vertebral endplates, with anterior spread to the disk region and the adjacent vertebral end plate.[4,38] Histologic examination of disk biopsy specimens from children with diskitis reveals subacute or chronic nonspecific inflammation. For some children with the characteristic clinical and radiologic findings of diskitis, histologic results are normal.[5,12]

Clinical Manifestations

The clinical manifestations of diskitis depend on the age of the child.[5,6,9,11,13,28] Onset is gradual, with symptoms often existing for several days to weeks before the child comes to medical attention. Younger children are more likely to have a history of irritability and reluctance to walk or bear weight.[39] Older children complain of back pain, hip pain, abdominal pain, or pain with walking. Some patients have abdominal complaints such as anorexia, vomiting, abdominal pain, and constipation (Table 78.3).

TABLE 78.3

Frequency of Presenting Symptoms in 165 Patients With Diskitis

Symptoms	Percentage of Patients
Limp, leg pain, or refusal to walk[a]	41
Back pain	41
Abdominal pain	15

[a] Children whose presenting symptom was refusal to bear weight or walk were younger (≥5 yr) when they came to medical attention.

Data from references 5, 6, 20, 28, 41, and 47.

On physical examination, the child often has a low-grade fever but appears well. Comfortable when lying still, the child refuses to bear weight or walks with a limp. Irritability with sitting or flexion of hips and pain with palpation over the lower back are common. The paraspinous muscles can spasm. The normal curvature of the spine sometimes can be altered, with loss of normal lumbar lordosis.[10,20,40,41] Gower sign (i.e., use of a hand push-off rather than use of the pelvic girdle to rise from sitting) can be seen in children with diskitis; it disappears after treatment.[42,43]

Abnormal neurologic findings are uncommon, but one retrospective case series described decreased muscle tone, muscle weakness, and decreased tendon reflexes in 7 of 17 children diagnosed with diskitis.[44] Neurologic abnormalities therefore do not exclude a diagnosis of diskitis. However, when detected, imaging studies are needed to exclude intraspinal involvement or an alternative diagnosis. Failure to consider a diagnosis of diskitis, to examine the lower back carefully, and to order the appropriate radiologic studies often results in delay in diagnosis and inappropriate use of tests.[45]

Differential Diagnosis

The differential diagnosis of diskitis includes vertebral osteomyelitis or osteomyelitis of the pelvis, pyogenic arthritis of the hip or sacroiliac joint, abscess of the psoas muscle or pelvic structures, spinal epidural abscess, meningitis, appendicitis, malignant processes, pyelonephritis, and tuberculosis of the spine. If a child appears to be ill and has a high fever, marked leukocytosis, neurologic abnormalities, or extensive involvement of the vertebral body, diskitis is not the likely diagnosis.[46] An immediate workup to rule out a more serious cause of symptoms should be initiated.

Diagnosis

The erythrocyte sedimentation rate (ESR) is typically elevated (rarely to more than 60 mm/hr) in children with diskitis.[10,11,28] The peripheral white blood cell (WBC) count is normal or slightly elevated.[11,47] The C-reactive protein (CRP) level can be elevated.[48] When a blood culture is obtained, the result usually is negative. A skin test for tuberculosis and chest radiograph are useful in circumstances in which tuberculosis is possible. When culture results are positive, therapy can be targeted to the causative pathogen.

Early in the course of diskitis, findings on plain radiography of the spine may be normal. Between 2 and 4 weeks after the onset of symptoms, the involved disk space is narrow, and the margins of the vertebral end plates exhibit demineralization and irregularity (Fig. 78.1). At 2 to 3 months after onset of symptoms, the disk space remains narrow, and remineralization of vertebral end plates has occurred. Long-term follow-up in most patients shows persistence of a narrow disk space and sclerotic changes at the vertebral end plates (Fig. 78.2). In some cases, involved vertebral bodies become fused or their shapes change.[10,11, 28,49,50]

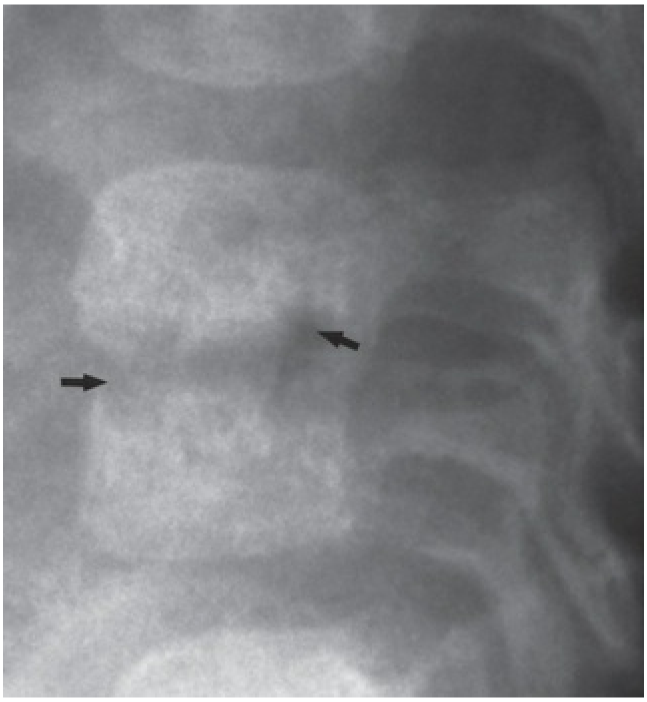

FIGURE 78.1 Diskitis involves the L4 to L5 space in an 18-month-old girl. Notice the narrowed disk space and irregularities of the adjacent vertebral end plates.

(Courtesy of Bruce Parker, MD, Palo Alto, CA.)

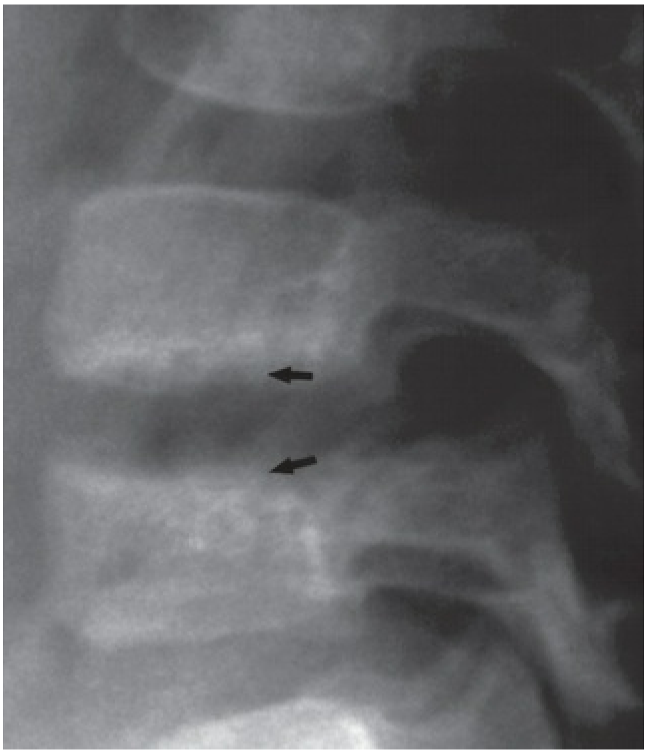

FIGURE 78.2 Follow-up radiograph of the same patient as in Fig. 78.1 was obtained 6 months after onset of symptoms. Some narrowing of disk space persists. Notice the sclerotic changes of the adjacent vertebral end plates. (Courtesy of Bruce Parker, MD, Palo Alto, CA.)

Other imaging modalities are useful if plain radiographic results are normal. Technetium bone scan has been used and frequently shows increased uptake at the disk space.[40,47] Computed tomography (CT) can demonstrate narrowing of the disk space and vertebral body involvement early in the course of disease.[20] MRI is the most sensitive technique for confirming the diagnosis of diskitis.[4,9,37,41,51] MRI is particularly useful for detecting paravertebral abscess, epidural abscess, severe protrusion of the disk, or significant vertebral body involvement.[48,52]

Aspiration of the disk space for culture in cases with compatible clinical findings and supportive imaging is controversial. Some investigators have reported a good yield from culture of material obtained from aspiration.[9,17,18] Identification of an organism, especially an unusual one such as *K. kingae,* may affect the choice of therapy. In many studies, most aspirates from a disk space are sterile even when antibiotics have not been administered.[5,13,28,47] Aspiration of the disk space therefore may be limited to cases in which there is no response to immobilization or empiric antibiotic therapy, cases with extensive involvement of the vertebral body, or cases that have other atypical features.[3,13,27,30,47] An aspirate or biopsy specimen of the disk space should be cultured for bacteria, mycobacteria, and fungus.

Management

Most children with diskitis respond promptly to bed rest, with decreased pain within 48 hours. Immobilization of the spine sometimes is required. Failure to respond to immobilization suggests that the diagnosis is incorrect. The optimal duration of immobilization is unknown. There has been no study correlating long-term outcome and duration of immobilization.

Some investigators suggest the use of antibiotic therapy only if culture results are positive or the child appears to be systemically ill or has not responded promptly to immobilization.[5,12,25,28,40,47] Although antibiotic therapy for diskitis does not appear to alter the long-term prognosis, one retrospective analysis of 47 patients showed that use of a short course of parenterally administered antibiotic agents followed by oral therapy hastened resolution of symptoms.[4] Because several cases have been associated with positive culture results, particularly for *S. aureus,* antibiotic treatment for an arbitrary length of time seems prudent.[1,3,4,6] In the absence of a positive culture result, empiric therapy for staphylococci and *K. kingae* is appropriate. Antibiotic agents can be administered intravenously for several days, until fever and pain have resolved and the ESR is decreasing, and then given orally. Optimal duration of therapy is unknown, but it should be continued until the patient is asymptomatic and the ESR or CRP level is normalizing.

Outcome

Most children with diskitis have persistently abnormal radiographic findings long after clinical symptoms have resolved.[12,37,49] The involved disk space may never regain its original height, and sclerotic changes in the vertebral end plates persist. Cases of recurrent symptoms have been reported.[5] Although reports of follow-up of patients with diskitis have included small numbers of patients and relatively short periods, most patients are asymptomatic and have no limitation of activity.[5,6,12,53] Younger children appear to have a lower rate of bony ankylosis compared with older children, presumably because of the increased vascular channels that promote more rapid healing.[53]

Some patients have mild, chronic back pain.[12,40] A study of 35 patients who were followed for an average of 17 years found that 42% complained of persistent backache. Extension of the spine was restricted in 30 patients. Most patients had been treated with bed rest or with a lengthy course of antibiotic agents and immobilization.[50]

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Transient Synovitis

C. Buddy Creech

Transient synovitis (TS) is a self-limited inflammation of the synovium, usually of the hip joint. TS is a common cause of limp in childhood. Synonyms for this condition include toxic synovitis, observation hip, irritable hip, and benign aseptic arthritis.[1–4]

Etiology and Epidemiology

The cause of TS is unknown. In the few cases for which biopsy specimens of the synovial membrane have been obtained, histologic examination shows nonspecific inflammation.[5,6] Considering that many children with TS have had a recent or concurrent upper respiratory or gastrointestinal viral infection and that elevated serum interferon levels have been demonstrated in some patients, TS likely represents a self-limited infection involving the synovial membrane or a postinfectious inflammatory response.[7–9]

Some investigators have found positive throat culture results for group A *Streptococcus* or elevated antistreptolysin O (ASO) titers, or both, for a small number of children with toxic synovitis.[8,10] However, no single organism has been implicated consistently as the cause of TS. In one series, an increase in antibody concentrations against rubella, enterovirus, Epstein-Barr virus, or *Mycoplasma* was demonstrated for 67 of 80 children with TS, but there was no unaffected control group; results of viral culture for synovial fluid were negative; and culture samples were not obtained from other sites.[11] In other reports, including one prospective study in which a control group was included and one study in which serologic evidence of acute parvovirus B19 or human herpesvirus 6 infection was sought, no evidence of viral or streptococcal causes was found.[5,12–15] Parvovirus B19 DNA has been detected by polymerase chain reaction (PCR) in the sera of a small number of children with TS.[16]

TS occurs predominantly in children 18 months to 12 years of age; in various studies, the mean age of occurrence is 5.6 to 5.9 years.[3,12,14,17] Boys are affected approximately twice as often as girls.[3,8,12,14,15,17–19] Although the annual incidence in the United States is unknown, TS frequently is referred to as the most common cause of hip pain in children.[20] The average annual incidence in one study of Swedish children was 0.2%.[19]

Clinical Manifestations

The usual manifestation of TS is acute onset of leg pain or limp in an otherwise healthy child. Symptoms are typically unilateral, with right and left hips affected equally. There have been rare reports of children with involvement of both hips.[3,12]

Leg pain can be localized to the hip, thigh, or knee. The intensity of pain ranges from mild to severe enough to awaken the child.[2,19] Most children are afebrile or have minimal temperature elevation.[21,22] The child usually appears minimally ill, with pain on movement of the knee, thigh, or hip on the affected side and limited internal rotation and adduction of the affected hip.[3,8]

The duration of symptoms ranges from 1 day to 3 weeks. Most children become asymptomatic approximately 1 week after the onset of symptoms.[13,14,23] Prolonged hip pain suggests another diagnosis.

Diagnosis

Laboratory and imaging studies can help to differentiate TS from more serious causes of hip pain. The white blood cell (WBC) count usually is normal, and the erythrocyte sedimentation rate (ESR) is normal or mildly elevated (<30 mm/hr). The mean C-reactive protein (CRP) level in one study of 64 patients with TS was 1.0

mg/dL.[24] Inflammatory markers for pyogenic (bacterial) arthritis and TS can overlap.[22,24] Blood and joint fluid cultures are helpful because a positive bacterial culture rules out TS.

Plain radiographs of the pelvis and hip often are normal.[18,19,25] They are obtained to rule out osteomyelitis, cancer, or Legg-Calvé-Perthes (LCP) disease.[10,25,26]

Ultrasound (US) is a useful noninvasive method for delineating the joint effusion[23,27–30] found in approximately 70% of children with TS.[12] US is helpful in guiding joint aspiration, particularly in children younger than 8 years, because cartilaginous structures are visualized well. In older children, fluoroscopic guidance is the preferred approach.[26] The bone scan is normal or shows increased uptake, especially in the blood pool phase.[31–33]

Magnetic resonance imaging (MRI) results are normal or reveal abnormal thickening of the articular surfaces and joint effusion.[34,35] Signal intensity alterations detected by MRI in bone marrow may help differentiate pyogenic arthritis from TS. Low-signal-intensity alterations on fat-suppressed T1-weighted images and high-signal-intensity alterations on fat-suppressed T2-weighted images are seen in the bone marrow of the affected joint in many of patients with bacterial arthritis and not seen in patients with TS.[36,37]

Differential Diagnosis

TS is a diagnosis of exclusion.[9,19] The differential diagnosis includes bacterial arthritis of the hip; osteomyelitis of the proximal femur, acetabulum, or sacroiliac joint; pyomyositis; psoas muscle or intra-abdominal abscess; trauma; pauciarticular arthritis; rheumatic fever; malignant tumor; slipped capital femoral epiphysis; LCP disease; fracture; and reactive arthritis.

Early differentiation of TS from bacterial arthritis of the hip is crucial because delay in surgical decompression for pyogenic arthritis can result in increased morbidity.[21,22] An evidence-based clinical prediction algorithm using four independent multivariate predictors (i.e. fever ≥38.5°C, refusal to bear weight, ESR >40 mm/hr, and peripheral WBC count >12,000 cells/mm^3) was proposed by Kocher and colleagues to estimate the probability of pyogenic arthritis.[38] Three or four predictors had a positive predictive value (PPV) for pyogenic arthritis of 93% or 99.6%

respectively, and one or two criteria had a PPV of 3% or 40%, respectively.[38] For a new cohort of children studied prospectively by the same investigators, performance of the algorithm was not as strong. In the prospective cohort, the area under the receiver operating characteristic curve was 0.86, compared with 0.96 in the original study.[39]

In a subsequent study of five independent clinical and laboratory markers (i.e., temperature >37°C, ESR >20 mm/hr, CRP ≥2 mg/dL, WBC >11,000 cells/mm^3, and difference of joint space distance >2 mm), identification of four predictors had a PPV for pyogenic arthritis of 99%; no or one predictor had PPV of 0.1% to 1.7%.[40]

A prospective study using the variables in the Kocher algorithm in addition to the CRP value found that fever was the best predictor of pyogenic arthritis, followed by an elevated CRP level, elevated ESR, refusal to bear weight, and an elevated WBC count.[41] In contrast, in a retrospective study of 311 children with hip effusion, a CRP >20 mg/L was the strongest independent risk factor for septic arthritis.[42]

In a retrospective application of five factors (with temperature ≥38.5°C, ESR ≥40 mm/hr, and CRP ≥2 mg/dL) in a general hospital, a finding of all five factors had a PPV of 60%, and fever was the single best predictor.[43] It is important to consider that the validity of clinical prediction algorithms can vary substantially between institutions and that no clinical prediction rule has been validated by large, prospective studies in different populations.[44–46]

Aspiration of fluid from the joint space frequently is attempted in patients with suspected TS because this is the most reliable method of excluding the diagnosis of pyogenic arthritis. The procedure also relieves pain. In cases of TS, the fluid is expected to be clear or slightly turbid, usually with a volume of less than 5 mL containing less than 1000 WBC/mm^3.

LCP disease frequently manifests as a limp in an otherwise healthy 5- to 9-year-old, afebrile child who has a normal peripheral WBC count and ESR. Boys are affected four times more often than girls. Initially, the clinical features, laboratory test results, and US findings may be indistinguishable from findings in TS. Plain films, bone scan, and MRI are useful differentiating tests; LCP disease shows ischemic necrosis of the head of the femur.[18,26,32,34,47] In children with LCP disease, bone age often is delayed from 6 months to 3 years.[2]

Treatment and Prognosis

Treatment of TS of the hip is rest. The usual duration of symptoms is 5 to 7 days. One small, double-blind, placebo-controlled trial of ibuprofen versus placebo demonstrated that ibuprofen shortened the duration of symptoms from 4.5 to 2 days in children with TS.[48] Close follow-up is necessary to detect development of signs and symptoms of pyogenic arthritis or osteomyelitis, which may be more challenging if patients have received anti-inflammatory drugs.

Children who are older than 6 years or who have protracted symptoms require careful evaluation and follow-up to differentiate LCP disease from other disorders. Some investigators suggest that children with TS are at higher risk for LCP disease,[7,9,18] whereas others have found no relationship between the two entities other than the similarity in initial clinical presentation.[14]

TS is self-limited and resolves with supportive therapy. Symptoms recur in a small number of children.[5,8,9] In some series, up to 30% of children who were followed for 1 to 30 years after an initial episode developed asymptomatic overgrowth (i.e., coxa magna) of the femoral head.[1,17] The long-term significance of this finding is unknown.

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Eye Infection

OUTLINE

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Conjunctivitis in the Neonatal Period (Ophthalmia Neonatorum)

Douglas R. Fredrick

Ophthalmia neonatorum is defined as conjunctivitis occurring within the first month of life. It is the most common eye disease of neonates, with an incidence ranging from 1.6% to 12%.[1–3] Incidence is directly related to the prevalence of sexually transmitted infection (STI) in adults. One hundred years ago, *Neisseria gonorrhoeae* was the most common pathogen and a major cause of blindness among children. With the advent of Credé prophylaxis (instillation of silver nitrate at time of birth) and changing trends in STI, *Chlamydia trachomatis* has become the most common sexually transmitted pathogen (Table 80.1).[4–14] In general, offspring of women who receive prenatal care have a lower incidence of infectious conjunctivitis.[12–14] In the absence of maternal STI, neonatal conjunctivitis is acquired postnatally and is caused by *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus* spp., and viridans streptococci. Viruses, with the exception of herpes simplex virus (HSV), are less common pathogens in this age group.

TABLE 80.1

Prevalence of *Chlamydia trachomatis, Neisseria gonorrhoeae*, and Other Bacterial Pathogens as Causes of Neonatal Conjunctivitis

Country of Study	**Decade of Publication**	**No. of Infants**	***Chlamydia trachomatis* (%) (Range Across Studies)**	***Neisseria gonorrhoeae* (%) (Range Across Studies)**	**Other Bacterial Pathogens[a,b] (%) (Range Across Studies)**	**References**
United States	1970s	402	24	4	26	4,5
			(13–28)	(0–15)	(22–39)	
United States and Europe[c]	1980s	477	30	0.2	51	2,6,7[d],8,10–12
			(1–51)	(0–1)	(10–80)	
Kenya	1980s	318	12	23	9	9,13[d]
			(11–13)	(5–43)		
United States	1990s	109	2	0	44	14

[a] Percentages represent approximations because most studies show total number of isolates, and multiple isolates were recovered from individual patients.

[b] Excludes coagulase-negative staphylococci, *Corynebacterium* spp., *Propionibacterium acnes*, and diphtheroids.

[c] US (references 6, 7, 8, and 10), United Kingdom (reference 2), Sweden (reference 11), Belgium (reference 12).

[d] Other bacterial pathogens not stated.

Hospital-associated infection can occur in neonatal intensive care units due to *S. aureus*, gram-negative bacilli (especially *Pseudomonas aeruginosa*), and adenovirus. Significant predictors of conjunctivitis include low birth weight, use of ventilator or nasal cannula, and continuous positive airway pressue.[15] Ophthalmologic examination has been associated with nosocomial bacterial conjunctivitis, and most notably adenovirus conjunctivitis (sometimes with dissemination and fatal outcome).[15,16]

Pathogenesis

Microbial pathogens can be transmitted to the eye by a variety of routes. Premature rupture of placental membranes allows for the retrograde spread of organisms to the fetal conjunctiva and cornea. Hematogenous spread can occur transplacentally as well. During vaginal delivery, the neonate's eyes can become infected by contact with infected maternal genital secretions. After birth, caregivers can transmit pathogens to the neonate's eyes through direct contact or aerosolization.

In addition to the immaturity of the immune system, the neonate has local risk factors for ocular infections. The secretory rate of tears under basal conditions in premature infants is about 20% of that in full-term infants,[17] and the blink frequency is decreased. The concentration of lysozyme, the enzyme in tears that catalyzes the breakdown of the bacterial cell wall, also is diminished in premature infants compared with full-term infants and adults.[18] A final reason for increased susceptibility of the neonatal eye is a lack of secretory immunoglobulin A (IgA) in the tears of neonates.[19]

Etiologic Agents

Chlamydia Trachomatis

Epidemiology

C. trachomatis has been the most common cause of infective neonatal conjunctivitis (see Table 80.1). Frequency of conjunctivitis reflects the prevalence of maternal genital infections, ranging from 18% to 23%.[20,21] The likelihood of transmission from untreated infected mothers to infants ranges from 18% to 61% (Table 80.2).[22–28]

TABLE 80.2

Prevalence of Chlamydial Conjunctivitis Among Infants Born to Mothers With Chlamydial Cervicitis

Country of Study	No. of Infants	Neonates Infected (%)	Reference
United States	18	44	22
United States	18	61	23
Sweden	23	22	24
United States	60	20	25
United States	95	28	20
United States	131	18	27
United States	120	25	28
Kenya	201	31	13

Clinical Manifestations

Chlamydial conjunctivitis is usually clinically evident within 5 to 14 days of birth, although it can appear as early as 3 days, especially after premature rupture of membranes, or as late as 60 days.[22,29] Typical findings are eyelid swelling, erythema, and unilateral or bilateral mucopurulent conjunctivitis; the cornea usually is not involved. On occasion, pseudomembranes and (rarely) true membranes develop. The expected lymphoid follicular response of the conjunctiva does not appear unless the infection persists beyond 6 weeks of age. In treated cases, healing usually occurs without sequelae. Infection in untreated or inadequately treated cases can persist for 2 to 12 months, and some cases remain clinically apparent for years. Persistent infection can lead to conjunctival scar formation and corneal micropannus.[30,31]

The major nonocular complication of chlamydial conjunctivitis is pneumonia. Pneumonia develops in 11% to 20% of infected infants and typically manifests at 1 to 3 months of age.[29,32,33] Infants usually are afebrile but have nasal congestion, prolonged cough, tachypnea, and rales. Hyperinflation with interstitial or alveolar infiltrates is evident radiographically. Total serum IgG and IgM antibody values are elevated, and eosinophilia sometimes occurs. Antibodies to *C. trachomatis* are detectable in tears and serum. Although infection usually is self-limited, systemic treatment is recommended because it shortens the duration of ocular and respiratory tract illness and because treatment of ocular infection prevents pneumonia.[33–35]

Diagnosis

In the past, *C. trachomatis* conjunctivitis was diagnosed by Giemsa staining of conjunctival scrapings showing blue-stained intracytoplasmic inclusions within epithelial cells. The sensitivity of Giemsa staining ranges widely, from 22% to 95%, reflecting varied technical and examiner skill.[5,6,36] Staining has been replaced by use of nucleic acid amplification test (NAAT) performed on conjunctival swabs. These tests are available widely and provide rapid results with high sensitivity.[37] Organism detection by direct fluorescence has lower sensitivity and is difficult to standardize but is less costly.[8,38–42] Cultivation of organisms in yolk sac or tissue culture is a sensitive means of confirming the diagnosis, but these techniques are laborious and slow and are used only in special circumstances.

Treatment

Systemic therapy for conjunctivitis due to *C. trachomatis* is recommended in all cases to treat conjunctivitis and prevent pneumonia.[26] Erythromycin estolate or ethylsuccinate, 50 mg/kg/day in 4 divided doses for 14 days, is curative in about 80% of cases.[34] A short course of azithromycin (20 mg/kg), given as a single dose or daily for 3 days, also may be effective and may be less associated with idiopathic hypertrophic pyloric stenosis.[25] Topical corticosteroid therapy is contraindicated because it can prolong the infection and possibly lead to conjunctival scarring.

Neisseria Gonorrhoeae

Epidemiology

In the past, *N. gonorrhoeae* was the most serious cause of ophthalmia neonatorum because of this organism's capacity to damage the eye; this infection accounted for 24% of children enrolled in schools for the blind between 1906 and 1911.[43] After the widespread use of perinatal ocular prophylaxis, the incidence of gonococcal ophthalmia neonatorum decreased, and the proportion of admissions to schools for the blind as a result of this infection dropped to 0.6% by 1959. In the United States, the emergence of penicillin-resistant gonococci and the increase in frequency of asymptomatic genital gonococcal infection resulted in a higher prevalence of infections in the 1970s.[44,45] In the US and England currently, neonatal gonococcal ophthalmia is rare.[46] In developing countries, the estimated incidence of gonococcal ophthalmia neonatorum is much higher than in the US, ranging from 15% to 34%. In Kenya, where ocular prophylaxis was discontinued in the mid-1970s and the prevalence of penicillinase-producing *N. gonorrhoeae* has risen to 60%, gonococcal ophthalmia has reached epidemic proportions.[9]

Clinical Manifestations

The clinical manifestations of gonococcal ophthalmia neonatorum typically appear 2 to 7 days after birth, although initial manifestations in the second week are not uncommon (Table 80.3). Later onset suggests postnatal exposure to the organism. Most neonates have edema of the eyelid and purulent conjunctivitis; however, some have a mild or catarrhal response.[47] The inflammatory response of the external ocular surface in infants tends to be less severe than that in the older child or adult. Even with treatment, exudative conjunctivitis can continue for 7 to 14 days before subsiding, contributing to the common complication of conjunctival scarring.

TABLE 80.3

Differential Diagnosis of Neonatal Conjunctivitis

Cause of Conjunctivitis	Time of Onset	Discharge	Corneal Involvement
Chemical	24 hours	Serous	No
Neisseria gonorrhoeae	2–7 days	Mucopurulent	Infiltrate
Chlamydia trachomatis	5–14 days	Mucopurulent	No
Herpes simplex virus	6–14 days	Serous	Dendrite, epithelial ulcer

Corneal involvement is the most serious complication because ulceration with resultant scarring is the major cause of visual impairment.[48] Initially, superficial keratitis gives the corneal surface a dull appearance. Subsequently, marginal and central infiltrates can appear, which then ulcerate, sometimes forming a ring abscess. Corneal perforation leads to abnormal apposition of the iris against the posterior cornea, which can persist as an adherent leukoma. The ulcerated or perforated cornea also can be the portal for invasion by other organisms, resulting in endophthalmitis. Prompt use of antibiotic therapy to treat gonococcal ophthalmia neonatorum can prevent such ocular complications.

Extraocular gonococcal infection may coexist with ocular infection and is more common than previously thought. Fransen and colleagues[9] reported that *N. gonorrhoeae* was isolated from pharyngeal specimens in 15% of infants with gonococcal ophthalmia. Although gonococcal pneumonia is not well documented, pharyngeal colonization can lead to bacteremic spread to distant sites, especially joints.[49,50]

Diagnosis

Gram stain of ocular exudate shows predominance of neutrophils with intracellular gram-negative diplococci. *Moraxella catarrhalis* and *Neisseria meningitidis* can be confused with *N. gonorrhoeae* on Gram stain.[51–54] Diagnosis of gonococcal ophthalmia is confirmed by culture on chocolate agar or Thayer-Martin media incubated at 37°C in humidified carbon dioxide. Appropriate culture specimens also should be obtained from the mother, and testing for *Chlamydia,* syphilis, and HIV should be performed. Blood and cerebrospinal fluid cultures (in an infant who is febrile or otherwise not behaving normally) also are obtained, as are tests for concurrent *C. trachomatis* infection.

Treatment

Neonates with gonococcal ophthalmia should be hospitalized and treated with parenteral therapy; topical therapy alone is ineffective. Because of the increased prevalence of penicillin resistance in *N. gonorrhoeae,* ceftriaxone (25–50 mg/kg, not to exceed 125 mg, is given once intravenously or intramuscularly).[55] Ceftriaxone should not be given to neonates with hyperbilirubinemia; cefotaxime given intravenously or intramuscularly is an alternative.[55] Most infants will be treated parenterally with ceftriaxone (25–50 mg/kg once daily) or cefotaxime (25–50 mg/kg/dose 2 or 3 times daily depending on age <7 or >7 days) until disseminated infections are excluded. In addition, the eye should be irrigated with saline solution at first hourly and then every 2 to 3 hours until discharge is eliminated. Instillation of topical antibiotic is not necessary after diagnosis is confirmed and appropriate systemic antibiotic therapy has been initiated. It is imperative that the mother of the child and all sexual partners be referred for testing for *Chlamydia* and other sexually transmitted infections. Gonococcal infections are designated as a notifiable disease.

Herpes Simplex Virus

Epidemiology

HSV can infect and seriously damage a neonate's eye. Before the availability of antiviral therapy, many infants with isolated perinatally acquired herpetic conjunctivitis or skin or other mucous membrane infection progressed to more serious infection.[56,57] Most neonatal infections are caused by HSV type 2, which has an estimated prevalence of nearly 25% among adults in the US.[58]

Clinical Manifestations

Ophthalmia neonatorum due to HSV typically becomes evident 6 to

14 days after birth, although infants born after prolonged rupture of placental membranes can have manifestations at birth.[59] Conjunctivitis, which can be unilateral or bilateral, is associated with ipsilateral eyelid edema and serous discharge. In the absence of herpetic lesions of the cornea or skin, herpetic conjunctivitis is indistinguishable from ophthalmia from other causes. Depending on the duration and severity of infection, examination of the cornea can reveal superficial keratitis, epithelial dendrite, geographic ulcer, or disciform stromal keratitis.[60] Although keratoconjunctivitis can be the sole manifestation of HSV infection in the neonate, it more commonly appears in association with other manifestations of systemic infections.[56,57] Most corneal infections in the neonate are detected with the use of a speculum to hold the eyelids apart and a cobalt blue light to illuminate the corneal surface, stained with a fluorescent dye.

Diagnosis

The diagnosis of HSV infection is confirmed by culture of specimens obtained from skin vesicles or conjunctival or corneal lesions. Plasma polymerase chain reaction (PCR) assay also can aid diagnosis. All neonates in whom HIV infection is suspected should undergo lumbar puncture and CSF testing for HSV DNA using PCR. Direct immunofluorescence assay or enzyme immunoassays also can be performed on swabs from the conjunctiva, but their sensitivity and specificity rates are lower than those of PCR.

Treatment

All infections caused by HSV in the neonatal period are treated with systemically administered acyclovir (60 mg/kg/day in three divided doses intravenously for 14 days; duration may be longer if other sites are involved. Keratoconjunctivitis usually responds to systemic treatment but may require the addition of topical therapy (1% trifluridine, 0.1% iododeoxyuridine, or 0.15% ganciclovir). Topical cycloplegics are indicated for relief of ciliary spasm if keratitis is present. Topical corticosteroid agents should be avoided because they may augment corneal damage.

Other Infectious Causes

The predominant bacterial pathogens recovered from young infants with nonchlamydial, nongonococcal conjunctivitis include *Haemophilus influenzae, Streptococcus pneumoniae,* and coagulase-negative staphylococci (CoNS) (see Table 80.1).[2–6,8–12,14,61] Although less common, various gram-negative organisms, such as *Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa* (especially in nosocomial settings), and *Neisseria cinerea,* collectively account for a sizable proportion of cases of conjunctivitis. Isolation of these bacteria from conjunctival specimens is not a priori evidence of causation. Demonstration of neutrophils and a single bacteria organism (especially when also present intracellularly) supports a pathogenic role.

Staphylococci have been implicated in ophthalmia neonatorum, but in most cases it is unclear whether the organisms resided on the conjunctiva or the eyelid (where CoNS is normal flora).[62,63] *S. aureus* can be acquired vertically or postnatally from the skin or nares of hospital personnel or from family members. Infection usually manifests as mild catarrhal conjunctivitis with mucoid or mucopurulent discharge. Potential ocular complication of such as corneal infiltrates and ulcers is perforation and resulting endophthalmitis. Systemic complications include infection at contiguous or distant sites (sinusitis, pneumonia, osteomyelitis, septicemia) or toxin-mediated disease (scalded-skin syndrome).[64] Localized staphylococcal conjunctivitis in a well infant can be treated with topical erythromycin, bacitracin ointment, or polymyxin B–trimethoprim eye drops. Susceptibility tests should be performed as community-associated and hospital-associated *S. aureus* can be multiply resistant.

P. aeruginosa is a rare but important cause of conjunctivitis in hospitalized infants. Prematurity, ventilatory support, and receipt of systemic antibiotic therapy are risk factors. Conjunctivitis can be self-limited and associated with moderate discharge or can progress rapidly, resulting in corneal abscess and endophthalmitis followed by septicemia and death.[65–67] The diagnosis should be suspected when Gram stain of exudate reveals slender gram-negative bacilli. Treatment is topical tobramycin drops, initially instilled every 3 hours. Some experts advocate the addition of subconjunctival tobramycin because of its high intraocular penetration.[68] Lack of response to therapy or progression to endophthalmitis, or periocular infection, requires systemic or intraocular antibiotic therapy, or both (see Chapter 84).

Prophylaxis

In 1881, Credé introduced ocular prophylaxis, consisting of cleansing of the eyelids immediately after birth followed by instillation of 2% silver nitrate drops into the conjunctival sac. Combined results of 24 studies conducted in North America and Europe between 1930 and 1979 indicated that only 0.06% of infants receiving topical silver nitrate experienced gonococcal ophthalmia.[69] Reported incidence was similar in the US among 12,431 infants born between 1986 and 1988.[70] However, use of silver nitrate is limited by its failure to prevent all cases of gonococcal ophthalmia,[71–73] chemical conjunctivitis, and corneal scarring after inadvertent use of a high concentration of silver nitrate. Silver nitrate is no longer available in most countries. Changes in the epidemiology of ophthalmia to a predominance of *C. trachomatis* in the early 1970s, however, prompted consideration of alternate prophylactic strategies.[74] Topical erythromycin and tetracycline were proposed because of their activity against *C. trachomatis*.[24] Two US studies have shown that, although silver nitrate, erythromycin, and tetracycline preparations are each effective prophylaxis against gonococcal ophthalmia, none prevents chlamydial ophthalmia.[13,70]

The American Academy of Pediatrics and the Centers for Disease Control and Prevention recommend the use of 1% tetracycline ointment or 0.5% erythromycin ointment for prophylaxis against *N. gonorrhoeae*.[55] Although this treatment is highly effective when administered properly and within 1 hour of birth, infants born to mothers with active infection also should be treated with a single dose of ceftriaxone given intravenously or intramuscularly (25–50 mg/kg; maximal dose 125 mg).[55] In developing countries, a single application of a 2.5% solution of povidone-iodine can be considered for ocular prophylaxis because it is inexpensive and has been shown to be more effective and less toxic than erythromycin and silver nitrate.[75] A second application of 2.5% povidone-iodine was found to be no more efficacious than a single application.[76] Reducing STIs and treating infected mothers before parturition are the best means of preventing infection in neonates.[77] As the incidence of neonatal conjunctivitis has decreased, several European countries have dropped their recommendation for antibiotic prophylaxis, and others have advocated abandoning routine prophylaxis with erythromycin because the incidence of resistance can be as high as 25%.[78] With concerns of underreporting and because the risk for treatment is low and consequences of infection from gonococcus substantial, routine prophylaxis continues to be recommended in the US.[79–80]

Key Points

Diagnosis and Management of Neonatal Conjunctivitis

Epidemiology

- Conjunctivitis occurring in infant in first 28 days of life
- Incidence 1%–12%; more common in developing countries where mothers do not receive prenatal care
- Risk for infant infection when mother has active gonorrhea is about 28%.
- Risk for infant infection when mother has active *Chlamydia* infection is up to 50%.
- In mothers who have received prenatal care and testing, most cases are due to *Staphylococcus, Streptococcus, Haemophilus,* and gram-negative species.

Clinical Features

- *Neisseria gonorrhea* manifests usually with hyperacute copious mucopurulent discharge between 2 and 7 days of age.
  - Can rapidly lead to corneal perforation if not treated
- *Chlamydia trachomatis* manifests with mucoid discharge between 5 and 14 days of age.

▪ If untreated, infants may develop pneumonia.

- HSV can manifest with or without corneal involvement and less mucoid discharge, characteristically between 6 and 14 days of age.

Diagnosis

- Swab for Gram stain, culture, and susceptibility testing
- Swab for *Chlamydia* culture, nucleic acid amplification test, or PCR
- Swab for HSV PCR assay if clinical suspicion (plus CSF and plasma PCR)

Treatment

- *Neisseria gonorrhoeae:* hospitalization and systemic ceftriaxone or cefotaxime plus very frequent irrigation
- *Chlamydia trachomatis:* erythromycin 50 mg/kg/day orally for 14 days
- Bacterial infection: polymyxin B−trimethoprim solution or polybacterial ointment applied topically; systemic therapy depending on clinical findings
- Must test mother for other STIs and report positive cases to public health officials

CSF, cerebrospinal fluid; HSV, herpes simplex virus; PCR, polymerase chain reaction; STI, sexually transmitted infection.

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81

Conjunctivitis Beyond the Neonatal Period

Douglas R. Fredrick

Conjunctivitis is the most common infectious disease of the eye in childhood. It is useful to separate conjunctivitis into acute infection (abrupt onset, lasting less than 10 to 14 days) and chronic infection (insidious onset, often persisting for several weeks, months, or even years). Most cases of acute conjunctivitis are self-limited and can be managed by primary care providers. Evaluation and successful management of chronic conjunctivitis, however, usually require consultation with an ophthalmologist for specialized diagnostic techniques and to prevent eventual vision-threatening damage.

Microorganisms can be transmitted to the ocular surface in a number of ways, but direct contact with contaminated fingers is the most common. Bacterial pathogens usually are found in nasopharyngeal secretions as well. Viral pathogens have specific tissue tropism, some rarely affecting conjunctival mucosa (e.g., influenza, respiratory syncytial virus), with others having a proclivity for conjunctival mucosa (e.g., adenovirus, herpes simplex). Organisms can be inoculated into the conjunctiva by airborne droplets produced by coughing and sneezing and, because many viruses can remain viable on dry surfaces for several hours, infection can result from exposure to infected fomites. Vector-borne ocular infections occur in some developing countries. For example, the filarial parasite *Onchocerca volvulus* is transmitted to the eye by the bite of an infested blackfly.

Conjunctivitis is a clinical diagnosis based on the presence of conjunctival hyperemia and ocular discharge. Typically, the palpebral conjunctiva is more inflamed than the bulbar conjunctiva, and the area surrounding the cornea (limbus) is spared. Thus, pulling down the lower lid and noting the predominant area of inflammation enables one to distinguish conjunctivitis from keratitis, uveitis, and other causes of red eye.[1,4] Conjunctival hyperemia associated with Kawasaki disease or bacterial toxin-mediated syndrome is distinguished by predominant involvement of bulbar conjunctivae and lack of exudate. The concurrent presence of a serous or purulent discharge confirms the diagnosis of conjunctivitis. Scant amounts of conjunctival discharge are best confirmed by asking the patient about the presence of eyelid crusting on awakening because dried exudate accumulates along the lid margins during sleep.

Acute Conjunctivitis

Etiologies

Bacteria and viruses cause acute conjunctivitis. An epidemiologic study of 99 children with conjunctivitis published in 1981 observed that 65% of cases of acute conjunctivitis were caused by bacteria and 20% of cases by a virus.[2] A similar study of 95 children published in 1993 confirmed that the majority (78%) of infections were caused by bacteria.[3] Differentiating features of bacterial conjunctivitis and viral conjunctivitis are shown in Table 81.1.

TABLE 81.1

Clinical Findings in Acute Bacterial and Viral Conjunctivitis

Clinical Finding	Bacterial Disease	Viral Disease
Bilateral disease at onset	50%–74%	35%
Conjunctival response[a]	Papillary[b] or nonspecific	Follicular[c]
Conjunctival discharge	Mucopurulent	Watery
Conjunctival membrane	Late onset	Early onset
Preauricular adenopathy	No[d]	Yes
Concurrent otitis media	20%–73%	10%

[a] Conjunctival response refers to conjunctival appearance on slit-lamp examination.

[b] Papillary response denotes focal area of inflamed conjunctiva centered on a blood vessel.

[c] Follicular response represents focal accumulation of lymphocytes encircled by blood vessels.

[d] Except granulomatous bacterial infection.

Data from Gigliotti F, Williams WT, Hayden FG, et al. Etiology of acute conjunctivitis in children. J Pediatr 1981;98:531–536; and Weiss A, Brinser JH, Nazar-Stewart V. Acute conjunctivitis in childhood. J Pediatr 1993;122:10–14.

Bacterial Causes

Haemophilus influenzae and *Streptococcus pneumoniae*.

Nontypable *Haemophilus influenza*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis* are most commonly isolated bacteria.[2,3] Collectively, these organisms are responsible for 55% to 72% of acute bacterial infections of the conjunctivae.[5] An outbreak of 698 cases of acute conjunctivitis on a college campus in 2002 was caused by an atypical, unencapsulated strain of *S. pneumoniae* that was identical to strains that had caused outbreaks two decades previously.[6]

Staphylococci.

Staphylococcus aureus and *S. epidermidis* often are recovered from “eye” cultures but are infrequently a cause of acute conjunctivitis.[3] Studies in which the lids and conjunctivae are sampled separately show that staphylococci can be recovered in relatively large numbers from lids, whereas few organisms are recovered from conjunctivae. Although staphylococci commonly colonize the lids without causing disease, they can cause blepharoconjunctivitis, a chronic infection of the lid margins.

Gram-Negative Bacilli.

Gram-negative bacilli other than *H. influenzae* occasionally cause conjunctivitis. Special clinical circumstances usually are pertinent, such as (1) exposure to broad-spectrum antibiotics that promote the emergence of gram-negative flora; (2) circumstances of poor hygiene in which children rub their eyes with fingers contaminated by feces or urine; and (3) prolonged hospitalization, especially in intensive care settings, where immobilization, exposure keratitis, and dragging of a tracheal suction catheter across the face raise the risk for direct inoculation.[7]

Neisseria gonorrhoeae.

Neisseria gonorrhoeae rarely causes conjunctivitis but is important to consider because infection can lead to corneal ulceration and blindness.[8,9] The organism binds avidly to surface receptors on the conjunctivae and cornea, triggering the release of bacterial toxins and inflammatory enzymes that damage the corneal epithelium and underlying collagenous stroma. Clinical hallmarks of infection are the onset of purulent conjunctivitis after an incubation period of less than 7 days and the presence of corneal opacification. Unusual cases of infection after incubation periods of up to 19 days and infection associated with minimal symptoms have been reported.[10,11] Beyond the neonatal period, gonococcal conjunctivitis is a result of sexual activity or abuse.[12] *N. gonorrhoeae* can be isolated from the pharynx, rectum, or genital mucosa as well as conjunctivae.

Neisseria meningitidis.

Neisseria meningitidis, a rare cause of conjunctivitis, is important because it can be complicated by meningococcemia and meningitis.[13–16] In a report of 21 cases and a review of 63 previously reported cases, Barquet and colleagues[15] noted that 18% of patients with conjunctivitis due to *N. meningitidis* experienced meningococcemia. Systemic infection was more common among those treated with topical antibiotics alone. Bilateral hyperacute conjunctivitis is typical. Conjunctival scrapings show the presence of gram-negative intracellular diplococci.

Haemophilus aegyptius.

Haemophilus aegyptius deserves special mention because it can cause a meningococcal-like illness (see Chapter 173). In South America, this organism is the cause of Brazilian purpuric fever.[17,18] Especially prominent in children younger than 10 years, this catastrophic illness typically begins as hyperacute conjunctivitis, which is followed by fever within 3 to 5 days. Disseminated purpura, hypotensive shock, and death ensue within 48 hours. Molecular studies show that all isolates causing Brazilian purpura fever are related genetically.[19] Initially, all reported cases came from São Paulo, Brazil, and the neighboring state of Parana, but new strains emerged in other regions, raising concern about the disease's potential to spread worldwide.[20] The genome of pathogenic *H. aegyptius* is larger than that of nonpathogenic strains. Frequent gene exchange between bacterial species has been shown to underlie this genetic addition.[21,22] In the United States *H. influenzae* biotype *aegyptius* (a nontypable *H. influenzae*) is associated with simple acute seasonal conjunctivitis.

Viral Causes

Viral conjunctivitis has an acute onset, spreading from one eye to the other within a week, and the inflammation lasts 4 days to 2 weeks. (Fig. 81.1) Involvement of the second eye usually is less severe than the first affected eye, and this pattern helps distinguish viral from bacterial causes. Conjunctival discharge is watery, and slit-lamp examination shows follicular hyperplasia of conjunctivae. Inflammatory membranes over the conjunctival surface can develop. Lid swelling can be minimal or marked. Invasion of the corneal epithelium (punctate keratitis) is associated with pain and photophobia. Superficial keratitis usually is transient but can evolve into an immune-mediated stromal keratitis that reduces vision. Ipsilateral preauricular adenopathy is common. Acute follicular conjunctivitis can be caused by a number of viruses, with associated ocular and nonocular clinical manifestations (Table 81.2).

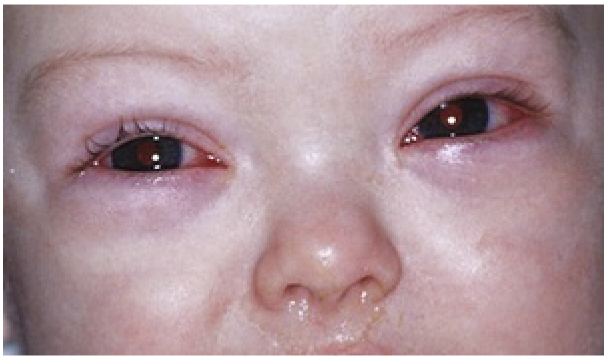

FIGURE 81.1 Bilateral conjunctivitis due to adenovirus.

(Courtesy of J. H. Brien ©.)

TABLE 81.2

Diagnostic Features of Acute Follicular Conjunctivitis

Clinical Syndrome	Etiologic Agent	Eyelid Lesions	Corneal Lesions	Nonocular Findings
Pharyngoconjunctival fever	Adenoviruses 3 and 7	None	Punctate epithelial keratitis	Fever, pharyngitis
Epidemic keratoconjunctivitis	Adenoviruses 8, 19, and 37	Lid swelling	Early: epithelial keratitis Late: subepithelial opacities	None
Herpetic keratoconjunctivitis	Herpes simplex virus	Vesicles	Punctate epithelial keratitis Dendritic keratitis	None
Acute hemorrhagic conjunctivitis	Enterovirus 70, coxsackievirus A24	None	Punctate epithelial keratitis	Neurologic sequelae Facial palsy Radiculomyelitis
Newcastle disease	Newcastle disease virus	None	Punctate epithelial keratitis	Usually occurs in poultry workers or veterinarians
Rubella, rubeola	Rubella and rubeola viruses	Skin exanthem	Punctate epithelial keratitis	Fever, diffuse exanthem, cough, rhinorrhea; occipital, postauricular adenopathy (rubella); Koplik spots (rubeola)

Modified from Dawson CR, Sheppard JD. Follicular conjunctivitis. In: Tasman W, Jaeger EA (eds). Duane's Clinical Ophthalmology, vol 4. Philadelphia, Lippincott-Raven, 1991, pp. 1–26.

Adenovirus.

Pharyngoconjunctival fever is characterized by the concurrent presence of fever, pharyngitis, and conjunctivitis.[23,24] It is caused by adenovirus (serotypes 3 and 7) and usually affects children younger than 10 years. Although direct contact with airborne droplets is the usual mode of transmission, prolonged fecal excretion of the virus may be responsible for epidemics associated with swimming pools.[24]

Epidemic keratoconjunctivitis is the most common ocular infection due to adenovirus (usually serotypes 8, 19, and 37) in older children.[25,26] Unassociated with fever or pharyngitis, conjunctivitis often is associated with corneal inflammation. The epithelia of the cornea and conjunctiva share a membrane cofactor protein (CD46) that attaches to and promotes entry of adenovirus type 37.[25] Diffuse punctate lesions of epithelial keratitis evolve over 7 to 10 days into circumscribed subepithelial opacities that can impair vision and result in local discomfort for weeks to months. Resolution occurs without scarring. In young children, adenovirus conjunctivitis often causes ocular adnexal inflammation, eyelid edema, and erythema simulating periorbital cellulitis; an inflammatory pseudomembranous or palpebral conjunctivitis is distinctive.[27] Direct contact with infected individuals is the usual mode of transmission,[28,29] but indirect spread by common-use instruments, particularly those used by ophthalmologists, also can occur.[30,31] Adenoviral conjunctivitis can be associated with an acute respiratory infection. Faden and colleagues reported an outbreak of adenovirus 30 disease in a neonatal nursery in which 6 infants with preexisting respiratory disease expired, and ophthalmologic procedures were the infectious source.[32,33]

Herpes Simplex Virus.

Both primary and recurrent herpes simplex virus (HSV) infections can result in unilateral follicular conjunctivitis or blepharoconjunctivitis.[26] Single or multiple clusters of vesicles characteristically appear on the eyelid and progress through pustular and crusted stages before healing (Fig. 81.2). When present, accompanying corneal ulcers manifest as marginal infiltrates, punctate epithelial defects, or classic dendrites. Whenever a child or adult has had an episode of herpetic blepharoconjunctivitis, it is imperative that subsequent episodes of conjunctivitis be promptly evaluated by an ophthalmologist because recurrent episodes usually involve the cornea. Prompt antiviral treatment of herpetic keratoconjunctivitis can prevent blindness resulting from corneal scarring.

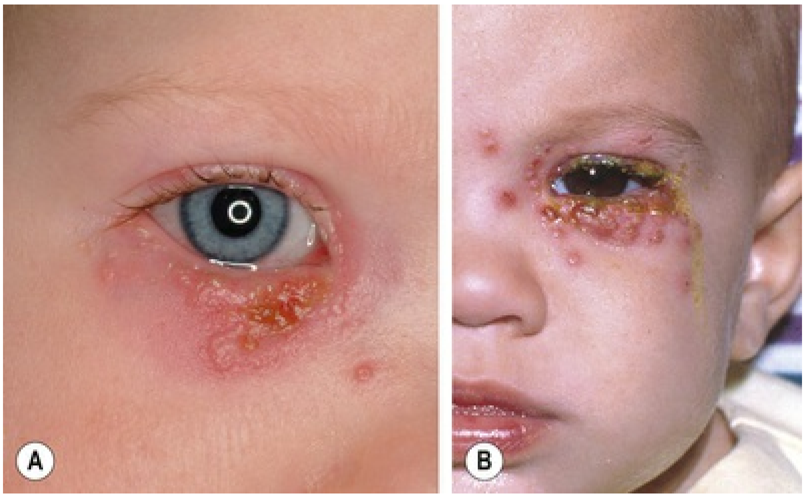

FIGURE 81.2 (A, B) Typical herpetic skin lesions of the eyelids associated with conjunctivitis in various stages of development and healing. (Courtesy of J. H. Brien ©.)

Picornaviruses.

Acute hemorrhagic conjunctivitis is a highly contagious illness usually caused by the picornaviruses, especially enterovirus 70 and coxsackievirus A24. Infection is characterized by the sudden onset of bilateral conjunctivitis associated with profuse watery discharge, lid edema, and fine, punctate epithelial keratitis.[34–36] A prominent distinguishing feature is the presence of subconjunctival hemorrhage, which can be pinpoint or confluent. The disease lasts for 3 to 5 days and resolves without adverse ocular sequelae. However, this pandemic infection can be accompanied by neurologic involvement, in particular radiculomyelitis with extremity weakness, unilateral facial nerve palsy, or other cranial neuropathies.[37,38]

Conjunctivitis-Otitis Syndrome

Because 20% to 73% of children with conjunctivitis have otitis media, children presenting with conjunctivitis should have otoscopic examinations. Nontypable *H. influenzae* is the major pathogen implicated.[39–42] In one study from France, 16% of children with acute otitis media had concurrent conjunctivitis; conjunctival exudates yielded growth of nontypable *H. influenzae* in 89% of 419 cases.[42]

Diagnosis

Most cases of acute conjunctivitis occurring in children do not require confirmation of bacterial cause because empiric therapy is cost-effective and efficacious. Conjunctival swabs should be obtained for microbiologic evaluation from affected neonates, immunocompromised children, hospitalized children, and those in whom infection caused by HSV is suspected. Etiologic agent usually cannot be predicted clinically. Bacterial cultures are more useful than viral cultures because their diagnostic yield is higher and their costs are lower. The combination of sterile culture of conjunctiva and low density of organisms from lid cultures is strong indirect evidence of a viral infection.[3] Molecular detection of adenovirus with real-time, polymerase chain reaction assay is rapid and is an acceptable alternative to viral cultures.[43,44] When HSV is a diagnostic consideration, viral cultures should be performed.

Although rarely necessary, conjunctival scraping can be helpful.[3,45] Specimens should include conjunctival epithelial cells to allow detection of intracellular pathogens. The conjunctival surface is scraped gently with a spatula after the instillation of topical anesthetic drops; swabbing of surface exudate with a cotton-tipped applicator is more likely to yield an amorphous mixture of fibrin and cellular debris than intact cells. Gram stain of the scraping provides preliminary information about the presence and relative quantity of bacteria. Giemsa stain can help to differentiate bacterial infections from viral infections; predominance of neutrophils typically is present in bacterial infections, and a predominance of lymphocytes suggests viral infection.

Treatment

Bacterial Disease

Acute conjunctivitis usually is self-limited. Topical antibiotic treatment is recommended because it speeds eradication of the offending pathogen and shortens the duration of symptoms.[46] Clinical factors for low risk for bacterial conjunctivitis, such as lack of discharge causing eyelid closure, age >6 years, and occurrence from April through November, are commonly associated with negative bacterial culture, reducing the value of treatment with antibiotics.[47,48] In general, treatment is empiric because cultures and cytologic examinations are not performed routinely. When the decision to treat with antibiotics is made, topical antibiotic therapy should be broad spectrum, nontoxic, and inexpensive.[49,50]

For infants, erythromycin ointment or polymyxin B–bacitracin ophthalmic ointment instilled 3 times a day for 5 to 7 days is well tolerated and treats most pathogens.[4,46] Ointments and solutions containing neomycin should be avoided because there is a high incidence of allergic sensitization with these agents. For older children, ophthalmic solutions should be used, and polymyxin B –trimethoprim solution or sodium sulfacetamide 5% solution are good choices for broad-spectrum coverage.[51–53] Tobramycin 3% solution is used commonly, but resistance of *Streptococcus* spp. limits effectiveness. Topical fluoroquinolones such as ciprofloxacin, ofloxacin, and norfloxacin are effective but expensive. The widespread use of topical fluoroquinolones has led to the emergence of resistant organisms; therefore their use should be restricted to infections involving the cornea or to those caused by gram-negative organisms in hospitalized patients.[54–63] Azithromycin 1.5% ophthalmic solution is well tolerated and has good coverage, especially against *Haemophilus* and many *Streptococcus* spp.[64]

Systemic antibiotics are effective in the treatment of bacterial conjunctivitis. Their use is recommended when there is concurrent acute otitis media (AOM) or streptococcal pharyngitis. Oral therapy may prevent the development of AOM. In one study, 11 of 42 (26%) patients treated with topical antibiotics alone, but only 2 of 41 (5%) patients treated with topical and systemic antibiotics, had evidence of AOM at a 2-week follow-up visit.[40] In another study, however, oral cefixime was no more effective than topical polymyxin B –bacitracin for either the eradication of conjunctival colonization or prevention of AOM.[4]

Intravenous antibiotics attain levels in the conjunctiva that are sufficient to eradicate potential pathogens. Efficacy of oral therapy is less clear because the conjunctival concentrations of drugs are substantially lower. In one study, 46 of 48 (96%) children with acute conjunctivitis treated with oral antibiotics alone had negative bacterial cultures after 3 to 5 days of therapy.[65] A controlled study by Isenberg and associates[66] indicated that topical solution of 1.25% povidone-iodine is as effective as neomycin–polymyxin B

−gramicidin in the treatment of acute conjunctivitis. Low cost and lack of microbial resistance make this an attractive option, especially in developing countries.

Herpes Simplex Virus

Treatment of HSV eye infections should be undertaken in collaboration with an ophthalmologist. Orally administered acyclovir and topical trifluridine are both effective, but intravenous therapy should be used when treating a patient with a history of atopy, a child with disseminated disease, an immunocompromised child, or a neonate.[67] Topical corticosteroid agents are contraindicated in suspected conjunctivitis and superficial keratitis due to HSV but are used by ophthalmologists on occasion, in conjunction with antiviral agents, for immune-mediated disease of the corneal stroma.

Adenovirus and Other Viruses

Treatment is supportive and may include cool compresses, use of artificial tears, and topical vasoconstrictors. Topical ketorolac 0.5%, a nonsteroidal anti-inflammatory agent, used 4 times daily is no better than artificial tears.[68] Topical cidofovir, a broad-spectrum antiviral agent, is not effective at 0.2% concentration, and the 1% concentration is limited by local toxicity.[69,70] Corticosteroid drops are contraindicated because they predispose to corneal involvement and can prolong viral shedding, as observed in an animal model.[71]

Chronic Conjunctivitis

Nasolacrimal Duct Obstruction

Nasolacrimal duct obstruction is the most common cause of chronic or recurrent eye infection of infants.[72] Although usually a developmental anomaly, sometimes obstruction can be acquired (as following local adenovirus or bacterial infection). Persistence of an imperforate membrane along the nasolacrimal duct blocks tear drainage and predisposes to secondary infection of retained tears. Consequently, tears pool in the conjunctival cul-de-sac and then spill over the lid margins, flowing onto the cheek (epiphora). At night or during sleep, spillage of infected material leads to accumulation of crusted exudate along the lid margins.

Digital compression of the lacrimal sac region usually elicits reflux of mucopurulent discharge. When reflux cannot be elicited, delayed clearance of 5% fluorescein dye instilled onto the eye confirms the diagnosis of a blocked tear duct. The conjunctiva appears normal or only minimally inflamed. The lower eyelid skin frequently becomes red and inflamed due to chronic wetness and rubbing, but the tissue is not edematous, painful, or tender, differentiating this condition from cellulitis. Topical antibiotics and digital massage of the lacrimal sac are the initial treatments of choice. Because 95% of obstructions resolve by 12 months of age, lacrimal duct probing is reserved for patients in whom obstruction persists beyond this age.

Blepharitis

Blepharitis is a primary infection of the eyelid with secondary inflammation of the conjunctiva. Blepharitis is the most common cause of chronic conjunctivitis in older children.[72,73] *S. aureus* or coagulase-negative staphylococci (CoNS) is the usual pathogen. Affected children come to medical attention because of red eyes, ocular irritation, chronic eye rubbing, and pulling of the eyelashes. Photophobia raises suspicion of corneal involvement.

Clinically, it is useful to separate blepharitis into anterior and posterior types. Anterior blepharitis is accompanied by crusting along the lid margin because of the buildup of epithelial debris and fibrin centered on the eyelashes (cilial collarettes). Close inspection reveals superficial excoriations of the lid margin and telangiectatic vessels. Chronic rubbing of the eyelid and eyelash pulling lead to breakage and partial loss of eyelashes. In posterior blepharitis, the meibomian gland orifices, located along the posterior lid margin, are blocked, causing retention of sebum and predisposing to meibomian cysts, chalazion, and secondary infections. The incidence of meibomitis peaks in young children[74] and during adolescence, when the sebaceous glands undergo hormonal stimulation. Examination reveals inspissation of meibomian glands, from which exudative material can be expressed by gentle compression of the lids with cotton applicators. Although blepharitis is a clinical diagnosis, the recovery of relatively more staphylococcal species from lid cultures than conjunctival cultures and cytologic evidence of neutrophils on Giemsa stains of conjunctival scrapings help to confirm the diagnosis.

The most common complication of blepharitis is chalazion formation. This results from obstruction of the meibomian gland orifices by debris and secondary infection. Blepharitis should be suspected in any child who demonstrates recurrent or multiple chalazions. Toxic epithelial changes of the cornea (punctate keratitis), immune-mediated subepithelial infiltrates, and marginal ulcerations can result from corneal contamination with exotoxins of staphylococci. Chronic staphylococcal keratitis can lead to corneal neovascularization and visual loss.

Blepharitis cannot be cured, but symptoms can be controlled through the use of eyelid hygiene and topical antibiotics. Lid hygiene entails applying a washcloth presoaked in warm water at least 2 to 4 times a day and scrubbing the lid margin with a cotton-tipped applicator presoaked in a 50 : 50 mixture of a nonirritating shampoo (or soap) and water. Attention to personal hygiene and avoidance of chronic eyelid rubbing are helpful in preventing contamination of the lids. Topical antibiotics should be used to treat secondary infection. Bacitracin or erythromycin ointments are appropriate choices. They should be applied 1 to 4 times daily for 1 to 2 weeks and then once daily for 4 to 8 weeks. Treatment is continued for 1 month after all signs of inflammation abate. Topical corticosteroids sometimes are required to suppress the inflammatory component but should be used only with the supervision of an ophthalmologist. Indiscriminate use of corticosteroids could lead to glaucoma and exacerbation of unrecognized herpetic eye disease. Systemic erythromycin in children younger than 8 years and systemic tetracycline in older children are effective treatment options in severe cases of blepharoconjunctivitis.[74,75] Erythromycin and tetracycline appear to accumulate in the meibomian glands, where they inhibit bacterial protein synthesis and lipase breakdown of sebum.

Chlamydial Infections

Trachoma

Trachoma is the most important ocular infection worldwide because it is a major, preventable cause of blindness.[76] *Chlamydia trachomatis*, usually serotype A, B, or C, is the usual cause of infection. Trachoma has an insidious onset in infants and young children, in whom the organism attaches to and invades the conjunctival and corneal epithelium, eliciting the formation of lymphoid follicles. Chronic inflammation causes a loss of conjunctival goblet cells with resulting mucin deficiency and subconjunctival fibrosis (particularly of the upper lid). As lymphoid follicles of the limbus regress, semilunar areas of thinned cornea, known as *Herbert pits*, appear and are pathognomonic of the disease. Progressive cicatrization of the conjunctiva can pull the lid margin inward, causing the eyelashes to rub on the cornea (trichiasis). The combined effects of chronic inflammation, mucin deficiency, and trichiasis can lead to corneal scarring, neovascularization, and blindness.

Trachoma is treated with topical erythromycin or tetracycline or with sulfacetamide ointment applied either twice daily for 2 months or twice daily for the first 5 days of the month for 6 months. Oral erythromycin or tetracycline therapy for 40 days is given if infection is severe. Single-dose azithromycin (20 mg/kg) also is effective and can be beneficial, especially in hyperendemic areas.[77–81] In one large study, the prevalence of infection fell from 9.5% before introduction of single-dose azithromycin therapy to 0.8% 24 months after introduction.[81] On the basis of a chlamydial recurrence rate of 11% at 6 months, one study proposed that repeat single-dose treatment biannually potentially could eliminate ocular *C. trachomatis*.[82]

Inclusion Conjunctivitis of the Adolescent

C. trachomatis (serotypes D through K) is the most common sexually transmitted infection, with disproportionate occurrence in sexually active adolescents.[83,84] The clinical hallmark of eye involvement is a unilateral follicular conjunctivitis with mucopurulent discharge, eyelid swelling, and ipsilateral preauricular adenopathy. Photophobia and severe irritation are symptoms consistent with corneal involvement. The organism invades the corneal epithelium, resulting in a superficial keratitis that can progress to subepithelial infiltrates and micropannus formation. If untreated, the disease can persist for months to years. Diagnosis is based on positive cultures, detection of chlamydial antigens, or molecular techniques. Treatment consists of systemic tetracycline, doxycycline, or erythromycin for 7 days or longer; or azithromycin in a single 1-g oral dose likely also would be effective.

Parinaud Oculoglandular Syndrome

Parinaud oculoglandular conjunctivitis is a syndrome characterized by the presence of granulomatous conjunctivitis and ipsilateral preauricular or submandibular adenopathy. Usually unilateral, there may be one or more granulomas of the upper or lower palpebral conjunctiva. Fever, malaise, and other systemic signs can be present. *Bartonella henselae* is the most common cause,[85] but oculoglandular syndrome also can be associated with tularemia, sporotrichosis, tuberculosis, syphilis, and infectious mononucleosis.

Viruses

Viruses rarely cause chronic conjunctivitis, with the exception of molluscum contagiosum, a poxvirus infection. One or more umbilicated papules of varying size on the eyelid is the cardinal feature. Rupture of lesions on the eyelid margin releases molluscum bodies onto the conjunctiva, inciting a follicular response.[86] Molluscum contagiosum of the eyelids can be a manifestation of human immunodeficiency virus infection.[87] Diagnosis is based on the presence of typical lesions on the lid and elsewhere on the skin. Treatment consists of excision, curettage, or cryopexy of individual lesions.[88]

Allergic Conjunctivitis

Children with allergic conjunctivitis can come to attention acutely, with sudden onset of conjunctival edema and redness, itching, and watery discharge, or can manifest chronic itchy red eyes with minimal discharge. Symptoms often are seasonal and may be accompanied by other signs of seasonal allergies such as nasal congestion and rhinorrhea, cough, and generalized pruritus. Children with atopy are particularly prone to developing allergic conjunctivitis. Treatment includes minimizing exposure to offending allergens, use of artificial tears, topical administration of antihistamine or mast cell stabilizers, or use of systemic antihistamines. Occasionally, topical corticosteroids are required to control severe disease.[89]

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Key Points

Pediatric Conjunctivitis

Epidemiology

- Common condition in children
- Usually self limited; exceptions when etiology is *Neisseria gonorrhoeae*, *Chlamydia trachomatis,* or herpes simplex virus

Clinical Features

- Allergic: red eyes; itchy, watery discharge with accompanying signs and symptoms of seasonal allergies (e.g., rhinorrhea, sneezing, urticaria)
- Viral: red eyes; itchy, watery discharge with accompanying signs of upper respiratory infection; sick contact; preauricular adenopathy if adenovirus; second eye less affected than first
- Bacterial: mucopurulent discharge, often unilateral, sometimes with accompanying acute otitis media
- Herpetic: foreign body sensation, follicular conjunctivitis, watery discharge; occurs more commonly in atopic children

Diagnosis

- Usually a clinical diagnosis

- If hyperpurulent or possibility of sexually transmitted infection, obtain bacterial culture and susceptibility testing, *Chlamydia* culture, nucleic acid amplification test, or immunofluorescent testing.

- If accompanying keratitis, obtain bacterial culture and susceptibility testing and obtain polymerase chain reaction for herpes simplex.

Treatment

- Allergic: avoid allergen; use artificial tears, topical antihistamine, topical mast cell stabilizer, oral antihistamine

- Viral: most cases self-limited and require only symptomatic relief, artificial tears, topical nonsteroidal agent; highly contagious

- Bacterial: broad-spectrum antibiotic polymyxin B−trimethoprim solution speeds resolution of symptoms

- Herpetic: if corneal involvement, use systemic acyclovir; topical agents also are effective but can cause local irritation

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82

Infective Keratitis

Douglas R. Fredrick

Infective keratitis is an uncommon but important infection because it has the potential to cause blindness. It can be caused by a wide variety of microorganisms. Most children with corneal infections come to medical attention because of a painful red eye. Distinguishing infectious keratitis from other causes of red eye accurately and promptly is extremely important.

Pathogenesis

The cornea is susceptible to microbial invasion because of its exposed position, avascularity, and limited inflammatory repertoire. Apart from epithelial Langerhans cells, the normal cornea lacks white cells, which must be recruited from the tear film, limbal lymphoid aggregates, and perilimbal circulation.[1,2] The epithelium and its basement membrane serve as a relative barrier to most infectious agents, but, once breached, the hypocellular stroma is vulnerable to infection, often with organisms of low virulence. Release of proteases, collagenases, and oxygen-derived free radicals from invasive organisms and infiltrating neutrophils degrades collagen and proteoglycans, the major constituents of the corneal stroma.

Trauma caused by the use of contact lenses is the most common factor predisposing to bacterial and fungal keratitis in children (Box 82.1).[3–7] Trauma from contact lenses can cause epithelial damage and corneal hypoxia. The risk for bacterial keratitis is 10- to 15-fold greater in subjects who wear contact lenses overnight compared with users of daily-wear lenses.[8] Orthokeratology, a procedure for reshaping the cornea by wearing nocturnal contact lenses, is popular among teenagers and predisposes to corneal infections.[9] Dry eyes, related to a deficient tear film or abnormality of the ocular surface, corneal anesthesia, and prior treatment with topical corticosteroid agents are other factors increasing the risk for bacterial keratitis. In developing countries, malnutrition, vitamin A deficiency, poor hygiene, and trachoma also predispose to corneal infections.[10]

Box 82.1

Risk Factors for Bacterial Keratitis in Children

Trauma

Corneal foreign body

Corneal abrasion or laceration

Contact lens wear

Trichiasis or distichiasis

Prior ocular or eyelid surgery

Corneal Exposure

Congenital and acquired disorders of the eyelids

Globe proptosis

Facial palsy

Moribund or sedated state

Abnormalities of the Ocular Surface

Dry-eye syndrome

Mucin deficiency from loss of goblet cells

Malnutrition

Corneal anesthesia

Ocular rosacea

Immunodeficiency States

Topical corticosteroid therapy

Immunosuppressive therapy

Immune deficiency syndrome

Atopy

Inadequate eyelid closure is another risk factor for infective keratitis. Corneal exposure in the severely ill or sedated child predisposes to breakdown of the epithelium and secondary infection.[3] Children with eyelid defects, facial nerve weakness, and proptotic globes, as well as those in intensive care under pharmacologic paralysis, are prone to exposure keratopathy and secondary infection. Protocols must be in place to ensure eyelid closure and lubrication in these patients.[11] Premature infants and older children receiving mechanical ventilators are particularly susceptible to conjunctival colonization with *Pseudomonas aeruginosa* and keratitis.[12–14]

Clinical Presentation

Severe pain is the hallmark of infective keratitis. Reflex tearing, redness of the eye, photophobia, and decreased vision are prominent symptoms. Keratitis usually is distinguished by the presence of greyish corneal opacification. Loss of the epithelium over the corneal infiltrate dulls the corneal light reflex and permits topically applied fluorescein dye to stain the area. Progressive destruction can lead to corneal thinning and eventual perforation. The anterior chamber can contain dispersed inflammatory cells or visible aggregates of neutrophils layering inferiorly (hypopyon). In an uncooperative child, examination of the eye is facilitated by the use of a topical anesthetic and a lid speculum.

Etiology

Herpes Simplex Virus

Keratoconjunctivitis caused by herpes simplex virus (HSV) usually is mild and, during the primary episode of infection, is indistinguishable from other causes of viral conjunctivitis except by the presence of skin or corneal lesions. The most common manifestations are unilateral follicular conjunctivitis, watery ocular discharge, and preauricular adenopathy.[15] Inspection of the swollen lids often reveals the presence of vesicles or lid margin ulcerations. Initially, the cornea is spared, but within a few days to 2 weeks, mild punctate keratitis or dendritic keratitis develops in about one half of infected children (Fig. 82.1). Primary herpetic keratitis is self-limited in most children beyond the neonatal period.

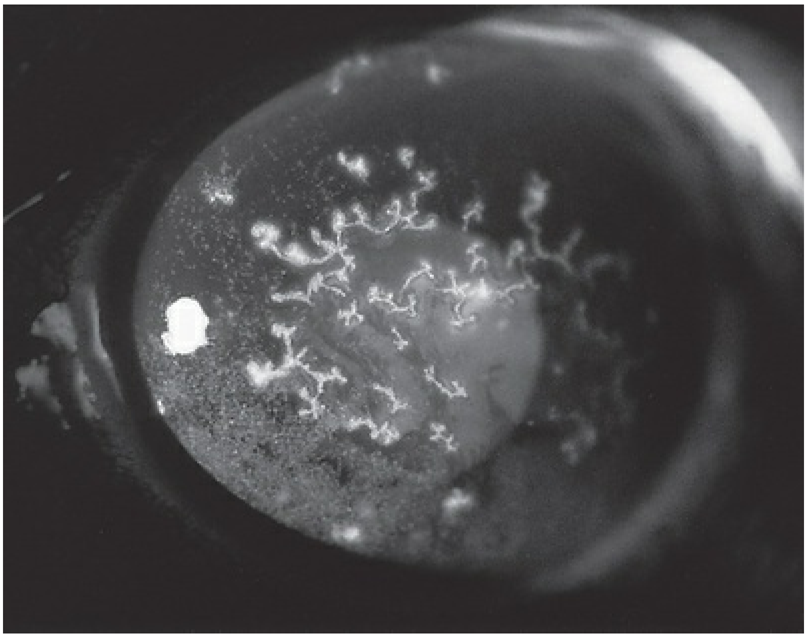

FIGURE 82.1 Classic appearance of primary herpes simplex virus keratitis stained with 1% fluorescein, showing multiple epithelial dendrites.

Most episodes of herpetic keratitis represent recurrent disease after primary infection that has resulted in latent infection of the cornea or trigeminal ganglion. Most recurrent episodes are not accompanied by vesicular skin lesions, but rather manifest as red eye, photophobia, watery discharge, and blurred vision. Up to 38% of children will develop recurrence during childhood. The number, frequency, and type of recurrences are highly variable, with worse vision developing in children who have multiple recurrences.[15–17] The spectrum of recurrent HSV keratitis includes epithelial dendrites (Fig. 82.2), large geographic defects, immune-mediated diskiform edema (Fig. 82.3), necrotizing keratitis complicated by corneal thinning or perforation, and chronic neurotrophic ulcerations. There are few serious sequelae if infection remains confined to the corneal epithelium, but if stromal disease ensues, progressive corneal scarring can result in permanent visual loss.

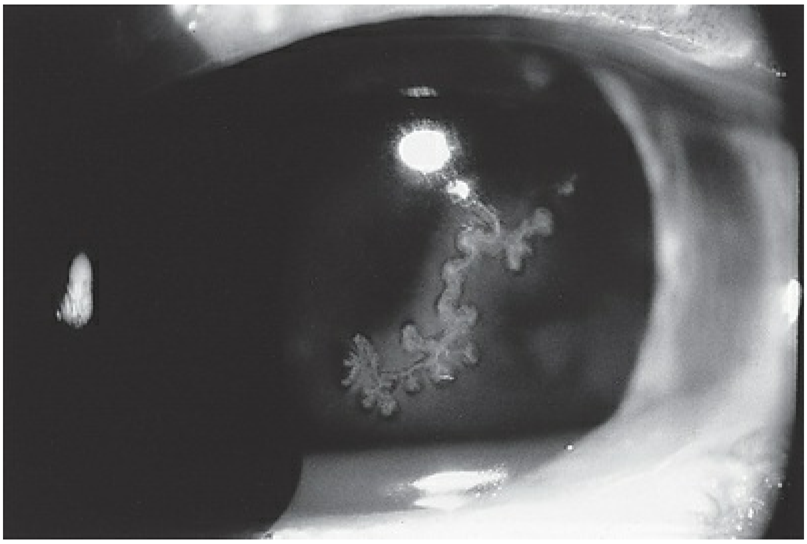

FIGURE 82.2 Slit-lamp appearance of recurrent dendritic keratitis due to herpes simplex virus stained with 1% fluorescein.

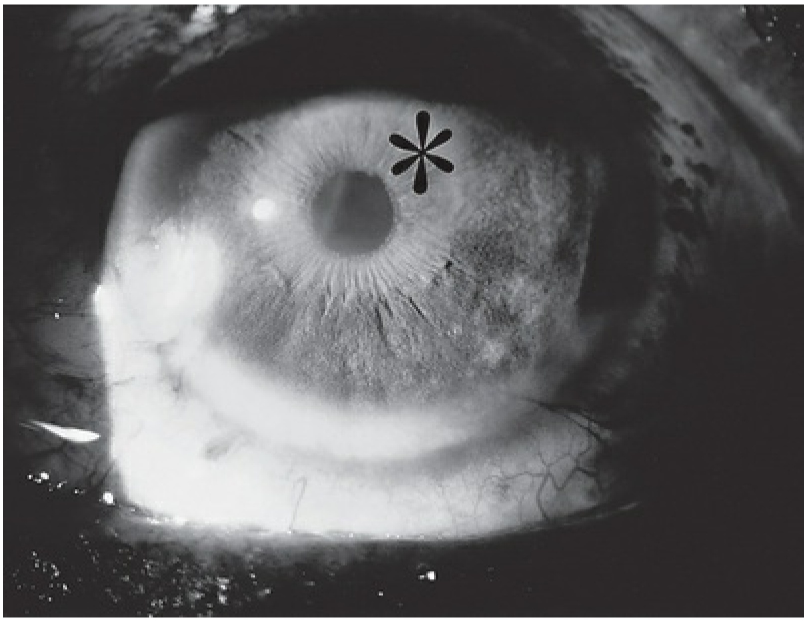

FIGURE 82.3 Herpes simplex virus diskiform keratitis, consisting of a disk-like area of stromal edema *(asterisk)* believed to be a cell-mediated immune response to residual herpes simplex virus antigen.

Varicella-Zoster Virus

Infection caused by varicella-zoster virus (VZV) can be associated with small vesicular or papular eruptions at the limbus. These lesions usually resolve without sequelae, but the affected conjunctiva often is red and painful. Less frequent corneal manifestations of VZV infection include superficial punctate epithelial defects, linear dendrites, and diskiform or necrotizing keratitis with ulceration. Recurrent epithelial or stromal keratitis also occurs.[16,18]

Herpes zoster ophthalmicus refers to reactivation of VZV along the sensory distribution of the ophthalmic division of the trigeminal nerve. Although uncommon in childhood, it can occur because of immunosuppression or after infection contracted during the first year of life.[19] A vesicular eruption is confined to the branches of the ophthalmic nerve. Uveitis and keratitis are the most common ocular manifestations. In the acute infectious stage, examination of the cornea can reveal punctate, dendritic, or geographic epithelial inflammation, which can progress to necrotizing stromal keratitis.[14,20] An immune-mediated response to varicella-related antigens appears as a delayed-onset diskiform or nummular (coin-shaped) keratitis. A chronic and recurrent epithelial or stromal keratitis can occur.[21] All children with zoster ophthalmicus must undergo a funduscopic examination because chorioretinitis can lead to permanent visual impairment. Although herpes zoster infections in previously vaccinated children tend to be mild, some children can have severe sclerokeratitis and anterior uveitis, which can lead to increased intraocular pressure and glaucoma.[22]

Other Viruses

Measles, mumps, rubella, adenovirus, coxsackievirus A24, and enterovirus 70 are associated commonly with a self-limited punctate epithelial keratitis; however, there are important exceptions. Epithelial lesions associated with adenovirus infections sometimes progress over 10 to 14 days to subepithelial opacities that can persist for months.[23] Measles keratitis usually is mild but can cause severe corneal disease when contracted by malnourished, immunocompromised, or vitamin A−deficient children.[24,25] Localized edema of the corneal stroma can, on occasion, be a delayed complication of mumps.[26]

Epstein-Barr virus can invade all layers of the cornea. Superficially there can be multiple epithelial dendrites. Stromal disease is more common and is characterized by multiple coin-shaped lesions in the anterior and mid stroma or recurrent infiltrate of the deeper layers associated with vascularization.[27–29] The condition resolves spontaneously without ocular sequelae; symptomatic treatment with artificial tears is sufficient.

Bacteria

Bacterial infection of the cornea is considered a medical emergency because it can progress rapidly and lead to severe visual loss. The presence of a dense greyish infiltrate and surface ulceration in an actively inflamed eye should be considered bacterial infection until proved otherwise (Fig. 82.4). Infection can be caused by a wide range of gram-positive and gram-negative organisms.[3–6] *Staphylococcus aureus* and streptococcal species are among the most common gram-positive isolates, especially in cooler climates. *Staphylococcus epidermidis* frequently is isolated from corneal cultures, but this often represents contamination from the eyelids. *P. aeruginosa* is the most common gram-negative isolate, especially among contact lens wearers. Ulcerative keratitis also can complicate bacterial conjunctivitis due to *Haemophilus influenzae* and *Moraxella catarrhalis*. *Shigella* and other enteric pathogens can cause keratitis after transfer to the eyes by fingers contaminated from extraocular sites of infection. The most common causes of bacterial keratitis in children are staphylococci and streptococci, seen in children who have chronic bacterial blepharokeratoconjunctivitis. These children often have itchy and burning eyes, photophobia, and tearing. On examination, debris on the eyelashes ("scurf") is seen, which represents protein exudate from inflamed eyelids. Lid margins are red, the myeibomian glands are inspissated with thickened oil, telangiectasia may be seen in ocular rosacea, and there is inflammation of the conjunctiva and cornea. The cornea may have infiltrates at the lid margins, and ulceration and neovascularization can result from chronic inflammation. Chronic cases can appear clinically similar to herpetic eye disease.[30]

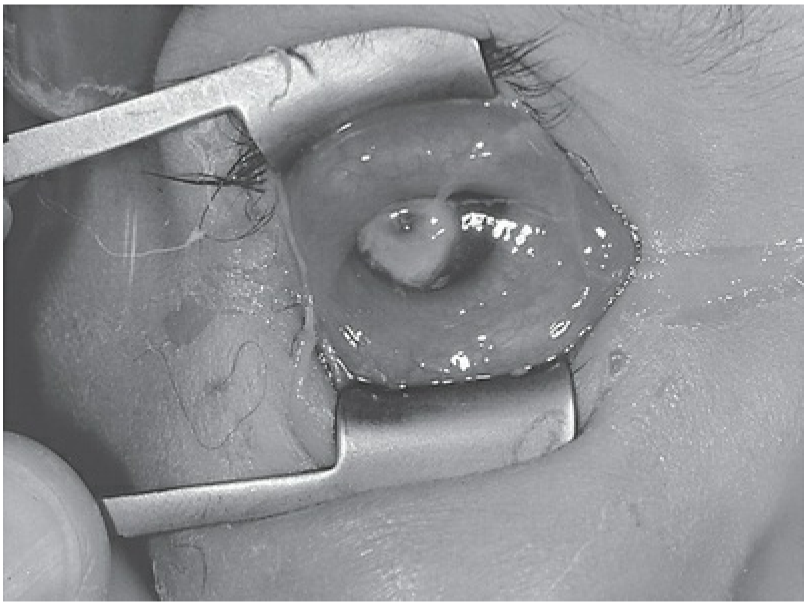

FIGURE 82.4 Perforated keratitis due to *Streptococcus pneumoniae* in a 3-year-old child after an eye injury.

Fungi

Fungal keratitis is rare in childhood and usually is the consequence of ocular trauma, especially with vegetable matter. The prior use of topical corticosteroid agents, systemic immunosuppression, preexisting corneal disease, and tropical environment increase the risk for fungal infection. *Fusarium* spp. were isolated in an outbreak of corneal ulcers associated with the use of a specific contact lens solution.[31] Typically, the ulcer has a subacute onset and progresses insidiously. Slit-lamp examination commonly reveals a yellow-white infiltrate with feathery edges; a dry, raised surface; and satellite lesions.[32,33] A wide range of fungi can be corneal pathogens. *Aspergillus* and *Fusarium* spp. are the most common pathogens worldwide.[3–6,33,34] In the United States, *F. solani* is the most common pathogen in southern states, whereas *Aspergillus* spp. and *Candida albicans* are most common elsewhere.[35,36] Dematiaceous (pigmented) fungi, particularly *Curvularia* spp., are emerging as important corneal pathogens.[33]

Acanthamoeba Keratitis

Acanthamoeba causes a recalcitrant keratitis that frequently leads to visual loss. It usually occurs in contact lens wearers or in persons exposed to contaminated water.[37,38] Severe pain, out of proportion to the severity of the keratitis, is common. This seems to be related to a propensity of the organism to infiltrate corneal nerve endings.[39] Initially, corneal epithelium is involved, and later a stromal infiltrate develops. As the infection progresses the infiltrate becomes most dense at the periphery, giving rise to a characteristic ring-shaped lesion.[40–42]

Interstitial and Marginal Keratitis

Interstitial keratitis usually is a delayed manifestation of a systemic infection from a variety of bacterial, viral, and parasitic pathogens. Congenital syphilis historically was the predominant cause of interstitial keratitis.[43,44] *Mycobacterium tuberculosis,* nontuberculous mycobacteria, *Borrelia burgdorferi,* herpesviruses, and onchocerciasis now are more common causes. Interstitial keratitis represents an immune-mediated reaction to retained microbial antigens rather than active infection. Pain, photophobia, and reflex tearing are the major symptoms. Examination reveals an intact corneal epithelium with underlying cellular infiltration of the superficial or deep stroma. Limbal blood vessels often proliferate and extend into the opacities. After the inflammation subsides, the opacities and blood vessels regress, leaving stromal scars and ghost vessels. Depending on the severity of scarring, final visual acuity ranges from 20/20 to 20/200.[45]

Staphylococcal lid disease is associated with a marginal keratitis in which infiltrates form in the peripheral cornea, often where the lid margins cross the limbus (at 2, 4, 8, and 10 o'clock). Cultures of the infiltrates are sterile, suggesting that they result from hypersensitivity reactions to staphylococcal antigens or exotoxins deposited on the ocular surface (Fig. 82.5). Ocular rosacea can lead to corneal ulceration and should be considered in patients with eyelid disease and recurrent keratitis.[46]

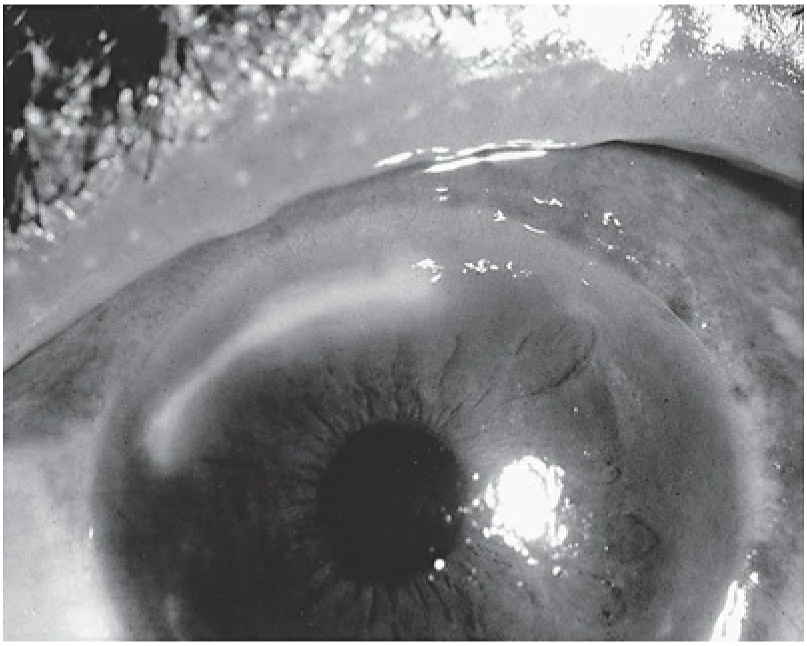

FIGURE 82.5 Extensive marginal keratitis in a child secondary to staphylococcal lid disease. Note the characteristic lucid interval between arcuate infiltrate and corneal limbus.

Diagnostic Procedures

Evaluation of infectious keratitis should include corneal scrapings for smears and cultures. Children often require sedation or examination under anesthesia to allow thorough evaluation and collection of appropriate specimens. Corneal specimens are obtained by scraping the leading edge and base of the ulcer with a sterilized Kimura spatula or Calgi swab.[47,48] Specimens from the lids and conjunctiva should be collected and cultured separately. Ideally, specimens should be inoculated directly onto the culture media because corneal scrapings contain small numbers of fastidious organisms. Amies transport media without charcoal is a useful alternative in the clinical setting.[49] Culture media should include blood and chocolate agar, anaerobic blood agar, Sabouraud dextrose agar (without cycloheximide), and enriched thioglycolate broth. *Acanthamoeba* spp. can be isolated using nonnutrient agar plates overlaid with a dried broth culture of *Escherichia coli.*

Staining of corneal scrapings is important for the early identification of bacteria, fungi, and *Acanthamoeba* and may provide the sole etiologic evidence in culture-negative cases.[47,48] Multiple specimens should be taken for Gram, Giemsa, and other specialized stains. Methenamine silver, acridine orange, and Calcofluor white stains are useful for the detection of fungi and *Acanthamoeba.*[50,51]

Microbial antigens can be detected using immunodiagnostic methods. Enzyme immunoassays and fluorescein-labeled monoclonal antibodies are especially useful in the diagnosis of chlamydial, herpetic, and other viral infections. Recombinant DNA methods have been applied to the detection of corneal fungi, herpes and other viruses, and *Acanthamoeba.*[52–54] Fungi and *Acanthamoeba* can be visualized directly in the cornea with confocal slit-lamp microscopy.[55]

Lumbar puncture should be performed in neonates with suspected herpetic eye disease. Diagnosis is done by polymerase chain reaction testing of cerebrospinal fluid and plasma for HSV.

Treatment

The mainstay of treatment for corneal infections is the intensive use of topical anti-infective agents.[56] Corneal ulcers are medical emergencies. Although some children with keratitis can be managed successfully in an outpatient setting,[57] most require inpatient care. Mydriatic drops should be used to avoid pupillary synechiae and provide comfort; ciliary spasm contributes to photophobia.

Viruses

With the exception of herpesvirus eye disease, the treatment of viral infections is symptomatic because infections are self-limited, and no effective therapy is currently available. Epithelial HSV infections can be debrided or treated with topical antiviral drugs, either vidarabine ointment (Vira-A) or trifluorothymidine (Viroptic) drops or systemic acyclovir. Drops are administered while the patient is awake every 2 hours during the first week and every 6 hours during the second week, and then rapidly tapered because these drugs are toxic to the corneal epithelium.[14] Acyclovir administered systemically is equally effective in the treatment of herpetic keratitis and represents an alternative to topical therapy.[17,58,59] Topical ganciclovir also is available and has similar efficacy to acyclovir. Children with recurrent episodes of herpetic keratitis may benefit from long-term prophylactic use of acyclovir to prevent recurrence, but resistance to acyclovir can develop over time.[60] Stromal HSV disease may require the addition of topical corticosteroid agents, but concomitant use with topical antiviral agents is necessary to prevent the reactivation of epithelial infection. Herpes zoster keratouveitis is unresponsive to available topical antiviral agents and is best managed with frequent application of corticosteroid topically and acyclovir (80 mg/kg/day) orally.

Bacteria

The mainstay of treatment for bacterial keratitis is a combination of a cephalosporin (50 mg/mL) drops and a fortified aminoglycoside, either tobramycin (15 mg/mL) or gentamicin (14 mg/mL).[45] Cefazolin is selected for gram-positive coverage, and ceftazidime is used when there is concern about *P. aeruginosa.* Toxicity, drug instability, and variability of concentration and pH of fortified antibiotics led to the use of topical fluoroquinolone antibiotics, including ciprofloxacin, ofloxacin, and norfloxacin. Several studies have shown ciprofloxacin to be an effective single agent in the treatment of bacterial keratitis.[61,62] Increasing resistance of gram-positive cocci and *Actinomyces* and *Pseudomonas* spp. to ciprofloxacin prompted the concurrent use of a cephalosporin and treatment of bacterial keratitis with a newer generation of fluoroquinolones.[63–67] Levofloxacin penetrates ocular tissues effectively and has superior gram-positive coverage; however, increasing resistance to this agent is reported.[67,68] Moxifloxacin has lower minimal inhibitory concentration (MIC) for gram-positive organisms, and gatifloxacin has lower MIC for gram-negative organisms. Both are active against methicillin-susceptible *S. aureus* isolates.[69] The newer fluoroquinolones are reported to have better in vitro activities, increased ocular penetration, and potentially lower rates of development of resistance than other fluoroquinolones.[70] Severe cases of bacterial keratitis should be treated with a cephalosporin combined with a fluoroquinolone or aminoglycoside. Choices for methicillin-resistant *S. aureus* are limited to gentamicin and vancomycin.

Because of their rapid clearance, topical antibiotics should be administered frequently, beginning with 1 drop every minute for 5 minutes, followed by doses every 15 to 30 minutes until culture results are available.[71] Subsequent therapy is modified according to culture results and clinical course, but treatment usually is continued for 7 to 14 days. A favorable therapeutic response is indicated by diminished pain, healing of the epithelium, decrease in size and density of the corneal infiltrate, and decrease in corneal edema and inflammation in the anterior chamber.

Patients with chronic staphylococcal blepharokeratoconjunctivitis require intensive eyelid hygiene, using warm compresses to liquefy inspissated material in the glands, eyelid scrubs with mild soap to remove debris, topical antibiotics such as erythromycin or bacitracin ointment to treat the bacteria, and sometimes a course of oral antibiotics.[30]

Fungi

Fungal keratitis is treated with topical natamycin, flucytosine, amphotericin B, miconazole, or flucytosine.[32,33] Frequent (hourly) initial instillation is slowly reduced over several weeks. Adequate treatment requires 6 to 12 weeks owing to poor corneal penetration and the slow growth of fungi. Lack of a therapeutic response should prompt the addition of parenteral therapy or consideration of excisional keratoplasty.[72] Deep fungal keratitis requires parenteral therapy from the outset because of the risk for fungal endophthalmitis. Subconjunctival fluconazole can be helpful in severe fungal keratitis unresponsive to topical and systemic therapy.[73]

Acanthamoeba Keratitis

Treatment of *Acanthamoeba* keratitis often is complicated by delayed diagnosis. Early and aggressive therapy with cationic disinfectants (polyhexamethylene biguanide or chlorhexidine), combined with dibrompropamidine isethionate (Brolene) and neomycin, can be curative.[74–79] Both cationic compounds result in rapid killing of the trophozoites and cysts at concentrations that are not toxic to corneal cells.[80] Clearance of *Acanthamoeba* trophozoites and cysts requires months of treatment.[81] Corneal transplantation is only recommended when the infection continues, and anti-infectives will be required long term to prevent recurrence in the graft.

Complications

Long-term complications usually are related to loss of corneal transparency and refractive changes. Central corneal scars (leukomas) that obstruct the visual axis can cause serious visual loss. Although the severity of scarring tends to diminish over time, even short periods of visual deprivation in children younger than 8 years of age can result in development of amblyopia. Although corneal transplants can restore vision,[81] corneal grafting in children may fail because of graft rejection.

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83

Infective Uveitis, Retinitis, and Chorioretinitis

Douglas R. Fredrick

Uveitis refers to any intraocular inflammation. *Anterior uveitis* is characterized by inflammation of the iris and ciliary body (*iridocyclitis*). *Intermediate uveitis* includes inflammation of the pars plana and vitreous (*pars planitis*, *vitritis*). *Posterior uveitis* features inflammation of the retina and choroid (*retinitis*, *choroiditis*). Uveitis is an uncommon disorder in childhood; among affected children, the anterior form is more common than the posterior form.

Anterior Uveitis

Table 83.1 summarizes the important pathogens and disorders responsible for anterior uveitis, with distinguishing features of each. After Kawasaki disease, at least one half of children with an identifiable cause of anterior uveitis have juvenile idiopathic arthritis or human leukocyte antigen (HLA)-B27−related spondyloarthropathy.[1,2]

TABLE 83.1

Common Causes of Anterior Uveitis

Organism or Condition	Duration	Associated Ocular Findings	Associated Systemic Findings
Varicella	Acute	Iris atrophy (rare)	Vesicular skin rash
Herpes simplex	Acute	Keratitis	None
Mumps	Acute	NS	Fever, headache, parotitis
Influenza	Acute	NS	Febrile respiratory illness
Epstein-Barr virus mononucleosis	Acute	NS	Fever, pharyngitis, lymphadenopathy
Measles	Acute	NS	Fever, coryza, Koplik spots
Kawasaki disease	Acute	NS	Fever, mucocutaneous findings, peripheral edema, unilateral lymphadenopathy
Herpes zoster	Chronic	Iris atrophy (common), KP	Fever, vesicular skin rash
Syphilis	Chronic	Iris nodules, chorioretinitis, optic neuritis	Maculopapular skin rash (palms and soles)
Tuberculosis	Chronic	Iris nodules, granulomatous KP, choroidal granulomas	Pulmonary lesions
Lyme disease	Chronic	Keratitis, optic neuritis	Erythema migrans, arthritis
Leprosy	Chronic	"Iris pearls" of iris atropy	Peripheral neuropathy, skin lesions

KP, keratitic precipitates that represent aggregates of inflammatory cells on the corneal endothelium; NS, nonspecific.

Clinical Manifestations

Patients with anterior uveitis come to attention because of ocular pain, photophobia, and blurred vision. The whole eye looks red, but closer inspection reveals that the predominant area of hyperemia is at the corneal limbus owing to the vascular engorgement of the underlying ciliary body. Slit-lamp examination allows visualization of (1) cells floating in the anterior chamber or adherent to the corneal endothelium (keratic precipitates) and (2) turbidity of the normally optically clear aqueous humor resulting from the spillover of protein (flare). Distortion of the pupil is related to formation of inflammatory scars between the iris and lens surface (synechiae). Dystrophic calcification of the epithelial basement membrane (band keratopathy), iris nodules, lens opacities, and phthisis bulbi can occur.

Etiologies

Viruses

Many viruses are associated with an acute nongranulomatous uveitis that is mild and self-limited.[3,4] Varicella-zoster virus (VZV) demonstrates the spectrum of disease involvement. Anterior uveitis resulting in mild inflammation occurs in up to 25% of patients with chickenpox.[5,6] It tends to be self-limited, resolving within 10 to 14 days. By contrast, uveitis associated with herpes zoster ophthalmicus is more severe and usually requires aggressive treatment with a topical corticosteroid, cycloplegic agents, and systemic acyclovir. Devastating visual complications can occur when there is concurrent involvement of structures of the posterior segment. Uveitis associated with herpes simplex virus (HSV) infection usually is a complication of a deep keratitis but can occur without antecedent keratitis.[7]

Mycobacterium tuberculosis

Chronic granulomatous uveitis, sometimes in association with iris nodules, once was caused commonly by *Mycobacterium tuberculosis*.[8] It is now uncommon, except in developing countries and in patients with acquired immunodeficiency syndrome (AIDS).

Treponema pallidum

The incidence of congenital syphilis parallels the incidence of syphilis among heterosexual persons in the United States. Congenital syphilis also remains a problem in developing countries. Chorioretinitis is a classic sign of early congenital syphilis, "salt-and-pepper" pigmentary changes of the peripheral retina being the most common finding.[9,10] Although anterior uveitis is a common presentation, some patients predominantly have intense posterior uveitis with necrotizing retinitis, retinal vasculitis, or optic neuritis.[11,12]

Borrelia burgdorferi

Borrelia burgdorferi, the organism responsible for Lyme borreliosis, can invade the cornea (keratitis) and uveal tract (iridocyclitis), and infection of the vitreous retina and choroid is documented with growing frequency.[13,14] Lyme uveitis can be a late manifestation of Lyme disease.[15,16]

Kawasaki Disease

Anterior uveitis is common in Kawasaki disease. In one prospective study, anterior uveitis was found in 83% of 41 patients with Kawasaki disease in the first week of the disease.[17] Iridocyclitis and periorbital vasculitis also have been described. Conjunctival hyperemia is present in >90% of cases.

Posterior Uveitis (Retinitis)

Table 83.2 summarizes the predominant ocular manifestations and associated findings for the infectious agents most commonly implicated in retinitis.

TABLE 83.2

Common Infectious Causes of Retinitis

Organism	Predominant Manifestation	Associated Findings
Toxoplasma gondii	Necrotizing retinitis	Vitritis, optic neuritis
Rubella virus	Pigmentary retinopathy	Cataract, microphthalmia
Cytomegalovirus	Hemorrhagic retinitis	Cotton-wool spots
Herpes simplex virus	Necrotizing retinitis	Vitritis, vasculitis, optic neuritis
Varicella-zoster virus	Necrotizing retinitis	Occlusive vasculitis, vitritis
Toxocara canis	Retinal granuloma	Vitritis, endophthalmitis

Bacteria and Fungi

Before the advent of effective antibacterial and antifungal therapies, the prevalence of septic emboli and secondary retinitis from bloodstream infection (BSI) was high. The presence of Roth spots (white-centered intraretinal hemorrhages, once believed to be pathognomonic for septic emboli) was a sign of endocarditis. In fact, white-centered hemorrhages are nonspecific and can be seen with septic emboli, clotting abnormalities, trauma, vascular occlusive disease, and vasculitis.[18] The white center can be composed of a fibrin aggregate or can be a mixture of inflammatory cells, bacteria, or fungal organisms. In patients with BSI from infective endocarditis or catheter-related infection, the appearance and resolution of septic emboli can be used to monitor antibacterial therapy.

The incidence of positive retinal findings in patients with fungal BSI ranges from 7% to 20%, with a highest incidence in neutropenic patients receiving chemotherapy or after organ or bone marrow transplantation.[19–22] The incidence in children is lower than in adults.[23] In premature infants, fungal emboli to the crystalline tunica vasculosa lentis can cause inflammatory ocular disease that mimics retinopathy of prematurity, congenital cataracts, or conjunctivitis. Systemic treatment of *Candida* and other fungi with amphotericin, an echinocandin, or voriconazole usually results in resolution of chorioretinal infection; the need for intravitreal injections and surgical vitrectomy has decreased in recent years.[24] For patients with BSI whose initial examination is negative but whose BSI persists, serial examinations should be performed to make certain that there are not new lesions.[25,26]

Toxoplasma gondii

Toxoplasmosis is the most common cause of posterior uveitis in immunocompetent individuals. Infection can be contracted prenatally or postnatally[27–29]; the proportion of prenatal versus postnatally acquired retinal infections varies geographically, and the latter by host conditions. Evidence of congenital infection may be identified at birth as active retinal lesions or inactive chorioretinal scars, or may not become clinically evident until months or years later.[30,31] Acquired infections can be associated with acute or delayed onset of ocular disease. Peak occurrence of acquired infection is between the second and fourth decades of life. Active lesions appear as fluffy, white areas of focal necrotizing retinitis attributable to proliferation of live parasites and reactive inflammatory cells in the overlying vitreous.[31] In some cases, the vitreal reaction is so severe that it obscures the underlying retina, giving the so-called "headlight-in-a-fog" appearance (Fig. 83.1). Healing of these lesions leaves atrophic chorioretinal scars, which can be located in the macula or the peripheral retina (Fig. 83.2). In addition to focal retinitis, there are atypical presentations. Punctate outer retinal toxoplasmosis is characterized by the presence of grey-white lesions of the outer retina with little or no overlying vitritis. In children, an asymptomatic scar is the most common finding, but infection can manifest as uveitis, retinitis, or optic neuritis in up to 20% of cases.[32] Healed lesions appear as granular white opacities. Neuroretinitis features optic disk swelling with macular exudates and visual loss and multifocal retinal infiltrates.[33] Optic neuritis can follow infections of the nerve or surrounding retina.

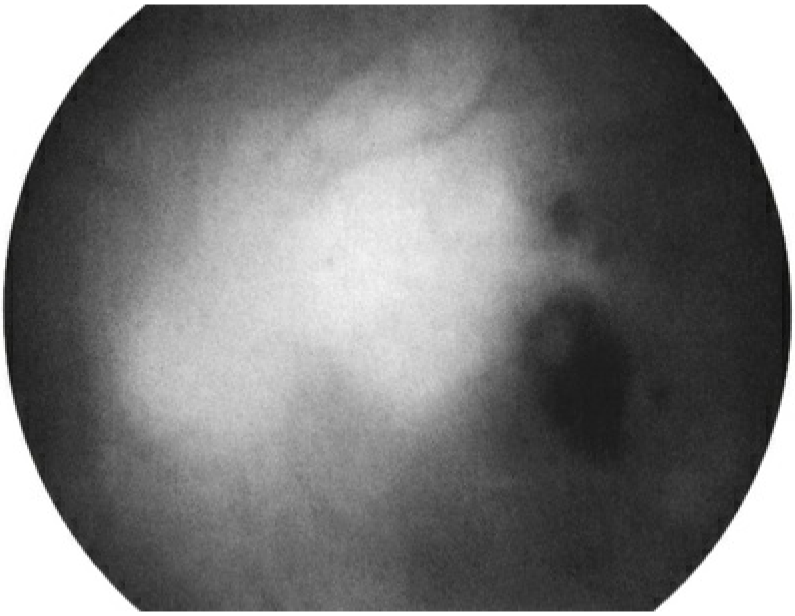

FIGURE 83.1 Fundus photograph shows an active toxoplasmic lesion situated at the edge of a pigmented chorioretinal scar; the view is hazy because there are inflammatory cells in the overlying vitreous.

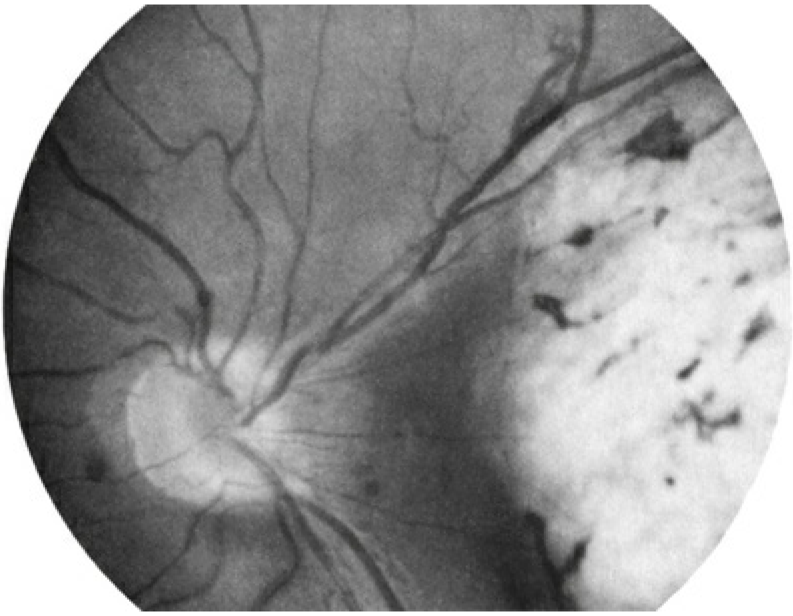

FIGURE 83.2 Fundus photograph shows a portion of a toxoplasmic chorioretinal scar centered on the macula with scattered clumping of retinal pigmentation.

Trapping of protozoa within the terminal branches of abundant perifoveal capillaries probably explains the high incidence of macular involvement. Additional causes of visual loss in toxoplasmosis are tractional distortion of the macula, optic atrophy, cataract, and retinal detachment. Recurrences usually appear at the edge of a quiescent scar, where dormant encysted organisms reactivate.[30,31] (See also Chapter 273.)

Toxoplasmosis acquired postnatally often manifests with isolated ocular involvement.[29,34,35] Solid organ transplant recipients can have evidence of toxoplasmosis infection that is delayed in onset because of the protective effect of trimethoprim-sulfamethoxazole prophylaxis.[36] Although necrotizing retinochoroiditis is the major sequela, early manifestations can be limited to vitritis, anterior uveitis, or retinal vasculitis.[36] Patients with AIDS commonly have multiple active lesions or extensive retinitis.[37]

The clinical diagnosis of ocular toxoplasmosis is confirmed in 50% to 80% of cases by serologic testing.[38,39] Detection of *Toxoplasma*-specific immunoglobulin G (IgG) and IgA in serum or aqueous humor by immunoblotting is the most sensitive method, providing confirmatory evidence in 70% of cases.[39] Identification of *Toxoplasma*-specific gene sequences by polymerase chain reaction (PCR) testing of aqueous humor has reported specificities of 83% to 100% and sensitivities ranging from 28% to 53%.[40,41] Invasive procedures to obtain aqueous humor or ocular tissue may be indicated in severe cases.

Although postnatally acquired active infections usually are treated with antiparasitic drugs, toxoplasmosis is a self-limited disease in immunocompetent individuals in whom long-term benefits of treatment for acute and recurrent toxoplasmic chorioretinitis are uncertain. Current regimens include the following: (1) pyrimethamine plus sulfadiazine and folinic acid; (2) trimethoprim-sulfamethoxazole; and (3) adjunctive clindamycin for coverage against the encysted form.[42–47] In murine models the combination of atovaquone and sulfadiazine is effective.[48] Systemic corticosteroid therapy is indicated when there is visual loss due to inflammation involving the optic nerve or macula.[31] Local destruction of solitary lesions with photocoagulation, cryotherapy, or surgical vitrectomy to remove preretinal membranes or relieve retinal traction may be beneficial in selected cases.[31,49]

Rubella

The most common ocular manifestations of congenital rubella are retinitis, cataract, microphthalmos, and glaucoma.[50–52] Retinitis is characterized by pigmentary mottling of the retinal pigment epithelium (RPE) due to viral invasion, which gives the fundus a “salt-and-pepper” appearance (Fig. 83.3). At birth, the fundi can be normal or can show pigmentary changes. Persistent infection of the RPE causes the pigmentary disturbances to develop or to progress during the first few years of life, after which they tend to remain stable.[51,53] Visual function is normal in patients with involvement of RPE alone. Choroidal neovascularization, macular detachment, and visual loss rarely can be late complications of rubella retinopathy.[54,55] Despite newer technology, cataract surgery frequently is associated with poor visual outcomes owing to postoperative inflammatory complications, glaucoma, and cortical visual impairment.[51,52] Virus can be isolated from lens material for several years after intrauterine infection.[56]

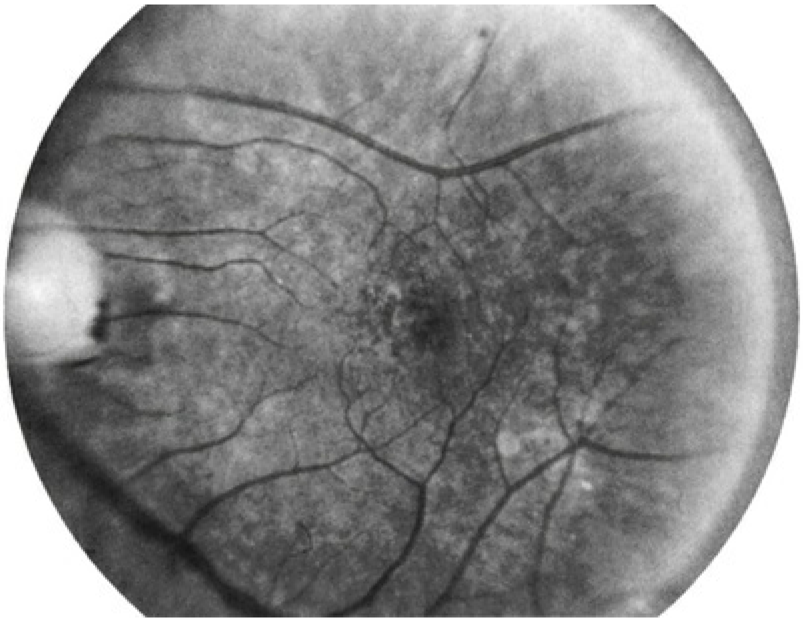

FIGURE 83.3 Fundus photograph shows “salt-and-pepper” retinopathy typical of congenital rubella.

Rubella can contribute to the development of Fuch heterochromic cyclitis, a chronic, unilateral uveitis with mild inflammation that leads to iris atrophy. Assay of aqueous humor revealed IgG rubella antibodies in all 52 patients in one study and the presence of rubella-specific gene sequence in 18% of patients.[57]

Cytomegalovirus

Chorioretinitis is the major ocular sequela in infants congenitally infected with cytomegalovirus (CMV).[58–60] Postinfectious scars appear as geographic areas of chorioretinal atrophy with surrounding hyperpigmentation (Fig. 83.4). Lesions vary in size from 0.5 to 5 mm (½ to 5 disk diameters) and are located in the macula or peripheral retina. Chorioretinal scars are present in 10% to 21% of systemically symptomatic infants but are uncommon in asymptomatic infants. Typically, chorioretinitis in congenital CMV is inactive, but individual congenital cases with postnatal progression and reactivation of chorioretinitis during childhood are reported.[61] Visual loss is associated with macular scarring but can be due to optic atrophy or cortical visual impairment.

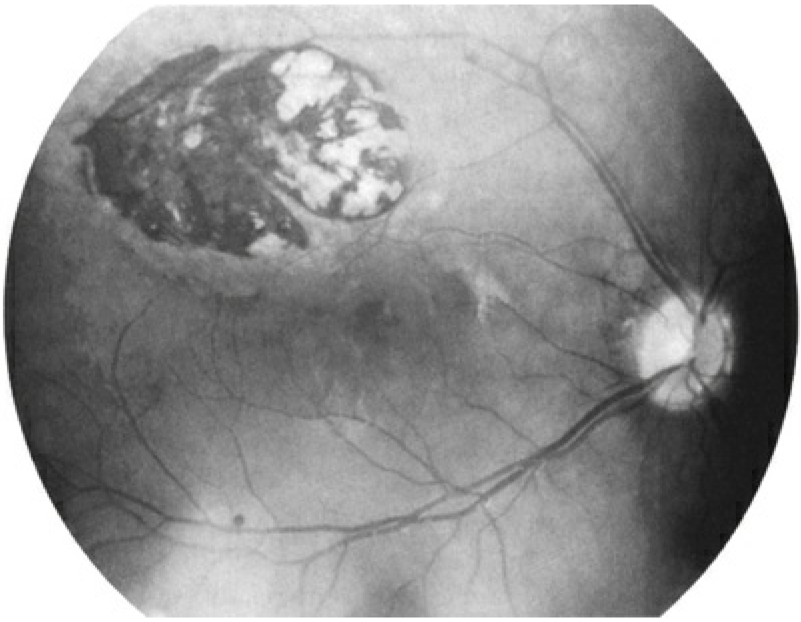

FIGURE 83.4 Fundus photograph shows a geographic chorioretinal scar related to congenital cytomegalovirus infection.

CMV retinitis also can be an acquired infection in immunosuppressed children, such as transplant recipients, those receiving chemotherapy for malignancy, and those with congenital or acquired immunodeficiencies, such as HIV/AIDS.[62–66] In the era of antiretroviral therapy (ART) for HIV, the incidence of CMV retinitis and rates of visual loss, retinal detachment, and mortality have decreased.[67–70] The clinical characteristics of CMV retinitis are similar for patients with and without HIV infection.[71] Early retinitis appears as small white lesions that can be mistaken for cotton-wool spots. The white lesions correspond histologically to areas of intracellular and extracellular edema and necrosis of the retina. These inflammatory changes frequently are associated with intraretinal hemorrhage and vasculitis of nearby retinal vessels, but the overlying vitreous is clear. As infection spreads, the size of the lesions increases along the course of the vessels, and new lesions develop (Fig. 83.5). When lesions heal, the necrotic retina is replaced by glial scar tissue with associated pigmentary clumping.[72–74] Retinitis in the region of the optic nerve and macula is associated with decreased visual acuity and a central visual field defect. Peripheral retinitis causes loss of peripheral visual field, but acuity can be normal.

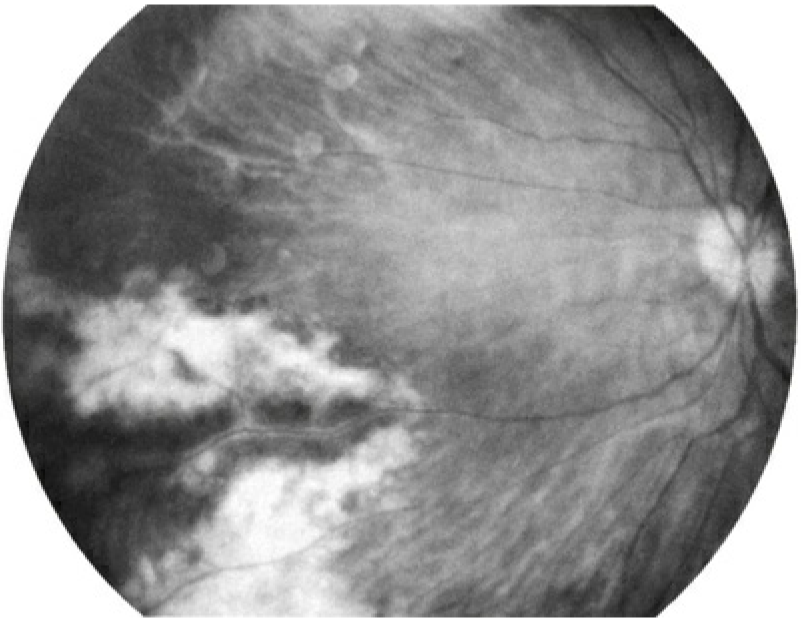

FIGURE 83.5 Fundus photograph shows a localized area of cytomegalovirus retinitis in the peripheral retina; a necrotizing lesion has spread along the course of a retinal vessel and is surrounded by hemorrhage.

Both neonates and immunosuppressed children with CMV chorioretinitis should be treated because active CMV infection can progress to blindness.[74–76] Ganciclovir, foscarnet, and cidofovir are parenteral therapies approved for initial induction and maintenance therapy of CMV retinitis.[77–87] Oral valganciclovir is an alternative to intravenous medications for treatment and maintenance, with fewer side effects.[88] For patients with progressive retinitis or drug-related toxicity (neutropenia, renal disease), local therapy given as an intravitreal injection or a surgically implanted “pellet” should be considered.[89] Local treatment is combined with a systemic antiviral agent to prevent systemic disease and to protect the second eye. Current drugs are virostatic and must be given for long periods of time to prevent progression or recurrence of disease. Children on maintenance chemotherapy for acute lymphoblastic leukemia are at risk for the development CMV retinitis even if they have not received a stem cell transplant.[90] Human monoclonal antibody directed against CMV appears to enhance the benefit of standard antiviral therapy.[91,92]

A subset of patients who become immunologically reconstituted with CD4$^+$ T-lymphocyte counts >100 cells/mm^3 after initiation of ART develop floaters because of vitritis, the incidence of which varies between centers. Complications include papillitis, macular abnormalities, and visual loss.[93,94]

Herpes Simplex Virus

Keratoconjunctivitis can be a manifestation of localized neonatal HSV infection, acquired perinatally. HSV retinitis in neonates generally indicates disseminated or CNS disease.[95,96] The presence of skin lesions, chorioretinitis, and brain abnormalities at birth is suggestive of intrauterine infection.[97] Ocular lesions consist of yellowish areas of necrotizing retinitis, which can be localized or diffuse. Marked vitritis, retinal vasculitis, and persistent fetal vasculature can occur; full-thickness necrosis can lead to optic atrophy and blindness.[98–100] Opsoclonus can be an early sign of encephalitis.[101] Acyclovir intravenously is the treatment of choice.

Congenital Varicella

During the first 20 weeks of pregnancy, approximately 2% of fetuses whose mothers have chickenpox develop an embryopathy.[102,103] Damage is mediated by direct neuropathic effects of the virus or by secondary vasculitis. Clinical features include skin scarring (76%), ocular defects in 51% (chorioretinitis, cataracts, and microphthalmia), skeletal anomalies (49%), and microcephaly and other neurologic deficits (60%).[104,105] Chorioretinitis associated with VZV is indistinguishable ophthalmoscopically from that due to other intrauterine infections. Reduced visual acuity is common because lesions frequently involve the macula.

Herpesvirus Retinochoroiditis and the Acute Retinal Necrosis Syndrome

Postnatally acquired primary varicella or herpes zoster ophthalmicus can be associated with optic disk swelling, macular exudates, multifocal retinitis, and retinal vascular occlusion.[106–108] Acute retinal necrosis (ARN) is an uncommon disease that can occur in immunocompetent or immunocompromised individuals due to VZV, HSV type 1 (HSV-1) or type 2 (HSV-2), CMV, or, rarely, Epstein-Barr virus.[109–114] HSV-2 is the most frequently identified cause of ARN in childhood[115] and often is attributed to reactivation of congenital or neonatal HSV infection.[112,115,116] Characteristic features include multifocal necrotizing retinitis, occlusive arteritis, panuveitis, and rapidly deteriorating vision. Thinning and atrophy of the retina in necrotic areas, combined with vitreous organization and traction, predispose to retinal detachment. Inflammatory optic neuropathy and panuveitis with visual loss can precede the retinopathy.[117] Diagnosis is based on detection of virus-specific gene sequence in aqueous or vitreous samples using the PCR assay. Disease progression is so rapid that visual loss often is irreversible despite aggressive antiviral treatment. However, early treatment with antiviral therapy can prevent further visual loss and the development of ARN in the second eye.[118]

In patients with AIDS, and, less frequently, in immunocompetent individuals, the retinopathy can be atypical, featuring a rapidly progressive necrotizing retinitis and severe bilateral visual loss.[119–122] Although progressive outer retinal necrosis has been emphasized, there is histopathologic evidence of panretinal necrosis.

West Nile Virus

West Nile virus (WNV) is an important cause of arboviral infections of the central nervous system (CNS) in the US.[123] The combined presence of acute encephalitis with multifocal chorioretinitis and vitritis should prompt consideration of WNV or other arbovirus infections. Detection of IgM antibody to WNV in serum confirms the diagnosis.[124,125]

Toxocara canis

Systemic migration of the nematode *Toxocara canis* usually occurs in 1- to 4-year-old children and results in the clinical syndrome of visceral larval migrans.[126,127] Ocular involvement is not concurrent with the visceral larva migrans stage and usually is detected between 4 and 8 years of age. Ocular toxocariasis takes one of the three forms: (1) inflammatory granuloma of the posterior pole; (2) diffuse endophthalmitis; and (3) solitary granuloma of the peripheral retina.[128,129] Common clinical findings include decreased vision, white pupil (leukocoria), and strabismus. The diagnosis is confirmed by the enzyme immunosorbent assay test. The specificity of this assay is high but sensitivity is low, unless a specimen from the aqueous humor is tested.[130] Treatment with periocular or systemic corticosteroids is directed at the inflammatory response incited by the death of larvae.[131] Surgical removal of vitreal membranes and reattachment of the retina can improve vision in individual cases.[132]

Diffuse Unilateral Subacute Neuroretinitis

Diffuse unilateral subacute neuroretinitis is an infection of the eye caused by nematodes endemic to the southeastern and midwestern regions of the US. Although the organisms have not been isolated, migratory larvae have been visualized directly in the subretinal space. One possible worm is *Ancylostoma caninum,* a dog hookworm, which is a common cause of cutaneous larval migrans. Initially, acute visual loss in one eye is noted. Examination of the fundus reveals grey-white lesions in the outer retina that fade over a few days and then reappear elsewhere. Invariably, cells are present in the vitreous, and the optic disk is swollen. Progressive involvement leads to further visual loss, diffuse pigmentary changes, and optic atrophy. Diminution of electroretinographic responses confirms retinal damage and probable visual loss.[133,134] *Baylisascaris procyonis,* a common intestinal raccoon roundworm, is another cause of neural larva migrans and ocular larva migrans. Although neurologic deterioration due to eosinophilic encephalomyelitis predominates clinically, ophthalmologic findings include diffuse unilateral neuroretinitis and choroidal infiltrates.[135,136] Treatment of active vitritis consists of either oral thiabendazole or ivermectin or direct photocoagulation of the larvae.[137–139]

Histoplasma capsulatum

Histoplasmosis of the choroid is believed to be due to invasion by *Histoplasma capsulatum.* Supporting evidence is largely epidemiologic because the organism has not been isolated from choroidal lesions.[140,141] Recent evidence for persistence of *H. capsulatum* DNA sequences in the lesions suggests that these products serve as immunogens and incite chronic inflammation.[142] Viable organisms have been isolated only from immunocompromised patients with endophthalmitis accompanying disseminated infection.[143,144]

This syndrome is characterized by the presence of multiple areas of atrophy in the peripheral retina, referred to as "histo spots." Curvilinear areas of clumped pigment and hypopigmentation surround the disk.[145] Focal scars do not contain viable organisms, but recurrent lymphocytic infiltration predisposes to the development of neovascular membranes and hemorrhagic macular detachment. Treatment options include laser photocoagulation, photodynamic therapy with verteporfin, and intravitreal instillation of corticosteroid, particularly when the macula is threatened.[146–148] Antifungal therapy has no role in the treatment of this disease because there are no actively replicating organisms.

Focal and Multifocal Choroiditis

Infectious organisms that spread hematogenously are more likely to become trapped in the choroid than in other parts of the eye because of high choroidal blood flow and the large number of fenestrated capillaries. Choroidal infiltrates can be single or multiple (Fig. 83.6). Tuberculosis can be associated with a focal choroidal mass, multiple choroidal masses, diffuse or multifocal choroiditis, or retinal vasculitis.[149] Additional infections associated with choroiditis include coccidioidomycosis, cryptococcosis, and nocardiosis.

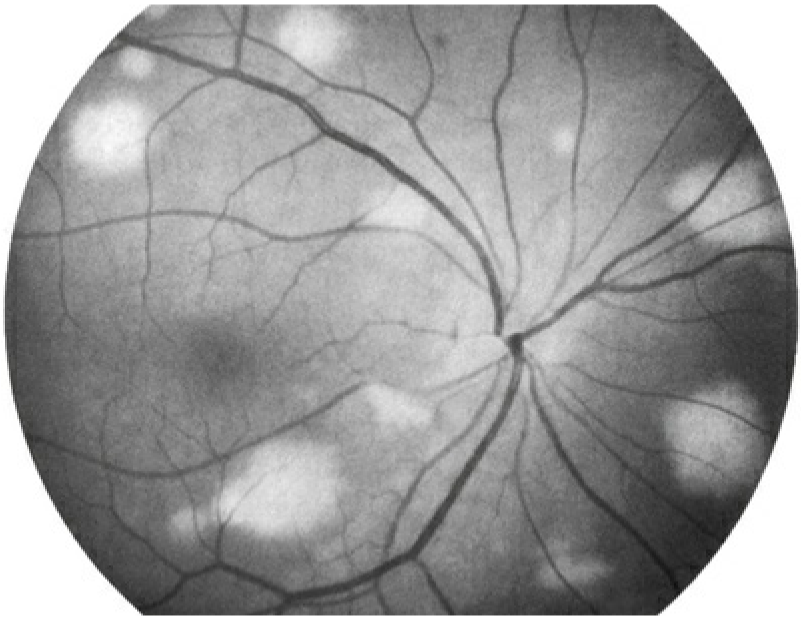

FIGURE 83.6 Fundus photograph shows multifocal choroidal infiltrates deep to the retina; there are no inflammatory cells in the overlying vitreous.

Multifocal choroiditis occurring in the context of AIDS deserves special mention because of its association with life-threatening systemic infections. Etiologic agents include *Pneumocystis jirovecii, Cryptococcus neoformans, M. tuberculosis, Candida, Mycobacterium avium* complex, and *H. capsulatum*.[149–151]

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84

Endophthalmitis

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The term *endophthalmitis* is applied to bacterial or fungal infection involving intraocular tissues (retina, uveal tract, or lens) or fluids (vitreous or aqueous). Two broad categories of infectious endophthalmitis are distinguished. *Exogenous* infection results from introduction of organisms into the eye through a surgical or traumatic penetrating wound; *endogenous* (or metastatic) infection is caused by organisms that enter the eye through the bloodstream. Both categories of infection are extremely serious, threatening sight and even loss of the globe.[1–3] Whereas most cases of endophthalmitis in adults occur after surgery or by endogenous routes, most cases of endophthalmitis in children occur after penetrating ocular trauma.[4]

Etiologic Agents

A wide variety of microorganisms can cause endophthalmitis. Gram-positive cocci (both staphylococci and streptococci) are leading pathogens for both exogenous and endogenous endophthalmitis. In recent years gram-positive isolates have become increasingly resistant to antibiotics, including early-generation fluoroquinolones, but resistance to vancomycin and fourth-generation fluoroquinolones remains uncommon.[5,6] *Staphylococcus epidermidis* is the organism most often identified in the postoperative setting and is a frequent agent of posttraumatic endophthalmitis as well.[1,2] Often, *S. epidermidis* infection has a subacute onset 1 week to 1 month after surgery. Neonatal group B streptococcal septicemia can be associated with endogenous endophthalmitis.[3]

The gram-positive anaerobic bacillus *Propionibacterium acnes* is one of the most common causes of endophthalmitis after cataract surgery. Characteristically, *P. acnes* endophthalmitis develops one to several months after surgery and follows a chronic smoldering course.[7] In contrast, *Bacillus cereus* is the most virulent organism inside the eye, capable of destroying the entire retina within hours of introduction by trauma or hematogenous seeding.[8]

Neisseria meningitidis was the most common cause of endogenous endophthalmitis before the advent of antibiotics and still must be recognized as having a predilection for intraocular localization.[3] Nontypable *Haemophilus influenzae* can cause endophthalmitis after accidental trauma and surgery.[9] During the past decade, *Klebsiella pneumoniae* has emerged as the predominant cause of endogenous endophthalmitis in East Asia.[8,10,11] Numerous other gram-negative bacilli (notably *Pseudomonas aeruginosa* and *Escherichia coli*) have been associated with both exogenous and endogenous endophthalmitis, especially after trauma or surgery, and in individuals with underlying conditions.[1,3,12]

Candida albicans bloodstream infection (BSI) remains the most common fungal precursor of endogenous endophthalmitis, although this complication appears to be decreasing in frequency with earlier initiation of systemic treatment for candidemia and invasive candidiasis.[1,13–15] Meta-analysis of neonatal *Candida* BSI showed 3% prevalence of endophthalmitis.[14] Non-*albicans Candida* spp. and a variety of other fungi (including *Aspergillus* and *Fusarium, Alternaría*, and *Scedosporium* spp.) have been implicated in both endogenous and exogenous endophthalmitis, especially in posttraumatic cases or immunocompromised hosts.[16,17] Fungal endophthalmitis tends to follow a more indolent course than that of most bacterial infections.

Epidemiology and Host Factors

Postoperative endophthalmitis most often follows cataract extraction but can be associated with any form of intraocular procedure or extraocular operations, such as strabismus repair (in which organisms presumably are introduced into the globe by inadvertent needle perforation of the sclera).[18,19] The rate of endophthalmitis after pediatric intraocular surgery is similar to that found in adults—approximately 1 in 1000 cases.[20–22] Extracapsular cataract surgery with intraocular lens implantation (increasingly being performed in childhood) predisposes particularly to chronic endophthalmitis caused by *P. acnes.*[7] A recent trend in cataract surgery toward use of unsutured "self-sealing" incisions through temporal clear cornea (as opposed to the superior limbus) has been associated with a small but substantial increase in the frequency of postoperative endophthalmitis.[23]

Filtering operations for glaucoma (which produce a fistulous connection for aqueous flow through the corneoscleral limbus between the anterior chamber and a conjunctival bleb) lower the physical resistance of the globe to invasion by microorganisms, creating a higher risk for intraocular infection that can persist for decades if the drainage tract remains patent. The frequency of late bleb-related endophthalmitis appears to have increased considerably in children as well as in adults because of increasing use of periocular antifibrotic agents (mitomycin C or 5-fluorouracil) administered intraoperatively or postoperatively. These drugs improve the rate of successful lowering of intraocular pressure after filtering surgery but tend to result in blebs that are large and thin-walled and, thus, particularly vulnerable to bacterial invasion.[9,24]

A recently recognized inflammatory condition that occurs after intraocular surgery, toxic anterior segment syndrome, can be confused with postoperative infectious endophthalmitis.[25] In this condition, toxins on surgical instruments that have been improperly sterilized lead to an inflammatory reaction within days after the anterior segment surgery. The diagnosis is made only after appropriate diagnostic aqueous and vitreous samples have been obtained for culture and sensitivity and intraocular empiric antibiotics have been administered because the consequence of not treating an infectious process could be devastating.

Endophthalmitis is a major concern after any penetrating trauma to the globe, especially in childhood, when contamination of the causative instrument with soil, saliva, or fecal material is common.[16,26,27] Occult penetration of the globe by a needle, thorn, or similarly shaped object can be unsuspected in a nonverbal child until days later when infection leads to obvious inflammatory signs. In a child with posttraumatic endophthalmitis, the possibility of an intraocular foreign body (which must be removed surgically) must be considered, and should be excluded, if necessary, with ultrasonographic or radiographic imaging.

Endogenous endophthalmitis usually occurs in a host who is already known to have BSI or is immunocompromised, but occasionally, ocular involvement is the first indication of the underlying problem.[3] Endocarditis and meningitis are the most important localized infections associated with endophthalmitis. Diabetic patients have the propensity for retinal spread of *K. pneumoniae* from hepatic abscesses and of *E. coli* from a urinary tract infection.[11,12] Intravenous drug abusers have increased risk for intraocular fungal infection and also for devastating *B. cereus* endophthalmitis.[3,8]

Although otherwise healthy persons are occasionally affected, most cases of endogenous candidal endophthalmitis are nosocomial, occurring in association with indwelling intravascular catheters, use of broad-spectrum antibiotics, or immunosuppressive or major surgical treatment. Infants with intraocular candidiasis or bacterial endophthalmitis usually have a history of premature birth and pulmonary disease.[13]

Pathophysiology

Microbial proliferation begins and remains concentrated in the aqueous or vitreous fluid in most cases of exogenous endophthalmitis. Damage to the retina and other intraocular structures occurs secondarily from exposure to toxins elaborated by the organisms and inflammatory cells.

By contrast, endogenous endophthalmitis typically originates in tissue within which a septic embolus has lodged.[3] When this process occurs in a small terminal branch of a vessel, ocular infection begins as either a microabscess in the iris or a focal lesion of retinitis or choroiditis. Diffuse involvement of the anterior ocular segment can develop rapidly after invasion of the iris, but posterior extension usually remains limited in such cases. Spillover of organisms and inflammatory cells from infected tissues of the posterior ocular segment leads to involvement of the vitreous, which subsequently can remain localized or become diffuse, extending ultimately to the anterior segment, sclera, and orbit (panophthalmitis). Occlusion of the central retinal artery by a large embolus can result in ischemia followed by massive dissemination of organisms directly into the retina that can lead to irreversible blindness within a short time.

Clinical Manifestations

The first external sign of endophthalmitis usually is injection of conjunctival vessels. Injection can be striking and associated with marked conjunctival and eyelid edema, or so mild that it scarcely attracts attention. Endophthalmitis must therefore be included in the differential diagnosis of every “red eye.” Careful inspection of the anterior segment with a hand light usually permits identification of a whitish *hypopyon,* which results from layering of abundant leukocytes from aqueous fluid onto the surface of the iris or in the most dependent portion of the anterior chamber (Fig. 84.1). Sometimes, however, the only readily identifiable sign in the anterior segment is blue-grey haziness or loss of clarity in visualization of the iris and the pupil, often accompanied by diminished or absent reactivity to light. Vision usually is reduced.

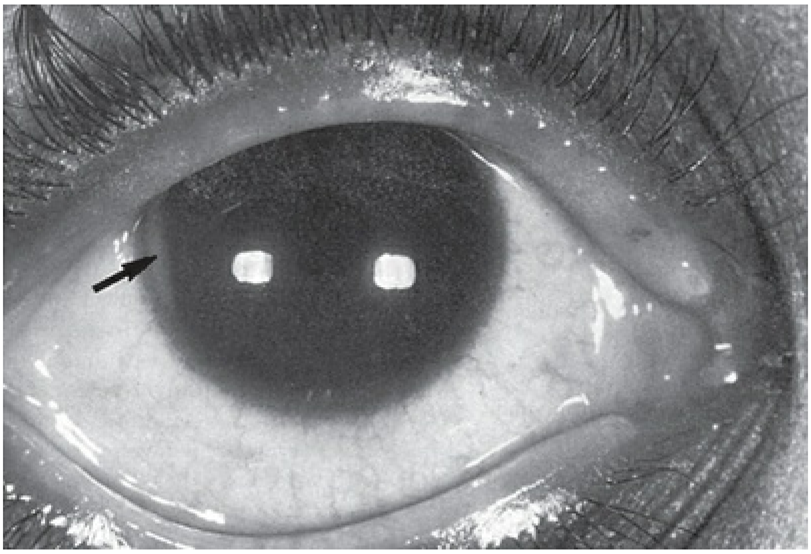

FIGURE 84.1 Right eye of a 15-year-old girl with acute meningococcal meningitis and bilateral endophthalmitis. Note the small hypopyon *(arrow),* layered temporally in the anterior chamber because

she had been lying on her right side.

Low-grade endophthalmitis localized to the posterior segment (including most cases of intraocular candidiasis) may produce no external signs. Typically, there is decreased clarity of ophthalmoscopic visualization and dimming of the fundus red reflex, resulting from vitritis, and visual acuity is reduced. In some cases, however, the problem only becomes evident when detailed examination of the fundus through a dilated pupil reveals the presence of one or more small whitish chorioretinal or vitreal infiltrates with indistinct borders.

Diagnostic Evaluation

Suspicion of endophthalmitis mandates consultation with an ophthalmologist, who can confirm the diagnosis, quantify the vision loss, and determine the extent of posterior-segment involvement (employing B-scan ultrasonography if the fundus cannot be visualized).

In the context of well-defined systemic infection with an identifiable organism, generally it is not necessary to perform additional microbiologic studies when making the diagnosis of endophthalmitis.[2] Otherwise, aspiration of ocular fluid for culture is required. If the patient is cooperative or immobilized easily, aqueous fluid (about 0.1 mL) can be obtained at the bedside with the use of a 27- or 30-gauge needle on a 1-mL syringe. Aspiration of the vitreous is a surgical procedure best performed in the operating room for children (Fig. 84.2). Vitreous culture has a substantially higher yield than aqueous culture in exogenous and posteriorly localized endogenous infection.[3,28,29] When fungal infection is suspected, polymerase chain reaction testing of vitreous aspirate can provide rapid confirmation of etiology.[30,31]

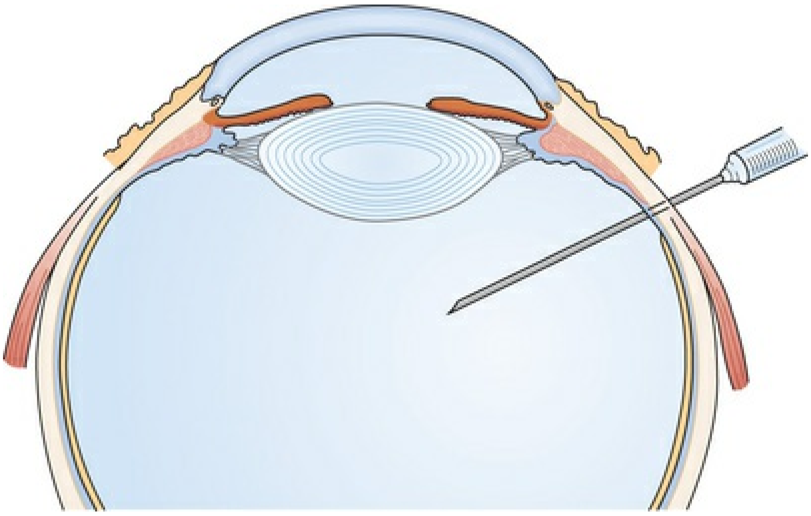

FIGURE 84.2 Diagrammatic illustration of needle passing through the pars plana of the ciliary body for diagnostic aspiration of vitreous or intravitreal injection of antibiotic. (Adapted from Bohigian GM. Endophthalmitis. In: Krupin T, Kolker AE, Rosenberg LF [eds]. Complications in Ophthalmic Surgery, 2nd ed. St. Louis, Mosby, 1999, pp. 19–36.)

In about 25% to 50% of cases of presumed infectious endophthalmitis, eye fluid cultures are sterile. For maximal yield, aspirates should be inoculated promptly into appropriate media, including media used for isolation of anaerobic and fungal organisms. Inoculation of fluid specimens into blood culture bottles also has been used successfully.[1]

With endophthalmitis of unknown origin, multiple blood cultures should be performed, followed by an exhaustive search for remote infections and predisposing conditions, including occult ocular trauma, diabetes, acquired immunodeficiency syndrome, and other immunodeficiency disorders.

Management

Antimicrobial agents for endophthalmitis can be delivered by a variety of routes. Intravenous antibiotic administration is the mainstay of treatment for endogenous bacterial infection.[3,10] The choice of drugs should be based on known or presumed susceptibility of documented or suspected pathogens, with dosage and duration at levels appropriate for meningitis (or greater if required for associated infection at another site). Endogenous fungal endophthalmitis usually responds well to treatment with intravenous amphotericin B; however, newer agents such as voriconazole (which can yield therapeutic intraocular concentration after oral as well as intravenous administration) are increasingly viewed as appropriate and possibly preferable alternative therapies.[32,33] If fungal chorioretinitis extends into the vitreous cavity, intravitreal injection with either amphotericin B (5–10 µg) or voriconazole (100 µg) is necessary, and vitrectomy may be required to remove fungal burden and inflammatory cells to minimize risk for retinal damage.

In the past, many cases of exogenous endophthalmitis were cured with combined intravenous, subconjunctival, and topical antibiotics, but intravitreal administration is now regarded as the most important route of drug delivery for this condition (see Fig. 84.2).[1,18,19] Initially, only a single injection is given (immediately after aspiration of vitreous for culture), followed by one or more additional injections if response to the first is incomplete. Gentamicin and cefazolin were formerly the intraocular antibiotics used most often, but growing concerns about aminoglycoside retinal toxicity and drug-resistant organisms have led to a shift toward other agents, particularly ceftazidime and vancomycin (Table 84.1; see also Table 294.4).[34]

TABLE 84.1

Intravitreal Injection for Endophthalmitis

Drug	Dose[a] (mg)	Comment
Vancomycin	1	Unless gram-positive bacteria can be excluded
Amikacin	0.4	Now seldom used because of potential retinal toxicity
Ceftazidime	2.25	Preferred agent for gram-negative coverage
Amphotericin B	0.005	If fungus suspected
Voriconazole	0.1	Increasingly used alternative to amphotericin
Dexamethasone	0.4	Recommended for anti-inflammatory effect by some authorities

[a] Each drug should be diluted to provide the indicated dose in a volume of 0.1 mL and should be injected using a separate 1 mL syringe.

Recommendations from references 1 and 18, and Hariprasad SM, Mieler WF, Flynn HW, et al. Advances in endophthalmitis management. Instruction course syllabus, American Academy of Ophthalmology Annual Meeting, Las Vegas, Nevada, 2006.

Controversy persists regarding the need for concurrent use of multiple routes of therapy.[35] Outcomes reported after combined intravitreal and systemic administration of antibiotics are similar to those seen with intravenous treatment alone in endogenous infections and with intravitreal treatment alone in most exogenous infections.[3,10,36,37] Many experienced clinicians continue to employ both modalities. Fourth-generation fluoroquinolones such as moxifloxacin can achieve therapeutic intraocular levels after oral administration (initial loading dose in an adult of 400 mg twice daily, followed by 400 mg once daily for 1 to 2 weeks) and have a favorable spectrum of coverage, making them an attractive used adjunct to intravitreal injection.[38] Moxifloxacin has become the antibiotic of choice for oral administration because of its high intraocular penetration, but caution should be exercised when used in children because of its association with potential tendon rupture. Minimal inhibitory concentrations for methicillin-resistant *S. aureus* (MRSA) are at least 10-fold those for methicillin-susceptible *S. aureus*. Intravitreal vancomycin is used for MRSA infection. Subconjunctival antibiotics (given as once- or twice-daily injections) are also sometimes used, although data to indicate incremental benefit are lacking. Cephalosporins often are used for treatment after discharge from the hospital, but intraocular and intravenous therapy is required at the time of initial diagnosis. Many clinicians also include corticosteroid agents (intraocular, subconjunctival, topical, systemic, or a combination) in the regimen in an attempt to reduce ocular inflammatory damage. No adverse effect on control of infection from this practice has been documented when appropriate antimicrobial therapy is given.[1,2,18]

The role of vitrectomy in the management of exogenous endophthalmitis was clarified by the results of a major multicenter, randomized clinical trial.[37] The investigators compared outcomes from treatment of postoperative endophthalmitis after cataract surgery using intravitreal antibiotics (amikacin and vancomycin) with or without immediate surgical removal of most of the infected vitreous. Vitrectomy provided significant benefit only when initial visual acuity was severely reduced to the level of light perception only. With better initial vision, outcomes were the same with and without vitrectomy. Vitrectomy with removal of infected lens material appears to be required for cure of most cases of chronic endophthalmitis caused by *P. acnes*.[7] Most authorities continue to view vitrectomy as warranted for endophthalmitis associated with penetrating trauma and glaucoma filtering blebs.[2,18]

Occasionally, even after intensive treatment, an eye is left blind and intractably inflamed by endophthalmitis. In such cases, it may be necessary to remove the entire ocular contents surgically (evisceration) or to remove the complete globe (enucleation).

Outcome

With current optimal therapy, the prognosis for infectious endophthalmitis is good. Recovery is the rule in (1) postoperative endophthalmitis due to *S. epidermidis* and *P. acnes;* (2) endogenous *Candida* endophthalmitis; and (3) endogenous bacterial endophthalmitis that shows either primarily anterior-segment or only focal posterior-segment involvement at the time of diagnosis, regardless of organism.[1,3,39] Mild to moderate permanent visual loss is common even in these favorable cases, however.

In situations other than those mentioned, endophthalmitis remains a grave disorder. Cases of bacterial infection due to trauma or to a hematogenous spread from other sites of infection that show diffuse posterior-segment involvement have a particularly poor prognosis, typically leaving the patient with a nonseeing eye or no eye at all.[3,8,16]

Overall, with current therapeutic methods, useful vision (finger-counting or better) is retained in about 60% of eyes treated for acute or subacute exogenous bacterial endophthalmitis and in 40% of eyes treated for endogenous bacterial endophthalmitis. These outcomes have remained unchanged over several decades.[3,25,40]

Prevention

Preoperative application of 1 drop of 5% povidone-iodine (half-strength dilution of the common commercially available solution) to the ocular surface has been shown to reduce the conjunctival bacterial population significantly and appears to lower the incidence of postoperative endophthalmitis.[21,41] It also remains common practice to administer a single subconjunctival injection of antibiotic (usually an aminoglycoside or a cephalosporin) at the conclusion of intraocular surgery and to prescribe a topical solution, to be applied several times a day for 1 week or longer. Use of moxifloxacin topically before and after surgery has been increasing. A minority of surgeons add antibiotic to the infusion fluid that circulates through the eye during cataract or vitrectomy surgery. Recent studies support the injection of antibiotic into the anterior chamber at the conclusion of surgery, but this approach has not been widely adopted in North America.[42]

Intensive prophylaxis against endophthalmitis is employed by most ophthalmologists after penetrating trauma. Intravenously administered vancomycin plus ceftazidime has largely replaced the traditional use of a first-generation cephalosporin, with or without an aminoglycoside.[2] Oral administration of a fluoroquinolone (e.g., moxifloxacin) can achieve therapeutic drug levels in the vitreous and reasonably good coverage for common infecting organisms, except MRSA and some coagulase-negative staphylococci.[43]

Some authorities recommend intravitreal injection as a preventive measure in cases of traumatic endophthalmitis that are likely to involve heavy contamination.[2,22,26] Culture of foreign material removed from the eye, aqueous or vitreous, exposed uveal tissue, or the conjunctiva (in roughly descending order of usefulness) at the time of surgical wound repair can provide valuable information for optimizing treatment should endophthalmitis develop.

Because of the risk for endophthalmitis, conjunctivitis that develops in an eye with a glaucoma filtering bleb should be treated promptly and aggressively with topical and, possibly, systemic antibiotics.[9]

Ophthalmologic evaluation to rule out ocular involvement in patients with *Candida albicans* fungemia or deep tissue infection appears to be justified, given the paucity of external signs heralding its development.[15] Ophthalmologic screening has a very low yield in patients who have fever of unknown origin or in whom *Candida* is isolated only from a superficial site or a catheter, and so is no longer recommended.

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85

Preseptal and Orbital Infections

Ellen R. Wald

The practitioner frequently has the opportunity to manage the child for whom the chief complaint is a "swollen eye" (Fig. 85.1). Some children have trivial or self-limited disorders, but others can have sight- or life-threatening problems. Noninfectious causes of the swollen eye can often be distinguished from infectious causes by a detailed history of the onset and progression of the eye swelling. Infectious causes of eye swelling are usually acute in presentation. Differentiating preseptal (common) and orbital (rare) causes of eye swelling is critical to management and can usually be accomplished on the basis of the physical examination.

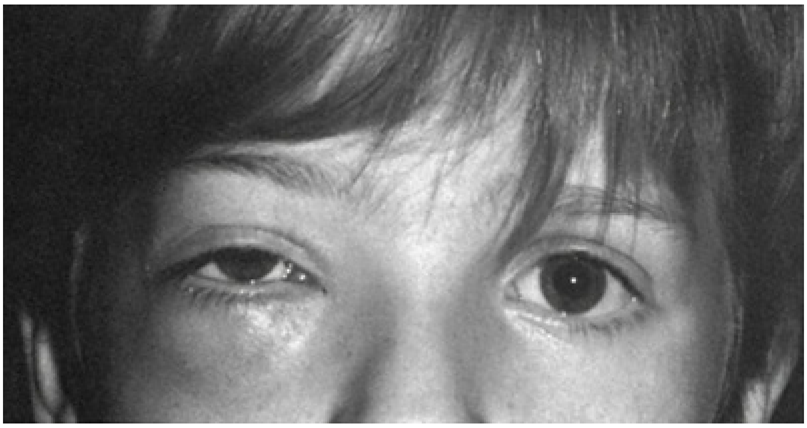

FIGURE 85.1 A 10-year-old boy with the complaint of swollen eye.

Differential Diagnosis

The noninfectious causes of swelling of or around the eye include (1) blunt trauma (leading to the proverbial "black" eye), (2) tumor, (3) local edema, and (4) allergy. In cases of blunt trauma, history provides the key to the diagnosis. Eyelid swelling continues to increase for 48 hours and then resolves over several days. Tumors that characteristically involve the eye include hemangioma of the lid, ocular tumors such as retinoblastoma and choroidal melanoma, and orbital neoplasms such as neuroblastoma and rhabdomyosarcoma.[1] Other tumors reported to cause orbital involvement are Langerhans cell histiocytosis and granulocytic sarcoma.[2,3] Tumors usually cause gradual onset of proptosis in the absence of inflammation. Orbital pseudotumor, an autoimmune inflammation of the orbital tissues, manifests as eyelid swelling, red eye, pain, and decreased ocular motility.[4] Hypoproteinemia and congestive heart failure cause eyelid swelling due to local edema; characteristic findings are bilateral, boggy, nontender, nondiscolored soft tissue swelling. Allergic inflammation includes angioneurotic edema or contact hypersensitivity.[5] Superficially, allergic inflammation can resemble acute infection; however, the presence of pruritus and the absence of tenderness are helpful distinguishing characteristics.

Pathogenesis

The anatomy of the eye is important for an understanding of its susceptibility to spread of infection from contiguous structures. Veins that drain the orbit, the ethmoid and maxillary sinuses, and the skin of the eye and periorbital tissues (Fig. 85.2) constitute an anastomosing and valveless network.[1] This venous system provides opportunities for spread of infection from one anatomic site to another and predisposes to involvement of the cavernous sinus.

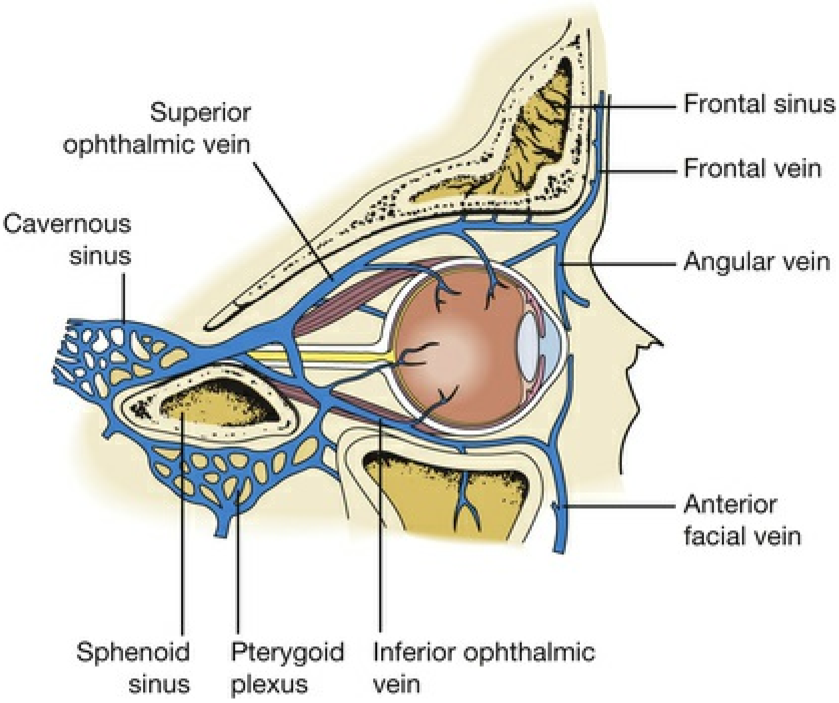

FIGURE 85.2 The valveless venous system of the orbit and its many anastomoses.

Fig. 85.3 demonstrates the relationship between the eye and the paranasal sinuses. The roof of the orbit is the floor of the frontal sinus, and the floor of the orbit is the roof of the maxillary sinus. The medial wall of the orbit is formed by the frontal maxillary process, the lacrimal bone, the lamina papyracea of the ethmoid bone, and a small part of the sphenoid bone.[6] Infection originating in the mucosa of the paranasal sinuses can spread to involve the bone (osteitis with or without subperiosteal abscess) and the intraorbital contents. Orbital infection can occur through natural bony dehiscences in the lamina papyracea of the ethmoid or frontal bones or through foramina through which the ethmoidal arteries pass.[5]

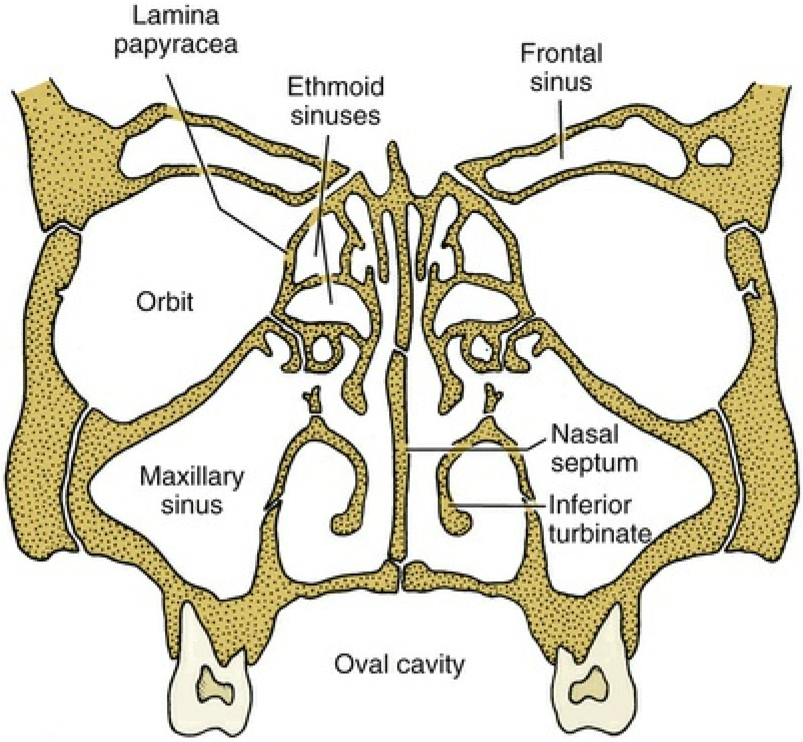

FIGURE 85.3 The relationship between the eye and the paranasal sinuses is shown schematically. The roof of the orbit, the medial wall, and the floor are shared by the frontal, ethmoid, and maxillary sinuses, respectively. (Redrawn from Shapiro ED, Wald ER, Brozanski BA. Periorbital cellulitis and paranasal sinusitis: a reappraisal. Pediatr Infect Dis J 1982;1:91–94.)

Fig. 85.4 shows the position of the orbital septum, a connective tissue extension of the periosteum (or periorbita) that is reflected into the upper and lower eyelids. Infection of tissues anterior to the orbital septum are described as *periorbital* or *preseptal*.[7] The septum provides a nearly impervious barrier to spread of infection to the orbit. Although preseptal cellulitis or periorbital cellulitis (the terms may be used interchangeably) often is considered a "diagnosis," either term is an inadequate diagnostic label unless accompanied by a modifier that indicates likely pathogenesis. In the remainder of this chapter, *preseptal cellulitis* is the preferred term.

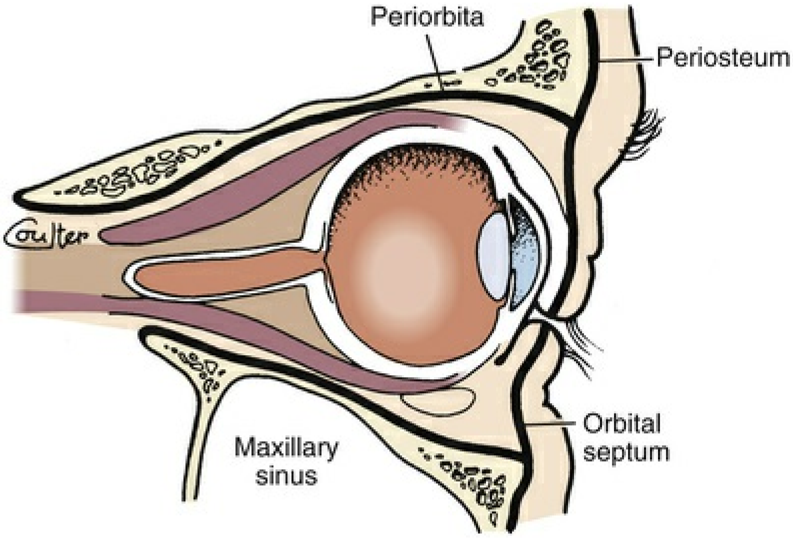

FIGURE 85.4 The orbital septum is a connective tissue extension of the periosteum that is reflected into the upper and lower lid. (Redrawn from Shapiro ED, Wald ER, Brozanski BA. Periorbital cellulitis and paranasal sinusitis: a reappraisal. Pediatr Infect Dis J 1982;1:91–94.)

Infectious causes of preseptal cellulitis occur in the following three settings: (1) secondary to a localized infection or inflammation of the conjunctiva, eyelids, or adjacent structures (e.g., conjunctivitis, hordeolum, acute chalazion, dacryocystitis, dacryoadenitis, impetigo, traumatic bacterial cellulitis); (2) secondary to hematogenous dissemination of nasopharyngeal pathogens to the periorbital tissue; and (3) as a manifestation of inflammatory edema in patients with acute sinusitis (Box 85.1).[7]

Box 85.1

Infectious Causes of Preseptal and Orbital Cellulitis

Preseptal Cellulitis

Localized infection of the eyelid or adjacent structure

Conjunctivitis

Hordeolum

Dacryoadenitis

Dacryocystitis

Bacterial cellulitis (trauma)

Hematogenous dissemination

Bacteremic periorbital cellulitis

Acute sinusitis

Inflammatory edema

Orbital Cellulitis

Acute sinusitis

Subperiosteal abscess

Orbital abscess

Orbital cellulitis

Cavernous sinus thrombosis

Hematogenous dissemination

Endophthalmitis

Traumatic inoculation

Endophthalmitis

Infections behind the septum that cause eye swelling include subperiosteal abscess, orbital abscess, orbital cellulitis, cavernous sinus thrombosis, panophthalmitis, and endophthalmitis. Although all of these entities can be labeled *orbital cellulitis,* a systematic approach allows a more specific diagnosis, thereby directing management. Infections intrinsic to the eye (i.e., conjunctivitis, keratitis, endophthalmitis, and panophthalmitis) are discussed in Chapters 80 through 84.

Preseptal Infections

Conjunctivitis

Conjunctivitis is the most common disorder of the eye for which children are brought for medical care. In most cases, the lids are crusted and thickened with hyperemic conjunctiva. The usual causes of conjunctivitis in children older than neonates but less than 6 years old are *Haemophilus influenzae* (nontypable) and *Streptococcus pneumoniae.*[8,9] In approximately 20% to 25% of children with conjunctivitis due to *H. influenzae,* acute otitis media is a complicating feature. In this case, systemic antibiotics are preferable to topical ophthalmic preparations. Adenovirus is the most common cause of viral conjunctivitis in children older than 6 years and frequently is associated with pharyngitis.[10] Occasionally young children with adenovirus infection have diffuse swelling of the lids that can be mistaken for a more serious problem.[11] Other viral causes of hemorrhagic conjunctivitis are enterovirus 70 and coxsackievirus A24 (see Chapter 80).

Hordeolum and Chalazion

An *external hordeolum,* or stye, is a bacterial infection of the gland of Zeis or Moll (sebaceous gland or sweat gland, respectively) associated with a hair follicle on the eyelid. In most cases, infection is localized and points to the lid margin as a pustule or inflammatory papule. The lid can be slightly swollen and erythematous around the area of involvement. An external hordeolum usually lasts a few days to a week and resolves spontaneously.

An *internal hordeolum* is a bacterial infection of a meibomian gland, a long sebaceous gland whose orifice is at the lid margin.[12] The infection usually causes inflammation and edema of the neck of the gland, which can result in obstruction. If there is no obstruction, infection points to the lid margin. If obstruction is present, infection points to the conjunctival surface of the eye.[12] Sometimes the swelling caused by an acute internal hordeolum is diffuse rather than localized, and a pustule is not obvious on the lid margin. To clarify the cause, it is necessary to evert the eyelid and examine the tarsal conjunctiva. A tiny, delicate pustule is diagnostic of an internal hordeolum.

The usual cause of acute internal or external hordeola is *Staphylococcus aureus.* An antibiotic ophthalmic ointment containing bacitracin can be applied to the site of infection. The main purpose of the topical therapy is to prevent spread of infection to adjacent hair follicles. Warm compresses may facilitate spontaneous drainage.

In contrast to the internal hordeolum, a *chalazion* manifests as a persistent (>2 weeks in duration), nontender, localized bulge or nodule (3–10 mm) in the lid; the overlying skin is completely normal. It is a sterile lipogranulomatous reaction. When a chalazion is large and causes local irritation, incision may be required.

Dacryoadenitis

Dacryoadenitis is an infection of the lacrimal gland. Sudden onset of soft tissue swelling that is maximum over the outer portion of the upper lid margin is typical. Occasionally, the eyeball is erythematous and the eyelid swollen, and the patient can have remarkable constitutional symptoms. The location of the swelling is a distinguishing characteristic (Fig. 85.5). When dacryoadenitis is caused by viral infection (mumps virus, Epstein-Barr virus,[13] cytomegalovirus, coxsackievirus, echoviruses, or varicella-zoster virus), the area is only modestly tender.[14] By contrast, when the infection is caused by bacterial agents, discomfort is prominent. In addition to *S. aureus,* which is the most common cause of bacterial dacryoadenitis, etiologic agents include streptococci, *Chlamydia trachomatis, Brucella melitensis,* and, occasionally, *Neisseria gonorrhoeae.*[15,16] Fungal and rare parasitic infections of the lacrimal gland have been reported, including those with *Cysticercus cellulosae* and *Schistosoma haematobium.*[14] If parenteral therapy is required for suspected bacterial dacryoadenitis due to *S. aureus,* nafcillin (150 mg/kg/day divided into doses every 6 hours) is appropriate. If methicillin-resistant *S. aureus* (MRSA) is suspected, vancomycin (60 mg/kg divided into doses every 6 hours) should be initiated. Oral treatment of acute dacryoadenitis is undertaken with a semisynthetic penicillin such as dicloxacillin (100 mg/kg/day divided into doses every 6 hours), cephalexin or cefadroxil (100 or 50 mg/kg/day, respectively, divided into doses every 6 or 12 hours, respectively), trimethoprim-sulfamethoxazole (based on 40 mg/kg/day of trimethoprim divided into doses every 12 hours), or clindamycin (40 mg/kg/day divided into doses every 6 hours). Treatment is continued until all signs and symptoms have disappeared.

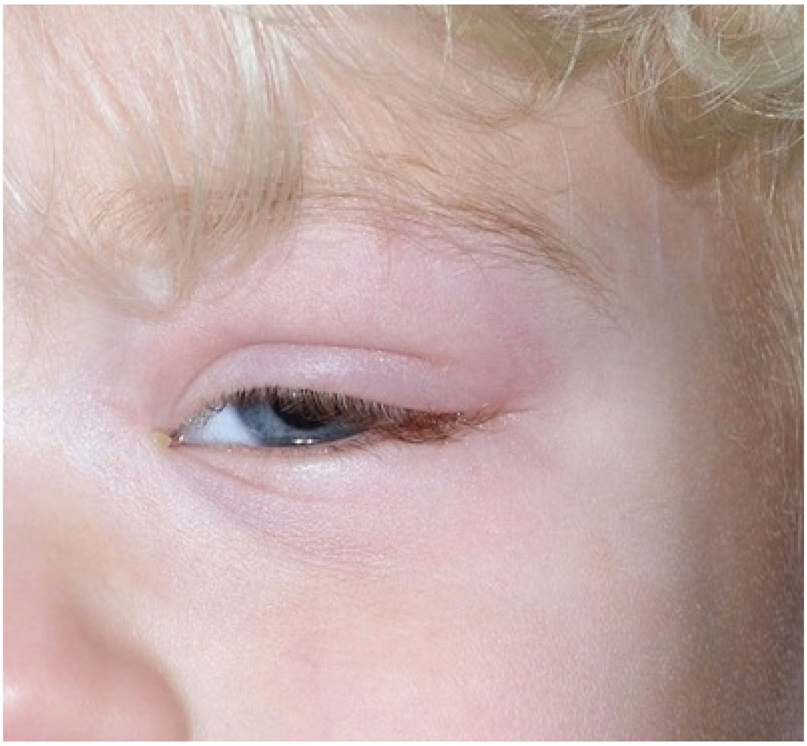

FIGURE 85.5 A patient with dacryoadenitis during a viral illness. The nontender swelling over the lateral portion of the left upper lid resolved without antibiotic treatment. (Courtesy of J. H. Briené.)

The differential diagnosis of swelling of the upper outer aspect of the eyelid includes inflammatory noninfectious problems such as Sjögren syndrome and sarcoidosis as well as benign and malignant tumors.[14]

Dacryocystitis

Dacryocystitis is a bacterial infection of the lacrimal sac. Although uncommon, dacryocystitis can occur at any age as a bacterial complication of a viral upper respiratory tract infection (URI). Because of the course traversed by the lacrimal duct, which drains to the inferior meatus within the nose, it is surprising that the duct and sac are not infected more often. Delayed opening of the duct, inspissated secretions, and anatomic abnormalities lead to disproportionate representation of infants younger than 3 months among children with dacryocystitis.

Patients with dacryocystitis usually have had a viral URI for several days. They then experience fever and impressive erythema and swelling in addition to exquisite tenderness, which is most prominent in the triangular area just below the medial canthus[17] (Fig. 85.6). Pressure over the lacrimal sac causes considerable discomfort but can result in expression of purulent material from the lacrimal puncta. Common causative organisms are gram-positive cocci. *S. pneumoniae* is most common in neonates, although *S. aureus, H. influenzae,* and *Streptococcus agalactiae* also have been reported.[15,18] *S. aureus* and *S. epidermidis* are most commonly implicated in acquired dacryocystitis in the older patient.[19] It is important to obtain material from the punctum because other organisms (including enteric gram-negative bacilli, anaerobic bacteria, and yeast) occasionally have been observed. Unusual pathogens, such as *Pasteurella multocida* and *Aeromonas hydrophilia,* have been reported rarely.[20]

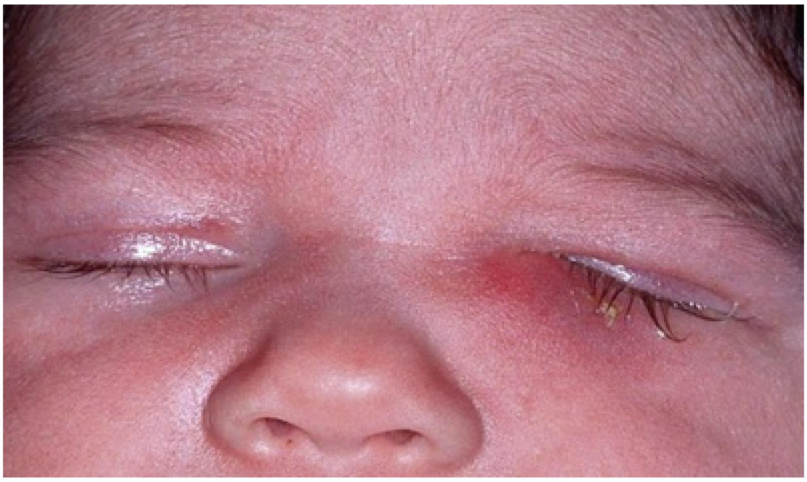

FIGURE 85.6 Dacrocystitis in an infant. The area at or beneath the medial canthus is erythematous, indurated, and exquisitely tender. (Courtesy of J. H. Briené.)

Most patients with dacryocystitis require admission to hospital. Often they appear ill or toxic. Because of the potential for any case of bacterial facial cellulitis to result in cavernous sinus thrombosis, therapy with parenteral antibiotics is indicated until the infection begins to subside. Nafcillin (at a dose of 150 mg/kg/day divided into doses every 6 hours) or cefazolin (at a dose of 100 mg/kg/day divided into doses every 8 hours) is appropriate. In penicillin-allergic patients, or when MRSA is suspected, vancomycin (60 mg/kg/day divided into doses every 6 hours) suffices. After substantial improvement is observed in local findings, an oral agent can be substituted to complete a 10- to 14-day course of therapy.

The role of nonmedical management of dacryocystitis is controversial. Although surgical manipulation of the lacrimal duct is not necessary for most patients, both probing of the duct and incision and drainage have been reported to be successful in neonates.[18] Incision and drainage and direct application of antibiotics inside the sac have been promoted by some practitioners who care for older children and adults.[21]

Preseptal Cellulitis After Trauma

Occasionally, preseptal cellulitis results from secondary bacterial infection of sites of local skin trauma (including insect bites) or with spread of infection from a focus of impetigo. The traumatic injury can be extremely modest or completely inapparent. Loosely bound periorbital soft tissues permit impressive swelling to accompany minor infection. The overlying skin can be bright red with subtle textural changes, or intense swelling can lead to a shiny appearance (Fig. 85.7). Some patients have fever, but many are afebrile despite dramatic local findings. The peripheral white blood cell count is variable. In these cases, cellulitis, similar to that on any other cutaneous area, is caused by *S. aureus* (including MRSA) or group A *Streptococcus*.[22,23] This is one of the most common causes of preseptal cellulitis.

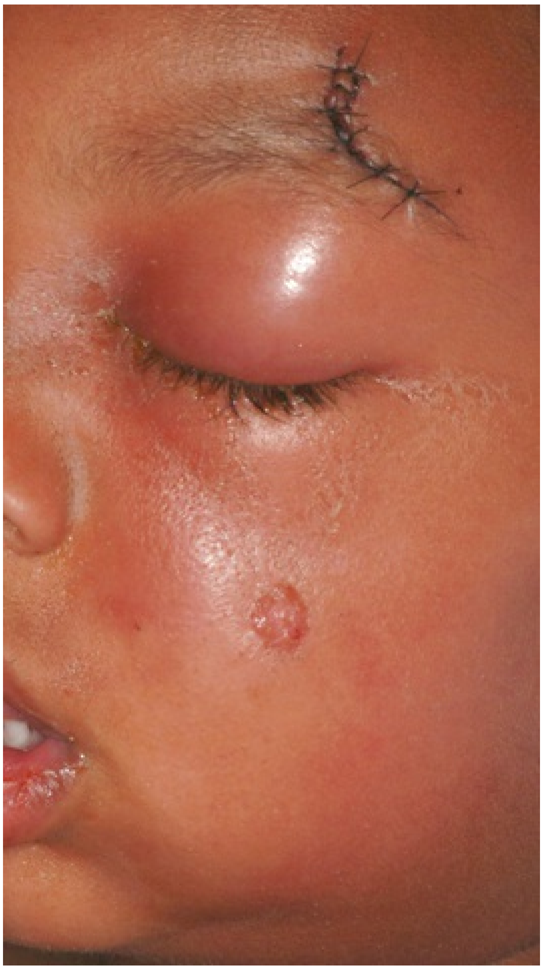

FIGURE 85.7 An infant with rapid onset of left eyelid swelling and erythema after a small laceration above the eye was sutured. Group A *Streptococcus* was recovered from the wound. (Courtesy of J. H. Briené.)

Several less common causes of lid cellulitis have been reported. Periocular cellulitis and abscess formation have resulted from infection with *P. multocida* in a healthy child who sustained a cat bite and cat scratch to the eyelid.[24] Ringworm (caused by *Trichophyton* spp.) also has been recognized as a cause of lid infection (leading to preseptal cellulitis) characterized by redness, swelling, ulceration, and vesicle formation.[25,26] A case of palpebral myiasis was reported in which larvae were extracted from a small draining fistula at the site of an erythematous and edematous lid.[27] Several cases of cellulitis of the eyelid due to *Bacillus anthracis* have been reported from Turkey.[28] The diagnosis was suspected when the erythematous and swollen lid developed an eschar. Scrapings showed the presence of gram-positive bacilli, which were confirmed by culture. A primary case of lymphocutaneous *Nocardia* *brasiliensis* of the eyelid has been reported in an adult hunting in England 2 weeks before presentation after a small abrasion on his lower eyelid.[29] In endemic countries, *Mycobacterium tuberculosis* should also be considered in patients who present with a swollen lid; in pediatric cases of tuberculous lesions of the eyelids, presentation usually is relatively indolent (2 days to 2 months), and intermittently draining cutaneous sinuses occur during the course of conventional antibiotic treatment for more typical bacterial disease.[30] Diagnosis is confirmed by a positive tuberculin skin test, the identification of a primary focus of tuberculosis in lung or bone, and response to antituberculous therapy. Intraorbital complications of mycobacterial infection also can occur.[31]

Patients with bacterial cellulitis of traumatized areas rarely have bacteremia. Precise bacteriologic diagnosis is made through culture of exudate from the wound. If there is no drainage, a careful attempt at tissue aspiration is undertaken if this can be done safely (i.e., at a distance far enough from the orbit that there can be no potential damage to the eye). A tuberculin syringe with a 25-gauge needle can be used for aspiration of "tissue juice." Usually, only a minuscule amount of infected material can be aspirated. A small volume of nonbacteriostatic saline (0.2 mL) is drawn into the syringe before the procedure. The saline is not injected into the skin; instead, it is used to expel the small volume of tissue fluid within the needle onto chocolate agar for culture.[32] Parenteral treatment similar to that for dacryocystitis is recommended in patients with bacterial cellulitis (unless an unexpected microbial etiology emerges), to hasten resolution and avoid spread of infection to the cavernous sinus.

Bacteremic Periorbital Cellulitis

Bacteremia as the pathogenetic mechanism of periorbital cellulitis has been very uncommon since the introduction of conjugate vaccines for *H. influenzae* type b (Hib) and *S. pneumoniae* (pneumococcal conjugate vaccine 7 [PCV7] and 13 [PCV13]) in 2000 and 2010, respectively.[33] In these cases, the child with bacteremic periorbital cellulitis, which most often is seen in infants younger than 18 months, has had a viral URI for several days. There is a sudden increase in temperature (to >39°C) accompanied by the acute onset and rapid progression of eyelid swelling. Swelling usually begins in the inner canthus of the upper and lower eyelid and can obscure the eyeball within 12 hours. Periorbital tissues are markedly discolored and usually erythematous, although if the swelling has been rapidly progressive, the area may have a violaceous discoloration.[34,35] The child's resistance to examination commonly leads to the erroneous impression of tenderness. Retraction or separation of the lids reveals that the globe is normally placed and extraocular eye movements are intact. If retraction of the lids is not possible, computed tomography of the orbit may be necessary.[36] The young age, high fever, and rapid progression of findings differentiate bacteremic preseptal cellulitis from other causes of swelling around the eye.

A precise bacteriologic diagnosis is made by recovery of the organism from blood culture. If a careful tissue aspiration is performed, culture of the specimen may have a positive result.

The pathogenesis of most of these infections, which usually occur during the course of a viral URI, is hematogenous dissemination from a portal of entry in the nasopharynx. This process is akin to the mechanism of most infections caused by Hib and some infections caused by *S. pneumoniae.*

In patients with bacteremic periorbital cellulitis, radiographs of the paranasal sinuses often are abnormal. However, the abnormalities almost certainly reflect the viral respiratory syndrome that precedes and probably predisposes to the bacteremic event, rather than a clinically significant sinusitis.[7] Bacteremic cellulitis rarely arises from the paranasal sinus cavities, as evidenced by the finding that typable *H. influenzae* organisms are almost never recovered from maxillary sinus aspirates and likewise are rarely recovered from abscess material in patients who have serious local complications of paranasal sinus disease, such as subperiosteal abscess. Although *S. pneumoniae* can cause subperiosteal abscess in patients with acute sinusitis, such patients usually are not bacteremic.

Treatment of suspected bacteremic periorbital cellulitis requires parenteral therapy. *S. pneumoniae* is the most likely cause in a child who has received both the Hib and PCV series. Because this infection usually is bacteremic in the age group in whom the meninges are susceptible to inoculation, it may be prudent to use an advanced-generation cephalosporin such as ceftazidime or ceftriaxone (150 or 100 mg/kg/day, respectively, divided into doses every 8 or 12 hours, respectively). Lumbar puncture should be performed unless the clinical picture precludes meningitis. Addition of vancomycin (60 mg/kg/day divided into doses every 6 hours) or rifampin (20 mg/kg once daily, not to exceed 600 mg/day) is appropriate if cerebrospinal fluid pleocytosis is present. When evidence of local infection has resolved and there is no meningitis, oral antimicrobial therapy is prescribed to complete a 10-day course.

Preseptal Cellulitis Caused by Inflammatory Edema of Sinusitis

Several complications of paranasal sinusitis can result in the development of swelling around the eye. The most common and least serious complication often is referred to as *inflammatory edema* or a *sympathetic effusion*.[6] This is a form of preseptal cellulitis, although infection is confined to the sinuses.

Typically, a child at least 2 years old has had a viral URI for several days when swelling is noted. Often, there is a history of intermittent early-morning periorbital swelling that resolves after a few hours. On the day of presentation, the eyelid swelling does not resolve typically but progresses gradually (see Fig. 85.1). Surprisingly, striking degrees of erythema also can be present. Eye pain and tenderness are variable. Eyelids can be very swollen and difficult to evert, requiring the assistance of an ophthalmologist. However, there is no displacement of the globe or impairment of extraocular eye movements. Fever, if present, is usually of low grade.

The peripheral white blood cell count is unremarkable, blood culture is sterile, and if a tissue aspiration is performed, culture is sterile. Sinus radiographs or other images show ipsilateral ethmoiditis or pansinusitis. The age of the child, gradual evolution of lid swelling, and modest fever differentiate inflammatory edema from bacteremic periorbital cellulitis.

The pathogenesis of sympathetic effusion or inflammatory edema is attributable to the venous drainage of the eyelid and surrounding structures. The inferior and superior ophthalmic veins, which drain the lower lid and upper lid, respectively, pass through or just next to the ethmoid sinus. When the ethmoid sinuses are completely congested, physical impedance of venous drainage occurs, resulting in soft tissue swelling of the eyelids, maximum at the medial aspect of the lids. In this instance, infection is confined within the paranasal sinuses. The globe is not displaced, and there is no impairment of the extraocular muscle movements. However, inflammatory edema is part of a continuum, with more serious complications resulting from the spread of infection outside the paranasal sinuses into the orbit.[37] Rarely, infection progresses despite initial optimal management of sympathetic effusions.

The infecting organisms in cases of inflammatory edema are the same as those that cause uncomplicated acute sinusitis (i.e., *S. pneumoniae,* nontypable *H. influenzae,* and *Moraxella catarrhalis*). Antibiotic therapy can be given orally if, at the time of the first examination, the eyelid swelling is modest (lid closure <50%), the child does not appear toxic, and the parents will adhere to management. Otherwise, admission to the hospital and parenteral treatment should be undertaken.

The only source of bacteriologic information is that obtainable by maxillary sinus aspiration, which is not usually performed. Appropriate agents for outpatient therapy should have activity against β-lactamase−producing organisms (e.g., amoxicillin −potassium clavulanate, cefuroxime axetil, and cefpodoxime proxetil). Parenteral agents include ceftriaxone (75 to 100 mg/kg/day, given as a single dose) or ampicillin-sulbactam (200 mg/kg/day divided into doses every 6 hours). The latter combination, although not approved for children younger than 12 years, is an attractive choice. Although the use of topically applied intranasal decongestants such as oxymetazoline has not been evaluated systematically, such agents may be helpful during the first 48 hours. After several days, when the affected eye has returned to near normal, an oral antimicrobial agent is substituted to complete a 14-day course of therapy.

A handful of children who present with a swollen eye experience one or more recurrences. In these cases anatomic abnormalities must be considered (natural or acquired bony dehiscences in the lamina papyracea,[38] or uncinate process[39]) in addition to reactivation of herpes simplex virus infection, sinusitis, allergic inflammation,[40] and orbital cysts derived from lacrimal tissue.[41]

Orbital Infection

The child or adolescent with true orbital disease secondary to sinusitis usually has sudden onset of erythema and swelling about the eye after several days of a viral URI (Fig. 85.8). Eye pain can precede swelling and often is dramatic. The presence of fever, systemic signs, and toxicity is variable. Orbital infection is suggested by proptosis (with the globe usually displaced anteriorly and downward), impairment of extraocular eye movements (most often upward gaze), or loss of visual acuity or chemosis (edema of the bulbar conjunctiva). Although most cases of orbital cellulitis secondary to sinusitis originate as a complication of viral URI, a few cases are of odontogenic origin.[42,43] Rarely, orbital abscess can occur without apparent underlying sinus or dental disease and absent acute signs of infection.[44] Fortunately, orbital infection is the least common cause of the "swollen eye."

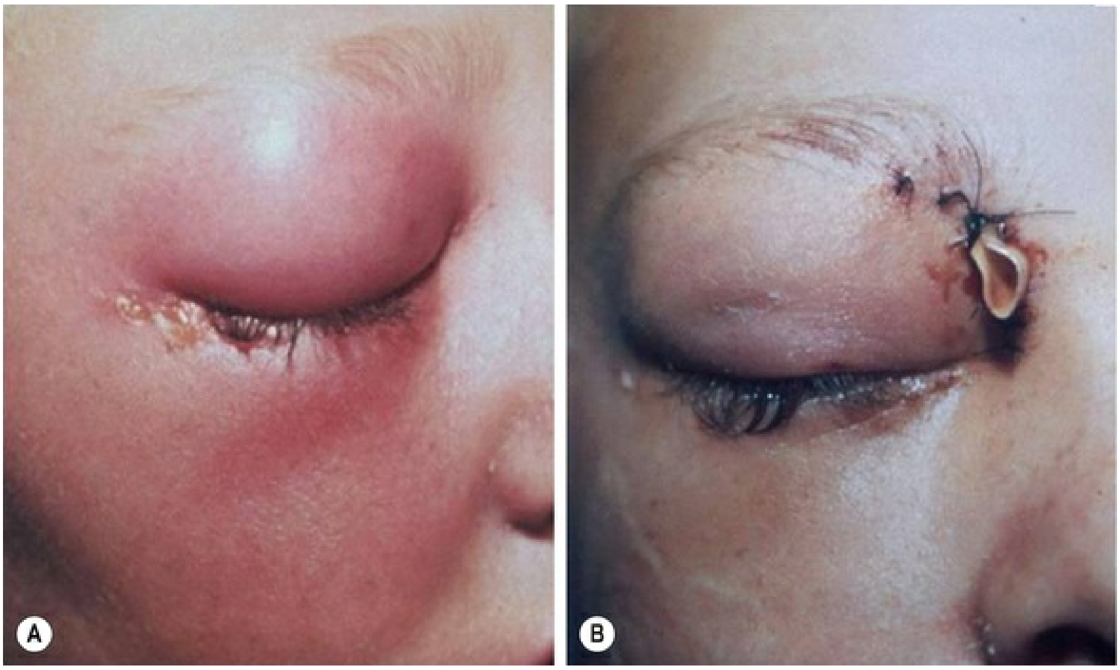

FIGURE 85.8 A boy with orbital cellulitis complicating sinusitis, before (A) and after (B) drainage. He had a 3-day history of eye pain with progressive swelling and erythema of the eyelids. He had proptosis, chemosis, and upward gaze palsy. (Courtesy of J. H. Briené.)

Most orbital infections involve the formation of a subperiosteal abscess. In young children, such an abscess results from ethmoiditis and ethmoid osteitis. In the adolescent, subperiosteal abscess can be a complication of frontal sinusitis and osteitis. Rarely, orbital cellulitis evolves, without formation of subperiosteal abscess, by direct spread from the ethmoid sinus to the orbit through natural bony dehiscences in the bones that form the medial wall of the orbit.

In addition to proptosis, impaired extraocular movements and loss of visual acuity, other factors, including age, extent of periorbital edema, absolute neutrophil count (>10,000/mm^3), and previous antibiotic treatment, may be used to estimate risk for orbital infection.[45] Imaging studies usually are performed if orbital disease is suspected to help determine whether subperiosteal abscess, orbital abscess, or orbital cellulitis is the cause of the clinical findings (Fig. 85.9).[46] In the presence of a large, well-defined abscess, complete ophthalmoplegia, or impairment of vision, prompt operative drainage of the paranasal sinuses and the abscess is performed.[47,48] Additional criteria include superior or inferior subperiosteal abscess, intracranial spread, frontal sinus involvement, and age greater than 9 years.[49] Subperiosteal abscess frequently can be drained successfully by endoscopy performed through an intranasal approach, thus avoiding an external incision.[50–52] In many cases, inflammatory tissue, rather than a well-defined abscess, is observed interposed between the lateral border of the ethmoid sinus and the swollen medial rectus muscle. Antimicrobial therapy alone usually is successful in such patients, as well as in patients with small abscesses that responded rapidly.[47,53–55] If the patient and ocular findings do not improve after 24 to 48 hours, surgical intervention is appropriate. Occasionally, computed tomography can suggest an abscess when only inflammatory edema is present[37,56]; accordingly, the clinical course is the ultimate guide to management.

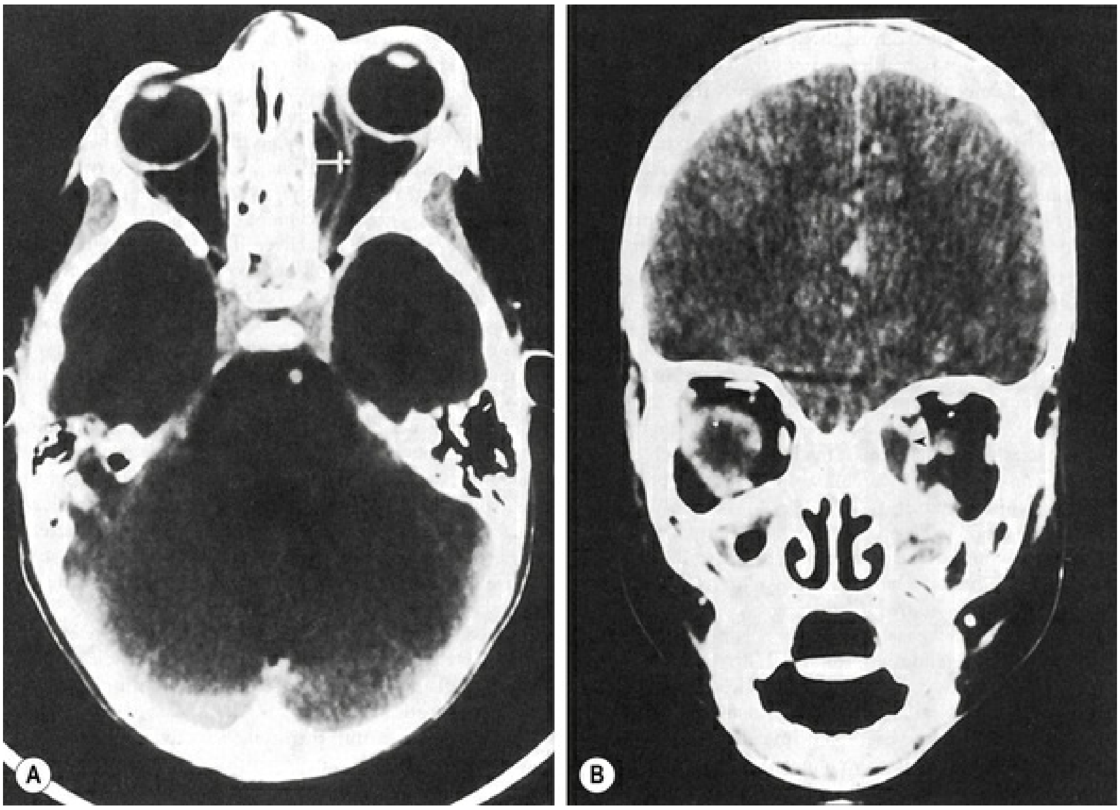

FIGURE 85.9 Axial (A) and coronal (B) computed tomography scans show a subperiosteal abscess extending from the left ethmoid sinus.

Empiric antimicrobial therapy should be chosen to provide activity against *S. aureus, S. pyogenes, Streptococcus anginosus,* and anaerobic bacteria of the upper respiratory tract (anaerobic cocci, *Bacteroides* spp., *Prevotella* spp., *Fusobacterium* spp., and *Veillonella* spp.) in addition to the usual pathogens associated with acute sinusitis (i.e., *S. pneumoniae, H. influenzae,* and *M. catarrhalis*).[49,57,58] An appropriate regimen is ampicillin-sulbactam (200 mg/kg/day divided into doses every 6 hours) plus vancomycin (60 mg/kg/day in 4 divided doses). Vancomycin will provide coverage in the event the causative organism is MRSA or if *S. pneumoniae* is highly resistant to penicillin. If surgery is performed, Gram stain of material drained from the sinuses or the abscess guides consideration of additional drugs or an altered regimen. When final results of culture and susceptibility tests are available, antibiotic therapy may be adjusted if necessary. Intravenous therapy is maintained until the eye appears nearly normal. At that time, oral antibiotic therapy can be substituted to complete a 3-week course of treatment.

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Infections Related to Trauma

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86

Infection Following Trauma

Sarah L. Wingerter

Trauma is a major cause of morbidity in children and is the leading cause of death in children older than 1 year. About 90% of childhood injuries are secondary to blunt trauma, often caused by motor vehicle crashes, falls, or abuse.[1,2] Infection that follows trauma can be due to the injury itself or, more commonly, can be a consequence of healthcare procedures and prolonged hospitalization. In one study, 10% of children admitted to a pediatric intensive care unit after trauma experienced infection.[3] The incidence of infection following trauma in adults may be as high as 25%; wound infections or other hospital-associated infections appear to be equally likely.[3] Hospital-associated infections are addressed in detail in Chapter 99. Trauma-associated infections, which can cause considerable morbidity, are the focus of this chapter.

Pathogenesis

Severe injuries increase a child's susceptibility to infection for several reasons. Breaks in the skin and mucosal barriers allow pathogens to gain entry, and accumulation of blood provides a favorable environment for bacterial growth. Devitalized or necrotic tissue at the injury site can harbor pathogens that can evade the host's defense mechanisms. Foreign bodies introduced by the injury itself or as a consequence of hospitalization (e.g., catheters) allow entry and persistence of pathogens. Risk factors for infection in patients hospitalized for trauma include the severity of the injury, the presence of shock, the number of organs injured, and the amount of blood lost.[4,5] Other potential risk factors are underlying host factors and the number and virulence of organisms introduced as a result of injury.

Trauma can adversely affect host defense mechanisms. Monocyte activation occurs rapidly after severe injury and hemorrhagic shock. After monocyte activation, inflammatory mediators can be released in a dysregulated pattern, leading to the systemic inflammatory response syndrome[6] (see Chapter 11). Complement is activated by injured tissue, thus decreasing complement levels, and antibody production also diminishes after blunt trauma.[7] Suboptimal nutrition can further impair immune responsiveness.

General Principles of Management

Patients who sustain trauma can exhibit signs and symptoms consistent with infection in the absence of infection. Retroperitoneal blood can cause fever, as can atelectasis. Pulmonary contusions can mimic pneumonia radiographically, and the signs and symptoms of hemorrhagic shock can be indistinguishable from those of septic shock. Thorough evaluation may be hampered by a patient's immobility or diminished neurologic status and by dressings that can obscure foci of infection. The decision to begin antibiotic therapy should be made carefully, after acquisition of appropriate microbiologic specimens. Appropriate use of antibiotics can benefit the patient, but inappropriate use has no benefit and can lead to adverse effects and promote the development of resistant organisms.

Measures to reduce infection include rapid surgical intervention when necessary, removal of unnecessary catheters, and strict attention to infection-control procedures and hand hygiene. Prophylactic or presumptive antibiotic therapy may be beneficial in some circumstances.

Immunity to tetanus should be assessed in any patient with an open wound. Tetanus toxoid-containing vaccine should be given to any child in whom the primary vaccination series has been delayed or who has not received tetanus vaccine in more than 5 years. Tetanus immune globulin should be used in conjunction with the vaccine in high-risk wounds (e.g., puncture wounds, wounds contaminated with soil, feces, or saliva) if the child has not received adequate prior immunization. Children 11 to 18 years old who were vaccinated against tetanus 5 years earlier and require a tetanus toxoid–containing vaccine as part of wound management should receive a tetanus toxoid, reduced diphtheria toxoid, acellular pertussis vaccine (Tdap) if they have not received Tdap previously.[8]

The use of prophylactic or presumptive antibiotic therapy in select situations can reduce the incidence of infection (Table 86.1); however, continuation of antibiotic therapy longer than 24 hours has not demonstrated additional benefit, as discussed in detail later.

TABLE 86.1

Common Pathogens and Recommended Prophylaxis Following Trauma

Type of Trauma	Common or Important Pathogens	Recommended Prophylaxis
All trauma	*Clostridium tetani*	Ensure tetanus immunity or give vaccine ± tetanus immune globulin
Penetrating abdominal injuries	Enteric gram-negative bacilli and anaerobic bacteria	Ceftriaxone plus metronidazole, or cefoxitin, or gentamicin plus metronidazole
Splenectomy	Encapsulated organisms, e.g., *Streptococcus pneumoniae, Haemophilus influenzae,* and *Neisseria* spp.	Ensure vaccination against all three organisms. Give penicillin prophylaxis
Basilar skull fracture	Meningitis due to respiratory tract organisms	No prophylaxis recommended
Open fractures (including skull)	*Staphylococcus aureus,* gram-negative bacilli	Nafcillin, or cefazolin, or clindamycin.[a] Add gram-negative coverage for grade III fractures
Thoracic trauma requiring chest tube	*S. aureus* and *Streptococcus* spp.	Nafcillin, or cefazolin, or clindamycin[a]

[a] Vancomycin may be appropriate if methicillin-resistant *S. aureus* (MRSA) is prevalent in the community or if the patient is known to be colonized with clindamycin-resistant MRSA.

Nutritional status also can affect infection risk. Patients with trauma who are given enteral nutrition have a lower risk for infectious complications than those given intravenous nutrition.[9,10]

There is conflicting evidence on whether injured patients fed an enteral diet rich in glutamine, arginine, and omega-3 fatty acids have a lower risk for infection than those fed a standard enteral diet or those who receive no early enteral nutrition.[11–13]

Skin and Soft Tissue Trauma

Factors associated with a greater risk for infection after injury to the skin and soft tissues are the severity of the wound, shock, and blood loss (Table 86.2).[4,7] Because wounds sustained in trauma are inherently contaminated, thorough cleansing and debridement of devitalized tissue have preeminent importance in preventing infection.

TABLE 86.2

Infection Risk and Management Following Trauma

Type of Trauma	Infection Risk	Intervention
Skin and soft tissue	*Streptococcus pyogenes* (GAS) <2 days Methicillin-susceptible/methicillin-resistant *Staphylococcus aureus* (MSSA/MRSA) ≥2 days	First-generation cephalosporin; wound culture; consider other antibiotics based on local resistance patterns (clindamycin, TMP-SMX, tetracycline, rifampin); vancomycin or linezolid if life-threatening
Animal/human bites	As above, plus *Pasteurella multocida, Eikenella corrodens,* anaerobic bacteria	Blood culture, needle aspirate; β-lactam/β-lactamase inhibitor agent, clindamycin plus TMP-SMX if penicillin-allergic
Body piercings, tattoos	Skin flora, *Pseudomonas aeruginosa*	Ceftazidime or piperacillin-tazobactam
Water associated		
Fresh water	*Aeromonas hydrophila*	Third- or fourth-generation cephalosporin or extended-spectrum β-lactam
Salt water or contact	*Vibrio vulnificus*	Third-generation cephalosporin with raw seafood exposure
Fish spines, fish tanks	*Mycobacterium marinum*	Surgical excision; combination antibacterial therapy
Blunt/penetrating trauma		
Pyomyositis	*S. aureus*, GAS	Surgical drainage, debridement; antibiotics
Necrotizing fasciitis/gas gangrene	*S. aureus*, GAS, *Clostridium* species	Fasciotomy; debridement; penicillin or nafcillin plus clindamycin (consider vancomycin)
Abdominal trauma		
Penetrating: higher risk for intestinal injury + spillage of bowel contents	Acute: peritonitis (±septicemia) Later: abscess, surgical	Surgical exploration, metronidazole plus aminoglycoside (see text)

Blunt: risk for duodenal/pancreatic hematoma (increased risk for infection if large-volume transfusion required)		Aminoglycoside or third-generation cephalosporin; surgical/CT-guided abscess drainage site of infection
Splenic rupture:		
Nonoperative	Blood transfusions pathogens	
Splenectomy	Postsplenectomy septicemia (encapsulated organisms)	Immunizations: Hib, pneumococcal, meningococcal vaccines; penicillin prophylaxis until at least 5 years of age and 1 year after splenectomy
Head trauma	Meningitis (especially with basilar skull fracture, penetrating trauma, or open wounds); ventriculitis; brain abscess, *S. pneumoniae, H. influenzae, N. meningitidis,* GAS, *S. aureus,* gram-negative bacilli	CSF analysis and culture; antibiotics with good CSF penetration; gram-positive coverage, e.g., vancomycin plus third-generation cephalosporin; gram-negative coverage if contaminated wound or extensive soft tissue damage; surgical intervention if persistent CSF leak
Fractures		
Open	Highest risk: grade IIIB or IIIC, internal/external fixation device, involvement of lower leg; *S. aureus, Enterobacter* spp., *Pseudomonas* spp.	Surgical debridement; antibiotic therapy. Antibiotic prophylaxis for open fractures: gram-positive coverage for open fractures; gram-negative coverage for grade III; add high-dose penicillin if fecal contamination or clostridial infection suspected clinically
Puncture wounds of the foot	Cellulitis, abscess, osteochondritis; *Pseudomonas* spp., *S. aureus,* GAS, *E. corrodens* (toothpick)	Surgical debridement; antibiotics
Thoracic trauma		
Pulmonary contusion, hemothorax, pneumothorax	Risk factors for hospital-associated pneumonia: prolonged intubation, poor pulmonary toilet, aspiration	Antibiotics active to cover oropharyngeal/nasopharyngeal organisms (including anaerobes) and defined gram-negative bacilli by local intensive care unit pathogens and respiratory culture. Empiric choices: clindamycin plus third-generation cephalosporin or aminoglycoside; or β-lactam/β-lactamase inhibitor

CSF, cerebrospinal fluid; CT, computed tomography; GAS, group A *Streptococcus;* Hib, *Haemophilus influenzae* type B; TMP-SMX, trimethoprim-sulfamethoxazole.

Cellulitis can follow minor or major trauma to the skin. Rapidly spreading cellulitis that occurs within 2 days of injury is more likely due to *Streptococcus pyogenes* (group A *Streptococcus* [GAS]), whereas staphylococcal cellulitis may not manifest for several days. Although GAS and *Staphylococcus aureus* are the most common causes of cellulitis, other pathogens should be considered in certain settings. Animal or human bites can lead to infection with

Pasteurella multocida or *Eikenella corrodens,* respectively, as well as with anaerobes, *S. aureus,* and GAS. Body piercings and tattoos, which are increasingly common in adolescents, also can lead to bacterial infection. Although skin flora usually is the cause, *Pseudomonas aeruginosa* is a common cause of infection following piercing of the auricular cartilage,[14] and there have been outbreaks of methicillin-resistant *S. aureus* (MRSA) infections in tattoo recipients.[15] Hepatitis B, hepatitis C, and human immunodeficiency virus (HIV) infection also can be transmitted through piercing and tattooing. *Aeromonas hydrophila* infection is associated with lacerations obtained while swimming in fresh water, and *Vibrio vulnificus* can cause skin or soft tissue wound infections after contact with salt water or drippings from raw seafood. *Mycobacterium marinum* can cause cutaneous infection after freshwater or salt-water injuries from fish spines or marine shellfish, or from contamination during exposure to fishtanks.[16]

Culture of blood and needle aspirate specimens have low yield in typical cases of cellulitis but can be revealing in cases of cellulitis associated with animal bites or other unusual injuries.

For mild to moderate cases of typical wound cellulitis, empiric therapy with a first-generation cephalosporin provides coverage for the most common pathogens, including *S. aureus* and GAS. The emergence of community-associated MRSA (CA-MRSA) in posttraumatic skin and soft tissue infections makes empiric treatment problematic.[17,18] Children colonized with MRSA have a greater risk for developing a wound infection after trauma. For more severe cases of cellulitis, for wound infections requiring hospitalization, or for an infection not responding to initial β-lactam antibiotic therapy, a diagnostic specimen should be obtained and treatment should include coverage of MRSA.[19] Although many CA-MRSA are susceptible to clindamycin,[20,21] some have inducible or constitutive clindamycin resistance.[22,23] Most strains also are susceptible to tetracycline (which should be avoided in children <9 years), trimethoprim-sulfamethoxazole, and rifampin. For life-threatening infections possibly due to MRSA, appropriate therapy would include vancomycin or linezolid.[24] Knowledge of local antibiotic resistance patterns should guide empiric therapy.[25]

Pyomyositis can occur after blunt or penetrating trauma and usually is caused by *S. aureus* or GAS. Treatment involves surgical drainage, debridement, and antibiotic therapy. Necrotizing fasciitis, due to GAS or *S. aureus,* and gas gangrene, usually due to *Clostridium* spp., can complicate traumatic wounds and are surgical emergencies. A characteristic symptom is intense pain, often out of proportion to findings on examination, which can include discoloration of the overlying skin, swelling, and crepitus. Patients with necrotizing fasciitis also can have concomitant toxic shock syndrome. Computed tomography (CT) or magnetic resonance imaging may show muscle swelling, fluid collections, or, in the case of gangrene, gas in the muscle. Leukocytosis, thrombocytopenia, a rising creatine kinase level, and hypocalcemia can be seen in these patients.

Therapy for necrotizing fasciitis involves immediate surgical fasciotomy and debridement. Penicillin or nafcillin plus clindamycin should be given for streptococcal and clostridial infections.[26,27] Although penicillin G is the drug of choice for invasive GAS infections, clindamycin also should be used for deep infections such as necrotizing fasciitis. In a mouse model of streptococcal myositis, clindamycin was found to be superior to penicillin.[28,29] The likely explanation is that the high density of GAS leads to reduced replication and decreased expression of penicillin-binding proteins.[29] Clindamycin, which inhibits protein synthesis, maintains its activity against these slowly replicating bacteria and also inhibits the production of bacterial toxins. Clindamycin should not be used alone until results of susceptibility testing are available because some GAS organisms are resistant.

Abdominal Trauma

Trauma to the abdomen can be blunt or penetrating. Penetrating trauma is less common but carries a higher risk for intestinal injury. Either penetrating or blunt trauma can cause intestinal tears that lead to spillage of bowel contents into the peritoneum. Injuries to the colon are associated with a higher risk for infection because of the higher density of organisms in the more distal bowel.[30] Blunt trauma related to physical abuse can cause hematoma of the duodenum and pancreatitis. Requirement for a large volume of transfusion is also a risk factor for infection after abdominal trauma.[5]

Infection can manifest acutely as peritonitis, with or without septicemia, or later, as an abscess or surgical site infection. Diagnosis is aided by CT or, in a patient who cannot be moved, ultrasonography. Needle aspiration of peritoneal fluid is performed in patients with peritonitis to confirm the diagnosis and establish the etiology. Treatment of an established infection requires empiric therapy with antibiotics effective against gram-negative and anaerobic bacteria, and surgical or CT-guided drainage if an abscess is present. Appropriate choices are metronidazole plus an aminoglycoside or third-generation cephalosporin, or piperacillin-tazobactam. It is not clear that empiric therapy with antienterococcal agents improves outcome in these patients; however, antienterococcal therapy should be considered for children who have persistent symptoms or when *Enterococcus* is isolated from peritoneal fluid cultures.

Surgical exploration is part of the routine management of penetrating abdominal injuries, and antibiotic therapy should be started as soon as possible. Fullen and associates[31] showed that patients with penetrating abdominal injuries who received antibiotics before surgery had a lower incidence of infection than patients who received the first dose of antibiotics intraoperatively or postoperatively. Because patients with penetrating abdominal injuries are presumed to have bacterial contamination of the peritoneum at the time of injury, antibiotic therapy should be considered as preemptive therapy.

The empiric antibiotic regimen should include agents effective against gram-negative enteric and anaerobic bacteria, which play a critical role in intra-abdominal infections after injury.[32] Single-drug therapy with a second-generation cephalosporin, such as cefoxitin or piperacillin-tazobactam, appears to be as effective as traditional three-drug antibiotic regimens in preventing infection in adults with penetrating abdominal injuries; resistance of anaerobic bacteria to cefoxitin and stimulation of production of extended-spectrum β-lactamases limit current use.[33,34] Other appropriate therapies include a third-generation cephalosporin plus metronidazole or an aminoglycoside plus metronidazole. Patients with trauma have a higher volume of drug distribution, so higher doses of aminoglycosides may be needed.[35,36]

Several studies have evaluated the appropriate length of presumptive therapy for patients with penetrating abdominal injuries. No significant difference in infection rate was found between patients treated for 24 hours and those treated for 5 days.[30,34,37–39] Therefore, current evidence does not support the use of antibiotics beyond 24 hours in patients with penetrating abdominal injuries, even if they have colonic injuries. Longer duration of antibiotic therapy promotes bacterial resistance and fungal overgrowth and may lead to additional side effects without further reducing the likelihood of infection.[40]

Splenic rupture after trauma deserves special consideration (see Chapter 106). If the rupture is managed nonoperatively, multiple blood transfusions may be required, placing the patient at risk for bloodborne pathogens. If splenectomy is performed, the child is at risk for overwhelming postsplenectomy septicemia, especially due to encapsulated organisms. The risk for septicemia in a child who has undergone traumatic splenectomy is as much as 350 times higher than that in a healthy child. Younger children are at higher risk for septicemia than older children. Although the period of greatest risk appears to be the first 2 years after splenectomy, septicemia has been reported up to 25 years after splenectomy. Therefore, observation or splenic repair is preferred if the child is clinically stable.[41,42]

If splenectomy is performed, immunizations should be reviewed to ensure that the child has been appropriately immunized with the *Haemophilus influenzae* type b and pneumococcal conjugate vaccines. Children 2 years and older who have been adequately immunized with the 13-valent pneumococcal conjugate vaccine (PCV13) should be given a dose of the 23-valent polysaccharide vaccine (PPSV23). They should receive a second PPSV23 dose 5 years after the first. Children 24 through 71 months of age who are fully immunized with PCV7 should receive one dose of the PCV13 as well as a dose of the PPSV23 at least 8 weeks later and then again 5 years later. Children 6 through 18 years of age also should receive the PCV13 and PPSV23 on a similar schedule (see Chapter 123 for additional circumstances). In addition, penicillin prophylaxis is recommended for children younger than 5 years and also for at least 1 year after trauma-related splenectomy in older children.[41] Meningococcal conjugate vaccine (ACWY or CY) should be administered to children 2 months and older (avoiding use of one product, MCV4-

D, Menactra, until 2 years of age or after completion of all indicated pneumococcal conjugate vaccines). Booster doses are required throughout life (see Chapter 125). Meningococcal B vaccine is indicated as a 2-dose (MenB-4C) or 3-dose (MenB-FHbp) series for those 10 years and older.[43]

Head Trauma

Head trauma is common in children, and central nervous system injury increases mortality among injured children.[1] As many as one half of patients with head trauma develop an infectious complication, most often a hospital-associated infection.[44] Trauma-related infectious complications include meningitis, ventriculitis, and brain abscess; common pathogens are *Streptococcus pneumoniae* and other upper respiratory tract organisms such as *H. influenzae, Neisseria meningitidis,* and GAS. Staphylococcal and gram-negative bacillary meningitis can occur after penetrating trauma, with open wounds, or postoperatively or can be associated with devices or occur after prolonged hospitalization.[45] It is essential to obtain cerebrospinal fluid (CSF) for culture if the diagnosis of meningitis is being considered after head trauma; CSF cell count as well as glucose and protein level can be difficult to interpret in the presence of subarachnoid hemorrhage. Treatment includes antibiotic therapy as well as possible surgical intervention in patients with device in place or after persistent CSF leakage.

Basilar skull fracture accounts for up to 20% of skull fractures and is associated with substantial risk for bacterial meningitis. Meningitis is a consequence of the communication created between the subarachnoid space and the colonized paranasal sinuses, nasopharynx, and middle ear. After basilar skull fracture, the incidence of meningitis can be as high as 17% and approaches 50% in patients who also have a CSF leak. However, a 1998 meta-analysis of 12 studies involving 1241 patients with basilar skull fractures suggested that antibiotic prophylaxis did not prevent meningitis.[46] Even when children and patients with CSF leakage were analyzed separately, there was no evidence that antibiotic prophylaxis decreased the risk for meningitis. In addition, the rate of meningitis in children after basilar skull fracture was only 3%, much lower than rates reported in adults. A 2006 Cochrane

Database review found that antibiotic prophylaxis had no significant effect on reducing the frequency of meningitis, all-cause mortality, or meningitis-related mortality in patients with basilar skull fractures.[47] Available data therefore do not support the use of prophylactic antibiotics in children with basilar skull fractures.

Prophylactic antibiotics usually are given after an open skull fracture, although there are few data to guide recommendations. Antibiotics chosen should have good CSF penetration and cover gram-positive organisms. Coverage for gram-negative organisms may be needed if the wound is heavily contaminated or there is extensive soft tissue damage.

Fractures

Fractures are common childhood injuries and can be either closed or open. Open fractures can be graded on a scale of I to III on the basis of wound size and amount of soft tissue damage. Grade III fractures are further subdivided (IIIA, IIIB, and IIIC) according to vascular injuries and soft tissue defects. Dellinger and colleagues,[48] evaluating factors associated with infection after open-extremity fractures, found the following independent risk factors: severity of fracture (grade IIIB or IIIC), the placement of an internal or external fixation device, and involvement of the lower leg. Organisms most commonly implicated in fracture-associated infections were *Staphylococcus* spp., *Enterobacter* spp., and *Pseudomonas* spp.[48–50] Therapy consists of surgical removal of infected tissue and antibiotics.

Infection rates associated with open fractures range from as high as 9% for grade I fractures to 50% for grade III fractures. Infection after open fracture can lead to delayed bone healing, prolonged hospitalization, and permanent disability. Open fractures have a higher risk for infection than closed fractures because bone and soft tissue contamination likely occurred at the time of injury.

Several studies have demonstrated a reduced risk for infection after open fractures in patients given prophylactic therapy with antibiotics effective against *S. aureus.*[51–53] In addition to *S. aureus,* gram-negative bacilli such as *Pseudomonas* and *Enterobacter* spp. can cause open-fracture–associated infections, especially with grade III fractures. The Eastern Association for the Surgery of Trauma

(EAST) guidelines revised in 2009 recommend the following: prophylactic antibiotics with gram-positive coverage as soon as possible after injury for all trauma with open fractures; additional coverage for gram-negative organisms for grade III fractures. For grade I and II fractures, antibiotics should be discontinued 24 hours after wound closure. Additionally, for grade III fractures, antibiotics should be continued for only 72 hours after the time of injury or not more than 24 hours after soft tissue coverage of the wound, whichever comes first. A Cochrane database review from 2010 also found evidence for benefit of antibiotic prophylaxis at the time of surgery for closed long-bone fractures.[54]

The use of antibiotic-impregnated beads, cement, and polymers has shown some promise in reducing open-fracture–associated infections.[50,52,55] Prospective randomized trials are needed to determine effectiveness.

Puncture Wounds

The management of infection after a puncture wound to the foot deserves special consideration. Up to 18% of such wounds are complicated by cellulitis or a soft tissue abscess, and up to 2% by osteochondritis. *P. aeruginosa* is responsible for as many as 90% of cases of osteochondritis after a puncture wound to the foot.[34] The liner of used sneakers has been found to contain *Pseudomonas,* making this a likely source; however, *Pseudomonas* can cause infection after a puncture wound through other shoes and even bare feet, and at other sites.[56] Other gram-negative bacilli, as well as *S. aureus* and GAS, also can cause osteochondritis after a puncture wound. *E. corrodens* and oral anaerobic bacteria have been reported after toothpick puncture injury to the foot.[57,58] Rarely, nontuberculous mycobacteria can be the primary pathogen.[59,60] Surgical debridement is the mainstay of management, both to obtain specimens for determining infectious etiology and to remove necrotic cartilage and any retained foreign body. After debridement, antipseudomonal therapy, if necessary, need only be continued for a week. Osteochondritis due to other organisms should be treated with a conventional course of therapy.

Thoracic Trauma

Thoracic injuries are a major cause of death in childhood trauma. Such injuries usually are blunt and often are due to a motor vehicle collision.[1] Significant chest trauma can lead to pulmonary contusion, hemothorax, and pneumothorax. Although any major trauma increases the risk for hospital-associated pneumonia due to prolonged intubation, poor pulmonary toilet, and the risk for aspiration, pulmonary contusions also lead to decreased pulmonary function, thereby further increasing the risk for pneumonia. The diagnosis of pneumonia can be challenging because fever and a pulmonary density can be due to the contusion itself. New onset of fever, leukocytosis, purulent secretions, and the need for increased ventilator settings are clues to the diagnosis. The antibiotic regimen for suspected pneumonia in this setting should take into account knowledge of the pathogens commonly identified in the local intensive care unit as well as results of culture of deep respiratory tract specimens, such as those collected by bronchoalveolar lavage when possible. Therapy consists of agents effective against defined oropharyngeal and nasopharyngeal or tracheal organisms, including anaerobic and gram-negative bacteria. Clindamycin plus either a third-generation cephalosporin or an aminoglycoside is appropriate, as is a β-lactam/β-lactamase–inhibiting agent.

Hemothorax due to blunt or penetrating thoracic trauma increases the risk for empyema, as does a thoracostomy tube placed to evacuate a hemothorax or pneumothorax. The risk increases with incomplete drainage of the pleural space or prolonged chest tube placement.[61] *S. aureus* and gram-negative bacilli predominate in these infections.[62] Prophylactic antibiotic therapy has been studied in the setting of tube thoracostomy after chest trauma. A meta-analysis of 9 prospective trials and 2 earlier meta-analyses found that prophylactic antibiotic therapy reduced the risk for subsequent pneumonia after thoracostomy tube placement.[63] A brief (24-hour) course of an antibiotic with good antistaphylococcal and antistreptococcal activity is appropriate after chest tube placement. Antibiotic prophylaxis for <24 hours also is recommended when open thoracotomy is performed for penetrating chest injury.[64]

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Infection Following Burns

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In 2013, unintentional injury was the leading cause of death in children 1 to 18 years of age in the United States. Of these deaths, burns were the fifth leading cause in children younger than 1 year, the fourth leading cause in children 1 to 4 years of age, and the third leading cause in children 5 to 9 years old.[1] Overall, the nonfatal burn injury rate per 100,000 population in the age group of 1 to 19 years was 156.6 in 2013.[1] Children younger than 4 years and children with disabilities are at the greatest risk for burn-related death and injury.[2] Most of these injuries are preventable. Most young children suffer scald injuries from hot liquids or flame burns from house fires. Older children are more likely to sustain flame burns from accidents with flammable liquids or fireworks and from house fires. On occasion, burn injuries can result from medical therapies, such as therapeutic application of heat, ignition of flammable medications (rubbing alcohol and hot oils), or burns from hot-air vaporizers.[3] The latest comprehensive analysis, performed in 2006, revealed a total annual cost of scald burn-related deaths and injuries among US children ≤14 years of age of approximately $44 million, with children <4 years of age accounting for 90% of these costs. Total charges for pediatric admissions to burn centers average $22,700 per case.[2]

The survival of children with burns depends on the following factors: (1) age, (2) the percentage of total body surface area (TBSA) burned, (3) the depth of the burn injury, (4) the type of burn, and (5) management. Young children, particularly those <2 years, have a lower survival rate for the same TBSA burned than older children and adults. Advances in burn care (improvements in resuscitation, intensive care, and care of the burn wound) have narrowed the gap in survival for small children.[4] Currently, the extent of burn associated with a 50% survival in patients older than 1 year is TBSA of about 80%.[5] Data suggest that the most common causes of death in burned children are smoke inhalation and hypoxic-ischemic brain injury. The enormous progress in burn survival and therapy is attributable to the following factors: care of patients in centers specializing in the treatment of burns; knowledge of the pathophysiology of shock and aggressive treatment of patients with fluid resuscitation and other adjunctive therapies; recognition of the importance of the caloric requirement of the burned patient and its role in wound healing; and advances in the care of the burn wound itself, especially early debridement and excision of the wound, use of topical antimicrobial agents, judicious use of antibiotics systemically, and improved grafting materials and techniques.[6]

TBSA can be estimated either from the Lund and Browder chart or with use of the size of the patient's palm, which roughly is 1% of the TBSA at any age, as a measure.[7] Depth of burn injury is determined by the extent of damage to tissue and is classified by degrees: a first-degree burn involves the epidermis only and is painful, red, and dry, resembling a sunburn; a second-degree burn involves the dermis, is severely painful, usually is erythematous and is moist, weeps, and may have blisters and bullae; a third-degree burn involves the subcutaneous tissue and is usually white or waxy-appearing, dry, avascular, and painless. Depth is alternatively classified as either partial thickness, involving the epidermis or superficial dermis, or full thickness, involving the deep dermis and subcutaneous tissue. The larger the percentage of TBSA involved and the deeper the burn, the higher the mortality, both immediately after injury (primarily from shock or occasionally from other associated injuries) and after successful resuscitation (from infectious complications). The type of burn also is important; scald burn is less commonly fatal than flame burn, especially if the latter is associated with pulmonary injury.

Children with burns >30% TBSA, flame and inhalation injuries, and full-thickness burns are at highest risk for infectious complications.[8] Burn victims are susceptible to a wide variety of infections associated with relative immunosuppression and complications of intensive care. Virtually any organ can become the target of an infection in such patients. The most common infections in burned children are those related to the burn wound and catheter-associated septicemia.[8] Infections related to intravascular and urinary catheters and endotracheal tubes are discussed in Chapter 100. Infection of the burn wound occurs with greatest frequency in children.[9] Burn wound septicemia is associated with at least an 80% mortality rate in children.

Diagnosis of infectious complications in a burn victim is challenging. Although fever and elevated peripheral white blood cell count with a left shift are usual indicators of infection, their positive predictive value for diagnosis of infectious complications in burn victims is very low because they are commonly seen in uninfected burned children whose wounds are uncovered.[10] Neither severity of fever (frequently >39°C) nor response to antipyretic therapy is a reliable indicator of infection.[10] Peak fever in burned children without infection usually occurs on the second day after the burn, with a second peak around the sixth and seventh days.[11] Fever is probably the result of an increase in metabolic rate and an alteration of hypothalamic temperature regulation. Fever usually subsides without specific therapy, coincident with re-epithelialization of the burn wound or successful grafting of all open areas. Thus, fever alone in the burned child is not a reliable indicator of infection or of the need to investigate for infection or prescribe antibiotic therapy.

Hypothermia usually is a more reliable indicator of infection, although children with burns affecting a high percentage of TBSA who are left uncovered for prolonged periods during dressing changes can have hypothermia that requires external warming. Hypotension due to fluid shifts is common early in the postburn period and usually can be differentiated from infectious causes because of rapid improvement with fluid resuscitation.

Several inflammatory mediators have been evaluated in attempts to distinguish infection from the normal response to thermal injury. They include tumor necrosis factor-α (TNF-α),[12–14] interleukin=1β (IL-1β),[12,14] IL-6,[12,14] IL-8,[13,15] procalcitonin,[16,17] and C-reactive protein.[18] Levels of mediators in burned patients are higher than those in healthy children, probably owing to nonspecific inflammation associated with thermal injury. Although several studies have shown significant differences in levels of these inflammatory mediators between burned patients with septicemia and those with uncomplicated thermal injury,[12,13,15–17] none is highly discriminatory. However, changes in serial C-reactive protein levels can occur in septicemia an average of 2.3 days earlier than a decrease in platelet count or clinical manifestations.[18]

Thus diagnosis of infectious complications is made through evaluation of all clinical signs, examination of the burn wound and all catheter sites, and consideration of supporting laboratory evidence and results of culture of blood, urine, or quantitative burn wound biopsy specimens.

Burn Wound Infection

Burn wound infection is defined as the invasion of microorganisms into viable tissue under the wound. Local infection can result in prolonged wound healing or sloughing of graft, toxin production leading to distant organ damage, and septicemia and infection at distant sites.[19]

The diagnosis of burn wound infection is made from local signs of wound infection, with or without systemic signs indicating septicemia or toxemia (Box 87.1), in conjunction with histologic and microbiologic evidence of infection in biopsy specimens of burn wounds (Box 87.2). The technique for quantitative biopsy requires a 1-g specimen of eschar, which is homogenized and cultured.[20] The procedure consists of cleaning the open wound with alcohol and obtaining the specimen with a scalpel or a dermal punch. Processing of the biopsy consists of aseptic weighing, alcohol dip and flaming to remove surface contamination, dilution in fixed-volume thioglycolate broth or saline, homogenization, and inoculation onto nutrient agar.[21,22] Although selection of the biopsy site, retained activity of topical antimicrobial agents, and multistep processing can be sources of error, quantitative biopsy culture yielding growth of a single or multiple organisms, each with a density of $>10^5$ colony-forming units per gram of tissue, correlates with infection. Histologic diagnosis of infection is supported by the presence of bacteria invading viable tissue and can be obtained with frozen or permanent sections, the latter of which is thought to be more accurate.[20] Blood culture results are positive in only 40% to 50% of patients with burn wound sepsis.

Box 87.1

Clinical Characteristics of Burn Wound Infection

Local Signs

Focal areas of discoloration or necrosis

Edema, erythema, discoloration of wound margin

Conversion of partial- to full-thickness burn

Unexpectedly rapid eschar separation

Hemorrhagic discoloration of subeschar tissue

Purulent exudate on burn wound

Systemic Signs

Hyperthermia

Hypothermia

Hypotension

Altered mentation

Glucose instability

Organ dysfunction

Adapted from Pruitt BA Jr, Yurt RW. Treating burn and soft tissue infections. Infect Surg 1983;2:623–650.

Box 87.2

Biopsy Findings of Burn Wound Infection

Histology

Characteristics of tissue underlying burn

Presence of microorganisms

Thrombosis or hemorrhage

Necrosis

Intense inflammatory response

Presence of intracellular viral inclusions

Microbiology

Positive quantitative Gram stain reaction

Isolation of single or multiple organisms, each $>10^5$ colony-forming units per gram of tissue

Adapted from Pruitt BA Jr, McManus AT. Opportunistic infections in severely burned patients. Am J Med 1984;76:146–154.

Factors that influence burn wound infection pertain to the wound, the host, and the causative organisms.

Wound Factors

Skin is a primary, critical local defense mechanism against infection, providing a mechanical barrier to penetration of organisms that normally reside on the surface. Skin saprophytes are thought to inhibit colonization by more pathogenic bacteria. Skin also produces antibacterial substances, such as unsaturated free fatty acids, that inhibit a number of microorganisms, particularly group A *Streptococcus* (GAS).[23] Thermal injury rapidly disrupts normal functions and produces an ideal culture medium.

After burn injury, the wound site rapidly becomes colonized with normal skin flora and gram-positive pathogens, and then by endogenous or environmental gram-negative bacilli and fungi if the course is protracted. Isolation of microbes from a burn wound is not a priori evidence of infection because invasion into underlying viable tissue must occur for infection to develop.

Adequacy of blood supply to the wound is critical. Avascularity of the burned tissue results from coagulation of vessels and tissue that make a protein-rich eschar and renders the site inaccessible to systemic antibiotics as well as humoral and cellular defenses. Infection in the burn wound can extend into the blood vessels, causing thrombosis that can compromise the blood supply further, converting a partial-thickness burn into a full-thickness burn. Wound factors such as the acidic, anaerobic, moist environment of the avascular burn tissue favor growth of certain pathogens such as fungi and impair activity of aminoglycoside antibiotics. The cooler temperature of the burn wound may influence infection because lower temperatures restrict blood flow, possibly causing further tissue necrosis and impairing phagocytic cell metabolism.[24] In addition, the location of the wound can contribute to the overall risk for infection, as is seen with exposure of the globe, bones, cartilage, and joints.[20] Likewise, the presence of foreign bodies in the wound also can promote infection.

Host Factors

Several host factors have been identified that influence the likelihood of burn wound infection. Children with underlying medical conditions, such as diabetes mellitus, neurologic disorder, and immunodeficiency, are more likely to experience burn wound septicemia, resulting in very high mortality.

Immunologic dysfunction is well described in patients who sustain burn injuries of >30% TBSA, with degree correlating directly with TBSA burned (Table 87.1).[25–52] The mechanism is unknown. It has been suggested that immunosuppression after injury evolves to protect against autoimmunity that might otherwise result from antigenic bombardment after intense tissue injury.[42,53,54] Immunosuppression of burned patients greatly increases their susceptibility to infection. Polymorphisms in the genes that encode toll-like receptor 4 and TNF-α are significantly associated with increased risk for severe septicemia after burn trauma.[55]

TABLE 87.1

Immunologic Dysfunction in Burned Children

Type of Dysfunction	References
HUMORAL IMMUNE FUNCTION	
Decreased numbers of B lymphocytes	25–27
Decreased total immunoglobulins	27–35
Decreased fibronectin	26, 27, 36–38
Aberrant production of immunomodulators	24, 26, 28, 39, 40
CELLULAR IMMUNE FUNCTION	
Anergy	26, 27, 41
Decreased mitogen and antigen responses	26, 29, 42
Increased suppressor T lymphocytes	27, 28, 42–44
Decreased helper T lymphocytes	28, 42, 43
NEUTROPHIL FUNCTION	
Decreased adherence	36
Decreased phagocytosis	29, 45–47
Decreased killing	27, 29, 45, 46, 48, 49
Decreased chemotaxis	26, 27, 29, 45, 46, 50, 51
OTHER	
Decreased macrophage and monocyte function	52
Complement-induced increase in release of immunosuppressive mediators	27

Causative Organisms

Organisms causing burn wound infection have changed during the past century. In the 1930s and 1940s, GAS was the predominant pathogen, followed by *Staphylococcus aureus.* In the 1950s and early 1960s, the predominant pathogen in such infections was *S. aureus.* Gram-negative bacilli, especially *Pseudomonas aeruginosa,* became the predominant pathogen in the 1960s and early 1970s. Since then, *S. aureus* has regained prominence (becoming the most common pathogen in many centers[8,56]), including methicillin-resistant *S. aureus* (MRSA), and the spectrum of gram-negative bacilli has broadened with increasing antimicrobial resistance.[57] Fungal and viral pathogens have become increasingly important. These changes are direct reflections of complications of aggressive therapy and survival of more severely affected patients.

The number of organisms present on the burn wound is an important factor in infectivity. It is theorized that high temperature initially sterilizes the burn wound. However, rapid colonization by normal skin flora and existent pathogens follows. At the time of hospitalization in our pediatric burn unit, routine cultures reveal that 9% and 54% of patients are colonized with GAS and *S. aureus*, respectively. Colonization of the wound surface is not equivalent to infection. Usually, a bacterial density of 10^5 organisms per gram of tissue is required before invasion of underlying viable tissue (burn wound infection) occurs. Infection can occur with lower bacterial densities, but rarely. The most common organisms to cause wound infections are *S. aureus* and *P. aeruginosa.*[20]

An organism's unique virulence, invasiveness, and motility also affect pathogenicity. It has been demonstrated that nonmotile strains of *Pseudomonas* spp. rarely cause infection.[58]

Early Infections

Colonization pattern of burn wounds is somewhat predictable over time. Initially, gram-positive organisms are present; infection that occurs in the first 48 hours after the burn usually is secondary to GAS. Because streptococcal infection can be rapidly invasive and fatal, it was once common practice to administer penicillin prophylactically to all burned patients at the time of admission. The incidence of GAS infections in burned patients has decreased, probably secondary to immediate use of topical antimicrobial therapy. Routine administration of penicillin prophylaxis is not recommended because it can hasten colonization and potential infection with more resistant organisms. *S. aureus* also causes early septicemia. If there is concomitant inhalation injury, organisms that colonize the respiratory tract can cause bacteremia and invade the burn wound.

In the latter part of the first week after injury, environmental and endogenous gram-negative bacilli colonize the wound. *P. aeruginosa* and Enterobacteriaceae are usual. Colonization of the gut is probably the primary event, followed by bacterial translocation and wound colonization. Bacterial translocation is frequent in burned patients because of the disruption of the mucosal barrier from nutritional factors, immunosuppression, disturbance of the normal barrier of bowel flora (from selective pressure of antibiotic administration), and overgrowth of hospital-associated pathogens. Early institution of enteral nutrition satisfies caloric requirements, improves immune function and tissue healing, and preserves the mucosal barrier, thereby decreasing the incidence of septicemia in burn victims.[59] Another proposed mechanism for acquisition of environmental organisms and subsequent infection is immersion of the patient in water or rolling of the patient in soil in an attempt to control the burning at the time of injury.[60]

Complication of burn injuries by tetanus is uncommon in the United States. In the nonimmune patient who has a wound contaminated with *Clostridium tetani,* neurologic manifestations of tetanus toxin and minor local infection can occur in the first week after injury.[61] Tetanus immunization is administered routinely to burned patients who have not had boosters within 60 months. Tetanus immunoglobulin is given in addition to patients with heavily contaminated wounds whose immunization status is unknown or who have received fewer than three doses of adsorbed tetanus toxoid.[62]

Later Infections

During the second week after injury, gram-negative bacilli continue to be important pathogens, but the burn wound also becomes colonized with fungi. Risk factors associated with fungal wound infection are preceding antibiotic therapy, presence of indwelling central venous catheters, and infusion of parenteral nutrition, especially of solutions containing lipids. Colonization with *Candida* spp. is common in burned patients, but burn wound septicemia is infrequent. When invasive infection occurs, mortality exceeds 90% despite aggressive medical and surgical therapy.[63]

Fungi such as *Aspergillus* spp. and *Fusarium* spp. and members of the Mucoraceae family are rare causes of infection; infection with such organisms is invasive, however, and usually fatal. These infections frequently follow successful treatment of gram-negative bacillary infection with broad-spectrum antibiotics, and they occur in patients with acidosis. Fungi invade tissue rapidly and cause thrombosis, leading to tissue infarction and systemic dissemination. Extremely aggressive surgical measures are indicated urgently, but mortality remains high. Other fungi isolated from burn wounds are *Geotrichum, Rhodotorula, Cephalosporium, Penicillium, Trichosporon, Trichophyton,* and *Fonsecaea* spp.; these usually do not invade tissue.[64]

Special Sites of Infection

Anaerobic infections are rare in burned pediatric patients. Anaerobic bacteria have been found to colonize burn wounds around the mouth and anus and can have a synergistic role in burn wound infection, however.[65]

Infections of burns involving the ear cartilage can result in suppurative auricular chondritis, which causes pain, fever, and rapidly progressive edema of the auricle followed by liquefaction of cartilage. Avascularity of this tissue makes treatment difficult. Iontophoresis, a technique that uses direct current to drive charged compounds (antibiotics) into local tissues, has been used in conjunction with topical antimicrobial therapy and grafting, with encouraging results.[66,67]

Corneal infections secondary to direct thermal injury, chemical burn, or ectropion and desiccation can cause permanent scarring requiring corneal transplantation. In addition, infected corneal ulcers can perforate and cause herniation of the lens and loss of the eye. Globe exposure secondary to progressive contracture of burned eyelids and facial skin can require acute eyelid release.[68]

Pyomyositis can occur secondary to vascular compromise in deep burns that leads to muscle necrosis or from the unsuspected deep muscle injury in electrical burns. Intracompartmental infection in which there may be associated pyomyositis can result from delayed escharotomy or extravasation of infused fluids or can occur as a complication of splinting and positioning.[69] Treatment is surgical. Osteomyelitis and pyogenic arthritis can occur when bone and joints are exposed.

Other Infections

Respiratory Tract Infections

Pneumonia is the second most common bacterial cause of death in the burned patient.[70] In patients with inhalation injuries, pneumonia occurs most frequently in the first week after injury. Thermal damage produced by inhalation injury predisposes the airway to infection by (1) producing structural damage to the respiratory tract epithelium; (2) impairing surfactant production, mucociliary transport, and macrophage function; and (3) producing atelectasis. Pneumonia or tracheobronchitis occurs in up to 35% of those with inhalation injury.[20] Less commonly, pneumonia can result from hematogenous spread of infection from other areas, most notably the infected burn wound; this typically occurs late in the postburn period. A chest tube that must be placed through a wound can result in empyema and should be removed as soon as is practical.[20]

Sinusitis and otitis media are infectious complications of the child requiring nasotracheal intubation for inhalation injury.

Bacteremia

Bacteremia is not uncommon in the burned patient. Risk factors include wound manipulation and the presence of an intravascular catheter. Suppurative thrombophlebitis or infected intravascular thrombus can cause persistent bacteremia. Endocarditis must be considered in any patient with prolonged bacteremia. Bloodstream infections are the most common cause of bacteria-related death in patients with severe burns.[70]

Daily dressing changes and surgical wound debridement have been associated with bacteremia in 7.7% to 65% of episodes.[71–74] The greater the percentage of TBSA burned (and thus manipulated), the higher the risk for bacteremia. Use of prophylactic systemic antibiotics before burn wound manipulation, particularly debridement, has been shown to reduce the incidence of bacteremia but has not had a beneficial effect on subsequent clinical course or incidence of burn wound infection.[71,73,74] Bacteremia can occur in the absence of wound manipulation or other identifiable risk factors, presumably from translocation of gut organisms. Bacteremia secondary to burn wound manipulation or gut translocation usually is transient and does not result in infection at distant sites or interfere with graft adherence. It is possible, however, that the higher incidence of endocarditis demonstrated in burned patients is attributable to the increased number of episodes of transient bacteremia. Pyogenic arthritis and brain abscesses secondary to *S. aureus* bacteremia have been described.[75,76]

Catheter-Related Infections

Burned patients have a high risk for acquiring intravascular catheter-related infections. In one study, the rate of catheter-associated infection correlated inversely with the distance of the catheter insertion site from the burn wound; infection occurred more commonly when the insertion site was <30 cm from the burn wound.[77] Suppurative thrombophlebitis, both peripheral and central, also can occur in burned patients and is difficult to diagnose if the affected vein underlies the burn; prolonged antibiotic therapy, systemic anticoagulation, and need for surgery are considered.[20]

Urinary tract infections are common in burned patients, especially associated with urinary catheters commonly used to care for perineal burns or to monitor fluid status. Catheters placed for fluid status monitoring should be removed as soon as the patient's clinical status is stable, and their use should never be prolonged for the convenience of caregivers.

Intra-Abdominal Infections

Acute cholecystitis can occur in older children and adolescents with burns if enteral nutrition is not instituted. Findings include fever without localizing signs and serum hepatic enzyme abnormalities consistent with cholestasis (mimicking findings in septicemia). Acute pancreatitis and pancreatic abscess can occur in severely burned patients. Peritonitis, as a result of splanchnic ischemia, increased gastrointestinal permeability, and bacterial translocation, can occur.[20] Early enteral feeding decreases the likelihood of these complications.

Central Nervous System Infections

Infectious complications in the central nervous system are infrequent and usually are associated with bacteremia or endocarditis in patients with a burn >30% TBSA, possibly related to inability to localize infection. In a postmortem review of burned victims, 53% had central nervous system complications, 16% of which were infectious. Microabscess, septic infarction, and meningitis occurred, and most were caused by *S. aureus, Candida* spp., or *P. aeruginosa.*[78]

Viral Infections

Viral infections must be considered in any burn victim with unexplained fever whose burn wound is healing adequately.[79–82] Viral infections can occur at any time but are most common in the second week after injury and can be due to reactivation or acquisition. Herpes simplex virus (HSV) and cytomegalovirus (CMV) have been isolated from up to 30% of pediatric burned patients[79]; infection correlates directly with the TBSA involved.

CMV infection in burn patients is a purported cause of unexplained fever as well as hepatitis, neutropenia, and thrombocytopenia. Other serious manifestations of CMV infections, such as pneumonia, are infrequent. CMV infection can result from reactivation of latent infection or from primary infection. The cell-mediated immune dysfunction experienced by burned patients enhances reactivation of CMV and exacerbates symptomatic infection. Primary infection can be acquired from blood transfusions or cadaveric skin allografts from seropositive donors. CMV infection is associated with greater risk for bacterial infection in patients with burns.

Orolabial reactivation of HSV is common, and the virus can disseminate locally or cause infection of the burn wound, impeding wound healing; disseminated infection also has been described in burned patients.[83,84]

Other viral infections associated with excessive morbidity, delayed wound healing, or unexplained fevers are varicella-zoster virus, Epstein-Barr virus, and adenovirus. One study, performed before testing of the blood supply for hepatitis C virus (HCV), demonstrated that 18% of burned patients acquired HCV. Chronic hepatitis was observed in 83% of burned patients, which is a high rate in comparison with that in other populations.[85] Nosocomially acquired respiratory syncytial virus, adenovirus, and rotavirus add considerable morbidity during the protracted hospitalization.

Treatment

Specialized care in burn centers, the surgical trend toward aggressive early and repeated debridement and wound closure, and the routine use of topical antimicrobial agents contribute immensely to the prevention and control of infections after burns.

Topical antimicrobial therapy is a mainstay of burn care; such therapy has had an enormous effect on the rates of wound infection and septicemia. The general objectives of topical therapy are to decrease water vapor loss, prevent desiccation of exposed viable tissues, contribute to pain control, and inhibit bacterial and fungal growth.[20] Although topical agents do not sterilize the wound, numbers of colonizing organisms decrease, thus reducing the risk for bacterial invasion of underlying tissue. Topical agents commonly used in burned patients differ in their antimicrobial spectrum and side effects (Table 87.2). Other topical agents used in burn care are discussed in Chapter 294. There is no ideal topical antimicrobial agent. An agent is selected on the basis of defined and expected colonizing organisms, time after injury, knowledge of organisms indigenous to the burn unit, and possible adverse reactions. Initially, silver sulfadiazine usually is used, and subsequent choices are based on results of isolation of organisms from the wound. Topical antimicrobials have demonstrated decreased activity against both gram-positive and gram-negative multidrug-resistant organisms.[86] Silver sulfadiazine has fair to poor eschar penetration, unlike mafenide acetate, a carbonic anhydrase inhibitor, which is capable of eschar penetration.[20]

TABLE 87.2

Topical Antimicrobial Agents Commonly Used in the Treatment of Burns

Agent	Antimicrobial Activity Against				Adverse/Other Effects
	Gram-Positive Organisms	Gram-Negative Organisms	Anaerobes	Fungi	
Silver sulfadiazine (Silvadene, Thermazene)	++	+++	++	++	Allergic reaction in 5%, leukopenia in 5%–15%
Mafenide acetate (Sulfamylon)	+	+++	++	+	Allergic reaction in 10%, pain, metatbolic acidosis, pulmonary edema
Nanocrystalline silver dressings (Acticoat A.B., Silverlon)	++	+++	++	++	Limited toxicity, less painful than silver nitrate
Nitrofurazone (Furacin)	+++	+++	++	–	Dermatitis
					Fungal overgrowth

+++, excellent activity; ++, good activity; +, limited activity; –, no activity.

Data from Church D, Elyased S, Reid D, et al. Burn wound infections. Clin Microbiol Rev 2006;19:403–434; and Lipsky BA, Hoey C. Topical antimicrobial therapy for treating chronic wounds. Clin Infect Dis 2009;49:1541–1549.

Debridement of the wound is essential. Both enzymatic and chemical means of debridement have been used in the care of burns as alternatives to surgical excision. Proteolytic and mucolytic enzymes rapidly debride nonviable tissue but have been associated with a higher risk for septicemia.[87] The recently developed Versajet (Smith & Nephew) tool, which uses the Venturi effect to create a stream of water for cutting and a vacuum, has been shown to provide more precise excision compared with blade excision in adults and children and may decrease the time required for excision.[88,89] Temporary membranes also are available to use on superficial wounds or donor sites to decrease infection and facilitate comfort.[90] Fresh or reconstituted porcine xenograft, synthetic bilaminates, hydrofibers, semipermeable membranes, hydrocolloid dressings, and human allografts, including human amnion and chorion membranes, are examples, some of which are impregnated with silver to reduce bacterial and fungal growth.[91–93] Patients with heavily contaminated wounds or septicemia, or both, are best managed with allografts initially and later with autografts.[20] A Cochrane systemic review of randomized controlled trials comparing recombinant human growth hormone (rhGH), which increases protein synthesis, with any comparator, including placebo, demonstrated some evidence that rhGH used in both adult and pediatric large surface area burns could produce more rapid healing of the burn wound and donor sites without increased mortality or scarring but with an increased risk for hyperglycemia.[94]

Systemic antimicrobial therapy is only used when systemic infection is strongly suspected, but its role is adjunctive, and it never replaces aggressive surgical debridement and the use of topical agents. Parenteral agents should be of the narrowest antimicrobial spectrum possible, being directed specifically at known pathogens, to avoid colonization with resistant bacteria or fungi. In burned patients, the pharmacokinetics of antibiotics are altered as a result of the multiple pathophysiologic changes that occur after the burn injury.[95,96] These changes must be considered in selection of agents and optimal dosage.

Aminoglycosides have a short elimination half-life in adult and pediatric burned patients, thus requiring increases in both dose and frequency of administration.[97–100] Once-daily aminoglycoside dosing (8 mg/kg) in burned patients (TBSA burned, 18% to 81%) has been evaluated and was associated with elevation of creatinine >0.5 mg/dL in 35% of patients and ototoxicity in 1 of 13 patients.[101] Thus, without further study, once-daily aminoglycoside dosing cannot be recommended in burned patients. Vancomycin clearance is increased in burned patients, possibly because of increased renal tubular secretion; higher dosages may be necessary.[102] Because burned patients may have renal dysfunction, serum levels of aminoglycosides or vancomycin are monitored to allow individual adjustment of dosages.

The pharmacokinetics of ceftazidime, ticarcillin-clavulanate, imipenem-cilastatin, and aztreonam have been evaluated in burned patients.[96,103–106] Alterations were found for ticarcillin-clavulanate and ceftazidime (increased total clearance and volume of distribution) and aztreonam (increased volume of distribution). Creatinine clearance does not adequately predict dosage requirements for these drugs; thus, specific dosage recommendations were not made in any study. It seems prudent to use the highest recommended dose in a burned patient who does not have evidence of renal or hepatic impairment.

Management of Outpatients

Partial-thickness burns covering a small TBSA (<10%−15%) can be treated on an outpatient basis in the following circumstances: (1) the burns are not circumferential or do not involve the face, hands, feet, or perineum; (2) no other injuries are present; (3) child abuse is not suspected; and (4) the caregivers are capable of adhering to management and follow-up. Appropriate treatment of smaller burns is imperative because inadequate care can lead to wound infection, septicemia, poor wound healing, and a poor functional or cosmetic result.

Outpatient management of burns consists of cleaning the wound thoroughly and removing devitalized tissue. Small blisters can be left intact. Because large blisters can interfere with wound healing, most burn surgeons advocate debridement, whereas others believe that this increases the risk for infection. After cleaning and debridement, gauze dressing containing a broad-spectrum topical antibiotic such as silver sulfadiazine is applied. The dressing is changed with new application of antibiotic twice daily, and the parent or caregiver is educated about the expected changes in appearance of the wound. The wound is inspected 24 to 48 hours later to observe the expected healing, to detect signs of local infection, and to assess adequacy of parents' understanding of wound care.

Prevention

Prevention of infection in a burn is paramount to prevent mortality and morbidity. Urgent and adequate care of all burns and use of dressings impregnated with topical antimicrobial agents, followed by meticulous care and assessment, usually are successful. Early closure of the burn wound is the most protective treatment against infection. Pulmonary toilet in the patient with inhalation injury and rapid removal of intravenous and urinary catheters are essential in prevention of nosocomial infections. Strict attention to infection control practices is essential.

Routine use of prophylactic systemic antibiotics is not beneficial in prevention of infections and can predispose to colonization with resistant organisms.[107] Replacement therapy with immune globulin intravenous (IGIV) has been studied because most burned patients show a decrease in serum immunoglobulin G (IgG) concentration immediately after injury (mean values, 300 mg/dL), with a gradual return to normal after 14 to 60 days.[34,35] In one study, patients younger than 4 years had the most severe and prolonged decreases of IgG levels.[30] Patients with persistent serum IgG concentrations of <500 mg/dL may have a higher risk for septic complications.[31] Although IgG levels normalized with administration of IGIV in the patients studied (from mean of 400 mg/dL before infusion to >1200 mg/dL after infusion), no beneficial effect on development of septicemia was evident.[108] Administration of hyper-IgG against *P. aeruginosa* and *S. aureus* decades ago as adjunctive treatment for septicemia caused by these organisms in burned patients showed some beneficial effect.[109–111]

Interferon-γ, because of its ability to enhance macrophage activity and stimulate host immune responses, has been evaluated as prophylaxis for infectious complications in burned patients. In a European multicenter trial of 216 patients with severe burn injuries, administration of interferon-γ did not give protection from infectious complications or affect the mortality from infections.[112] A vaccine directed against *P. aeruginosa* was developed decades ago and shown to be efficacious.[113–117] In one study of 322 burned patients, administration of maximal-dose vaccine reduced the rate of invasive disease. A lower mortality rate was seen, however, only in patients who received parenteral antibiotic therapy and adjunctive hyperimmune globulin. Vaccination did not prevent colonization, and 90% of the patients had an adverse reaction to vaccination.[114] In 2000 a double-blind, randomized, placebo-controlled clinical trial of a *P. aeruginosa* vaccine involving 95 adult patients with burn injuries of ≥10% TBSA demonstrated high immunogenicity and a significantly lower incidence of *P. aeruginosa* bacteremia in vaccine recipients.[118] Additional controlled studies are required to assess the benefit of immunotherapy, in view of changes in predominant pathogens, improved supportive measures, and the trend toward early excision and wound closure.

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88

Infection Following Bites

Marvin B. Harper, Sarah L. Wingerter

In the United States, it is estimated that 5 million bites occur every year, 90% of which are dog bites.[1] Dog bites alone result in approximately 330,000 emergency department visits (42% among children <14 years of age), 13,000 hospitalizations, and 20 deaths annually (mostly children).[2] Dogs, cats, and humans account for >90% of non–insect-related bite injuries, with rabbits and rodents responsible for most of the remainder.[1,3] Contact with wild animals and nontraditional pets poses a risk for both infection and injury. Worldwide, as many as 5 million people are bitten by snakes each year, with most bites occurring in Africa and Southeast Asia, and monkey bites represent up to 21% of animal bite injuries.[4] The trauma caused by these bites can be serious, and infection is the most common late complication.

Etiologic Agents

The organisms causing bite wound infections generally derive from the microbial flora of the biting animal's mouth rather than the victim's skin. Therefore the infecting organisms vary by species. Bite wound infections should be considered polymicrobial infections; in a large, prospective study of infected dog and cat bites, cultures done at a central reference laboratory yielded a median of five bacterial isolates per culture.[5] Mixed aerobic and anaerobic infection occurred in more than 50% of cases. Specimens sent concomitantly to local microbiology laboratories identified significantly fewer organisms, emphasizing the need for careful microbiologic analysis.

Table 88.1 shows the aerobic and anaerobic bacteria isolated from 50 patients with dog, 57 with cat, and 50 with human bite wounds.[5,6] *Pasteurella* spp. were the most common isolates from dog and cat bites, with *P. canis* the predominant organism isolated from dog bites and *P. multocida* the most common from cat bites. Other species isolated from these patients included streptococci, staphylococci, and *Moraxella* and *Neisseria* spp. Common anaerobic isolates included *Fusobacterium, Bacteroides, Porphyromonas, Prevotella, Propionibacterium,* and *Peptostreptococcus* spp. A number of other bacterial isolates previously had not been recognized as bite wound pathogens.

TABLE 88.1

Frequency of Isolation of Aerobic and Anaerobic Bacteria After 50 Dog, 57 Cat, and 50 Human Bite Wounds at Presentation for Management of Infection

	Dog	Cat	Human
AEROBIC AND FACULTATIVE			
Acinetobacter	+	+	
Aggregatibacter (formerly Actinobacillus)		+	+
Aerococcus viridans			+
Aeromonas		+	+
Agrobacterium radiobacter			+
Alcaligenes		+	+
Bacillus	+	++	
Brevibacterium	+	+	
Candida			+
Capnocytophaga	+	+	+
CDC group EF-4a	+		
CDC group EF-4b	++	++	
CDC group NO-2			+
Citrobacter			+
Corynebacterium spp.	++	+++	++
Corynebacterium jeikeium	+	+	
Corynebacterium pseudodiphtheriticum	+		+
Dermabacter hominis	+		
Eikenella corrodens	+	+	++++
Enterobacter cloacae		+	+
Enterococcus	++	++	+
Erysipelothrix		+	

Flavimonas	+	+	
Flavobacterium	+		
Gemella	+	+	++
Haemophilus			+++
Kingella			+
Klebsiella	+	+	+
Kocuria			+
Lactobacillus	+	+	+
Leclercia			+
Micrococcus	+		+
Moraxella	++	++++	+
Neisseria	++	++	+
Oerskovia	+		
Pantoea endophytica		+	+
Pasteurella	+++++	+++++	
Pasteurella canis	+++	+	
Pasteurella multocida ssp. *multocida*	++	+++++	
Pasteurella multocida ssp. *septica*	++	+++	
Pediococcus	+		
Proteus	+		+
Pseudomonas aeruginosa	+		
Pseudomonas non-*aeruginosa*	+	+	
Reimerella anatipestifer		+	
Rhodococcus		+	
Rothia		+	+
Staphylococcus aureus	+++	+	++++
Staphylococcus coagulase-negative	+++++	+++++	++++
Stenotrophomonas maltophilia	+		
Stomatococcus mucilaginosus	+		+
Streptococcus spp.	+++++	+++++	+++++
Streptococcus pyogenes (group A)	++		++
Streptococcus agalactiae (group B)	+	+	
Streptococcus group C/G	+		+
Streptococcus group F		+	
Streptococcus viridans group	+++++	+++++	+++++
Streptococcus milleri group *(Streptococcus intermedius, Streptococcus anginosus, Streptococcus constellatus)*	++	+	+++++
Streptomyces		+	
Weeksella	+	+	
ANAEROBIC			
Actinomyces			+
Arcanobacterium bernardiae			+
Bacteroides	++++	+++	+
Campylobacter			++
Clostridium		+	
Collinsella (Eubacterium) aerofaciens			+
Dialister pneumosintes			+
Eubacterium	+	+	++
Filifactor villosus		+	
Fusobacterium spp.	++++	++++	++++
Fusobacterium necrophorum			+
Fusobacterium nucleatum	++	+++	++++
Lactobacillus	+		+
Peptostreptococcus	++	+	+++
Porphyromonas	+++	++++	+

Prevotella	+++	++	++++
Propionibacterium	+++	++	+
Veillonella		+	+++

++++, very common; +++, common; ++ not uncommon; +, occasional

Other studies confirm the polymicrobial nature of bite wounds.[7,8] *Pasteurella multocida* is only seen in animal bites, more commonly from cats,[9] whereas *Eikenella corrodens* and *Streptococcus pyogenes* are more closely associated with human bites, although they are sometimes seen with animal bites as well. *Capnocytophaga canimorsus,*[10,11] *C. cynodegmi,*[10] *Neisseria weaveri* (formerly M-5),[12,13] *Bergeyella zoohelcum,*[14] *Neisseria canis,*[15] *Staphylococcus intermedius,*[16] NO-1,[17] and *Paracoccus yeeii* (EO-2)[18] are all uncommon organisms to recover from general clinical specimens but are isolated from bite wound infections, particularly from dog bites.

The cause of infections resulting from bites of species other than humans, dogs, and cats is less well described. Simian bites appear to be similar to human bites in microbiology.[19] Polymicrobial infections with *Staphylococcus aureus, S. pyogenes, Pseudomonas aeruginosa,* and *Bacillus* spp. have been reported with camel bites.[20] Bites of large cat species such as leopards and tigers are associated with organisms typical of domestic cat bites, with isolation of *P. multocida* and *N. weaveri*.[21] Snake bites do not routinely require antibiotic management unless there is necrosis, in which case aerobic gram-positive cocci and gram-negative bacilli are thought to predominate.[22] A *Pasteurella caballi* infection was seen after a horse bite,[23] *Pasteurella aerogenes* and a *Chryseobacterium*-like organism have been isolated from infected pig bites,[24,25] *Actinobacillus* spp. have been reported from horse and sheep bite wounds,[26] and *Halomonas venusta* has been isolated from a fish bite.[27] In bites occurring in marine settings, organisms associated with water, such as *Vibrio* spp., *Aeromonas hydrophila, Plesiomonas shigelloides,* and *Pseudomonas* spp., have caused infections from bites of catfish, eel, crocodile, and swan.[28–32] Additionally, systemic diseases have been transmitted by bites, including tularemia from cats,[33] rat-bite (Haverhill) fever and sodoku from rats, herpesvirus B infection from monkeys, hepatitis B from humans, and leptospirosis from dogs and rodents. A rare infectious entity acquired from contact with seals, known as seal finger, is likely caused by a marine mycoplasma.[34] Human immunodeficiency virus (HIV) appears to be difficult to transmit by human bite.[35–37]

Epidemiology

Dog bites account for >90% of bite wounds that come to medical attention. The annual incidence of dog bites of children has been estimated at 1 to 3 per 1000 children per year[38–41] in developed countries, to rates as high as 26 per 1000 per year in developing countries.[42] Dog bite injuries alone account for 0.3% to 0.4% of all emergency department visits.[2,38] Data from the Agency for Healthcare Research and Quality indicate that in 2008 there were more than 300,000 emergency department visits and 9500 hospitalizations related to dog bites, an average of 866 emergency department visits and 26 hospitalizations per day.[43] The incidence and body part involved with dog bites vary by age. Children are more likely than adults to sustain a dog bite, with the highest risk in the second year of life and steadily decreasing each year thereafter (based on data from Austria) or with peak incidence in the 5- to 9-year age group (based on US data).[38,39] A recent study of patients receiving care for dog bites at a level 1 pediatric trauma center demonstrated a median age of 5 years, a male predominance, and a majority of dogs belonging to the patient's immediate or extended family.[44] Several studies have identified pit bulls as the most common breed involved in dog bites coming to medical attention.[44,45] Injuries to the face, head, and neck are most common, accounting for two thirds of dog bite injuries in preschool-aged children (extremities accounting for 27%). Injuries to the extremities (upper more than lower) become more common with increasing age, accounting for 55% beyond 14 years of age (at which age only 9% involve the head or neck).[39] Between 7% and 25% of children sustaining dog bites require hospital admission, depending on use of general anesthesia for primary wound management and the rate of infectious complications.[38,46]

Fatalities from bites occur primarily from massive blood loss after mauling by large dogs, particularly Rottweiler and pitbull-type dogs, or as the result of intracranial injury, particularly in smaller children.[47] Children <5 years of age are particularly vulnerable to attack and are more likely to sustain injury from smaller dogs. Overall, the relative risk for attack is significantly higher from

German shepherd, Doberman, pitbull, and Rottweiler breeds than from Labrador/retriever or cross-bred dogs, but because cross-bred dogs are so much more common, they represent the majority of bite injuries. Approximately 20 deaths occur each year in the United States as a result of dog bite attacks. Deaths due to infection after dog bites are uncommon but can occur as the result of septicemia or intracranial infection. In developing countries, rabies remains a significant late cause of death from dog bites. The estimated risk for infection in the otherwise healthy child depends on the location and extent of the dog bite injury and the initial management but is estimated to be 5% to 15%.

Cat bites are spread more evenly across age groups and cause less overall initial injury because cats have smaller mouths and less biting force, which results in less tearing of the tissues. However, their thin, sharp teeth produce small, deep wounds that are difficult to cleanse and are more likely to result in clinical infection, estimated to occur after 10% to 50% of bites.

Human bites may be sustained somewhat differently than bites of other animals and generally are defined as any disruption in the skin as a result of contact with the mouth. These can be self-inflicted (e.g., thumb-sucking resulting in skin breakdown, or self-injury as with autism), the result of a punch to the mouth of another person that results in a laceration of the hand, or the result of a typical bite but resulting from sexual activity or abuse that might be concealed from the medical provider. One study of human bite wounds in children seen at a single institution over a 6-year period identified 322 patients, representing 0.2% of all emergency department visits. Infection was seen in 9%, and 2%, overall, were hospitalized for treatment of infection.[48]

Table 88.2 displays the rate of infection of bite wounds from any source by bite site.[48,49] The two studies enrolled subjects at the time of initial evaluation in the outpatient setting. Bites to the hand are significantly more likely to become infected compared with bites at other sites. Wounds to the face are the least likely to become infected, probably because of its extensive vascularity. In one of these studies,[49] 12% of the wounds became infected, and the risk for infection differed on the basis of the biting species. Only 4% of 80 dog bites became infected, but 16% of 37 human bites and 50% of 22 cat bites became infected. Cat bites also can transmit *Bartonella* *henselae* and *Sporothrix schenckii*.[50,51] The paucity of reports regarding infection after rodent or rabbit bites makes the rate difficult to estimate, but it appears to be small, perhaps related to smaller and less penetrating wounds. Rat bites are associated with *Streptobacillus moniliformis* infections, hamster bites have caused *Francisella tularensis* and *Pasteurella aerogenes* infections,[52,53] and guinea pigs have caused *Haemophilus influenzae* infections.[54] Bat bite is important because it can transmit rabies virus. Infections transmitted by biting insects are addressed in other chapters.

TABLE 88.2

Rates of Infection of Bite Wounds by Body Site

Location of Bite	Rate (%)	No. Infected/No. Bites
Face/head/neck	6	3/49
Arm/leg	10	7/68
Trunk	10	1/10
Hand	28	21/76
Total	16	32/203

Data from Baker MD, Moore SE. Human bites in children. Pediatrics 1991;88:55; and Aghabian RV, Conte JE Jr. Mammalian bite wounds. Ann Emerg Med 1980;9:79.

Pathogenesis

Bite wounds become infected by inoculation of microorganisms into subcutaneous or deeper tissues. Modifying factors include the type and depth of inoculation, the amount of crush injury and devitalized tissue, the involvement of infection-prone structures, the ability to cleanse and debride the wound, and the pathogenicity of the infecting microorganism. Most series show a higher infection rate in bite wounds to the hand. Cat bites have the highest infection rates because of deep inoculation and high prevalence of *P. multocida* (Fig. 88.1). Dog bites are more likely to cause lacerations or avulsion injuries that are easier to clean and debride.

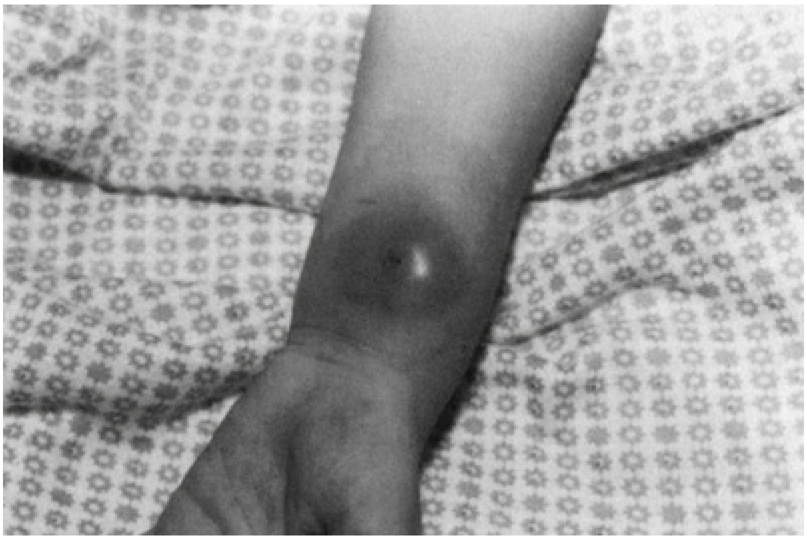

FIGURE 88.1 Cat bite abscess of the wrist with presentation for care delayed 1 month after injury. *Pasteurella multocida* was isolated in pure culture.

Most infections manifest as localized cellulitis or simple abscess. Infection can extend to adjacent areas, particularly if the teeth penetrate structures such as bones, joints, or the cranium. Regional lymphadenopathy, lymphangitis, fasciitis, toxic shock syndrome, septicemia, and shock also can develop. Septicemia occurs primarily in immunocompromised hosts, particularly asplenic individuals, who are prone to fulminant septicemia and shock with infection caused by *C. canimorsus*[55–59] or *Eubacterium plautii*[60] after dog bites.

Clinical Manifestations, Differential Diagnosis, and Clinical Approach

The history and physical examination readily lead to the likely organisms of most bite wound infections (Box 88.1). If infected, signs and symptoms (erythema, pain, tenderness, and swelling) almost always become apparent within 24 to 48 hours after the bite. Infections caused by *P. multocida* tend to have a more rapid onset, often within 12 to 18 hours. There may be purulent or serosanguineous discharge. Most patients are afebrile,[5] although fever can occur in patients with severe cellulitis or in the rare instance of bacteremia. Eschars at bite sites in individuals who appear ill may indicate *C. canimorsus* infection.[58]

Box 88.1

Key Elements of History and Physical Examination in Evaluating Bite Wounds With Regard to Possible Infection

History

The Animal

Record type of animal, health of animal, and whether attack was provoked or unprovoked, and consider the availability for testing or quarantine for signs of rabies, if applicable. Query whether local authorities notified (e.g., animal control or police officers)

The Patient

Consider special risks such as immunosuppression, asplenia, diabetes mellitus, antibiotic allergies, and history of tetanus and hepatitis B immunizations

Physical Examination

Systemic

Note state of well-being, fever, tachycardia, tachypnea, hypotension, or widened pulse pressure

Local

Note type of wound (e.g., puncture, laceration, avulsion), depth of penetration, involvement of underlying structures (e.g., joint, tendon, bone, cranial contents), extent of edema, erythema, tenderness (with measurements), range of motion, type of drainage (e.g., purulent, serosanguineous, malodorous), neurovascular function, lymphangitic streaking, and regional lymphadenopathy. Consider possibility of retained foreign body (e.g., tooth)

Even apparently trivial bites require careful evaluation for penetration of the skull or other body cavities or possible damage to underlying structures, such as joint spaces, bone, tendons, nerves, and blood vessels. The physician should consider the mouth size of the biter and, if there are puncture wounds, should examine carefully for punctures due to the apposing teeth. With cosmetically important bite wounds to the face in young children, there may be more life-threatening puncture wounds in the scalp or neck found only by careful examination.[61] Assessing deep structures is particularly important for scalp injuries that can penetrate the skull and for clenched-fist injuries in which joint or tendon injury could be missed.[62] Lacerations sustained when punching and striking teeth with a closed fist most commonly occur on the dorsal aspect of the third metacarpophalangeal joint and can be missed if the hand is examined only in the relaxed position. In addition, the initially linear path of injury becomes obstructed, hindering drainage of deep structures.

Paronychial infections in young children can result from thumb- or finger-sucking, and oral flora should be considered as a possible cause, especially when a history of injury is lacking. Herpetic whitlow, which can be confused with bacterial infection, should be suspected when erythematous or dusky-appearing vesicular or vesiculobullous lesions are present, particularly in cluster arrangement. Seal finger, which occurs in association with either seal bites or scratches or other contact with seals, has a longer incubation (4 to 8 days); edema and severe pain are prominent; and lymphangitis, lymphadenitis, and arthritis occur more frequently than in other bite wound infections.[63] Water organisms, such as *P. aeruginosa* and *Aeromonas* spp., should be considered after water animal bites.

Laboratory Findings and Diagnosis

Microbiologic confirmation of infection can be highly beneficial in management regardless of the biting species. Laboratory personnel should be notified to consider multiple isolates as pathogenic and to be vigilant for *P. multocida* or *E. corrodens.* Specimens should be sent for both aerobic and anaerobic bacterial culture (using anaerobic transport medium). For wounds contaminated by soil or vegetative debris, culture for mycobacteria and fungi should be considered. Gram stain and culture of fresh, uninfected bite wounds are not recommended because they do not predict the risk for subsequent infection or the pathogens that cause them.

Blood specimens for aerobic and anaerobic culture should be obtained from febrile children, particularly if they are immunocompromised or asplenic. Radiographs should be obtained after penetrating injuries overlying bones or joints, or when a fracture or a foreign body is suspected.

Management and Presumptive Therapy

Steps of Immediate Postexposure Management

1. **Evaluate the extent of injury and contamination.** New, uninfected bites should be carefully examined for foreign bodies, and visible dirt and debris should be sponged or irrigated away.

2. **Debride and cleanse the wound.** The wound should be copiously irrigated with sterile normal saline by high-pressure syringe irrigation, taking care not to inject into the tissue or inflict additional trauma.

a. *Consider use of a surgical-type scrub sponge for highly contaminated wounds*, especially if particulate matter is present. (Hibiclens or Betadine should not be used, unless diluted to 1% to avoid tissue toxicity. Agents such as Pluronic-68 or Shur-Clens are suggested.)

b. *Irrigate with ≥250 mL of saline*. There is no demonstrated benefit to irrigation with other solutions such as 1% Betadine solution or Pluronic F-68.[64] A recent Cochrane review indicated tap water may be a suitable alternative to saline for wound irrigation.[65] Antibiotic irrigation has not been shown to have additional benefit; rarely it may be used in special, high-risk circumstances. Animal models suggest high-pressure irrigation reduces bacterial wound counts better and reduces wound infection rates. Irrigation pressures of 5 to 8 pounds per square inch (psi) are recommended and correspond to gentle use of commercially available splash-guard shields (e.g., Zerowet) or an 18G catheter/needle attached to a 30- or 60-mL syringe.

c. Perform imaging to establish the presence or absence of foreign material such as embedded teeth or fragments as well as to identify bone damage.

d. Debride devitalized tissue and remove foreign material. Operative exploration and debridement should be considered if there is extensive tissue damage, involvement of a joint space, or cranial injury. There is no role for culture of the wound unless there is clinical evidence of infection.

3. **Consider wound closure.** The role of suturing, in general, is controversial. One study evaluated the practice of primary closure for mammalian bites in a series of 145 consecutive bites (88 dog, 45 cat, 12 human) treated with primary closure. Patients presented a mean of 2 hours after injury; 6% (95% confidence interval 2% to 9%) experienced wound infections, suggesting that when cosmesis is a primary concern, this rate of infection may be acceptable.[66] Increasing time to closure has been associated with increasing risk for infection, but more likely the time to closure is simply a proxy for the time to adequate wound cleansing. This has led to specific recommendations against closure for high-risk wounds >8 to 12 hours after the time of injury. No prospective or pediatric study has been performed to validate this approach with bite wounds. Until there are further data, it may be prudent to avoid primary closure if time since trauma is >8 hours or it is difficult to irrigate a deep puncture wound (unless the wound must be repaired for important cosmetic or functional reasons).[1,67] When closure is appropriate, the placement of a drain, microdrains, or only loose approximation of the skin is the optimal approach when feasible. The use of subcutaneous sutures has been associated with increased risk for

infection in retrospective studies, and their use should be avoided. An underused practice is delayed closure (after 48–72 hours) of this type of wound. Delayed closure has been recommended for human bites to the head and neck, especially those with exposed cartilage.[68] Elevation and immobilization of the wound are common practice.

4. **Consider postexposure prophylaxis.**

a. *Antibiotic prophylaxis*. The role of antimicrobial prophylaxis is discussed in Chapter 7. Limited data are available from clinical trials. A Cochrane analysis concluded that there is evidence that antibiotic administration significantly reduces infection rates with bites to the hand or human bites.[69] One meta-analysis suggested that antibiotic treatment also lowered the risk for infection after dog bites.[70] One small study randomized patients with human bite wounds to placebo or cephalexin-penicillin combination and identified a low rate of infection in both groups (1 of 62 individuals receiving placebo and 0 of 63 receiving antibiotic).[71] Antibiotic prophylaxis commonly is recommended for infection-prone bite wounds: moderate to severe wounds (especially if edema or crush injury is present), wounds that are difficult to clean or debride adequately, penetrating cat bites, and human bite wounds. Less severe wounds or more easily cleansed and dog bite wounds to areas other than the face, hands, feet, or genital area do not require antibiotic prophylaxis routinely. The ability of the host to control infection, should it occur, also is considered (Box 88.2).[1,62] The drug of choice is amoxicillin-clavulanic acid, which is given for 2 to 3 days. For penicillin-allergic patients, a combination of trimethoprim-sulfamethoxazole and clindamycin is recommended. All patients with bite wounds should be re-evaluated within 24 to 48 hours for signs of infection (Box 88.3).

Box 88.2

Indications for Infection Prophylaxis

Antibiotic Recommended

Characteristics of the Wound

Bite wounds of the face, hands, feet, or genital area

Wounds that cannot be reliably cleansed or completely debrided (e.g., deep punctures)

Bite wounds involving tendon, bone, or joint

Wounds with moderate or severe edema, crush injury, or devitalized tissue

Characteristics of the Host

Immunocompromised or asplenic host

Other Postexposure Prophylaxis Recommended

Hepatitis B

Begin vaccine if a human bite and the patient is not previously immunized. The use of hepatitis B immune globulin is limited to cases in which the biter is known to test positive for hepatitis B surface antigen

Human Immunodeficiency Virus (HIV)

Prophylaxis is limited to high-risk human bite exposures from a known HIV-positive biter (the need for HIV postexposure prophylaxis of bite wounds is uncommon)

Rabies

Administer rabies immune globulin and begin vaccine series for appropriate mammalian bites (see Chapter 228)

Tetanus

For patients who have received <3 doses of adsorbed tetanus toxoid or if immunization history is unknown, give:

1. DTaP if <7 years old, Tdap if ≥7 years old and has not previously received Tdap, or Td if previously has received Tdap

2. Tetanus immune globulin (TIG) or immune globulin intravenous (IGIV) if TIG not available
   For patients who have received ≥3 doses of adsorbed tetanus toxoid, give:

a. No tetanus booster if <5 years since last tetanus-containing vaccine dose

b. Tetanus booster if ≥5 years since last tetanus-containing vaccine dose (DTaP if ≤7 years old, Tdap if ≥7 years old and has not previously received Tdap, or Td if previously has received Tdap)

c. 3. No TIG

Box 88.3

Recommended Antibiotic Therapy

Wound Prophylaxis if Indicated

Amoxicillin-clavulanate; if penicillin-allergic, trimethoprim-sulfamethoxazole plus clindamycin

Treatment of Wound Infection

Oral therapy as above unless febrile, rapidly spreading, or high risk (then use parenteral therapy)

Parenteral therapy if indicated:

- Ampicillin-sulbactam (consider adding aminoglycoside if reptile or water-related species)
- If penicillin-allergic without anaphylaxis, consider using extended-spectrum cephalosporin or carbapenem (e.g., ceftriaxone, cefipime, or meropenem), *or* if severe allergy, use trimethoprim-sulfamethoxazole plus clindamycin and consider adding aminoglycoside if reptile or water-associated
- Vancomycin is considered in severe infections if methicillin-resistant *Staphylococcus aureus* (MRSA) is a possibility
- Clindamycin, doxycycline, or trimethoprim-sulfamethoxazole is considered for less serious, possible MRSA infection
- Bite wound infection can include many other pathogens in the immunocompromised host; treatment is individualized

b. *Tetanus prophylaxis.* Bites generally are not tetanus-prone injuries unless there is additional contamination with soil. They are, however, an opportunity to assess the patient's vaccination status. For persons with tetanus-prone injuries who have not completed their primary series, tetanus immune globulin and vaccine should be administered (see Chapter 188).

c. *Rabies prophylaxis*. The possibility of rabies must be considered after animal bites (see Chapter 228). Bites from bats are considered high risk for rabies in the US, and postexposure prophylaxis for these bites is routine. Local public health authorities can assist in determining the need for postexposure rabies prophylaxis for other bites.

d. *Consideration of systemic infectious agents related to human bites*. Hepatitis B, hepatitis C, and HIV could be transmitted potentially by a human bite. Hepatitis B prophylaxis should be considered for human bites. Human bites do not efficiently transmit HIV; postexposure prophylaxis for HIV is not routinely indicated but is considered in some special circumstances.[35,36]

e. *Consideration of cercopithecine herpesvirus 1 (herpes simiae or B virus) after bites from an Old World macaque monkey*. Little is known regarding the risk for infection after a monkey bite, but most macaque monkeys are seropositive for herpes simiae by 2 years of age, and more than 20 cases of transmission to humans have been reported with development of encephalitis (75% fatal). As a result, copious wound irrigation is recommended; irrigation with diluted sodium hypochlorite (household bleach diluted 1 : 10 with 0.9% saline) is considered, as is postexposure antiviral chemoprophylaxis with acyclovir or valacyclovir for 14 days.[72–74]

Most jurisdictions require bite injuries to be reported to the local health department. In cases with multiple or severe bites, there is a high risk for posttraumatic stress disorder, and referral for counseling should be considered.[75]

Empiric Management When Infection Occurs

When a patient comes to medical attention with an infected bite wound, basic principles of management should be followed. Sutured wounds should be opened, purulent collections drained, and necrotic tissue, foreign bodies, and debris removed. Specimens should be obtained for aerobic and anaerobic culture. Infected wounds should not be sutured. If bone or joint penetration has occurred, exploration and debridement of these areas may be necessary.

Empiric antimicrobial therapy should be based on pathogens that are most likely to be associated with the biting species and the clinical setting. Oral antibiotic therapy is appropriate for mild to moderate infections when adherence to the treatment plan is assured. Amoxicillin-clavulanic acid is an excellent choice because it provides activity against all common bite wound pathogens, including anaerobic bacteria, methicillin-susceptible *S. aureus, S. pyogenes, E. corrodens,* and *P. multocida.* Comparable parenteral agents, such as ampicillin-sulbactam or piperacillin-tazobactam, can be used for patients who require hospitalization because of rapidly spreading cellulitis or lymphangitis, large abscesses, bone or joint infection, or suspected sepsis. Appropriate alternative regimens include an extended-spectrum cephalosporin (cefotaxime or ceftriaxone) plus clindamycin. Trimethoprim-sulfamethoxazole has activity against *Pasteurella* and *Eikenella* spp., and a combination of trimethoprim-sulfamethoxazole and clindamycin is acceptable for individuals with a history of anaphylactic reactions to penicillins or cephalosporins. Antibiotics commonly used for other skin and soft tissue infections, such as the antistaphylococcal penicillins, first-generation cephalosporins, vancomycin, clindamycin, and erythromycin, are less active or inactive against *Pasteurella* and *Eikenella* spp. and cannot be used alone.[5,76] Azithromycin and fluoroquinolone agents have in vitro activity against the organisms that commonly cause bite wound infections,[77,78] but data on their clinical effectiveness are limited. Tetracycline is the treatment of choice for seal finger and also is active against most aerobic bacteria that cause bite wound infections, including *Pasteurella*.[77]

A 7- to 14-day course of antibiotic treatment usually is sufficient for infections limited to the soft tissues. A >3-week course generally is given for bone or joint infections. In all cases, the duration and route of antibiotic therapy should be individualized, based on the site, infecting organisms, antimicrobial susceptibility, and response to treatment.

Complications

The most common complications are related to tissue destruction. Soft tissue necrosis can result from infection or from crush injury during the bite. Pyogenic arthritis or osteomyelitis, particularly in cases in which diagnosis is delayed, can result in permanent injury to the joint or bone. Depending on the site of the bite, other complications, such as brain abscess, can develop.[79] Septicemia and meningitis can occur, especially in immunocompromised individuals.

Prognosis and Sequelae

Long-term follow-up studies of children sustaining bite wound infections are not available. In general, soft tissue infections that are treated promptly and appropriately are expected to heal completely, unless the injury itself has resulted in extensive tissue devitalization. Infections involving underlying bone, tendon, or joint structures have a more guarded prognosis for return to normal function. Goldstein[62] reported residual sequelae in 25% to 50% of patients after clenched-fist injury. In other series, permanent disabilities of the involved extremity were less common and often were related to delayed or inappropriate therapy.[80,81] A delay in therapy, particularly that caused by a failure to recognize deep (bone, joint, or tendon) involvement, may be the most important factor leading to poor outcome.

Prevention

Prevention of bites is most important. Education of the public to limit exposure of preschool-aged children to dogs, selection of specific dog breeds, spaying or neutering dogs (which makes them less likely to bite), and education of children on proper behavior around animals and the proper respect for dogs are important strategies. Healthcare providers should counsel parents regarding selection of appropriate pets, dog ownership, and avoiding dog breeds implicated most frequently in dog bite injuries and on matching pet size and temperament to a child's age and behavior.[1] Households with children younger than 8 years should avoid ownership of nontraditional pets such as ferrets, iguanas, or wild animals.[1] Proper cleansing and debridement of wounds remain the cornerstone for the prevention of wound infections, although antimicrobial prophylaxis also can play an important role in preventing infection for certain bite wounds.

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89

Infections Related to Pets and Exotic Animals

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Contact with animals can provide benefits for children and adults. However, exposure to nontraditional pets in the home and animals in public settings poses potential risks to children, including injuries and transmission of pathogenic organisms. Potential risks can be minimized or prevented by knowledge and use of educational materials, regulations, and guidelines that have been developed for this purpose.[1,2] Healthcare personnel (HCP), including pediatricians and veterinarians, can provide advice on selection of appropriate pets as well as prevention of disease transmission from nontraditional pets and when children contact animals in public settings.

Pet Exposures

Most households in the United States include one or more pets. In national surveys conducted by the American Pet Products Manufacturers Association, US households with one or more pets increased from 56% in 1998 to 65% (79.7 million homes) in 2015–16.[3] Numbers of households in the US owning pets were as follows: for dogs, 54.4 million; cats, 42.9 million; freshwater fish, 12.3 million; birds, 6.1 million; small animals (including sloths, porcupines, kinkajous, wallabies, sugar gliders, hedgehogs), 5.4 million; reptiles, 4.9 million; horses, 2.5 million; and saltwater fish, 1.3 million. Total US expenditures in the pet industry in 2015 were estimated at $60 billion.[3] In recent years, the number of families choosing nontraditional pets has increased.

Categories of Pets

Animals that become pets can be classified as *traditional* pets and *nontraditional* pets. Traditional pets generally include dogs and cats. Nontraditional pets include exotic animals, defined either as imported, nonnative species or species that originally were nonnative but now are bred in the US; indigenous wildlife; and wildlife hybrids (wildlife crossbred with domestic animals, producing offspring known as hybrids). The definition of nontraditional pets includes reptiles and certain species of mammals. In addition to exposure to animals in their homes, children may come in contact with animals in a variety of public settings.[2] Although there are many benefits to experiences with animals outside the home, contact with animals in public settings can be associated with substantial risks to children, including infections and injuries. These potential risks are exaggerated when there is inadequate understanding of disease transmission, methods of transmission prevention, or animal behavior, or lack of appropriate facilities for the care of animals.

Traditional Pets

Pets have become part of many families and are often considered to be extended family—living, eating, and even sleeping with human family members.[4] Among dog owners in the US, 53% consider their dog to be a member of the family, and 56% of dog owners sleep with their dogs next to them. In developed countries, 21% to 23% of dogs and 60% of cats sleep on or in their owner's bed.[4] Transmission of zoonotic agents by close contact between healthy traditional pets and family members through kissing, licking, or biting by pets or through vectors has been documented.[1,4–7]

In children, bite injuries are caused by a wide variety of traditional and nontraditional pets, but most wounds result in minor injuries and are not reported. Most systematic studies are limited to dog or cat bites. Bacteria from animal bites are reflective of the oral flora of the biting animal or less commonly of victim's own skin. The oral flora of the biting animal also may contain flora of ingested prey and other foods.[5]

Nontraditional Pets

Nontraditional pets are increasing in popularity among families because lifestyle choices of owners may favor smaller or more unusual pets. A survey by the American Veterinary Medical Association estimated that in 2011, 11% of US households owned “specialty or exotic pets” other than dogs, cats, birds, and horses, and the total population of exotic companion animals was estimated to be 8 million.[8] Table 89.1 provides examples of animals that are considered nontraditional pets as well as animals to which children may be exposed in public settings.

TABLE 89.1

Animals That Are Considered Nontraditional Pets and Animals That Can Be Encountered in Public Settings

Categories	Examples
Amphibians	Frogs, toads, newts, salamanders
Fish	Many types
Mammals	
Wildlife	Raccoons, skunks, foxes, coyotes, civet cats, tigers, lions, bears, kinkajous, coatis, olingos, ringtails, nonhuman primates
Domesticated livestock	Cattle, pigs, goats, sheep
Equines	Horses, mules, donkeys, zebras
Weasels	Ferrets, minks, sables, skunks
Lagomorphs	Rabbits, hares, pikas
Rodents	Mice, rats, hamsters, gerbils, guinea pigs, chinchillas, gophers, lemmings, squirrels, chipmunks, prairie dogs, hedgehogs
Feral animals	Cats, dogs, horses, swine
Birds	Canaries, finches, sparrows, parrots, parakeets, love birds
Reptiles	Turtles, lizards, iguanas, snakes, alligators
Arachnids	Spiders, scorpions, tarantulas
Insects	Madagascar hissing cockroaches, millipedes, stick insects

Modified from Pickering LK, Marano N, Bocchini JA, et al. Exposure to nontraditional pets at home and to animals in public settings: risk to children. Pediatrics 2008:122;876–886.

In addition to legal importation, there is a worldwide illegal trade in exotic animals, estimated at up to $10 billion annually,[9–10] only exceeded by the trafficking of arms and drugs. This illegal trade subverts rules established by regulatory agencies to reduce introduction of disease and potentially dangerous animals through importation restriction, inspection, and quarantine.[9]

Human contact with nontraditional pets and, specifically, with exotic animals raises several public health concerns. Most imported nonnative species are caught in the wild rather than bred in captivity. Health screening generally is not performed before shipment of these animals to the US, and often there is mixing of animal species in holding locations where exposure occurs of healthy animals to animals that might be ill, incubating, or asymptomatically carrying potential pathogens. In addition, the significant wildlife black market, through which a large number of exotic animals enter the US, compounds the risks for introduction of zoonoses.[10] After making the initial decision to acquire a nontraditional pet, owners may discover they are unable to provide the animal with the environment or nutrition required for a healthy life and often subsequently abandon or release the animal into the wild, posing risks for introduction of zoonotic disease, disruption of ecosystems, and injury to people, domestic wildlife, and the environment.

Diseases (Zoonoses) Associated With Nontraditional Pets

Zoonotic diseases or zoonoses are infections transmitted between other vertebrate animals and humans. Most emerging infectious diseases in humans are zoonotic in origin.[10–13] Of 1415 human pathogens, 61% are known to be zoonotic, and pathogens with multiple host species are twice as likely to be associated with an emerging infectious disease.[13] From 1980 to 2003, more than 35 new infectious diseases emerged in humans, many of which are zoonoses.[13] The leading causes of their emergence are human behavior and modifications of natural habitats, including expansion of human populations and encroachment on wildlife habitats, changes in food production processes, changes in agricultural practices, and global trade in wildlife.[9,10,14] Wild animals also can serve as reservoirs for transmission of zoonotic agents to domesticated animals and to humans.[12] Domestic animals and humans also can acquire zoonotic pathogens from exposure to nontraditional pets. An outbreak of tularemia in wild prairie dogs caught in the US and held in a commercial facility in Texas led to human transmission.[15] Some of the infected animals were distributed to a pet shop in Texas and were exported as far away as the Czech Republic.

Contact between animals from different areas of the world, including exotic animals imported into the US, can lead to disease in a new species and establishment of a pathogen in a new geographic area. In 2003, human monkeypox was introduced into the US. The source of monkeypox was imported African Gambian rats that were held in close proximity to prairie dogs being sold as pets. The prairie dogs became infected, which ultimately led to infection of humans with whom they had close contact.[16] Prompt recognition and public health efforts controlled this outbreak and may have prevented the establishment of monkeypox in North America.

Zoonotic transmission of bacteria, viruses, fungi, and parasites from household pets or animals to children through contact in their homes or public settings is common.[7] Transmission can be direct or indirect—through contact, aerosols, bites or scratches, contamination of the environment or food or water sources, or disease-carrying vectors. Animals can become ill but more commonly are asymptomatic carriers of specific organisms and can contaminate the environment to which children are exposed. Infants and children aged <5 years are at greatest risk, in part because they have suboptimal hygiene practices, have attraction to or curiosity about animals, and have developing immune systems, but also because these infections tend to be more severe in infants and young children.[17] People of all ages with primary or secondary immunodeficiencies are at risk for more severe zoonotic disease, as are pregnant women and elderly people.[18]

Reptiles and Amphibians

Reptiles pose a significant risk because of high carriage rates and intermittent shedding of *Salmonella* in their feces and because of persistence of *Salmonella* organisms in the environment.[17,19–21] A federal prohibition against commercial distribution of turtles with shells <4 inches in diameter was enacted in 1975 after investigations demonstrated that small turtles were a major source of human salmonellosis, particularly in children. This resulted in an important and sustained reduction of human salmonellosis. Despite this ban, however, illegal distribution of small turtles with subsequent human disease continues to occur.[22–25] In addition, young children without direct turtle exposure are at risk for turtle-associated salmonellosis through person-to-person transmission in childcare settings.[23] Amphibians also serve as a source of salmonellosis in households.[17,26] In the US, 6% of all sporadic *Salmonella* infections (11% among people <21 years of age)—approximately 74,000 cases annually—are the result of direct or indirect contact with reptiles or amphibians.[17]

Rodents

Contact with hamsters,[27] guinea pigs[28] and other rodents[29] purchased from retail pet stores has resulted in multistate outbreaks of salmonellosis. Hamsters have been associated with outbreaks of disease attributable to lymphocytic choriomeningitis virus (LCMV).[30] Guidelines for minimizing risk for human LCMV infection associated with pet rodents have been published.[31] Hedgehogs, originally from Europe, Asia, and Africa, have proved to be an important source of *Salmonella* serotype Tilene in the US.[32] *Yersinia pseudotuberculosis, Mycobacterium marinum,* rabies virus, and other *Salmonella* serotypes also are zoonotic pathogens carried by hedgehogs.

Plague, caused by *Yersinia pestis,* is enzootic among rodents in the western US. Humans become infected through bites of infected rodent fleas, inhalation of respiratory secretion from infected animals or humans, and handling of infected animals, especially rodents, lagomorphs, and domestic cats and dogs.[4,33–35] In parts of the US where plague is endemic, people with rodent-seeking animals can be exposed to *Y. pestis* through direct contact with plague-infected pets or their fleas.[4,34,35] People who live in areas where plague is endemic should follow a flea-control program designed by their veterinarians to keep their cats and dogs free from fleas.

Association with nontraditional pets also can result in skin infections, including ringworm, monkeypox, orf, cutaneous anthrax, tularemia, erysipeloid, ectoparasites, and endoparasites.[36–42] Hedgehogs pose a significant risk because their spines readily penetrate skin and can be the source of *M. marinum* and *Y. pseudotuberculosis* infections.[32]

Nonhuman Primates

Herpes B virus (cercopithecine herpesvirus 1) is a naturally occurring infectious agent that is endemic among macaque monkeys (including rhesus macaques, pig-tailed macaques, cynomolgus monkeys, and other macaques). Infected monkeys usually are asymptomatic or have mild oral lesions. Exposure occurs when monkeys are kept as pets or displayed in public settings. Herpes B virus infections in humans have been reported after animal bites, scratches, or percutaneous inoculation with infected material or splashes on mucous membranes. Human infections most often result in fatal meningoencephalitis.[43]

Fish

The major zoonoses transmitted by aquarium fish are mycobacterial infections,[44] but other organisms have been reported after exposure to aquarium water, tanks, filtration equipment, or other tank contents. Infection usually is sporadic and immunocompromised people have increased risk.[45–47] Typical organisms include *Aeromonas*, *Vibrio*, *Edwardsiella*, and *Salmonella* spp., *Streptococcus iniae*, and *Erysipelothrix rhusiopathiae.*[48]

Other Sources of Infection

Contact with chicks and other baby poultry purchased at agricultural feed stores have resulted in outbreaks of *Salmonella* infections.[49] The growing popularity of owning backyard poultry also has been linked to an increasing number of *Salmonella* outbreaks.[50] Parents who purchase these birds for their children or for fresh eggs generally are not often aware that *Salmonella* can be transmitted from live poultry to humans. In addition to direct exposure to animals, exposure to animal-derived pet food treats, such as pig ear chews, and to dry dog and cat food has resulted in human infections attributable to *Salmonella*.[51–53] Animals can become colonized after ingesting contaminated pet food treats, dry pet food, or raw meats. Animals can be asymptomatic and become unrecognized sources of contamination in the household. Handling contaminated pet food treats and pet food by humans also can result in infection.[52] In the US, pet treats are regulated by the US Food and Drug Administration (FDA). *Salmonella*-contaminated pet treats are considered adulterated under the Federal Food, Drug, and Cosmetic Act (21 USC §301−399). In 2004, the FDA initiated annual nationwide testing of pet treats for *Salmonella* spp. A multinational outbreak of antibiotic-resistant *Salmonella* was related to frozen feeder rodents.[54] Pet birds have been associated with the transmission of ectoparasites (mites), psittacosis, *Salmonella* spp., *Campylobacter* spp., and cryptococcus, among others.[55] From 2005 through 2009, 66 human cases of psittacosis were reported to the Centers for Disease Control and Prevention (CDC), most commonly after exposure to infected pet birds, usually cockatiels, parakeets, parrots, and macaws.[56]

Diseases Associated With Animals in Public Settings

Certain venues encourage or permit infants and children to come in contact with many different animal species (see Table 89.1) in a variety of public settings (Box 89.1), potentially resulting in millions of human-animal interactions annually. Infectious diseases, rabies exposure, injuries, and other health problems associated with these venues are well documented.[1,2,57] Of particular concern are instances in which zoonoses result in many people becoming ill. A systematic review of the literature documented that animal contact in pet stores and animals purchased from pet stores have been associated with the transmission of a wide spectrum of zoonotic infections.[58] Infections due to animals' enteric bacteria and parasites pose the highest risk in public settings. Although ruminant livestock (cattle, sheep, and goats) are the major source of infection, live poultry, reptiles, rodents, amphibians, and other domestic and wild animals also are potential sources.[2] These outbreaks have medical, public health, economic, and legal implications.

Box 89.1

Locations Where Contact With Animals in Public Settings Can Occur

Agricultural feed stores

Animal displays

Animal swap meets

Carnivals

Childcare facilities or schools

Circuses

County or state agricultural fairs

Educational farms or farm tours

Feed stores

Fish tanks

Livestock-birthing exhibits

Metropolitan zoos

Nature parks

Pet stores

Petting zoos

Rodeo events

Wildlife photography exhibits

Zoologic institutions

During 1996 through 2012, approximately 200 outbreaks of human infectious disease involving animals in public settings were reported to the CDC.[2] Most commonly, these involved enteric bacteria and parasites.[57] Serious infections with *Escherichia coli* O157:H7 and other Shiga toxin–producing *E. coli* (STEC) have been associated with multiple animals in public settings.[59–71] The primary reservoir of *E. coli* O157:H7 and other STEC is ruminant livestock, which are colonized asymptomatically. In many studies, the primary route of transmission has been foodborne,[65] including unpasteurized milk,[66] but person-to-person spread, direct animal contact, and contact with environmental items contaminated by animals are common.[61] Some pathogens are shed by animals intermittently and remain viable in the environment for months or longer.[72] In 2004 and 2005, there were 3 outbreaks in 3 states of *E. coli* O157:H7, accounting for 173 cases associated with direct and indirect animal contact at petting zoos.[62] Outbreaks[19] and sporadic cases of salmonellosis and outbreaks of cryptosporidiosis[73–75] have been described after visits to farms where visitors had either direct or indirect contact with animals. Additional illnesses after exposures in public settings include campylobacteriosis, tuberculosis, rabies, orf virus infection, giardiasis, tularemia, ringworm, and infected bites or wounds.[2,15,20,36,67,69,76,77] Poxvirus has been transmitted from pet rats to humans.[78]

The risk of human infection is increased by certain factors and behaviors, especially in children, including direct contact with animals (especially young animals), contamination of the environment or food or water sources, inadequate handwashing facilities or lack of education about hand hygiene, hand-to-mouth activities, lack of close supervision, and inappropriate layout and maintenance of facilities at animal exhibits.[2] For example, in a study of observations of practices at petting zoos in Canada, hand hygiene facilities were provided but often not used, items that would come into contact with mouths of infants and children (pacifiers, baby bottles, sippy cups) were carried into the petting zoos, and education about hygiene was lacking.[79] The recommendation to wash hands immediately after leaving an animal exhibit is the single most important prevention step for reducing the risk for disease transmission, even if an animal was not touched.

Rabies

People who have contact with rabid animals can be exposed to rabies virus through a bite or mucous membrane or wound contamination with infected saliva or nerve tissue.[80] Although human rabies deaths caused by animal contact in public exhibits have not been reported, exposures to rabid mammals at pet stores,[81] county fairs,[82] petting zoos,[83,84] and rodeo events[84] have required extensive public health investigations and medical follow-up. Raccoon-variant rabies in pet rabbits and a guinea pig has led to postexposure prophylaxis of adults and children.[85] Prevention of rabies in domestic cats, dogs, and ferrets can be achieved by regular rabies immunization and reimmunization.[80] Control of rabies among wildlife reservoirs is difficult, and use of licensed oral vaccines for mass immunization of free-ranging wildlife depends on the circumstances surrounding each animal rabies outbreak and is restricted to use through state and federal rabies-control programs.[80] No parenteral rabies vaccine is licensed for use in wild animals or hybrids. Because of the risk for rabies in wild animals (especially raccoons, skunks, coyotes, foxes, and bats), the American Veterinary Medical Association (AVMA), American Public Health Association, Council of State and Territorial Epidemiologists (CSTE), National Animal Care and Control Association, and National Association of State and Public Health Veterinarians (NASPHV) strongly recommend enactment and enforcement of state laws prohibiting importation, distribution, translocation, and private ownership of these animals. The AVMA has concerns about a number of aspects relative to ownership or possession of wild animals or hybrids, including the welfare of the animal, public health and safety, and environmental effects.[86]

Injuries and Allergies

Bites, scratches, kicks, falls, and crush injuries of hands or feet or from being pinned between an animal and a fixed object can occur at home or during exposure to animals in a public setting. Serious and fatal injuries can result from a large animal or any animal with aggressive behavior. Some nontraditional pets are chosen when they are young and small without consideration that they may grow into dangerous, aggressive adults. For example, iguanas sold shortly after birth measure <8 inches but by 2 to 3 years grow to several feet, and baby chicks become full-grown chickens and have a lifespan of up to 20 years.

An estimated 4 to 5 million animal bites occur in the US annually.[5] Although approximately 90% of bites are from dogs or cats, severe and fatal bites can occur from large or aggressive nontraditional pets. Animal bites or scratches often become infected. Infectious organisms, depending on the biting animal, include *Pasteurella multocida, Francisella tularensis, Capnocytophaga canimorsus*, *Staphylococcus* spp., *Streptobacillus moniliformis* (rat-bite fever), *Bartonella henselae* (cat-scratch disease), *Leptospira,* and herpes B virus. Tularemia occurred in a 3-year-old child bitten by an infected hamster purchased at a pet store.[42] Reptiles can produce injuries by bites, with claws, or with tails. Severe hand injury[41] and cellulitis[38] have been reported after green iguana bites. Between 33 and 50 nonnative (exotic) snake envenomations were reported annually in 2005–11 to US Poison Centers, 4% of which occurred in children <6 years of age, 3% in 6- to 12-year-olds, and 10% in 13- to 19-year-olds. Seventy percent of the envenomations occurred in a private residence.[87] Unprovoked attacks of children by ferrets, particularly of infants sleeping or lying down, can be severe, with mutilation of the ears or nose.[88,89] Attacks on sleeping infants are similar to those inflicted by rats.[90]

Although the frequency is not known precisely, the potential for having an allergy to nontraditional pets is likely to be substantial. The American Academy of Allergy, Asthma, and Immunology estimates that approximately 15% of the population experiences allergies to dogs and cats,[91] usually owing to sensitization to their dander, scales, fur, feathers, body waste, or saliva. Flea bites also can lead to allergic manifestations. Hives have been described in people who have contact with hedgehogs.[92] Although scaly animals are not as likely to be as allergenic as furry animals, there are case reports of allergic rhinitis, asthma, and contact hypersensitivity reactions to iguanas.[40] In addition, an iguana bite–induced hypersensitivity reaction has been reported.[41]

Reportable Diseases Acquired From

Nontraditional Pets and Animals in Public Settings

Many national and state notifiable diseases can be transmitted from animals. Public health officials at state health departments and the CDC collaborate in determining which infectious diseases should be nationally notifiable; states determine which diseases are reportable within states. A disease may be added to the national or state list as a new pathogen emerges or removed if disease incidence decreases. Because disease reporting varies by state, specific requirements should be obtained from relevant state health departments. Provisional data are published weekly in the *Morbidity and Mortality Weekly Report,* and final data are published each year by the CDC in the annual "Summary of Notifiable Diseases," which can be found online (http://www.cdc.gov/mmwr/mmwr_nd/index.html). These data are necessary for study of epidemiologic trends and development of disease prevention policies. HCP should report suspected cases of human illness to local and state health departments as soon as possible, including when the patient has a history of visiting an animal in a public setting during his or her incubation period.

Prevention Measures

HCP and veterinarians play an important role in guiding parents and their children about prevention of risks associated with ownership of traditional and nontraditional pets as well as contact with animals in public settings. Parents and pet owners typically lack knowledge about the multiple modes of transmission of zoonotic infectious diseases from pets. Although pediatricians recognize the importance of anticipatory guidance about pet-related hazards, only 5% reported that they regularly educated patients or families about pet-associated salmonellosis or toxoplasmosis.[93]

Pediatricians and veterinarians together can remind parents, children, and pet owners about the importance of measures to avoid illness. Simple and effective advice includes frequent handwashing and avoiding direct contact with animals and their environments. This is particularly important with animals from which transmission of enteric pathogens is a risk, including young ruminants, young poultry, reptiles, rodents, amphibians, and animals who are ill. Young children always should be supervised closely when in contact with animals in public settings. The NASPHV has developed an excellent compendium with standardized recommendations for use by public health officials, veterinarians, animal venue operators, animal exhibitors, visitors to animal venues and exhibits, and others concerned with disease control and with minimizing risks associated with animals in public settings.[2]

To reduce the possibility of injury, HCP should remind pet owners about matching the size and temperament of a pet to the age and behavior of an infant or child, providing direct supervision of younger children, and educating all children about appropriate human-animal interactions.

The decision to obtain a nontraditional pet by parents with children in the household is often not discussed with HCP or veterinarians. However, as trusted sources of healthcare information, HCP and veterinarians are in a unique position to offer information and advice to families who already have or are considering the purchase of a nontraditional pet. Informational brochures and posters available for display or referral to websites can educate parents without significantly increasing time of healthcare visits. Proper pet health maintenance, immunization, flea and tick control, deworming, and diet and activity can minimize the risk for infection or injury and ensure health of the pet. Referral to a veterinarian also can be helpful when parents are contemplating purchase of a nontraditional animal. Veterinarians can provide information about appropriate pet selection, the size of an animal when it attains adulthood, the temperament as well as husbandry needs of an animal, and suitability as a pet.

A history of contact with pets in the home or animals in public settings should be part of every well-child evaluation and especially should be part of an evaluation of a suspected infectious disease. A history of nontraditional pets in the home or contact with animals in public settings can lead to specific testing and additional or optimized management and occasionally will result in early identification of an unusual infection from another part of the world.

Recommendations and Guidelines

Recommendations for dealing with nontraditional pets and exposures to animals in public settings have been developed by several organizations including the American Academy of Pediatrics, whose recommendations are summarized in Box 89.2. The NASPHV and CDC have established recommendations to prevent disease outbreaks associated with animals in public settings.[2] The CDC has issued recommendations for preventing transmission of *Salmonella* from reptiles to humans[23] and information regarding health risks from *Salmonella* posed by contact with baby poultry.[49] Guidelines for prevention of zoonoses in immunosuppressed people also are available.[18,94]

Box 89.2

Guidelines for Prevention of Human Diseases Acquired From Nontraditional Pets at Home and Exposure to Animals in Public Settings

General

- Wash hands immediately after contact with animals, animal products, or their environment
- Supervise handwashing for children <5 years of age
- Wash hands after handling animal-derived pet treats
- Never bring wild animals home, and never adopt wild animals as pets
- Teach children never to handle unfamiliar, wild, or domestic animals even if the animals appear friendly
- Avoid rough play with animals to prevent scratches or bites
- Do not permit children to kiss pets or put their hands or other objects into their mouths after handling animals
- Do not permit nontraditional pets to roam or fly freely in the

house or allow nontraditional or domestic pets to have contact with wild animals

- Do not permit animals in areas where food or drink are prepared or consumed
- Administer rabies vaccine to mammals as appropriate
- Keep animals clean and free of intestinal parasites, fleas, ticks, mites, and lice
- People at increased risk for infection or serious complications of salmonellosis (e.g., children <5 years of age, elderly people, and immunocompromised hosts) should avoid contact with animal-derived pet treats

Animals Visiting Schools and Childcare Facilities

- Designate specific areas for animal contact
- Display animals in enclosed cages or under appropriate restraint
- Do not allow food in animal-contact areas
- Always supervise children, especially those <5 years of age, during interaction with animals
- Obtain a certificate of veterinary inspection for visiting animals and/or proof of rabies immunization according to local or state requirements
- Properly clean and disinfect all areas where animals have been present
- Consult with parents or guardians to determine special considerations needed for children who are immunocompromised or who have allergies or asthma
- Certain animals are not recommended in schools, childcare settings, and hospitals. These include nonhuman primates, inherently dangerous animals (lions, tigers, cougars, bears,

wolfdog hybrids), mammals at high risk for transmitting rabies (bats, raccoons, skunks, foxes, coyotes), aggressive animals or animals with unpredictable behavior, stray animals with unknown health history, reptiles, and amphibians

- Ensure that people who provide animals for educational purposes are knowledgeable regarding animal handling and zoonotic disease issues

Public Settings

- Venue operators must know about risks for disease and injury
- Venue operators and staff must maintain a safe environment
- Venue operators and staff must educate visitors about the risk for disease and injury and provide appropriate preventive measures

Animal-Specific Guidelines

- Children <5 years of age and immunocompromised people should avoid contact in public settings with reptiles, amphibians, rodents, ferrets, baby poultry (chicks, ducklings), and any items that have been in contact with these animals or their environments
- Reptiles, amphibians, rodents, ferrets, and baby poultry (chicks, ducklings) should be kept out of households that contain children <5 years of age, immunocompromised people, or people with sickle cell disease and should not be allowed in childcare facilities
- Reptiles, amphibians, rodents, and baby poultry should not be permitted to roam freely throughout a home or living area and should not be permitted in kitchens or other food-preparation areas
- Disposable gloves should be worn when cleaning fish aquariums, and aquarium water should not be disposed in sinks used for food preparation or for obtaining drinking water
- Mammals at high risk for transmitting rabies (bats, raccoons,

skunks, foxes, and coyotes) should not be touched by children

Modified from Pickering LK, Marano N, Bocchini JA, et al. Exposure to nontraditional pets at home and to animals in public settings: risk to children. Pediatrics 2008:122;876–886.

The AVMA supports the view that exotic animals, wildlife, and wildlife-domestic hybrids do not make good pets. These animals are dangerous and are a hazard to human health, other animals, and the environment. The AVMA also recommends that ferret owners have knowledge about the species and stress that no one who is incapable of removing himself or herself from the bite of a ferret should be left unattended with a ferret. Measures to control and prevent psittacosis in humans and birds were published by a committee formed by the NASPHV and were endorsed by AVMA, CSTE, and the Association of Avian Veterinarians.[56]

Guidelines for animals that might have contact with children in childcare settings have been published by the National Resource Center for Health and Safety in Child Care and Early Education.[95] These guidelines state that any pet or animal present at the facility (indoors or outdoors) should be in good health, show no evidence of carrying any disease, be fully immunized, and be maintained on a flea-, tick-, and worm-control program. A current (time-specified) certificate from a veterinarian should be on file in the facility, stating that the specific pet meets these conditions. All contact between animals and children should be supervised by a caregiver who is close enough to remove the child immediately if the animal shows signs of distress or the child shows signs of treating the animal inappropriately. The caregiver should instruct children on safe procedures to follow when in close proximity to animals—for example, not to provoke or startle animals or touch them when they are near their food. Potentially aggressive animals should not be in the same physical space with children. The facility should not keep or bring in turtles, iguanas, lizards, or other reptiles; ferrets; psittacine birds; or any wild or dangerous animals. Recommendations for handwashing by staff, volunteers, and children, as well as maintenance of animals housed on the premises, are provided in the guidelines.[95] In addition to exposures to animals within a center, childcare and school field trips can result in disease.

HCP and veterinarians are encouraged to work together to educate one other and to communicate a common message to pet owners regarding the benefits and risks of pet ownership and of contact with animals outside the home. Joint training seminars and joint sponsorship of health communication campaigns in pediatrician and veterinarian offices would greatly increase awareness of pet owners. The One Health initiative supported by AVMA to increase veterinary collaboration with counterparts in human medicine is an excellent step forward to benefit clinical medicine and public health and will build and reinforce partnerships between the professions to create a holistic approach to reduce human illness and injury related to animal contact.[96] A conceptual framework to support "one-health research" for policy on emerging zoonoses has been published.[97]

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90

Tickborne Infections

Kristina Bryant

Ticks are obligate blood-sucking arthropods that transmit a variety of pathogenic organisms, including bacteria, viruses, and protozoa.[1–4] Along with mites, ticks are arachnids of the subclass Acari. More than 800 species comprise two major families within the suborder Ixodida.[1] Hard-bodied ticks (family Ixodidae) are distinguished from soft-bodied ticks (family Argasidae) by the presence of a dorsal sclerotized plate or scutum. A third family, the Nuttalliellidae, contains a single species of tick found only in southern Africa.

Hard ticks may survive for several months to 3 years, whereas soft ticks may live for more than 10 years and are highly resistant to starvation.[1] The longevity of ticks serves to perpetuate the pathogens that they carry.

Epidemiology

Although ticks are found throughout the world, individual species have evolved with requirements for specific hosts, habitats, and climates. Most tickborne diseases also have a specific geographic distribution (Table 90.1).[2–8] Several factors influence the incidence of tickborne infections. Human factors include the degree and duration of exposure to tick-infested habitats and host immunity. Tick-related factors include the prevalence of ticks and their usual hosts, infection rates, seasonal activity, and the relative likelihood of individual species to feed on humans.

TABLE 90.1

Tickborne Diseases: Agents, Vectors, and Geographic Distribution

Disease	Agent	Principal Vectors	Approximate Distribution
Lyme disease	*Borrelia burgdorferi*	*Ixodes scapularis, I. pacificus, I. ricinis*	Northeast, Midwest, and West of United.States; Europe
Babesiosis	*Babesia microti, B. duncani, B. divergens*	*Ixodes scapularis, I. ricinis*	Northeast, upper Midwest, and West (e.g., Washington, California) of US; Europe
Rocky Mountain spotted fever (RMSF)	*Rickettsia rickettsii*	*Dermacentor variabilis* (American dog tick), *D. andersoni* (Rocky Mountain wood tick), *Rhipicephalus sanguineus* (brown dog tick)	*D. variabilis:* widely distributed east of the Rocky Mountains and in limited areas of Pacific Coast. *D. andersoni:* Rocky Mountain states and Southwestern Canada *Rhipicephalus sanguineus:* widespread but associated with disease transmission in southwestern US and along the US-Mexico border)
***Rickettsia parkeri* rickettsiosis**	*Rickettsia parkeri*	*Amblyomma maculatum* (Gulf Coast tick)	East and South of US, especially coastal regions
***Rickettsia species* 364D–associated spotted fever**	*Rickettsia species* 364D	*Dermacentor occidentalis (Pacific Coast tick)*	US Pacific Coast (e.g., northern California)
Mediterranean spotted fever (MSF)	*Rickettsia conorii*	*Rhipicephalus sanguineus*	Mediterranean region, Africa, Western Asia
Human monocytic ehrlichiosis	*Ehrlichia chaffeensis*	*Amblyomma americanum* (lone star tick)	Southern and middle Atlantic regions of US, north and south central regions of US; isolated areas of New England
Human granulocytic anaplasmosis	*Anaplasma phagocytophilum*	*Ixodes scapularis, I. pacificus*	New England; north central and Pacific regions of US
***Ehrlichia ewingii* infection**	*Ehrlichia ewingii*	*Amblyomma americanum* (lone star tick)	Southeastern and south central regions of US; isolated areas of New England
Southeastern tick–associated rash illness (STARI)	Not identified	*Amblyomma americanum* (lone star tick)	South central region of US
Tularemia	*Francisella tularensis*	*Amblyomma americanum, Dermacentor variabilis, D. andersoni*	All US states except Hawaii; Europe, Asia
Powassan virus disease	Powassan virus	*Ixodes cookei, I. marxi, I. spinipalpus, Dermacentor andersoni*	Maine, New York, Michigan, Minnesota, Wisconsin, Virginia
Colorado tick fever virus disease	Colorado tick virus	*Dermacentor andersoni*	Western US and southwestern Canada (elevations of 4000 to 10,000 feet)
Tickborne	Tickborne	*Ixodes ricinus, I. persulcatus*	Europe and northern parts of

encephalitis virus disease	encephalitis virus		Asia
Tickborne relapsing fever	*Borrelia hermsii*, *B. miyamotoi*	*Ornithodoros* species, *Ixodes scapularis*, *I. pacificus*, *I. ricinus*, *I. persulcatus*, *I. ovatus*, *I pavlovski*	Worldwide, US, Canada, Europe, Russia, Asia
Crimean-Congo hemorrhagic fever	Crimean-Congo hemorrhagic fever virus	*Hyalomma marginatum* complex	Europe, Asia, Africa

Not all diseases caused by ticks are infectious. Tick paralysis may result after exposure of the host to neurotoxic substances produced salivary glands of engorged female ticks, usually after attachment for at least 5 days.[9,10] This rare disease manifests as ataxia or acute flaccid paralysis without sensory loss or pain. Symptoms may be confused with botulism or Guillain-Barré syndrome. Most cases occur in children, with girls affected more often than boys.[11] There are no diagnostic tests for tick paralysis. The diagnosis is made by finding an embedded tick and watching for improvement after tick removal. Symptoms usually resolve within 24 hours.[9,10]

Cases of tick paralysis have been reported worldwide, and 43 tick species have been implicated.[12] In North America, most episodes occur in the western United States and Canada and are associated with *Dermacentor andersoni* or *D. variabilis*. Cases cluster in April through June, when *Dermacentor* species ticks emerge from hibernation.[9]

Pathogenesis

The tick life cycle includes three stages: larvae, nymph, and adult. Both the larva and the nymph must take a blood meal to progress from one stage to the next. Hard-bodied ticks feed slowly over several days and only once per stage. Soft-bodied ticks may take up to 10 short blood meals (i.e., minutes to hours) that involve multiple hosts. Ticks become infected with microorganisms when this blood meal is taken from an infected host. Some pathogens (e.g., *Borrelia* spp., *Rickettsia* spp., *Francisella tularensis*) are also transmitted transovarially and transtadially (i.e., from larva to nymph to adult), allowing ticks to serve as reservoirs and vectors. Horizontal transmission when ticks are cofeeding on a host has been described but is rare.

Transmission of pathogens to humans usually occurs when the feeding site of an attached tick is contaminated with infected salivary secretions, regurgitated midgut contents, feces, or coxal fluid.[2] The duration of tick attachment necessary for transmission varies widely. Transmission of bacterial agents usually requires more than 24 hours, although *Anaplasma phagocytophilum* can be transmitted more rapidly.[13] Tick-borne encephalitis virus (TBEV) is transmitted within minutes of a tick bite, and early removal does not decrease transmission.[14] Transmission occasionally occurs in the absence of attachment, as is seen when nonintact skin or conjunctiva are touched after crushing an infected tick.

Clinical Manifestations

A careful travel history can help determine which pathogens should be considered in a patient with signs and symptoms consistent with a tickborne illness. A history of recent tick bite and occupational or recreational exposures that could result in tick exposure should be sought, but their absence does not exclude infection with a tickborne illness. Because tick bites are usually painless, individuals with confirmed tickborne illnesses may be unaware of their exposure to ticks. For example, in several published case series, tick bites were reported by only about 60% of those with confirmed Rocky Mountain spotted fever (RMSF) and 68% of people with ehrlichiosis.[15–17] Tick bites may confused with spider bites, chigger bites, or other insect bites. Because clustering of some tickborne illnesses is well-documented, similar illness in family members, other close contacts who share environmental exposures, or even pet dogs should prompt consideration of tickborne infection.[18]

Fever, headache, malaise, arthralgia, and myalgia are features common to many tickborne diseases and a variety of other infectious and noninfectious conditions. It is therefore not surprising that many tickborne diseases represent a diagnostic challenge. As many as 75% of patients ultimately proved to have tickborne rickettsial disease are given another diagnosis when they first seek for medical care.[19,20] Tickborne rickettsioses, for example, must be differentiated from a variety of other illnesses that cause fever and a maculopapular or petechial rash, including human herpesvirus 6, enterovirus, group A *Streptococcus*, human parvovirus B19, and *Neisseria meningitidis* infection.[21] As with bacterial sepsis, hypotension and disseminated intravascular coagulation also can occur.[22] Gastrointestinal tract manifestations, including anorexia, nausea, vomiting, and diarrhea, are often reported with tickborne diseases.[23] Severe abdominal pain mimicking acute appendicitis has been described with RMSF.[24]

The erythema migrans skin lesions seen with Lyme disease and southeastern tick-associated rash illness (STARI) can be confused with bacterial cellulitis, eczema, tinea corporis, granuloma annulare, and insect envenomations.[25] Lyme arthritis must be distinguished from septic arthritis, postinfectious arthritis, and rheumatologic disease. A variety of pathogens, including *F. tularensis*, *Bartonella henselae,* and several *Rickettsia* species, have been associated with a syndrome characterized by a scalp eschar at the site of tick attachment and neck lymphadenopathy.[26] When the eschar is overlooked, any of these diseases can mimic cat-scratch disease or bacterial lymphadenitis due to *Staphylococcus aureus* or group A *Streptococcus*.

Concomitant pharyngitis or malaise can suggest Epstein-Barr virus infection. The symptoms of babesiosis overlap with those of malaria. The differential diagnosis for tickborne relapsing fever includes diseases characterized by recurrent or biphasic fever patterns, including malaria, yellow fever, dengue fever, brucellosis, leptospirosis, rat-bite fever, chronic meningococcemia, and some African hemorrhagic fevers. Heartland virus, a phlebovirus, shares clinical manifestations with *Ehrlichia* and *Anaplasma*, including fever, leukopenia, and thrombocytopenia.[8]

Clinical clues and common laboratory abnormalities that suggest tickborne diseases are provided in Table 90.2, along with characteristic skin findings.[8,27,28] The spectrum of illness for more recently described infections has not been fully elucidated.

TABLE 90.2

Clinical and Laboratory Manifestations of Selected Tickborne Illnesses

Disease	Clinical Clues	Skin Findings	Common Hematologic Abnormalities	Other Laboratory Abnormalities

Lyme disease[29–32]	Monoarticular arthritis Aseptic meningitis Facial nerve palsy	Erythema migrans (single or multiple)	Leukopenia Thrombocytopenia	Hepatic transaminase elevation
Babesiosis[33]	Malaria-like illness with fever, hepatosplenomegaly, and jaundice	Rash not usually detected	Anemia (severe) WBC count normal to mildly decreased Elevated reticulocyte count Thrombocytopenia Decreased haptoglobin Positive direct Coombs test	Hepatic transaminase elevation (mild) Hemoglobinuria Elevated lactate dehydrogenase Elevated BUN, creatinine
Rocky Mountain spotted fever[20,34]	Febrile illness with rash, headache, myalgias	Maculopapular rash in >90% of children, often involving the palms and soles; may become petechial	Thrombocytopenia CSF pleocytosis (<100 cells) with moderate protein elevation	Hyponatremia Hepatic transaminase elevation
***Rickettsia parkeri* rickettsiosis**[6]	Febrile illness with myalgia, headache, lymphadenopathy	Eschar at inoculation site Multiple eschars in <20% Maculopapular or less commonly petechial rash; may involve palms or soles	Thrombocytopenia, leukopenia	Mild hepatic transaminase elevation
Mediterranean spotted fever[35–37]	Febrile illness with rash, headache, myalgia, and lymphadenopathy	Eschar at site of tick bite Maculopapular rash on trunk, extremities, palms and soles (96% of children)	Lymphopenia Thrombocytopenia	Hepatic transaminase elevation Elevated lactate dehydrogenase
Human monocytic ehrlichiosis[38–41]	Febrile illness with rash, headache, myalgias	Petechial, maculopapular, or diffuse erythema (66% of children)	Leukopenia Thrombocytopenia CSF pleocytosis (<100 cells) with moderate protein elevation	Hepatic transaminase elevation
Human granulocytic anaplasmosis[42]	Febrile illness with headache, myalgias	Rash rare	Leukopenia Thrombocytopenia	Hepatic transaminase elevation
***Ehrlichia ewingii* infection**[43]	Febrile illness with headache, myalgias	Rash rare	Leukopenia Thrombocytopenia	Hepatic transaminase elevation

Southern tick–associated rash. illness[44–46]	Mild Lyme-like illness manifesting outside a Lyme-endemic area	Erythema migrans–like	Usually normal	Not reported
Tularemia[47–50]	Regional lymphadenopathy Pulse-temperature dissociation	Papule or necrotic ulcer at site of tick bite	—	—
Powassan virus[51]	Meningitis or meningoencephalitis Profound muscle weakness Hemiplegia	—	—	Lymphocytic pleocytosis in CSF
Colorado tick fever virus[52]	Biphasic febrile illness with fever, myalgias	Maculopapular or petechial rash in 5%-12%	Leukopenia Atypical lymphocytosis Thrombocytopenia	Lymphocytic pleocytosis in CSF with elevated protein level
Tickborne encephalitis (TBE) virus[53–55]	Biphasic illness with meningoencephalitis occurring 7 days after self-limited, flu-like illness		Initial leukopenia; thrombocytopenia later Leukocytosis	Elevated hepatic transaminases Moderate PMN pleocytosis in CSF
Tickborne relapsing fever[56,57]	Recurring febrile episodes lasting 2–7 days Headache, myalgia, chills, nausea, vomiting, arthralgia Jarisch-Herxheimer reaction with antibiotic therapy	Petechiae concentrated in the trunk, extremities, and mucous membranes	Thrombocytopenia	Hematuria Proteinuria
Crimean-Congo hemorrhagic fever[58,59]	Febrile illness with rash, myalgia and mucosal bleeding Tonsillopharyngitis common	Maculopapular rash Petechiae	Leukopenia Lymphopenia Thrombocytopenia	Elevated AST Hematuria Proteinuria
Heartland virus[8]	Fever, fatigue, anorexia headache, nausea, diarrhea myalgia, arthralgia	Not described	Leukopenia Thrombocytopenia	Elevated hepatic transaminases

[a] Mortality rates are higher for immunocompromised patients and asplenics.

[b] Requires biosafety level 4 facilities.

[c] Among the initial six patients described with this disease, one patient with multiple comorbidities died.

AST, aspartate aminotransferase; BUN, blood urea nitrogen; CSF, cerebrospinal fluid; PCR, polymerase chain reaction; PMN, polymorphonuclear cell; WBC, white blood cell.

Tickborne infections can be asymptomatic, and symptomatic infections range from mild, self-limited illness to severe disease and death.[60–62] Case-fatality rates of selected pathogens in the absence of treatment are provided in Table 90.2. Some tick species are vectors for multiple pathogens, and a single tick bite may result in two or more simultaneous infections.[63,64] Concurrent bacterial and viral infections have been described.[65] Coinfections may result in atypical clinical manifestations or increased severity of disease.[66,67]

Diagnosis

Because different tick species are known to transmit specific pathogens, the ability to identify ticks may assist with diagnosis. Pictorial guides are available.[68] Estimating the degree of engorgement can suggest the duration of attachment and therefore the potential risk of infection. Testing ticks for pathogens is not routinely recommended for clinical diagnosis. Diagnostic strategies are outlined in Table 90.2.

The clinician should be aware of the limitations of current diagnostic tests, especially serology. Antibody tests may be negative at the onset of symptoms, necessitating acute and convalescent serology. Asymptomatic or clinically inapparent infection can result in high seroprevalence rates for some tickborne disease in endemic regions.[69,70] Antibodies can persist for years after infection and may exhibit significant cross-reactivity. For example, *A. phagocytophila* and *E. chaffeensis* have a more than 50% cross-reactivity.[71] Serologic cross-reactivity also has been seen between *B. burgdorferi* and several other organisms, including other relapsing fever *Borrelia*, *Ehrlichia*, and *Leptospira* species.[72] This cross-reactivity makes knowledge of clinical and ecologic factors associated with these diseases essential for diagnosis.

Treatment

Detailed treatment recommendations can be found in pathogen-specific chapters. Severe or fatal disease may result when treatment is delayed, and prompt, empiric antibiotic therapy with doxycycline is essential when spotted fever rickettsioses, ehrlichiosis, or anaplasmosis are suspected. A retrospective cohort study failed to reveal dental staining, enamel hypoplasia, or tooth color differences involving children younger than 8 years of age who were treated with doxycycline for suspected RMSF.[73] Doxycycline also is the preferred treatment for tickborne relapsing fever and for children 8 years or older with early Lyme disease.

Macrolides, including azithromycin and clarithromycin, are alternatives for the treatment of some tickborne infections.[74,75] Trimethoprim-sulfamethoxazole therapy has been associated with increased severity of ehrlichiosis and should be avoided when this diagnosis is considered.[76] Intravenous gentamicin is recommended for the treatment of tularemia, although fluoroquinolones also are active against *F. tularensis.* Most cases of babesiosis may resolve without treatment, but quinine plus clindamycin or atovaquone plus azithromycin are indicated for severe disease.

Supportive care is indicated for the most viral tick-transmitted diseases. Ribavirin has been used to treat Crimean-Congo hemorrhagic fever, but the quality of evidence supporting a benefit is low and is derived primarily from observational studies.[77]

Prevention

Avoidance of tick-infected areas remains a key strategy for the prevention of tickborne illnesses. When tick habitats cannot be avoided, wearing a hat, long-sleeved shirt, pants, socks, and closed-toe shoes may prevent ticks from reaching the skin. Light-colored clothing permits visualization of crawling ticks. Outer clothing may be treated with permethrin. This synthetic pyrethroid should be sprayed onto each side of the fabric in well-ventilated areas only, and treated items should be allowed to dry completely before they are worn.[78] This insecticide retains its potency for 2 or more weeks, even if clothing is laundered.

N,*N*-diethyl-*m*-toluamide (DEET) is an over-the-counter tick repellant used on skin. Although rare toxicity has been reported with inappropriate or excessive use, the product is safe when used as directed on children.[79,80] For children 2 months of age or older, products with up to 30% DEET are recommended.[81] DEET-containing products are not recommended for children younger than 2 months of age. Products containing picaridin, oil of eucalyptus, IR3535, and 2-undecanone have also been registered by the US Environmental Protection Agency for use as tick repellants, but hourly protection times vary considerably.[82]

Those living in tick-endemic areas should be educated about tickborne diseases and the need to perform routine checks for ticks after possible exposures.[83] After leaving grassy and wooded areas, skin should be inspected for ticks. Prompt removal of ticks may prevent the transmission of pathogens. Common sites of tick attachment include the scalp, waist, armpits, groin, and under socks and the beltline. Ideally, attached ticks are grasped with tweezers or fine-tipped forceps and are removed with gentle, steady pulling perpendicular to the skin. Use of folk remedies, including application of gasoline, kerosene, fingernail polish, petroleum jelly, or a lit match, are never recommended for tick removal.[84]

Controlling tick populations is difficult and may have adverse environmental consequences.[85] In selected areas, populations of black-legged nymphal ticks and lone star ticks have been reduced through the use of deer feeding stations that result in the transfer of a topical acaricide to the animal.[86] In residential areas, landscape management practices can reduce potential exposure to ticks. These include removal of leaf litter, tall grasses, and brush around homes and using wood chips or gravel between lawns and wooded areas.[87] Judicious use of a chemical control agent also is beneficial, and a single springtime application of an acaricide has been shown to reduce the population of ticks that cause Lyme disease by 68% to 100%.

Control of host reservoirs is another potentially important prevention strategy for some tickborne diseases. For example, rodent-proofing homes is recommended in areas where tickborne relapsing fever is endemic.[88] Keeping pet animals free of ticks also is recommended.

Most tickborne diseases are not vaccine preventable. Distribution of a vaccine developed for the prevention of Lyme disease was discontinued in 2002, with the manufacturer citing insufficient consumer demand.[89] Two inactivated vaccines for the prevention of tickborne encephalitis virus are licensed in Europe.[90] The pediatric formulation of FSME-IMMUN (Baxter, Austria) is available for children 1 to 15 years of age, and the pediatric formulation of Encepur (Novartis, Germany) is recommended for children 1 to 11 years of age. The adult formulation of FSME-IMMUN also is licensed in Canada. Both vaccines are well-tolerated and immunogenic, with seroconversion rates approaching 100%.[91–93]

The primary series of FSME-IMMUN and Encepur consist of three doses, with an initial booster dose after 3 years. Subsequent booster doses are given every 3 to 5 years, depending on age, local epidemiology, and national recommendation. Travelers to endemic areas may be vaccinated according to an accelerated schedule that varies by vaccine.

Individuals who develop fever within 4 weeks of a known tick bite should undergo medical evaluation. However, prophylactic antibiotics after a tick bite to prevent bacterial diseases are not routinely recommended. Even in areas where tickborne diseases are endemic, limited numbers of ticks are infected with pathogenic organisms.[94] The efficacy of preventive antibiotics varies. For example, antibiotic therapy delays but does not prevent the symptoms associated with RMSF.[95]

According to guidelines published by the Infectious Disease Society of America, prophylaxis to prevent Lyme disease may be considered when all of the following criteria can be met. First, the attached tick is reliably identified as an adult or nymphal *Ixodes scapularis* tick that is estimated to have been attached for 36 or more hours based on the degree of engorgement or certainty about time of exposure. Second, antibiotics can be started within 72 hours of the time the tick was removed. Third, ecologic information indicates that the local rate of infection of *I. scapularis* ticks is at least 20%. Fourth, doxycycline is not contraindicated.[96] A single dose of doxycycline (200 mg for adults or 4 mg/kg up to 200 mg/dose for children ≥8 years) is the only recommended prophylactic regimen.

Standard precautions are indicated for the care of hospitalized patients with most tickborne infections. A notable exception is Crimean-Congo hemorrhagic fever virus, for which blood and body fluids of infected patients are highly infectious and healthcare-associated outbreaks have been reported.[97] Strict observation of droplet and contact precautions, along with thorough environmental disinfection are necessary.

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Infections of the Fetus and Newborn

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Clinical Approach to the Infected Neonate

Jessica E. Ericson, Daniel K. Benjamin Jr.

Neonates are uniquely susceptible to infection. An immature immune system is coupled with exposure to the variety of maternal and environmental pathogens that can affect this population.

This chapter outlines the clinical approach to the neonate with signs or symptoms consistent with infection. Supportive measures should be the first priority: respiratory support, correction of metabolic and hematologic derangements, fluid management, and use of inotropic drugs when indicated. The clinician then should obtain diagnostic studies and institute antimicrobial therapy considering the timing of infection and the neonate's previous exposure to maternal and environmental factors.

Etiologic Agents

Timing is important in determining the cause of neonatal infections. Infections can be acquired prenatally, perinatally, or postnatally (Table 91.1). Detailed discussions of infections can be found in Chapters 92, 93, and 94.

TABLE 91.1

Periods of Transmission of Neonatal Pathogens[36]

Pathogen	**Prenatal**	**Perinatal**	**Postnatal**
VIRUSES			
Cytomegalovirus	x	x	x
Enterovirus	Rare	x	x
Hepatitis B virus	Rare	x	—
Hepatitis C virus	x	x	—
Herpes simplex virus	Rare	x	Rare
Human immunodeficiency virus	x	x	x
Parvovirus B19	x	—	—
Rubella virus	x	—	—
Varicella-zoster virus	x	x	x
Zika virus	x	—	—
BACTERIA			
Chlamydia trachomatis	—	x	—
Group B *Streptococcus*	x	x	x
Enterococcus species	—	x	x
Enterobacteriaceae	—	x	x
Listeria monocytogenes	x	x	x
Neisseria gonorrhoeae	—	x	—
Staphylococcus species	—	—	x
Treponema pallidum	x	—	—
Ureaplasma urealyticum	—	x	—
FUNGI			
Candida species	—	x	x
PROTOZOA			
Toxoplasma gondii	x	—	—

x, period of transmission.

Epidemiology

Infections acquired in utero result from organisms such as *Toxoplasma gondii*, rubella virus, cytomegalovirus (CMV), herpes simplex virus (HSV), parvovirus B19, hepatitis C virus, Zika virus, and *Treponema pallidum*. These infections typically result from transplacental transmission. Risk of transmission depends on the trimester of pregnancy during which the maternal infection occurs. For example, *Toxoplasma* transmission rates range from almost 0% during the first weeks of pregnancy to 60% in the third trimester.[1]

Severity of the infection also depends on the stage of pregnancy at which maternal infection occurred. Congenital toxoplasmosis, parvovirus B19, and rubella acquired during the first trimester often result in stillbirth or severe anomalies. Transmission of infection often depends on whether the maternal infection is a primary infection or a recurrence. For example, almost 40% of neonates born to mothers with a primary CMV infection during pregnancy are infected, and most infections are associated with signs and symptoms at birth, whereas less than 2% of neonates are infected in pregnancies of CMV-infected, seropositive mothers.[2]

Perinatal infections are acquired just before birth (often after rupture of membranes) or as the neonate passes through the birth canal. The neonate initially is colonized after exposure to maternal microflora, including with nonpathogenic organisms such as *Lactobacillus, Peptostreptococcus,* and *Saccharomyces*. However, the neonate also can be exposed to potential pathogens such as group B *Streptococcus* (GBS) and other bacteria, HSV, human immunodeficiency virus (HIV), hepatitis B virus, CMV, and *Candida* species. Perinatally acquired infections can manifest any time from immediately after birth to weeks or months later (e.g., HIV). Early-onset sepsis (<72 hours of life) typically is caused by perinatally acquired infections. Risk factors for early-onset sepsis include preterm delivery, prolonged rupture of membranes (>18 hours), maternal fever, and chorioamnionitis.[3,4] Although GBS is still the most common cause of early-onset sepsis, the institution of intrapartum chemoprophylaxis has decreased the incidence of GBS early-onset sepsis by 70%.[5] Chorioamnionitis is a major risk factor for early-onset sepsis predominantly in prematurely born neonates, and *Escherichia coli* is the most common cause.[6,7]

Late-onset sepsis (4 to 30 days of life) can be caused by perinatally or postnatally acquired organisms. The incidence of late-onset sepsis and meningitis caused by GBS has not been reduced with the use of intrapartum chemoprophylaxis.[5] Late-onset and late-late onset (>30 days of life) infections are found increasingly in very low birth weight (VLBW) neonates.[8] Common organisms include *Staphylococcus aureus, Enterococcus* species, or gram-negative bacilli that are likely to be acquired from the environment rather than periantally.[8,9] Coagulase-negative staphylococci, once the most common cause of catheter-associated bloodstream infection (BSI), and *Candida* spp. that cause late-onset BSI have receded dramatically in neonatal intensive care units using bundled best practices of infection prevention.[10]

Clinical Manifestations

Although a variety of organisms can cause congenital infections, some aspects of the clinical presentation frequently occur independent of the underlying cause (Table 91.2). Intrauterine growth retardation (IUGR), jaundice, hepatosplenomegaly, rash, intracranial calcifications, microcephaly, chorioretinitis, and thrombocytopenia can be manifestations of several congenital infections. Although many sequelae of congenital infections are present at birth, others (e.g., hearing loss, developmental delay) can manifest months or years later.

TABLE 91.2

Characteristic Manifestations of Congenital Infections

Manifestation	Toxoplasma	Rubella	CMV	Treponema	Parvovirus B19	VZV	Herpes	Ent
Anemia	x	—	—	x	x	—	—	—
Bony abnormalities	x	x	—	x	—	x	x	—
Cardiac anomalies	—	x	—	—	x	—	—	x
Cataracts	x	x	—	—	—	—	x	—
Chorioretinitis	x	x	x	x	—	x	x	—
Hearing impairment	x	x	x	x	—	—	x	—
Hepatosplenomegaly	x	x	x	x	—	x	x	x
Hydrocephalus	x	x	x	x	—	—	—	—
Hydrops fetalis	—	—	—	x	x	—	—	—
Intracranial calcifications	x	—	x	—	—	x	x	—
IUGR	x	x	x	—	—	x	—	—
Microcephaly	x	—	x	—	—	x	x	—
Rash	x	x	x	x	—	x	x	x
Thrombocytopenia	x	x	x	x	x	x	—	—

CMV, cytomegalovirus; IUGR, intrauterine growth retardation; VZV, varicella-zoster virus; x, manifestation of the disease.

From Neu N, Duchon J, Zachariah P. TORCH infections. Clin Perinatol 2015;42:77–103.

Early-onset bacterial septicemia often is nonfocal and fulminant in onset, in contrast to late-onset sepsis that can progress more slowly and often manifests as a focal infection (e.g., meningitis, urinary tract infection, pyogenic arthritis, osteomyelitis, pneumonia). More than 90% of neonates with early-onset sepsis have clinical manifestations in the first 24 hours, with most of the remainder within 48 hours of birth.[11]

Signs of perinatally and nosocomially acquired septicemia often are nonspecific and subtle, but bacteremia is uncommon in asymptomatic neonates.[11,12] Signs consistent with neonatal systemic infection can include temperature instability, lethargy, irritability, apnea, respiratory distress, hypotension, bradycardia, tachycardia, cyanosis, abdominal distention, hyperglycemia, hypoglycemia, jaundice, and feeding intolerance.[12,13] These signs overlap with those of other diseases in the neonatal period, including anemia, congenital heart disease, respiratory distress syndrome, and metabolic disorders.

Laboratory Findings and Diagnosis

If bacterial or fungal infection is suspected, prompt investigation should be accompanied by administration of empiric antimicrobial therapy. White blood cell counts and acute phase reactants such as C-reactive protein (CRP) have poor positive predictive values for septic neonates (14% for neonates at risk for sepsis).[14,15] There currently are no screening laboratory tests with sufficient sensitivity and specificity to discriminate among well-appearing neonates at risk for early-onset sepsis.[7]

For bacterial and fungal infections, culture of normally sterile body fluids remains the gold standard for diagnosis. The sensitivity of blood culture to detect candidemia and bacteremia depends on a collection of at least 0.5 mL blood,[16–18] and this volume may not detect low levels of bacteremia or candidemia.[14] Although obtaining multiple-site blood samples concurrently may help distinguish between cultures contaminated with skin flora and those representing true infection,[19] obtaining serial blood cultures increases detection by only a few percentage points. Sensitivity of blood cultures also can be compromised by antibiotic administration to the mother intrapartum or to the neonate.

The incidence of bacterial meningitis is higher in the first month of life than at any other time and complicates approximately 25% of BSIs.[20] Diagnosis of meningitis and identification of the offending organisms require examination of cerebrospinal fluid (CSF). Unless neurologic signs are present at the time of the sepsis evaluation, some clinicians defer performance of lumbar puncture unless the blood culture detects a pathogenic organism.[21] Blood cultures, however, can be negative for neonates with meningitis. Blood cultures were negative for 38% (35 of 92) of neonates 34 or more weeks' gestational age with meningitis in one study[22] and 34% (45 of 134) of VLBW neonates with culture-proven meningitis in another study.[23] The delay inherent in waiting for a positive blood culture to obtain CSF cultures decreases the likelihood of confirming meningitis.[24] The American Academy of Pediatrics and the Centers for Disease Control and Prevention recommend that a lumbar puncture be performed when neonatal sepsis is suspected provided that the infant is stable enough to tolerate the procedure.[3,25]

A urine culture should be obtained as part of the sepsis evaluation of neonates after the third day of life, but it has limited utility before this age.[26] Urine cultures should be obtained by suprapubic aspiration or in-and-out bladder catheterization. Bag specimens are difficult to evaluate due to frequent contamination and can lead to unnecessary antibiotic administration and imaging studies.

Disseminated HSV can manifest as sepsis with or without vesicular skin lesions; clues are hepatic dysfunction and consumptive coagulopathy. Evaluation of neonates suspected of having HSV infection should include viral cultures or DNA polymerase chain reaction testing performed on swabs obtained from the conjunctivae, mouth, skin, anus, CSF, and blood.[27]

Table 91.3 outlines the primary diagnostic tests for congenital infections. Characteristics of the clinical presentation and a review of the maternal history and laboratory test results can provide additional clues to the priority of pathogen testing.

TABLE 91.3

Diagnostic Tests for Congenital Infection[36]

Pathogen	Method
Cytomegalovirus	Shell vial, culture on urine; DNA PCR on plasma; IgM antibody in serum
Human immunodeficiency virus	DNA PCR on plasma
Parvovirus B19	DNA PCR on plasma; IgM antibody in serum
Rubella virus	IgM antibody in serum; culture from nasal specimen
Varicella-zoster virus	IgM antibody in serum; DNA PCR on plasma, lesions
Herpes simplex virus	DNA PCR on CSF and plasma; culture or DNA PCR of skin-eye-mouth lesions or swab specimens from mouth, nasopharynx, conjunctiva if no lesions
Treponema	Quantitative nontreponemal test on serum; CSF VDRL test; dark-field examination for spirochetes, direct fluorescent antibody test of lesions
Toxoplasma	Detection of IgM or IgA antibody in serum; DNA PCR on plasma, CSF, or urine

CSF, cerebrospinal fluid; IgM, immunoglobulin M; PCR, polymerase chain reaction test; VDRL, Venereal Diseases Research Laboratory.

Management: Empiric and Definitive Therapy

A high index of suspicion and timely, empiric antimicrobial therapy are important in the management of septicemia in neonates. Ampicillin plus an aminoglycoside are the most commonly used antibiotics.[28] Ampicillin provides coverage for gram-positive infections (e.g., GBS, *Listeria monocytogenes*). Gentamicin is active against most gram-negative pathogens causing early-onset disease (e.g., *E. coli,* other Enterobacteriaceae) and provides synergy with ampicillin against GBS and *Listeria*. Cefotaxime, a third-generation cephalosporin with superior CSF penetration compared with gentamicin, may be considered in cases of suspected or proven gram-negative bacillary meningitis. However, the use of empiric cefotaxime rather than gentamicin among infants at birth has been associated with an increased risk of death among term and preterm infants[29] and development of invasive candidiasis and necrotizing enterocolitis in premature infants.[30,31] Vancomycin or nafcillin sometimes is substituted for ampicillin for suspected nosocomial infections, especially in the setting of an indwelling central venous catheter.

After the organism and its susceptibilities are available, antibiotic therapy should be changed to the narrowest effective regimen. Vancomycin should not be continued unless a pathogen is identified that is resistant to β-lactam agents. Duration of antibiotic therapy typically is 10 days for a confirmed uncomplicated BSI. For meningitis caused by GBS, the usual duration of therapy is 14 to 21 days, and for enteric bacilli, the duration is at least 14 days after sterilization of CSF or 21 days total, whichever is longer. Increasingly, magnetic resonance imaging (MRI) is performed near anticipated end of therapy to detect cerebritis, infarction, or abscesses that may lengthen therapy.

Although uncommon in term infants, the cumulative incidence of candidemia among extremely low birth weight neonates (<1000 g) may be as high as 9%.[32] Empiric therapy for *Candida* should be considered for hospital-associated infection in symptomatic neonates with risk factors for fungal infections, including extreme prematurity, thrombocytopenia, and recent exposure to broad-spectrum antibiotics.[32] Options for antifungal therapy include amphotericin B deoxycholate, lipid products of amphotericin B, fluconazole, and micafungin.

Empiric high-dose acyclovir therapy should be considered for neonates with elevated hepatic transaminase levels, skin-eye-mouth lesions consistent with herpes infection, maternal peripartum HSV infection, and those who do not improve with antibiotics and have negative blood cultures at 48 hours.[33] The use of acyclovir empirically is debated.[34,35]

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92

Bacterial Infections in the Neonate

Morven S. Edwards, Carol J. Baker

Perspective

Neonatal sepsis and pneumonia account globally for approximately 500,000 deaths annually and almost 50% of deaths of infants 7 through 27 days of age.[1] The mortality rate in developed countries also is substantial, estimated at 5% to 10%. Neonatal sepsis is characterized by systemic signs and bloodstream infections (BSIs) occurring in the first month of life. The survival of very low birth weight (VLBW) (<1500 g) and extremely low birth weight (ELBW) (<1000 g) infants in the United States and other resource-rich countries has expanded use of this terminology to infants requiring prolonged hospitalization for complications of prematurity.

Etiologic Agents

Over past decades, the incidence of early-onset sepsis has declined in developed countries, and that of later-onset sepsis has remained unchanged or has increased.[2] The incidence of early-onset group B streptococcal (GBS) infection has declined by 85% to about 0.25 cases per 1000 live births, in association with implementation of maternal intrapartum antibiotic prophylaxis.[3] The predominant pathogens causing early-onset bacterial infections continue to be

GBS and *Escherichia coli,* which together account for approximately 70% of infections (Table 92.1).[2,4,5] Most infants with early-onset sepsis due to GBS are term (≈75%), and most with *E. coli* are preterm (≈80%).[6] The remaining early-onset infections are caused by other streptococci, including viridans streptococci and *Enterococcus;* enteric gram-negative bacilli; and *Listeria monocytogenes* or other maternal genital flora. Maternal vaginal colonization with methicillin-susceptible *Staphylococcus aureus* (MSSA) or methicillin-resistant *S. aureus* (MRSA), although uncommon, poses potential for vertical transmission and resultant neonatal infection.[7]

TABLE 92.1

Bacteria Causing Neonatal Septicemia

Bacteria	Importance of Pathogen	
	Early Onset	Later Onset[a]
GRAM-POSITIVE BACTERIA		
Group B *Streptococcus*	+++	+
Viridans streptococci	+	+
Enterococcus spp.	+	++
Coagulase-negative staphylococci	−	+++
Staphylococcus aureus	+	+++
Streptococcus pneumoniae	+	+
Listeria monocytogenes	+	+
GRAM-NEGATIVE BACTERIA		
Escherichia coli	+++	++
Klebsiella spp.	+	++
Enterobacter spp.	+	++
Citrobacter spp.	−	+
Serratia marcescens	−	+
Pseudomonas spp.	−	+
Salmonella spp.	−	+
Haemophilus influenzae	+	−
Neisseria meningitidis	−	+
Other nonenteric gram-negative bacilli	−	+
Other enteric gram-negative bacilli	+	+
ANAEROBIC BACTERIA		
Bacteroides spp.	+	+
Clostridium spp.	−	+
Others	−	+

[a] Includes late onset and late, late onset.

+++, commonly associated; ++, frequently associated; +, occasionally associated; −, rarely associated.

In late preterm infants (34 to 36 weeks' gestational age), gram-positive organisms cause most cases of early-onset sepsis,[8] but among VLBW infants, GBS has declined, and the relative importance of *E. coli* has increased.[9,10] More than one half of early-onset infections in a cohort of VLBW infants at centers of the National Institute for Child Health and Human Development Neonatal Research Network (NICHD NRN) were caused by gram-negative enteric organisms, especially *E. coli*.[11] Each of the bacteria causing early-onset sepsis can cause late-onset disease. Septicemia due to *E. coli* or GBS remains common (see Table 92.1).

The predominant organism among VLBW neonates is coagulase-negative staphylococci (CoNS), which can occur in association with a medical device (e.g., intravascular catheter), result from a gastrointestinal disorder (e.g., necrotizing enterocolitis), or occur de novo.[2,12] Among VLBW infants, most late-onset infections are caused by gram-positive organisms (70%), and CoNS accounted for almost one half of infections in the NICHD NRN.[13] True infection, based on isolation of CoNS from two or more blood cultures or one blood culture and a sterile site, is unlikely in infants with a birth weight exceeding 2000 g or gestation exceeding 34 weeks.[14] Infection rates due to CoNS can be reduced with implementation of infection-prevention initiatives.[15]

Gram-negative enteric bacilli, such as *Enterobacter* and *Klebsiella* spp., and nosocomial gram-negative pathogens, such as *Pseudomonas aeruginosa* and *Serratia marcescens,* also are encountered. *Streptococcus pneumoniae* and *Haemophilus influenzae* are uncommon causal organisms. Infants with late-onset sepsis due to *S. pneumoniae* usually are term and have infection at 3 weeks of life or later.[16]

S. aureus is cause of healthcare-associated infection, accounting for 8% of late-onset infections in the NICHD NRN.[13] The incidence of late-onset MRSA infections increased by more than 300% among all birth categories between 1995 and 2004 according to data reported by the National Nosocomial Infections Surveillance (NNIS) system.[17] MRSA emerged as a cause of late-onset sepsis in neonates hospitalized in the neonatal intensive care unit (NICU) since birth.[18] MRSA strains from 75% of infants with late-onset BSIs due to *S. aureus* in one large NICU included MRSA USA300, the dominant clone in the United States. Outbreaks of MRSA neonatal pustulosis among term infants have been reported from many states.[19] Although the mortality rate is high among VLBW infants with invasive staphylococcal infections, BSIs due to MRSA and MSSA have equivalent morbidity and mortality rates.[20] Enterococci and *Candida* must be considered in infections that arise from the intestine or with use of intravascular devices. A national point-prevalence survey cited enterococci and fungi as the next most common bloodstream isolates after staphylococci in the NICU setting.[21]

Anaerobes and several unusual bacteria have caused infections in neonates.[22] Any bacterial isolate from blood or a normally sterile body site of a clinically ill neonate should be considered a true pathogen unless there is sufficient evidence to conclude that it is a contaminant.

Epidemiology

Systemic bacterial infections affect approximately 1 to 2 of 1000 liveborn neonates, with incidence inversely related to gestation. Characterized by age at onset, infections are called *early* or *late* (Table 92.2). The age at onset for early-onset bacterial infection is defined as 72 hours or less, usually with reference to neonates hospitalized in an intensive care unit compared with less than 7 days, often with reference to illness in term infants. The burden of early-onset sepsis in the United States is about 3300 cases annually; preterm and black infants are affected disproportionately.[23]

TABLE 92.2

Features Distinguishing Early-Onset From Later-Onset Bacterial Infection in Neonates

Feature	Early Onset[a]	Late Onset	Late, Late Onset
Time of onset (days of age)	≤3 or <7	>3 or ≥7–89	≥90
Maternal complications of labor or delivery	Common	Less common	Common
Incidence of prematurity	25%	Less common	Median birth weight <1000 g
Source of organism	Maternal genital tract	Maternal genital tract; nosocomial; community	Nosocomial; community
Usual clinical presentation	Nonspecific or respiratory distress	Nonspecific or focal	Nonspecific or focal
Mortality rate (%)	5–15	2–10	5–60

[a] The age at onset for early-onset bacterial infection is defined as ≤72 hours, usually

with reference to infants hospitalized in a neonatal intensive care unit or as <7 days, often with reference to illness in term infants.

Most infants with early-onset infection are ill at or within 48 hours of birth. Maternal obstetric complications are common, and the source of pathogens is the maternal genital tract. The typical clinical presentation is respiratory distress or nonspecific signs, often indistinguishable from noninfectious disorders, but without evidence of focal infection other than pneumonia. Among VLBW infants, early-onset sepsis does not increase the risk for late-onset sepsis.[24]

For infants with late-onset infection, maternal obstetric complications other than preterm delivery are uncommon. The incidence of infection is similar for singleton and multiple birth infants.[25] The source can be the maternal genital tract, the hospital environment if duration of hospitalization exceeds a few days, or the community. The usual clinical presentation is one of nonspecific signs but focal manifestations, such as skin or soft tissue infection, pneumonia, or meningitis, are more frequent than with early-onset infection.

The survival of VLBW or ELBW neonates has prompted the use of a third category: *late, late* or *very late* onset. Although these infants are strictly speaking no longer neonates, their median gestational age of less than 28 weeks at birth and their continuing hospitalization for postnatal complications accord them an extended interval as “newborns” on the basis of postmenstrual age. These infants almost always have devices (e.g., catheters) that can lead to infection by commensal species. The mortality rate ranges from 5% to 60%, depending on the infecting agent.

Pathogenesis

Infants who experience early-onset sepsis, especially preterm infants, often have one or more risk factors associated with their mother's labor and delivery (Table 92.3). Although term infants with early-onset sepsis can have associated maternal intrapartum complications, 50% to 70% of those with early-onset GBS sepsis have no identifiable maternal factors. Maternal factors enhancing risk for early-onset septicemia include preterm delivery, premature rupture of membranes (i.e., rupture of membranes before onset of labor at any gestation), prolonged rupture of membranes (>18 hours), chorioamnionitis, GBS bacteriuria during pregnancy, early postpartum febrile conditions (including maternal bacteremia, endometritis, and wound infection), and complications of delivery causing or associated with fetal hypoxia.

TABLE 92.3

Maternal Peripartum Risk Factors for Early-Onset Bacterial Infection

Risk Factor	Comment
Preterm delivery	Attack rate inversely related to gestation <37 wk
Premature rupture of membranes	Rupture of membranes >1 hr before onset of labor at any gestation
Chorioamnionitis[a]	Risk of neonatal septicemia is 5%–15%
Urinary tract infection	Higher neonatal risk even when mother asymptomatic
Multiple pregnancy	Only for group B streptococcal septicemia
Prolonged rupture of membranes	Attack rate directly proportional to duration of rupture of membranes >18 hr
Early postpartum febrile morbidity	Maternal fever (>38°C) during the first 24 hr postpartum
No prenatal care	Higher neonatal risk
Fetal hypoxia	Apgar score <6 associated with higher risk

[a] Chorioamnionitis or intrauterine amniotic infection when a strict definition is employed (i.e., maternal fever ≥38° C *plus* ≥2 of the following: maternal tachycardia [>100 beats/min], fetal tachycardia [>160 beats/min], peripheral white blood cell count >15,000 cells/mm^3, uterine tenderness, foul smelling lochia of amniotic fluid, and exclusion of maternal respiratory or urinary tract infection).

The pathogenesis of neonatal septicemia is multifactorial and encompasses microbial, host, metabolic, and environmental factors. Infants with exposure to a high maternal genital inoculum (>10^5 colony-forming units/mL) of GBS, for example, are at a greater risk for septicemia than those exposed to a maternal carrier who has low-density colonization. Compared with term infants, premature neonates are at increased risk of septicemia because of passive acquisition of lower levels of maternally derived total immunoglobulin G (IgG) and specific antibodies to bacterial pathogens; immature function of neutrophils and decreased neutrophil storage pools; and immature immune responses to pulmonary invasion and bacteremia. Decreased expression of lectin family proteins is an additional form of neonatal immunodeficiency.[26]

Metabolic factors such as hypoxia, acidosis, and hyperbilirubinemia further compromise host response. Interruption of mucosal or skin barriers by endotracheal or nasogastric tubes, intravascular access devices, blood sampling, and monitoring equipment promote bacterial invasion, particularly for late, late-onset infection. Prior therapy with broad-spectrum antimicrobial agents increases the likelihood that bacteria resistant to routinely employed antimicrobial regimens will cause late-onset infection.

Clinical Manifestations

Septicemia and Meningitis

The risk of bacterial infection in healthy-appearing neonates is low.[27] Clinical signs of bacterial infection, however, can be subtle, and even minimal deviation from usual activity can be the first indication of invasive infection (Table 92.4). In one series of 647 infants, hypoglycemia and hypothermia were the most common findings in cases of early-onset and late-onset sepsis.[2] In another report, hyperthermia was the most common sign among 455 neonates, but only one half of the infants had fever as a sign of septicemia.[22] Temperature elevation without infection in term infants is uncommon (except for fever associated with prostaglandin therapy). Only 1% of healthy infants have fever, defined as an axillary temperature in excess of 37.5°C to 37.8°C.

TABLE 92.4

Clinical Signs of Bacterial Infections in the Newborn

Clinical Sign	Frequency of Sign	
	Septicemia	Meningitis
Hyperthermia	+++	+++
Hypothermia	++	++
Respiratory distress	++	++
Apnea	+	+
Jaundice	++	++
Lethargy	++	+++
Anorexia or vomiting	++	++
Irritability	+	++
Convulsions	−	++
Bulging or full fontanel	−	++
Diarrhea or abdominal distention	+	+
Hypotension	++	+

+++, encountered in ≥50%; ++, frequently associated (25%–49%); +, occasionally observed (15%–24%); −, rarely associated (<15%).

Adapted from Nizet V, Klein JO. Bacterial sepsis and meningitis. In Wilson CB, Nizet V, Maldonado YA, et al. (eds). Remington and Klein's Infectious Diseases of the Fetus and Newborn Infant, 8th ed. Philadelphia: Elsevier Saunders; 2016, pp 217–271.

Infants with a temperature abnormality should be examined closely for other accompanying signs. One third to one half of infants with septicemia have signs of respiratory distress, including tachypnea and grunting. Among term infants returning for evaluation after the first week of life, jaundice can be a presenting feature. Findings such as lethargy, irritability, abdominal distention, and diarrhea are less common clues, occurring in less than one fourth of infants.

Neonates with meningitis generally have the same signs as those with septicemia (see Table 92.4). Seizures also occur in up to 50%, a bulging or full fontanel in up to 30%, and nuchal rigidity in approximately 15%. These signs suggest meningitis, but their absence does not exclude central nervous system infection.

Infants should be examined for signs suggesting foci of bacterial infection, including otitis media, conjunctivitis, pneumonia, cellulitis, and abdominal findings of distention and diminished bowel sounds. Necrotizing enterocolitis is associated with BSI in almost half of affected infants and is typically attributed to gram-negative bacilli.[28] Extremities should be examined for limitation of motion, swelling, warmth, erythema, and pain with palpation. The signs of osteomyelitis and pyogenic arthritis are subtle. Skin lesions, including pustular lesions consistent with staphylococcal infection, should be sought.

Acute Otitis Media.

Healthy term infants have otoscopic findings in the immediate neonatal period (e.g., diminution or absence of mobility, a pink appearance) that would suggest middle ear inflammation in an older infant. These features are progressively less common by age 1 month. For most neonates, a diagnosis of AOM is established presumptively with pneumatic otoscopy and confirmed by tympanocentesis.[29] Common presenting features are respiratory signs and fever.[30] The usual pathogens are *S. pneumoniae* and *H.*

influenzae; gram-negative bacilli, and *S. aureus*, each comprising less than 10% of isolates.

Conjunctivitis.

Infectious conjunctivitis in neonates is caused by *Chlamydia trachomatis* and various gram-positive and gram-negative bacteria, including *S. aureus, S. pneumoniae, Enterococcus,* and *Haemophilus* spp.[31] *Neisseria gonorrhoeae,* herpes simplex virus, and adenovirus are infrequent but important pathogens. Regardless of the pathogen, eyelid edema, hyperemia of the palpebral conjunctivae, and purulent discharge are common findings. Findings frequently are bilateral. Hospitalized ELBW infants are more likely to have gram-negative enteric bacteria causing conjunctivitis compared with higher birth weight NICU infants.[32]

Osteomyelitis and Pyogenic Arthritis.

Two clinical syndromes are associated with bone or joint infection in neonates (Table 92.5). The mild or subacute form is a consequence of low-grade and transient bacteremia. Edema and swelling of the extremity or joint, usually without warmth or erythema, can occur for several weeks before the diagnosis. Typically, pain is elicited by moving the infant during diaper or clothing changes. Spontaneous movement is decreased in the involved extremity, a consequence of pain (i.e., pseudoparalysis) or weakness. This presentation is typical of GBS. Erb palsy sometimes is diagnosed erroneously when the proximal humerus is involved.

TABLE 92.5

Clinical Presentation of Bone and Joint Infections in Newborn Infants

Manifestation	Mild Form	Severe Form
Preceding bacteremia	Low-grade or transient	Prolonged or intense
Duration of signs	Can be several weeks	Simultaneously with bacteremia or in days after initiation of therapy
Physical findings	Subtle	Prominent
Multiple bone involvement	Uncommon	Common

The severe presentation is a consequence of a prolonged or intense BSI. Staphylococci, including MRSA or MSSA, are the usual pathogens. Severe systemic signs overshadow early localizing signs of hematogenous seeding of bones. Bone or joint foci can be seen concurrently with a BSI or days after initiation of therapy. Inflammatory changes, such as swelling, tenderness, erythema, and warmth, are prominent. Because of spread across transphyseal vessels, infection in the metaphysis spreads to the contiguous epiphysis and into the joint.[33]

The presenting signs of osteomyelitis in 121 neonates consisted of swelling in 64%, pseudoparalysis in 55%, tenderness in 32%, erythema in 30%, fever in 45%, and irritability or lethargy in 36%.[34] Common sites of infection are the femur, humerus, and tibia. Cuboidal bones, primarily bones of the hands or feet, and the flat bones of the ribs, skull, sternum, and scapula account for one fourth of sites. Osteomyelitis due to *Serratia marcescens* should raise suspicion for chronic granulomatous disease as an underlying condition.[35] Infants with osteomyelitis due to *Candida* spp. have a similar presentation, with subtle signs and sometimes involving multiple sites; *Candida* osteomyelitis has become rare if there is early institution of therapy and rapid control of BSI.

Skin and Soft Tissue Infections.

Skin or soft tissue foci infection can lead to BSI. Pustular lesions can be a presenting feature of staphylococcal BSI, more often with *S. aureus* than with CoNS. Other skin manifestations of infection in the neonate include cellulitis, abscess, impetigo, omphalitis, and necrotizing fasciitis.[16,18,36] They usually are a consequence of gram-positive infection, especially *S. aureus,* but gram-negative bacteria should be considered until excluded by culture. Occasionally, infection due to *Candida* spp. can manifest as soft tissue abscesses.

Laboratory Findings and Diagnosis

Septicemia Screening Tests

The difficulty in early diagnosis of bacterial infection in neonates has prompted investigation of a number of screening tests. However, no single biomarker or panel is sufficiently sensitive to obviate evaluation of infants with clinical signs of illness.[37,38] Taken in the context of limitations, the total white blood cell (WBC) count with a differential leukocyte count and other screening tests (Table 92.6) can be moderately useful in sepsis screening and in minimizing the duration of antibiotic exposure.[39]

TABLE 92.6

Screening Tests for Septicemia: Uses and Limitations

Test Finding	Finding Supporting Possible Infection	Comments
Total white blood cell count (cells/mm^3)	<5000	High likelihood ratio when test performed at ≥4 hr of life
Absolute neutrophil (polymorphonuclear [PMN]) count (cells/mm^3)	<1000	High likelihood ratio when test performed at ≥4 hr of life
Total immature PMN count (cells/mm^3)	>1100 (cord blood) >1500 (12 hr) >600 (>60 hr)	Relatively insensitive; finding unusual in uninfected infants
Ratio of immature PMNs to total PMNs	>0.2	Sensitivity 30%–90%; good negative predictive value
Platelet count (cells/mm^3)	<100,000	Insensitive, nonspecific, and late finding
C-reactive protein (mg/dL)	>1	Sensitivity 50%–90% at onset
Interleukin-6 (pg/mL)	>15	Sensitivity >80%; cutoff points vary; serial determinations may be required
Interleukin-8 (pg/mL)	>18	High sensitivity and negative predictive value
Procalcitonin (ng/mL)	>0.5	Promising for early- and late-onset infection
Erythrocyte sedimentation rate (mm/hr)	>5 (first 24 hr) > Infant's age in days + 3 (through age 14 days) >20 (>2 wk of age)	Individual laboratories must establish normal values; normal value varies inversely with hematocrit
Fibronectin (μg/mL)	<120–145	Sensitivity 30%–70%
Serum amyloid A (mg/dL)	>0.8–1.0	High sensitivity and negative predictive value; commercial kit available

A retrospective cross-sectional study of more than 67,000 term and late preterm newborns who had complete blood cell (CBC) count and blood culture obtained within 1 hour of each other for newborns younger than 72 hours of age determined that optimal interpretation of the CBC count requires using interval likelihood ratios according to the newborn's age in hours.[40] The WBC and absolute neutrophil counts were most informative when they were low and when testing was performed at 4 hours of age or later. A normal WBC count does not exclude bacterial BSI, especially in VLBW neonates, but serial assessment of neutrophil values can predict the absence of early-onset sepsis.[41,42]

The C-reactive protein (CRP) level has a high sensitivity for diagnosing infection, but it can be elevated in many noninfectious conditions (e.g., respiratory distress syndrome, hypoxia, intraventricular hemorrhage, surgery) associated with tissue injury or inflammation, limiting its value as a screening test.[43,44] Procalcitonin is an acute phase reactant produced by monocytes and hepatocytes; expression increases several hours after exposure to bacterial endotoxin, and levels remain elevated for at least 24 hours. The utility of elevated procalcitonin level is limited by its rapid postnatal endogenous increase.[38,43,44]

Neutrophil CD64 expression increases when neutrophils are activated by infectious stimuli. The neutrophil CD64 index appears to have a high sensitivity and high negative predictive value for bacterial sepsis.[45,46] Mass spectrometry-based proteomic profiling offers promise in identifying signature host-response biomarkers relevant in neonatal infection.[47]

Microbiologic Techniques

Blood culture is the gold standard for the diagnosis of BSI. The desired volume of 0.75 to 1 mL has a sensitivity of approximately 90%. Multiple blood cultures only modestly increase sensitivity and can delay initiation of therapy.[48] Documentation of BSI is absent for approximately 10% of infants with clinical signs, and infection is presumed by the clinical course.

It is appropriate to initiate empiric antimicrobial therapy after an evaluation for sepsis. Meningeal drug dosing should be employed for neonates with suspected BSI until cerebrospinal fluid (CSF) is examined and meningitis is excluded. With computer-assisted automated blood culture systems, virtually all cultures containing clinically relevant bacteria are positive by 24 to 36 hours of incubation, and cultures containing CoNS or *Candida* spp are positive within 48 hours.[49] Antibiotic therapy should be discontinued if an infant has a benign clinical course and culture results are negative at 36 to 48 hours.

A lumbar puncture should be considered in all neonates evaluated for sepsis. If deferred because of clinical instability, CSF should be examined as soon as the infant's condition permits. In the era of intrapartum antibiotic prophylaxis, 20% of infants with GBS meningitis have sterile blood cultures.[50] Because the yield of lumbar puncture is low among healthy-appearing term neonates evaluated because of maternal risk factors and premature infants with respiratory distress, some experts omit lumbar puncture in evaluating such neonates. Wiswell and colleagues[51] observed that meningitis would have been missed or the diagnosis delayed in up to one third of neonates younger than 7 days of age if CSF had not been assessed. Weighing the benefits of early diagnosis against the minimal procedural risk, it is our practice to examine CSF in all neonates evaluated for early- and late-onset sepsis.

Urine culture is not required when evaluating infants with possible early-onset infection. Bladder tap or catheter-obtained urine should be obtained for culture for infants older than 6 days of age. Cultures from foci of clinically apparent infection are obtained for Gram stain and culture. Examples are purulent drainage from the eye, joint fluid or metaphyseal bone aspirate for suspicion of osteoarthritis, peritoneal fluid, and purulent material from pustules or soft tissue abscesses.

Cultures from surface sites or mucous membranes are not helpful. Isolates from sites such as the ear canal, nasopharynx, axilla, umbilicus, groin, rectum, stomach, and endotracheal tube are uncommonly the same as those from blood, CSF, or other sterile sites and have a positive predictive value of less than 10%.[52] Positive cultures from the placenta or gastric aspirate indicate exposure to a potential pathogen. Positive cultures from placenta or surface specimens do not dictate further evaluation if an infant has no signs or risk factors predisposing to septicemia.

Management: Empiric and Definitive Therapy

The choice of empiric antimicrobial therapy is influenced by likely etiologic agents, susceptibility patterns of isolates from infants in the NICU, the antimicrobial agent's CSF penetration, potential toxicity, and the infant's hepatic and renal function. Dosage schedules by age and weight should be available and used for agents selected.

Empiric Therapy

Early-Onset Sepsis.

Empiric therapy for early-onset sepsis, unchanged after 4 decades of use, consists of ampicillin in combination with gentamicin. After meningitis is excluded, ampicillin and gentamicin at the doses shown in Table 92.7 are employed. Gentamicin serum levels are not required unless therapy is given for more than 72 hours, renal function is abnormal or unstable, or birth weight is less than 1500 g. A 10-year retrospective review found that more than 90% of isolates from cases of culture-proven early-onset sepsis in term or late preterm infants were susceptible to ampicillin or gentamicin, or both.[53] Most nonsusceptible isolates were *S. aureus*, and infants had an uncomplicated course when therapy was modified appropriately.

TABLE 92.7

Empiric Antimicrobial Therapy for Neonatal Bacterial Infections

Clinical Presentation	Antibiotics (dose/kg, IV)	Frequency (hr)	Expected Duration (days)
Septicemia			
Early-onset (term infant)	Ampicillin (50 mg) *plus* gentamicin (4 mg)	q8 + q24[a]	10
Late-onset (term infant readmitted)	Ampicillin (75 mg) *plus* gentamicin (4–5 mg) or cefotaxime (50 mg) until meningitis excluded; then ampicillin (50 mg) q6	q6 + q24[a] or q 8	10
Late-onset (inpatient)	Vancomycin (15 mg)[b] *plus* gentamicin (5 mg) or amikacin (15–17.5 mg)	q36[a] or q24	10–14
Meningitis			
Early-onset	Ampicillin (100 mg) *plus* gentamicin (4 mg) *plus* cefotaxime (50 mg)	q8 + q8[a] q12	14–21
Late-onset	Ampicillin (75 mg) *plus* gentamicin (4–5 mg) or amikacin (15–17.5 mg) *plus* cefotaxime (50 mg)	q6 + q24[a] or q24[c] q8	14–21
Bone or joint infection	Vancomycin[b] *plus* gentamicin (4–5 mg)	q24[a]	3–6 wk
Suspected gastrointestinal infection	Include clindamycin (5 mg) or piperacillin-tazobactam (100 mg piperacillin component) *plus* aminoglycoside	q6–12 q8–12	10–14

[a] For age ≤7 days and body weight ≥2 kg, gentamicin dose is 4 mg every 24 hr; for age ≤7 days and body weight <2 kg, gentamicin dose is 5 mg/kg every 48 hr; for age 8–28 days and body weight >2 kg, gentamicin dose is 4–5 mg/kg every 24 hr; for age 8–28 days and body weight ≤2 kg, gentamicin dose is 5 mg/kg every 36 hr. Serum levels should be monitored if administered for >2 doses to achieve a peak of

5–10 µg/mL and a trough of <1.5 µg/mL.

[b] Dosing algorithm for vancomycin is based on serum creatinine level that reasonably reflects neonatal renal function at approximately 5 days after birth; if <0.7 mg/dL, the dose is 15 mg/kg every 12 hr; if 0.7–0.9 mg/dL, the dose is 20 mg/kg every 24 hr; if 1–1.2 mg/dL, the dose is 15 mg/kg every 24 hr; if 1.3–1.6 mg/dL the dose is 10 mg/kg every 24 hr; if >1.6 mg/dL the dose is 15 mg/kg every 48 hr.

[c] Serum levels should be monitored to achieve an amikacin peak of 20–35 µg/mL and a trough of <10 µg/mL.

Use of maternal intrapartum antibiotic prophylaxis for prevention of early-onset GBS infection has raised concern about increasing ampicillin resistance among *E. coli* isolates. Results of a nationally representative sample published in 2002 indicated that the proportion of *E. coli* infections resistant to ampicillin increased only among preterm infants.[54] In a later study, intrapartum ampicillin exposure was not associated with an increase in the incidence of ampicillin-resistant early-onset sepsis over 18 years.[55]

Including a third-generation cephalosporin for the empiric treatment of presumed meningitis is advisable. Some experts advocate substitution of cefotaxime for gentamicin for empiric treatment of presumed nonmeningeal early-onset infection in neonates. This is inadvisable for the following reasons: superior efficacy compared with ampicillin plus gentamicin has not been demonstrated; third-generation cephalosporins are not active against *Listeria* or *Enterococcus* spp.; routine use of these agents exerts selective pressure for colonization with and BSI caused by multidrug-resistant gram-negative organisms[56]; and for NICU patients, the concurrent use of ampicillin and cefotaxime within the first 3 days of life is associated with an increased risk of death compared with the use of ampicillin and gentamicin.[57]

Late-Onset Sepsis.

For the term infant up to 8 weeks of age who is readmitted to the hospital for possible septicemia without an apparent focus of infection, ampicillin plus gentamicin or ampicillin plus cefotaxime is appropriate for empiric therapy unless *S. aureus* infection is suspected. For skin, soft tissue, and bone and joint infection, vancomycin is substituted for ampicillin. For meningitis, cefotaxime is given in addition to ampicillin plus gentamicin or instead of gentamicin. For infection of suspected gastrointestinal origin, clindamycin or another agent active against anaerobes (i.e., metronidazole) should be included. For infants previously treated with gentamicin, amikacin could be substituted, but gentamicin-resistant organisms are uncommon outside of NICU outbreak settings.

Definitive Therapy

Definitive therapy is based on the susceptibility of the isolated pathogen. Suggested duration of therapy is summarized in Table 92.7. The drug of choice for invasive GBS infection is penicillin (see Chapter 119). Infants with ampicillin-susceptible *E. coli* BSI can receive ampicillin monotherapy. For ampicillin-resistant isolates, an aminoglycoside or cefotaxime is appropriate for treatment. Combination therapy with a β-lactam agent plus an aminoglycoside can be considered for BSI caused by *Enterobacter*, *Serratia*, or *Pseudomonas*. Infants with BSI caused by extended-spectrum, β-lactamase–producing, and multidrug-resistant gram-negative organisms should receive meropenem.[58]

Topical mupirocin has been used for mild cases of neonatal staphylococcal pustulosis. For localized pustulosis in a preterm or VLBW infant or for more extensive disease in term infants, vancomycin administered parenterally is recommended, at least until a BSI is excluded.[59] Therapy for MSSA infections can be completed with nafcillin. Vancomycin is the drug of choice for MRSA sepsis and for associated bone and joint infections. Limited experience indicates that linezolid is well tolerated and is as effective as vancomycin in treatment of resistant gram-positive infections in neonates.[60]

Infants with meningitis typically have progression of clinical illness after antimicrobial therapy is initiated, and observation under intensive care is recommended for a minimum of 24 hours. Bactericidal agents should be chosen, and for gram-negative bacillary meningitis, concurrent use of two active agents (e.g., cefotaxime plus gentamicin) is ideal. Doses used should be high enough to achieve bactericidal concentrations in the CSF but to avoid associated toxicity (see Table 92.7).

After the pathogen has been identified, antimicrobial susceptibility determined, and the CSF proved to be sterile, therapy is modified to the most active, narrow-spectrum agents with the least toxicity. The drugs of choice are penicillin G alone (450,000–500,000 units/kg/day) for GBS and ampicillin (300 mg/kg/day) for *L. monocytogenes*. For enteric pathogens, the first 7 days of treatment consists of a β-lactam agent plus an aminoglycoside. Some exceptions occur, such as ampicillin-susceptible *E. coli* or *Proteus mirabilis* meningitis, for which ampicillin alone is efficacious. Meningitis due to multidrug-resistant gram-negative bacilli necessitates the use of meropenem.

Failure of antibiotic therapy to sterilize the CSF within 24 to 36 hours suggests focal involvement, such as cerebritis, ventriculitis (often with obstruction), subdural empyema, or early abscess formation. For meningitis caused by GBS, therapy is administered for a total of 14 to 21 days; for *L. monocytogenes,* 14 days is recommended; and for enteric bacilli, 14 days after sterilization of CSF or 21 total days (whichever is longer) is indicated. For optimal management, sterility of CSF should be documented at 24 to 48 hours after initiation of therapy. The diagnosis of meningitis in the neonate mandates supportive care not routinely given to infants with septicemia, such as careful observation for and control of respiratory failure and seizures, fluid administration with consideration of potential inappropriate secretion of antidiuretic hormone secretion, and care that minimizes elevation of intracranial pressure.

Prognosis and Sequelae

Infection in VLBW infants adversely affects their outcomes. VLBW infants with infection during their hospitalization are significantly more likely than are those without infection to have impaired neurodevelopmental outcomes in early childhood, including cerebral palsy.[61] For ELBW infants, antenatal exposure to chorioamnionitis, particularly histologically confirmed plus clinical chorioamnionitis, compared with no exposure also is associated with an increased risk of cognitive impairment.[62]

The outcome for neonatal bacterial meningitis is guarded, regardless of birth weight and age at onset. Among infants surviving an episode of GBS meningitis, 22% have neurologic sequelae at hospital discharge, including persistent seizures, hypertonicity, and dysphagia.[63] Among 88 term or near-term survivors of meningitis in one report, 17 had moderate or severe disability at 1 year of age.[64] In a report comparing 5-year outcomes, more children surviving neonatal meningitis had serious disability (23%) than children from a general pediatric practice (2%).[65]

Recent Advances

Ongoing morbidity and mortality from neonatal sepsis despite the use of potent antimicrobial agents and advances in critical care medicine have prompted interest in early pathogen identification through tools such as multiplex polymerase chain reaction (PCR), multiplex pyrosequencing PCR assays, and matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) mass spectrometry to identify pathogens directly from whole blood. Real-time PCR and pyrosequencing of the universal 23S rRNA gene has been used successfully in testing neonatal blood culture samples.[66]

Efforts are ongoing to define more efficient strategies for evaluation and treatment of early-onset sepsis in term and late preterm infants. Risk assessment based only on objective clinical data available at birth has been proposed.[67] An accurate multivariate predictive model of sepsis has been developed for infants born at 34 weeks' gestation or later.[68] Escobar and colleagues[69] conducted a retrospective, nested case-control study combining objective maternal data with evolving neonatal clinical findings. A risk stratification scheme that divided the neonatal population into groups treated empirically, those observed and evaluated, and those managed by continued observation was proposed that could result in substantially decreased antibiotic treatment. Prospective evaluation is required to determine the feasibility of using such a model to guide clinical decision making.

Results of clinical trials evaluating adjunctive therapies have become available. A large, randomized, multicenter, placebo-controlled trial found that therapy with immune globulin intravenous (IGIV) did not reduce neonatal sepsis deaths or major disabilities at 2 years of age.[70] Routine administration of IGIV in suspected or documented neonatal bacterial infection is not recommended.[71] A multicenter trial (i.e., PROGRAMS trial) found that early postnatal prophylactic granulocyte-macrophage colony-stimulating factor corrected neutropenia in ELBW infants but did not reduce the incidence of sepsis or improve outcomes.[72]

The impact of intestinal microbiota composition on prevention of neonatal sepsis is being investigated, as is the potential for promotion of gut microbiome diversity through administration of probiotics. Antibiotic use perinatally and during in the first week of life has sustained effects on the gut microbiota of preterm infants, increasing the relative abundance of *Enterobacter* or the Enterobacteriaceae family of organisms and lowering bacterial diversity.[73,74] Dysbiosis caused by antibiotic use can precede and potentially precipitate sepsis and necrotizing enterocolitis. Use of probiotics to colonize the premature gut and normalize the fecal microbiota can potentially prevent bacterial infections.[73] Prospective, controlled clinical trials based on these hypotheses are needed.

Prevention

Three general approaches for the prevention of neonatal septicemia have been suggested, and the first two have been efficacious: improvement in prenatal care resulting in delivery of infants at term gestation and without maternal risk factors for septicemia, maternal intrapartum antibiotic prophylaxis for prevention of early-onset GBS septicemia, and maternal immunization to provide pathogen-specific, IgG-mediated passive immunity for the infant.

Although the first approach, provision of prenatal care, especially for women younger than 20 years, is self-evident, its achievement continues to elude even urban centers. A decline in the rate of preterm deliveries can reduce the incidence of neonatal septicemia and would eliminate most very-late-onset BSIs and healthcare-associated infections in NICUs. The second approach, intrapartum antibiotic prophylaxis, targets women who are antenatally identified as carriers of GBS to prevent early-onset neonatal GBS septicemia. Sepsis caused by other organisms is more often associated with preterm birth.[75] Implementation of intrapartum antibiotic prophylaxis has been associated with an 85% decrease in the incidence of early-onset GBS infection[3] (see Chapter 119).

Whereas intrapartum antibiotic prophylaxis is a desirable interim approach, prevention of all GBS infections, irrespective of age at onset or presence of maternal risk factors, awaits availability of suitable maternal vaccines. Candidate capsular polysaccharide-protein conjugate vaccines are in development. If efficacy can be documented, women can be immunized to protect their neonates against early- and late-onset GBS disease. This approach also could be successful in prevention of infection caused by other neonatal pathogens.

Key Points

Diagnosis and Management of Bacterial Infections in the Neonate

Epidemiology

- Bacterial infections affect 1 or 2 of every 1000 live births, with a mortality rate in developed countries of 5% to10%.
- Early-onset disease manifests signs of illness within the first hours to a few days of life, often in association with maternal obstetric complications.
- Late-onset infection, variously defined as occurring at 4 days or 7 days of life or older, can have focal manifestations.
- Clinical features typically are nonspecific in early- and late-onset disease.
- Common causes of early-onset infection are group B *Streptococcus* (GBS) and *Escherichia coli.*
- Common causes of late-onset infection are coagulase-negative staphylococci, gram-negative enteric bacilli, *Staphylococcus aureus*, and GBS.

Diagnosis

- Isolation of a pathogen from blood or a normally sterile site, such as cerebrospinal fluid, establishes the diagnosis.
- No single biomarker or panel of tests has sufficient positive or negative predictive value to provide an unequivocal diagnosis.

Treatment

- Empiric antimicrobial agents, broadly targeting gram-positive and gram-negative pathogens, are employed in suspect cases while awaiting culture results.

- Definitive therapy targets the infecting microorganism.

- The recommended duration of treatment is 10 days for sepsis and 14 to 21 days for meningitis.

Prevention

- Intrapartum antibiotic prophylaxis has been associated with a significant reduction in early-onset GBS disease.

- Maternal immunization holds promise for prevention of GBS in neonates and young infants.

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93

Viral Infections in the Fetus and Neonate

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Neonates, like older children and adults, are subject to viral infections acquired by horizontal routes, such as those due to influenza, rotavirus, and enteroviruses. They also are at risk for viruses through routes that are unique to the perinatal setting in which mother-to-child transmission can occur transplacentally, during birth, or from breast milk. The ability of cytomegalovirus (CMV), herpes simplex virus (HSV), human immunodeficiency virus (HIV), and human T-lymphotrophic virus type 1 (HTLV-1) to establish chronic infection in the mother with persistence of infectious virus in blood, mucosa, or milk accounts for the role vertical transmission plays in their epidemiology and potential clinical impact.

Whether viruses that produce acute, self-limited infections in the mother are transmitted to the fetus or newborn depends on the timing of maternal infection in relation to gestation and parturition. The clinical settings in which fetal and neonatal viral infections must be considered include pregnancy, the newborn nursery, and the evaluation of an ill newborn.

This chapter provides an overview of the viral infections that occur in these settings. Detailed discussions of epidemiology, diagnosis, treatment, and prevention are presented in the chapters focused on specific viruses.

Pathogenesis

Viral infection of the fetus probably follows maternal secondary viremia or viral replication in the placenta. Developmental immaturity of fetal and neonatal innate and adaptive immune function is important in pathogenesis.[1] The innate immune system and transplacentally transferred maternal antibodies are the first line of defense against viral infections because the fetus and newborn have little or no prior experience to prime adaptive immune responses. Their adaptive immune systems are slow to respond compared with adults. Fetal and neonatal antigen-presenting cells (i.e., monocytes and dendritic cells) have reduced functionality compared with cells from adults.

Toll-like receptors (TLRs) and natural killer (NK) cells are key components of the innate immune system. NK cells have the ability to lyse virus-infected cells, and they are important sources of interferon γ (IFγ). IFγ can inhibit viral replication directly and enhance innate and adaptive immune responses.

TLRs recognize distinct features of viruses (e.g., nucleic acids), triggering induction of cytokine production and proinflammatory pathways that activate NK cells. TLRs also play a key role in increasing cell surface expression of major histocompatibility complex (MHC) class II molecules and costimulatory molecules CD40, CD80, and CD86 on the surface of plasmacytoid dendritic cells, which leads to activation of adaptive immunity, including cytotoxic T lymphocytes and B lymphocytes.[2] TLR stimulation of newborn antigen-presenting cells results in deficient production of tumor necrosis factor and IFγ and a predominantly anti-inflammatory cytokine profile compared with adults.

NK cells from newborns have an immature phenotype, decreased cytolytic ability, and markedly decreased production of IFγ compared with adults. Newborns also have higher proportions of circulating myeloid cells with a neutrophil phenotype that suppress T-lymphocyte proliferation, cytokine secretion, and NK cell cytotoxicity.

Maternal antibody acquired transplacentally and antibody and immunocompetent cells present in colostrum and mother's milk are important components of the neonate's defense against viral infection. A neonate infected by a virus to which the mother lacks immunity is prone to severe infection; neonatal infections caused by herpesviruses are illustrative. Transfusion-acquired CMV infection rarely is evident clinically in term infants of seropositive mothers, but it can cause severe illness in small, antibody-negative premature infants. HSV and varicella-zoster virus (VZV) are more likely to cause severe disease in the neonate with absent or low concentrations of maternal antibodies.

Epidemiology

Virus Transmission From Mother to Child

Viruses for which mother-to-child transmission has well-characterized clinical consequences are listed in Table 93.1. Whether maternal viral infection is spread to the fetus or neonate is determined by the occurrence of viremia, exposure to virus during labor and delivery, or from virolactia. For many viruses, the prevalence of infection among women of childbearing age and the incidence of new infections during pregnancy contribute to the overall prevalence of fetal or neonatal infection. Transmission of VZV, rubella virus, parvovirus B19, hepatitis E virus, and several agents not listed in Table 93.1 is based on the incidence and timing of maternal infection in relation to pregnancy and delivery. Rates of maternal infection due to viruses are listed in Table 93.1. The risk of transmission and the consequences of infection for the fetus or newborn are described elsewhere in this textbook.

TABLE 93.1

Viruses for Which Mother-to-Child Transmission Has Well-Characterized Clinical Consequences

Virus	Clinical Features	Transmission Route[a]
Chikungunya virus	Fever, sepsis, encephalopathy	Transplacental, intrapartum
CMV	Congenital infection syndrome	Transplacental
Dengue virus	Fever, rash, hepatosplenomegaly, thrombocytopenia, pleural effusion	Transplacental, intrapartum
Hepatitis B virus	Chronic liver disease	Intrapartum

Hepatitis C virus	Chronic liver disease	Intrapartum
Hepatitis E virus	Jaundice, hepatitis, liver failure	Transplacental, intrapartum?
HSV	Neonatal herpes	Intrapartum
HIV	Perinatal HIV/AIDS	Intrapartum, breast milk
Human papillomavirus	Laryngeal papillomatosis	Intrapartum
HTLV-1	Adult T-cell leukemia	Breast milk
LCMV	Encephalopathy, chorioretinitis	Transplacental
Parvovirus B19	Anemia, hydrops	Transplacental
Rubella virus	Congenital rubella syndrome	Transplacental
Zika virus	Microcephaly and other anomalies	Transplacental

[a] Principal route responsible for clinical consequences.

AIDS, acquired immunodeficiency syndrome; CMV, cytomegalovirus; HSV, herpes simplex virus; HIV, human immunodeficiency virus; HTLV-1, human T-cell lymphotrophic virus; LCMV, lymphocytic choriomeningitis virus.

Mother-to-child transmission of some viruses not listed in Table 93.1 is known to occur. Studies of GB virus C (i.e., hepatitis G virus), a hepatotrophic flavivirus that produces chronic infection, show that 60% to 80% of infants born to mothers with viral RNA in their blood are infected. Transiently elevated serum alanine aminotransferase concentrations have been found, but no illness in infants has been associated with perinatal infection.[3] Zika virus, a member of the flavivirus family that is transmitted by the *Aedes aegypti* mosquito, can be transmitted transplacentally and has been associated with microcephaly and central nervous system damage.[4–6] Sporadic reports of congenital disease due to enteroviruses or adenovirus and detection of viral nucleic acid by polymerase chain reaction (PCR) testing of amniotic fluid suggest that transplacental transmission of these viruses may be more common than appreciated.[7–9]

Infection of the newborn at birth occurs through exposure to virus in the genital tract or perineum; it is the major route of acquisition of HSV, HIV, hepatitis B, and hepatitis C. Labor and delivery prolong the contact between the neonate's mucosal surfaces and maternal surfaces, secretions, and blood, facilitating the transfer of viruses. The newborn who acquires virus during birth typically becomes viremic or sheds virus in other body fluids within days to a few months postpartum. Intrapartum acquisition of HSV and HIV has well-known clinical consequences. Acquisition of hepatitis B and hepatitis C lead to chronic infection that can progress to chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Intrapartum acquisition of CMV is common, but infection usually is not clinically significant except in a small proportion of very low birth weight premature infants.

Mother-to-child transmission of viruses through human milk is important in the epidemiology of CMV, HTLV-I, and HIV. The nursing infant is exposed to this potential source of infection many times each day for months. Breastfeeding is the major route for infant acquisition of CMV, which rarely causes acute illness and is not associated with adverse sequelae. In populations with high rates of maternal seropositivity and breastfeeding, most infants acquire CMV during the first year of life.[10] Breast milk–acquired CMV infection in very low birth weight premature newborns is a possible exception (see Chapter 206).

HIV and HTLV-I can be transmitted through human milk; the onset of infection usually is after 1 month of age.[11–13] Breast milk also may be the source of GB virus C and torque teno virus, but neither has been proved to cause disease when transmitted through human milk.[3,14] Perinatal transmission likely involving breastfeeding has been reported for rubella virus, HSV, echovirus 18, dengue virus, West Nile virus, and Zika virus.[15–19] Viruses that are transmitted through blood can be transmitted during breastfeeding in the setting of bleeding or cracked nipples.

Because of the association of higher infant mortality with formula feeding, the potential transmission of maternal viral infection rarely should be a reason to interdict breastfeeding in developing countries, with the possible exception of HIV infection. In the context of maternal HIV infection, the 2010 World Health Organization guidelines on infant feeding recommend that national authorities in each country decide which infant feeding practice should be supported.[20] The previous recommendation that "…replacement feeding should not be used unless it is acceptable, feasible, affordable, sustainable, and safe" remains, but stronger support is stated for maternal antiretroviral treatment and continued breastfeeding, especially in countries where not breastfeeding is associated with increased infant mortality and rates of mother-to-child transmission of HIV are high. In 2013, the American Academy of Pediatrics (AAP) Committee on Pediatric AIDS reiterated its recommendation for the United States of complete avoidance of breastfeeding "…regardless of maternal viral load and antiretroviral therapy."[21] The AAP's 2015 guidance is summarized in Table 93.2.[22]

TABLE 93.2

Prevention of Transmission of Viruses Through Human Milk in the United States

Virus	Recommendation
Cytomegalovirus	Risk for only very low birth weight preterm; no clear recommendation
Hepatitis B virus (HBV)	Administer first dose of HBV vaccine and hepatitis B immune globulin within 12 hours of birth; no restriction on breastfeeding after immunization.
Hepatitis C virus	Not a contraindication to breastfeeding. Abstain from breastfeeding if nipples are cracked or bleeding.
Herpes simplex virus	Avoid any contact between baby and herpetic lesions. Use good hand hygiene. Avoid nursing from an affected breast until lesions are resolved.
Human immunodeficiency virus	Do not breastfeed.
Human T-lymphotrophic virus I	Do not breastfeed.
Human T-lymphotrophic virus II	Do not breastfeed.
Rubella	Neither acute rubella nor recent receipt of rubella vaccine is a reason to avoid breastfeeding.
Varicella	Follow age-based recommendations for administration of hyperimmune globulin; no recommendations regarding breastfeeding.
West Nile virus	Breastfeeding is recommended in endemic area; no recommendation for acute infection during lactation.

From Kimberlin DW, Brady MT, Jackson MA, Long SS (eds). The Red Book: 2015 Report of the Committee on Infectious Diseases, 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015, pp 128–131.

Sources of Maternal Infection

The risk of maternal infection is related to the epidemiology of the specific virus and type of exposure. CMV infection is common among young children who shed CMV chronically. Exposure to young children is probably the most important risk factor for maternal CMV infection. Sexual activity is a risk factor for HSV, CMV, HIV, and hepatitis B virus infection. Injecting drug use is a risk factor for HIV, hepatitis B virus, and hepatitis C virus. For viruses that cause acute, self-limited infections with seasonal or periodic epidemics such as parvovirus B19, rubella, and enteroviruses, risk of maternal and congenital infection is related to epidemic activity in the community. Endemic rubella and congenital rubella have been eliminated from the United States and the Region of the Americas through the widespread use of rubella vaccine.

Animal and insect vectors can be the source of maternal viral infections that are spread to the fetus or newborn. Congenital infection due to lymphocytic choriomeningitis virus (LCMV) is likely underdiagnosed in the United States. Maternal LCMV infection, especially in the first trimester, can lead to fetal infection with subsequent chorioretinitis, microcephaly or macrocephaly, and intracranial calcifications. Maternal exposure to rodents may be the key epidemiologic clue.[23,24] West Nile virus is an arthropod-borne pathogen with transplacental and breast milk transmission reported in the United States.[25,26] However, mother-to-child transmission appears to be rare. Dengue virus, chikungunya virus, and Zika virus are transmitted to humans by *A. aegypti* mosquitoes and cause similar acute febrile illnesses. Maternal chikungunya virus infection can be transmitted to the fetus and neonate; a transmission rate of almost 50% has been reported with maternal viremia at term.[27]

Although it is unclear whether maternal infection affects the outcome of pregnancy, newborn infection can manifest as sepsis and encephalopathy, often associated with central nervous system sequelae.[27,28] Dengue virus infection is common in tropical areas, and rates of mother-to-child transmission range from 12% to 60% when infection occurs during pregnancy. Similar to chikungunya virus infection, maternal dengue viremia at term is associated with neonatal infection that can manifest as sepsis with fever, thrombocytopenia, hepatosplenomegaly, rash, and pleural effusion.[29]

Community-Acquired and Nosocomial Postnatal Infection

Horizontal transmission of viruses to neonates from caregivers or family members occurs primarily through infected droplets or contaminated hands. Neonates are more vulnerable than older hosts because they are immunologically naïve and their care requires repeated handling and close contact. Outbreaks of many viruses in newborn nurseries have been described; enterovirus, adenovirus, rotavirus, and RSV are notable because they are common, are difficult to control, and have substantial clinical consequences.[6,30] Neonates can be infected by the mother, other family members, or hospital personnel. Enterovirus and respiratory virus outbreaks in hospital nurseries usually are associated with community outbreaks. Blood products are a potential source of nosocomial CMV infection, especially in premature infants born to CMV-seronegative mothers. These infections can be prevented by using only CMV-negative blood products or by filtering blood to remove leukocytes.

Viruses are the leading cause of illness in infants who come to medical attention with fever before 3 months of age.[31] Enteroviruses are particularly common in this age group. Data from the US National Enterovirus Surveillance System (NESS) covering the 1983–2003 period showed that 11% of all reported enterovirus infections occurred in neonates.[32] During summer and fall, enteroviruses account for most hospitalizations of young infants with suspected sepsis.[6,31] A study of hospitalized, febrile infants reported PCR detection of enterovirus in 28% of CSF samples collected during enterovirus season (i.e., June through October) compared with 11% detected during other months.[33] Enteroviruses and parechoviruses (previously echovirus 22 and 23) are common causes of sepsis-like illness, rash, and central nervous system infections in newborns.[34,35] Infections caused by adenovirus, rotavirus, norovirus, astrovirus, influenza, RSV, influenza, and others are common sporadic or seasonal causes of fever, systemic illness, gastrointestinal disease, and respiratory disease in newborns.[36–38]

Clinical Manifestations

Prematurity and Low Birth Weight.

Maternal viral infection can affect the outcome for the infant, even if fetal infection does not occur. Maternal herpangina has been associated with premature birth, low birth weight, and poor intrauterine growth.[39] Placental adenovirus infection has been associated with chorioamnionitis and preterm birth.[40] A study testing PCR on newborn dried blood spots to detect enterovirus RNA and herpesvirus DNA found an association between detection of CMV DNA and pregnancy-induced hypertension and preterm birth.[41] Adeno-associated virus-2, a member of the parvovirus family, has been associated with pre-eclampsia, stillbirth, and preterm birth.[42]

Increased risk of prematurity, low birth weight, and other unfavorable pregnancy outcomes has been ascribed to maternal dengue infection, but a review of 30 published studies concluded that evidence linking maternal infection to adverse pregnancy outcomes was inconclusive.[29] A virologic and serologic study of small-for-gestational-age neonates in Sweden did not find evidence of association with viral infection.[43] Infections that affect fetal growth or lead to premature birth usually produce other abnormalities suggesting congenital infection. A Dutch study of neonates with isolated intrauterine growth retardation concluded that screening small-for-gestational-age babies for congenital infection was not justified, with the possible exception of congenital CMV infection, which was found in 2% of cases.[44]

Spontaneous Abortion and Stillbirth.

Associations between spontaneous abortion or stillbirth and several viruses, including poliovirus, measles, rubella, mumps, influenza, parvovirus B19, HSV, CMV, and nonpolio enterovirus infection, have been reported.[45] The extent to which maternal HIV infection in the absence of immune deficiency increases the risk of fetal death or stillbirth is not clear.[45] Declining CD4 cell count and comorbidities are associated with increased risk of stillbirth, and in countries with high maternal seroprevalence, HIV can be an important cause of stillbirth.

Comparing estimates of the frequency of fetal deaths due to viral causes based on healthcare data with estimates from studies that used PCR for virus detection suggests that viral infections may play an important role in spontaneous abortion and fetal death. A study from northern England examined viral causes of fetal death (20–23 weeks) and stillbirths (≥24 weeks) over a 21-year period.[46] A viral cause was implicated in 0.5% (16 of 2953) of late fetal deaths and 0.6% (24 of 3954) of stillbirths. Studies that used molecular techniques for virus detection are summarized in Table 93.3. These studies suggest that viral infections may account for many cases of unexplained fetal death and stillbirth.[47–50]

TABLE 93.3

Viral Infections as Causes of Intrauterine Fetal Death and Stillbirth

Study	Method	Study Population	Results
Sweden, 2001	Placental and fetal tissue: PV B19 PCR, immunohistochemistry, histopathology	47 fetal deaths	15% PV B19
		37 miscarriages	5% PV B19
		29 induced abortions	0
		53 term, normal pregnancies	0
Germany, 2004	Prospective study of 1018 pregnancies with PV B19 infection	Infection before 20 weeks	11% fetal deaths
		Infection after 20 weeks	0 fetal deaths
Greece, 2008	Placental tissue: virus specific PCR	62 fetal deaths after 15 weeks	16% CMV; 13% PV B19; 5% HSV
		35 term, healthy newborns	3% CMV; 3% PV B19; 0 HSV
Australia, 2011	Liver, kidney, placenta: CMV PCR	130 stillbirths	15% CMV

CMV, cytomegalovirus; HSV, herpes simplex virus; PCR, polymerase chain reaction; PV, parvovirus.

Only a few studies have used modern laboratory methods to detect viral infection in spontaneous abortions, intrauterine fetal deaths, and stillbirths, and most focused on one or a few viruses and were performed in developed countries. It is likely that application of molecular methods in a wider variety of cultures and geographic areas will identify more viral causes and demonstrate that viruses are common causes fetal death and stillbirth.

Syndrome of Congenital Infection.

Hepatomegaly, splenomegaly, microcephaly, petechiae, jaundice, dermal manifestations of erythropoiesis, poor intrauterine growth, chorioretinitis, intracranial calcifications, deafness, thrombocytopenia, direct hyperbilirubinemia, or hepatitis in the neonate suggests prenatal infection. Other findings occasionally associated with congenital infection are cardiac defects, hydrocephalus, prematurity, and anemia. Clinical findings suggesting infection by a specific viral agent are listed in Table 93.4.

However, clinical findings alone are not diagnostic; laboratory evaluation is necessary to confirm the cause of congenital infection.

TABLE 93.4

Clinical Findings for Newborns Suggesting a Specific Congenital Viral Infection

Virus	Clinical Features
Cytomegalovirus	Microcephaly, hearing loss, petechiae, cholestatic jaundice
Rubella	Cataracts, heart disease, deafness
Varicella-zoster virus	Scarring of skin, limb hypoplasia, ocular abnormalities
Herpes simplex virus	Hydranencephaly, ocular disease, skin scars
Lymphocytic choriomeningitis virus	Microcephaly or macrocephaly, chorioretinitis
Zika virus	Microcephaly, retinal atrophy

Central Nervous System Infection.

Viral encephalitis or meningitis in the neonate can result from prenatal or postnatal infection. Abnormalities suggesting viral central nervous system disease often are subtle and nonspecific. They include lethargy, hypotonia, irritability, poor feeding, apnea, fever, and seizures. Prenatal viral infections can affect brain growth, leading to microcephaly. Although encephalopathy or encephalitis has been found in the neonate with many viral infections, CMV, enteroviruses, parechoviruses, and HSV are the most common known causes.

Sepsis Syndrome.

Clinical manifestations suggesting septicemia sometimes are associated with neonatal enterovirus, coxsackievirus, parechovirus, adenovirus, HSV, RSV, or influenza infections. Neonates with echovirus, parechovirus, or coxsackievirus infection can have pallor, lethargy, hypotension, apnea, acidosis, and respiratory impairment.[6] Rapid progression of disseminated HSV infection can produce shock, coagulopathy, fulminant hepatitis, and diffuse lung disease, often in the absence of vesicular skin lesions.[51] Postnatal CMV infection in very low birth weight premature newborns can cause a sepsis-like syndrome.[52,53] Neonatal infections due to RSV, adenovirus, and likely many other viruses sometimes manifest nonspecifically with apnea, lethargy, irritability, and poor feeding mimicking sepsis.[36,54]

Cardiac Insufficiency.

Viral infections produce congestive heart failure in the fetus or neonate by causing anemia or by directly damaging the myocardium. Fetal infection with human parvovirus B19 characteristically leads to profound anemia. Although many fetuses appear to recover in utero, hydrops fetalis and fetal death can result.[55] Rare cases of nonimmune hydrops fetalis also have been attributed to intrauterine CMV and adenovirus infection.[56,57] Viral myocarditis usually is caused by group B coxsackieviruses or echoviruses in the neonate, manifesting as cardiac failure or shock.[6]

Pulmonary Disease.

Lower respiratory tract disease is an unusual manifestation of congenital or perinatal viral infection, and when it occurs, usually is part of multisystem disease such as disseminated HSV or VZV infection. Postnatal lower respiratory infection or pneumonia in the neonate can be caused by any respiratory tract virus. Infection in newborns is associated with more severe lung disease than in older children, and systemic symptoms can mimic sepsis.

Ocular Abnormalities.

Table 93.5 lists ocular abnormalities found in patients with congenital and neonatal viral infections.[58–60] Abnormalities of the cornea and iris, chorioretinitis, vitritis, optic atrophy, and pigment retinopathy are associated most often with congenital infection. Chorioretinitis can be evident as scarring or as active lesions, sometimes accompanied by vitritis. In infants with microcephaly and possible congenital Zika virus infection, the most striking retinal abnormality is retinal atrophy, with evidence of uveitis and vasculitis notably absent.[5] Ocular abnormalities in newborns with congenital infection usually are associated with evidence of involvement of other organ systems, especially the central nervous system.

TABLE 93.5

Newborn Ocular Abnormalities Associated With Congenital and Neonatal Viral Infection

Ocular Abnormality	Viruses

Cataracts	Rubella, CMV, HSV, LCMV, VZV
Chorioretinitis	CMV, HSV, LCMV, VZV, Zika
Optic atrophy	HSV, VZV, rubella, CMV, LCMV, Zika
Microphthalmia	CMV, rubella, HSV, LCMV
Coloboma	CMV, rubella
Keratoconjunctivitis	HSV
Pigment retinopathy	Rubella
Glaucoma	Rubella
Iritis	HSV, rubella
Anophthalmia	CMV
Peter anomaly[a]	CMV
Horner syndrome[b]	VZV

[a] Central corneal or anterior chamber synechiae or cataract.

[b] Ptosis, meiosis, and ipsilateral absence of facial sweating.

CMV, cytomegalovirus; HSV, herpes simplex virus; LCMV, lymphocytic choriomeningitis virus; VZV, varicella-zoster virus.

Deafness.

Deafness commonly is associated with congenital infection caused by rubella virus and CMV. Newborns with diminished hearing of unknown origin should be evaluated for congenital infection. Congenital CMV infection accounts for approximately 15% to 20% of cases of bilateral, moderate to profound sensorineural hearing loss in the US children.[61] Because congenital CMV infection can cause progressive hearing loss, serial hearing evaluations throughout infancy and early childhood are recommended.

Approach to the Neonate With Suspected Viral Infection

Differential Diagnosis

Hepatomegaly, splenomegaly, petechiae, purpura, jaundice, microcephaly, encephalopathy, ocular abnormalities, anemia, thrombocytopenia, conjugated hyperbilirubinemia, or elevated serum hepatic transaminases should prompt the consideration of congenital viral infection. Nonspecific signs, such as fever, lethargy, anorexia, respiratory symptoms, and a sepsis-like syndrome, suggest possible perinatal viral, bacterial, or fungal infection. Congenital syphilis and toxoplasmosis can be indistinguishable clinically from congenital viral infection. Disseminated tuberculosis with central nervous system manifestations, hepatomegaly, and splenomegaly may initially suggest congenital viral infection.

Inborn errors of metabolism can cause encephalopathy, elevation of serum hepatic enzymes, thrombocytopenia, anemia, enlarged liver and spleen, jaundice, retinal pigment defects, and cataracts. Hypoglycemia, acidosis or alkalosis, hyperammonemia, crystalluria, urinary reducing substances, and a positive urine ferric chloride test result are clues to metabolic disease. Genetic abnormalities can produce central nervous system and other abnormalities similar to those seen with congenital infection.[62–64] Liver disease associated with neonatal giant cell hepatitis, biliary atresia, choledochal cyst, or intestinal obstruction can lead to hepatomegaly, splenomegaly, serum transaminase elevation, and cholestatic jaundice. Anemia, hyperbilirubinemia or hepatosplenomegaly due to rhesus or ABO isoimmunization, red blood cell biochemical defects, red blood cell structural defects, or immunologically mediated thrombocytopenia can be confused with congenital infection.

Fetal exposure to alcohol, anticonvulsants, or cocaine can impair brain growth, leading to microcephaly and neonatal encephalopathy similar to those observed in congenital infection. The prolonged use of intravenous vitamin E in premature infants has been associated with thrombocytopenia, encephalopathy, and cholestatic jaundice. Congenital leukemia and neuroblastoma can manifest as anemia, thrombocytopenia, and organomegaly.

Laboratory Diagnosis

Laboratory testing should focus on identification of virus by culture or molecular detection. The most likely causes should be selected on the basis of signs, laboratory abnormalities, and clinical context. The specimens required and the approach used for laboratory diagnosis depend on the specific virus considered, and they are discussed in those chapters.

Measurement of maternal or neonatal antibody responses is of limited value but can contribute useful information in certain circumstances. Negative immunoglobulin G (IgG) antibody results for specific agents indicate that maternal infection is absent or is very recent, virtually eliminating the likelihood of prenatal infection. The accuracy of IgM antibody testing of neonatal serum for viral diagnosis varies and depends on the virus, assay used, and laboratory. Results of test panels for IgG or IgM antibody to multiple possible causes of infection (i.e., TORCH titers) usually fail to establish an etiologic diagnosis or are not relevant, and they should not be used as the sole laboratory diagnostic assay.[65,66] Virus culture or PCR testing should be used to confirm IgM antibody test results.

Prevention and Treatment

Specific action to prevent or treat viral infection is required for newborns with or at risk for HSV, CMV, VZV, HIV, measles, influenza, and hepatitis B virus and is discussed in respective chapters. Antiviral treatment in the newborn is recommended for congenital CMV and perinatal HSV, HIV, VZV, and influenza virus infections. Management of infants with congenital or neonatal viral infection includes supportive care and anticipation of complications, such as hearing loss, cognitive impairment, seizures, cerebral palsy, impaired vision, and chronic liver disease.

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94

Healthcare-Associated Infections in the Neonate

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As progressively smaller premature infants survive beyond the first few days of life, healthcare-associated infections (HAIs) have emerged as a major cause of morbidity and late mortality in the neonatal intensive care unit (NICU). Effective prevention and treatment of HAIs in the NICU require an understanding of the distribution of pathogens, the various patient-related risk factors for these infections, and the roles of medications and invasive procedures in predisposing to their occurrence.

Epidemiology and Anatomic Sites of Infection

Bloodstream infections (BSIs) are the most common HAIs in the NICU. They can occur in isolation or in association with urinary tract infections (UTIs)[1] and meningitis.[2] Endocarditis, osteomyelitis, pyogenic arthritis, ventilator associated pneumonia, peritonitis, conjunctivitis, and skin abscesses are important, less common HAIs (Table 94.1).

TABLE 94.1

Common Sites and Causes of Healthcare-Associated Infections in the Neonatal Intensive Care Unit

Site of Infection	Anticipated Causal Organisms					
	CoNS	*S. aureus*	Enterococci	GNR	*Candida*	Viruses
BSI	+++	++	++	++	+	−
CLABSI	+++	++	+	++	++	−
Osteomyelitis/septic arthritis	−	+++	−	+	+	−
Endocarditis	+	+++	+	+	+	−
Meningitis	+++	+	+	++	++	+
VAP	−	+	−	+++	+	+[a]
Peritonitis	+	−	+	+++	+	−
UTI	−	−	+	+++	++	−
Conjunctivitis	+	+	−	+	−	−
Skin or subcutaneous tissue	+	+++	−	+	+	+

[a] Includes respiratory syncytial virus, influenza virus, parainfluenza viruses, and enterovirus.

BSI, bloodstream infection; CLABSI, central line–associated bloodstream infection; CoNS, coagulase-negative staphylococci; GNR, gram-negative rods; *S. aureus, Staphylococcus aureus;* UTI, urinary tract infection; VAP, ventilator-associated pneumonia; +++, most common isolate; ++, frequently isolated; +, occasionally isolated; −, rarely or not isolated.

Late-Onset Sepsis

Late-onset sepsis is defined by the National Institute for Child Health and Human Development Neonatal Research Network (NICHD NRN) as BSIs occurring in neonates at or after 72 hours of age. Late-onset sepsis is most common in very low birth weight (VLBW) infants (<1500 g), for whom HAIs increase hospital length of stay by 19 days and cause 45% of deaths beyond 2 weeks of age.[3] Late-onset sepsis occurred in 21% of VLBW infants who survived beyond 3 days of age in the NICHD NRN study,[3] and similar rates have been reported from the Neonatal Networks in Canada (24%)[4] and Israel (30%).[5]

At the institutional level, the prevalence of late-onset sepsis in VLBW infants varies more: 11% to 32% in the NICUs of the NICHD NRN[3] and 7% to 74% in the NICUs participating in the Canadian Neonatal Network.[4] Data from the NICHD NRN confirm the risk of late-onset sepsis despite advances in medical care for the extremely premature infant, with 36% of infants born between 22 and 28 weeks' gestation having late-onset sepsis. The rate of late-onset sepsis is strongly and inversely associated with birth weight and gestational age, decreasing from about 60% among neonates with a gestational age of less than 25 weeks to 20% among infants born at 28 weeks' gestation.[6] Consequently, institutions caring for more extremely low birth weight (ELBW) infants have higher rates. Management practices, particularly those concerning the use and maintenance care of central venous catheters (CVCs) or peripherally inserted central catheters (PICCs), can further impact these rates of infection.[7]

Most cases of late-onset sepsis in neonates are associated with a central catheter (i.e., CVC or PICC)[3] and are referred to as central line–associated bloodstream infections (CLABSIs). The Centers for Disease Control and Prevention (CDC) and National Healthcare Safety Network (NHSN) definition[8] for a CLABSI includes isolation of a pathogen from one blood culture or of a skin commensal from two blood cultures, one or more clinical signs of infection (e.g., apnea, bradycardia, temperature instability) that are not related to an infection at another site, and presence of a CVC at the time the blood culture is obtained or within 48 hours before the development of the infection.

A rate of HAI that is linked to device use, such as for a CLABSI, helps control for variation in management practices from institution to institution. The preferred unit of measure is infections per 1000 catheter-days. The NHSN continues to recommend that CLABSI should be a major focus of surveillance and prevention efforts in NICUs and that institutions provide summary data on CLABSI rates for different birth weight groups. Values at the extremes of the NHSN data indicate problems with effective infection control or underreporting of CLABSI events, respectively. Individual NICUs are encouraged to monitor and compare their CLABSI rates with NHSN data, which are updated annually and usually published in December.[9]

In 2015, data on CLABSI rates from NHSN participating level III NICUs for the year 2013 showed a median number BSIs per 1000 catheter-days of 1 for infants weighing 750 g or less, 0 for those weighing 751 to 1000 g, and 0 for those weighing 1001 to 1500 g at birth.[9] The 90th percentile of BSIs per 1000 catheter-days was 6.3 for infants weighing 750 g or less, 4.4 for those weighing 751 to 1000 g, and 3.2 for those weighing 1001 to 1500 g at birth. These values represent a continuing decline in CLABSIs and device use. Data also were obtained for umbilical catheter–associated BSIs for the same period, which revealed low rates of infection in all weight categories.[9]

Coexistence of endocarditis, an infected intravascular thrombus, osteomyelitis, or pyogenic arthritis should be considered when BSIs persist in neonates. *Staphylococcus aureus* is the most common cause of endocarditis[10,11] and osteomyelitis[12,13] in neonates. These complications are uncommon, but the diagnosis should be considered when multiple blood cultures are positive in a neonate with a CVC.

Late-Onset Meningitis

Until recently, there were few surveillance data on the incidence of late-onset meningitis in the NICU. Consequently, considerable variation has existed in clinical practice concerning performance of a lumbar puncture in neonates with suspected late-onset sepsis. In a prospective study of 9641 VLBW infants who survived more than 3 days, late-onset meningitis occurred in 134 infants. This represented 1.4% of all infants and 5% of those who had a lumbar puncture performed. Compared with infants without septicemia, VLBW infants with meningitis were more likely to have seizures (25% vs. 2%), and were more likely to die (23% vs. 2%).[2] One third (45 of 134) of the infants with meningitis had blood cultures drawn simultaneously that were negative.

Because meningitis can alter duration of antibiotic therapy, affect long-term prognosis, and be complicated by parameningeal or brain abscess, all VLBW infants with suspected late-onset sepsis should have a lumbar puncture as part of the initial diagnostic evaluation, unless they are too critically ill to tolerate the procedure. In the latter case, lumbar puncture should be performed when clinical stabilization is achieved.

Urinary Tract Infection

UTI is a common HAI in adults and frequently is associated with an indwelling urinary catheter,[9] which seldom is used in VLBW infants. There is considerable variation in performing urine culture and analysis when late-onset sepsis is suspected.[14] Urine specimens obtained by bag collection from infants have notoriously high rates of contamination—up to 63%[15]—and are not recommended. Suprapubic bladder aspiration is performed less commonly because of the risk of serious, albeit rare, complications such as bowel perforation[16] and increased pain.[17] Sterile urethral catheterization can be performed easily by experienced nurses, even in ELBW infants, and has a potentially higher rate of success in obtaining urine compared with suprapubic bladder aspiration.[18,19]

Although prospective studies have not been performed, UTI, may be the second most common HAI in the NICU. The reported prevalence among premature infants ranges from 4% to 25%, but these reports are from the 1960s and do not represent the typical population in NICUs currently. A retrospective study reported an 8% rate of late-onset UTI among 762 VLBW infants in one NICU over an 11-year period.[20] UTI was more common in ELBW infants (12%) than in infants with birth weights between 1001 and 1500 g (6%). In a prospective study of one NICU over a 1-year period, the rate of HAIs was 17.5%, with only a 0.7% rate if UTIs.[21] When intervention-associated infections were examined, urinary catheter–associated UTIs (CAUTIs) accounted for up to 17.3%. The highest risk of HAIs was found for patients with a birth weight of less than 1000 g (relative risk, 11.8).[21]

Examining paired blood and urine cultures for 189 VLBW infants suspected of having late-onset sepsis, Tamim and colleagues detected UTI in 25%.[14] Among VLBW infants with UTIs, 62% (30 of 48) had a negative blood culture. Phillips and Karlowicz[1] reported a case series of 60 UTIs among NICU patients, primarily documented through specimens obtained by urethral catheterization when late-onset sepsis was suspected. Simultaneous BSIs with the same pathogen were detected in 52% of cases of *Candida* UTI and 8% of cases of bacterial UTI. Because most VLBW infants with UTI do not have a BSI, it is our practice to obtain urine for culture by sterile urethral catheterization or by suprapubic aspiration, when late-onset sepsis is suspected.

Ventilator-Associated Pneumonia

It is difficult to diagnosis healthcare-associated pneumonia in any patient population and particularly in the NICU population. New definitions from the CDC and NHSN in 2008 attempted to provide reproducible criteria for surveillance, classifying pneumonia as three specific types: clinically defined (PNU1), pneumonia with laboratory findings (PNU2), and pneumonia in immunocompromised patients (PNU3).[8] Infants and children usually fall into category PNU1. Diagnosis of ventilator-associated pneumonia (VAP) is especially difficult in neonates because noninfectious conditions such as respiratory distress syndrome and bronchopulmonary dysplasia are common and frequently cause radiologic abnormalities.

The NHSN has published specific guidelines adapted to infants younger than 1 year of age, but they are not specific to the premature infant. New benchmark data are becoming available through the NHSN. The highest incidence of VAP (i.e., 1.3 cases per 1000 ventilator days) occurs among infants with a median birth weight of less than 750 grams.[9]

A few investigators have attempted to establish reproducible criteria for VAP specific to the neonatal population. Cordero and coworkers[22] showed that finding purulent tracheal aspirate fluid with a positive tracheal culture in mechanically ventilated neonates in the absence of worsening clinical or radiologic findings is more consistent with clinically insignificant tracheal colonization than with VAP.

Apisarnthanarak and colleagues[23] performed a prospective cohort study addressing risk factors, microbiology, and outcomes of VAP in neonates. Their definition of VAP required new and persistent radiologic evidence of focal infiltrates more than 48 hours after initiating mechanical ventilation and treatment with antibiotics for more than 7 days for presumed VAP. By this definition, 19 (28%) of 67 of mechanically ventilated VLBW infants developed VAP, with a rate of 6.5 per 1000 ventilator-days.[23] Gram-negative bacteria were isolated from tracheal aspirates in 94% of VAP episodes, and most cases were polymicrobial. VAP developed in neonates at a median of ventilation day 30, and the risk of VAP increased by 11% for every additional week an infant was mechanically ventilated. VAP was strongly associated with mortality among neonates who required NICU care more than 30 days.[23]

Intestinal Perforation and Peritonitis

Peritonitis associated with intestinal perforation is a serious HAI in the NICU. Coates and associates[24] reported striking differences in the distribution of pathogens associated with peritonitis in 36 infants with focal intestinal perforation (FIP) compared with 80 infants with necrotizing enterocolitis (NEC). Enterobacteriaceae were found in 75% of NEC cases, compared with 25% of FIP cases. *Candida* species were found in 44% of FIP cases and in 15% of NEC cases. Coagulase-negative staphylococci (CoNS) were found in 50% of FIP cases and in 14% of NEC cases.

Peritoneal fluid cultures were positive and helped direct antimicrobial therapy in 40% (46 of 116) of cases.[24] Peritoneal fluid culture should be obtained for all neonates with intestinal perforation, regardless of cause.

Other Infections

Conjunctivitis is common in healthy term newborns. Few studies address its occurrence in the NICU. Diagnosis can be complicated because conjunctival colonization, especially with CoNS, is common in the NICU.[25] Occurrence rates of conjunctivitis in NICUs vary, with Haas and colleagues[26] reporting 5% in a prospective study and Couto and coworkers[27] reporting 12% (although infants of all birth weights were included). The most common pathogens are enteric gram-negative bacilli, but nonenteric flora such as *Pseudomonas aeruginosa* also can occur.[28]

Most neonatal skin infections are caused by *S. aureus*. Clinical manifestations include impetigo, cellulitis, soft tissue abscesses, and toxin-mediated diseases such as staphylococcal scalded skin and toxic shock syndromes.[29] Methicillin-resistant and methicillin-susceptible *S. aureus* (MRSA and MSSA) cause similar infections. Carey and associates reported an incidence of 4.8% for MSSA and 1.8% for MRSA among ELBW (<1000 g) infants' skin infections, with 53% of all NICU skin infections occurring in the ELBW cohort.[30] *P. aeruginosa* can cause ecthyma gangrenosum lesions even in a VLBW or ELBW infant.[31] Zygomycetes can cause progressive necrotizing skin lesions in neonates, with or without gastrointestinal manifestations.[32]

Pathogens of Late-Onset Infections

Gram-positive organisms are the predominant cause of late-onset sepsis in the NICU (48% to 70% of cases), but gram-negative organisms (19% to 25% of cases) and fungi (12% to 18% of cases) also are important.[3,33–36] Across many reports, the same pathogens cause most episodes: CoNS, *Candida* species, *S. aureus,* and Enterobacteriaceae (Table 94.2).

TABLE 94.2

Pathogens That Commonly Cause Late-Onset Sepsis in the Neonatal Intensive Care Unit

Pathogen	**Relative Frequency of Isolation**	**Comment**
CoNS	+++	Most common cause of CLABSI but decreasing with implementation of multipronged infection prevention
Staphylococcus aureus	++	Highest rate of focal complications; MRSA is a problem in some NICUs
Candida species	++	*Candida albicans* and C, *parapsilosis* are the most common species
Enteric GNR	++	Most common cause of fulminant sepsis; *Klebsiella* species is the most common GNR
Pseudomonas aeruginosa	+	GNR with highest case-fatality rate
Enterococcus species	+	Increased in importance as a nosocomial pathogen since the 1990s
Group B streptococci	+	Rate of late-onset cases unchanged, in contrast to dramatic decrease in early-onset cases with intrapartum antibiotics

CoNS, Coagulase-negative staphylococci; CLABSI, central line–associated bloodstream infection; GNR, gram-negative rods; MRSA, methicillin-resistant *Staphylococcus aureus*; NICU, neonatal intensive care unit; +++, most frequently isolated; ++, commonly isolated; +, occasionally isolated.

Very-late-onset sepsis (VLOS) is becoming more common as VLBW infants are living longer with ongoing needs for interventions. VLOS is defined as an infection after 120 days of life. The organisms that cause late-onset sepsis also cause VLOS.[34,37]

Usual Pathogens

The frequency of pathogens and likelihood that certain pathogens cause rapid progression to severe complications and death (i.e., fulminant sepsis) must be considered when choosing empiric therapy. Karlowicz and colleagues[33] reported that although gram-negative organisms caused only 25% of BSIs in their series, they caused 69% of *fulminant* late-onset BSIs. Of the gram-negative bacilli, *P. aeruginosa* caused 42% of fulminant cases and overall had a case-fatality rate of 56%, which contrasts with a case-fatality rate of less than 1% for CoNS.[33] Similar findings have been reported by others.[3,38]

CoNS are the most common pathogens causing late-onset sepsis, accounting for 35%[29] to 48%[3] of cases. Distinguishing between true BSI and pseudobacteremia can be difficult. The CDC and NHSN define a laboratory-confirmed bloodstream infection (LCBI) with common skin contaminant flora as ≥2 positive blood cultures drawn on separate occasions.[8] In the report of Stoll and coworkers[3] of late-onset sepsis, a rate of 48% for CoNS would have fallen to 29% if LCBSIs had been included, a rate similar to the 35% reported by Karlowicz and colleagues.[33] There has been a substantial decline in late-onset CoNS BSIs the past decade due to implementation of several infection prevention initiatives.[39]

Gram-positive organisms are the predominant pathogens in VLOS, although *S. aureus* and *Enterococcus* species can be more common than CoNS. Wynn and associates found that 48% of infections in VLBW infants were caused by gram-positive organisms, followed by gram-negative bacilli and then fungi. *Candida* species produced the highest organism-specific mortality rate in their cohort (33%), followed by gram-positive cocci (28%), but the highest organism-specific mortality rate (44%) was attributed to *S. aureus*, followed by *P. aeruginosa* (38%), similar to late-onset sepsis.[34]

Emerging Pathogens

The prevalence of pathogens in the community, healthcare, and NICU environments and the selective pressure of antibiotic use contribute to antibiotic-resistant infections in NICUs.[40] Gram-positive bacteria, including hospital- and community-associated MRSA (CA-MRSA)[30,41–45] and vancomycin-resistant *Enterococcus* *faecium,*[46] are serious problems in NICUs. The incidence of CA-MRSA varies widely across NICUs, and mortality rates for MRSA and MSSA infections remain high and frequently are not catheter related.[47] Gram-negative enteric organisms (e.g., extended-spectrum β-lactamase-carrying *E. coli* and *Klebsiella* spp.,[48–50] *AmpC* β-lactamase-carrying *Enterobacter* spp.,[51] metallo-β-lactamase–carrying enteric bacilli,[52] multidrug-resistant *Serratia marcescens,*[53,54] *Leclercia adecarboxylata*[55,56]), nonenteric organisms (e.g., *P. aeruginosa,*[57,58] *Burkholderia cepacia,*[59] *Chryseobacterium meningosepticum*[60]), and recently, highly resistant *Acinetobacter* spp. have emerged in NICU environments.[61,62]

In many instances, reservoirs containing the organism exist within the healthcare environment. Patients are exposed through the use of contaminated medical equipment or by the hands of caretakers, including family members. The former often results from breakdowns in the cleaning procedures used in the NICU or hospital environment,[44,52,54,63] and the latter results from ineffective use of hand hygiene.[57,64,65] Molecular fingerprinting of organisms has been useful for characterizing and controlling some outbreaks.[42,48,52,54,60] Control of NICU outbreaks of antibiotic-resistant organisms frequently requires vigorous application of infection control procedures (e.g., surveillance cultures, patient and staff cohorting, hand hygiene education interventions[66,67]) and active education about the factors that predispose to infection. The CDC began a 12-Step Campaign in 2002 to prevent antimicrobial resistance in various healthcare settings, and these valuable methods can be applied successfully to the NICU.[68]

Viral Infections

HAIs caused by viruses are uncommon in the NICU (incidence <1%),[69] but because of patient vulnerability and the propensity of viruses to spread patient to patient, the impact can be substantial. NICU outbreaks have been caused by respiratory syncytial virus (RSV),[70,71] influenza virus,[72] enteroviruses,[73,74] rotavirus,[75,76] adenovirus,[77] coronavirus,[78] parainfluenza,[79] and norovirus,[80,81] sometimes concurrently.[82] Attack rates can be as high as 33%.[72,74,77] Patients can be asymptomatic or have disease that is lethal,[76] and attributable costs can be high.[70] Viruses can be introduced into the

NICU by family members and by ill healthcare personnel (HCP).

RSV, adenovirus and parainfluenza infections manifest with cough, congestion, apnea, increasing oxygen requirement, or respiratory failure.[69,70] Parainfluenza and adenovirus infections manifest with epidemic conjunctivitis (in which ophthalmologic procedures can contribute to spread).[77] Coronavirus infection manifests with respiratory decompensation or abdominal distention and fever.[78] Infections with enteroviruses manifest with NEC-like signs, overwhelming septicemia, rash, or aseptic meningitis.[73] Rotavirus infection manifests with diarrhea that is frequent and watery in term infants, whereas in preterm infants, it more often is bloody and associated with abdominal distention and intestinal dilatation.[75]

Clinical Manifestations

The clinical features of sepsis in neonates are nonspecific. The most common clinical features are an increase in apnea or bradycardia (55%), gastrointestinal problems (46%) (i.e., feeding intolerance, abdominal distention, or bloody stools), need for respiratory support (29%), and lethargy or hypotonia (23%).[83] Predominant laboratory indicators are an abnormal white blood cell count (46%) (e.g., leukocytosis, increased immature white blood cells, or neutropenia), unexplained metabolic acidosis (11%), and hyperglycemia (10%). Unfortunately, the predictive values of these features are low; the best positive predictive value is for hypotension (31%).[83]

Abnormal heart rate characteristics (i.e., reduced variability and transient decelerations) occur early in the course of neonatal sepsis.[84] Although technology has been developed to calculate a heart rate characteristic index (HRCi),[85] Griffin and colleagues found that the HRCi performed similar to a clinical scoring system in predicting sepsis.[86]

The most common signs of CLABSI in neonates are fever (49%) and respiratory distress (30%).[87] Only 20% of patients had erythema or purulent discharge at the catheter insertion site.

Laboratory Diagnosis

The pretreatment diagnostic evaluation of suspected HAI should include at least two blood cultures (e.g., from any indwelling catheter along with peripheral sites), cerebrospinal fluid (CSF) culture, and urine culture. The isolation of CoNS from a single blood culture usually should be interpreted as a contaminant. A definitive diagnosis of a HAI due to bacterial or fungal species requires isolation of the organism from blood or another normally sterile body site or fluid. Exceptions are fungi such as *Aspergillus* and Zygomycetes, which can cause potentially fatal disseminated multiorgan infection but rarely are isolated from blood.[32,88] The use of serum biomarkers for fungal disease such as the 1,3-β-ᴅ-glucan assay in neonates requires more study.[89]

When viral infection is suspected, a presumptive diagnosis can be made by rapid diagnostic testing (e.g., positive direct fluorescent antibody [DFA] test for adenovirus, herpes simplex virus; enzyme immunoassay [EIA] for influenza, respiratory syncytial virus, or rotavirus; polymerase chain reaction tests) and a definitive diagnosis by isolation in viral culture. As they become available and validated for testing of body fluids such as blood, CSF, nasal washings, tracheal secretions, bronchoalveolar lavage fluid, or stool, they permit rapid viral diagnosis.

Attempts to identify dependable serum markers for diagnosis, severity, or prognosis have been somewhat successful, including use of the complete blood cell count,[90] C-reactive protein (CRP), various proinflammatory cytokines, serum hepcidin,[91] and procalcitonin (PCT) levels. Two meta-analysis of PCT showed potential for its use in the diagnosis of late-onset sepsis.[92,93] One study found PCT more accurate than the CRP level,[93] but studies have not had consistent results.[94]

Treatment

Empiric Therapy

Empiric antimicrobial therapy for suspected HAIs without a clinical focus in neonates should be guided by knowledge of the distribution, case-fatality rates of pathogens, and local susceptibility patterns of likely pathogens. An empiric antibiotic regimen should effectively treat gram-negative pathogens, particularly *P. aeruginosa* and other nonenteric flora. An aminoglycoside should be used for empiric treatment of possible gram-negative septicemia, the choice of which is determined by the antimicrobial susceptibility patterns of isolates from the NICU. Third-generation cephalosporins are not recommended for routine empiric therapy in neonates (unless knowledge of the patient's flora or the NICU pattern of infections specifically dictates) because: they do not have activity against most *P. aeruginosa* and some Enterobacteriaceae, routine use in NICUs has been associated with emergence of cephalosporin-resistant gram-negative bacilli,[95,96] and use has been associated with increased risk of candidemia in VLBW neonates.[97]

Ampicillin may be considered for empiric treatment of possible gram-positive septicemia, especially if *Enterococcus* and *Streptococcus agalactiae* are common pathogens causing late-onset sepsis in the NICU. If MRSA is prevalent in the community or NICU, vancomycin should be used as first-line therapy.[98] If MRSA is not identified, vancomycin should be discontinued promptly. If MSSA is identified, nafcillin is therapeutically superior to vancomycin.

Because CoNS sepsis is common, some physicians advocate broad empiric use of vancomycin.[99] This creates additional problems. Stoll and associates[3] found it alarming that 44% of all VLBW infants in the NICHD NRN were treated with vancomycin whether they had CoNS BSI or not. The Hospital Infection Control and Practices Advisory Committee of the CDC recommend avoiding empiric vancomycin therapy in patients with suspected sepsis to prevent the emergence and spread of vancomycin-resistant enterococci.[100] Karlowicz and coworkers[33] showed that avoidance of empiric use of vancomycin had no impact on the very low rate of fulminant CoNS sepsis and that the practice of beginning vancomycin only after CoNS was identified in blood culture did not prolong the duration of BSI.

Despite ongoing education, vancomycin continues to be the most commonly used drug in NICUs surveyed and was used inappropriately in 32% of instances.[68] In one study, application of guidelines for vancomycin use decreased neonatal vancomycin exposure from 5.2 to 3.1 per 1000 patient-days (40% reduction) and 10.8 to 5.5 per 1000 patient-days (49% reduction) in two NICUs with no change in causes of infection, duration of BSI, or incidence of complications or attributable deaths.[101] In a retrospective study of 4364 infants with CoNS BSIs across 348 NICUs, there was no 30-day survival benefit of empiric therapy with vancomycin versus therapy delayed 1 to 3 days after a first positive blood culture.[102]

In a retrospective review of 126 VLBW infants with CoNS sepsis (≥2 positive blood cultures), there was no difference in outcomes when infants were treated with vancomycin for 5 days after the last positive blood culture compared with a longer course (infants with endocarditis or infected thrombi were excluded).[103] This approach requires prospective study but is promising for reducing vancomycin use. Antibiotic stewardship specific to each NICU remains critical to the prevention of spread of resistant bacteria and avoidance of use of medications unnecessarily.

The use of empiric antifungal therapy for VLBW infants at high risk for candidemia is not standardized. Some studies suggest that empiric therapy may reduce mortality rates and improve outcomes for VLBW infants.[104] In a small, retrospective study, empiric antifungal treatment was given to critically ill neonates (<1500 g) with additional risk factors for invasive *Candida* infection who had received vancomycin or a third-generation cephalosporin, or both, for 7 days and had one or more of the following risks: receipt of total parenteral nutrition, mechanical ventilation, postnatal corticosteroid therapy, or an H_2-blocking agent or had a mucocutaneous *Candida* infection.[105] No *Candida*-related mortality occurred for patients who received empiric amphotericin B (0 of 6) compared with historical controls (11 of 18).[105] The decision to use an empiric antifungal agent for late-onset sepsis should be made on an individual basis.[106,107]

The suggested duration of therapy for HAIs by anatomic site is summarized in Table 94.3. The duration of treatment for individual patients should be determined by virulence of the pathogen, time it takes for follow-up cultures to become negative, rapidity of clinical response, time to negative blood culture, removal or retention of a CVC, and adequate drainage of any purulent foci.

TABLE 94.3

Suggested Duration of Therapy for Selected Healthcare Infections

Site or Manifestation of Infection	Duration of Therapy (Days)

BSI	10–14
Meningitis	14–21
CLABSI without removal of CVC	14[a]
Osteomyelitis or pyogenic arthritis	4–6 wk
VAP	10–14
UTI	10–14
Endocarditis	4–6 wk
Candidemia, catheter removed, rapidly resolving	10–14
Fungemia, disseminated	≈4 wk
Skin or subcutaneous lesion	7–10

[a] After first negative blood culture.

BSI, bloodstream infection; CLABSI, central line-associated bloodstream infection; CVC, central venous catheter; UTI, urinary tract infection; VAP, ventilator-associated pneumonia.

Adjunctive Therapy

Several adjunctive therapies have been investigated for late-onset sepsis, including immune globulin intravenous (IGIV), hematopoietic growth factors (i.e., granulocyte colony-stimulating factor [G-CSF] and granulocyte-macrophage colony-stimulating factor [GM-CSF]), granulocyte transfusions, and pentoxifylline. IGIV,[108] G-CSF and GM-CSF administration[109] and granulocyte transfusions[110] have been evaluated in the Cochrane Database of Systematic Reviews, with the conclusion that there is insufficient evidence to support routine use in the treatment of neonates with sepsis. Pentoxifylline also has been reviewed in the Cochrane Database as an adjunct to antibiotics for treatment of suspected or confirmed sepsis or NEC, with results showing a decrease in all-cause mortality and decrease in length of stay, but the studies evaluated were small.[111,112] Larger clinical trials are needed to determine the usefulness of this adjunctive agent, but it may be promising.

A larger, multicenter trial used GM-CSF for prophylaxis of late-onset sepsis in neonates younger than 31 weeks' gestation and small for gestational age but did not show significant difference in sepsis-free survival.[113] A review of the data from studies of granulocyte transfusions in septic neonates demonstrated improved outcome in the situation of neutropenic depletion of the marrow storage pool, but associated morbidities included fluid overload, worsening hypoxia, respiratory distress from leukocyte sequestration in the lung, graft-versus-host disease, and risk of transmission of viral infections.[110] Careful assessment of the risks and benefits of leukocyte administration is required, as is the use of any of the other adjunctive therapy.[114]

Management of Central Line–Associated Bloodstream Infections

Removal of an intravascular catheter constitutes optimal management when a BSI occurs. Nevertheless, the vital importance of CVCs in critically ill neonates must be acknowledged, especially because successful treatment of CLABSI in situ has become more common.[115] BSIs can occur without being CLABSIs; differentiation of these two conditions can be difficult.

There have been no randomized trials to guide management of CLABSIs in the NICU, but several large, observational cohort studies have compared outcomes of late-onset sepsis in neonates with CVCs treated with or without CVC removal. Data suggest that management strategies depend on the pathogen and clinical condition of the infant. If treatment with the CVC in situ is attempted, antimicrobial agents should be administered through the contaminated catheter. The algorithm shown in Fig. 94.1 provides a framework for the management of CLABSIs in neonates until evidence becomes available from randomized trials.

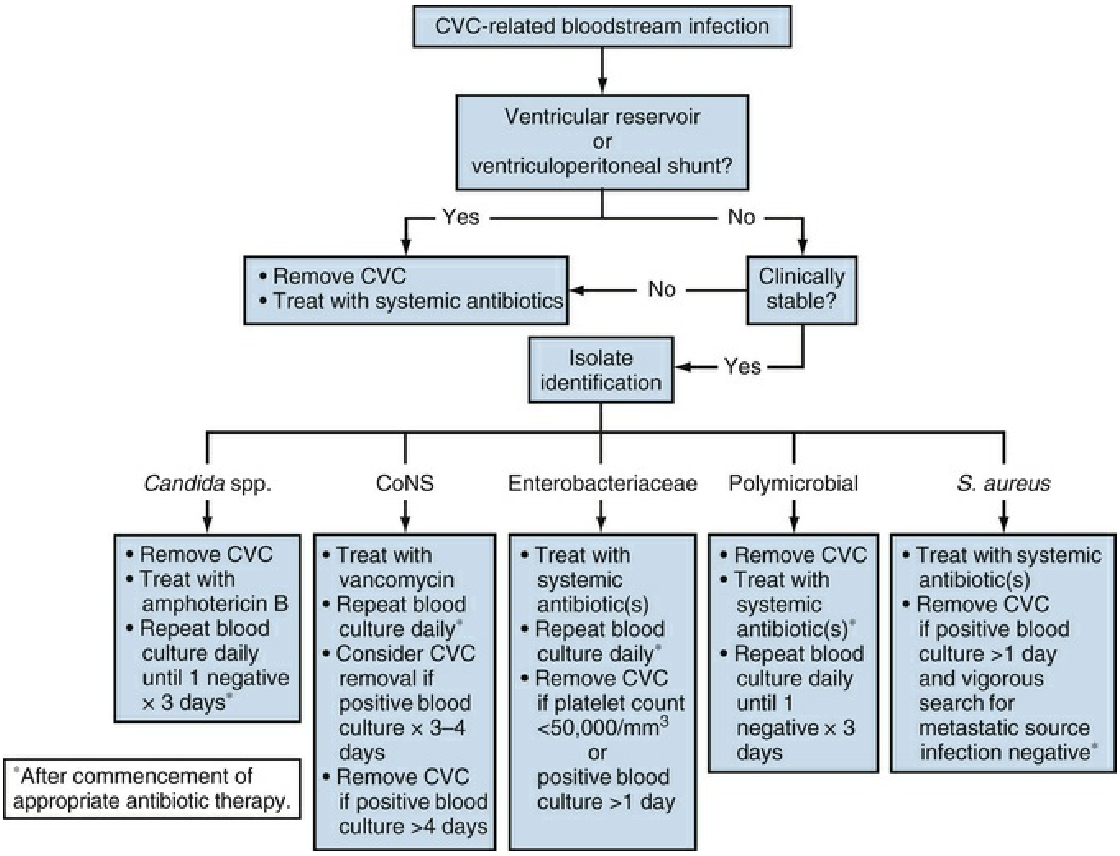
CVC-related bloodstream infection
Ventricular reservoir or ventriculoperitoneal shunt?
Yes
No
• Remove CVC
• Treat with systemic antibiotics
No
Clinically stable?
Isolate identification
Yes
Candida spp.
CoNS
Enterobacteriaceae
Polymicrobial
S. aureus
• Remove CVC
• Treat with amphotericin B
• Repeat blood culture daily until 1 negative × 3 days*
• Treat with vancomycin
• Repeat blood culture daily*
• Consider CVC removal if positive blood culture × 3–4 days
• Remove CVC if positive blood culture >4 days
• Treat with systemic antibiotic(s)
• Repeat blood culture daily*
• Remove CVC if platelet count <50,000/mm3 or positive blood culture >1 day
• Remove CVC
• Treat with systemic antibiotic(s)*
• Repeat blood culture daily until 1 negative × 3 days
• Treat with systemic antibiotic(s)
• Remove CVC if positive blood culture >1 day and vigorous search for metastatic source infection negative*
*After commencement of appropriate antibiotic therapy.

FIGURE 94.1 Suggested management of central line–associated bloodstream infection (CLABSI) in neonates. CoNS, coagulase-negative staphylococci; CVC, central venous catheter.

Candida Species.

A single-center, retrospective study of 104 cases reported that failure to remove CVCs as soon as *Candida* sepsis was detected in neonates was associated with significantly increased mortality rates for *C. albicans* sepsis (i.e., case-fatality risk increase of 39%; number needed to harm of 2.6) and significantly prolonged duration of *Candida* sepsis regardless of the *Candida* species (i.e., median of 6 days vs. 3 days).[116] These findings were confirmed in a retrospective, multicenter study of ELBW infants with systemic candidiasis.[104]

The Infectious Diseases Society of America (IDSA) guidelines for treatment of catheter-related infections[115] and guidelines for management of candidiasis in NICU patients[117] strongly recommend that CVCs be removed as soon as *Candida* sepsis is detected (if feasible) and that a lumbar puncture and dilated retinal examination be performed.

Coagulase-Negative Staphylococci.

It has been difficult to interpret clinical studies of CoNS CLABSI in neonates because many studies required only a single positive blood culture for inclusion, including many cases of pseudobacteremia. In a series of 119 cases[118] of CoNS CLABSI with at least two positive blood cultures, investigators concluded that treatment in situ often could be successful, but they observed it was unclear how long clinicians should wait before abandoning sterilizing attempts and removing the CVC.

Karlowicz and colleagues reported that treatment in situ with vancomycin was successful in 46% of cases with CoNS CLABSI,[118] but none of 19 patients with CoNS BSI for more than 4 days after institution of antibiotic therapy had resolution until the CVC was removed. In contrast, 79% of cases with CoNS BSI for 2 days or less were successfully treated without CVC removal; the successful treatment rate decreased to 44% when BSI persisted for 3 to 4 days.[118] When CoNS CLABSI persists in neonates whose catheter is vital to clinical care, it is our practice to administer antibiotic treatment through the CVC for 2 days and perhaps as long as 3 to 4 days in special circumstances but never beyond 4 days of persistent bacteremia before removing a CVC.

Although the use of antibiotic lock therapy for 10 to 14 days in combination with systemic antibiotic treatment for the treatment of CoNS CLABSI is part of the 2009 IDSA treatment guidelines for short- and long-term CVC,[115] the role of a vancomycin lock for therapy or prevention in the NICU requires further study.[119]

Enterobacteriaceae.

Although Enterobacteriaceae are a common cause of late-onset sepsis, data are limited concerning CLABSI. In a report of 53 cases of Enterobacteriaceae CLABSI in neonates, resolution of infection was reported in 45% of cases with the use of gentamicin or tobramycin without CVC removal.[120] Successful treatment of Enterobacteriaceae with a BSI of more than 1 day's duration was uncommon without removal of the CVC.

Attempting to treat Enterobacteriaceae BSI with CVC in situ was not associated with an observable increase in mortality, morbidity, or recurrence. Severe thrombocytopenia (platelet count <50,000/mm^3) on the first day of Enterobacteriaceae BSI did not resolve until the CVC was removed in 82% of cases.[120] It is our practice to remove the CVC in cases associated with severe thrombocytopenia or if Enterobacteriaceae BSI persists for more than 1 day after commencing appropriate antibiotic treatment.

Staphylococcus aureus.

For adults, removal of the CVC is advised in cases of *S. aureus* BSI, unless there is a compelling reason to conserve the catheter.[115] There are few published reports concerning *S. aureus* CLABSI in neonates or children. In a review of 154 cases of *S. aureus* CLABSI in 112 patients in one institution (including 12 premature neonates),[14] patients had complications related to infection (excluding prolonged bacteremia), with recurrence being most common. The rate of complications was lower among the patients whose catheter was removed less than 4 days after onset of infection compared with those whose catheter was not removed or was removed more than 4 days after onset.[121]

Data on treating *S. aureus* CLABSI in situ are conflicting, with some showing poor success.[122] Most cases that were treated successfully with a CVC in situ showed resolution of MSSA BSI within 24 hours of starting a penicillinase-resistant penicillin. Focal complications (e.g., soft tissue abscesses, endocarditis, osteomyelitis) may be more important risk factors for persistent *S. aureus* BSI than retention of the CVC. It is our practice to use a cautious approach, removing the CVC immediately if infection persists more than 1 day after initiation of appropriate antibiotic treatment, especially if no other source of *S. aureus* infection is identified.

Polymicrobial Infections.

Polymicrobial BSI in neonates accounts for about 10% of cases of late-onset sepsis.[123] It usually occurs later than monomicrobial sepsis in neonates with a severe underlying condition and among those with longer-indwelling CVCs.

CoNS is the most common organism recovered from culture, and it is seen in combination with other gram-positive and gram-negative organisms.[123] It is prudent to remove CVCs as soon as possible in cases of polymicrobial sepsis.

Management of Persistent Bloodstream Infections

The likelihood of adverse outcomes, such as focal complications, increases when BSI persists in neonates. Although it is uncertain whether focal complications are the cause or the consequence of persistent BSI, it is imperative that clinicians obtain serial blood cultures to document resolution of BSI and perform thorough diagnostic evaluations searching for focal complications if BSI persists. When BSI persists, clinicians must make management decisions concerning the timing of CVC removal and changes in antimicrobial therapy. Several cases have been reported of successful treatment of persistent CoNS CLABSIs with CVCs in situ without adverse consequences by adding rifampin to standard antistaphylococcal antimicrobial therapy.[124,125]

Some pathogens, especially *Candida* species, may continue to be isolated from blood cultures despite prompt removal of the CVC and administration of antifungal therapy. In one series of 96 neonatal cases, candidiasis lasted more than 7 days in 30% of cases.[126] The risk of focal complications of invasive candidiasis was significantly increased in cases with persistent compared with nonpersistent BSI (48% vs. 13%). The most common focal complications were "fungus ball" uropathy (29%), renal infiltration (20%), abscess (19%), and endocarditis (9%).[126]

Because more than one half of neonates with persistent candidiasis do not have focal complications, Chapman and Faix[126] suggested that aggressive imaging for focal complications be reserved for cases in which blood cultures remain positive despite several days of antifungal therapy or if there are clinical signs suggesting focal complications. Noyola and associates[127] documented focal complications in 23% of 86 neonates with candidemia, including some with only one positive blood culture, and the investigators recommended renal, cardiac, and ophthalmologic diagnostic evaluations for all neonates with candidemia because the existence of focal complications may affect the duration of therapy and outcome.

The prevalence of persistent BSI was 22% in a series of 335 cases of bacteremia in one NICU.[128] In this case series, the frequent decision to treat bacterial BSI with a CVC in situ contributed to the high prevalence of persistent cases. The prevalence of focal suppurative complications (i.e., osteomyelitis, septic arthritis, abscess, infected thrombus, or endocarditis) was significantly increased with the duration of BSI and was greater with persistent non-CoNS BSI compared with persistent CoNS BSI (28% vs. 3%).[128] *S. aureus* caused 50% of persistent non-CoNS BSIs and 67% of the cases with focal complications.

The study authors recommended that all neonates with persistent BSI undergo extensive evaluation for focal complications, especially for endocarditis, osteomyelitis, and soft tissue abscesses.[128] This evaluation is especially important in cases of persistent BSI caused by *S. aureus* or Enterobacteriaceae because the bacteremia does not resolve until the soft tissue abscesses (sometimes suppurative phlebitis) or bone or joint infections are drained or until the intravascular clot dissolves.

Prevention of Healthcare-Associated Infections

Risk factors for CLABSI have been extensively examined and include the use of total parenteral nutrition,[3] mechanical ventilation,[3] previous BSIs,[105] and previous exposure to third-generation cephalosporins.[96] A cohort study of monozygotic and dizygotic premature infants concluded that 49% of variance in the occurrence of late-onset sepsis might result from genetic factors and 51% from environmental factors.[129]

Manipulation of the central line increases the risk of CLABSI, including placement of the lines, maintenance of the dressing, and repeated entry into the CVC system. Approaches that minimize these interventions decrease the rate of CLABSI. Successful programs address technical and contextual factors, often with the use of care bundles and guidelines.[130] Bizzarro and coworkers performed a quality improvement initiative designed to reduce their NICU infection rate by implementing several interventions using a multidisciplinary approach and using guidelines for CVC care.[7] Interventions were associated with a decrease in the rates of CLABSI from 8.40 to 1.28 cases per 1000 central line–days and late-onset sepsis from 5.84 to 1.42 cases per 1000 patient-days.[7]

Hand decontamination by HCP is the most effective means of preventing HAIs,[131] but it often is overlooked or performed poorly in the NICU environment.[67,132] Activities such as skin contact, respiratory care, and diaper changes are independently associated with increased hand contamination.[131] The CDC recommends that HCP use alcohol-based hand rubs rather than antimicrobial soaps.[131] Alcohol-based hand rubs have excellent antimicrobial spectrum against bacteria, fungi, and viruses. The alcohol-based hand rubs also have a rapid speed of action and are the least likely to cause hand dermatitis in HCP.[131] The institution of a hand hygiene taskforce that includes problem-based and task-oriented education programs can help with hand hygiene compliance and a concurrent decrease in the infection rate. It is important to have continuous staff involvement to ensure success.[67,133]

The use of chlorhexidine gluconate (CHG) in the NICU for CVC care is increasing, with one survey showing 62% of respondents using CHG as off-label use because it is not approved by the US Food and Drug Administration for use in children younger than 2 months of age.[134] There are no data to support the use of CHG for patient bathing in the neonatal or pediatric population.

CHG antisepsis has been part of the Central Venous Catheter Guidelines in the United Kingdom since 2007,[135] but evidence from clinical trials has been lacking. In 2009, Soothill and colleagues at Great Ormond Street Hospital (GOSH) for Children reported a “profound, sustained fall” in CLABSIs from 12 to 3 per 1000 line-days in their hematopoietic stem cell transplantation pediatric patients.[136] This profound, sustained fall in CLABSIs occurred after changing from 30-second CVC hub antisepsis with 70% isopropyl alcohol to a 30-second CVC hub antisepsis with 2% CHG. Because the 30-second hub scrub was identical in the CHG and the 70% isopropyl alcohol groups, the significant reduction in the CLABSI rate was more likely associated with the introduction of CHG CVC hub antisepsis and not the friction of the 30-second hub scrub.

Soothill and colleagues[136] also reported that CVC hub antisepsis with 2% CHG was associated with a “marked fall” in the CLABSI rate throughout GOSH. The advantage of 3.15% CHG CVC hub antisepsis over 2% CHG CVC hub antisepsis, as used by Soothill and colleagues at GOSH,[136] is that 3.15 % CHG has similar effectiveness but requires only one half of the time. The 3.15% CHG CVC hub antisepsis takes 30 seconds (i.e., 15-second hub scrub followed by a 15-second drying time) compared with 60 seconds for the 2% CHG CVC hub antisepsis (i.e., 30-second hub scrub followed by a 30-second drying time), as described in the 3.15% and 2% CHG package inserts.

Premature infants require respiratory and enteral support. Systemic corticosteroid and H_2-blocking agents have been used to prevent chronic lung disease and enhance gastrointestinal function, respectively. Dexamethasone therapy for VLBW infants is associated with increased risk of late-onset sepsis.[104] Use of H_2-blocking agents in VLBW infants is associated with higher rates of NEC,[137] BSIs,[104] and candidemia.[104,138] Avoiding the use of dexamethasone and H_2-blocking agents should reduce rates of late-onset sepsis.[139]

Human milk contains several substances that provide a beneficial effect to the premature infant, including enhancement of innate immunity and enhancement of mucosal barriers. Establishing full enteral feedings with human milk is associated with lower risks of late-onset sepsis in ELBW infants.[140] Human milk was found to reduce the development of NEC by sixfold in a study of 202 VLBW infants who received more than 50% compared with those who received less than 50% human milk in the first 14 days of life.[141]

The use of bovine lactoferrin (bLF) also is being studied for the prevention of sepsis. The Italian Study Group for Neonatal Infections studied the effect of lactoferrin with or without probiotics (*Lactobacillus* GG) and found a decrease in the rate of infection in infants who were given bLF (6%) compared with the placebo group (18%).[142] The use of oral lactoferrin was reviewed in a 2015 Cochrane Database, which concluded that evidence of low to moderate quality suggests that oral lactoferrin prophylaxis decreases late-onset sepsis in preterm infants. Completion of several ongoing trials may improve the quality of the evidence.[143]

The American Academy of Pediatrics Red Book 2015 Committee on Infectious Diseases said that the use of fluconazole prophylaxis to prevent invasive candidiasis in ELBW infants should be considered in nurseries with moderate (5%–10%) to high (>10%) rates of invasive candidiasis after infection control practices are optimized.[144] Kaufman and colleagues demonstrated a significant reduction in invasive fungal disease in 100 ELBW infants given fluconazole prophylaxis or placebo (0% vs. 20%, respectively), but the level of invasive candidiasis was higher in their NICU than in centers in the NICHD NRN at that time.[145]

The strongest effect appears to occur when prophylaxis is targeted to high-risk patients with birth weights of less than 1000 g and with use of CVCs. It may be reasonable to use fluconazole with dosing of 3 mg/kg twice per week until intravenous (central or peripheral) access is no longer needed in the high-risk populations, starting in the first 2 days of life.[139] Nystatin prophylaxis also has been studied, although not as extensively, and it shows potential effectiveness in the same high-risk population but may have increased gastrointestinal side effects compared with fluconazole.[139]

The use of probiotics in the NICU is controversial because probiotics used in studies have varied and not all probiotics can be considered the same. Different strains of probiotic may have common characteristics and action but also may have unique properties and actions toward specific targets; generalization is difficult.[146] A meta-analysis of 15 randomized, controlled trials of enteral probiotic supplementation recommended the use of probiotics in preterm infants if a suitable product is available because the benefits of the reduction of death and NEC disease were clear to the inestigators.[147]

One multicenter, randomized, controlled trial showed a higher prevalence of sepsis and periventricular leukomalacia among infants weighing 500 to750 g in the probiotic group.[148] Another randomized, controlled trial showed an increased association of vancomycin-resistant enterococcus colonization in VLBW infants given probiotics.[149] Despite some studies showing benefit, evidence of infection prevention and product safety require further elucidation before a universal recommendation of probiotic supplementation, especially with regard to the strains used.

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Infections and Transplantation

OUTLINE

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Infections in Solid Organ Transplant Recipients

Michael Green, Marian G. Michaels

Solid-organ transplantation (SOT) is an accepted therapy for end-stage disease of many organs. Survival after transplantation has increased substantially, and the expanding numbers of immunosuppressed children are at risk for infection after transplantation.

Predisposing Factors

Factors predisposing to infection after SOT can be divided into those that exist before transplantation and those due to intraoperative and posttransplantation events (Box 95.1).

Box 95.1

Predisposing Factors for Infections After Organ Transplantation in Children

Pretransplantation Factors

Underlying diseases, malnutrition

Specific organ to be transplanted

Age of patient

Previous exposures to infectious agents

Previous immunizations

Intraoperative Factors

Duration of transplantation surgery

Exposure to blood products

Technical problems

Organisms transmitted in donor tissue

Posttransplantation Factors

Immunosuppression

- Immediate posttransplant immunosuppression
- Maintenance immunosuppression
- Augmented therapy for rejection episodes

Indwelling cannulas

Nosocomial exposures

Community exposures

Pretransplantation Factors

The specific organ that is transplanted is the most important determinant of the location of infection, especially during the first 3 postoperative months.[1] The chest, abdomen, and urinary tract are the most common sites of infection after thoracic, liver, and kidney transplantation, respectively. Explanations for these site-specific infections include local ischemic injury, bleeding, and potential intraoperative contamination.[2]

The underlying condition causing organ failure also can increase the risk of infection after SOT. For example, cystic fibrosis (CF) predisposes to pseudomonal and fungal infections after lung transplantation. Palliative surgery, such as for cardiac, biliary, and urologic conditions, increases the technical difficulty of the transplantation procedure, enhancing the risk of subsequent infection.[3] The severity of disease at the time of transplantation correlates with the risk of postoperative morbidity and mortality.[4] Longstanding malnutrition predisposes children to infection; attempts to correct nutritional deficits with parenteral alimentation carry attendant risks of catheter-associated infection. Mechanical ventilation while awaiting transplantation increases the risk of colonization and infection with nosocomial pathogens, many of which have multidrug resistance.

Age is an important determinant of susceptibility to and severity of infection after transplantation. Young compared with older children undergoing transplantation can experience greater disease severity due to respiratory viruses. Primary infection with cytomegalovirus (CMV) or Epstein-Barr virus (EBV) is associated with worse outcomes compared with reactivation infections.[5,6] In contrast, infections with other pathogens (e.g., *Cryptococcus* species) rarely occur before young adulthood. Younger age at the time of transplantation also is associated with an increased rate of infection during the first few years after transplantation.[7] Young children who are not immunized fully before transplantation remain susceptible to vaccine-preventable infections, and those immunized after transplantation may respond suboptimally due to immunosuppression.[8]

Transplant recipients can acquire pathogens from their donors who have active or latent infections at the time of organ harvesting. Examples include CMV,[9–11] EBV, *Toxoplasma gondii, Histoplasma* spp., West Nile virus (WNV), hepatitis B (HBV) and C viruses (HCV), and human immunodeficiency virus (HIV).[12] Screening to exclude donors with HIV or active HBV infection is standard practice, whereas organs from HCV-positive donors sometimes are used in HCV-positive recipients. Similarly, organs from HBV core antibody–positive donors sometimes are used in individual cases. Bacteria or fungi colonizing the donor's respiratory tract can cause disease after lung transplantation.[13] Unrecognized bacteremia or viremia in the donor also creates a risk for any recipient.

Intraoperative Factors

Operative factors unique to each SOT procedure can affect the risk of infection. For example, the type of biliary reconstruction used in liver transplantation influences the risk of infectious complications.[14] Surgical events during the operation also alter the risk of infection. Injury to the phrenic, vagal, or recurrent laryngeal nerves affect pulmonary toilet, predisposing a lung transplant recipient to pneumonia. Additional factors, including ischemia, prolonged operative time, contamination of the operative field, and bleeding at or near surgical sites, increase the risk of postoperative infections.

Posttransplantation Factors

Immunosuppression is the major risk for infection after transplantation. Although immunosuppressive regimens evolve to achieve more specific control of rejection with less impairment of immune function, all regimens interfere with host defenses. Treatment of rejection exacerbates this risk, as does use of antilymphocyte preparations or other biologic agents[11,14,15] (see Chapter 108). As newer immunosuppressive agents are introduced, clinicians must be alert for known and unknown infectious risks and manifestations.[16]

Technical problems after transplantation are major risk factors for infectious complications. Thrombosis of the hepatic artery predisposes to hepatic abscesses and bloodstream infections (BSIs) after liver transplantation.[17] Vesicoureteral reflux predisposes to graft pyelonephritis in renal transplant recipients.[15,18] Mediastinal bleeding requiring re-exploration predisposes to mediastinitis and BSI in thoracic organ transplant recipients.[19]

Indwelling cannulas and nosocomial exposures are a significant risk for infection. Central venous catheters (CVCs) are a risk factor for BSI. Urethral catheters predispose to urinary tract infection (UTI), and prolonged endotracheal intubation is associated with pneumonia. All transplant recipients are at risk for transfusion-associated pathogens. Children undergoing transplantation during the winter often are exposed nosocomially to common respiratory viruses. Areas of the hospital with heavy contamination with pathogenic fungi (e.g., *Aspergillus* species) increase the risk of invasive fungal disease. Nosocomial transmission of multidrug-resistant bacteria predisposes to infection with these pathogens.

Timing of Infections

The timing of specific infections usually is predictable, regardless of the type of organ transplanted. Most clinically important infections occur within the first 180 days and tend to manifest at stereotypical times after transplantation. However, the timing of certain pathogens (e.g., CMV) can be affected by the use of prophylactic strategies, augmentation in immune suppression, or the need for additional surgery.

In evaluating possible infection, it is useful to divide risk periods after transplantation into three major intervals: early (0–30 days after transplantation), intermediate (30–180 days), and late (>180 days). Some infections can occur throughout the posttransplantation course. Although exceptions occur, these divisions provide a useful framework for the approach to and differential diagnosis of a patient with fever after transplantation (Table 95.1).

TABLE 95.1

Timing of Infectious Complications After Transplantation[a]

Early Period (0–1 mo)	Middle Period (1–6 mo)	Late Period (≥6 mo)
BACTERIAL INFECTIONS	**VIRAL INFECTIONS**	**VIRAL INFECTIONS**
Gram-negative enteric bacilli Small bowel, liver, neonatal heart *Pseudomonas* and *Burkholderia* spp. Cystic fibrosis: lung Gram-positive organisms All transplant types **FUNGAL INFECTIONS** All transplant types	Cytomegalovirus All transplant types Seronegative recipient of seropositive donor Epstein-Barr virus All transplant types Seronegative recipient Small bowel highest risk group Varicella-zoster virus All transplant types **OPPORTUNISTIC INFECTIONS** *Pneumocystis jirovecii* All transplant types	Epstein-Barr virus All transplant types, but less than middle period Varicella-zoster virus All transplant types Community-acquired viral infections All transplant types **BACTERIAL INFECTIONS** *Pseudomonas* and *Burkholderia* spp. Cystic fibrosis: lung Lung recipients with chronic

VIRAL INFECTIONS Herpes simplex virus All transplant types Nosocomial respiratory viruses All transplant types	*Toxoplasma gondii* Seronegative recipient of a heart from a seropositive donor **BACTERIAL INFECTIONS** *Pseudomonas* and *Burkholderia* spp. pneumonia Cystic fibrosis: lung Gram-negative enteric bacilli Small bowel highest risk group	rejection Gram-negative enteric bacilli Small bowel highest risk group **FUNGAL INFECTIONS** *Aspergillus* spp. Lung transplants with chronic rejection

[a] Listed in decreasing order of relative importance.

Early Infections.

Early infections (0–30 days after transplantation) usually are associated with pre-existing conditions or surgical complications. Bacteria or yeast are the most frequent pathogens; 50% or more of all bacterial infections after transplantation occur during the early posttransplantation period.[19,20] Superficial or deep surgical wound infections predominate.

Technical difficulties, particularly those resulting in anastomotic leaks or stenoses, are important risk factors after most types of SOT. Donor-derived infections also can manifest. They most frequently are bacterial infections such as bacteremia (relevant to all SOT recipients), subclinical bacterial infection of the airway in lung transplant recipients, or urinary tract infection in renal transplant recipients.[12] Acute donor viral infections, such as West Nile virus or adenovirus, also can manifest in recipient.

Intermediate Period Infections.

The intermediate period (31–180 days after transplantation) is the typical time for manifestation of infection due to latent organisms transmitted from donor organs or blood products and for reactivation of latent infections in the recipient. This period also is the time when classic opportunistic infections are seen. In the absence of antiviral prophylaxis, CMV infection peaks,[9–11] and EBV-associated posttransplantation lymphoproliferative disorders (PTLDs),[6,21,22] *Pneumocystis jirovecii* pneumonia (PCP),[23–25] and toxoplasmosis[26] typically manifest.

Late Infections.

Published data on late infectious complications (>180 days after transplantation) are limited. Rates and severity of infection in children 6 months or more after transplantation are similar to those observed for otherwise healthy children[7] because most pediatric transplant recipients are by then maintained on low levels of immunosuppressing drugs. However, chronic or recurrent infections occur in a subset of transplant recipients who have uncorrected anatomic or functional abnormalities (e.g., vesicoureteral reflux, biliary stricture).

Children experiencing chronic lung rejection that manifests as bronchiolitis obliterans syndrome (BOS) frequently become infected with *Pseudomonas, Stenotrophomonas,* and *Aspergillus* species.[13,27] Infections due to varicella-zoster virus (VZV)[28] and CMV, particularly in children who receive prolonged prophylaxis,[29] and EBV-associated PTLDs can manifest in the late period.[30]

Infections Occurring Throughout the Postoperative and Posttransplantation Course.

Central venous catheters, percutaneous indwelling catheters, and nasotracheal or endotracheal tubes pose a risk of infection for the entire time of cannulation. The risk of community-acquired respiratory viruses is seasonal. Diagnostic studies should be modified according to these considerations.

Bacterial and Fungal Infection

Except for infections related to the use of indwelling catheters, bacterial infections tend to occur at sites near the transplanted organ. Recovery of bacteria with multidrug resistance is common. Knowledge of prior culture results and local antimicrobial resistance patterns help guide empiric antibiotic use.

Renal Transplantation.

Septicemia originating from the urinary tract, the lower respiratory tract, or the operative wound accounts for most life-threatening infections early after renal transplantation.[18,31] UTI, especially pyelonephritis, is the most common infectious complication, accounting for up to 50% of episodes.[32,33] Gram-negative organisms predominate.[31–33] One third of pediatric renal transplant recipients experience recurrent UTIs.[34] The incidence may be decreased with the use of ureteroneocystostomy and daily prophylactic use of trimethoprim-sulfamethoxazole (TMP-SMX).[19,35]

Infection of the lower respiratory tract occurs in 10% to 25% of adult recipients and can occur more than 1 year after transplantation.[31,34] Episodes of pneumonia caused by gram-negative and gram-positive bacteria can be severe.[36]

Fungal infections are uncommon. *Candida* spp. predominate, and the urinary tract is the most common site.[18] However, patients also are at risk for infection with opportunistic fungi such as *Aspergillus* spp.[34,37] Those with fungal infections appear to be at higher risk for graft loss.[38]

Liver Transplantation.

Bacterial and fungal infections are common early.[39–42] Intra-abdominal infection or a CVC predispose to BSIs, but these infections can occur without an obvious source. Enteric gram-negative organisms account for more than 50% of episodes. Bacterial infections involving the abdomen or surgical wound are common. Infectious complications in the transplanted liver also occur. Historically, the most important complication was hepatic abscess, which was associated with hepatic artery or portal vein thrombosis. However, the introduction of frequent Doppler surveillance studies to assess for thrombosis, coupled with the use of operative thrombectomy and thrombolysis, has marked reduced the frequency of hepatic abscesses.

Ascending cholangitis is common after liver transplantation, and it usually is associated with biliary tract abnormalities. The diagnosis is made on clinical grounds for a patient with fever and biochemical evidence of biliary tract inflammation (see Chapter 64). Enteric gram-negative bacilli and enterococcal species predominate. However, cholangitis and acute graft rejection can mimic one another, and a liver biopsy should be performed to differentiate these processes. Cholangiography is performed to assess the status of the biliary tract for patients with proven cholangitis.

As many as 40% of children develop a fungal infection during the first year after liver transplantation.[41] *Candida* spp. predominate, and infection usually is associated with an intra-abdominal focus or CVC. Data suggest the rate of invasive candidiasis is only 2.5%.[43] Episodes of invasive aspergillosis are uncommon but can be fatal.[44]

Children undergoing liver transplantation for CF are at increased risk for *Aspergillus* infection.[41]

Intestinal Transplantation.

As increasing numbers of children undergo intestinal transplantation, many have combined procedures with transplantation of liver or multiviscera. Bacterial infection (most commonly with BSI) occurs frequently,[20,44–46] at a rate of approximately 1.4 episodes per pediatric intestinal transplant recipient.[47] Disruption of the mucosal barrier associated with harvest injury or rejection commonly leads to BSI.[45,46] Coagulase-negative staphylococci, enterococci, gram-negative bacilli, and *Candida* spp. account for most episodes.

Although most episodes of BSI occur in the first 3 to 6 months after transplantation, later episodes also occur. Intra-abdominal and wound infections occur in more than one third of patients, typically soon after transplantation.

Heart Transplantation.

Death from infection after pediatric heart transplantation has decreased in recent years. Infection now accounts for less than 15% of deaths in the first year and between 5% and 10% of later deaths.[48] Infection of the lower respiratory tract (including pneumonia and lung abscess) is the most common infection after pediatric heart transplantation.[9,49–52] Mediastinitis also is an important infection, particularly if re-exploration of the chest is required. Pathogens associated with mediastinitis include *Staphylococcus aureus* and gram-negative bacilli. Young children are at increased risk for invasive infection due to *Streptococcus pneumoniae*.[52,53] Infants represent a unique population and have an increased risk of serious bacterial and fungal disease.[52,54,55]

Fungal infections, although uncommon, can be severe after heart transplantation. *Candida* spp. predominate, but serious *Aspergillus* infection also occur.[49]

Lung and Heart–Lung Transplantation.

Infection is the major cause of death in the first year after pediatric lung transplantation.[56] Infection was the primary or contributing cause of death for most patients who died after the perioperative period in one series,[27] and it was second only to graft failure in the 2013 International Registry data.[56] Infection is the third major cause of death, following bronchiolitis obliterans syndrome and primary graft failure, for children who die more than 1 year after transplantation.[56] Recipients are at high risk for bacterial and fungal infection of the respiratory tract, which derive from their native flora from the donor lungs.

Pneumonia, the most important infectious complication, is difficult to differentiate from chronic colonization. Gram-negative pathogens and *S. aureus* can be recovered in the presence or absence of disease. Radiographic abnormalities are found almost universally for patients with pneumonia or graft rejection.[57–59] Bronchoalveolar lavage with transbronchial biopsy often is required to distinguish between causes.

Children undergoing lung transplantation because of CF have a high rate of infectious complications due to bacteria and fungi.[60] Patients usually are colonized with *Pseudomonas* or *Aspergillus* spp. Colonization with *Burkholderia cenocepacia* (formerly *B. cepacia* genomovar III) has been associated with excessive mortality rates.[61–63] BSI due to organisms present before transplantation is common after lung transplantation in these patients.[64,65] Because of the importance and difficulty in treating these bacterial complications, protocols at most transplantation centers include thorough interrogation of the microbial flora of candidates before transplantation, including evaluation of isolates of *B. cepacia* complex species at reference laboratories.

Fungal infection frequently complicates pediatric lung transplantation. Infections occur early and late after transplantation, particularly if patients develop BOS.[27,66] Many lung centers have instituted guidelines for fungal prophylaxis.[66,67]

Viral Infections

Viral pathogens, especially herpesviruses, are a major source of morbidity and mortality after SOT. Patterns of disease associated with individual viruses usually are similar among all transplant recipients. However, frequency, mode of presentation, and relative severity can be different according to the type of organ transplanted and the pretransplantation serologic status of the recipient.

Cytomegalovirus.

CMV remains one of the most common and important causes of viral infection after SOT. Infection can be asymptomatic or symptomatic and can be caused by primary infection, reactivation of latent CMV, or acquisition of a new CMV strain. Before the use of prophylaxis against CMV, the reported incidence of disease among children after transplantation was 22% for kidney,[68] 40% for liver,[11] and 26% for thoracic[9] organs. Preventive strategies and treatment with ganciclovir have resulted in decreased rates and severity of CMV disease.

Primary CMV infection, typically acquired from the donated organ, is associated with the highest morbidity and mortality rates. Reactivation of latent infection or superinfection with a new CMV strain tends to result in milder illness.[5] Patients treated with high doses of immunosuppressive agents, especially antilymphocyte products, have increased rates of CMV disease, regardless of previous immunity.[9,14,68]

CMV disease is characterized by the constellation of fever (which can be high grade, prolonged, and hectic) and hematologic abnormalities (including leukopenia, atypical lymphocytosis, and thrombocytopenia). Disseminated CMV disease, often referred to as *tissue invasive disease*, can cause signs and symptoms related to specific organ involvement. Common sites include the gastrointestinal tract, liver, and lungs. The site of involvement can vary according to the type of transplant.

CMV chorioretinitis is uncommon in SOT recipients. Before the availability of ganciclovir, fatal, disseminated CMV disease occurred in 4%, 14%, and 19% of infected children after kidney,[68] heart or heart-lung,[9] and liver transplantation,[11] respectively. Although death due to CMV is rare in the ganciclovir era, CMV viremia still is associated with an increased rate of death and retransplantation among pediatric lung transplant recipients.[69,70] CMV also is associated with a risk for secondary infections, rejection, and late graft loss in some adult series.[71]

Diagnosis of CMV disease is confirmed in a patient with a compatible clinical syndrome by means of quantitative nucleic acid based tests or, less frequently, by CMV pp65 antigenemia, histopathology, or culture.[16] However, results of viral cultures of urine and respiratory secretions (including bronchoalveolar lavage specimens) can be difficult to interpret because patients frequently shed CMV in these secretions asymptomatically. Quantitative tests have been valuable in predicting which patients are at risk for disease, allowing pre-emptive initiation of therapy. Past problems with interlaboratory variations in results led to the development and implementation of international standards.[71,72] Histologic examination of involved organs remains the gold standard to confirm the presence of invasive CMV disease.

Antiviral agents with activity against CMV (e.g., ganciclovir, valganciclovir, foscarnet, cidofovir) have improved dramatically the outcome of SOT recipients. For clinical CMV disease (i.e., fever with cytopenia or visceral disease), ganciclovir or valganciclovir is given in conjunction with a reduction of immunosuppression unless there is evidence of concurrent rejection. The clinical response usually occurs 5 to 7 days after treatment is begun. The duration of therapy is guided by serial measurements of the CMV viral load using quantitative assays.[29,71]

The role of CMV hyperimmune globulin in combination with ganciclovir in the treatment of CMV disease is controversial, although some evidence for improved outcome with combination therapy has been reported in the treatment of CMV pneumonia in adult transplant recipients.[73] Studies of the use of oral valganciclovir in adults have shown valganciclovir to be comparable to intravenous ganciclovir for clearance of viremia, and its use has been recommended for adults with mild to moderate CMV disease.[29,74] Although anecdotal reports of the use of oral valganciclovir for the treatment of CMV disease in pediatric transplant recipients are increasing, published data remain limited.[29]

The clinical response typically precedes the virologic response, especially when using sensitive nucleic acid amplification testing,[7] but resistance should be suspected in children whose tests fail to show any change by at least 14 days of therapy.[71] Confirmation of antiviral resistance in CMV infections should be confirmed using genotypic assays. Foscarnet and cidofovir use is restricted to patients with apparent or proven resistance to ganciclovir.

Epstein-Barr Virus.

EBV is an important cause of morbidity and mortality for pediatric

SOT recipients.[10,21,22,75,76] A wide spectrum of EBV disease is recognized, including nonspecific viral illness, mononucleosis, and PTLDs, including lymphoma. Histologic evaluation is important in differentiating among these categories, and manifestations can evolve in individual patients. Asymptomatic seroconversion also occurs.

Variation in severity and extent of disease is related to the degree of immunosuppression and adequacy of the host immune response. Symptomatic EBV infection in general and PTLD in particular are more common after primary EBV infection, affecting children disproportionately.[6] In one study, 4% of children undergoing SOT and 10% of children with primary EBV infection developed PTLD between 1 month and 5 years after transplantation.[6] In the absence of preventive interventions, cumulative occurrence can be as high as 12% to 20% by 7 to 12 years after liver transplantation.[30,77] The onset of a viral syndrome, mononucleosis, and PTLD occurs primarily within the first year after transplantation, whereas lymphoma tends to occur later. The introduction of new immunosuppressive agents and regimens invariably impacts the incidence and timing of EBV disease.[78–80] Careful monitoring of patients receiving newer regimens is warranted.

The diagnosis of EBV-associated PTLD is made on the basis of clinical, laboratory, and histopathologic findings and should be suspected in patients with protracted fever, exudative tonsillitis, lymphadenopathy, organomegaly, leukopenia, or atypical lymphocytosis (see Chapter 208).[21,22] Gastrointestinal involvement should be suspected in patients with persistent fever and diarrhea.

The serologic diagnosis often is confounded by the presence of passive antibody. Quantitative EBV polymerase chain reaction (PCR) assays to predict risk for or presence of EBV viremia or PTLD are used widely.[22,81–83] Although extremely sensitive, these assays lack specificity; the viral load often is elevated in asymptomatic patients.[84] Every effort should be made to confirm the diagnosis of EBV disease or PTLD histologically.

Occult sites of PTLD are assessed with computed tomography of the chest and abdomen. Data suggest a potential role for position-emission tomography (PET). Palpable nodes or lesions identified by imaging should be biopsied. Endoscopy should be considered in patients with an elevated viral load and diarrheal illnesses.

Histologic evaluation can be augmented through the use of the Epstein-Barr–encoded RNA (EBER) probe.[85]

Guidelines for the management of patients with EBV disease and PTLD recommend a stepwise approach to therapy, starting with reduced immunosuppression. Further escalation of treatment is based primarily on the patient's clinical response and the histopathologic characteristics of the PTLD lesion.[86] Although antiviral agents and immune globulin intravenous (IGIV) are used frequently as part of this initial strategy,[81,87] their efficacy in the treatment of EBV-associated PTLD has not been established. Reduction of immunosuppression, alone or in combination with antiviral therapy, results in an approximately 67% cure rate of EBV-associated PTLD.

For patients who fail to respond to the initial approach, two alternative treatment strategies have been proposed. Rituximab, an anti-CD20 antibody, has been used increasingly for the treatment of EBV disease.[86] Experience suggests that as many as two thirds of patients who fail to respond after the initial withdrawal of immunosuppression respond to a 4-week course of rituximab.[88,89] However, relapse of EBV disease has been observed in 20% to 25% of treated patients 6 to 8 months after completion of therapy, at the time when rituximab antibody has waned. The second alternative for patients failing initial reduction or withdrawal of immunosuppressive therapy is the use of modified doses of cyclophosphamide and prednisone; therapy is successful in approximately two thirds of patients.[90] Unfortunately, relapse of PTLD has occurred in 22% of treated patients, and outright treatment failures have occurred in patients with fulminant disease. The addition of rituximab to this protocol improved outcomes of patients with fulminant disease, but relapses occur.[91] Studies comparing these second-line therapies are needed to define optimal treatment for children who fail initial modification of immunosuppression.

Cytotoxic chemotherapy should be considered for patients who fail to respond to the stepwise approach. It can be considered as first-line therapy for those with T-lymphocyte–associated PTLD, PTLD of the central nervous system, and monomorphic PTLD occurring late in the posttransplantation course.[86]

Adenovirus.

After pediatric liver transplantation, adenovirus is the third most important viral infection, occurring in 10% of recipients in one large early series.[92] Symptomatic disease, which ranges from self-limited fever, gastroenteritis, and cystitis to devastating illness with necrotizing hepatitis or pneumonia, occurred in more than 60% of infected patients. Infections occurred within the first 3 months after transplantation. The frequency of invasive adenovirus infections after pediatric liver transplantation appears to have decreased with the use of tacrolimus-based immunosuppression. This may reflect the ability to decrease the overall amount of immunosuppressive agents.[93,94]

Adenovirus infection in other pediatric organ recipients is less well characterized but can be severe, particularly after lung transplantation, and it can be fatal when disease manifests soon after transplantation.[27,95–98] Adenovirus DNA found in cardiac biopsies after pediatric heart transplantation was significantly associated with poor graft survival in one series.[99] Adenovirus also has been associated with hemorrhagic cystitis and graft dysfunction in adult renal transplant recipients.[100] High rates of adenovirus infection have been found after pediatric intestinal transplantation, although clinical disease does not always occur.[94,100–103]

The diagnosis of adenovirus infection can be challenging as this virus, like CMV, can be latent and can reactivate asymptomatically. Ascribing a causative role in the pathologic process sometimes is difficult. The use of nucleotide amplification testing (NAT) to detect adenovirus in the peripheral blood or other sites (e.g., bronchoalveolar lavage) can be helpful or confusing because adenovirus can be detectable in blood or other body fluids in the absence of clinical disease. Definitive diagnosis of adenovirus disease is made by histologic evidence of the virus by direct inspection of typical inclusions or immunofluorescent antibody, or both.[102]

Although no antiviral agent is approved for the treatment of adenovirus, many experts consider cidofovir to have clinical antiviral activity against the virus. Brincidofovir (i.e., liposomal derivative of cidofovir) is undergoing formal evaluation in clinical trials for the treatment of adenovirus infection.[102]

Varicella-Zoster Virus.

Many children have undergone SOT without immunity against VZV. Early experience found severe and potentially fatal disease in children developing varicella infection after transplantation.[104,105] Some fatal cases occurred despite the use of intravenous acyclovir, and disease developed in approximately 50% of patients who received postexposure varicella-zoster immune globulin (VZIG). Recently, few or no patients have developed significant complications of VZV infection after SOT.[28,106] These results were achieved in children treated with acyclovir intravenously, although a small subset thought to be at low risk for severe disease were treated with oral acyclovir or valacyclovir.

Current recommendations favor an aggressive response to varicella exposure and disease.[107] Administration of VariZIG is recommended up to 10 days after exposure of nonimmune patients; administration as soon as possible is preferred. Alternatives include the use of an intravenous immunoglobulin or off-label use of oral acyclovir or valacyclovir starting at day 7 after a known exposure date or starting as soon as possible if the date of exposure is not known (unpublished data). If varicella lesions develop, it is prudent to hospitalize patients and administer acyclovir intravenously until fever abates, no new lesions erupt, and existent lesions begin to crust.[108] Some centers have managed patients with mild disease using oral acyclovir or valacyclovir in the outpatient setting when close follow-up can be ensured.

The use of VZV vaccine after SOT is an area of active research. Limited experience in pediatric renal[109] and liver transplant recipients[109] is encouraging. Immunogenicity and safety appear to be acceptable in children who are more than 1 year out from transplantation and who have stable and relatively low levels of immunosuppression. However, these patients have received vaccine under study protocols with close follow-up, and 25% had vaccine-associated rash, prompting antiviral therapy.[109] Additional experience is needed before recommending a standard protocol for VZV vaccination after transplantation.

Common Community-Acquired Viruses.

Limited published data suggest that most children who receive SOT experience the usual childhood respiratory and gastrointestinal tract illnesses without significant problems.[7,50] This is especially true when they occur long after transplantation and are not associated with an episode of rejection.[7] However, infections caused by respiratory syncytial virus (RSV), influenza virus, or parainfluenza virus (PIV) have led to more severe disease in young children, especially when occurring soon after transplantation and during periods of maximal immunosuppression.[110,111]

A retrospective review of 576 pediatric lung transplant recipients from 14 centers found that 79 (14%) patients who had confirmed respiratory virus infections during the first year had a decreased 1-year survival rate.[97] Shirali and colleagues found that DNA from community-associated viruses such as enterovirus, adenovirus, and parvovirus in heart biopsies of children after cardiac transplantation was associated with increased adverse events, but the timing of the biopsies relative to the time of transplantation was not evaluated.[98]

Opportunistic Infections

Pneumocystis jirovecii Pneumonia.

Pneumocystis pneumonia (PCP) is a well-documented complication of SOT. Before the introduction of prophylaxis, the incidence of PCP was 4% to 35%.[23–25] However, use of TMP-SMX prophylaxis has essentially eliminated this problem.

PCP typically occurs after the first month after transplantation, reflecting indolent infection before transplantation. Most cases occur within the first year after transplantation, but PCP can occur later and should remain in the differential diagnosis for patients with fever and lower respiratory tract symptoms, particularly if they are not receiving PCP prophylaxis.

Toxoplasmosis.

Toxoplasma gondii can cause significant infection in immunocompromised hosts.[112] A rare cause of disease in renal and liver transplant recipients,[113] toxoplasmosis more often is an infectious complication after cardiac transplantation.[26,114] The risk for cardiac recipients may be explained by tropism of the organism for cardiac muscle and subsequent donor transmission.

Reactivation of cysts within the graft occurs in the immunosuppressed recipient without previous immunity. This contrasts with adult patients with AIDS who develop reactivation disease despite the presence of antibody.

Clinical manifestations usually occur 2 to 24 weeks after transplantation and include fever, pulmonary disease, chorioretinitis, myocarditis, and neurologic disorders. Use of pyrimethamine or TMP-SMX prophylaxis has been effective in adult patients.[115,116]

Tuberculosis.

Tuberculosis is a special concern in immunosuppressed hosts, including SOT recipients. Although the development of tuberculosis is rare in US centers, an incidence of 2.4% was reported from a pediatric liver transplantation center in the United Kingdom.[117] Although most cases in this series were thought to represent primary infection acquired after transplantation, transplant recipients with a reactive tuberculin skin test (TST) result or who come from areas where tuberculosis is endemic are at increased risk for symptomatic reactivation.[118–120] The risk of reactivation tuberculosis appears greatest for patients who received no, inadequate, or incomplete prior treatment for latent infection.

A careful history of exposure, a TST, or an interferon γ release assay (for children >5 years of age)[121] and a chest radiograph are evaluated before transplantation. Patients with latent tuberculosis who received no or inadequate treatment should receive isoniazid for at least 9 months after transplantation.[117,122] When possible, treatment should begin before transplantation. Attempts at a more definitive diagnosis are indicated for a patient from an endemic area who has a negative TST result but a suspicious radiograph. Combination-drug antituberculosis therapy is indicated for those thought to have disease due to *Mycobacterium tuberculosis*. Evidence of side effects, particularly hepatotoxicity, should be monitored carefully in all pediatric transplant recipients receiving therapy for tuberculosis.

Other Opportunistic Infections.

Endemic fungal infections such as coccidioidomycosis and histoplasmosis are concerns for patients with exposure to specific geographic areas. Parasitic infections (e.g., *Trypanosoma cruzi*) have occurred in adult transplant recipients. Because patients often travel to transplantation centers distant from their homes, physicians caring for SOT candidates or recipients must be cognizant of the environmental risks for each patient. Experience with coccidioidomycosis in transplant recipients suggests that a minimum of 4 months of antifungal therapy, such as fluconazole, should be given to transplant recipients with this history.[123]

Management and Preventive Measures

Pretransplantation Evaluation

Pretransplantation evaluation permits preventive intervention and anticipation of posttransplantation complications. A history should be obtained and a physical examination performed with particular attention to previous infections, exposures, immunizations, and drug allergies. Children with CF or those with a prolonged stay under intensive care just before transplantation can be colonized with antimicrobial-resistant organisms. Pretransplantation surveillance cultures are useful in guiding subsequent empiric selection of antimicrobial agents in these patients.

Screening for tuberculosis is performed along with serologic studies for CMV, EBV, HSV, VZV, HBV, HCV, HIV, and syphilis. Other serologic tests, such as for *T. gondii* (particularly for heart transplant candidates) and hepatitis A serology for liver transplant candidates, should be performed. Donor serologic testing is performed for microbes proved to be transmitted by blood or organs (Tables 95.2 and 95.3). WNV has been transmitted by organ donation from undiagnosed cases, resulting in severe disease in the recipient. Currently, blood donor screening but not organ donor screening by WNV nucleic acid amplification test is performed routinely.[124] However, screening should be considered in specific geographic areas during periods of WNV activity.

TABLE 95.2

Screening Tests for Transplant Candidates[a]

Test and Pathogen	Comment
SEROLOGIC TESTS[b]	
HIV-1 and -2	
HTLV-1 and -2	
Hepatitis A virus	IgG and IgM screening test
Hepatitis B virus	Hepatitis B surface antigen and anti–core antibody indicate active disease; anti–hepatitis B surface antigen indicates serologic conversion after immunization
Hepatitis C virus	
Hepatitis D virus	Test if hepatitis B virus positive
CMV	IgG test; urine culture if positive
EBV	Antiviral capsid antigen IgG and EBNA
Herpes simplex virus	
Varicella-zoster virus	If history of age-appropriate vaccinations, confirmed disease, or serology is negative, consider age-appropriate immunizations, the last ≥4 weeks before anticipated transplantation
Toxoplasma gondii	Obtain for heart and heart-lung transplant candidates in particular; some centers screen all candidates
Measles virus	If serology is negative, consider immunization if ≥4 weeks anticipated before transplantation
Mumps virus	If serology is negative, consider immunization if ≥4 weeks anticipated before transplantation
Rubella virus	If serology is negative, consider immunization if ≥4 weeks anticipated before transplantation
OTHER TESTS	
Mycobacterium tuberculosis	Tuberculin skin test (TST) and/or interferon γ release assay (IGRA)
Respiratory tract pathogens	Sputum culture for patients with cystic fibrosis and other lung transplant candidates

[a] All tests performed on all candidates except where noted.

[b] IgG antibody measured except where noted.

CMV, cytomegalovirus; EBNA, Epstein-Barr virus nuclear antigen; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; HTLV, human T-lymphotropic virus; Ig, immunoglobulin.

TABLE 95.3

Recommended Screening Using Serologic Testing or Nucleotide Amplification Testing of Organ Donor[a]

Pathogen	Comment
HIV-1 and -2	Positive result contraindicates organ use (fourth-generation HIV antigen/antibody allowed for all donors in the US. HIV NAT *or* combined HIV antigen/antibody testing required for donors at increased risk for HIV, HBV, and/or HCV in the US)
Hepatitis A virus	Positive result for IgM test contraindicates organ use
Hepatitis	Obtain HBV core antibody and HBV surface antigen; result suggesting current

B virus	infection contraindicates organ use
Hepatitis C virus	Some centers use positive donor only for positive candidate (HCV NAT required on all donors in US)
CMV	Obtain IgG test; obtain urine culture if positive neonatal donor
EBV	Obtain antiviral capsid IgG and IgM
Toxoplasma gondii	Obtain for heart and heart-lung donors in particular
Treponema pallidum	Obtain treponemal-specific assays, followed by reagin test (specific test if positive) or regain test alone; positive result contraindicates organ use

[a] IgG antibody measured except where noted.

CMV, cytomegalovirus; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; Ig, immunoglobulin; NAT, nucleotide amplification testing; US, United States.

Strategies should be implemented to optimize immunizations during the pretransplantation period. This is particularly relevant for young organ transplant candidates who may not have completed their primary vaccination series. These infants should start vaccinations at 6 weeks of age and follow an accelerated schedule.[125] Immunizations sometimes are delayed and often overlooked while these children are waiting for transplantation because of their medical conditions. Despite their underlying illnesses, vaccine responses are likely to be better in the transplant candidate than in the transplant recipient.[126]

Inactivated and purified antigen vaccines are given to maximize protection before immunosuppression. Influenza vaccine should be given to children 6 months of age or older and to all family members. After receipt of pneumococcal conjugate vaccines (e.g., PCV13), 23-valent pneumococcal polysaccharide vaccine (PPSV23) should be given to those 2 years of age or older.[127] Children expected to have at least 4 weeks before transplantation should be given live virus vaccines at the earliest ages recommended.

In many centers, immunologic response is assessed by serologic testing, at least for measles, mumps, and varicella. If seroconversion is not documented, revaccination can be attempted if time permits. Living donors should be current with vaccines based on age, vaccination history, and exposure history according to the Centers for Disease Control and Prevention (CDC) annual schedule. Live virus vaccines should be avoided within 4 weeks of organ donation.[127]

Preventive Strategies

Antimicrobial and Immunoglobulin Prophylaxis

Prophylactic regimens for SOT vary by center and type of transplant. Perioperative antibiotics are used for the first 48 to 72 hours to provide protection against intraoperative soilage, septicemia, and wound infection. The choice of antimicrobial agents is dictated by the organ being transplanted, patient characteristics, expected flora, and knowledge of the antimicrobial susceptibilities of local pathogens and the patient's flora if known. Surveillance cultures of the donor bronchi or trachea also are useful in heart-lung or lung transplantation. CF patients usually require a more prolonged period of prophylaxis.

The frequency and severity of CMV infections in transplant recipients prompt consideration of prophylactic strategies.[128] Although published guidelines provide evidenced-based recommendations for adult organ transplant recipients,[29,71,129–131] definitive data to inform recommendations for pediatric SOT recipients are not available. Accordingly, various strategies are used.[132]

The CMV prevention strategies used at the Children's Hospital of Pittsburgh (CHP) vary by organ type and the donor and recipient status. All pediatric recipients deemed to be at risk for CMV disease are begun at transplantation on intravenous ganciclovir; oral valganciclovir is considered for those requiring prophylactic therapy beyond 2 weeks. High-risk (i.e., CMV-positive donor and CMV-negative recipient) intestinal transplant recipients also receive CMV IGIV at CHP.

At the completion of prophylaxis, many recipients undergo serial monitoring by quantitative blood PCR testing in what some experts have called a *hybrid* or *sequential prevention approach*. Change of virus density over time is more useful than a quantitative cutoff point. Serial quantitative monitoring of the blood CMV load (or less commonly, pp65 antigenemia assays) from the time of transplantation also has been used to inform the use of pre-emptive antiviral therapy.[71,133] In this approach, only patients demonstrating an increasing viral load are treated. Although this strategy has gained acceptance at some centers, experience in pediatric transplant recipients remains limited.

Several strategies are being explored (e.g., immunoprophylaxis, monitoring, pre-emptive therapy) to prevent EBV-associated

PTLD.[134–136] Their relative efficacies have not been established. Serial monitoring of the viral load to inform pre-emptive reductions in immunosuppression appears to be the most promising strategy.[136]

Nystatin suspension can be used in pediatric transplant recipients for the first 3 months after transplantation to prevent oropharyngeal candidiasis. TMP-SMX is used to prevent PCP. When given on a daily basis, the use of TMP-SMX also decreases the incidence of posttransplantation UTI in renal transplant recipients.[32] The duration of prophylaxis for PCP is controversial. Most cases occur during the first year after transplantation. However, because late cases occur, TMP-SMX is given indefinitely at some centers. Fungal prophylaxis against *Aspergillus* is used for children undergoing lung transplantation for various durations.

Immunizations After Transplantation

Centers use various protocols for immunization after transplantation.[137,138] The decision about when to initiate immunizations after organ transplantation should be individualized. For some patients, induction immunosuppression or recurrent treatment of rejection may require a prolonged delay in starting immunizations due to significant ongoing immunosuppression. For others who have an uncomplicated posttransplantation course, immunizations with inactivated agents may be resumed as early as 3 to 6 months after transplantation, depending on baseline immunosuppression. However, earlier use of inactivated influenza vaccine should be considered for children who were not immunized before transplantation and who undergo transplantation just before or during the influenza season.

Live vaccines usually are not administered after transplantation, although several small clinical trials evaluating the measles, mumps, and rubella (MMR) and varicella vaccines demonstrated promising safety profiles.[109,138–142] There are insufficient data regarding the safety of rotavirus vaccines to recommend their use after transplantation, and limitations of age at commencement exclude most SOT recipients from consideration.

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96

Infections in Hematopoietic Stem Cell Transplant Recipients

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Hematopoietic stem cell transplantation (HSCT) has broad indications in pediatrics, including treatment of cancer, primary immunodeficiency syndromes, bone marrow failure syndromes, hemoglobinopathies, and an assortment of genetic conditions, including inborn errors of metabolism, and nonmalignant conditions such as osteopetrosis.[1–3] Patients undergoing HSCT have increased risks of infections that are somewhat predictable based on the acquired immune deficiencies that occur after HSCT.[4–7]

Etiologic Agents

Patients who have had HSCT have immune deficiencies in the phagocytic, humoral, and cellular arms of the immune system.[4] These immune defects lead to pathogen susceptibility and infectious complications in three predictable risk periods (Fig. 96.1).[4] After the conditioning regimen, a period of neutropenia occurs for 3 to 4 weeks, during which bacteria and fungi cause most infections. Herpes simplex virus (HSV) and seasonal respiratory viral infections also can occur.[4,7,8]

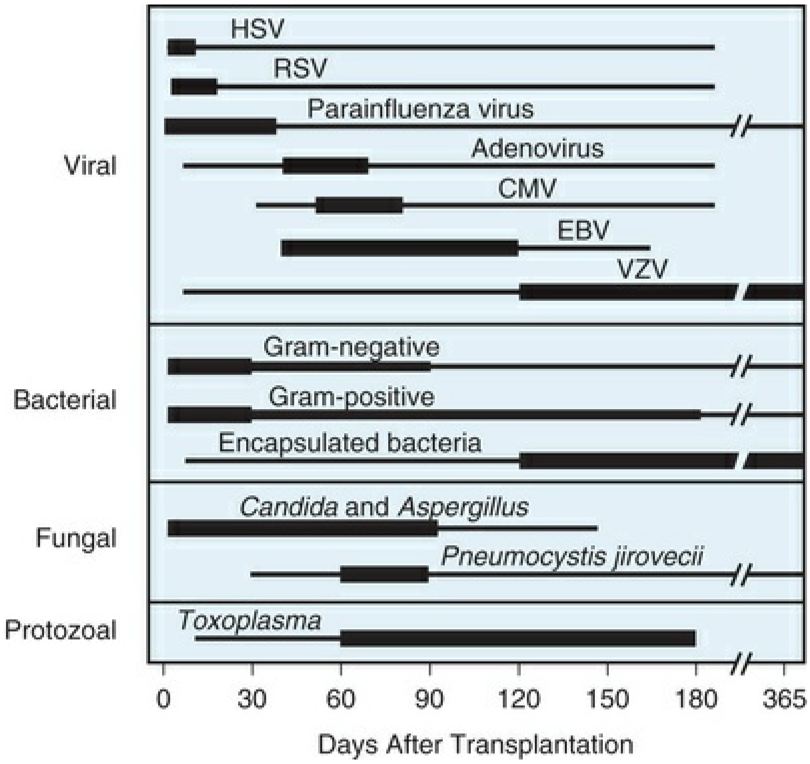

FIGURE 96.1 Temporal association of infectious agents and hematopoietic stem cell transplantation. Day 0 is the time of stem cell infusion. *Boldness* of the line denotes increasing frequency of infection with the offending agent. CMV, cytomegalovirus; EBV, Epstein–Barr virus; HSV, herpes simplex virus; RSV; respiratory syncytial virus; VZV, varicella–zoster virus.

The middle period occurs after granulocyte recovery and continues until approximately 100 days after HSCT. Infectious complications during this period are associated with profound impairment of humoral and cellular immunity. Although bacterial and fungal infections still can occur, they are much less frequent than during the neutropenic period. Cytomegalovirus (CMV) is a major infecting agent, but *Pneumocystis jirovecii* disease also can occur. With the advent of effective prophylaxis against both of these agents, the incidence of associated disease has decreased. Infections due to adenovirus and Epstein–Barr virus (EBV) can occur, especially with the use of mismatched HSCT and T-lymphocyte–

depleted HSCT.[9–11]

The late period is associated with deficits in humoral immune responses, cellular immune responses, and reticuloendothelial function begins 100 days after HSCT. Varicella-zoster virus (VZV) and encapsulated bacteria, particularly *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib), are major pathogens during this period.

Epidemiology

Among HSCT recipients, most infections are derived from their microbial flora or reactivation of latent infections. Many factors account for the high risk of infectious complications among HSCT recipients (Box 96.1). Immune deficiency associated with the underlying disease is a determinant of the degree of immune suppression.

Box 96.1

Predisposing Factors for Infectious Complications in Hematopoietic Stem Cell Transplant Recipients

- Underlying illness
- Type of transplant
- Conditioning regimen
- Infectious disease history
- Indwelling medical device
- Occurrence and severity of graft-versus-host disease
- Immunosuppressive regimen administered to prevent graft-versus-host disease
- Epidemiology of infection in hospital or transplantation care unit

Allogeneic HSCT recipients (i.e., matched unrelated donor or unrelated cord blood transplantation) are at high risk for graft-versus-host disease (GvHD), which enhances the infection rate by delaying the return of normal immune function and by ulceration of the gastrointestinal tract. Moreover, the risk of infection is directly related to the degree of donor-recipient mismatch. To abrogate GvHD, immune-suppressing medications are administered as prophylaxis. These agents increase the risk of infection by depressing the cell-mediated immune response and by disrupting mucosal barriers.

The conditioning regimen with or without concomitant irradiation compromises the immune system and can disrupt mucosal barriers. Purging of the bone marrow in autologous transplants to reduce the load of malignant cells and T-lymphocyte depletion used in allogeneic transplants to reduce the incidence of GvHD predispose the host to infection.

The serologic status of the donor and the recipient is important because many infections in transplant recipients are caused by reactivation (Table 96.1). This is most notable for the herpesviruses. CMV is a major cause of pneumonitis in allogeneic transplant recipients. Other herpesviruses, especially HSV, VZV, and EBV; *Toxoplasma gondii*; and adenovirus infections are prone to reactivate after the transplantation.

TABLE 96.1

Evaluation of Patients Before Hematopoietic Stem Cell Transplantation

Study Type	Organism or Test
Serum antibody assay	CMV
	EBV
	HSV
	VZV
	Hepatitis B (HBsAg, HBsAb, HBcAb)
	Hepatitis C
	RPR
	Human immunodeficiency virus
Other laboratory tests	Serum hepatic enzymes (ALT, AST, bilirubin)
	Renal function tests (BUN, creatinine)
	Complete blood cell count with differential leukocyte count
	Stool for ova and parasites
Tuberculosis test	Tuberculin skin test (TST); for children >5 years of age, interferon γ release assay (blood) is acceptable
Radiographic testing	Chest, posteroanterior and lateral
	Sinus series, if clinically indicated

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; cAb, core antibody; CMV, cytomegalovirus; EBV, Epstein–Barr virus; RPR, rapid plasma reagin; sAb, surface antibody; sAg, surface antigen.

All HSCT recipients have a central venous catheter (CVC) placed before transplantation, providing a potential site for infection. Patients who have other indwelling medical devices (e.g., cerebrospinal fluid shunts) have an increased risk of infection. Patients with a history of invasive aspergillosis who are undergoing HSCT require adequate antifungal prophylaxis and treatment to prevent relapse of the disease.[12]

Knowledge of the epidemiology of pathogens associated with the local hospital and the transplantation unit allows assessment of the risk of environmental organisms such as *Aspergillus* and *Legionella* species. Rates of infection can be reduced substantially by preventive mechanisms that inhibit aerosolization of organisms, such as the use of laminar flow rooms or high-efficiency particulate air (HEPA)–filtered rooms.[6]

Clinical Syndromes, Differential Diagnosis, and Clinical Approach

The approach to a patient who has had HSCT takes into account the infections that can occur during each of the risk periods (see Fig. 96.1). This provides the framework for matching possible causative agents with the clinical syndrome. Because some of these clinical syndromes are highlighted in Chapters 97 and 98, the following discussion focuses on the clinical approach to the HSCT recipient.

Early Period

Several types of infection are more likely to occur during the early period (i.e., before engraftment) of the transplantation process.

Herpes Simplex Virus Gingivostomatitis.

HSV infection occurs primarily as a result of reactivation in seropositive patients undergoing HSCT. The diagnosis is difficult because lip lesions are rare and mucosal ulcerations are similar to those that occur as a result of the conditioning regimen.

Central Venous Catheter–Related Bloodstream Infections.

During the neutropenic period, HSCT recipients are at high risk for bacterial infection, comparable with the risk for patients with cancer who develop chemotherapy-induced neutropenia. Central line–associated bloodstream infections (CLABSIs) are common because of the uniform use of indwelling CVCs in HSCT patients for administration of medications, hyperalimentation, blood products, and blood sampling. Measures to prevent CLABSIs should be followed.[6,13]

Staphylococcus epidermidis and other coagulase-negative staphylococci are the most common causes of bloodstream infections (BSIs) during the three periods after transplantation.[14–16] Other gram-positive organisms associated with BSIs in HSCT recipients include viridans streptococci and *S. aureus.*[14–16] Viridans streptococci infections have been associated with chemotherapy-induced mucositis and poor dental hygiene.[17,18] Most gram-positive catheter-related infections can be treated successfully without removal of the catheter.

Gram-negative bacillary infections occur after mucosal damage with bacterial translocation from the intestinal mucosa into the bloodstream and are the second most frequent cause of BSI. The predominant organisms in this class include *Escherichia coli, Klebsiella* spp., and *Pseudomonas aeruginosa,* although other gram-negative organisms are common.[14,16] Antibiotic resistance among these organisms is common. Catheter-related infections with some gram-negative bacilli, *Candida* spp., and *Bacillus cereus* can be problematic and require catheter removal.

Fungal Infections.

The major causes of fungal infection include *Aspergillus* spp., *Candida* spp., and agents of mucormycosis (e.g., *Mucor, Absidia, Rhizopus* spp.).[19–21] Other fungi recognized as pathogens include *Trichosporon* spp., *Fusarium* spp., *Curvularia* spp., and *Alternaría* spp.[21–23] Infection with these organisms usually occurs after a period of antibiotic therapy and correlates with the degree and duration of neutropenia. Although *Candida albicans* is the most frequent *Candida* species causing BSI, *C. tropicalis* may cause more severe disease. Other *Candida* species, including *C. glabrata, C. parapsilosis,* and *C. krusei,* also have emerged because of resistance to fluconazole, which is used as prophylaxis.[20–22]

The portal of entry for *Aspergillus* and agents of mucormycosis is the respiratory tract, as opposed to that for *Candida* spp., which is the gastrointestinal tract. *Aspergillus* is associated with sinopulmonary disease and dissemination (Fig. 96.2), but it is rarely recovered from blood cultures. Diagnosis usually depends on tissue histology and culture of material obtained from bronchoscopy, lung aspiration, or open-lung biopsy. The galactomannan assay can be useful in the early diagnosis of invasive aspergillosis in high-risk patients.[12,24]

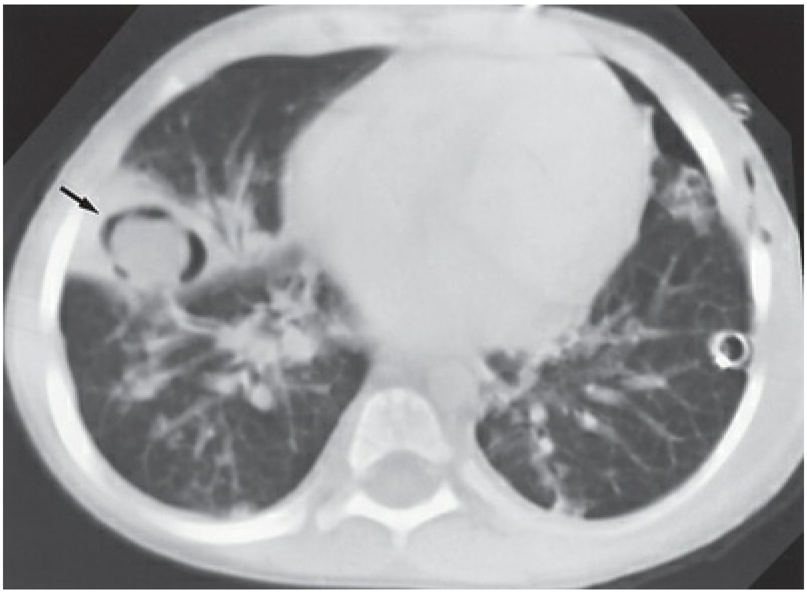

FIGURE 96.2 Invasive aspergillosis in a patient after hematopoietic stem cell transplantation. Computed tomography of the chest shows bilateral pulmonary involvement, including aspergilloma in the right middle lobe *(arrow)*.

Hemorrhagic Cystitis.

Hemorrhagic cystitis is associated with a variety of infectious and noninfectious causes (Box 96.2).[25] The onset can occur at any time during the transplantation period; chemotherapy-induced cystitis occurs soon after commencing the conditioning regimen. The most common infectious causes are polyomaviruses (BK virus and JC virus) and adenovirus.[25–27] Bacterial and fungal pathogens also must be considered.

Box 96.2

Differential Diagnosis of Hemorrhagic Cystitis in Hematopoietic Stem Cell Transplant Recipients

Infectious Causes

Virus

Adenovirus

Cytomegalovirus

Polyomaviruses, especially BK virus and JC virus

Herpes simplex virus

Bacteria

Urinary tract infection, predominantly gram-negative bacilli

Fungus

Urinary tract infection

Fungus ball

Noninfectious Causes

Chemotherapy (e.g., cyclophosphamide)

Graft-versus-host disease

Mechanical trauma from Foley catheter

Enteric Infections.

Diarrhea after transplantation is caused most commonly by mucositis and GvHD. Enteric infections can occur throughout the transplantation period. Antibiotic-associated diarrhea, including that due to *Clostridium difficile,* usually occurs during the neutropenic period, when antimicrobial agents are frequently administered. Other infecting agents, including enteric adenovirus, rotavirus, coxsackievirus, and noroviruses, should also be considered.[11,28] Infections caused by enteric viruses typically are seasonal in occurrence.

Middle Period

The middle period (i.e., early engraftment), which spans days 30 through 100 after transplantation, was once was dominated by CMV infection, but the incidence of CMV infection has diminished with the use of ganciclovir as pre-emptive therapy. Bacterial infections are less problematic during this period, except for those associated with indwelling catheters. Fungal infections occur in patients with GvHD.

Pneumonitis.

Pulmonary infiltrates can have infectious or noninfectious causes (Box 96.3). Although signs and symptoms can occur throughout the transplantation period, viral infections are more common during the early engraftment period.

Box 96.3

Causes of Pneumonitis in Hematopoietic Stem Cell Transplant Recipients

Infectious Causes

Bacteria

- Enterobacteriaceae
- *Staphylococcus aureus*
- *Legionella pneumophila*

Fungi

- *Aspergillus* species
- Mucormycosis
- *Pneumocystis jirovecii*

- *Candida* species

Viruses

- Parainfluenza types 1–4
- Adenovirus
- Respiratory syncytial virus
- Human metapneumovirus
- Cytomegalovirus
- Influenza
- Human herpesvirus 6
- Coxsackievirus and echoviruses
- Rhinovirus

Noninfectious Causes

Pulmonary damage by radiation exposure

Pulmonary damage by chemotherapeutic agents (e.g., bleomycin)

Underlying cancer

Pulmonary edema

Alveolar hemorrhage

Idiopathic interstitial pneumonia

Pulmonary vascular disease

Pneumomediastinum

CMV manifests at a median time of 40 to 50 days after the transplantation period (see Fig. 96.1). CMV most commonly occurs because of reactivation of latent virus in seropositive individuals but also can occur in seronegative patients who receive a transplant from a seropositive donor. Risk factors for CMV pneumonia include seropositivity of the donor, type of transplant (i.e., allogeneic more than autologous), human leukocyte antigen (HLA)–mismatched transplant, older age of the patient (>10 years), and development of acute GvHD.[29]

CMV infection occurs in 30% to 50% of patients undergoing HSCT; pneumonia occurs in 10% to 15% of these patients and has a mortality rate of 85%. CMV infection and disease also occur in autologous HSCT recipients, although at a much lower incidence. The clinical manifestations of CMV disease vary from asymptomatic infection to the constellation of fever, hepatitis, and leukopenia to life-threatening diseases such as interstitial pneumonitis, esophagitis, and encephalitis.[30]

Other viral causes of respiratory tract infections include adenovirus, respiratory syncytial virus (RSV), human metapneumovirus, parainfluenza virus, influenza virus, human herpesvirus 6 (HHV-6), coxsackievirus, and rhinovirus.[31–37] RSV, influenza virus, and parainfluenza virus can cause sinusitis and life-threatening pneumonia.[31,32,37]

Pneumocystis jirovecii also causes pneumonia after engraftment.[38] Clinical manifestations are similar to those in other immunocompromised hosts. The incidence of *Pneumocystis* pneumonia (PCP) has been curtailed markedly by routine prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) and pentamidine.

Adenovirus Infection.

Adenovirus infection occurs in approximately 30% of pediatric HSCT recipients and can become latent in lymphoid tissue and kidneys.[39] The most common clinical manifestations of infection include diarrhea, febrile illness, hemorrhagic cystitis, and pneumonia but also can include hepatitis and encephalitis.[39]

Toxoplasmosis.

Toxoplasmosis is a rare but almost always fatal infection after HSCT. Toxoplasmosis usually occurs 2 to 6 months after HSCT, and the central nervous system is affected most often. Symptoms include focal neurologic signs, fever, seizures, and altered mental status. Imaging of the brain typically shows multiple lesions in both hemispheres and the basal ganglia.[40,41]

Encephalopathy.

Encephalopathy is a poorly characterized complication of HSCT. It has a very poor prognosis for pediatric patients, with a mortality rate of 65% in one study.[42] Several infectious and noninfectious causes have been described (Box 96.4).[33,41,42] HHV-6 has been associated with encephalitis and delayed platelet engraftment.[35,36,43]

Box 96.4

Differential Diagnosis of Meningitis, Encephalitis, and Encephalopathy in Hematopoietic Stem Cell Transplantation Recipients

Infectious Causes

Viruses

- Adenovirus
- Human herpesvirus 6 and 7
- Polyomaviruses, especially BK virus and JC virus (progressive multifocal leukoencephalopathy)
- Herpes simplex virus and varicella-zoster virus
- Postviral (acute disseminated encephalomyelitis)

Bacteria

- *Streptococcus pneumoniae*

Fungi

- *Aspergillus* species

Protozoa

- *Toxoplasma gondii*

Noninfectious Causes

Medications (e.g., cyclosporine, amphotericin B)

Nonconvulsive seizures

Thrombotic thrombocytopenic purpura

Multiorgan system failure

Stroke

Late Period

At 100 days after transplantation, the late period begins. It lasts for 6 to 12 months or longer, depending on the complications of transplantation, especially GvHD.

Bloodstream Infection.

Bacterial infections occur less commonly during the late period, but patients continue to be immunosuppressed and susceptible to bacterial infection and BSI. Chronic GvHD augments this immunosuppression. Encapsulated bacteria, especially *S. pneumoniae* and Hib, are the most common agents responsible for bacterial infections that are not related to the existence of an indwelling catheter.[4]

Varicella-Zoster Virus Infection.

VZV infections occur in 25% to 40% of patients after HSCT.[44] Reactivation occurs more frequently in association with chronic GvHD but also has been described in patients after autologous HSCT. A prodrome of a burning sensation or pain over the involved dermatome can occur. Groups of vesicles appear in the distribution of one to three sensory dermatomes. If appropriate therapy with acyclovir is not instituted, dissemination can occur in 36% of infected patients, with a mortality rate of 10%.

Hepatitis.

Acute or chronic hepatitis can follow HSCT and has infectious and noninfectious causes (Box 96.5). Hepatitis C virus can infect HSCT recipients, and activation occurs at the time of discontinuation of immunosuppressive therapy.[45]

Box 96.5

Differential Diagnosis of Hepatitis After Hematopoietic Stem Cell Transplantation

Infectious Causes

Hepatitis viruses A, B, C, D, and E

Herpes simplex virus

Cytomegalovirus

Adenovirus

Echovirus

Epstein–Barr virus

Varicella-zoster virus

Human herpesvirus 6

Noninfectious Causes

Veno-occlusive disease

Graft-versus-host disease

Chemotherapy-induced hepatitis

Hepatopathy of total parenteral nutrition

Cholestatic liver injury due to septicemia

Nonchemotherapeutic drugs, including acetaminophen and antibiotics

Laboratory Findings and Diagnosis

Microbiologic evaluation is the gold standard for the diagnosis of infection. Microbiologic tests include blood cultures for bacteria and fungi. Blood cultures should be obtained from each lumen of the central venous line and a peripheral vein.[46] If bacteria or fungi are detected in the blood culture, use of real-time polymerase chain reaction (PCR) can reduce the time to identification of microorganisms and can identify certain antimicrobial resistance genes.[47] When clinically indicated, additional testing includes detection of viral infection by serology, culture, PCR, and immunohistochemical stains on pathologic specimens.

PCR testing is extremely helpful for the screening and diagnosis of viral infections. PCR is available for all the herpesviruses, adenovirus, and polyomaviruses.[11,26,35,48] PCR panels can be used to detect viruses from respiratory specimens, allowing rapid detection of influenza virus, RSV, parainfluenza virus, metapneumovirus, adenovirus, and others.[49,50]

Other laboratory tests are of limited value. The use of the (1-3)-β-D-glucan assay as a screening tool for fungal infection has limited value primarily because several factors can confound the interpretation of the results.[23,46,51] The galactomannan assay is best used longitudinally and only for patients at risk for invasive aspergillosis.[46] A single negative serum test should never be used to rule out invasive fungal infection.[46] Complete blood cell counts can be used to assess engraftment status. An absolute neutrophil count of $<500/\text{mm}^3$ is associated with higher incidence of bacterial infections. Serum hepatic enzyme levels and renal function tests can provide evidence of pathology from an infectious agent or insults from chemotherapy or GvHD (see Boxes 96.2 and 96.5).

Management and Presumptive Therapy

Initial management of patients with fever and neutropenia is similar to management of patients with chemotherapy-induced fever and neutropenia (see Chapter 97). An empiric antibiotic therapy regimen consists of an antipseudomonal β-lactam, cefepime or piperacillin-tazobactam, or carbapenem.[46,51] With rising antimicrobial resistance, every effort should be made to reserve carbapenems for patients with antibiotic allergy or resistant gram-negative infections.

Monotherapy has shown to be noninferior to combination therapy.[46,51] β-Lactam monotherapy avoids the use of aminoglycoside in patients who have received nephrotoxic drugs. Cefepime and piperacillin-tazobactam provide empiric coverage for *Pseudomonas aeruginosa*, other gram-negative, and susceptible gram-positive bacteria. Vancomycin may be added for high-risk patients such as those with severe mucositis, those at risk for infection with methicillin-resistant *Staphylococcus aureus* (MRSA) or other resistant gram-positive bacteria and those with severe sepsis.[46] Vancomycin should be discontinued 2 to 3 days after initiation if no gram-positive resistant bacteria are identified.[46] Choice of antibiotic regimens should take into account isolates indicating the patient's colonization status, the hospital environment, and the antimicrobial resistance pattern within the community and hospital.

For persistently febrile neutropenic patients without an identified bacterial source at 96 or more hours, empiric antifungal therapy should be initiated.[46,51] Lipid or liposomal formulations of amphotericin B, caspofungin, and voriconazole may be used as empiric therapy.[46,51] Liposomal amphotericin B may be less nephrotoxic than amphotericin B deoxycholate.[51] Azole agents such as posaconazole and voriconazole are effective for the treatment of invasive aspergillosis in immunocompromised hosts.[12,52] The echinocandins, caspofungin, and micafungin, alone or in combination therapy with an azole or amphotericin B, are effective for *Candida* spp. infections and invasive aspergillosis.[53–55] Micafungin has been evaluated for salvage therapy for pulmonary aspergillosis, but the dosage has not been established.[12]

Viral infections are treated after a diagnosis is made if therapy is available. Acyclovir is the treatment of choice for HSV and VZV infections. Orally administered valacyclovir and famciclovir also can be used to treat HSV infections. CMV pneumonitis is treated with ganciclovir and immune globulin intravenous (IGIV) to inhibit proliferation of CMV and possibly to abrogate the immune response contributing to the pneumonitis. Foscarnet can be used in cases of ganciclovir-resistant CMV or acyclovir-resistant HSV infections. Cidofovir is used to treat adenovirus and BK virus, and it is used as a second-line agent for herpesvirus infections.[56–59] There are no randomized, controlled trials of pediatric HSCT to demonstrate the efficacy of treatment of adenovirus infection.[56] In a nonrandomized, single-dose pilot study, cidofovir was well tolerated by most children, and the pharmacokinetics, other than a longer drug half-life, were similar to published adult data.[56]

Adoptive immunotherapy, by transferring virus-specific cytotoxic T lymphocytes to patients after allogeneic HSCT, has been used to treat infections caused by EBV and CMV.[60] It also is used selectively to reconstitute immune function against these viruses.[61]

For respiratory viral infections, pre-emptive aerosolized ribavirin for upper respiratory RSV infection appears to be safe and may decrease the RSV nasal viral load.[62] Ribavirin has not been proved efficacious for the treatment of parainfluenza virus infection.[63] Current evidence does not support the therapeutic use of palivizumab, an RSV-specific monoclonal antibody, because it may not prevent RSV progression to lower respiratory tract disease.[64] Limited data are available for the treatment of human metapneumovirus infection.[63] The use of neuraminidase inhibitors should be considered for patients with influenza infection, even if initiation of therapy is delayed, because a beneficial effect still may be observed.[63]

Prevention

Prevention of infectious complications is a high priority for recipients of HSCT. Prophylaxis against PCP using TMP-SMX is started after engraftment and is given orally three times per week until 6 months after transplantation. The dose is 5 to 10 mg/kg/day divided into 2 doses or 150 mg/m^2/day divided into 2 doses for 3 consecutive days per week.

For HSCT recipients with neutropenia, fluconazole, posaconazole, or micafungin is recommended during the period of risk of neutropenia for prophylaxis against candidiasis.[55,65] However, the use of fluconazole has been complicated by the emergence of resistant pathogens such as *Candida krusei* and other *Candida* species.[20] Antifungal prophylaxis using posaconazole can be recommended for HSCT recipients with GvHD who are at high risk for invasive aspergillosis.[12]

The risk of primary CMV infection can be decreased for the CMV-seronegative HSCT recipient by using leukocyte-filtered blood products for transfusion. Since the introduction of prophylaxis with ganciclovir for CMV infection, the incidence of CMV disease has been reduced substantially.[30] Pre-emptive therapy with ganciclovir or foscarnet is used in seropositive HSCT recipients or in patients receiving a transplant from a seropositive donor. The use of ganciclovir as prophylaxis can cause neutropenia, which increases the risk of a bacterial infection, but the risk of CMV pneumonia justifies its use. Pre-emptive ganciclovir therapy administered early in the course of HSCT delays the median time of onset of CMV infection from 1 to 2 months to 4 to 6 months, when immune reconstitution is more advanced.[66]

Active Immunizations

Reimmunization is important because most allogeneic and a large proportion of autologous recipients of HSCT lose their immunity to vaccine-preventable diseases. When reimmunizing transplant recipients, recent administration of immunoglobulin preparations (except monoclonal antibody to RSV) must be considered because of interference with the response to live virus vaccine (i.e., measles, mumps, rubella, and varicella).

Immunization can be started 3 months after HSCT. One schema (Table 96.2) is based on the Infectious Diseases Society of America (IDSA) guidelines for vaccination of the immunocompromised host.[67] Inactivated influenza vaccine should be administered annually in early autumn to recipients of HSCT beginning 6 months after transplantation. For people who are less than 6 months after HSCT during the influenza season, chemoprophylaxis should be considered. The live attenuated influenza vaccine should not be administered to HSCT recipients.[6,67–71] Vaccination of the donor for the benefit of the recipient is not recommended.[67] Inactivated vaccines pose no risk to HSCT recipients. Live vaccines should not be administered to HSCT patients with active GvHD or ongoing immunosuppression.[67,69]

TABLE 96.2

Immunization Schedule for Hematopoietic Stem Cell Transplant Recipients

Months After Transplantation	Vaccines
3–6	Pneumococcal[a]
6–12	DTaP,[b,c] IPV[c], Hib[c], meningococcal,[d] hepatitis A[e] and B[c], HPV[c,f]
24	MMR,[g] varicella

[a] Three doses of 13-valent conjugate vaccine should be given between 3 to 6 months post-HSCT followed by a dose of 23-valent pneumococcal vaccine at 12 months after hematopoietic stem cell transplantation (see Chapters 6 and 123).

[b] For patients ≥7 years of age, a dose of Tdap should replace DTaP, and it should be followed by 2 doses of TD or Td vaccine.

[c] Three doses between 6 to 12 months after transplantation.

[d] Two doses of meningococcal conjugate vaccine if indicated by age.

[e] Consider for patients who have chronic liver disease or chronic GvHD or those who live in areas with endemic infection.

[f] For patients between 11 and 26 years of age.

[g] Two-dose series starting 24 months after hematopoietic stem cell transplantation. Do not use live virus vaccines in patients with chronic GvHD or those receiving corticosteroid therapy.

DTaP, Diphtheria and tetanus toxoids and acellular pertussis; GvHD, graft-versus-host disease; Hib, *Haemophilus influenzae* type B; IPV, poliovirus vaccine inactivated; MMR, measles, mumps, rubella; Tdap, diphtheria, tetanus toxoid, acellular pertussis vaccine; HPV, human papillomavirus vaccine.

Passive Immunization and Immunoglobulin Use

Because of its antimicrobial and immunomodulatory effect, IGIV has been administered to HSCT recipients with no advantage in terms of survival or infection prevention.[72] The indications for passive immunization with specific immune globulin preparations (e.g., hepatitis B, tetanus, rabies) in patients after HSCT are similar to those in otherwise healthy people. Passive immunization is recommended for susceptible people with known exposure to varicella (see Chapter 205).

Key Points

Infections in Hematopoietic Stem Cell Transplantation Recipients

Epidemiology and Etiologic Agents

- Immune deficiencies after HSCT in the phagocytic, humoral, and cellular arms of the immune system cause susceptibility to infectious agents in three distinct periods.

- Most infections are derived from the patient's microbial flora or reactivation of a latent infection.

- ▪ Allogeneic HSCT recipients are at higher risk for infection than autologous HSCT recipients.

Clinical Syndromes, Differential Diagnosis, and Clinical Approach

- Approach according to the risk period after transplantation

- ▪ Early period (i.e., before engraftment): HSV, CLABSI, and fungal infection

- ▪ Middle period (i.e., early engraftment): CLABSI, adenovirus, CMV, pneumonitis, and toxoplasmosis

- ▪ Late period: CLABSI, VZV, and hepatitis

Laboratory Findings and Diagnosis

- Microbiologic testing is the gold standard for diagnosis.

- PCR testing is helpful for screening and confirmation of viral infections.

Management and Presumptive Therapy

- Manage HSCT patients as for febrile neutropenic patients with cancer.

- Begin antifungal therapy if fever continues ≥96 hours after commencement of antibiotic therapy.

- Begin antiviral treatment when the diagnosis is made.

Prevention

- Antimicrobial prophylaxis is important to prevent certain infections (e.g., PCP, CMV).

- Reimmunization is important because most recipients of HSCT lose prior immunity to vaccine-preventable diseases.

CLABSI, Central line–associated bloodstream infection; CMV, cytomegalovirus; HSCT, hematopoietic stem cell transplantation; HSV, herpes simplex virus; PCP, *Pneumocystis* pneumonia; PCR, polymerase chain reaction; VZV, varicella-zoster virus.

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P

Infections and Cancer

OUTLINE

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97

Fever and Granulocytopenia

Monica I. Ardura, Andrew Y. Koh

Infection remains a major cause of morbidity in children with cancer. Fever and neutropenia are among the most common complications of cancer therapy in children. The use of empiric antimicrobial regimens in this patient population began with the observation that febrile neutropenic patients with cancer who had potentially fatal infections could not be distinguished from patients who had less serious or noninfectious illnesses and has since led to a reduction in infection-related morbidity and mortality rates.

Epidemiology and Outcome

Fever may be the first or only manifestation of an infection in a neutropenic patient. Studies completed in the late 1970s suggested that more than one half of children with fever and neutropenia had a clinically or microbiologically proven infection, with a causative agent documented in almost two thirds of infectious episodes.[1] More recent data demonstrate that the incidence of microbiologically proven infection in febrile and neutropenic children is lower and that bloodstream infection (BSI) is the most frequently documented infection. (10%–40%)[2–7] In several large series published in the 1990s, the mortality rates for febrile and neutropenic patients ranged from 1% to 19%.[8–13] Fever without documented cause now accounts for approximately two thirds of febrile episodes, perhaps because of earlier use of empiric antibiotic therapy. Neutropenic patients can have serious infections in the absence of fever. Therefore, neutropenic patients who develop signs or symptoms suggestive of a localized infection should be managed according to the same principles as neutropenic patients who present with fever. The same is true for afebrile neutropenic patients with hypothermia, hemodynamic instability, or localized pain despite the lack of erythema, purulence, or swelling because signs of an inflammatory response may be attenuated in the setting of severe neutropenia.

Children with cancer differ from their adult counterparts in several ways. Febrile children often do not have a clinically apparent site of infection. When a clinically apparent site is present, children are more likely than adults to have upper respiratory tract findings. Whereas the incidence of BSI is similar in children and adults, the rate of death during fever and neutropenia is 1% in children compared with 4% in adults.[8]

Pathogenesis and Etiologic Factors

The interactions of complex factors in cancer and its treatment lead to the high risk for serious infection in patients undergoing cancer treatment (see Tables 97.1 to 97.4).

TABLE 97.1

Predominant Pathogens Infecting Children With Anatomic Disruptions

Site	Bacteria	Fungi	Other
Oral cavity	α-Hemolytic streptococci Oral anaerobes	*Candida* spp.	Herpes simplex virus
Esophagus	Staphylococci Other colonizing organisms	*Candida* spp.	Herpes simplex virus Cytomegalovirus
Lower gastrointestinal tract	Gram-positive: group D streptococci Gram-negative: enteric organisms Anaerobes: *Bacteroides fragilis*, *Clostridium perfringens*	*Candida* spp.	Cytomegalovirus *Strongyloides stercoralis*
Skin (intravenous catheter)	Gram-positive: staphylococci, streptococci, corynebacteria, *Bacillus* spp.	*Candida* spp. *Aspergillus* spp. *Malassezia furfur*	

	Gram-negative: *Pseudomonas aeruginosa*, enteric organisms		
Urinary tract	Gram-positive: group D streptococci Gram-negative: enteric organisms, *P. aeruginosa*	*Candida* spp.	

TABLE 97.2

Predominant Pathogens Infecting Children With Neutropenia

Category	Organisms
Bacteria	Gram-negative enteric organisms: *Escherichia coli, Klebsiella pneumoniae, Enterobacter* spp., *Citrobacter* spp., *Pseudomonas aeruginosa, Bacteroides* spp.
	Gram-positive: Staphylococci: coagulase-negative, coagulase-positive Streptococci: group D, α-hemolytic, anaerobic Clostridia
Fungi	*Candida* spp. *(C. albicans, C. tropicalis, other species)*
	Aspergillus spp. *(A. fumigatus, A. flavus)*

TABLE 97.3

Predominant Pathogens Infecting Children With Defects in Cell-Mediated Immunity

Bacteria	Fungi	Viruses	Other
Legionella	*Cryptococcus neoformans*	Varicella-zoster virus	*Toxoplasma gondii*
Nocardia asteroides	*Histoplasma capsulatum*	Herpes simplex virus	*Cryptosporidium*
Salmonella spp.	*Coccidioides immitis*	Cytomegalovirus	*Strongyloides stercoralis*
Mycobacteria	*Candida* spp.	Epstein-Barr virus	
Mycobacterium tuberculosis and nontuberculous mycobacteria	*Pneumocystis jirovecii*	Hepatitis B	
Disseminated bacille Calmette-Guérin			Disseminated infection from live virus vaccines (vaccinia, measles, rubella, mumps, yellow fever, or poliovirus)

TABLE 97.4

Predominant Pathogens Infecting Children With Defects in Immunoglobulins, Complement, and Splenic Function[a]

Defect	Organisms
Immunoglobulin abnormalities	Gram-positive:

	Streptococcus pneumoniae
	Staphylococcus aureus
	Gram-negative:
	Haemophilus influenzae
	Neisseria spp.
	Enteric organisms
	Viruses: enteroviruses (including polioviruses)
	Protozoa: *Giardia lamblia*
Complement abnormalities	
C3–C5	Gram-positive:
	S. pneumoniae
	Staphylococcus spp.
	Gram-negative:
	H. influenzae
	Neisseria spp.
	Enteric organisms
C5–C9	*Neisseria* spp.:
	N. gonorrhoeae
	N. meningitidis
Splenectomy	Gram-positive:
	S. pneumoniae
	Capnocytophaga canimorsus (formerly known as DF2 bacillus)
	Gram-negative:
	H. influenzae
	Salmonella spp.
	Babesia spp.

[a] See also Chapters 102, 103, and 106.

Anatomic Disruptions and Devices

Alteration of skin or mucosal integrity or obstruction of an organ or body cavity predisposes to infection (Table 97.1). Cytotoxic chemotherapy damages oral and gastrointestinal tract mucosa while concomitantly inducing neutropenia. Devices that violate skin integrity, such as central venous catheters (CVCs) and peripherally inserted central catheters, also significantly increase (~40-fold) the risk of infection.[14,15] Depending on the specific patient population, techniques of catheter insertion and care, treatment regimens, and the definition of CVC-related infections, infections occur in 9% to 80% of patients.[16,17]

Some studies have suggested that the incidence of infection is lower for patients with totally implanted devices (e.g., Port-A-Cath, Smiths Medical, Dublin, Ohio) compared with patients with external, tunneled CVCs (Hickman-Broviac–type catheters).[18–20] A prospective, randomized study, however, failed to demonstrate a difference in rates of infection.[21] The use of a central catheter for delivery of parenteral nutrition increases the risk of infection by ~2.4 fold, independent of the type of catheter used.[22] A systematic review of published studies concluded that all types of intravascular catheters pose a risk for local and catheter-associated BSI and that appropriate guidelines for prevention of catheter-related infections, from insertion to maintenance, should be followed.[23,24]

Devices other than CVCs also have been associated with an increased risk of infection in immunocompromised patients. Limb-sparing procedures for patients with osteosarcoma use prosthetic bone and joint hardware that has been associated with high rate of infections.[25] In some institutions, children with such prosthetic devices are not considered candidates for permanent CVCs because of the higher risk of BSI and seeding of the prosthesis. The relative risk of infection in children with limb prostheses is not known, and optimal management has not been defined. With any device, the importance of microbial biofilm formation and the mechanisms by which these organisms may perpetuate seeding of the bloodstream and promote emergence of antibiotic resistance cannot be overemphasized.[26,27]

Neutropenia

The most important risk factor in the development of infections in children with cancer is neutropenia resulting from cytotoxic chemotherapy. The relationship between neutrophil numbers and the risk of infectious complications in patients with leukemia was first described in 1966 by Bodey and colleagues[28] at the National Cancer Institute. The investigators concluded the following: (1) the risk of infection was inversely related to the absolute neutrophil count (ANC), with infections being more prevalent when the ANC fell to less than 1000 cells/mm^3 and increasing in likelihood and severity with ANC <500 cells/mm^3 and further with ANC ≤100 cells/mm^3; (2) relapse of leukemia was associated with higher rates of infection than remission at all levels of neutrophil count; and (3) the duration of neutropenia was the single most important factor in predicting risk of infection. Severe neutropenia that lasted longer than 3 weeks was associated with a 100% risk of infection and the highest mortality rates.[28] These observations were confirmed over ensuing years and led to the current approach to management of patients with fever and neutropenia.[29–31] Organisms causing infections in children with neutropenia are listed in Table 97.2.

Normal Microbiota

Commensal microbes stimulate the gastrointestinal epithelium to produce antimicrobial peptides (AMPs) that act as a first line of defense against invading pathogenic bacteria.[32] When indigenous commensals are depleted after antibiotic administration, select pathogenic bacteria (e.g., vancomycin-resistant enterococci [VRE]) can overgrow and cause invasive disease.[33] Stimulating intestinal toll-like receptor 4 (TLR4) by oral administration of lipopolysaccharide,[33] or stimulating TLR5 with purified flagellin,[34] reinduces AMP RegIIIγ and results in a decrease of VRE in the gastrointestinal tract. Thus, methods for maintaining microbial homeostasis during chemotherapy and antibiotic therapies may provide a novel means for preventing colonization and dissemination of pathogenic microbes.

Other Defects

Repeated cycles of cytotoxic therapy not only decrease circulating neutrophils but also deplete lymphocytes and natural killer cells.[35] Reduced lymphocyte subset populations were associated with opportunistic infections in a group of patients receiving dose-intensive chemotherapeutic regimens.[35] Because TLRs are key components of innate host response, responsible for recognition of pathogens and cytokine response to surface molecules,[36,37] it is not surprising that an association exists between donor TLR4 haplotype and the risk of invasive aspergillosis.[38] Similarly, other TLR4 single nucleotide polymorphisms have been associated with susceptibility to infections caused by gram-negative bacteria,[39] *Candida albicans*,[40] and respiratory syncytial virus.[41] Organisms causing infections in children that are related to defects in cell-mediated immunity are listed in Table 97.3, and organisms related to immunoglobulin and complement abnormalities, as well as splenic dysfunction (or absence), are listed in Table 97.4.

Etiologic Agents

Infections in immunocompromised children can result from bacteria, fungi, viruses, or protozoa. Changes in the epidemiology of these infections in the neutropenic host are multifactorial, including fluctuations in antimicrobial practices, increased use of indwelling devices, more intensive chemotherapy regimens, evolving infection control measures, and emergence of resistant organisms.

Bacteria

Infections in immunocompromised children can result from organisms from the host's endogenous bacterial flora. With hospitalization and antibiotic therapy (including antineoplastic chemotherapy), a shift in normal flora occurs to include potentially pathogenic gram-negative bacteria.[42] Underlying disease and exposure to broad-spectrum antibiotics likely contribute to changes in microbial populations.[43] Approximately one half of pathogens responsible for documented infections are acquired by oncology patients after initial admission to the hospital,[44] including antibiotic-resistant gram-positive and gram-negative organisms.

The relative incidence of gram-negative infections has decreased since the early 1980s, whereas the incidence of gram-positive infections in this population has risen.[8,45] Currently, gram-positive organisms, particularly coagulase-negative staphylococci, *Staphylococcus aureus* (and especially methicillin-resistant *S. aureus* [MRSA]), α-hemolytic streptococci, enterococci, and *Corynebacterium* spp., account for more than one half of documented infections in patients with cancer. *Escherichia coli, Pseudomonas* species, and the *Enterobacter-Klebsiella-Serratia* group are identified in a smaller but significant proportion of patients.[8,45–47]

Although BSI with gram-positive organisms generally is associated with lower mortality rates than is BSI associated with gram-negative organisms, the syndrome of α-hemolytic streptococcal septicemia deserves special attention.[48] The α-hemolytic streptococci (viridans group streptococci) are normal inhabitants of the oral cavity and the gastrointestinal and respiratory tracts.[49] Neutropenic patients with acute myeloid leukemia, those receiving cytosine arabinoside, and hematopoietic stem cell transplant (HSCT) recipients are at highest risk of viridans streptococcal sepsis syndrome.[50,51] *Streptococcus mitis* and *Streptococcus sanguis* are the most commonly associated α-hemolytic streptococci. Septic shock and respiratory distress can progress rapidly to death; mortality rates range from 10% to 100%.[52,53] Fever often persists despite sterilization of blood, and patients can progress to shock after 48 to 72 hours despite clearance of BSI. Secondary myositis and even myocarditis rarely have been reported with α-hemolytic streptococcal BSI.[54,55] Penicillin resistance is not uncommon among these previously susceptible organisms.[47,56] Increased use of systemic antibiotics for treatment and prophylaxis (especially with fluoroquinolones and trimethoprim-sulfamethoxazole) has led to an increase in penicillin-resistant α-hemolytic streptococci. It is important to know local antibiotic resistance patterns and to request antimicrobial susceptibility testing on all clinically relevant isolates.

Widespread use of vancomycin has been linked with increasingly vancomycin-resistant *Enterococcus* spp. and *Staphylococcus* spp.[57,58] Community-acquired MRSA (CA-MRSA) is an important cause of invasive infections including sepsis,[59] necrotizing fasciitis,[60] and pneumonia[61] in adults and children without recognized risk factors.[62,63] *S. aureus* can cause serious infections in pediatric oncology patients.[64,65] Increasing prevalence of CA-MRSA nasal and rectal colonization was described in children at a large US pediatric cancer center; patients colonized with Panton-Valentine leukocidin–positive strains are more likely to develop infection and recurring infection. Although CA-MRSA isolates are likely to be susceptible to non–β-lactam antibiotics (such as clindamycin, trimethoprim-sulfamethoxazole, and rifampin), macrolide-lincosamide-streptogramin resistance and constitutive and inducible resistance to clindamycin have occurred at variable prevalence geographically.[63,66]

Infections resulting from gram-negative bacilli, particularly *Pseudomonas aeruginosa* BSI, continue to carry high mortality rates.[67] Therefore, although these infections have become less frequent than gram-positive infections, empiric antimicrobial coverage, especially for *P. aeruginosa,* remains important in children with fever and neutropenia. Increasing antibiotic resistance of gram-negative organisms to β-lactam agents (e.g., extended-spectrum penicillins and cephalosporins) and to carbapenems, aminoglycosides, and quinolones has been observed.[68] Of particular concern are *Enterobacter* and *Serratia* spp., which are prone to rapid development of resistance caused by inducible β-lactamases.

Infections with anaerobic organisms occur infrequently in febrile, neutropenic patients despite the predominance of these organisms in the normal gut microbiota. Nonetheless, anaerobic infections, often polymicrobial, can cause BSI (<5%) with associated high mortality rates.[69,70] The most commonly isolated anaerobic organisms are *Bacteroides* spp. and *Clostridium* spp.,[71,72] which have been associated with specific syndromes, such as peritonitis, abdominal or pelvic abscesses, and perirectal cellulitis.[73,74] Anaerobes also contribute to infections of the oral cavity, especially necrotizing gingivitis. *Clostridium perfringens and Clostridium septicum* can cause a devastating infection characterized by septic shock and rapidly progressive necrotizing fasciitis with myonecrosis. Infection may arise from a traumatic or surgical wound or spontaneously from an abdominal source, such as necrotic bowel. Pseudomembranous colitis caused by toxins of *Clostridium difficile* can result in a wide spectrum of clinical manifestations, from mild diarrhea and cramping to toxic megacolon and intestinal perforation. *Fusobacterium* spp. BSI has been associated with severe mucositis and fluoroquinolone prophylaxis.[75] The possibility of an anaerobic infection should be considered in neutropenic patients with severe mucositis, abdominal or perirectal symptoms, or necrotic skin lesions or in patients who remain hemodynamically unstable despite broad antibiotic therapy that does not cover anaerobic bacteria (e.g., cefepime).

Fungi

With improved treatment and better survival from bacterial infections in febrile neutropenic patients, prevention and treatment of fungal infections have great importance, especially in patients with prolonged neutropenia. In the 1980s, investigators noted that prolonged or relapsing fever that occurred during ≥7 days of antibiotic therapy for fever and neutropenia was associated with invasive fungal infections and that empiric antifungal therapy improved outcomes.[76] Fungi are rarely the cause of the initial episode of fever and neutropenia.[2,77]

Historically, *C. albicans* was the most common species isolated. It accounted for approximately 50% of isolates, with non-*albicans Candida* species (e.g., *Candida tropicalis, Candida parapsilosis, Candida krusei*, and *Candida glabrata*) making up the remaining one half of isolates.[78–80] More recent prospective pediatric studies demonstrated the emergence of non-*albicans Candida* species causing invasive disease.[81] This changing pattern may reflect, in part, the use of oral antifungal agents prophylactically, as well as factors related to the host and fungal species.[82–84]

Aspergillus spp. are the second most common causes of invasive fungal infections in neutropenic patients in most hospitals. *Aspergillus fumigatus* and *Aspergillus flavus* are the species most frequently isolated. Other fungi that cause serious infection in neutropenic children are *Mucor, Fusarium, Trichosporon* spp., and the Phaeohyphomyces (also known as dematiaceous molds including *Curvularia, Bipolaris, Alternaria*, and *Exserohilum*). These organisms are not part of the normal flora of the respiratory or gastrointestinal tract, but after colonization, they can become invasive when chemotherapy renders the host susceptible. These molds are ubiquitous in the environment; temporal relationships between construction and an increase in invasive mold infection in neutropenic patients have been described.[85–88] Infection with yeasts such as *Histoplasma, Cryptococcus*, and *Coccidioides* are more commonly associated with defects of cell-mediated immunity, but they can occur in neutropenic patients as primary infections or reactivated disease.

Pneumocystis jirovecii (formerly *Pneumocystis carinii*) is a major fungal pathogen in children with cancer.[89] In patients with cancer, *P. jirovecii* infection generally is caused by reactivation of latent organisms. It appears to be associated with more rapidly progressive pneumonia than that seen in adults and older children infected with human immunodeficiency virus (HIV).[90,91] The risk of *Pneumocystis* pneumonia (PCP) and the severity of disease are related to the underlying malignant disease, the intensity of immunosuppressive regimens including corticosteroids (a feature that explains particular occurrence in children with leukemia, lymphomas, and brain tumors), and the use of prophylaxis. Symptomatic disease has been strongly associated with tapering and discontinuation of corticosteroids.[91–93] The possibility of PCP should be considered in children with cancer who have diffuse pulmonary infiltrates and hypoxemia. Confirmation of the diagnosis requires detection in respiratory specimens by using traditional microscopy with staining demonstrating cysts or trophozoites in sputum or bronchoalveolar lavage specimens. The use of PCP polymerase chain reaction and (1,3)-β-D glucan assays on respiratory fluid samples has improved diagnostic yields in patients with hematologic malignant diseases.

Viruses

Herpes simplex virus and varicella-zoster virus were identified as the most common viral pathogens in a prospective study of children with leukemia.[94] The incidence of viral infections is higher in children undergoing induction or during relapse than during remission.[95] Other viruses, including influenza virus, parainfluenza virus, cytomegalovirus, human herpesviruses 6 and 8, adenovirus, measles virus, respiratory syncytial virus, and enteroviruses, also can lead to substantial morbidity. Although some viral illnesses (e.g., dermatomal zoster or herpetic stomatitis) cause clinically recognizable lesions that are easily confirmable, others illnesses have nonspecific symptoms or localize to areas that are less accessible (e.g., cytomegalovirus hepatitis or viral encephalitis). Common respiratory tract viruses can cause lower respiratory tract infection. Respiratory viral infection has been documented in 34% to 57% of febrile, neutropenic patients.[3,96,97]

Parasites

Parasites such as *Toxoplasma gondii* and *Cryptosporidium* rarely occur in children with cancer, but they can be associated with significant morbidity. *T. gondii* can cause fulminant disseminated disease but most often is localized to the central nervous system. Stem cell transplant recipients are at the highest risk of developing toxoplasmosis of the central nervous system.[98] *Cryptosporidium* should always be considered in any pediatric patient with cancer who has severe or prolonged diarrhea.[99]

Differential Diagnosis and Clinical Approach to Diagnosis

Many oncology centers have adopted a standardized approach to the evaluation of febrile, neutropenic patients to ensure that all potentially dangerous causes of fever are considered (Box 97.1). *Neutropenia* is defined as an existing ANC of fewer than 500 neutrophils/mm^3 or ANC <1000 neutrophils/mm^3 and expected decrease to <500 neutrophils/mm^3 in the subsequent 48 hours. Severe or profound neutropenia describes an ANC <100 cell/mm^3. *Fever* is defined as a single oral-equivalent temperature of at least 38.3°C (101°F), or a temperature recorded that is higher than 38.0°C (100.4°F) sustained over a 1-hour period. Documentation of fever by the patient or caretaker should always be accepted, even if the child is afebrile at the time of medical evaluation. Some life-threatening infections can occur in the absence of fever in profoundly neutropenic patients with localizing signs or symptoms (e.g., right lower quadrant abdominal pain).[100]

Box 97.1

Initial Diagnostic Evaluation of Children With Fever and Neutropenia

Careful medical history

Physical examination (which should be repeated at least daily in febrile neutropenic patients) with attention to the skin, perirectal area, and other mucosal sites

Specimens for diagnostic evaluation:

- Blood: specimens from every lumen or accessed port of intravascular catheters for blood culture; consideration of specimen from a peripheral site
- Urine for culture

- Respiratory secretions: for bacteria and viruses if symptoms are present
- Any site with clinical signs of infection, including bacterial or fungal cultures from skin sites, *Clostridium difficile* toxin assay if diarrhea present

Chest imaging if lower respiratory tract symptoms

- Other imaging studies or diagnostic procedures as clinically indicated
- Sinus radiograph or computed tomography
- Abdominal ultrasonography or computed tomography

The diagnostic evaluation of the child with fever and neutropenia should be guided by clinical history and physical examination findings. A history of possible infectious exposures should be sought, and careful physical examination should be repeated frequently throughout the period of observation and empiric treatment. Unfortunately, such examinations identify a potential site of serious infection in a minority of patients. The traditional markers of inflammation can be muted or even absent in children who lack neutrophils, and thus the usual manifestations of serious infection, such as chills, rigors, and "toxic appearance," may not help distinguish patients with BSI or other serious infection. Examination of the oral and nasal cavity, perirectal area, and skin (including the CVC site) must not be overlooked.[2,13]

Specimens for culture from suggestive sites should be obtained. Blood cultures should be obtained from each lumen of the CVC before institution of antibiotic therapy. The utility of concomitant blood cultures from a peripheral site is controversial. Peripheral cultures may be useful in diagnosing CVC-associated BSI and aiding in CVC management (e.g., salvage versus removal).[101] The proportion of true BSI detected by peripheral blood cultures when CVC cultures were negative was 13% (95% confidence interval, 8% to 18%) in one study.[31] Optimal blood culture volume should always be obtained to ensure an adequate diagnostic yield. Because urinary tract infections are among the most prevalent infections (with frequencies of 8.6% during fever and neutropenia episodes) and can be subclinical, urine should be obtained for culture from all patients. Pyuria can be absent in children with neutropenia.[13,102] During seasonal outbreaks of viral infection of the respiratory tract, a throat or nasopharyngeal specimen should be obtained for viral antigen or polymerase chain reaction testing. Pulmonary imaging should be considered at the time of initial evaluation of fever and neutropenia in patients with lower respiratory tract symptoms; the yield in asymptomatic neutropenic patients is small.[103,104] Pulmonary infiltrates not present initially may become apparent with bone marrow recovery, when neutrophils are recruited to a site of previously "silent" infection.

The value of surveillance cultures in patients undergoing chemotherapy has been studied. In a survey of 652 episodes of fever and neutropenia in which surveillance cultures of nose, throat, urine, and stool were performed, 62% of patients who developed BSI had been colonized with the infecting organism. However, management of these patients was not substantially influenced by this information because multiple potential pathogens often were isolated from the same site. No single site was predictive of BSI, and the blood isolate frequently was identified before results of surveillance cultures were available.[105]

Management and Empiric Therapy

An empiric antibiotic regimen for febrile neutropenic episodes should: (1) provide a broad spectrum of activity against a variety of pathogenic organisms, including but not limited to *Pseudomonas*; (2) be bactericidal; and (3) have low potential for adverse effects or emergence of resistant organisms. Because large randomized controlled trials to determine the optimal management of children with fever and neutropenia are lacking, recommendations mainly are derived from studies conducted in adults, consensus guidelines, and historical data.

Empiric Therapeutic Regimens

Empiric, broad-spectrum antibiotic therapy continues to be the standard of care for patients with fever and neutropenia. Numerous regimens have been evaluated over the last several decades, with most large comparative clinical efficacy trials including both adults and children. No single empiric regimen has demonstrable superiority; many of the regimens studied are similar in efficacy, although study designs and definitions of success have not been uniform. Evidence-based clinical practice guidelines are published[30,31]; however, the choice of a specific agent or combination should be based on multiple factors including the patient's clinical presentation (severity, manifestation, risk factors), previous history of infection or colonization with resistant organisms, prophylactic antimicrobial regimens, and specific patterns of infection and susceptibility profiles in one's own institution.

Historically, empiric regimens consisted of 2 agents with antipseudomonal activity. Monotherapy was pioneered by the National Cancer Institute to simplify antibiotic regimens and reduce toxicity in children who often receive complex chemotherapeutic regimens. Monotherapy with ceftazidime had equivalent efficacy (i.e., survival of patients with fever and neutropenia) compared with combination regimens regardless of whether a site of infection could be documented. However, many patients required modifications of the initial regimen if they had a documented site of infection or >7 days of neutropenia. Additional studies evaluating cephalosporins (e.g., cefepime[106–108]), as well as carbapenems,[9,109,110–112] as single agents for fever and neutropenia showed comparable efficacy and provided options for management. In both adults and children, monotherapy with an antipseudomonal antibiotic was found to be as effective as combination regimens and was associated with fewer toxicities.[113,114] Furthermore, no differences were reported in treatment failures, adverse events, or mortality rates when comparing monotherapy with antipseudomonal penicillins versus antipseudomonal cephalosporins or carbapenems. Ceftazidime may no longer be a reliable agent in many centers because of increasing resistance of gram-negative bacteria and poor coverage against gram-positive pathogens. Piperacillin-tazobactam, cefepime, or meropenem is used for first-line empiric monotherapy in high-risk neutropenic patients with fever who are otherwise stable.[30,31] A patient's clinical syndrome should further guide antibiotic choice (e.g., to use piperacillin-tazobactam or meropenem compared with cefepime for suspected intra-abdominal infection).

In patients who are clinically unstable, initiation of additional empiric antibiotics is prudent pending results of cultures and clinical progression. Routine use of vancomycin as part of the empiric antimicrobial regimen in patients with fever and neutropenia is not recommended. Results from randomized trials concluded that empiric use of vancomycin did not improve treatment success, shorten duration of fever, or improve mortality rates, and it was associated with significantly more adverse events, including nephrotoxicity.[115,116] Vancomycin should be chosen empirically for patients with higher likelihood of gram-positive infections, including patients who have hemodynamic instability, evidence of skin or soft tissue infection or catheter-associated pocket or tunnel infection, lobar pneumonia, or a history of previous infection or colonization with MRSA. Another indication for the addition of vancomycin is for patients with severe mucositis who have been receiving fluoroquinolone prophylaxis.[30] The addition of a second antibiotic with activity against gram-negative bacteria should be considered in patients who are clinically unstable or if antimicrobial resistance is suspected (e.g., history of previous colonization with multidrug-resistant gram-negative bacteria). A meta-analysis of randomized controlled trials comparing ciprofloxacin plus β-lactam with aminoglycoside plus β-lactam combinations for the empiric treatment of febrile neutropenia showed comparable or better outcomes with the ciprofloxacin plus β-lactam combination. The authors of this analysis suggested that this combination should be considered only for patients who have not received a fluoroquinolone for prevention of infections and in settings in which fluoroquinolone resistance is not common.[117]

Duration and Modification of Therapy

Modifications of initial empiric antimicrobial therapy should be guided by clinical evolution and microbiologic data. Continued fever alone in an asymptomatic and clinically stable patient without an identified focus of infection does not warrant the addition of antibiotics to the empiric regimen. Conversely, patients who remain hemodynamically unstable after initial empiric antibiotics should have antibiotic coverage broadened to provide additional gram-negative, gram-positive, anaerobic, and fungal coverage. Even when a bacterial pathogen is isolated from a febrile, neutropenic child, evidence supports the continuation of broad-spectrum antibiotic therapy.[118] Obtaining tissue may be necessary for both diagnosis and optimal antimicrobial therapy when fever and neutropenia persist, radiographic imaging is abnormal, and no corroborative microbiologic confirmation occurs. Specific clinical events that may require modification of the initial treatment regimen are described in Chapter 98; recommendations are summarized in Table 97.5.

TABLE 97.5

Modifications of Antimicrobial Therapy During Fever and Neutropenia

Clinical Event	Possible Modifications in Therapy
Breakthrough bacteremia on empiric regimen	If gram-positive isolate, add vancomycin or other gram- positive agent in patient with known history of VRE
	If gram-negative isolate (presumably resistant), change regimen and consider addition of second gram-negative agent
Catheter-associated soft tissue infection	Add vancomycin
Severe oral mucositis or necrotizing gingivitis	Add agent active against β-lactamase–producing anaerobic bacteria; consider acyclovir
Esophagitis	Clotrimazole, ketoconazole, fluconazole, voriconazole, caspofungin, or amphotericin B; consider acyclovir
Diffuse or interstitial pneumonitis	Trimethoprim-sulfamethoxazole; macrolide
New infiltrate in neutropenic patient receiving antibiotics	If neutrophil count rising, can observe If neutrophil count not recovering or has been severe and prolonged, pursue further diagnostics, including possible biopsy; if biopsy not possible, consider agent active against molds
Perianal cellulitis	Add agent active against β-lactamase–producing anaerobic bacteria if not already included in broad-spectrum therapy
Prolonged fever and neutropenia	After 1 week of antibiotics, add antifungal agent

VRE, vancomycin-resistant enterococci.

The duration of antibiotic therapy depends on several factors, including isolation of the presumed pathogen, clinical identification of a presumed infectious process, duration of fever and neutropenia, and the patient's schedule of chemotherapy. Patients who had additional antibiotics (e.g., vancomycin and a second gram-negative agent) added to their empiric regimen, who remain clinically stable without a clinical focus of infection, and whose culture results are negative at 48 to 72 hours can have the additional antibiotics discontinued. If the preantibiotic blood and catheter culture results are negative and no site of infection is determined, the additional gram-positive and gram-negative specific antibiotics may be discontinued, and monotherapy with an antipseudomonal antibiotic may be continued evidence of resolution of neutropenia is noted. If the culture results are positive, a therapeutic course is warranted.

Traditionally, empiric therapy is continued until the ANC has returned to >500 cells/mm^3 and the patient is afebrile.[30] For patients whose infection has been documented (either microbiologically or clinically) and whose resolution of fever and neutropenia has been prompt, the course of antibiotic treatment should be appropriate for the infection identified. Parenteral antibiotics are preferred for patients with serious infections. For patients without a defined site of infection who show signs of bone marrow recovery, antibiotics usually can be discontinued, even before the ANC reaches 500/mm^3. The optimal duration of antibiotic therapy in high-risk patients without a clinical or microbiologic focus of infection who remain profoundly neutropenic is unknown.

Empiric Antifungal Therapy

Patients at high risk for invasive fungal infections include those with acute myeloid leukemia, patients with relapsed acute lymphoblastic leukemia, those receiving intensive myelosuppressive chemotherapy, and HSCT recipients. Additive risk factors include persistent fever despite prolonged broad-spectrum antibiotics and severe or prolonged neutropenia. Fungi have emerged as important causes of infections in patients with prolonged neutropenia by affecting 9% to 31% of this population.[76,119]

Historically, amphotericin B was the only available systemic antifungal agent available. Its use in empiric regimens for prolonged or recurrent fever in neutropenic patients reduced the incidence of documented fungal infections and attributable mortality rates.[76] As a result, antifungal therapy became standard of care, and current guidelines recommend the use of empiric antifungal agents in high-risk patients with no identified fever source whose fever persists or recurs despite 4 to 7 days of broad-spectrum antibiotic therapy.[30,31] Empiric use of amphotericin B deoxycholate has been supplanted by less toxic agents. Choices include polyenes, triazoles, and echinocandin classes of antifungal agents.[30,120]

Two prospective studies suggested that fluconazole is an equally effective but less toxic alternative to amphotericin B when it is given as empiric antifungal therapy in patients with cancer who have prolonged fever and neutropenia.[121,122] The azoles, however, may be less active than amphotericin B against some species and should not be used as empiric therapy in patients who are receiving fluconazole prophylaxis or have had recent azole exposure. Fluconazole has no useful activity against *Aspergillus* and has less activity than amphotericin B against *C. tropicalis, C. krusei, Candida lusitaniae*, and *C. glabrata*. Itraconazole and voriconazole have activity against *Candida* spp., *Aspergillus* spp., and some of the less common fungi, but no activity against Zygomycetes. Voriconazole compared favorably with liposomal amphotericin B in adult patients with cancer who had fever and neutropenia.[123] Newer azoles such as posaconazole and isavuconazonium sulfate provide broad activity against *Aspergillus* and *Mucorales* spp. The use of posaconazole is approved by the Food and Drug Administration for prophylaxis against invasive *Aspergillus* and *Candida* infections in immunocompromised patients 13 years of age and older. Posaconazole is distinct in having been successfully used in salvage treatment of infections caused by Zygomycetes, but its efficacy as an empiric antifungal agent in febrile and neutropenic patients with cancer has not been evaluated.

Considerable interest has been expressed in preparations of liposomal or lipid-associated amphotericin because of lower toxicity. In the only randomized, double-blind trial comparing liposomal amphotericin with conventional amphotericin B as empiric antifungal therapy, outcomes were similar with respect to survival, resolution of fever, and discontinuation of study drug because of toxic effects or lack of efficacy.[124] Liposomal amphotericin B was associated with fewer breakthrough fungal infections, less infusion-related toxicity, less nephrotoxicity,[124] and lower hospital costs.[125]

The echinocandins (i.e., caspofungin, micafungin, anidulafungin) are large lipopeptide molecules that are inhibitors of β-(1,3)-glucan synthesis, which is essential for fungal cell wall synthesis. Both in vitro and in vivo, the echinocandins are rapidly fungicidal against most *Candida* spp. and are fungistatic against *Aspergillus* spp., but they intrinsically are not active against Zygomycetes, *Cryptococcus neoformans*, or *Fusarium* spp.[126] Because the drug target is not present in mammalian cells, adverse events are generally mild, including (for caspofungin) local phlebitis, fever, abnormal serum hepatic enzymes, and mild hemolysis. In a prospective randomized, double-blind trial comparing the efficacy and safety of caspofungin with that of liposomal amphotericin B, caspofungin was as effective as and generally better tolerated than liposomal amphotericin B when it was given as empiric antifungal therapy in patients with persistent fever and neutropenia.[127] Caution is warranted in using echinocandins for the treatment of *C. parapsilosis* infection, given that patients with *C. parapsilosis* infection had persistently positive blood culture results when they were treated with caspofungin but achieved clearance when treated with amphotericin.[128] This agent is licensed for adult use, and the optimal caspofungin dosing for pediatric patients is not known. One small prospective study investigated the pharmacokinetics and safety of caspofungin in children and demonstrated that a caspofungin dose of 50 mg/m^2/day provided comparable exposure to that of adult patients treated with 50 mg/day without any serious drug-related adverse events or toxicity[129] (see Chapter 293). The newer echinocandins, micafungin and anidulafungin, also appear to be well tolerated in pediatric oncology patients.[130,131] In the absence of potential mechanistic antagonism with other antifungal drugs and a mild adverse event profile, combination antifungal therapy could become a general feature of echinocandin use, particularly for invasive aspergillosis.

Preemptive antifungal therapy has been shown to be a safe and effective management alternative in a subset of adult patients with continued fever and neutropenia. Prospective clinical trials have demonstrated that high-risk adults receiving prophylaxis against *Candida* spp. who remain febrile but are clinically stable and have no evidence of invasive fungal infections based on lack of clinical or radiologic (chest and sinus computed tomography) signs, negative serum mycologic assays (e.g., *Aspergillus* galactomannan, β-[1,3]-D glucan, fungal polymerase chain reaction tests), and sterile cultures may be closely monitored without starting empiric antifungal therapy.[132,133] The performance characteristics of the *Aspergillus* galactomannan assay in children are improved when this test is performed serially in the highest-risk children and during periods of neutropenia.[134,135] Additional data are required regarding the utility of mycologic assays in high-risk children hospitalized with fever and neutropenia; data are insufficient to construct an evidence-based preemptive antifungal treatment algorithm in the management of the high-risk child with persistent fever and neutropenia.

Risk Stratification

The following are extrapolated from the published literature as key factors increasing the risk of infectious complications in patients with fever and neutropenia: (1) anticipated duration of neutropenia[136]; (2) significant medical comorbidity[136,137]; (3) cancer status and cancer type; (4) documented infection on presentation; (5) evidence of bone marrow recovery[138,139]; and (6) height of fever.[8,138] The prospect of accurately and reliably identifying patients with fever and neutropenia who are at lower risk for complications is a desirable goal and integral to optimizing antimicrobial management strategies. In adults with fever and neutropenia, a risk stratification schema proposed from the Multinational Association of Supportive Care in Cancer (MASCC) has been validated and applied to identify adults with fever and neutropenia who are at low risk for complications and are thereby candidates for oral antimicrobials and outpatient therapy.[140] The MASCC score has not been evaluated in the pediatric oncology population. Multiple risk prediction studies have been conducted,[141] and certain low-risk stratification schemas have been validated in children.[138,139,142–147] However, no consensus exists on a single risk stratification schema and management algorithm that can be reliably and universally incorporated across pediatric clinical centers.

Investigations of oral antibiotic therapy have used many antibiotic regimens (pefloxacin,[148] ofloxacin,[149–153] ciprofloxacin,[154–156] cefixime,[157,158] moxifloxacin[159]) for empiric coverage in low-risk febrile and neutropenic patients with cancer. Although the results of these studies are encouraging, many of the clinical trials were statistically underpowered and limited by methodologic issues. Two large, prospective randomized studies of low-risk patients evaluated the efficacy of oral ciprofloxacin in combination with oral amoxicillin-clavulanate with more conventional parenteral antibiotic therapies in an inpatient setting.[160,161] Although the relative efficacies of oral and intravenous regimens were comparable in both these clinical trials, limited experience precludes this practice as an established standard for treating low-risk pediatric patients. A prospective, outpatient trial in children with low-risk febrile neutropenia that compared oral amoxicillin-clavulanate and ofloxacin with intravenous ceftriaxone and amikacin also found that outpatient therapy was safe, with no differences in outcome in oral versus intravenous therapy.[162,163] Outpatient and oral antibiotic management of children with low-risk fever and neutropenia was found to be effective in a meta-analysis.[164] When analyzing the spectrum of infections in a large cohort of low-risk febrile neutropenic patients (757 episodes of fever and neutropenia) at MD Anderson Cancer Center in Houston, Texas, investigators found that episodes of unexplained fever were predominant (58% of episodes), but both clinically documented and microbiologically documented infections were seen with equal frequency (21% respectively).[165] Among microbiologically documented infections, gram-positive (49%), gram-negative (36%), and polymicrobial (15%) infections were documented. Thus, although these patients were considered at low risk for developing infectious complications, many patients developed serious infections necessitating broad-spectrum antibiotic therapy.

Recombinant Human Colony-

Stimulating Factors

The use of hematopoietic growth factors, such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF), has been implemented widely in the management of neutropenia in patients with cancer and bone marrow transplants. Both G-CSF and GM-CSF have been evaluated as adjuncts to chemotherapy to assist bone marrow reconstitution and possibly prevent neutropenia and reduce infectious complications.

The use of CSFs as adjunctive treatment for fever and neutropenia has been studied in clinical trials. Primary use of G-CSF was shown to lower the incidence of febrile neutropenic episodes by approximately 50% in 3 randomized studies in which the incidence of fever and neutropenia in the control group was >40%. Prophylactic use of G-CSFs in adults reduced the risk of fever and neutropenia episodes, as well as infection-related mortality rates.[166] A meta-analysis of 13 studies revealed that the use of CSFs in patients with fever and neutropenia reduced the amount of time spent in the hospital and the neutrophil recovery period; the overall mortality rate was not affected by the use of CSFs.[167,168] A meta-analysis of randomized, controlled trials using prophylactic CSFs in children with cancer found a reduction in the rate of fever and neutropenia by 20%, decreased duration of both neutropenia and hospitalization, and reduction in documented infections rates by 22%. However, the use of CSFs did not reduce infection-related mortality rates.[169] Data are inconsistent regarding whether significant clinical benefits of starting CSFs during an episode of fever and neutropenia (beyond shortening time to resolution of neutropenia) exist to warrant routine use.[170,171]

Guidelines published by the American Society of Clinical Oncology recommend the use of G-CSF as primary prophylaxis, before the onset of neutropenia, if the expected incidence of fever and neutropenia is ≥40% (rate seen in control patients in the randomized trials), but not routinely at presentation with fever and neutropenia.[172] Clinical practice guidelines published by the Infectious Disease Society of America and the European Organisation for Research and Treatment of Cancer suggest consideration of prophylactic G-CSF when the anticipated risk of fever and neutropenia is ≥20%, but not for treatment of established fever and neutropenia.[30,173]

Secondary use of G-CSF or GM-CSF in subsequent cycles of chemotherapy has not demonstrated disease-free or overall survival benefits when the dose of chemotherapy was maintained. Therefore reduction in chemotherapy dose should be considered the primary therapeutic option in a patient who experiences neutropenic fever or severe or prolonged neutropenia after the previous cycle of treatment. If G-CSF is administered within the first few days of chemotherapy for the initial induction or the first postremission course for acute lymphoblastic leukemia, the duration of neutropenia of <1000/mm^3 can be shortened by approximately 1 week. These studies and guidelines for the use of hematopoietic growth factors are summarized in a consensus paper by the American Society of Clinical Oncology.[172]

Prevention

Preventive strategies have been evaluated, including the use of hematopoietic growth factors, isolation measures, active and passive immunization, and prophylactic antimicrobial regimens.

Active Immunization

Guidelines for vaccination of immunocompromised children, including children receiving cancer chemotherapy and HSCT recipients, have been published.[174–176] Annual inactivated influenza vaccination is routinely recommended for patients ≥6 months of age with hematologic and solid tumor malignant diseases. Although vaccination is safe, efficacy is reduced in patients receiving intensive chemotherapy (e.g., induction or consolidation in acute leukemia) or in patients receiving anti–B-lymphocyte antibodies. Killed virus or subunit vaccines are considered safe for even the most compromised patients, but the efficacy in these patients may be reduced. Inactivated vaccines (other than influenza) that are given during maintenance chemotherapy are not considered valid doses and must be given 3 months after completion of chemotherapy unless a protective antibody level is documented. Vaccine administration should be delayed for at least 6 months after receiving monoclonal antibodies directed against B lymphocytes. Children recovering from allogeneic bone marrow transplantation may acquire the immunity of their donor but generally should be regarded as unimmunized. Because antibody concentrations against vaccine-preventable diseases typically decline after HSCT, recipients are candidates for revaccination.[176] Generally, revaccination for both autologous and allogeneic HSCT recipients should begin 6 to 12 months after HSCT. However, pneumococcal conjugate and inactivated influenza vaccines can be administered as early as 3 and 4 months after HSCT, respectively. If influenza vaccine is given earlier than 6 months after HSCT, a second dose should be contemplated regardless of the conditioning regimen. Thereafter, lifelong seasonal influenza vaccination is recommended for all HSCT recipients. Live-virus vaccines can be administered 2 years after successful transplantation if the patient has no evidence of graft-versus-host disease and is not receiving immunosuppressive drugs. Vaccinations for family members, close household contacts, and healthcare workers is strongly recommended.

Passive Immunization

Passive immunization also has been evaluated. In certain circumstances, infection-specific or hyperimmune globulins have proved to be particularly helpful, as in the case of postexposure use of varicella-zoster immune globulin (VariZIG) in persons who lack evidence of immunity to varicella and in whom varicella vaccine is contraindicated. VariZIG reduces the incidence of primary varicella and its complications in nonimmune persons if it is given ideally within 96 hours and up to 10 days after exposure.[177] Approval by the Food and Drug Administration was based on the clinical use of varicella immunoglobulin in exposed immunocompromised children that resulted in fewer clinical varicella cases and less severity in the subgroup of children who did develop disease, compared with historical controls. Because protection lasts for only 3 to 4 weeks after VariZIG administration, repeated doses may be necessary in the setting of community outbreaks and repeated exposure. Patients receiving high-dose immune globulin intravenous (≥400 mg/kg IGIV) are likely protected if the dose of the IGIV was administered in the preceding 3 weeks. IGIV can be used as prophylaxis for measles in susceptible patients during epidemics.

Prophylactic Antimicrobial Therapy

Many clinical trials have focused on the use of prophylactic antibiotics to prevent infections in neutropenic patients without fever. The oral fluoroquinolone antibiotics have been investigated because of their good bioavailability and broad activity against aerobic gram-negative bacteria. A meta-analysis of published randomized controlled trials of fluoroquinolone prophylaxis (18 trials with 1408 patients) found that prophylaxis significantly reduced the incidence of gram-negative bacterial infections, total infections, and fevers but did not alter the incidence of gram-positive infections or infection-related deaths.[178] A large, randomized, prospective trial evaluating the use of oral levofloxacin (500 mg daily) in adults with cancer before anticipated chemotherapy-induced neutropenia showed that the levofloxacin-treated group had a lower rate of microbiologically documented infections did than the placebo group. The mortality rates were similar in the 2 groups, and the effect of prophylaxis was similar between patients with acute leukemia and those with solid tumors or lymphomas.[179] Two studies evaluating the use of prophylactic oral levofloxacin (500 mg daily) in patients receiving chemotherapy for either solid tumors or lymphoma[180] or hematologic malignant diseases[181] both showed a reduction in documented infections. A meta-analysis of antibiotic prophylaxis in neutropenic patients with cancer (95 trials performed between 1973 and 2004) concluded that antibiotic prophylaxis (various antibiotic regimens) compared with placebo or no treatment significantly decreased the risk for death.[182] When trials that used fluoroquinolone prophylaxis (52 trials) were separately analyzed, a significant reduction was observed in the risk for all cause-mortality, as well as infection-related mortality, fever, clinically documented infections, and microbiologically documented infections. Many of these studies reported increasing rates of antimicrobial resistance to fluoroquinolones.[179,181,182] Thus, if fluoroquinolone prophylaxis is implemented, vigilant monitoring of the incidence of BSI (specifically gram-negative BSI) is important to detect the loss of efficacy of fluoroquinolone prophylaxis.

Fluoroquinolone prophylaxis should be considered for high-risk adult patients in whom severe neutropenia (ANC ≤ 100 cells/mm^3) is expected to last for more than 7 days.[30,175] Data on fluoroquinolone prophylaxis is children are less robust and raise concerns about adverse effects on antibiotic resistance patterns. The use of ciprofloxacin prophylaxis in 95 children with acute lymphoblastic leukemia or acute myeloid leukemia led to a 23% reduction in fever and neutropenia episodes in patients with acute lymphoblastic leukemia during induction chemotherapy, but not in patients receiving consolidation or in those with lymphoma.[183] Of concern, after only 2 weeks, the proportion of ciprofloxacin-resistant gram-negative bacteria colonizing patients who received fluoroquinolone prophylaxis was 95% compared with 27% of those patients randomized to receive placebo. Significantly increased rates of emerging resistance after fluoroquinolone use have been documented in other pediatric studies.[4] Given an incidence of gram-negative BSI of 10% to 15% in this population, it was estimated that fluoroquinolone prophylaxis would need to be administered unnecessarily in 96 to 97 patients to prevent an episode in 3 to 4 patients.[184] Routine fluoroquinolone prophylaxis precludes its empiric use for fever and neutropenia.[185,186] Further study in children is necessary before widespread use is adopted.

In meta-analyses, antifungal prophylaxis was found to reduce superficial and invasive fungal infections, fungal infection–related morbidity, and mortality rates in some patients, particularly patients with prolonged neutropenia or HSCT receipt.[187,188] Thus, prophylaxis against *Candida* species is recommended in patients at high risk for invasive infection, including allogeneic HSCT recipients and patients undergoing remission-induction or salvage-induction chemotherapy for acute leukemia. Broad use of fluconazole prophylaxis has changed the epidemiology of infections with *Candida* spp. In several studies investigating fluconazole, infections with fungi known to be resistant to fluconazole (i.e., *Aspergillus* or other molds and non-*albicans Candida* spp. such as *C. glabrata*) have been major causes of morbidity and mortality.[121,189,190] Antifungal prophylaxis with agents active against molds such as voriconazole or posaconazole should be considered in selected patients, including those with a previous history of

Aspergillus infection, patients with a prolonged period of neutropenia before HSCT, patients with anticipated prolonged neutropenia of >2 weeks, and HSCT recipients with acute graft-versus-host disease receiving augmented immunosuppression, as well as in centers where the rate of invasive aspergillosis is ≥6%.[30,191,192] The potential for serious drug interactions with azole agents necessitates close monitoring, especially when these drugs are given concomitantly with other medications (e.g., vincristine, high doses of cyclophosphamide) that are metabolized by cytochrome P450 isoenzymes.

The incidence of PCP in children with cancer can be decreased by the use of trimethoprim-sulfamethoxazole, which has become a standard part of medical management.[193,194] The incidence of recurrent herpes simplex disease in patients receiving intensive chemotherapy or bone marrow transplantation has been reduced with the prophylactic use of acyclovir.[195] In addition, the use of viral surveillance and preemptive ganciclovir therapy in preventing cytomegalovirus disease and the use of acyclovir or valacyclovir in preventing varicella-zoster virus reactivation after bone marrow transplantation has been shown to be effective.[196,197]

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98

Infections in Children With Cancer

Monica I. Ardura, Andrew Y. Koh

Approximately one third of pediatric patients with cancer who have fever and neutropenia have a clinically or microbiologically proven site of infection. Table 98.1 summarizes documented infections identified in 3 large clinical trials of empiric antibiotic therapy administered to patients admitted to the National Cancer Institute for fever during episodes of neutropenia.[1–3]

TABLE 98.1

Documented Sites of Infection in Patients with Cancer, Fever, and Neutropenia

Site or Type of Infection	Pizzo et al.[1] No. (%)	Pizzo et al.[2] No. (%)	Freifeld et al.[3] No. (%)	Total No. (%)
Bloodstream	81 (43)	109 (27)	20 (17)	210 (29)
Pulmonary	28 (15)	88 (21)	16 (13)	132 (18)
Cutaneous	42 (22)	43 (10)	19 (16)	104 (14)
Head, eyes, ears, nose, throat	11 (6)	69 (17)	28[a] (23)	108 (15)
Gastrointestinal	4 (2)	35 (9)	30 (25)	69 (10)
Urinary tract	22 (11)	29 (7)	NR	51 (7)
Other	2 (1)	38 (9)	7 (6)	47 (7)

[a] Includes cases of severe mucositis.

NR, not reported separately.

Diagnosis and Management of Specific Clinical Syndromes of Infection

Catheter-Associated Bacteremia

Several series evaluating the use of central venous catheters in patients with cancer confirmed that these devices increase the incidence of bloodstream infection (BSI), regardless of the level of bone marrow suppression.[4,5] Although gram-positive organisms, particularly coagulase-negative staphylococci, emerged as the predominant pathogens, almost any bacteria can be responsible for central line–associated BSI (CLABSI) bacteremia. Fungi, most often *Candida* spp., also can cause CLABSI and are difficult to eradicate without removal of the contaminated device.[6,7] Mixed flora bacteremia should prompt an investigation to identify a causative event (e.g., swimming with the catheter unprotected, dropping of catheter tubing into bathwater, chewing on catheter tubing by young children, disconnection of catheter caps or tubing) so that appropriate education can be provided.

In evaluating children for CLABSI, cultures should be obtained from all lumens of a multilumen device. Because of the increased risk of CLABSI, empiric antibiotics may also be warranted in non-neutropenic patients with central venous catheters who have fever with no localizing findings. The choice of agent used for empiric antibiotic therapy in children with cancer should have a broad spectrum of activity, and take into account the severity of illness, associated neutropenia, history of infection or colonization with multidrug-resistant bacteria, and antimicrobial prophylaxis regimens. Vancomycin may not be necessary empirically unless the patient has evidence of soft tissue infection at the catheter site or elsewhere, clinical instability, or a history of a resistant gram-positive pathogen.[8–10]

Infection of soft tissue at the catheter site can be confined to the skin immediately surrounding the exit site of a catheter or can involve deeper soft tissue around the subcutaneously tunneled portion of the catheter or access port. Localizing findings in a neutropenic child should be considered evidence of infection, thus mandating hospitalization and administration of broad-spectrum antibiotics, including an antistaphylococcal agent. Induration, erythema, tenderness, or fluctuance along the subcutaneous tunnel tract generally requires removal of the catheter, debridement of infected tissue, and systemic antibiotic therapy.

Catheter management (salvage or removal) depends on the pathogen, the type of catheter, the patient's clinical manifestations, and complications. Most episodes of bacterial CLABSI can be successfully treated with the catheter in place, even when multiple organisms are identified.[4,11] Although current guidelines recommend the addition of antibiotic lock therapy for catheter salvage, data on an additional benefit of antibiotic or ethanol lock therapy in pediatric oncology patients with CLABSI are inconclusive, warranting prospective study.[12,13] Removal of the catheter is recommended if the patient has erythema or exudate at the catheter site (concerning for a catheter pocket or tunnel infection), bacteremia with certain pathogens, persistence of bacteremia despite 72 hours of appropriate antimicrobial therapy, or the presence of concomitant endocarditis, suppurative thrombophlebitis, or metastatic infection.[14] Specific organisms require removal of the catheter: *Staphylococcus aureus*,[11,12] *Bacillus* spp.,[14,15] *Mycobacterium* spp.,[16] *Pseudomonas aeruginosa* and multidrug-resistant gram-negative bacteria (e.g., *Acinetobacter* spp.), and fungi (including *Candida* spp.)[6,7,9,14] Polymicrobial infections may require removal of the catheter.

Skin Infections

Cutaneous infections are common in immunocompromised patients. These infections accounted for 22% to 33% of infections in an older series,[17] as well as 16% of infections present at the time of hospitalization for fever and neutropenia in another study.[3] Infections of the skin can be caused by bacteria, fungi, or viruses.

Bacteria.

Bacterial skin infections usually are caused by staphylococci or streptococci. In immunocompromised patients, both gram-positive and gram-negative bacteria, including enteric organisms and *Pseudomonas,* can be isolated either from the blood or from material obtained from fine-needle aspiration of the area of cellulitis.[18] *P. aeruginosa* infection classically is associated with the severe necrotic skin lesion *ecthyma gangrenosum* (Fig. 98.1), although invasive infections with other gram-negative organisms, staphylococci, mycobacteria, and fungi can cause ecthyma gangrenosum. Empiric therapy for suspected bacterial cellulitis should provide broad-spectrum coverage. Every effort should be made to establish a microbiologic diagnosis; new skin lesions should be examined using biopsy and culture.

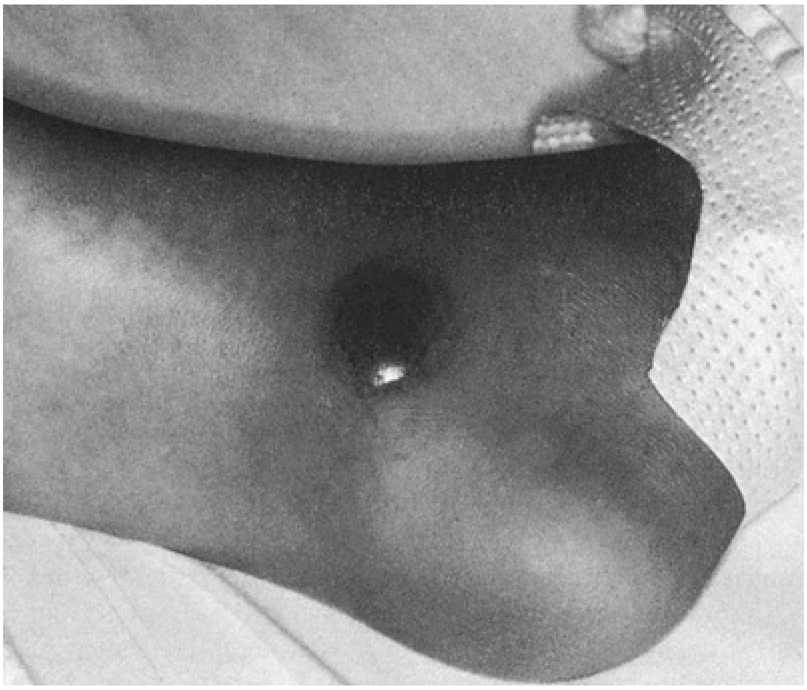

FIGURE 98.1 Ecthyma gangrenosum in an 8-year-old boy with newly diagnosed acute lymphocytic leukemia, fever, and bacteremia caused by *Pseudomonas aeruginosa.*

Fungi.

Fungal pathogens including *Candida, Aspergillus, Fusarium, Scedosporium,* and agents of mucormycosis can cause cutaneous lesions either as isolated, primary infections or as manifestations of disseminated infection.[19] Routine blood and fungal blood cultures and tissue histologic examination and culture should be obtained. Black, rapidly progressing, necrotic eschars should prompt immediate evaluation for fungal infection. Tender, erythematous skin nodules or pustules can develop during candidemia; examination can aid diagnosis while awaiting culture results. Superficial cultures of suggestive skin lesions may not provide adequate material for diagnosis of fungal infections; biopsy generally is more useful. A cutaneous fungal infection resulting from *Aspergillus* or other molds often is a manifestation of hematogenous spread or local angioinvasive infection, requiring surgical debridement in addition to prolonged antifungal therapy.

Viruses.

Cutaneous viral infections can result from either primary infection or viral reactivation. Herpes simplex virus (HSV) and varicella-zoster virus (VZV) can cause painful or pruritic vesicular lesions that can become secondarily infected. The diagnosis is confirmed by unroofing a fresh vesicle, scraping the base of the lesion, and testing the sample by direct fluorescent antibody or polymerase chain reaction (PCR) for HSV and VZV. Differentiation is important because VZV infection requires higher doses of acyclovir (10 mg/kg/dose or 500 mg/m^2/dose every 8 hours) than does HSV infection. Acyclovir prophylaxis has demonstrated benefit in preventing reactivation in HSV- and VZV-seropositive recipients of allogeneic hematopoietic cell transplantation (HCT) and in patients receiving induction therapy for acute leukemia.[9,20–22]

Patients with cancer who develop primary varicella, especially patients who are actively receiving chemotherapy, are at increased risk of serious disseminated disease, including giant cell pneumonia, encephalitis, hepatitis, and purpura fulminans. Rates of dissemination and subsequent mortality (estimated as 7% to 20% in untreated patients[23]) have been reduced by rapid initiation of intravenous acyclovir therapy.[24] Although recurrent disease in the form of herpes zoster is rarely associated with severe complications when VZV infection remains localized to the skin, dissemination occurs in up to 25% of patients with immunocompromising conditions.[25] Severe abdominal pain, back pain, or evidence of inappropriate antidiuretic hormone secretion can herald multisystem involvement, indicating an urgent need to initiate intravenous acyclovir therapy.[26]

Scabies.

A severe variant of scabies (caused by *Sarcoptes scabiei)*, called Norwegian or crusted scabies, occurs in immunodeficient patients, especially patients with leukemia or lymphoma, and is characterized by the presence of 10^3 to 10^6 viable mites, resulting in widespread, hyperkeratotic, crusted lesions. This form of scabies is highly contagious and also can be recalcitrant to standard topical scabicidal therapy. Oral ivermectin is highly effective for treating both routine scabies and Norwegian scabies after a single administration, although additional treatment often is given.[27,28]

Pulmonary Infections

The lungs are the most common sites of localized infection in patients with neutropenia, and pulmonary infection in this population produces a wide variety of symptoms, signs, and radiographic appearances. Table 98.2 summarizes causative agents suggested by radiographic findings.

TABLE 98.2

Causes of Pulmonary Processes in Patients with Cancer as Suggested by Radiographic Abnormality

Radiographic Manifestation	Infectious Cause	Noninfectious Process
Focal consolidation (lobar or segmental)	Bacteria (routine and nosocomial pathogens) *Legionella* Oral flora (aspiration and postobstructive) *Mycobacterium tuberculosis* Fungi (*Cryptococcus, Histoplasma, Coccidioides*)	Pulmonary hemorrhage Pulmonary infarction Atelectasis Radiation pneumonitis Drug-related pneumonitis Tumor
Diffuse interstitial infiltrate	Viruses *Pneumocystis jirovecii* Mycobacteria, including miliary tuberculosis Disseminated fungi (*Cryptococcus, Histoplasma, Coccidioides*) *Mycoplasma* *Chlamydophila*	Pulmonary edema Adult respiratory distress syndrome Drug-related pneumonitis Radiation pneumonitis Lymphangitic metastasis Lymphocytic interstitial pneumonitis (HIV)
Nodular infiltrate (with	Molds: *Aspergillus, Mucor, Fusarium*	Tumor

or without cavitation)	Bacteria (especially *Staphylococcus aureus, Pseudomonas, Klebsiella,* anaerobic bacteria), *Nocardia* Mycobacteria, including *M. tuberculosis* Viruses (e.g., CMV, HSV, VZV, EBV, RSV)	

CMV, cytomegalovirus; EBV, Epstein-Bar virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; RSV, respiratory syncytial virus; VZV, varicella-zoster virus.

Localized Infiltrates

Acute localized infiltrates at the onset of fever in a patient with cancer, with or without neutropenia, are most often caused by bacterial pathogens. Because both community-acquired and healthcare-associated pathogens can be responsible for pneumonia in neutropenic patients, initial antibiotic therapy should provide coverage for organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae,* as well as *Pseudomonas* spp. and other gram-negative bacteria. *Legionella* also is considered in febrile, immunocompromised patients with patchy infiltrates. *Legionella* can colonize air conditioning equipment and showerheads and can be spread by aerosolization of contaminated water. Antigen testing of urine is sensitive and specific for *L. pneumophila,* serogroup 1. Patients with pulmonary metastases of cancers also can have an increased risk for postobstructive pneumonia resulting from mouth flora, including anaerobic bacteria. The antibiotic regimens used for empiric therapy for fever without localizing findings in a patient with neutropenia (e.g., fourth-generation cephalosporin, extended-spectrum penicillin, or carbapenem) are appropriate for initial management of pneumonia. In some cases, the addition of a macrolide or fluoroquinolone for possible *Mycoplasma* or *Legionella* infections is warranted. In children with clinical or imaging findings consistent with possible community-associated *Staphylococcus aureus* pneumonia, vancomycin or clindamycin should be added to the beta-lactam therapy.

Viruses, such as influenza and parainfluenza viruses, respiratory syncytial virus, and adenovirus, also can cause localized infiltrates in immunocompromised children, although a diffuse process is more common. In one study, respiratory viruses were detected in 52% of 50 episodes of fever in neutropenic children with negative bacterial cultures, though ascribing a causal role in the clinical illness is challenging.[29] Consideration of a viral infection can lead to specific therapy (e.g., as in influenza), but it does not obviate the need for broad-spectrum antibiotic therapy in a patient with neutropenia, fever, and a pulmonary infiltrate.

A patient with localized infiltrates who fails to respond to broad-spectrum antibiotics has broad differential diagnostic possibilities. Guidelines recommend bronchoalveolar lavage (BAL) fluid sampling in patients with fever, neutropenia, and an infiltrate of uncertain origin.[9] Infection resulting from fungi, *Nocardia,* mycobacteria (including *Mycobacteria tuberculosis*),[30] or antibiotic-resistant, healthcare-associated bacteria can manifest with localized infiltrates. Endemic fungi, *Histoplasma, Cryptococcus,* and *Coccidioides* also can cause localized pneumonitis in selected geographic regions and, in compromised hosts, can also be associated with extrapulmonary infection. The presence of *Candida* in upper respiratory tract or tracheal secretions, even in patients with pulmonary infiltrates, correlates poorly with causation because of the high frequency of colonization of the oral cavity and tracheobronchial tree. Blood culture results that are positive for *Candida* or typical retinal lesions of endophthalmitis are associated with disseminated infection, which can include pneumonia. In the absence of these findings, definitive diagnosis usually requires histopathologic confirmation.

The fungal pathogens of most concern in the patient with neutropenia include *Aspergillus, Fusarium,* agents of mucormycosis, *Scedosporium,* and *Trichosporon* because these organisms cause rapidly progressive, extensively destructive infection. Unlikely to be identified at the onset of neutropenia and fever, the finding of a progressive or new infiltrate, accompanied by fever, nonproductive cough or hemoptysis, and pleuritic chest pain, in a persistently neutropenic patient during broad-spectrum antibiotic therapy suggests the diagnosis of invasive fungal pneumonia (most frequently with *Aspergillus*). Computed tomography (CT) may reveal multiple pulmonary nodules (sometimes with cavitation) that are not readily apparent on routine chest radiographs.[31] The classic histopathologic findings in aspergillosis are invasion of the blood vessels with thrombosis and resulting infarction and hemorrhage. Whereas recovery of *Aspergillus* from the respiratory tract of patients without neutropenia can represent colonization, isolation of this organism in the setting of prolonged neutropenia and pulmonary infiltrate is highly predictive of invasive disease,[32] and is sufficient evidence for initiation of antifungal therapy. In biopsy-proven *Aspergillus* pneumonia, BAL has a recovery rate of only 50%, and transbronchial biopsy has a recovery rate of only 20%. Open lung biopsy may be required.[33,34] *Aspergillus* galactomannan testing on blood and BAL specimens can facilitate the diagnosis of invasive pulmonary aspergillosis in patients with hematologic diseases, with overall sensitivity and specificity for proven invasive aspergillosis of 71% and 89%, respectively.[35–39] Thus, a positive galactomannan assay coupled with a consistent CT appearance can suggest probable invasive aspergillosis in a neutropenic patient with cancer or a history of HCT[40]; a positive culture result of a specimen obtained from a normally sterile site remains the gold standard for proven infection. Other non–culture-based assays, including β-D-glucan and fungal PCR, show promise as adjuncts to diagnosis, but they remain investigational in pediatrics.[40a]

Voriconazole is considered the drug of choice for primary treatment of invasive aspergillosis based on the findings of an international, randomized, open-label trial demonstrating that voriconazole conferred a significant benefit of survival and overall therapeutic response compared with patients treated with amphotericin.[41–43] Liposomal amphotericin can be considered as alternative or salvage therapy.[44] The echinocandin agent caspofungin initially was approved for use in patients with refractory aspergillosis. A prospective study enrolling 90 patients with invasive aspergillosis who were refractory to (86%) or intolerant of amphotericin B, liposomal amphotericin B, or triazoles (14%) and who were treated with caspofungin showed a favorable response to caspofungin therapy in 45% of patients (50% with pulmonary aspergillosis and 23% with disseminated aspergillosis).[45] Although successful use of caspofungin as first-line monotherapy for invasive aspergillosis has been reported,[46,47] no randomized controlled trials comparing efficacy with other antifungal agents have been conducted. Finally, given few adverse effects and a theoretical lack of antagonism, combination therapy with voriconazole and an echinocandin for invasive aspergillosis can be considered.[48–50] Results of a randomized, double-blind, placebo-controlled trial in adults with hematologic malignant diseases and after HCT who had suspected or documented invasive aspergillosis demonstrated improved survival rates in patients who received combination therapy with voriconazole and an echinocandin compared with patients who received voriconazole monotherapy.[51] Other fungal pathogens, such as *Histoplasma capsulatum, Coccidioides immitis,* and *Cryptococcus neoformans,* can also cause focal infiltrates in patients with neutropenia who are receiving corticosteroid therapy or with epidemiologic exposures.[52]

Diffuse or Interstitial Infiltrates

Diffuse or interstitial infiltrates can represent a nonbacterial process, although both gram-positive and gram-negative bacteria can cause interstitial pneumonitis. In children not receiving antimicrobial prophylaxis, *Pneumocystis jirovecii* is the organism most often identified in the setting of diffuse, interstitial infiltrates. Historically, in children with leukemia during maintenance chemotherapy who did not receive prophylaxis, incidence rates of *Pneumocystis* pneumonia (PCP) were 2% to 22%.[53] The incidence of PCP in patients with cancer has been reduced substantially with the standard use of prophylactic trimethoprim-sulfamethoxazole (TMP-SMX). Nonetheless, *P. jirovecii* should be considered in children receiving corticosteroid therapy or in children with significant cell-mediated immune deficiency who have fever, nonproductive cough, tachypnea, and hypoxemia. In a review of oncology patients with confirmed PCP, 70% of patients became symptomatic while corticosteroid dosages were being tapered.[54] The chest radiograph in PCP typically reveals bilateral perihilar interstitial, or alveolar, infiltrates that spread to involve all lobes (Fig. 98.2), but virtually any radiographic pattern can occur. The diagnosis is established by microscopic findings of either cysts or trophozoites on smears of respiratory tract secretions obtained by sputum induction, BAL, or open lung biopsy. Because *Pneumocystis* cannot be cultured, and the sensitivity of microscopy is lower in patients who do not have human immunodeficiency virus (HIV) infection, additional assays have been applied, including *Pneumocystis* PCR and β-D-glucan assays, to improve diagnostic yield. *Pneumocystis* PCR performed on BAL or sputum specimens from non-HIV immunocompromised patients compared with conventional microscopy methods in one study showed sensitivity of 87% and specificity of 92% for PCP, with a negative predictive value of 100%.[55] A positive serum (1,3)-β-D glucan assay may be an early indicator of PCP and has been used clinically in children with malignant diseases; the assay has positive and negative predictive values of 61% to 64% and 98% to 99%, respectively.[56–58] In non-neutropenic patients with diffuse infiltrates who are unable to undergo BAL or biopsy, an empiric course of TMP-SMX can be considered.[59] Definitive therapy for PCP is TMP-SMX, 15 to 20 mg/kg/day divided into every 6 hour doses for 21 days. Patients with severe PCP who have an absolute contraindication to TMP-SMX therapy should receive pentamidine intravenously. Prednisone usually is given to patients with moderate or severe PCP concomitantly with antibiotic therapy. Other therapies found to be effective for PCP in HIV-infected patients include pentamidine, trimetrexate, atovaquone, and clindamycin plus primaquine. Recurrence of PCP or breakthrough infection is unusual in children with cancer receiving TMP-SMX prophylaxis, but it is reported in HIV-infected children.[60]

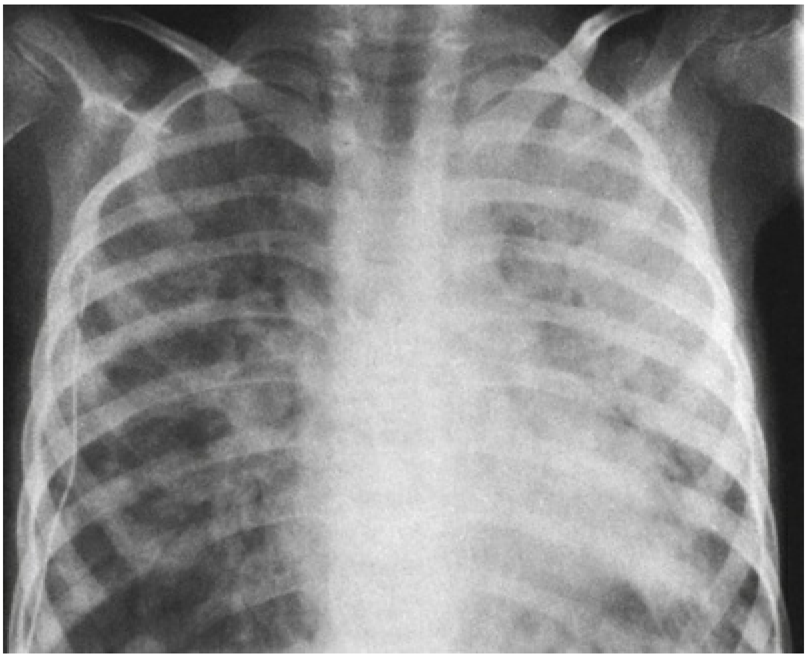

FIGURE 98.2 Chest radiograph showing bilateral interstitial and alveolar infiltrates in a child with acute lymphocytic leukemia and *Pneumocystis* pneumonia.

Viral infections also can cause pneumonia with diffuse or interstitial infiltrates. Whereas the common respiratory tract viruses cause more severe disease in immunocompromised patients, the most serious cases are caused by cytomegalovirus (CMV). CMV pneumonitis has been seen most often in patients receiving allogeneic bone marrow transplants, within the first 3 months after transplantation. Clinical presentation includes fever and rapidly progressive diffuse pulmonary infiltrates, often requiring ventilatory assistance. Risk factors for CMV pneumonitis include the presence of pretransplant CMV seronegativity in the donor and seropositivity in the, receipt of total body irradiation as part of the pretransplant regimen, and development of graft-versus-host disease.[61] The definitive diagnosis of CMV lower respiratory tract disease requires identification of viral cytopathic effect on lung tissue obtained by biopsy. Historically, CMV pneumonitis had a mortality rate of more than 80%. Antiviral treatment with ganciclovir or foscarnet has improved outcomes, with overall survival rates of 50% to 70%. The added benefit of pooled or CMV-specific intravenous immunoglobulin is less clear.[62–64] Standard practice in many transplant centers now includes preemptive strategies including surveillance testing (quantitative CMV DNA or RNA PCR tests) and preemptive therapy with intravenous ganciclovir for patients who have CMV isolated from any site during the early post-HCT period.[21,65]

Other herpesviruses, particularly VZV and HSV, can cause diffuse pneumonitis in patients with cancer. Respiratory syncytial virus also can cause severe lower respiratory tract disease with a high mortality rate, notably in patients undergoing therapy for acute myelogenous leukemia or after HCT.[66,67] Parainfluenza virus, influenza virus (including H1N1), human metapneumovirus, adenovirus, and human herpesvirus 6 can cause interstitial pneumonitis in pediatric patients with cancer.[68,69] Respiratory virus detection before HCT, even of rhinovirus alone, has been associated with lower survival rates at day 100.[70]

Infections of the Ears and Sinuses

Patients who have been hospitalized or who are receiving chemotherapy may have altered microbial flora. In addition to the usual bacterial pathogens responsible for otitis media (*S.*

pneumoniae, H. influenzae, Moraxella catarrhalis), nosocomial pathogens (such as gram-negative organisms) must be considered. In the neutropenic child, ear infections can be accompanied by pain, with minimal erythema of the tympanic membrane and canal. Malignant otitis externa resulting from invasive infection of the auditory canal with *P. aeruginosa* (and occasionally invasive fungi) occurs more commonly in patients with diabetes mellitus or patients receiving corticosteroids, but it also is seen in patients receiving chemotherapy and requires aggressive debridement and intravenous antimicrobial therapy.

Although mastoiditis is an uncommon infection in pediatric patients with cancer, those children with anatomic abnormalities of the middle ear and children with prolonged neutropenia are at increased risk. Fungi (particularly *Aspergillus*) can cause mastoiditis in neutropenic patients. Surgical debridement usually is required for cure.[71]

The paranasal sinuses also can become infected with typical pathogens or the altered bacterial flora in hospitalized patients. Sinusitis was found more commonly in children with hematologic malignant diseases than in those with solid tumors in one series, and 41% of 91 children with acute lymphoblastic leukemia had abnormal sinus radiographs at the time of induction chemotherapy.[72] Children with tumors involving the sinuses (e.g., nasopharyngeal carcinoma, Burkitt lymphoma, rhabdomyosarcoma) are at particular risk for recurrent or chronic sinusitis; distinguishing between progressive or necrotizing tumor and infection is challenging. Sinus radiography and CT are helpful tools in the diagnosis. Broad-spectrum antibiotics, including an agent with activity against anaerobic organisms, are necessary for treatment of sinusitis in neutropenic patients. If symptoms do not improve within 48 to 72 hours of empiric antibiotic therapy, aspiration or biopsy should be performed.

Patients who remain neutropenic for more than 7 days are at increased risk of fungal infection, including sinusitis. In a series of fungal sinusitis in children, facial pain or headache, fever, facial swelling (which developed in 50% of patients), and abnormal findings on sinus radiographs were the most common manifestations.[72] In a 10-year retrospective analysis of invasive fungal sinusitis, *Aspergillus flavus* accounted for >50% of cases, and periorbital swelling (41% of patients) was the most common presenting symptom.[73] Other fungal pathogens include *Mucor, Fusarium, Scedosporium, Rhizopus,* among others. A small, blackened eschar within the nose or sinus can be the first manifestation, with rapid progression, significant tissue invasion, necrosis secondary to vascular thrombosis, and ultimate extension into the orbits or brain. Obtaining biopsy material for histopathologic examination and culture is necessary to establish the diagnosis definitively. Management of rhinocerebral fungal infection requires aggressive surgical debridement and longterm therapy with voriconazole for *Aspergillus* sinusitis and amphotericin B and posaconazole considerations for zygomycosis.

Gastrointestinal Tract Infections

Underlying diseases and the cytotoxic and radiation regimens used in therapy predispose pediatric patients with cancer to alterations of the gastrointestinal mucosa that lead to local infections and portals of entry for resident microorganisms.

Mucositis and Esophagitis

Mucositis can range in severity from isolated, small oral ulcers to extensive mucosal sloughing of the oral cavity and more distal gastrointestinal tract. A recognizable complication of mucositis is necrotizing or marginal gingivitis, characterized by a periapical line of erythema and tenderness. Because this condition presumably results from anaerobic infection, empiric antibiotic therapy should include an effective agent (e.g., clindamycin, metronidazole, piperacillin-tazobactam, or meropenem). In addition, children who have had prolonged hospitalization or have received broad-spectrum antibiotics can have oral colonization with gram-negative organisms or fungi. Chemotherapy-induced mucositis also can become superinfected with *Candida, Aspergillus,*[74] or HSV. A Gram stain of scrapings (swab or tongue depressor) may identify yeast or hyphae, and immunofluorescent stain, PCR, or culture may confirm HSV infection. Mild *Candida* infection may respond to topical treatment with clotrimazole troches, but fluconazole, voriconazole,[75] caspofungin,[76–78] or amphotericin B usually is given because stomatitis can lead to locally invasive or disseminated fungal infection, or both. Oral or intravenous acyclovir is given for HSV stomatitis. Because 70% to 80% of children with a past history of HSV infection have reactivation during induction chemotherapy for leukemia or after HCT, oral acyclovir is given prophylactically during the high-risk period of leukopenia.[79] Septicemia caused by α-hemolytic streptococci can complicate mucositis and has high rates of shock and central nervous system (CNS) infection. Penicillin nonsusceptibility as high as 75% is reported in such cases.[80]

Although the differential diagnosis of substernal burning chest pain and odynophagia includes both infectious and noninfectious causes of esophagitis, establishing a specific cause can be difficult. Neither barium swallow nor endoscopic visualization reliably distinguishes among *Candida,* HSV, and noninfectious causes (e.g., mucositis secondary to chemotherapy or radiation). In one study, 21 of 22 patients with cancer who had a clinical and microbiologic diagnosis of oral candidiasis also had endoscopic and microbiologic findings diagnostic of candidal esophagitis, a finding suggesting that oropharyngeal candidiasis can represent a reliable marker for esophageal candidiasis in patients with cancer.[81] Definitive diagnosis, however, requires endoscopically performed biopsy and culture. When biopsy is considered too risky (e.g., a patient with a platelet count of $<50,000/\text{mm}^3$), a sequential approach can begin with empiric azole therapy (for *Candida* esophagitis), and if there is a lack of clinical improvement within 48 hours, change to amphotericin or caspofungin. Failure to improve within 48 hours of amphotericin or caspofungin makes *Candida* spp a less likely cause of esophagitis, and endoscopic biopsy should be reconsidered. If a biopsy cannot be performed, an empirical trial of acyclovir for presumptive HSV esophagitis could be considered. In the patient without neutropenia, infectious causes of esophagitis are uncommon; symptomatic treatment with antacids or histamine-blocking agents can be appropriate.

Intra-Abdominal Infections

The epidemiology of infectious diarrhea in children with fever and neutropenia is not well described. Infectious causes are broad, but most common viruses, including norovirus, enterovirus, adenovirus, and rotavirus, are responsible. More severe or protracted illness and prolonged viral shedding are expected in immunocompromised patients, especially in HCT recipients.[82] CMV also can cause severe colitis in HCT recipients and in patients receiving anti-CD52 monoclonal antibody therapy; case reports also describe CMV-associated colitis in patients receiving systemic chemotherapy for hematologic malignant diseases and lymphomas.[83,84] A history of travel, food consumption, water exposure (water park, well water), and animal exposure should be sought in children with fever and acute diarrhea. Fever and bloody diarrhea make the possibility of bacterial enteritis more likely, and stool samples should be tested by culture or PCR. Evaluation for parasitic infections (e.g., enzyme immunoassays for *Giardia* and *Cryptosporidium*, stool ova and parasite testing) is determined by exposure history.

Clostridium difficile Infection.

Pseudomembranous or antibiotic-associated colitis can follow antibiotic administration for empiric therapy in febrile neutropenic patients. Many patients become colonized with *Clostridium difficile* during hospitalization and can have prolonged shedding.[85] The incidence of *C. difficile* infection in hospitalized children is 15-fold greater in children with cancer compared with children without cancer.[86–88] Symptoms of *C. difficile* disease range from mild abdominal pain to severe bloody colitis. Diarrheal stool samples should be tested for *C. difficile* toxin whenever diarrhea or abdominal pain develops in a patient with neutropenia. Metronidazole is the drug of choice for the initial episode of mild to moderate infection, and oral vancomycin is given for more severe infections.[89] Children with malignant diseases have a higher risk for recurrent disease.[90] Treatment of first recurrence usually is with the same regimen as for the initial episode, but additional recurrences generally are treated with oral vancomycin therapy using a tapered regimen.[89] A trial of adding rifampicin to metronidazole therapy did not show a trend toward better efficacy.[91] Nitazoxanide[92,93] and teicoplanin[94] are potential alternatives to traditional therapy.

Typhlitis.

The immunosuppressed patient with cancer is at increased risk of intra-abdominal infections because of invasion or obstruction of the bowel by tumor, extension of mucosal ulcerations, or sloughing secondary to chemotherapy. Typhlitis, or neutropenic cecitis, is a necrotizing process involving the cecum and terminal ileum that is seen almost exclusively in patients with cancer who have profound neutropenia (most often associated with treatment of acute myeloid leukemia).[95] Additional risk factors identified in children include the presence of mucositis, HCT, and receipt of chemotherapy in the preceding 2 weeks.[96] Typhlitis manifests with nausea, vomiting, diarrhea, and abdominal pain localized to the right lower quadrant (mimicking appendicitis) that can become generalized and usually is accompanied by fever and systemic symptoms. Because of neutropenia, many patients with peritonitis lack classic signs.[97] Concomitant bacteremia or fungemia can occur. Plain radiographs are nonspecifically abnormal unless free air or intramural pneumatosis is noted. Abdominal ultrasound examination or CT can better demonstrate cecal wall thickening, pericecal edema, fat stranding, and intramural pneumatosis of the cecum. Histopathologic examination of the bowel reveals infiltration of the bowel wall with bacteria, usually gram-negative bacilli (especially *Pseudomonas*), with little or no surrounding inflammation, and progression to necrosis in some areas. In a review of 24 cases of typhlitis over 30 years, bacteremia was documented in 8 of 24 children, and thickening of the bowel wall was present on CT scans in 17 of 20 patients studied.[81] Most patients with typhlitis respond to medical management, including complete bowel rest, parenteral nutrition, broad-spectrum antibiotic therapy, and recovery from effects of cancer therapies, including resolution of neutropenia.[98] No controlled trials have evaluated optimal antibiotic therapy for typhlitis; empiric therapy should include agents active against enteric gram-negative bacteria and *Pseudomonas*, enterococci, and anaerobes. In patients with protracted fever despite broad-spectrum antibiotics, the addition of an antifungal agent is prudent. Surgical resection of necrotic bowel can be necessary when perforation, abscess formation, uncontrolled bleeding, or necrosis occurs.[99] In adults with neutropenic enterocolitis, mortality rates can exceed 50%.[100]

Clostridium septicum Infection.

Although uncommon, a catastrophic complication of typhlitis consists of spontaneous peritonitis and septicemia caused by *Clostridium septicum.* Neutrophil dysfunction and bowel ischemia are factors associated with increased risk and severity with *C. septicum* infection.[101] Peritonitis classically manifests fulminantly with rapidly progressive abdominal wall myonecrosis, crepitance, hemolysis, and shock; fever can be absent. *C. septicum* can be part of the natural flora of the gastrointestinal tract, is more aerotolerant than *Clostridium perfringens*, and can grow in viable, non-necrotic tissue. More than 80% of patients with *C. septicum* septicemia have an underlying malignant disease.[102,103] The steps in pathogenesis are thought to be loss of mucosal integrity secondary to malignant disease or chemotherapy, microbial invasion of the bowel wall, and rapid proliferation in the setting of immunosuppression or granulocytopenia.[104] Additionally, *C. septicum* produces an α toxin that may play some role in the severity of infection. Antibiotics with anticlostridial activity must be initiated urgently if *C. septicum* infection is suspected.

Hepatosplenic candidiasis.

Hepatosplenic candidiasis (also referred to as chronic disseminated candidiasis) is an invasive form of candidiasis that occurs in patients with cancer, especially patients with prolonged neutropenia. Clinical clues are persistent fever during neutropenia that is unresponsive to broad-spectrum antibiotics and, sometimes, right upper quadrant abdominal pain or tenderness and an elevated serum alkaline phosphatase level. Hepatosplenic candidiasis can occur despite antifungal therapy. Most often, multiple cultures from blood, urine, and other sites are sterile. Typical hepatic “bull's eye” lesions noted on ultrasonography or hypodense lesions can be seen as the neutrophil count begins to recover. Magnetic resonance imaging may be the most sensitive study. Before recovery of the inflammatory response, hepatic lesions can be missed by all imaging techniques available. The detection of *Candida* enolase antigen and d-arabinitol and mannan antibodies in serum has been used as an additional tool for diagnosing invasive candidiasis.[105–107] Confirmation of the diagnosis can require liver biopsy. Treatment usually requires a prolonged course of antifungal therapy.[108] Amphotericin B lipid complex has been shown to be effective in the treatment of hepatosplenic candidiasis.[109] Fluconazole has been used as salvage therapy in patients in whom amphotericin B treatment failed or who had serious amphotericin B–related toxicities, or as step-down oral therapy in improved patients.[31,52,110,111] Treatment failures with fluconazole in this setting, however, have been reported. Determining the appropriate end point of antifungal therapy is challenging, often depending on resolution or calcification of visualized lesions; antifungal therapy should be continued through periods of chemotherapy-induced immunosuppression.

Perianal Cellulitis

Although, in general, children have fewer chemotherapy-related perirectal lesions than do adults, children are prone to develop mucositis involving the rectal mucosa. These lesions provide a focus for local cellulitis or abscess, usually involving enteric gram-negative facultative and anaerobic organisms. Multiple organisms, most commonly anaerobes, are identified in most cases in which surgical drainage or needle aspiration is performed.[112] Most patients can be treated effectively with antibiotics alone. Appropriate choices include piperacillin-tazobactam, meropenem, or a fourth-generation cephalosporin, in combination with metronidazole.

Central Nervous System Infections

Infections of the CNS occur infrequently in children undergoing chemotherapy for cancer. These infections must be considered in children who have had a neurosurgical procedure. Placement of an intraventricular shunt poses an additional risk of infection; 25% of children experience a related CNS infection, but death is rare.[113] Indolent infections are most common with organisms of low pathogenicity, such as *Staphylococcus epidermidis* and *Propionibacterium acnes*; many shunt-associated infections can be resolved without removing the device. Because of the vague nature of associated symptoms, any child with a CNS device who has fever and no localizing findings should have cerebrospinal fluid sampled for cell count, chemical evaluation, and culture.

Although meningitis in patients with cancer is uncommon (one study noted that less than 0.9% of febrile neutropenic episodes in pediatric patients with cancer were caused by CNS infections[114]), but it is associated with significant mortality and morbidity rates.[115] Patients with fever and a change in mental status should be evaluated, diagnostic tests should be performed, and empiric therapy should be initiated promptly. Some studies have reported meningeal signs only in a minority of neutropenic patients or in patients who have had neurosurgical manipulation who develop meningitis[116–118]; thus the absence of meningeal signs does not exclude the diagnosis of meningitis. In a retrospective review of 40 cases of bacterial or fungal meningitis in pediatric patients with cancer, most patients (65%) had had recent neurosurgical procedures, a CNS device placed, or a cerebrospinal fluid leak, and one third of patients had neutropenia.[115] Fever and altered mental status were the most consistent signs; meningismus was notably less frequent in neutropenic patients. *S. aureus* and *S. pneumoniae* were the most common pathogens. Of the 5 patients with fatal outcomes, all were neutropenic at presentation. Candidal meningitis in children with cancer is rare but has high mortality rates.[119] Similarly, although the incidence of CNS *Aspergillus* infection is low, the mortality rate approaches 100%. A retrospective review of 81 adults with definite or probable CNS aspergillosis who were treated with voriconazole showed complete or partial response in approximately one third, as well as improved survival rates in patients who underwent therapeutic neurosurgical procedures.[120] In published data in children, CNS aspergillosis commonly manifested as brain abscesses, and as in adults, surgical management was associated independently with improved survival rates.[121,122]

Cystitis

Hemorrhagic cystitis, manifesting as bladder pain and significant gross hematuria, has been reported in bone marrow transplant recipients. Adenovirus (particularly type 11), CMV, and polyomavirus (BK virus) are causative agents. PCR detection of viruses is possible in both urine and blood.[123] Older age, receipt of HCT, and detection of BK virus were associated with risk of hemorrhagic cystitis and greater disease severity in children.[124] Although case reports documenting successful treatment of adenovirus and polyomavirus hemorrhagic cystitis with intravenous ribavirin, vidarabine, cidofovir, and ganciclovir have been reported, case-controlled randomized studies have not been performed to confirm benefit.[125–128]

Osteoarticular Infections

Bone and joint infections occurring in patients with cancer also are relatively rare. Children with soft tissue or bone tumors are at risk of infectious complications related to surgical tissue trauma or to destruction by the tumor. It can be difficult to distinguish osteomyelitis from tumor or the effects of local radiation. Any organism that can lead to bacteremia or fungemia (e.g., *Aspergillus* spp.,[129]) can cause osteomyelitis or arthritis. Diagnosis and treatment can be particularly complex in children who have had limb-sparing procedures involving bone and joint prostheses and whose longterm stability of the prosthesis is of concern. Serial imaging studies can suggest infection, but biopsy and culture of the involved bone are necessary for definitive diagnosis. Longterm antimicrobial therapy is mandatory when infection occurs, and revision of the prosthesis often is required for cure.[130]

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Infections Associated With Hospitalization and Medical Devices

OUTLINE

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99

Healthcare-Associated Infections

Jane M. Gould, Susan E. Coffin

A *healthcare-associated infection (HAI)* is defined as any infection not present or incubating at the time of the patient's initial contact with a healthcare setting. Originally termed *nosocomial, hospital-acquired,* or *hospital-onset infections,* the scope of HAI has expanded because patients now receive medical care in a wide variety of healthcare settings. Many HAIs are preventable and thus should be targeted for aggressive infection prevention programs (see Chapter 2). In 1985, the Study on the Efficacy of Nosocomial Infection Control (SENIC) project found that 5.7% of 169,526 patients hospitalized in 338 randomly selected US hospitals had an infection.[1] This group of investigators estimated that 32% of these hospital-onset infections could have been averted by the application of known principles and practices of infection prevention. We now know that most HAIs are preventable. Marked reductions in the rates of central line–associated bloodstream infections (CLABSIs), ventilator-associated pneumonia (VAP), and surgical site infections (SSIs) have been achieved through meticulous adherence to evidence-based practices.[2–6]

HAIs are common in children[7,8] (Tables 99.1 and 99.2). Rates, sites of infection, and microbiologic features of pediatric HAIs differ from those of HAIs in adults. Although children are less likely to have comorbid conditions that increase the risk of specific device-associated HAIs, they have greater risk of acquiring nosocomial viral infections because of the large reservoir of easily transmissible viruses in sites where children receive medical care. Bloodstream infections (BSIs) are the most common HAIs in children, whereas catheter-related urinary tract infections predominate in adults.[8] Rates of HAI in children vary by birth weight, age, underlying diseases, and intensity of medical care. Rates are highest in children <1 year of age and in children who require intensive care, especially in neonatal intensive care units (NICUs).[9–13] Risk factors in these patients are similar to those that predispose older patients to infections, such as severe underlying illness, loss of skin and mucosal barrier integrity, or the presence of multiple medical devices that breach normal defense mechanisms. Multidrug-resistant organisms are becoming more prevalent as causes of HAIs in both adult and pediatric populations. Of hospitals reporting to the National Healthcare Safety Network (NHSN) during the 2-year period from 2009 through 2010, approximately 20% of all HAIs were caused by multidrug-resistant organisms.[5] In a study matching patients infected with the same organism, antimicrobial resistance in both HAIs and community-associated infections was associated with higher charges, longer hospitalizations, and increased death rates.[14]

TABLE 99.1

Distribution of Pathogens by Infection Type Reported to the National Healthcare Safety Network, 2009 to 2010[a]

Pathogen	Number of Infections	Percentage (%)
CENTRAL LINE–ASSOCIATED BLOODSTREAM INFECTION		
Coagulase-negative staphylococci	6245	20.5
Enterococcus spp.	5501	18.1
Candida spp.	4439	14.6
Staphylococcus aureus	3735	12.3
Klebsiella pneumoniae/oytoca	2407	7.9
Enterobacter spp.	1365	4.5
Escherichia coli	1206	4
Pseudomonas aeruginosa	1166	3.8
VENTILATOR-ASSOCIATED PNEUMONIA		
S. aureus	2043	24.1
P. aeruginosa	1408	16.6
K. pneumoniae/oxytoca	854	10.1
Enterobacter spp.	727	8.6
Acinetobacter baumannii	557	6.6
Escherichia coli	504	5.9
CATHETER-ASSOCIATED URINARY TRACT INFECTION		

Escherichia coli	5660	26.8
Enterococcus spp.	3183	15.1
Candida spp.	2698	12.7
P. aeruginosa	2381	11.3
K. pneumoniae/oxytoca	2365	11.2

[a]Data include pathogens reported from adult and pediatric patients.

TABLE 99.2

Rates of Pediatric Healthcare-Associated Infections by Site in Hospital, From the National Healthcare Safety Network, 2013

Infection Type and Hospital Site	Pooled Mean[a]	Median (25%, 75%)[a]	Device Use[b]
CENTRAL LINE–ASSOCIATED BLOODSTREAM INFECTION			
PICU (medical/surgical)	1.2	0.7 (0, 1.7)	0.45
Pediatric CICU	1.3	1.2 (0.5, 2.0)	0.72
Pediatric inpatient unit	1.1	0 (0, 1.5)	0.20
Pediatric hematology/oncology unit	2.1	0.7 (0, 3.1)	0.20
Level III NICU (by birth weight):			
≤750 g	2.1	1 (0, 3.5)	0.39
751–1000 g	1.3	0 (0, 1.9)	0.33
1001–1500 g	0.8	0 (0, 0.9)	0.26
1501–2500 g	0.6	0 (0, 0)	0.17
≥2500 g	0.7	0 (0, 0)	0.23
CATHETER-ASSOCIATED URINARY TRACT INFECTION			
PICU (medical/surgical)	2.5	1.4 (0, 3.6)	0.21
Pediatric CICU	1.2	0.5 (0, 1.6)	0.21
Pediatric inpatient unit	3.4	0 (0, 5.0)	0.16
VENTILATOR-ASSOCIATED PNEUMONIA			
PICU (medical/surgical)	0.7	0 (0, 0.8)	0.37
Pediatric CICU	0.4	NA	0.39
Level III NICU (by birth weight):			
≤750 g	1	0 (0, 1.5)	0.38
751–1000 g	1.1	0 (0, 0)	0.22
1001–1500 g	0.7	0 (0, 0)	0.10
1501–2500 g	0.5	0 (0, 0)	0.06
≥2500 g	0.1	0 (0, 0)	0.1

[a]Rate of device-related infection per 1000 device-days.

[b]Device use = number of device-patient days / number of total patient days × 100.

CICU, cardiac intensive care unit; NICU; neonatal intensive care unit; PICU, pediatric intensive care unit.

From Centers for Disease Control and Prevention, National Healthcare Safety Network. Annual Report, 2013. http://www.cdc.gov/nhsn/datastat/index.html.

The NHSN, which is the most widely recognized source of US national data on hospital infections, is coordinated by the Centers for Disease Control and Prevention (CDC). Definitions of select neonatal HAIs are included, as are unique clinical manifestations in young children. Criteria for definitions of pneumonia and BSI are aged based: for patients ≤12 months and >12 months of age.[15] Because the NHSN provides HAI definitions and standard surveillance protocols, NHSN data are used commonly for benchmarking purposes.[16–18] Investigators have demonstrated repeatedly that significant differences in the application of standardized HAI definitions can undermine their valid use for interinstitutional comparisons.[19,20]

Bloodstream Infections

Device-Associated Infections

BSIs are the most common HAIs (see Table 99.1).[8] Among hospitalized and chronically ill patients, most CLABSIs and non-CLABSIs are related to the use of intravascular catheters. (see Chapter 100). In addition, pediatric patients are at risk for BSIs as a result of contaminated intravenous fluids or medications, blood or blood products, or dissemination from a distant site of infection.

Infections Associated With the Transfusion of Blood and Blood Products

Epidemiology and Pathogenesis.

The overall rate of infectious complications of blood transfusions is unknown, with estimated rates of contamination by bacteria, viruses, and protozoa varying substantially. The rate of bacterial contamination is estimated at 1 per 500,000 units of red blood cells and 1 per 10,200 units of random-donor platelets.[21] Use of apheresis platelets reduces the risk of transfusion-associated sepsis resulting from platelet contamination. In addition, blood transfusion is an independent risk factor for a variety of HAIs.[22] Although all fatalities associated with the transfusion of blood and blood products must be reported by law to the US Food and Drug Administration (FDA), some fatalities associated with transfusions can go unrecognized.

Although relatively rare, a wide variety of pathogens can be transmitted by blood transfusion. (Table 99.3). At present, the American Red Cross Blood Services screens each donor for risk of transmissible disease by questionnaire. Additionally, each unit of donated blood undergoes the following tests: rapid plasma reagin antibody for syphilis; surface antigen and core antibody for hepatitis B virus (HBV); nucleic acid amplification test for HBV DNA (since 2009), HIV-1 RNA (since 1999), HCV RNA (since 1999) and West Nile virus RNA (since 2003); antibody to hepatitis C virus (HCV); antibody to HIV types 1 and 2; antibody to human T-lymphotropic virus (HTLV) types 1 and 2; and enzyme immunoassay for *Trypanosoma cruzi* (Chagas disease) (since 2007).[23–26] Selective screening is performed in at-risk geographic areas for pathogens such as Dengue virus and *Babesia microti*. Since the introduction of screening for bloodborne pathogens and active education programs to pre-screen potential donors, the risk of infection is extremely low: 1 in 1,000,000 donations for HBV, 1 in 2,135,000 donations for HIV, 1 in 1,930,000 donations for HCV infection.[27,28] At present, the combined risk of transfusion-related infection with HIV-1, HIV-2, HTLV-1, HTLV-2, HBV or HCV is lower than the risk of a transfusion-related bacterial infection.[29,27,28]

TABLE 99.3

Predominant Infectious Agents Associated With Specific Blood Products

Blood Component	Storage Conditions	Predominant Organisms
Red blood cells	1°–6°C for 35–42 days	*Yersinia enterocolitica* *Pseudomonas* spp.
		Other gram-negative organisms
		Staphylococcus spp. *Propionibacterium* spp.
Platelets	20°–24°C for 5 days	*Staphylococcus* spp.
		Diphtheroids
		Bacillus spp.
		Salmonella spp. *Serratia* spp.
		Escherichia coli
		Enterococcus spp.
		Flavobacterium spp.
		Streptococcus spp.
Whole blood	1°–6°C for 35–42 days	Skin organisms, gram-negative organisms
Plasma	−18°C; thawed, 1°–6°C for ≥24 hr	*Staphylococcus* spp. *Propionibacterium* spp. *Pseudomonas aeruginosa*

Almost all reported acute infectious complications and most fatalities associated with the transfusion of blood products are due to bacterial pathogens. The manner in which a blood product is obtained, processed, and stored is a major determinant of pathogens transmitted.[30] For example, *Yersinia enterocolitica* and *Pseudomonas* species are associated with cold storage of red blood cells, while skin flora and gram-negative bacilli are more associated with whole blood and platelet transfusions (see Table 99.3). The FDA and the AABB (originally known as the American Association of Blood Banks) dictate the safe storage and handling of various blood products.[21] Various additional sources for contamination of blood and blood products have been identified, including the donor, equipment used to obtain and process the blood product, and procedures used for blood product administration. The FDA approved 3 new pathogen-reduction technologies capable of inactivating pathogens in donated blood components (i.e., platelets and plasma). Additional tests of whole blood and red blood cells are in phase II and III studies, which, if implemented, would further improve the safety of the blood component transfusion.[31]

Clinical Manifestations and Management.

Signs and symptoms associated with the transfusion of contaminated blood or blood products vary according to the characteristics and concentration of the microorganism and the severity of the recipient's underlying illness and immunologic compromise. Signs and symptoms of transfusion-related BSI range from mild fever to overwhelming septicemia with endotoxic shock.

In a patient who is receiving or has recently received (usually within 2 hours) a transfusion, the sudden onset of high fever and chills should raise the suspicion of transfusion-associated BSI. The transfusion must be discontinued immediately; the blood product should be examined visually for abnormalities such as hemolysis, clumping, and discoloration, and the residual blood product and the administration set should be refrigerated for further testing. Culture-confirmed episodes of transfusion-associated septicemia should be reported to the FDA Center for Biologics Evaluation and Research (301-827-6220; e-mail: fatalities2@cber.fda.gov).

Prevention.

Donor self-deferral and appropriate screening are essential to identify and exclude donors with potentially transmissible diseases.[30] Screening consists of a full history of recent illnesses and travel, as well as serologic and nucleic acid amplification test screening of donor blood. Despite laboratory-based screening, donors with asymptomatic or incubating infections can be missed. To enhance the safety of transfused blood, potential blood donors are asked to defer donation if they are known or suspected to have infection with West Nile virus or have recently returned from an area where malaria is endemic. Blood donation also is prohibited by people with a history of babesiosis or Chagas disease or people at risk of Creutzfeldt-Jakob disease or variant Creutzfeldt-Jakob disease.[32]

Meticulous aseptic technique must be used when performing venipuncture to avoid transfusion-related BSI resulting from skin flora. Contamination can occur from introduction of bacteria during blood collection or through withdrawal of a skin plug during venipuncture.[33,34] Even with appropriate skin antisepsis, skin plugs can harbor normal skin flora that could proliferate (especially in platelet concentrates stored at room temperature). Use of contaminated equipment during the collection or processing of blood also can lead to transfusion-associated infections.[35–37]

Respiratory Tract Infections

Epidemiology and Pathogenesis

Various healthcare-associated respiratory tract infections threaten hospitalized children, including pneumonia secondary to aspiration and VAP. Absence of preexisting immunity, an abundant reservoir of viruses in pediatric facilities and units, and children's behaviors and caretaking needs contribute to the increased risk of viral respiratory tract infection among children compared with adults. A nasopharyngeal or nasogastric tube can interfere with normal drainage of the sinuses and the eustachian tubes,[38,39] and these devices have been associated with healthcare-associated sinusitis and otitis media.[40,41]

Pneumonia.

The CDC estimated that 157,500 cases of healthcare-associated pneumonia occurred in acute care hospitals in the United States in 2011.[42] Overall, pneumonia and SSIs were the most common HAIs, each representing 21.8% of the total HAI burden as identified by the CDC Emerging Infections Program.[43,44] The NHSN data summary for 2013 reported that VAP was the third most prevalent device-associated infection in children and that VAP occurred more frequently in the neonatal population.[8] VAP is associated with increased morbidity and hospital costs.[45] The attributable mortality rate of VAP is estimated to be approximately 10% in adults.[46–48] Data from pediatric populations are more limited, but mortality rates appear to be lower in children; however, multivariate analyses of predictors of death have not been performed in children with VAP.[49–51]

Aspiration Pneumonia.

Although bacterial pneumonia can occur through hematogenous spread or aerosolization, most cases result from aspiration of bacteria that colonize the upper airway or gastric mucosa of a hospitalized or chronically ill patient.[52–55] Although the most common source of organisms is controversial, studies of ventilated patients have shown that enteric and gram-positive organisms begin to colonize these areas within hours of intubation.[52,55] Microaspiration of bacteria into the trachea is hypothesized to be a primary mode of pathogenesis.[56] Risk factors for aspiration include preexisting neurologic or neuromuscular conditions, decreased gastric motility, placement of an endotracheal tube, and sedation, which can lead to pooling of oral secretions.[57,58] When oropharyngeal secretions carrying pathogenic bacteria are aspirated into the lower airway, a polymicrobial pneumonia can ensue. In contrast, a noninfectious chemical pneumonitis can follow aspiration of gastric secretions; it typically has a more rapid onset (e.g., within 6 hours of aspiration) and often is not accompanied by fever.[59] Nonetheless, differentiation of bacterial from chemical causes of lower respiratory tract disease can be difficult.

Ventilator-Associated Pneumonia.

The epidemiology of VAP is well described in adults, but few data exist for pediatric patients, who appear to have a lower incidence of VAP. Pathogenesis of VAP in adults and children presumably is similar. Alterations in the glycoprotein fibronectin, which coats the respiratory epithelium, can occur within hours of hospitalization and can enhance the adherence of gram-negative bacilli to the respiratory mucosa.[60–62] An endotracheal or nasotracheal tube provides the conduit by which organisms colonizing the oropharynx or nasopharynx migrate to the lower respiratory tract. Artificial airway devices also inhibit host defenses such as the gag reflex and ciliary function, and they provide a substrate for the formation of biofilms.[52,55] Biofilms, another reservoir of pathogenic bacteria, can be dislodged through mechanical suctioning or high-pressure airflow and delivered directly to the lower respiratory tract. Mechanical ventilation also has been shown in animals to increase toll-like receptor 3–mediated lung inflammation and permeability.[63]

Bacteria that cause VAP also can arise from aspirated material from the digestive tract. A study of adults in intensive care units (ICUs) found significantly higher levels of total bile acids in oral secretions of patients with VAP compared with control subjects, a finding suggesting that gastroesophageal reflux can play a role in the development of VAP.[64] At normal pH (1–2), the gastric mucosa does not support the growth of bacteria that typically cause VAP. However, use of proton-pump inhibitors and histamine type 2 (H_2)–receptor antagonists for prophylaxis against stress ulcer promotes changes in the colonization of the upper gastrointestinal tract. Studies of critically ill adults have shown repeatedly that patients receiving such prophylactic agents have a higher rate of VAP than do patients who receive the cytoprotective agent sucralfate.[65,66] Thus the risk of pneumonia must be balanced against the risk of clinically significant gastrointestinal bleeding.

Risk factors for VAP in children also include the presence of a genetic syndrome, reintubation, neuromuscular blockade, and immunosuppression.[49] The risk of VAP in neonates increases with decreasing postconceptual age, antecedent BSI, and increasing duration of intubation.[12,67,68]

Pseudomonas aeruginosa and methicillin-resistant *Staphylococcus aureus* (MRSA) are the most common organisms recovered from critically ill children with VAP.[13,49,69,70] NICU patients also have a risk of VAP caused by *Enterococcus* (group B *Streptococcus*) and methicillin-susceptible *S. aureus* (MSSA).[68] Respiratory viruses have been recovered from the lower respiratory tract in children with VAP in the absence of other pathogens.

Viral Respiratory Tract Infections.

Viruses are the most common causes of healthcare-associated upper and lower respiratory tract infections in children. Most nosocomial viral infections have exogenous sources (e.g., from family members or other visitors), occur during community outbreaks, and have the potential for widespread transmission within healthcare settings.[71–73] The hospital environment can become contaminated with respiratory viruses that can persist on inanimate surfaces. Factors such as visitation (especially of young siblings), playroom use, reluctance by ill healthcare personnel (HCP) to use sick leave, and low influenza vaccination rates among HCP contribute to an increased burden of viral HAIs. A survey of advanced-practice clinicians and physicians at a children's hospital revealed knowledge that working while ill put their patients at risk, but most HCP worked while ill (for a variety of reasons). The most common symptoms of HCP working while ill were respiratory, but 30% of HCP who worked while ill reported diarrhea, and 16% reported fever.[74]

Both children with underlying conditions and acutely ill patients are at risk for viral pneumonia.[65] Many viruses, including adenovirus, influenza virus, measles virus, parainfluenza virus, respiratory syncytial virus (RSV), human metapneumovirus, rhinoviruses, and varicella-zoster virus, can cause healthcare-associated pneumonia. Among viral respiratory tract pathogens, the modes of transmission of RSV have been studied most carefully.[71,75–77] Both droplet transmission from close contact with infectious people and indirect contact transmission through hands or fomites contaminated by secretions occur during hospital-based outbreaks, RSV-contaminated hands probably are the predominant means of cross-infection.[78,79] Other respiratory viruses, such as influenza virus, most often are transmitted by respiratory droplets. However, the possible role of airborne transmission of influenza has led to newer recommendations for the use of enhanced respiratory protection and environmental controls when performing aerosol-generating procedures on patients with known or suspected influenza virus infection.[80]

Clinical Manifestations and Laboratory Diagnosis

Ventilator-Associated Pneumonia.

VAP is difficult to confirm. The classic findings associated with lower respiratory tract infection (fever, cough, production of purulent sputum, and a new or progressive pulmonary infiltrate on chest radiographs) are not present consistently or can represent another process, such as atelectasis or acute respiratory distress syndrome.[81] The NHSN developed guidelines for the diagnosis of VAP in pediatric patients based on clinical and radiographic criteria; the sensitivity and specificity of these criteria are poor.[82–86] Because of the inherent subjectivity associated with elements of the VAP diagnostic criteria, the NHSN implemented a surveillance definition for adult *ventilator-associated events* (VAE) in 2013 that uses objective criteria and expands the focus of surveillance to include additional complications of mechanical ventilation, both infectious and noninfectious. VAE includes ventilator-associated condition (VAC), defined by respiratory deterioration after a period of stability while the patient is being mechanically ventilated; and infection-related ventilator-associated complication (iVAC), a subset of which can be VAP. CDC studies addressing performance of these definitions in pediatrics are ongoing, but preliminary data suggest that pediatric patients, including neonates with VAC, have higher risks of morbidity and death regardless of ventilatory thresholds (fraction of inspired oxygen and mean airway pressure) used.[87]

According to the NHSN, VAP should be considered when pneumonia develops in a patient who has received mechanical ventilation for >2 calendar days (with day of ventilator placement being day 1, and the ventilator being used 1 day before or on the day of the event). If the patient is admitted or transferred into a facility while he or she is on a ventilator, the day of admission is considered day 1. Currently, 3 NHSN pneumonia definitions (PNU1, PNU2, and PNU3) exist, according to the microbial origin of the infection or the immune status of the intubated patient. Each definition requires compatible signs and symptoms of lower respiratory infection, imaging findings, and laboratory evidence of infection. PNU1 is further differentiated by the age of the patient.[83] Accurate diagnosis is more likely when specimens are obtained by bronchoscopy, lung biopsy, lung aspiration, protected-specimen brush technique (whether bronchoscopic or nonbronchoscopic), or transtracheal aspiration rather than by aspiration of tracheal contents through an endotracheal tube.[84–88] The isolation of potentially pathogenic bacteria from such specimens does not confirm VAP because recovery of bacteria could represent lung colonization or infection at another site (e.g., sinusitis or tracheobronchitis). The use of clinical criteria in addition to positive sputum or tracheal culture results has low specificity for VAP.[89,90] Advances in the diagnosis of VAP in adults have included the use of bronchoalveolar lavage or protected sample brush to obtain secretions of the lower respiratory tract for quantitative culture. However, these procedures are not used routinely in children because of technical difficulties and the potential for complications. In NICU patients, it is difficult to obtain any specimen through the endotracheal tube other than suctioned secretions. In a study comparing diagnostic methods in children, quantitative culture of lower respiratory tract secretions obtained by blind, protected bronchoalveolar lavage was the most reliable diagnostic test; a bacterial index (the sum of the $\log_{10}$ of all species obtained by bronchoalveolar lavage) of >5 was predictive of VAP.[81]

The Clinical Pulmonary Infection Score (CPIS), a tool used to identify adult ICU patients with pulmonary infection, demonstrated good correlation and subsequently was modified and evaluated as a tool to limit unnecessary antibiotic use in an adult ICU. Patients found to be at low risk for infection by the modified CPIS were managed successfully with a short course of empiric antibiotic therapy.[91] Additionally, use of the modified CPIS resulted in significantly lower antimicrobial therapy costs and antibiotic resistance, without adversely affecting patients' mortality rates and lengths of ICU stay. Clinical scoring systems to establish a diagnosis of bacterial pulmonary infection have not been validated in pediatrics. Many children with presumed VAP may not have significant bacterial infections.

Viral and Other Respiratory Tract Infections.

The accurate diagnosis of healthcare-associated (HA) viral respiratory tract infections relies on the availability of certain viral diagnostic procedures. Although few antiviral therapies exist, accurate diagnosis can uncover a problem, permit prompt infection prevention measures to reduce widespread transmission, and reduce unnecessary use of antibiotics.[92,93] Detection of virus (by culture), viral antigen (by immunoassays), or viral genome (by polymerase chain reaction [PCR]) in a specimen obtained from the respiratory tract, combined with clinical and radiographic findings consistent with lower respiratory tract infection, generally is accepted as confirmation of viral pneumonia.[83] For viruses that can be shed for prolonged periods (e.g., bocavirus, rhinoviruses, and some adenoviruses) or are latent and can reactivate (e.g., herpes simplex virus or cytomegalovirus), confirmation of a causal role is more difficult and can require histologic examination of tissue or demonstration of increasing viral load determined by quantitative PCR. The NHSN definition of viral pneumonia and of *Legionella* and other bacterial pneumonias (PNU2) includes imaging evidence in addition to signs and symptoms compatible with pneumonia (as described earlier) and laboratory evidence by at least one of the following means: culture of virus, *Legionella,* or *Chlamydophila* from respiratory secretions; nonculture diagnostic tests of secretions or tissue for virus, *Bordetella*, *Chlamydophila*, *Mycoplasma*, or *Legionella* spp. (e.g., enzyme immunoassay, shell vial assay, PCR); a fourfold rise in pathogen anti–immunoglobulin G in paired acute and convalescent sera; or detection of *Legionella pneumophila* serogroup 1 antigen in urine by radioimmunoassay or enzyme immunoassay.[83]

Management and Outcome

Ventilator-Associated Pneumonia.

Empiric management of suspected bacterial pneumonia depends on both patient-specific and hospital-related considerations. All of the following should be considered: the patient's underlying disease, previous antimicrobial therapy, mental status (and other conditions that increase the risk of aspiration), and length of hospitalization; the results of Gram stain examination of respiratory tract specimens; and detailed knowledge of the hospital's antibiogram for bacterial pathogens derived from microbiologic surveillance data.

Empiric treatment for VAP generally is given when a new infiltrate is visualized on chest radiographs in association with fever, an increase in quantity or purulence of respiratory tract secretions, a rising neutrophil count, or an unexplained decrease in oxygen saturation. Gram stain and culture of respiratory tract secretions commonly are used to support the diagnosis. Guidelines for the treatment of adults with HA pneumonia and VAP are available from the Infectious Diseases Society of America,[94] but many of the principles likely apply well to children.

The outcome of HA pneumonia varies by the characteristics of both the patient and the pathogen. VAP is associated with significant morbidity and death, particularly in neonates; the case-fatality rate for neonates is reported to be 10%, and extremely premature infants have a fatality rate of 27%. Among pediatric ICU (PICU) patients, the reported fatality rate is approximately 6%. VAP is associated with prolonged ICU and hospital stay in both NICU and PICU patients.[49] Because delays in the initiation of appropriate therapy have been associated with increased morbidity and mortality rates,[95,96] empiric therapy should be broad based. Negative results of lower respiratory tract cultures from specimens taken before a recent change in antibiotic therapy can be used to discontinue empiric therapy. Microbiologic results of respiratory cultures should be used to narrow antibiotic therapy. Short courses (5–7 days) of appropriate antibiotic therapy may be adequate in patients with uncomplicated VAP who have a good initial clinical response to treatment.[97]

Viral Respiratory Tract Infections.

Children with HA influenza virus infection should receive age-appropriate antiviral therapy, ideally within 48 hours of symptom onset. Data on hospitalized patients who show improved outcomes related to antiviral therapy are limited.

Although ribavirin has in vitro activity against RSV, ribavirin generally is not given for uncomplicated RSV infection.[98,99] Clinical improvement achieved during aerosolized ribavirin administration in studies has been limited or sometimes insignificant. Several studies reported therapy-associated clinical improvement and subsequent reductions in length of mechanical ventilator support;

however, findings have varied.[99,100] Treatment may be prudent in selected patients, such as patients with hemodynamically significant congenital heart disease, profound immunocompromise, or potentially life-threatening infection.

Immunotherapy with RSV monoclonal antibody has been evaluated for therapy; with no significant impact on hospital course.[101–103] RSV monoclonal antibody is not recommended or approved by the FDA for the treatment of RSV infection in any patient group.

Prevention.

The Society for Healthcare Epidemiology and the Infectious Diseases Society of America produced an evidence-based practice recommendation entitled "Strategies to Prevent Ventilator-Associated Pneumonia in Acute Care Hospitals: 2014 Update."[104] A summary of the recommendations to prevent VAP is shown in Box 99.1. Major areas for preventive interventions include avoiding aspiration, minimizing contamination of respiratory mucosa and equipment, and reducing the exposure to mechanical ventilation. Taken together, these interventions, sometimes called "bundles," can reduce the incidence of VAP substantially.[105–107]

Box 99.1

Prevention of Ventilator-Associated Pneumonia

General Strategies

- Conduct active surveillance for VAP.
- Pay careful attention to hand hygiene.
- Use noninvasive ventilation when possible.
- Minimize the duration of mechanical ventilation (assess extubation readiness daily in patients without contraindications).
- Interrupt sedation once a day.
- Educate staff on VAP prevention strategies.

Strategies to Prevent Aspiration

- Maintain patients in a semirecumbent position (30–45-degree elevation). Consider lateral recumbent or reverse Trendelenburg positioning in preterm neonates.
- Avoid gastric overdistention.
- Avoid unplanned extubations and reintubations.
- Use a cuffed endotracheal tube with in-line or subglottic suction. Suction oral secretions before each position change.

Strategies to Reduce Colonization of Respiratory Mucosa

- Perform regular oral care with an antiseptic solution or sterile water for preterm neonates.
- Avoid nasotracheal intubation when possible.
- Consider using alternative acid-suppressing therapy (e.g., sucralfate) in patients at low risk of gastrointestinal bleeding.
- Consider prophylactic probiotics.

Strategies to Minimize Contamination of Equipment

- Use sterile water to rinse reusable respiratory equipment.
- Drain condensate regularly, but keep circuit closed when removing condensate.
- Change circuit only when visibly soiled or malfunctioning.
- Store and disinfect respiratory therapy equipment properly.

VAP, ventilator-associated pneumonia.

Adapted from A compendium of strategies to prevent healthcare-associated infections in acute care hospitals: 2014 updates. Infect Control Hosp Epidemiol 2014;35(Suppl 2):S22–S30.

Additional study is needed to define the optimal methods to prevent HA viral respiratory tract infection in children. Macartney and colleagues[79] demonstrated that a targeted, multicomponent program designed to reduce nosocomial transmission of RSV was effective and cost-efficient. Components include: (1) prompt laboratory confirmation of infection, (2) cohorting of patients and nursing staff, and (3) use of contact precautions (gloves and gowns). Little is known about the efficacy and cost-efficiency of similar programs targeted at other pathogens. Other institutional factors, such as appropriate use of HCP sick leave, consistent visitor screening or visitor restriction (either hospitalwide or in certain units during respiratory viral season or community outbreaks), and mandatory influenza vaccination of HCP, also are important strategies to prevent transmission of respiratory viruses in healthcare settings.

Gastrointestinal Tract Infections

Epidemiology and Pathogenesis

HA gastroenteritis is relatively common but frequently overlooked because many episodes resolve quickly without specific therapy.[108] Infants and older adults are at greatest risk; a point prevalence survey in multiple pediatric acute care hospitals estimated rates of HA gastroenteritis (viral gastroenteritis in addition to *Clostridium difficile* infection) from ~1% in neonates to 3.5% in school-aged children.[108] Several factors are affecting changes in the epidemiology of nosocomial gastroenteritis. The introduction of rotavirus vaccine has led to substantial reductions in community-onset infections and appears to be associated with similar reductions in nosocomial rotavirus infections.[109] The incidence of *C. difficile* colitis among hospitalized children has risen.[110–113] Norovirus has emerged as a commonly recognized cause of both community-onset gastroenteritis and HA gastroenteritis.[114,115]

Intrinsic factors heighten the risk of gastrointestinal infections in hospitalized patients, including impairment of immunity, alterations in gastric acidity, and changes in gastric motility and intestinal flora. Several studies have shown that hematopoietic cell transplant recipients and patients with severe immunodeficiencies are at risk of repeated and prolonged episodes of HA viral gastroenteritis and *C. difficile* gastroenteritis.[116–119] Furthermore, immunocompromised people excrete high density of viruses for prolonged periods and are important reservoirs within healthcare settings.[120]

Extrinsic factors also influence the risk of HA gastroenteritis, including adherence to hand hygiene practices, use of nasogastric tubes, and use of gastric acid–suppressing medications.[121] Indirect contact through fomites or environmental contamination plays a role in the transmission of *C. difficile* and norovirus, likely related to the relative resistance of these organisms to commonly used disinfectants. Contaminated foods or other common vehicles have been associated with the transmission of *Salmonella, Shigella, Yersinia enterocolitica, Escherichia coli,* noroviruses, and *Cryptosporidium* species.[122–126]

Viral Gastroenteritis.

Viruses are among the most common causes of HA gastroenteritis in children. Norovirus infections are increasingly recognized as the cause of both sporadic and outbreak-related cases of nosocomial gastroenteritis,[127–129] and they have surpassed declining rotavirus cases.[130–132] Noroviruses cause approximately two thirds of the identified HA outbreaks of gastroenteritis, likely related to ease of transmission by direct and indirect contact, including through food or water sources.[126,127,129,130,131] Environmental contamination frequently is implicated as a cause of protracted norovirus outbreaks.[132] Immediate cohorting of ill patients, furlough of ill HCP, and implementation of stringent environmental control measures are necessary to halt transmission.

Clostridium difficile Infection.

In both children and adults, *C. difficile* infection is the most important bacterial HA gastrointestinal disease. The epidemiology of *C. difficile* infection is complex in the pediatric population, with an unsettled role of this agent in gastroenteritis in infants and young children (see also Chapter 190).[133–135] Up to 50% of healthy neonates may be colonized with toxigenic forms of *C. difficile,*[136–138] and infants can be reservoirs for community-onset *C. difficile* infection among older children and adults.[139] After the age of 2 years, colonization rates decrease to adult levels of <5%, although colonization is substantially more prevalent in hospitalized patients with or without exposure to antimicrobial agents.[133,134]

Clinically apparent disease occurs when the microbial ecology of the gut is disrupted. *C. difficile* can proliferate and elaborate potent toxins A and B, which stimulate secretory diarrhea and inflammatory colitis.[140] Although a few cases of antibiotic-associated diarrhea and not all cases of pseudomembranous colitis are caused by *C. difficile*, *C. difficile* is the most commonly identified pathogen.[141] The major risk factors for HA *C. difficile* colitis in children are exposure to a wide variety of antimicrobial agents, underlying gastrointestinal disease (including the use of percutaneous feeding tubes), and immunocompromising conditions.[142–144]

Clinical Manifestations and Laboratory Diagnosis

Viral Gastroenteritis.

Rotavirus and norovirus typically cause noninflammatory diarrhea, often associated with fever and vomiting, that frequently leads to dehydration.[145] In immunocompetent children, symptoms typically resolve within 2 to 4 days. Norovirus and rotavirus are detectable in stool samples by PCR, and rotavirus can be identified by antigen detection assays. Other agents identified in children with HA gastroenteritis include sapovirus, adenovirus 40/41, and astrovirus.[115]

Clostridium difficile Gastroenteritis.

Symptoms of *C. difficile* infection typically begin 1 to 21 days (mean, 4 days) after initiation of antimicrobial therapy. However, occasionally symptoms begin after the drug is discontinued. Associated signs and symptoms include fever, cramping abdominal pain, distention, nausea, and vomiting. Typically, overt hematochezia does not occur, although stools frequently are foul smelling and can contain occult blood.[146] Severe disease occurs in 10% to 20% of patients with HA *C. difficile* infection and includes toxic megacolon, pneumatosis intestinalis, and intestinal perforation.[140,141,146–148] HA *C. difficile* infection has been associated with an almost sevenfold increased risk of death and prolonged hospital stay in children.[149]

Advances in diagnostic assays and improved algorithms for rejecting samples (formed stools) from patients unlikely to have *C. difficile* infection have improved the predictive value of diagnostic assays.[150,151] Two-step testing algorithms that include detection of *C. difficile* organisms by glutamate dehydrogenase assays coupled with more sensitive assays to detect *C. difficile* toxin (e.g., nucleic acid amplification tests) have excellent predictive values.[152,153] Occasionally, endoscopy is required for definitive diagnosis. Lesions in the colon or small bowel are red, edematous, and friable, with multiple raised, yellowish plaques (pseudomembranes) that consist of mucus, fibrin, necrotic cells, and polymorphonuclear cells.

Management, Outcome, and Control

Viral Gastroenteritis.

Viral gastroenteritis typically is self-limited. Supportive care with careful attention to hydration status remains the cornerstone of management.[154] Rotavirus and norovirus have been shown to contaminate the fomites and persist on inanimate objects for long periods.[155] Appropriate cohorting of patients and staff, use of contact precautions, and careful attention to hand hygiene and environmental cleaning are critical to preventing transmission.[132,156,157] Because norovirus and *C. difficile* spores are resistant to alcohol, many institutions use soap and water for hand hygiene when providing care for these patients. Some experts argue that appropriate use of standard precautions (including use of gloves) obviates the need for this practice divergence when only sporadic cases of infection occur. When a cluster of norovirus or *C. difficile* cases occurs, the use of soap and water for hand hygiene is advisable.

Clostridium difficile Infection.

First-line therapy for *C. difficile* infection is discontinuation of antibiotics whenever possible and supportive care. Oral metronidazole and vancomycin are effective therapies generally, although data in adults suggest that treatment with oral vancomycin is associated with improved clinical outcomes and lower rates of recurrence.[158] Similar studies have not been performed in children. Response to treatment generally occurs within 48 hours, but some patients may not have full resolution of diarrhea and other symptoms for up to 1 week after starting therapy.

Relapse after therapy occurs in up to 35% of patients and can reflect infection with a different strain, reinfection with the same organism (often from a persistent environmental reservoir), or relapse secondary to failure to eradicate the initial infection.[159,160] Host factors such as preexisting gastrointestinal disease, immunologic impairment, and repeated exposure to antimicrobial agents, as well as the severity of the initial episode, can affect the frequency.[160] A Cochrane meta-analysis concluded that "moderate quality evidence suggests that use of probiotic agents is safe and effective for preventing *C. difficile*-associated diarrhea" in adults and children[161]; however, adoption of this practice has not been universal.

Strict adherence to infection control practices is critical to prevent nosocomial transmission of *C. difficile* gastroenteritis. Contact isolation precautions should be instituted for any patient with symptomatic infection. Because *C. difficile* commonly contaminates the inanimate environment, care should be taken to use gloves appropriately and perform hand hygiene immediately on glove removal after any contact with the patient or the patient's environment.[162] One study demonstrated an increased risk of *C. difficile* among patients occupying a room that was previously occupied by an infected patient. Careful terminal environmental cleaning of patients' rooms with a sporocidal agent is essential.

Surgical Site Infections

Epidemiology and Pathogenesis

SSIs represent 14% to 16% of all infections reported to the NHSN.[18] Using a structured sampling strategy, investigators for the Pediatric National Surgery Quality Improvement Project calculated a standardized, risk-adjusted ratio of SSIs after >30,000 pediatric surgical procedures of 1.8% and noted the highest rate of SSIs following neurosurgical procedures (Table 99.4).[163] Specific pediatric SSIs, including mediastinitis, ventricular shunt infection, and infection after placement of orthopedic prostheses, are associated with substantial morbidity and have been targeted by several different improvement collaboratives.

TABLE 99.4

Rates of Surgical Site Infections for Specific Pediatric Specialties, American College of Surgeons National Surgical Quality Improvement Program, 2010

Specialty	Surgical Site Infection Rates (%)[a]	
	All Cases	Neonates
General surgery	3.8	6.2
Otolaryngology	1.1	0
Orthopedics	2.5	2.7
Urology	1.5	2.4
Neurosurgery	6.3	12.6
Plastic surgery	3.1	0

[a] Rates have been risk adjusted using the National Surgical Quality Improvement Program hierarchical model.

Adapted from Bruny JL, Hall BL, Barnhart DC, et al. American College of Surgeons National Surgical Quality Improvement Program Pediatric: a beta phase report. J Pediatr Surg 2013;48:74–80.

Development of an SSI requires a reservoir of microorganisms, a mode of transmission, and a suitable wound. Surgical infections usually result from intraoperative seeding of the site by the patient's own flora or by inoculation with exogenous bacteria (Table 99.5). At present, the relative contribution of postoperative factors (e.g., wound management) is understood poorly.[164]

TABLE 99.5

Microbiology of Postoperative Infections in Surgical Patients

Nature of Operation	Likely Pathogens (in Alphabetic Order)
"CLEAN" SURGERY[a]	
Cardiac[b]	
Prosthetic valve, coronary artery bypass, other open heart surgery, pacemaker implant	(CoNS, *Corynebacterium* spp., enteric gram-negative bacilli, *Staphylococcus aureus*
Vascular	
Arterial surgery involving the abdominal aorta,	CoNS, enteric gram-negative bacilli, *S. aureus*

a prosthesis, or a groin incision	
Lower extremity amputation for ischemia	CoNS, *Clostridium* spp., enteric gram-negative bacilli, *S. aureus*
Orthopedic	
Total joint replacement, internal fixation of fractures	CoNS, *S. aureus*
Ophthalmic	CoNS, enteric gram-negative bacilli, *Pseudomonas, S. aureus, Streptococcus* spp.
Head and Neck	
Incisions through oral cavity or pharynx	Anaerobic bacteria, enteric gram-negative bacilli, *S. aureus*
Craniotomy	CoNS, *S. aureus*
Abdominal	
Gastroduodenal[c]	Enteric gram-negative bacilli, gram-positive cocci
Biliary tract[d]	*Clostridium* spp., enteric gram-negative bacilli, *Enterococcus* spp.
Colorectal	Anaerobic bacteria, enteric gram-negative bacilli, *Enterococcus* spp.
Appendectomy, nonperforated	Anaerobes, enteric gram-negative bacilli, *Enterococcus* spp.
“DIRTY” SURGERY[e]	
Ruptured viscus	Anaerobes, enteric gram-negative bacilli, *Enterococcus* spp.
Traumatic wound[f]	*Clostridium* spp., group A *Streptococcus, S. aureus*

[a] Parenteral prophylactic antimicrobial agents can be given as a single intravenous dose just before the operation. For prolonged operations, additional intraoperative doses should be given every 4 hours for the duration of the procedure.

[b] An additional dose can be given after patients are removed from bypass during open heart operations.

[c] Morbid obesity, decreased gastric acidity, or decreased gastrointestinal motility.

[d] Acute cholecystitis, nonfunctioning gallbladder, obstructive jaundice, or common duct stones.

[e] For “dirty” surgical procedures, therapy usually should be continued for 5 to 10 days.

[f] For bite wounds, likely pathogens also can include oral anaerobic bacteria, *Eikenella corrodens* (human), and *Pasteurella multocida* (dog and cat).

CoNS, Coagulase-negative staphylococci.

Adapted from Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm 2013;70:195–283.

The risk of an SSI is influenced strongly by both patient-related and procedure-related risk factors. Patient-related risk factors in children associated with SSIs include comorbid conditions (including genetic syndromes),[165–167] obesity,[168,169] and prematurity.[170,171] Race also may be an independent risk factor for SSIs, although further understanding and confirmation are needed.[172,173] Procedure-related factors include the type (clean vs.

clean-contaminated vs. dirty) and length of the surgical procedure,[17,174,175] appropriate use of perioperative antibiotics,[166,176,177] use of a medical device during the procedure,[171,172] and the presence of a remote infection.[178,179] Although evidence from pediatric studies is sparse, other risk factors associated with SSIs include immune status, method of preoperative hair removal,[180] and surgical technique.[181,182]

Cardiac Surgery.

Children who undergo surgical repair of congenital heart disease have a high risk of SSI. The incidence of superficial wound infections after median sternotomy is difficult to estimate because of the challenges differentiating normal wound healing from changes associated with early infection. Sternal osteomyelitis after median sternotomy is a rare but serious complication, often requiring reoperation for debridement and prolonged courses of antibiotics. The most serious infectious complication after pediatric cardiac operations is mediastinitis, with an estimated incidence ranging from 0.1% to 5%. Procedures performed in neonates or that involve delayed sternal closure have the highest reported rates of mediastinitis.[183,184] Factors independently associated with pediatric mediastinitis include young age, prolonged preoperative hospitalization, preoperative ventilator support, and genetic abnormalities.[184,185] Other risk factors for pediatric cardiac SSIs (including superficial infections, deep infections, and mediastinitis) include prolonged use of intracardiac pacing wires, previous operation, colonization with MRSA, and delayed sternal closure.[165,186–189]

Staphylococci are the predominant pathogens causing postoperative mediastinitis.[190] In children, *S. aureus* accounts for 38% to 96% and coagulase-negative staphylococci account for 10% to 52% of episodes of mediastinitis.[191–193] Gram-negative organisms and *Candida* spp. are less common, although a case series reported that gram-negative pathogens caused 30% of cases.[193,194]

Ventricular Shunt Placement.

Each year in the US, approximately 20,000 pediatric neurosurgical procedures are performed to place a shunt to drain cerebrospinal fluid (CSF). Substantial risk exists for both superficial and deep postoperative infections.[195] Because the proximal tip of the shunt catheter usually is placed within the ventricular cavity, SSIs often consist of localized ventriculitis (in children with obstructive hydrocephalus) or meningitis (in children with free circulation of CSF). Approximately 10% of newly placed CSF shunts become infected within 1 year, with an escalating risk with each subsequent CSF shunt procedure.[196] Additional risk factors include prematurity, shunt revision within 90 days, postoperative CSF leak, and intraoperative breach in aseptic technique.[197–199] Skin organisms such as *S. aureus* and *Staphylococcus epidermidis* are the most common causes of CSF shunt infections.[200,201] Infections with *Proprionibacterium spp.* can be particularly indolent and difficult to diagnose because of the fastidious nature of these organisms.

Spinal Fusion.

The risk of SSI after pediatric spinal fusion is highly associated with specific patient-related characteristics. Adolescents undergoing spinal fusion for idiopathic scoliosis a have 0.5% to 1.6% risk of SSI, whereas children with associated neurologic or neuromuscular conditions have an SSI risk of ≥20%.[167] Factors such as bowel incontinence, malnutrition, and a need for instrumentation that extends to the pelvis are thought to underlie a heightened risk.[202] The microbiology of SSI after spinal fusion also varies by patient-related factors. *S. aureus, S. epidermidis,* and *Propionibacterium acnes* are common causes of SSI in teens with idiopathic scoliosis, whereas gram-negative bacilli are more prevalent in children with nonidiopathic scoliosis.[167]

Clinical Manifestations and Laboratory Diagnosis

A surgical wound is not infected if it heals primarily without discharge. In contrast, a wound can be considered infected if purulent discharge develops, even if microorganisms are not recovered from culture of discharge fluid.

For surveillance purposes, the NHSN classifies SSIs into incisional infections and organ or space (i.e., involving the surgical bed or other tissues) infections. Incisional infections are subdivided into superficial (involving only the skin and subcutaneous tissue) and deep (involving fascia and muscle) categories.[18] By definition, a *superficial incisional SSI* must occur within 30 days of the operative procedure and meet at least one of the following criteria: (1) purulent fluid is draining from the incision; (2) an organism is isolated from an aseptically obtained wound culture; (3) a symptom such as pain, tenderness, localized swelling, redness, or heat induces the surgeon to open the incision; or (4) a diagnosis of infection is made by the surgeon.

By definition, a *deep incisional SSI* must occur within 30 days after most procedures, or within 90 days after selected procedures that include placement of a homograft or prosthetic material, and meet at least one of the following criteria: (1) purulent fluid is draining from the deep incision (but not from the organ or space component of the site); (2) the deep incision spontaneously dehisces or is opened by the surgeon when the patient has fever (>38°C), localized pain, or tenderness (unless the incision is culture negative); (3) an abscess or other evidence of infection is identified on direct examination, by an imaging study, or by histopathologic specimen examination.

An *organ or space infection* involves deeper spaces entered or manipulated during the operative procedure; examples are mediastinitis after surgical repair of complex congenital heart disease and osteomyelitis after laminectomy. By definition, an organ or space SSI must occur within 30 days after most procedures, or within 90 days after selected procedures that include placement of a homograft or prosthetic material, and meet at least one of the following criteria: (1) purulent fluid is emitting from a drain placed into the organ or space; (2) an organism is isolated from an aseptically obtained culture from the organ or space; (3) an abscess or other evidence of infection is identified on direct examination, by an imaging study, or by histopathologic specimen examination.

Cardiac Surgery.

Common signs and symptoms of postoperative mediastinitis include local tenderness, wound dehiscence, increased erythema of the wound with or without purulence, and an unstable sternum. Infants can manifest minimal symptoms initially, with only fussiness and expiratory grunting (likely related to pain associated with respiratory effort). Fever occurs on average 5 days postoperatively, and local signs occur a mean of 9 days postoperatively.[118,194] In older children, signs and symptoms can appear later; in one study, infections were diagnosed at a mean of 15 days postoperatively.[191]

Laboratory test results usually reveal moderate leukocytosis with increased neutrophils. Typically, inflammatory markers are elevated. The diagnosis of acute suppurative mediastinitis is suggested by radiographic evidence of a widened mediastinum, mediastinal emphysema, and pleural effusions. Computed tomography and magnetic resonance imaging both have been used to diagnose mediastinitis; however, differentiating mediastinitis from postoperative changes can be difficult.[203]

Ventricular Shunt Placement.

Shunt-related infection should be suspected if a child has fever and no other localizing source and has undergone shunt placement, revision, or manipulation in the previous 3 months.[199] Children with a previous shunt infection are at increased risk.[183] Peripheral blood leukocytosis occurs frequently.[199] A sample of CSF obtained from the shunt bulb typically yields a positive culture result; positive and negative predictive values of other CSF laboratory test results are confounded by residual postoperative inflammation or by organisms causing only low-grade inflammation.

Spinal Fusion.

Infection after spinal fusion should be suspected in a child who has warmth, swelling, or excessive tenderness over the surgical incision within 3 months of the operation. Constitutional signs and symptoms of infection can be present and include fever, leukocytosis, and elevated inflammatory markers. Postoperative drains are risk factors.[204] Approximately two thirds of SSIs after spinal fusion operations occur within 30 days postoperatively, with an additional 20% of infections becoming apparent 1 to 6 months postoperatively. Approximately 10% of pediatric spinal surgical SSIs have delayed onset (>6 months) postoperatively.[167]

Management and Outcome

Antimicrobial therapy is only one aspect of management of SSIs; source control and nutritional support also are important. In patients with pyogenic abscesses, clostridial myonecrosis, streptococcal gangrene, or other infections with extensive tissue necrosis, surgical drainage or debridement is the primary treatment, and antimicrobial therapy is adjunctive. Empiric antimicrobial therapy for SSIs is based on the location of the initial surgical procedure, the suspected pathogen or pathogens, and local antibiogram. Holding therapy until acquisition of a protected specimen is desirable when safe.

Cardiac Surgery.

Surgical drainage and debridement, often with irrigation of the surgical bed, generally are required to treat postoperative mediastinitis. In patients with severe infections, the wound must be left open, with subsequent secondary closure.[205] The use of negative-pressure wound therapy can be associated with improved outcome in children who require delayed sternal closure.[185]

Empiric antimicrobial therapy is targeted at institutional cardiac SSI pathogens and the patient's endogenous flora if known; additionally, therapy also should target *S. aureus* and coagulase-negative staphylococci. No studies have been conducted to evaluate the optimal regimen or duration of antimicrobial therapy for mediastinitis; however, a course lasting 3 to 8 weeks generally is recommended, depending on the severity of the infection and the involvement of bone.[206]

Sternal osteomyelitis can accompany severe, deep mediastinal infections. These infections most commonly follow operations involving median sternotomy. Pathogens are similar to those in mediastinitis. Treatment of sternal osteomyelitis requires debridement of infected bone and a minimum of 4 to 6 weeks of antimicrobial therapy.[207]

Ventricular Shunt Placement.

Optimal management of CSF shunt infections usually entails removal of the shunt tubing and administration of systemic antibiotic therapy.[208] For children with ongoing hydrocephalus, a temporary method of CSF drainage is needed (either placement of an external ventriculostomy drain or regular ventricular taps for fluid removal) until a new shunt can be placed. Daily CSF samples are obtained to monitor the organism burden (by Gram stain), days to sterility, and in some cases cell counts and chemical values. Ventricular administration of antibiotics sometimes is required to sterilize CSF that fails to clear after several days of appropriate systemic antibiotics; however, care must be taken to ensure that the drug selected and the dose administered are appropriate and safe for direct instillation into the ventricular system.[209] Typically, several days of treatment are given after proven sterility of CSF before reinsertion of a new shunt. Antibiotic therapy is discontinued within 48 hours after placement of a new shunt system. The occurrence of infection but not the duration of initial treatment appears to affect the risk of reinfection.[183]

Spinal Fusion.

Therapy for superficial infections after spinal fusion includes systemic antibiotic therapy and enhanced wound care, which, depending on the extent of infection, can include debridement, irrigation, and packing. The management of deep SSI is challenging. Decisions about retention of grafts and prosthetic material must be considered when determining whether a wound should be closed or allowed to close by secondary intention and whether a negative-pressure dressing system should be used.[210] Selection of the appropriate agent and duration of antibiotic therapy are challenging when wound culture results are sterile or difficult to interpret.

Prevention

Key measures to prevent postoperative SSIs were introduced into surgical practice in the last century and are reviewed comprehensively.[211–213] These practices include preoperative measures such as removal of hair and application of antiseptic agents to the patient's skin, performance of surgical procedures in a properly designed and ventilated operating room, and appropriate hand antisepsis by surgical staff. Despite only limited high-quality, pediatric-specific evidence, national experts have convened working groups to develop “best practice guidelines” through consensus.

The American College of Surgeons[214] recommended perioperative antimicrobial prophylaxis when (1) prosthetic material is implanted, (2) the rate of infection is relatively high (e.g., clean-contaminated or contaminated procedures), and (3) the consequences of a postoperative infection are severe. The appropriate selection and timing of administration of perioperative antimicrobial prophylaxis have been shown repeatedly to reduce the risk of SSIs[176,215] (see Chapter 7). In a study of children undergoing general, cardiac, and spinal surgical procedures, the risk of SSI was 70% greater for patients who did not receive appropriate perioperative antimicrobial prophylaxis.[184] Although difficulties exist in establishing evidence-based recommendations for antimicrobial prophylaxis in pediatrics, the Committee on Infectious Diseases of the American Academy of Pediatrics provided recommendations based on expert consensus.[216] In addition, the guideline of the American Society of Health Systems Pharmacists provides detailed, procedure-specific recommendations on the selection and dosing of perioperative antibiotics; although these recommendations were developed for adult patients, many experts believe that they can be applied reasonably to children in most situtations.[217] General principles reiterated in guidelines include the importance of timing of the initial dose (within 60 minutes of incision), weight-based dosing for children and obese patients, and redosing for prolonged procedures and after excess blood loss.

Selection of prophylactic agents should depend on the procedure, the potentially associated pathogens, local antimicrobial susceptibility patterns, and the patient's age and hepatic and renal function. For most operative procedures that do not involve the gastrointestinal tract, cefazolin is the most commonly recommended agent because of its spectrum of activity that includes many relevant gram-positive pathogens, its serum half-life, and the low incidence of side effects. The regional prevalence of MRSA colonization among healthy children can require alteration of prophylactic strategies. Use of adjunctive agents (e.g., parenteral or topical vancomycin) for high-risk procedures (e.g., cardiac or spinal repair with placement of prosthetic material) in patients known to be colonized with MRSA is debated.[218] A meta-analysis of randomized clinical trials comparing vancomycin with a β-lactam agent for perioperative prophylaxis of SSIs in adult cardiac, vascular, or orthopedic procedures reported no difference in rates of SSI; however, investigators noted a vancomycin-associated reduced rate of infection with *Enterococcus* spp. and MRSA.[219] Large pediatric trials will be required to provide evidence-based practices for pediatric surgical patients.

Many centers develop practices based on local expertise, consensus, and available published reports. Because no benefit derives from prolonged postoperative antibiotic prophylaxis,[220] which increases the risk of wound infections caused by resistant bacteria,[164] perioperative antibiotic prophylaxis should be discontinued within 24 hours of completion of the surgical procedure.

Additional SSI prevention practices are emerging, but because high-quality evidence of efficacy in children often is limited, many of these practices have not been adopted fully by pediatric facilities. For example, the role of preoperative antiseptic bathing remains uncertain. Although it is being adopted with increasing frequency in adult and pediatric institutions, a meta-analysis performed in 2015 was unable to demonstrate that preoperative bathing with chlorhexidine gluconate was associated with lower SSI rates.[221] In contrast, multiple studies demonstrated that selective decolonization of adults known to harbor *S. aureus* reduces the risk of wound infection after high-risk orthopedic[222] and cardiac[223] operations, although substantial variation exists in the screening and decolonizing practices across US hospitals.[224] Because of the cost and complexity of identifying and decolonizing patients preoperatively, this practice is recommended only when rates of SSI remain high after full implementation of all other prevention measures.[212] Successful reductions in pediatric SSI are associated with participation in multicenter learning collaboratives.[225]

Cardiac Surgery.

Although in placebo-controlled trials antimicrobial prophylaxis was not shown to decrease the risk of pediatric mediastinitis, prophylaxis typically is used because mediastinitis can be catastrophic. The study demonstrating an increased risk of SSI among children undergoing cardiac surgical procedures who did not receive appropriate perioperative antimicrobial prophylaxis is noteworthy.[215] A review of 43 academic centers performing pediatric cardiothoracic operations showed that prophylactic antimicrobial agents frequently were continued while certain devices remained in place, such as thoracostomy or mediastinal tubes, transthoracic vascular catheters, central venous catheters, or temporary pacing wires.[226] Lack of benefit from prolonged postoperative antibiotic prophylaxis[220] and an increased risk of wound infections with resistant bacteria indicate that this practice should be abandoned.

Other preventive practices used in centers with lower rates of mediastinitis include: (1) strict adherence to aseptic technique; (2) attention to hemostasis and precise sternal closure; and (3) interventions targeted to identified risk factors.[220,227,228]

Ventricular Shunt Placement.

Prevention of SSIs after ventricular shunt placement requires adherence to the evidence-based practices described earlier. A report from the Hydrocephalus Clinical Research Network demonstrated a 36% relative reduction in the rate of infection across a 4-hospital network after adoption of a standardized protocol that included the intravenous administration of cefazolin 30 mg/kg (vancomycin 15 mg/kg for patients with substantial allergy) before incision, no use of razors for hair removal, and administration of vancomycin and gentamicin into the shunt reservoir before skin closure.[183] The role of antibiotic-impregnated shunt tubing remains unclear. Although many small retrospective studies did not find a difference in SSI rate among children who did and did not receive an antibiotic-impregnated shunt,[229–231] a large study conducted in the United Kingdom found that the use of an antibiotic-coated shunt was associated with a 40% reduction in the risk of SSI.[232] A meta-analysis concluded a lower SSI risk with "unclear degree of clinical certainty."[233] Additional study is needed.

Spinal Fusion.

Unfortunately, high-quality evidence to guide recommendations to prevent SSI after spinal fusion in children is limited. A group of orthopedic surgeons and infectious diseases specialists used the Delphi process to identify consensus practices.[218] A total of 14 prevention strategies were recommended for use in all spinal fusion procedures other than initial fusion for idiopathic scoliosis in patients without comorbid conditions. Key elements of this best practice guideline include (1) preoperative nutritional assessment, (2) a chlorhexidine gluconate bath the night before the operation, (3) perioperative antimicrobial prophylaxis that targets both skin and enteric organisms, (4) monitoring of adherence to perioperative antimicrobial regimens, and (5) limited movement into and out of the operating room during the procedure.[218] Participating centers are currently gathering data to assess the impact of these practices on SSIs.

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100

Clinical Syndromes of Device-Associated Infections

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The use of medical devices has increased dramatically over recent decades.[1] In children, the most common device-associated infections involve intravascular catheters; cardiac devices, such as prosthetic valves, patches, vascular grafts, pacemakers, and ventricular assist devices; cerebrospinal fluid shunts; peritoneal dialysis catheters; orthopedic implants; and urinary catheters. Such infections contribute to the substantial burden of emergency department visits, hospitalizations, and nosocomial illnesses in children.[2,3] This chapter addresses device-associated infections in children beyond the neonatal period. For device-associated infections in the neonate, see Chapter 94.

Certain general principles apply to infections involving medical devices. Factors that influence the risk for developing a device-associated infection include the properties of the device, of potential pathogens, and of the host (Box 100.1).[4] In addition, colonization and subsequent infection associated with medical devices are facilitated by biofilm formation—a complex matrix of colonizing organisms and extracellular proteins.[5,6] Immediately after implantation, biofilms begin to form with the deposition of host proteins on the device surface. Microorganisms adhere, multiply, and contribute additional extracellular proteins to this coating. Properties inherent to biofilms can inhibit host defenses[7,8] and sequester organisms away from antimicrobial agents.[9–11]

Box 100.1

Determinants of Medical Device–Associated Infections

Properties of the Device

Material: inert, plastic, rubber

Design: hollow, solid

Location: implanted, percutaneous, vascular/nonvascular site

Properties of Potential Pathogens

Source: endogenous, environment, contaminated disinfectant/device/solution

Susceptibility: in vitro and in biofilm

Properties of the Host

Host defenses: skin, mucous membranes, immune system

Medication: anti-inflammatory agents, immunosuppressive agents

Altered flora due to diet, medications (antacids, antimicrobial agents)

The microbiology of device-associated infections varies by device (Box 100.2). Organisms found as part of the normal skin flora are the most common etiologic agents in foreign body infections in infants and children.[8,12] Certain species are particularly well suited to colonizing devices. *Staphylococcus aureus* adheres specifically to fibrinogen, a component of biofilms.[13,14] Coagulase-negative staphylococci (CoNS), *Pseudomonas aeruginosa,* and *Corynebacterium* spp. produce proteinaceous slime, capsular polysaccharides, and adhesins that enhance adherence and protect the organism from host defenses and the effects of antimicrobial agents.[12,15–17]

Box 100.2

Pathogens Recovered From Medical Device–Associated Infections

Most Common

Coagulase-negative staphylococci

Staphylococcus aureus

Other skin flora

Common

Gram-negative enteric bacilli

Environmental organisms

Candida spp., especially *C. albicans* and *C. glabrata*

Occasional

Other fungi

Nontuberculous mycobacteria

Common clinical findings in foreign body infection include malfunction of the device (e.g., occlusion of catheters and shunts or loosening of prosthetic joints),[18,19] pain at the site of the device or insertion site, and failure of wound healing after implantation. Fever, leukocytosis, and other systemic signs can be absent; thus, a high index of suspicion is required for timely diagnosis. Cultures are essential to both establish the diagnosis and guide definitive therapy. Antimicrobial therapy alone sometimes is curative, but frequently the foreign body must be removed. The risk for device-associated infections can be reduced by consistent application of several principles and evidence-based practices, referred to as "bundles."[20] Devices should only be used in circumstances in which they are essential and, when feasible, removed as soon as possible; strict aseptic technique must be observed during insertion or manipulation of a device; and the frequency of device access or manipulation should be limited to reduce the likelihood of contamination. Although the use of antimicrobial prophylaxis at the time of insertion is commonplace, the efficacy of such measures for many devices has not been established.[21–23] Recent advances in materials used for catheters and prosthetic devices have resulted in decreased rates of infection. The use of central venous catheters (CVCs) impregnated with either minocycline and rifampin or chlorhexidine and silver sulfadiazine has been shown to be effective in reducing the incidence of both catheter colonization and central line−associated bloodstream infection (CLABSI) in adult patients[24–26]; however, few efficacy studies of these devices have been performed in children.[27–31]

Intravascular Catheter-Related Infections

Epidemiology and Pathogenesis

With focused prevention efforts, rates of CLABSI in the United States have decreased dramatically. The Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN) reporting system noted a 46% decline in CLABSI between 2008 and 2013.[32] Still, device-associated infections comprise approximately 25% of all healthcare-associated infection (HAI) reported to NHSN,[33] and CLABSIs represent the most common device-associated infection experienced by hospitalized children.[32] Critically ill children who develop CLABSI have longer duration of intensive care unit (ICU) and hospital stay, and the crude attributable mortality has been estimated to be 19%.[34] In addition, using a propensity score matched case-control study, the attributable cost and length of stay between matched CLABSI cases and non-CLABSI controls was found to be $55,646 (2011 dollars) and 19 days, respectively.[35]

The terminology describing catheter-related infections can be confusing. Catheter-related bloodstream infection (CRBSI) identifies the catheter as the source of infection. CLABSI, however, is a term used by NHSN to facilitate surveillance (and, therefore, has been widely adopted as a surrogate for CRBSI in the literature describing its epidemiology) and may overestimate the true incidence of CRBSI. Also, several different types of CVCs are used in children. A CVC generally is classified by its intended duration of use (short term vs. long term); its site and mode of insertion (peripheral, femoral, subclavian; tunneled vs. nontunneled); or other specific characteristics (antibiotic-coated, multilumen). Lastly, multiple types of catheter-related infections can be identified. Infection can occur at the exit site, in the subcutaneous tunnel or pocket, or in the bloodstream.[36] Pathogens can be introduced during insertion, manipulation, calibration, and flushing of monitoring devices (all modes of direct contamination influenced by hand hygiene practices), or through contaminated parenteral fluids, flush solutions, or skin antiseptics. Translocation of organisms from colonizing sites with resultant transient bacteremia also can lead to CLABSI. (Box 100.3).[37–41]

Box 100.3

Origins of Medical Device–Associated Infection

Inoculation at the Time of Insertion of the Device

Endogenous flora of the host

Environmental flora

Inoculation During Manipulation of the Device

Breaks in aseptic technique

Hematogenous Seeding

Transient bacteremia

Nonintact mucous membranes or gastrointestinal tract

EXTENSION OF LOCAL INFECTION

Gram-positive organisms, including CoNS, *S. aureus,* and enterococci, are most commonly isolated in intravascular catheter-associated infections.[34,42–44] In fact, although incidence density rates of CLABSI have decreased overall in recent years, the incidence density rate of *S. aureus* CLABSIs among pediatric ICUs in the US has remained the same.[45] Identification of gram-negative bacilli, including *Enterobacter* spp., *P. aeruginosa, Klebsiella pneumoniae,* and *Escherichia coli,* has increased to approximately one third of reported infections (Box 100.4).[44] *Candida* spp. are increasingly prevalent and now are the fourth most common cause of nosocomial bloodstream infection (BSI) in the US.[44,46–48] Among 29 hospitals participating in the Children's Hospital Association Quality Transformation Network, the majority of CLABSIs in pediatric ICUs were caused by a single organism, most commonly gram-positive cocci.[49] Of *S. aureus* isolates, methicillin-resistant *S. aureus* (MRSA) represented nearly 50%. Gram-negative bacilli were identified in one third of cases and *Candida* spp. in 15%. Other relatively common organisms include *Corynebacterium, Propionibacterium,* and *Bacillus* spp., *Serratia marcescens, Acinetobacter* spp., *Citrobacter* spp., and nontuberculous mycobacteria.[36] The frequency and distribution of organisms may be influenced by the child's exposure to (or level of illness associated with) the ICU[50] particular medications, such as intravenous (IV) prostanoid agents[51] or underlying cancer or chemotherapy.[52,53]

Box 100.4

Pathogens Recovered in Vascular Catheter-Related Infections

Most Common

Coagulase-negative staphylococci

Common

Staphylococcus aureus

Enterococcus spp.

Candida spp.

Escherichia coli

Klebsiella spp.

Pseudomonas aeruginosa

Enterobacter spp.

Occasional

Other gram-negative bacilli, including *Acinetobacter* spp. and *Citrobacter* spp.

Nontuberculous mycobacteria

Corynebacterium spp.

Bacillus spp.

Catheter-Related Factors

Risk for infection varies by catheter type. Rates are higher for CVCs than for peripheral venous or arterial catheters.[36] Although some studies showed similar infection risks for tunneled and nontunneled catheters,[54,55] later randomized studies showed that tunneling of femoral catheters[56] and internal jugular catheters[57] is associated with lower infection risk (Box 100.5). Peripherally inserted central catheters (PICCs) now are used more commonly because of their perceived lower risk for infection; however, two outpatient studies demonstrated a 10% PICC infection rate,[58,59] and analyses of critically ill patients have revealed that the risk for catheter infection is similar among patients with a PICC and those with a centrally inserted percutaneous catheter.[60] A correlation between increasing number of lumens and incidence of infection has been noted in some studies, but not others.[61,62] In addition, the presence of multiple venous catheters was found to be an independent risk factor associated with nosocomial BSIs.[34] The site of placement determines the types and burden of organisms in proximity to the catheter entry site because organisms present at the site of catheter insertion can move from the entry site along the dermal tunnel to the catheter tip within hours.[63] Quantitative cultures of potential catheter sites in adults and neonates show that the upper extremity and chest wall have the lowest burden of bacteria, whereas the groin and jugular areas are more heavily colonized.[64] In adults, catheters placed in the groin are associated with a greater risk for infection than those placed in the neck[65];

however, this does not appear to be consistently supported in pediatric studies,[49,66–69] and recent guidelines do not support preferential placement in children.[41,43]

Box 100.5

Risk Factors for Vascular Catheter-Related Infections

Catheter

Site of insertion

Manipulations: entry into the system

Duration of catheterization

Thrombosis

Lumens, stopcocks, monitoring devices

Antiseptic/antibiotic-coated or not

Tunneled or not; implanted or not

Infusant

Parenteral nutrition

Lipids

Blood

Host

Skin integrity

Skin flora

Immune competence

The duration of catheter placement is directly related to the risk for infection, a concept that has been substantiated in multiple pediatric studies.[50,70–74] Biofilm formation, which increases with dwell time, clearly increases the opportunity for catheter colonization. In addition, each manipulation of a catheter, stopcock, or needleless device provides an opportunity for the introduction of organisms.[36,75,76] Outbreaks of bacteremia have resulted from contamination of pressure transducers.[65,77–80] Replacing the catheter over a guidewire does not decrease the incidence of infection, and may even increase it.[81] Finally, the effect of transparent versus gauze dressing use on infection risk remains an unresolved issue.[82] A recent meta-analysis found an association between CLABSI and transparent dressing use; however, the source studies for the meta-analysis were of low quality.[82–84]

Certain infusates are more likely than others to be associated with BSI. Use of parenteral nutrition fluids increases the risk for CLABSI in multiple pediatric studies.[50,71,85,86] In addition, receipt of blood transfusion has been identified as an independent risk factor for CLABSI in pediatric ICU patients.[87,88] Intrinsically or extrinsically contaminated infusates also can cause CLABSI. Although intrinsic contamination of intravenous fluids is rarely reported in the US, episodes of extrinsic contamination of intravenous fluids and medications continue to occur.

Host Factors

Host factors influence the risk of CLABSI. Skin flora varies according to a person's hygiene and medications. Topical antimicrobial agents may alter the nature and density of local flora, and chlorhexidine gluconate (CHG) is now the preferred agent for preinsertion decontamination and daily maintenance (see "Prevention" section later). Systemic antimicrobial agents alter stool and skin flora and increase the risk for infection by *Candida* spp.[72,89] Factors that lead to a break in the integrity of skin or mucous membranes can increase the risk for catheter infections. Thus patients with immature skin (premature infants), impaired integrity of the gut epithelium (patients with short-gut syndrome),[90,91] or burn patients may be at risk for bacteremia and subsequent colonization of an indwelling catheter, although the true contribution of these putative mechanisms (as opposed to confounding risks such as illness severity and increased need for intravascular access) remains unclear. Similarly, patients with a distant site of infection (such as an abscess) or who develop a spontaneous bacteremia are also at risk for developing a secondary CRBSI.

Children undergoing cancer chemotherapy are at risk for infection because of neutropenia; infection rates in these patients are increased 2- to 4-fold by the use of indwelling CVCs.[92] In addition, mucositis may raise the risk for bacterial gastrointestinal wall translocation and bacteremia and may account for differences in the microbiology of BSIs that occur in neutropenic, compared with nonneutropenic, patients. In a prospective study of more than 24,000 episodes of nosocomial BSIs, neutropenic patients were at greater risk for infection due to *Candida* spp., enterococci, and viridans group streptococci.[93] It remains unclear, however, whether the increased infection rate and variable microbiology are attributable to mucositis or to the associated illness severity, immune suppression, and care environment of such patients. In light of these issues, the CDC recently incorporated a new category for CLABSI surveillance known as *mucosal barrier injury–laboratory confirmed bloodstream infection* (MBI-LCBI); these infections include primary BSI due to select organisms in patients with neutropenia or in patients with allogeneic hematopoietic stem cell transplantation with gastrointestinal graft-versus-host disease or diarrhea.[94,95]

Patients with human immunodeficiency virus (HIV) infection are at greater risk for a variety of infections; use of CVCs for nutritional support and for medications increases the risk for bacteremia in HIV-infected and other patients.[96,97] Patients with uremia are at higher risk for CLABSI, particularly those with hemodialysis catheters.[98–100] In patients undergoing hemodialysis, the type of bloodstream access used influences the risk for infection; the risk is lowest with native arteriovenous fistulas, intermediate with artificial arteriovenous grafts, and highest with CVCs.[101,102]

Clinical factors related to the severity of illness also have been found to influence the risk for infection. In a cohort of critically ill pediatric patients, the need for transport out of the care unit and for a procedure performed within an ICU were both independently associated with a 3- to 4-fold increase in the risk for developing a nosocomial BSI.[34] Need for ICU exposure, ICU placement of the central line, mechanical ventilation, medical cardiac disease, malignancy, genetic syndrome, metabolic disease, presence of a gastrostomy tube, and history of prior CVC also have been associated with CLABSI in children.[50,70,71,85,87,88]

Clinical Manifestations and Laboratory Diagnosis

Fever usually is present in patients with catheter-related infections. Patients with localized infection of the exit site, pocket, or tunnel frequently have infection in the absence of fever. When a catheter-related infection is suspected, the exit site should be examined for the presence of local suppuration or cellulitis; however, normal appearance of the exit site does not exclude a local or systemic infection involving the catheter. Any catheter malfunction (including decrease in flow or unidirectional flow) should prompt an evaluation for infection. Findings suggestive of disseminated infection include the presence of emboli in the retina, skin, bone, and viscera (lungs, kidneys, liver, and spleen) and organ dysfunction due to immune complex deposition (e.g., nephritis).

Infections attributable to a CVC include exit, tunnel, and pocket infections as well as BSI (Table 100.1).[103] A CRBSI is defined as bacteremia or fungemia in a patient with a centrally placed intravascular catheter in which the catheter is the presumed source of infection. Establishing that the catheter is the source of infection is not always straightforward. For example, a BSI in a patient with an indwelling catheter can originate from an undocumented source of infection (e.g., a postoperative wound infection or a urinary tract infection [UTI]) rather than from the catheter. In adult patients, only 15% to 20% of CVCs removed in the context of a BSI are implicated ultimately as the primary source of infection.

TABLE 100.1

Types of Catheter-Related Infections

Infection	Clinical Diagnosis
Exit site infection	Erythema or induration within 2 cm of catheter exit site
Tunnel infection	Tenderness, erythema, or induration along the subcutaneous tract of a tunneled catheter and more than 2 cm from catheter exit site
Pocket infection	Purulent fluid in the subcutaneous pocket of a totally implanted venous access device. May be accompanied by overlying tenderness, erythema, induration, visible drainage, and skin necrosis

Catheter-associated bloodstream infection	Positive simultaneous blood cultures from the central venous catheter and peripheral vein yielding the same organism in the presence of at least one of the following:
	▪ Simultaneous quantitative blood cultures in which the number of CFUs/mL isolated from blood drawn through the central catheter is ≥5-fold the number isolated from blood drawn peripherally
	▪ Positive semiquantitative (≥15 CFUs/catheter segment) or quantitative (≥100 CFUs/catheter segment) catheter tip cultures
	▪ Simultaneous blood cultures of equal volume in which the central blood culture has growth in an automated system ≥2 hours earlier than the peripheral blood culture

CFU, colony-forming unit.

Several methods have been used to identify the catheter as the source of infection, although no microbiologic gold standard for diagnosis of catheter-related BSIs exists.[104] Proposed methods include quantitative cultures of blood obtained through the catheter and a peripheral vein simultaneously; quantitative and semiquantitative cultures of a catheter segment; and differential time to blood culture positivity[105] (see Table 100.1). Until recently, the most commonly accepted methods of diagnosing a CRBSI have involved either quantitative or semiquantitative cultures of the catheter tip. This strategy relies on the prompt removal of the catheter and is thus not appropriate in many clinical settings. A positive catheter culture result is defined as growth of at least 15 colony-forming units (CFU) on an agar surface over which the catheter tip was rolled.[106] An alternative method involves sonicating the catheter tip in fluid to dislodge the intraluminal biofilm; this method is associated with a higher rate of positive cultures than the roll technique.[107] A catheter tip culture that yields ≥15 CFU is a valid indication of catheter colonization, which in turn is associated with a higher risk for BSI. However, a relatively small number of patients with colonized catheters have CRBSI.[108] In fact, electron microscopy of catheter tips reveals universal colonization with bacteria.[107,109] Thus the positive predictive value (PPV) of a positive catheter tip culture result is low, ranging from 5% to 30% in most studies, and this method has not been evaluated for antimicrobial agent- or antiseptic-impregnated catheters.

Differential time to positivity of paired blood cultures is the simplest of the three methods and does not require specialized laboratory culture methods (other than a continuous-monitoring blood culture system) or catheter removal, but requires that peripheral and central cultures are drawn simultaneously and are of equal volume. If the same organism is isolated from both blood cultures and the time to positivity of the catheter-obtained specimen is >2 hours shorter than that of the peripherally obtained culture, catheter colonization and CRBSI are likely.[105,110] Compared with quantitative and semiquantitative methods, differential time to positivity of >2 hours had a sensitivity of 93% and a specificity of 75% for catheters in place for >30 days and a sensitivity of 81% and a specificity of 92% for catheters in place for <30 days.[111] Several smaller studies have demonstrated similar results.[112–114] In an analysis of semiquantitative cultures obtained from different lumens of multilumen catheters in pediatric oncology patients with double-lumen catheters in place and no peripheral blood cultures available, PPV of more than fivefold difference in CFU/mL of isolates from samples from the two lumens was 92% predictive of a CRBSI.[115]

Few studies have evaluated the optimal timing of blood cultures, although timing should be guided by patient acuity. Compared with obtaining multiple specimens at the same time, obtaining multiple samples over a 24-hour period appears to increase the ability to detect intermittent bacteremia.[114,116] In patients already receiving antibiotics, samples obtained close to the time that antibiotic concentrations have reached trough levels (i.e., just before next dose) theoretically could improve recovery of organisms in blood cultures[117]; however, this issue has not been studied and may not be practical clinically.

The volume of blood that is obtained is the most important factor in successfully recovering bacteria and fungi.[104,118] Studies have demonstrated that the likelihood of growth is lower and the time to detection is delayed when small volumes (<0.5 mL) of blood are used to inoculate blood culture bottles[108]; however, advancements in blood culture detection system technology continue to improve in efficiency. Although multiple cultures enhance the recovery of pathogens, the volume of blood cultured may be more important than the total number of blood cultures obtained. One study found that the pathogen recovery rate at 24 hours was 72% for a large-volume (6 mL) single culture compared with a 47% combined yield of two smaller (2 mL) samples inoculated into separate culture bottles.[119] Similar results were found in studies of adult patients in which standard "adult-volume" cultures (mean, 8.7 mL) had a higher detection rate (92%) than "low-volume" cultures (mean, 2.7 mL), in which the detection rate was only 69%.[120] Investigators estimated that the yield of adult blood cultures increased approximately 3% per mL of blood cultured.

Other technical issues can affect the sensitivity of blood cultures. Diluting the blood into the blood culture broth enhances recovery of pathogens, perhaps by diluting antimicrobial agents (if applicable) and blood components such as phagocytes, antibodies, and complement factors that are known to have bactericidal activity.[121] The ideal blood-to-broth ratio depends on the blood culture system used, but a ratio between 1 : 5 and 1 : 10 generally is considered ideal[122]; it is essential to identify the optimal blood volume suitable for the culture system in one's clinical microbiology laboratory. For recovery of certain bacteria, fungi, and mycobacteria, special handling of blood cultures is required. For example, filamentous fungi require solid media for growth, *Malassezia furfur* requires lipid supplementation, and certain gram-negative species and some mycobacteria need prolonged incubation (see Chapter 286). Failure of culture to identify a pathogen in the patient with continued clinical evidence of infection should prompt consideration of less common, more fastidious organisms and discussion with microbiology laboratory personnel about additional collection, culture and detection techniques.

Distinguishing between cultures that represent "contamination" and those that represent "true" BSI can be challenging, especially when a skin organism (e.g., CoNS, *Bacillus* spp., micrococci) is isolated. Obtaining multiple cultures can clarify most situations. A study using a mathematical model of blood cultures positive for CoNS in patients with a CVC found that the PPV of a single positive culture (if only one culture was obtained) was 55%; however, if only 1 of 2 cultures obtained was positive, the PPV was 20%, and if only 1 of 3 cultures was positive, the PPV was only 5%. Investigators developed a similar model for blood culture positivity depending on sampling site. If 2 of 2 cultures were positive, the PPV was 98% if both samples were obtained from a peripheral vein, 96% if 1 sample was obtained through a catheter and the other was obtained through the vein, and only 50% if both samples were obtained through a catheter.[123] Furthermore, the distinction between pathogen and contaminant is influenced by age and underlying conditions. Although CoNS often is considered a true pathogen in neonates, this issue remains controversial.[124] Because the isolation of CoNS from a blood culture often results in a clinical intervention and administration of vancomycin, it is particularly important to obtain multiple blood cultures. Overuse of vancomycin has implications for adverse events, and the continued increase of vancomycin resistance among gram-positive organisms.[125–127]

Repeatedly positive blood culture results despite appropriate antimicrobial therapy suggests the presence of an intravascular focus of infection such as the catheter itself, complicating suppurative thrombophlebitis or endocarditis (especially if the catheter has been removed).[128,129] Among patients with intravascular catheters, the risk for endocarditis is highest with Swan-Ganz catheters and lowest with peripheral catheters. In an autopsy series, 53% of patients who had undergone pulmonary artery catheterization had right-sided endocardial lesions; 7% had infective endocarditis.[130] Centrally placed catheters often traverse and damage the tricuspid valve, increasing the risk for right-sided endocarditis. Thrombi within the heart can become infected or can obstruct outflow.

Ultrasonography is useful in detecting thrombosis of vessels or formation of vegetations. The value of a negative transcutaneous ultrasonography result is debated; in adults, the use of transesophageal echocardiography increases the likelihood of detecting intracardiac vegetations.[131] Gadolinium-enhanced magnetic resonance venography can be useful in detecting central venous thromboses.[132]

Management and Outcome

Exit site infections can be treated by removal of the catheter and local care. If the catheter remains in place, local topical therapy can be successful in controlling this type of infection; however, systemic antimicrobial therapy and catheter removal usually are required if an exit site infection extends to involve the soft tissues that surround the catheter (i.e., the subcutaneous tunnel or pocket) or is associated with a CLABSI. Limited data guide the management of

CLABSI in children. Even in adults, there are insufficient randomized or controlled studies to address optimal management of CLABSI.[105] To help address this uncertainly, the Infectious Diseases Society of America has published guidelines for the diagnosis and management of CLABSI. Although focused on adult patients, this guideline contains recommendations for the management of children with CLABSI and is endorsed by the Pediatric Infectious Diseases Society.[105]

Empiric therapy in children with suspected CLABSI should include an antimicrobial agent with activity against gram-positive bacteria, such as nafcillin, oxacillin, or vancomycin, and an agent effective against gram-negative bacteria, including *Pseudomonas* spp., such as ceftazidime or cefipime. The empiric use of both an antipseudomonal β-lactam and an aminoglycoside may be appropriate in severely ill patients or when infection with a resistant gram-negative organism is suspected. In institutions in which MRSA is prevalent, the use of vancomycin is appropriate. Aztreonam or fluoroquinolones can be used when β-lactam allergy is present and broad-spectrum gram-negative coverage is required.

Limited data guide clinical decisions regarding the need for catheter removal (Table 100.2). In adults with CLABSI, it is recommended that most nontunneled CVCs be removed.[105] In children, removal of a catheter may not always be feasible because of the potential for complications associated with reinsertion and limited vascular access sites. Children treated without catheter removal should be monitored closely and additional blood cultures drawn; the catheter should be removed with clinical deterioration or persistent or recurrent CLABSI. In patients with CLABSI associated with a tunneled catheter or implantable device such as a port catheter, the decision to remove the catheter is more complicated; however, good evidence favors the removal of the CVC in patients with evidence of a tunnel infection or infection in the subcutaneous pocket of an implanted device.[105] When culture data are available, treatment decisions can be tailored to the specific organism isolated. Several studies have reported successful treatment of CLABSI without catheter removal, depending on the pathogen identified.[133–136]

TABLE 100.2

Management of the Catheter in Patients With a Central Venous Catheter−Related Infection

Type of Infection	Catheter Management
Exit site infection	Remove CVC if:
	▪ No longer required
	▪ Alternate site exists
	▪ Patient critically ill (e.g., hypotension)
	▪ Infection due to *Pseudomonas aeruginosa* or fungi
Tunnel infection	Remove CVC
Pocket infection	Remove CVC
Catheter-related bloodstream infection	Remove CVC if: ▪ No longer required
	▪ Infection caused by *Staphylococcus aureus, Candida* spp., or mycobacteria
	▪ Patient critically ill
	▪ Failure to clear bacteremia in 48–72 hours
	▪ Persistent symptoms of bloodstream infection beyond 48–72 hours
	▪ Noninfectious valvular heart disease (increased risk for endocarditis)
	▪ Endocarditis
	▪ Metastatic infection
	▪ Septic thrombophlebitis

CVC, central venous catheter.

The aforementioned management guideline also includes the use of antimicrobial lock therapy in management of CLABSI when catheter salvage is the goal.[41] The concept underpinning lock therapy is that bacteria embedded in biofilms on intraluminal surfaces of catheters may be killed more effectively by antibiotic concentrations 100 to 1000 times higher than standard concentrations of intravenous antibiotics. Lock solutions typically are mixed with heparin in sufficient volumes to fill the lumen, allowed to dwell, then removed. This approach is currently recommended in conjunction with systemic therapy for select organisms.[41]

Few data exist regarding the duration of antibiotic therapy for CLABSI. The duration of therapy depends in part on the pathogen; whether the catheter is removed; and whether infection is complicated by septic thrombosis, endocarditis, osteomyelitis, or other metastatic foci of bacteria. For complicated infections, the duration of therapy is based on the length of therapy needed to treat the suppurative complication. There are no data to determine the optimal duration of intravenous versus oral antibiotics for the treatment of CLABSI when the catheter is removed. Certain antibiotics with excellent oral bioavailability may be considered an alternative to parenteral therapy after the catheter has been removed (or lock therapy begun), the BSI has cleared, and the patient has shown clinical improvement. Some pathogen-specific recommendations are provided below.

Coagulase-Negative Staphylococci (Other Than *S. lugdunensis*)

A relatively low-virulence organism, CoNS infection usually presents with fever alone or catheter malfunction, with or without inflammation at the catheter exit site. CoNS CLABSI can resolve with catheter removal alone, although guidelines recommend a short course of antibiotic therapy (3–5 days) even after removal of the catheter.[105] If the catheter is retained, the recommended duration of treatment is 10 to 14 days after a negative culture from blood drawn through the CVC has been obtained. In neonates with CoNS BSI, treatment without removal of the catheter can be attempted; however, if a neonate has 3 positive blood cultures despite appropriate antimicrobial therapy, the catheter should be removed because of the increased risk for end-organ damage[137] (see Chapter 94). The relapse rate in adults with CoNS CLABSI is 20% if the catheter is not removed, compared with 3% if the catheter is removed.[138]

Staphylococcus aureus

Serious complications, including endocarditis and other deep tissue infections, have been reported in association with *S. aureus* CLABSI.[40,129] Adults with *S. aureus* BSI who have a medical device are at substantial risk for endocarditis; echocardiography is performed routinely as part of management.[139,140] In contrast, the frequency of infective endocarditis is low in children with structurally normal hearts who have *S. aureus* BSI; therefore, echocardiography is not recommended routinely.[141] In a prospective study of 51 children with *S. aureus* BSI, definite or possible endocarditis was diagnosed in 52% of patients with congenital heart disease but in only 3% of children with structurally normal hearts.[141] Echocardiography should be considered in children with (1) prolonged BSI before treatment, (2) persistent BSI while receiving appropriate antimicrobial therapy, (3) a new murmur identified on physical examination, or (4) congenital heart disease. Neonates may be more vulnerable than older infants to complications of *S. aureus* BSI.[137] Some experts recommend catheter removal for neonates with a single positive blood culture when *S. aureus* or a gram-negative bacillus is the isolate because this significantly improves outcome. Two weeks of appropriate antimicrobial therapy, chosen based on susceptibility test results, is recommended for uncomplicated *S. aureus* CLABSI.[90] Longer duration of therapy (4–6 weeks) may be necessary for patients with prolonged BSI (>3 days), persistent fever, or complicated infection.[142]

Gram-Negative Bacilli

Few data address the appropriate duration of therapy and the need for catheter removal in patients with CLABSI caused by gram-negative bacilli. In general, for uncomplicated infections, antimicrobial therapy should be administered for 10 to 14 days after documented blood culture negativity.[105] Although children with CLABSI caused by gram-negative bacilli have been successfully treated without catheter removal, catheter removal has been shown to be beneficial in the treatment of infections with specific gram-negative bacilli such as *Pseudomonas* spp., *Burkholderia cepacia, Acinetobacter baumannii,* and *Stenotrophomonas* spp.[40,103] In a study of adults with CLABSI caused by gram-negative bacilli, catheter removal was associated with a reduced rate of relapse.[143]

Candida Species

Treatment of candidemia without removal of the catheter has been associated with poor outcomes in children and adults[144–146]; however, these studies have not accounted for confounding effects of the severity of illness.[147] Failure to remove the catheter promptly is associated with prolonged candidemia, which in turn has been associated with higher rates of disseminated infection. However, a recent retrospective study among adults with catheter-associated candidemia found no difference in outcomes between early versus late catheter removal, but the study did not address long-term outcomes such as recurrence.[148] In a study of 153 children with candidemia, the overall rate of disseminated candidiasis (to lung, liver, spleen, eye, brain, heart) was 17%; the crude mortality rate was 26%.[149] Guidelines recommend that catheters should be removed in patients with candidemia whenever clinically feasible.[150] Patients with candidemia should be treated with an echinocandin, amphotericin B, or fluconazole for at least 2 weeks. Azole susceptibility testing should be performed for all bloodstream isolates, and echinocandin testing is done for those from patients previously treated with an echinocandin and for non-*albicans* species.[150] Many experts would recommend performance of an ophthalmologic examination to evaluate for candidal endophthalmitis, preferably after the infection is controlled and further disseminated disease is unlikely.[150] Risk for dissemination is multifactorial, depending on the pathogen, host, and duration of candidemia.

Nontuberculous Mycobacteria

Infections due to nontuberculous mycobacteria should be managed by removal of the catheter and antimicrobial therapy. The choice of agents is individualized. The empiric combination of clarithromycin and tobramycin *(M. chelonae),* amikacin and meropenem *(M. fortuitum),*[151,152] or other drugs in combination should be considered depending on the species of pathogen and expected and then proven antimicrobial susceptibility.

Complications

Complications of CRBSI include thrombosis with or without thrombophlebitis, sepsis, septic endocarditis, and metastatic infection with seeding of bone and organs (lung, kidneys, liver, spleen, brain, skin). The prognosis for patients with CRBSI is influenced by factors related to the pathogen, host, and therapy. If the infection is recognized and appropriate antimicrobial therapy is instituted promptly, there can be a high rate of cure, and even salvage of the catheter; delayed treatment is associated with increased morbidity and mortality.[105]

CVC-related thrombosis is common. In one study of children who had CVCs for home parenteral nutrition, venography revealed blockage of central vessels in 66%.[153] In a study of femoral venous catheters, evidence of thrombosis was found in 69% of children. Positive blood culture results were obtained in 38% of patients who had thrombosis versus 3% of patients who did not. The incidence of thrombosis was lower in patients who had heparin-bonded catheters.[154] If a patient with a thrombosed vessel develops BSI, the clot can become infected and lead to thrombophlebitis and persistent BSI.[155] The optimal treatment for septic thrombophlebitis of a CVC is unclear. Phlebitis of peripheral veins is commonly delayed in onset, often becoming apparent ≥24 hours after removal of the catheter.[156,157] Suppurative thrombophlebitis sometimes resolves after catheter removal. Fluctuance at a subcutaneous venous site; persistent erythema, swelling, and tenderness; or persistent BSI despite antimicrobial therapy are clues that aspiration, surgical drainage, or resection of the vein may be necessary for cure.[158] Removal of the catheter and prompt therapy with appropriate antimicrobial agents are essential. Although urokinase has been demonstrated to be effective in restoring catheter patency in up to 75% of patients with occluded catheters,[159] the role of anticoagulation or thrombolytic agents in the face of a catheter infection is uncertain.

Overall, fatality rates for CLABSI are 10% to 25%, with rates as high as 50% in critically ill patients and neonates.[160,161] One study demonstrated that only the presence of underlying malignancy or immunodeficiency was independently associated with an increased risk for mortality due to a CLABSI.[162] Relapse of a catheter-associated infection can occur, and reinfection with a new organism is more common in catheters that have been infected previously.[142,151] Frequent recurrences should raise concerns regarding the care of the catheter, particularly in children who are outpatients. Munchausen syndrome by proxy has been implicated as a cause of recurrent central catheter septicemia.[163]

Prevention

The elimination of CLABSI in all patient care areas is the stated goal of many national organizations.[43] Although this target has not been reached in many pediatric settings, considerable progress has been made, particularly within the context of organized initiatives and with use of care bundles for both catheter insertion and maintenance[20,164–166] (see Chapter 2). Still, the success of bundled practices depends on adherence to the individual elements and is optimized in settings with a preexisting culture of patient safety.

The simplest way to reduce the risk for CLABSI is to avoid catheterization (Box 100.6). If a catheter is essential, however, a variety of practical measures can be taken to lower the risk for CLABSI.[41,167,168] Catheters that are no longer needed should be removed promptly. The presence of an idle catheter is common, accounting for 20% of catheter days in one study, and poses an unacceptable risk to the patient.[169] Performance of hand hygiene and the use of maximal barrier precautions (the wearing of sterile gloves, long-sleeved sterile gown, mask, and cap and the use of a large sterile sheet drape) before and during insertion of central catheters help reduce infection risk substantially.[170] In addition, use of checklists, as well as all-inclusive catheter carts or kits, can help to ensure that optimal insertion practices are followed.[41] These measures have been shown to be cost-effective over a wide variety of clinical conditions.[171]

Box 100.6

Prevention of Vascular Catheter-Related Infections

General

Avoid unnecessary catheter insertion

Remove unneeded catheters as soon as possible

Catheter Insertion

Apply skin site antisepsis; use chlorhexidine gluconate for central venous catheter placement

Use strict aseptic technique

Use sterile technique and maximal barrier precautions when inserting central venous or arterial catheters

Catheter Care

Minimize manipulation of catheters

Perform hand hygiene before and after palpating, inserting, replacing, or dressing any catheter

Perform catheter site care (chlorhexidine); consider use chlorhexidine biopatch

Inspect hub design; avoid preslit cover

Prepare hub before injection or aspiration through the hub

Replace end caps frequently

Catheter Selection

Select a catheter with the fewest lumens needed for management of the patient

Consider use of antiseptic- or antimicrobial-coated central catheters and silver-impregnated, collagen-cuffed catheters when infection rates remain high despite other measures (e.g., maximal barrier precautions)

For long-term (>30 days) access in children older than 4 years, consider peripherally inserted central catheters or tunneled or totally implantable devices; for children younger than 4 years, consider totally implantable devices

Stopcocks

Cover all openings

Minimize use

Monitoring Devices (Transducers, etc.)

Sterilize if being reused; avoid contamination during use

Careful skin antisepsis before insertion is an important preventive measure. Several randomized trials have demonstrated that antisepsis with 2% chlorhexidine is superior to povidone-iodine for preventing CLABSI,[172–174] and an alcoholic chlorhexidine antiseptic is now recommended for skin preparation before CVC insertion.[41] Further, numerous studies have demonstrated the benefit of daily chlorhexidine bathing in reducing CLABSI and other HAIs in adult settings[175–180] and in pediatric ICUs[181]; this practice is now recommended for all ICU patients with CVCs.[34,41] The optimal choice of antiseptic agent for children <2 months of age remains an unresolved issue, although chlorhexidine products frequently are used in neonatal populations,[182] and daily chlorhexidine bathing has been shown to reduce rates of CLABSI in a tertiary care neonatal ICU.[183] The U.S. Food and Drug Administration (FDA) recommends "use with care in premature infants or infants under 2 months of age; these products may cause irritation or chemical burns." Routine changing of percutaneously inserted lines over guidewires should not be performed to prevent infection[81,167] or to replace a catheter with suspected infection.[34] Systemic antimicrobial prophylaxis before insertion of the CVC or for catheter maintenance has not been demonstrated to reduce the risk for CRBSI and is not recommended.[34,41,168,184] Continuous infusion of vancomycin through the CVC was effective in reducing CoNS BSI in neonates in one study, but did not reduce either length of stay in the ICU or mortality.[185] Moreover, routine use of systemic vancomycin for prophylaxis carries the risk for inducing vancomycin resistance and is not recommended.[186]

Attention to daily catheter care and maintenance is essential to preventing infection. Hand hygiene should be performed before any catheter manipulation. Education and training of staff, as well as ensuring appropriate staffing levels, are paramount.[34,41] Infection rates may be lower when catheter care is provided by a specially trained team.[187] Transparent catheter site dressings should be changed every 5 to 7 days and site care performed with a chlorhexidine-based antiseptic; dressings should be changed immediately if visibly soiled, loose, or damp.[41] Recommended frequency of changes for gauze dressings is every 2 days. Catheter hubs repeatedly have been demonstrated to be common sites of colonization.[188] Thus the hub of the catheter should be cleansed each time it is accessed with either 70% ethanol, alcoholic chlorhexidine, or povidone-iodine,[41] although use of chlorhexidine for disinfection may have longer lasting residual activity.[189] Mechanical friction should be applied to the hub for no less than 5 seconds.[70] Administration sets need to be changed no more frequently than at 96-hour intervals,[41] unless blood- or lipid-containing solutions are administered, in which case tubing should be changed within 24 hours after the infusion is initiated.[167,190]

Antimicrobial-based preventive strategies for select populations or individuals at higher risk for CLABSI include antimicrobial lock therapy, use of antimicrobial-impregnated catheters, and antimicrobial-impregnated dressings. As described previously, antimicrobial "locks" involve use of supratherapeutic concentrations of an antimicrobial agent (e.g., antibiotic or 70% ethanol) that is confined to the catheter lumen while the CVC is idle. Numerous studies of antimicrobial lock therapy have shown significant reductions in CLABSI risk, including a recent meta-analysis of randomized clinical trials that demonstrated a 69% reduction in CLABSI rate among a variety of patient populations, including hemodialysis patients, adult and pediatric oncology patients, critically ill neonates, and patients receiving total parenteral nutrition.[191–195] This effect appears to be additive to traditional preventive measures. However, because of concerns regarding the emergence of antimicrobial resistance in exposed organisms, antimicrobial lock therapy is recommended in patients at highest risk, including those with long-term hemodialysis catheters, patients with limited venous access and history of recurrent CLABSI, and those at risk for severe sequelae from infection.[41]

Catheters that are coated or impregnated with antimicrobial or antiseptic agents, such as chlorhexidine–silver sulfadiazine[30] or minocycline-rifampin,[196] can decrease the risk for infection and have been shown to decrease hospital costs, despite the additional expense of these devices.[24] The anti-infective effect of these catheters, however, is not permanent and may be limited to a relatively short period after insertion; data are lacking on their efficacy for longer insertion times (e.g., ≥2 weeks).[73] Although the efficacy has not been widely demonstrated in children, data from observational studies suggest that impregnated or coated catheters are safe and may be effective in reducing CLABSI in pediatric ICU patients,[39,197–199a] including a single-center study that demonstrated that minocycline-rifampin–coated CVCs delayed the occurrence of infection in critically ill children.[34] Such catheters are approved by the FDA for use in patients weighing >3 kg and are recommended for clinical situations in which the incidence of CLABSI is high despite implementation of other preventive measures.[34,41,67]

Use of chlorhexidine-impregnated dressings also has been shown to be protective against CLABSI, including in a randomized trial in adult patients,[200] although it is unclear whether their use provides additional benefit if daily chlorhexidine bathing is performed. In a randomized study performed in children with cardiac disease, use of a chlorhexidine-impregnated dressing reduced the rate of catheter colonization but not of catheter-related BSI.[201] Luminal contamination may be reduced through use of closed catheter connection systems[202] or a self-disinfecting CVC hub (containing iodinated alcohol).[203–205] Use of a chlorhexidine-impregnated dressing is recommended for patients older than 2 months when CLABSI rates are not decreasing despite adherence to all preventive measures.[34,41]

There are few guidelines for outpatient management of vascular catheters, although most CLABSIs occur in hospital units outside of the ICU or in outpatients. Issues that require further study include the safety of bathing or swimming; the optimal frequency of dressing, cap, and tubing changes; and optimal care of the insertion site. One study suggested that children with subcutaneously implanted catheters who swim (while the catheter is not being accessed) are not at higher risk for infection.[206] Nevertheless, when patients are discharged with indwelling venous catheters, they and their caregivers should understand the need to protect the catheter and catheter site and avoid contamination with tap water.

Infections of Prosthetic Valves, Patches, and Vascular Grafts

Epidemiology and Pathogenesis

Prosthetic valve and patch infections are classified as *early* (occurring ≤60 days after implantation) or *late* (occurring >60 days after implantation). Agents causing early infection are presumed to have been introduced at the time of the surgery or soon thereafter (Box 100.7). *S. aureus* is the most common cause of prosthetic valve endocarditis and vascular graft infection, followed by CoNS.[12,207–209] Other pathogens are *Enterococcus* spp., *Corynebacterium* spp., fungi, and gram-negative enteric bacilli; and rarely *Mycoplasma hominis*, *Brucella melitensis*, *Legionella* spp., *Pasteurella multocida*, and *Kingella kingae*.[210–216]

Box 100.7

Routes of Infection in Prosthetic Valve Endocarditis

Early Infection

Inoculation during insertion

Seeding from catheter-associated bacteremia

Spread from infected wound

Late Infection

Hematogenous spread: bacteremia due to tooth/gum disease, surgical procedures, infection elsewhere

Bacteremia in patients with prosthetic valves often is related to medical devices, particularly vascular catheters; one third of infections are HAIs.[188] In a prospective study of patients with prosthetic valves and healthcare-associated BSI, 43% had endocarditis.[217] The rate of infection of prosthetic valves is 1% to 4% for early infection and about 1% annually for late infections (after the prosthesis has become endothelialized).[209,218] Reported rates of infection of vascular grafts range from 0.5% to 4%.[189] Grafts in the lower extremities, especially the groin, are more likely to become infected. Hemodialysis grafts and fistulas most often are infected with *S. aureus*. Infection with gram-negative bacilli or nontuberculous mycobacteria can be associated with improper sterilization of hemodialyzers.[219–223]

Clinical Manifestations and Laboratory Diagnosis

Patients with infected prosthetic valves or patches typically come to medical attention with fever. Hemodynamic changes can be present in patients infected with more virulent organisms (Box 100.8).[209] Valve ring abscesses can lead to perivalvular leakage. The leakage may be appreciated as a new murmur and can be complicated by congestive heart failure and rhythm disturbances, such as heart block. Late infections generally give rise to the usual signs and symptoms of subacute bacterial endocarditis but can be more acute and fulminant depending on the pathogen (e.g., *S. aureus*, *Streptococcus pyogenes*).

Box 100.8

Diagnosis of Prosthetic Valve Infection

Physical Findings

New murmur

Congestive heart failure

Arrhythmia

Skin lesions (Osler nodes, Janeway lesions)

Petechiae; splinter and subconjunctival hemorrhages

Laboratory Findings

Positive blood culture

Elevated C-reactive protein/erythrocyte sedimentation rate

Elevated white blood cell count

Microscopic hematuria

Echocardiogram

Cardiac failure/valve dysfunction

Vegetation

Blood cultures are essential to optimal management. Bacteremia generally is continuous; however, culture results can be negative because of prior exposure to antimicrobial therapy or the presence of a fastidious organism. Echocardiography is another key component of the evaluation of patients with suspected endocarditis.[209,224] In children, adequate imaging often can be achieved by transthoracic echocardiography. The sensitivity of transesophageal echocardiography, however, generally is greater than transthoracic studies.[225] A negative echocardiogram does not exclude endocarditis; negative studies can occur if vegetations are small or have already embolized, or if prosthetic material obscures or distorts the images.

Graft infection can manifest as local wound purulence, pseudoaneurysm at the graft-vessel anastomosis, hemorrhage, or thrombosis. Physical examination often identifies infection in superficially located grafts. Ultrasonography is useful to detect pseudoaneurysms and thromboses. Other studies, such as angiography, computed tomography, and magnetic resonance imaging, are occasionally needed to determine the extent of infection and the presence of complications.[219]

Management and Outcome

Antimicrobial therapy and surgery are the main therapeutic modalities for infections of prosthetic valves and patches. For both early and late infections, combination therapy using synergistic antimicrobial agents is recommended,[209,224] although the benefit of combination therapy remains unclear. Because CoNS almost always is resistant to β-lactam agents, vancomycin and an aminoglycoside plus rifampin often are used empirically until culture results are known. Consensus guidelines for the treatment and prevention of endocarditis for patients with prosthetic valves have been published.[209,226]

Surgical consultation is advisable, particularly for patients early in the course and with acute infection. The benefit of surgery over medical therapy in adults with prosthetic valve endocarditis has not been demonstrated clearly,[227] and large pediatric studies have not been performed. Indications for surgery early in the course of infection include hemodynamic instability, repeated major embolizations, inability to control infection, and relapse of infection. Indications for surgery later in the course of acute infection include new regurgitant murmur, moderate to severe heart failure, or a myocardial abscess unresponsive to medical therapy.[228–231] When surgery has been undertaken during acute infection, studies have demonstrated that infection of new valves implanted at this time is relatively uncommon.[207–209,232] A retrospective analysis of *S. aureus* prosthetic valve endocarditis revealed significantly lower mortality when valves were replaced during antimicrobial therapy.[233] Therapy for infected grafts often requires surgical resection or revision for cure.[219] Antimicrobial agents have limited penetration in areas with poor blood flow (i.e., a thrombosed graft).

The role of anticoagulation in infection of prosthetic valves or grafts is still debated. Most patients with prosthetic valves are treated with anticoagulants; discontinuation of this therapy is associated with a higher incidence of thrombosis and embolic phenomena.[208,209] The risk for death, however, from neurologic events is higher if anticoagulation is continued.[234]

Complications of intravascular infections include thrombosis, hemorrhage, embolic infarction and infection, graft dysfunction, heart failure, overwhelming infection, and death, with 1-year mortality rates of more than 30% in adults.[227] Prognosis of prosthetic valve endocarditis depends on the organism, the condition of the patient at the time of diagnosis, the rapidity and appropriateness of antimicrobial therapy, and the timely use of surgical intervention if appropriate.[209,218,224,232,235]

Prevention

Important measures to prevent infection of prosthetic valves and grafts include proper timing of surgical procedures (e.g., avoiding elective surgery in a patient with an intravascular device and an active distant infection), appropriate administration of periprocedural prophylactic antibiotics,[233] meticulous attention to surgical asepsis, and prompt removal of catheters and other potential infectious foci (Box 100.9). The common practice of continuing perioperative antimicrobial prophylaxis until catheters or drains are removed is inappropriate and may prevent the timely identification of pathogens in early prosthetic valve endocarditis.

Box 100.9

Prevention of Prosthetic Valve Infection

Use prophylactic perioperative antimicrobial agents at time of placement and subsequent dental/surgical procedures

Minimize intraoperative contamination

Remove catheters as soon as possible

Use meticulous wound care: handwashing, removal of necrotic tissue, avoidance of contamination

Minimize antimicrobial agents to maintain normal flora

Avoid antacids to diminish colonization of stomach and subsequent spread to lungs

Prevention of graft infection starts with meticulous attention to sterile technique at the time of implantation. Hemodialysis grafts are at risk for contamination and subsequent infection with each dialysis procedure, so good hygiene and care of the graft site with each access are essential.[218] Because *S. aureus* is by far the most common pathogen associated with dialysis grafts, attempts have been made to decrease patient colonization through the use of intranasal mupirocin or systemic rifampin and cloxacillin; these attempts have met with some success.[234,236–238]

If dialyzers are reused, strict adherence to sterilization and reuse protocols is crucial. The Association for the Advancement of Medical Instrumentation and the CDC recommend that hemodialysis fluids be monitored at least monthly with quantitative culture and endotoxin assay. Water used to prepare dialysate must have ≤200 CFU/mL in culture, and water used to reprocess hemodialyzers should have ≤200 CFU/mL in culture and <1 ng/mL of endotoxin on assay. Dialysate colony counts should be ≤2000 CFU/mL.[239]

Infections Associated With Pacemakers and Left Ventricular Assist Devices

Epidemiology and Pathogenesis

Temporary pacemaker wires, which generally are inserted percutaneously into the bloodstream, are associated with infection risks similar to those for vascular catheters. In addition, pacemaker wires typically are embedded into the myocardium, posing a risk for myocardial abscess. Permanent pacemakers consist of a battery, which is inserted into a soft tissue pocket, and wires that pass across tissue planes to reach the myocardium. During initial placement either the battery or wires can become contaminated.[240] Infection in children occurs in 1% to 8% of patients.[209] Although most infections are limited to the pocket site, roughly 10% of adult pacemaker infections result in endocarditis.[226]

Left ventricular assist devices (LVADs) consist of a pump with an inflow conduit from the left ventricular apex and an outflow conduit to the ascending aorta. Although original models used bioprosthetic valves to maintain unidirectional flow, newer continuous flow pumps do not require valves.[241] The pump is placed into a pocket formed in the lateral rectus sheath. A driveline, tunneled from the pump, connects to an external power source through an exit site on the lower abdominal wall. LVAD-related infection is a common complication, occurring in 25% to 70% of patients,[242–248] and can include local infection of the driveline or pocket as well as LVAD-related BSI with or without endocarditis.[244,249]

Clinical Manifestations and Laboratory Diagnosis

Signs of pacemaker infection include tenderness and erythema around the battery pocket, fever, and, occasionally, BSI.[250,251] Although most studies of pacemaker and LVAD infections focus on adults, pediatric case series suggest similar etiologies and outcomes of infection.[247] The most common organisms are CoNS (42%) and *S. aureus* (29%), although gram-negative enteric bacilli and yeast can be isolated.[226] Signs of LVAD driveline infection include localized purulent drainage from the abdominal exit site. Device pocket infection is characterized by tenderness and erythema around the pump pocket and purulence within the subcutaneous space. BSI can cause fever, chills, and other constitutional symptoms. The distribution of pathogens identified in LVAD infection is similar to that encountered in pacemaker infections,[242,243,246–248] although recent reports suggest that fungal infections may be becoming more common.[244] Diagnosis is made by culturing relevant purulent drainage and obtaining blood cultures.

Management and Outcome

Treatment of pacemaker infections depends on the extent of the infection.[226] Localized cellulitis without device involvement often can be managed with systemic antimicrobial therapy without removal of the pacemaker battery. Indications for removal and replacement of the wire include (1) valvular or lead endocarditis or sepsis; (2) pocket infection with abscess formation, device erosion, skin adherence, or chronic draining or recurrent sinus; or (3) occult BSI. The outcome depends on the site of infection, the pathogen, and the condition of the patient. Local infections usually resolve without sequelae; deeper infections are associated with greater morbidity and mortality.

LVAD infections are difficult to eradicate and are associated with significant mortality.[244,246–248] Evidence for optimal treatment for LVAD-associated infection is derived largely from single-center case series with almost entirely adults. Although the optimal duration of therapy for LVAD-associated infection is unknown, continuous antimicrobial therapy before, during, and beyond transplantation may be required. Intraoperative debridement or, in rare cases, device removal and exchange may be required.[246,248,252] The results of a large single-center study suggested that continuous antimicrobial therapy is associated with fewer relapses than a limited course of therapy.[243] The potential benefits of prolonged antimicrobial therapy, however, must be balanced against the risk for developing antimicrobial resistance.

Prevention

Evidence-based data on the efficacy of measures to prevent infections in patients with pacemakers and LVADs are lacking. Antibiotic prophylaxis recommendations for pacemakers and

LVADs are modeled after those used to prevent surgical site infection.[226,253] For LVAD drivelines, exit site care usually consists of daily sterile cleansing with povidone-iodine and isopropyl alcohol, dilute hydrogen peroxide, or chlorhexidine and placement of an occlusive dressing.[243] Although fungal LVAD infections are associated with a worse prognosis than bacterial infections, systemic antifungal prophylaxis does not appear to prevent fungal infection.[244]

Infections of Central Nervous System Devices

Epidemiology and Pathogenesis

Central nervous system (CNS) devices include cerebrospinal fluid (CSF) shunts, subarachnoid screws and bolts, and subdural catheters.[254] Infections usually are caused by skin flora introduced during surgical insertion. Skin-associated tract infections and ascending infection can occur postoperatively in patients with ventriculoperitoneal (VP) shunts.[255] The latter develops when the distal end of a VP shunt penetrates the bowel (or is surrounded by a collection of contaminated mesenteric/peritoneal fluid, i.e., “CSFoma”) and typically are polymicrobial. Rarely, the VP catheter tip perforates the genitourinary system and becomes contaminated with local flora. Ventriculostomy catheters exit percutaneously to an external monitoring system and can become contaminated during placement or manipulation.[256,257] Moreover, skin flora can ascend from the exit site along the catheter and into the ventricle. Subcutaneous reservoirs can be contaminated during placement or subsequent access.

Infection rates for VP shunts range from 3% to 35%.[1,258–263] In general, rates are higher for second procedures (especially for replacement of an infected shunt, although the causative organisms may be dissimilar),[254] among those with perioperative CSF leak or myelomeningocele, and for shunts placed for hydrocephalus due to intraventricular hemorrhage fluid shunt infections in children.[263–265] Infections rates generally are higher in children than adults.[266] Most infections occur within 2 months of shunt placement.[267] In a study from 41 free-standing children's hospitals, the rates of shunt infection at 24 months were 11.7% per patient and 7.2% per procedure, although rates varied widely across institutions.[268] A follow-up analysis revealed a reinfection rate of 14.8%, most of which occurred within the first 2 months after reinsertion.[269] One study found that rates of infection were highest in July, possibly correlating with the arrival of new neurosurgical fellows in hospital programs.[260] As with other indwelling catheters, the rate of infection depends on the duration of catheterization.[270] Infection rates have been reported to be approximately 20% to 25% for subcutaneous reservoirs[270] and 10% for percutaneous ventriculostomies.

Clinical Manifestations and Laboratory Diagnosis

Catheter malfunction is the most common manifestation of infection. For shunts, malfunction produces signs of increased intracranial pressure (i.e., headache, vomiting, irritability, or mental status changes). Fever is usually but not always present.[254,256] Abdominal symptoms can predominate when the gastrointestinal tract is the source of shunt infection or if primary ventricular infection causes clinical peritonitis. Seizure occasionally is a presenting sign. Shunt malfunction due to occlusion or disconnection is the major alternative diagnosis. A malfunctioning shunt should be considered infected until proven otherwise, even in the absence of systemic manifestations and CSF pleocytosis.[256] Up to 30% of malfunctioning shunts are ultimately proven infected.[260]

Most infections are caused by CoNS and other skin flora; gram-negative bacteria account for about 20%.[256–260,271,272] Skin flora, including *Corynebacterium* spp. and *Propionibacterium acnes*, can cause particularly indolent infections. Fungal infections most commonly are caused by *Candida* spp. and occur most commonly in prematurely born infants.[273]

Diagnosis requires examination and culture of ventricular fluid; lumbar CSF is not sufficient.[274] Pleocytosis is typical but can range from none to thousands of cells per cubic millimeter.[5,258,263,274] Elevated ventricular fluid protein is more common than abnormal glucose concentration. Clinical and laboratory findings often are subtle in infections due to CoNS. Blood culture results usually are positive with ventriculoatrial shunt infection; likewise, pleural fluid culture can be positive in ventriculopleural shunt infections, and peritoneal fluid in VP shunt infections. Blood culture is rarely positive in VP shunt infection. Abdominal complications of VP shunts, including formation of pseudocyst (CSFoma), are best diagnosed with ultrasonography or computed tomography.[275,276] Lumbar puncture for CSF examination should be performed for a child with a lumboperitoneal shunt, or a VP shunt when the diagnosis of meningitis is suspected and ventricular shunt fluid is normal.

Management and Outcome

Treatment includes antimicrobial therapy and surgery.[254,256,260] Cure with systemic antimicrobial therapy alone is unusual. A common approach to treatment includes (1) removing the ventriculostomy or shunt or externalizing the peritoneal end of the shunt; (2) beginning systemic antimicrobial therapy; and (3) sampling ventricular fluid daily. Empiric therapy consists of an antistaphylococcal agent with adequate CSF penetration (nafcillin, oxacillin, or vancomycin); if abdominal signs are present or if a gram-negative infection is suspected, a broad-spectrum cephalosporin, such as cefotaxime, ceftriaxone, or cefepime, plus an aminoglycoside is added. Definitive therapy is based on susceptibility test results of isolates and ability of the antimicrobial agent to penetrate the CSF. Rifampin may be useful in combination therapy for patients with infection due to staphylococci, especially when the shunt cannot be removed. If the infection does not resolve promptly, antimicrobial agents also can be administered intraventricularly.[277–279]

Cultures should be repeated frequently to ensure that the infection is controlled and to use time-to-sterilization as a basis for duration of therapy. The system is replaced after the infection is fully controlled and cultures are negative. Limited data inform duration of antimicrobial therapy or optimal timing for shunt replacement.[256,257,280] Some experts recommend 7 to 10 days of antimicrobial therapy after sterilizing CSF, with extension to 10 to 14 days for more virulent pathogens such as *S. aureus*.[279,281] Timing of shunt replacement must balance the risks for superinfection associated with prolonged externalization against the risk for premature internalization with contamination of a new system.

The major complication of ventriculitis is brain injury. Studies of children with myelomeningocele reveal that the number of shunt infections is a major determinant of low intelligence.[282] The prognosis for ventriculitis depends on the virulence of the pathogen and condition of the underlying host. Infections caused by slime-producing strains of CoNS may be more difficult to cure.[283] Infection in the immunocompromised host is more likely to result in morbidity or mortality. Complications of peritonitis include adhesions, bowel obstruction, and loss of fluid-absorptive capacity. Respiratory distress due to pleural effusion or infection can complicate infections of ventriculopleural shunts (Box 100.10). Ventriculoatrial infection can lead to endocarditis and immune complex-related glomerulonephritis.

Box 100.10

Complications of Central Nervous System Devices

All Shunts

Ventriculitis: loss of neurons

Ventriculoperitoneal Shunts

Peritonitis: bowel obstruction, abdominal pseudocyst ("CSFoma"), loss of absorptive surface

Ventriculopleural Shunts

Pleural effusion, empyema

Ventriculoatrial Shunts

Bacteremia, endocarditis, nephritis

CSF, cerebrospinal fluid.

Prevention

Prevention of infection depends on the appropriateness of antimicrobial prophylaxis as well as meticulous sterile technique during device placement and with each sampling of CSF. Shaving the scalp over the shunt button before CSF collection damages the skin and increases the risk for infection at subsequent samplings; if hair removal is required, clipping should be performed. Although some individual studies of antimicrobial prophylaxis have failed to show a significant effect on infection rate, a meta-analysis suggests that perioperative prophylaxis reduces the incidence of shunt infection.[284] The optimal antimicrobial regimen remains unclear.[259,285,286] Administration of antimicrobial agents for the duration of continuous intracranial pressure monitoring is not appropriate.[287]

Prophylaxis for CNS devices should be limited to the perioperative period. Catheters and shunts impregnated with antimicrobial agents, such as rifampin and clindamycin, have been shown in vitro and in animal models to inhibit bacterial colonization.[288,289] Small clinical trials in adults[290–292] and children[293,294] and a meta-analysis[284] also support the efficacy of antimicrobial catheters for infection prevention.

Similar to prevention strategies for other device-related infections, the use of a standardized prevention protocol was recently evaluated among a collaborative of pediatric neurosurgical centers in the management of hydrocephalus.[295] Elements of the protocol included posting signs on the door to limit traffic during the procedure, positioning the head away from the main operating room door, providing specific guidance around perioperative prophylaxis and timing, and using an alcoholic chlorhexidine solution for skin antisepsis. The network infection rate decreased from 8.8% to 5.7% over a 6-month period with implementation of the protocol across centers; compliance with the protocol was reported at 74% overall but improved over the study period.

Infections Associated With Peritoneal Catheters

Epidemiology and Pathogenesis

Peritoneal catheters are most often inserted for continuous ambulatory peritoneal dialysis (CAPD). Peritoneal dialysis removes complement and immunoglobulins and thus impairs host defenses.[296,297] In addition, the low pH of dialysate inhibits neutrophil function.[297] Peritoneal catheter-associated infections include catheter exit site and tunnel infections as well as peritonitis; the incidence of peritonitis in children is approximately 0.67 episodes per patient-year.[298,299] Longer duration of dialysis therapy, younger age, and decreased serum concentrations of immunoglobulin G are associated with a higher incidence of peritonitis.[299,300]

Organisms can enter the peritoneum during placement and subsequent manipulation of the catheter, through intrinsically or extrinsically contaminated peritoneal dialysis fluid, or after perforation of the bowel by the catheter tip.[301] Hematogenous seeding, ascending infection through the fallopian tubes, and transmural migration of bacteria across the bowel wall are less common routes of infection.[296] The most common organisms are those that colonize the skin around the catheter insertion site and that may enter the peritoneum through the catheter tract: *S. aureus* and CoNS, which are isolated in 50% to 60% of infections; gram-negative enteric bacilli in 20% to 30%; and, less frequently, *Candida* spp., nontuberculous mycobacteria, molds, and *Nocardia* spp.[296,300,302,303]

Clinical Manifestations and Laboratory Diagnosis

Clinical findings in peritonitis include fever, abdominal tenderness, and cloudy dialysate. Presentations range from subtle pain to sepsis syndrome.[301] The differential diagnosis includes chemical peritonitis, eosinophilic peritonitis, hemoperitoneum, chylous ascites, and (rarely) malignancy.[299] Examination of the dialysate fluid usually reveals pleocytosis. Cell counts vary, depending on fluid dwell time and the causal pathogen, but leukocyte counts of >100 cells/mm^3 with neutrophil counts of >50% suggest infection.[296,304,305] There is no consensus on the optimal method to culture fluid. Consensus guidelines recommend centrifugation of a large volume (50 mL) of fluid for inoculation of blood culture media.[296,304–306] Exit site infection causes pericathether swelling, erythema, and tenderness localized to the catheter insertion site, whereas a tunnel infection causes these same signs and symptoms along the subcutaneous portion of the catheter.[305] Ultrasonography of the catheter tunnel can be useful in diagnosing tunnel site infection (particularly when exit site infection is apparent or in the setting of peritonitis) and after response to therapy.[307–311]

Management and Outcome

Exit site infections often respond to local therapy and oral antimicrobial therapy for 2 to 3 weeks depending on the organism isolated.[305] Infections of the tunnel often require catheter removal.[296] Peritonitis is usually managed with intraperitoneal antimicrobial therapy and continuous dialysis.[301] Most patients with CAPD-associated peritonitis can be treated in the ambulatory setting. If the patient is systemically ill or if attempts to eradicate the bacteria fail, hospital admission and systemic antimicrobial therapy are warranted, and catheter removal should be considered. Catheter removal is essential for cure of fungal infection[303] and often is necessary for enterococcal and *Pseudomonas* infections.[302] Several reports indicate that simultaneous removal and replacement of the catheter is successful in selected instances,[310–312] particularly when infection is caused by staphylococci, when the tunnel is involved, or in cases of recurrent peritonitis that clears intermittently with treatment.[305] This approach is less likely to be effective in infections due to gram-negative organisms or fungi, or if there is ongoing inflammation between episodes of recurrent peritonitis.[312] There are no controlled studies on optimal duration of therapy; the recommended course for children is 2 weeks, extended to 3 weeks for *S. aureus*.[313] Complications include intra-abdominal abscess formation, adhesions with subsequent bowel obstruction, and impairment of the diffusable peritoneal surface available for dialysis.

Prevention

Staphylococcal carriage predisposes to peritonitis. Eradication of nasal or skin carriage with antistaphylococcal agents has been shown to decrease the incidence of peritonitis due to *S. aureus*.[314–317] Systemic administration of rifampin, combined with an antistaphylococcal agent for 7 days, appears to be most effective.[314] Extensive guidelines for the prevention of infections associated with peritoneal dialysis in children have been published and include a standardized approach to training of nursing staff; catheter type, placement, and connection; exit sit care; and antimicrobial prophylaxis for catheter placement and in high-risk exposures.[305]

Infections of Orthopedic Devices

Epidemiology and Pathogenesis

Prosthetic joints are used less commonly in children than in adults, but pins, medullary nails, and rods are commonly placed in children for stabilization of fractures and during corrective surgery. Infection is a major complication of orthopedic devices[318,319]; incidence varies with type of procedure and patient population.[1] Infection after pediatric spinal fusion procedures varies by the underlying diagnosis: correction of adolescent idiopathic scoliosis is complicated by surgical site infection only 1% to 2% of cases, whereas infection rates for nonidiopathic scoliosis can be >10%.[320] For hip and knee replacements in adults, cumulative incidence of infection is roughly 1% to 2% over the life of the prosthesis but varies depending on the type of prosthesis or whether it is a primary implant or revision.[321] Risk for infection is higher in the presence of underlying malignancy; in a surgical site infection not involving the prosthesis; with a National Nosocomial Infections Surveillance System surgical patient risk index of >1[322]; and after surgery related to a previously infected site.[323,324] Pin site infections are common because the pin track creates a direct pathway for skin flora and contaminating organisms to reach soft tissues and bone. Infection risk depends on the mode and site of injury, amount of associated soft tissue injury, and time before pin removal. Solid medullary nails are associated with lower infection risk than hollow nails.[325]

Most infections are caused by CoNS and *S. aureus*. Other gram-positive cocci, such as group A streptococci, oral streptococci, and enterococci, as well as gram-negative enteric bacilli, are occasionally involved. Anaerobic bacteria account for <10% of infections.

Organisms gain access to the joint and bone at the time of implantation and later by spread from contiguous infections or (less commonly) by hematogenous seeding.[318,319]

Clinical Manifestations and Laboratory Diagnosis

Clinical manifestations of implanted orthopedic device–associated infection frequently are subtle. Findings include pain, wound dehiscence, or loosening or malfunction of prosthetic joints. With pin-related infections, there is usually purulence at the skin exit site, but the depth of involvement is difficult to determine; infection can extend to the intramedullary cavity.[326] Toxic shock has been reported as a complication of pin site infection,[327] as has brain abscess secondary to a halo orthosis pin site infection.[328]

The diagnostic utility of most radiographic techniques in pin, nail, and joint infection is limited because the appearance of infection mimics that of healing bone. For prosthetic joints, radiographs sometimes are helpful; periosteal reaction occurs with infection but also can occur with normal healing. An area of radiolucency surrounded by a sclerotic edge is suggestive of infection.[329] Radionuclide scans are sensitive but not specific and do not reliably differentiate infection from fracture and healing bone.[330,331] Computed tomography and magnetic resonance imaging are rarely helpful because the device often causes artifacts, obscuring the area of interest.[318] Assessment of inflammatory markers, including erythrocyte sedimentation rate and C-reactive protein, may help guide diagnosis and treatment.

Culture of superficial drainage from pin sites or draining sinuses can yield colonizing or contaminating organisms rather than the true etiologic agent. Direct sampling of the bone or joint for histologic examination and culture usually is required for definitive diagnosis.[319] Intraoperative specimens evaluated by frozen-section examination are useful in excluding active infection during surgery to revise loosened prostheses.[332]

Management and Outcome

The treatment of infections associated with surgical implants is challenging.[333] Therapy for superficial pin track infections involves pin removal and prolonged antimicrobial therapy. For infected rods and joints, removing the device offers the best chance of cure but is complicated by prolonged disability and deformity. Often, a two-step approach is used, in which the infection is first brought under control with systemic antimicrobial therapy and the device and all devitalized tissue and cement are removed. At a later date, the device is replaced.[334,335] There is no consensus regarding the ideal interval before replacement.

If removal of the device is not feasible, a combination of antimicrobial therapy and debridement can be attempted. Although retaining the prosthesis had historically met with limited success,[336,337] some studies of adults with infected hip and knee prostheses demonstrated successful treatment with prolonged oral antimicrobial therapy, primarily with combinations of ciprofloxacin and rifampin and retention of the prosthesis after initial debridement.[338,339]

Antimicrobial therapy for infected orthopedic devices typically is prolonged. For staphylococcal infections, the combination of a β-lactam or fluoroquinolone plus rifampin may be considered if the organism is susceptible and the device cannot be removed.[340] For cases in which the device is left in place, vacuum device to enhance blood flow, and long-term suppressive therapy may be warranted. If there are large tissue defects over the involved area, skin and muscle flaps may help by providing a vascular source to enhance host defenses and improve antimicrobial delivery.[341]

Prevention

Methods designed to decrease contamination of the operative field during implantation of orthopedic devices have been studied, including increasing the number of operating room air exchanges as well as use of high-efficiency particulate air filters, laminar flow systems, and special barrier suits for surgeons.[342] A large prospective study involving >7000 patients showed no difference in rates of infection between the use of conventional operating suites and laminar flow rooms,[319] and more recent analyses suggest that laminar flow may increase the rate of surgical site infection after some orthopedic implantation procedures.[343]

Perioperative prophylaxis, primarily with intravenous antistaphylococcal agents, is beneficial. Administration of prophylactic agents should be confined to the immediate perioperative period (i.e., from just before the procedure to 24 hours afterward). The appropriate drug, dose, and timing of antimicrobial prophylaxis before orthopedic implantation is critical,[344] and guidelines for perioperative prophylaxis of pediatric orthopedic procedures have been published.[345] The clinical efficacy of dipping implants in antimicrobial solutions, antimicrobial coating of implants, use of antimicrobial carriers (e.g., cements, beads), or topical application of antimicrobials to the surgical bed before closure (e.g., vancomycin "powder") has not been established.[345–349] Antimicrobial prophylaxis in persons with orthopedic implants who undergo dental or surgical procedures typically is not recommended.[350,351]

Infection of Urinary Catheters

Epidemiology and Pathogenesis

The literature describing catheter-associated urinary tract infections (CAUTIs) in children largely is limited by two factors: (1) studies often fail to distinguish symptomatic from asymptomatic infections (i.e., catheter-associated bacteriuria from CAUTI), and (2) data describing epidemiology and strategies for the management and prevention of infections are limited. Despite these limitations, many principles of adult CAUTI are reasonably adapted to pediatrics.

Infection is the most common complication of urinary catheterization,[352,353] and CAUTI is the most common HAI in adults worldwide.[354] CAUTI makes up a much smaller proportion of device-related HAI in pediatric patients, likely owing to differences in urinary tract catheterization between adults and children. However, data from the CDC NHSN show that pooled mean rates of CAUTI are similar between adult and pediatric ICUs.[32] Isolated cystitis occurs most commonly, but pyelonephritis and secondary BSI also can develop. Limited data exist on the epidemiology of pediatric CAUTI. A recent retrospective analysis of CAUTI in a tertiary care children's hospital found that >80% of CAUTIs were identified in critically ill children and 75% were in females; nearly all patients had at least one chronic underlying condition, and approximately one third had either an anatomic or functional abnormality of the genitourinary tract.[355]

Microbial colonization of the urine is the first step in the pathogenesis of CAUTI, although many chronically catheterized patients may have evidence of bladder colonization without clinical evidence of infection. Pathogens can be introduced during catheter insertion, by ascending from the perineum along the external surface of the catheter, or intraluminally through contamination of the collecting tube or drainage bag.[356,357] After insertion, microbes begin to adhere along the internal and external surfaces of the catheter, leading to the rapid formation of polymicrobic biofilms that migrate to the bladder within 1 to 3 days.[354,358,359] Duration of catheterization is the most important risk factor for CAUTI.[353] The incidence of catheter-associated bacteriuria is estimated at 3% to 8% per day[354]; estimates are lower in the presence of a closed drainage system and higher with open drainage, when diarrhea is present, and when there is diminished urine flow or urinary stasis (as occurs with ureteral reflux, bladder diverticula, and stenosis of the urethra).[1,116,357–361]

The most common organisms that cause CAUTIs are members of the perineal flora.[44] Infections in patients with short-term indwelling catheters (<30 days) are typically caused by a single organism, whereas infections in patients with long-term catheters (>30 days) are more often polymicrobial.[314] *E. coli* is most commonly identified; other enteric gram-negative bacilli, *Enterococcus* spp., and *Candida* spp. also are frequent. Patients receiving antimicrobial agents are at high risk for infection due to resistant bacteria and fungi.[357,362]

Clinical Manifestations and Laboratory Diagnosis

Bacteriuria in patients with indwelling urinary catheters typically is asymptomatic.[363] Signs and symptoms of CAUTI can be challenging to identify because many catheterized patients do not manifest typical symptoms of UTI, such as urgency, frequency, and dysuria. Fever is often the most commonly identified sign. Other symptoms can include enuresis and cloudy or foul-smelling urine. Urinalysis and culture are useful to confirm infection. Urinalysis can reveal pyuria, but pyuria alone is not diagnostic of infection in a catheterized patient, particularly those with long-term indwelling catheters. Diagnosis of CAUTI is established by isolation of organisms with colony counts of $>10^5$ CFU/mL from a urine specimen that is obtained aseptically from the catheter.

Management and Outcome

Therapy for bacteriuria and infection should include removal of the catheter if possible. If the catheter remains in place, infection often persists despite appropriate antimicrobial treatment or recurs immediately after cessation of therapy. The need for antimicrobial therapy for bacteriuria or cystitis is debatable because infection often resolves spontaneously with removal of the catheter.[357] For complicating pyelonephritis and BSI, systemic therapy is necessary; the optimal duration is unclear.

The major complications of CAUTI are pyelonephritis, renal damage,[360] and BSI.[360,364] It is important to exclude UTI before major surgical interventions in catheterized patients. Prognosis is related to extent of the infection, the pathogen involved, and underlying host factors.

Prevention

Detailed guidelines for the prevention of CAUTI in acute care hospitals have been published and recently updated.[353] Many of these strategies have been incorporated into CAUTI prevention bundles that include standardized training and catheter insertion and maintenance practices; use of a CAUTI prevention bundle was recently associated with a significant reduction in CAUTI rates in a tertiary care children's hospital.[355] Important strategies to prevent CAUTI include (1) limiting catheterization to those for whom it is medically necessary; (2) using aseptic technique during catheter insertion; (3) properly securing the catheter and maintaining a sterile, continuously closed drainage system with unobstructed urine flow; and (4) removing the catheter as soon as possible. Using collection tubing that is free of kinks or dependent loops and positioning the collecting system below the level of the bladder avoid bladder urinary stasis or reflux.[23,353] In general, applying creams or attempting to wash the perineum raises the risk for UTI, probably because of movement of the catheter and an increase in introduction of perineal flora along the catheter and into the bladder.[365]

Catheters commonly are "forgotten" and left in place for too long. One study of adult medical inpatients revealed that clinicians were unaware that their patients had a catheter 28% of the time.[366]

Prophylactic antimicrobial therapy has been demonstrated to provide brief protection against bacteriuria[367]; however, few guidelines recommend this strategy because the risk for progression from asymptomatic bacteriuria to UTI remains low for most patients.[354] In addition, prolonged antimicrobial therapy is not protective and often is harmful because of the promotion of antimicrobial resistance and development of *Clostridium difficile* infection.[356]

Clean intermittent catheterization is preferred to indwelling catheterization in children with neurogenic bladder.[368] The abdominal Credé method does not empty the bladder and may increase the risk for infection.[19,356,369] Antiseptic-impregnated catheters have been shown to delay the onset of bacteriuria, but few studies have examined cost versus benefit and the risk for emerging resistant organisms associated with the use of these catheters.[370]

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Infections in Patients With Deficient Defenses

OUTLINE

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101

Evaluation of the Child With Suspected Immunodeficiency

E. Stephen Buescher

Although primary immunodeficiency disorders are uncommon, referral for evaluation of these conditions in children with frequent infections is common. Epidemiologic studies show that children aged <2 years have an average of 5 to 6 acute respiratory tract illnesses per year, with a range up of to 11 or 12 per year.[1,2] Infections such as otitis media and gastroenteritis occur with similar frequencies in children <2 years of age, with up to 14 episodes per year at the far end of the normal spectrum.[3] Attendance at group childcare and exposure to secondhand smoke further increase frequency of these infections.[4] An approach that includes a carefully obtained history, a thorough physical examination, and selected laboratory tests often is required to differentiate the uncommon, immunologically abnormal child who requires more extensive evaluation from the common, “normal but unlucky” child.[5] Because normal children can experience large numbers of infections, criteria other than the number of illnesses should be considered. These include (1) a history of documented, deep infections at multiple sites; (2) abnormal growth or development; (3) abnormal morphology or physiology between infections; or (4) a family history of immunodeficiency. Further investigation is warranted in children with one or more of these characteristics and focuses on categorizing patients as to the likely cause for their recurrent infections.

Anatomic and Physiologic Abnormalities

A variety of anatomic abnormalities can alter natural host defenses and predispose a child to recurrent infections (Table 101.1). Anatomy-related infections often localize with recurrent infections at or near the site of the abnormality. In instances of congenital malformation, infections usually begin during infancy. Compared with the incidence of primary immunodeficiency disorders, congenital malformation as a cause of recurrent infections is common.

TABLE 101.1

Anatomic and Physiologic Abnormalities That Predispose to Recurrent Infections

Type of Infection	Predisposing Abnormality
Bloodstream infection	Asplenia
	Cardiac valve abnormality
	Intravascular cannula or thrombus
	Neutropenia
Bone infection	Foreign body
	Orthopedic device
Meningitis	Cochlear implant
	Dura mater (meningeal) defect
	Midline dermal sinus
	Mondini defect of inner ear
	Neuroenteric fistula
	Occult skull fracture
	Ventricular cannula
Pneumonia	Abnormal cough reflex
	Atelectasis
	Bronchiectasis
	Endotracheal intubation
	Extrinsic airway compression
	Foreign body
	Gastroesophageal reflux

	Polyps
	Pulmonary cyst, fistula
	Pulmonary sequestration
	Tracheal web
	Tracheoesophageal fistula
	Tracheomalacia
	Tracheostomy
	Vascular ring
Soft tissue infection	Diminished sensation
	Foreign body
	Lymphedema
	Thermal injury
Urinary tract infection	Genitourinary tract duplication, cyst, fistula, or obstruction
	Nephrostomy
	Urinary catheter
	Vesicostomy

Underlying Conditions

The presence of underlying conditions, either natural or iatrogenic, can alter host defenses and predispose to recurrent infections or may be associated with an immunodeficiency (Box 101.1). In addition to the primary immunodeficiency syndromes, recurrent infections occur in more than 100 other syndromes, which include growth deficiencies, specific organ system dysfunctions, inborn errors of metabolism, and miscellaneous and chromosomal anomalies.[6] Some underlying conditions only become serious diagnostic considerations when specific data are obtained during a detailed history. Some conditions are suspected when constellations of noninfectious signs and symptoms are revealed by history and physical examination. Recurrent infections associated with underlying conditions either can be localized or disseminated and may or may not respond well even when appropriate treatment is given. Compared with the incidence of primary immunodeficiency disorders, this category of causes of recurrent infections also is common.

Box 101.1

Underlying Conditions That Can Predispose to Recurrent Infections

Asplenia syndromes/conditions

Asthma

Bone marrow and solid-organ transplantation

Chemotherapy

Collagen vascular diseases

Congenital malformation

Corticosteroid therapy

Cystic fibrosis

Dermatologic syndrome with immunodeficiency

Diabetes mellitus

Down syndrome

Drug-induced cytopenia

Galactosemia

Gastrointestinal tract syndrome with immunodeficiency

Genetic/metabolic conditions

Glycogen storage disease type IB

Growth deficiency/immunodeficiency syndrome

Hematopoietic/immunologic conditions

Hemoglobinopathy

Ichthyosis

Immunosuppression

Isovaleric acidemia

Lymphohematopoietic malignancy

Malnutrition

α-Mannosidosis

Methylmalonic aciduria

Mucolipidosis II

Myelokathexis (WHIM syndrome)

Myotonic dystrophy

Nephrotic syndrome

Neurologic syndrome with immunodeficiency

Newborn state

Nutritional conditions

Orotic aciduria

Prematurity

Propionic acidemia

Protein-losing enteropathy

Radiation therapy

Renal conditions

Renal failure

Sarcoidosis

Tumor necrosis factor antagonist therapy

Werdnig-Hoffmann disease

WHIM (warts, hypogammaglobulinemia, infections, myelokathexis)

Primary Immunodeficiency Disorders

Recurrent infections due to primary immunodeficiency disorders are rare in the general population and are relatively rare compared with other causes of recurrent infection (Table 101.2). Common characteristics in children with primary immunodeficiency disorders are shown in Box 101.2.

TABLE 101.2

Estimated Frequencies of Selected Chronic Underlying Illnesses, Primary Immunodeficiency Disorders, and HIV Infection

Condition	Frequency
Asthma[26]	1 in 26
IgA deficiency	1 in 500 to 700
Diabetes mellitus[26]	1 in 556
HIV infection	1 in 1000
Sickle cell disease[26]	1 in 2200
Cystic fibrosis[27]	1 in 2500
Acute lymphocytic leukemia[26]	1 in 9000
Phenylketonuria[26]	1 in 10,000
Agammaglobulinemia[26]	1 in 50,000 to 100,000
Severe combined immunodeficiency	1 in 100,000 to 500,000
Chronic granulomatous disease[28]	1 in 255,000

HIV, human immunodeficiency virus; IgA, immunoglobulin A.

Box 101.2

Characteristics of Children Wth Primary Immunodeficiency Disorders

Infectious symptoms often begin in first days to weeks of life

Therapeutic response is slow despite identification of a pathogen and administration of appropriate antimicrobial therapy

Infection is suppressed rather than eradicated by appropriate therapy

Common organisms cause severe manifestations or recurrent infection

Unusual (sometimes sentinel) or "nonpathogenic" organisms cause infections

Growth and development are delayed

Multiple infections occur simultaneously

Infection with common organisms leads to unexpected complications

The relative frequency of primary immunodeficiency disorders is shown in Table 101.3.[7,8] The list of recognized immunodeficiency conditions is ever-expanding, and the component due to recognized disorders of the innate immune system is growing.[8] The International Union of Immunological Societies frequently publishes updates on the classification of primary immunodeficiencies, which include names of conditions, presumed pathogenesis, genetics, inheritance, immunologic parameters, associated features, and Online Mendelian Inheritance in Man (OMIM) reference numbers.[9] More than 250 conditions presently are identified.[9,10] Some are well characterized, their pathologic mechanisms are understood, and numerous affected patients have been described (e.g., chronic granulomatous disease, X-linked severe combined immunodeficiency syndrome, X-linked agammaglobulinemia, leukocyte adhesive deficiency type I, and adenosine deaminase deficiency).[11–15] Other conditions remain incompletely characterized, are poorly understood, or have been observed in so few patients that they have not been studied extensively (e.g., lazy leukocyte syndrome, generalized pustular psoriasis, reticular dysgenesis).[16–18]

TABLE 101.3

Relative Frequency of Primary Immunodeficiency Disorders

Factors	Percentage
B lymphocytes	50–70
T lymphocytes	20–30
T and B lymphocytes	10–15
Phagocytic cells	15–20
Complement	2–5
Other innate immunity factors	<1

Clinical Approach to the Child With

Recurrent Infections

History

A detailed history is the most powerful evaluation tool and should gather information using all available sources, including medical records, parent or patient interviews, radiographs, and laboratory test results. Information is assembled into a chronology of data and events to determine whether episodes of illness have been characterized well enough to confirm that the patient truly has had recurrent infections. Additional important considerations are whether treatment of infectious episodes was appropriate, response to treatment was as expected, or other explanations exist (e.g., fever from inflammatory rather than infectious disease).

Medical History

A description of each infectious episode is obtained, specifically: (1) date, duration, and site of infection; (2) how the diagnosis was established (i.e., specific cultures and diagnostic tests performed and their results); (3) severity of the episode (shock, tissue destruction, ventilator support, end-organ damage); (4) what treatment (need for parenteral or prolonged) was used and responses to specific treatments; (5) need for surgical intervention and quality of wound healing; and (6) temporal relationships to previous episodes. This level of detail often necessitates a prolonged interview but is crucial for establishing whether an immunodeficiency is likely. Additional helpful details of the patient's history include immunizations administered and any clinical illnesses associated with them, pattern of growth and development, medications given (including long-term antibiotic use) and their effect on course of disease, compliance with treatments, presence of conditions that can predispose to or masquerade as infections, unusual blood phenotypes (e.g., McLeod phenotype in chronic granulomatous disease, Bombay phenotype in leukocyte adhesion deficiency type II), and healing pattern after skin and soft tissue infection, injuries, or surgery. If infections have been localized around an anatomic site, details should be obtained to focus on foreign body aspiration, injuries or surgery at the site, medical problems involving the site, and timing of onset of infections relative to other events.

Historical details that decrease concern for a primary immunodeficiency are rapid responses to appropriate therapy, rapid resolution (vs. suppression) of infected foci, healing without scarring, and inability to document infection. Details that are difficult to assess are poorly documented "infections," "infections" in the presence of allergic inflammation, and infections occurring in association with underlying conditions.

The category of microorganisms (and certain sentinel organisms) causing infections can suggest specific disorders (Table 101.4). Recurrent infections with extracellular, encapsulated microorganisms or chronic sinopulmonary infections frequently occur in people with asplenia, antibody deficiency conditions, or pattern recognition molecule (e.g., mannose-binding lectin or toll-like receptor) dysfunction. Deep fungal infections, multiple liver abscesses, or osteomyelitis suggests a phagocytic cell disorder. Recurrent infections accompanied by autoimmune symptoms or recurrent infections with *Neisseria meningitidis* suggest complement deficiencies. Recurrent infections due to opportunistic viral, protozoal, bacterial, mycobacterial, or fungal agents suggest T-lymphocyte deficiency. Unusual susceptibility to human papillomavirus infections occurs in WHIM (warts, hypogammaglobulinemia, infections, myelokathexis) syndrome and severe and disseminated mycobacterial infections are seen in defects related to interferon γ production and signaling.

TABLE 101.4

Sentinel Pathogens of Infections and Associated Conditions

Infectious Agent	**Condition**
Mucoid *Pseudomonas aeruginosa*	Cystic fibrosis
Nocardia spp., *Aspergillus* spp.	Chronic granulomatous disease
Burkholderia cepacia pneumonia	Chronic granulomatous disease, cystic fibrosis
Recurrent *Neisseria* spp. infections	Terminal complement component deficiency
Escherichia coli bloodstream infection	Galactosemia
Deep *Candida* spp. infection	Myeloperoxidase deficiency
Disseminated *Mycobacterium* spp. infection	T-lymphocyte deficiency, IFNγ receptor deficiency, IL-12 defects
Pneumocystis jirovecii	T-lymphocyte deficiency
Recurrent/severe *Streptococcus pneumoniae* bloodstream	Asplenia, hemoglobinopathy, agammaglobulinemia, mannose-binding lectin deficiency, IRAK4 deficiency

infection	
Recurrent/severe *Staphylococcus aureus* infection	Chronic granulomatous disease, hyper-IgE/recurrent infection syndrome, Chédiak-Higashi syndrome, IRAK4 deficiency

IFNγ, interferon γ; IgE, immunoglobulin E; IL, interleukin; IRAK4, interleukin 1 receptor−associated kinase 4.

Family History

Specific questions regarding the parents' ethnic heritage, the likelihood of parental consanguinity, early childhood deaths in the two previous generations, and gender bias in medical problems should be asked. Survival and significant illnesses and hospitalizations in all family members within two previous generations, as well as occurrence of peculiar infections or certain syndromes (e.g., collagen vascular diseases and lymphoreticular malignancy), should be documented. Consanguinity or close ethnic heritage of the parents, occurrence of multiple early childhood deaths (particularly of male sex) in the family, serious infections in other family members, or presence of recognized syndromes in other family members (e.g., discoid lupus in heterozygous carriers for X-linked chronic granulomatous disease) heighten concern. Collagen vascular diseases in family members (associated with some complement deficiency states) and the presence of lymphoreticular malignancies (associated with a variety of immunodeficiency diseases) are noteworthy.[19]

Birth History

Both congenital anatomic malformations and primary immunodeficiency disorders can manifest within days to weeks of birth. History is sought about the mother's prenatal care, prenatal illnesses, and exposures as well as the infant's length of gestation and peripartum problems, delayed separation of the umbilical stump (leukocyte adhesion deficiency type I), requirement for blood transfusion (graft-versus-host disease), and need for ventilator support. Historical details of concern include lack of prenatal care, maternal drug use or multiple sexual partners (human immunodeficiency virus or other congenital infection), presence of congenital malformations, absence of a thymic shadow on a neonatal chest radiograph, perinatal blood transfusion, perinatal ventilator therapy (resulting in chronic lung disease), onset of infection in the first days of life, intracranial hemorrhage (resulting in dysfunction of hypothalamic temperature regulation), prenatal exposure to a teratogen, and the need for surgical removal of the umbilical stump. Separation of the umbilical stump normally occurs within 14 days, and failure to separate is associated with leukocyte adhesion deficiency type 1. Of note, assiduous umbilical cord care (aggressive application of triple dye and isopropyl alcohol to "keep the cord stump clean") can lead to its desiccation and resultant failure to separate in normal infants.

Social History

Because the frequency of infection in small children mirrors frequency of exposure, details are sought of the patient's contacts with other children (e.g., siblings, classmates, playmates in childcare, nursery school, playgroups) that increase the frequency of exposures. In addition, exposure to tobacco smoke or other environmental pollutants affects infection rates and symptomatology, particularly in association with underlying atopy.

Review of the patient's dietary habits should include estimates of caloric intake and whether raw egg ingestion occurs (excessive intake of avidin can lead to nutritional biotin deficiency). The length of time at the current residence, the type and duration of parental employment, and the child's daily activities or school performance can yield insights into the continuity of medical care. The effect that "recurrent infections" has had on the child and family gives a measure of their severity.

Review of Systems

The review of systems should focus on infection by organ systems involved. Skin, mouth, nasopharynx, lungs, and gastrointestinal tract are sites of constant contact with the microbially contaminated external environment and are common sites of infection. The liver, spleen, and lungs provide defenses against systemic spread of infection and as a result can become sites of infection. The occurrence of cutaneous abscesses and extent of scarring when wounds heal, rashes (e.g., discoid lupus), rhinitis, dermatitis (generalized or localized, particularly behind the ears and in the diaper area), and paronychia provide clues to underlying disorders and the integrity of skin defenses. Questions about sinusitis, seasonal allergies, allergic shiners, snoring, and sleep disturbance (i.e., upper airway obstruction) explore the possibility of an allergic diathesis. Gingivitis, periodontal disease, retained primary teeth, and aphthous stomatitis can be associated with specific primary immunodeficiency disorders. Focused questioning about pneumonia, diarrhea, perirectal or pararectal abscess, liver abscess, lymphadenitis, and bloodstream infections can reveal details sometimes missed in general review of systems.

Physical Examination

Points to be addressed by the physical examination are (1) the physical status of the patient, (2) the presence of physical findings that confirm points of history, and (3) previously unrecognized but significant physiologic or anatomic abnormalities. Specific considerations during the physical examination are shown in Box 101.3.

Box 101.3

Specific Considerations During the Physical Examination

Reconcile vital signs with historical details (e.g., normal pulse and respiratory rate despite significant lung disease infers physiologic compensation and, therefore, chronicity)

Assess general habitus, growth, and development (chronically ill versus robust; developmental delay; dysmorphism suggesting a genetic syndrome)

Seek markers for atopy, nasopharyngeal lymphoid hyperplasia, or both

Identify lymphoid tissue (absence of palpable or visible lymphoid tissue suggesting T-lymphocyte deficiency)

Examine for midline defects in the head, neck, spine, or sacrum; or the presence of glucose-containing rhinorrhea

Examine for scarring of tympanic membranes

Examine for gingivitis, ulcerations, tooth loss, or periodontal disease (typical of immunodeficiency)

Identify cutaneous stigmata:

- Petechiae (suggesting Wiskott-Aldrich syndrome)
- Skin or conjunctival telangiectases (ataxia-telangiectasia syndrome)
- Eczematoid rash (Wiskott-Aldrich syndrome, hyperimmunoglobulinemia E [hyper-IgE] syndrome)
- Seborrhea-like dermatitis localized behind the ears (chronic granulomatous disease)
- Generalized seborrhea-like dermatitis (Langerhans histiocytosis, graft-versus-host disease, or T-lymphocyte deficiency)
- Nose-tip dermatitis (chronic granulomatous disease)
- Alopecia (graft-versus-host disease)
- Ectodermal dysplasia (anhidrotic ectodermal dysplasia with immunodeficiency)
- Cutaneous scars, with thin/poor formation at site of previous surgery or with tissue loss at site of previous infection (leukocyte defects)

Seek markers for chronic lung disease (pulmonary osteoarthropathy)

Assess for acute or chronic sinus disease

Identify the size of the liver and spleen

Examine for pararectal inflammation, scarring from previous infections, or persistent inflammation

Examine exhaustively any anatomic site where infections repeatedly localize, assessing normalcy of local anatomy and physiology

Laboratory Findings and Diagnosis

If the history and physical findings are consistent with an anatomic cause of infection or the presence of an underlying condition, laboratory evaluation of the patient is directed at either defining the anatomic problem or diagnosing the underlying condition. If the history and physical findings do not point to a cause for recurrent, significant infections, a screening laboratory analysis provides a reasonable first evaluation (Table 101.5).

TABLE 101.5

Screening Laboratory Tests and Their Purposes in the Evaluation of Immunodeficiency Disorders

Test	Purposes
Complete blood count differential	Assess numbers and morphology of cellular blood elements: leukopenia, leukocytosis, anemia, neutropenia, lymphopenia, Howell-Jolly bodies, bizarre erythrocyte forms, leukocyte morphology, thrombocytopenia
Total lymphocyte, T-lymphocyte, and B-lymphocyte quantification	CD3 marker is used to estimate total lymphocyte number by flow cytometry; CD4 and CD8 markers are used to estimate T-lymphocyte subsets; B-lymphocyte numbers are estimated using surface Ig expression or CD19 or CD20 markers
Skin testing	Simple assessment of cell-mediated immunity (T-lymphocyte function)
Serum immunoglobulin quantification (IgA, IgG, IgM, IgE)	Assess for hypergammaglobulinemia, hypogammaglobulinemia, or agammaglobulinemia
IgG subclass determinations	Assess for specific subclass deficiency
Specific antibody determinations	Assess production of antibody in responses to tetanus or diphtheria toxoid immunization as well as boosting; assess quantitative

	isohemagglutinin levels
Assess for Underlying Conditions	**Test**
Cystic fibrosis	Sweat test
HIV	HIV serology (and PCR testing, depending on patient age)
Sickle cell disease, thalassemia	Hemoglobin electrophoresis
Multiple congenital and acquired anomalies/conditions	Assess chest radiograph for chronic lung disease, foreign body, presence of thymus, situs inversus, anatomic abnormality, or end-organ damage If anatomic definition is inadequate, consider chest computed tomography
Terminal complement component deficiency	Total hemolytic complement activity (CH50)[a]

[a] Test performance is altered easily and unpredictably by inappropriate specimen handling and/or poor laboratory technique.

CD, cluster designation (for antigens); CH50, 50% hemolyzing dose of complement; HIV, human immunodeficiency virus; Ig, immunoglobulin; PCR, polymerase chain reaction.

Further Assessment

After the history, physical examination, and a screening laboratory evaluation have been completed, either the diagnosis will be clear and a plan of action can be proposed, or a diagnosis will be lacking and the decision must be made as to whether further, more detailed evaluation is appropriate. This decision is based on an overall impression of the severity, end-organ effects, documentation, and pathogens of the child's recurrent infections, family history, and physical findings. In the absence of repeated, documented infections in a patient in whom physical findings, growth and development, and appetite and activity are normal and the screening laboratory examination are unrevealing, the likelihood of a predisposing condition or immunodeficiency is remote and the child is assessed as “normal but unlucky.” Prospective observation and documentation should be planned and reassurance given.

Problems may resolve spontaneously, or documentation of continuing problems may reveal their cause or lead to a need for specialized evaluation. If there are major incongruities between physical findings, historical details, and laboratory results, or when an unexplained lack of continuity in patient care is obvious, Munchausen syndrome or Munchausen syndrome by proxy should be considered.[20]

Specialized Testing

If anatomic problems or underlying conditions are suspected, appropriate testing and imaging are pursued. If immunodeficiency is suspected or is likely, specialized, targeted testing is planned. Because the range of specialized testing is broad, an all-inclusive testing approach is both labor and time intensive, extremely costly, and inappropriate in most circumstances. Focused testing should be performed in a stepwise fashion, pursuing abnormalities uncovered by history, physical examination, and screening laboratory tests (Table 101.6).

TABLE 101.6

Specific Testing Approaches for Immunodeficiency Disorders

Disorder	Possible Testing Approaches
Cytopenia	Bone marrow examination/histochemistry
	Cytokine, colony-stimulating factor levels
Antibody deficiency	In vitro antibody production (Ig isotypes and subclasses)
	Cytokine levels
	In vitro specific antibody production
	Bruton thymidine kinase gene
T-lymphocyte deficiency	Adenosine deaminase activity
	Nucleoside phosphorylase activity
	In vitro proliferation responses (mitogens and specific antigens)
	Cytokine, growth factor levels
	Skin biopsy, intestinal biopsy (graft-versus-host disease)
Phagocytic cell dysfunction	Bactericidal activity Respiratory burst activity (nitroblue tetrazolium reduction, superoxide, dihydrorhodamine 123 oxidation test, or H_2O_2 production) Chemotaxis
Complement deficiency	CH50 Individual complement component quantitation Serum opsonic activity

CH50, 50% hemolyzing dose of complement; Ig, immunoglobulin.

Genetic Testing

Genetic testing is a powerful diagnostic tool in primary immunodeficiency disorders. Current information on characteristics and genetics of most disorders is available at the OMIM website (www.omim.org). The genes responsible for all of the known X-linked and most of the known autosomal primary immunodeficiency disorders have been elucidated. For the X-linked disorders, approximately one third of new cases are due to new mutations, and two thirds are inherited.[21] Carriers of some X-linked conditions (e.g., X-linked severe combined immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome) sometimes can be identified through the use of X-chromosome inactivation analysis because cells expressing the normal X chromosome have a survival advantage over cells expressing the abnormal X chromosome.[22–25] Carriers are recognized because of their homogeneous X-chromosome expression pattern (except in situations of "extreme" lyonization). In classical autosomal recessive conditions, recurrence risks follow mendelian inheritance.

Well over 100 genes have now been associated with primary immunodeficiency diseases.[9] Although the availability of appropriate gene probes or diagnostic methods for most currently recognized primary immunodeficiency syndromes makes their diagnosis easier than in the past, clinical suspicion remains the fulcrum for testing. In some instances, the suspicion only arises after the death of an index patient; if specimens of tissues are appropriately preserved, genetic testing can be performed postmortem.

Management

When a child is identified with an anatomic abnormality, an underlying condition, or a primary immunodeficiency disorder, management is based on existing knowledge about the specific condition, as described in subsequent chapters. Management is more difficult for patients whose history or physical findings are suggestive of a defect but in whom diagnostic testing is unrevealing. Such patients often require management based more on skilled judgment and careful reassessment than on scientific knowledge. It is important to emphasize to parents that, although negative diagnostic test results cannot exclude all potential underlying conditions, they eliminate specific serious conditions; this information can be comforting and helpful. In addition, delineating a specific plan for ongoing observation communicates a commitment to the child's well-being, which will help to ensure adherence to medically recommended interventions and continued contact with the patient.

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102

Infectious Complications of Antibody Deficiency

Elisabeth E. Adderson

Antibodies play a central role in protective immunity against bacterial and certain viral infections. Immunoglobulin (Ig) molecules consist of two identical light chains and two identical heavy chains held together by disulfide bonds. There are two types of light chains (κ and λ) and five classes, or isotypes, of heavy chains (IgG, IgA, IgM, IgD, and IgE). There also are subclasses of IgG (IgG_1, IgG_2, IgG_3, and IgG_4) and of IgA (IgA_1 and IgA_2). The antigen-binding amino-terminal variable regions of Ig molecules are unique for each B-lymphocyte clone. The carboxyl-terminal constant regions are the same for each isotype or subclass.

Antibodies bind to specific antigens through the variable region of the Ig molecule. The constant region then performs an effector function, such as activation of complement, binding to a phagocytic cell, or antibody-dependent cell-mediated cytotoxicity. In some circumstances, the antigen-specific binding region functions alone by blocking the binding of a toxin or an infectious agent to the surface of a target cell. Different antibody isotypes are more or less efficient at providing different effector functions.

B lymphocytes develop from a pluripotent precursor stem cell to IgM-expressing immature cells in the bone marrow, a process that does not require contact with antigen (Fig. 102.1). Further differentiation to mature B lymphocyte and to memory B or plasma cells takes place in peripheral lymphoid organs beginning about a week after antigen stimulation. Activated B lymphocytes can undergo a change in isotype expression from IgM to IgG, IgA, or IgE. Genes encoding variable regions also can undergo somatic hypermutation, a process that increases the affinity of antigen binding by antibody. Re-exposure to an antigen results in an accelerated memory (or secondary) immunologic response—this is responsible for the more rapid and greater magnitude of Ig responses to "booster" vaccinations compared with primary antigen exposures.

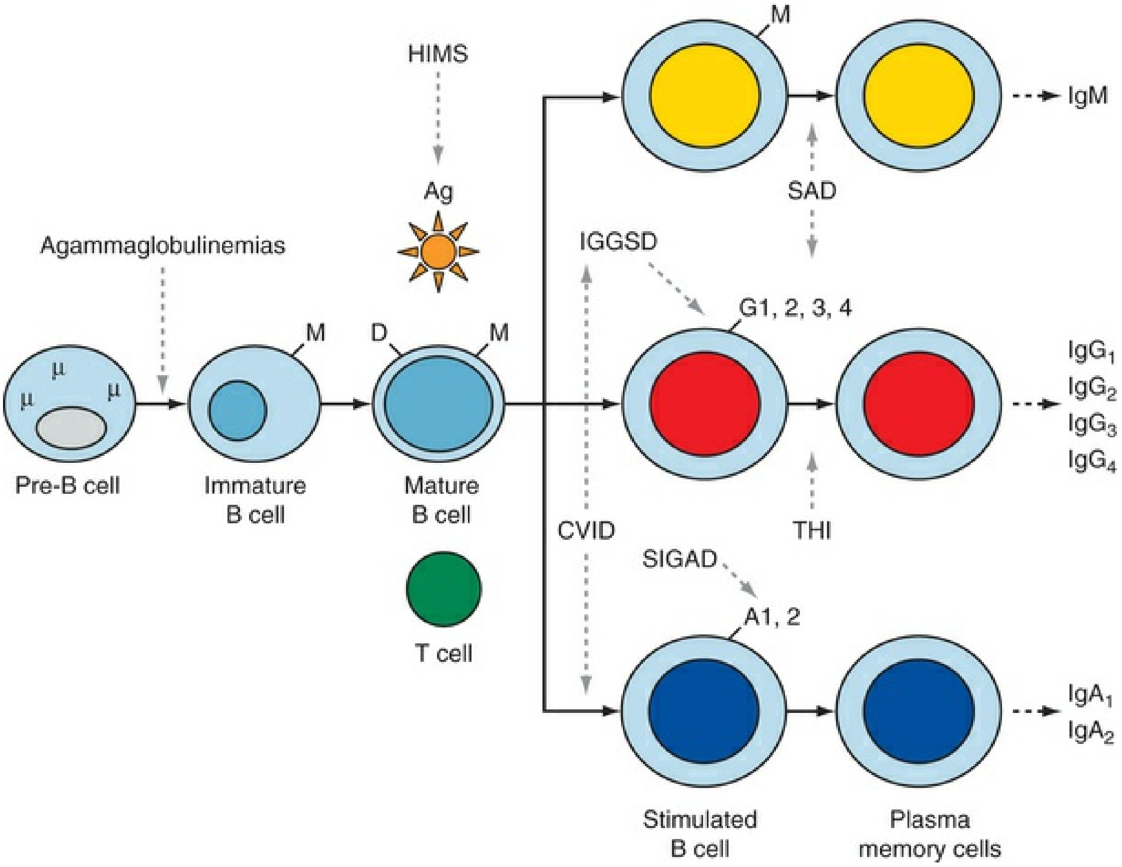

FIGURE 102.1 Normal antibody synthesis and primary deficiencies. μ, heavy chain of immunoglobulin (Ig) M; A, IgA; Ag, antigen; CVID, common variable immunodeficiency; D, IgD; G, IgG; M, IgM; HIMS, hyper-IgM syndromes; IgGSD, IgG subclass deficiency; SAD, specific antibody deficiency; SIgAD, selective IgA deficiency; THI, transient hypogammaglobulinemia of infancy.

Primary humoral immunodeficiencies have a prevalence of 13.9 to 18.1 per 100,000 persons in the United States.[1] The classification of these disorders was updated in 2014 by the International Union of Immunological Societies (Table 102.1), and diagnostic criteria for some have been published.[2,3] Antibody-mediated or humoral immunity is particularly important in the defense against infection caused by polysaccharide-encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae,* as well as some viral (poliovirus, nonpolio enteroviruses) and protozoan *(Giardia lamblia)* pathogens. In some antibody deficiency disorders, immunodeficiency is present prenatally, but transplacental transfer of maternal IgG in pregnancy protects infants against infection in the first several months of life. Children with severe antibody deficiency typically become symptomatic after this passively transferred immunity wanes. The onset of other humoral immunodeficiencies can be delayed until adolescence or adulthood, and some may be progressive. Among children, the average prevalence of humoral immunodeficiencies is highest in those aged 1 to 5 years (29–67 per 100,000).[1]

TABLE 102.1

Immunodeficiencies Predominantly Involving Antibody Deficiency

Category	Immunologic Features	Genetic Defects	Clinical Features
Agammaglobulinemias	All Ig isotypes severely reduced Absent (<2%) B lymphocytes Absent specific antibody responses	X-linked agammaglobulinemia (mutations in *BTK*) AR agammaglobulinemia [mutations in μ heavy chain, λ5, *Iga* (*CD79a*), *Igb* (*CD79b*), *BLNK*, *PIK3R1*] AD agammaglobulinemia (mutations in *TCF3*)	Recurrent and severe bacterial infections Chronic diarrhea Chronic enteroviral infections
Common variable immunodeficiency-like disorders	IgG low, IgA normal or low, IgM normal or low Normal or low numbers of B lymphocytes Poor specific antibody responses	Common variable immunodeficiency (unknown mutation) AR inheritance [mutations in *ICOS*, *CD19*, *CD81*, *CD20*, *CD21*, *TACI*, *LRBA*, *BAFF-R* (*TNFRSF13C*)] AD inheritance (mutations in *TWEAK*, *NFKB2*, *TACI*) WHIM (warts, hypogammaglobulinemia,	Recurrent infections Allergic disease Autoimmune disorders Malignancy

		infections, myelokathexis) syndrome (AD inheritance, mutations in *CXCR4*)	
Class switch recombination defects (hyperimmunoglobulin M syndromes)	IgG and IgA low, IgM normal or elevated Normal numbers of B lymphocytes Absent or poor specific antibody responses	X-linked inheritance (mutations in *CD40LG*) AR inheritance (mutations in *CD40*, *AICDA*, *UNG*)	Recurrent infections Opportunistic infections Lymphoid hyperplasia Autoimmune disorders
Isotype or light chain deficiencies with generally normal numbers of B lymphocytes			
Isotype deficiency	At least 1 IgG, IgA isotype and/or IgE absent Normal specific antibody responses	AR inheritance (mutations in 14q32 of chromosome 14)	Most asymptomatic
Kappa light chain deficiency	Kappa light chains absent Normal specific antibody responses	AR inheritance (mutations in *Cκ*)	Asymptomatic
IgG subclass deficiency	Normal total IgG and IgM At least 1 IgG subclass low Variable specific antibody responses	Unknown mutation	Most asymptomatic Recurrent sinopulmonary infections Allergic disease Autoimmune disorders
Selective IgA deficiency	IgG and IgM normal, IgA low; secretory IgA usually absent Specific antibody responses usually normal	Unknown mutation	Most asymptomatic Recurrent sinopulmonary infections Allergic disease Autoimmune disorders Anaphylactic reaction to IgA containing blood products
IgA deficiency with IgG subclass deficiency	Total IgG and IgM normal, IgA low, at least 1 IgG subclasses low	Unknown mutation	Recurrent sinopulmonary infections Allergic disease Autoimmune

	Specific antibody responses usually normal		disorders Anaphylactic reaction to IgA containing blood products
Activated phosphatidylinositol-3-OH kinase-delta (PI3K-∂) syndrome (immunodeficiency 14)	IgG and IgA low, IgM normal or elevated Decreased numbers of T and B memory lymphocytes Absent or poor specific antibody responses	AD inheritance (mutation in *PIK3CD*)	Recurrent sinopulmonary infections beginning in childhood Chronic viral infection Lymphoproliferation Epstein-Barr virus associated lymphoma
Protein kinase C delta (PRKC∂) deficiency	IgG low, IgA and IgM elevated Progressive decrease in numbers of B lymphocytes	AR inheritance (mutations in *PRKCD*)	Recurrent infection Autoimmune disorders Autoimmune lymphoproliferative syndrome
Specific antibody deficiency	Normal IgG, IgA and IgM Normal numbers of B lymphocytes Poor IgG response to polysaccharide antigens	Unknown	Recurrent sinopulmonary infections Allergic disease
Transient hypogammaglobulinemia of infancy	Low IgG, variable IgA and IgM Normal numbers of B lymphocytes Specific antibody responses usually normal	Unknown	Recurrent infections

AD, autosomal dominant; AR, autosomal recessive.

Approach to the Patient With Suspected Antibody Deficiency

A primary antibody deficiency should be considered in children with recurrent or chronic sinopulmonary infections, particularly in association with (1) poor growth, (2) unusual or unusually severe infections, (3) chronic or recurrent diarrhea, (4) a family history of recurrent and severe infections or of early childhood deaths, or (5) granulomatous or autoimmune disease.[4] Physical features suggesting humoral immunodeficiency include absent or small lymph nodes and tonsils, chronic lymphadenopathy, a dermatomyositis-like rash, and hypertrophic osteoarthropathy.[5,6]

Timely diagnosis of primary antibody deficiency and institution of immunoglobulin replacement therapy reduces the morbidity and mortality associated with these disorders. Quantitative serum immunoglobulin concentrations should be compared with normal values for age, and reduced levels of IgG, IgM, or IgA (or normal levels in the presence of a clinical picture strongly suggestive of antibody deficiency) should prompt additional investigations (Fig. 102.2). B lymphocytes (CD19$^+$) are quantified by flow cytometry. The ability to generate a specific antibody response is assessed by measuring serum isohemagglutinins (naturally occurring antibodies to ABO blood group antigens) and antigen-specific serum antibody concentrations before and after vaccination with protein (e.g., tetanus, diphtheria, pertussis) and polysaccharide antigens (e.g., pneumococcal polysaccharide vaccine in children older than 2 years). Quantifying IgG subclasses may be helpful in some cases, but the wide range of normal values and an inconsistent correlation between low serum concentrations and clinical disease complicate the interpretation of results, particularly in younger children. Evidence of the decreased expression or function of a specific gene product may be useful, but these tests generally are available on a research basis only. A definitive diagnosis is possible for disorders caused by known genetic mutations. Carrier detection and prenatal diagnosis also are possible in some cases.

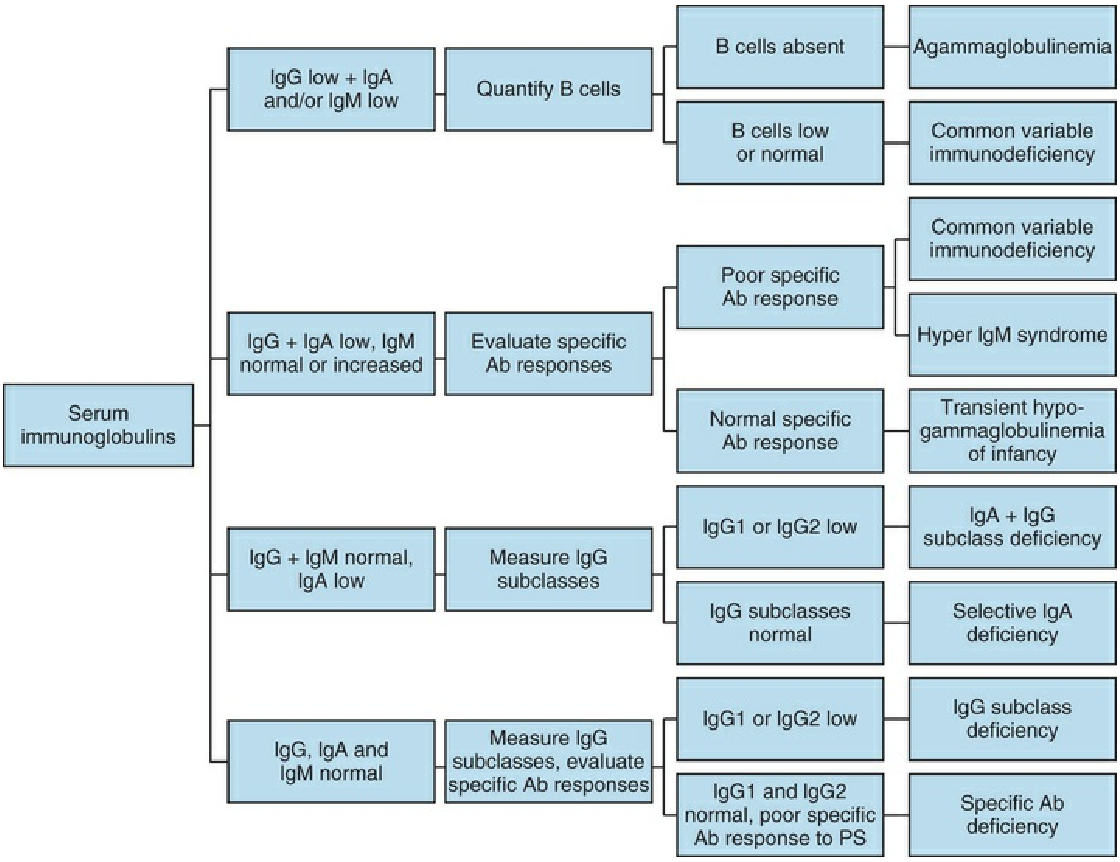
Serum immunoglobulins
IgG low + IgA and/or IgM low
Quantify B cells
B cells absent
Agammaglobulinemia
B cells low or normal
Common variable immunodeficiency
IgG + IgA low, IgM normal or increased
Evaluate specific Ab responses
Poor specific Ab response
Common variable immunodeficiency
Hyper IgM syndrome
Normal specific Ab response
Transient hypo-gammaglobulinemia of infancy
IgG + IgM normal, IgA low
Measure IgG subclasses
IgG1 or IgG2 low
IgA + IgG subclass deficiency
IgG subclasses normal
Selective IgA deficiency
IgG, IgA and IgM normal
Measure IgG subclasses, evaluate specific Ab responses
IgG1 or IgG2 low
IgG subclass deficiency
IgG1 and IgG2 normal, poor specific Ab response to PS
Specific Ab deficiency

FIGURE 102.2 Algorithm for the evaluation of common primary antibody deficiency disorders. Ab, antibody; PS, polysaccharide.

Patients with primary antibody deficiencies and severe symptoms should receive immunoglobulin replacement therapy, which reduces the rate and severity of infections. Ideally, trough serum IgG concentrations (immediately before the next administration of immunoglobulin) should be within the normal range of healthy persons. Increasing use has been made of rapid subcutaneous infusion and home or infusion center programs.[7] Immunoglobulin replacement therapy does not prevent all infections, however, and signs and symptoms of infection should be evaluated promptly and breakthrough infections treated aggressively. Some patients, particularly those with frequent or chronic respiratory infections, may benefit from prophylactic antibacterial therapy. Patients with hyperimmunoglobulin M syndrome (HIMS) caused by CD40L or CD40 deficiency have an increased susceptibility to *Pneumocystis jirovecii* infection and should receive trimethoprim-sulfamethoxazole or other effective prophylaxis. Vaccines composed of live, attenuated virus should not be administered to patients known or suspected of having a clinically significant primary antibody deficiency, with the exception of persons with selective IgA deficiency.

Infectious Complications of Antibody Deficiency Syndrome

Severely Reduced IgG, IgA, and IgM Levels With Absent B Lymphocytes (Agammaglobulinemia)

The prototype of antibody deficiency syndromes is X-linked agammaglobulinemia (XLA), which has an incidence of approximately 1 in 200,000 persons and accounts for about 85% of cases of agammaglobulinemia (Box 102.1).[2–5] XLA is caused by mutations in the Bruton tyrosine kinase gene, *BTK,* which is required for the normal differentiation of pro–B lymphocytes to pre–B lymphocytes and mature B lymphocytes.[8,9] A family history of male relatives with recurrent infections is common, but about one half of patients represent new mutations. The severity of infectious complications can differ among family members with the same mutation. Prenatal diagnosis and carrier detection are possible if the mutation is known. Rare autosomal recessive agammaglobulinemias result from mutations in other genes important to B-lymphocyte development, including μ heavy chain, *λ5*, *Igα* (*CD79a*), *Igb* (*CD79b*), B-cell linker (*BLNK*), phosphoinositide 3-kinase (*PIK3R1*), and transcription factor 3 (E47 transcription factor).[2–5,10–16]

Box 102.1

Agammaglobulinemia

Clinical Presentation

- Onset in infancy or early childhood
- Recurrent respiratory and invasive infections, especially *Haemophilus influenzae* type b, *Streptococcus pneumoniae*
- Chronic diarrhea, malabsorption, chronic *Giardia* and rotavirus infection

- Chronic enteroviral meningoencephalitis, poliomyelitis, dermatomyositis-like syndrome
- Neutropenia with infection
- Lymph nodes and tonsils absent or small

Diagnosis

- IgG, IgM, and IgA >2 standard deviations below mean for age
- Peripheral blood $CD19^+$ B lymphocytes <2%
- Poor specific antibody responses, including isohemagglutinins
- Genetic testing

Treatment

- Immunoglobulin replacement

Serum IgG, IgA, and IgM levels are very low (>2 standard deviations [SD] below the mean value for age), and patients have poor or no specific antibody responses after infection or immunization.[3] Circulating $CD19^+$ B lymphocytes are absent or present in very low proportions (generally <2%). Plasma cells are absent from lymph nodes and bone marrow, and lymph nodes and tonsils are absent or small. T lymphocytes are normal in both number and function. Neutropenia can occur in association with acute infections.[17]

Transplacentally acquired maternal IgG typically protects infants with agammaglobulinemia from infection in the first few months of life. Thereafter, affected children have recurrent bacterial infections, particularly otitis media, sinusitis, and pneumonia. More than one half of patients are symptomatic by 1 year of age, and almost all are by 5 years of age.[18] Invasive bacterial infections (septicemia, meningitis, osteoarticular infections) also are common. Encapsulated bacteria, particularly *H. influenzae* type b (Hib), *S. pneumoniae, Staphylococcus aureus,* and *Pseudomonas* spp. cause most infections. Up to 50% of patients experience chronic diarrhea, steatorrhea, or malabsorption. In some cases, these symptoms have been associated with chronic rotavirus and *Giardia lamblia* infections.[19,20] The incidence of enteritis due to *Salmonella* spp. and *Campylobacter jejuni* is higher in persons with agammaglobulinemia than in the general population. Persistent *Mycoplasma* and *Ureaplasma* infections of the respiratory tract, joints, and urogenital tract also occur.

Although children with antibody deficiencies usually manifest greater susceptibility to bacterial than to viral infections, some children with agammaglobulinemia have severe and chronic enteroviral infections. In regions of the world where wild-type poliovirus or live vaccine strain polioviruses circulate, paralytic disease in patients with agammaglobulinemia can occur.[21] Meningitis caused by nonpolio enteroviruses also can occur and either can have an insidious onset with ataxia, loss of cognitive skills, and paresthesias or present more acutely with fever, headache, and seizures. Central nervous system (CNS) enterovirus infection may be the initial manifestation of XLA and can occur despite immune globulin intravenous (IGIV) replacement therapy. Cerebrospinal fluid (CSF) pleocytosis with a lymphocytic predominance, increased protein levels, and decreased glucose levels are typical, although some children have normal or only mildly abnormal findings. CSF abnormalities tend to worsen with clinical exacerbations. Some individuals with chronic enteroviral infections develop a dermatomyositis-like syndrome characterized by muscle weakness, edema and woody induration of the skin, and a violaceous rash over the extensor surfaces of joints, often accompanied by hepatitis.[21]

The prognosis of XLA has improved greatly with IGIV therapy, particularly when therapy is initiated at an early age. Aggressive and prolonged treatment of bacterial infections is critical. Patients with chronic enteroviral meningoencephalitis are treated with high doses of IgG (to maintain trough levels of >1000 mg/dL) or with plasma or immune serum known to have high antibody titers to the enterovirus causing the infection.[21] Intrathecal IGIV also has been used. The most common causes of death among patients with agammaglobulinemia are chronic enteroviral and pulmonary infections.

Severely Reduced IgG, IgA, and /or IgM Levels With Normal or Low Numbers of B Lymphocytes (Common Variable Immunodeficiency Disorder)

Common variable immunodeficiency disorder (CVID) represents a heterogeneous group of disorders characterized by low serum Ig concentrations, defective production of specific antibodies, and an increased susceptibility to respiratory and gastrointestinal tract infections (Box 102.2).[2,3,22] CVID affects 1 in 25,000 to 1 in 50,000 persons and has an equal prevalence in males and females. Persons with CVID have serum total IgG concentration ≥2 SD below the mean for their age, a marked decrease in IgA, normal or low IgM, and impaired specific antibody responses.[3] Numbers of peripheral B lymphocytes can be normal, reduced, or increased. Current diagnostic criteria restrict CVID to children who are older than 4 years, in part owing to the need to exclude other immunodeficiencies that manifest earlier in life. CVID can develop in persons who initially present with clinical and laboratory findings suggestive of selective IgA or IgG subclass deficiencies. Immunodeficiency can be progressive.[22]

Box 102.2

Common Variable Immunodeficiency

Clinical Presentation

- Onset 2 years of age to adulthood
- Recurrent and severe sinopulmonary infections, especially *Streptococcus pneumoniae, Haemophilus influenzae*
- Gastrointestinal infections, especially *Giardia, Campylobacter jejuni, Salmonella* spp.
- Chronic *Mycoplasma* infection
- Severe infections due to hepatitis C, cytomegalovirus, varicella-zoster virus, enteroviruses
- Autoimmune and inflammatory disorders (gastrointestinal

lymphoid hyperplasia, inflammatory bowel disease, autoimmune cytopenias, arthritis, vasculitis)

- Lymphoid hyperplasia, splenomegaly, peripheral lymphadenopathy
- Increased risk for lymphoma, gastric carcinoma

Diagnosis

- IgG usually >2 standard deviations below mean for age; young children may present with progressive IgG subclass deficiency
- IgA usually >2 standard deviations below mean for age
- IgM normal or low
- Peripheral blood CD19$^+$ B lymphocytes normal or reduced
- Poor specific antibody responses, absent isohemagglutinins
- Genetic testing available for some forms

Treatment

- Immunoglobulin replacement

The genetic basis of most CVIDs is not known. Approximately 25% of cases are familial.[23] Most have autosomal recessive inheritance and result from mutations in B-lymphocyte surface receptors, transmembrane proteins involved in B-lymphocyte signaling pathways, or costimulatory molecules expressed on T lymphocytes.[24–27] Other immunodeficiencies, including the agammaglobulinemias, class switch recombination defects, X-linked lymphoproliferative disease, and "leaky" severe combined immunodeficiency syndromes can resemble CVID. Warts, hypogammaglobulinemia, infections, and myelokathexis, also known as *WHIM syndrome*, represent an autosomal dominantly inherited disorder characterized by hypogammaglobulinemia, recurrent sinopulmonary and invasive bacterial infections, peripheral neutropenia with bone marrow hypercellularity, a distinctive neutrophil morphology, and increased susceptibility to human papillomavirus infection.[28] Certain drugs, chromosomal abnormalities, infection, malignancy, and systemic illnesses are associated with secondary CVID.

Symptoms of CVID are unusual in children younger than 2 years. Bimodal peaks of incidence are recognized at 2 to 5 and 16 to 28 years of age.[29] Patients most commonly have recurrent sinopulmonary infections, chiefly due to bacteria such as *S. pneumoniae, H. influenzae, Moraxella catarrhalis,* and *Mycoplasma pneumoniae.* Recurrent pneumonia sometimes progresses to bronchiectasis. Invasive bacterial infections occur in 10% to 25%. Enteric infections caused by *Giardia* spp., *C. jejuni,* and *Salmonella* spp. are frequent and can be more severe and prolonged than in immunocompetent persons. Chronic genitourinary tract, joint, and systemic infections caused by *Mycoplasma* spp. have been described. Although most viral infections are not complicated in patients with CVID, an increased frequency and severity of hepatitis C virus, cytomegalovirus (CMV), measles, and varicella-zoster virus infection has been reported.[22,29] Complications of enteroviral infection, including chronic encephalomyelitis and dermatomyositis-like syndrome, occur but are less frequent than with the agammaglobulinemias.[4]

Allergic disorders are found in more than 30% of children and adolescents with CVID.[30] Inflammatory or autoimmune diseases occur in 20% to 35% of patients and can cause more serious morbidity than infections. Granulomatous pulmonary disease, lymphocytic interstitial pneumonitis, and chronic lymphadenopathy have been reported. Inflammatory bowel disease, lymphonodular hyperplasia, or malabsorption affect up to 25% of patients, and hematologic disorders such as autoimmune thrombocytopenia, hemolytic anemia, neutropenia, and pernicious anemia occur in 10%. About one fourth of patients have significant growth restriction.[30] The incidence of some cancers, particularly lymphomas and gastric carcinoma, is markedly elevated in patients with CVID, occurring predominantly in adults.

Most patients with CVID require Ig replacement therapy. Prophylactic antibiotics may benefit some patients, particularly those with recurrent respiratory infections and bronchiectasis. Patients require careful monitoring for autoimmune and lymphoproliferative complications.

Reduced IgG and IgA With Normal or Elevated IgM and Normal Numbers of B Lymphocytes (Class Switch Recombination Defects, Hyperimmunoglobulin M Syndrome)

Children with HIMS have recurrent or serious infections in the first 5 years of life, absent or low levels of serum IgG, normal or elevated serum IgM, absent or poor specific immune responses, normal or elevated numbers of B lymphocytes, and normal numbers of T lymphocytes (Box 102.3).[3,5,31]

Box 102.3

Class Switch Recombination Disorders (Hyper-IgM Syndromes)

Clinical Presentation

- Onset in infancy or early childhood
- Recurrent and severe sinopulmonary infections
- *Pneumocystis jirovecii* infection
- Severe or chronic *Cryptosporidium* and *Giardia* infections
- Neutropenia, parvovirus-induced aplastic anemia
- Autoimmune and lymphoproliferative disorders (sclerosing cholangitis, diabetes, arthritis, inflammatory bowel disease, uveitis)

Diagnosis

- Serum IgG >2 standard deviations below mean for age
- Normal or elevated numbers of B lymphocytes
- Normal numbers of T lymphocytes

- Absent specific IgG immune response; normal isohemagglutinins
- Genetic testing

Treatment

- Immunoglobulin replacement
- *P. jirovecii* prophylaxis for patients with CD40L or CD40 deficiency
- Granulocyte colony-stimulating factor for chronic neutropenia
- Hematopoietic stem cell transplantation

HIMS is rare, affecting about 1 in 300,000 persons. Approximately 65% of cases are inherited in an X-linked recessive fashion and are due to mutations of the gene encoding CD40L *(TNFSF5)*.[32,33] Rare mutations of CD40 *(TNFRSF5)* cause a similar disorder with autosomal recessive inheritance.[34] B-lymphocyte signaling through CD40, which is required for isotype switching and the affinity maturation of antibody responses, is impaired in these disorders. Other cases of autosomal recessively inherited HIMS result from mutations of the activation-induced cytidine deaminase gene, *AICDA*, or activation-induced cytidine deaminase, *UNG*, the products of which are required for isotype switching from IgM to IgG and IgA.[2]

Patients with HIMS have serum total IgG concentration >2 SD below the mean for their age and impaired specific IgG responses, but most patients have normal isohemagglutinins, which are of the IgM isotype. Serum IgM levels are normal or increased. Circulating T- and B-lymphocyte numbers are within the normal range, but T-lymphocyte proliferation is impaired in patients with CD40L and CD40 deficiency.

Patients with CD40L and CD40 deficiency typically come to attention at 1 to 2 years of age.[35,36] Patients with CD40L/CD40 deficiency, who have impaired humoral and cellular immune responses, generally are more ill than patients with other antibody deficiency disorders. Most have recurrent or severe bacterial infections, especially affecting the respiratory and gastrointestinal tracts. A predisposition to *P. jirovecii* pneumonia, which is reported in 40% of patients, and to disseminated infections caused by *Cryptococcus* spp. CMV and herpes simplex virus infections distinguishes these disorders from other antibody deficiency disorders. More than one half of affected patients have diarrhea, commonly associated with *Cryptosporidium, Salmonella,* or *Giardia* spp., and poor growth. Sclerosing cholangitis, sometimes progressing to cirrhosis, is common and can be idiopathic or a complication of *Cryptosporidium* infection. Patients have a significantly increased risk for gastrointestinal and hepatic malignancies. Neutropenia and anemia occur in 25% to 65% of patients; neutropenia can be chronic or cyclic. Chronic anemia and pancytopenia also occur in association with human parvovirus B19 infection.

Patients with *AICDA* and *UNG* deficiency may be diagnosed only in adolescence or adulthood. Opportunistic infections are uncommon, but lymphoid hyperplasia, especially of cervical lymph nodes and tonsils, is more common than in CD40L/CD40 deficiency. Autoimmune and inflammatory complications, including neutropenia, diabetes, arthritis, hepatitis, and inflammatory bowel disease, are identified in approximately 20% of patients, including young children. Unlike CD40L/CD40 deficiency, patients with AICDA or UNG deficiency do not have an increased risk for malignancy.

IgG replacement therapy is the mainstay for therapy of the class switch recombination defect disorders. Patients with CD40L and CD40 deficiency should receive trimethoprim-sulfamethoxazole or other effective prophylaxis to prevent *P. jirovecii* infection. Patients should be counseled in regard to measures to prevent *Cryptosporidium* infections. Granulocyte colony-stimulating factor may be helpful to manage chronic neutropenia. Hematopoietic stem cell transplantation may be curative; younger patients and those without liver disease appear to have the best outcomes.[31] Carrier detection and prenatal diagnosis are possible if the specific mutation is known.

Isotype or Light Chain Deficiencies With Normal Numbers of B Lymphocytes

Ig Heavy Chain Deficiency.

Rarely, deletions in the heavy chain constant region genes affect the expression of one or more Ig isotypes. Decreased serum concentrations of one or more IgG or IgA isotypes, or both, with or without IgE deficiency, are the most common abnormalities. Most affected people do not have significant problems with recurrent or severe infections.

Kappa Light Chain Deficiency.

Individuals with partial or complete deficiencies of serum antibody containing kappa light chain have been described rarely.[37] Most have symptoms; lambda light chains appear to compensate for the absence of kappa light chains.

Isolated IgG Subclass Deficiency.

IgG subclass deficiency is defined as ≥1 serum IgG subclass levels >2 SD below the mean for the individual's age but with normal total serum IgG and IgM levels (Box 102.4).[2] Several biologic and technical problems complicate the study of selective IgG subclass deficiencies in children, including the wide range of normal values for each of the subclasses and marked differences among the subclasses in the length of time required to mature to adult serum levels. Some cases of absolute IgG subclass deficiency result from mutations in genes encoding the IgG constant regions, but the etiology of most defects is unknown.[38]

Box 102.4

IgG Subclass Deficiency and IgA Deficiency With IgG Subclass Deficiency

Clinical Presentation

- Age of onset variable
- Most are asymptomatic
- Recurrent sinopulmonary infections, bacteremia (*Haemophilus influenzae* type b, *Streptococcus pneumoniae*) more common in patients with IgA plus IgG subclass deficiency than those with isolated IgG subclass deficiency

Diagnosis

- ≥1 IgG subclass >2 standard deviations below mean for age
- Total IgG and IgM normal, IgA normal or low
- Normal numbers of B lymphocytes
- Antibody responses usually normal, impaired antipolysaccharide antibody responses in some patients with IgG_2 deficiency; normal isohemagglutinins

Treatment

- Immunoglobulin replacement in patients with recurrent or severe infections

Although some patients experience recurrent sinopulmonary infections or allergic or autoimmune disease, most patients with IgG subclass deficiencies are symptom free, and some deficiencies resolve over time.[39–41] The ability to make specific antibody is most relevant to symptoms and prognosis in Ig subclass deficiency, and evaluation should focus on this function. Patients should be managed according to their specific antibody responses and clinical status. Ig replacement therapy is reserved for patients with poor specific antibody responses and severe or recurrent infections.

Selective IgA Deficiency.

Selective IgA deficiency is defined as a serum IgA concentration of <0.07 g/L in the presence of normal total serum IgG and IgM levels. Usually, secretory IgA also is absent. Isolated IgA deficiency is the most common primary immunodeficiency, with an incidence ranging from 1 in 400 to 1 in 5000 persons. Children <5 years of age may have a physiologic delay in IgA expression, and some transient cases of IgA deficiency result from an exaggeration of this maturational delay.

The cause of most cases of selective IgA deficiency is unknown. Up to 20% are hereditary. IgA deficiency, CVID, and IgG subclass deficiency have been reported in the same family, suggesting that these conditions may be part of a spectrum of abnormalities caused by the failure of appropriate signaling for B-lymphocyte maturation.[42] Secondary IgA deficiency can result from the use of certain anti-inflammatory and anticonvulsant drugs.

Most patients with selective IgA deficiency have no related symptoms. One third have recurrent infections, particularly of the respiratory tract. People with selective IgA deficiency also have a higher incidence of allergy and autoimmune disorders than the general population.

As with IgG subclass deficiency, evaluation should focus on the patient's ability to generate specific antibody. Rarely, patients can benefit from Ig replacement therapy; however, minor amounts of IgA in IGIV preparations or other blood products may lead to the development of anti-IgA antibodies and result in severe anaphylactic reactions in IgA-deficient patients who receive such tranfusions.[43] Products low in IgA should be used if replacement therapy is necessary. In contrast to other primary antibody deficiency syndromes, routine vaccination with live, attenuated viral vaccines is not contraindicated in selective IgA deficiency.

Iga Deficiency With IgG Subclass Deficiency.

Persons with IgA deficiency who also have deficiencies in IgG subclasses or specific antibody production have a greater predisposition to infection than those with selective IgA deficiency alone (see Box 102.4). In addition to recurrent sinopulmonary infections, these patients have an increased risk for allergy, inflammatory gastrointestinal disease, and autoimmune disorders. Deficiency of IgG_2, in particular, is associated with recurrent otitis media and sinopulmonary infections in children.[44] The defects most commonly associated with IgA deficiency are deficiencies of IgG_4 (40%), IgG_2 (28%), and IgG_3 (17%). IgA, IgG_4, and IgG_2 deficiency sometimes coexist. Patients should be evaluated and managed in the same manner as those with selective IgA deficiency.

Protein Kinase C Delta (PRKCδ) Deficiency.

PRKCδ deficiency plays an important role in the negative regulation of B-lymphocyte proliferation and the development of immunologic tolerance.[45] A small number of patients with mutations in *PRKCδ* have been reported; these persons had recurrent infections, hypogammaglobulinemia, elevated IgA and IgM levels, progressive B-lymphocytic lymphopenia, and autoimmune disease or autoimmune lymphoproliferative syndrome–like disease.[46–48]

Activated Phosphatidylinositol-3-OH Kinase Delta (PI3Kδ) Syndrome (Immunodeficiency 14).

The p110δ subunit of phosphoinositide 3-kinase is selectively expressed in leukocytes and is critical for the differentiation of naïve T lymphocytes into memory precursor effector cells.[49] Patients with autosomal dominantly inherited gain-of-function mutations in *PI3Kδ* have been described who have recurrent sinopulmonary infections, class switch recombination defects (low IgG and IgA, elevated IgM), markedly diminished memory T and B lymphocytes, lymphoproliferative disorders, chronic Epstein-Barr virus or CMV viremia, Epstein-Barr virus–associated lymphomas, and autoimmune disease.[49–51]

Specific Antibody Deficiency With Normal IgG Concentrations and Normal B-Lymphocyte Numbers

Patients with specific antibody deficiency (SAD) have poor IgG responses to polysaccharide antigens such as pneumococcal and *H. influenzae* capsular polysaccharide (specific serum IgG <1.3 μg/mL, or less than a fourfold rise in specific antibody levels 1 month after vaccination) but have normal levels of serum Ig and IgG subclasses (Box 102.5). The incidence of SAD ranges from 0% to 10% in children with allergic disease and recurrent respiratory infections, but incidence in the general population is not known.[52,53] The defects responsible for SAD have not been identified; some cases are familial.

Box 102.5

Specific Antibody Deficiency

Clinical Presentation

- Age of onset variable

- Recurrent otitis media, sinopulmonary infections (*Haemophilus influenzae* type b, *Streptococcus pneumoniae*)
- Occasional invasive infections
- Allergic disease common

Diagnosis

- Normal serum total IgG, IgA, and IgM
- Normal numbers of B lymphocytes
- Poor response to vaccination with polysaccharide antigen (less than fourfold rise in serum specific IgG titer 4 weeks after vaccination or postvaccination serum-specific IgG <1.3 g/mL

Treatment

- Immunoglobuin replacement if severe or persistent infections

Children with SAD typically come to attention with recurrent sinopulmonary infections. Serious infections such as septicemia and meningitis can occur. Many children have associated allergic disease. The diagnosis of SAD in children is complicated by the physiologic delay in the development of specific immune responses to polysaccharide antigens and the poor standardization of laboratory testing for antipolysaccharide antibodies.[5,54] Responses of healthy children younger than 2 years to polysaccharide antigens generally are poor and may be unreliable until middle childhood. Serial testing often is required to conclude that a persistent deficiency exists. The natural history of the disorder is not well described. Although antibody responses generally improve with age, some patients progress to CVID. Most children who fail to respond to immunization with polysaccharide vaccines have adequate responses to polysaccharide-protein conjugate formulations. Rarely, children with SAD may benefit from a trial of Ig or prophylactic antibiotics if symptoms are severe and persistent.

Transient Hypogammaglobulinemia of Infancy

After birth, a healthy infant actively begins first making IgM, then IgG, and finally IgA. Simultaneously, passively transferred maternal IgG normally decreases with a half-life of 25 to 30 days, reaching a nadir between 3 and 6 months of age. Sometimes this physiologic trough in serum IgG concentrations persists beyond 6 months of age; this condition is called transient hypogammaglobulinemia of infancy (THI) (Box 102.6). The incidence of THI has been estimated to be 20 to 60 per 100,000 live births, and THI is slightly more common in males.[55] Children come to attention with recurrent respiratory or gastrointestinal tract infections. Rarely, patients experience invasive bacterial, fungal, or severe viral infections. Infants with THI have normal numbers of circulating B lymphocytes and generally have normal specific immune responses. Low serum concentrations of IgA are present in up to 80% of patients, and a smaller proportion of children have low serum IgM levels.

Box 102.6

Transient Hypogammaglobulinemia of Infancy

Clinical Presentation

- Onset 3 months to 3 years
- Recurrent sinopulmonary and respiratory viral infections
- Rarely invasive bacterial infections

Diagnosis

- IgG >2 standard deviations below mean for age
- IgM usually normal, IgA variable
- B-lymphocyte numbers usually normal
- Specific antibody responses usually normal, normal

isohemagglutinins

Treatment

- Most resolve by 2–4 years
- Immunoglobuin replacement if severe or persistent infections

The cause of the maturational delay in IgG production in THI is unknown. THI occurs with greater frequency in families with other immunodeficiency syndromes, but no specific genetic defects have been identified. THI is self-limited, with antibody concentrations typically normalizing by 2 to 4 years of age. The presence of invasive infections or poor specific antitetanus antibody responses at the time of presentation may identify children who will have more persistent immunodeficiency.[56] Most children with THI do not require specific treatment, but IGIV should be considered in children with frequent or severe infections. If initiated, the continued need for IGIV should be reassessed after 3 to 6 months.[5]

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103

Complement in Control of Infectious Agents

Michael M. Frank

The collective term *complement* refers to a large group of plasma- and cell membrane–bound proteins that play a major role in first-line innate defense against a wide variety of infectious agents. The group contains at least 30 plasma- and cell membrane–bound proteins that function cooperatively in antimicrobial and inflammatory reactions.[1–5] A large number of additional proteins, perhaps 20 more, have been found to interact with selected proteins on the system. The complement proteins are evolutionarily old, and some were incorporated into the adaptive immune system as it developed to help promote a healthy immune response.[6,7] This chapter reviews the biochemistry and biology of complement and its role in host defense against infection, and illustrates infectious complications in individuals with inherited or acquired deficiencies of complement proteins; neither aspects are covered exhaustively. Hundreds of infectious agents are more pathogenic in the absence of complement-mediated host defense. Relatively few patients have complete complement protein deficiencies.[8,9] It has been thought that the system almost always functions normally and that defects generally are limited to a few clinical situations. Our understanding of complement has broadened in the past decade, and that definition of deficiency may have been too narrow.

Biochemistry and Biology of Complement

The basic biochemistry of the complement system was clarified decades ago.[10–12] Many biologically significant effects of the complement system are mediated by the third component of complement (C3) and the late acting proteins (C5, C6, C7, C8, and C9). However, C3 and C5 through C9 first must be activated by one of three effector pathways before generating biologic activities: the classical pathway, the alternative pathway, or the lectin pathway[11,12] (Fig. 103.1).

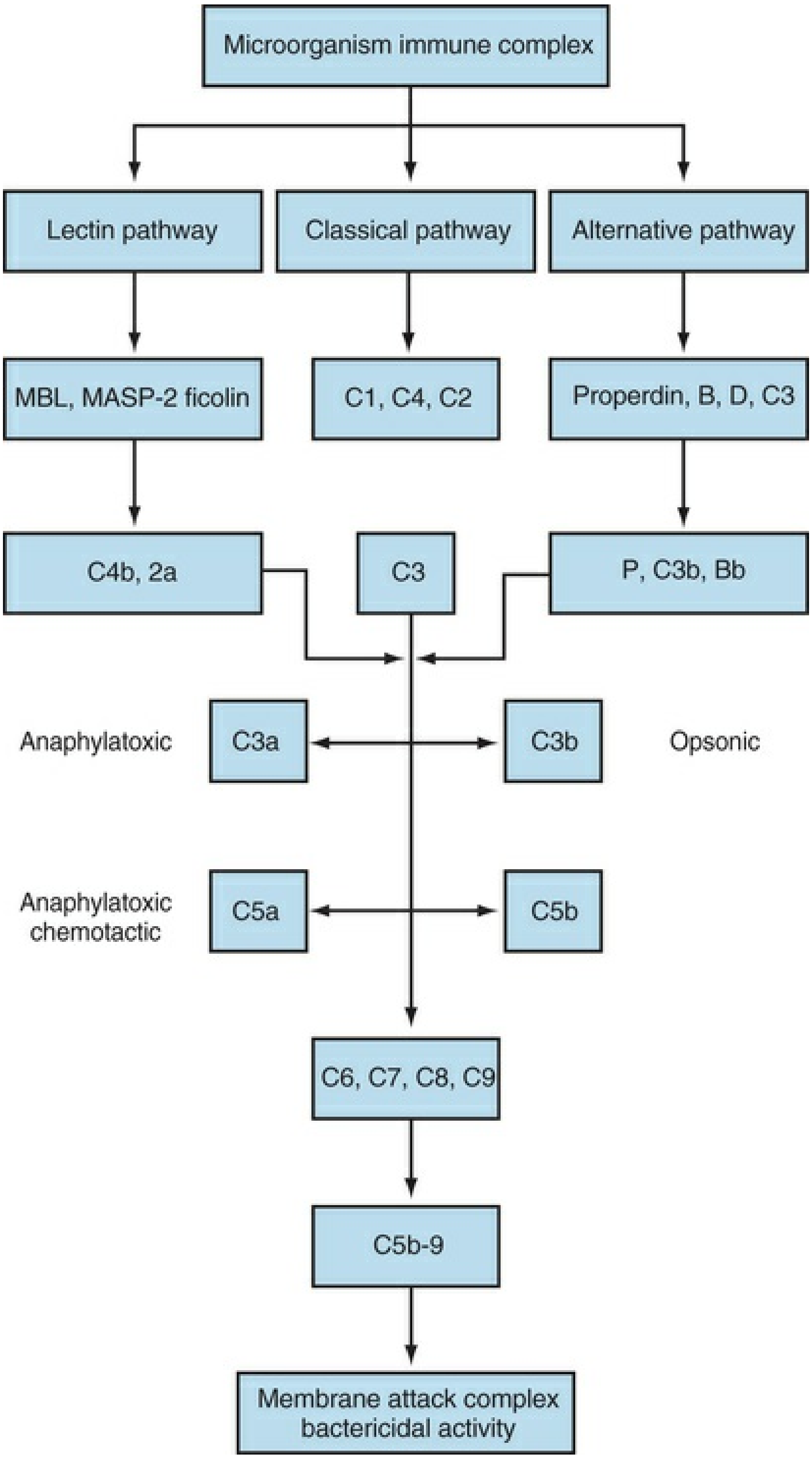

FIGURE 103.1 The complement system.

The Classical Pathway

The *classical pathway* is so termed because it was the first pathway of activation, studied more than 100 years ago.[10] In traditional experiments, complement activity was shown by the ability of the fluid phase complement proteins (components) to lyse antibody-sensitized erythrocytes. Activation of the classical pathway usually is initiated by antigen-antibody complexes. Antibodies of the appropriate class (immunoglobulin M [IgM] or IgG subclass IgG1, IgG2, IgG3) combine with microbial or other antigens to form an immune complex, which then binds and activates the first component of complement (C1). Only one molecule of pentameric IgM, deposited on a surface such as a cell membrane, is needed for activation of C1. In contrast, two IgG molecules, side by side, are necessary for C1 to bind and cause activation. The requirement for an IgG doublet greatly reduces the efficiency of IgG compared with IgM in activating C1 and the classical pathway because thousands of IgG molecules may need to be deposited on a microbial surface in order for two to be aligned in close proximity.[13]

C1 is a macromolecular complex composed of three biochemically distinct subcomponents, designated as C1q, C1r, and C1s. C1q binds to the Fc fragment of immunoglobulin molecules in the immune complex.[14] Binding is followed by cleavage of the bound C1r and then cleavage of C1s. Activated C1s then cleaves both the fourth component of complement (C4) and the second component (C2), each into smaller and larger products. The larger fragment of C2 (C2a) remains complexed with the larger fragment of C4 (C4b) to form a bimolecular enzyme, C4b2a, which is responsible for activating C3 and initiating the assembly of the terminal components.

Because the classical pathway usually is activated by antibody, it is considered to be important especially in "acquired" immunity. However, some enveloped RNA viruses, some *Mycoplasma* spp., and certain strains and species of both gram-negative and gram-positive bacteria bind C1q directly and activate the classical pathway.[5] Thus, under some circumstances, the classical pathway also can be activated in an antibody-independent fashion and functions in "natural" immunity.

Activation of C3

Because C3 function and structure play a critical role in the activation of the alternative pathway, C3 activation is considered before the alternative and lectin pathways.[15] C3 is a two-chain molecule with the chains designated α and β. One C3-activating enzyme (convertase) is formed by proteins of the classical and lectin pathways, as described. A second convertase is formed by the proteins of the alternative pathway. Hundreds of C3 molecules can be cleaved by each C3 convertase molecule, allowing for amplification of the response. C3 cleavage releases a small peptide (C3a) from the α chain into the fluid phase, where it acts as an anaphylatoxin.[16] C3a is a cell-activating molecule, and one of its actions is to induce histamine release from mast cells and basophils generating an anaphylaxis-like response. C3a also acts as an immune regulator, downregulating some immune responses.[16] The larger C3 fragment, C3b, binds to the activating complex. It is rapidly inactivated by hydrolysis, preventing its binding to targets. However, some C3b binds covalently to the microbial cell surface, where it acts as an opsonin.[15] The target-bound C3b can be degraded by circulating complement control proteins, factor H and factor I, the latter which interacts with C3b after binding to factor H, as well as by other proteases, yielding a variety of products.[17] However, if C3b is not degraded, it joins an alternative pathway C3 convertase to continue the complement cascade. C3b degradation is complex, and specific cellular membrane receptors recognize each of the degradation products; each appears to have a different biologic function. C3b itself is recognized by a specific receptor present on phagocytes and B lymphocytes, CD35 (sometimes termed *complement receptor 1* [CR1]). Binding of microbes to CD35 markedly enhances phagocytosis. The first step in C3b degradation leads to the decay fragment iC3b. This fragment with a cleaved α chain is recognized by the opsonization receptors CD11b/CD18 and CD11c/CD18 (two of the B2 integrins, also termed CR3 and CR4). These receptors are deficient or abnormal in leukocyte adhesion deficiency (LAD).[18] With this cleavage of the α chain, iC3b no longer supports the continued activation of the complement cascade. This fragment is further degraded in several steps to the final fragment C3d that is recognized by CD21 (CR2), a receptor present on B lymphocytes and follicular dendritic cells, which is important in antigen processing and immune response.

The Alternative Pathway

The alternative pathway provides an evolutionarily old and quite primitive innate immune defense mechanism.[15,18] Activation commonly begins with the C3 molecule itself. Native C3 contains an internal thiol ester in its α chain that, under normal physiologic conditions, undergoes continuous low-grade hydrolysis to create a "C3b-like" molecule, C3(H_2O). C3(H_2O) can bind a circulating alternative pathway protein, factor B, which allows factor B to be cleaved by a serine protease, factor D. Two cleavage products of factor B are generated: the larger Bb and smaller Ba. The association of the hydrolyzed C3 with Bb creates a new C3-cleaving enzyme, C3(H_2O)Bb (termed the *priming C3-convertase*), which is responsible for a continuous, low-grade cleavage of C3 and, hence, the generation of further nascent C3b. If nascent C3b binds covalently to a suitable surface, such as a bacterium, it can form a reversible complex with native factor B. This complex is cleaved by factor D to create a highly efficient C3-cleaving enzyme, C3bBb, termed the *amplification C3-convertase*. These convertases of the alternative pathway are not stable and, like the C3 convertase of the classical pathway, decay over time. Decay in the classical pathway is associated with release of C2, and in the alternative pathway it is associated with release of factor B of the convertase. Another circulating protein, properdin, stabilizes the alternative pathway convertase, and properdin binding to C3 appears also to act as an initiating factor of the alternative pathway.[19]

Antibody is not required for the activation of the alternative pathway; however, antibody enhances activation. Thus, the alternative pathway can participate in both innate and "acquired" antibody-mediated host defense.

Because C3b is both the product of the alternative pathway C3-cleaving enzyme and also forms part of it, the activation of C3 through the alternative pathway creates a positive-feedback amplification loop (see Fig. 103.1). Moreover, activation of the classical pathway, by creating nascent C3b, amplifies activation of the alternative pathway.

The Lectin Pathway

The lectin pathway is a third C3 activation pathway and, like the alternative pathway, is evolutionarily ancient.[20] Mannose-binding lectin (MBL) is a naturally occurring member of the collectin family of proteins and is capable of binding to a number of sugars on the surface of a variety of microorganisms, including human immunodeficiency virus (HIV), *Haemophilus influenzae, Neisseria meningitidis,* streptococci, and many others. In the circulation MBL is associated with three serine proteases: MBL-associated serine proteases 1 to 3 (MASP1, MASP2, and MASP3). The principal activation pathway involves MASP2, which, when activated, cleaves both C4 and C2 to create C4b2a with its C3 cleaving activity. Another less studied group of proteins of the lectin pathway, the ficolins, have similar structure and presumably similar function to MBL, but bind to acetylated sugars as targets.

Activation of Terminal Complement Components

After C3 convertases are formed and bind C3, leading ultimately to bound C3b, the convertase can then bind C5 and function as a C5 convertase. Activation of C5 by either the alternative or classical pathway by C5 convertases results in cleavage of the α chain of the C5 molecule to create a low-molecular-weight product, C5a, and a high-molecular-weight product, C5b, which remains bound to the activation site. The smaller cleavage product, C5a, is released into the fluid phase, where it, like C3a, acts as an anaphylatoxin.[21] In addition, C5a possesses potent chemotactic activity for neutrophils and monocytes and acts to activate a series of cells with C5a receptors (CD88). C5a facilitates phagocytosis by neutrophils and appears to play a role in the generation of FoxP3-positive induced regulatory T cells (iTregs). Nascent C5b combines with native C6 to initiate formation of the membrane attack complex, a multimolecular assembly of C5b, C6, C7, C8, and C9, which is capable of cytolytic and bactericidal activity.[22]

Control of Complement Activation

Uncontrolled complement activation can result in widespread immunopathologic damage to the host, and each step in the cascade is under complex control.[23] Each enzyme undergoes spontaneous decay under physiologic conditions. In addition, a number of control proteins inhibit the classical pathway (i.e., C1 esterase inhibitor, C4-binding protein, factor I, and decay-accelerating factor, CD55) and the alternative pathway (i.e., factors H and I and membrane cofactor protein, CD46).[17] The membrane attack complex, composed of C5b through C9, also is regulated by control proteins (i.e., CD59). Thus the activation of complement proceeds in a highly controlled process and is limited to the immediate vicinity of the initiating substance (e.g., a microbial surface). Infectious agents have evolved proteins that control or prevent complement activation or binding or specifically bind complement control proteins from serum, allowing them to evade host defense. Well-studied examples involve staphylococci,[24] gonococci,[25] and vaccinia virus.[26,27]

Role of Complement in Host Defense

The complement system is critical in the host's defense against infection caused by a wide variety of bacteria, viruses, and fungi.[27] Animals that are pharmacologically depleted of complement or genetically deficient in individual complement proteins are more susceptible to infection with *H. influenza*,[28] *S. pneumoniae*,[27,29] *Staphylococcus* spp.,[30] Sindbis virus,[31] influenza A virus,[27] meningococcus,[32] West Nile virus,[33] and *Candida* spp.[34] to name just a few.

The protective effects of complement appear to be most important in the first hours following the onset of infection, when complement helps to limit the spread of microorganisms from an initial focus of infection.[35] Complement also plays a critical role in the clearance of pathogens from the bloodstream.[5] Different proteins of the system participate in different aspects of host defense. For example, in vivo studies have shown that the chemotactic cell-activating activities associated with C5a are important in attracting neutrophils to the initial site of infection, whereas the opsonic activity of C3b is critical in the clearance of bacteria from the bloodstream.[5] After the invading organism has established an infection, complement activation can contribute to further tissue damage.

Genetically Determined Deficiencies

of Complement

Complete deficiency of a specific complement protein is relatively uncommon; only 78 patients throughout Europe were identified in a 2015 publication.[9] Most of the genetically determined deficiencies of the complement system are inherited as autosomal recessive traits.[36] However, C1 esterase inhibitor deficiency is inherited as an autosomal dominant trait, and properdin deficiency is inherited as an X-linked recessive trait (Table 103.1). Heterozygous individuals with one half the normal level of complement proteins usually do not have an increased incidence of infections, but susceptibility to infection is increased in many complete deficiencies. Many deficiencies are associated with rheumatic disorders and one, C1 esterase inhibitor deficiency, is associated with episodic attacks of angioedema.[37] A discussion of each protein deficiency is beyond the scope of this chapter, but each is reviewed in *Immune Deficiencies*, edited by Sullivan and Stiehm.[36]

TABLE 103.1

Genetically Determined Deficiencies of Complement Associated With an Increased Susceptibility to Infection

Deficiency	Chromosomal Location	Inheritance	Major Clinical Manifestations
C1q	1p	Autosomal recessive	Rheumatic disorders and pyogenic infections
C1r or C1s	12p	Autosomal recessive	Rheumatic disorders and pyogenic infections
C4	6p	Autosomal recessive	Rheumatic disorders and pyogenic infections
C2	6p	Autosomal recessive	Rheumatic disorders and pyogenic infections
C3	19p	Autosomal recessive	Pyogenic infections and rheumatic disorders
C5	9q	Autosomal recessive	Meningococcal septicemia and meningitis
C6	5q	Autosomal recessive	Meningococcal septicemia and meningitis
C7	5q	Autosomal recessive	Meningococcal septicemia and meningitis
C8	1p(a,b)	Autosomal recessive	Meningococcal septicemia and meningitis
	9q(γ)	Autosomal recessive	Meningococcal septicemia and meningitis
C9	5p	Autosomal recessive	Meningococcal septicemia and meningitis
Factor I	4q	Autosomal	Pyogenic infections

		recessive	
Factor D	19p	Autosomal recessive	Systemic meningococcal infections
Properdin	Xp	X-linked recessive	Meningococcal septicemia and meningitis
Mannose binding lectin	10q11	Autosomal dominant	Infection and increased rheumatic disease

Patients with inherited total deficiency of complement proteins develop certain types of infection depending on the function of the deficient protein in host defense. Patients with a deficiency in C3-dependent opsonization have increased susceptibility to organisms for which C3b-dependent opsonization and phagocytosis plays an important role—organisms such as pneumococci, streptococci, and *H. influenzae* type b. Patients with deficiencies of C5, C6, C7, C8, or C9 are able to generate opsonically active C3b and thus have less susceptibility to these organisms.[27] However, because they lack the ability to generate C5- through C9-dependent bactericidal activity, these deficient patients are susceptible especially to *Neisseria* spp., for which bactericidal activity is a critical host defense mechanism. Between 5% and 15% of patients with systemic meningococcal infections have an inherited deficiency of a terminal component (C5–C9).[27] The risk for having a complement deficiency is higher if the infection is caused by an uncommon serotype (i.e., X, Y, and W135) or if the individual or a first-degree relative has had meningococcal infection. In-depth study of diseases, such as atypical hemolytic uremic syndrome and macular degeneration in elderly people, has uncovered a much more subtle type of complement deficiency that has not yet been explored in detail as a factor in host defense against infection.[23]

C1q Deficiency

Patients with C1q deficiency are unable to activate C3 and C5 through C9 by the classical pathway and thus have decreased antibody and C3b-dependent opsonizing activity as well as C5b- through C9-dependent bactericidal activity.[38] Interestingly, their predominant clinical presentation is a lupus-like syndrome with 75% of the relatively rare C1q-deficient individuals reported as having severe systemic lupus erythematosus (SLE). This genetic defect has the closest known association with SLE. Some patients also have contracted septicemia or meningitis caused by encapsulated bacteria.

C1r or C1s Deficiency

Patients with C1r or C1s deficiency have markedly reduced concentrations of the deficient protein (<1% of normal) and levels of the related protein that are 20% to 50% of normal.[39] Similar to patients with C1q deficiency, C1r- or C1s-deficient patients are unable to activate C3 and C5 through C9 by the classical pathway and thus have decreased C3b-dependent opsonizing activity and C5- through C9-dependent bactericidal activity. Many C1r- or C1s-deficient patients have SLE or isolated glomerulonephritis rather than infection.

Mannose-Binding Lectin Deficiency

MBL deficiency is the most common deficiency of a complement protein, accounting for up to one third of cases.[20] The normal serum level of MBL is low, 1 to 2 μg/mL. In about one third of the population, mutations in either the chain-coding or promoter regions of the gene lead to blood levels that are about ⅒ of normal. The literature suggests that individuals with MBL deficiency have a statistically increased frequency of infection, especially in the newborn period. Moreover, patients with cystic fibrosis with low MBL levels are more likely to die earlier in life from infection than are patients with normal levels, although the reasons for this are unclear. Patients with MBL deficiency may have increased frequency of rheumatologic diseases.

C4 and C2 Deficiency

C4 is encoded by two closely linked distinct loci (C4A and C4B) within the major histocompatibility complex (MHC) locus. Individuals with complete C4 deficiency are therefore deficient at both loci. As with other deficiencies of the classical pathway, C4-deficient patients do not generate C3b-dependent opsonizing activity or classical C5- through C9-dependent bactericidal activity. Serum deficient in C4 is capable of opsonization and bactericidal activity through microbial activation of the alternative pathway but not as quickly or to the same degree as serum containing C4. The most common clinical manifestation of complete C4 deficiency has been a lupus-like syndrome, and some patients have had bacterial septicemia or meningitis. Homozygous C4B deficiency predisposes children to bacterial meningitis, presumably because they need to depend on the less functionally active C4A isotype to activate C3 through the classical pathway.[36]

C2 Deficiency

Although the ability of C2-deficient patients to generate complement-dependent opsonic and bactericidal activity by the classical pathway is reduced, activity is generated by the alternative pathway.[36,40] Affected individuals may be healthy, but a subset have an increased susceptibility to infection and several rheumatologic disorders. Typical infections are septicemia or meningitis. Usual pathogens include encapsulated pyogenic bacteria such as the pneumococci and typable *H. influenzae,* pseudomonas, and meningococci.

C3 Deficiency

C3 is central to the function of all activation pathways, and C3-deficient individuals have deficient opsonic and bactericidal activity.[15,18] Affected patients typically manifest an increased susceptibility to infection and a variety of rheumatologic diseases. Localized infections, such as recurrent otitis media, sinusitis, and pneumonia, also can occur. The most common etiologic organisms are pneumococci, typable *H. influenzae,* and meningococci.

In normal hosts, iC3b interacts with CD11b/CD18 and CD11c/CD18; these receptors are deficient in patients with leukocyte adhesion deficiency.[18,41] The defect usually is in the protein CD18, and these patients are deficient in all of the B2 integrins including LFA1, known to be important in T-lymphocyte function (see Chapter 104).

C5 Deficiency

Patients with C5 deficiency can generate opsonically active C3b through activation of the classical or alternative pathway, but cannot generate C5b- through C9-dependent bactericidal activity.[18,29] They do not have an increased susceptibility to infection with encapsulated bacteria; however, because normal host defense against *Neisseria* spp. depends on intact serum bactericidal activity, C5-deficient patients have increased susceptibility to systemic *Neisseria* spp. infections.[18,27] Patients with C5 deficiency fail to generate normal C5a, which is thought to contribute to their increased risk for infectious disease complications.

C6, C7, C8, C9, and Properdin Deficiency

Patients with C6, C7, or C8 deficiency can opsonize microbes but are unable to generate complement-dependent bactericidal activity. They have an increased risk for systemic meningococcal and gonococcal infections.[36]

Native C8 is composed of three distinct chains. The α and γ chains are covalently linked to form one subunit, which is noncovalently bound to the second subunit composed of the β chain.[36] There are two genetically distinct forms of C8 deficiency, one in which the α-γ subunit is deficient, and the other in which the β subunit is deficient. Blacks tend to have C8 α-γ chain deficiency, and whites tend to have deficiency of the β chain. In both forms, C8 functional activity and serum bactericidal activity are reduced markedly. The predominant clinical expression of C8 deficiency is an increased susceptibility to systemic *Neisseria* spp. infections.[8]

The assembly of C5b through C8 results in an unstable membrane attack complex that possesses limited bactericidal activity. The first patient described with C9 deficiency had no apparent consequence. Subsequently, an epidemiologic study has demonstrated the relationship between C9 deficiency and systemic meningococcal and other infections.[42,43]

Properdin acts to stabilize the alternative pathway C3-cleaving enzyme, C3bBb, thereby retarding its intrinsic decay. Deficiency of properdin increases susceptibility to bacterial infections, particularly those caused by *Neisseria*.

Deficiency of Factors H and I

Factor H is one of a set of 5 proteins that have elements of similar structure. Factor H deficiency is associated with atypical hemolytic uremic syndrome.[44] Abnormalities in factor H also are associated with age-related macular degeneration.[45] Complement may be important in the clearance of debris from various sites of deposition, such as in the back of the eye.[45] A wide variety of microbes have been found to bind factor H specifically in plasma, thereby helping to downregulate the ability of complement to destroy the organism.[46,47] Factor I is a cofactor for the cleavage of factor H–bound C3b to iC3b. Factor I also functions with additional membrane proteins that act as cofactors for the cleavage of C3b and iC3b to form C3d. These are the C3b receptor itself (CD35) and CD46.[18,48] Patients with factor I deficiency have uncontrolled activation of C3, with resulting secondary serum C3 deficiency. Afflicted patients have an increased susceptibility to infection with the same encapsulated bacteria to which C3-deficient patients are susceptible. Patients with mutations in factor I also have increased incidence of atypical hemolytic uremic syndrome.[44]

Patients with factor D deficiency are unable to activate C3 by the alternative pathway. Rare families have been described in which patients with mutations of factor D have had systemic meningococcal infections.[36] Factor B is the protein in the alternative pathway that functions like C2 of the classical pathway; only a few instances of factor B deficiency in humans have been reported.

Secondary Deficiencies of Complement

Secondary deficiencies of complement can contribute to increased susceptibility to infection. For example, children with the idiopathic nephrotic syndrome who lose complement proteins in their urine have an increased susceptibility to pneumococcal peritonitis and sepsis.[49]

Infants

Complement proteins in general do not cross the placenta, and serum concentrations of most complement proteins in term infants are reduced to between 50% and 80% of those found in adults. Even lower concentrations are found in premature infants.[50] These deficiencies contribute to susceptibility to infection.

Sickle Cell Disease

Patients with sickle cell disease have a markedly increased susceptibility to systemic infections caused by *Streptococcus pneumoniae*.[51] Two defects in host defense contribute to this increased susceptibility: functional asplenia and a decrease in serum opsonizing activity. Deficient serum opsonizing activity is secondary to defective activation of the alternative pathway, although the exact basis for this defect is unknown.

New Research in Genetic Deficiencies

Defects in the synthesis of individual complement proteins are rare. Defects in the control proteins are far more common. An autosomal dominant defect in synthesis of functional C1 inhibitor has been known to be causal in hereditary angioedema (HAE). Type 1 HAE defects lead to low levels of circulating protein. Type 2 defects are associated with normal or elevated levels, but functional levels are low because of amino acid defects.[37] Defects in the control proteins that regulate the degradation of C3 often are associated with the development of atypical hemolytic uremic syndrome,[23] even when defects are only in heterozygous form, emphasizing the fine balance between activation and downregulation of complement. In examining the causes of glomerulonephritis in patients and in macular degeneration, it has been learned that minor alterations in either complement proteins or control proteins with small alterations in amino acid sequence can upregulate slightly the activity of complement proteins such as C3 or factor B, or downregulate slightly the activity of a control protein. The sum of a number of these small changes can upregulate or downregulate complement function, thereby causing disease.[23,45]

Diagnosis of Complement Deficiencies

Screening for deficiencies of the early components of the classical pathway (C1, C4, and C2), C3, and the terminal components (C5–C9) can be accomplished by measuring total serum hemolytic complement activity (CH50), an assay that examines the lysis of antibody sensitized sheep erythrocytes.[52,53] Deficiency of any complement protein leads to a reduction or absence of total hemolytic complement activity.

Deficiencies of factors B and D and properdin can be detected by a hemolytic assay that assesses lysis of rabbit erythrocytes mediated by the alternative pathway.[53] This assay also is abnormal in patients with deficiencies of C3 or C5 through C9. Defects of MBL can be identified by enzyme immunoassay. The specific abnormality can be confirmed by sequencing relevant genes.

In some cases the concentration of serum protein in question is a reliable test for a genetic defect. In other cases, such as in type 2 hereditary angioedema, the protein is present but nonfunctional; therefore, functional assays are needed for diagnosis. Patients with C8 deficiency lack either one (C8β) or two (C8α and γ) chains of the complete three-chain molecule. Therefore, C8 antigen is detected in the serum of such patients, but C8 function is reduced markedly. Individuals who are heterozygous for a deficiency of a single component usually have normal CH50 levels because this assay is not sufficiently sensitive to detect mild to moderate reductions in a single component.

Identification of the complement receptors or membrane-bound complement control proteins usually is established by flow cytometry.

Management

Replacement of specific components usually is not practical because of the short half-life of the complement proteins and the generation of an immune response to infused protein. Patients with complement deficiencies that predispose to an increased susceptibility to infection may benefit from the administration of prophylactic antibiotics.

Immunization against vaccine-preventable infections in complement-deficient patients is critically important. Because antibody can act directly as an opsonin through engagement of Fc receptors on phagocytic cells, increasing concentrations of specific anticapsular antibody can provide increased opsonic activity independent of complement. In addition, increased levels of specific antibody may increase activation of the classical pathway in patients with alternative pathway defects. Thus, complement-deficient individuals (see Chapter 6) should be immunized on a schedule for hosts at increased risk for *S. pneumoniae, H. influenzae* type b, and *N. meningitidis*[27] (see Chapters 6 and 126).

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104

Infectious Complications of Dysfunction or Deficiency of Polymorphonuclear and Mononuclear Phagocytes

E. Stephen Buescher

Phagocytes perform critical roles in human host defense. Polymorphonuclear phagocytes (neutrophils, eosinophils, and basophils) defend against microbial invasion and contribute to various aspects of the inflammatory response. Mononuclear phagocytes (monocytes and macrophages) perform similar complementary functions in defense and cognate immunity. Despite their rarity, inherited disorders of these cell types provide insight into the critical role of phagocytes in human survival and health. One of the first phagocyte disorders to be recognized, chronic granulomatous disease (CGD), was described in 1957.[1,2] Despite its rare occurrence, CGD has been studied intensively and has become the paradigm for clinical management of infectious and inflammation-related problems common to disorders of phagocyte function.

Etiologic Agents

The major phagocyte function disorders and their abnormalities are outlined in Table 104.1. Because phagocytic cell responses are important both in normal host defense against extracellular microorganisms and in acute inflammatory responses, most of these conditions have the dual characteristics of recurrent infection plus deranged inflammatory responses. True pathogens or typically opportunistic agents cause infections in people with these disorders. Bacterial agents predominate in most conditions, but fungi are significant pathogens in many disorders (Table 104.2).

TABLE 104.1

Characteristic Abnormalities of Disorders of Phagocytic Function

Disorder	Characteristics of Phagocytic Cells			
	Numbers	Chemotaxis	Adherence	Microbicidal Activity
Chronic granulomatous disease	NL	NL	NL	↓
Leukocyte adhesion deficiency	↑	↓	↓	NL
Chédiak-Higashi syndrome	↓[a]	↓	NL	↓
Myeloperoxidase deficiency	NL	NL	NL	NL[b]
Specific granule deficiency	↑/NL	↓	NL	↓
Hyper-IgE–recurrent infection syndrome	NL	↓/NL	NL	NL

[a] Neutropenia is common during the accelerated phase.

[b] In vitro microbicidal activity against *Candida* spp. is deficient.

Hyper-IgE, hyperimmunoglobulin E; NL, normal; ↑, increased; ↓, decreased.

TABLE 104.2

Pathogens Associated With Disorders of Phagocytic Function

	Chronic	Leukocyte	Chédiak-	Hyper-IgE	Specific

Organism	Granulomatous Disease	Adhesion Deficiency	Higashi Syndrome	–Recurrent Infection Syndrome	Granule Deficiency	Myeloperox Deficiency
Staphylococcus aureus	++++	+++	++++	++++	+++	–
Streptococcus spp.	+	+	+++	+++	+++	–
Escherichia coli	++	+++	+	+	+	–
Burkholderia cepacia	+++	++	+	+	+	–
Serratia marcescens	+++	++	+	+	+	–
Candida spp.	++	++	+	++++	+	++++
Aspergillus spp.	+++	++	+	++	+	–
Nocardia spp.	+++	+	+	+	+	–
Pseudomonas aeruginosa	+	+++	+	+	++	–

Hyper-IgE, hyperimmunoglobulin E; ++++, most common or distinctive pathogen; +++, common pathogen; ++, less common pathogen; +, occasional pathogen; –, never associated.

Pathologic Findings

Infections can occur at any anatomic site. However, interfaces between host and environment are the sites most commonly affected; skin and soft tissue infections or abscesses, pneumonia, and infections of the upper airway or sinuses are typical (Table 104.3). Clinical manifestations depend on the nature of the underlying disorder. CGD phagocytes circulate in adequate numbers, move to tissues appropriately with normal locomotive and phagocytic function, and localize infection, but fail to develop the respiratory burst required to kill certain pathogens. As a result, abscess formation is common, but progressive, rapidly spreading cellulitis or septicemia is not. By contrast, disorders involving locomotive abnormalities (e.g., Chédiak-Higashi syndrome, leukocyte adhesion deficiency type 1) demonstrate failure to localize infection, often resulting in rapid progression of infection or systemic spread, with a delayed appearance of inflammation.

TABLE 104.3

Infectious Complications of Disorders of Phagocytic Function

	Chronic	Leukocyte	Chédiak-	Hyper-IgE	Specific

Infection	Chronic Granulomatous Disease	Leukocyte Adhesion Deficiency	Chédiak-Higashi Syndrome	–Recurrent Infection Syndrome	Specific Granule Deficiency	Myeloperox Deficiency
Lymphadenitis	++++	+	+	++	+	–
Septicemia	+	+++	++	++	+	++
Osteomyelitis	+++	+	+	++	++	++
Pneumonia	+++	++	+++	++++	++	+
Sinusitis	+	+	+	+++	+	–
Liver abscess	++	++	+	++++	+	++++
Meningitis	++	++	+	++	+	–
Poor healing	+++	+	+	+	+	–
Cellulitis	+	+++	+	+	++	–

Hyper-IgE, hyperimmunoglobulin E; ++++, most common; +++, common; ++, less common; +, occasional; –, rare.

Abnormal acute inflammatory responses contribute to ineffective wound healing that is characteristic of these conditions. At sites of injury, histologic examination can show disordered inflammatory responses, such as combinations of acute and chronic inflammation (Fig. 104.1) or poor accumulation of inflammatory cells. In some instances, abnormal inflammatory responses, rather than infection, are the major cause of pathology.[3]

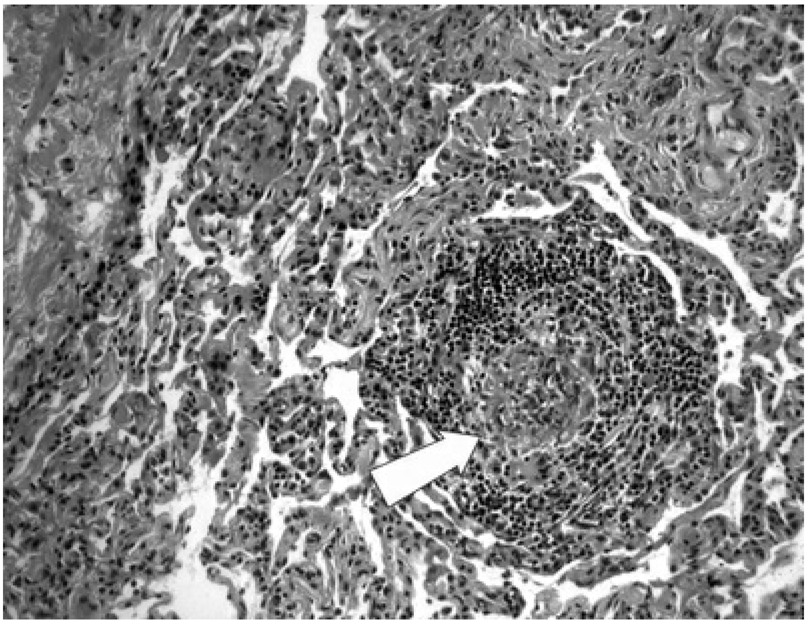

FIGURE 104.1 Pyogranuloma (acute inflammatory cells within granulomatous inflammatory response) *(arrow)* in the lung of patient with chronic granulomatous disease and *Aspergillus* spp. pneumonia.

Clinical Manifestations

Manifestations of disorders of phagocyte function are highly variable. In some instances, inflammatory (rather than infectious) manifestations occur first.[4] Age at presentation varies from neonates to adults, but presentation early in life is more typical.[5,6] Infections can be caused by well-known pathogens, opportunistic pathogens, or nonpathogens. Although few rules invariably apply, certain characteristics of infections raise concern for an underlying disorder, and specific physical findings or infectious agents may suggest specific disorders (Tables 104.2 to 104.4).

TABLE 104.4

Patterns of Clinical Illness Associated With Disorders of Phagocytic Function

Disorder	Clinical Illness
Chronic granulomatous disease	Liver abscess, aphthous stomatitis, discoid lupus erythematosus, McLeod blood phenotype, *Burkholderia cepacia* pneumonia, *Nocardia* spp. infections, *Aspergillus* spp. infections, retinitis pigmentosa, Duchenne muscular dystrophy, gastric or genitourinary tract wall thickening
Leukocyte adhesion deficiency type 1	Failure of umbilical stump separation, early periodontal disease
Myeloperoxidase deficiency	Severe infections with *Candida* spp., often in presence of diabetes mellitus
Hyper-IgE –recurrent infection syndrome	Lung cysts or pneumatoceles, soft tissue abscesses with minimal inflammation, retention of primary teeth, multiple bone fractures, scoliosis
Chédiak-Higashi syndrome	Recurrent cutaneous abscesses and cellulitis, invasive infections, progressive neuropathy, leukemia-like myeloproliferative process
Specific granule deficiency	Recurrent cutaneous and invasive infections

Hyper-IgE, hyperimmunoglobulin E.

Clinical Approach

The clinical approach to these patients involves regular, repeated examination of target organ systems, preventive therapies, and prompt evaluation of acute clinical complaints. At the time of diagnosis, studies to define the anatomy of organ systems likely to be involved with future infection can provide baseline information for comparison. These studies include scintigraphy of the skeleton and computed tomography (CT) or magnetic resonance imaging (MRI) of the chest and abdomen (liver, spleen, para-aortic nodes, kidneys, and bladder). Regular examination of the hemogram, blood chemistry, coagulation, erythrocyte sedimentation rate, and C-reactive protein values aids in monitoring the patient's general state of health and provides data for comparison during illness.

Prompt evaluation of clinical complaints permits early recognition and treatment of conditions before serious complications or tissue damage occurs. The typical inflammatory response can be absent in these patients, and fever is variable. Simple problems (e.g., hangnail, insect bite, or minor injury) can become a source of progressive infection; expectant management, with attention to local care and administration of antibiotics, is required to prevent serious complications.

Any microorganism recovered from a normally sterile site, regardless of its nominal pathogenic potential, should be regarded as a likely infectious agent. This includes normal human flora or environmental organisms when the same organism is recovered repeatedly from the same site or from multiple sites. Recovery of multiple organisms from aspiration or biopsy materials should not be discounted because polymicrobial infections (including bacteria or fungi) are well described in these patients.

Management

Identification of the Site of Infection

The ease with which sites of infection can be identified often varies from episode to episode. Skin, upper and lower respiratory tract, liver, bone, and lymph nodes are common sites of infection; spleen, gastrointestinal tract, central nervous system, and blood are less common. When the site of infection is accessible, material for culture and histology should be promptly obtained, preferably before administration of antimicrobial agents. When deep infections occur, clinical judgment must be used to decide whether antibiotic treatment can be delayed for 12 to 24 hours to acquire a surgical specimen. For patients with fever but no localizing signs or symptoms, a plan must be formulated early to define the length of clinical observation, while awaiting culture results or evolution of localizing findings, before initiating empiric antibiotic therapy. Anatomic sites previously infected should be carefully scrutinized because recurrent infections are common: bone scan and imaging studies of the chest and abdomen should be considered. Anatomic sites containing lymph nodes (hila of the lungs, paravertebral areas, mediastinum, retroperitoneum) should receive special attention because of the frequency of nodal suppuration in conditions such as CGD (see Table 104.3). Use of different imaging methods to examine the same anatomic areas (e.g., CT vs. MRI) can be helpful (Fig. 104.2). If, after 24 to 48 hours of close observation, the patient has no clinical change or has worsened, empiric antibiotic therapy should begin, usually with an antistaphylococcal agent plus an aminoglycoside or third-generation cephalosporin. In some instances, a previously unrecognized site of infection becomes evident after initiating empiric antibiotic therapy. If this occurs, appropriate surgical biopsy or drainage with culture of the specimen should be considered. Empiric antibiotic therapy alone rarely leads to resolution of unrecognized infection; repeated careful examinations of the patient and monitoring studies should be performed until the site of infection is identified or infection is ruled out.

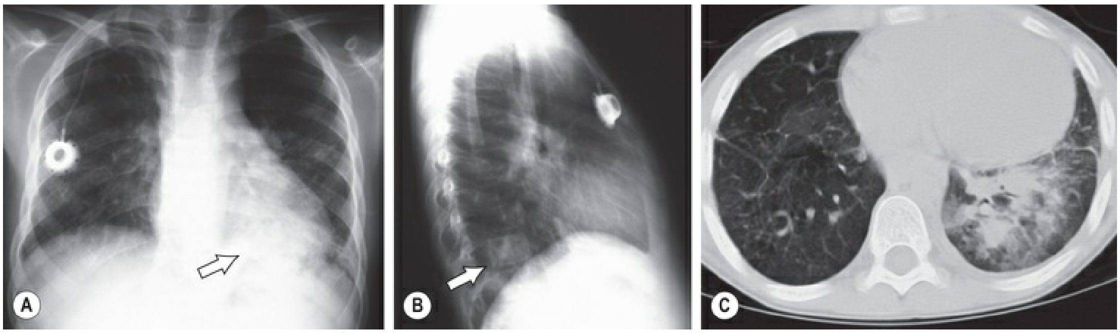

FIGURE 104.2 Chest radiograph and chest computed tomography (CT) scan of a 7-year-old child with chronic granulomatous disease with fever and dry cough. Plain films show a retrocardiac left lower lobe infiltrate *(arrow)* (A), which appears small on the lateral view *(arrow)* (B). (C) CT demonstrated more extensive disease throughout the left lower lobe. *Burkholderia cepacia* was isolated from the open-lung biopsy. Because this child had an episode of pneumonia caused by the same organism 12 months previously,

the exposure history was more intensively examined, revealing that the child had a favorite outdoor activity of pulling up wild onions.

Identification of the Infectious Agent

The importance of obtaining specimens for culture from sites of infection cannot be overemphasized; the variety of potential agents and the complicated nature of management require definitive knowledge for optimal treatment. Cultures of blood, urine, and cerebrospinal fluid (if appropriate), as well as cultures from all infected sites, should be obtained before initiation of treatment. Surgical or imaging-guided biopsy is performed for deep infection (see Fig. 104.2).

Delineation of Tissue Involvement and Debridement

For deep infections, meticulous and vigorous debridement of involved tissue should be performed at the time of biopsy; delayed control of infection, recurrence of infection, and slow healing all can result in excessive scarring and fibrosis. Tissue specimens (not swabs) should be sent for culture. For fungal infections, cure may require surgical removal of the affected tissue. Close collaboration with the surgeon, including the subspecialist's attendance at operative procedures, is required for optimal surgical intervention.

Initiation of Appropriate and Specific Treatment

When a surgical intervention is performed, prolonged postoperative drainage should be ensured by slow advancement of drains, allowing perhaps twice the usual time for drainage to be achieved. Skin and soft tissue sutures must be of maximal mechanical strength and left in place for a prolonged period because poor wound healing and weak scars in these patients lead to dehiscence. The duration of antimicrobial treatment typically is extended to approximately twice that required to treat an immunocompetent child with the same infection, with further tailoring of treatment based on the extent of disease, antimicrobial susceptibility of microorganisms, effectiveness of surgery and therapy, and complications. Intravenous therapy is the standard for acute management, with oral treatment only used for chronic phases of therapy. Central venous catheters, if used, should be managed with meticulous aseptic technique because of associated risks for infection. Defervescence in patients receiving appropriate management may be slow, but ineffective drainage, failure to identify and drain all foci, and iatrogenic causes, such as thrombophlebitis or drug fever, also must be considered when fever persists.

The frequency and severity of fungal infections, especially in patients with CGD, deserve specific comment (see Table 104.2).[7] Experience with CGD suggests that surgical resection of fungal infection offers the best chance of cure, but often, complete surgical resection is impossible. Amphotericin B, the mainstay of therapy in the past, remains effective against many fungi, but newer agents with less attendant toxicity, including itraconazole, voriconazole, caspofungin, and posaconazole, are supplanting its use.[8]

Inadequate treatment of infectious episodes is common in these patients. When infection is suppressed instead of eradicated, smoldering infection and chronic inflammation lead to end-organ damage and scarring that eventually become insurmountable clinically, negatively affecting the patient's long-term prognosis.

Aggressive conventional approaches to treatment are not always successful. Unconventional adjunctive modalities must be considered in some situations, especially for fungal infections. Administration of functionally competent leukocytes by transfusion can be considered in situations of failure of aggressively applied conventional therapies, lack of localization of an infectious process, or life-threatening infection.[9] Most experience with leukocyte transfusions is based on care of patients with CGD, often in the context of extensive, nonresectable fungal infection.[7,10] When used in this situation, it is prudent to separate leukocyte transfusion administration and infusion of amphotericin B by at least 6 hours to avoid acute pulmonary decompensation.[11] If used, it is important to understand that antileukocyte antibodies develop in approximately three fourths of patients.[12]

Inflammatory Diseases

With widespread, routine use of prophylactic antibacterial and antifungal agents, disease due to dysfunction of acute inflammatory responses in patients with CGD is more frequently recognized and reported. Inflammatory processes without obvious infection (inflammatory bowel disease–like manifestations, genitourinary and gastrointestinal tract granulomatous masses) clearly occur in these patients, and although infection should always be the primary concern, failure to identify an infectious process should lead to consideration of an inflammatory process, with management approaches shifting away from anti-infectious therapies to anti-inflammation therapies.[13]

Complications

Progressive tissue damage with associated loss of physiologic function or extension of infection is the most serious consequence of ineffective treatment of infection (Fig. 104.3). Progressive loss of pulmonary function, with parenchymal loss, bronchiectasis, and restrictive lung disease, is a typical irreversible complication, which can be minimized or avoided by prompt definitive diagnosis and aggressive management.

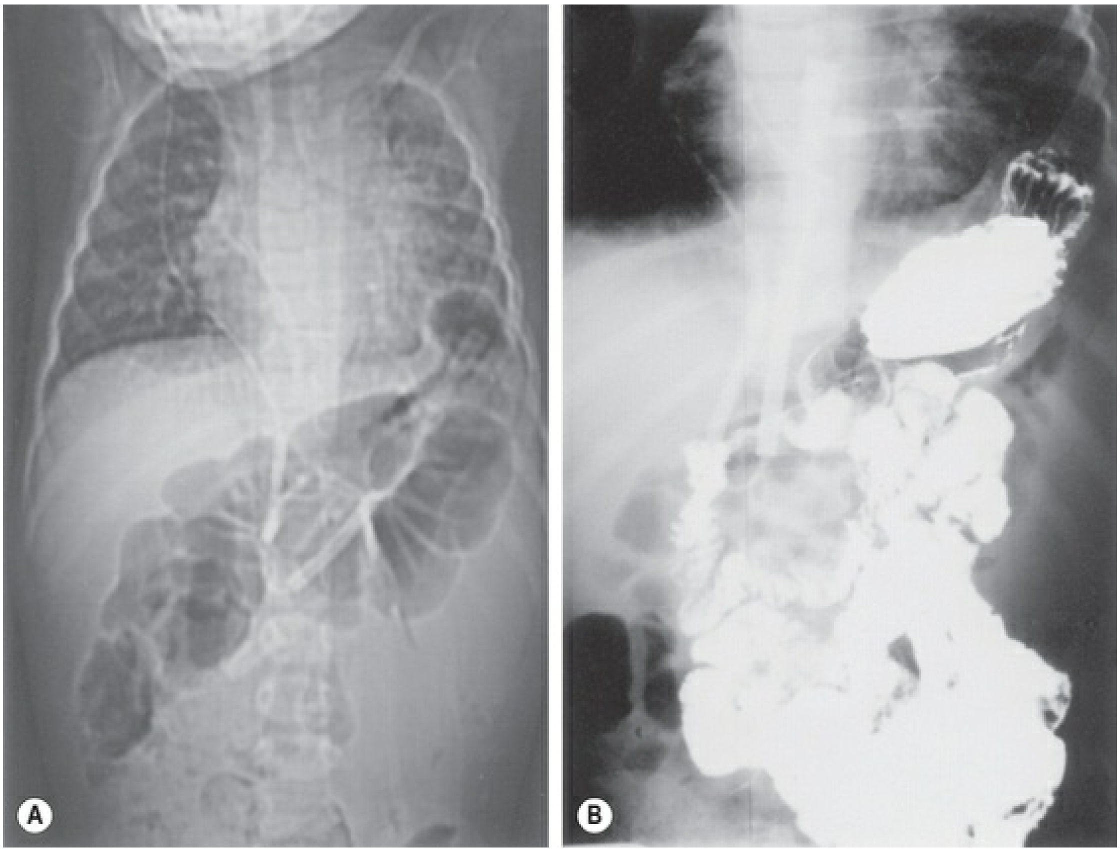

FIGURE 104.3 Plain radiograph (A) and barium study (B) illustrating herniation of the stomach through the incompetent left hemidiaphragm in a patient with chronic granulomatous disease. The left anterior chest wall, left lung, and left hemidiaphragm had been infected with *Aspergillus fumigatus* 2 years previously and had been effectively treated with white blood cell transfusions and parenteral antifungal treatment.

Effects of inflammation-related masses, wound dehiscence, and mechanical failure of scar tissue are other major complications (Fig. 104.4). In CGD, obstruction of the gastrointestinal or urinary tract by masses of granulomatous tissue, often without evidence of active infection, is a manifestation of the abnormal inflammatory response.[14,15] In some patients with CGD, gastric outlet obstruction is the first manifestation (Fig. 104.5).[14] Corticosteroid therapy is used to re-establish normal function.[13] Inflammatory bowel disease-like colitis occurs in some patients with CGD and can be difficult to control. Complications of poor wound healing generally can be avoided by careful surgical technique and delayed removal of suture material.

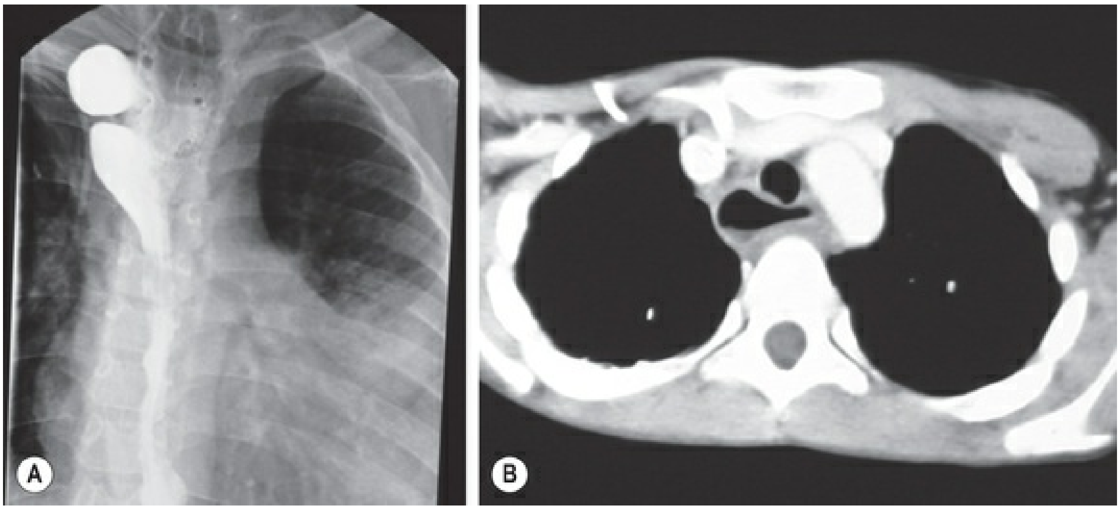

FIGURE 104.4 Barium swallow (A) and chest computed tomography (CT) images (B) of a 10-year-old patient with chronic granulomatous disease. Gastrointestinal granulomatosus was first diagnosed at 3 years of age and treated since with intermittent-pulse corticosteroid therapy for symptoms. Upper esophageal diverticulum formed spontaneously over 4 years, during which time right upper lobe aspergillosis was diagnosed and treated. At age 7 years, right upper lobe resection was performed, with subsequent development of the lower diverticulum.

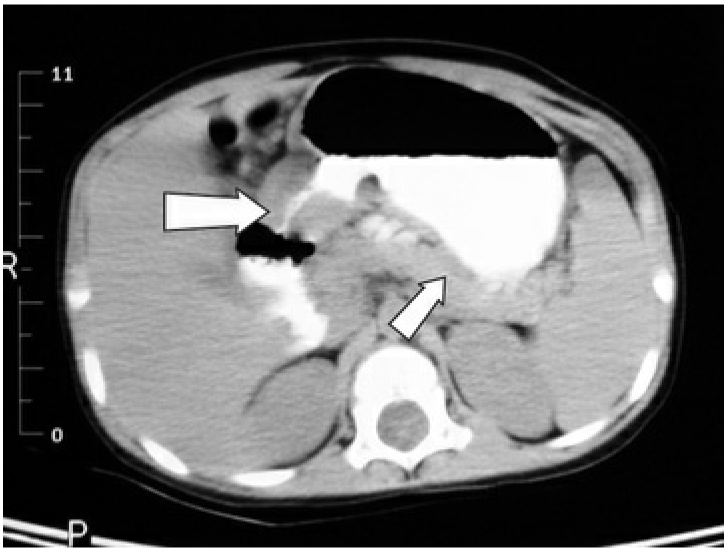

FIGURE 104.5 Abdominal computed tomography (CT) study of a 2-year-old boy with chronic granulomatous disease and persistent vomiting. Contrast material in the stomach forms an “apple-core” shadow as it passes through the pylorus *(upper large arrow),* which

is thickened by granulomatous inflammation. The posterior antral wall is also severely thickened *(lower small arrow).* Vomiting resolved within 24 hours of starting oral prednisone treatment.

Prognosis and Sequelae

The prognosis for patients with phagocyte functional disorders has improved steadily over time. With aggressive management of infections and careful follow-up, 10-year survival in conditions such as CGD has improved from 15% to 25% previously to 80% or greater.[16,17] Survival data for other conditions are not readily available. Rates of infection in patients with CGD can be reduced by prophylaxis with cotrimoxazole, itraconazole or voriconazole, and interferon γ.[18–21] Patients with CGD and fungal pneumonia or disseminated fungal infection have mortality rates as high as 45%.[7] Bone marrow stem cell transplantation has been more commonly performed since the mid-2000s in patients, including some with CGD and Chédiak-Higashi syndrome.[22,23] Gene insertion therapies have been successful in animal models of CGD, but are not available for humans.[24]

Recent Advances

Use of recombinant human hematopoietic growth factors has been examined in many phagocytic cell disorders and, in general, has not proved helpful, except in situations in which neutropenia accompanies abnormal function (e.g., glycogen storage disease type Ib).[25] Use of cytokines in nonmalignant syndromes of cytopenia (congenital neutropenia, myelokathexis) also shows some promise.[26,27]

Prevention

Prevention of infections in people with phagocyte function disorders is based on prophylactic administration of antimicrobial agents, prompt attention and care of minor injuries, and avoidance of potentially harmful environments. Chronic administration of oral antibiotics has not been examined definitively in any of these conditions. Daily cotrimoxazole appears to prolong infection-free periods in CGD but has less clear effects in other conditions (Table 104.5). Perioperative antibiotics should be administered before elective surgical and dental procedures (Table 104.6). Continuous prophylactic use of itraconazole to prevent fungal infections in patients with CGD results in significantly fewer invasive fungal infections.[19] Administration of ascorbic acid may be effective in reversing functional defects of phagocytes in Chédiak-Higashi syndrome and CGD, although beneficial effects have not been observed in all patients.[23,28,29] In several conditions, administration of recombinant interferon γ appears to prolong infection-free periods. Administration of subcutaneous interferon γ (50 μg/m^2) 3 times a week significantly prolongs periods between serious infections in patients with CGD, and long-term treatment is safe.[21] In hyperimmunoglobulin E (hyper-IgE) syndrome, in vitro interferon γ exposure alters polymorphonuclear leukocyte locomotive responses, but clinical trials have not been performed.[30]

TABLE 104.5

Prophylactic Antimicrobial Administration in Disorders of Phagocytic Function

Drug	Dose (Per Day)		
	<40 kg	>40 kg	Comments
Trimethoprim–sulfamethoxazole	5 mg/kg[a]	160 mg[a]	Penetrates phagocytes
Dicloxacillin	12–25 mg/kg[a]	500 mg[a]	Remains extracellular
Clindamycin	10 mg/kg[a]	300 mg[a]	Penetrates phagocytes
Itraconazole	100 mg	200 mg	

[a] Divided into 2 equal doses.

TABLE 104.6

Antibiotics and Dosages for Surgical Prophylaxis in Patients With Disorders of Phagocytic Function

Drug	Dose	Schedule	Alternative Drug
Cefazolin	Child: 20–30 mg/kg IV	20–30 min before cut; repeat every 2–3 hours during procedure[a] and 8 hours and 16 hours after procedure	Vancomycin: 15 mg/kg IV (over 1 hour) before cut; repeat (over 1 hour) every 8–12 hours during procedure
	Adult: 2 g IV	20–30 min before cut; repeat every 4 hours during procedure[a] and 8	Adult: 15 mg/kg IV over 1 hour before cut; repeat (over 1 hour)

		hours and 16 hours after procedure	every 8–12 hours during procedure
Gentamicin	Child: 2.5 mg/kg IM or IV	30–60 min before cut; do not repeat dose before 24 hours	Cefotaxime: Child: 50 mg/kg IV 20–30 minutes before cut; repeat every 3 hours during procedure[a]
	Adult: 5 mg/kg IM or IV	20–30 minutes before cut; do not repeat dose before 24 hours	Adult: 1 g IV 20–30 minutes before cut; repeat every 3 hours during procedure[a]

[a] To maintain blood level above minimal inhibitory concentration of target organism throughout procedure.

IM, intramuscular; IV, intravenous.

Minor wounds should be cleaned promptly and thoroughly and treated topically with an antiseptic or antibiotic agent. To minimize gingivitis and periodontal disease, oral hygiene should include twice-daily brushing of teeth with 3% H_2O_2 and baking soda. Activities or environments that might predispose to infection should be avoided, including active and passive smoking; environments containing decaying plants, vegetables, or wood (e.g., hay, sawdust, compost, garden mulch) where *Burkholderia* spp., spores of *Aspergillus* spp., or other fungi might be aerosolized (see Fig. 104.2).[31]

Specific Conditions

Chronic Granulomatous Disease

CGD is characterized by a defective or absent phagocyte respiratory burst in both polymorphonuclear and mononuclear phagocytes. Absence of the respiratory burst results in failure to produce reactive oxygen metabolites and H_2O_2. Microbicidal activity against catalase-positive bacteria and fungi is defective; recurrent, life-threatening infections with these organisms result. CGD occurs in 1:250,000 births. For initial screening, flow cytometric analysis of dihydrorhodamine 123 oxidation by blood leukocytes is used widely, but the nitroblue tetrazolium test remains rapid, relatively simple, and accurate. For confirmation, a quantitative test of the respiratory burst (superoxide assay or H_2O_2 assay) or demonstration of an appropriate gene defect is necessary.

Both infectious and inflammatory syndromes are associated with

CGD (see Table 104.2). Hepatic abscesses commonly cause fever, anorexia, and variable degrees of abdominal pain, often without abnormalities in serum transaminase levels. Abscesses can be multiple and variable in size (1 to >20 cm in diameter) (Fig. 104.6). Surgical excision is the preferred management.[32,33] Suppurative adenitis can involve a single node, multiple contiguous nodes, or multiple geographically separate nodes. Surgical excision is preferred, followed by prolonged antibiotic therapy. Pneumonia, caused by either bacterial or fungal agents, requires aggressive, early diagnostic efforts (e.g., bronchoalveolar lavage or open-lung biopsy). Fungal pneumonia initially can be asymptomatic and is difficult to eradicate; excisional biopsy should be seriously considered if pneumonia is localized discretely to one lung area. Osteomyelitis can cause fever with or without initial bone pain. Hematogenous spread or local extension from a nearby nonosseous infection can occur. Bone scan usually is diagnostic, and bone biopsy for identification of organisms should be performed. Concomitant antimicrobial prophylaxis may interfere with recovery of infectious agents, including fungi, so prophylactic antimicrobials should be held before diagnostic procedures. Vertebral osteomyelitis caused by *Aspergillus* spp. is difficult to treat and is associated with a poor prognosis.[34] Inflammatory syndromes include granulomatous changes in viscera that produce mass effects, poorly controlled inflammatory responses, poor scar formation, and slow wound healing (see Fig. 104.5).

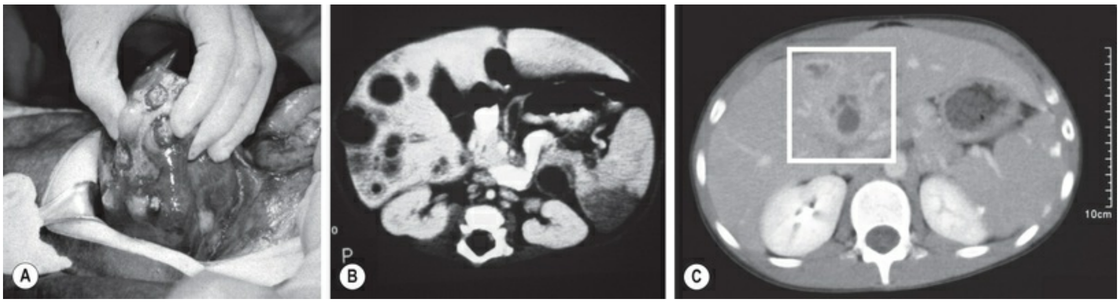

FIGURE 104.6 Intraoperative photograph (A) and abdominal computed tomography (CT) section (B) through the liver of a 3-month-old patient with chronic granulomatous disease, illustrating multiple liver abscesses, the number and location of which preclude resection en bloc. Abscesses were successfully treated using intraoperative, ultrasound-guided

aspirations, followed by prolonged antibiotic therapy. (C) Single complex liver abscess *(white box)* in a 12-year-old patient with chronic granulomatous disease. Abscess is in the medial left lobe *(box),* in contact with the portal vein. Drainage was achieved by intraoperative ultrasound-guided needle aspiration, followed by prolonged antibiotic therapy.

Myeloperoxidase Deficiency

Myeloperoxidase (MPO) deficiency is the most common syndrome of phagocyte defect, occurring in approximately 1 in 2100 persons.[35,36] MPO deficiency affects both polymorphonuclear and mononuclear phagocytes, resulting in deficient conversion of chloride and H_2O_2 to hypochlorous acid and its microbicidal byproducts. The diagnosis of MPO deficiency relies on biochemical or histochemical determination of absence of peroxidase activity in blood polymorphonuclear leukocytes. In vitro, MPO-deficient cells have only minor microbicidal abnormalities against bacterial pathogens, but killing of *Candida* spp. is dramatically deficient and may explain the severe candidal infections reported in some affected individuals.[37] Appropriate surgical debridement with antifungal treatment appears to be effective for these infections. MPO deficiency should be considered in any patient with a severe candidal infection that is not caused by an indwelling device or cytopenia.

Hyperimmunoglobulin E−Recurrent Infection Syndrome

Originally termed *Job syndrome*, hyper-IgE−recurrent infection syndrome (DOCK8 deficiency) is a multisystem disorder of at least three different forms characterized by extreme elevations of serum IgE (at least 10 times the upper limit of normal levels), recurrent skin and sinopulmonary infections, and eczematoid rashes.[38] Clinically, patients often have coarse facial features, retention of primary teeth, and candidiasis of the mouth, nails, or vagina. Recurrent sinopulmonary and cutaneous infections often begin in infancy; pneumonia frequently is severe and often is associated with pulmonary cyst or pneumatocele formation.[39,40] Bronchitis and sinusitis are common. Cutaneous infections typically are manifest as either abscesses (often with little associated evidence of inflammation) or cellulitis, but other types of cutaneous infections can occur. When osteomyelitis occurs, it is often in proximity to a soft tissue focus. Expected infectious agents include *Staphylococcus aureus*, *Haemophilus influenzae, Candida albicans, Streptococcus pneumoniae,* and *S. pyogenes,* but other organisms also are described.[41] Noninfectious manifestations include arthritis, arthralgia, multiple bone fractures, hyperextensibility of joints, scoliosis, keratoconjunctivitis, pulmonary cysts or pneumatocele, and lymphoid cancer.[38,39,42] No single laboratory study establishes the diagnosis, but extreme elevation of serum IgE level and eosinophilia are common. Most cases are associated with mutations in *STAT3* and its signaling systems.[38] Although originally proposed as a syndrome of primary phagocyte defect, it is now clear that the hyper-IgE–recurrent infection syndrome is a multisystem disease involving dentition, bones, connective tissues, and defense systems; aberrant intracellular signaling through the dedicator of cytokinesis 8 (DOCK8) protein causes the associated abnormalities of phagocyte function (i.e., chemotaxis).

Leukocyte Adhesion Deficiency Types 1, 2, and 3

Three separate conditions involving abnormalities of leukocyte adhesion are identified as leukocyte adhesion deficiency types 1, 2, and 3. The first descriptions of the condition now called leukocyte adhesion deficiency type 1 reported patients with recurrent infections, defective neutrophil mobility, and delayed separation of the umbilical cord.[43] Subsequently, the additional characteristics of severe periodontal disease, poor wound healing, and multiple adhesion-related abnormalities of phagocyte function, including poor adherence, spreading, chemotaxis, phagocytosis, and antibody-dependent cellular cytotoxicity responses, were described.[44] Partial ("moderate phenotype") or complete ("severe phenotype") absence of β_2 integrins ("leukocyte integrins," CD11/CD18) on mononuclear and polymorphonuclear phagocytic cells occur. The result is slow mobilization and poor localization of phagocytic cells at inflammatory foci, resulting in severe, systemic, life-threatening infections, often resulting in death during infancy.[44] Infections involving cutaneous ulceration, delayed wound healing, pneumonia, and peritonitis are common. Periodontal disease is common and can result in premature tooth loss. Leukocytosis without infection also is common, with marked leukocytosis often accompanying episodes of infection. Natural killer cell responses are diminished in vitro, but whether this results in abnormal cell-mediated immunity is controversial.[44] Spontaneous "regain of function" mutations in the defective β_2-integrin genes of three patients with leukocyte adhesion deficiency type 1 have been documented.[45]

Leukocyte adhesion deficiency type 2 is an unrelated disorder in which absence of fucosylated ligands (sialyl-Lewis X antigen), which are the ligands for endothelial cell selectins on the surface of phagocytes, results in ineffective phagocyte–endothelial cell interactions.[46] Associated findings are severe mental retardation, short stature, and the Bombay erythrocyte phenotype. Dietary supplementation with oral fucose reverses the adhesive defect.[47]

Leukocyte adhesion deficiency type 3 is the most recently recognized leukocyte adhesion deficiency, involving failure of integrins to respond to activation signals. Multiple mutations in the *KINDLIN3* gene have been described, with resultant defects in leukocyte adhesion and platelet aggregation. Although it is unclear presently whether the type 3 condition is one or several distinct entities, all cases recognized to date have the common clinical characteristics of recurrent infection and severe bleeding tendencies.[48]

Chédiak-Higashi Syndrome

Chédiak-Higashi syndrome is a rare, autosomal recessive disorder that results in recurrent pyogenic infections, partial oculocutaneous albinism with photophobia and nystagmus, and giant intracellular granules. Abnormal packaging of lysosomes is characteristic; all blood leukocytes show the diagnostic characteristic of abnormal, giant intracellular granules. In polymorphonuclear cells, these granules contain both primary and secondary granule markers and are deficient in elastase and cathepsin G.[46,50] In vitro, microbial killing is delayed, degranulation is abnormal, and chemotactic responsiveness is impaired.[51] Dysfunction of the lysosomal trafficking regulator gene *(LYST)* underlies the functional abnormalities of phagocytes in Chédiak-Higashi syndrome. Recurrent infections involving the respiratory tract and skin are most common, with *S. aureus* being the most common causative agent. Progressive neuropathy is common, and a lymphoma-like “accelerated phase,” accompanied by hepatosplenomegaly, lymphadenopathy, lymphohistiocytic proliferation or infiltration, anemia, neutropenia, and thrombocytopenia, develops in most patients during their first decade of life. Limited studies addressing the use of prophylaxis with antibiotic agents in these patients have shown little effect. In some patients, ascorbic acid treatment is reported to improve phagocytic cell function, but this effect does not occur in all patients.[23,28] Ascorbic acid treatment does not alter progression to the accelerated phase, prompting investigation of bone marrow transplantation to correct this syndrome.[23]

Secondary Granule Deficiency

Secondary granule deficiency is a rare condition characterized by severe, recurrent infections, and deficiency of the secondary granule marker lactoferrin due to dysfunction of the myeloid-specific transcription factor CEBPE.[52,53] These patients' phagocytes also lack all defensins, a class of phagocytic antimicrobial proteins.[50] Phagocytes from these patients have multiple functional abnormalities.[54,55] The diagnosis is made by demonstrating absence of antigenic lactoferrin in polymorphonuclear leukocytes. Clinically, patients manifest delayed localization of acute inflammatory cells at sites of injury, which leads to recurrent bacterial infections (both cutaneous and deep) and poor wound healing.[54]

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Infectious Complications of Cell-Mediated Immunity Other Than AIDS

Primary Immunodeficiencies

David B. Lewis

This chapter focuses on the infectious complications of primary immunodeficiencies in which lymphocyte-mediated immunity is compromised. Genetic disorders of cell-mediated immunity that are mainly associated with hemophagocytic syndrome are discussed in Chapter 12. Acquired autoantibody syndromes that result in infectious complications that mimic inherited immunodeficiencies are included, whereas inherited immunodeficiencies that mainly result in an autoimmune diathesis rather than compromised host defense, such as FoxP3 deficiency (IPEX syndrome) or CTLA-4 haploinsufficiency,[1,2] are not discussed here.

Overview of Cell-Mediated Immunity and Its Role in Control of Infections

Disorders of cell-mediated immunity that predispose to infection can be due to quantitative or qualitative deficiencies of thymus-derived lymphocytes (T lymphocytes, T cells) or innate lymphocyte cells (ILCs), such as natural killer (NK) cells, as well as abnormalities in antigen-processing or presentation to T cells by antigen-presenting cells (APCs).[1,2] Limitations in cytokine production or cytokine responsiveness (e.g., genetic deficiencies in cytokine receptors), in downstream signaling and transcriptional regulatory molecules (e.g., JAKs [*Ja*nus tyrosine *k*inases] and STAT [*s*ignal *t*ransduction and *a*ctivator of *t*ranscription] proteins[3]), and in acquired autoantibodies to cytokines[4] are also are important causes of opportunistic and severe infections.

T cells that express a heterodimeric T-cell receptor (TCR) for antigen consisting of an α and a β chain (α/β T cells) play a critical role in the initiation and maintenance of antigen-specific immunity.[5] Most α/β T cells recognize antigens in the form of short peptides bound to histocompatibility leukocyte antigen (HLA) molecules on APCs, and this recognition involves a highly diverse repertoire of αβ TCRs that are clonally distributed on T cells. The CD4 subset of α/β T cells recognizes peptide antigens presented by major histocompatibility complex (MHC) class II molecules, which consist of HLA-DR, HLA-DP, and HLA-DQ in humans. CD4 T cells regulate the adaptive immune response by producing soluble cytokines, such as interleukin-2 (IL-2), IL-4, IL-5, IL-9, IL-13, IL-17, IL-21, IL-22, interferon γ (IFNγ), and tumor necrosis factor- α (TNF-α), and by expressing surface molecules, such as CD40-ligand (CD154), which interact with cognate ligands on other cells.[5] This CD4 T-cell regulation includes promoting B-cell responses to protein antigens (by CD4 T follicular helper [Tfh] cells secreting IL-21 and expressing CD40-ligand, which binds to CD40 on B cells), augmenting the microbicidal activity of mononuclear phagocytes (by CD4 T helper 1 [Th1] cells secreting IFNγ, IL-2, and TNF-α), enhancing the production of and tissue microbicidal activity of neutrophils (by CD4 Th17 cells secreting IL-17 and IL-22), and helping maintain CD8 effector T cells that are involved in the control of persistent viral infections. Effector CD4 T cells, especially Th1 cells, are important for the control of pathogens that infect cells for at least part of their life cycle, particularly certain bacteria (e.g., *Mycobacterium, Salmonella, Listeria*), fungi (e.g., *Pneumocystis*), protozoa (e.g., *Toxoplasma* and *Leishmania*), and viruses (e.g., herpesviruses). Effector Th17 cells are important for the control of mucocutaneous candidal infections and, based on murine studies, also may help control pulmonary infection due to gram-negative bacteria.

The human CD8 α/β T-cell subset recognizes peptide antigens presented by MHC class I molecules, which consists of HLA-A, HLA-B, and HLA-C molecules. CD8 T cells are particularly important in killing infected host cells, such as those harboring viruses, by inducing them to undergo apoptosis (cell-mediated cytotoxicity). The most important mechanism of cytotoxicity involves the secretion of perforin and granzymes from the CD8 T cell, which bind to the target cell and result in the induction of death by apoptosis.

The human α/β T-cell compartment includes additional cell populations, such as NK T cells and mucosal-associated invariant T (MAIT) cells, that express canonical or highly restricted types of αβ-TCRs and that recognize nonpeptide antigens presented by nonclassical HLA molecules. Because the importance of deficits of these human T-cell subsets, as well of γ/δ T cells, which express a TCR heterodimer consisting of an γ and a δ chain, in increasing vulnerability to infection remains unclear, they are not discussed further in detail in this chapter.

APCs are not only involved in antigen presentation but also produce cytokines, such as IL-12p70 (a heterodimer of IL-12p40 and IL-12p35 chains), IL-23 (an IL-12p40 and IL-23p19 heterodimer), and others that play an important role in directing the adaptive immune response. The CD11c$^+$ subset of dendritic cells is particularly important in initiating the immune response of naïve CD4 and CD8 T cells to viral, bacterial, and fungal pathogens. The plasmacytoid subset of dendritic cells produces very high levels of interferon type I (multiple types of IFNα and IFNβ) and may be particularly important in the early response to viruses.

ILCs are distinct from T or B cells in that they lack TCRs or B-cell receptors (BCRs), respectively. NK cells are a subgroup of ILCs that have the innate ability to kill host cells (natural cytotoxicity) that are infected with intracellular pathogens, particularly herpesviruses. As for CD8 T cells, the major pathway for NK cell–mediated cytotoxicity is secretion of perforin and granzymes. Other ILC populations lack the capacity for cell-mediated cytotoxicity but have the innate ability to secrete the cytokines characteristic of Th1, Th2, or Th17 CD4 T cells.

More than 260 monogenic primary immunodeficiency disorders in humans have been identified.[6] Most of the classical monogenic lymphocyte-mediated immunodeficiency disorders are inherited as either autosomal recessive (AR) or X-linked disorders and compromise immunity from birth (e.g., severe combined immunodeficiency [SCID]).[1,2,6] With the advent of next-generation sequencing technologies, particularly for evaluation of the exome, a growing number of primary immunodeficiency disorders have been identified that are due to heterozygous mutations and act in a dominant activating or inhibitory way ultimately to cause immunodeficiency.[6] Although primary lymphocyte-mediated immunodeficiencies collectively are rarer than acquired immunodeficiency disorders, they often manifest as unusual, severe, or recurrent infections, and they frequently require more aggressive approaches for specific microbial diagnosis and therapy. Some primary immunodeficiency disorders may require a specific infectious trigger for immunodeficiency to become manifest (e.g., Epstein-Barr virus [EBV] infection in the X-linked lymphoproliferative [XLP] syndrome).[7]

Severe Combined Immunodeficiency Syndrome

Definition

SCID, which occurs in about 1 in 58,000 live births in the United States,[8] is an inherited severe immunodeficiency with marked quantitative deficiency of the de novo production by the thymus of peripheral antigenically naïve ($CD45RA^{high}CD45RO^{low}$) T cells. The profound T-cell lymphopenia is either due to reduced intrathymic production (most etiologies) or, rarely, to a block in their egress from the thymus to the periphery [coronin 1A (*CORO1A*) deficiency].[9] The “combined” term in SCID reflects the fact that severe T-cell deficiency invariably compromises B-cell function, regardless of whether B cells are present in normal numbers, which they are in a number of common etiologies. This is because CD4 T-cell help for B-cell antibody production in the form of surface CD40 ligand and secreted cytokines, such as IL-21, is required for most antigens. In addition, in some forms of SCID the B cells that are present may have intrinsic functional defects, such as a lack of cytokine responsiveness, that further compromise B-cell function.[10] There is variable loss of NK cell numbers, depending on the specific defect (Table 105.1).[1,2,9]

TABLE 105.1

Clinical Characteristics of Some Well-Defined Forms of Severe Combined Immunodeficiency

Syndrome/Gene Defect(s)/Mode of Inheritance	Gene Product Function	Mechanism of Immunodeficiency	Effect on Lymphocyte Numbers and Function	Characteristic N –Infection-Relat Features
Common gamma chain (IL-2 receptor gamma chain) deficiency/*IL2RG*/X-linked	Component of IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 receptors	Lack of IL-7 signaling leads to ↓↓ thymocyte development; lack of IL-15 signaling arrests NK cell development	↓↓ T and NK; nl B but nonfunctional	None
JAK-3 deficiency/*JAK3*/AR	Signaling of cytokine receptors that use γc	Same as for *IL2RG* deficiency	Same as for *IL2RG* deficiency	None
IL-7 receptor α chain deficiency/*IL7R*/AR	Specific component of IL-7 receptor	Same as for *IL2RG* except that intact IL-15 function allows NK cell development	↓↓ T; nl NK and B	None
RAG-1 or RAG-2 deficiency/*RAG1* or *RAG2*/AR	Enzymes required for TCR and Ig gene rearrangement	↓↓ T- and B-cell precursors	↓↓ T and B; nl NK	None
Artemis deficiency/*DCLRE1C*/AR	Required for DNA repair process involved in TCR and Ig gene rearrangement	↓↓ T and B precursors	↓↓ T and B; nl NK	Radiation sensiti
MHC class II	Transcription	↓ Intrathymic	↓ or ↓↓ CD4	None

deficiency/*CTIIA, RFX5, RFXANK*, or *RFXAP*/AR	of MHC class II (HLA-DR, -DP, and -DQ) genes	maturation of CD4$^+$CD8$^-$ lineage cells and ↓↓ antigen presentation to peripheral CD4 T cells	T; nl or ↑ CD8 T; nl NK and B	
ZAP-70 kinase deficiency/*ZAP70*/AR	TCR signaling of thymocytes and T lymphocytes	↓ Intrathymic development of CD8$^+$ T cells; CD4$^+$ T cells have ↓↓ function	↓↓ CD8$^+$ T; nl or ↑ CD4$^+$ T; nl B and NK	None
Cartilage hair hypoplasia (CHH) syndrome/*RMRP*/AR	*RMRP* encodes an RNA that is component of mitochondria	RMRP RNA/protein required for normal thymocyte growth	↓ to ↓↓ T – SCID only occurs with severe ↓↓	Absence of scalp eyebrow hair, sh limb dwarfism
Adenosine deaminase deficiency/*ADA*/AR	Enzyme in purine salvage pathway	Thymocytes, immature B cells, and NK cells die from toxic effects of accumulated purine metabolites	↓↓ T and B in infantile-onset cases; ↓ NK cells	Rachitic flaring c costochondral junctions (50% o infantile-onset ca renal mesangial sclerosis
Purine nucleoside phosphorylase deficiency/*PNP*/AR	Enzyme in purine salvage pathway	Purine metabolites that accumulate are less toxic to B than to T cells	↓↓ T; variable ↓ in B with poor function	Central nervous system disorder autoimmune/alle disorders
Reticular dysgenesis/*AK2*/AR	Adenylate kinase 2 is an enzyme in the inner mitochondrial space required for hematopoietic stem cell development	Stem cell defect required for lymphocytes and granulocytes	↓↓ T, B, and NK ↓↓ PMNs	Bilateral sensorineural deafness
Omenn syndrome/biallelic hypomorphic deficiency of *RAG1* or *RAG2*, rarely *IL2RG, LIG4, IL7R, ADA, DCLRE1C, AK2, RMRP, ZAP70, CHD7, CARD11*	See RAG-1, RAG-2/AR	↓ T- and ↓↓ B-cell development; ↑ peripheral T cells with ↓↓ TCR repertoire	Nl or ↑ T cells with Th2 cytokine profile; ↓ regulatory T cells; ↓↓ B cells	Congenital or neonatal onset erythroderma, lymphadenopat hepatosplenome ↑↑ eosinophils a IgE

AR, autosomal recessive; B, B cell; HLA, human leukocyte antigen; Ig, immunoglobulin; IL, interleukin; MHC, major histocompatibility complex; NK, natural killer; nl, normal; ↓, moderately decreased; ↓↓, very decreased; ↑, moderately increased; PMN, polymorphonuclear leukocyte; SCID, severe combined immunodeficiency; TCR, T-cell receptor; T, T cell.

Specific Gene Defects and Their Inheritance Pattern

SCID can be due to single X-linked or biallelic AR gene defects[1,2,9] (the specific genes involved are indicated in italics) or, less commonly, to chromosomal abnormalities (e.g., complete DiGeorge syndrome).[11] Most types of SCID are due to gene defects with hematopoietic cell autonomous effects so that the disease can be cured by hematopoietic stem cell (HSC) transplantation or HSC-based gene therapy. X-linked SCID, the most common form of these hematopoietic cell autonomous defects, comprises about 50% of cases of SCID in most series and is due to deficiency of the common gamma chain gene (also known as the IL-2 receptor gamma chain gene [*IL2RG*]) encoded in the Xq13.1 region. The common gamma chain protein (CD132), along with the IL-7Rα chain (CD127), comprises the specific receptor for the cytokine IL-7, and a lack of functional IL-7 receptors on developing thymocytes results in their arrested development.[1,2,9] Deficiency of the common gamma chain protein also results in the loss of functional surface receptors for IL-2, IL-4, IL-9, IL-15, and IL-21 and compromises the ability of *IL2RG*-deficient B cells to receive IL-21–mediated help for immunoglobulin production.[7] Thymocyte deficiency of the IL-7Rα chain or of Janus kinase-3 (*JAK3*), which is associated with the common gamma chain, results in a form of SCID similar to *IL2RG* deficiency—except that these have an AR rather than an X-linked inheritance pattern.[1,2,9] SCID with an AR inheritance pattern also can be due to defects in the ability of the thymocyte TCRs to transmit survival signals to the thymocyte (e.g., deficiencies of CD3-δ [*CD3D*], CD3-ε [*CD3E*], TCR-zeta [*CD247*], zeta-associated protein of 70-kd kinase [*ZAP70*], *CD45*, or the proteins encoded by *ORAI1* or *STIM1* molecules that are involved in calcium signaling); defective thymocyte rearrangement of TCR genes (deficiencies of recombination activating gene proteins encoded by *RAG1* and *RAG2*, Artemis (*DCLRE1C*), Cernunos (*NHEJ1*), DNA ligase IV (*LIG4*), or DNA-dependent protein kinase catalytic subunit (*PRKDC*); increased thymocyte death from toxic effects of accumulated purine metabolites (deficiency of adenosine deaminase [*ADA*] or purine nucleoside phosphorylase [*PNP*]); a failure of the development of bone marrow hematopoietic cell precursors that normally colonize the thymus and give rise to thymocytes (reticular dysgenesis due to deficiency of adenylate kinase 2 [*AK2*]); and impaired expression of MHC class II molecules (deficiency of transcription factors encoded by *RFXAP*, *RFXANK*, *RFX5*, or *CIITA*), which are required for the intrathymic development of CD4 T cells from CD4$^+$CD8$^+$ thymocytes as well as antigen presentation to mature peripheral CD4 T cells.

Likely owing to variable expressivity of null mutations, AR SCID also can occur in some cases of the cartilage hair hypoplasia (CHH) syndrome[12] due to biallelic mutations of *RMRP*, (unpublished observations), which encodes an RNA involved in mitochrondrial RNA processing. SCID also can occur in some cases of immunodeficiency with multiple intestinal atresias due to biallelic mutations of the *TTC7A* gene,[13] which encodes a cytoplasmic protein that may be involved in phosphatidyl inositol signaling. Some genetic immunodeficiencies may result in substantial or even normal numbers of peripheral naïve T cells that have profound functional impairments, resulting in a SCID clinical presentation. A recent example is caspase recruitment domain 11 (CARD11) deficiency, in which there is normal production of T cells by the thymus that have profound defects in TCR activation of the NF-κB pathway.[14]

A few types of SCID are due to thymic epithelial cell abnormalities resulting in a secondary perturbation of thymocyte differentiation and proliferation. These include complete DiGeorge syndrome, which occurs in about 1% to 2% of cases of the hemizygous interstitial chromosome 22q11.2 deletion.[15] Biallelic mutations of *CHD7* (CHARGE syndrome: *c*oloboma, *h*eart defect, *a*tresia choanae, *r*etarded growth and development, *g*enital hypoplasia, *e*ar anomalies/deafness) also rarely can result in a complete DiGeorge syndrome–like clinical presentation.[16] Biallelic mutations of the gene encoding the forkhead box N1 (FoxN1) transcription factor also results in SCID due to perturbed thymic epithelial development.[1,2,9] These forms of SCID are currently treatable only by the allogeneic transplantation of thymic epithelium.[15,17]

Characteristic Infections

Even with the growing adoption of neonatal screening for SCID, it remains important for the clinician to be aware of the frequent initial presentation of SCID so that the diagnosis can be confirmed rapidly and potentially life-saving therapies, such as immune reconstitution, can be considered. SCID disorders typically manifest early in infancy with infections caused by opportunistic organisms or with severe or protracted infections caused by common pathogens, especially viruses.[9,18,19] The infectious complications of SCID are similar regardless of the particular genetic defect and reflect a failure of T cells and, in some cases, NK cells to control and ultimately eliminate intracellular viruses in these and other tissues. Infections due to adenovirus, enterovirus, parainfluenza and influenza viruses, respiratory syncytial virus (RSV), and herpesviruses, such as cytomegalovirus (CMV), herpes simplex virus (HSV), and varicella-zoster virus (VZV), can be severe, with marked pulmonary, hepatic, or central nervous system involvement.[9,18,19] Failure to thrive is a prominent manifestation in most patients and usually is due to persistent gastroenteritis from common pathogens, such as rotavirus, adenovirus, enteroviruses, or norovirus. SCID patients also have increased risk for complications from live vaccines, such as paralytic disease from oral poliovirus vaccine and diarrhea due to persistent vaccine-acquired rotavirus infection.[20]

Fungal infections, which are suggestive of severe CD4 T-cell immune deficiency, include persistent and severe mucocutaneous candidiasis and *Pneumocystis jirovecii* pneumonia (PCP). *Pneumocystis* infection always should prompt a comprehensive search for SCID or another primary immunodeficiency involving CD4 T cells.

Severe bacterial infections with pathogens that have a predominant intracellular presence, such as *Legionella, Listeria, Mycobacterium* (e.g., after vaccination with bacille Calmette-Guérin [BCG]),[21] and *Salmonella* can occur and illustrate the requirement for CD4 T-cell−mediated immunity in control of these pathogens. Other gram-negative bacteria, such as *Pseudomonas, Serratia, Klebsiella,* and *Escherichia coli,* also have been reported as causes of infection even before hematopoietic cell transplantation,[22] and this may be explained by defects in Th17 cells.[5] Some cases of SCID can be complicated before transplantation by hemophagocytic syndrome,[22] which can include neutropenia that increases the risk for invasive bacterial disease, such as gram-negative septicemia. As maternally derived immunoglobulin G (IgG) level decreases over the first several months of life, patients develop marked and persistent hypogammaglobulinemia and have increased risk for recurrent sinopulmonary infections from encapsulated bacteria, such as *Streptococcus pneumoniae* and *Haemophilus influenzae.*

Routine neonatal screening for SCID using Guthrie card blood spots for measurement of signal joint T-cell receptor excision circles (sjTRECs) is now being carried out in most states of the United States.[8] Results typically are available by approximately 3 weeks of age, after which confirmed SCID patients can be put into some form of protective isolation, treated with prophylactic antimicrobial agents to prevent infections (e.g., PCP) and begun on immunoglobulin replacement therapy. However, because CMV frequently is acquired during vaginal delivery or by breastfeeding, the current screening process will not be able to prevent the acquisition of CMV in all cases of SCID.[23]

In addition to infectious complications, some infants with SCID develop a skin rash and other organ dysfunction, such as hepatitis and gastrointestinal inflammation, from graft-versus-host-disease (GvHD). GvHD is mediated by T cells acquired transplacentally from the mother or from unirradiated blood transfusions, especially whole blood or platelets. Such maternally derived T cells also can cause hemophagocytic syndrome in untransplanted SCID patients.[22] Severe GvHD also should be distinguished from Omenn syndrome (OS), a form of SCID that classically is due to biallelic hypomorphic (i.e., not null) mutations of either *RAG1* or *RAG2*, but also can occur in cases of SCID due to other gene deficiencies, including *IL2RG*, *LIG4*, *IL7R*, *ADA*, *DCLRE1C*, *AK2*, *RMRP*, *ZAP70*, *CHD7*, and *CARD11*.[24,25] Patients with OS often have extensive erythroderma, which resembles primary dermatologic conditions, such as Netherton syndrome, lymphadenopathy, hepatosplenomegaly, and failure to thrive. OS due to hypomorphic *RAG* mutations typically includes marked peripheral eosinophilia, highly elevated serum levels of IgE, increased levels of CD4 T cells producing Th2-type cytokines (IL-4, IL-5, and IL-13), and markedly reduced peripheral CD8 T cells and B cells.[24]

About one third of infant patients with complete DiGeorge syndrome have an atypical course in which an OS-like syndrome of erythroderma that may be accompanied by enteritis and hepatitis occurs starting at several months of age.[15] The OS-like syndrome coincides with the appearance of increased numbers of circulating oligoclonal T cells that are produced by the infant (and not the mother). These T cells are highly activated, express memory/effector markers, (i.e., CD45RO^{high} CD45RA^{low}), and appear to be autoreactive against the skin, gastrointestinal tract, liver, and potentially other organs.

Diagnosis

A history of other family members who experienced severe or recurrent infections in infancy or who died of unknown cause is suggestive of the diagnosis. However, a substantial number of cases of SCID, even cases of X-linked disease, result from new mutations, in which case the family history is not informative. Because SCID usually is due to severe thymic hypoplasia, there typically is a reduced or absent thymic shadow on imaging studies. Exceptions may include *CORO1* or *CARD11* deficiency. In cases of early-onset adenosine deaminase (ADA) deficiency, lateral chest radiograph also can reveal the rachitic-like flaring of the costochondral junctions. On physical examination, peripheral lymph node tissue typically is reduced, although there are exceptions, such as in OS, in which lymphadenopathy and hepatosplenomegaly are common. In a minority of cases, findings point to a specific disorder (e.g., the findings of short-limbed dwarfism and the absence of eyebrows and hair in the CHH syndrome [*RMRP* deficiency], the absence of hair in deficiency of *FOXNI*, or the characteristic facies and congenital heart disease typical of DiGeorge syndrome; see Table 105.1).

In most cases of SCID, a complete blood count reveals a reduced absolute lymphocyte count (ALC) for age. This finding in early infancy never should be ignored, even in a well-appearing infant, because it can lead to an early diagnosis of immunodeficiency. A severely reduced ALC is typical of forms of SCID that result in an arrest of both naïve T-cell and B-cell development, such as null mutations of *RAG* or ADA deficiency. A less severely decreased ALC is characteristic of forms of SCID due to defects of *IL7R* because this spares human B-cell and NK cell development (see Table 105.1). However, the ALC in some forms of SCID can be normal (e.g., some cases of X-linked SCID, MHC class II deficiency, and ZAP-70 deficiency) or even increased (e.g., some cases of ZAP-70 deficiency and most cases of OS). Normal or increased counts may reflect a compensatory increase in one lymphocyte population that masks the loss of another (e.g., the absolute increase in circulating numbers of CD4 T cells masking the absence of CD8 T cells in ZAP-70 deficiency) or a pathologic expansion (e.g., the marked expansion of a small population of activated CD4 T cells with a limited αβ TCR repertoire in OS or of CD4 T cells or CD8 T cells in maternal engraftment or in atypical complete DiGeorge syndrome). In these pathologic expansions, these oligoclonal T-cell populations uniformly express memory/effector markers (CD45RO) rather than the CD45RA isoform of naïve T cells.[15,22,24] Gene defects in which there is retention of residual function may also result in ALCs that are normal or even elevated. Therefore, regardless of the result of the ALC or T-cell subset analysis, if SCID is suspected clinically it is critical to enlist the help of a clinical immunologist so that appropriate tests can be performed to evaluate lymphocyte subpopulations (e.g., phenotype by flow cytometry), and T-cell function (e.g., mitogen- and antigen-induced proliferation, flow cytometric analysis of cytokine secretion capacity), specific gene sequencing, αβ TCR repertoire analysis, and determination of T-cell receptor excision circles if this has not already been performed as part of neonatal screening.

Treatment

After SCID is diagnosed and appropriate blood samples for total and antigen-specific immunoglobulin levels have been obtained, immune globulin intravenous (IGIV) usually is administered pending a definitive treatment plan. All live vaccines, including oral poliovirus vaccine, rotavirus vaccine, measles, mumps and rubella, varicella vaccine, vaccinia, BCG, and attenuated influenza vaccine and oral *Salmonella* Typhi vaccine, are contraindicated. IGIV therapy obviates the benefit of vaccination with “killed” vaccines (e.g., inactivated poliovirus vaccine) by providing passive antibody. Therefore, inactivated or protein/polysaccharide component vaccines, although safe in SCID and other immunodeficiencies, typically are not administered after IGIV therapy is begun. For ADA deficiency, specific enzyme replacement with polyethylene glycol–associated ADA (pegademase [Adagen]) is available but should only be used in consultation with an experienced immunologist. For most SCID patients, the early transplantation of HSCs contained in bone marrow, peripheral blood, or cord blood, ideally from an HLA-matched relative, is standard treatment for immune reconstitution. For certain disorders, HSC gene therapy has been successfully employed for SCID due to *ADA* deficiency using gammaretroviral vectors to insert a transgene into HSC progenitors followed by administration to the patient.[26] For *IL2RG* SCID, clinical gene therapy trials are underway using self-inactivating gammaretroviral vectors and lentiviral vectors.[26] These newer vectors appear to be safe and effective and avoid the potentially serious effects of dysregulation of endogenous genes near the viral insertion site using conventional gammaretroviral vectors that led to the development of T-cell lymphoid cancers in a number of gene therapy recipients.

Pneumonia in Severe Combined Immunodeficiency Disease

Pneumonia often is a presenting feature of SCID, as well as other serious disorders of T-cell immunity. Because virtually any microorganism can cause pneumonia in these hosts, it is imperative to establish a specific etiologic diagnosis, particularly if the patient shows signs of severe disease or deterioration. Some clinicians advocate initially relying on bronchoalveolar lavage to make a diagnosis, reserving thoracoscopic lung biopsy for those who do not have a prompt response to initial therapy and who lack a specific identified agent.[27] Others argue that early lung biopsy potentially can improve patient outcome and that delay in biopsy accounts for lack of its beneficial effect on survival.[28] (See discussion at end of reference 28.)

Selected Non–Severe Combined Immunodeficiency Disease Disorders of T Cells and Natural Killer Cells

Numerous non-SCID primary immunodeficiencies of T cells and/or NK cells can manifest with serious infections.[1,2] The genetic basis, clinical features (including infection predilection, diagnosis, and treatment of some of the better characterized classic disorders), and infectious disease presentations are discussed next and summarized in Table 105.2.

TABLE 105.2

Genetic and Clinical Features of Selected T-Cell and Natural Killer Cell Immunodeficiencies

Syndrome/Gene Defect/Mode of Inheritance	Gene Product Function and Mechanism of Immunodeficiency	Characteristic Noninfectious and Immune Features	Characteristic
Ataxia telangiectasia/*ATM*/ biallelic autosomal recessive (AR)	Protects from radiation-induced chromosomal damage by cell cycle arrest, allowing DNA repair; impaired V(D)J recombination and antibody isotype switching	Progressive cerebellar ataxia, bulbar and cutaneous telangiectasia; cellular hypersensitivity to radiation; ↓ IgA, IgM, T cells	Severe sinopu infections and bronchiectasis occasionally opportunistic T-cell immun is severe
Autoimmune polyendocrinopathy–candidiasis–ectodermal dysplasia (APECED) syndrome/*AIRE*/biallelic AR	Elimination of autoreactive thymocytes in thymic medulla, which if allowed to survive can contribute to autoimmunity	Autoimmune endocrinopathies, hepatitis, vitiligo, keratopathy; ↓ Th17 and Th22 immunity due to autoantibodies against IL-17A, IL-17F, and IL-22	Chronic muco candidiasis (
DiGeorge syndrome (DGS) /interstitial deletion of chromosome 22q11.2/haploinsufficiency	Haploinsufficiency for the *TBX1* and *CRKL* genes result in hypoplasia of third and fourth branchial arch derivatives, including the thymus	Truncoconal congenital heart disease, characteristic facies, hypocalcemia; ↓ T cells (CD8 subset often ↓ more than CD4)	Usually asym T cells >500/μ DiGeorge syn (naïve CD45R T cells <50/μL manifest as S
Hyper-IgE–AD syndrome/*STAT3* /monoallelic AD	*STAT3* mutations that allow expression of mutated full-length protein inhibit the activity of STAT3 encoded by the normal allele	Eczema/dermatitis; osteoporosis, pathologic fractures, retention of deciduous teeth; coarse facies, joint hyperextensibility, aneurysms; ↑↑ IgE; ↓↓ IL-17– and IL-	*Staphylococcus* boils (↓ IL-22); pneumonia a empyema due and other bac 17); pneumat secondarily in *Aspergillus,* ot nontuberculo

		22–producing CD4 T cells	*Mycobacterium*
Hyper-IgE–AR syndrome/*DOCK8*/biallelic AR	*DOCK8* is involved in intracellular signaling and possibly in cell migration of multiple hematopoietic cell types	Eczema, dermatitis, ↑↑ IgE with allergies to drugs, foods; eosinophilia; ↓ T cells; ↓ Ig response to bacterial polysaccharides	Viral infection (HSV, VZV, H molluscum co CMC, PCP; re bacterial sino infections
Hyper-IgM syndrome/*CD154*/X-linked	Binds to CD40 and activates B cells and APCs; CD40 ligand/CD40 interaction required for generation of memory T and B cells, and isotype switching	Neutropenia and stomatitis common; normal or elevated IgM in 50% with ↓↓ serum IgG and IgA; poor specific antibody formation to protein antigens	Bacterial sino infections and parvovirus (↓ immunity); *Pr* *Cryptococcus,* *Cryptosporidiu* *Toxoplasma,* Cl T-cell immuni
IL-17 pathway disorders/*ACT1, IL17F, IL17RA, IL17RC, RORC, STAT1* (GOF), *STAT3* (AD)/mostly biallelic AR; *STAT1* and *STAT3* monoallelic	Genes of this pathway are involved in the generation and function of T cells that produce IL-17A and IL-17F	Deficiency of IL-17–producing T cells (deficiencies of *IL17F, RORC,* GOF *STAT1,* AD *STAT3*) or lack of responsiveness to IL-17A and IL-17F (deficiencies of *IL17RA, IL17RC, ACT1*)	CMC
IFNγ receptor deficiency/*IFNGR1* or *IFNGR2* genes/mostly biallelic AR	Specific cell surface receptor for IFNγ, a potent activator of mononuclear phagocytes	Poor granuloma formation in response to mycobacterial infections	Disseminated nontuberculou *Mycobacterium* *Salmonella, Lis* *Toxoplasma*; re and respirator infections?
IL-12 or IL-12 receptor chain deficiency/*IL12B* or *IL12RB1*/biallelic AR	IL-12p40 is a component of IL-12p70 and IL-23, which respectively induce Th1 (IFNγ) and Th17 (IL-17A and IL-17F) immunity by CD4 T cells	Granuloma formation in response to mycobacterial infection is normal	Nontuberculo mycobacteria, disseminated *Salmonella, Lis* (mild and onl patients)
***NEMO* mutation with immunodeficiency/*IKBKG* /X-linked hypomorphic mutations**	Impaired activation of the NF-κB transcription factor impairs innate (e.g., NK cell function) and adaptive immunity by T and B cells	Hypohidrosis; conical/peg teeth, oligodontia, delayed tooth eruption; ↓ T-cell –specific and ↓↓ specific antibody responses; ↓ NK cell–mediated cytotoxicity	Disseminated nontuberculou *Mycobacterium* positive or gra bloodstream i sinopulmonar severe herpes infections; *Pne*
NK cell	Transcription	Lack of NK cells	Severe primar

deficiency/*GATA2*/haploinsufficiency (monoallelic AD)	factor regulates Unknown; lack of NK results in initially severe herpesvirus infections until T-cell immunity develops	based on CD16 and CD56 staining; may progress to involve other cell lineages, e.g., B cells and monocytes; aplastic anemia; hemophagocytic syndrome; (HPV-induced cancers	HSV, and CM but no ↑ in rec infection with viruses; HPV
Wiskott-Aldrich syndrome/*WASP*/X-linked	Regulates leukocyte cytoskeletal function; required for normal function of T cells, B cells, and APCs, including dendritic cells	Thrombocytopenia with decreased mean platelet volume; eczema; IgA-mediated autoimmune disease; ↑ IgA and IgE, ↓ IgM and antigen-specific B cell responses	Recurrent sin infections, her infections, EB lymphoprolife disease; *Pneu* *Aspergillus,* C
X-linked lymphoproliferative syndrome/*SH2D1A*/X-linked	Lymphocyte signal transduction molecule involved in T-cell and NK cell function	Lymphoid neoplasm can occur in the absence of EBV infection (rare)	Primary EBV with fulminan hemophagocy syndrome, ne later hypogammag

AD, autosomal dominant; APC, antigen-presenting cell; AR, autosomal recessive; BCG, bacille Calmette-Guérin; CMC, chronic mucocutaneous candidiasis; CMV, cytomegalovirus; EBV, Epstein-Barr virus; GOF, gain-of-function; HPV, human papillomavirus; HSV, herpes simplex virus; hyper-IgE, hyperimmunoglobulin E; IFN, interferon; Ig, immunoglobulin; IL, interleukin; MHC, major histocompatibility complex; nl, normal; PCP, *Pneumocystis jirovecii* pneumonia; PML, polymorphonuclear leukocyte; SCID, severe combined immunodeficiency; TCR, T-cell receptor; VZV, varicella-zoster virus; ↓, moderately decreased; ↓↓, very decreased; ↑, increased; ↑↑, markedly increased.

Adenosine Deaminase and Purine Nucleoside Phosphorylase Deficiency (Late Onset)

ADA, or purine nucleoside phosphorylase (PNP) deficiency, should be considered in HIV-negative patients of any age, including adults, in whom there is unexplained lymphopenia and recurrent infections. Notable infections include recurrent sinopulmonary disease, pneumonia, bacteremia, severe local papilloma infections, and recurrent herpes zoster. Late-onset infections associated with allergic or autoimmune hematologic disorders suggest partial enzyme defects.[29]

Ataxia-Telangiectasia

Ataxia-telangiectasia (AT) is an AR progressive disorder with cerebellar degeneration and a high risk for cancer due to biallelic mutations of the *ATM* (ataxia-telangiectasia mutated) gene. About two thirds of patients also develop immunologic dysfunction, which includes reduced antibody responses to polysaccharide antigens, such as unconjugated pneumococcal polysaccharide vaccine (PPV23) absent IgA in serum, and progressive loss of T cells. Patients frequently have severe and recurrent bacterial sinopulmonary infections, which likely is a reflection of markedly decreased antibody-mediated immunity.[30] Infections typical of compromised T-cell immunity are unusual, although reduced T-cell immunosurveillance may contribute to the high risk for EBV-related lymphoma. The *ATM* gene encodes a cytoplasmic protein that helps arrest the progression of the cell cycle after radiation, allowing DNA repair to be completed before resumption of cycling. This accounts for the unusual sensitivity of AT patients to radiation-induced chromosomal breakage and the development of neoplasms. The *ATM* gene product also is required for normal rearrangement by V(D)J recombination of T-cell receptor and immunoglobulin genes. The serum concentration of α-fetoprotein usually is elevated and is a useful screening test for AT. Treatment is problematic because the immunodeficiency and neurologic disease are progressive and the risk for developing cancer is high.

Autoimmune Polyendocrinopathy–Candidiasis–Ectodermal Dysplasia Syndrome

Chronic mucocutaneous candidiasis is an invariable component of the autoimmune polyendocrinopathy–candidiasis–ectodermal dysplasia (APECED) syndrome, also known as *autoimmune polyglandular syndrome type 1*, an AR disorder. The APECED syndrome can include autoimmune-mediated hypocortisolism, hypoparathyroidism, hypothyroidism, growth hormone abnormalities, hypogonadism, hepatitis, and vitiligo as well as corneal and nail abnormalities. Chronic, intractable *Candida* infection of the oral mucosa, fingers, toes, and face is frequent,[31] and occasional patients have disseminated fungal infection. Prolonged antifungal therapy and prophylaxis are the mainstay of treatment. The APECED syndrome is due to a defect in the autoimmune regulator (*AIRE*) gene, and specific diagnosis is based on DNA sequence analysis. The *AIRE* gene is required for optimal transcription of genes encoding self-proteins by thymic epithelial cells of the thymic medulla so that developing T cells reactive with these self-proteins can be eliminated by a process known as *negative selection*. This may account for the frequent detection of T-cell −dependent autoantibodies against endocrine organ targets. The increased susceptibility to candidal infection, which often starts in early childhood, is explained at least in part by autoantibodies to the cytokines IL-17A, IL-17F, and IL-22,[32,33] all of which provide important protection against fungal infection. The rest of immunologic function usually is normal.

DiGeorge Syndrome due to Interstitial Deletions of Chromosome 22 (22q11.2 Deletion Syndrome)

Patients who are hemizygous for an interstitial deletion that includes the chromosomal 22q11.2 region typically have features of classic DiGeorge syndrome. These include moderate T-cell immunodeficiency due to reduced thymocyte production because of thymic epithelial defects; transient postnatal hypocalcemia secondary to hypoparathyroidism; truncoconal cardiovascular anomalies (found in 80% of patients), especially interrupted aortic arch, truncus arteriosus, and tetralogy of Fallot; and characteristic facial anomalies.[34] Peripheral α/β T cells appear to function normally in most respects. This probably accounts for the observation that patients with circulating T-cell counts in the range of 500 to 1500/µL usually do not show signs of immunodeficiency. In most moderately lymphopenic infants with this syndrome, the peripheral CD4 and CD8 T-cell counts normalize during the first year of life. However, the assay of antigen-specific T-cell responses is particularly important because peripheral T cells can undergo homeostatic expansion in a lymphopenic environment, giving the misleading impression that thymic function is relatively intact when actually it is substantially reduced. If such responses are normal, and the patient has a CD4 T-cell count of >400/μL, live vaccines appear to be well tolerated. Moderately lymphopenic patients are at an increased risk for autoimmune hematologic and other diseases in later childhood, suggesting that the thymic defect includes limitations in the induction of T-cell tolerance or its maintenance by regulatory T cells. A small fraction of cases (<2%) can result in severe thymic hypoplasia or aplasia, so peripheral naive (CD45RA^{high}CD62-L^{high}) T-cell counts are persistently <50/μL. These patients typically have SCID-like manifestations with severe infections (see Table 105.1). In this case, immune reconstitution by thymic transplantation[15] may be effective.

Hyperimmunoglobulin E–Autosomal Dominant Syndrome

Most cases of the hyperimmunoglobulin E (hyper-IgE)−autosomal dominant (AD) syndrome are due to heterozygosity for loss-of-function mutations of the *STAT3* gene that allow protein expression.[35] These patients have a clinical triad of markedly elevated levels of IgE, recurrent pulmonary and skin infections, and eczema (the onset of the rash typically occurs in the neonatal period). Pneumonia due to *Staphylococcus aureus* and other bacteria, such as *S. pneumoniae* and *H. influenzae,* often results in a striking amount of disease but a relative lack of symptoms, such as cough and fever. Pneumonias often are complicated by the development of empyema, pneumatocoeles, and bronchiectasis. The pneumatocoeles and bronchiectatic airways often serve as sites for secondary infection with fungi, such as *Aspergillus,* or with nontuberculous *Mycobacterium* spp. The eczematous rash usually is present in the neonatal period, and skin furunculosis with *S. aureus* is invariably part of the syndrome. The predisposition to *S. aureus* pneumonia is likely due to impaired development of Th17 cells, and the predisposition to skin infections likely reflects a lack of CD4 T cells producing IL-22 (Th22 cells).[35] Children with hyper-IgE–AD syndrome frequently also have retention of their primary teeth beyond the usual age of exfoliation and joint hyperextensibility.

They also develop coarse facies, osteoporosis, and pathologic fractures, particularly after childhood, and are at risk for a variety of vascular abnormalities, including aneurysms.

Hyperimmunoglobulin E–Autosomal Recessive Syndrome (DOCK8 Deficiency)

Most cases of autosomal recessive hyper-IgE syndrome are due to biallelic mutations of the *DOCK8* (dedicator of cytokinesis 8) gene resulting in a combined immunodeficiency with impairment of both T-cell and B-cell function.[35] DOCK8 is an intracellular protein involved in cell signaling, but its normal role in immune function remains poorly understood. DOCK8-deficient patients have markedly elevated levels of IgE, usually eosinophilia, and invariably severe eczema that is often superinfected with gram-positive bacteria, sometimes resulting in skin abscesses. Susceptibility to viral infections of the skin is characteristic, including herpesviruses (HSV, VZV), human papillomavirus (HPV), and molluscum contagiosum virus.[36] DOCK8 deficiency results in progressive loss of naïve T-cell numbers with aging due to reduced thymic output of new T cells, which is accompanied by a progressive risk for developing classic opportunistic infections, such as chronic mucocutaneous candidiasis, PCP, or cryptococcosis. B-cell function is impaired, and low total serum IgM is characteristic. The antibody responses to PPV23 is minimal, and this impaired antibody response to encapsulated organisms likely contributes to the observed susceptibility to recurrent upper respiratory tract infections, such as otitis media and sinusitis, and pneumonia due to gram-positive and gram-negative bacteria. In contrast to hyper-IgE−AD syndrome, DOCK8-deficient patients are at a high risk for developing cancer, both hematologic and epithelial, and they should be considered for early HSC transplantation.

Hyperimmunoglobulin M Syndromes

The hyper-IgM syndromes have the frequent findings of elevated serum level of IgM and low levels of other immunoglobulin isotypes, particularly IgG.[37] The classic X-linked form of disease is due to genetic deficiency in CD40 ligand, a surface protein that is expressed at high levels by activated CD4 T cells. The interaction between CD40 ligand on the CD4 T cells and the CD40 molecule on dendritic cells, mononuclear phagocytes, and B cells is essential for many adaptive immune responses, but this interaction is not required for normal T-cell or B-cell development. Patients have severe qualitative defects in B-cell function and a partial but important qualitative defect in T-cell function. Markedly reduced B-cell function frequently results in recurrent sinopulmonary infections with encapsulated bacteria and rarely results in chronic parvovirus-induced anemia or enteroviral meningoencephalitis. These patients are extremely susceptible during infancy to PCP, an indication of the importance of CD40 ligand produced by CD4 T cells in the normal control of this fungus. A variety of other infections indicative of T-cell immunodeficiency have also been reported, including hepatobiliary infection with *Cryptosporidium,* cryptococcal meningitis, disseminated histoplasmosis, oral candidiasis, disseminated toxoplasmosis, severe CMV disease, and progressive multifocal leukoencephalopathy due to JC virus. Because the numbers of T and B cells (and ALC) are normal, diagnosis requires assaying for functional CD40 ligand surface expression on activated CD4 T cells using flow cytometry. Another frequent abnormality is neutropenia, which may be due to antineutrophil autoantibodies. Oral ulcers often accompany neutropenia but can occur independently. Patients should be treated with IGIV and should receive PCP prophylaxis. Some cases of severe neutropenia may respond to treatment with granulocyte colony-stimulating factor. Prognosis is poor even with these therapies; approximately 50% of patients die by the fourth decade of life. Transplantation of HSCs from bone marrow, cord blood, or peripheral blood is curative of all features of the disease.

The hyper-IgM syndrome also can occur in an AR inheritance pattern due to biallelic CD40 genetic deficiency. This is rare but clinically indistinguishable from its X-linked counterpart except that girls and boys are affected equally. The identical immunologic phenotype and clinical consequences for CD40 ligand and CD40 deficiency is consistent with CD40 being the only biologically important receptor for CD40 ligand. Other forms of AR hyper-IgM syndrome do not result in T-cell immunodeficiency but are associated with selective B-cell intrinsic defects in isotype switching and somatic hypermutation of immunoglobulin genes. These include defects in two enzymes, activation-induced cytidine deaminase (AID), and uracil *N*-glycolyase (UNG).[37] Patients with AID or UNG deficiency are predisposed to recurrent sinopulmonary and gastrointestinal infections associated with severe antibody deficiency, but are not susceptible to severe infections with intracellular pathogens, such as PCP.

Impaired T Helper 1 Immunity

Th1 CD4 T cells produce IFNγ in response to their TCR engaging specific antigen. The secreted IFNγ binds to specific IFNγ receptors, which are heterodimers encoded by the *IFNGR1* and *IFNGR2* genes expressed on the surface or target cells, such as mononuclear phagocytes. This leads to activation of homodimers encoded by *STAT1* and the enhancement of their antimicrobial activity by STAT1-dependent transcription.[5,38] Th1 cells are derived from naïve CD4 T-cell precursors that receive critical differentiation signals from cytokines produced by dendritic cells and other APCs, particularly IL-12p70, a heterodimer that consists of a p35 and p40 subunit respectively encoded by *IL12A* and *IL12B*. IL-12p70 binds to its specific receptor, which is also a heterodimer that is encoded by *IL12RB1* and *IL12RB2*, leading to Tyk2 tyrosine kinase-dependent STAT4 activation and the induction of Tbet, a master transcription factor for Th1 differentiation encoded by the *TBX21* gene.[5,38,39] Infections with nontuberculous relatively avirulent mycobacteria or dissemination after BCG immunization are the hallmark of human Th1 immune deficiencies and have been observed in patients with mutations of *IFNGR1*, *IFNGR2*, *STAT1*, *IL12B*, *IL12RB1*, and *TYK2*.[38,40] In addition, biallelic mutations of a transcription factor encoded by the *RORC* gene have also been associated with infection with avirulent *Mycobacterium*, and in this case there is not general impairment Th1 immunity but rather a specific inability of T cells to produce IFNγ in response to mycobacterial antigens.[41] *IL12B* or *IL12RB1* deficiency predominantly presents with disseminated (extraintestinal) *Salmonella* infection, and, to a lesser degree with *Mycobacterium* infection. The exquisite sensitivity of *IL12B*- or *IL12RB1*-deficient patients for disseminated *Salmonella* infection is not completely understood but likely reflects the importance of a synergy between IL-12p70 and host defense mechanisms mediated by IL-23 (a cytokine discussed subsequently). Other infectious agents that have been infrequently noted with IFNγ receptor defects include *Klebsiella*, *Legionella*, *Listeria monocytogenes*, *Mycoplasma*, *Toxoplasma gondii*, and herpesviruses (CMV, VZV, HSV).[38] In patients with acquired neutralizing autoantibodies for IFNγ, a similar pattern of infections is observed with predominance of weakly virulent mycobacteria and, less frequently, nontyphoidal *Salmonella* infections. In addition, these IFNγ autoantibody patients have also been reported to have more frequent infections with *Penicillium*, *Histoplasma*, *Cryptococcus*, and *Burkholderia* spp. and *Toxoplasma gondii* and to have higher frequency than expected for age of both dermatomal and disseminated VZV reactivation.[4]

Impaired T Helper 17 Immunity

Activated Th17 CD4 T cells produce IL-17A, IL-17F, and IL-22. These cytokines, which are also produced by a number of other subsets of T cells, such as γ/δ T cells, and ILCs promote granulocyte colony-stimulating factor–dependent neutrophil production by the bone marrow, the induction of chemokines that chemoattract neutrophils to local sites of inflammation, and increased local epithelial expression of antimicrobial peptides, such as defensins.[5,42] Collectively, these effects provide important mucosal host defense against fungal infections, such as *Candida* spp. infections, and, based on mouse models, also may provide protection against gram-negative bacterial pneumonia. Secreted IL-17A and IL-17F homodimers and IL-17A/IL-17F heterodimers bind a specific heterodimeric receptor encoded by the *IL17RA* and *IL17RC* genes,[42] and IL-22 binds to a specific heterodimeric receptor consisting of the IL-22R1 consisting of IL-10R2 chains. Engagement of the IL-17 receptor leads to activation of the receptor-associated ACT1 cytoplasmic protein that signals through pathways, such as NF-κB, leading to proinflammatory gene expression.[42] IL-22 receptor engagement leads to the tyrosine phosphorylation and activation of cytoplasmic STAT3, which translocates to the nucleus to induce gene transcription. The differentiation of Th17 cells from naïve CD4 T cells involves a number of cytokines produced by local APCs, including IL-23, IL-1β, IL-6, and transforming growth factor-β. IL-23 is a heterodimeric cytokine that consists of the IL-12p40 subunit and a p19 subunit that specifically binds to a heterodimeric specific receptor that is encoded by *IL12RB1* and *IL-23R,* leading to tyrosine phosphorylation and activation of STAT3 and STAT4.[42] IL-23 signaling helps maintain Th17 cell identity, which depends on the master transcription factor RORγt, which is one of two isoforms encoded by the *RORC* gene.[42] The hallmark infection of genetic disorders of Th17 immunity is chronic mucocutaneous candidiasis (CMC), an infectious complication that has been observed with mutations of *IL17F*, *IL17RA*, *IL17RC*, *ACT1*, *STAT3* (see earlier section "Hyperimmunoglobulin E–Autosomal Dominant Syndrome"), *IL12B*, *IL12RB1,* and *RORC*.[41,43] In the case of *IL12B* and *IL12RB1* deficiencies, which modestly affect Th17 immunity by abrogating IL-23 signaling, CMC is relatively mild and only affects about 30% of these patients, whereas disseminated *Salmonella* is a prominent complication in most patients. The fact that disseminated *Salmonella* is not a complication of "pure" IL-17 pathway defects, such as *IL17F*, *IL17RA*, *IL17RC*, and *ACT1*, suggests that IL-23 has a special role in contributing to *Salmonella* host defense that is independent of Th17 immunity. Interestingly, gain-of-function mutations of *STAT1* that result in its prolonged nuclear localization after cytokine engagement of receptors results in impaired STAT3 signaling, reduced Th17 effector CD4 T cells, and a vulnerability to CMC as well as other fungal pathogens.[43] The mechanism by which enhanced Th1 differentiation signals block Th17 development remains unclear. Finally, acquired autoantibodies to IL-17A, IL-17F, or IL-22 also result in CMC[4,43] and are the predominant mechanism for this infectious complication in *AIRE* deficiency (see earlier section "Autoimmune Polyendocrinopathy–Candidiasis–Ectodermal Dysplasia Syndrome").

Natural Killer Cell Deficiency

A few patients of both sexes have been identified with an apparent selective and complete deficiency of NK cells.[44] This selective defect in NK cells must be distinguished from a large number of primary immunodeficiencies in which there are NK cell functional defects and normal or moderately decreased numbers of NK cells.[44] Most of these patients have presented after infancy with initially severe primary herpesvirus infections, including VZV, HSV, and CMV, requiring intravenous antiviral drug therapy. After recovery from a particular herpesvirus infection, these patients do not experience an increased frequency of recurrent infection, indicating the development of durable viral-specific T-cell immunity (D. Lewis, unpublished observations). There is a complete absence of circulating NK cells, based on flow cytometry using the $CD16^+$ and $CD56^+$ markers, and absent in vitro NK cell activity in peripheral blood samples.[44] T-cell numbers and function appear to be normal in most cases, although in at least 1 patient there was also evidence of progressive loss of B-cell dysfunction with recurrent pneumonia and a poor response to PPV23 (D. Lewis, unpublished observations). Genetic sequencing indicates that a substantial fraction of patients may have haploinsufficiency for the GATA2 transcription factor.[44] IGIV has been used for therapy because theoretically this can increase antiviral function of cells other than NK cells, such as neutrophils and monocytes.

NF-κB Essential Modulator Mutation With Immunodeficiency

The NF-κB essential modulator (NEMO) protein is encoded on the X chromosome by the *IKBK* (*i*nhibitor of *k*appa *l*ight *p*olypeptide *g*ene *e*nhancer in *B* cells, *k*inase *g*amma) gene and plays a critical role in the activation of the NF-κB protein by facilitating its release from the inhibitor of NF-κB (IκB) protein complex. NEMO immunodeficiency occurs in boys with hypomorphic mutations of *IKBK*; null mutations are lethal for the embryo. Ectodermal dysplasia, including hypohidrosis, sparse hair, conical or peg-shaped teeth, oligodontia, or delayed tooth eruption, occur in >90% of cases and reflect impaired function of the ectodysplasin A receptor, which uses NF-κB for signaling. NF-κB activation also plays a central role in both innate and adaptive immune responses, including those downstream of engagement of members of the TNF receptor family (e.g., the TNF receptor and CD40), and of the antigen-specific TCR and BCR. Thus it is not surprising that the immunologic phenotype and predilection to infectious disease complications in hypomorphic *IKBK* deficiency are complex and vary depending on the particular mutation and its location within the coding region of the gene.[45] Decreased NF-κB–dependent signaling by toll-like receptors (TLRs), which can be evaluated by measuring the production by blood monocytes of cytokines such as TNF-α in response to TLR ligands (e.g., lipopolysaccharide), is observed with many mutations,[45] This block likely compromises the activation of mononuclear phagocytes and dendritic cells by pathogens and pathogen-derived products in vivo, which explains the susceptibility to sepsis caused by a variety of bacteria, including *S. pneumoniae, H. influenzae,* and *Listeria, Klebsiella,* and *Pseudomonas* spp.[46] Severe and disseminated infections with nontuberculous *Mycobacterium* spp. also are frequent and may reflect limitations in innate immunity, such as a lack of signaling by CD40 and TNF receptors.[46] PCP, CMV colitis, and severe herpesvirus infections also have been observed. NEMO-deficient NK cells often have markedly impaired natural cytotoxic activity, which may contribute to the severity of herpesvirus infections.[46] Finally, antibody responses to T-independent antigens, such as in PPV23, almost invariably are decreased and may be the only clinically evident abnormality with some mutations. Consistent with impaired CD40 signaling by B cells, some patients have a phenotype reminiscent of deficiency of CD40 ligand or of CD40 (i.e., increased levels of IgM and low levels of IgG and IgA).[45] Poor specific antibody responses, in combination with limitations in neutrophil function, likely contribute to the risk for bloodstream and other invasive infections caused by encapsulated organisms[46] and recurrent sinopulmonary infections.

Most patients have abnormalities of TLR function, which can be screened using assays such as lipopolysaccharide-induced production of TNF-α, and decreased NK cell–mediated cytotoxicity. Genetic sequencing is important for confirmation. IGIV replacement therapy is indicated routinely because of the severity of humoral immunodeficiency. HSC transplantation is curative for the immunodeficiency component of this disorder but may not correct enterocolitis, which most likely is a consequence of epithelial cell abnormalities of NF-κB signaling.

Wiskott-Aldrich Syndrome

Wiskott-Aldrich syndrome (WAS) is an X-linked disorder characterized by thrombocytopenia with small platelets, eczema of variable severity, and recurrent or severe infections due to mutations of the WAS protein gene *(WASP)*. Frequent immune abnormalities include naïve T-cell lymphopenia, particularly for CD8 T cells; impaired Th1 immune responses and regulatory T lymphocyte (Treg) activity; decreased NK cell activity; severely depressed antibody response to PPV23; moderately depressed response to protein antigens; low serum IgM levels; and elevated serum IgA and IgE levels.[47] IgE elevation, often accompanied by eosinophilia, presumably is associated with the atopic diathesis of these patients.

WASP is widely expressed by hematopoietic cells and involved in the regulation of the cytoskeleton during cell signaling in the cytoplasm and also regulates gene transcription in the nucleus involved in the generation of Th1 immune cells.[48] WASP deficiency appears to substantially but selectively compromise the intrinsic function of T cells, B cells, NK cells, and APCs.[47] In addition to recurrent pyogenic infections, especially otitis media, patients with WASP deficiency also are at increased risk for severe infection with certain viruses, particularly herpesviruses, such as VZV, HSV, and CMV,[47] and these patients appear to be at high risk for chronic recurrent infection with acyclovir-resistant HSV. Patients with complete WASP deficiency also can develop nonviral infections suggestive of severe compromised T-cell–mediated immunity, such as PCP, invasive *Aspergillus* infections, and severe CMC. A substantial fraction of patients with WASP deficiency eventually develop autoimmune vasculitis associated with deposition of IgA-containing immune complexes that has many similarities to Henoch–Schönlein purpura. Autoimmune manifestations can include intussusception, arthritis, and nephritis. The increased risk for autoimmune disease may be multifactorial, with defective B-cell tolerance, decreased Treg activity, and dysregulated secretion of interferon type I by plasmacytoid dendritic cells as contributing factors.[47] Bleeding can be severe or life-threatening in cases with profound thrombocytopenia. Splenectomy may be helpful in raising platelet counts, but this also increases the risk for life-threatening septicemia. Patients with WASP deficiency are at high risk for developing malignancy, especially lymphomas, starting after the second decade of life.

The diagnosis usually is evident, is based on the distinct features of the syndrome, can be screened for by evaluating intracellular expression of WASP using flow cytometry, and can be confirmed genetically by DNA sequencing of the *WASP* genetic locus. Immune reconstitution by HSC transplantation is curative of all disease manifestations and appears to have the best outcome if performed early in life. Gene therapy using lentiviral vectors is a promising therapeutic alternative.[47]

X-Linked Lymphoproliferative Disease and Other Genetic Immunodeficiencies With Selective Susceptibility to Severe Epstein-Barr Virus Infection

XLP disease is an X-linked immunodeficiency of males that affects T cells and B cells and is due to a mutation in the *SH2D1A* (SH2 domain protein 1A) gene.[49] The *SH2D1* gene encodes SAP (SLAM-associated protein), a cytoplasmic protein associated with the SLAM receptor (CD150) that is involved in T-cell and NK-cell signal transduction. The immunodeficiency usually is silent clinically until primary infection with EBV results in a fatal infectious mononucleosis syndrome in about 50% to 60% of cases; a lymphoproliferative disorder, including malignant lymphoma in about 25 to 30% of cases; or persistent dysgammaglobulinemia with decreased levels of IgG in about 30% of patients. Rarely, genetically affected individuals develop either lymphoma or dysgammaglobulinemia without prior EBV infection.

The mean age at development of infectious mononucleosis is about 5 years, and infection usually is accompanied by severe hepatitis with periportal lymphocytic infiltration and bone marrow dysfunction with accompanying viral-associated hemophagocytic syndrome. In cases of hemophagocytosis, there are highly activated mononuclear phagocytes, many of which have internalized red blood cells in the bone marrow, lymph nodes, liver, and spleen (see Chapter 12). Meningoencephalitis also is common. Although there are no simple screening tests for diagnosis of this disorder, an absence of invariant NK T cells, a T-cell population that has some features of NK cells and a characteristic T-cell receptor, is suggestive but not pathognomonic of the disorder.[49] The diagnosis of XLP can be established definitively by analysis of SAP protein expression or of the *SH2D1A* gene sequence. Patients with post-EBV hypogammaglobulinemia are treated with IGIV. The prognosis without definitive treatment, such as HSC transplantation, is poor, with most patients dying before 40 years of age.

In addition to *SH2D1A* gene deficiency, there are a number of other more recently identified primary immunodeficiencies that characteristically present with severe EBV infection but not with infectious complications from other viruses. These include disorders due to mutations in the *BIRC4*, *CD27*, *CORO1A*, *ITK*, *LRBA*, and *MAGT1* genes.[50] Most of these disorders are associated with a markedly increased risk for EBV-induced lymphoproliferative disease and lymphoma.

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Infectious Complications in Special Hosts

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Sickle Hemoglobinopathy

The decrease in splenic function in young children with hemoglobin SS (Hb SS) disease results in increased susceptibility to fulminant bacterial infection, especially in early childhood. Since the recognition in the 1970s that rates of septicemia and meningitis due to *Streptococcus pneumoniae* were excessive in patients with sickle cell disease,[1] and with the evolution of pneumococcal vaccines, mortality and morbidity due to pneumococcal disease have decreased substantially.[1–3] Retrospective studies reported rates of invasive infection in children 0 to 10 years of age with Hb SS disease, before licensure of pneumococcal conjugate vaccine (PCV), to be 63.4 cases per 1000 person-years. More striking, mortality rates due to pneumococcal infections in US children with Hb SS disease were as high as 100 times that in the general population.[4] Patients with less severe hemoglobinopathies (sickle cell hemoglobin C [Hb SC] disease, sickle cell thalassemia [Hb S-thalassemia]) appear to have risk for severe pneumococcal disease that is lower than patients with more severe hemoglobinopathies, although still higher than that of otherwise healthy children.[5,6] Bone and joint infections are relatively more common in patients with hemoglobinopathies, and *Salmonella* spp. are isolated from these infections with greater frequency.[7,8]

Etiologic Agents

Encapsulated organisms such as *S. pneumoniae, Haemophilus influenzae* type b (Hib), *Neisseria meningitidis,* and *Salmonella* spp. are historically among the most common pathogens in patients with sickle cell disease.[9,10] In African countries, infections with *Staphylococcus aureus, Escherichia coli,* and *Salmonella* and *Klebsiella* spp. predominate, and *S. pneumoniae* is responsible for fewer cases of infection than previously reported.[11] The incidence of Hib infections in the United States has dropped to very low levels since the introduction of Hib conjugate vaccines in infancy.[12] Other microbes with special significance for patients with Hb SS disease are *Edwardsiella tarda,*[13] *Yersinia enterocolítica,*[14] *Mycoplasma* spp.,[15] *Chlamydophila* spp.,[16,17] and parvovirus B19.[18,19]

Epidemiology

Several studies of the natural history of Hb SS disease in the US, Saudi Arabia, and Jamaica have demonstrated increased mortality in young children: rates of pneumococcal infection have been 20-fold to 100-fold higher than in unaffected children in the first 5 years of life.[4,20] A study in Kenya reported an age-adjusted odds ratio for bloodstream infection (BSI) in children with Hb SS of 26 (95% confidence interval [CI], 14–48), with pneumococcus, *Salmonella,* and Hib disease documented most commonly.[21] Persistence of fetal hemoglobin is associated with fewer episodes of infection. Nasopharyngeal carriage rates and serotypes of pneumococci infecting children with Hb SS disease have been similar to those infecting unaffected hosts.[3,22] Due to the frequent use of antimicrobial agents, close contact with many children in group childcare, and penicillin prophylaxis, up to 72% of the pneumococci colonizing children with Hb SS disease are penicillin nonsusceptible.[23,24]

Although infection was the major cause of death in a cohort of patients between the ages of 1 and 3 years with Hb SS who were monitored from 1979 to 1989, cerebrovascular accidents and trauma were more common causes in those older than 10 years.[25] Other life expectancy studies suggest that at least 50% of patients with Hb SS currently followed survive beyond the fifth decade and that mortality most often is related to renal failure, chest syndrome, or stroke rather than infection.[26,27] Overall mortality associated with BSI in children with Hb SS has been documented as up to 23%, with median survival estimated to be <5 years of age.[11]

The incidence of bacterial infection in Hb SC disease, although greater than that in healthy children, is less than that in Hb SS disease. Functional asplenia has been documented in adults with Hb SC by radionuclide liver-spleen scans or by quantification of pitted erythrocytes. In one series, 4 of 51 children with Hb SC observed for 370 person-years were found to have 7 serious but nonfatal bacterial infections.[5] A second report describes 7 fatal episodes of pneumococcal septicemia in patients aged 1 to 15 years with Hb SC.[6]

Pathogenesis and Pathology

The increased incidence and morbidity of infections due to encapsulated microorganisms in patients with sickle hemoglobinopathies are attributable primarily to splenic dysfunction. The spleen is important as a reticuloendothelial filter and is involved in processing bacterial antigens to promote helper T-lymphocyte and B-lymphocyte responses. Encapsulated organisms cannot be phagocytosed efficiently without opsonization; thus, presence of type-specific antibody is critical to clearance of organisms. The spleen and the liver (to a lesser extent) are important in clearing pneumococci from the blood. Additionally, activation of complement by the alternative pathway, critical for phagocytosis in the absence of specific antibody, may be altered in patients with Hb SS.

S. pneumoniae itself elicits a profound inflammatory response. Pneumococcal cell wall fragments trigger the expression of interleukin-1 and tumor necrosis factor, cytokines that in turn mediate systemic reactions associated with the clinical syndrome of septic shock. Thus, inability of the functionally asplenic, nonimmune child with Hb SS to phagocytose and efficiently kill pneumococci results in bacteremia, multiple metastatic foci of infection, and unremitting upregulation of inflammatory mediators.

Clinical Manifestations

The clinical manifestations of infection (i.e., fever, pain, erythema, swelling) are no different from those in hosts without hemoglobinopathy. Differentiation of symptoms due to vaso-occlusive ischemia from those due to infection (e.g., osteomyelitis) remains problematic, and even advanced imaging sometimes is insufficient to discriminate between diagnoses. Children with Hb SS who appear “ill” should be treated aggressively for presumed infection and sepsis while a specific diagnosis, including meningitis, is sought.

Pulmonary Symptoms.

Bacterial pneumonia caused by *S. pneumoniae* is suspected in a patient with fever, cough, chest pain, sputum production (older patients), and abnormal chest radiograph (lobar infiltrate or other parenchymal or pleural abnormalities). Patients often appear toxic. Laboratory findings include leukocytosis, frequently with an increase in immature forms. Additional causative agents include other encapsulated bacteria, *Mycoplasma pneumoniae,*[28] and *Chlamydophila pneumoniae,*[17] all of which have been shown to cause excessive morbidity in patients with sickle hemoglobinopathy.

Acute chest syndrome, described as fever and new pulmonary symptoms in a patient with Hb SS or Hb SC, commonly is precipitated by fat embolism and infection, usually community-acquired pneumonia.[29,30] Specific causes may be difficult to differentiate.[29,31] Patients have chest pain, rales on auscultation, and infiltrates caused by focal vaso-occlusive necrosis or frank pulmonary infarction, although the latter may be less frequent in children. Radiographic abnormalities can be minimum during the first few days of symptoms. Precipitating infections are bacteria, *Chlamydophila,*[17] and viruses (especially influenza).[32] In contrast, primary vaso-occlusive crisis involving ribs can cause splinting, diminished pulmonary clearance, and secondary bacterial pneumonia.

Laboratory data helpful in differentiating bacterial infection from vaso-occlusive processes are increased band count and either extremely high or low white blood cell count (>30,000 or <5000 cells/mm^3).[33] Blood gas determinations in patients with acute pneumonia show oxygen desaturation, but patients with acute chest syndrome due to vaso-occlusion also can exhibit abnormal blood gases as a result of ventilation-perfusion mismatch. Patients with significant vaso-occlusive pulmonary disease require prompt treatment with transfusion or exchange transfusion.

Central Nervous System Symptoms.

In 1971, Barrett-Connor calculated that children with Hb SS had a 300-fold higher risk for pneumococcal meningitis than unaffected children.[1] Children with Hb SS in industrialized countries have a 6% to 8% chance of experiencing bacterial meningitis, and those in Africa have a 19% risk.[21] Of all children with Hb SS infected with *S. pneumoniae* in the pre-PCV era, meningitis developed in 20%, and 15% of these children died.[4] Factors historically associated with death in children with Hb SS and Hb SC included age >4 years, serotype 19F *S. pneumoniae,* and not being followed by a hematologist.[4] However, a significant decline in the rate of pneumococcal meningitis was documented in the 1980s, and this rate has been reduced further in recent years by the use of prophylactic penicillin in young children with Hb SS, immunization with PCV7 and PCV13, and prompt use of antimicrobial agents for febrile illnesses.[3,25,33,34] Current rates of invasive pneumococcal infection in children with Hb SS and fever probably are ≤4%.[35]

Lumbar puncture should be performed immediately in all febrile children with Hb SS who appear ill. This practice is particularly important in infants whose mental status can be difficult to evaluate and in children who have received oral antibiotics that can mitigate or delay signs of serious infection. In children with Hb SS, the incidence of overt central nervous system (CNS) vaso-occlusive disease (stroke) has been reduced to ~1%, and this condition typically manifests with neurologic abnormalities in the absence of signs of infection.[36] The management of pneumococcal meningitis includes consideration of early adjunctive corticosteroid therapy in an attempt to decrease the CNS inflammatory response.

Bone and Joint Infections.

Bone and joint infection frequently is associated with bone ischemia and can manifest as dactylitis (in infants), pyogenic arthritis, or osteomyelitis, with erythema, swelling, and pain.[7,8] An infectious cause sometimes is suggested by the clinical presentation (e.g., as a complication of septicemia due to *S. pneumoniae* or a subacute presentation with less systemic illness due to *Salmonella*). Limp or refusal to bear weight may be the only clinical complaint. Bone and joint infections are associated most often with *S. aureus*, as in unaffected children. *Salmonella* spp., including serotypes associated specifically with bone and joint infections *(S. enterica* [formerly *choleraesuis*], *S. heidelberg),* also are important because of splenic dysfunction and can manifest either as systemic infection or with localized signs and symptoms.[37] Blood and stool specimens, as well as aspirates from infected sites, should be obtained for culture before empiric antibiotic therapy is begun. It is important to determine specific etiology and antimicrobial susceptibility because prolonged therapy generally is required.

Clinical differentiation between osteomyelitis and vaso-occlusive ischemia in the bone is difficult. Pain and tenderness out of proportion to physical findings, bilateral or symmetric involvement, and diffuse (as opposed to focal) symptoms over the diaphysis or the diaphysis and metaphysis of long bones (or dorsum of the hands and fingers in infants) may indicate infarction. Laboratory findings may be helpful. Elevated erythrocyte sedimentation rate (which usually is depressed in Hb SS) suggests bacterial infection, whereas leukocyte count and C-reactive protein level can be elevated during infarction. Bony destruction (“crumbling-bone disease”) and periosteal new bone formation visualized on plain radiograph can occur with either condition. Needle aspiration of involved bone, or open bone biopsy, often is necessary to establish a definite bacterial cause. Imaging studies can be useful in establishing an etiology, but differentiation of infarction from infection remains difficult in some cases (Fig. 106.1). Magnetic resonance imaging can identify a subperiosteal fluid collection that signifies osteomyelitis and can distinguish bone from muscle involvement.[38] In addition, higher fat-saturated T1 signal intensity has been proposed as a sensitive finding in bone infarction.[39] Ultrasound has been proposed as another helpful modality.[40] However, definitive studies (e.g., prospective imaging and universal sampling for microbiologic confirmation) have not been performed. Radionuclide bone scanning is difficult to interpret in this context and is infrequently useful.

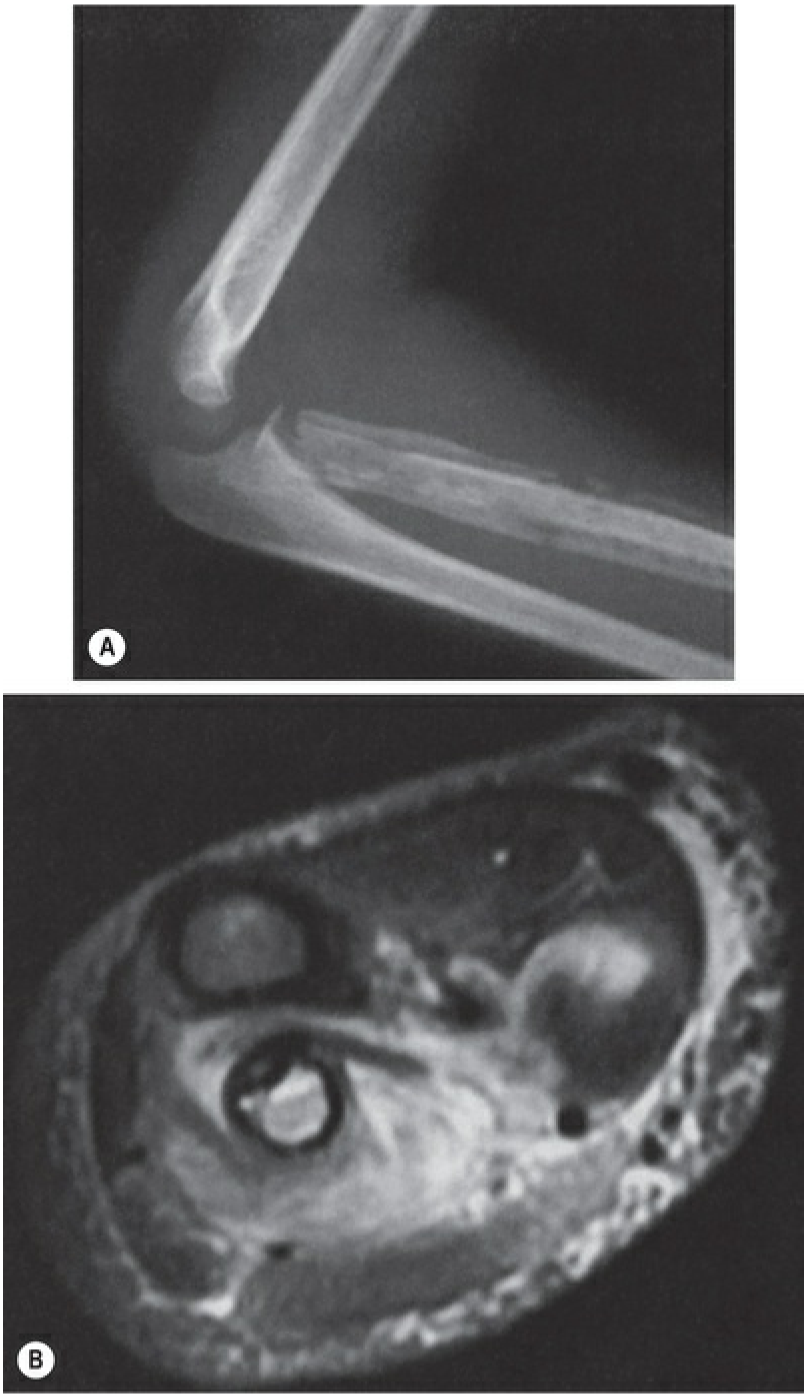

FIGURE 106.1 (A) Radiograph of elbow of 30-month-old patient with hemoglobin SS disease and osteomyelitis due to *Salmonella* spp. There is joint effusion, marked destruction of bone, involucrum, and periosteal new bone formation. (B) Magnetic resonance imaging of elbow showing fat-saturated T_2-

weighted image in the axial plane. There is joint effusion, edema of the supinator muscle, and an active process within the radius more consistent with osteomyelitis than with infarction.

Management and Presumptive Therapy

Meningitis, Septicemia, and Pneumonia.

Infants and young children with Hb SS and fever should be evaluated and treated for presumed bacterial infection. Initial evaluation usually includes a complete blood cell count, blood culture, and chest radiograph, particularly in young children in whom the physical examination may not be optimal. Patients who are at high risk for infection (i.e., those who look ill and who have a body temperature >40°C or a white blood cell count >30,000 or <5000 cells/mm^3) are more likely to have systemic bacterial infection and should be hospitalized for aggressive therapy.[33] Children who have had previous episodes of pneumococcal BSI are at increased risk for repeated infection and warrant special consideration.[41]

Patients who are febrile but do not appear ill have been managed successfully in a variety of ways, including (1) observation in a short-stay area of the hospital for several hours after institution of antimicrobial therapy and (2) parenteral administration of ceftriaxone and close observation on an outpatient basis.[33] Enthusiasm for the latter approach is tempered by case reports of severe and rapidly fatal immune-mediated hemolysis due to ceftriaxone in patients with Hb SS and in other patients who have received multiple courses of the drug.[42,43] All febrile children with Hb SS should be given an antibiotic. In the case of disease that is highly likely to be a vaso-occlusive crisis, therapy can be given orally with close follow-up.

S. pneumoniae that is nonsusceptible to penicillin or cephalosporins poses a particular challenge,[23,44,45] especially for children younger than 3 years who are receiving penicillin prophylaxis. Most commonly, vancomycin plus a third-generation cephalosporin is considered presumptive therapy for BSI (i.e., pending culture and susceptibility results). Fluoroquinolones may be considered for therapy in developing countries where widespread antibiotic resistance is present.[21] For meningitis, particularly when corticosteroids are used, vancomycin (60 mg/kg/day) plus cefotaxime or ceftriaxone is given empirically.

Bone and Joint Infections.

Empiric therapy for bone or joint infection includes agents effective against *S. aureus* (e.g., oxacillin, nafcillin, vancomycin) and *Salmonella* (e.g., third-generation cephalosporin or fluoroquinolone) as well as surgical consultation. Extensive disease, particularly that due to *Salmonella* spp., usually requires debridement and prolonged antimicrobial therapy (e.g., ≥6 months), as for chronic osteomyelitis.

Prevention

The widespread use of PCV has drastically reduced incidence of pneumococcal disease in children. The 13-valent (PCV13) series is recommended for all children, beginning at 2 months of age (see Chapter 123), including those with Hb SS.[46–49] PCV given in infancy decreases nasal colonization with *S. pneumoniae* as well as invasive disease.[50] For children with Hb SS who have previously received a complete course of the 7-valent PCV vaccine, one dose of PCV13 is given.[49] For children with Hb SS or other causes of functional asplenia, 23-valent pneumococcal polysaccharide vaccine (PPSV23) also should be given after the PCV series, at >24 months of age.[46,49] One additional dose of PPSV23 should be given 5 years after the first dose.[46,49] A quadrivalent meningococcal conjugate vaccine (MCV4) series also is recommended for children with Hb SS or Hb SC disease beginning at 2 months of age, with booster 3 years after completion of the primary series and then every 5 years.[51–53] Group B meningococcal (MenB) vaccine series also is given to children with sickle cell disease starting at 10 years of age.[54] Influenza vaccine should be targeted annually for children with Hb SS (as well as for all children 6 months and older)[48] because of the significant risk for complications due to influenza, including invasive pneumococcal infection.

Substantial reduction in morbidity and mortality due to *S. pneumoniae* has been demonstrated in children younger than 3 years with Hb SS through the use of prophylactic penicillin.[3] The major placebo-controlled study (performed before availability of PCV) demonstrated a decrease in the rate of pneumococcal infection from 9.8 to 1.5 per 100 patient-years.[34] Prophylactic penicillin is begun at 3 months of age. There is no consensus regarding the age at which prophylaxis should be stopped, but studies do not indicate benefit of continuing beyond 5 years of age.[55,56] Adherence to an oral regimen may be erratic; monthly injections of penicillin G benzathine are efficacious.

Special Considerations

Parvovirus B19 Infection.

Transient aplastic crisis in Hb SS disease (worsening anemia and profound reticulocytopenia) has been associated with parvovirus B19 infection.[18] The cellular receptor for this virus is the blood group P antigen, explaining the tropism of the virus for erythroid progenitor cells; viral infection appears to trigger apoptosis.[57] Serologic studies of patients with Hb SS who have transient aplastic crisis demonstrate acute parvovirus B19 infection in >70%.[18,19,58] Patients have a high burden of virus, are highly contagious, and do not demonstrate the characteristic rash of erythema infectiosum. Neither chronic nor recurrent disease is reported in this patient group, and anti-B19 immunoglobulin G (IgG) antibodies remain detectable for several years after infection, suggesting protection.

Asplenia and Polysplenia

Asplenic patients have increased risk for overwhelming, life-threatening infections, most commonly due to *S. pneumoniae*.[59–62] The level of risk appears to correlate inversely with the amount of time a patient has had a functioning spleen. Adults who undergo splenectomy after trauma have a lower risk for serious infection than infants with congenital asplenia syndrome and children who undergo splenectomy after trauma. Children who undergo splenectomy as part of treatment for malignancy are at great risk. Overall, approximately 3% of children whose spleen is removed before the age of 4 years have significant infections, with a mortality rate of about 40%.[63] Risk for infection is greatest in the year after splenectomy (regardless of age) and continues to be significant for the next 7 to 10 years, after which time risk is low but never as low as for people with normal splenic function.

Children with congenital asplenia and polysplenia syndromes are at increased risk for overwhelming septicemia.[64,65] Splenic function should be evaluated in children with congenital abnormalities of embryonic lateralization, such as heterotaxy syndromes involving a variety of abnormalities across the left-right axis of the body (i.e., situs inversus)[64] and a wide variety of cardiac defects including conotruncal abnormalities, transposition of the great vessels, and endocardial cushion defects. Asplenia and polysplenia often are associated with other types of congenital abnormalities, including gastrointestinal malformations such as biliary atresia, neural tube anomalies, genitourinary defects, skeletal defects, and bronchopulmonary defects, such as Kartagener syndrome, as well as bilobed and mirror-image lungs. Isolated congenital asplenia also occurs in rare kindred, with an autosomal dominant inheritance pattern.[66] Success with living-donor liver transplantation in children with polysplenia syndrome has translated into more of these high-risk patients surviving. The polysplenia syndrome also has been reported as an incidental finding on computed tomography in adults, suggesting that some individuals may have immunologic impairment that is not as significant as that of asplenic patients.

Functional asplenia is confirmed by the presence of Howell-Jolly bodies in a peripheral blood smear (obtained after the first week of life), absence of splenic uptake on a technetium-99m sulfur colloid scan, or increased percentage (>3.5%) of pitted or pocked erythrocytes in peripheral blood. The last test is not widely available but is useful in monitoring splenic function after trauma and partial splenectomy because the pocked erythrocyte count rises to >10% with absent splenic function.[67] Of note, although abdominal ultrasound readily identifies the normal or enlarged spleen, it is not 100% sensitive in patients with asplenia or polysplenia.[68] Children with severe or repeated pneumococcal infection should undergo evaluation of splenic function as well as tests for immunoglobulin deficiency and HIV infection.

Etiologic Agents

Encapsulated organisms represent the greatest risk for asplenic patients. *S. pneumoniae* has been associated with 50% to 90% of the overwhelming infections occurring after splenectomy. Other pathogens are *H. influenzae* type b and *N. meningitidis*. Fatal cases frequently are associated with meningitis.[61] It is not well documented that *N. meningitidis* infection is more fulminant in asplenic patients. Other streptococci, such as *Streptococcus agalactiae* (group B streptococcus) and *Enterococcus* spp., can cause fatal infection in asplenic hosts. Infections due to *Salmonella* spp. have been reported in asplenic patients, although the risk appears lower than with sickle hemoglobinopathy. Fulminant septicemia due to *Capnocytophaga canimorsus*, part of the mouth flora of dogs, occurs in asplenic patients, whose contact frequently is merely with a pet's saliva.[69] Asplenic patients also have substantially higher risk for infection due to *Babesia microti,* an intraerythrocytic parasite endemic in coastal areas of the northeastern US. There is increasing concern that asplenic patients are at greater risk for severe infection from *Plasmodium* spp. because the spleen plays a central role in parasite clearance.[60,70]

Pathogenesis

The central roles of the spleen include (1) mechanical clearance of antigen and foreign material; (2) synthesis of factors that enhance phagocytosis; and (3) coordination of interactions of the T-lymphocyte and B-lymphocyte responses to organisms. The spleen is important in the *initial* response to a pathogen, perhaps as a result of its role in IgM production; the asplenic host is therefore at a disadvantage when encountering a polysaccharide antigen (e.g., pneumococcal capsule) for the first time. Asplenic patients are unduly affected by encapsulated organisms that require antibody and complement for opsonization and clearance. In the absence of preformed antibody, the spleen is critical in clearing the bloodstream. This may explain why adults who have developed a broad immunologic repertoire and older children who have been given pneumococcal vaccines, and then undergo splenectomy, have a lower risk than asplenic children for overwhelming infection.[60] Infants with congenital asplenia have profoundly impaired reticuloendothelial clearance mechanisms. Additionally, they have diminished T-lymphocyte responsiveness to a variety of antigens compared with age-matched controls.[71]

Management

Seemingly trivial febrile illnesses can herald life-threatening pneumococcal septicemia in the asplenic patient. Bacterial sepsis in a cohort of patients with visceral heterotaxy and asplenia has been reported to carry a 44% mortality rate.[64] Febrile episodes require careful evaluation and empiric antibiotic therapy. Many physicians instruct patients to begin taking oral antibiotics at the earliest signs of infection, particularly if medical evaluation is not available immediately. For patients requiring parenteral antibiotics, empiric therapy is the same as for patients with Hb SS disease, typically comprising vancomycin and a third-generation cephalosporin.[72]

Prevention

Routinely recommended immunizations, especially PCV13 and PPSV23, should be given on schedule as for patients with Hb SS.[46,49] Hib conjugate vaccine and varicella vaccine are critically important for all asplenic children.[73] The series of meningococcal conjugate vaccine (MenACWY) should be begun as early as 2 months of age,[51,52] and the series of MenB vaccine and boosters is begun at 10 years of age.[74] When splenectomy is elective, patients should be fully immunized at least 2 weeks (or 4 weeks for live virus vaccines) before surgery.[75]

It is less clear whether children with asplenia benefit from prophylactic antibiotics to the same extent as children with Hb SS. Most experts recommend penicillin prophylaxis for (1) children who have congenital asplenia; (2) children who undergo splenectomy for hemolytic anemia, malignancy, or liver transplantation at any age; (3) children who undergo splenectomy before age 5 years; and (4) persons of any age during the initial years after splenectomy. There is no consensus as to when penicillin prophylaxis should be discontinued.[60] It is important to recognize that patients receiving penicillin prophylaxis are at continued risk for fulminant infection and, thus, require the same careful and urgent evaluation for febrile illness.

Renal Disease

Children with renal disease have increased risk for infection for a variety of reasons, including underlying disease, immunosuppressive therapeutic modalities, and indwelling intravascular and peritoneal dialysis catheters.[76] Children with nephrotic syndrome and accompanying hypogammaglobulinemia have increased risk for infection with encapsulated organisms, particularly *S. pneumoniae,* which require preformed IgG for efficient opsonization. In addition, gram-negative organisms, including *N. meningitidis* and *Salmonella* spp., as well as gut flora (*E. coli, Klebsiella* spp., and *Enterobacter* spp.), account for one half of infections in this population.[77] Such patients require careful evaluation and empiric therapy effective against bowel flora as well as the encapsulated pathogens associated with BSI in patients with immunoglobulin deficiency. Patients with nephrotic syndrome also have an apparently higher frequency of urinary tract infections.[78–80]

Children with nephrotic syndrome as well as other patients with chronic renal disease should be immunized with routine pediatric vaccines, including PCV13, plus PPSV23.[46,76] Antibody levels in these patients are lower than in healthy children, but geometric mean antibody titers generally reach a protective range after immunization.[81] Duration of antibody protection may be reduced.[82] Higher doses of hepatitis B vaccine have proved more immunogenic than routine doses in children with renal failure.[83] The benefit of prophylactic penicillin in children with nephrotic syndrome is unclear because the risk for selection of multidrug-resistant organisms is of concern. Some clinicians use prophylactic penicillin in children with nephrotic syndrome who are younger than 2 or 3 years of age and have had an episode of *S. pneumoniae* bacteremia.

Patients with end-stage renal disease who are undergoing ambulatory peritoneal dialysis or hemodialysis have additional risk for infection. Patients receiving chronic ambulatory peritoneal dialysis commonly experience low-grade peritonitis, which often is due to catheter-related coagulase-negative staphylococci (CoNS). Gram-negative organisms or fungi from the bowel (e.g., *Candida* spp.) can contaminate peritoneal fluid and cause frank peritonitis. The repeated use of vancomycin in these patients may predispose to multidrug-resistant pathogens, such as vancomycin-resistant enterococci (VRE). Linezolid currently is considered the drug of choice for VRE infections in adults and often in children.[84,85] The creation of arteriovenous shunts for hemodialysis also can lead to infection, usually due to CoNS but also to *S. aureus* or other nosocomial pathogens.

Children with nephrotic syndrome who are being treated with corticosteroids (>2 mg/kg or >20 mg/day of prednisone) are at significant risk for severe varicella infection. A study of varicella vaccination in 20 children with corticosteroid-sensitive nephrotic syndrome found that antivaricella antibodies remained high 2 years after vaccination, with only 3 subjects becoming mildly infected.[86] The use of varicella-zoster immune globulin after known exposures in susceptible nephrotic children is recommended, and some clinicians also treat exposed patients with acyclovir pre-emptively, although the oral dosages used may not achieve sufficient levels to be effective.

Ascites

Patients with ascites due to either hepatic or renal dysfunction have increased risk for infection, particularly primary (spontaneous) peritonitis. Historically, these infections often were due to pneumococci or group A *Streptococcus*. Although pneumococcal peritonitis remains a major problem in children with nephrotic syndrome, children with ascites of hepatic origin also have increased risk for peritonitis due to gram-negative bacteria. The close association of primary peritonitis and ascites due to hepatic disease suggests that the compromised reticuloendothelial function of the liver associated with cirrhosis and portal hypertension allows organisms, which normally would be cleared, to contaminate hepatic lymph and pass into the peritoneal fluid. Because the liver is an important site for the clearance of bacteria from the bloodstream, significant compromise of this function leads to peritoneal infection, bloodstream infection, or both.[87,88] Experimental data suggest that bacteria also can traverse the intestinal wall to seed the peritoneal cavity. Of note, the composition of ascitic fluid contributes significantly to the development of clinically significant peritonitis; low levels of complement and immunoglobulins permit bacterial proliferation.

Although peritoneal fluid cultures are positive in most patients with ascites and peritonitis, culture techniques inadequate for recovery of anaerobic organisms may explain some negative culture results.[89] Choice of therapy is informed by peritoneal fluid Gram stain and culture as well as blood culture results. A third-generation cephalosporin such as cefotaxime may be useful for activity against possible aerobic and facultative bowel flora and *S. pneumoniae.* In children repeatedly exposed to the healthcare environment who have received multiple courses of antibiotics, the use of a carbapenem, for activity against *Pseudomonas aeruginosa,* multidrug-resistant Enterobacteriaceae (*Enterobacter, Citrobacter, Serratia, Klebsiella* spp.), and anaerobic bacteria, may be warranted initially. In adults with uncomplicated spontaneous bacterial peritonitis, a therapeutic course of a fluoroquinolone orally often is used.[87] In adults with cirrhosis, prophylactic use of a fluoroquinolone decreases the number of episodes of primary peritonitis, although it also raises the risk for selecting multidrug-resistant pathogens and *Clostridium difficile*.[90]

Iron Overload States

Patients with increased availability of free iron are at greater risk for serious infection due to *Yersinia enterocolítica*[91] and, less commonly, *Listeria monocytogenes, Vibrio vulnificus,* and *Klebsiella* spp.[92–96] Children at risk include those with (1) β-thalassemia who require chronic transfusions and iron-aluminum chelation therapy with desferoxamine[97]; (2) hemolysis due to glucose-6-phosphate dehydrogenase deficiency and other conditions[98]; (3) idiopathic hemochromatosis; and (4) chronic kidney disease managed with chronic transfusions and chelation. The use of erythropoietin in chronic anemia should decrease the use of transfusion and incidence of these infections.

Many in vitro studies demonstrate the importance of iron-scavenging systems in the virulence of bacteria and parasites as well as of free iron-depleting defense mechanisms of the host during acute infection.[94,96] As a means of innate defense, humans have evolved numerous methods of limiting availability of extracellular iron for potential pathogens. Bacteria have, in turn, evolved means to subvert innate defenses and gain access to iron. For example, uropathogenic *E. coli* have been studied extensively for their ability to produce multiple siderophores that bind iron in iron-poor conditions, which are imperative for virulence in the urinary tract.[99,100] In addition to scavenging iron from the host, *Vibrio* spp. are able to access iron by degrading host heme-containing compounds through proteolytic enzymes.[101] The importance of iron and its role in infection continues to be an active and productive area of research.[96,102,103]

Most patients with iron overload syndromes have other deficiencies in immune function due to reticuloendothelial blockade and functional asplenia. However, increased free iron itself predisposes to *Yersinia* spp. infections and has been reported even as a complication of acute iron ingestion.[104] In addition, a high rate of gram-negative BSI has been associated with the intramuscular injection of iron-dextran in neonates.[105] Acidosis, particularly diabetic ketoacidosis, leads to a greater availability of iron through a number of mechanisms and has been associated with zygomycosis in patients with acidosis.[106]

Etiologic Agents and Pathogenesis

Y. enterocolitica has been associated with septicemia, mesenteric lymphadenitis, liver and splenic abscesses, and an acute appendicitis-like syndrome in patients with thalassemia and hemochromatosis.[97,107] Organisms can be found in blood, stool, and lymph nodes. *V. vulnificus* can cause severe and often fatal BSI in these patients and also has been reported in necrotizing fasciitis in a child with congenital spherocytosis.[108] Infections caused by *L. monocytogenes, Salmonella* spp., *Klebsiella* spp., and zygomycetes are reported in patients who are treated with desferoxamine for iron overload associated with chronic transfusion.[93]

Yersinia spp., like other bacteria and fungi, require iron for growth. Unlike most other organisms, however, *Yersinia* spp. and the zygomycetes are able to use iron complexed with the siderophore desferoxamine and thrive under conditions of increased iron.[104] Several studies have demonstrated diminished host immune function (decreased phagocytic function, impaired T-lymphocyte responsiveness) in the presence of elevated serum iron levels.[109] Thus both host and bacterial factors contribute to the greater susceptibility to infection.

Clinical Manifestations and Management

The most common presentation of *Y. enterocolitica* infection in patients with thalassemia consists of fever, chills, and gastrointestinal complaints ranging from bloody diarrhea to frank peritonitis. Findings suggestive of acute appendicitis are associated with recovery of *Y. enterocolitica* from mesenteric lymph nodes. Normal hosts generally limit the organism to the intestinal mucosa, and extraintestinal infection is uncommon.

Early recognition and specific antibiotic treatment are important. Iron chelation therapy with desferoxamine should be temporarily discontinued in infected patients. Almost all *Y. enterocolitica* isolates are susceptible to trimethoprim-sulfamethoxazole, aminoglycosides, fluoroquinolones, and certain third-generation cephalosporins (cefotaxime and ceftriaxone).[110] Parenteral therapy with cefotaxime or ceftriaxone is appropriate for febrile, ill patients without focal signs of infection.

Ciliary Dysfunction

Primary ciliary dyskinesia (PCD) is an autosomal recessive disease with an incidence of approximately 1 in 15,000 to 30,000 births. At least 21 distinct ultrastructural abnormalities of cilia have been associated with the immotile cilia syndrome.[111] Approximately one half of patients with immotile cilia syndrome have situs inversus, which may be associated with Kartagener syndrome, dextrocardia, asplenia, or polysplenia. Lack of normal mucociliary clearance in the respiratory tract leads to a higher incidence of local infection. Patients with ciliary dysfunction have respiratory symptoms in the first month of life and often are colonized with *H. influenzae.*[112]

Recurrent mucopurulent rhinitis, otitis media, and bronchitis lead to bronchiectasis in as many as 85% of PCD patients. Risk for invasive infection is not increased (unless there is an associated splenic abnormality), and pulmonary function usually is preserved until late in the course of disease. Longitudinal studies suggest that patients diagnosed early in life who are treated aggressively for infection have significantly better pulmonary function than those who are not treated for infection.[113] Bronchiectasis is the most significant complication, but young infants with PCD have frequent acute otitis media, sometimes leading to hearing impairment.[114] The most common infecting organisms associated with bronchiectasis in primary ciliary dyskinesia are nontypable *H. influenzae* (47%), *S. pneumoniae* (32%), and *P. aeruginosa* (16%).[115] In upper airway infections, typical agents of acute otitis media and sinusitis are common.

Bronchodilator therapy may be useful in some patients. Antimicrobial therapy is aimed at treating existent infection and decreasing inflammation. Chest physiotherapy aids in clearance of secretions and prevention of atelectasis. Unlike cystic fibrosis (CF), ciliary dysfunction does not reduce life expectancy significantly.

Cystic Fibrosis

CF is the most common lethal genetic disease of white people. It is caused by mutations in the CF transmembrane regulator (CFTR), an adenosine triphosphate−dependent chloride channel primarily expressed in the lung and exocrine glands.[116] Patients have chronic pulmonary infection with airway inflammation and poor growth secondary to pancreatic exocrine insufficiency and malabsorption. Sinusitis secondary to abnormal secretions and nasal polyps, as well as pancreatic endocrine insufficiency, can cause significant morbidity. Aggressive medical management of the pulmonary and gastrointestinal manifestations of CF has more than doubled the life expectancy of affected patients from a median of 14 years in 1969 to a median of 40.7 years in 2013.[117,118]

Etiologic Agents

The spectrum of bacterial pathogens colonizing and infecting the lungs of patients with CF is relatively limited (Table 106.1). *S. aureus* (both methicillin-sensitive and methicillin-resistant *S. aureus*), *P. aeruginosa, and H. influenzae* (mostly nontypable) are the most commonly isolated bacterial pathogens,[119,120] and several studies demonstrate bacterial lung infections within the first 3 years of life.[121,122] *P. aeruginosa* is considered the predominant pathogen in

CF and is seen in 45% to 62% of pediatric patients.[123] Although infection with both nonmucoid and mucoid phenotypes of *P. aeruginosa* is associated with a more rapid decline in lung function, mucoid isolates signal chronic infection and are very difficult to eradicate.[124,125] Methicillin-resistant *S. aureus* also is associated with functional decline, increased number of exacerbations, and mortality in recent experience.[126–128] Later in the course of disease, multidrug-resistant gram-negative organisms such as *Burkholderia cepacia* complex, *Stenotrophomonas maltophilia,* and *Achromobacter xylosoxidans* are isolated. In recent years, the prevalence of these organisms has increased.[129,130] *B. cepacia* complex organisms, particularly *B. cenocepacia* (genomovar III) and *B. multivorans* (genomovar II), have been associated with both fulminant pulmonary infection and chronic colonization.[131] The clinical significance of *S. maltophilia* and *A. xylosoxidans* is less well characterized; however, emerging data suggest that chronic infection with *S. maltophilia* is not associated with decreasing lung function.[132–134]

TABLE 106.1

Age-Related Appearance of Pathogens in Cystic Fibrosis

Patient Age	Pathogens
Early infancy	*Staphylococcus aureus*
Early childhood	*Haemophilus influenzae*
Adolescence	*Pseudomonas aeruginosa*
Late in disease	*Burkholderia cepacia* complex *Stenotrophomonas maltophilia* *Achromobacter xylosoxidans* *Aspergillus fumigatus*

Fungi such as *Aspergillus* and *Fusarium* also cause disease in patients with CF. *A. fumigatus* can manifest as allergic bronchopulmonary aspergillosis,[135] invasive dissemination (possibly related to corticosteroid use),[136] and pulmonary or invasive disease, especially after lung transplantation.[137] In a multicenter study, nontuberculous mycobacteria were isolated from sputum in up to 13% of patients with CF—more commonly in older patients, those with a higher 1-second forced expiratory volume, those with lower body mass, and those with *S. aureus,* but not *P. aeruginosa,* isolated from sputum.[138] The effect of nontuberculous mycobacteria appears to be species driven, and *Mycobacterium* *abscessus* is associated with more rapid decline in lung function.[139,140] Whether other species of mycobacteria affect pulmonary decline remains unclear.[138] The role of infection with respiratory viruses in patients with CF has been examined in several studies. There appears to be no difference in the numbers of upper respiratory tract viral infections between children with CF and unaffected controls. However, children with cystic fibrosis have significantly more episodes of lower respiratory tract disease.[141,142] Studies support a causative role for influenza and other respiratory viruses in acute pulmonary exacerbations[143,144]; high morbidity and occasional fatality during acute influenza infection are recognized. During infancy, respiratory syncytial virus may be an important cause of early pulmonary morbidity, requiring hospitalization.[145] Rhinovirus and influenza play larger roles in early childhood and adolescence.[146,147]

Epidemiology

The epidemiology of the acquisition of *P. aeruginosa* in CF is increasingly being examined. Most children with CF appear to have unique strains,[148,149] and these early isolates share many phenotypic characteristics with environmental isolates.[150] Studies in siblings and at summer camps identify common strains in patients with close contact; it is uncertain whether these findings result from person-to-person spread or a common environmental source. Outbreaks of multidrug-resistant *P. aeruginosa* in CF centers in Europe and Australia have identified epidemic strains that appear capable of person-to-person transmission.[151,152] In addition, emerging data suggest the potential for environmental transmission through infectious droplets.[153]

Epidemiologic studies also support the conclusion that *B. cepacia* complex can be spread from person to person. Molecular typing of *B. cepacia* complex has identified unique strains in each CF center, and studies of the epidemiology in summer camps attended by patients from different geographic areas have demonstrated cross-infection.[154] Social contact outside the hospital also has been implicated in the spread of *B. cepacia* complex.[155] Of the 9 named species in the complex, *B. cenocepacia* has specific clones, especially ET12, that most clearly have been associated with transmissibility.[156] A significant problem in understanding the epidemiology of *B. cepacia* complex is the demonstration that up to 2 years may elapse from the time of acquisition of the organism until it is detected by sputum culture.[157]

Pathogenesis

The molecular events responsible for the close association between *P. aeruginosa* and the lungs of patients with CF have not been defined fully. Inspissated secretions and dehydrated mucus decrease normal mucociliary clearance of organisms and facilitate chronic infection. Expression of increased numbers of asialylated glycolipid receptors for *P. aeruginosa* pili on the epithelium of the lung in such patients may predispose them to colonization.[158] Some studies suggest that naturally occurring airway antimicrobial peptides are functionally inhibited in the milieu of the CF lung.[159] After colonization, *P. aeruginosa* grows in microcolonies, forming biofilms within the airway.[160,161] The environment within the CF lung favors the proliferation of mucoid mutants of *P. aeruginosa* that produce large amounts of alginate exopolysaccharide, interfering with effective phagocytosis. After chronic infection is established, organisms are rarely, if ever, eradicated. Infection is endobronchial in location, with bacteria loosely enmeshed in a viscous layer of mucus that contains large amounts of cellular debris, neutrophil DNA, and actin. Histopathologic analysis shows areas of focal infection surrounded by neutrophils. Eventually, chronic infection, fibrosis, and loss of the normal pulmonary parenchyma result. Much of the observed pathology is due to the inflammatory response to *P. aeruginosa.*

Clinical Manifestations

Due to their inability to eradicate bacterial pathogens from the lower airways, patients with CF have chronic pulmonary symptoms, including persistent cough, expectoration of sputum, and progressive deterioration in pulmonary function. Acute episodes of clinical exacerbation are superimposed on chronic pulmonary symptoms. The wide variation in severity of underlying chronic manifestations makes it difficult to define a pulmonary exacerbation by clinical criteria alone.[162] Rather than new symptoms, an exacerbation more often is heralded by a quantitative change in ongoing symptoms, for example, an increase in frequency and intensity of cough or in the quantity and purulence of sputum. The acute and chronic symptoms are the result of vigorous inflammatory responses to endobronchial infection. Increased airway disease manifests as tachypnea and increased work of breathing (retractions, use of accessory respiratory muscles, and wheezing). Systemic manifestations of pulmonary exacerbation include malaise, myalgia, anorexia, weight loss, and (rarely) low-grade fever. Epidemiologic studies attempt to clarify the definition of acute exacerbation with the presence of four distinct clinical characteristics: new crackles, increased cough, increased sputum, and weight decline.[163] However, clinical responses to these symptoms, even when three or more are present, is inconsistent across providers at CF centers, complicating the interpretation of the proposed definition.[164]

Nonpulmonary symptoms of CF that can mimic infection include immune complex−mediated manifestations, such as vasculitic rashes[165] and arthritis.[166] In addition to pancreatic insufficiency, gastrointestinal manifestations include severe constipation, intestinal obstruction, and unrecognized or unusual presentations of acute appendicitis. Sinusitis secondary to nasal polyps is common.[167] Etiologic agents include the usual sinus pathogens plus organisms colonizing the lower airways in this population. In addition to episodes of acute and chronic infections, sinuses can serve as a reservoir for antibiotic-resistant organisms in patients undergoing lung transplantation.

Laboratory Findings

Decline in results of pulmonary function studies is the most accurate and objective indicator of pulmonary exacerbation. Unfortunately, most patients younger than 5 years cannot perform pulmonary function tests reproducibly, making the diagnosis of an exacerbation more difficult. The appearance of a new pulmonary infiltrate on a chest radiograph can be helpful; however, most pulmonary exacerbations, especially in patients with advanced disease, are unassociated with significant radiographic changes, probably because of the marked abnormalities present at baseline (Fig. 106.2).

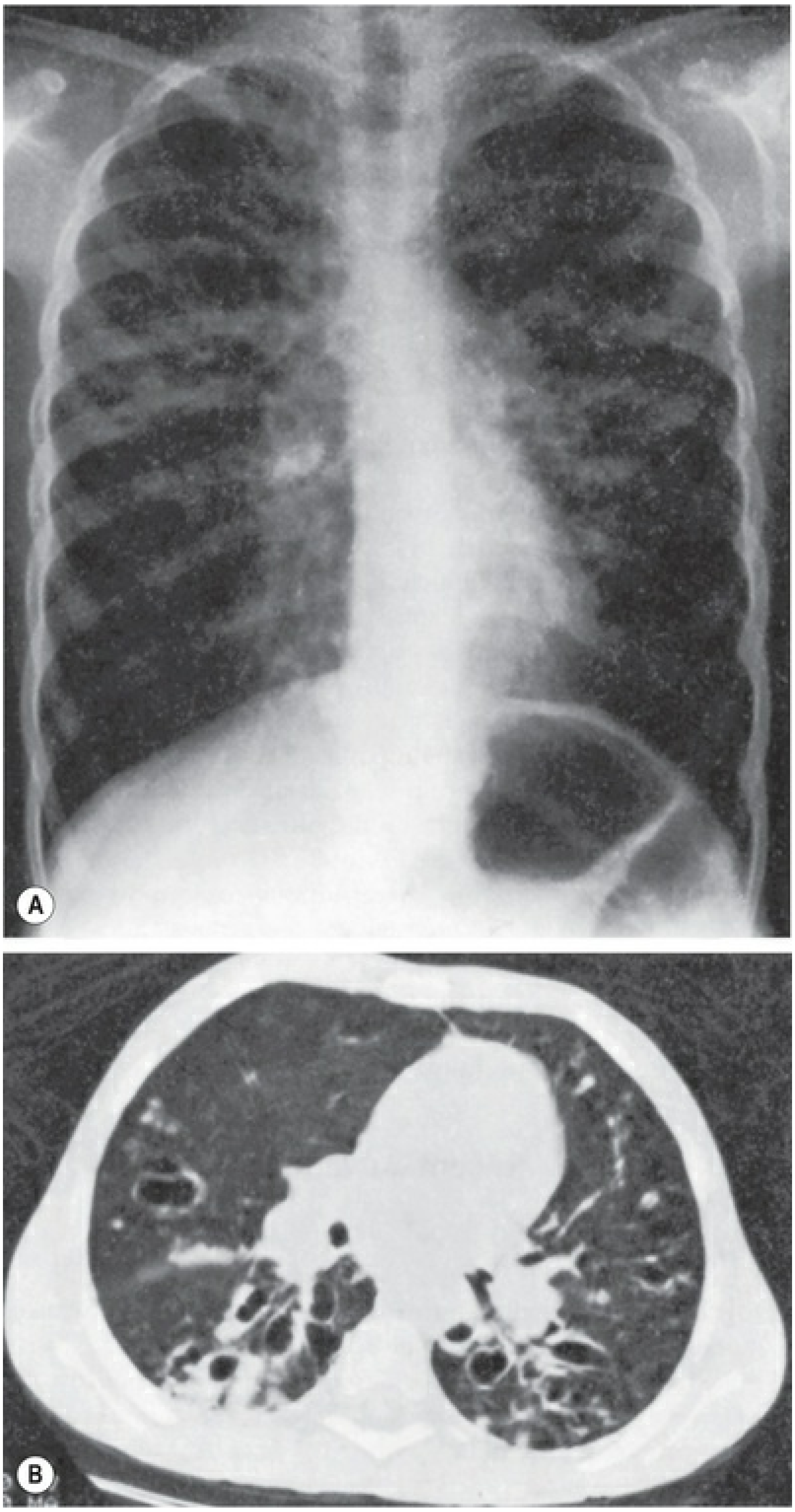

FIGURE 106.2 (A) Chest radiograph of a 14-year-old boy with cystic fibrosis demonstrating typical changes of hyperinflation, bronchial wall thickening, and areas of bronchiectasis and consolidation. (B) Computed

tomography demonstrates the magnitude of changes and diffuse nature of the pulmonary involvement.

Sputum culture can accurately identify the bacterial pathogens colonizing lower airway secretions.[168] Oropharyngeal culture (a suggested alternative in the nonexpectorating patient) is a relatively insensitive measure of lower airway pathogens.[169] Sputum induction is an alternative strategy, with organism recovery similar to bronchoalveolar lavage.[170,171] A technique combining the use of selective media and quantitative culture methods to identify infecting organisms in sputum also is used to evaluate therapeutic response.[172] This method circumvents the problem of rapidly growing mucoid strains of *P. aeruginosa,* which obscure the growth of more fastidious organisms such as *H. influenzae.*

Other laboratory studies helpful in defining a pulmonary exacerbation are white blood cell count with differential and measurements of acute-phase reactants, such as erythrocyte sedimentation rate and serum C-reactive protein level.[173] These tests have limited value without baseline measurements for comparison. BSI rarely is seen, except in a subpopulation of patients infected with *B. cepacia* complex, patients with an indwelling catheter, and immunosuppressed patients after lung transplantation.[174] Blood cultures are not indicated routinely in patients with CF unless they have one of these risk factors.

Management

The goal of acute and long-term treatment in CF is to prevent pulmonary damage from chronic infection and inflammation. Mainstays of therapy include nutritional support with pancreatic enzyme supplementation, chest physiotherapy to improve the drainage of pulmonary secretions, bronchodilator therapy to treat reactive airway disease, and antibiotic treatment to decrease bacterial density in the lungs. Antibiotic therapy in CF can take three forms: (1) early treatment of colonization (pre-emptive therapy); (2) suppression of chronic infection; and (3) treatment of acute pulmonary exacerbations.

Aggressive pre-emptive therapy for CF patients with their first *P. aeruginosa*–positive airway culture is the standard of care.[175] Several studies to decrease acquisition of chronic colonization or to eradicate first colonization of *P. aeruginosa* show clinical and microbiologic efficacy.[176–180] Danish groups have used ciprofloxacin in combination with inhaled colistin, whereas other studies have employed inhaled tobramycin and inhaled aztreonam.[181] After prolonged eradication, when *P. aeruginosa* did reappear, the organism most frequently was a new strain.[176,178]

The role of suppressive therapy in individuals with chronic *P. aeruginosa* infections also has been demonstrated, using antibiotics that may or may not have in vitro or in vivo antibacterial activity. Tobramycin has been used parenterally in pulmonary exacerbations for many years; most isolates of *P. aeruginosa* in patients with CF are susceptible. Use of high-dose inhaled tobramycin is associated with improvement in pulmonary function, decrease in the risk for hospitalization, and reduction in *P. aeruginosa* density in sputum without detectable ototoxicity or nephrotoxicity. Although a substantially higher rate of tobramycin resistance does not appear in individual studies,[182] resistance rates for tobramycin are increasing in longitudinal cohorts studied.[129,176–180] More recently, inhaled aztreonam lysinate has been shown to be safe and efficacious in CF, and its availability has resulted in increased use of combination inhaled therapy.[183,184] Several randomized controlled trials of treatment with oral azithromycin, a macrolide agent with anti-inflammatory properties, to which *P. aeruginosa* routinely is resistant in vitro, have demonstrated clinical improvement in lung function, body weight, number of exacerbations, and quality of life, but without a decrease in sputum bacterial density.[185–187]

Optimal antibiotic management of pulmonary exacerbations depends on knowledge of each patient's recent sputum bacteriology and susceptibility test results. Most often, two drugs with antipseudomonal activity are given—typically a β-lactam agent or fluoroquinolone plus an aminoglycoside.[188] Because of the potential for the induction of expression of the *Pseudomonas* chromosomal β-lactamase, combinations comprising two β-lactam agents generally are avoided. Late in the course of disease, multidrug-resistant strains are isolated frequently. Of note, in a controlled clinical trial in subjects with clinical exacerbations, antibiotic therapy directed by combination susceptibility (“synergy”) testing of *P. aeruginosa, B. cepacia* complex, *S. maltophilia,* and *A. xylosoxidans* did not result in better clinical or bacteriologic outcomes compared with therapy directed by standard testing.[189] Similar results were reported for therapy based on biofilm susceptibility testing.[190]

Several problems make the selection and use of antibiotics in patients with CF challenging. Chronic inflammation in the lung and localization of infection in the lumen of the airway make achievement of adequate levels of bioactive drug at the site of the infection difficult. The lack of a microbiologic end point for treating infections (organisms are never eradicated) makes definition of antibiotic resistance problematic. The differences in antibiotic pharmacokinetics identified in individuals with CF require the modification of drug dosing because the clearance of many drugs is high compared with that in unaffected controls.[191–193]

Recombinant human deoxyribonuclease has been demonstrated to improve pulmonary function and decrease the frequency of pulmonary exacerbations in patients with CF.[194] Improved mucociliary clearance results from lysis of the high concentrations of leukocyte DNA in the sputum of such patients.[195] Nebulized hypertonic saline, shown to improve mucociliary clearance, also has been demonstrated in short-term trials to improve mucociliary clearance, but is not recommended routinely in management.[196]

Bilateral lung transplantation is a potential life-extending therapy for selected patients with end-stage pulmonary disease. However, infectious complications caused by multidrug-resistant bacteria and fungi are a serious posttransplantation problem given the immunosuppression required for transplantation.[137] Although infected lungs are removed, colonization of upper respiratory and gastrointestinal tracts persists. Bronchiolitis obliterans also is a potentially fatal complication of transplantation.

Recent Advances

Investigational efforts in CF have been divided between anti-infective or anti-inflammatory strategies and potentially curative therapies. Aerosol administration of antimicrobial agents in addition to tobramycin and aztreonam is potentially advantageous because high concentrations of drug can be delivered directly to the site of infection while avoiding toxicity. The potential role of anti-inflammatory medications, including corticosteroids and ibuprofen, has been demonstrated in well-controlled clinical trials, although treatment with systemic corticosteroids has unacceptable side effects.[197,198] Other anti-inflammatory strategies currently being examined include inhibitors of proinflammatory mediators, anti-inflammatory cytokines, modulators of proinflammatory signaling cascades, antioxidants, and protease inhibitors.[199]

Potentially curative therapies for CF include gene therapy and pharmacologic approaches to correct the phenotype resulting from mutant CFTR. Although many CF-associated gene mutations have been identified, and administration of CFTR cyclic DNA to humans can complement the defect in vivo, the development of effective vectors to deliver the gene to the appropriate target cells and maintain its expression is challenging.[200,201] Another therapeutic strategy is the use of agents that restore activity of the mutant gene product such as CFTR potentiators, drugs that target protein folding and trafficking, and agents that induce translational read-through of stop codons and other nonsense mutations.[202] Recently, a CFTR potentiator, ivacaftor, was approved for use in CF patients 6 years and older with 1 of 10 specific CF mutations.[203] Additional studies using ivacaftor in combination with another CFTR ion transport corrector, lumacaftor, have shown promise for patients with the more common ΔF508 CFTR mutation.[204]

Prevention

Approaches to the prevention of *P. aeruginosa* colonization have included the aggressive use of prophylactic antibiotics and the development of antipseudomonal vaccines for use in noncolonized patients. Preliminary studies of at least two different vaccines against *P. aeruginosa* demonstrated safety and immunogenicity[205,206]; long-term follow-up of the polyvalent conjugate vaccine in 26 young children demonstrated a longer time to *P. aeruginosa* infection and fewer chronic infections in the study group compared with matched controls.[207]

Patients with CF should receive all routine childhood and adolescent immunizations, including acellular pertussis, PCV, varicella-zoster, and inactivated influenza vaccine.[208] In addition, their families should receive acellular pertussis and annual influenza vaccine because of the high rate of morbidity associated with these infections in CF patients.[143,147] There is no specific recommendation for routine administration of PPSV23 in patients with CF; however, a single dose of PPSV23 is recommended at 2 years or older for any immunocompetent child with chronic illness (including chronic lung disease).[49]

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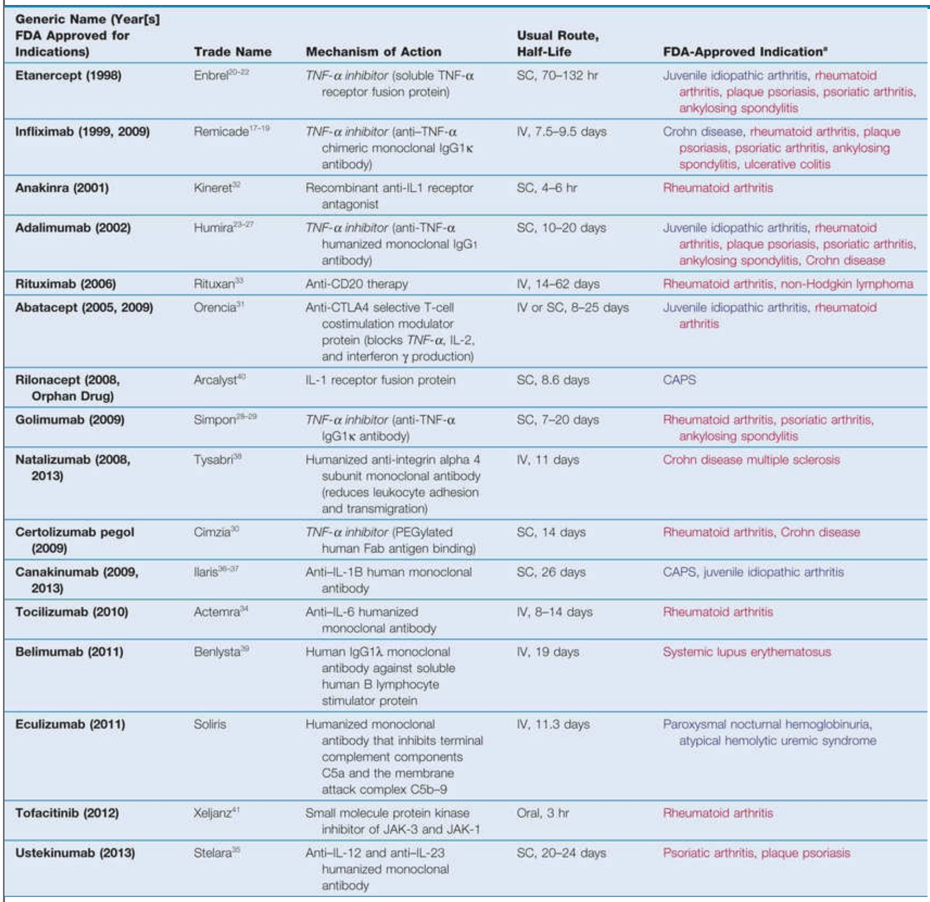
Infections Related to Biologic Modifier Therapy

H. Dele Davies

Biologic response modifiers (BRMs) have been developed to modify host immune responses, such as cytokines, chemokines, and antibodies that naturally protect against infections, but have become pathologic. Synthetic BRMs generally target or mimic natural cytokines or inhibitors, including tumor necrosis factor-α (TNF-α); interleukin-6 (IL-6), IL-12, and IL-23; and the receptors for IL-1α and IL-1β, and are used to restore, boost, or dampen the host immune response. This chapter deals only with BRMs that are used to dampen the response in autoinflammatory and autoimmune conditions. Although highly effective in reducing the underlying symptoms of the targeted condition and associated disability, BRMs also can lead to immunosuppression that persists for weeks to months after therapy.[1] Consequently, many of these drugs have been associated with an increased risk for infection with certain viral and mycobacterial pathogens as well as some fungal, other bacterial, and intracellular pathogens.[2–4] Most of the data on effects of BRMs are from adults,[5–9] with recommendations for children primarily from small case series and cohort studies.[2,10–16] Table 107.1 summarizes the BRMs currently approved by the US Food and Drug Administration (FDA), including their mechanisms of action, routes of administration, half-lives, and indications.[17–41]

TABLE 107.1

FDA-Approved Biologic Response Modifiers and Indications



Generic Name (Year[s] FDA Approved for Indications)	Trade Name	Mechanism of Action	Usual Route, Half-Life	FDA-Approved Indication[a]
Etanercept (1998)	Enbrel[20–22]	*TNF-α inhibitor* (soluble TNF-α receptor fusion protein)	SC, 70–132 hr	Juvenile idiopathic arthritis, rheumatoid arthritis, plaque psoriasis, psoriatic arthritis, ankylosing spondylitis
Infliximab (1999, 2009)	Remicade[17–19]	*TNF-α inhibitor* (anti–TNF-α chimeric monoclonal IgG1κ antibody)	IV, 7.5–9.5 days	Crohn disease, rheumatoid arthritis, plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis
Anakinra (2001)	Kineret[32]	Recombinant anti-IL1 receptor antagonist	SC, 4–6 hr	Rheumatoid arthritis
Adalimumab (2002)	Humira[23–27]	*TNF-α inhibitor* (anti-TNF-α humanized monoclonal IgG1 antibody)	SC, 10–20 days	Juvenile idiopathic arthritis, rheumatoid arthritis, plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, Crohn disease
Rituximab (2006)	Rituxan[33]	Anti-CD20 therapy	IV, 14–62 days	Rheumatoid arthritis, non-Hodgkin lymphoma
Abatacept (2005, 2009)	Orencia[31]	Anti-CTLA4 selective T-cell costimulation modulator protein (blocks *TNF-α*, IL-2, and interferon γ production)	IV or SC, 8–25 days	Juvenile idiopathic arthritis, rheumatoid arthritis
Rilonacept (2008, Orphan Drug)	Arcalyst[40]	IL-1 receptor fusion protein	SC, 8.6 days	CAPS
Golimumab (2009)	Simpon[28–29]	*TNF-α inhibitor* (anti-TNF-α IgG1κ antibody)	SC, 7–20 days	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis
Natalizumab (2008, 2013)	Tysabri[38]	Humanized anti-integrin alpha 4 subunit monoclonal antibody (reduces leukocyte adhesion and transmigration)	IV, 11 days	Crohn disease multiple sclerosis
Certolizumab pegol (2009)	Cimzia[30]	*TNF-α inhibitor* (PEGylated human Fab antigen binding)	SC, 14 days	Rheumatoid arthritis, Crohn disease
Canakinumab (2009, 2013)	Ilaris[36–37]	Anti–IL-1B human monoclonal antibody	SC, 26 days	CAPS, juvenile idiopathic arthritis
Tocilizumab (2010)	Actemra[34]	Anti–IL-6 humanized monoclonal antibody	IV, 8–14 days	Rheumatoid arthritis
Belimumab (2011)	Benlysta[39]	Human IgG1λ monoclonal antibody against soluble human B lymphocyte stimulator protein	IV, 19 days	Systemic lupus erythematosus
Eculizumab (2011)	Soliris	Humanized monoclonal antibody that inhibits terminal complement components C5a and the membrane attack complex C5b-9	IV, 11.3 days	Paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome
Tofacitinib (2012)	Xeljanz[41]	Small molecule protein kinase inhibitor of JAK-3 and JAK-1	Oral, 3 hr	Rheumatoid arthritis
Ustekinumab (2013)	Stelara[35]	Anti–IL-12 and anti–IL-23 humanized monoclonal antibody	SC, 20–24 days	Psoriatic arthritis, plaque psoriasis

[a] FDA approved indication: for conditions in *purple*, safety and efficacy have been established in children <18 years; for indications in *red*, safety and efficacy have only been shown in adults. Infliximab, etanercept, and adalimumab have been used off-label for scleritis, but none is FDA approved for this condition.

CAPS, cryopyrin-associated periodic syndromes (consisting of familial cold autoinflammatory syndrome and Muckle-Wells syndrome); FDA, U.S. Food and Drug Administration; IV, intravenous; SC, subcutaneous.

Data are from references 17 to 41.

Infections Associated With Use of Biologic Response Modifiers

Overall Rate of Serious Infections

Use of BRMs has been associated with elevated risk for developing certain bacterial (especially mycobacterial), viral, and fungal infections. The increased risk for infection likely is also contributed to by the concomitant use of other immunosuppressive agents, such as corticosteroids and methotrexate, and the underlying inflammatory disease.[20,42,43]

A Cochrane review involving more than 60,000 (primarily adult) participants receiving 9 different BRMs (adalimumab, certolizumab, etanercept, golimumab, infliximab, anakinra, tocilizumab, abatacept, and rituximab) for treatment of either rheumatoid arthritis (RA) or cancer[44] showed an overall increased risk for serious infections (defined as associated with death, hospitalization, or use of intravenous antibiotics) with an odds ratio [OR] of 1.37 and 95% confidence interval [CI] of 1.04–1.82, compared with placebo recipients.[44] The highest risks were seen with certolizumab (OR, 4.75; 95% CI, 1.52–18.5) and anakinra (OR, 4.05; 95% CI, 1.22–16.8). The risk for reactivation of tuberculosis (TB) among patients receiving BRMs also was elevated compared with those receiving placebo. Eculizumab (Soliris) is a humanized monoclonal antibody used for the treatment of paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. This drug inhibits terminal complement components and increases the risk for invasive meningococcal infection markedly, a risk not completely ameliorated by conjugate vaccine administration (www.soliris.net).

In pediatric studies, risk for nonmycobacterial infection among patients receiving a BRM (e.g., etanercept) is similar to risk in those receiving the BRM plus conventional disease-modifying antirheumatic drugs (DMARDs) such as methotrexate.[21,22,45–52] Infections in those receiving BRMs are primarily lower respiratory tract and gastrointestinal infections, sepsis, skin infections, and abscesses. Nonetheless, even though there is no clear evidence of increased risk for nonmycobacterial infections in these patients compared with those receiving DMARDs alone, case reports of sepsis and even death among patients receiving a BRM have warranted vigilance and caution when using a BRM in a patient with active infection.

Rituximab-Associated Neutropenia

Rituximab-associated neutropenia is prolonged, lasting from 4 days to 1 year during or after completion of therapy, as reported primarily among adult patients being treated for lymphomas.[53–61] Neutropenia occurs in 0.02% to 6% of treated patients, but occurred in up to 25% in one series. In contrast to other BRMs in which the primary risk is for mycobacterial infections, rituximab is associated with fever and sepsis involving bacterial pathogens, especially *Pseudomonas* spp. Circulating antibodies against neutrophils have been postulated, but not proved as the cause.[61] Among 55 children treated with rituximab for juvenile idiopathic arthritis (JIA) after failure to respond to infliximab and other DMARDs, 17 (31%) developed neutropenia between weeks 6 and 28 of treatment. During a 96-week follow-up period among this cohort, 8 serious infections occurred—all lower respiratory tract infections, including *Pneumocystis jirovecii* and *Mycoplasma* pneumonia—but there were no cases of sepsis or neutropenia-associated fever without a focus.[60] Milder infections were noted, including ear, nose, and throat (14%) and skin (11%) infections and four cases of herpetic infections. The neutrophil count was less than 1500/mm^3 in 9 (16%) of the patients, 1000/mm^3 in 5 (9%) of the patients, and 500/mm^3 in 3 (6%) of the patients. All patients were treated with granulocyte-macrophage colony-stimulating factor (5 μg/kg/day). In 80% of patients, complete depletion of B lymphocytes (CD20$^+$ cells) occurred and persisted at low counts throughout the follow-up period. Serum immunoglobulin M (IgM) and IgG levels also were reduced below the age-related lower limits of normal in 11 patients (20%).

Specific Infections

Tuberculosis.

Use of TNF inhibitors has been associated with reactivation of infections caused by organisms in the *Mycobacterium tuberculosis* complex. In mouse models, TNF-α is known to contribute to granuloma formation and induces and maintains latency of *M. tuberculosis* infection[62]; blockage of TNF-α leads to failure to control bacillary growth and form protective granulomas.[63–66] In a Cochrane review of trials in which patients received BRMs or placebo,[44] the overall OR for Mtb reactivation in BRM recipients was 4.7 (95% CI, 1.2–18.6), with an absolute risk of 20 cases per 10,000 compared with 4 per 10,000 patients receiving placebo.

Studies in adults suggest that the risk for Mtb reactivation may be related to the class of TNF inhibitor, with TNF antibodies (e.g., infliximab and adalimumab) associated with the highest risk, and soluble TNF receptor antibodies (e.g., etanercept) appear to have the lowest risk.[67–70] Although risk appears lower with etanercept, the risk appears increased compared with the general population, but disease tends to be localized, although disseminated infection has been reported.[68,70–74]

In adult patients receiving BRMs, particularly TNF-α inhibitors, Mtb infection is associated with a substantial increase in extrapulmonary and disseminated disease, diagnoses that often require an invasive procedure.[75] In TNF-α–associated tuberculosis, 56% to 62% are reported to have extrapulmonary disease, and 24% to 28% have disseminated disease, compared with rates of 18% and 2%, respectively, in patients with non-HIV–related tuberculosis.[4,69] Because of the diminished host response, many patients do not develop granulomas. The median time to clinical disease varies by BRM—from 12 weeks (infliximab) to 30 weeks (adalimumab) to 46 weeks (etanercept).[74] It should be noted that the risk for Mtb reactivation associated with the underlying autoimmune or inflammatory conditions alone, without medications, is estimated to be twice that of the general population.[76]

Although data are limited for children, several case reports of Mtb reactivation are reported with use of TNF-α inhibitors.[36,68,77,78] However, screening and treating for latent tuberculosis infection (LTBI) before initiating BRM appears to reduce the risk for reactivation substantially. In 2210 adults treated worldwide with golimumab for a variety of rheumatologic conditions, none of 317 who were assessed and treated with isoniazid for LTBI developed disease, whereas 5 cases developed in patients not assessed and treated by week 52.[27]

Nontuberculous *Mycobacterium* Species.

Disease due to nontuberculous mycobacteria (NTM) has been reported to be twice as common as tuberculosis in adults receiving BRMs.[79–81] Pulmonary disease occurs most commonly (56%), but as with tuberculosis, 44% of patients come to attention with extrapulmonary disease. *Mycobacterium avium* complex is most commonly isolated. Absence of an accurate (sensitive and specific) screening test precludes baseline screening.[81]

Varicella-Zoster Virus.

Primary or reactivated varicella-zoster virus (VZV) infections frequently are reported as complications among patients receiving BRM.[2,46,49,82] These data support the importance of appropriate varicella immunization before immunosuppressive and BRM therapy and the recognition of exposures in patients taking any BRM. In at least one study involving the use of etanercept, all 3 patients with primary VZV infection recovered with acyclovir therapy and discontinuation of the BRM.[49]

Data on increased risk for herpes zoster are almost exclusively from adults.[83–86] Patients receiving monoclonal antibodies (infliximab or adalimumab) especially appear to have heightened risk for zoster compared with those receiving etanercept or DMARDs alone.[83] Encephalitis and meningitis attributable to herpes simples virus (HSV) and VZV also have been described in postmarketing surveillance of patients receiving natalizumab.[38]

Herpes Simplex.

Although uncommon, cases of HSV encephalitis, disseminated cutaneous HSV, and localized disease have reported complicating treatment with TNF-α inhibitors.[5,87–91] In one report, a girl with Crohn disease and relapsing HSV-1 peribuccal labialis was successfully treated with infliximab while receiving valacyclovir prophylaxis.[92]

Hepatitis B.

Patients receiving BRMs have an increased risk for hepatitis B virus (HBV) reactivation.[93,94] Patients who test positive for hepatitis B surface antigen (HBsAg) have the greatest (up to 39%) risk, but up to 5% of patients with hepatitis B core antibody (HBcAb) who are HBsAg negative (indicating immunity due to previous infection rather than vaccine) have had HBV reactivation up to 2 years after immunosuppression with BRMs.[95,96] In patients taking rituximab or TNF-α antagonists, the highest risk for reactivation is found among those with the lowest levels of hepatitis B surface antibody (HBsAb).[93,94]

Endemic Mycoses and Other Fungi.

Numerous cases and case series of fungal infections (*Aspergillus*,[89,91,97] *Coccidioides*,[98–100] *Histoplasma*, *Cryptococcus*, *Sporothrix*, and *Candida* spp.)[3,5,80,89,97,101–104] have been reported during treatment with BRMs. *Histoplasma* is the most common invasive fungal agent, reported 3 times more frequently than tuberculosis among recipients of BRMs.[3,80,102,103] Histoplasmosis and acute tuberculosis share symptoms, signs, (cough, fever, chills, night sweats, weight loss, and possible skin or mouth lesions), and chest radiographic findings, making it difficult yet critical to establish the correct diagnosis. Histoplasmosis generally manifests as fever of unknown origin due to disseminated disease in up to three fourths of patients and has high mortality (50%); pulmonary histoplasmosis is less common.[102] Nonspecific diagnostic clues include pancytopenia and elevated serum hepatic enzymes; definitive diagnosis requires antigen detection in the urine and serum or isolation in culture of bone marrow. Other fungal infections identified less commonly include *P. jirovecii* pneumonia (PCP), aspergillosis, and severe *Candida* spp. infections.[4]

Pneumocystis jirovecii and Rituximab Treatment.

P. jirovecii colonizes 16% to 29% of adults with systemic autoimmune inflammatory diseases.[105–107] Although PCP has been identified in patients receiving several BRMs,[108–110] rituximab (which depletes B lymphocytes that are crucial to control *P. jirovecii*) particularly is associated with increased risk for PCP.[111] There is no clear benefit of screening for PCP by use of induced sputum or of chemoprophylaxis for PCP in patients receiving rituximab.[106,112]

Human Immunodeficiency Virus.

There are no reports of increased rate of HIV infections among patients receiving BRMs.

Other Infections.

Opportunistic-type infections, including those due to cytomegalovirus, Epstein-Barr virus (EBV),[89] and *Listeria*[113–115] and *Legionella* spp.,[116,117] have been noted in case reports or case series during treatment with BRMs used alone or with other DMARDs. However, in one study of infliximab over 6 weeks to 5 years, there was no evidence of EBV or cytomegalovirus reactivation during treatment based on viral load or polymerase chain reaction testing.[118,119]

Considerations for Patients Before Initiation, During Use, and After Discontinuation of Biologic Response Modifier Therapy

General Precautions

Table 107.2 summarizes recommended screening and immunization practices for patients before initiating, during, and after discontinuation of BRM. Consideration of whether to defer BRMs in order to immunize against vaccine preventable diseases, or to delay immunizations, involves tradeoffs and should be made with the specialist managing the patient (e.g., gastroenterologist, rheumatologist, dermatologist). Nonetheless, application of some common principles can help minimize the risk for serious infections for patients receiving BRMs:

TABLE 107.2

Summary of Suggested Screening/Immunizations Before Initiating, During, and After Discontinuation of Biologic Response Modifier Therapy[a]

Before Initiating BRM[a]	
Thorough history	Document prior vaccines, antibody testing when indicated (routine antibody testing not recommended for varicella) Query about possible exposure and epidemiologic risk factors for histoplasmosis and coccidioidomycosis Query about history of recurrent HSV Consider serologic testing for Epstein-Barr virus Screen for past hepatitis B and determine need for vaccine (see Table 107.3)

Routine immunizations	Follow current AAP, CDC, and American Academy of Family Physician guidelines[b,132] Give recommended inactivated or subunit vaccines ≥2 weeks before initiation of BRM Consider safety of giving live virus vaccine(s); if appropriate, give ≥4 weeks before initiating BRM[122]
Tuberculosis	Test for latent tuberculosis and manage based on result (see reference 148 for algorithm)
During BRM[a]	
Routine immunizations	Should still receive routine inactivated, polysaccharide, recombinant, or subunit vaccine[b,c] Give annual inactivated influenza vaccine[122] Avoid live vaccines, unless under special circumstances with help of infectious diseases specialist[122]
Immunizing immunocompetent household contacts (before or during treatment)?	Follow AAP guidelines for immunizing household contacts of immunocompromised patients[122]
Risk for listeriosis	Avoid unpasteurized milk and milk products, uncooked meats[133]
Febrile or serious respiratory illness during BRM therapy	Consider stopping BRM and actively search for infections, including bacterial, mycobacterial, and opportunistic infections
After Discontinuation of BRM[a]	
Routine inactivated immunizations	Should receive routine inactivated, polysaccharide, recombinant, or subunit vaccine[b,c]
Live virus vaccines	See text and consult infectious diseases specialist for timing

[a] Guidance should be considered only as such. Each situation should be guided by clinical scenario and with the help of an infectious diseases consultant.

[b] If receiving/received eculizumab, should be given meningococcal conjugate vaccines (serogroup B as well as ACWY) as for high-risk patients (see Chapter 125).

[c] If receiving (received) rituximab, may respond adequately.

AAP, American Academy of Pediatrics; *BRM,* biologic response modifier; *CDC,* Centers for Disease Control and Prevention; *HSV,* herpes simplex virus.

- Consider all patients with new diagnoses of rheumatologic or immune-mediated conditions, such as Crohn disease or JIA, as current or future candidates for a BRM and screen for potential opportunistic infections *at the time of diagnosis* and before starting immunosuppressive agents.
- Do not give BRMs to patients during clinically significant acute infections.
- Exercise caution in prescribing BRMs to children receiving treatment for chronic infections, have a history of recurrent infections, or have underlying conditions that may predispose them to chronic infection (including HIV).[70]
- Consider potential opportunistic infections endemic in the

patient's area of residence (e.g., histoplasmosis, coccidioidomycoses) before starting a BRM, including determination of prior exposure and potential risk for reactivation or infection during treatment with the BRM.

- Withhold the BRM immediately if the patient develops symptoms suggestive of an opportunistic infection; aggressively seek confirmation of the diagnosis, appropriately manage the infection, and await resolution of symptoms.
- Monitor neutrophil counts weekly and measure serum immunoglobulin levels if there are recurrent ear, nose, or throat infections in patients receiving rituximab.

Managing Immunizations

Immunization Before Initiating Biologic Response Modifier Therapy.

All children planned to receive a BRM first should receive immunizations guided by current recommendations of expert organizations (see http://aapredbook.aappublications.org/site/resources/IZSchedule.pd
Recommendations include the following:

- Obtain a thorough immunization history and history of prior vaccine preventable disease. Consider specific antibody serologic testing when the history is inadequate, except for varicella, for which vaccination is the recommended course if there is adequate time for safe administration (4 weeks minimum) before initiating BRM.
- Administer inactivated vaccines at least 2 weeks before initiating BRM.
- Administer live virus vaccines (varicella; measles, mumps, and rubella [MMR]; rotavirus; live, attenuated influenza) at least 4 weeks before initiating BRM. Both MMR vaccine and a tuberculin skin test (TST) can be administered on the same day; otherwise, if MMR has been given, TST should be delayed for 4 to 6 weeks because of suppression of TST response by MMR vaccine.[121] Interpretation of TST is not affected by inactivated, toxoid, polysaccharide, or recombinant or subunit vaccines.

- *Do not* administer live virus vaccines to children who have underlying conditions that suppress the immune system (e.g., lupus) or who are receiving medications that suppress the immune system, except in very special circumstances.[122] Live virus vaccines should not be administered for at least 1 month after discontinuation in patients receiving high-dose corticosteroids (i.e., ≥2 mg/kg/day of prednisone or its equivalent, or ≥20 mg/day for those weighing more than 10 kg >14 days).[122]

Immunization During Biologic Response Modifier Therapy.

Responses to inactivated, polysaccharide, recombinant, or subunit vaccines, including the inactivated influenza vaccines, are reduced but adequate; inactivated vaccines should be given to patients receiving BRMs when indicated.[123–126] The possible exception is receipt of rituximab, which significantly impairs antibody response, especially for pneumococcal conjugate vaccines, during therapy and for up to 6 months after discontinuation.[127–131] Every effort should be made to immunize patients who will receive rituximab before commencement. To guide need for additional vaccine doses and to manage future exposures during BRM therapy, postimmunization serum antibody levels measured 4 to 6 weeks after immunization may be helpful.[122] Patients receiving BRMs or other immunosuppressive drugs during treatment should not be given live, attenuated influenza vaccine or other live vaccines because of risk for dissemination and adverse outcomes, except in special circumstances as recommended by an infectious diseases specialist.[122] Inactivated influenza vaccine should be administered annually.

Immunization After a Biologic Response Modifier Is Discontinued.

Data are insufficient currently to guide how soon live vaccine may be given after discontinuation of BRM.[122]

Immunizing Immunocompetent Household Contacts of Patients Receiving Biologic Response Modifiers.

Household members should all receive recommended inactivated vaccines following guidelines recommended by the American

Academy of Pediatrics for household contacts of immunocompromised patients.[122] Household contacts of people receiving BRM should not be given oral polio vaccine (no longer given in the United States). MMR, varicella, and rotavirus vaccines should be given to household contacts as recommended. Vaccine strain transmission is very low, and the disease associated with the virus is expected to be mild. If a household contact develops a vesicular rash after receipt of the varicella vaccine, separation of that contact from the BRM recipient may be prudent for the duration of the rash. Administration of varicella-zoster immune globulin is not indicated. Influenza vaccine should be given annually to all household contacts who are 6 months or older,[122] using any age-appropriate vaccine.

Evaluation and Treatment of *Mycobacterium tuberculosis* Infection

Screening for LTBI and treatment should be performed in all patients immediately after diagnosis of rheumatologic or inflammatory and autoimmune conditions for which BRM therapy may be needed regardless of risk factors and using the following principles[134–136]:

- Consider options for screening based on the clinical scenario. Use a TST or an interferon γ release assay (IGRA) or both. Either QuantiFERON-TB Gold in-tube assay (QFT; Cellestis/Qiagen, Carnegie, Australia) or the T-SPOT.*TB* assay (T-SPOT; Oxford Immunotec, Abingdon, United Kingdom) IGRA is acceptable.[136,137]
- If there are no risk factors for LTBI (prior history of TB, prior history of positive TST, history of exposure to someone with active TB, travel to an area with endemic TB in the past 12 months, or foreign-born patient or parents from area with endemic TB) and *no* symptoms suggestive of TB, choose baseline screening method based on age. In general, TST should be used to screen children younger than 5 years, while an IGRA should be used for children older than 5 years.[137]
- If *any risk factor* for LTBI is present or any symptom is suggestive of TB, test for LTBI with *both* the TST and an IGRA. If either test is positive, perform chest radiography (posteroanterior and lateral)

and begin appropriate treatment for either LTBI or TB disease (after further evaluation), depending on clinical and laboratory findings.[137] IGRA should not be relied on to test for LTBI in children younger than 2 years because of lack of data and high risk for progression to disease. IGRA can be considered in children 2 years and older, especially those who have received bacille Calmette-Guérin vaccine.[137]

- Query patients for TB symptoms and risk factors *each year*; routine annual TST or IGRA is not recommended.
- If change in risk or new symptoms suggestive of TB infection develop during BRM, further investigate and reassess risk (i.e., repeat both the TST and IGRA if the baseline was negative and perform chest radiography).
- Treat all patients with LTBI.[134,135]
- Withhold BRM and other DMARDs if active TB is suspected until infection is excluded or is under control. An infectious diseases specialist should guide isolation precautions and management, including considerations of risks for drug-resistant infection and presence of disseminated or extrapulmonary disease.[138]

Evaluation for Nontuberculous Mycobacteria and Fungi

No screening is recommended, but NTM should be considered in the differential diagnosis of patients taking BRMs for whom TB is being considered, or those with febrile illnesses, cervical or unexplained lymphadenitis, or other focal infections.

Both histoplasmosis and coccidioidomycosis have signs and symptoms that overlap substantially with tuberculosis; patients should be queried about possible exposure and epidemiologic risk factors.[102,104,139–141] Routine serologic screening is not indicated for histoplasmosis because up to 90% of persons living in a histoplasmosis belt will have acquired the fungus with self-resolving infection and positive serology before adulthood, and negative serology does not predict risk for development of histoplasmosis during therapy.[102] Similarly, residence in endemic geographic areas (e.g., southwestern United States and southern California) is a risk for developing coccidioidomycoses,[98,99,141–144] and certain racial groups (Filipino, Hispanic, black, American Indian, and Asian people), pregnant women during the third trimester, and women in the immediate postpartum period have heightened risk for severe disease. Invasive and disseminated disease occurs in about 2% of patients receiving BRM who reside in at-risk regions. For patients with signs or symptoms compatible with acute histoplasmosis[102,104,139,140] or coccidioidomycosis[98–100,142–144] during treatment, BRM should be withheld immediately and evaluation performed urgently (e.g., chest radiography and serologic, antigen detection, and culture tests).

Evaluation for Certain Viruses

Varicella-Zoster Virus and Herpes Simplex Virus.

Routine serologic testing should not be performed for VZV because of wide variability in the sensitivity of the assays in assessing immunity after VZV immunization. If there is doubt about immunity based on the history or inadequacy of records, the patient should be immunized (with the timing and other precautions discussed earlier for live vaccines).[145]

BRM therapy should be stopped immediately in patients suspected of having VZV or HSV infection and diagnosis sought using a combination of clinical, serologic, and polymerase chain reaction testing of skin lesions (i.e., vesicles or papules). Therapy should be initiated with acyclovir or valacyclovir pending confirmation of diagnosis. Prophylaxis with valacyclovir or acyclovir is considered in patients with recurrent HSV who are being considered for BRM therapy.

Epstein-Barr Virus.

Baseline serologic testing for EBV should be assessed at the time of diagnosis of the underlying rheumatologic condition and subsequent testing should be considered if the patient develops becomes symptomatic or has signs associated with EBV such as a mononucleosis-like illness or excessive fatigue.

Hepatitis B Virus.

Table 107.3 summarizes the approach to screening for previous hepatitis B infection before initiating BRM, based on the serology and immunization records, along with suggested management. Baseline serum hepatic enzyme levels should be obtained.[146–151] Patients recommended for immunization (those who are negative for HBsAg, HBcAb, and HBsAb or who are positive only for HBsAb positive) should be immunized with the first dose of hepatitis B vaccine at least 2 weeks before initiation of BRM.[1,152] The decision to give the full series of HBV vaccinations before starting BRM includes weighing benefits versus risks of delaying BRM.[125,153] It should be noted that a transiently positive serologic test result can occur after receipt of immune globulin intravenous. Regular monitoring (every 1–3 months, depending on underlying HBV infection) hepatic enzymes, HBsAg, hepatitis B core e antigen, and HBV DNA levels should be conducted for all patients considered at risk for HBV reactivation (chronic, resolved, or occult infection) and continued for at least 6 months after discontinuing BRM.

TABLE 107.3

Screening Tests for Hepatitis B Virus Infection, Interpretation, and Recommendations Before Biologic Response Modifier Therapy

HBV Infection	HBsAg	HBsAb	HBcAb	HBcIgM	Abnormal Lfts and/or Symptoms	Additional Testing	Management	Comm
Uninfected, nonimmune	−	−	−	−	−	−	Safely treat with BRM	Admin HBV vaccin before BRM therap
Vaccinated	−	+	−	−	−	−	Safely treat with BRM	For HB <10 mIU/m sugges HBV booste
Acute	+	−	+	+	+	−	Defer BRM therapy	
Chronic	+	−	+	−	+/−	HBeAg, HBeAb, HBV DNA	Treat with BRM in consultation with ID consultant or hepatologist	
Resolved	−	+	+	−	−	HBV DNA	Treat with BRM in consultation	

							with ID consultant or hepatologist	
Occult	−	−	+	−	−	HBV DNA	Treat with BRM in consultation with ID consultant or hepatologist	

HBcAb, hepatitis B core antibody; HBcIgM, hepatitis B core antibody; HBeAb, hepatitis B core antibody; HBeAg, hepatitis B core e antigen; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; ID, infectious disease; LFT, liver function test; *BRM,* biologic response modifier.

From Motaparthi K, Stanisic V, Van Voorhees AS, et al. From the Medical Board of the National Psoriasis Foundation: recommendations for screening for hepatitis B infection prior to initiating anti-tumor necrosis factor-alfa inhibitors or other immunosuppressive agents in patients with psoriasis. J Am Acad Dermatol 2014;70:178–186.

Key Points

Biologic Response Modifiers

- Biologic response–modifiers (BRMs) are effective for management of patients with a variety of autoimmune and inflammatory conditions but also can lead to immunosuppression that persists for weeks to months after discontinuation of therapy.

- BRMs are associated with an increased risk for acquisition or reactivation of some serious and opportunistic infections, especially *Mycobacterium tuberculosis*, nontuberculous mycobacteria, certain fungal and intracellular pathogens and viral infections, including hepatitis B.

- Screening, appropriate immunization, and anticipatory guidance are critical before initiating BRMs to reduce the risk for infection and disease and for negative outcomes from infections.

- In general, BRMs should be withheld when active infection is suspected or proved until adequately controlled.

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108

Infectious Complications of Corticosteroid Therapy

Kari A. Simonsen, H. Dele Davies

Corticosteroids play a key role in the management of many neoplastic, autoimmune, allergic, and autoinflammatory disorders. Corticosteroids also sometimes are used for their lifesaving lympholytic and anti-inflammatory effect during infection, for example, to prevent airway obstruction during croup or Epstein-Barr virus–associated tonsillitis, or to dampen immune reconstitution inflammatory syndrome (IRIS) when treating pulmonary or brain infection in patients with acquired immunodeficiency syndrome (AIDS). Corticosteroid also is given almost universally after surgery on airway structures or before extubation. Despite widespread applications, utility is tempered by the occurrence of myriad adverse effects, including increased risk and severity of infections.

Corticosteroids can be either naturally produced or laboratory-synthesized hormones; glucocorticoids generally regulate inflammation and metabolism, whereas mineralocorticoids regulate water and sodium.[1] Glucocorticoids are highly lipid soluble and readily penetrate cell membranes, binding to a specific receptor present in all nucleated cells, which allows both anti-inflammatory and metabolic effects without specificity.[2] Corticosteroids generally are metabolized by the hepatic P450 system. Direct application to sites of inflammation (e.g., topical, inhaled, epidural) provides high local concentrations and bypasses rapid metabolism.[3]

Glucocorticoids exert anti-inflammatory effects through multiple mechanisms: reduction in circulating leukocyte populations, including neutrophils, lymphocytes, monocytes, eosinophils, and basophils; inhibition of production of cytokine and other proinflammatory molecules; inhibition of synthesis of interleukin-2 (IL-2) receptor; and reduction of expression of major histocompatibility complex (MHC) molecules on the surface of antigen-presenting cells, leading to suppression of immunologic response. With prolonged administration, cell-mediated immunity is suppressed.[4]

Initially, administration of a glucocorticoid causes a temporary increase in the peripheral circulation of neutrophils due to enhanced release from bone marrow and reduced migration from blood vessels. Ultimately, the peripheral leukocyte count declines because of migration of lymphocytes, monocytes, basophils, and eosinophils from the peripheral vasculature to the lymphoid tissues.[5] Neutrophil function and bactericidal activity are impaired at least in part owing to reduced adherence to vascular endothelium and diapedesis into interstitial spaces.[6]

Infectious Adverse Effects of Glucocorticoids

It is challenging to confirm a direct causal relationship between corticosteroid use and increased risk or severity of infection because of the wide range of underlying diseases for which corticosteroids are prescribed and the combination immunosuppressive therapies that many patients receive. Although much of available data are derived from observational studies in adults, the body of data in children suggest that extrapolation of effects to children is reasonable. Corticosteroids have been associated with increased risk for infection across multiple immunocompromised states as well as in previously immunocompetent hosts.[7,8] In a meta-analysis of adult and pediatric patients receiving corticosteroids, the relative risk (RR) for infectious complications was 1.6 (95% confidence interval [CI], 1.3–1.9; $P < 0.001$).[9] Confining analysis to adults taking daily doses of prednisone between 20 mg and 40 mg, the RR of infection was 2.1 (95% CI, 1.3–3.6): a pediatric subset analysis was not reported. Increased rates of infection were not seen in adult and pediatric patients given prednisone at daily doses of <10 mg or cumulative doses of <700 mg when analyzed together.[9] Thus higher doses of glucocorticoids and combination therapy with other immunosuppressive agents elevate the risk for infectious complications.[10] Excess risk or severity or infections caused by bacterial, fungal, viral, and parasitic pathogens has been reported in patients receiving glucocorticoid therapy (Table 108.1). The anti-inflammatory properties of the glucocorticoids also can modify typical signs and symptoms of infection, resulting in presentation at a later stage of the infection.[11]

TABLE 108.1

Infections Reported With Excess Risk or Severity in Patients Treated With Corticosteroids

Bacteria	Gram-positive—*Staphylococcus aureus, Listeria monocytogenes, Nocardia* spp. Gram-negative—*Pseudomonas, Klebsiella, Salmonella, Legionella* spp. *Mycobacterium* spp.
Fungi	*Aspergillus, Candida, Cryptococcus*, endemic mycoses, *Fusarium, Scedosporium, Trichosporon*, zygomycetes
Viruses	Herpesviruses, enteroviruses, hepatitis B and hepatitis C
Parasites	*Strongyloides stercoralis*

Bacterial Infections

Bacterial infections are the most common complication of corticosteroid use, and potentially any bacterial pathogen can be causative.[9] Bacterial sepsis occurred 1.5 times more frequently in adult and pediatric patients receiving systemic corticosteroids in one meta-analysis; among all patients in the dataset, the mean daily drug exposure was equivalent to 35 mg of prednisone, with the mean total exposure of 2200 mg.[12] A meta-analysis of prediction models for neonatal intensive care unit (NICU)–associated sepsis found postnatal corticosteroid use to have a statistically significant predictive association.[13] Other studies of NICU-associated sepsis have demonstrated increased rates associated with antenatal corticosteroids to promote pulmonary maturation as well as postnatal corticosteroids, primarily dexamethasone. These risks must be considered in context of demonstrated benefits of antenatal corticosteroids to reduce intraventricular hemorrhage, respiratory distress syndrome, bronchopulmonary dysplasia, and all-cause neonatal mortality.[14]

Surgical site infections are significantly increased among patients receiving long-term corticosteroid immunosuppressive therapy, including neonatal and pediatric patients younger than 5 years undergoing complex cardiac surgery,[15,16] and data suggest that corticosteroids may be associated with increased overall morbidity after cardiac surgery, particularly in lower risk patients.[17] An increased risk for surgical site infection has been associated with corticosteroid use in adults with ulcerative colitis.[18]

Long-term corticosteroid use increases the risk for bacterial opportunistic infections related to impaired cell-mediated immunity. Bacterial pathogens include mycobacteria and *Nocardia* and *Legionella* spp.[19,20] In a large case-control study of adults, the adjusted odds ratio of tuberculosis in the group receiving corticosteroids compared with no steroid use was 4.9 (95% CI, 2.9, 8.3).[21] Pediatric-specific data are limited.

Fungal Infections

Invasive fungal infections are most frequently observed in patients receiving chronic corticosteroid therapy who are profoundly immunocompromised, such as hematopoietic stem cell transplantation (HSCT) and solid organ transplantation patients, oncology patients, and patients with collagen-vascular disorders.[22] Higher doses and longer duration of glucocorticoid therapy are associated with higher risk and worse prognosis for invasive fungal infection, and lower doses and alternate-day regimens have been shown to be protective.[23,24] In addition to increasing risk for invasive fungal infection, the anti-inflammatory properties of glucocorticoids also can result in delayed recognition because of modified signs and symptoms of infection.[22] Invasive aspergillosis is an important pathogen in allogeneic bone marrow transplantation and is the most common cause of infectious death among these patients, resulting in 10% of mortality in the late posttransplantation period.[22-23] However, invasive aspergillosis, the most common mold infection associated with glucocorticoid administration, has been reported in patients receiving only high-potency inhaled glucocorticoids, without other immunosuppressive therapies.[25]

Glucocorticoids are an independent risk factor for invasive yeast infections, including invasive candidiasis and candidemia. Increased risk is reported in patients with cancer and HSCT, hemodialysis, systemic lupus erythematosus, or surgery and in premature neonates.[22,26–29] In one study of premature neonates, risk for invasive candidiasis was 7.5-fold higher in infants treated with glucocorticoids for hypotension compared with unexposed infants.[29] In a recent study during routine use of antifungal prophylaxis in premature infants, corticosteroid use was not a statistically significant risk factor for invasive candidiasis, suggesting that risk can be successfully mitigated.[30]

Pneumocystis jirovecii pneumonia (PCP) is associated with prolonged and high-dose glucocorticoid administration in children and adults with cancer, solid-organ and allogeneic bone marrow transplantations, and collagen-vascular disorders.[22] PCP also has occurred in asthmatic children treated with high doses of systemic corticosteroids.[20] Crypotococcal infections, including meningitis, have been described in non-AIDS patients receiving glucocorticoids, although no specific pediatric data are available.[22] Primary and reactivated endemic fungal infections also are reported in patients receiving long-term glucocorticoids. Although histoplasmosis is reported most frequently, coccidioidomycosis, blastomycosis, penicilliosis, and sporotrichosis also have been reported, primarily in adults.[22]

Viral Infections

Herpesviruses.

The most frequently described viral complication of corticosteroid use is reactivated herpesvirus infections. Oncology and transplantation patients with significant immunosuppression are at greatest risk. Severe fulminant hepatitis is associated with herpes simplex virus (HSV) or varicella-zoster virus (VZV), and cytomegalovirus (CMV) is an important cause of pneumonia in immunosuppressed patients with prominent T-lymphocyte dysfunction.[19] Pediatric data show mixed results regarding the risk for severe primary VZV infection in patients receiving corticosteroids. In a case-control population chosen to represent immunocompetent children exposed to corticosteroids, there was no increased risk for severe VZV (odds ratio [OR], 1.6; 95% CI, 0.2,16.9); conversely, in a case-control cohort inclusive of immunosuppressed patients receiving glucocorticoids, including children undergoing treatment for acute leukemia, the OR for severe varicella was a remarkable at 178 (95% CI, 59, 541).[31,32] Of note, both of these studies were conducted before the era of universal varicella immunization in the US. When primary VZV infection is diagnosed in children receiving 2 mg/kg/day of corticosteroids for >14 days, intravenous acyclovir therapy is recommended to reduce the risk for severe infection.[33]

Other Common Viruses.

The course of viral infections can be more severe when corticosteroids are given as therapeutics. A meta-analysis of data from the 2009 H1N1 influenza pandemic did not support the use of corticosteroids for severe influenza and showed a trend toward increased mortality among corticosteroid-treated patients of all ages.[34] In addition, during enterovirus 71 outbreaks, children receiving injectable glucocorticoids early in the illness as outpatients were more likely to progress to severe, life-threatening infection.[35]

Hepatitis B and C Viruses.

Reactivation to active replication of hepatitis B virus (HBV) and hepatitis C virus (HCV) can follow corticosteroid therapy with clinically significant consequences. In addition to the immunosuppressive effects, corticosteroids stimulate HBV replication in vitro. Although most clinical data are in adults receiving chemotherapy for malignancies, in a meta-analysis of risk factors among oncology patients, younger age and corticosteroid use were significant risks for HBV reactivation.[36–38]

Parasitic Infections.

Corticosteroid use increases the risk for symptomatic strongyloidiasis (RR, 2.29–3.3).[39] Severe strongyloidiasis due to amplification of the parasite's autoinfective cycle has been associated with glucocorticoids used for chemotherapy, after transplantation, and for rheumatologic conditions in adults. Disease can occur 30 years or later after infestation in endemic areas, and overall mortality is high (59%), with secondary bacterial or fungal sepsis significantly contributing to morbidity and mortality.[40]

Other Considerations

Administration of Vaccines

For patients receiving corticosteroid therapy lasting >2 weeks at doses ≥2 mg/kg/day of prednisone or its equivalent, or ≥20 mg/day for those weighing more than 10 kg, live virus vaccines should be deferred for 1 month after corticosteroid discontinuation. Prolonged corticosteroid therapy can reduce the immunologic responses to vaccines, including influenza and pneumococcal vaccines.[41,42] Inactivated vaccines can be given routinely while children are receiving corticosteroid therapy, or they can be deferred until therapy ends if the condition requiring corticosteroid treatment is anticipated to resolve and the patient can be recalled for vaccine administration.[33] When initiation of corticosteroid therapy can be anticipated, live virus vaccines should be given ≥4 weeks before, and inactivated vaccines ≥2 weeks before commencement of immune suppression with corticosteroids.[33]

Respiratory syncytial virus (RSV) prophylaxis with palivizumab may be indicated for certain patients requiring chronic corticosteroid use. The American Academy of Pediatrics recommends RSV seasonal palivizumab administration for former preterm infants born before 32 weeks, 0 days of estimated gestational age who required at least 28 days of oxygen after birth and who continue to require supplemental oxygen, chronic systemic corticosteroid therapy, or bronchodilator therapy within 6 months of the start of their first or second RSV season.[43]

Prevention of Opportunistic Infection

Patients initiating long-term corticosteroid therapy first should be screened with a tuberculin skin test or interferon γ release assay, and those identified with latent tuberculosis infection should be treated with an appropriate regimen.[44,45] Patients requiring prednisone doses of ≥20 mg/day for >30 days should also be considered for PCP prophylaxis using trimethoprim-sulfamethoxazole, dapsone, or atovaquone.[46] To prevent severe strongyloidiasis, oral ivermectin or albendazole is recommended for patients who have lived in or traveled to endemic areas even if the risk was years before initiation of immunosuppression with corticosteroids.[47]

Management of Patients Receiving Cortiocosteroid Therapy

Clinicians should maintain a low threshold for considering infection in patients receiving corticosteroids because classical signs and symptoms can be altered. Diagnostic and therapeutic considerations should include both typical and opportunistic infections. Decisions regarding whether corticosteroids should be continued in the presence of documented infection should be individualized, considering adverse infectious complications with continuation, the patient's underlying condition, and the potential for corticosteroid-related hypothalamic-pituitary-adrenal axis suppression and adrenal insufficiency with discontinuation.[48]

Future Directions

Future directions in the management of immunosuppressive agents and the conditions requiring them should include investigation into more specific targets for immunosuppression that minimize adverse effects and degree of immune impairment, along with improved diagnostics to identify infectious complications expeditiously in patients who may not manifest typical inflammatory signs and symptoms. Use of molecular diagnostics to identify respiratory virus should enlighten potential risks of corticosteroid use for status asthmaticus in acutely infected children.

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Human Immunodeficiency Virus and the Acquired Immunodeficiency Syndrome

OUTLINE

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Epidemiology and Prevention of HIV Infection in Children and Adolescents

Jennifer S. Read

The epidemiology of infection with human immunodeficiency virus type 1 (HIV) in children and adolescents has evolved dramatically since the first case of pediatric HIV infection was described in 1983.[1] This evolution is due in part to improvements in the management of HIV infection, with resultant increased survival of infected individuals. This chapter addresses the epidemiology of HIV infection among children and adolescents, clinical manifestations and progression of disease, and prevention of HIV infection in children and adolescents.

Epidemiology

The epidemiology of HIV infection varies dramatically between resource-poor and resource-rich settings around the world. Estimates of the extent of the HIV epidemic, globally and in the United States, are updated regularly by the Joint United Nations

Programme on HIV/AIDS (UNAIDS)[2] and by the US Centers for Disease Control and Prevention (CDC),[3] respectively. In the US, black and other minority infants, children, and adolescents are disproportionately affected by HIV infection.[3] HIV transmission to infants, children, and adolescents can occur through sexual contact (vaginal, anal, or orogenital), percutaneous blood exposure (from contaminated needles or other sharp instruments), mucous membrane exposure to contaminated blood or other body fluids, and transfusion with contaminated blood products.[4] Children also can acquire HIV infection through mother-to-child transmission.[4]

Of the estimated 36.7 million people living with HIV infection in 2015, 17.8 million were women and 1.8 million were children younger than 15 years, and most HIV-infected people (25.5 million) resided in sub-Saharan Africa.[2] An estimated 2.4 million HIV-infected individuals were in western and central Europe and North America. Of the estimated 2.1 million new infections in 2015 (91,000 in western and central Europe and North America), 1.9 million were among adults and 150,000 among children.[2] Finally, there were an estimated 1.1 million AIDS-related deaths in 2015 (22,000 in western and central Europe and North America).[2] In 2014, the number of persons living with a diagnosis of HIV infection in the US and dependent areas with confidential name-based HIV infection reporting included 2494 children (<13 years of age).[3]

Both in the US and globally, mother-to-child transmission is the most common means of acquisition of HIV infection by children (Table 109.1). For example, of the 2494 children reported to be living with HIV infection in the US in 2014,[3] 2012 (81%) were classified as having acquired infection through mother-to-child transmission.[3] Although there has been a dramatic decrease in the rate of mother-to-child transmission of HIV and in the number of pediatric HIV infections and AIDS cases in the US, mother-to-child transmission has not been eliminated in the US. In 2006, there were an estimated 171,400 HIV-infected women aged 13 to 44 years in the US and five dependent areas, with an estimated 8700 births to these women.[5] The estimated number of cases of mother-to-child transmission of HIV in the US peaked in 1991 (1650 cases).[6] By 2005, the number of cases of mother-to-child transmission in the US had decreased to an estimated 215 to 370, representing a transmission rate of approximately 2.8%.[7]

TABLE 109.1

Modes of Acquisition of HIV Infection in Children and Adolescents

Children	Adolescents
MOST COMMON	
Mother-to-child transmission	Sexual transmission • Males: male-to-male sexual transmission • Females: heterosexual transmission • Injection drug use
OTHER	
Transfusion of contaminated blood or blood products if effective screening not available (e.g., among patients with hemophilia early in the HIV epidemic in the US) Mucous membrane exposure to contaminated blood or other body fluids (e.g., through receipt of food that has been prechewed by an HIV-infected caregiver with bleeding gums or open sores in the mouth) Sexual abuse	Percutaneous blood exposure (from contaminated needles or other sharp instruments, e.g., with tattooing)

Mother-to-child transmission of HIV can occur during pregnancy, around the time of labor and delivery, and postnatally (through breastfeeding).[8] Most transmission occurs during the intrapartum period (both in breastfeeding and nonbreastfeeding populations).[9] Rates of mother-to-child transmission of HIV were calculated in studies conducted in various countries before the development and implementation of interventions to decrease transmission.[10] Usually a transmission rate in the range of 25% to 30% was reported. Higher transmission rates were observed in resource-poor settings (13%–42%) compared with rates in resource-rich settings (14%–25%), in part attributed to the greater proportion of breastfeeding women in resource-poor settings.

Various risk factors for mother-to-child transmission of HIV have been identified or are under investigation and can be categorized as follows: (1) the amount of virus to which the child is exposed (e.g., maternal viral load,[11–15] expressed as copies/mL of HIV RNA); (2) the duration of such exposure (e.g., the duration of ruptured membranes[16] or of breastfeeding,[17] vaginal versus cesarean delivery before labor and before ruptured membranes[18,19]); and (3) other factors, including those facilitating the transfer of virus from mother to child (e.g., mixed breastfeeding,[20,21] maternal breast pathology,[13,22–24] and infant oral candidiasis[23,24]). In addition to these risk factors, characteristics of the virus and the child's susceptibility to infection are important.

Improved estimation of HIV incidence is now possible with newer assays that differentiate between recent and chronic HIV infections.[25] Many cases of HIV infection in young adults represent infections that actually were acquired during adolescence, but were not recognized until several years later. In 2014, the number of persons living with a diagnosis of HIV infection in US and dependent areas with confidential name-based HIV infection reporting included 6161 adolescents (13–19 years of age) and 32,195 young adults (20–24 years of age).[3] Among the estimated 734,506 male adults and adolescents living with HIV infection in 2014, 513,045 (70%) of these infections were acquired through male-to-male sexual contact, 83,020 (11%) were due to injection drug use, 53,166 (7%) were due to male-to-male sexual contact and injection drug use, and 77,479 (10%) were due to heterosexual contact[3] (see Table 109.1). In contrast, among the estimated 235,613 female adults and adolescents living with HIV infection in 2014, 175,581 (74%) were acquired through heterosexual contact and 53,222 (23%) from injection drug use[3] (see Table 109.1).

Aside from mother-to-child transmission, sexual transmission, and transmission related to intravenous drug use, other means of acquisition of HIV infection include transfusion of contaminated blood or blood products in settings in which routine and effective screening of blood is not available, percutaneous blood exposure (from contaminated needles or other sharp instruments), and mucous membrane exposure to contaminated blood or other body fluids (see Table 109.1).[4] The first case of pediatric HIV infection in the US was an infant who acquired HIV infection through a transfusion of contaminated blood.[1] Thousands of patients with hemophilia and other recipients of contaminated blood and blood products acquired HIV infection before screening of blood and blood products for HIV. Now, in the US and many other countries, blood, blood components, and clotting factors undergo effective screening procedures. As a result, transmission of HIV through transfusion of blood or blood products in the US has decreased substantially.[26–29] The risk for transmission of HIV through blood transfusions in the US in 2010 was estimated at 1 per 1,467,000.[29] In addition to intravenous drug use, other exposure to contaminated needles (e.g., with tattooing)[30] can result in HIV transmission. Possible transmission of HIV through receipt of food that has been prechewed by an HIV-infected caregiver with bleeding gums or open sores in the mouth has been reported.[31,32] There have been rare cases of household transmission of HIV between siblings,[33] but in these cases, there were opportunities for skin or mucous membrane exposure to HIV-infected blood. Thus all caregivers of HIV-infected children should receive education regarding universal precautions.[34,35] Transmission of HIV has not been described as a result of routine outpatient or inpatient care or in schools or childcare settings in the US.[4,36–38] Cases of HIV transmission to children through sexual abuse have been reported.[39–41]

Clinical Manifestations and Progression

Infection with HIV can result in a myriad of clinical manifestations. Acquired immunodeficiency syndrome, or AIDS, refers to the most advanced disease stage of HIV infection. AIDS is defined by the development of life-threatening manifestations, including opportunistic infections and neoplasms, due to progressive immunosuppression induced by HIV infection.

Previously, the CDC had classified HIV-infected children (below 13 years of age) according to their clinical status (ranging from N [not symptomatic], through A and B, to C [severely symptomatic; AIDS]) and immunologic status (category 1 [$CD4^+$ T-lymphocyte count or percentage indicating no evidence of immune suppression] to category 3 [severe suppression]).[42] Thus, combining both the clinical and immunologic staging of children resulted in categories of N1 through C3. This classification system took into account the age-related changes (<1 year, 1–5 years, 6–12 years) in the normal ranges of $CD4^+$ lymphocyte counts. The classification system for adolescents and adults similarly classified HIV-infected individuals according to their clinical and immunologic status, except that the clinical staging ranged from A to C (no category N).[43] In 2014, the CDC revised the surveillance case definition for HIV infection.[44] According to this new case definition, a confirmed case of HIV infection (whether in children [<13 years of age] or in adolescents and adults) can be classified into one of five HIV infection stages (stages 0, 1, 2, 3, or unknown).[44] Early infection is classified as stage 0, and AIDS is classified as stage 3.[44]

The natural history of HIV infection in infants who acquired HIV infection through mother-to-child transmission differs from that in adults. Plasma viral loads among untreated, infected infants increase rapidly after birth,[45] peaking at 1 to 2 months of age (median values of 318,000 and 256,000 copies/mL, respectively).[45] Untreated, viral loads decline slowly during the first 2 years of life,[46] reaching values observed in HIV-infected adults only at approximately 5 years of age.[47]

Studies of HIV-infected infants who acquired infection through mother-to-child transmission[48,49] that were published in the late 1990s, at a time when pediatric antiretroviral treatment was limited, described rapid progression of disease. For example, in a study of 128 HIV-infected children in North America,[48] the median ages of progression to clinical classes A, B, and C were 5, 11, and 48 months, respectively. In another study of 392 HIV-infected children in Europe, about 20% progressed to class C disease or death during the first year of life, and approximately 5% progressed per year thereafter.[49] The mortality rate at 6 years was 26%.[49] Early onset of clinical manifestations of HIV infection (lymphadenopathy, hepatomegaly, splenomegaly at 3 months of age or earlier) and positive HIV diagnostic testing within the first week of life were associated with more rapid disease progression.[48] In subsequent studies of HIV-infected children in Africa, more than one third of untreated, HIV-infected infants died by 12 months of age,[50] and approximately one half died by 24 months of age.[51]

After the introduction of more effective antiretroviral regimens, the morbidity and mortality associated with HIV infection among infants, children, adolescents, and adults has decreased substantially.[52–64] Opportunistic and other infections were uncommon among HIV-infected children in 2000 to 2004,[65] and infection rates were lower than those reported in earlier years.[66] Similarly, the incidence of certain noninfectious conditions (encephalopathy, pancreatitis, cardiac disorders) decreased between 2001 and 2006 among HIV-infected children and adolescents.[67]

In a randomized clinical trial conducted in South Africa, infants with early time-limited antiretroviral therapy had better clinical and immunologic outcomes than infants with deferred therapy.

Also, infants with early antiretroviral therapy did not have excess disease progression during subsequent treatment interruption.[68,69] Based on these data and the high risk for rapid progression of HIV infection in infants, urgent antiretroviral therapy for all HIV-infected infants is recommended, regardless of clinical, immunologic ($CD4^+$ lymphocyte percentage), or viral load status.[70] For children aged 1 to <6 years, urgent treatment is recommended for those with CDC stage 3-defining opportunistic infections or stage 3 immunodeficiency ($CD4^+$ cell count <500 cells/mm^3).[70] Antiretroviral treatment is recommended for children aged 1 to <6 years with moderate HIV-related symptoms, those with a $CD4^+$ cell count of 500 to 999 cells/mm^3, and those who are asymptomatic or mildly symptomatic and who have a CD4 cell count ≥1000 cells/mm^3.[70] For children ≥6 years of age, urgent antiretroviral treatment is recommended for those with CDC stage 3-defining opportunistic infections or stage 3 immunodeficiency ($CD4^+$ cell count <200 cells/mm^3).[70] Antiretroviral treatment is recommended for children ≥6 years of age with moderate HIV-related symptoms, those with a $CD4^+$ cell count of 200 to 499 cells/mm^3, and those who are asymptomatic or mildly symptomatic and with a CD4 cell count ≥500 cells/mm^3.[70]

There is substantial variation in HIV disease progression among adolescents and adults; some individuals progress to AIDS in less than 5 years,[71] but some untreated individuals (so-called long-term nonprogressors) do not deteriorate clinically or immunologically for many years.[72,73] Current guidelines for initiation of antiretroviral therapy in HIV-infected adolescents and adults[74] recommend the initiation of antiretroviral therapy in all HIV-infected individuals, regardless of $CD4^+$ count, to decrease morbidity and mortality related to HIV infection. Antiretroviral therapy should be initiated as soon as possible after diagnosis of HIV infection, although in certain circumstances (i.e., related to clinical and/or psychosocial factors), therapy may be deferred.[74]

Prevention

Mother-to-child transmission represents the means by which virtually all infants and young children acquire HIV infection. Most adults and adolescents acquire HIV infection through sexual transmission or percutaneous exposure (e.g., intravenous drug use). Discussion of prevention of HIV transmission to children and adolescents focuses on these routes of transmission.

Prevention of Mother-to-Child Transmission

Prevention of mother-to-child transmission of HIV is just one component of the overall management of HIV-infected women and their children (Box 109.1). The World Health Organization (WHO) Strategic Approach to Prevention of Pediatric HIV Infection[75] includes four components: primary prevention of HIV infection; prevention of unintended pregnancies among HIV-infected women; prevention of transmission of HIV infection from mothers to children; and provision of ongoing support, care, and treatment to HIV-infected women and their families. Ideally, primary prevention of HIV infection occurs (e.g., an HIV-uninfected woman does not acquire HIV infection either before or during pregnancy). To facilitate prevention of acquisition of HIV infection, individuals should know their own and their sexual partners' HIV infection status. This is accomplished through provision of and access to HIV counseling and testing. Prevention of unintended pregnancies is crucial for women who acquire HIV infection. Antiretroviral therapy for HIV-infected women, for their own health and for prevention of mother-to-child transmission of HIV, as well as other interventions to prevent mother-to-child transmission, should be available. Finally, HIV-infected women and their children need ongoing support, care, and treatment, including infant feeding counseling and support.

Box 109.1

Prevention of Mother-to-Child Transmission of HIV

Antiretroviral agent(s)

- For the mother (for treatment of the mother's own HIV infection, for prevention of mother-to-child transmission of HIV)

- For the nonbreastfeeding infant (early postnatal period)

Cesarean delivery before labor and before rupture of membranes

Interventions to prevent breast milk transmission of HIV

- Complete avoidance of breastfeeding
- Exclusive breastfeeding when complete avoidance of breastfeeding is not feasible or safe
- Antiretroviral prophylaxis for the breastfeeding infant

Although different interventions to prevent mother-to-child transmission of HIV have been and are being investigated, efficacy has been demonstrated to date for only the following: antiretroviral use during pregnancy by HIV-infected women,[76–83] cesarean delivery before labor and before ruptured membranes,[18] complete avoidance of breastfeeding,[84] and (in settings where complete avoidance of breastfeeding is not feasible) exclusive breastfeeding,[85] antiretroviral prophylaxis administered to the infant while breastfeeding,[86–89] and antiretroviral use by breastfeeding mothers.[88,90]

Antiretroviral Agents

Maternal use of antiretroviral agents during the antepartum and intrapartum periods, and during the postpartum period if breastfeeding, as well as infant antiretroviral prophylaxis while breastfeeding, are associated with significant reduction in the rates of mother-to-child transmission of HIV. In the first efficacy trial of antiretroviral prophylaxis, zidovudine alone was given to mothers during pregnancy and the intrapartum period and to their infants.[76] Subsequently, the US Public Health Service issued guidelines regarding the use of zidovudine prophylaxis,[91] and such prophylaxis played a central role in the prevention of mother-to-child transmission in the US[92] and other resource-rich settings. More recently, an increasing number of HIV-infected women have been using combination antiretroviral therapy (cART) during pregnancy.[93] In 2015, results from a randomized trial demonstrated lower rates of mother-to-child transmission with cART regimens including three drugs (zidovudine, lamivudine, and lopinavir/ritonavir [0.5%] or tenofovir, emtricitabine, and lopinavir/ritonavir [0.6%]) compared with zidovudine, with a single dose of nevirapine at delivery, plus tenofovir and emtricitabine (1.8%).[83]

Antiretroviral agents prevent mother-to-child transmission of HIV by decreasing the viral load in maternal blood and genital secretions,[12,94] an important risk factor for vertical transmission.[94–96] In addition to decreasing viral load, other mechanisms of action of antiretroviral therapy in reducing vertical transmission are suggested by several observations. First, there is no threshold maternal plasma viral load below which transmission does not occur; transmission has been observed at all levels of maternal viral load.[94,96,97] Second, among women with lower plasma viral loads (<1000 copies/mL), more intensive maternal antiretroviral regimens are associated with lower risks for transmission.[98] Also, maternal plasma load at delivery and antepartum antiretroviral use are each independent risk factors for transmission.[93] Pre-exposure infant prophylaxis can be accomplished through the maternal use of antiretroviral agents that cross the placenta and result in adequate systemic drug concentrations in the infant. Postexposure infant prophylaxis can be achieved through administration of antiretroviral agents to the infant after birth. In this situation, the antiretroviral agents can protect the infant from acquiring infection through maternal microtransfusions of blood during labor or from virus swallowed by the infant during delivery. The efficacy and effectiveness of intrapartum or neonatal antiretroviral regimens for prevention of mother-to-child transmission (i.e., initiated too late to prevent transmission by decreasing maternal viral load)[81,99–104] lend further support to the benefit of infant pre-exposure and postexposure prophylaxis.

Guidelines addressing the use of antiretroviral therapy during pregnancy have been developed by the US Department of Health and Human Services (DHHS) Panel on Treatment of HIV-Infected

Pregnant Women and Prevention of Perinatal Transmission,[105] the WHO,[107] and other groups. Guidelines for the use of antiretroviral agents in HIV-infected pregnant women in the US have evolved over the years.[105] Current recommendations are for all pregnant, HIV-infected women to use cART to prevent mother-to-child transmission of the virus, irrespective of the woman's plasma $CD4^+$ count or viral load (copies/mL), and such therapy should be initiated as early in pregnancy as possible.[105] In general, indications for initiation of antiretroviral therapy in women of reproductive age, pregnant women, or postpartum women are the same as those for other HIV-infected adults and adolescents.[74] British guidelines for the management of HIV-infected women include zidovudine alone as a valid option for women with higher $CD4^+$ counts and lower pretreatment plasma viral loads (<10,000 copies/mL) who do not want to use cART during pregnancy and who are willing to give birth by planned cesarean delivery.[108]

Antiretroviral resistance testing should be performed in all HIV-infected, antiretroviral-naïve pregnant women before initiation of antiretroviral treatment (if the pretreatment viral load is above the threshold for resistance testing [i.e., >500−1000 copies/mL]).[105] For women with viral loads above the threshold for resistance testing while using antiretroviral agents and for those who have suboptimal viral suppression after initiating antiretroviral therapy during pregnancy, resistance testing should be performed before modifying antiretroviral regimens.[105] Of note, for women who come to attention late in pregnancy, empiric antiretroviral therapy should be initiated without waiting for resistance testing results. After results become available, the antiretroviral regimen can be modified if necessary.[105]

Women using cART during pregnancy should continue this regimen as much as possible around the time of delivery, and intrapartum (intravenous) zidovudine is not required for women with good adherence to cART who have viral loads ≤1000 copies/mL.[105] However, intravenous zidovudine should be administered to other HIV-infected women, especially those with a viral load of >1000 copies/mL or an unknown viral load near delivery.[105] For women of unknown HIV infection status who present in labor, expedited antigen/antibody testing should be performed. If this testing is positive, maternal intravenous zidovudine and infant cART should be initiated immediately, without waiting for the results of an HIV-1/HIV-2 antibody differentiation assay.[105]

All newborn infants of HIV-infected women should receive antiretroviral postexposure prophylaxis, irrespective of whether the mother used antiretroviral agents during pregnancy.[105] A 4-week regimen of zidovudine is recommended for transmission prophylaxis for full-term infants whose mothers adhered to a cART regimen during pregnancy (with sustained viral suppression).[105] A longer (6-week) regimen of antiretroviral prophylaxis (with a combination ARV regimen) is recommended for all high-risk infants (i.e., those whose mothers did not use antepartum or intrapartum ARVs or whose mothers used only intrapartum ARVs, and those whose mothers used cART but without sustained viral suppression).[105] In the United Kingdom, a 4-week infant antiretroviral prophylaxis regimen is recommended.[108] Antiretroviral prophylaxis for infants should begin as soon as possible (preferably within 6–12 hours) after birth.[105] Clinical trials are planned to address the question of whether using cART for HIV-exposed, high-risk infants will affect the establishment and persistence of HIV infection, as well as to assess the safety of such an approach.

The effectiveness of antiretroviral therapy in improving maternal $CD4^+$ lymphocyte counts and decreasing plasma viral load should be monitored carefully in any HIV-treated patient population, including infected pregnant women.[105] Laboratory monitoring to assess antiretroviral drug-related toxicities is based on the known adverse events related to the drugs being used.[105]

In addition, the benefits of antiretroviral agents for HIV-infected women and their infants (treatment of the mother's own HIV infection, prevention of mother-to-child transmission of HIV) must be weighed against adverse events associated with these drugs. Potential adverse events related to in utero exposure to antiretroviral agents include congenital anomalies, malignancies, mitochondrial toxicity, and preterm birth.

Studies evaluating in utero exposure to antiretroviral agents, especially first-trimester exposure, generally have not demonstrated significant associations between exposure and infant congenital anomalies.[111–116] Some studies[116,117] have reported a higher risk for congenital anomalies among infants with first-trimester exposure to efavirenz, but more research regarding first-trimester exposure to the drug is necessary to evaluate potential risks more conclusively. However, because of potential central nervous system abnormalities with first-trimester exposure to efavirenz and similar findings in primates, the use of efavirenz during the first trimester of pregnancy should be avoided.[105]

Findings to date regarding the short-term (e.g., within the first 2–4 years of life) risk for malignancies among infants with in utero antiretroviral exposure are reassuring.[118–121] Nonetheless, the possibility that children with in utero exposure are at increased risk for cancer at older ages remains. Children with exposure to antiretroviral agents should have follow-up into adulthood because of the potential for carcinogenicity of antiretroviral agents.[105]

In utero exposure to nucleoside and nucleotide analogue reverse transcriptase inhibitors has been linked to mitochondrial dysfunction in French infants.[122,123] However, results of other studies from the US and Europe[124–129] have not corroborated these results. Further research in this area is needed. Even if a clear association between in utero antiretroviral exposure and mitochondrial dysfunction is delineated, the absolute risk for severe mitochondrial dysfunction appears to be low and outweighed by the benefit of antiretroviral agents in reducing the risk for mother-to-child transmission of HIV.

The possibility of an association between use of cART, especially those regimens containing protease inhibitors, during pregnancy and infant preterm birth should be considered, although currently available data are conflicting.[130–150] In general, however, the benefits of antiretroviral use during pregnancy are considered to outweigh the small possible risk for preterm birth.

Neonatal anemia has been associated with in utero or early postnatal exposure to antiretroviral agents; therefore treated babies should have routine hematologic evaluation. Based on studies suggesting other laboratory abnormalities among infants with in utero or early postnatal exposure to antiretroviral agents,[151–157] some experts recommend more extensive laboratory assessments, such as a complete blood count with differential of white cells and hepatic transaminase assays.

WHO guidelines regarding the use of antiretroviral agents[107] recommend initiation in all HIV-infected pregnant or breastfeeding women regardless of WHO clinical stage or $CD4^+$ count and continuation lifelong. All infants born to HIV-infected mothers should receive antiretroviral prophylaxis. For infants of women who are using ART and are breastfeeding, 6 weeks of infant prophylaxis with daily nevirapine is recommended.[107] For infants receiving replacement feeding, 4 to 6 weeks of infant prophylaxis is recommended (with daily nevirapine or twice-daily zidovudine).[107] High-risk infants (infants who are at high risk of acquiring HIV infection because they are [1] born to mothers with chronic HIV infection who received less than 4 weeks of antiretroviral therapy by the time of delivery; [2] born to mothers with chronic HIV infection and a viral load above 1000 copies/mL in the 4 weeks prior to delivery; [3] born to mothers with acute HIV infection during pregnancy or during breastfeeding; or [4] born to mothers identified for the first time as HIV-infected during the postpartum period) should receive prophylaxis with twice-daily zidovudine and once-daily nevirapine for the first 6 weeks of life (irrespective of whether breastfed or formula fed).[107] Such breastfed infants should continue prophylaxis for an additional 6 weeks (for a total of 12 weeks of infant prophylaxis).[107] The WHO guidelines recommend initiation of antiretroviral therapy in all HIV-infected children younger than 10 years of age, regardless of WHO clinical stage or $CD4^+$ cell count.

Cesarean Delivery Before Labor and Before Ruptured Membranes

In the late 1990s, results from both a multicenter, randomized clinical trial conducted in Europe and a meta-analysis of prospective cohort studies conducted in North America and Europe demonstrated the effectiveness of cesarean delivery before labor and before ruptured membranes in reducing mother-to-child transmission of HIV.[18,19] In the clinical trial, the risk for mother-to-child transmission of HIV was 80% lower among women allocated to the group who underwent cesarean delivery before labor and before rupture of membranes; the risk for transmission was highest among women who delivered vaginally (10.2%), followed by those who had a cesarean delivery after onset of labor or ruptured membranes (8.8%), with the lowest risk among those who underwent cesarean delivery before labor and before rupture of membranes (2.4%).[18] The individual patient meta-analysis of data from 15 prospective cohort studies found that, after controlling for maternal age, use of antiretroviral agents during pregnancy (mostly zidovudine alone), and infant birth weight, cesarean delivery before labor and before ruptured membranes was associated with a lower risk for transmission of HIV (adjusted odds ratio [OR], 0.43; 95% confidence interval [CI], 0.33–0.56) compared with other modes of delivery.[19]

A large proportion of mother-to-child transmission of HIV occurs during the intrapartum period.[8,9] One potential mechanism of intrapartum HIV transmission is fetal exposure to infected maternal blood and cervicovaginal secretions. An early study of twins born to HIV-infected women found that the first-born twin was at higher risk for HIV transmission compared with the second twin,[158] suggesting that time spent with exposure to infected blood and secretions in the vagina increased risk. In addition, a longer duration of ruptured membranes is associated with a greater risk for mother-to-child transmission of HIV.[159] For each hour increase in the duration of ruptured membranes, there is an approximate 2% increase in the risk for mother-to-child transmission of HIV.[158] This association suggests that intrapartum transmission results from ascending infection from the lower genital tract, after the integrity of the amniotic membranes is disrupted. Another potential mechanism for mother-to-child transmission of HIV is microtransfusions of maternal blood during uterine contractions. Placental microtransfusions occur when a small amount of maternal blood crosses the placenta to the fetus. Two studies assessing the levels of placental alkaline phosphatase found that the lowest cord placental alkaline phosphatase levels, and thus the lowest volumes of maternal-fetal transfusion, were among those undergoing cesarean delivery before labor and before rupture of membranes.[160,161]

Based on these studies, the American College of Obstetricians and Gynecologists (ACOG) recommended that: (1) HIV-infected women with plasma viral loads >1000 copies/mL should be counseled on the benefits of cesarean delivery before labor and before rupture of membranes to prevent mother-to-child transmission; (2) cesarean delivery should be performed at 38 completed gestational weeks, based on the best clinical estimate, to minimize the odds for onset of labor and rupture of the membranes; (3) HIV-infected women should receive antiretroviral agents during pregnancy and without interruption before the cesarean delivery; and (4) women should receive intravenous zidovudine 3 hours before the cesarean delivery, before labor and before rupture of membranes.[161] After the release of data regarding mode of delivery and mother-to-child transmission of HIV,[18,19] cesarean delivery for HIV-infected women was performed with increasing frequency in clinical centers in the US.[163] However, HIV-preventive cesarean delivery generally is not feasible in resource-poor settings because of the lack of a skilled attendant during labor and for other reasons. Scheduled cesarean delivery at 38 weeks' gestation is recommended for HIV-infected women in the US with plasma viral loads above 1000 copies/mL or unknown plasma viral loads near the time of delivery, irrespective of use of antepartum antiretroviral agents.[105]

Because cesarean delivery is a major operative procedure, there are concerns about potential risks to the mothers and infants. Compared with vaginal delivery among HIV-uninfected women, cesarean delivery is associated with increased risk for intraoperative and postoperative complications, particularly after emergency cesarean delivery.[164–167] Several studies have compared postpartum morbidity according to mode of delivery among HIV-infected women.[18,168–171] The results of these studies, summarized in a Cochrane review,[172] indicate that the risk for postpartum morbidity, primarily infectious (i.e., urinary tract infection, pneumonia, wound infection, septicemia, and episiotomy infection), was highest with nonelective cesarean delivery, intermediate with elective cesarean delivery, and lowest with vaginal delivery. The DHHS Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission[105] has concluded that the observed postpartum morbidity associated with cesarean delivery before labor and before ruptured membranes among HIV-infected women is not of sufficient frequency or severity to outweigh the benefit of decreased transmission of HIV to the infant.

Studies among HIV-uninfected women have demonstrated that infants who are delivered before 39 weeks' gestation are at an increased risk for neonatal respiratory morbidity and other complications. In two recent analyses of data from prospective cohort studies,[173,174] respiratory morbidity among neonates of HIV-infected pregnant women was assessed according to mode of delivery. In an analysis of more than 1000 mother-infant pairs in North America, the authors concluded that there was minimal neonatal respiratory morbidity risk in near-term infants born by cesarean delivery before labor and rupture of membranes.[173] In an analysis of more than 1400 HIV-infected women and their infants in Latin America, few children born by cesarean delivery before labor and before ruptured membranes for prevention of mother-to-child transmission of HIV had respiratory distress syndrome or transient tachypnea of the newborn, and only a minority required ventilator support.[174] It therefore appears that the benefits of cesarean delivery for prevention of mother-to-child transmission of HIV outweigh the small risk for respiratory morbidity among near-term infants.[173,174]

To strike a balance between minimizing the risks for iatrogenic prematurity and ensuring that the cesarean delivery before labor and before rupture of membranes is performed before the onset of labor, the ACOG recommends that infants of HIV-infected women should be delivered a week earlier (at 38 completed weeks of gestation) than is customary among uninfected women (39 completed weeks of gestation).[162] Although the ACOG generally recommends testing amniotic fluid if elective delivery is being considered before 39 week to determine fetal pulmonary maturity,[175] amniocentesis should not be performed routinely in HIV-infected women. Therefore clinicians should depend on the best clinical estimate of gestational age to determine when to deliver.[176]

Unresolved questions regarding mode of delivery and prevention of mother-to-child transmission of HIV include whether cesarean delivery before labor and before ruptured membranes is beneficial among HIV-infected, pregnant women with low plasma viral loads (<1000 copies/mL) and whether there is a benefit of cesarean delivery before labor and before rupture of membranes among women who are using cART. In one recent study, the mother-to-child transmission rate in term births (including all modes of delivery) according to maternal viral load at delivery was 0.6% (<400 copies/mL).[177] A similarly low rate of transmission (0.8%) has been observed among women using cART for at least the last 14 days of pregnancy, regardless of mode of delivery.[178] However, analyses of data from the European Collaborative Study[179] demonstrated an 80% lower risk for transmission with cesarean delivery before labor and before rupture of membranes when adjusting for use of cART and preterm birth (adjusted OR, 0.20; 95% CI, 0.05–0.65). Similarly, among 560 women with undetectable viral loads, cesarean delivery before labor and before rupture of membranes was associated with a 90% lower risk for transmission (OR, 0.10; 95% CI, 0.03–0.33).[180] More recent data from the UK and Ireland regarding HIV-infected women with plasma viral loads of 50 to 399 copies/mL suggest the risk for mother-to-child transmission among women with a scheduled cesarean delivery is less than one half that in women intending to delivery vaginally.[181]

Interventions to Prevent Breast Milk Transmission of HIV

Both the CDC[182] and the American Academy of Pediatrics (AAP)[183,184] recommend that HIV-infected women in the US not breastfeed their children. These recommendations are based in large part on the results of a randomized clinical trial conducted in Kenya, where the observed rate of mother-to-child transmission of HIV among mothers randomized to not breastfeed was significantly lower than among mothers randomized to breastfeed (20.5% vs. 36.7% at 2 years, $P < 0.001$).[84]

The evidence for breast milk transmission of HIV and risk factors for such transmission have been summarized[185]; these include longer duration of breastfeeding, more advanced HIV disease in the mother, the child's susceptibility to infection, and factors that may facilitate transfer of HIV from mother to child or are otherwise associated with an increased risk for breast milk transmission. A meta-analysis incorporating data from thousands of breastfeeding children of HIV-infected women in sub-Saharan Africa[17] demonstrated that breast milk transmission of HIV contributes substantially to overall mother-to-child transmission. The longer breastfeeding continues, the greater the cumulative risk for HIV transmission. More advanced maternal disease stage, as manifested by lower $CD4^+$ lymphocyte counts, is a risk factor for breast milk transmission of HIV,[13,24] along with higher maternal peripheral blood or human milk viral load.[13–15] Factors that facilitate the transfer of the virus from mother to child and other factors, including maternal breast abnormalities, infant candidiasis, and mixed feeding, are associated with breast milk transmission of HIV.[13–15,20,22–24]

If complete avoidance of breastfeeding is not safe or feasible, specific interventions to prevent breast milk transmission of HIV can be implemented. Some of these interventions have been evaluated in clinical trials, whereas others are currently under study.

Because a longer duration of breastfeeding is associated with a greater risk for transmission,[17,84] early weaning was thought to be a reasonable intervention to decrease the risk for transmission. However, the morbidity associated with complete avoidance of breastfeeding and with early weaning, owing to contaminated water used in the preparation of replacement feeds, serves to counterbalance the benefits of such interventions to prevent mother-to-child transmission of HIV. For example, in the clinical trial of formula feeding versus breastfeeding, the two groups of children experienced similar mortality and malnutrition rates during the first 2 years of life.[186] Similarly, studies in Malawi and Uganda documented increased risks for severe gastroenteritis[187,188] and gastroenteritis-associated mortality[187] among HIV-exposed infants. In a randomized trial evaluating the safety and efficacy of early weaning,[189] there was no statistically significant difference in HIV-free survival between those children who ceased breastfeeding at about 4 months of age and those who continued breastfeeding ($P = 0.27$).

Because more advanced maternal disease (e.g., as manifested by a higher maternal viral load in breast milk) is associated with a greater risk for mother-to-child transmission of HIV, two types of interventions have been proposed to decrease the infectiousness of the breast milk of HIV-infected mothers: maternal use of antiretroviral agents while breastfeeding, and treatment (chemical or heat) of breast milk. Two randomized clinical trials conducted in sub-Saharan Africa evaluated the use of antiretroviral prophylaxis by breastfeeding women in the reduction of mother-to-child transmission of HIV.[88,90] In the BAN trial, HIV-infected, breastfeeding mothers with a $CD4^+$ lymphocyte count of ≥250 cells/mm^3 and their infants were randomized at 1 week after delivery to receive maternal antiretroviral regimen for 28 weeks, infant nevirapine for 28 weeks, or no prophylaxis beyond the first week of age. Before randomization, all mothers and infants had received standard perinatal prophylaxis, which included a single dose of oral nevirapine given to mothers in labor and to their infants immediately after birth. In addition, all mothers had received zidovudine and lamivudine as a single tablet every 12 hours from the onset of labor to 7 days after birth, and all infants received zidovudine until 7 days of age. Of 2369 mother-infant pairs who were randomized, 5% of infants were HIV-infected at 2 weeks of life. The estimated risk for mother-to-child transmission of HIV between 2 and 28 weeks was higher in the control group (5.7%) than in the other groups (maternal regimen group: 2.9%, $P = 0.009$; infant regimen group: 1.7%, $P < 0.001$). The estimated risks for infant HIV infection or death between 2 and 28 weeks were 7% in the control group, 4.1% in the maternal regimen group ($P = 0.02$), and 2.6% in the infant regimen group ($P < 0.001$).[88] In the Kesho Bora study, women with $CD4^+$ lymphocyte counts between 200 and 500 cells/mm^3 were randomized to either (1) zidovudine with lamivudine and lopinavir/ritonavir (triple-ARV) at 28 to 36 weeks' gestation until 6 months postpartum; or (2) zidovudine at 28 to 36 weeks' gestation until the onset of labor, and then zidovudine with lamivudine and one dose of nevirapine at the onset of labor, followed by (in a later version of the protocol) zidovudine with lamivudine until 1 week after delivery (ZDV/sdNVP). All infants received one dose of nevirapine within 72 hours of birth along with 1 week of zidovudine. Among 882 enrolled women, 824 were randomized and delivered 805 singleton or first, live-born infants. The cumulative risk for HIV transmission at 12 months was 5.4% in the triple-ARV arm and 9.5% in the ZDV/sdNVP arm ($P = 0.03$), a 43% risk reduction.[90] Heat and chemical (e.g., sodium dodecyl sulfate) treatments of breast milk to decrease the amount of cell-free and cell-associated HIV have been evaluated in several studies.[190,191] In addition, a method of “flash heating” of breast milk[102] may be evaluated further in East Africa.

Because various factors facilitate the transfer of the virus from mother to child or are otherwise associated with a greater risk for mother-to-child transmission (e.g., maternal breast abnormalities, infant candidiasis, mixed breastfeeding), interventions to prevent or treat such factors have been developed. For example, programs have been developed to educate HIV-infected women who choose to breastfeed, addressing proper positioning during breastfeeding, promptly seeking medical care if breast abnormalities develop or if the infant develops oral candidiasis or other lesions, and avoiding breastfeeding from a breast with mastitis or other abnormalities. Studies conducted in Brazil and South Africa suggest a lower risk for transmission with exclusive breastfeeding compared with mixed breastfeeding.[20,193] Additional studies in Zimbabwe,[21] South Africa,[85] and Zambia[189] support the association of exclusive breastfeeding with a lower risk for mother-to-child transmission of HIV. For example, the transmission rate among infants who were still exclusively breastfeeding at 6 months of age was 15%, but the rate was higher among those with mixed feeding at 6 months of age (27% among those who initiated mixed feeding before 14 weeks and 26% for those who initiated mixed breastfeeding after 14 weeks).[85] It is noteworthy that although mixed feeding has been hypothesized to damage the intestinal mucosa, thus facilitating HIV infection of the infant through increased permeability or intestinal immune activation, the evidence to date do not support this hypothesis.[194] The exact mechanism by which mixed feeding is associated with a higher risk for transmission of HIV remains controversial.

Finally, interventions to decrease infant susceptibility to infection while breastfeeding (e.g., active and passive immunization of the infant, administration of antiretroviral prophylaxis to the infant while breastfeeding) have been or are being evaluated. Studies of the safety and immunogenicity of active immunization for prevention of mother-to-child transmission of HIV have been initiated.[195,196] Similarly, passive immunization with polyclonal immune globulin has been evaluated in clinical trials in the US (formula-fed infants) and Uganda (predominantly breastfed infants).[195,196]

Several major studies have evaluated the efficacy of extended administration of antiretroviral prophylaxis to breastfeeding infants.[86–89,197] In a clinical trial in Botswana, infants were randomized to 6 months of breastfeeding along with zidovudine prophylaxis, or to formula feeding with 1 month of zidovudine prophylaxis. HIV-free survival at 18 months was similar with both strategies.[197] Other studies evaluating extended antiretroviral prophylaxis to breastfeeding infants (with nevirapine alone or with nevirapine and zidovudine)[86–89] indicated that extended prophylaxis is efficacious in preventing breast milk transmission of HIV, with a longer duration of prophylaxis associated with a lower risk for mother-to-child transmission. Durations of extended infant antiretroviral prophylaxis ranged from 6 weeks to 6 months. The results of these studies led to the concept that, if infant antiretroviral prophylaxis will be used to prevent breast milk transmission of HIV, it should be used for the duration of breastfeeding. This idea is being evaluated in an ongoing clinical trial (PROMISE), which is being conducted at multiple sites around the world.

Prevention of HIV Transmission in Adolescents

Adolescents may have acquired HIV infection through mother-to-child transmission (already discussed) or can acquire through behaviors (e.g., sexual transmission or injection drug use). Prevention of behaviorally acquired HIV infection in adolescents is the focus of this section.

Essential components of the care of adolescents (Box 109.2) are counseling regarding behaviors that may put them at risk for acquisition of HIV and interventions to decrease the risk for transmission of HIV. In addition, adolescents should be educated regarding testing for HIV, pre-exposure prophylaxis, and postexposure prophylaxis. The most effective strategy for prevention of transmission of HIV in adolescents and adults will likely be to combine various types of interventions (behavioral and biological)

Box 109.2

Prevention of HIV Transmission in Adolescents

Counseling and education regarding *behaviors* that put them at risk for acquisition of HIV infection and interventions to decrease that risk

- Counseling and education regarding safer *sexual practices* and about sexually transmitted infections
- Counseling and education regarding prevention of initiation of *substance abuse* and prevention of HIV acquisition among those with an existing substance abuse problem

Screening for sexually transmitted infections

HIV testing

Pre-exposure prophylaxis

Postexposure prophylaxis

Sexual transmission accounts for most cases of HIV infection among adolescents and adults.[3] Although abstinence from sexual activity is the most effective means of avoiding acquisition of sexually transmitted infections (STIs), it is not possible to predict which adolescents will abstain. The AAP views provision of information regarding sex and STIs as an essential part of anticipatory guidance that pediatricians provide to their adolescent patients.[198] The AAP recommends that this information explicitly underscores the potential consequences of STIs, including HIV.[198] Adolescents with STIs, especially ulcerative diseases such as herpes simplex virus infection or syphilis, should be made aware of the association between such infections and transmission of HIV.[198] Screening for STIs in both public and private clinical settings represents an important component of prevention of HIV infection among adolescents and adults.[199]

Injection drug use or other percutaneous exposure to HIV is another important means of acquisition of HIV infection by adolescents and adults.[3] Adolescents should be informed about the dangers of injection drug use as well as precautions to decrease the risk for transmission of HIV and other bloodborne viral pathogens due to contact with blood or open wounds (e.g., during contact sports).[198,200] In addition to injection drug use or other percutaneous exposures, the use of noninjection drugs (e.g., alcohol, cocaine, marijuana) is associated with an increased risk for acquisition of HIV infection due to impaired judgment associated with the use of these substances, which in turn may increase the likelihood of unsafe sexual practices.[198] Efforts to reduce the risk for adolescents initiating substance abuse and to prevent acquisition of HIV infection among adolescents with a substance abuse problem should be encouraged.[201]

The CDC recommends at least annual testing for sexually active men who have sex with men between the ages of 13 and 64 years.[202] HIV testing is treated as part of routine care, and it is performed unless the patient objects ("opts out"). General consent for medical care is considered to encompass consent for HIV testing, and no specific consent for HIV testing would be required.[202] Testing for HIV infection is important in the prevention of HIV transmission because it provides the individual with knowledge of his or her HIV infection status, and, with this knowledge, most individuals reduce high-risk sexual behaviors.[203] In addition, testing is the first step in linking an HIV-infected person to appropriate care and treatment.

Antiretroviral therapy can be used to decrease the transmission of HIV. Lower plasma viral loads are associated with lower viral loads in genital secretions.[204–207] However, the concentrations of most antiretroviral agents vary among different fluids.[205–208] Associations between lower serum or genital viral loads and lower transmission rates among HIV serodiscordant heterosexual couples have been observed.[204,209,210] Ecologic studies of communities with high concentrations of injection drug users and of men who have sex with men suggest that increased use of antiretrovirals is associated with a decreased community viral load and a lower rate of new HIV infections.[211–213] In a trial of HIV-discordant couples, almost all heterosexual, HIV-infected sexual partners who were antiretroviral naïve and had $CD4^+$ counts between 350 and 550 cells/mm^3 were randomized to initiate or delay antiretroviral therapy.[214] Those who initiated antiretroviral therapy had a 96% decrease in transmission of HIV to uninfected partners. Suppression of viral load in blood and genital secretions with antiretroviral therapy should protect against transmission in other patient populations (e.g., men who have sex with men, injection drug users), but the effectiveness of such an intervention for groups other than heterosexual couples has not yet been established. The effectiveness of antiretroviral therapy in the prevention of transmission of HIV is predicated on the following: agents can effectively suppress viral loads in blood and genital fluids; adherence to therapy is high; and there is not a concomitant STI. Of note, when cART is available, rates of HIV risk behaviors may increase, sometimes substantially.[215]

Recommendations for postexposure prophylaxis in children and adolescents for nonoccupational exposure to HIV have been developed.[216] If postexposure prophylaxis is used, it should be initiated as soon as possible after exposure (no later than 72 hours) and continued for 28 days. Close follow-up is necessary to monitor adherence to and toxicity related to the prophylaxis, to provide psychological support, and to complete serial HIV testing.

Summary

HIV infection among children and adolescents in the US disproportionately affects minorities. Effective antiretroviral treatment and other care and support for HIV-infected children and adolescents have resulted in significantly decreased morbidity and mortality. Major successes have been achieved in prevention of mother-to-child transmission of HIV, but such transmission has not been eliminated. In addition, acquisition of HIV infection among adolescents and adults continues at an alarming rate. Essential components of the care of adolescents include HIV testing, counseling and education regarding behaviors that put them at risk for acquisition of HIV infection, and interventions to reduce that risk.

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Immunopathogenesis of HIV-1 Infection

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In the absence of antiretroviral therapy, most human immunodeficiency virus type 1 (HIV-1) infections in children are due to mother-to-child transmission during pregnancy, birth, or breastfeeding. In settings where maternal HIV testing and treatment are available, most infections occur during adolescence (see Chapter 109) as a result of sexual activity or injection drug use. In this chapter we review the main features of HIV-1 immunopathogenesis, with an emphasis on the unique features of pediatric infection. We also describe how antiretroviral therapy (ART) allows preservation and reconstitution of immune function and alters the latent reservoir.

HIV Replication

Activated $CD4^+$ T lymphocytes represent the main cellular target of HIV-1, and most of these cells reside in the gastrointestinal tract. During acute infection, adolescents and adults frequently have nonspecific “viral” symptoms (see Chapter 111), but infants usually are symptom free.[1,2] In adolescents and adults, plasma viremia decreases and peripheral blood $CD4^+$ T-lymphocyte counts rise after a few weeks, even in the absence of ART. $CD8^+$ cytotoxic T lymphocytes (CTLs) play a major role in this early control of viral replication.[3–5] Additional adaptive immune responses, as well as innate immune responses, increasingly are being recognized as important factors in the control of initial viral replication.[6–8] After this acute period, adults and older children have relatively constant levels of viremia, which is referred to as a *set point*. This level of viremia is highly predictive of the later course of disease progression.[9,10]

In contrast to older children and adults, HIV-1-infected infants have high levels of plasma viremia and do not achieve a set point for several years.[11] These high and persistent levels of viremia are attributed to immunologic immaturity.[12,13] HIV-specific CTL responses can be detected at birth in infants infected in utero, but these responses are insufficient to control infection.[14] Studies suggest that this failure is due to decreased functional capacity, lack of CD4$^+$ T-lymphocyte help, and targeting of epitopes that inhibit the virus less effectively.[14,15] The relatively high frequency of regulatory T lymphocytes also may contribute to the suppression of virus-specific T-lymphocyte responses.[16,17] Other immune factors that may play a role include a decreased capacity of neonatal natural killer cells to mediate antibody-dependent cell-mediated cytotoxicity.

The availability of increased numbers of target cells also may contribute to the high level of viremia. The absolute number and relative percentage of CD4$^+$ T lymphocytes are much higher in infants and children.[18] Relative to their body size, the mass of the thymus is increased, and thymopoiesis is much more active during childhood.[19] Thus a large renewable source of CD4$^+$ T lymphocytes may serve as “fuel” for HIV infection and may account for the rapid tempo of disease progression observed in children.

Immune Consequences of Untreated HIV-1 Infection

CD4$^+$ T-lymphocyte depletion is the hallmark of HIV-1 infection. Direct infection leading to apoptosis by caspase-3 accounts for only 5% of this depletion. Approximately 95% of CD4$^+$ T lymphocytes die by caspase-1-mediated pyroptosis, a cellular defense mechanism in which nonproductive fragments of HIV-1 genomic

DNA activate a host DNA sensor, resulting in formation of an inflammasome. The inflammasome fragments nuclear DNA, secretes interferon 1β (attracting other CD4$^+$ T lymphocytes to their fiery death), and ruptures the cell.[20,21] Other potential mechanisms of CD4$^+$ T-lymphocyte depletion include decreased production of bone marrow precursors and thymic dysfunction. The function and repertoire of the remaining CD4$^+$ T lymphocytes are significantly perturbed, resulting in defects in both B-lymphocyte antibody formation and the generation of effective CD8$^+$ T-lymphocyte responses.[22–25] Other immune cell perturbations in HIV-1 infection are shown in Box 110.1.

Box 110.1

Immunopathologic Consequences of HIV-1 Infection

T Lymphocytes

Laboratory Manifestations

Lymphopenia

Selective CD4$^+$ T-lymphocyte depletion

Decreased CD4$^+$/CD8$^+$ T-lymphocyte ratio

Impairments in other T-lymphocyte subsets (Th17 and Treg depletion; switch Th1→Th2-type response) and gamma-delta cells

Impaired Functions

Impaired delayed-type hypersensitivity (new and recall)

Impaired mitogen-antigen responses

Impaired alloantigen reactivity

Impaired T-lymphocyte cytotoxicity

Impaired cytokine production (IL-2, IFNγ, others)

Clinical Manifestations

Chronic active viral infections (i.e., varicella-zoster virus, cytomegalovirus, Epstein-Barr virus)

Neoplasms

B Lymphocytes

Phenotypic Perturbations

Overrepresentation of activated, exhausted, and terminally differentiated B lymphocytes

Overrepresentation of immature/transitional B lymphocytes

Reduced representation of $CD27^+$ memory B lymphocytes

Impaired Functions

Polyclonal B-lymphocyte activation

Hypergammaglobulinemia

Polyclonal immunoglobulin class switch recombination (switch from IgM to nonprotective IgG, IgA, and IgE)

Impaired antibody responses (primary and secondary responses; T-lymphocyte-dependent and T-lymphocyte-independent antigens)

Reduced proliferative capacity

Stunted immunoglobulin diversification

Increased circulating immune complexes

Loss of serologic antibody memory

Clinical Manifestations

Impaired vaccine responses

B-lymphocyte malignancies

Autoimmune diseases

Monocytes and Macrophages

(including bone marrow precursors and microglial cells in the central nervous system)

Laboratory Manifestations

Increased levels of circulating “pocked” red blood cells

Elevated serum levels of TNF

Impaired splenic clearance (antibody-coated red blood cells)

Impaired Functions

Noncytopathic latent infection

Impaired delayed-type hypersensitivity

Impaired granuloma formation

Clinical Manifestations

Opportunistic infections (mainly mycobacterial)

Invasive pneumococcal infections

HIV-associated encephalopathy

Natural Killer Lymphocytes

Laboratory Manifestations

Reduced percentage of NK cells

Depletion of mature cytotoxic NK cell subsets (CD161$^+$, CD56$^+$, or CD16$^+$)

Selective depletion of invariant NKT lymphocytes

Impaired Functions

Impaired cytolytic activity

Impaired immunoregulatory activity (DC-mediated helper function for Th1 and CTL responses)

Clinical Manifestations

Chronic viral infection (i.e., herpesvirus)

Neoplasms

Dendritic Cells

Laboratory Manifestations

Decreased numbers of both plasmacytoid and myeloid DCs in peripheral blood

Impaired Functions

Impaired IFNα production

Increased secretion of inflammatory cytokines and chemokines (including TNF and IL-6)

Neutrophils

Laboratory Manifestations

Neutropenia

Impaired Functions

Impaired chemotaxis and expression of cellular adhesion molecules

Impaired phagocytosis

Impaired production of toxic oxygen species

Clinical Manifestations

Opportunistic bacterial and fungal infections

CTL, cytotoxic T lymphocyte; DC, dendritic cell; Ig, immunoglobulin; IL, interleukin; IFN, interferon; NK, natural killer; NKT, natural killer T; Th, T helper; TNF, tumor necrosis factor; Treg, regulatory T lymphocyte.

Destruction of up to 60% of CD4$^+$ T lymphocytes residing in the gastrointestinal tract has been identified as a critical early event in HIV-1 pathogenesis.[26–31] Unlike their counterparts in the blood, the numbers of these cells in the gastrointestinal tract do not recover after the acute phase, and even with ART, their numbers rarely are restored.[32–34] Most of the CD4$^+$ T lymphocytes destroyed in the gut belong to the recently identified Th17 subset.[35–37] These cells regulate responses to bacterial and fungal pathogens at mucosal surfaces. This loss is associated with increased microbial translocation and immune activation, which contribute to enhanced HIV spread and CD4$^+$ T-lymphocyte loss.[38,39]

The chronic phase of HIV-1 infection is characterized by a pathologic activation of the immune system. The extent of immune activation predicts disease progression better than either plasma viremia or CD4$^+$ T-lymphocyte counts.[40,41] This activation is linked to immune exhaustion, impaired T-lymphocyte homeostasis, hypergammaglobulinemia, and other perturbations that result in increased susceptibility to opportunistic infections and cancers that characterize AIDS.[42,43]

Effects of Antiviral Therapy on Immune Function and Viral Reservoirs

The advent of effective ARTs has transformed HIV-1 infection into a chronic manageable disease. Higher levels of plasma viremia, variable pharmacokinetics, and poor adherence to therapy offer unique challenges to HIV-1 suppression in children. Nevertheless, with contemporary regimens, most children can achieve viral suppression with corresponding improvements in immune function. Normalization of both T- and B-lymphocyte numbers and function has been documented in many studies, particularly if therapy is initiated early in infection.[44–51] In contrast to adults, some infants who achieve and maintain viral suppression in the first few months of life do not develop detectable HIV-specific responses (antibodies, $CD4^+$, and CTL responses).[44,52] These infants mount appropriate responses to vaccines and viral infections, suggesting that this defect is specific to HIV-1. Increased thymic function also confers an advantage in HIV-infected adolescents.[53] Children who start therapy at low $CD4^+$ T-lymphocyte levels may not experience full immunologic recovery.[35]

Early infant treatment modifies clinical disease progression, and ART also can influence both the size and composition of latent viral reservoirs. An important barrier to HIV eradication is the early seeding of long-term reservoirs. HIV persists in multiple memory T-lymphocyte subsets with varying half-lives and modes of maintenance, which contribute to the latent reservoirs to varying degrees.[54] T-lymphocyte subset composition differs in infants and children.[55] Because very early treatment in adults alters which T-lymphocyte subsets make up the reservoir, it is likely that very early treatment in infants, which decreases the size of reservoirs, also can alter its composition.[56–58] The recent case of an HIV-infected infant who, after 18 months of very early ART, remained aviremic without ART for 27 months (rather than the typical days to weeks) before experiencing viral rebound, is encouraging and currently is under investigation in clinical trials.[59–62]

Notably, at the initiation of ART, between 10% and 40% of individuals develop a pathologic immune response to antigens, especially latent or persistent mycobacterial and cryptococcal infection.[63–65] This acute inflammatory condition is referred to as *immune reconstitution inflammatory syndrome* (IRIS). It is similar to "paradoxical reactions" long recognized in *Mycobacterium tuberculosis* infection. It is more common in individuals with low $CD4^+$ T-lymphocyte levels, and recent data suggest that infants may be at greater risk.[66,67] Most individuals can be managed by the use of anti-inflammatory agents without interrupting ART.

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111

Diagnosis and Clinical Manifestations of HIV Infection

Paul Krogstad

Most cases of human immunodeficiency virus (HIV) infection in infants and young children result from mother-to-child transmission. Infection acquired by sexual contact and injectable drug use contributes to the growing number of infections in adolescents and young adults. The early clinical manifestations of HIV infection are varied and sometimes indistinct, particularly in infants and young children. Early diagnosis is a prerequisite to timely provision of effective antiretroviral therapy and potentially life-saving prophylactic medications. Accurate detection of HIV infection in children younger than 18 months rests on specialized laboratory testing to detect the virus itself, owing to the confounding effects of transplacentally acquired maternal antibody. This chapter outlines diagnostic approaches for HIV infection in infants, children, and adolescents and young adults and provides an overview of the pathologic effects of HIV on various organ systems seen in these age groups. Infectious complications of HIV infection are discussed in Chapter 112.

Diagnosis

Most HIV infections in infants and children are acquired through mother-to-child transmission of the virus in utero, during labor and delivery, or postnatally during breastfeeding. Transplacentally acquired antibodies specific for HIV are present in the serum of newborns born to infected women, yielding positive serologic tests regardless of whether infection has actually occurred. Because seroreversion usually does not occur until 12 to 18 months of age, and may not occur until 24 months of age, the diagnosis of HIV infection in infants must be based on virologic tests. Virus culture has been used in the past but is slow and technically cumbersome. Instead, detection of HIV RNA or DNA by polymerase chain reaction (PCR) or other nucleic acid tests (NATs) is recommended by the World Health Organization (WHO) and public health authorities and experts in the United States.[1–3] WHO also endorses the use of specialized ultrasensitive enzyme immunoassay (EIA) methods to detect the HIV p24 protein in plasma or dried blood spots because this method is less expensive and more readily available in some resource-poor settings.[3]

The sensitivity of DNA PCR detection of HIV in blood leukocytes is about 55% at birth, increases to more than 90% by 2 to 4 weeks of age, and approaches 100% by 3 months of age. False-positive tests are rare after the immediate newborn period, with a reported specificity of 100% thereafter.[1,4–6]

HIV RNA assays detect the presence of the viral genome in plasma. The specificity of HIV RNA assays for diagnosis of viral infection is essentially 100%. Using a threshold of 5000 copies/mL of plasma as a minimal threshold for positivity, the sensitivity of HIV RNA assays for detection of infection in infants is 25% to 58% during the first several weeks of life, 89% at age 1 month, and 90% to 100% by age 2 to 3 months. HIV RNA testing should be sensitive despite antiretroviral therapy. The impact of maternal therapy or postnatal treatment of infants on the sensitivity of HIV RNA tests remains the subject of investigation due to continuous changes in the composition and potency of the antiretroviral agents used.[1,2]

For infants born to HIV-infected mothers, the US Public Health Service recommendations include HIV DNA PCR or HIV RNA NAT testing at 14 to 21 days, 1 to 2 months, and 4 to 6 months of age.[2] Some experts also recommend testing immediately after birth for infants whose mothers have poorly controlled HIV disease and other infants at higher risk for acquiring infection. Cord blood specimens should not be used for HIV RNA or DNA testing because contamination of specimens with maternal blood may cause false-positive results. Any positive virologic test should be confirmed as soon as possible by a test on a second specimen. An HIV RNA assay can be used as the confirmatory test for infants who have an initial positive HIV DNA PCR test.[2]

HIV infection is *presumptively* excluded in nonbreastfed infants who have had two or more negative virologic tests, with one test obtained at ≥14 days of age and the other obtained at ≥4 weeks of age. Children with one negative virologic test result obtained at ≥2 months of age also are presumed to be uninfected. *Definitive* exclusion of HIV infection in a nonbreastfed infant requires two or more negative virologic tests, with one obtained at ≥1 month of age and the other at ≥4 months of age. Ideally, these tests to exclude HIV infection should have been performed 2 to 4 weeks after cessation of any antiretroviral prophylaxis.[2]

The worldwide genetic variability of HIV has an impact on the choice of nucleic acid tests used for diagnosis and monitoring of infection. HIV exists in a variety of genetically distinguishable subtypes.[7] Subtype B is the predominate variant found in North America, South America, and Western Europe. Subtype C is the major subtype in most of sub-Saharan Africa and India, and a recombinant variant of HIV, CRF01, predominates in Southeast Asia. HIV DNA tests used in the United States will not detect all non-B subtypes of HIV. HIV RNA assays are more sensitive for detecting non−subtype B HIV and should be preferentially used when infection is thought to have originated in Asia or Africa. These technical limitations of HIV nucleic acid testing, and the possibility of infection with HIV-2, should be kept in mind if the clinical presentation of a child leads to concerns about undiagnosed HIV infection. Unexpected cases of non−subtype B HIV have been documented in the US.[8,9]

The diagnosis of HIV infection in children older than 24 months, adolescents, and adults primarily relies on HIV antibody tests or on antigen-antibody combination tests that also detect the viral p24 HIV-specific antigen (Table 111.1). The recommended schema for diagnostic evaluation of patients 24 months or older is outlined in Fig. 111.1.[10] In brief, testing should begin with a combination immunoassay that detects HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen. An immunoassay to detect HIV-1/2 antibodies is an alternative, but the combination assay permits detection of infection before antibody responses to HIV antigens have developed. All specimens reactive on this initial assay should then undergo supplemental testing with an immunoassay that differentiates HIV-1 from HIV-2 antibodies. Specimens that are reactive on the initial immunoassay and nonreactive or indeterminate on the antibody differentiation assay proceed to HIV-1 nucleic acid testing to resolve the diagnostic ambiguity. Additional testing, including HIV-1 viral RNA measurement and $CD4^+$ T-lymphocyte quantitation, are then recommended to determine the need for prophylactic therapy against opportunistic infections and in preparation for institution of antiretroviral therapy.[2]

TABLE 111.1

Assays to Detect HIV Infection

Assay	Type	Advantages	Disadvantages
PCR and other NATs to detect HIV DNA and RNA	Virologic	Very highly sensitive	Small risk for false-positive results if HIV RNA value <5000 copies/mL is considered positive
Ultrasensitive p24 antigen detection assays for plasma/dried blood spots	Virologic	Inexpensive	Less sensitive than NAT; false-positive results in the first week of life
Culture	Virologic	Sensitive, highly specific	Requires weeks to complete, technically complex; research use only. Not currently recommended for diagnosis.
Ultrasensitive p24 antigen detection assays for plasma/dried blood spots	Virologic	Inexpensive	Less sensitive than NAT; false-positive results in the first week of life
HIV-1/2 antibody/HIV-1 antigen combination immunoassays	Virologic and antibody Based	Sensitive, highly specific. Detection of antigen allows early diagnosis before an individual develops HIV antibody.	Recommended for initial testing to screen for established infection with HIV-1 or HIV-2 and for acute HIV-1 infection.
HIV-1/2 immunoassays	Antibody	Highly sensitive	Alternative for initial testing
HIV-1 Western blot and HIV-1 indirect	Antibody		Technically more difficult than immunoassay methods.

IFAs			Recommended as an alternative for supplemental testing. Will not detect acute HIV infection.
HIV-1/HIV-2 antibody differentiation immunoassay	Antibody	Used to clarify ambiguous results from HIV-1/2 combination assays	Recommended for supplemental testing.

IFA, immunofluorescence assay; NAT, nucleic acid testing; PCR, polymerase chain reaction.

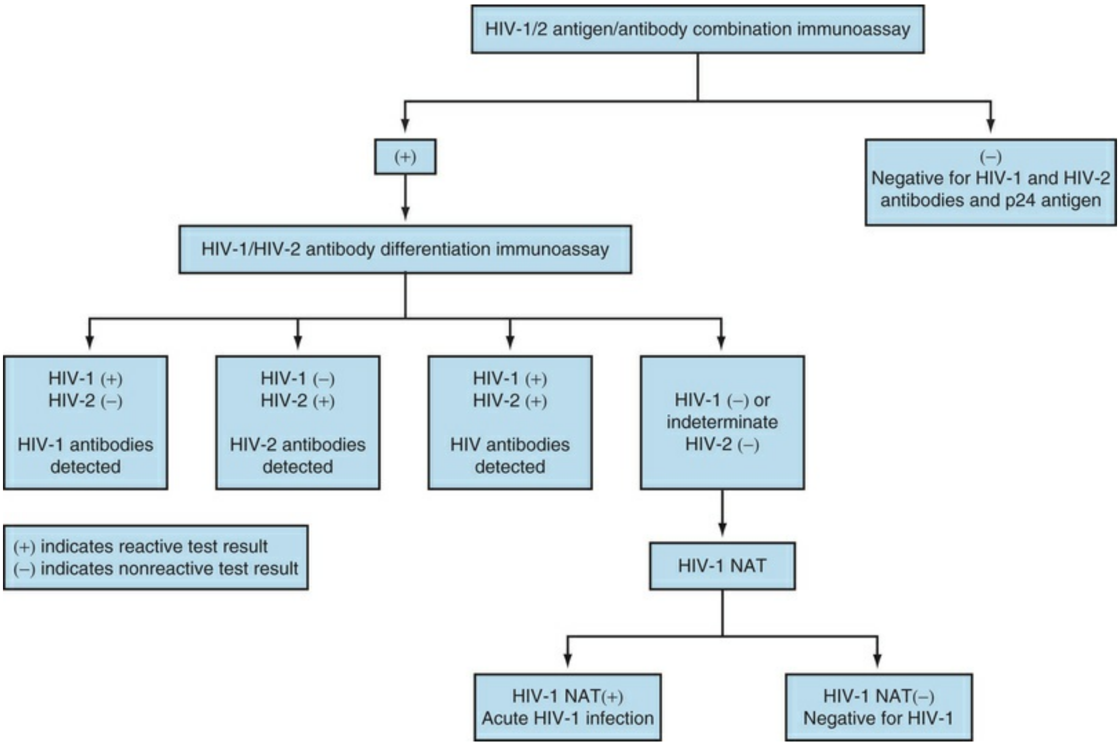
HIV-1/2 antigen/antibody combination immunoassay
(+)
(–)
Negative for HIV-1 and HIV-2 antibodies and p24 antigen
HIV-1/HIV-2 antibody differentiation immunoassay
HIV-1 (+)
HIV-2 (–)
HIV-1 antibodies detected
HIV-1 (–)
HIV-2 (+)
HIV-2 antibodies detected
HIV-1 (+)
HIV-2 (+)
HIV antibodies detected
HIV-1 (–) or indeterminate
HIV-2 (–)
(+) indicates reactive test result
(–) indicates nonreactive test result
HIV-1 NAT
HIV-1 NAT(+)
Acute HIV-1 infection
HIV-1 NAT(–)
Negative for HIV-1

FIGURE 111.1 Schema for diagnosis of HIV infection in children older than 24 months, adolescents, and adults. NAT, nuclear acid test.

Several rapid tests also are available to detect HIV antibody in blood specimens collected by fingerstick or by venipuncture. These tests are useful for point-of-care testing because the results of rapid tests are available promptly, thereby enhancing the effectiveness of posttest counseling.[10] Rapid tests also facilitate the determination of HIV status of pregnant women, allowing the timely administration of antiretroviral therapy to prevent mother-to-child transmission at the time of delivery.[5] Individuals with positive (reactive) rapid tests should be evaluated as in Fig. 111.1, beginning with an antigen/antibody combination immunoassay. In areas with a high prevalence of HIV, a second enzyme immunoassay (EIA) or use of a rapid diagnostic test may be an acceptable approach for confirmation of an EIA or an initial rapid test result.[3,11] However, rapid tests, like other antibody tests, will yield false-positive results in uninfected infants and toddlers with maternally derived HIV antibody.

Some experts confirm the absence of HIV infection after ≥12 months of age in children with prior negative virologic tests by performing an antibody test to document loss of maternal HIV antibodies.[2] Two or more negative HIV antibody tests from separate specimens obtained at ≥6 months of age also allow infection to be excluded, if an infant has not been breastfed. If breastfeeding has occurred, HIV infection cannot be definitively excluded until the infant has a negative diagnostic test ≥6 weeks after breastfeeding has ceased.[2]

Early Signs, Symptoms, and Laboratory Abnormalities After Mother-to-Child Transmission

Infants born to HIV-infected women are more often of low birth weight than unexposed infants but have normal physical findings and are symptom free during the neonatal period. The earliest manifestations of HIV infection in infants frequently are nonspecific.[12,13] Lymphadenopathy, often associated with hepatosplenomegaly, is a commonly observed early sign. Oral candidiasis, parotitis, poor weight gain, dermatitis, developmental regression, or failure to achieve developmental milestones are other common presenting features. Before prophylactic therapy with trimethoprim-sulfamethoxazole and other agents became routine, *Pneumocystis jirovecii* pneumonia (PCP) accounted for about half of all AIDS-defining conditions diagnosed during the first year of life in the US.[14]

Laboratory abnormalities indicative of immunologic derangement also are seen in infancy. By 1 or 2 months of age, many HIV-infected infants have $CD4^+$ lymphocyte counts that are significantly lower than those in HIV-exposed, uninfected infants.[15] Hyperimmunoglobulinemia G, A, E, or M is present in up to 90% of HIV-infected infants by 6 months of age.[13,16]

The Centers for Disease Control and Prevention (CDC) recently revised surveillance staging of disease (Table 111.2). This classification ranges from stage 1 (mild abnormality in $CD4^+$ T-lymphocyte parameters) to stage 3 (laboratory evidence of substantial immunodeficiency). An individual also is said to have stage 3 disease, regardless of $CD4^+$ T-lymphocyte parameters, if they have experienced an AIDS defining illnesses (Box 111.1).[17] The WHO clinical classification of HIV infection is similar in concept and ranges from stage 1 (symptom free) to stage 4 (advanced symptoms).[18]

TABLE 111.2

HIV Infection Stage Based on Age-Specific $CD4^+$ T-lymphocyte Count or $CD4^+$ T-Lymphocyte Percentage of Total Lymphocytes

Stage[a]	Age at Which $CD4^+$ T Lymphocytes Tested					
	<1 yr		1–5 yr		≥6 yr	
	Cells/mm^3	%	Cells/mm^3	%	Cells/mm^3	%
1	≥1500	≥34	≥1000	≥30	≥500	≥26
2	750–1499	26–33	500–999	22–29	200–499	14–25
3	<750	<26	<500	<22	<200	<14

[a] The stage is based primarily on the $CD4^+$ T-lymphocyte count; the $CD4^+$ T-lymphocyte count takes precedence over the $CD4^+$ T-lymphocyte percentage, and the percentage is considered only if the count is missing.

From Centers for Disease Control and Prevention. Revised surveillance case definition for HIV infection—United States, 2014. MMWR Recomm Rep 2014;63(RR-3):1–10.

Box 111.1

Stage 3–Defining Opportunistic Illnesses in HIV Infection

Bacterial infections, multiple or recurrent[a]

Candidiasis of bronchi, trachea, or lungs

Candidiasis of esophagus

Cervical cancer, invasive[b]

Coccidioidomycosis, disseminated or extrapulmonary

Cryptococcosis, extrapulmonary

Cryptosporidiosis, chronic intestinal (>1 month's duration)

Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month

Cytomegalovirus retinitis (with loss of vision)

Encephalopathy attributed to HIV[c]

Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis with onset at age >1 month

Histoplasmosis, disseminated or extrapulmonary

Isosporiasis, chronic intestinal (>1 month's duration)

Kaposi sarcoma

Lymphoma, Burkitt (or equivalent term)

Lymphoma, immunoblastic (or equivalent term)

Lymphoma, primary, of brain

Mycobacterium avium complex or *Mycobacterium kansasii*, disseminated or extrapulmonary

Mycobacterium tuberculosis of any site, pulmonary,[b] disseminated, or extrapulmonary

Mycobacterium, other species or unidentified species, disseminated or extrapulmonary

Pneumocystis jirovecii (PCP) pneumonia

Pneumonia, recurrent[b]

Progressive multifocal leukoencephalopathy

Salmonella septicemia, recurrent

Toxoplasmosis of brain with onset at age >1 month

Wasting syndrome attributed to HIV[c]

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[a] Only among children aged <6 years.

[b] Only among adults, adolescents, and children aged ≥6 years.

[c] Suggested diagnostic criteria for these illnesses, which might be particularly important for HIV encephalopathy and HIV wasting syndrome, are described in the following references: Center for Disease Control and Prevention. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR Recomm Rep 1994;43(RR-12); and Centers for Disease Control and Prevention. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep 1992;41(RR-17).

Organ System–Specific Manifestations of HIV Infection

HIV infection has the potential to cause injury directly or indirectly to many organ systems. The following sections summarize the most common manifestations of HIV infection and AIDS in infants, children, and adolescents.

Neurologic Manifestations

Central nervous system (CNS) pathology and neurocognitive dysfunction are extremely common in untreated HIV-infected children.[19–21] Before the availability of antiretroviral therapy, progressive HIV encephalopathy accounted for about 15% of all pediatric AIDS-defining conditions reported to the CDC.[22]

Clinical features of HIV-associated encephalopathy in young children are shown in Table 111.3. Developmental delay or loss of developmental milestones are common manifestations and may be associated with poor weight gain. Characteristic computed tomography (CT) and magnetic resonance imaging findings in such children include cerebral atrophy (85%–100% of cases) and bilateral symmetric calcification of the basal ganglia (15%–40% of cases)[21,23,24] (Fig. 111.2). Evidence of cerebrovascular disease can be seen, and strokes occur in a small fraction of children.[25] Results of cerebrospinal fluid (CSF) studies usually are normal; mild pleocytosis is observed in some cases.[26]

TABLE 111.3

Features of Encephalopathy Associated With Human Immunodeficiency Virus Infection in Infants and Children

Clinical Features	**Neuroimaging Features**
Impaired brain growth/microcephaly	Cerebral atrophy
Developmental delay or regression Expressive language impairment Spastic weakness	Symmetric calcifications in basal ganglia
Pathologic reflexes	
Dystonia	
Gait disturbance	

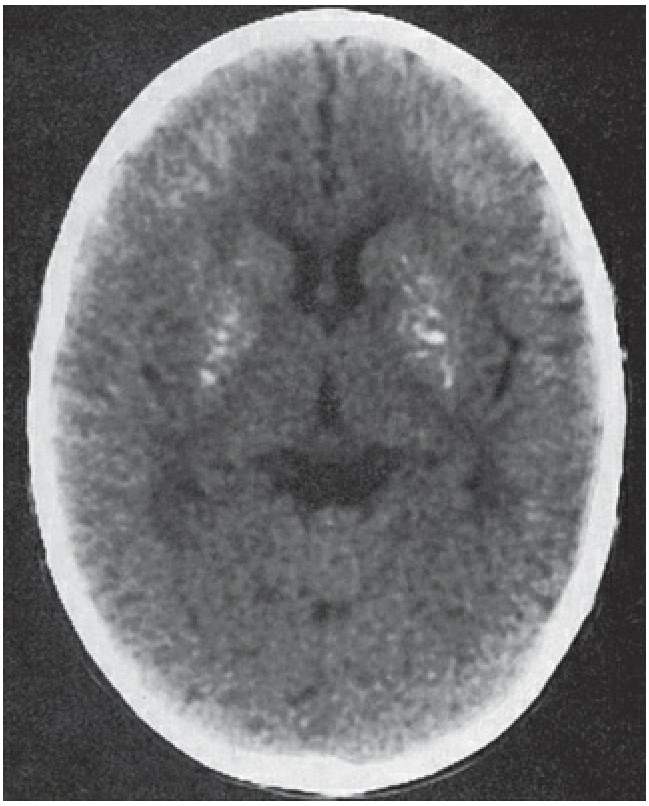

FIGURE 111.2 Computed tomography scan of the brain showing bilateral symmetric calcification of the basal ganglia in a 2-year-old boy with vertically acquired HIV infection.

HIV-related neuropathology is likely the result of HIV infection rather than from complicating infection or malignancy. Evidence supporting this view includes virus isolation from or detection of RNA by PCR in the CSF, intrathecal synthesis of HIV antibody, and identification of HIV nucleotide sequences in brain tissue at autopsy.[26–30] Neuropathologic features noted in the brains of HIV-infected children include atrophy, subcortical inflammatory lesions, multinucleated giant cells, and vascular calcification[27,29]

Blood-derived macrophages, resident microglia, their derivatives (including multinucleated giant cells), and astrocytes are the only cells that consistently have been shown to harbor HIV in the CNS.[20,27,31] It is hypothesized that activation of these cells by HIV results in overproduction of certain cytokines, arachidonic acid metabolites, nitric oxide, and quinolinic acid, which in turn may be responsible for some of the neuropathologic changes.[32–35] Elevated serum concentration of tumor necrosis factor-α (TNF-α) has been associated with progressive encephalopathy in HIV-infected children,[33–35] and TNF-α can produce white-matter destruction in vitro similar to that observed clinically and pathologically in children with encephalopathy.[36] Platelet-activating factor and products of arachidonic acid metabolism also may mediate CNS injury, possibly through upregulation of TNF-α or other cytokines.[37]

The rate of progression and severity of HIV encephalopathy vary tremendously and are modified by antiretroviral therapy. The effectiveness of antiretroviral therapy in preventing or reversing CNS abnormalities may depend on the CNS penetration of the specific agents used and how early therapy is begun, although conflicting data are reported.[23,38]

Residual behavioral problems, as well as neurologic, cognitive, and scholastic impairments, still appear to be common with current antiretroviral therapy, and some antiretroviral drugs have been associated with neuropsychiatric symptoms.[23,38] Consequently, frequent evaluation of developmental milestones, neuropsychological testing, counseling, and supportive and symptomatic care are critical in the care of HIV-infected children.[2]

Pulmonary Conditions

Before the development of multidrug antiretroviral therapy, lymphoid interstitial pneumonia (LIP) and the clinically similar, but histologically distinct, pulmonary lymphoid hyperplasia (PLH) were second only to PCP as pulmonary diseases indicative of HIV infection and AIDS in children.[22] Although LIP and PLH no longer are considered AIDS-defining illnesses because of their relatively benign course, one retrospective study showed twice the rate of hospitalization due to serious respiratory infections in patients with LIP-PLH than in HIV-infected children who did not have evidence of LIP-PLH.[39]

Although the radiographic features of LIP-PLH and PCP can be similar, clinical features distinguish the conditions (Table 111.4). The onset of LIP-PLH usually is insidious. Cough and tachypnea often are present. Examination of the chest generally reveals few auscultatory abnormalities. Marked generalized lymphadenopathy, hepatosplenomegaly, and salivary gland, especially parotid gland, enlargement may be noted. Digital clubbing is observed in advanced cases of LIP-PLH. A chest radiograph typically reveals symmetric bilateral reticulonodular and interstitial infiltrates, sometimes in association with hilar adenopathy (Fig. 111.3). Differentiation from miliary tuberculosis sometimes is difficult, although patients with LIP-PLH are more likely to be afebrile and relatively well appearing, and the chest radiograph shows less distinct (sometimes larger) lesions and more interstitial abnormality than in tuberculosis. There is no typical laboratory abnormality, but a marked increase in serum immunoglobulin concentrations often is present in patients with LIP-PLH, reflecting the presence of immunologic activation.

TABLE 111.4

Clinical Differentiation of LIP-PLH from PCP Pneumonia

Finding	LIP-PLH	PCP
CLINICAL		
Acute onset	No	Yes
Fever	No	Yes (usually)
Retractions	Late	Early
Crackles	No	Yes
Hypoxia	Late	Early
Clubbing	Yes	No
Salivary gland enlargement	Yes	No
BAL FLUID		

Lymphocyte predominance	Yes	No
Neutrophil predominance	No	Yes

BAL, bronchoalveolar lavage; LIP-PLH, lymphoid interstitial pneumonitis or pulmonary lymphoid hyperplasia; PCP, *Pneumocystis jirovecii* pneumonia.

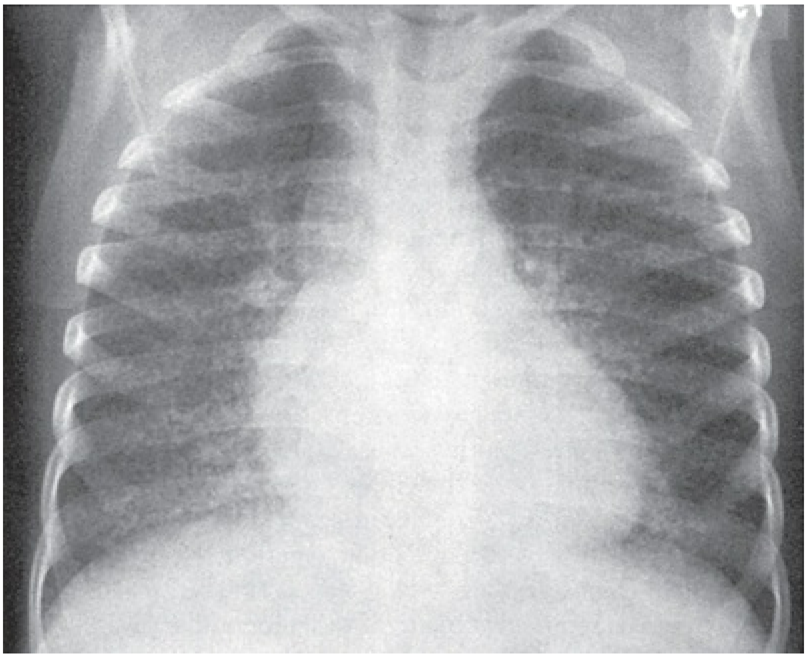

FIGURE 111.3 Chest radiograph demonstrating bilateral reticulonodular interstitial infiltrates of lymphoid interstitial pneumonitis/pulmonary lymphoid hyperplasia in a 4-year-old boy with vertically acquired HIV infection.

With careful evaluation to exclude tuberculosis or other infections, a presumptive diagnosis of LIP-PLH can be made on the basis of characteristic radiographic features persisting for 2 months or longer; CT can enhance diagnostic evaluation.[39,40] A definitive diagnosis requires lung biopsy. Histopathologic and immunocytochemical analyses reveal a mononuclear interstitial infiltrate surrounding the airways composed of immunoblasts, plasma cells, and $CD8^+$ lymphocytes. The pathogenesis of LIP-PLH is poorly understood, but Epstein-Barr virus (EBV) has been repeatedly implicated as a cofactor because EBV nucleic and antigens are frequently detected in histologic sections.[41]

The clinical course of LIP-PLH is variable. Spontaneous clinical remission sometimes is observed. In severe cases, there is progressive hypoxia and respiratory failure. Exacerbation of clinical signs and symptoms can occur in association with intercurrent viral respiratory illnesses. Antiretroviral treatment is associated with clinical improvement, including full resolution.[42] Supportive care is essential, including immunization against common viral and bacterial pathogens (e.g., influenza virus, *Streptococcus pneumoniae*), which often complicate LIP, and appropriate use of antibiotics and antiviral drugs for acute infections.[39] Some patients require supplemental oxygen, and anecdotal reports suggest that some cases with progressive hypoxemia may respond to systemic corticosteroid therapy.[40,43]

Malignancy

Cancers are uncommon among HIV-infected children but occur at much higher rates than in the general population.[44] Malignancy is most common among children with severe immunosuppression and in those who had been receiving multidrug antiretroviral therapy for 2 years or less.[44] The most common cancer is non-Hodgkin lymphoma (Burkitt or immunoblastic types).[45–47] Patients often manifest fever, weight loss, and evidence of "extranodal" disease (e.g., hepatomegaly and jaundice, abdominal distention, myelophthisis, or neurologic abnormalities). Children with CNS lymphoma can have delay or loss of developmental milestones, cranial nerve palsies, seizures, or hemiparesis.[48] Contrast-enhanced CT of the brain reveals hyperdense periventricular mass lesions similar to those seen in cerebral toxoplasmosis. CNS lymphoma more commonly causes an isolated brain mass in children than toxoplasmosis or other infectious agents. In addition to elevated protein and depressed glucose concentrations, examination of CSF can reveal malignant cells. Brain biopsy for definitive diagnosis is indicated for those children who have rapidly progressive disease or clinical or radiographic progression despite empiric therapy for toxoplasmosis.

The pathogenesis of AIDS-associated non-Hodgkin lymphoma is poorly defined; both EBV and mutations or rearrangements in the *c-myc* oncogene have been implicated.[49–51] Effective chemotherapeutic regimens are available.[52]

Hodgkin lymphoma, leiomyosarcoma, leiomyoma, and Kaposi sarcoma also occur with greater frequency in children with HIV infection than in the general population.[52] A strong association exists between EBV and leiomyosarcoma or leiomyoma. Endobronchial leiomyosarcoma or leiomyoma can manifest with fever or cyanosis.[47] Multiple pulmonary parenchymal nodules can be visualized radiographically. Clinical manifestations of pulmonary Kaposi sarcoma, which is triggered by infection with human herpesvirus 8, include fever, cough, dyspnea, and hemoptysis. The radiographic features are diffuse reticulonodular infiltrates resembling those seen in LIP-PLH or PCP. Kaposi sarcoma also can present with involvement of lymph nodes, the oral cavity (hard palate or tonsils), or skin. Gastrointestinal lesions can occur with any of these malignancies, resulting in gastrointestinal bleeding, abdominal pain, or bowel obstruction.[46,47]

Gastrointestinal Disease

Wasting Syndrome

In some areas of Africa, HIV infection was originally referred to as “slim disease.”[53] Weight loss, or failure to gain appropriate weight, is a common presenting symptom in HIV-infected infants and children and may appear within the first 2 to 3 months of life.[54] Several factors contribute to wasting. HIV infection itself increases a child's nutritional requirements. In addition, opportunistic infections, especially those associated with fever, contribute to increased metabolic requirements. Oral lesions (e.g., thrush, herpes simplex virus infection, recurrent aphthous ulcers) can interfere with feeding. Chronic diarrhea and malabsorptive syndromes can inhibit caloric uptake. Effective antiretroviral therapy and nutritional support are the primary approaches to treating wasting syndrome and can include the use of nasogastric or gastrostomy tube feedings in some cases.

Hepatitis

Hepatomegaly, moderate increases in serum concentrations of hepatic enzymes (e.g., 5- to 10-fold increases in aspartate aminotransferase and/or alanine aminotransferase), are common in HIV-infected children but often are unaccompanied by clinical manifestations.[55] The differential diagnosis of hepatitis in HIV-infected children is broad and includes a variety of infectious causes, neoplasms, and effects of medications (Box 111.2).[56] In addition, elevation of transaminase concentrations has been reported in association with the use of virtually all antiretroviral medications.[2] These elevations usually are clinically insignificant in children but can necessitate discontinuation of antiretroviral medications in some cases. The clinical course of HIV-associated hepatitis is variable. Histopathologic studies of liver tissue obtained from HIV-infected children have identified giant cell transformation of hepatocytes, fatty degeneration, and lymphoplasmacytic infiltration as prominent features.[57,58] Coinfection with HIV can hasten the progression of liver disease caused by hepatitis B or C. The presence of hepatitis B coinfection also influences the selection of antiretroviral medications because worsening of liver disease can occur with discontinuation of antiretroviral agents that have activity against hepatitis B virus.[59]

Box 111.2

Differential Diagnosis of Hepatitis in Children Infected With HIV

Infection

Bacteria (e.g., *Mycobacterium avium* complex, *Mycobacterium tuberculosis,* or *Bartonella* spp.–induced bacillary peliosis hepatis)

Viruses (e.g., hepatitis A, B, or C; cytomegalovirus; Epstein-Barr virus; herpes simplex virus; adenovirus; or HIV)

Fungi (e.g., *Candida* spp., *Cryptococcus neoformans, Histoplasma capsulatum, Pneumocystis jirovecii*)

Protozoans (e.g., *Toxoplasma gondii*)

Malignancy

Lymphoma

Sarcoma

Drug-Induced

Sulfonamides

Antiretroviral agents (especially nonnucleoside reverse transcriptase inhibitors, tipranavir)

Antimycobacterial medications

Pentamidine

Cardiovascular Disease

Cardiac abnormalities are commonly observed in untreated HIV-infected children. Electrocardiographic abnormalities include conduction defects, unexplained sinus tachycardia, voltage abnormalities compatible with chamber enlargement, and dysrhythmias. Echocardiographic findings include ventricular dysfunction and pericardial effusion.[60] Many abnormalities are not apparent clinically, but in one retrospective study of 81 HIV-infected children, serious dysrhythmia, congestive heart failure, and unexpected cardiac arrest occurred in 28 (35%), 8 (10%), and 7 (9%) patients, respectively.[61]

The pathogenesis of cardiac disease in HIV-infected children is poorly understood, but epidemiologic associations between coinfection with EBV and bradycardia and congestive heart failure have been reported.[61] Adenovirus and cytomegalovirus gene sequences have been identified in a postmortem study of cardiac tissue from HIV-infected children with myocarditis, suggesting a possible etiologic role.[62] Rare cases exist in which HIV-infected cells were demonstrated in the myocardium.[63] The relationship between antiretroviral agents and cardiomyopathy remains unclear. Antiretroviral therapy has been associated with a marked reduction in the risk for cardiomyopathy, and infected children with cardiomyopathy and congestive heart failure generally improve with antiretroviral therapy and specific management of the cardiac disease. The use of either zalcitabine, an obsolete antiretroviral medication, or zidovudine has been linked to the development of cardiomyopathy.[64] Abnormalities of serum lipid concentrations and effect on electrocardiographic findings are adverse effects of antiretroviral medications, especially the HIV protease inhibitors. When dyslipidemia is encountered, changes in diet and other lifestyle modifications, substitution of other medications, or pharmacologic treatment may be needed.[2]

Renal Dysfunction

Nephropathy was initially described among children with advanced HIV disease.[65–67] In one early study, progressive renal disease with nephrotic syndrome and renal failure developed in 5 of 12 children with AIDS and proteinuria.[67] Persistent proteinuria now is recognized as a common finding and can be the initial evidence of renal disease in HIV-infected children and adolescents.[65,68,69] Most frequently, renal biopsies reveal histopathologic evidence of HIV-associated nephropathy (HIVAN), a collapsing form of focal and segmental glomerulosclerosis with microcystic tubulointerstitial injury. In vitro and in vivo studies suggest that HIV infection of renal epithelial parenchymal cells is involved in the development of HIVAN and that HIV replication in the kidney is compartmentalized after it occurs.[70–73] Immune complex glomerulonephritis and other forms of medical renal disease, as well as medication-induced renal injury, also can occur in HIV-infected individuals. Biopsy confirmation is recommended when HIVAN is suspected.[65,66,68,74] Progression of HIVAN to renal failure is more commonly seen among those of African ancestry.[74] Before the availability of antiretroviral therapy, HIVAN was strongly associated with increased mortality.[66,68] Antiretroviral therapy appears to be the most effective therapy, but angiotensin-converting enzyme inhibitors are used commonly in children with proteinuria. Corticosteroid therapy is not consistently effective among children with HIVAN, but cyclosporine-induced remission of HIV-associated nephrotic syndrome also has been reported.[65,67,75]

Hematologic Disorders

Anemia, leukopenia, neutropenia, and thrombocytopenia are common manifestations of HIV infection in children. Many cases of normocytic or microcytic anemia are attributable to chronic disease; macrocytic anemia most often is secondary to zidovudine therapy.[2] Other causes of anemia are iron deficiency, hemoglobinopathies, and red blood cell enzyme defects. Infectious diseases resulting in anemia in HIV-infected children include disseminated *Mycobacterium avium* complex infection, cytomegalovirus infection, and chronic parvovirus infection.[76]

The treatment of anemia in HIV-infected patients depends on the etiology. Therapy with recombinant human erythropoietin facilitates continued use of zidovudine if alternative antiretroviral agents cannot be substituted.[2,77] Some patients with chronic parvovirus infection respond to high-dose immune globulin intravenous (IGIV) therapy.[76]

Leukopenia and neutropenia often result from medication-induced bone marrow depression caused by zidovudine, trimethoprim-sulfamethoxazole, ganciclovir, pentamidine, and other medications. Neutropenia also is observed during the course of various chronic and opportunistic infections, including those caused by parvovirus B19 and *Mycobacterium avium* complex. Granulocyte colony-stimulating factor therapy can be helpful in reversing drug- or disease-induced neutropenia and preventing infectious complications.[78]

Thrombocytopenia in HIV-infected children can occur as a result of either underproduction or shortened survival of platelets. Immune-mediated destruction is a common cause of thrombocytopenia, and antiplatelet antibodies are detectable in most patients. Antiretroviral therapy often leads to resolution of thrombocytopenia. Some children can exhibit an initial response to corticosteroid, IGIV therapy, or the use of intravenous anti-D antibody, but improvement often is short-lived and incomplete. Splenectomy may be indicated for the HIV-infected child with severe thrombocytopenia that is refractory to other measures.[79] Rituximab also has been used in chronic, recurrent HIV-associated immune thrombocytopenia.[80]

Dermatologic Conditions

A wide variety of bacterial, fungal, viral, and parasitic infections of the skin occur in children with HIV infection.[81–83] In particular, molluscum contagiosum, scabies, tinea infections, and oropharyngeal candidiasis occur and recur at high frequency and often are severe and refractory to therapy. Prolonged development of vesicular lesions and recurrences of varicella also may occur.[84] HIV-infected children have a higher than expected incidence of noninfectious inflammatory, eczematoid, psoriatic, neoplastic, and drug hypersensitivity skin conditions.[85] Seborrheic dermatitis manifests as erythema and scaling of the face and scalp in HIV-infected infants or of the nasolabial folds, eyebrows, and postauricular areas in older children. Pruritic papular eruption (PPE) is a chronic eruption of papular lesions commonly encountered in children.[81,86] The etiology is uncertain, but PPE may represent a hypersensitivity reaction to insect bites.[83,86] PPE can cause substantial discomfort and is treated with oral antihistamine medications and topical corticosteroids.[83] Cutaneous eruptions occur with a variety of oral and parenteral medications, cotrimoxazole, and nonnucleoside reverse transcriptase inhibitors being the most commonly implicated.[2] Cutaneous Kaposi sarcoma occurs in HIV-infected children internationally but is rarely seen in the US.[45,52]

Prognosis

In general, children with vertically acquired HIV infection have shorter asymptomatic periods and more rapid disease progression than other individuals with HIV infection.[12,87,88] However, many children demonstrate late onset of symptoms and longterm survival.[87,89] Both the age at diagnosis of an AIDS-defining condition and clinical presentation are important determinants of prognosis. In one study in the US conducted before the advent of antiretroviral therapy, the overall median survival time for children with vertically acquired HIV infection was 30 months. Children who demonstrated AIDS in the first year of life had a median survival time of only about 7 months.[12] Even shorter periods of survival are common in resource-poor countries of the world.[88] Presentation during infancy with opportunistic infection (especially PCP) or HIV encephalopathy portends a poor prognosis, whereas slow decline of $CD4^+$ lymphocyte count, late onset of signs and symptoms of HIV infection,[12,21,87] and occurrence of LIP-PLH have been associated with longer survival.[89]

Beyond infancy, $CD4^+$ T-lymphocyte counts and measurements of plasma HIV viral load have strong prognostic value. The HIV Paediatric Prognostic Markers Collaborative Study[90] was a metaanalysis based on data from 3941 children (with 7297 child-years of follow-up) who had received no antiretroviral therapy, or zidovudine alone. In this study, $CD4^+$ lymphocyte percentage and HIV RNA levels were both independently predictive of the risk for clinical progression or death in children older than 12 months. The CD4⁺ lymphocyte percentage was a stronger predictor of risk than HIV RNA concentration (Fig. 111.4).

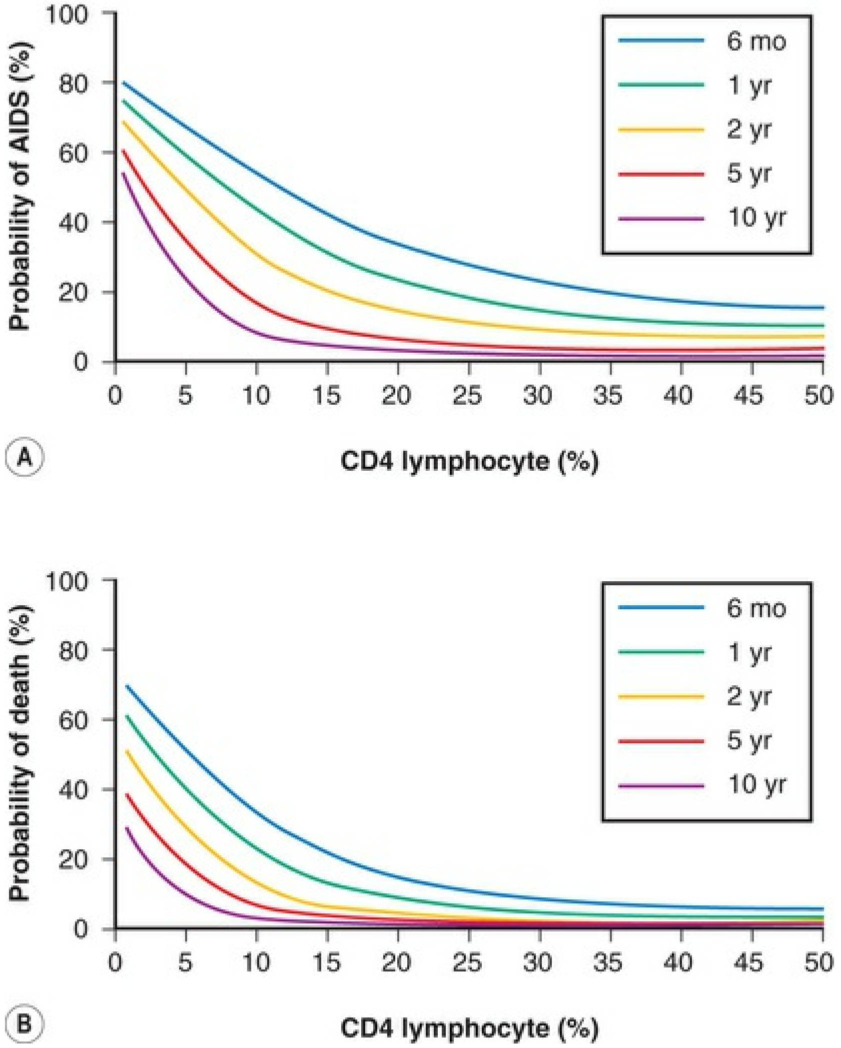

FIGURE 111.4 (A) Estimated probability of AIDS within 12 months by age and CD4 lymphocyte percentage in HIV-infected children receiving no therapy or zidovudine monotherapy. (B) Estimated probability of death within 12 months by age and CD4 lymphocyte percentage in HIV-infected children receiving no therapy or zidovudine monotherapy. (From Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. https://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf.)

The outlook for children with HIV continues to improve. Combination antiretroviral therapy (cART) is increasingly available throughout the world. It is recommended for all children by the WHO and experts in the US[2,91] because it is able to prevent, ameliorate, or reverse most of the clinical manifestations of HIV infection and reduce morbidity and mortality. Although adherence to antiretroviral medications and tolerance of their side effects remain problematic, the number of pediatric deaths due to HIV/AIDS has been reduced markedly wherever cART has been introduced. Unfortunately, even with cART, the mortality rate for HIV-infected children, adolescents, and young adults remains about 30-fold higher than that for other children in the US.[92] Moreover, opportunistic infections and malignancies may occur for many months after normalization of $CD4^+$ T-lymphocyte counts.[93]

Behaviorally Acquired HIV Infection

In the US and throughout the world, adolescents and young adults are the fastest growing group of HIV-infected individuals. In 2013, youth 13 to 24 years of age represented 21% of all Americans who were newly diagnosed. The youth most often infected were black or Hispanic/Latino; most were young men who have sex with men or who reported injection drug use.[94]

Some of those with behaviorally acquired infection will come to attention with acute retroviral syndrome (fever, sore throat, swollen lymph nodes or tonsils, rash, and other nonspecific symptoms). Acute gastrointestinal complaints (vomiting, diarrhea, oral ulcers) and neurologic findings (including encephalitis, facial nerve palsy, psychosis) also are common with acute retroviral syndrome.[95] Many cases of early HIV infection will be diagnosed after EBV-related mononucleosis was initially suspected.[95] A small fraction (~10%) of new infections will come to medical attention with severe opportunistic infections or AIDS-defining conditions such as cytomegalovirus infections of the gastrointestinal tract.[95] Not all newly diagnosed adolescents are newly infected. Some patients will present with conditions that indicate long established HIV infection and immunologic dysfunction, such as thrush, immune thrombocytopenia, or shingles (varicella-zoster virus). HIV testing should be routinely performed when ostensibly healthy individuals present with these indicator conditions or during evaluation for either sexually transmitted infections or tuberculosis. Some newly diagnosed youth are symptom free at the time of presentation but obtain HIV testing through testing campaigns, partner notification, or provider-initiated testing in their primary care settings.

Clinical care for infected youth includes starting treatment or prophylaxis against opportunistic infections and assessing readiness for antiretroviral treatment. Most youth respond well to antiretroviral therapy.[93,96] Psychological support is critical in caring for those youth who are infected because of behavioral risks, who may have preexisting mental health and substance abuse issues.[96,97] For the newly diagnosed adolescent, care must include a focus on building a therapeutic relationship[98] and on education about HIV diseases and the prevention of transmission of HIV to others.

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112

Infectious Complications of HIV Infection

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Opportunistic infections were central to the identification of the acquired immunodeficiency syndrome (AIDS) and have been a major cause of human immunodeficiency virus (HIV)–associated morbidity and mortality. An unusual clustering of cases of *Pneumocystis jirovecii* (formally *P. carinii*) pneumonia (PCP) in the early 1980s led in part to the recognition of AIDS. Other AIDS-associated opportunistic infections, including disseminated mycobacterial disease, cryptococcal meningitis, cerebral toxoplasmosis, and cytomegalovirus (CMV) retinitis, were recognized soon thereafter.

In the mid-1990s, improved treatment and prevention strategies and the introduction of combination antiretroviral therapy (cART), previously referred to as highly active antiretroviral therapy (HAART), dramatically reduced the incidence of opportunistic infections and the mortality rate for HIV. Between 1994 and 2000, the overall mortality rate for HIV-infected children in the United States decreased from 7.2 to 0.8 deaths per 100 person-years.[1] Likewise, the incidence of most opportunistic infections fell dramatically[2,3] (Table 112.1). Despite these advances, opportunistic infections continue to occur, and physicians must be familiar with the epidemiology and other features of these infections to optimize early identification, prevention, and treatment.[4,5]

TABLE 112.1

Incidence of Infections per 100 Patient-Years Among HIV-Infected Children Before and After the Advent of Combination Antiretroviral Therapy

Condition	Before cART 1986–1998[3,19]	After cART 1997–2014[2,3,5]
OPPORTUNISTIC INFECTIONS		
Pneumocystis jirovecii pneumonia	1.3–5.8	0.09–0.3
Nontuberculous mycobacterial infection	1.3–1.8	0.2–0.15
Cytomegalovirus disease	0.7–1.5	0.03–0.1
Toxoplasmosis	0.06	NA
Progressive multifocal leukoencephalopathy	0.06	NA
Cryptosporidiosis	0.3–0.6	0–0.03
OTHER INFECTIONS		
Otitis media	57	NA
Upper respiratory infection	47	NA
Sinusitis	15	NA
Bloodstream infection	3.3	0.35
Bacterial pneumonia	11.1	1.2–2.1
Bacterial meningitis	0.1	0.05
Varicella	4.7	0.44
Herpes zoster	2.9	0.76–1.1
Candidiasis, esophageal or pulmonary	1.2–1.4	0.04–0.44
Urinary tract infection	1.6	0.35
Tuberculosis	0.4	<0.5

cART, combination antiretroviral therapy; NA, not available.

Increasing numbers of children are being born to HIV-infected mothers. Due to the advances in antiretroviral therapy for the prevention of mother-to-child transmission, most of these HIV-exposed children are HIV-uninfected and do not have the same risk of infections as HIV-infected children.[6] However, HIV-exposed but uninfected children have immunologic abnormalities resulting in an increased susceptibility to childhood illnesses, including diarrhea, pneumonia, and sepsis.[7–11]

Pathogenesis

Healthy neonates are at risk for serious infection because of immaturity of several components of the immune system, including B and T lymphocytes, phagocytes, and complement. The naïvety of the developing immune system is invoked as a possible explanation for susceptibility of the HIV-infected infant or child to rapid HIV disease progression and complicating infections.

HIV infection of the fetus or neonate can have profound effects on cellular immunity. Destruction of the thymus gland is observed in spontaneous abortuses from HIV-infected mothers. Surprisingly, depletion of $CD4^+$ lymphocytes is not recognized at the time of birth. However, as early as 1 or 2 months of age, HIV-infected infants have $CD4^+$ lymphocyte counts significantly lower than those of HIV-exposed but uninfected infants.[12] Suppression of cell-mediated immunity is responsible in large part for the susceptibility of HIV-infected individuals to PCP and opportunistic mycobacterial, fungal, and viral infections.

Despite hypergammaglobulinemia, humoral immune dysfunction occurs in most children with symptomatic HIV infection and predisposes to recurrent bacterial infections. Humoral deficiency results from dysregulation of T-lymphocyte–mediated responses and polyclonal stimulation of B lymphocytes by poorly controlled infectious agents.[13–17] In vitro lymphoproliferative responses to B-lymphocyte mitogens and specific antigens often are poor. In vivo, there is impaired specific antibody production after immunization with T-lymphocyte–independent antigens (e.g., capsular polysaccharide of *Streptococcus pneumoniae*) and T-lymphocyte–dependent antigens, particularly in those not receiving cART or with a low $CD4^+$ count. Primary humoral immune responses and recall responses (i.e., amplification and immunoglobulin class switch) are defective in children with HIV infection.

Phagocytic function can be altered by HIV infection. Neutropenia and defects in neutrophil chemotaxis and bactericidal activity have been described.[18,19] Neutrophil superoxide production can be depressed in children with advanced HIV disease.[20,21] This combination of phagocyte abnormalities compromises the ability of an HIV-infected person to kill bacterial and fungal pathogens. Although the precise pathogenesis of these abnormalities is unknown, studies suggest that neutropenia and neutrophil dysfunction are partly mediated by abnormal regulation by cytokines (e.g., granulocyte colony-stimulating factor [G-CSF]).[22] Recombinant G-CSF administration in HIV-infected adults has reversed neutropenia and corrected neutrophil-killing defects.[23]

Immune Reconstitution Inflammatory Syndrome

Children with advanced immunosuppression who initiate cART often have a rapid improvement in immune competence, reflected by increased $CD4^+$ cell counts. In the setting of an underlying infection, this can result in the appearance or worsening of the infection's symptoms. The infection unrecognized before starting cART can be unmasked by the resulting inflammatory response.

In children, immune reconstitution inflammatory syndrome (IRIS) most often occurs with mycobacterial infections (i.e., *Mycobacterium avium* complex [MAC], *M. tuberculosis,* and the bacille Calmette-Guérin [BCG] vaccine), varicella-zoster virus (VZV), herpes simplex virus (HSV), and cryptococcal infections, but it can be seen with PCP, CMV, hepatitis B and C, toxoplasmosis, and JC virus (i.e., progressive multifocal leukoencephalopathy [PML]).[24,25] IRIS usually occurs within the first 2 to 3 months after initiating cART and is associated with virologic suppression and a rapid rise in the $CD4^+$ lymphocyte count. IRIS should not be interpreted as a failure of cART.

Children should be evaluated carefully for underlying occult infections before initiating cART. The optimal time to start cART in a child with an active opportunistic infection often is not clear and depends on the specific infection. For opportunistic infections without effective therapy (e.g., PML, Kaposi sarcoma), cART should be initiated promptly because immune reconstitution may resolve the infection. For opportunistic infections with effective therapy (e.g., *M. tuberculosis,* MAC, PCP, cryptococcal meningitis), initiating treatment of the opportunistic infection before starting cART may prevent IRIS. The sequencing of opportunistic infection treatment and cART has been studied for several infections and should be reviewed before initiation cART. If symptoms of IRIS develop after cART, the opportunistic infection should be treated, cART usually is continued, and immunomodulating therapy may be considered.

Epidemiology and Etiologic Agents

In children, as in adults, untreated HIV infection is characterized by an increased frequency of a specific group of serious opportunistic and nonopportunistic infections. The increased frequency of common childhood infections of a less serious nature also contributes to the overall morbidity of the disease. The frequency of the various opportunistic infections among HIV-infected children in the years preceding cART varied by age, pathogen, and immunologic status.[26] The most common opportunistic infections among children in the United States included serious bacterial infections (SBIs) such as pneumonia and bloodstream infection (BSI), PCP, nontuberculous mycobacterial infections, and CMV disease (see Table 112.1).[2,3,26] Despite a dramatic decrease in the rate of opportunistic infections among patients receiving cART,[3,27,28] the types of infections that occur are similar.[29,30]

Table 112.1 compares the incidence of infections in children before and after the widespread use of cART. Before cART and the use of PCP prophylaxis in early infancy, 7% to 20% of HIV-infected infants developed PCP, making it the most common AIDS-defining opportunistic infection in children (Table 112.2). More than 50% of cases occurred between 3 and 6 months of age.[31] A low age-adjusted CD4$^+$ lymphocyte count or percentage was the major determinant of risk. Although PCP still is observed in HIV-infected infants and children, the incidence has decreased dramatically in the United States.[3]

TABLE 112.2

Common AIDS-Defining Infections in Children <13 Years of Age Before the Combination Antiretroviral Therapy Era

AIDS-Defining Infection	Proportion of Children (%)
Pneumocystis jirovecii pneumonia	35
Lymphoid interstitial pneumonitis	23
Recurrent bacterial infections	21
Esophageal or pulmonary candidiasis	21
Cytomegalovirus disease	11
Mycobacterium avium complex infection	9
Severe herpes simplex infection	5
Cryptosporidiosis	5

AIDS, acquired immunodeficiency syndrome.

From Centers of Disease Control and Prevention. Personal communication, 2011.

Oral candidiasis occurs in 15% to 40% of children with HIV infection and is more common among children with low CD4$^+$ lymphocyte counts or symptomatic HIV disease.[32,33] Whereas oral candidiasis is common at all stages of HIV disease, esophageal and pulmonary candidiasis are far less common and typically restricted to patients with advanced HIV disease.[4] Esophageal and pulmonary candidiasis accounted for approximately 17% and 4%, respectively, of AIDS-defining illnesses in children before cART.

SBIs (e.g., BSI, pneumonia, sinusitis, meningitis, osteomyelitis, pyogenic arthritis, mastoiditis, abscess of an internal organ) were reported for 40% to 60% of HIV-infected children before cART, with an overall incidence of 44 cases per 100 patient-years of follow-up.[34–36] Recurrent bacterial infections represent an AIDS-defining condition and accounted for 21% of all pediatric AIDS-defining illnesses reported to the Centers for Disease Control and Prevention (CDC) through 2007 (see Table 112.2). Minor infections (e.g., otitis media, urinary tract infection, infections of skin or soft tissue) were threefold more common than serious infections. Use of cART has resulted in a dramatic drop in the incidence of SBIs, but rates remain higher than those for HIV-uninfected children (see Table 112.1).[5]

The incidence of SBIs among HIV-infected children is highest in children younger than 1 year of age who have low CD4$^+$ lymphocyte counts.[37] The Pediatric Spectrum of Disease Project evaluated 21,167 vertically infected children and found 1063 SBIs among 570 children. Sixty-four percent were severely immunocompromised (i.e., CDC immunologic category 3) when the first SBI occurred; 25% had a first infection in the first 6 months of life and 37% by 12 months of age. BSI, pneumonia, and urinary tract infection were the most common.[38]

Streptococcus pneumoniae is the single most common cause of SBIs in HIV-infected children.[34–36,38,39] In a study of HIV-infected children younger than 36 months of age, pneumococcal BSI occurred with an annualized rate of 11.3 episodes per 100 patient-years[40]; this rate is more than threefold that observed for children with sickle cell anemia[41] and 12-fold that reported in one study of adults with AIDS.[42] Other bacteria causing these infections include *Salmonella* species, *Staphylococcus aureus,* and *Neisseria meningitidis*.

Although CMV infection is common, disseminated disease, chorioretinitis, and colitis caused by CMV are uncommon in children.[43] The role of CMV as a cause of pneumonia in HIV-infected children is controversial; CMV usually is associated with another opportunistic pathogen (often *P. jirovecii*). HSV commonly causes infection of the oral or genital mucous membranes that is more severe and prolonged than would be expected[44]; esophageal or pulmonary disease occurs rarely. CMV disease, cryptosporidiosis,[45] and disseminated MAC[46,47] occur predominantly in children with advanced HIV disease and severely depressed $CD4^+$ lymphocyte counts. Without prophylaxis, up to 20% of HIV-infected children with $CD4^+$ lymphocyte counts of less than 50 $cells/mm^3$ develop disseminated MAC infection.

Approach to the HIV-Infected Child With Suspected Systemic or Focal Infection

Fever

Clinical manifestations and diagnostic considerations for HIV-infected children with fever are as diverse as among uninfected children. Fever is a common reason for unscheduled outpatient clinic visits and hospital admissions of HIV-infected children. Although most HIV-infected children with acute febrile illnesses have mild, self-limited illnesses presumably caused by a viral infection, they are at increased risk for more serious illnesses. Differentiation can be difficult (Box 112.1).

Box 112.1

Causes of Fever Without an Obvious Source in HIV-Infected Children

Common causes (e.g., respiratory viruses, urinary tract pathogens)

Bacteremia

Focal bacterial infection (e.g., sinusitis, pneumonia, organ abscess)

Catheter infection

Salmonellosis

Tuberculous or nontuberculous mycobacterial infection

Fungal infection (e.g., candidal esophagitis, cryptococcal meningitis, pneumonia)

Pneumocystis jirovecii infection

Toxoplasmosis

Cytomegalovirus infection

Epstein-Barr virus infection

Herpes simplex virus infection

Hepatitis

Esophagitis

Lymphoma and other types of malignancy

Drug fever

Febrile HIV-infected children require a thorough medical history and physical examination. The character and duration of symptoms, HIV disease status (including the most recent $CD4^+$ lymphocyte count), adherence to cART and opportunistic infection prophylaxis, and history of recent exposures are important. A careful search for evidence of focal infection or inflammation and an assessment of the severity of illness (i.e., toxicity) should be performed. Clinical features of focal infection in HIV-infected children are similar to those observed in immunologically healthy children, with fever and local signs of inflammation often found. BSI should be suspected in an acutely ill child with a serious focal infection such as pneumonia, cellulitis, or osteomyelitis.

The approach to the acutely febrile HIV-infected child without localizing signs can be problematic. Not all patients require diagnostic testing or antibiotic therapy, although both should be considered, especially for those with high fever (>39.4°C) or advanced HIV disease. The likelihood of an opportunistic infection such as disseminated MAC, *Cryptococcus neoformans,* or CMV enteritis or retinitis typically increases as the patient's $CD4^+$ lymphocyte count decreases.

The white blood cell count, often used as a screening test for SBI in immunologically normal children, must be interpreted in the context of the patient's baseline values. Neutropenia commonly results from trimethoprim-sulfamethoxazole (TMP-SMX) use and can result from HIV infection and the use of other medications. Other diagnostic studies can include radiographs of the chest and sinuses; culture of blood for routine bacteria, mycobacteria, and fungi; culture of the urine; culture or testing by molecular methods of throat or nasopharyngeal specimens and blood for viruses (including CMV); cryptococcal and other fungal antigen tests; Epstein-Barr virus serologic tests; hepatic enzyme measurements; and ophthalmologic examination for chorioretinitis. Examination of cerebrospinal fluid (CSF) sometimes is indicated for routine blood cell counts and protein and glucose concentration; bacterial, fungal, and viral polymerase chain reaction (PCR) assays; cryptococcal antigen test; and cytologic tests.

Empiric antibiotic therapy for children who have mild or asymptomatic HIV infection who have an acute febrile illness should be similar to that used in the treatment of immunologically normal children with comparable clinical manifestations. Oral antibiotic therapy is appropriate in most cases. Children with more advanced HIV disease may require agents with broader activity that are administered parenterally.

The selection of antibiotic agents for expectant therapy is influenced by factors such as the likely source of infection (e.g., community-acquired vs. healthcare-associated infection), presence of a central venous catheter, immunization status, use of prophylactic antibiotics, and $CD4^+$ count. Empiric antibiotic therapy should be directed against a limited number of likely pathogens. Unless convincing clinical or laboratory evidence exists for serious opportunistic fungal, mycobacterial, or viral infection, therapy usually is directed against potential bacterial pathogens.

Pneumonia

In the pre-cART era, more than one half of infants with vertically acquired HIV infection initially came to medical attention with lung disease and PCP, bacterial pneumonia, and lymphocytic interstitial pneumonitis (LIP) or pulmonary lymphoid hyperplasia were the most common causes.[48] The likelihood of an opportunistic infection increases as the patient's CD4$^+$ lymphocyte count decreases. With cART and appropriate prophylaxis, PCP and LIP have become rare in the United States, and the incidence of pneumonia overall continues to fall.[5]

The predominant bacterial causes of pneumonia include *S. pneumoniae, S. aureus, M. tuberculosis,* and occasionally gram-negative organisms. The rate of tuberculosis is increased among HIV-infected children and adults, and unlike other opportunistic infections, the CD4$^+$ lymphocyte count is not a good indicator of tuberculosis risk. Other infectious causes of pneumonia include community-acquired respiratory viruses, CMV, HSV, and fungi (e.g., *Candida, Cryptococcus neoformans, Histoplasma capsulatum*).

The clinical manifestations of bacterial pneumonia are similar to those seen in immunologically normal children. The usual manifestations of PCP include acute onset of fever, cough, tachypnea, hypoxia, and respiratory distress. However, PCP also can progress in a slow and insidious manner. Decreased breath sounds and hypoxia can occur, but crackles are uncommon. LIP usually is insidious and slowly progressive. Patients can have cough and wheezing. Associated findings include generalized lymphadenopathy, hepatosplenomegaly, parotid enlargement, and digital clubbing.

Radiographic features of pneumonia in HIV-infected children usually are not distinctive. Bacterial pneumonia can be associated with focal or diffuse infiltrates. The typical radiographic picture of PCP is diffuse, reticular interstitial and alveolar infiltrates that are most prominent in the perihilar areas (Fig. 112.1). Air bronchograms, focal infiltrates, pneumatoceles, or pneumothorax can occur in some cases. The chest radiograph can be normal at the time of presentation. The radiographic features of tuberculosis can be similar to those of HIV-uninfected children, although atypical findings, such as multilobar infiltrates and diffuse interstitial disease, can occur in HIV-infected children.[49] The typical radiographic features of LIP include diffuse, reticulonodular densities and hilar adenopathy (Fig. 112.2).

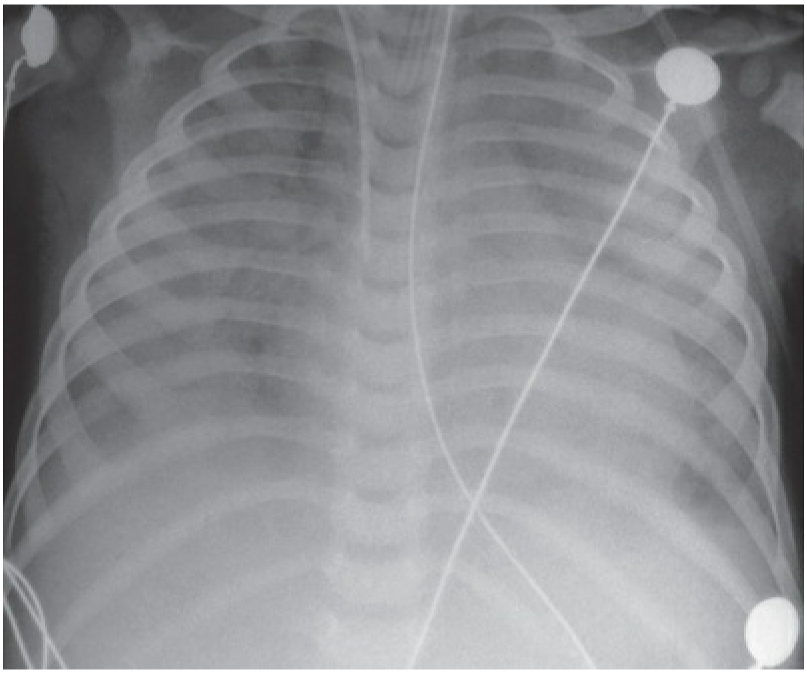

FIGURE 112.1 Chest radiograph shows *Pneumocystis jirovecii* pneumonia in a 2-year-old boy with vertically acquired human immunodeficiency virus infection. The interstitial lung disease is bilateral.

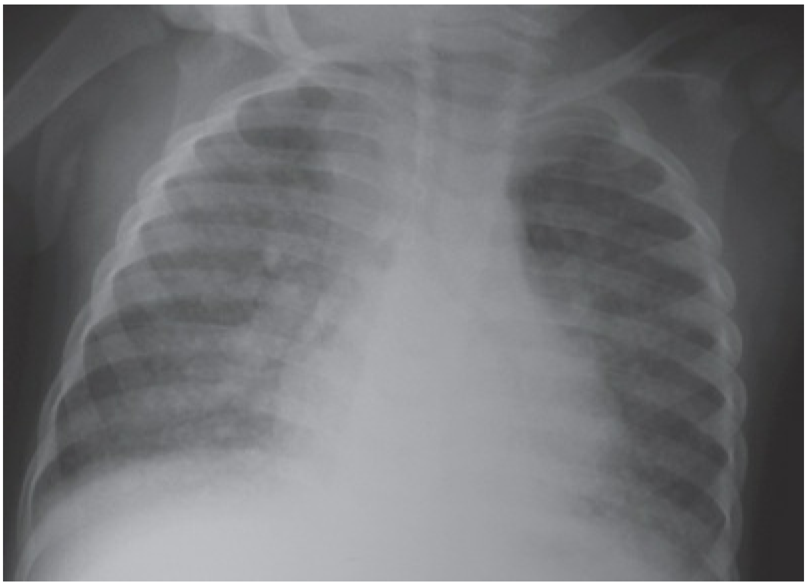

FIGURE 112.2 Typical lymphocytic interstitial pneumonitis or pulmonary lymphoid hyperplasia is the presenting feature of vertically acquired human immunodeficiency virus infection in a 23-month-old

infant with slowly worsening bronchiolitis and hypoxia. Fungal, bacterial, and other viral causes were excluded. Plain radiograph shows diffuse reticulonodular infiltration and perihilar adenopathy. There was complete resolution 4 months after starting combination antiretroviral therapy. (Courtesy E.N. Faerber, J. Chen, and J. Foster, St. Christopher's Hospital for Children, Philadelphia, PA.)

A complete blood cell count, measure of oxygen saturation, and blood cultures should be obtained. A tuberculin skin test (TST) or an interferon γ release assay (IGRA) should be performed for every appropriate-age, HIV-infected child with pneumonia. A negative TST result (i.e., induration of ≤5 mm) or IGRA result does not exclude tuberculosis. Most children with a normal (or unchanged from previous) chest radiograph and normal arterial oxygen saturation value have self-limited (presumably viral) illness. A nasopharyngeal specimen for rapid diagnostic tests (e.g., fluorescent antibody test, enzyme immunoassay), nucleic acid testing, or culture for viruses may be helpful.

Positive results for the blood culture or evidence of a segmental or lobar infiltrate suggests bacterial pneumonia. PCP is likely in a child with a low CD4$^+$ lymphocyte count, the acute onset of respiratory distress, typical reticular interstitial infiltrates, and hypoxemia. Marked elevation of the serum lactate dehydrogenase concentration (>1000 IU/L) supports a diagnosis of PCP. Bronchoalveolar lavage is indicated for confirmation of suspected PCP and exclusion of other opportunistic infections in children with advanced HIV disease. If tuberculosis is strongly suspected for a child with a pulmonary infiltrate and negative TST results, gastric or bronchoalveolar lavage is warranted.

Atypical features of pneumonia may necessitate bronchoscopy or open-lung biopsy for histology, molecular testing, and cultures to evaluate the wide array of diagnostic possibilities. A presumptive diagnosis of LIP can be made on the basis of characteristic clinical features and radiographic changes persisting for more than 2 months in the absence of another explanation, particularly in a child with newly diagnosed HIV disease.

Empiric antibiotic therapy is indicated for children with characteristic features of bacterial pneumonia. A β-lactum agent, with or without a β-lactamase inhibitor, or a third-generation cephalosporin is appropriate for children with normal CD4$^+$ lymphocyte counts. Including treatment of *Mycoplasma* is appropriate for school-aged children. Coverage for methicillin-resistant *S. aureus* (MRSA) is appropriate for children with severe disease or profoundly depressed CD4$^+$ lymphocyte counts.

Treatment of tuberculosis in HIV-infected children is complex because there are multiple drug interactions between antiretroviral drugs, other prophylactic agents such as the macrolides and azoles, and antimycobacterial drugs. Guidelines should be consulted and advice obtained from an expert in the treatment of the two diseases.[4] Tuberculosis treatment should be started immediately, and the child's antiretroviral therapy should be altered as necessary. Directly observed therapy is essential. Specific considerations include the importance of rifampin in tuberculosis therapy and its potent induction of the hepatic CYP3A enzyme system that precludes the use of all protease inhibitors. Rifabutin should be substituted with appropriate dosage adjustments, or cART should not include a protease inhibitor.

Central Nervous System Infections

Except for children with advanced HIV disease, the causative agents, clinical manifestations, and CSF findings of meningitis and encephalitis are similar to those observed in immunocompetent hosts. *C. neoformans* and JC virus are two opportunistic pathogens that can cause central nervous system (CNS) infection in HIV-infected children. *C. neoformans* is a common cause of meningitis in patients with advanced HIV disease and severely depressed CD4$^+$ lymphocyte counts. Cryptococcal meningitis often is characterized by an indolent course of illness. Complaints of fever, intermittent headache, and vomiting are common. Signs of meningeal inflammation can be absent. Rarely, cryptococcal CNS infection can cause acute focal neurologic signs and symptoms.[50,51] The CSF cell count and the glucose and protein values can be normal. Important CSF diagnostic studies include an India ink stain, cryptococcal antigen testing, and culture.

JC virus is a polyomavirus that causes progressive multifocal leukoencephalopathy (PML) in people with advanced immunosuppression. PML is a progressive, demyelinating disease of the CNS, characterized by focal neurologic abnormalities (e.g., visual deficits, motor weakness), personality and cognitive changes, confusion, ataxia, and seizures. Neuroimaging reveals focal white matter lesions without a mass effect (Fig. 112.3). Most cases of PML occur in patients with advanced HIV disease. PML was uncommon in HIV-infected children before cART and has become rare.[3,26]

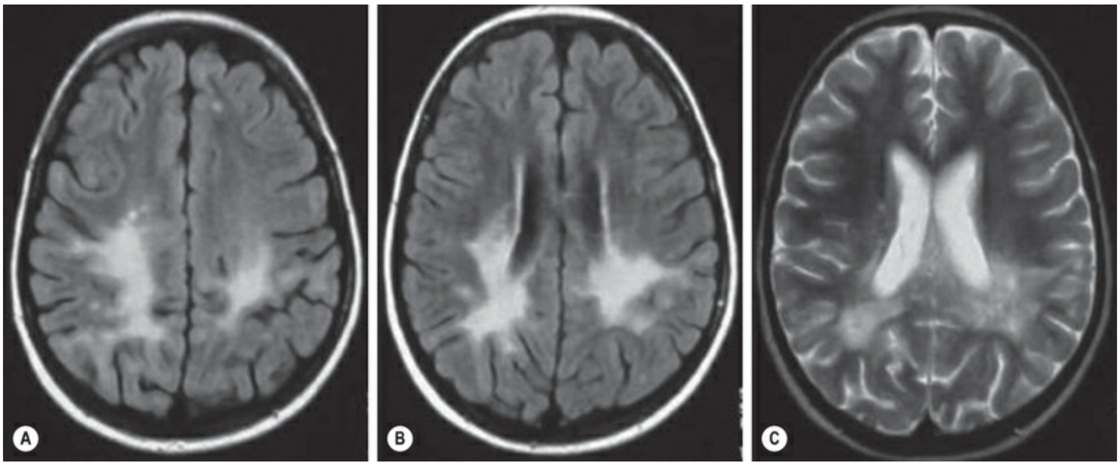

FIGURE 112.3 Progressive multifocal leukoencephalopathy. A 12-year-old boy, who recently immigrated from Zambia and was newly diagnosed with acquired immunodeficiency syndrome, had a 2- to 3-year history of severe headache and diarrhea. Magnetic resonance imaging (MRI) showed predominantly right-sided white matter lesions. Antimicrobials and combination antiretroviral therapy (cART) were begun; 9 weeks after starting cART, the human immunodeficiency virus viral load was low, but he was subdued and tearful, and had decreased strength and reflexes on the left side. Imaging showed progression of previous abnormalities. Cerebrospinal fluid (CSF) appeared normal, but the CSF polymerase chain reaction result was positive for JC virus. The fluid-attenuated inversion recovery (FLAIR) (A and B) and T2-weighted MRI (C) scans show increased signal within the periventricular white matter tracts extending outward to the subcortical areas, involving the parietal lobes, both hemispheres, corpus callosum, and brainstem, with no mass effect. (Courtesy A.R. Feingold and D. Meislich, Cooper University Hospital, Camden, NJ.)

The usual clinical course of PML is inexorable deterioration of

CNS function, leading to death within a few months of diagnosis. The mainstay of therapy is to optimize antiretroviral therapy because an improved immune status can produce clinical improvement. Antiviral agents directed against JC virus, including cytosine arabinoside and cidofovir, have no demonstrated efficacy.

Cerebral toxoplasmosis occurs in patients with advanced HIV disease and severely depressed $CD4^+$ lymphocyte counts. Presenting features include fever, headache, seizures, focal neurologic abnormalities, and altered consciousness. Computed tomography or magnetic resonance imaging of the brain typically reveals multiple ring-enhancing lesions with surrounding edema. Toxoplasmosis almost invariably represents reactivation of prior infection. Patients who are seronegative for *Toxoplasma* are unlikely to have cerebral toxoplasmosis, and it is useful to periodically document the serologic status of HIV-infected children.

The differential diagnosis of CNS toxoplasmosis includes bacterial and fungal infections and CNS lymphoma. Brain biopsy, the definitive diagnostic procedure, usually is reserved for patients who fail to respond clinically and radiographically to empiric therapy for toxoplasmosis. Risk factors for toxoplasmosis include direct and indirect contact with cats (e.g., litter boxes) and consumption of undercooked meats. Families should be counseled about the risk.

CNS mass lesions in children with HIV infection pose special diagnostic considerations. Definitive diagnosis may require tissue examination. Infectious causes include bacterial brain abscess, toxoplasmosis, cryptococcoma, and tuberculoma. Noninfectious causes such as lymphoma also should be considered.

Diarrhea

As for uninfected children, episodes of diarrhea in HIV-infected children are often acute and self-limited, with no apparent long-term effects. Persistent or recurrent diarrhea, however, can adversely affect quality of life and place the child at risk for malnutrition and further immunologic impairment.

Gastroenteritis can be caused by any of the usual enteric pathogens, including rotavirus, *Salmonella, Shigella,* enterotoxigenic *Escherichia coli, Campylobacter, Vibrio cholera, Clostridium difficile,* *Entamoeba histolytica,* enteric adenoviruses, and *Giardia intestinalis,* irrespective of the child's $CD4^+$ count. Opportunistic pathogens, such as CMV, MAC, *Cryptosporidium,* microsporidia, and *Cystoisospora (Isospora)*, usually occur with advanced immunosuppression. The diagnostic evaluation should be guided by the patient's $CD4^+$ count and clinical presentation.

Many episodes of acute enteritis do not require diagnostic evaluation. However, if gastrointestinal symptoms are severe or persistent, several investigations should be considered. Examination of the stool for rotavirus (i.e., antigen or nucleic acid test) and for ova and parasites (i.e., routine and acid-fast staining) for detection of *Cryptosporidium* and *Cystoisospora* spp. should be considered. Stool cultures for bacterial enteric pathogens are obtained if the child has fever. Blood culture is obtained to exclude *Salmonella* bacteremia. Studies for *C. difficile* are performed if there is a history of recent antibiotic use. Documentation of active CMV replication by blood antigenemia, nucleic acid testing, or culture can be helpful. Stool cultures for CMV and MAC typically are not useful.

Upper endoscopy is reserved for patients with persistent diarrhea of unknown cause. Colonoscopy should be considered in patients with dysentery without an identified pathogen. Biopsies are obtained for evaluation of bowel histology and detection of *Giardia,* CMV, *Cryptosporidium,* and MAC.

Management must include close attention to nutritional support. Empiric antibiotic therapy for *Salmonella* spp. should be considered for the child with dysentery and signs of toxicity. Other therapeutic interventions are guided by results of diagnostic studies. Treatment guidelines are available for the management of specific opportunistic infections causing diarrhea.[4] Some of the antiretroviral agents can cause diarrhea and always should be considered, particularly if no infectious cause is identified.

Esophagitis

Esophagitis is common among people with AIDS. Symptoms include irritability, pain in the esophagus or chest, difficulty swallowing, hiccups, and fever. Esophagitis can have infectious and noninfectious causes. *Candida* species are the most common infectious cause. Children with esophageal candidiasis do not always have concomitant oral candidiasis. Viral causes of esophagitis include CMV and HSV.[52] Esophageal disease caused by bacteria (including mycobacteria) is uncommon. Other causes of esophageal disease in HIV-infected children include lymphoma, acid reflux, and aphthous ulcers.

Empiric antifungal therapy is given when oral candidiasis and typical clinical features of esophagitis are identified. Barium esophagography or endoscopy is considered if the presentation is atypical or the patient fails to improve within 5 to 7 days. Radiographic differentiation of various types of esophageal ulcerative disease (e.g., candidiasis vs. CMV disease) and recognition of dual infection are impossible. If ulcerative or nodular lesions are identified radiographically, esophagoscopy and biopsy should be performed.

Oral Infections

Candidiasis is the most common oral infection in HIV-infected children.[44] Several clinical variants are recognized, including pseudomembranous, hyperplastic, and erythematous candidiasis and angular cheilitis. Although oral candidiasis may respond to oral nystatin or clotrimazole, oral fluconazole is more effective.

Oral ulcers are common in HIV-infected children. CMV and HSV are common infectious causes. Three types of aphthous ulcers occur frequently: aphthous major (i.e., large ulcers persisting >3 weeks), aphthous minor (i.e., smaller ulcers that heal spontaneously within 5–10 days), and aphthous herpetiformis (i.e., multiple, discrete ulcers resembling those caused by HSV). Aphthous major is the most common form observed in HIV-infected patients; concomitant pharyngeal and esophageal ulcers occur in some cases.

Diagnostic evaluation and management of children with oral ulcers are based on clinical presentation. A surface culture for HSV and empiric therapy with acyclovir may suffice for patients with lesions typical of herpetic stomatitis. Biopsy and cultures for viruses, mycobacteria, and fungi should be considered if initial diagnostic studies are negative, the ulcers are large or deep, or the ulcers fail to heal in an appropriate length of time with or without empiric therapy.

Prevention of Infection

Guidelines for the prevention and treatment of opportunistic infections in HIV-infected and HIV-exposed children and HIV-infected adolescents and adults are published by the US Public Health Service and are updated regularly.[4] Guidelines for vaccination of the immunocompromised host were published from the Infectious Diseases Society of America in 2014.[53]

Routine Immunization

A modified immunization schedule for HIV-infected children and HIV-exposed infants with undefined HIV infection status is available and should be consulted.[4] Children immunized before cART usually have poor vaccine responses associated with a low $CD4^+$ count and high viral load at the time of immunization. With immune reconstitution after cART, the response to immunization is much improved, although protective immunity can wane over time.[54] Although it is likely that children with immune reconstitution after severe immunosuppression can benefit from reimmunization, data are not readily available to support reimmunization with most vaccines. However, some data demonstrate low antibody titers to measles, mumps, and rubella in children immunized before cART, and reimmunization is recommended. Reimmunization may be considered for children at increased risk of exposure to vaccine-preventable diseases (e.g., child traveling to an endemic region who was initially vaccinated at a low $CD4^+$ count).

The bacterial vaccines (i.e., diphtheria, tetanus, pertussis, *H. influenzae* type b, and pneumococcus) should be administered to all HIV-infected children according to the routine childhood schedule.[4,55] Because HIV-infected people are at increased risk of meningococcal C, W, and Y infection related directly to viral load and inversely to $CD4^+$ count, the MenACWY conjugate vaccine is recommended beginning at 2 months of age, with catch-up inoculations for older children and repeated booster doses.[56] HIV-infected children should receive pneumococcal immunization as recommended in the modified immunization schedule.[4,55] Key points include the following:

- HIV-exposed and infected infants and children between the ages of 2 and 59 months should receive the 13-valent pneumococcal vaccine (PCV13) on the same schedule as that recommended for healthy infants and children, including series completion with PCV13 for those who initiated immunization with PCV7.
- A single dose of PCV13 should be administered routinely to HIV-infected children between 6 and 18 years who did not receive PCV13 before 6 years of age.
- HIV-infected children 2 years of age or older should receive the 23-valent pneumococcal polysaccharide vaccine (PPSV23) at least 8 months after their last PCV dose, with a single revaccination with PPSV23 5 years later.
- If not previously vaccinated with PPSV23, children and adolescents between 6 and 18 years of age should receive 1 dose of PPSV23.
- HIV-infected children 2 months of age and older should receive meningococcal ACWY conjugate vaccination, with booster doses as necessary for other children at high risk of infection.[55]

Beginning at 12 months of age, two doses of the live attenuated measles, mumps, and rubella (MMR) vaccine and varicella (V) vaccine should be administered to HIV-infected children, except those who are severely immunosuppressed (i.e., CDC immunologic category 3 and $CD4^+$ lymphocytes <15%), who are at risk for dissemination of the vaccine virus.[4] The quadrivalent measles-mumps-rubella-varicella (MMRV) vaccine should not be administered to HIV-infected children because immunogenicity and efficacy data for MMRV are lacking. Reimmunization with two additional doses of the MMR vaccine is recommended for children who were immunized before starting cART unless immunity has been demonstrated serologically.[57,58] Use of the rotavirus vaccine in HIV-infected children should be considered in accordance with guidelines.[4] Inactivated viral vaccines (i.e., hepatitis A, hepatitis B, poliovirus, and human papillomavirus) should be administered to all HIV-infected children according to the routine childhood immunization schedule. Inactivated influenza immunization is recommended annually for all HIV-infected children beginning at 6 months of age. It is important to immunize family members and other close contacts.

Passive Immunization

Varicella immune globulin (see Chapter 205) should be administered as early as possible after exposure of a susceptible HIV-infected child to an individual with chickenpox or zoster.[4]

The beneficial effects of immune globulin intravenous (IGIV) for HIV-infected children was demonstrated in the pre-cART era.[36,59] However, cART and the widespread use of TMP-SMX prophylaxis have limited the value of IGIV. Current guidelines limit its use to HIV-infected children with hypogammaglobulinemia (i.e., immunoglobulin G <400 mg/dL) or with recurrent bacterial infections despite appropriate immunization and antibiotic prophylaxis.[4]

Pneumocystis jirovecii Pneumonia Prophylaxis

Identification of children at risk for PCP is complicated by two factors. First, HIV-infected infants, who are at greatest risk for PCP, may not be known to be at risk for HIV infection (i.e., mother is not known to be HIV infected) or may be known to be at risk but not have a confirmed infection. Second, because normal $CD4^+$ lymphocyte counts are age specific, a single $CD4^+$ lymphocyte threshold cannot be used for defining the risk of PCP in all children. Guidelines for primary prophylaxis against PCP published by the CDC take these issues into account.[4] All HIV-infected infants should receive PCP prophylaxis until they are 12 months of age, at which time the need for prophylaxis is determined by age-specific $CD4^+$ lymphocyte values. HIV-infected children 12 months of age or older who meet criteria for CDC immunologic category 3 should receive prophylaxis. All HIV-exposed infants should be started on PCP prophylaxis at 4 to 6 weeks of age unless demonstrated to be uninfected or presumptively uninfected (Box 112.2). Infants with indeterminate infection status should receive prophylaxis until shown to be uninfected or presumptively uninfected. Children 12 months of age or older who experience immune reconstitution after cART can have primary prophylaxis stopped safely if they have received more than 6 months of cART and have $CD4^+$ cell counts exceeding CDC immunologic category 3 for more than 3 consecutive months. Children who have had an episode of PCP should receive secondary prophylaxis to prevent recurrence. Most children can have secondary prophylaxis safely stopped if they meet the criteria for stopping primary prophylaxis.

Box 112.2

Classification of HIV Infection Status of Children Born to HIV-Infected Mothers

Definitive Infection

- Positive virologic results on two separate specimens at any age, *or*
- Age >18 months plus a positive virologic test or a positive confirmed HIV-antibody test[a]

Presumptive Exclusion of Infection in a Nonbreastfed Infant

- No clinical or laboratory evidence of HIV infection, two negative virologic tests, both obtained at ≥14 days of age and one obtained at ≥4 weeks of age plus no positive virologic tests, *or*
- One negative virologic test at ≥8 weeks of age plus no positive virologic test, *or*
- One negative HIV antibody test at ≥6 months of age plus no positive virologic test

Definitive Exclusion of Infection in a Nonbreastfed Infant

- No clinical or laboratory evidence of HIV infection plus two negative virologic tests, both obtained at ≥1 month of age and one obtained at ≥4 months of age, plus no positive virologic tests, *or*
- Two or more negative HIV antibody tests at ≥6 months of age

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[a] A discussion testing can be found in reference 68.

From Mofenson LM, Brady MT, Danner SP, et al. Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. MMWR Recomm Rep 2009;58(RR-11):1–166.

TMP-SMX is the drug of choice for PCP prophylaxis. It is given orally at 5 to 10 mg/kg of TMP component per day (maximum of 320 mg) in 2 divided doses on 3 consecutive days per week.[4] Alternative oral dosing schedules include a single dose on 3 consecutive days per week or 2 divided daily doses. TMP-SMX also is effective in preventing toxoplasmosis and some bacterial infections. Alternative regimens for children who are intolerant of TMP-SMX include oral dapsone, oral atovaquone, and aerosolized pentamidine.[4]

Mycobacterial Infection

An annual TST or IGRA, depending on age, is recommended for all HIV-infected children to diagnose latent mycobacterial infection. The use of control skin testing to identify anergy is not recommended. When identified, treatment for latent tuberculosis should be instituted.

Clinical trials have demonstrated the effectiveness of clarithromycin and azithromycin as primary prophylaxis for MAC infection.[60,61] Although rifabutin also is effective for the prevention of MAC infection, rifabutin should be used as an alternative agent for patients who are unable to tolerate macrolides. Current guidelines recommend that HIV-infected adults and adolescents receive prophylaxis if their $CD4^+$ lymphocyte count is less than 50 cells/mm^3. Recommendations for starting MAC prophylaxis in children are based on the child's age and $CD4^+$ lymphocyte count: ≥6 years of age, <50 cells/mm^3; 2 to 6 years of age, <75 cells/mm^3; 1 to 2 years of age, <500 cells/mm^3; and <12 months, <750 cells/mm^3. The pediatric dose is 7.5 mg of clarithromycin/kg/dose (maximum, 500 mg) orally twice each day or 20 mg of azithromycin/kg/dose (maximum, 1200 mg) orally once weekly.

Fungal Infections

Several trials of prophylaxis against *Candida* infections in adults receiving daily or weekly fluconazole indicate that clinical relapses can be prevented. Emergence of resistance to fluconazole, particularly among species of *Candida* other than *C. albicans*, is a concern.[62,63] Primary prophylaxis of candidiasis in HIV-infected infants and children is not recommended.[4] For children with infrequent recurrences, it is reasonable to treat each clinical episode. Children with frequent recurrences or a history of esophageal candidiasis are candidates for prophylaxis with oral fluconazole.

Specific circumstances dictate the use of antifungal agents for prophylaxis of systemic noncandidal fungal infections in HIV-infected patients.[4] Prospective, controlled trials indicate that fluconazole and itraconazole are effective in the prevention of cryptococcosis in adults with advanced HIV disease (CD4$^+$ lymphocyte count <50 cells/mm^3).[4] Primary prophylaxis for cryptococcosis usually is not appropriate for children. Secondary prophylaxis is administered if a child has had cryptococcosis. Although secondary prophylaxis has not been studied for children and decisions should be made for each case, secondary prophylaxis usually can be discontinued in children 6 years of age or older after 1 year and when they have had a CD4$^+$ count of ≥100 cells/mm^3 and a suppressed viral load while on cART for at least 3 months.[4]

Prognosis

Opportunistic infections and nonopportunistic infections are important clinical indicators of HIV disease progression, immunologic deterioration, and early death. PCP, especially when it occurs during the first year of life, portends a poor prognosis for long-term survival in the absence of cART.[64,65] In one study, children with recurrent bacterial infections or LIP had at least a fourfold longer survival time than those with PCP, disseminated MAC disease, CMV infection, tumors, or PML.[64]

Administration of cART has resulted in a marked reduction in the progression to AIDS, opportunistic infections, and hospitalizations and provided improved survival.[1,66–68] However, the mortality rate for HIV-infected children and youth remains 30 times that for healthy children. Many of these deaths are caused by opportunistic infections, resulting from virologic failure due to poor adherence and viral resistance.[5] As HIV has become a chronic condition, there are concerns about long-term toxicities resulting from HIV and its treatment, including cardiovascular, metabolic, neurologic, and other end-organ disease.[5]

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113

Management of HIV Infection

George Kelly Siberry

The treatment and prognosis of pediatric human immunodeficiency virus (HIV) infection have changed dramatically since the start of the epidemic in the 1980s. The Department of Health and Human Services (DHHS) Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children has developed guidelines for use of antiretroviral agents in pediatric HIV infection.[1] These guidelines are updated regularly to ensure that recommendations are based on the most recent evidence. Similarly, specialists in pediatric HIV infection periodically update guidelines for the prevention and treatment of opportunistic infections (OIs) in HIV-infected and HIV-exposed, uninfected children.[2] This chapter emphasizes the predominantly outpatient care-based approach to use of antiretroviral therapy (ART).

Antiretroviral Therapy

The terms *highly active ART* (HAART) and *combination ART* (cART) have been used to distinguish the potent, multidrug ART regimen that is the current standard of care from single-drug, two-drug, and other less potent drug regimens used early in the HIV epidemic. In this chapter, the term ART will be used, instead of HAART or cART, to describe the multidrug regimens in current use.

Therapeutic Agents

As of 2015, more than 20 antiretroviral drugs (ARVs) are available for use in HIV-infected adults and adolescents, most of which have an approved pediatric treatment indication and are available as a pediatric formulation or in capsule size (Table 113.1). The therapeutic efficacy of these agents results from interruption of viral replication via several mechanisms (Fig. 113.1):

TABLE 113.1

Antiretroviral Drug Formulations and Pediatric Approval Status (as of June 2015)

Name (Abbreviation)	Formulations	Pediatric Approval (Age)
NUCLEOSIDE/NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS		
Abacavir (ABC)	Solution, tablet	>3 mo
Didanosine (ddI)	Powder for solution, tablet for suspension, capsule	>2 wk
Emtricitabine (FTC)	Solution, capsule	All ages
Lamivudine (3TC)	Solution, tablet	All ages
Stavudine (d4T)	Solution, capsule	All ages
Tenofovir disoproxil fumarate (TDF)	Powder (for mixing with food), tablet	≥2 yr
Zidovudine (ZDV)	Syrup, capsule, tablet	All ages, including premature infants
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS		
Efavirenz (EFV)	Capsule, tablet	≥3 kg and ≥3 mo
Etravirine (ETR)	Dispersible tablet	≥6 yr
Nevirapine (NVP)	Suspension, tablet (immediate-release and extended release)	≥15 days[a]
Rilpivirine (RPV)	Tablet	No
PROTEASE INHIBITORS		
Atazanavir (ATV)	Powder, capsule	>3 mo and ≥10 kg
Darunavir (DRV)	Suspension, tablet	≥3 yr
Fosamprenavir (FPV)	Suspension, tablet	≥4 wk
Indinavir (IDV)	Capsule	No
Lopinavir/ritonavir (LPV/r)	Solution, tablet	≥14 days
Nelfinavir (NFV)	Tablet (dissolvable)	≥2 yr
Saquinavir (SQV)	Capsule, tablet	No
Tipranavir (TPV)	Solution, capsule	≥2 yr
ENTRY INHIBITORS		
Enfuvirtide (T-20)	Injection	≥6 yr
Maraviroc (MVC)	Tablet	≥2 yr
INTEGRASE STRAND TRANSFER INHIBITORS		
Dolutegravir (DTG)	Tablet	≥30 kg and ≥6 yr
Elvitegravir (EVG)	Tablet	No
Raltegravir (RAL)	Tablets	≥4 wk
PHARMACOLOGIC ENHANCERS		
Ritonavir (RTV)	Solution, capsule, tablet	—[b]
Cobicistat (COBI)	Tablet	No

[a] Approved for infants <14 days of age as prophylaxis against maternal–child transmission.

[b] RTV is approved for and but is no longer used as an antiretroviral agent in children as young as 4 wk. As a pharmacokinetic enhancer in coformulated LPV/r, it is approved for those ≥14 days of age.

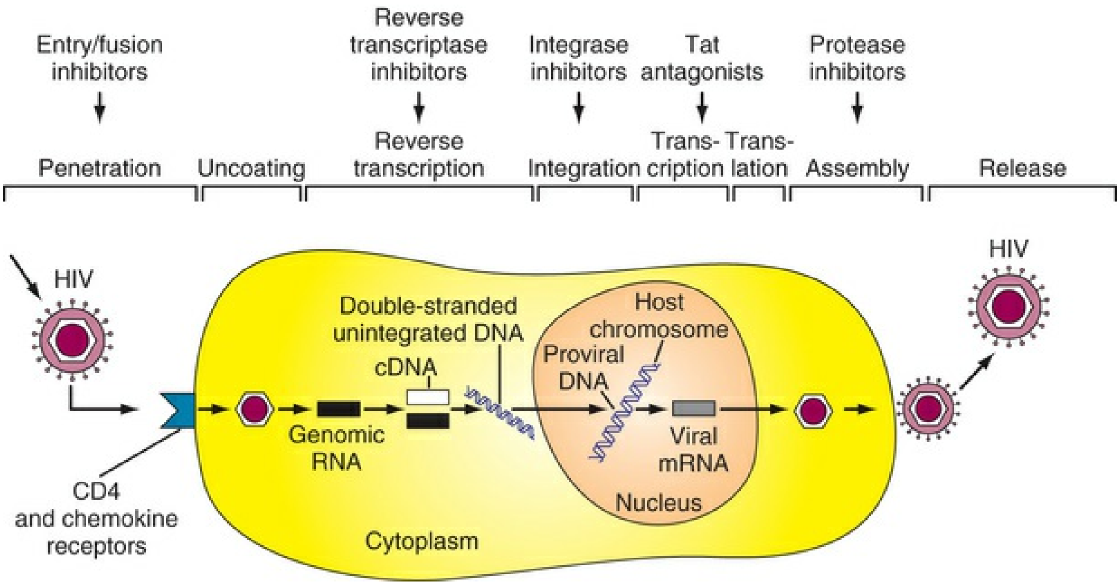

FIGURE 113.1 Human immunodeficiency virus (HIV) life cycle and location of action of various antiretroviral medications. cDNA, complementary DNA; mRNA, messenger RNA.

- Prevention of viral entry: C-C chemokine receptor type (CCR5) antagonists and fusion inhibitors
- Blockade of the early stage of viral replication: nucleoside/nucleotide analogue reverse transcriptase inhibitors (NRTIs/NtRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Inhibition of integrase-mediated strand transfer, which is necessary for integration of the viral genome: integrase strand transfer inhibitors (INSTI) or, simply, integrase inhibitors
- Interference with cleavage of HIV proteins by the viral protease: protease inhibitors (PIs)

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors

The NRTIs were the first class of ARVs available for the treatment of HIV infection. NRTIs inhibit the HIV reverse transcriptase enzyme, which is responsible for the reverse transcription of viral RNA into DNA. Like the NRTIs, the NtRTI tenofovir competitively inhibits viral reverse transcriptase, but because it already possesses a phosphate molecule, it bypasses the initial phosphorylation step that is required for activation of NRTIs.

NRTIs/NtRTIs are the backbone of ART. In general, two of these agents are used with a PI, NNRTI, or INSTI as first-line therapy. Fixed-dose combinations of NRTIs/NtRTIs are available to simplify dosing. With subsequent regimens, one or more of the NRTIs used in an earlier regimen are often used again to take advantage of a favorable resistance profile.[3]

NRTIs/NtRTIs inhibit the synthesis of mitochondrial DNA (mtDNA), leading to depletion of mtDNA and impaired mitochondrial function. This effect contributes to the toxicities associated with NRTIs/NtRTIs, such as peripheral neuropathy, pancreatitis, and myopathy. Unusual but serious toxicities that can occur with use of NRTIs/NtRTIs include lactic acidosis, hepatic steatosis, cardiomyopathy, and rapidly ascending muscular weakness. The order of potency of the NRTIs/NtRTIs in inhibiting mtDNA synthesis in vitro is didanosine (ddI) > stavudine (d4T) > zidovudine (ZDV) > lamivudine (3TC), abacavir (ABC), and tenofovir.[4] ddI and d4T are not used as first-line agents because of these toxicities. Tenofovir appears to cause fewer mitochondrial toxicities, but concerns about its deleterious effects on bone and kidneys limit its use in children; studies in adults suggest that tenofovir alafenamide (TAF), a different oral form of tenofovir, can achieve therapeutic activity with less risk of bone and kidney toxicity than the oral form, tenofovir disoproxil fumarate (TDF).[5]

Non-Nucleoside Analogue Reverse Transcriptase Inhibitors

The NNRTIs have specific activity against HIV-1 but not HIV-2 or other retroviruses. They noncompetitively bind to and disrupt the catalytic site of reverse transcriptase. Because drug resistance to NNRTIs requires a single mutation that does not appear to affect viral fitness, resistance can develop rapidly after initiation of NNRTI as part of a nonsuppressive regimen. Cross-resistance readily occurs between the NNRTIs efavirenz (EFV), nevirapine (NVP), and rilpivirine (RPV); cross-resistance is less common with etravirine (ETR). NNRTI-based ART regimens are at least as effective as PI-based regimens in achieving durable viral suppression. In addition, NNRTIs appear to be associated with less long-term toxicity than PIs.[1]

NNRTIs are associated with several types of hepatic toxicity, including asymptomatic elevation in transaminases, clinical hepatitis, and hypersensitivity reactions with hepatitis. In HIV-infected adults, risk factors for hepatic toxicity with NVP include elevated baseline serum transaminases, hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, female gender, and higher CD4$^+$ lymphocyte counts (CD4 counts). However, serious liver dysfunction appears to occur much less commonly in children receiving NVP than in adults.[6]

Hypersensitivity reactions are reported more commonly with NNRTIs (especially NVP) than with other antiretroviral agents. Effects of EFV on the central nervous system (CNS) include confusion, hallucinations, and nightmares. Concern about increased risk of neural tube defects with EFV has led to avoidance of this drug in early pregnancy, although accumulating evidence continues to provide reassurance that it can be used safely during pregnancy.[7] The US Food and Drug Administration (FDA) continues to recommend against use of EFV in women who may become pregnant and during early pregnancy, but the DHHS Guidelines and the World Health Organization (WHO) assessment is that EFV is a safe component of ART at any time in pregnancy.[8,9,11] ETR has been approved for children 6 years or older, and it is typically used in combination with PIs and other ARVs in children for whom other ART regimens have failed. RPV is not currently approved for use in children.

Protease Inhibitors

PIs inhibit the HIV protease enzyme, which is required to cleave viral polyprotein precursors and generate functional viral proteins. The protease enzyme is crucial for viral assembly.

PIs have a potent antiretroviral effect, especially when used in combination with NRTIs and/or NNRTIs. Because resistance to PIs requires multiple mutations, some of which reduce viral fitness, PI resistance usually develops slowly. However, compared with NNRTIs, PIs are associated with more long-term toxicity, such as fat redistribution, lipodystrophy syndrome, hyperlipidemia, diabetes mellitus, and hyperglycemia. In children, most PIs require coadministration with a pharmacologic enhancer, usually ritonavir (RTV) because cobicistat (COBI) is not yet approved for use in children. The pharmacologic enhancer inhibits cytochrome P450 (CYP) 3A4 enzymes and increases the concentrations of other PIs. RTV is no longer used in therapeutic doses for anti-HIV activity. The most commonly used PI in children is a coformulation of lopinavir (LPV) and RTV known as LPV/r. Other PIs coadministered with a pharmacologic enhancer include atazanavir (ATV), darunavir (DRV), fosamprenavir (FPV), and tipranavir (TPV).[1] All PIs are metabolized by and/or inhibit enzymes in the CYP system; therefore, attention to potential drug–drug interactions is required.

Entry and Fusion Inhibitors

HIV enters target cells via a multistep process. First, HIV binds to the CD4 receptor, leading to conformational changes in the viral gp120 envelope protein that enable binding to chemokine coreceptors for HIV. Chemokine receptor engagement triggers conformational changes in the HIV gp41 envelope protein, leading to fusion of HIV and the target cell and resulting in delivery to the viral core.

Enfuvirtide (T-20), the only FDA-approved fusion inhibitor, requires twice-daily subcutaneous injections. Maraviroc (MVC) binds to and alters the structure of the CCR5 chemokine receptor, preventing it from being used as a coreceptor by HIV. Because some strains of HIV also can infect cells by using the C-X-C chemokine receptor type 4 (CXCR4) molecule as a coreceptor, MVC is ineffective in individuals who harbor CXCR4-tropic HIV virus or dual-tropic virus (i.e., able bind to both CCR5 and CXCR4). These two drugs are seldom used in children.

Integrase Inhibitors

The three drugs in this class—raltegravir (RAL), dolutegravir (DTG), and elvitegravir (EVG)—inhibit the viral integrase, preventing the strand transfer step that is necessary for integration of the viral genome into the host cell genome. RAL is approved for use in infants as young as 4 weeks of age but requires twice-daily dosing and has a lower barrier to resistance than the newer, once-daily DTG (licensed for ages ≥6 years and body weight ≥30 kg) or EVG (licensed only for adults).

Indications for Initiation of Antiretroviral Therapy

The high mortality rate of HIV-infected infants younger than 12 months of age and the relatively poor ability of the CD4 count and other factors to predict which infants will have rapid disease progression have led to a longstanding recommendation in the United States that ART should commence in all infected infants as soon as they are identified.[1] The CHER trial provided clear evidence in resource-limited settings of the benefit of initiating ART in any infant younger than 12 months of age regardless of CD4 count.[8] In that study, infected infants (6–12 weeks old) with greater than 25% $CD4^+$ lymphocytes were randomized to either initiation of ART or delay until certain defined criteria were met. The fourfold higher mortality rate in the delayed initiation arm led the WHO in 2010 to recommend ART for all infants. Because of the increased mortality and poor predictive capacity of CD4 counts in those aged 1 to 2 years, the WHO also recommended therapy for all 1- to 2-year-old children, although supporting clinical trial evidence was lacking.[11]

Initiation of ART in children older than 1 to 2 years of age was long based on clinical and immunologic staging. Based on evidence from large trials in adults demonstrating clinical benefit of immediate ART initiation irrespective of CD4 count and on availability of expanding safe, potent treatment options for children, ART is now recommended by DHHS and WHO guidelines for all people with HIV infection, including children of all ages.[1,8,12a,12b]

Limited virologic testing capabilities in many countries hinder timely diagnosis of perinatally infected children. Delayed recognition of children with HIV infection still occurs in the United States, usually because of unrecognized perinatal HIV exposure.[12]

Given the need to start multiple agents, comorbid conditions, such as tuberculosis (TB), that require treatment with other medications that can interact with the ARVs, as well as many other complicating factors in the lives of families affected by HIV, should be addressed by intensive counseling and support before treatment begins. Families should be educated about the medications and the critical importance of adherence, and such counseling and support should continue at every visit.

Selection of Antiretroviral Drugs for the Initial ART Regimen

Guidelines for the treatment of pediatric HIV are published and updated regularly.[1,11] Initial therapy with three antiretroviral agents, usually two NRTIs and a PI, an INSTI or an NNRTI, is recommended. The P1060 trial demonstrated that LPV/r-based ART was superior to NVP-based ART for children younger than 3 years old in resource-limited settings[13,14]; however, PENPACT-1 did not demonstrate an advantage of PI-based over NNRTI-based ART in children in higher-resource settings with higher average age and more diverse drug regimens.[15] Factors to consider when deciding on an initial ART regimen for an infant or child include the following[1]:

- Availability of appropriate (and palatable) drug formulations and pharmacokinetic information for the child's age group
- Potency, dosing frequency, food and fluid requirements, and potential short- and long-term adverse effects of the antiretroviral regimen
- Effect of initial regimen on later options
- Presence of comorbidity, such as TB, HBV or HCV infection or chronic renal or liver disease
- Potential interactions of ARVs with other prescribed, over-the-counter, or complementary or alternative medications
- Ability of the caregiver and child to adhere to the regimen
- Results of baseline ARV drug resistance testing

Clinical and Laboratory Monitoring

Table 113.2 displays the schedule of clinical and laboratory evaluations during pediatric HIV management, based on ART status.[1,16] When HIV infection is diagnosed, it is important to stage the disease, evaluate for coinfections and complications, assess the need for OI prevention, provide elements of routine primary health care, and address psychosocial needs. It is important to assess knowledge, attitudes, and potential barriers for taking ART. Adherence counseling begins with readiness assessments before ART initiation and includes monitoring at every clinical encounter once ART has been prescribed. Clinical evaluations are recommended approximately every 3 months for HIV-infected children who have not yet met indications for initiation of ART.

TABLE 113.2

Routine Monitoring Schedule for Management of Children With HIV-Infection by ART Treatment Status

Visit Interval	Monitoring of Treatment Efficacy and Adherence[a]	Toxicity Monitoring, Other Care and Monitoring[a,b]
INITIAL VISIT		
N/A	Assess attitudes and readiness for ART HIV viral load CD4 count and percentage HIV drug resistance genotype	History: complete clinical history, including pregnancy and delivery, OIs, and other HIV-related illnesses; ARV exposure and treatment; immunization record; comprehensive medical and family history Pyschosocial assessment; status of HIV disclosure to child and other family members or contacts Disclosure counseling; guardianship, permanency planning Complete physical examination Growth and nutritional assessment; pubertal and neurodevelopmental assessment; educational assessment General laboratory studies: complete blood count and differential; chemistry panel (liver function, renal function, electrolytes, calcium, phosphate, amylase, lipase); lipid panel[c]; urinalysis (dipstick and microscopic); G6PD-deficiency screening; 25-hydroxy vitamin D level[d] HBsAg, HBsAb, and HBcAb; age-appropriate hepatitis C testing; *Toxoplasma* IgG, varicella IgG TB assessment: exposure, symptoms, STS STI testing (syphilis, chlamydia, gonorrhea) based on maternal history (for infants); STI testing including cervical/anal Pap smear for sexually active youth; reproductive planning and risk reduction counseling for youth
ART INITIATION		
1–2 wk (in	Adherence	Adverse effects history

person or by phone), usually for at least the first 4 wk	counseling and assessment Reinforce medication instructions Viral load (optional)	Targeted physical examination Additional problem-based evaluations Interim clinical and psychosocial history
EARLY ART		
4–8 wk	Adherence counseling and assessment Reinforce medication instructions Viral load CD4 count (optional)	Adverse effects history Targeted physical examination Complete blood count with differential Chemistry panel (liver function, renal function, electrolytes) Additional problem-based evaluations Interim clinical and psychosocial history Intensive, interdisciplinary psychosocial support
STABLE ART		
3 mo	Adherence counseling and assessment Reinforce medication instructions Adjust ARV dosing for growth Consider ARV changes for convenience or tolerability, especially as child learns to swallow pills Viral load HIV viral load CD4 count and percentage[f]	Interim clinical history, including targeted history of adverse effects Targeted physical examination Additional problem-based evaluations Complete blood count and differential Chemistry panel (liver function, renal function, electrolytes, calcium) Drug-specific toxicity monitoring[e] (e.g., phosphate for TDF; amylase, lipase for ddI) Interim psychosocial history Immunization and OI prophylaxis assessment **Every 6–12 mo:** Complete interim history and physical examination Growth and nutritional assessment, pubertal and neurodevelopmental assessment; educational assessment Update family and psychosocial history Disclosure counseling HBsAb (annually, if at ongoing risk) Hepatitis C antibody testing (if at ongoing risk) TB assessment (yearly): history, STS STI testing including cervical/anal Pap smear for sexually active youth Reproductive planning and risk reduction counseling for youth. Optional or in selected patients: 25-hydroxy vitamin D level[e]; bone mineral density assessment (by DXA[e])
SUSPECTED TREATMENT FAILURE		
2–4 weeks (in person and/or by phone)	Adherence counseling and assessment Reinforce medication instructions Confirm drug dosing, food and fasting requirements, interacting drugs Viral load (once at failure, then every ≥8–12 wk if persistent failure	Interim clinical history, including targeted history of adverse effects Targeted physical examination Complete blood count and differential Chemistry panel (liver function, renal function, electrolytes, calcium) Additional problem-based evaluations Interim clinical and psychosocial history Intensive, interdisciplinary psychosocial support

	and ready to start new ART regimen) HIV drug resistance genotype; also phenotype, if multidrug resistance is present	

[a] Monitoring elements performed at each visit interval unless otherwise specified.

[b] No toxicity monitoring is done before ART is initiated.

[c] If lipid panel results are abnormal on a nonfasting specimen, obtain at least one fasting lipid panel per year.

[d] Criteria for vitamin D level and DXA screening are not well established.

[e] Toxicities and monitoring of individual ARV agents are covered elsewhere.

[f] Some experts monitor CD4 count and percentage less frequently (e.g., every 6–12 mo) if adherence is good, CD4 values are greater than the threshold for OI risk, viral suppression is sustained, and clinical status is stable for more than 2–3 yr.

ART, Antiretroviral therapy; ARV, antiretroviral drug; CD4 count, CD4$^+$ lymphocyte count; ddI, didanosine; DXA, dual-energy X-ray absorptiometry; G6PD, glucose-6-phosphate dehydrogenase HBcAb, hepatitis B core antibody; HBsAb, antibody to hepatitis B surface antigen; HBsAg, hepatitis B surface antigen; HIV, human immunodeficiency virus; IgG, immunoglobulin G; N/A, not applicable; OI, opportunistic infection; STI, sexually transmitted infection; STS, skin test for TB; TB, tuberculosis; TDF, tenofovir.

Adapted from Department of Health and Human Services, Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. AIDS Info: Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Last updated March 1, 2016. http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf.

Frequency of visits, assessment, and counseling are intensified at the time ART is initiated, allowing the provider to identify and intervene early in case of problems with adherence or adverse effects. Some patients require counseling every 1 to 2 weeks for several weeks to work through adherence and medication intolerance problems. By 4 weeks after ART initiation, a visit should occur to allow for physical examination and laboratory testing to monitor toxicity and virologic response (see Table 113.2). Additional monitoring may be indicated based on individual antiretroviral toxicity profiles. HIV viral load should be measured to confirm the expected response to ART. Clinical assessments should continue every 4 to 8 weeks or at shorter intervals if there are problems with adherence, intolerance, laboratory abnormalities, or lack of virologic response. In an uncomplicated case, encounters occur at 1 to 2 weeks, at 4 weeks, and at 12 weeks after initiation.

Successful ART is expected to reduce viral load by at least 1 log from baseline at 8 to 12 weeks, and a viral load of less than 200 copies/mL should be attained by 6 months.[1] Children whose pretreatment viral load is extremely high (>10^6 copies/mL) may take longer to achieve viral load suppression, but they should nonetheless demonstrate a 1-log drop in viral load by 12 weeks and a consistent pattern of declining viral load measurements thereafter. For children who begin ART with CD4 counts greater than the age-specific threshold that would indicate immunosuppression,[17] successful ART is expected to be associated with sustained or increased CD4 counts. Infants and children whose CD4 counts are depressed at ART initiation should achieve CD4 counts greater than the level associated with immunosuppression within 6 to 12 months, although those with severe immunosuppression at ART initiation may take 2 years or longer to reach healthy CD4 counts, and some may never achieve CD4 reconstitution.[18]

Once patients have a documented response to therapy on stable ART, routine monitoring visits should take place approximately every 3 months with the goals of assessing adherence, documenting ongoing treatment success (by viral load and CD4 count), evaluating for toxicity, and ensuring that other aspects of comprehensive care are provided. Some experts monitor CD4 count every 6 to 12 months in those children who have maintained CD4 counts greater than the threshold for OI risk, sustained viral suppression, and stable clinical status for longer than 2 to 3 years.[1,19]

Illnesses that occur during the initial 3 to 6 months of treatment do not always represent treatment failure, especially in the context of good virologic response; such illnesses may be the result of incomplete reversal of baseline immunosuppression or an immune-reconstitution inflammatory syndrome (IRIS) that occurs as an exaggerated or unmasked response to an infection in the context of an imbalanced, recovering immune system.[20] Mycobacterial infections, toxoplasmosis, cryptococcosis, and varicella-zoster virus infection account for most IRIS events; in lower-resource settings, TB and bacille Calmette-Guérin (BCG) disease are especially common. Noninfectious IRIS syndromes, such as sarcoidosis and inflammatory response to Kaposi sarcoma, can occur. In addition to management of the underlying infection or condition, IRIS may require treatment with nonsteroidal anti-inflammatory agents and, when more severe, with systemic corticosteroids. ART rarely is withheld and only in the most severe cases. Mortality is most often related to complications of CNS IRIS syndromes.

Treatment failure can manifest as lack of virologic suppression, decline or inadequate increase in CD4 count, or new HIV-related clinical illness. The most common manifestation of treatment failure is lack or loss of virologic suppression; the most common underlying reason is medication nonadherence. Drug resistance can be a primary cause of treatment failure or can emerge during periods of poor virologic control attributable to nonadherence. Poor virologic response or relapse after virologic suppression merits prompt reassessment. Isolated episodes of low-level viremia (<500 copies/mL) usually do not represent virologic failure.[21] However, repeated detection of even low-level viremia may signify failure.[19] If virologic failure is confirmed, assessment and counseling visits should emphasize adherence improvement, evaluate for drug resistance with HIV genotypic testing, confirm ARV dosing and food and fasting requirements for individual ARVs, and exclude use of other drugs that interfere with absorption, metabolism, or action of ARVs (e.g., proton-pump inhibitors that reduce absorption of ATV). Changing to a new ART regimen should be undertaken only after these problems—especially adherence—have been addressed.

Infection Prevention: Immunizations and Chemoprophylaxis

Chapter 112 provides a detailed discussion of prevention and management of infectious disease complications of HIV infection, and specific guidelines are published and updated periodically.[2] Indications for chemoprophylaxis against OIs and eligibility for vaccines should be reviewed at every clinical evaluation.

All HIV-infected infants require prophylaxis against *Pneumocystis* pneumonia (PCP) caused by *P. jirovecii* regardless of clinical, immunologic, or treatment status. Beyond the first year of life, indications for OI chemoprophylaxis should be based on the CD4 count obtained at the prior visit, interpreted according to normative values by age. Declines in CD4 values, resulting in new need for OI chemoprophylaxis, are most likely to occur in children who are not yet receiving ART.

Primary and secondary OI chemoprophylaxis for PCP and for toxoplasmosis can be safely discontinued in children older than 1 year of age who are receiving stable ART and have immune reconstitution.[2] It is important to assess for the need to restart prophylaxis at each HIV monitoring visit.

Specific recommendations for routine immunization have been developed for HIV-infected children[2] because the safety, immunogenicity, efficacy, and protective durability of vaccines may be different from those observed in non–HIV-infected children.[22] These differences vary by specific vaccine and by demographic and clinical characteristics of the vaccine recipients, including use of ART and degree of immunosuppression.

The increase in HIV viral load and decline in CD4 count that can follow immunization are transient and without clinical consequences. Although increased mortality was reported after administration of pneumococcal polysaccharide vaccine compared with placebo in a trial involving HIV-infected African adults who were not receiving ART,[23] there is no evidence of increased toxicity with use of pneumococcal or other non-live vaccines in adults receiving ART or in HIV-infected children.[22] Therefore, non-live vaccines are regarded as safe for use in HIV-infected children. Because serious and even fatal illnesses have occurred in severely immunocompromised HIV-infected children after administration of live virus vaccines, measles, mumps, rubella, and varicella vaccines are not recommended for such children, although they should be used in those without severe immunosuppression. Increasing evidence suggests that both rotavirus vaccines[24] and cold-adapted live-attenuated intranasal influenza vaccine can be used safely in HIV-infected children.[25] BCG vaccine should not be given to infants with known HIV infection or to those with perinatal HIV exposure accompanied by symptoms suspicious for HIV infection. However, BCG vaccine may be given to infants who are asymptomatic, including those of undetermined HIV status born to HIV-infected mothers, in countries with high TB burden and established neonatal BCG vaccination programs.[26]

HIV-infected children demonstrate blunted humoral responses compared with uninfected children. Impaired response is particularly common in children with advanced HIV disease, lower CD4 counts, higher viral loads, and lack of ART.[22] With effective ART, most HIV-infected children respond adequately, although not as well as uninfected children. Potential strategies that have been explored to optimize protection of HIV-infected children include additional vaccine doses in primary series, higher-titer vaccine doses, more frequent booster doses, postimmunization confirmation of serologic response, and reimmunization after immune reconstitution. Most children who initiate ART beyond infancy lack immunity related to vaccines they received before ART.[27,28] Older children who received measles-mumps-rubella (MMR) vaccine before starting effective ART should have MMR doses repeated once they are receiving stable ART and have improved CD4 counts.[29,30] Routine reimmunization may be indicated for other vaccines in such children, but further evidence is needed.[27]

Growth and Nutrition

With effective ART, HIV-infected children in the United States rarely suffer the AIDS-defining growth failure and severe malnutrition that were typical in the pre-ART era. These manifestations, now observed largely in those patients who are failing ART, portend a poor prognosis. High-calorie supplementation (orally or by gastrostomy tube) and appetite stimulants may be used as adjunctive, supportive therapy, but the most important intervention is institution of effective ART. Whereas effective ART routinely improves weight gain and linear growth, normal final height may not be attained, especially in children who are already stunted when ART is begun.[31]

Growth failure that occurs in the setting of successful ART merits a comprehensive evaluation, including for causes unrelated to HIV infection. There are no established associations of specific ARVs and growth failure, but alterations in body appearance and fat distribution and metabolic derangements in ART-treated children are common. Body mass index (BMI) should be monitored routinely, and overweight children should be given nutrition and exercise counseling.

Evidence of delayed puberty in HIV-infected children is limited largely to the pre-ART era. More recent data suggest that pubertal delay among children receiving ART is less common and is largely confined to those with poor response to ART.[32]

Vitamin D deficiency is common in HIV-infected children; ensuring vitamin D sufficiency and adequate intake of calcium should be emphasized.

Disclosure

Developmentally appropriate disclosure of HIV infection status to children is recommended strongly.[33,34] Informing and educating children about their HIV infection takes place in stages, often over years, beginning with general information about reasons for taking medicine and having an infection. Discussing HIV by name requires the child to have an intellectual ability to understand the information and a capacity to understand the principle of keeping medical information private, usually at 8 to 10 years of age. A multidisciplinary team should provide ongoing counseling to parents and other caregivers about the purpose and process of disclosure. Some parents prefer to have disclosure discussions with their children at home, whereas others prefer to have staff present to participate in or even lead the disclosure discussions. Delaying disclosure until older ages increases the risk of inadvertent or unplanned disclosure and poor outcomes. Awareness of HIV status before onset of sexual activity is especially important for prevention of secondary transmission.

Consequences of Infection and Antiretroviral Therapy by Organ Systems

Neurologic Function

HIV infection commonly affects both the CNS and the peripheral nervous system. In the pre-ART era, the impact of infection of the CNS was devastating in infants and children, with up to 50% of infected infants developing encephalopathy with substantial morbidity and mortality. Pathologic findings have included focal cerebral mass lesions, myelopathies, myopathies, seizures, cerebral vascular accidents, and peripheral neuropathies. Since the advent of ART, encephalopathy has almost disappeared.[35,36] However, an emerging concern is for more subtle CNS problems, such as cognitive deficits, problems with attention, and psychiatric disorders.[37,38] The etiology of these problems is not completely understood and likely is multifactorial. Potential causes include ongoing CNS infection or ongoing damage secondary to the initial CNS infection,[39] inflammatory changes,[40] ARV toxicities,[41] HIV- and ARV-related metabolic derangements, other exposures (e.g., in utero exposure, current substance use), and social and demographic influences.

Many of the NRTIs can exacerbate or trigger peripheral neuropathy, although peripheral neuropathy also can occur in HIV-infected children who are not receiving ARVs. EFV can cause impaired concentration, sleep disturbances, anxiety, vivid dreams, nightmares, and psychosis. In most patients, these symptoms are self-limited or manageable with nighttime administration of EFV; EFV probably should not be used in children with psychiatric disorders.

Cardiovascular Health

Cardiomyopathy caused by ARVs (especially ZDV) and HIV was a major cause of morbidity and mortality in the pre-ART era.[42] In the ART era, the proportion of deaths due to cardiomyopathy has remained relatively stable, but the absolute number of cases has declined along with the dramatic decreases in overall mortality.[43] An emerging concern is the long-term effect of dyslipidemia and other metabolic derangements in children with well-controlled HIV disease. HIV itself is known to cause dyslipidemia, marked primarily by low concentrations of high-density lipoprotein. A substantial proportion of perinatally infected children, especially those treated with NRTIs and PIs, have dyslipidemia (elevated cholesterol, elevated triglycerides, or both), other metabolic derangements (e.g., insulin resistance), and fat redistribution (with an overall appearance of peripheral wasting and central obesity that is associated with increased risk of cardiovascular disease).[44,45] Appropriate prevention and management include standard recommendations about diet and exercise. The roles of statins and other pharmacologic therapies that have been recommended for other high-risk pediatric groups[46] have not been evaluated fully. Consideration may be given to substitution of lipodystrophy-promoting ARVs with ARVs associated with less lipid and metabolic derangement (e.g., RAL in place of LPV/r).

Another potential cardiac complication of the specific PIs ATV LPV/r, saquinavir (SQV), and RTV is prolongation of the PR interval and other conduction problems. Caution should be exercised when using these agents in patients known to have preexisting conduction problems and in those receiving other drugs that also are associated with conduction problems.

Hepatic Function

All perinatally HIV-infected children should be evaluated for HBV and HCV infections. The rate of HCV maternal–infant transmission is estimated to be 4% for HIV-uninfected women but rises to about 20% in women with HIV/HCV coinfection.[47] It is not clear whether the rate of HBV maternal–infant transmission is different if the mother also is HIV-infected. Infants of HBV/HIV-coinfected women should receive the same HBV preventive management as infants of HBV-monoinfected women. HBV surface antigen and HCV antibody testing also should be performed in older HIV-infected children for whom maternal information is lacking.

Several ARVs, including 3TC, emtricitabine (FTC), and TDF, have activity against HBV. For this reason, TDF is included routinely in ART regimens for HBV/HIV-coinfected older children; its use in younger children is limited by potential adverse effects.[1] Once HBV-active drugs are initiated, caution is advised against discontinuing these drugs because flares of hepatic inflammation have been reported.

In children who have persistent, severe immunosuppression (CD4 counts <50–100/mm^3 or <15%), several OIs can involve the biliary system and produce a syndrome of right upper quadrant pain, fever, direct hyperbilirubinemia, and elevation of serum aminotransferase levels. Ultrasonography or other imaging is indicated. Detection of the offending pathogen may require direct aspiration, biopsy, and/or endoscopic retrograde cholangiopancreatography (ERCP)-guided sphincterotomy and fluid sampling. Ascending bacterial cholangitis and obstructive conditions also should be considered. Such biliary problems are rare in children receiving ART.

Tests of hepatic inflammation and function are part of routine monitoring. Jaundice due to indirect hyperbilirubinemia is commonly associated with ATV. This benign drug effect is thought to be related to inhibition of a uridine diphosphate glucuronyltransferase. At first occurrence, it is important to exclude elevated direct bilirubin and increased hepatic transaminases, abnormalities that would suggest a different etiology. Even with continued use of the precipitating ARV, the indirect hyperbilirubinemia may abate. Hepatic transaminase elevation is common in HIV-infected children, and frequently no specific explanation is found; HIV infection itself, ARVs (especially NNRTIs), non-ARV agents, and hepatotropic viral infections should be considered. Persistent or moderate elevations deserve further evaluation. Intercurrent viral infections (e.g., Epstein-Barr virus, enteroviruses) and effects of ARVs and non-ARV agents are the most common causes. It is important also to consider HBV and HCV infection, withdrawal of HBV-active drugs in HBV-coinfected children, and HBV- or HCV-related IRIS. There is concern that ongoing mild or subclinical liver inflammation may pose a long-term risk of progressive liver dysfunction, liver fibrosis, and cirrhosis.[48]

Renal Health

In the pre-ART era, HIV infection frequently caused kidney disease. HIV-associated renal disease has been classified into four groups: acute tubular disease, immune-mediated glomerulopathies, thrombotic microangiopathies, and HIV-associated nephropathy. In the ART era, the proportion of deaths due to renal disease has increased relatively; fatalities probably reflect end-stage HIV disease.[43] The rate of glomerular disease has decreased, and the rate of proteinuria, as high as 33% in the pre-ART era, has fallen to less than 10% in the ART era.[49,50] Specific ARVs, such as TDF and many of the PIs, are associated with renal disease. TDF-associated renal disease is a tubulopathy characterized by proteinuria, glycosuria, and renal phosphate wasting. Treatment with some PIs has been associated with renal calculi.[51] In most cases, these toxic effects on the kidney are reversible with discontinuation of the offending ARV.

Appropriate monitoring for kidney disease includes measurements of serum creatinine and other electrolytes along with urinalysis before ARVs are started and then periodically during treatment. More intensive monitoring may be necessary for those receiving TDF.[52] Renal complications can develop as an insidious, progressive, chronic process exacerbated by nephrotoxic agents or other metabolic effects of longstanding HIV infection.[53] All of the NRTIs (except ABC) and TDF are excreted by the kidney and require appropriate dose adjustments in the setting of impaired renal function.

Bone Health

HIV infection in adults increases the risk of osteonecrosis (avascular necrosis), a condition that results from ischemic death of the cellular elements of bone.[54] The femoral head is affected most commonly, but other involved structures may include humeral heads and wrist bones. HIV-infected children appear to be at increased risk, with an approximately 0.2% prevalence of avascular necrosis of the hip.[55] The most important osteonecrosis risk factor is corticosteroid use, which can be exacerbated by PI-mediated alterations in corticosteroid metabolism. Other risk factors include alcohol use, hemoglobinopathies, hyperlipidemia, pancreatitis, low bone mineral density (BMD), and hypercoagulable states. Specific risk factors for HIV-infected children have not been determined. Limp, hip pain or periarticular pain and tenderness, and limited range of motion at affected joints are typical. Imaging is used to confirm the diagnosis. Less advanced osteonecrosis can be managed with avoidance of weight bearing and use of analgesics, but surgical intervention often is required; consultation with an orthopedic specialist should be obtained early. Corticosteroid use and alcohol intake should be minimized.

Decreased BMD is recognized as an emerging metabolic complication of HIV infection in adults and children.[56,57] Declining bone mass (osteopenia) frequently precedes osteoporosis. Decreased BMD occurs in about 15% to 20% of HIV-infected adults and children in the ART era. Increased risk of fracture has been demonstrated in HIV-infected adults compared with uninfected adults,[58] but such findings have not been reported for children. The impact on bone health of perinatally HIV-infected children will likely not be understood fully until these children reach adulthood because of the normal maturational changes in BMD. The dual concern is that infected youths may not attain a normal peak bone mass in early adulthood and will continue to have high rates of ongoing bone loss, which would lead to high rates of osteoporosis and fractures in adulthood.

The causes of low BMD and osteoporosis in HIV-infected children and adolescents, in addition to HIV-specific factors such as effects of HIV infection and ARV use, include low BMI, malnutrition, corticosteroid use, and vitamin D insufficiency; in older adolescents, smoking, alcohol consumption, or use of medroxyprogesterone injectable contraception may be a cause. Lower BMD was observed in HIV-infected patients in the pre-ART era. Initiation of ART has been associated repeatedly with loss of BMD. Specifically implicated ARVs include d4T, TDF, and PIs.

There is no recommendation at the present time for routine radiographic assessment of BMD in children and youths.[1,56] Given the high rates of vitamin D insufficiency in children with HIV infection, periodic assessment of vitamin D status is recommended.[59] Ensuring calcium and vitamin D sufficiency, encouraging weight-bearing exercise, and minimizing use of tobacco, alcohol, corticosteroids, and other drugs that compromise bone health are important interventions for maintenance and restoration of bone health. Substitution of TDF with a different ARV—balanced against the feasibility of maintaining virologic suppression without TDF—may be warranted if very low BMD or osteoporosis is diagnosed.

Pulmonary Conditions

In the pre-ART era, pulmonary infections in HIV-infected children were common. PCP was a common presentation for infants with unrecognized HIV infection. PCP and recurrent bacterial pneumonia are now uncommon in the United States and occur predominantly in children whose severe immunosuppression is a result of lack of effective ART. Asthma may be more common in HIV-infected children with increasing use of ART.[60]

TB commonly complicates HIV infection in children who live in TB-endemic areas. Although this is less of a problem for children in the United States, HIV-infected US children are at increased risk of exposure to *Mycobacterium tuberculosis* if they live with HIV-infected, immunosuppressed adults with TB; have immigrated from TB-endemic areas; or have household contacts who immigrated from TB-endemic areas. HIV-infected children should have annual screening for TB risk and symptoms as well as testing with a tuberculin skin test or interferon γ release assay. Once infected with *M. tuberculosis*, HIV-infected children are at increased risk of developing TB disease, especially if CD4 counts have not been preserved or restored by ART.

Lymphocytic interstitial pneumonitis (LIP) is a chronic lymphoproliferative disorder that was observed in about one third of HIV-infected children in the pre-ART era (see Fig. 111.3 in Chapter 111). LIP can lead to bronchiectasis and progressive pulmonary decompensation. Distinguishing the radiographic appearance of LIP from that of TB or PCP can be difficult. Epstein-Barr virus has been implicated in the pathogenesis of LIP, but the etiology is not definitively established. Episodic pulmonary exacerbations respond to systemic corticosteroids. LIP appears to be both prevented and treated by ART.[61]

Hematologic Abnormalities

Anemia, thrombocytopenia, and neutropenia are observed commonly in HIV-infected children. These abnormalities can be related to the HIV infection itself, toxicity of ARVs or other commonly used drugs, malnutrition or micronutrient deficiency, superinfection (e.g., parvovirus, B19, *Mycobacterium avium* complex), or malignancy.

Anemia usually results from direct bone marrow suppression by HIV or from autoimmune hemolytic anemia. Both typically improve with ART, although control of autoimmune hemolytic anemia may require use of corticosteroids. Anemia related to concomitant infection, malignancy, or other conditions improves with treatment of the underlying condition. Drug-related anemia usually is the result of marrow suppression (e.g., due to ZDV, cotrimoxazole) but also can be related to hemolysis in glucose-6-phosphate dehydrogenase (G6PD)-deficient patients taking drugs such as dapsone or sulfonamides. ZDV-related anemia is common and usually is macrocytic. Erythropoietin injections have been used to mitigate severe nonhemolytic anemia and avoid transfusions in children without an alternative to ZDV or an immediate option for treatment of an underlying condition, but this approach is rarely needed now.

Neutropenia in HIV-infected children does not seem to carry the same risk of infection as neutropenia in children with malignancies. ZDV is the most common drug-related cause. Neutropenia also can be caused by direct effects of untreated HIV infection, other drugs, intercurrent infections, or malignancy. Effective HIV treatment, substitution of offending drugs, and/or treatment of underlying conditions usually is sufficient. Injections of granulocyte colony-stimulating factor (G-CSF) have been effective for severe or persistent neutropenia but are rarely needed today.[1]

Thrombocytopenia is more likely the result of HIV infection than the result of HIV treatment. Thrombocytopenia typically responds to ART and is uncommon among children receiving effective ART. Other causes include indinavir (IDV), non-ARV agents (e.g., cotrimoxazole), opportunistic and non-opportunistic infections, recent live-virus immunizations, and malignancy. Severe thrombocytopenia has been managed successfully with the same therapeutic approaches as for HIV-unrelated immune thrombocytopenic purpura.[1]

Lactic Acidosis and Mitochondrial Dysfunction

NRTIs/NtRTIs inhibit mtDNA synthesis and impair mitochondrial function in vitro. HIV itself also can cause mitochondrial dysfunction. Clinical manifestations are broad, ranging from asymptomatic elevations in lactic acid (2.1–5.0 mmol/L); to a combination of symptoms and signs including fatigue, weakness, myalgia, abdominal pain, and dyspnea; to severe multiorgan involvement (hepatic toxicity, pancreatitis, and respiratory failure) with elevated lactic acid concentrations. Mitochondrial toxicity also can play a role in peripheral neuropathy, cardiomyopathy, and CNS toxicity. Because asymptomatic elevations of lactic acid are common and of uncertain significance, routine assessment of lactic acid levels is not recommended. However, measurements should be performed whenever signs or symptoms of lactic acidosis are present.[1]

In the setting of symptomatic lactic acid elevations, all ARVs should be discontinued. After resolution of symptoms and normalization of lactic acid concentrations, a new ARV regimen that does not include the likely offending agents should be started. Although in vitro data suggest that ddI and d4T are most likely—and 3TC and TDF are less likely—to cause lactic acidosis, the clinical situation can be more complicated.[62,63] Therefore, NRTI/NtRTI-sparing regimens may be preferred in a patient who has experienced mitochondrial toxicity and lactic acidosis.

Malignancies

HIV-infected adults are at high risk for several cancers, including Kaposi sarcoma and non-Hodgkin lymphoma. In the ART era, HIV-infected adults are much less likely to develop Kaposi sarcoma, but because of improved survival and other risk factors, a much broader array of malignancies is now seen. Cancer is a leading cause of death among adults infected with HIV in the United States.[64] Cancer rates are low in infants and children infected with HIV but still higher than in the general pediatric population.[65]

Reproductive Health

By 19 years of age, 17% of perinatally infected girls in one cohort had been pregnant at least once.[66] In this same cohort, 27% of 13- to 24-year-old girls were sexually active. Those who were sexually active had higher viral loads and lower CD4 counts, factors that increase the risk of HIV transmission.

Whereas screening for cervical dysplasia (i.e., by Pap smear) is generally deferred in adolescents (regardless of the age at onset of sexual activity) until age 21 years, sexually active HIV-infected adolescents should undergo cervical cytology screening twice during the first year after sexual activity onset and annually thereafter.[2,67] Human papilloma virus (HPV) vaccines are safe and immunogenic in perinatally HIV-infected children and youths[68]; HPV vaccine should be offered to all children, preferably by 11 years of age. Even those with evidence of HPV disease should receive HPV vaccine. Anal dysplasia screening (by anal Pap smear) also may be beneficial for HIV-infected women and men who have sex with men.[2]

Routine HIV care for perinatally infected adolescents should include regular reproductive health screening and counseling. Discussion and prevention counseling should include current and planned sexual activity; reducing the risk of acquiring and transmitting sexually transmitted infections (STIs), including HIV infection; partner disclosure; screening for STIs and for HPV-associated dysplasia; and pregnancy planning and contraception. Condoms are recommended to prevent transmission of HIV, HPV, and other STIs and for pregnancy prevention. Many forms of hormonal contraception can be used safely and effectively by HIV-infected women, but providers should be aware of potential drug interactions, especially between many PIs and oral contraceptives.[69] Most often, the infected youth's partner is not HIV-infected; periodic HIV testing and counseling about preexposure prophylaxis (PrEP) for the partner is recommended, and consultation with an obstetrician can be helpful for counseling about approaches to safe conception for the HIV-discordant couple.

International Settings

In resource-limited countries, HIV remains a devastating problem, but improving access to ARVs is transforming the pediatric HIV epidemic in those countries, as it has in the United States. Numerous studies have shown that despite treatment initiation in children at more advanced stages of disease, response to ART in resource-limited settings is similar to results in the United States and Europe.[70] Nevertheless, many challenges remain, including the cost of treatment, limited infrastructure for medical care, nutritional deficiencies and food insecurity, and comorbid conditions, especially TB and malaria, that are rarely seen in HIV-infected children in the United States.

Transition of Care

The advent of effective ART has transformed perinatal HIV from a progressive, fatal infection into a chronic disease. In addition to the possibility of cardiovascular and other long-term complications, survivors of perinatal HIV infection confront the same challenges of adolescence and adulthood faced by peers without HIV infection. Rather than focusing just on survival and avoidance of opportunistic illnesses, counseling of HIV-infected adolescents and young adults must also focus on school success and career choices, reproductive health and plans for marriage and family, and the transition to adult medical care. Transition to adult medical care takes time and advance planning because the pediatric and adult chronic care models are different. Awareness of patient and provider factors that facilitate or enhance transition can inform programs for perinatally HIV-infected young adults to enroll successfully in adult medical care.[71] Routine advance care planning with HIV-infected youths and their families is as important as in any youth with chronic illness and has been shown to be well received and beneficial.

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PART III

Etiologic Agents of Infectious Diseases

OUTLINE

A Bacteria
B Viruses
C Fungi
D Human Parasites and Vectors

A

Bacteria

OUTLINE

114 Classification of Bacteria
Gram-Positive Cocci
Gram-Negative Cocci
Gram-Positive Bacilli
Enterobacteriaceae: Gram-Negative Bacilli
Nonenterobacteriaceae: Gram-Negative Bacilli
Gram-Negative Coccobacilli
Gram-Negative Coccobacilli
Anaerobic Bacteria
Mycoplasma
Diseases of Possible Infectious or Unknown Etiology

114

Classification of Bacteria

Joseph W. St. Geme III, Katherine A. Rempe

The ability to discriminate among distinct groups of organisms and to communicate with a common language about organisms in the context of disease is essential for clinical microbiologists and for physicians caring for patients. The official taxonomic ranks for naming bacterial organisms are kingdom, division, class, order, family, genus, and species. A bacterial *species* is defined as a distinct group of organisms that share a constellation of properties. This definition is somewhat subjective, and as new data become available, reclassification is necessary occasionally.

Identification by Phenotypic Characteristics

Historically, bacterial classification has been based on phenotypic characteristics. A useful first approach to classification was developed in 1884 by Christian Gram, who observed that some bacteria retain crystal violet dye after decoloration with ethanol and others do not; in this test, now called Gram staining, the former group of bacteria remain blue and are called *gram positive*, whereas the latter appear red and are called *gram negative*. These staining characteristics reflect differences in cell wall structure. As shown in Fig. 114.1, gram-positive cells have a relatively simple cell wall composed of an inner membrane and a surrounding peptidoglycan layer between 30 and 200 molecules thick. The gram-positive cell wall also contains teichoic acids and lipoteichoic acids, which are water-soluble polymers of polyol phosphates. Gram-negative organisms have a more complex cell wall characterized by the presence of an inner membrane, a surrounding peptidoglycan layer one to two molecules thick, and an outer membrane (see Fig. 114.1). The outer membrane contains lipopolysaccharide (endotoxin), which is unique to gram-negative organisms. The compartment between the inner and outer membranes, called the periplasm, contains a number of degradative enzymes and transport-related proteins.

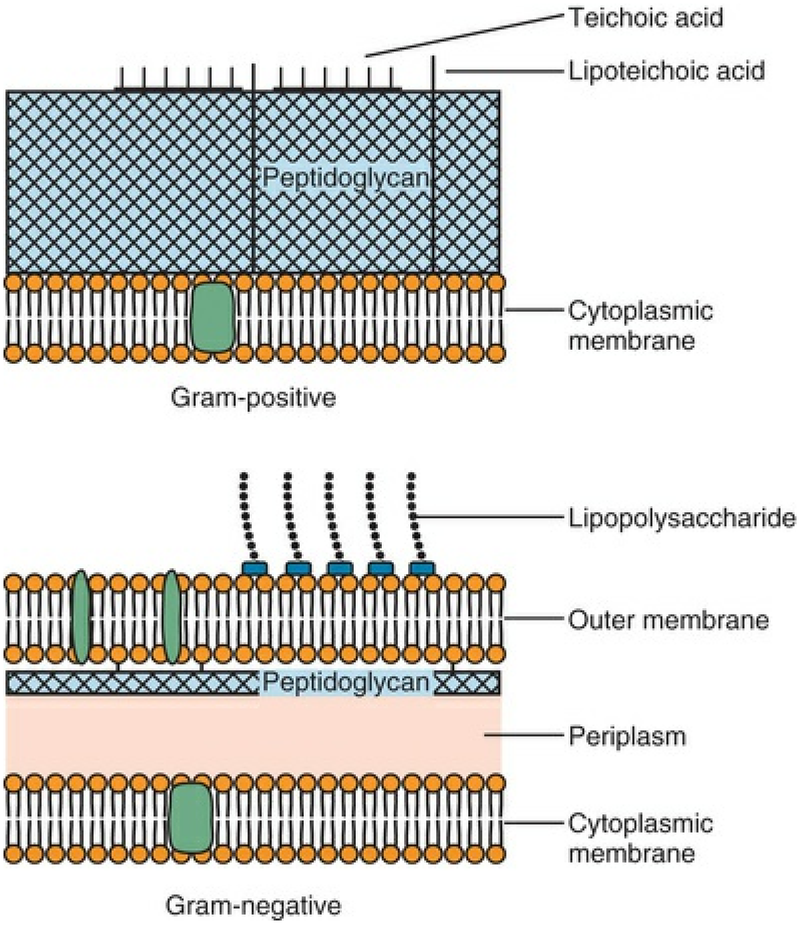

FIGURE 114.1 Schematic diagram of the cell wall structures of gram-positive and gram-negative bacteria.

Whereas most bacteria are gram-positive or gram-negative, some stain poorly or fail to stain at all with Gram reagents. Examples are mycobacteria, some actinomycetes, treponemes, rickettsiae, anaplasmae, chlamydiae, and mycoplasmas. Mycobacteria possess a complex cell wall that is rich in lipids; they have been referred to as *acid fast* because of their resistance to decolorization with acid solutions. These organisms are best visualized microscopically with Ziehl-Neelsen or Kinyoun acid-fast stain. Most actinomycetes are gram positive, but *Nocardia* and *Rhodococcus* characteristically take up Gram stain irregularly. They have a cell wall structure similar to that of mycobacteria, and, like the mycobacteria, they are acid fast.

The family Treponemataceae contains five genera, namely *Treponema, Borrelia, Leptospira, Brachyspira,* and *Spirillum.* The treponemes generally do not stain with Gram reagents or other standard laboratory stains and usually are best seen with darkfield microscopy. Members of the family Rickettsiaceae and the family Anaplasmataceae *(Ehrlichia, Anaplasma, Wolbachia,* and *Neorickettsia)* possess a cell wall typical of gram-negative bacilli but react weakly with Gram stain and are visualized optimally with Giemsa or Gimenez stain. Members of the family Chlamydiaceae *(Chlamydia trachomatis, Chlamydophila psittaci,* and *Chlamydophila pneumoniae)* are obligate intracellular organisms that possess inner and outer membranes similar to those of gram-negative bacteria but lack a peptidoglycan layer and do not take up Gram stain. The two important members of the family Mycoplasmataceae are *Mycoplasma* and *Ureaplasma.* Mycoplasmas do not have a cell wall; their cytoplasmic contents are enclosed only by a well-developed plasma membrane.

Cellular morphology also plays an important role in classification. Bacteria can be separated into five major groups on the basis of morphology as viewed through the light microscope. Bacteria that are spherical or oval in appearance are described as *cocci.* Those that are rod-like or cylindrical are referred to as *bacilli.* Those with a comma-like or curved rod appearance are referred to as *vibrios*. Bacteria with a helical or more undulating appearance are called *spirochetes* if they are flexible or *spirilla* if they are rigid.

After cell division, the cell wall between daughter cells in some species may not separate completely, giving rise to various cell arrangements. These cell arrangements are typically distinctive and may be helpful in identifying related organisms. Common arrangements are cocci in pairs, cocci in chains, cocci in irregular clusters, cocci in packets of four or eight (called *sarcina*), bacilli in pairs, bacilli in chains, unusually short bacilli (called *coccobacilli*), and bacilli with tapered ends (called *fusiform bacilli*).

A wide range of other phenotypic characteristics also are employed for the purpose of bacterial classification. For example, aerobic and facultative anaerobic organisms are distinguished from strictly anaerobic organisms, and spore-forming bacteria are distinguished from non–spore-forming species. Additional useful properties are carbohydrate fermentation ability, susceptibility to antibiotics and inorganic compounds, and reactivity with well-defined serologic reagents.

Identification by Molecular Techniques

Beyond phenotypic characteristics, molecular analysis also plays a major role in determining phylogenetic relationships among organisms and in classifying bacteria. The historical standard in this respect is DNA-DNA hybridization, which allows the total DNA from one organism to be compared with the total DNA of any other organism.[1] This technique involves incubating single-stranded DNA from one strain with single-stranded DNA from a second strain and assessing the formation of a double-stranded DNA molecule. DNA reassociation is a specific, temperature-dependent reaction. The optimal temperature for DNA reassociation is 25°C to 30°C below the temperature at which native double-stranded DNA is denatured into single strands. Experience with several hundred species has led taxonomists to conclude that organisms with 70% or greater DNA-DNA relatedness belong to the same species. Occasionally, the 70% species-relatedness rule has been ignored when the existing nomenclature is both deeply ingrained and useful. Examples include *Escherichia coli* and the four species of *Shigella*. These organisms all are more than 70% related and should therefore be grouped into a single species instead of the present five species in two genera. However, to avoid confusion among the medical community, no change has been made.

Mole percent guanine plus cytosine (G + C) content and genome size are two other measurements of DNA that often are helpful in classifying organisms.[2] The G + C content in bacterial DNA ranges from about 25% to about 75%. The G + C percentage is specific for a given species but is not unique to that species. Therefore, two strains with similar G + C contents may or may not belong to the same species. On the other hand, if the G + C contents are very different, the strains cannot be members of the same species. *Genome size,* or the molecular mass of bacterial DNA, ranges between 1×10^9 and 8×10^9 daltons. In certain circumstances, genome size determinations can distinguish between groups. Such determinations were used to distinguish *Legionella pneumophila* from *Bartonella quintana. L. pneumophila* has a genome size of 3×10^9 daltons, whereas the *B. quintana* genome is roughly 1×10^9 daltons.

In a number of cases, multilocus enzyme electrophoresis (MEE) has been applied to classify bacteria.[3] This method detects differences in the electrophoretic mobilities of individual soluble metabolic enzymes. The cellular proteins of an organism are separated by starch gel electrophoresis, and the individual enzymes are detected with the use of specific substrates. Variations in electrophoretic mobility of a given enzyme typically reflect amino acid substitutions that alter protein charge; these variations thus represent different alleles of the gene encoding the enzyme. In analyses of a relatively large number of enzymes, a positive correlation between estimates of relatedness obtained by MEE and by DNA hybridization of whole chromosomal DNA has been demonstrated. Therefore, it is possible to use MEE to determine the level of relatedness of two strains or a group of strains. This method has been particularly useful in yielding quantitative data about the relationships among organisms within a given species. In addition, it has provided insights into bacterial evolution.

Two additional methods are useful to determine genetic relatedness between strains and to characterize the population structure of a given species: pulsed-field gel electrophoresis (PFGE) and amplified fragment length polymorphism (AFLP) analysis.[4,5] PFGE has been the accepted gold standard for many species and involves extraction of chromosomal DNA and then digestion of the DNA with a rare-cutting restriction enzyme, giving rise to a number of large (80–100 kb) fragments, which can be separated by applying an electrical field alternatively in two directions. The critical experimental variable is the *pulse time,* which is defined as the time during which a field is applied in one direction before it is abruptly switched to another direction. Each strain gives rise to a reproducible pattern of bands (a fingerprint), and the number of bands shared between strains provides a measure of relatedness. AFLP analysis involves extraction of genomic DNA and then digestion of this DNA with two restriction enzymes. Subsequently, two different double-stranded oligonucleotide adapters are added to the digested DNA, one compatible with the first restriction enzyme and the other compatible with the second enzyme. After ligation, an aliquot of the DNA sample is subjected to polymerase chain reaction (PCR) amplification under highly stringent conditions with adapter-specific primers that have an extension of one to three bases at their 3-prime ends, running into the unknown chromosomal fragment. An extension of one base (e.g., adenine) in one primer results in amplification of one-fourth of the ligated fragments (e.g., those with a thymine but not those with adenine, guanine, or cytidine at the complementary position), whereas an extension of two or three bases results in amplification of a smaller fraction of fragments. After polyacrylamide gel electrophoresis, a highly informative pattern of 40 to 200 bands is obtained.

The molecular technique that has taken on greatest importance for classifying bacteria is 16S (small subunit) ribosomal RNA (rRNA) gene sequencing. The 16S rRNA folds in a precise fashion with the large subunit rRNA to form ribosomes. *Ribosomes* are highly conserved structures found in all living cells that perform the crucial task of protein synthesis. Because the genes for 16S rRNA contain some sequences that have been highly conserved through the course of evolution and others that are highly variable, 16S rRNA gene sequencing can be used to determine evolutionary and genetic relationships among organisms.[6] A further attribute of 16S rRNA gene sequencing is that cultivation of the organism is not required; for example, through the use of PCR and oligonucleotide primers that correspond to conserved regions of the bacterial 16S rRNA gene, a stretch of bacterial DNA can be amplified directly from diseased tissue or any other relevant source.[7] The variable regions of the resultant DNA sequence form the basis for specific phylogenetic analysis. In general, consensus primers can be designed for any discrete group of organisms with common ancestry. On the basis of 16S rRNA sequence comparisons, the evolutionary relationships among all known extant bacterial species can be represented in a phylogenetic tree (Fig. 114.2).[7]

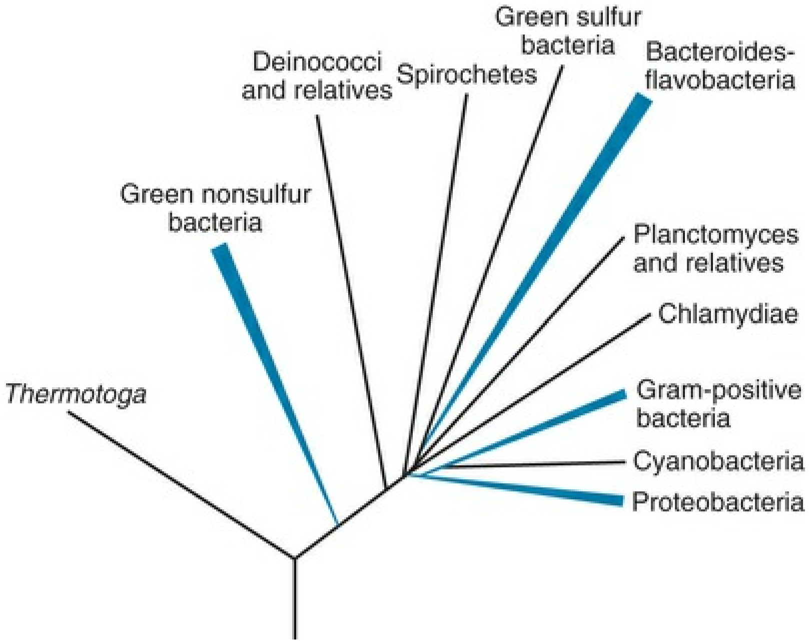

FIGURE 114.2 Phylogenic tree of the domain Bacteria based on comparison of 16S ribosomal RNA sequences. Divisions that contain human pathogens are denoted by boldface branches. (Redrawn from Relman DA. The identification of uncultured microbial pathogens. J Infect Dis 1993;168:1–8.)

Although 16S rRNA gene sequencing has clear strengths related to defining genetic relationships and classifying bacteria, use of this technique alone has limitations. For example, isolates that have divergent 16S rRNA gene sequences are consistently unrelated, but isolates that have almost identical 16S rRNA gene sequences may or may not belong to the same species, resulting in the need for another method to explore further whether isolates are sufficiently similar to be assigned to the same species. Consequently, multilocus sequence typing (MLST), which circumvents the potential effects of simple stochastic variation or recombination at a single locus, is becoming more common. MLST uses profiles of alleles at multiple (usually about seven) housekeeping gene sites to group isolates and determine relatedness between strains.[8,9] MLST has been especially useful in tracking the epidemiology of community-associated methicillin-resistant *Staphylococcus aureus* infections and the spread of virulent clones.[10,11]

Over the past decade, there has been a steady increase in the number of completely sequenced bacterial genomes, reflecting advances in sequencing technology. The availability of this information has led to the development of DNA microarrays and has allowed comparison of the whole genomes of individual isolates. Increasingly, whole genome information is used to assist with bacterial classification in general terms and in clinical settings.[12,13]

Beyond nucleic acid–based approaches to bacterial classification, whole-cell matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry has been demonstrated to be useful in classifying bacteria and comparing isolates for strain identity.[14,15] MALDI-TOF relies on the ionization of biomolecules, including whole proteins, and comparison of the resulting spectrum to a reference library. Identification by MALDI-TOF has the advantage of requiring significantly less time than other methods; samples can be analyzed directly from a colony on a plate with no special culturing needed.[16] However, the method is currently limited by the necessity of using proprietary rather than publicly available databases.[17]

Additional genetic and proteomic information continues to spur reclassifications.[18]

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Gram-Positive Cocci

OUTLINE

115 Staphylococcus aureus
116 Staphylococcus epidermidis and Other Coagulase-Negative Staphylococci
117 Classification of Streptococci
118 Streptococcus pyogenes (Group A Streptococcus)
119 Streptococcus agalactiae (Group B Streptococcus)
120 Enterococcus Species
121 Viridans Streptococci, Abiotrophia and Granulicatella Species, and Streptococcus bovis Group
122 Groups C and G Streptococci
123 Streptococcus pneumoniae
124 Other Gram-Positive, Catalase-Negative Cocci Leuconostoc and Pediococcus Species and Other Genera

115

Staphylococcus aureus

Robert S. Daum

Staphylococcus aureus is the most virulent species of the genus *Staphylococcus* and the most common pathogen isolated among pediatric patients in North America. The pathogenicity of *S. aureus* reflects its ability to acquire and integrate accessory genetic elements that confer virulence. *S. aureus* is responsible for community- and healthcare-associated infections and toxin-mediated diseases, and it is a major cause of mortality. The species also is adept at evolving strategies to elude antimicrobial therapy, leading to limited therapeutic options.

Microbiology and Pathogenesis

Staphylococci are aerobic or facultatively anaerobic gram-positive cocci that can persist in distressed environments, such as acidic conditions, high sodium concentrations, and wide temperature variations. Staphylococci can survive on fomites, in dust, or on clothing for at least several days. The defining characteristics of *S. aureus* are the production of the extracellular enzyme coagulase and protein A (Fig. 115.1). Clinical manifestations of *S. aureus* infection can result from tissue invasion, hematogenous dissemination, or toxin release, which incite inflammatory cascades and tissue necrosis. Isolation of *S. aureus* from skin and mucosal sites also may represent asymptomatic colonization because the organism can be a commensal flora.

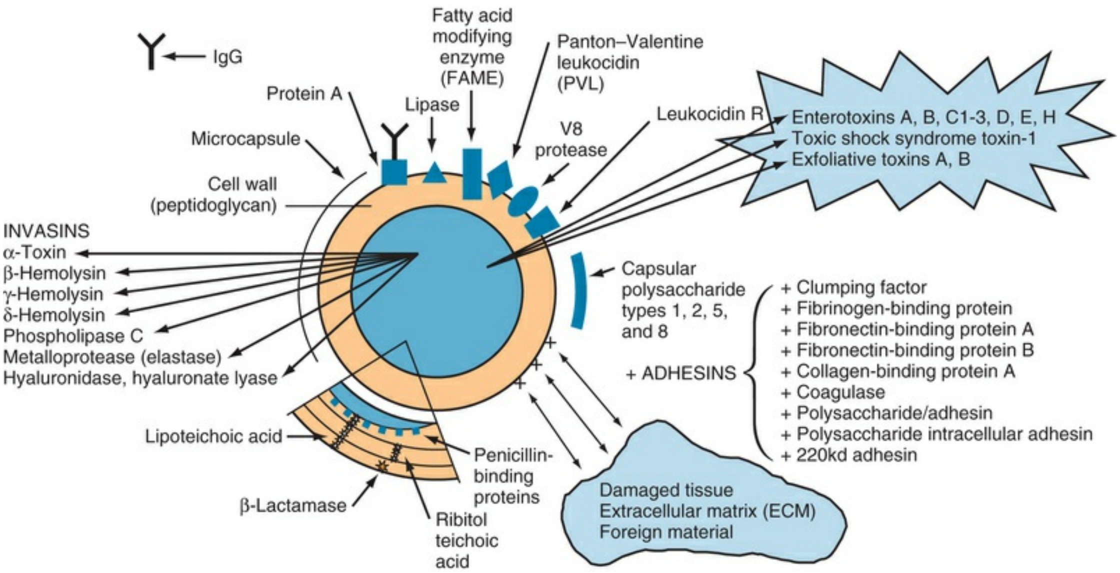

IgG
Protein A
Fatty acid modifying enzyme (FAME)
Lipase
Panton–Valentine leukocidin (PVL)
V8 protease
Leukocidin R
Microcapsule
Cell wall (peptidoglycan)
Enterotoxins A, B, C1-3, D, E, H
Toxic shock syndrome toxin-1
Exfoliative toxins A, B
INVASINS
α-Toxin
β-Hemolysin
γ-Hemolysin
δ-Hemolysin
Phospholipase C
Metalloprotease (elastase)
Hyaluronidase, hyaluronate lyase
Capsular polysaccharide types 1, 2, 5, and 8
+ ADHESINS
+ Clumping factor
+ Fibrinogen-binding protein
+ Fibronectin-binding protein A
+ Fibronectin-binding protein B
+ Collagen-binding protein A
+ Coagulase
+ Polysaccharide/adhesin
+ Polysaccharide intracellular adhesin
+ 220kd adhesin
Lipoteichoic acid
Penicillin-binding proteins
β-Lactamase
Ribitol teichoic acid
Damaged tissue
Extracellular matrix (ECM)
Foreign material

FIGURE 115.1 Virulence factors and relevant surface adhesins of *Staphylococcus aureus.* (Redrawn from Daum RS. *Staphylococcus aureus* vaccine. In: Plotkin SA, Orenstein WA (eds). Vaccines. 7th ed. Philadelphia, Saunders/Elsevier, 2016.)

Capsule and Cell Wall

Many clinical *S. aureus* isolates have a polysaccharide capsule; 11 capsular serotypes have been described, but most experts believe that probably only 4 exist.[1] The high prevalence of two of the capsular polysaccharide types (5 and 8) in almost all collections of clinically important human and veterinary isolates suggests an important but uncertain role in pathogenesis. Bloodstream infection (BSI) has also been caused by unencapsulated organisms; for example, the so-called type 336 isolates and USA300.[2,3] Immunization with the type 5 and 8 polysaccharide conjugated to *Pseudomonas* exotoxoid A was the basis for two recent immunization trials, neither of which met primary end points.[4–6]

The cell wall of *S. aureus* is composed of peptidoglycan, capsular polysaccharide when present, ribitol teichoic acid, lipoteichoic acid, and many surface proteins, including protein A, which binds to the Fc region of the immunoglobulin G (IgG) molecule.[7] Binding of IgG antibody to the staphylococcal cell surface in this nonphysiologic manner is ineffectual and decreases the efficiency with which *S. aureus* is opsonized and phagocytosed.[8–10]

Surface Proteins

Many proteins found on the surface of *S. aureus* isolates have been implicated in pathogenesis. Adherence of *S. aureus* to mammalian extracellular matrix components is mediated by a family of adhesins, the microbial surface components that recognize adhesive matrix molecules (MSCRAMMs).[11] Coagulase is found on the bacterial cell surface and in its environment. Coagulase binds to host prothrombin and forms staphylothrombin, an enzyme that catalyzes the formation of fibrin from fibrinogen.[12] The A and B clumping factors are cell surface proteins that bind to fibrinogen, producing the typical clusters of staphylococci when mixed with plasma.[13] Coagulase and the clumping factors breach host defenses by causing localized clotting; the clumping factors also may aid adherence to traumatized skin, endothelial structures, and foreign surfaces. Recognition of the role of *S. aureus* clumping factors has prompted investigation into their potential use as vaccine antigens.[14]

Iron is an essential component of cytochromes and other redox proteins. A cell wall–bound system of iron acquisition and importation has been identified in *S. aureus* and is under investigation to define an apparently essential role in pathogenesis.[15] However, a trial of an iron-scavenging protein, ISDB, was terminated prematurely for lack of demonstrable benefit.[16]

Toxins

The virulence of *S. aureus* is due to a combination of variously elaborated proteins, including extracellular products (e.g., the α, β, γ, and δ hemolysins [also called toxins]), leukocidins, proteases, lipase, deoxyribonuclease, a fatty acid–modifying enzyme, and hyaluronidase.[17–23] The most extensively studied of the exotoxins is α-hemolysin, which causes hemolysis of erythrocytes, necrosis of the skin, and the release of cytokines and eicosanoids that can produce shock. *S. aureus* is lethal when injected into animals. *S.*

aureus mutants lacking α-hemolysin generally are less virulent,[24] although pathogenic *S. aureus* isolates that do not produce α-hemolysin have been identified. *S. aureus* β-hemolysin is a sphingomyelinase that can injure lipid-rich membranes; however, most human isolates do not express β-hemolysin. The high prevalence of γ-leukocidin genes in isolates that cause necrotizing skin infections suggests the importance of this toxin in causing dermonecrosis. *S. aureus* has several leukocidins, which are synergohymenotropic toxins that damage membranes of certain cells as a result of the concerted action of two elaborated, secreted proteins. The Panton-Valentine leukocidin (PVL) is a pore-forming cytotoxin,[25] and its toxic effect is said to result from the synergistic action of the proteins lukS-PV and lukF-PV.[26] PVL has been associated with severe inflammatory lesions, presumably through the activation of granulocytes.[27] PVL-producing strains have been associated with severe skin infections and lung infections,[28] specifically necrotizing pneumonia.[29] The importance of PVL in the pathogenesis of *S. aureus* infections, a controversial topic because of variation in the susceptibility of host species, has been clarified in human infections.[30–32]

S. aureus causes a variety of so-called toxin-mediated diseases, including staphylococcal scalded skin syndrome (SSSS), toxic shock syndrome (TSS), and staphylococcal food poisoning; all of these are caused by the action of exotoxins and enterotoxins. Exfoliative toxins A (ETA) and B (ETB) cleave the glycoprotein desmoglein 1, promoting the spread of *S. aureus* under the stratum corneum[33,34] and resulting in blistering of the superficial epidermis, which is characteristic of SSSS and bullous impetigo (Fig. 115.2). Toxic shock syndrome toxin-1 (TSST-1) and staphylococcal enterotoxins B (SEB) and C (SEC) have been implicated in most cases of TSS. These toxins have superantigen activity; that is, they stimulate T lymphocytes nonspecifically, resulting in cytokine release and clinical toxic shock. At a skin or mucosal port of entry TSST-1 can interfere with the release of inflammatory mediators locally, which may account for a surprisingly benign appearance at the local infective site. An expanding family of enterotoxins has been implicated in staphylococcal food poisoning, but the most frequently implicated molecule is enterotoxin A (SEA).

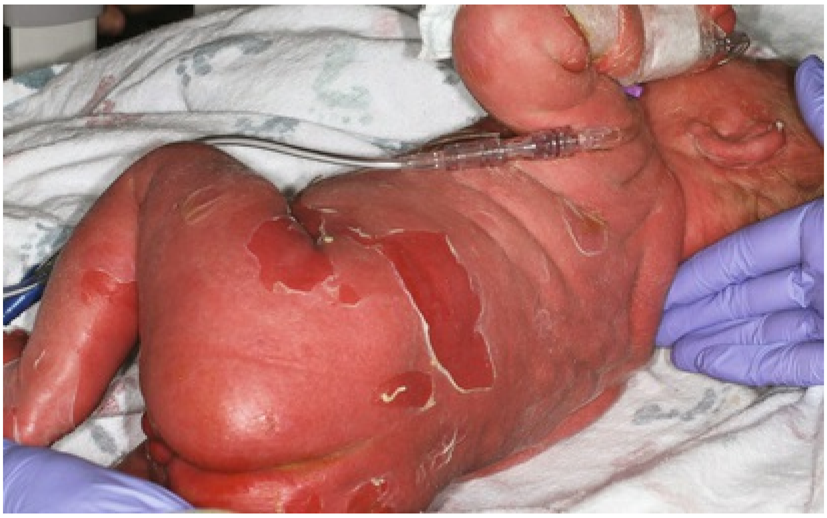


FIGURE 115.2 Staphylococcal scalded skin syndrome (Ritter disease) in an infant 1 week old. (Courtesy of J.H. Brien©.)

Genetic Basis and Regulation of Pathogenicity Factors and Antimicrobial Resistance

The whole genome of *S. aureus* has been sequenced many times. It has a circular chromosome of about 2.8 million base pairs.[35] Genes for many housekeeping functions are highly conserved. The genome also carries mobile genetic elements, such as plasmids, transposons, prophages, and pathogenicity islands, many of which encode virulence factors or determinants of antibiotic resistance. These factors represent a subset of a large class of accessory gene products (including surface proteins, exotoxins, and other enzymes) that provide one or more advantages in particular environments, although these accessory products are not required for growth and cell division.

S. aureus has evolved a remarkable network of regulatory mechanisms that control subsets of genes that are upregulated or downregulated under certain growth and environmental conditions. The most extensively studied is the *agr* locus with its two-component signal transduction system and its effector RNAIII molecule. The *agr* locus upregulates genes that encode capsular polysaccharides; α-δ toxins; two-component synergohymenotropic toxins; enterotoxins; exfoliatins; and proteases; it downregulates other genes, such as those that encode MSCRAMMs, other adhesins, and protein A. Other two-component signal transduction systems implicated in pathogenesis are *saeRS, srrAB, arlSR,* and *lytRS.* Protein systems that bind deoxyribonucleic acid (DNA), such as *sarA* and its regulatory homologues, also regulate virulence factors. Additionally, the σ-factor, σ^B, can combine with the ribonucleic acid (RNA) polymerase core enzyme to form a holoenzyme that can recognize promoter elements for at least 36 *S. aureus* genes involved in bacterial stress responses. Taken together, membrane sensing systems (e.g., *agr*) and DNA-binding regulatory systems afford *S. aureus* a versatile environmental response system and confer the capacity to respond to a myriad of environmental stimuli, such as high or low sodium chloride concentrations, subinhibitory concentrations of protein synthesis inhibitors, a low pH, or a condition in which essential nutrients (e.g., amino acids) are limited.

S. aureus can overcome environmental antibiotic pressure through the acquisition and transmission of resistance genes from other, usually less pathogenic, species and isolates of the same species. Resistance to β-lactam antibiotics (e.g., penicillins, cephalosporins, and carbapenems) is one example. The β-lactam antibiotics bind to *S. aureus* penicillin-binding proteins (PBPs), thereby inhibiting cell wall synthesis.

Resistance to penicillin was documented almost immediately after the medication's introduction into clinical practice in the 1940s. It is mediated by the elaboration of a β-lactamase, which is encoded by a transposon borne on a plasmid. Almost all clinical isolates of *S. aureus* can elaborate this enzyme, rendering antibiotics susceptible to β-lactamase hydrolysis clinically ineffective.

The development of β-lactamase–resistant semisynthetic penicillins temporarily overcame this widely prevalent clinical problem. However, some strains became resistant to semisynthetic compounds by acquiring *mecA,* a gene that elaborates PBP2a, a peptidoglycan-synthesizing enzyme that has decreased affinity for β-lactam antibiotics.[36,37] These resistant strains are called methicillin-resistant *Staphylococcus aureus* (MRSA) and are responsible for nosocomial outbreaks and for the current community-based MRSA epidemic. MRSA strains are resistant to all β-lactams except ceftaroline.

The *mecA* resistance gene is located on a mobile genetic element called the staphylococcal chromosome cassette *mec* (SCC*mec*),[38] which is present in all MRSA isolates, with occasional exceptions. SCC*mec* contains a *mec* complex, comprised of *mecA* and its variably present *mec1* and *mecR1* regulatory genes, and a *ccr* complex, comprised of genes that mediate insertion and excision of SCC*mec* from the genome. Insertion of SCC*mec* into the *S. aureus* genome is the genetic event that converts a methicillin-susceptible strain into a methicillin-resistant one. Currently 11 SCC*mec* elements have been sequenced or partially characterized. In the United States, mobile elements SCC*mec* types I to III generally are found in healthcare-associated MRSA (HA-MRSA) isolates, and SCC*mec* types IV and V generally are found in community-associated MRSA (CA-MRSA) isolates, although these distinctions are blurring.[39]

Although the mechanism of the movement of SCC*mec* elements from strain to strain is unknown, the large size of types I to III is believed to limit easy transfer of the elements. Types IV and V, however, are small and mobile. Types IV and V have been found in multiple *S. aureus* genetic backgrounds, which supports the hypothesis that they are readily transferred from strain to strain.[40–42] To date, types VI through XI have been identified in only a limited number of strains.

Epidemiology

Colonization

Humans and other mammals are the natural reservoirs for *S. aureus*. Asymptomatic colonization is frequent in humans, and traditionally the anterior nares were thought to be a predominant site. However, the skin, nails, pharynx, axillae, perineum, throat, rectum, and vagina are common sites of colonization. Colonization rates range from 25% to 50%; higher rates are found in children, in people with dermatologic conditions (e.g., eczema), in those who perform needle injections frequently (e.g., intravenous drug abusers), in those with indwelling intravascular devices (e.g., patients receiving dialysis), and in healthcare personnel (HCP). Even higher rates have been documented with the use of highly sensitive detection methods, leading some to speculate that colonization may be universal.[43] Although it has been held that most people are colonized intermittently (and fewer are persistently or rarely colonized[44]), scant explicit data are available. Traditionally, nasal *S. aureus* carriage has been a risk factor for developing an infection,[45–47] although most colonized individuals do not do so. CA-MRSA colonization affects more body sites, which correlates with an increased risk of infection.

Healthcare-Associated Infections

S. aureus can develop resistance to all classes of antimicrobial agents. The first MRSA strain was reported less than a year after the introduction of semisynthetic penicillins in the early 1960s, even though these penicillins were active against β-lactamase–producing, so-called methicillin-susceptible *S. aureus* (MSSA). Multidrug-resistant HA-MRSA strains spread worldwide in hospital settings. The National Healthcare Safety Network (NHSN) (formerly the National Nosocomial Infections Surveillance System), an agency of the Centers for Disease Control and Prevention (CDC), has reported *S. aureus* as a major pathogen of HAIs. In 2003 MRSA accounted for 64% of nosocomial *S. aureus* isolates in intensive care units (ICUs) in U.S. hospitals, an increase from 36% in 1992.[48] From January, 2006, to October, 2007, *S. aureus* was the second most common cause of HAIs, exceeded only by coagulase-negative staphylococci (CoNS).[49]

In pediatric ICUs in the U.S., *S. aureus* is the major nosocomial pathogen in a variety of clinical situations; it accounts for 9% of HA bloodstream infections (HA-BSIs), 17% of cases of HA pneumonia, and 20% of surgical site infections.[50] Current patterns of HA-MRSA isolates reveal decreasing rates of isolation[51] and decreasing resistance to non–β-lactam antibiotics; this suggests a shift in nosocomial MRSA epidemiology, probably reflecting the movement of “biologically fit” CA-MRSA isolates into the hospital.[40,52]

In recent years MSSA has become a healthcare-associated pathogen, predominantly over MRSA in some settings, but more frequently associated with BSI and the requirement for intensive care.

Community-Associated MRSA Infections

Prevalent MRSA infection outside the healthcare setting was first reported in 1982 in Detroit, Michigan, among intravenous (IV) drug users.[53] This and subsequent reports of CA-MRSA were associated with risk factors for infection similar to those for HA-MRSA, including IV drug administration, recent hospitalization or surgery, presence of indwelling catheters or devices, dialysis, or residence in a longterm care facility.[54–57] In the late 1990s CA-MRSA infections emerged; these infections occurred mostly in children with no identifiable predisposing MRSA risk factors,[58–62] and they commonly resulted in skin and soft tissue infections (SSTIs). Some serious infections required hospitalization or were fatal.[63] The number and geographic distribution of CA-MRSA infections grew substantially. Strong evidence supports the de novo rise of MRSA in the community, rather than movement of HA-MRSA into the community.[64,65]

A CA-MRSA infection can be defined as one that occurs in an outpatient or that develops within 72 hours of admission to the hospital in a patient without any of the factors used to define risk for HA-MRSA: recent hospitalization or surgery, prolonged antibiotic therapy, underlying chronic disease, indwelling catheter or other device, healthcare contact, or residence in a longterm facility.[66] Molecular definitions also have been used to distinguish HA-MRSA from CA-MRSA strains.[67] Outbreaks of CA-MRSA infections have been reported in group childcare settings,[57,68] sports teams,[69,70] correctional facilities,[71,72] and military units,[73,74] which suggests that close contact and suboptimal hygiene practices play a role in the spread of infection.

CA-MRSA isolates also can be distinguished from HA-MRSA by their lack of multidrug resistance. Most CA-MRSA isolates are susceptible to clindamycin, trimethoprim-sulfamethoxazole (TMP-SMX), and doxycycline, whereas HA-MRSA isolates usually are resistant to these agents. Multilocus sequence typing, SCC*mec* typing, and pulsed-field gel electrophoresis have elucidated important differences between HA-MRSA and CA-MRSA isolates. In the U.S., HA-MRSA usually contain SCC*mec* type II and genes that mediate resistance to several non–β-lactam antibiotics. In contrast, CA-MRSA isolates usually contain SCC*mec* type IV or type

V and lack non–β-lactam antibiotic resistance genes.[59] Even among CA-MRSA isolates, however, determinants of non–β-lactam agent resistance can be found elsewhere in the cell, such as on plasmids or in the chromosome. For example, erythromycin resistance is common among both HA-MRSA and CA-MRSA strains and can be mediated by a variety of phenotypic and genetic mechanisms. When the *erm* gene that commonly mediates erythromycin resistance is present, the constitutive or inducible MLS_B phenotype (discussed later in the chapter) is conferred.[75,76]

Another difference between CA-MRSA and HA-MRSA isolates is their repertoire of toxin genes.[77] The most striking examples are the *lukS-PV* and *lukF-PV* genes that encode for PVL and are transferred from strain to strain by an as yet unknown mechanism.[78] These toxin genes have been associated with MSSA and MRSA strains that cause SSTIs, necrotizing pneumonia, and empyema.[79–81] More severe infections, such as severe sepsis, thrombosis, and thromboembolism, also are caused by isolates containing the PVL genes.[30] Interestingly, although SCC*mec* IV or SCC*mec* V and PVL together seem to confer a selective advantage for spread (i.e., transmission and colonization) and pathogenicity (i.e., excess rate of infection per colonized individual), the genes encoding PVL are transferred separately from the SCC*mec* element. Most circulating CA-MRSA organisms in the U.S. belong to a genetic lineage called USA 300 (from a nomenclature scheme based on pulsed-field gel electrophoretic pattern). These organisms contain an island of foreign DNA called the arginine catabolic mobile element (ACME)–encoded *arc* cluster. The role of ACME is the subject of controversy, but it is believed to confer an improved survival advantage on skin and spermidine susceptibility.[82–84]

Vancomycin-Intermediate *S. aureus* and Vancomycin-Resistant *S. aureus* Infections

S. aureus isolates with decreased susceptibility to vancomycin also emerged in the late 1990s. These vancomycin-intermediate *S. aureus* (VISA) strains, defined as having a minimal inhibitory concentration (MIC) of vancomycin greater than 2 μg/mL, typically have been isolated from patients with underlying medical conditions in whom vancomycin therapy has failed[85,86]; these strains usually also are resistant to teicoplanin (a glycopeptide not licensed in the U.S.). Therefore, the term glycopeptide-intermediately susceptible *S. aureus* (GISA) may be more appropriate. In 2002 the first high-level vancomycin-resistant *S. aureus* (VRSA) strain was reported (MIC of vancomycin >16 μg/mL); this isolate apparently acquired the *vanA* vancomycin resistance genes from *Enterococcus* organisms. To date, 13 VRSA isolates have been reported in the U.S., and all strains evaluated have carried the *vanA* gene.[87–89]

Clinical Manifestations

Skin and Soft Tissue Infections

Impetigo

S. aureus is a major cause of several infections of the skin and its appendages. The most superficial is impetigo, which begins as a small, tender, erythematous papule. Often the integument has been interrupted, such as by an insect bite, a varicella vesicle, eczema, or a minor abrasion from trauma. Bullous impetigo is a specific *S. aureus* infection in which transparent bullae rupture easily, exposing a moist base surrounded by a thin rim of scale (Fig. 115.3). Bullous impetigo is mediated by the production of ETA and ETB.[90,91]

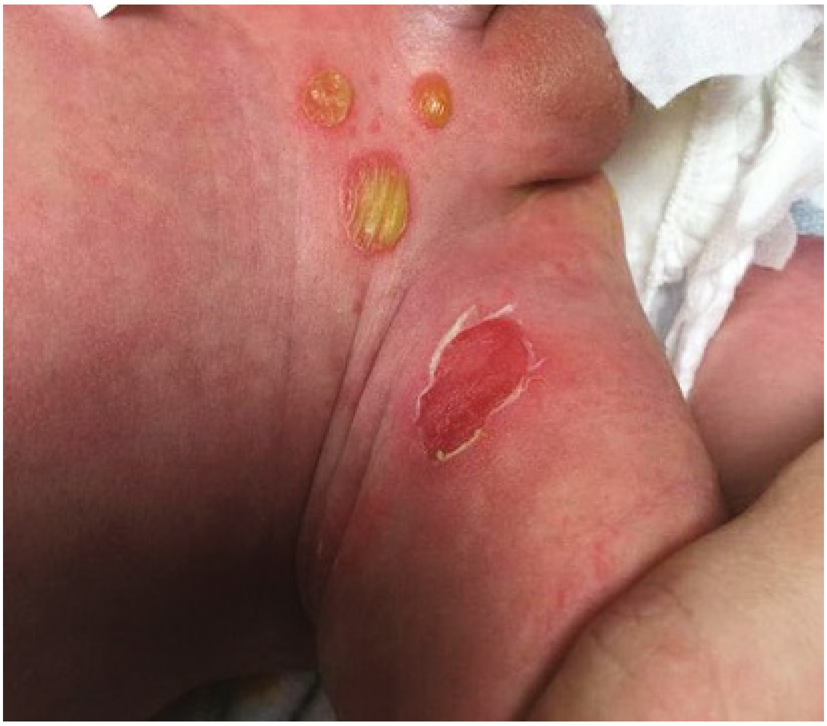


FIGURE 115.3 Bullous impetigo in a neonate. (Courtesy of J.H. Brien©.)

Several studies have demonstrated the superiority of topical or systemic antibiotics over simple cleansing for the treatment of impetigo. For uncomplicated singular sites of impetigo in children outside the neonatal period, topical mupirocin can be appropriate. Mupirocin ointment should be applied 3 times daily for 7 to 10 days. Retapamulin recently was licensed for topical therapy for children 9 months of age or older who have impetigo caused by *Streptococcus pyogenes* or MSSA (but not MRSA).[92] This drug's place in the therapeutic armamentarium has yet to be determined. Many experts prefer systemic antimicrobial therapy for the treatment of bullous impetigo.[93]

Oral or parenteral antimicrobial therapy should be considered if the impetigo is widespread. Because of the high prevalence of MRSA, a culture should be performed before the initiation of systemic therapy in most patients. Neonates with minor bullous impetigo (frequently near the umbilicus) who are afebrile and well sometimes can be managed with oral empiric systemic antimicrobial therapy with an agent active against MRSA.

Abscess

S. aureus commonly causes superficial abscesses of the skin. Moist and hairy skin is particularly susceptible to furuncles, boils, folliculitis, and hidradenitis. When the lesion is associated with a hair shaft, the term furuncle is often used (see Fig. 68.6). Rupture yields a purulent discharge. A carbuncle is a larger lesion formed by the coalescence of furuncles. With most small skin abscesses the symptoms pain and erythema are local, although fever can be present. Systemic signs can accompany larger lesions. In the neonate a skin abscess or boil can progress rapidly to BSI and clinical sepsis.

S. aureus is the leading cause of breast abscess in infants, which commonly occurs within the first 3 weeks of life, when the breasts are enlarged physiologically (Fig. 115.4) The abscess usually is unilateral and accompanied by erythema and induration. Occasionally fever, leukocytosis, or BSI can occur. Isolation of the pathogen from the abscess's discharge aids management.[94]

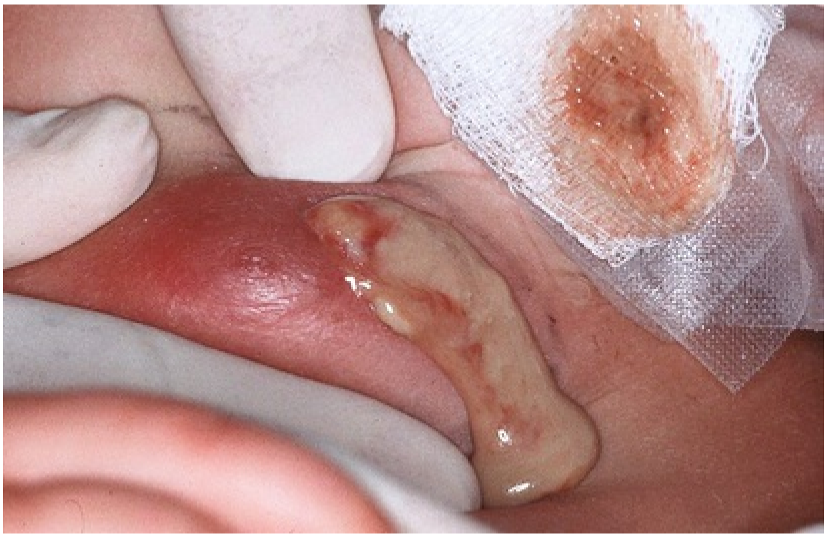


FIGURE 115.4 Abscess and cellulitis due to community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA). (Courtesy of J. H. Brien©.)

Local cleansing and incision and drainage are essential components of the management of abscesses.[95,96] Sometimes small abscesses (<5 cm) can be treated without systemic antimicrobial therapy[95]; however, in a randomized, placebo-controlled trial, TMP-SMX had a higher clinical cure rate.[97] Neonates with skin abscesses and infants with a breast abscess should be treated. Systemic antibiotic treatment also is required for any patient with severe or extensive disease, rapid progression of associated cellulitis, systemic illness, associated comorbidity or immunosuppression, abscess in an area difficult to drain (e.g., face, genitalia, hand), or associated phlebitis.[98]

Any abscess can heal with scarring. Some patients may suffer from recurrent furunculosis, which can be difficult to manage. Systemic and topical antimicrobial agents, along with careful hand and nail hygiene, may help reduce recurrences.

Recurring MRSA SSTIs are common and pose a management challenge. Underlying skin conditions (e.g., eczema, diaper dermatitis) should be managed aggressively. Attempts to decolonize a patient with nasal mupirocin or applications of an antiseptic (e.g., chlorhexidine) often are unsuccessful; in addition, the right time to attempt such decolonization is unclear. Consideration of congenital or acquired immunodeficiency may be warranted in patients with recurrent disease, especially if the response to therapy is slow or healing occurs with remarkable scarring.[99]

Cellulitis

Cellulitis is an infection of the subcutaneous tissues and the dermis that manifests as an area of erythema, warmth, edema, and tenderness. *S. aureus* is a major cause of the infection in all age groups and at all clinical sites. If systemic signs are present, a blood culture should be performed before antimicrobial therapy is started. When present, purulent material should be cultured. Culturing an aspirate or biopsy specimen from a patient with nonpurulent cellulitis can yield the infecting bacterium.[100]

Treatment involves oral or parenteral antimicrobial therapy, depending on the extent of disease and whether systemic signs or toxicity is present.

Wound Infection

The likelihood of a postoperative or posttraumatic wound infection increases with the use of sutures, especially in poorly vascularized tissues. Measures that often can prevent infections include frequent dressing changes, meticulous daily wound care, and strict handwashing. *S. aureus* wound infections generally are recognized within a few days after trauma or surgery; inflammation is a local sign, and constitutional signs of illness may be present. The exudate often is cloudy, hemorrhagic, and notably odorless. Extension of a wound infection into deeper tissues can occur, resulting in cellulitis, lymphadenitis, lymphangitis, or necrotizing fasciitis. Bursitis usually is the complication of a contiguous skin infection, frequently with trauma, and must be differentiated from pyogenic arthritis.

Treatment of a wound infection includes exploration of the wound, drainage, removal of any foreign material, and optimization of skin hygiene. Topical or systemic antimicrobial therapy may be a useful adjunct for mild infections. Parenteral antimicrobial therapy should be considered for clinically serious or extensive infections and for wound infections on the head and neck.

Ocular Infections

S. aureus is an important cause of purulent conjunctivitis. The causative organism can be visualized by Gram stain or isolated from purulent discharge. Conjunctivitis usually resolves without treatment, although topical ophthalmic antimicrobial agents frequently are used. *S. aureus* is the most frequently recognized cause of a stye or a hordeolum, an infection of the sebaceous gland or the eyelash follicle, respectively. Use of a topical antimicrobial agent may prevent the spread of infection to adjacent hair follicles, but frequent application of warm compresses usually suffices for treatment.[101]

Preseptal (periorbital) cellulitis can result from extension of sinusitis or from autoinoculation of skin flora after a break in the skin due to local trauma, an insect bite, an abscess, or impetigo.[102] (Fig. 115.5). *S. aureus* is the leading cause of skin lesion–related preseptal cellulitis. Because of the elasticity and thinness of the skin in and around the eyelid, the clinical presentation can be dramatic, with a rapid onset of lid swelling, erythema, and tenderness.[103] Low-grade fever and leukocytosis can be present, although typically the child does not appear systemically ill. Visual acuity is not affected, and movement of the globe is not painful or limited. Treatment of preseptal cellulitis usually is initiated parenterally; oral therapy can be substituted after a clinical response has been demonstrated.

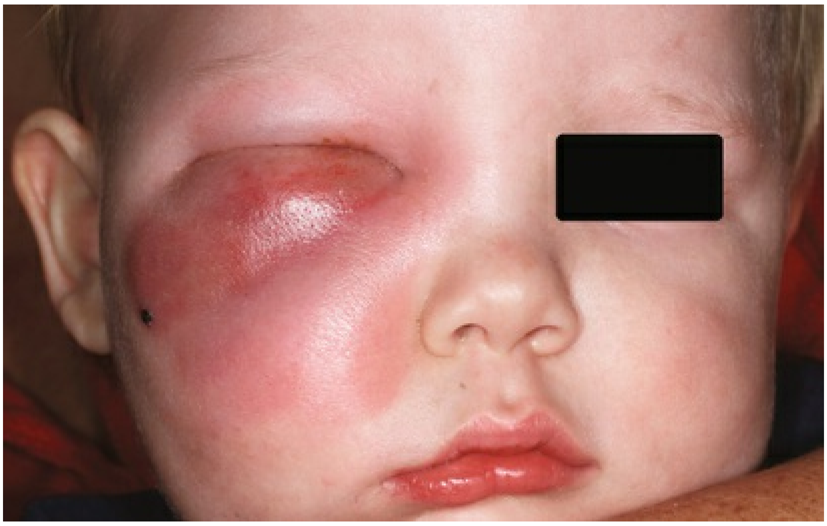


FIGURE 115.5 Preseptal cellulitis due to MRSA infection after minor trauma. (Courtesy of J.H. Brien©.)

S. aureus is presumed to be the leading cause of orbital (postseptal) cellulitis after surgical or accidental trauma to the orbit, and it can be responsible for orbital cellulitis that complicates sinusitis.[104] Patients or parents note a red, swollen "eye"; the physical examination reveals one or more of the following: decreased or painful movement of the globe, impaired visual acuity, chemosis, or proptosis.[103] Complicating cavernous sinus thrombosis should be suspected if the patient has abnormal neurologic findings.[105] Treatment requires confirmation of the pathogen and antimicrobial susceptibility. CT helps distinguish between orbital phlegmon, subperiosteal abscess, and orbital abscess; staphylococci are more often associated with abscesses. These diagnoses mandate assessment for surgical drainage in addition to IV antibiotics.[106] An extended course of antimicrobial therapy is given parenterally.

S. aureus endophthalmitis is an uncommon infection in children and usually follows ocular surgery or penetrating trauma to the globe.[107] Symptoms include blurred vision, redness, pain, lid swelling, and the presence of a hypopyon. Systemic signs or fever and lethargy often are present. Treatment includes antibiotics, both given parenterally and instilled directly into the vitreal cavity, and vitrectomy. Visual outcomes are poor.[108]

Invasive Infections

Osteomyelitis

S. aureus is the major cause of hematogenous osteomyelitis, accounting for up to 90% of cases. The metaphyses of long, tubular bones are affected most frequently, although infection can occur in any bone.[109–112] Previous minor trauma may predispose a person to infection, probably as the result of subclinical minor vascular injury or because a small area of bony necrosis acts as a nidus for seeding during what otherwise would have been asymptomatic bacteremia.[113] The classic clinical picture includes fever and point tenderness over the affected area of bone (usually at the metaphysis), decreased range of motion, and minor local signs of inflammation. Infants and toddlers can manifest only irritability, limp, or refusal to bear weight. Diagnosis requires a high degree of suspicion. Symptoms usually are present 1 week or less before they come to medical attention, but occasionally they are present for several weeks before recognition.[114]

Evaluation should include a blood culture because BSI is detectable in about 50% of patients.[115] At the time of clinical presentation the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level usually are elevated, although normal values can be seen, particularly among neonates or patients with sickle cell disease, distal digital infection, or subacute cases (e.g., Brodie abscess). Other acute phase reactants (e.g., leukocyte count) may be normal.[116] A radiograph of the affected bone is likely to have a normal appearance in the first days after the onset of symptoms, or it may show only deep soft tissue swelling adjacent to the bony metaphysis; periosteal elevation or lucencies within the bone typically are not apparent until 10 to 21 days after the onset of infection. A technetium-99 methylene phosphonate scan, performed in three phases, identifies increases in regional perfusion and tracer uptake by inflamed bone. Scintigraphy is especially useful for detecting multifocal infection. Although scintigraphy is sensitive, the results can be normal in neonates and patients with sickle cell disease with osteomyelitis. MRI is the most accurate diagnostic test, and it also can identify critical fascial and deep muscle phlegmon and abscess.[117]

Establishing the causative organism by needle aspiration or biopsy of the bone is important, especially if blood cultures are negative. Surgical intervention beyond a diagnostic needle aspiration usually is not required for simple acute osteomyelitis, but it can be indicated urgently if extensive subperiosteal or soft tissue infection or ischemic compartment syndrome is present, and it must be repeated frequently. Surgery often is required for chronic infection to remove sequestra and to debride affected bone.

IV antibiotics should be initiated and subsequently modified according to microbiology test results. Most experts recommend a course of antimicrobial therapy extending up to 4 weeks or longer for *S. aureus* osteomyelitis, with parenteral therapy used initially. Deep vein thrombosis adjacent to the bony site of infection and septic thromboembolism increasingly have become recognized as complications of *S. aureus* osteomyelitis, especially when they are caused by CA-MRSA or PVL-positive MSSA. These conditions usually develop in the proximal long bones and vertebrae.[118] The total duration of the therapy and the transition to oral therapy is individualized, depending on the extent of infection, susceptibility test results, the clinical setting and course.[114,119,120] One study has shown that a total course of therapy of 3 weeks to be noninferior,[120] and another study has shown that early transition to oral therapy also is effective, even when CA-MRSA is the cause.[121]

Techniques for monitoring the therapeutic response vary, and few explicit data are available. Most experts use a rapid fall in the CRP level as evidence of an appropriate antibiotic choice, and an eventual fall in the ESR as a guide to an adequate duration of therapy. In general, serial imaging of the infected bone does not provide useful information about the duration of therapy.

S. aureus can cause osteomyelitis secondary to an adjacent deep soft tissue focus; by concurrent direct inoculation; or by contiguous spread, such as through an accidental puncture wound of the foot or the patella, a bite, trauma, an infected paronychia, or a surgical procedure.[122] Osteomyelitis that develops after a puncture wound frequently is called osteochondritis, partly to remind clinicians of the clinical and pathophysiologic features that distinguish it from hematogenous osteomyelitis. Symptoms and signs of acute hematogenous osteomyelitis usually are absent, although many patients have localized pain, fever, and erythema. The blood typically is sterile, and the CRP level can be minimally increased or normal. Surgical debridement is an important component of the therapeutic strategy in nonhematogenous osteomyelitis/osteochondritis syndromes; antimicrobial therapy is adjunctive. The optimal duration of antimicrobial therapy for osteochondritis is unclear, but it frequently can be short (e.g., 7 to 14 days) after adequate surgical debridement in selected cases.[114]

Diskitis

Diskitis, or inflammation of an intervertebral disk, is uncommon and occurs primarily in children younger than 5 years of age. Diskitis may be difficult to distinguish from vertebral osteomyelitis, and the two entities probably have a similar pathogenesis (see chapters 76 and 78). Children with diskitis usually are not febrile or ill, but they refuse to walk, limp or, in older children, have back pain. MRI helps distinguish diskitis from vertebral osteomyelitis. *S. aureus* is the most frequently identified organism in both entities, although specimens are collected more frequently and are positive more frequently in patients with vertebral osteomyelitis. Diskitis may resolve spontaneously without antimicrobial therapy; vertebral osteomyelitis does not.

Diskitis without adjacent vertebral involvement sometimes can be managed with observation alone. If the adjacent vertebrae are involved, vertebral osteomyelitis cannot be excluded, and these patients should receive a course of antimicrobial therapy appropriate for osteomyelitis. Follow-up imaging studies are appropriate in this circumstance.[123]

Pyogenic Arthritis

Hematogenous seeding of the synovium during *S. aureus* BSI is the most common pathogenesis of infectious arthritis in children. Pyogenic arthritis usually is heralded by warmth, tenderness, erythema, and limited range of motion of the involved joint. Manifestations of a hip infection can be more subtle because of the depth of tissue surrounding the joint. In infants a subtle increase in resistance to movement or pain with movement may be the only clue. An imaging study (e.g., ultrasonography) is valuable.[124] Infants with osteomyelitis of the femur or humerus especially are prone to pyogenic arthritis of the contiguous joint due to the vascular and capsular anatomy in this region at this age[125] (see Fig. 76.4).

If pyogenic arthritis is suspected, blood culture and aspiration of joint fluid are performed urgently; the hip usually is drained surgically. The fluid is evaluated by Gram stain and culture, total and differential cell counts, and glucose and protein levels. In occasional cases of *S. aureus* arthritis, bacteria visualized on Gram stain are not isolated in culture because of the bacteriostatic nature of synovial fluid or previous antimicrobial therapy.

Treatment consists of surgical drainage and antimicrobial therapy. Antimicrobial therapy should be initiated when clinical suspicion is high and is continued for at least 3 weeks. Multiple aspiration procedures may be necessary. Open surgical drainage is used when serial aspiration does not produce a rapid response; as initial management when the hip or shoulder joint is affected; or when establishing effective drainage by simple aspiration is technically difficult and the risk of longterm complications is high.[114] A poor outcome is associated with delay of appropriate management and concomitant osteomyelitis.[126]

Abscesses of Muscle and Viscera

S. aureus is the most common cause of pyomyositis (including iliopsoas and obturator internus abscess) and liver abscess, and it is an important cause of renal, perinephric, splenic, and pancreatic abscesses. These are all complications of BSI, which may have been asymptomatic; the patient may come to medical attention because of symptoms related to the focal infection or for fever of unknown origin (FUO) or associated with severe sepsis. Necrotizing fasciitis, especially due to CA-MRSA, usually occurs as a complication of skin infection but also can occur after seeding of a deep site during BSI (see Fig. 75.2). Pyomyositis usually manifests with fever and an insidious or acute onset of cramping muscle pain, tenderness and, especially, induration of a large muscle group, such as those near the buttock, thigh, or hip. An obturator internus abscess can cause a painful limp, pelvic girdle pain, or refusal to walk. An iliopsoas abscess can cause predominantly flank pain and tenderness. A visceral abscess and nephric abscesses are most likely to manifest as FUO, possibly accompanied by nonspecific abdominal or flank symptoms. A blood culture is positive in fewer than one half of cases that present because of FUO or localized complaints.

CT or MRI is highly likely to identify abnormalities. Management usually entails surgical decompression, debridement and drainage, and prolonged parenteral antibiotic therapy. Multiple, small visceral abscesses frequently can be treated with antibiotic therapy alone if the pathogen is identified and susceptibility test results are available. Necrotizing fasciitis is a surgical emergency and requires decompression and debridement of the involved tissue and antimicrobial therapy.

Upper Respiratory Tract Infections

Head and Neck Infections

S. aureus is an infrequent cause of acute otitis media or sinusitis, but it should be considered in a child who fails multiple courses of empiric, oral antimicrobial therapy and in chronic or complicated disease. Both MSSA and MRSA increasingly have been isolated in cases of otorrhea that develops after tympanostomy tube insertion, and as complications of paranasal sinusitis.[104,127,128]

S. aureus is the leading cause of nasolacrimal duct abscess, suppurative parotitis, abscess of a lymph node below the angle of the jaw in very young infants (Fig. 115.6), and retropharyngeal abscess in children younger than 3 years of age (see Fig. 28.1). Infection occurs presumably after nasopharyngeal or oropharyngeal colonization, sometimes in association with a viral infection. In older children and adolescents *S. aureus* is the leading cause of peritonsillar and parapharyngeal abscess associated with recurrent pharyngeal infections and suppurative cervical lymphadenitis.

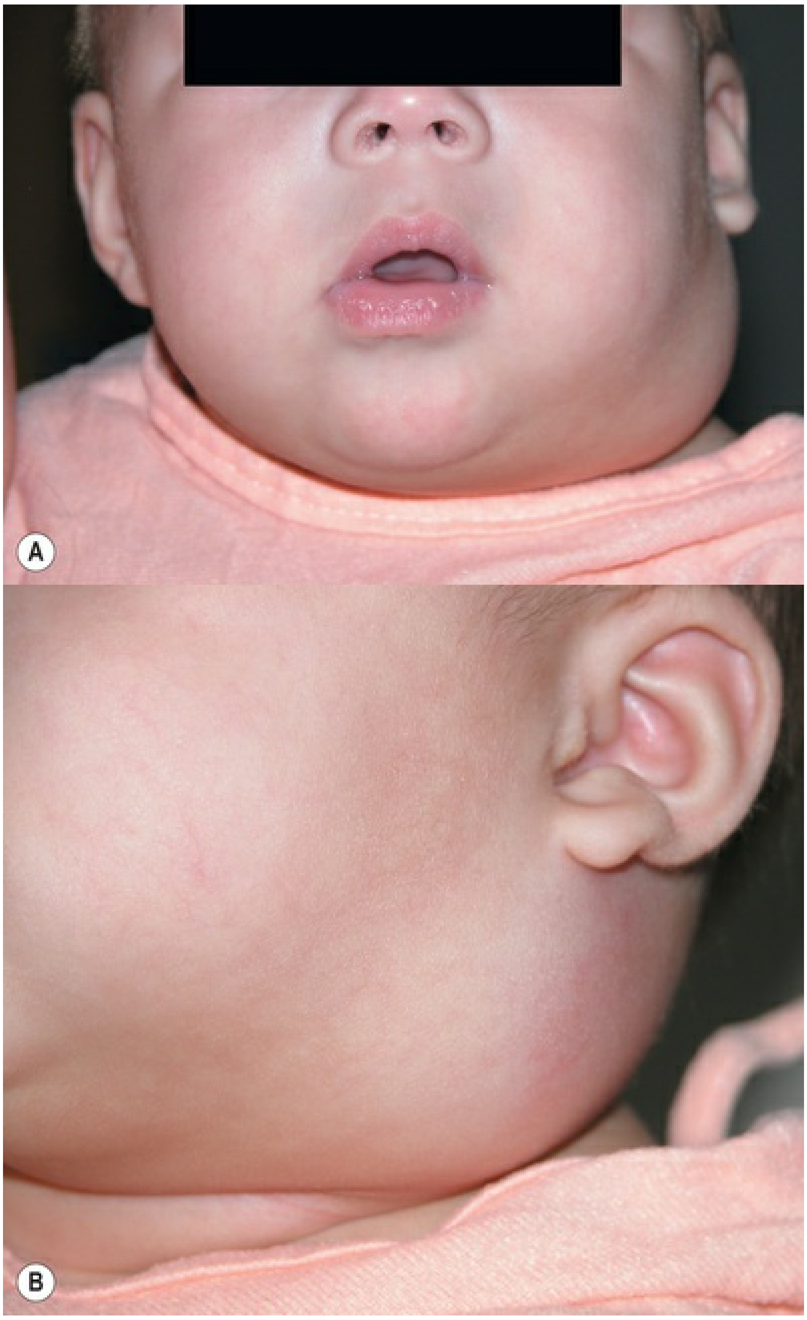


FIGURE 115.6 Two-month-old infant with necrotizing lymphadenitis due to MSSA. The infant had no intraoral, skin, or middle-ear abnormality. Note the location of the mass (A and B) and elevation of the earlobe (A). (Courtesy of J.H. Brien©.)

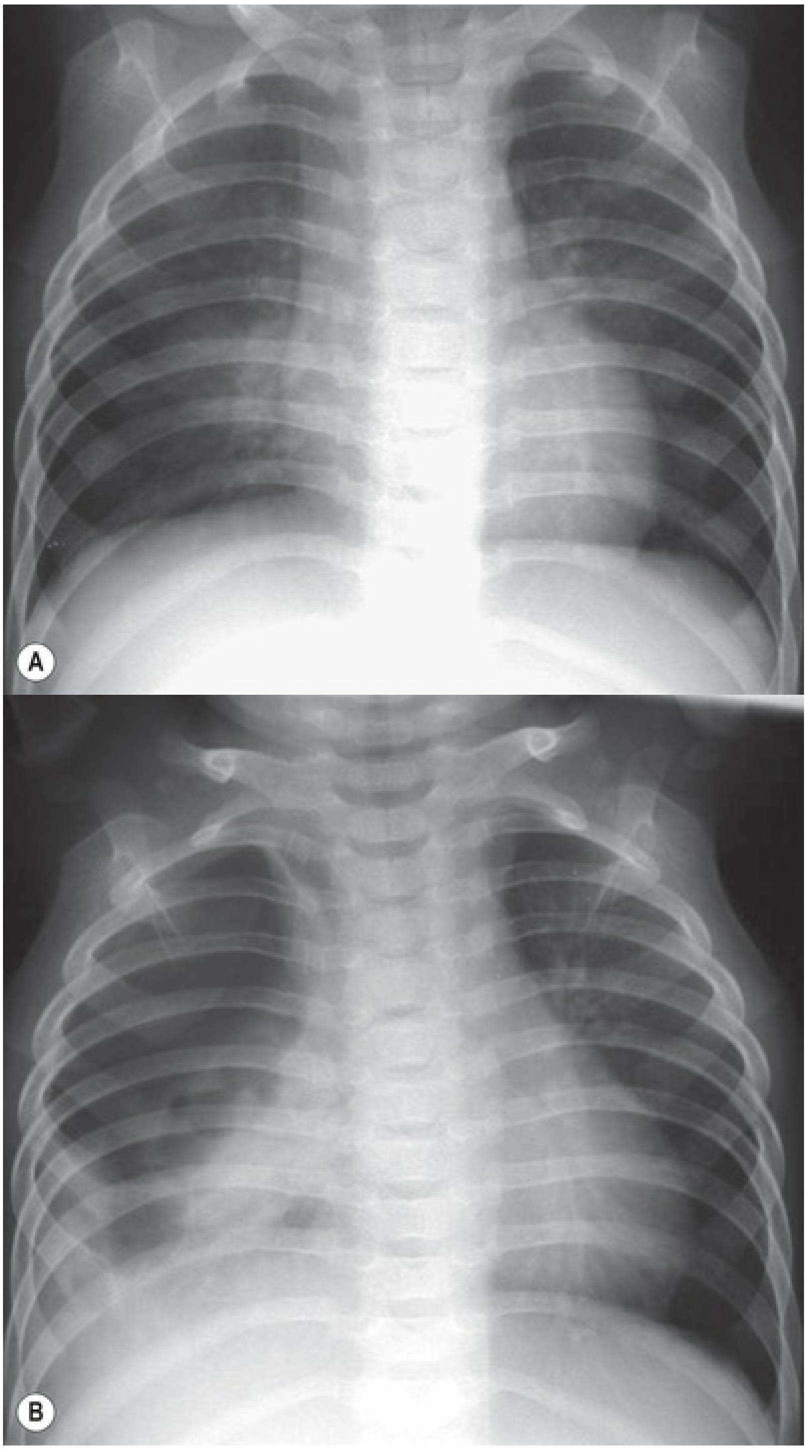
Tracheitis

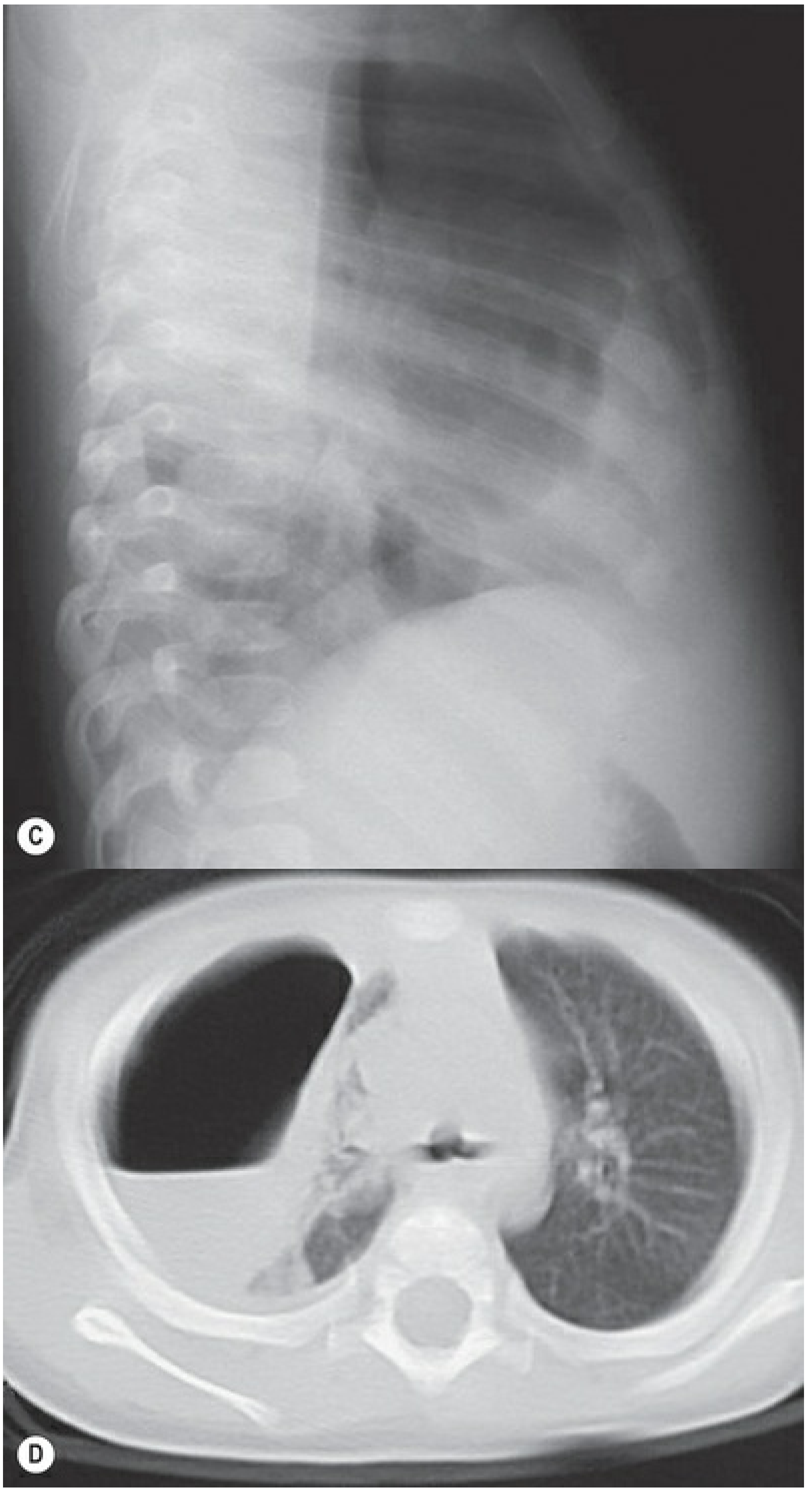
Bacterial tracheitis caused by *S. aureus* can occur in an airway inflamed by a viral process or injured by medical manipulation. Affected patients manifest hoarseness and stridor (if the larynx is involved concomitantly) and can deteriorate suddenly, showing respiratory distress and s high temperature. The diagnosis can be suspected by the results of imaging studies and is confirmed by direct visualization of thick, purulent secretions in the trachea and subglottic edema, along with a positive Gram stain of secretions and recovery of *S. aureus* upon culture. Management includes establishment of an artificial airway and IV antibiotic therapy[129] (see Chapter 28).

Lower Respiratory Tract Infections

Pneumonia

S. aureus can cause rapidly progressive pneumonia after inhalation of the organism or seeding of the lungs during BSI. Clinical features include fever, cough, grunting, and tachypnea, which can evolve into rapidly progressive and severe respiratory distress. A chest radiograph demonstrates multiple, patchy alveolar infiltrates that tend to coalesce to form large consolidations (Fig. 115.7). Pleural effusion and empyema accompany about 90% of pulmonary infections; spontaneous pneumothorax occurs in 25% to 50%. A pneumatocele (an air- or fluid-filled cavitation resulting from dissolution of intra-alveolar septa) occurs in more than 50% of cases. Most cases occur in previously healthy children, although predisposing factors (e.g., young age [younger than 1 year], chronic lung disease, immunosuppression, and presence of a foreign body or skin infection) may increase the likelihood of *S. aureus* pneumonia. A seasonal peak in *S. aureus* pneumonia is associated with viral respiratory tract infections such as influenza, presumably because viral illness transiently alters pulmonary defense mechanisms.[130]


A
B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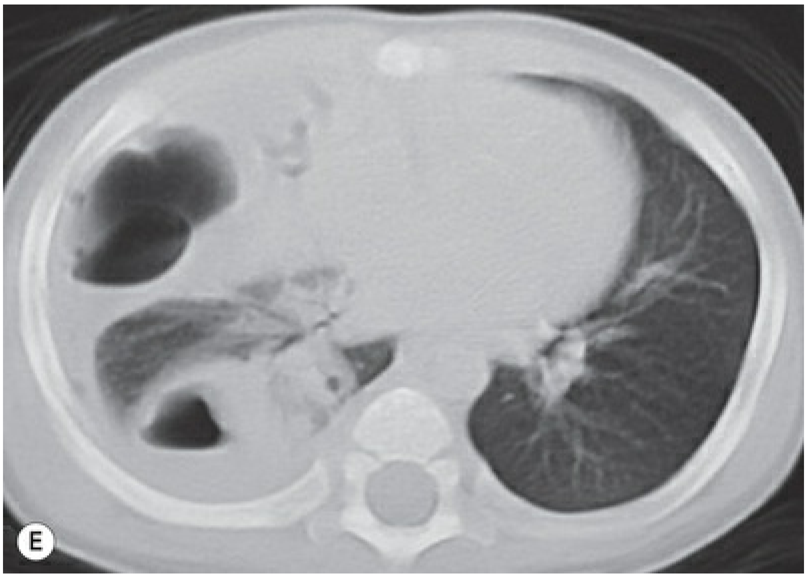

FIGURE 115.7 Progressive MRSA pneumonia with pneumatoceles in a previously healthy 9-month-old boy. Chest radiographic findings spanning 4 days showed a perihilar right lower lobe infiltrate (A) progressing to a worsening infiltrate and large hydropneumothorax with mediastinal shift (B and C) despite appropriate therapy. Axial CT of the chest without contrast (lung windows) showed partial loculation of hydropneumothorax, multilobar consolidation, pneumatoceles, and atelectasis (D and E). Video-assisted thoracoscopic surgery (VATS) was performed, and a chest tube was placed for 3 days. MRSA was isolated from pleural fluid. After 2 weeks of clindamycin therapy the chest radiograph had only minor abnormalities. (Courtesy of S.S. Long.)

S. aureus necrotizing community-acquired pneumonia (CAP) has increased dramatically in immunocompetent children. It can be caused by both MSSA and MRSA strains, which usually contain the PVL genes.[28,131–134] Leukopenia, and rapidly progressive unilateral or bilateral diffuse parenchymal pulmonary infiltrates are typical.[29] Severe sepsis syndrome can be present and has a high fatality rate. Histologic findings at autopsy reveal dense *S. aureus* with necrosis extending from the tracheobronchial epithelium to the congested and hemorrhagic parenchyma of the lung[29,80] (Fig. 115.8).

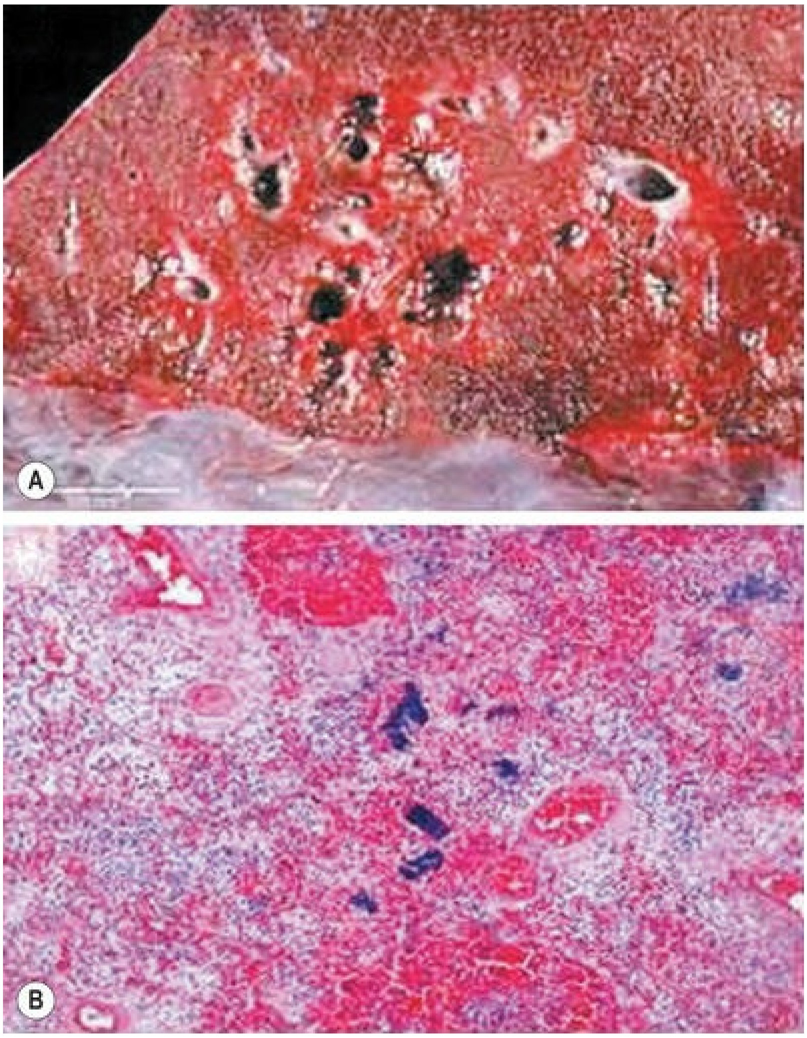

FIGURE 115.8 Pathologic findings from a patient with fatal necrotizing pneumonia due to *S. aureus* show a gross specimen of lung with microabscesses (A), and the histologic appearance of a section of lung with *S. aureus* colonies and hemorrhage (B). (Hematoxylin-eosin stain.) (From Adem PV, et al. *Staphylococcus aureus* sepsis and the Waterhouse-Friderichsen syndrome in children. N Engl J Med 2005;353:1245–1251.)

A high index of suspicion for *S. aureus* is critical in evaluating possible cases and aggressively treating them with empiric therapy active against MRSA and MSSA. The diagnosis is confirmed by recovery of the organism from pleural fluid, blood, or tracheobronchial aspirate. The duration of parenteral antimicrobial therapy depends on the clinical course. When compared with nonoperative treatment, early intervention for empyema with video-assisted thoracoscopic surgery (VATS) or open surgical debridement reduces mortality and the duration of antimicrobial therapy.[135]

Lung Abscess

Lung abscess can result as a complication of aspiration of infected material or a foreign body, can develop during pneumonia, or can result from hematogenous seeding during *S. aureus* BSI or septic thrombophlebitis. When bacteriology is proved as the mechanism of infection in children with aspiration, *S. aureus* can be recovered with or without facultative and anaerobic oral bacteria.[136,137]

Clinical features of *S. aureus* lung abscess include fever, cough, chest pain, dyspnea, anorexia, and weight loss.[136] CT helps determine the extent of disease and aids in following abscess resolution. Despite a dramatic appearance on radiographs, lung abscesses uncomplicated by pleural empyema usually can be treated adequately with IV antimicrobial therapy alone, as evidenced by resolution seen on follow-up chest radiographs.[138] Surgical drainage occasionally is required.[139] In these situations percutaneous drainage is a well-established technique.[140–142]

Cardiovascular Infections

Endocarditis

S. aureus is the most common cause of infective endocarditis (IE).[143] IE occurs more frequently in patients with congenital heart disease, whether surgically repaired or not, but can follow *S. aureus* BSI in any patient; or, it can be associated with device-associated persistent BSI.[144] Children whose cardiac lesions cause high-velocity blood flow and those with prosthetic valves or patches have an increased risk of developing *S. aureus* IE.[145,146]

Fever, a new or changed heart murmur, and continuous BSI are the hallmarks of IE. The presentation can be indolent or acute; common complaints include myalgia, arthralgia, general malaise, weight loss, and anorexia. Clinical progression can be rapid, with associated lethargy and cardiac failure, particularly when the aortic valve is involved. Right-sided endocarditis can be the source of emboli to the lungs, causing lung abscesses. Small vessel embolic phenomena, such as petechiae, splinter and conjunctival hemorrhages, and Janeway lesions, rarely manifest in children.[145]

The diagnosis is straightforward when echocardiography demonstrates a vegetation or abscess. However, this evidence may be lacking in children. A negative finding on a transthoracic or transesophageal echocardiogram does not exclude IE.[147,148] The modified Duke criteria have been used to identify children with IE based on major and minor clinical criteria (see Chapter 37).

Treatment requires 4 to 6 weeks of high-dose bactericidal antimicrobial therapy, administered intravenously, because of the relatively avascular nature of valves, the high organism load, and the decreased ability of polymorphonuclear leukocytes to function in endocarditis lesions. Guidelines for the treatment of *S. aureus* endocarditis, including consideration of combination therapy with aminoglycosides, can be found in Baltimore and colleagues[149] and Chapter 37. Fever may persist for about 1 week after the start of antimicrobial therapy.[150] Sustained bacteremia that spans several days in usual. Serial blood cultures should be obtained until sterility is demonstrated. Occasionally, surgical intervention is necessary, particularly when embolic phenomena to major organs, intractable cardiac failure, or aortic insufficiency is documented, or when BSI persists despite appropriate antimicrobial therapy, particularly when a prosthetic valve or other foreign material is involved. Prosthetic valve endocarditis caused by *S. aureus* poses a risk of mortality.[151,152]

Close follow-up should be maintained after therapy has been concluded because some patients can relapse and require definitive surgical intervention or removal of foreign material.

Pericarditis

Bacterial pericarditis in children is a rare complication of *S. aureus* BSI or other focal (usually pleural) infection. Pericarditis should be suspected in any patient with BSI and cardiomegaly. Signs and symptoms include fever, dyspnea, cough, and precordial chest pain. The chest radiograph shows an enlarged heart, and echocardiography demonstrates the presence of pericardial fluid. The diagnosis is made by examination of the pericardial fluid for inflammatory cells and bacteria. Management includes urgent pericardial decompression, closed or open pericardial drainage, and parenteral antimicrobial therapy.[153–155] Mortality is due to cardiac tamponade or the systemic inflammatory response syndrome; the likelihood of both these complications is decreased by early medical and surgical treatment. Patients who develop constrictive pericarditis require pericardiectomy.

Suppurative Phlebitis and Septic Thrombophlebitis

Suppurative phlebitis and septic thrombophlebitis are serious endovascular infections that occur along a continuum of clinical severity; they are most commonly caused by *S. aureus.* Suppurative phlebitis usually occurs in a catheterized vessel wall and is characterized by a fluctuant, palpable vein that is warm, tender, and erythematous; pus sometimes can be found at the catheter insertion site or by needle aspiration. Infection can progress to obstruction of the vessel or dissemination of infected thrombi to other sites, or both. The treatment of suppurative phlebitis includes removal of a device, drainage or resection of the infected segment of the vessel, and IV antimicrobial therapy.

Septic thrombophlebitis also occurs in association with invasive *S. aureus* infection without catheterization of the infected vessel. The veins involved usually are major deep veins, especially pelvic or lower extremity vessels, and they commonly are contiguous with an area of osteomyelitis, pyogenic arthritis, pyomyositis, or other soft tissue infection.[118] Longterm IV antibiotic therapy is warranted for this serious endovascular infection, with its attendant severe complications and mortality. Anticoagulant therapy and placement of an inferior vena cava filter are considered when infected clots disperse septic emboli to the lungs.[156]

Central Nervous System Infections

Meningitis

S. aureus meningitis can occur as a complication of BSI or endocarditis, or from extension of a parameningeal focus, including sinusitis, osteomyelitis of the skull bone, subdural empyema, epidural abscess, or rupture of a brain abscess into the lateral cerebral ventricles or the subarachnoid space. Congenital anomalies, such as a dermal sinus or meningomyelocele, can provide a portal of entry. Any neurosurgical procedure increases the risk of staphylococcal meningitis; insertion of a cerebrospinal fluid (CSF) shunt is the most common predisposing procedure.[157]

Treatment consists of parenteral antimicrobial therapy for 3 to 6 weeks, depending on the pathophysiology of the meningitis and removal of a device when present. (Treatment of device-related infection is discussed later in the chapter.)

Brain Abscess

A brain abscess caused by *S. aureus* can result from direct extension of an adjacent infectious focus (e.g., sinusitis,[104] mastoiditis, otitis media); from inoculation of bacteria during a surgical procedure or as a consequence of trauma; or from seeding of the brain during bacteremia. A brain abscess more frequently complicates *S. aureus* BSI than BSI due to other pathogens[158,159] (see Chapter 46). An *S. aureus* etiology should be considered, especially when brain abscess complicates severe *S. aureus* BSI or the patient has had a neurosurgical procedure or penetrating trauma. Cyanotic congenital heart disease also is a predisposing risk factor.[160]

Clinical features of brain abscess in children include headache, vomiting, irritability, focal neurologic defect, seizures, or other manifestations of increased intracranial pressure. The onset of symptoms can be insidious, depending on the pathophysiology; fever can be absent or low grade. The physical examination findings depend on the location of the abscess. Signs of meningitis are expected only if the abscess ruptures into a ventricle.

Imaging techniques are most often definitive in diagnosing a brain abscess. Enhanced MRI is superior to CT, although both modalities are useful.[161] The principal advantages of MRI are the abilities to distinguish the central core of an abscess from a surrounding area of ring enhancement, identify adjacent areas of cerebral edema, and detect abscesses in the posterior fossa.

Treatment consists of parenteral antimicrobial therapy and surgical drainage of the abscess, frequently by aspiration. In rare cases enucleation of the abscess is performed. Evolving abscesses in the non-necrotizing cerebritis stage and some small intracerebral abscesses can be treated with antimicrobial agents alone.[158] Corticosteroid therapy is limited to cases in which increased intracranial pressure is an important component. Patients typically are treated with antimicrobial agents parenterally for 6 weeks. Mortality associated with brain abscess is relatively low, but up to 60% of patients have neurologic sequelae, most commonly seizures.[162]

Spinal Epidural Abscess

S. aureus is the most common cause of a spinal epidural abscess, which is a collection of purulent material external to the dura in the spinal canal, usually in the posterior aspect of the thoracic or lumbar vertebrae. Abscesses arise as a result of seeding of the epidural space during BSI or through direct extension of an adjacent focus of infection, such as pyomyositis or osteomyelitis. Complaints in children can be nonspecific and include fever, vomiting, lethargy, and irritability. Localized tenderness and refusal to lie prone also can be noted. In older children, localized or radicular pain can be present. Paresis of limb muscles and loss of bowel or bladder control are specific and ominous signs because paralysis and loss of sensory modalities at levels below the affected area can ensue rapidly. A history of a clinical illness compatible with bacteremia sometimes is elicited.[163]

Spinal epidural abscess must be distinguished from diskitis, extradural neoplasm, hematoma, disk herniation, and vertebral osteomyelitis. MRI is the diagnostic procedure of choice.[164] Lumbar puncture is deferred when this diagnosis is suspected; if it is performed, CSF findings are similar to those in other parameningeal infections (i.e., a variable, modest pleocytosis, normal glucose, and modestly increased protein concentration).

Therapy includes immediate surgical decompression, debridement of the epidural space, and parenteral antimicrobial therapy, which generally is administered for 6 weeks.[165] Medical management alone is rarely considered in immunocompetent patients with a normal or stable neurologic examination and no signs of septicemia. Continuous reassessment is necessary to identify progressive pain or the onset of any neurologic abnormality that necessitates urgent surgery.[166]

Device-Related Infections

Indwelling Vascular Catheters

Staphylococci are the most common causes of catheter-associated infections. For peripheral venous catheters, *S. aureus* is the most common infecting species; for central venous catheters (CVCs), coagulase-negative staphylococci are recovered more commonly. Cutaneous colonization at the insertion site is the most important predictor of catheter-associated infections related to short-term, percutaneously inserted catheters. For surgically implanted CVCs, organisms introduced through the hub and lumen are the most important source of infection.

Local redness, pain, and warmth at the site of a simple peripheral catheter suggest local phlebitis, which is managed by removal of the device. Diagnosing a central line–associated BSI (CLABSI) can be more difficult. Fever and the presence of pain, fluctuance, erythema, purulence or soft tissue infection at the site suggest CLABSI. Most often, however, the catheter entrance site appears normal.

Blood for culture is taken via the catheter; a positive culture can represent CLABSI or BSI from another source. Isolation of *S. aureus* should not be regarded as the result of a procedural contaminant; repeated samplings or, occasionally, blood drawn simultaneously by venipuncture help to clarify the issue. Semiquantitative culture of the catheter tip after removal can implicate the catheter as the infectious nidus when the colony count exceeds 15 colonies; a negative culture of the catheter tip does not exclude CLABSI.

S. aureus exit-site infections, whether in the presence of a tunnel track infection or BSI, are managed by removing the catheter and administering antimicrobial therapy. Because of the propensity of *S. aureus* BSI to persist and to cause clinical sepsis or to seed the endocardium, abdominal viscera, brain, lung, or bone, many experts recommend removal of an intravascular catheter when *S. aureus* infection is documented, even in the absence of an exit-site infection.

Vancomycin is the preferred empiric therapy for suspected *S. aureus* catheter-associated infection. Combination bactericidal therapy and an extended course of antimicrobial therapy (e.g., 4 to 6 weeks) frequently are recommended because of the known tendency of *S. aureus* BSI to seed and form abscesses at multiple sites. This point is controversial because of the lack of specific data (see Chapter 100). Consistent use of a "bundle" of techniques for placing and handling catheters is among the measures that have been shown to reduce the infection rate; these measures include skin disinfection with chlorhexidine, an aseptic placement technique, use of a BioPatch dressing, dedicated teams for ongoing catheter care, and the earliest possible removal of the catheter.

Cerebrospinal Fluid Shunt Devices

A contaminated CSF shunt or subcutaneous reservoir device is the most common predisposing cause of staphylococcal meningitis.[157] Presumably *S. aureus* gains access to the catheter during surgical insertion, although the device and CSF can be seeded by a subsequent adjacent primary SSTI or tract infection or during BSI – the presence of the catheter increases the likelihood that the organism will survive and multiply.

Most CSF shunt infections occur within 2 months of shunt placement or revision. Low-grade fever and dysfunction of the shunt are variably present. For ventriculoperitoneal (VP) shunts, symptoms and signs attributable to peritonitis commonly can be present.[167,168] If the patient had recently undergone surgery, a wound infection may be evident. A first episode of an *S. aureus* shunt infection is predictive of a subsequent *S. aureus* shunt infection.[169]

Examination of the CSF (typically obtained by percutaneous puncture of the shunt reservoir/tubing) may reveal only mild abnormalities, such as modest pleocytosis, a normal glucose level, and a normal or minimally elevated protein concentration. Microorganisms infrequently are visualized on Gram stain. Culture of CSF is the most sensitive test; however, culture of CSF obtained by lumbar puncture frequently is not diagnostic of a VP shunt infection.

Most experts recommend combined medical and surgical treatment for CSF shunt infections. Typically a temporary external ventricular drain is used, while IV antimicrobial therapy is administered, until the CSF is sterile and inflammation subsides, at which time a new shunt can be placed.[170,171] The timing of this procedure is important – insertion of the new catheter into an infected field must be avoided. However, maintaining an externalized catheter as a drainage device carries its own risk of infection, which accelerates after 5 to 7 days of use.

Toxin-Mediated Syndromes

Staphylococcal Food Poisoning

Staphylococcal food poisoning is caused by ingestion of *S. aureus* enterotoxins. It accounts for up to one third of foodborne gastrointestinal illnesses (see Chapter 59). Protein-rich foods (e.g., ham and chicken) often are implicated as the outbreak source, as are dairy products and egg and potato salads. The individual who inadvertently inoculates the food with *S. aureus* may have a clinical infection but usually is colonized asymptomatically.[172,173]

Illness begins shortly after consumption (4 hours on average) because ingestion of preformed toxin causes the clinical manifestation. Classic symptoms are nausea, vomiting, abdominal pain, and diarrhea; headache and prostration are less common. Fever occurs in about 25% of patients. Hospitalization is required infrequently, and death occurs rarely.

S. aureus can be isolated from the vomitus or feces of ill people. Culture of the contaminated food may yield the offending organism. Therapy is supportive; antibiotics are not useful. The syndrome can be prevented by proper handling of food and careful hygiene practices by food handlers. When cases are recognized, the Department of Public Health must be notified.

Staphylococcal Scalded Skin Syndrome

SSSS is an illness mediated by exfoliative toxins ETA and ETB.[90,91] Hematogenous spread of the toxins produces fever and widespread erythema of the skin, which can be tender and quickly forms thin-walled, fluid-containing bullae that rupture, leaving a moist base of skin. Gentle friction applied to the skin produces Nikolsky sign, a sloughing of superficial sheets of skin (see Fig. 13.2). Desquamation follows rapidly and can be widespread, especially in the neonate.[174,175]

SSSS is diagnosed clinically or by isolation of *S. aureus* from a local site (not necessarily the exfoliating site), ideally with demonstration by the isolate of toxin production or the toxin gene. Histologic evaluation of the skin reveals the separation of skin layers at the granular layer within the epidermis, rather than the separation of the dermis and epidermis seen in drug-induced toxic epidermal necrolysis.[176]

Management of SSSS is primarily supportive, and careful attention is paid to electrolyte levels because fluid shifts can occur across the denuded skin. Antiseptic measures should be taken to prevent infection of the unprotected, affected areas. Parenteral antimicrobial therapy is administered to reduce the staphylococcal burden. Topical antimicrobial agents are not helpful.[176]

Toxic Shock Syndrome

TSS is caused by *S. aureus* strains that produce TSST-1 or certain enterotoxins (specifically SEB and SEC).[177] It is characterized by fever, rash, hypotension, and multisystem organ dysfunction[178] (Box 115.1). The incidence of TSS peaked in the early 1980s; the condition was attributed to the use of superabsorbent tampons by menstruating adolescents and women.[179] Subsequent public education and manufacturing regulations helped reduce the number of TSS cases, and now nonmenstrual TSS accounts for approximately one half of all TSS cases.[180]

Box 115.1

Staphylococcal Toxic Shock Syndrome: Clinical Case Definition

An illness with the following clinical manifestations:

Fever: Temperature >38.9°C (102°F)

Rash: Diffuse macular erythroderma

Desquamation: 1–2 weeks after onset of illness, particularly on palms and soles

Hypotension: Systolic blood pressure ≥90 mm Hg for adults or less than 5th percentile by age for children <16 years; orthostatic drop in diastolic blood pressure ≥15 mm Hg from lying to sitting, orthostatic syncope, or orthostatic dizziness

Multisystem involvement: 3 or more of the following:

1. Gastrointestinal: Vomiting or diarrhea at onset of illness
2. Muscular: Severe myalgia or creatine phosphokinase level ≥2 times the upper limit of normal for laboratory

3. Mucous membrane: Vaginal, oropharyngeal, or conjunctival hyperemia

4. Renal: Blood urea nitrogen or creatinine ≥2 times the upper limit of normal for laboratory or urinary sediment with pyuria (≥5 leukocytes per high-power field) in the absence of urinary tract infection

5. Hepatic: Total bilirubin, serum glutamic-oxaloacetic transaminase (SGOT), or serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥2× the upper limit of normal for laboratory

6. Hematologic: Platelets $<100{,}000/\text{mm}^3$

7. CNS: Disorientation or alteration in consciousness without focal neurologic signs when fever and hypotension are absent

Negative results on the following tests, if obtained:

1. Blood, throat, or cerebrospinal fluid cultures (for all microorganisms except *Staphylococcus aureus*)

2. Rise in antibody titer to *Rickettsia* or *Leptospira* species or rubeola

Modified from Wharton M, Chorba TL, Vogt RL, et al. Case definitions for public health surveillance. MMWR Recomm Rep 1990;39:1–43.

Risk factors for TSS include colonization and disruption of the skin, colonization of mucous membranes, or any infection caused by a toxin-producing strain of *S. aureus.* TSS often is associated with surgery or trauma, manifesting several days after the event. The sudden onset of fever, chills, headache, vomiting, sore throat, myalgia, and diarrhea is followed by hypotension, respiratory distress, edema, and rash within 24 to 48 hours. Dizziness, listlessness, and disorientation are clues to hypotension and cerebral dysfunction; coma can ensue.

The initial *S. aureus* focus can show no signs of inflammation or purulence. Initially the rash can appear like that seen in scarlet fever, but it classically is described as diffuse erythroderma, or "sunburn." The rash typically desquamates 1 to 2 weeks after the onset of illness, most notably on the palms and soles.

Mucous membrane involvement includes conjunctival hyperemia, strawberry tongue, beefy red oropharyngeal membranes (sometimes with ulcerations), and lesions representing reactivation of the herpes simplex virus.

A vaginal culture yields the organism in 85% of menstrual TSS cases. In nonmenstrual TSS cases a nasopharyngeal or a wound culture may yield *S. aureus;* a blood culture should be obtained (to diagnose concurrent BSI) but is seldom positive.

Management consists of treating intravascular volume depletion, shock, and respiratory failure, in addition to the *S. aureus* infection. Any relevant focus of infection should be drained and any foreign body removed if possible. IV antimicrobial therapy, including an antibiotic that inhibits protein synthesis (e.g., clindamycin or linezolid), may be preferable. The response to effective therapy can be rapid. For a patient who does not respond to these interventions, most experts recommend immune globulin intravenous (IGIV), based on the presence of antibody to staphylococcal enterotoxins and TSST-1.[181,182] End-organ failure, particularly renal failure and acute respiratory distress syndrome, can occur within the first few days of illness and are responsible for the attendant 3% mortality rate.

Severe Sepsis Syndrome

Severe sepsis syndrome is defined as isolation of *S. aureus* from a clinically important site, hypotension (i.e., systolic blood pressure less than the 5th percentile for age for children or less than 90 mm Hg for adults), and respiratory distress syndrome or respiratory failure, in addition to involvement of the central nervous system (CNS), liver, kidneys, muscles, or skin; or abnormal hemostasis; or the presence of leukopenia or thrombocytopenia. Severe sepsis syndrome is similar to TSS but does not meet all the clinical criteria for TSS, and the *S. aureus* isolates do not produce TSST-1.[81]

Increasingly, severe sepsis occurs in children and adolescents with no underlying medical conditions or other identifiable risk factors.[81,183–185] Both MSSA and MRSA are implicated; genes encoding PVL frequently are identified in the infecting strain.

A primary infectious process (e.g., pyogenic arthritis or pneumonia) often is identified before clinical deterioration begins. However, patients can have an overwhelming infection and experience subsequent rapid decline without a primary tissue site of infection.[81,183,184] Skin lesions are common and manifest as erythroderma, pustules, petechiae, and/or purpura. Waterhouse-Friderichsen syndrome,[186] staphylococcal purpura fulminans,[187] and necrotizing fasciitis have been reported.[188]

The diagnosis is made by isolation of *S. aureus* from a clinically important site, such as the blood, a joint space, or respiratory secretions (with concomitant systemic illness). A high index of suspicion is critical to instituting appropriate parenteral antimicrobial therapy and aggressive cardiopulmonary support. Mortality rates based on reviews of case reports approach 64%.[183]

Management

Treatment of invasive *S. aureus* infections should be rapid and aggressive. IV antimicrobial therapy should be started promptly, and the source of BSI and sites of possible metastatic infection should be sought aggressively. Abscesses should be drained, and CVCs or other foreign bodies should be removed when possible. Associated endocarditis or other endovascular infections always should be considered in patients with *S. aureus* BSI because this species has a tropism for endothelial cells, and organisms with the PVL gene have the propensity to cause thrombosis and thromboembolism.[118,189,190]

If rapid improvement does not occur or BSI continues after more than 24 hours of therapy, the therapeutic approach should be carefully reevaluated because irreversible organ damage can progress rapidly. Once the antimicrobial susceptibility of the organism is known, therapy should be tailored to use the appropriate antimicrobial agent or agents with the narrowest appropriate spectrum of activity.

The CA-MRSA epidemic has refocused attention on the importance of adjunctive local treatments, such as incision and drainage. For many purulent SSTIs, incision and drainage may suffice. Guidelines have been published for management involving antibiotics and drainage.[98,191] Because susceptibility to β-lactam antibiotics cannot be assumed, obtaining a specimen for culture is essential for patients who require antibiotic treatment, to further guide therapy.[192]

Antistaphylococcal Agents

The compounds presented in the following sections are discussed further in Chapter 292.

β-Lactam Antibiotics

Previously, semisynthetic β-lactam penicillins (nafcillin, oxacillin, cloxacillin, and dicloxacillin), were the gold standard for treatment of staphylococcal infections. These agents inhibit cell wall synthesis and thus are bactericidal, well tolerated, and have a long record of therapeutic effectiveness. When an MSSA strain is isolated, β-lactams are the drugs of choice for serious staphylococcal infections. Parenteral compounds in wide use in the U.S. include oxacillin and nafcillin; dicloxacillin is available for oral use, although some children find the taste of the suspension unpleasant.

The combination drugs made up of a β-lactam plus a β-lactamase inhibitor (i.e., (ampicillin-sulbactam, amoxicillin-clavulanate, ticarcillin-clavulanate, and piperacillin-tazobactam) are active against MSSA but offer no advantage over the semisynthetic penicillins. The antistaphylococcal activity of the so-called first-generation cephalosporins is superior to that of later generations of cephalosporins. Cefazolin (for parenteral administration) and cephalexin (for oral administration) are useful class compound examples; their efficacy is similar to that of the semisynthetic penicillins for the treatment of MSSA infections that are not life threatening, and cefazolin is associated with fewer episodes of premature drug discontinuation and drug-emergent events.[193]

Until 2010 none of the β-lactam antibiotics, β-lactamase inhibitors, or cephalosporins had proved useful for therapy of MRSA infections. However, in 2010 the drug ceftaroline was licensed for treatment of CAP and complicated SSTIs. Designated a fifth-generation cephalosporin, ceftaroline is active against MRSA strains and has broad-spectrum activity against many gram-positive and gram-negative bacteria. Ceftaroline has been used as salvage therapy in adults with invasive MRSA infections who have responded slowly to vancomycin. No data have been reported on the drug's use in children,[194] although evaluation is underway.

Clindamycin

Clindamycin is a lincosamide antibiotic that inhibits protein synthesis at the chain elongation step by interfering with transpeptidation of the 50S ribosomal subunit. Most HA-MRSA isolates are resistant to clindamycin, but most CA-MRSA isolates are susceptible,[191] particularly in children.[60,77,98,195,196] Despite its increasingly frequent use in the treatment of CA-MRSA infections, clindamycin is not licensed by the U.S. Food and Drug Administration (FDA) for this purpose.

Erythromycin resistance of *S. aureus* is prevalent and can impair the effectiveness of clindamycin. The erythromycin ribosomal methylase *(erm)* gene codes for the enzyme that modifies the binding site not only for macrolides, but also for lincosamides and streptogramin B antibiotics. Consequently, cross-resistance to these three classes of antibiotics, the so-called macrolide–lincosamide–streptogramin B (MLS_B) phenotype, is common among *S. aureus* isolates.[197] Phenotypic expression of the MLS_B phenotype can be constitutive or inducible with exposure to a macrolide. When it is constitutive, the isolate tests as resistant to all MLS_B antibiotics. When it is inducible, however, the isolate tests as resistant to erythromycin and susceptible to clindamycin.

Clinical laboratories test for inducible clindamycin resistance with the disk diffusion D-test or with automated simultaneous broth dilution testing in the presence of erythromycin (see Chapter 290 and Fig. 290.4).[198,198] To date, although the incidence of erythromycin resistance among CA-MRSA isolates is high, the incidence of clindamycin resistance is not. Clinicians should be aware that treatment failure with clindamycin is possible if the target organisms have demonstrable inducible resistance in vitro.[198,199]

Clindamycin also is a potent suppressor of bacterial toxin synthesis. Clindamycin therapy may be clinically superior in toxin-mediated staphylococcal syndromes, although explicit data are lacking. When clindamycin is used in this setting, combination therapy with oxacillin or nafcillin, or with vancomycin, frequently is used.

Clindamycin is bacteriostatic and does not cross the blood-brain barrier; it is not used alone in the treatment of endocarditis or other intravascular or CNS infections that can occur during *S. aureus* invasive infection. The poor taste of clindamycin suspensions can hamper adherence to oral therapy in outpatients.

Clindamycin resistance rates among *S. aureus* isolates, both MRSA and MSSA, should be monitored locally. In areas where the resistance rates exceed 10% to 15%, empiric therapy with this agent probably should be avoided.[200–202]

Vancomycin

Vancomycin is a glycopeptide that inhibits synthesis and assembly of the second stage of cell wall peptidoglycan in gram-positive bacteria. It is the therapeutic agent of choice for HA-MRSA infections. However, the emergence of VISA and VRSA isolates, in addition to the so-called MIC creep to 1 to 2 μg/mL, has the potential to limit the effectiveness of vancomycin.[203–205] Some experts recommend the use of higher doses in serious infections to elicit higher serum trough levels of vancomycin; however, the effectiveness, necessity, and safety of these strategies in children is controversial.[98]

Vancomycin should be considered for children suspected of having serious CA-MRSA infections, such as SSTIs with systemic manifestations that require hospitalization, severe sepsis, TSS, CNS infection, necrotizing pneumonia, and necrotizing fasciitis. Considerations for empiric use for osteoarticular infections include the local prevalence of CA-MRSA, degree of illness, site of infection, and adequacy of culture specimens obtained to guide therapy.

Because vancomycin is less bactericidal than oxacillin or nafcillin for MSSA and can result in treatment failure or relapse, it should not be used for therapy of MSSA infections unless it is necessary (e.g., the patient has a type 1 allergic reaction to β-lactam agents). In severely ill patients, semisynthetic penicillin frequently is given in addition to vancomycin until culture and susceptibility test results are available. Vancomycin is available only in IV form for use in the therapy of *S. aureus* infections, and the concentration obtained in the alveolar space is poor. Oral vancomycin is not absorbed.

Oritavancin

Oritavancin is a semisynthetic lipoglycopeptide that was approved by the FDA in 2014 for the treatment of SSTIs caused by gram-positive organisms. Oritavancin is active against MRSA, VISA, VRSA, daptomycin-nonsusceptible isolates and vancomycin-resistant *Enterococcus*. Due to a long serum half-life (393 hours), concentration-dependent bactericidal activity, and a three-pronged mechanism of action, a single dose of oritivancin has been shown to be noninferior to repeated vancomycin dosing for treatment of SSTI in adults.[206,207] Due to slow tissue elimination, no oritivancin dosing adjustments are needed in patients with renal or hepatic insufficiency.

In addition to achieving steric inhibition of transglycosylation, oritavancin can bind pentaglycyl cross-bridges, which inhibits peptidoglycan transpeptidation and cross-linking. It interacts with the bacterial cell membrane, leading to depolarization, increased membrane permeability, and cell death of both stationary and exponential growth phase bacteria. These mechanisms distinguish oritavancin from vancomycin.[208] Membrane depolarization also provides effectiveness against daptomycin-nonsusceptible bacteria. To date, no oritavancin resistance has been detected in clinical isolates of *S. aureus*. Lack of evaluation in children and expense currently limit its use.

Dalbavancin

Dalbavancin is a semisynthetic lipoglycopeptide derivative of teicoplanin. It contains a long lipophilic side chain that extends its potency and half-life. Dalbavancin has been approved by the FDA for the treatment of SSTI caused by gram-positive organisms, and it is dosed once per week. Dalbavancin binds to the D-ala-D-ala residue, destabilizing the cell membrane and resulting in bacterial cell death. Active against both MSSA and MRSA, dalbavancin is more potent than vancomycin against strains with a vancomycin MIC of 2 μg/mL or less. The kinetics in children 12 to 17 years of age appear to be similar to those in adults[209]; no data are available for younger children. Dalbavancin is noninferior to vancomycin and linezolid. Because of its extended half-life, one or two doses of dalbavancin can be used after incision and drainage to treat SSTIs in ambulatory patients. The drug is very expensive and must be given parenterally.

Linezolid and Tedizolid

Linezolid and tedizolid are oxazolidinones that inhibit protein synthesis by binding to the 50S ribosomal subunit during the formation of the initiation complex.[210] They have broad in vitro activity against MRSA, GISA, VISA, and VRSA isolates. They are well tolerated, and linezolid is as effective as vancomycin in children with SSTIs and pneumonia caused by MRSA.[211–213] The oral bioavailability of both compounds is almost 100%, which facilitates transition from IV to oral therapy.

Linezolid and tedizolid are bacteriostatic against *S. aureus* and therefore are not preferred for the treatment of endocarditis or other intravascular infections. If possible, linezolid should be avoided in patients taking adrenergic or serotonergic agents.[214] Drug interactions may occur less frequently with tedizolid than with linezolid. Both compounds can be associated (possibly to a lesser degree for tedizolid) with the development of thrombocytopenia, which can be idiosyncratic and severe; anemia; and neutropenia.[215] The complete blood count should be monitored in patients receiving therapy for longer than 2 weeks, those with underlying myelosuppression, or those taking other drugs that cause bone marrow suppression. A small number of cases of optic and peripheral neuropathy and lactic acidosis have been reported in adults during prolonged courses of therapy with linezolid.

Resistance to linezolid has emerged in patients receiving longterm therapy. Resistant isolates have mutations in the 23S rRNA gene in the domain V region, of which *S. aureus* has five copies.[216,217] A mutation in two or more of the rRNA genes is required for the resistant phenotype. This kind of resistance probably also occurs with tedizolid. Additional resistance mechanisms have been identified in ribosomal proteins L4 and L3. Plasmid-borne *cfr* genes have been identified that encode a methyltransferase that mediates linezolid resistance by methylation of carbon-8 on the 23S rRNA base. *cfr* genes confer cross-resistance to phenicols, lincosamides, pleuromutilins, and streptogramin A antibiotics.[218] Available data suggest that isolates with *cfr* genes are nonetheless responsive to tedizolid therapy.[219]

Both linezolid and tedizolid are available in IV and oral forms. Linezolid is available in a convenient pediatric suspension. The compounds are extremely expensive, and negotiation with some third-party payers may be required for each use. Patients also can experience delays in procuring linezolid from private pharmacies that do not stock it routinely. A generic form of linezolid was recently released that costs about 20% less.

Trimethoprim-Sulfamethoxazole

TMP-SMX interferes with the biosynthesis of tetrahydrofolic acid, which is essential for microbial synthesis of proteins and nucleotides. Although most *S. aureus* isolates are susceptible in vitro, TMP-SMX was seldom used to treat *S. aureus* infections until the recent epidemic of CA-MRSA. Reports now are available on clinical experience using TMP-SMX to treat CA-MRSA SSTIs[220] or more severe *S. aureus* infections. One study suggested that the efficacy of TMP-SMX was similar to that of clindamycin for skin infections of unspecified cause, including cellulitis.[220] For the treatment of invasive *S. aureus* infection, data show IV TMP-SMX to be inferior to vancomycin for MSSA and only equivalent to vancomycin for MRSA (these data were obtained before the CA-MRSA era[221]). The observation that thymidine can be released from injured tissue or bacteria has suggested a possible explanation for discordant in vitro and clinical outcomes.[222] Additional information is needed to establish the appropriate role for TMP-SMX in the anti–*S. aureus* armamentarium.

Tetracyclines (Including Tigecycline)

Tetracyclines inhibit bacterial protein synthesis by binding to the

30S ribosomal subunit, thereby blocking the attachment of the transfer RNA amino acid to the ribosome. Tetracyclines such as doxycycline and minocycline have emerged as alternative oral antimicrobial agents for mildly to moderately ill patients with MRSA SSTIs. Most isolates are susceptible in vitro.[191,223]

Tigecycline, a novel glycylcycline that was recently licensed for parenteral use, has potent activity against *S. aureus* in vitro, regardless of methicillin or vancomycin susceptibility.[224,225] However, in 2010 the FDA issued a warning linking tigecycline to an increased mortality risk in patients being treated for hospital-acquired pneumonia, CAP, complicated intra-abdominal infections, and complicated SSTIs; this suggests that tigecycline should not be used in the treatment of *S. aureus* infections.

All tetracyclines are bacteriostatic and should not be used for the treatment of endocarditis or other intravascular or CNS infections. Tetracyclines also should not be used to treat pregnant women.

Quinupristin-Dalfopristin

The drug Synercid is a combination of two streptogramin antibiotics, one from group B (quinupristin) and one from group A (dalfopristin), in a 30/70 ratio. Quinupristin-dalfopristin has good in vitro activity against *S. aureus,* including MRSA. The two streptogramins bind to sequential sites on the 50S ribosomal subunit and have a synergistic bactericidal effect that results from inhibition of protein synthesis.[226] Recent trials have shown a lower bacteriologic success rate compared with standard therapy.[227] Quinupristin-dalfopristin is not cross-resistant to *S. aureus* isolates with MLS_B resistance because the streptogramin A component remains active; however, few data are available to ensure the clinical validity of this issue. Quinupristin-dalfopristin is available only in IV form, and evaluation in children has been minimal. Infusion site inflammation, thrombophlebitis, arthralgias, drug-drug interactions, myalgias, gastrointestinal toxic effects, and increased serum unconjugated bilirubin concentrations have limited widespread use.

Daptomycin

Daptomycin is a novel cyclic lipopeptide with a mechanism of action that is not completely understood. It appears to bind to the gram-positive bacterial cell membrane, which is followed by calcium-dependent insertion[228] that results in a decrease in membrane potential, causing cell death by rapidly stopping DNA, RNA, and protein synthesis. It has potent bactericidal activity against MRSA.[229] Daptomycin was comparable to vancomycin in the treatment of complicated SSTIs[230]; however, it showed decreased effectiveness for the treatment of CAP compared with standard treatment, probably because of its propensity for binding surfactant.[231] Daptomycin has been licensed by the FDA for the treatment of complicated SSTIs, BSI, and right-sided endocarditis; however, it is not approved for the treatment of left-sided endocarditis.[232] Daptomycin is available in IV form only. Studies evaluating its use in children suggest good efficacy.[233] When the cell wall is thickened (e.g., in a VISA isolate or after exposure of an *S. aureus* isolate to vancomycin), resistance to daptomycin becomes evident, presumably because the compound cannot reach its cell membrane target.[234,235] Resistance to daptomycin can occur during therapy and was documented in 6 of 120 patients receiving daptomycin for endocarditis, or BSI.[236] In addition, daptomycin-resistant isolates can be cross-resistant to vancomycin.[235]

Telavancin

Telavancin is a lipoglycopeptide that was licensed by the FDA in 2009 for the treatment of complicated SSTIs. The compound depolarizes bacterial membranes and inhibits cell wall formation. No formal evaluation has been done in children. The drug is administered once daily. Telavancin carries a “black box” warning that it worsens renal dysfunction. As can vancomycin, telavancin can cause red man syndrome. A few resistant isolates have been, obtained although the mechanism is not known.

Rifampin

Rifampin is a bactericidal agent that blocks protein synthesis by inhibiting RNA polymerase. It is highly active against almost all *S. aureus* isolates, but resistance emerges rapidly when rifampin is used as monotherapy. Combination regimens using rifampin with clindamycin, TMP-SMX, or doxycycline sometimes are recommended for the treatment of CA-MRSA infections or for treating device- or prosthesis-associated *S. aureus* infections. Whether such regimens are more effective is unclear. Rifampin is available in both oral and IV forms, although a suspension suitable for use in young children is not available.

Aminoglycosides

Aminoglycosides (e.g., gentamicin) are potent bactericidal inhibitors of protein synthesis. Aminoglycosides alone are believed to be poorly efficacious against *S. aureus* infections, although they are synergistic with β-lactam antibiotics and vancomycin in vitro. They are commonly used in combination therapy for severe infections, such as endocarditis, but whether this offers a clinical advantage is the subject of controversy.

Empiric Therapy for Community-Associated Infections

CA-MSSA and CA-MRSA skin infections cannot be differentiated on clinical grounds.[192] In areas where CA-MRSA is prevalent, empiric β-lactam therapy is not appropriate. Fig. 115.9 suggests an approach to the management of these cases. Therapy should be adjusted according to in vitro test results. A study sponsored by the National Institutes of Health is underway to determine the optimal oral therapy of *S. aureus* large-lesion SSTI in outpatients.[220] A similar study comparing clindamycin, TMP-SMX and placebo therapies for small abscess will be published (Daum R, et al. In press).

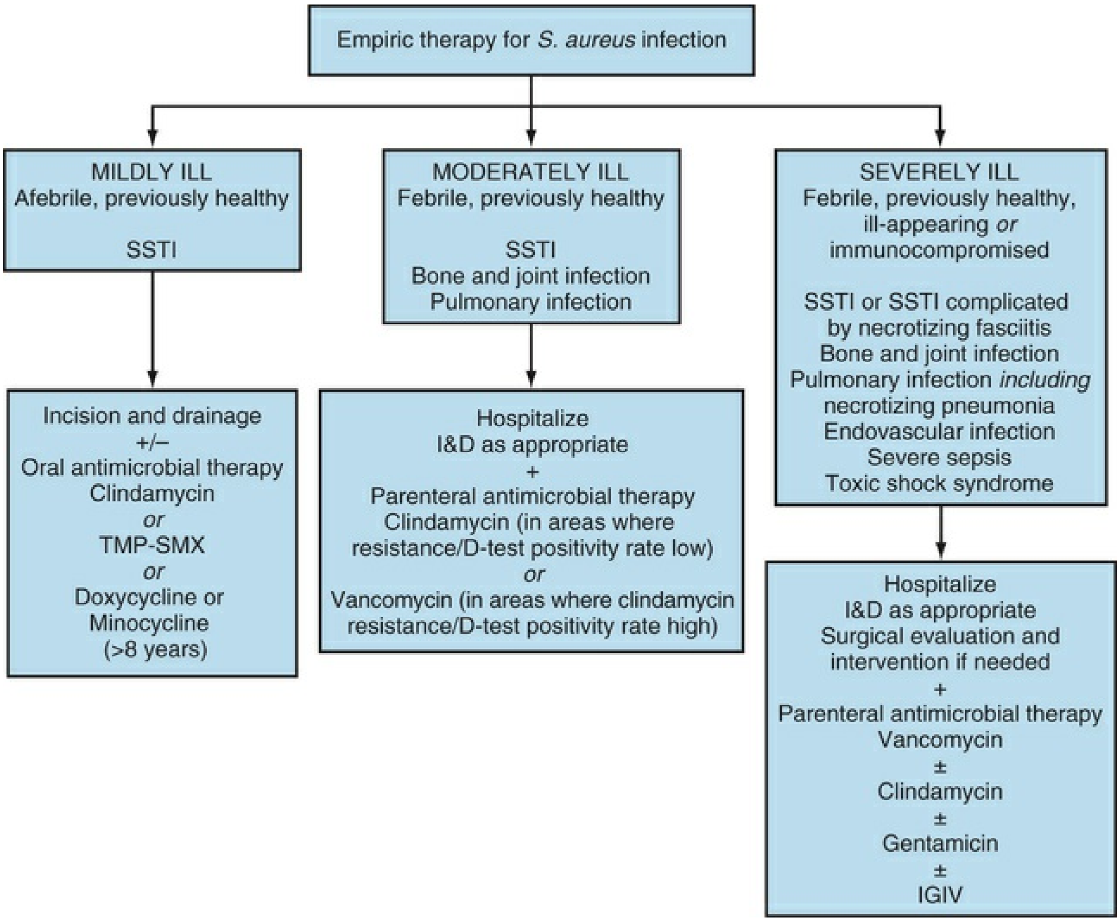

FIGURE 115.9 Schema for the empiric treatment of community-associated *S. aureus* infections, determined by the severity of the illness. SSTI, Skin and soft tissue infection; I&D, incision and drainage; TMP-SMX, trimethoprim-sulfamethoxazole; IGIV, immune globulin for intravenous use.

Empiric Therapy for MRSA Infections Requiring Hospitalization

Vancomycin is indicated for empiric therapy of putative *S. aureus* infections when the patient is severely ill.[98,237] VISA isolates have been identified that are associated with vancomycin treatment failure.[238,239] The Clinical and Laboratory Standards Institute defines VISA as an MIC of vancomycin greater than 2 μg/mL. In 2002 the CDC reported the first documented infection caused by *S. aureus* with high-level resistance (MIC >16 μg/mL) to vancomycin, or VRSA; 12 additional VRSA strains have been isolated since.[87–89,240,241] VISA and VRSA isolates probably occur more frequently than is documented because optimal tests to detect decreased vancomycin susceptibility often are not performed in clinical laboratories.[242]

Information about parenteral therapy with clindamycin, daptomycin, tigecycline, linezolid, telavancin, and other agents useful in the therapy of MRSA infections in hospitalized children can be found in Chapter 292 and in the guidelines established by the Infectious Diseases Society of America.[98,243]

Prevention

Efforts to prevent *S. aureus* HAIs have included general measures such as improved hand hygiene and attention to careful implementation of measures aimed at diminishing infections associated with intravascular catheters. Other efforts aimed specifically at reducing infections caused by MRSA have included identification of MRSA carriers upon hospitalization, and isolation and cohorting of patients who are colonized. Contact Precautions are used in the care of patients with a MRSA infection. Some states have legislated mandatory screening for MRSA upon admission to the hospital or, in some cases, to an intensive care unit. However, such a screening approach has several problems: high cost, focusing finite resources on a single pathogen, lack of agreement on best practices to determine MRSA carriage, lack of evidence-based management when colonization is found, and the insignificant impact of an effective institution-based strategy on MRSA infections in the community.[243]

In the community setting, some sports teams have increased efforts to schedule equipment washing, discourage towel sharing, restrict infected members from play until lesions have healed, and encourage good hygiene among team members.[244,245] Several correctional facilities have introduced practices to reduce the spread of CA-MRSA, as recommended by the Federal Bureau of Prisons.[72] Chlorhexidine-impregnated cloths were used successfully in prisons to reduce the density of skin colonization,[246] and they are frequently are used preoperatively; however, this approach was unsuccessful in preventing SSTIs among military recruits.[247]

MRSA decolonization has been attempted in outbreak situations and to prevent recurrent SSTI, with little success. Few randomized, controlled trials have evaluated the efficacy of topical antibiotics and skin antisepsis in the eradication of *S. aureus* carriage.[99,248–251]

Intranasal mupirocin ointment appears to have the most success in reducing previous HA-MRSA nasal colonization, and it has shown a subsequent decrease in carriage at other body sites. A 5-day application of intranasal mupirocin resulted in decreased short-term rates of colonization, but recolonization occurred in at least one half of the treated subjects, usually within a few months.[99] Unacceptably high recolonization rates, concern about mupirocin resistance,[252,253] and limited data about the drug's effectiveness against CA-MRSA prevent intranasal mupirocin from being recommended for routine use. Focusing on reducing the density of colonization and environmental contamination, as well as improving underlying skin conditions, may be more prudent.

Vaccine Development

A vaccine to prevent *S. aureus* infection remains a formidable challenge. Experts disagree on whether *S. aureus* infections can be prevented by vaccination and, if so, whether such a vaccine should be deployed universally or targeted to high-risk groups.

The traditional idea that production of an opsonophagocytic antibody (or antibodies) correlates with protection has been challenged by available data. In two vaccine trials of types 5 and 8 polysaccharide conjugate vaccine, immunization failed to provide protection against BSI.[254] Recently a protein vaccine containing an iron-scavenging, cell wall–anchored protein (ISDB) was developed. Enrollees in the study of this vaccine were adults undergoing elective cardiac surgery that required a sternotomy. The clinical end point was the occurrence of *S. aureus* mediastinitis or bacteremia. However, the study was halted for lack of efficacy and because of concern that vaccine recipients who developed *S. aureus* invasive infection had a worse outcome than placebo recipients.[16] A clinical trial of a 4-component vaccine, including the capsular antigens manufactured by Pfizer, currently is enrolling adults undergoing elective spinal surgery.

In an initial trial, attempts to protect neonates passively with a high-titer, anti–clumping factor A polyclonal antibody product (Veronate) appeared to have promising results; however, a confirmatory trial did not confirm efficacy (Hetherington S. Personal communication, 2006.). A clinical trial using a monoclonal antibody (pagibaximab) directed against lipoteichoic acid was conducted among small premature infants in an attempt to prevent infections caused by *S. aureus* and coagulase-negative staphylococci; however, efficacy was lacking.

Recent attention has focused on the role of the Th17/IL-17 lymphocyte pathway.[255] One candidate vaccine (rAls3p-N) derived from a *Candida* adhesin protected mice against bacteremic challenge. Efficacy was retained in mice that were B-lymphocyte deficient but not in those that were T-lymphocyte deficient. Adoptive transfer of $CD4^+$ lymphocytes, but not $B220^+$ lymphocytes, transferred immunity. The vaccine apparently stimulates proinflammatory Th1, Th17, and Th1/Th17 lymphocytes, and these cytokines enhance neutrophil recruitment and activation. As of February, 2015, the manufacturer had yet to decide whether to evaluate this vaccine against *S. aureus* in an efficacy trial.

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Staphylococcus epidermidis and Other Coagulase-Negative Staphylococci

Philip Toltzis

Staphylococcus epidermidis and other coagulase-negative staphylococci (CoNS), once considered nonpathogenic commensal organisms, now are recognized clearly as potential true pathogens, particularly in hospitalized patients and those with indwelling foreign bodies. Multiple surveys have shown that CoNS are the most frequent cause of nosocomial bloodstream infections (BSIs) around the globe.[1–6] These organisms are implicated particularly in bacteremic disease in patients in the intensive care unit (ICU)[4,5,7–10] and in patients immunocompromised by cancer[11–18] or solid-organ transplantation.[19,20] CoNS account for 20% to 50% of all nosocomial BSIs in these patient groups.

Description of the Pathogen

Staphylococci are members of the family Staphylococcaceae. They are nonmotile, nonspore-forming, catalase-positive bacteria.[21] These organisms are gram-positive cocci that grow in irregular clusters. Staphylococci are among the hardiest of nonspore-forming bacteria and can survive many nonphysiologic environmental conditions. Colonies are round, smooth, raised, and glistening and can be surrounded by a zone of hemolysis when grown on blood-containing media.

In the clinical microbiology laboratory, CoNS are distinguished from *Staphylococcus aureus* by their failure to produce coagulase, an enzyme that coagulates rabbit plasma. Originally, all CoNS were grouped together under the designation *Staphylococcus albus;* by 2015, however, 50 species and numerous subspecies of CoNS had been recognized, based on biochemical and genetic differences (for the current classifications, see the website http://www.bacterio.cict.fr/). Fifteen species are normal human flora: *S. epidermidis, S. haemolyticus, S. hominis, S. saccharolyticus, S. capitis, S. warneri, S. caprae, S. pasteuri, S. saprophyticus, S. cohnii, S. xylosus, S. simulans, S. auricularis, S. lugdunensis,* and *S. schleiferi*.[21] All CoNS primarily are skin commensals, but they can colonize the upper respiratory tract, gastrointestinal tract, genitourinary tract, and mammary glands. Some species exhibit preferential niches for certain areas of the skin, such as *S. capitis* for the sebaceous gland-rich scalp, *S. auricularis* for the external auditory canal, *S. hominis* and *S. haemolyticus* for the apocrine gland–rich axillae and pubis, and *S. saprophyticus* for the female genitourinary tract.

Many clinical microbiology laboratories continue to characterize isolates simply as CoNS. However, commercially available kits can rapidly distinguish CoNS species with an accuracy of 70% to greater than 90%.[21] Most kits include a series of biochemical reactions, although systems based on polymerase chain reaction amplification of ribosomal ribonucleic acid *(rRNA)* and other conserved genes also have been described.[21] Species identification of *S. lugdunensis* and *S. schleiferi* is particularly important because these species cause aggressive disease more typical of *S. aureus*.[22,23] In the laboratory they can be distinguished from most other CoNS because they produce a positive result on a rapid coagulase slide test (reflecting the presence of “clumping factor” rather than bound coagulase); as do other CoNS, however, they test negative with the more definitive coagulase tube assay.[21] Both *S. lugdunensis* and *S. schleiferi* are relatively uncommon on normal human skin, but they can colonize implanted materials, such as catheters and drains. *S. lugdunensis* has been implicated in natural and prosthetic valve endocarditis, septicemia, brain abscess, peritonitis, soft tissue infection, vascular graft infection, prosthetic joint infection, and catheter-related infection.[22–27] *S. schleiferi* rarely has been reported as a pathogen in the United States, but in some European countries it has caused brain empyema, wound infection, osteomyelitis, and BSI.[23,28,29]

Pathogenesis

Colonization is a prerequisite for CoNS disease. CoNS can be isolated from multiple skin surfaces, which suggests that most infections originate from organisms on the skin.[30,31] Most patients who develop a CoNS infection have an obvious disruption of the skin barrier, caused by surgery, placement of a catheter, or insertion of a prosthesis. Systemic infection also can originate from colonized mucous membranes of the pharynx and gastrointestinal tract when organisms enter the bloodstream, either through breaks in the mucosa or by translocation through mesenteric lymph nodes.[32,33]

Unlike *S. aureus,* CoNS typically do not elaborate virulent exotoxins. Consequently, infections caused by most CoNS characteristically are indolent and prolonged, even in compromised patients. The prominence of CoNS as nosocomial pathogens stems largely from their propensity to adhere to the inanimate surfaces of catheters and prostheses and also in their ability, once established, to evade host defense mechanisms and antibiotic activity. Both characteristics are mediated by the production of biofilm, a thick accumulation of bacteria arranged in multilayered clusters that are covered by an extracellular matrix. The importance of biofilm in CoNS pathogenesis has been confirmed repeatedly by demonstrations that mutants deficient in biofilm-related molecules are less likely to cause disease than their isogenic counterparts.[34,35]

The formation of biofilm occurs in three overlapping stages: attachment of the CoNS to polymer surfaces; maturation of the organisms within the biofilm to form a complex, multilayered structure; and detachment, which allows the organisms within the biofilm to disseminate to distant sites.[36–38] (Fig. 116.1). In the first stage, nonspecific factors, including long-range electromagnetic forces and surface hydrophobicity, promote attachment.[39,40] Several bacteria-specific products mediate this seminal stage of attachment. Chief among these is the surface-associated autolysin AtlE, which shows significant homology to the major autolysin of *S. aureus*.[41] AtlE mediates binding to unmodified plastic surfaces indirectly, by altering the hydrophobicity of the bacterial cell wall.[36,37] Two related staphylococcal surface proteins, SSP-1 and SSP-2, are fimbria-like polymers encoded by *S. epidermidis* that further mediate adherence to polymers.[42,43] Once inserted into the body, plastic surfaces become coated with plasma and extracellular host proteins such as fibronectin, fibrinogen, vitronectin, thrombospondin, and von Willebrand factor, and bacterial molecules also bind these host molecules (Fig. 116.1). Several such molecules have been characterized; they are known collectively as microbial surface components recognizing adhesive matrix molecules (MSCRAMMs).[36–38,44,45]

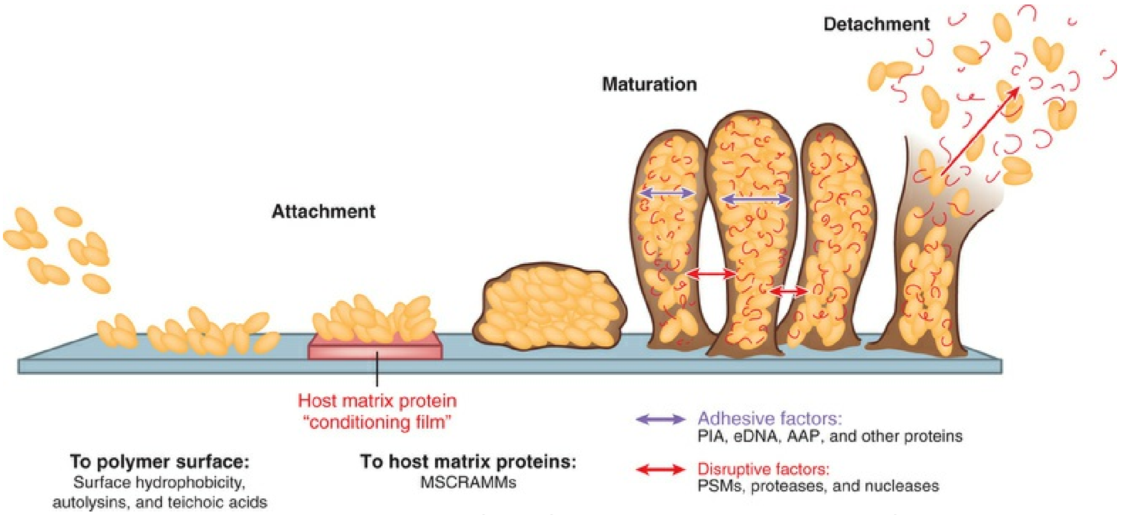

FIGURE 116.1 Phases of biofilm development. Biofilm development includes initial attachment, maturation, and detachment. Attachment can occur directly to a surface (e.g., a polymeric surface of an indwelling medical device) or to a "conditioning film" formed by host matrix molecules. Then biofilm maturation proceeds via the agglomeration of cells, which is dependent on adhesive molecules. Formation of the characteristic channel-containing biofilm structure depends on disruptive forces, which also ultimately

facilitates the last phase of biofilm development, detachment. Molecular determinants that have been shown or are suspected to be involved in the biofilm development phases in staphylococci are noted at the bottom of the illustration. AAP, accumulation-associated protein; eDNA, extracellular DNA; MSCRAMMs, microbial surface *components recognizing adhesive matrix molecules*; PIA, *polysaccharide intercellular adhesin*; PSMs, phenol-soluble modulins. (From Otto M. Staphylococcal infections: mechanisms of biofilm maturation and detachment as critical determinants of pathogenicity. Annu Rev Med 2013;64:175–188.)

After attachment and during the maturation phase, organisms accumulate and form multilayered aggregates; this is the critical stage of biofilm formation (see Fig. 116.1). In 1994, Mack and coworkers found that a *S. epidermidis* transposon mutant that lacked a polysaccharide antigen, called polysaccharide intercellular adhesin (PIA), was unable to form multilayered cell clusters.[46] PIA since has been confirmed as the central molecule in CoNS biofilm production. PIA is encoded by the *icaADBC* gene cluster, which is responsible for its synthesis and modification; mutation of any of the four open reading frames in the *ica* gene locus interferes with maturation of the CoNS biofilm.[36,37,44] The control of *ica* expression is incompletely understood but is influenced by several negative and positive regulators, which presumably promote the production of biofilm under specific environmental conditions.[44,47,48] However, *ica*-negative CoNS that produce biofilm have been identified, indicating the existence of PIA-independent mechanisms of biofilm formation.[49–51] Three candidates are a 140-kd extracellular protein called accumulation-associated protein[52,53]; extracellular matrix binding protein; and extracellular deoxyribonucleic acid (eDNA) released from lysed bacteria; all three of these also may participate in the first (attachment) phase of biofilm formation.[36] These additional molecules add redundancy to the synthetic mechanisms of CoNS, mediating accumulation in organisms with a compromised ability to express PIA.[37]

After attachment and maturation, most biofilm isolates elaborate copious amounts of a complex extracellular material generally referred to as slime.[54] In a hospital-wide survey Ishak and associates[55] found slime production in 13 of 14 clinically significant bloodstream isolates of *S. epidermidis*, but in only 3 of 13 blood culture contaminants and 4 of 27 skin isolates. Studies of infants with CoNS infection have yielded similar results. In independent studies, slime production was noted in 82% of isolates from infants with invasive disease.[56]

The third phase of biofilm formation, detachment, likely is mediated by the formation of channels within the structure that allow the resident bacteria access to nutrients.[37] Quorum-sensing mechanisms in CoNS recognize the bacterial density in the biofilm and convert the replicating populations to a more stationary phase.[37] Additionally, these mechanisms activate the expression of a family of surfactants called phenol-soluble modulins (PSMs), which affect the volume of biofilm and the formation of channels. Under flow conditions such biofilms detach, allowing dissemination of organisms to distant sites.[37] CoNS with disrupted PSM function form biofilms that are more compact and tightly adherent to the plastic surface than the biofilms produced by CoNS with functional PSMs; however, the ability of the former to spread is diminished.

Several biofilm-related molecules are implicated in immune evasion.[57] PIA may render the organism more resistant to neutrophil clearance; *S. epidermidis* organisms that contain *ica* gene mutations and deficient PIA are phagocytosed more readily in vitro and are more susceptible to the toxic effects of neutrophil granules than their isogenic correlates.[35,58] These antiphagocytic properties may make the organism particularly pathogenic in premature infants, who have depressed neutrophil function compared with that of term infants and adults.[59] Slime further functions as a nonspecific physical barrier to cellular and humoral defense mechanisms. In addition, it inhibits neutrophil chemotaxis and phagocytosis and suppresses lymphocyte blastogenesis.[60] Crude extracts of slime can inhibit the antimicrobial action of the glycopeptide antibiotics vancomycin and teicoplanin.[61] This effect appears to be limited to the glycopeptide class of antibiotics because slime extracts produce no change in the minimal inhibitory concentration (MIC) of cefazolin, clindamycin, or rifampin.

CoNS also elaborate a variety of exoproteins. Examples include urease, lipase/esterase, fibrinolysin, DNase, and a number of proteases. For the most part the specific function of these bacterial products remains undetermined. In addition, some isolates produce δ-like toxin, an extracellular hemolysin that resembles the enteropathic δ-toxin of *S. aureus* in size, biologic properties, and antigenicity.[38] This δ-like toxin has cytotoxic effects on intestinal epithelium, and investigators have correlated free toxin in the stool of premature infants with the development of necrotizing enterocolitis (NEC).[62] *S. epidermidis* further produces a number of lantibiotics, or antibiotic peptides containing the unusual amino acids lanthionine or methyllanthionine that can suppress the growth of competing bacteria on skin and mucous membrane surfaces.[38]

S. saprophyticus elaborates a number of factors that may contribute to its ability to cause urinary tract infections (UTIs). A hemagglutinin/adhesin expressed on the surface of *S. saprophyticus* and the surface fibrillar protein SSP both bind to uroepithelial cells, which may explain the peculiar tropism of this species for the urinary tract. *S. saprophyticus* further elaborates a urease, which damages bladder tissue once infection has been established.[63]

Epidemiology

CoNS are acquired early in life; virtually all infants carry them at multiple sites by 2 to 4 days of age.[64] Colonization among healthy people remains ubiquitous beyond the newborn period. Many CoNS responsible for community-associated infections previously were methicillin susceptible, but community strains increasingly have become resistant.[65,66] In one Japanese study, nearly one third of healthy children had nasal colonization with methicillin-resistant CoNS.[66] Although community CoNS have a diverse lineage, a substantial proportion carry the same staphylococcal cassette chromosome mec cassette (SCC*mec*) IV, which is responsible for methicillin resistance in community-associated methicillin-resistant *S. aureus*.[65,66]

Accumulating evidence suggests that, in contrast to the diversity of community-derived CoNS strains, one or more CoNS strains in an individual hospital unit can become predominant over a protracted period. Genetically identical or strongly related organisms have been isolated from a number of patients in an ICU,[67–72] a hematology-oncology unit,[73] a dialysis unit,[74] and even among several wards in a particular hospital.[75,76] Dominant strains can circulate in affected units for many years.[70] The hands of nurses become colonized by hospital-associated CoNS strains soon after employment,[77,78] which highlights the importance of personnel in patient-to-patient transmission. The biologic properties that confer strain predominance are not known, but interference with the growth of surrounding organisms and superior adherence to colonizing surfaces have been speculated to provide a relative survival advantage.

Clinical Manifestations

Bloodstream Infection and Intravascular Catheter–Associated Infection Outside the Newborn Period

CoNS account for roughly one third of all BSIs in children undergoing therapy for leukemia, lymphoma, or solid tumors.[79] In addition, CoNS are an important cause of septicemia in recipients of stem cell transplants.[80] The strongest risk factor for CoNS BSI in these patients is the presence of a central venous catheter (CVC), although immunosuppressive therapy, neutropenia, and chemotherapy-induced gastrointestinal mucositis also are associated risk factors. Mortality from CoNS BSI in this group is reported to be as high as 11%.[79,81] Additionally, *S. epidermidis* is the most common species associated with CVC-associated infections in patients in ICUs with temporary, percutaneously inserted catheters.[82] Infection related to a CVC can occur at the exit site, along the catheter tunnel, or on the intravascular portion. Heavy skin colonization followed by tracking of the organisms along the external surface of the catheter is the principal mechanism of CoNS catheter-associated BSI (also referred to as *central line associated BSI* [CLABSI]).[30,83] Additionally, the catheter hub can become contaminated and organisms can reach the intravascular portion along the inner surface.[30]

In addition to being a frequent cause of CLABSI, CoNS are the most common contaminants of blood cultures, and distinguishing true infection from contamination often is difficult. Some patients who show a positive result on a blood culture for CoNS experience systemic manifestations of infection, such as fever, tachycardia, tachypnea, and hypotension[84]; this makes the diagnosis of true infection relatively secure. In the patient with more subtle signs and symptoms, the most important evidence of true infection is repeated positive results on blood cultures drawn at separate samplings over 1 to 2 days.[85–88] In 2008 the Centers for Disease Control and Prevention established the diagnostic criteria currently used for catheter-associated BSI caused by CoNS (and other skin commensals). These criteria include at least two blood cultures showing a positive result (www.cdc.gov/nhsn/PDFs/pscManual/4PSC/_CLABSIcurrent.pdf).

Several investigators have attempted to define additional diagnostic methods to confirm that the catheter is the source of bacteremia. Quantitative blood cultures are most useful in this regard; specifically, the catheter is likely the source of the infection if the density of organisms in blood obtained through the catheter is at least 5- to 10-fold greater than that in blood drawn simultaneously from a peripheral vessel.[89] When quantitative cultures are unavailable, the relative concentrations of bacteria in central and peripheral blood can be estimated by comparing the time-to-positivity of blood samples taken from the central line and from a peripheral site; a difference in time-to-positivity greater than 120 to 180 minutes suggests that the catheter is the source of infection. However, this comparison is valid only if the samples are of equal volume.[90,91]

Culturing the intravascular portion of the catheter itself is the most reliable method of establishing the catheter as the source. Maki and associates[92] determined that CLA BSI can be confirmed by removing the catheter, rolling the distal 5 to 7 cm of the catheter over an agar surface, and finding growth of 15 or more colonies. The drawback to this method is that it requires removal of the catheter. Fortunately most patients with CoNS exit site infection and roughly 75% of those with BSI arising from a surgically implanted, tunneled catheter can be cured without removing the catheter.[89] Although the risks of recurrent CoNS BSI are increased if the BSI is treated with the line in situ,[93,94] in one study this practice did not contribute to increased mortality.[93] Treatment typically is continued for 10 to 14 days after sterilization of the blood. Catheter removal is almost always necessary when tunnel infection is present. In percutaneous catheters that are not placed surgically, particularly those commonly inserted into patients in the ICU, catheter-related BSI generally requires catheter removal.

Neonatal Septicemia

In the neonatal intensive care unit (NICU), CoNS are recognized worldwide as the most frequent cause of late onset sepsis (sepsis that occurs 7 days or more after hospitalization) in very low birth weight infants.[7,95–99] CoNS also have been implicated as principal pathogens in early onset neonatal sepsis.[8,100–102] In fact, as intrapartum antibiotic prophylaxis to prevent early onset neonatal group B streptococcal infection has become standard, CoNS are second only to gram-negative bacteria as a cause of early onset sepsis.[102,103] Unlike older patients, neonates (especially very low birth weight infants) with CoNS BSI often have focal complications, which frequently are heralded by persistent bacteremia.[104–106] Sites of localized disease include the skin, the heart, an intravenous thrombus, the central nervous system, the lungs, and bones and joints.[96] As in older children, CoNS BSI in the newborn often is a consequence of CVC contamination. CVCs have been implicated in greater than 50% of cases of neonatal CoNS BSI, especially catheters used to infuse parenteral nutrition, particularly lipid emulsions,[107] because intralipid may provide an enriched medium for proliferation of CoNS. Alternatively, the skin, upper airway, and gastrointestinal tract of the critically ill neonate frequently become colonized by CoNS, particularly with prolonged hospitalization, and these sites also may serve as a nidus for bloodborne infection.[95,108–111]

In a critically ill neonate, performing more than a single blood culture before starting antibiotic therapy often is impossible. When CoNS are isolated from a single blood culture, assessment of the likelihood of true infection may be difficult.[112] Infants with septicemia are significantly more likely to have a central catheter or an abnormal hematologic value (white blood cell count $>20{,}000/\text{mm}^3$ or $<5000/\text{mm}^3$, an immature to total neutrophil ratio >0.12, or a platelet count $<150{,}000/\text{mm}^3$). Culture contamination is more likely when infants lack these clinical features.[113,114]

Necrotizing Enterocolitis and Neonatal Focal Intestinal Perforation

Severe, even fatal cases of NEC have been associated with *S. epidermidis* infection.[115] CoNS are a component of the perturbed gut microbiome typical of the critically ill neonate,[116] and this abnormally developing colonic microflora is a key factor potentiating NEC.[117] In one study examining infants who simultaneously experienced NEC and bacteremia, CoNS were the most commonly isolated gram-positive species.[118] Gruskay and associates[119] described a series of neonates who, in contrast to typical NEC, had *S. epidermidis* BSI and associated acute enterocolitis. By definition, all 19 infants had bloody stools with mucus, in addition to signs and symptoms of enterocolitis and an abnormal abdominal radiographic finding. The clinical courses in this series were mild; only one infant had pneumatosis intestinalis, and none required surgical intervention or died. These findings are consistent with CoNS peritonitis caused by focal intestinal perforation, a condition that, in contrast to typical NEC, involves only a limited area of bowel.[120]

Endocarditis

CoNS are an important cause of infective endocarditis. In older children and adults CoNS account for approximately 5% of cases of endocarditis involving previously normal valves.[121,122] Endocarditis in this situation develops after a period of transient BSI with seeding of the valve. CoNS also have been implicated in native valve endocarditis in children with congenital heart disease; inoculation most often occurs at the time of surgical repair. CoNS also are the most common cause of prosthetic valve endocarditis, accounting for 25% to 40% of all such cases. The pathogenesis is believed to involve contamination at the time of surgery, with subsequent formation of an abscess at the valvular ring.[123–125]

Although some cases of CoNS endocarditis are caused by the intrinsically pathogenic *S. lugdunensis,* most are caused by *S. epidermidis.*[121,123–125] Therefore, the course of CoNS endocarditis typically is indolent, sometimes evolving over several months, although acute onset with valvular destruction that requires surgical intervention also can occur.[121,126,127] Fever, the most common finding, is present in approximately 90% of patients. Other findings include splenomegaly, petechiae, and a new or changed murmur. Classic manifestations of bacterial endocarditis, including Osler nodes, Roth spots, Janeway lesions, and splinter hemorrhages, are uncommon. In practice, the initial blood culture isolation of CoNS in patients who later prove to have endocarditis frequently is dismissed.[128] Timely diagnosis, therefore, requires a high level of suspicion.

In neonates, CoNS endocarditis usually is right sided and tends to occur when the tip of an intravascular catheter is positioned in the right atrium.[129] Although the mortality associated with neonatal infective endocarditis caused by other pathogens is high, the outcome of CoNS endocarditis is more favorable. An important diagnostic clue to the presence of endocarditis in the neonate is persistent bacteremia despite removal of the catheter and appropriate antibiotic therapy, especially in the presence of thrombocytopenia. Distinguishing endocarditis from an infected intravascular thrombus at an extracardiac site sometimes is difficult. The diagnosis is confirmed by echocardiography, which reveals intracardiac lesions associated with a valve or the endocardial wall. Removal of the catheter is fundamental to cure.

Cerebrospinal Fluid Shunt Infections and Meningitis

In approximately 10% of cerebrospinal shunts placed in children, infectious complications occur within 24 months of the shunt's insertion,[130] and CoNS are the principal organisms implicated. *S. epidermidis* alone accounts for 60% to 75% of cerebrospinal fluid (CSF) shunt infections. Seventy percent of shunt infections occur within 2 months of placement, which suggests that in most cases seeding occurs at the time of surgery.[131] Because infection is associated commonly with shunt or catheter obstruction, signs and symptoms frequently reflect increased intracranial pressure, such as headache, vomiting, and depressed mental status. In addition, many patients have a low-grade fever. Examination of the CSF most often reveals modest pleocytosis, typically with an elevated protein concentration and sometimes with a slightly depressed glucose level. The Gram stain result is variably positive. In some patients the result of CSF analysis is completely normal; in these cases, repeated isolation of the same strain is required to establish causation.

Few data guide the optimal approach to an infected CSF shunt. Most practitioners remove the contaminated apparatus and eradicate infection with parenteral antibiotics; meanwhile the CSF is drained through a temporary external ventricular drain. A new internal shunt then is placed. Using mostly experiential data, a decision analysis concluded that this approach results in fewer deaths and treatment failures compared with strategies using antibiotics plus immediate shunt replacement or antibiotics alone.[132] In addition, some clinicians instill antibiotics directly into the ventricles through the drain,[133–135] but the benefits of this practice beyond those derived from systemic antibiotics and shunt removal are not known.

Isolated CoNS meningitis in the absence of an intraventricular foreign body has been reported in neonates, presumably as a result of undetected BSI.[106,136] One study described 10 infants with *S. epidermidis* meningitis who had unremarkable CSF white blood cell counts (mean, 6 cells/mm^3; range, 0 to 14) and normal glucose and protein concentrations.[136] In this series, no death or case of hydrocephalus secondary to meningitis was reported.[136] The possibility of more subtle, longterm sequelae was not assessed.[136]

Peritonitis Associated With a Peritoneal Dialysis Catheter

Infection remains the most common complication of peritoneal dialysis.[137,138] According to several studies the cumulative risk of peritonitis in patients undergoing continuous ambulatory peritoneal dialysis (CAPD) is approximately 60%.[138] *S. epidermidis,* the most common bacterial pathogen, accounts for roughly 40% of infections.[138] The most frequent symptoms of catheter-related peritonitis include abdominal pain, nausea, and vomiting. Fever is present in a minority of patients. The physical examination typically reveals abdominal tenderness, and in nearly all cases cloudy peritoneal fluid is present.

The criteria for the diagnosis of catheter-related peritonitis are not uniform from one study to another, but generally they include some combination of abdominal pain, peritoneal fluid with more than 100 neutrophils/mm^3, and a positive result on a peritoneal fluid culture.[138] In the absence of CoNS tunnel infection, antibiotic treatment without removal of the catheter usually is successful.[139,140] Effective regimens have included intraperitoneal, parenteral, oral, or intraperitoneal plus oral administration of antibiotics. Treatment failure requires retreatment or removal of the catheter.

Urinary Tract Infection

CoNS are an important cause of UTI, particularly in adolescent girls and young adult women.[141–145] *S. saprophyticus,* the species implicated most often, is identified readily in the clinical microbiology laboratory on the basis of its resistance to a 5-μg novobiocin disk.[146] *S. saprophyticus* UTI is almost always symptomatic, and it involves the upper urinary tract in approximately one half of cases. Sexual intercourse is an important risk factor for infection, presumably by facilitating the spread of bacteria from the urethra and periurethral area into the bladder. In one study nearly 70% of females with *S. saprophyticus* UTI gave a history of sexual intercourse within the 24 hours preceding the onset of symptoms.[142]

Other species of CoNS occasionally cause UTI, such as *S. epidermidis* and *S. haemolyticus.* In contrast to *S. saprophyticus,* these species most commonly produce disease in hospitalized patients, generally those with an indwelling urinary catheter. On occasion CoNS cause UTI in otherwise healthy children.[147]

Miscellaneous Infections

CoNS can cause a number of other infections, many described primarily in neonates. Pneumonia caused by CoNS occurs almost exclusively in ill premature infants. In general, the diagnosis is assigned when CoNS are isolated from blood of an infant with respiratory distress and a pulmonary infiltrate. A series by Hall and coworkers[56] identified 12 infants with hospital-acquired pneumonia among 27 with CoNS BSI; 9 of these 12 were intubated when a positive result on a blood culture and pulmonary infiltrate were identified, and 3 had been intubated previously. Neonates also can experience omphalitis and abscesses caused by CoNS.[148] Omphalitis is characterized by purulent discharge at the umbilical stump, along with erythema, edema, and tenderness in the periumbilical area. Abscess formation secondary to CoNS can occur at a variety of sites, but the most frequent are the breast and the scalp. Breast abscess is encountered most often during the second or third week of life and occurs more frequently in females. Scalp abscess usually is a complication of a scalp electrode used for fetal monitoring. In rare cases, CoNS can cause primary or secondary osteomyelitis in neonates, particularly in premature infants.[96,149] CoNS further has been implicated as a cause of hospital-acquired conjunctivitis in the NICU.[150]

In older children, CoNS are an important cause of endophthalmitis and keratitis,[151] which most frequently occur after intraocular trauma.[152] CoNS infections of the ocular surface also can result from prolonged use of contact lenses, including those used for orthokeratology.[153–155] Mediastinitis caused by CoNS can occur after median sternotomy for open heart surgery.[156] Additionally, BSI from CoNS may be potentiated by delayed sternal closure after surgery for congenital heart malformations, even in the absence of overt soft tissue infection.[157] CoNS infection also has been associated with a variety of implanted foreign bodies, including pacemaker wires, left ventricular assist devices, baclofen pumps, hemodialysis shunts, intravascular grafts, and prosthetic joints.[158–161]

Antibiotic Treatment

Resistance to penicillin, methicillin, and gentamicin is common among hospital-associated CoNS isolates.[56,113,162] Full resistance to vancomycin is rare but has been reported in isolates of *S. haemolyticus*.[163] Higher, “creeping” MICs of vancomycin for CoNS are a concern. Intermediate resistance to vancomycin has been observed in *S. epidermidis*, and the percentage of all clinical isolates of CoNS with a vancomycin or teicoplanin MIC of 4 μg/mL has increased with continued use of glycopeptides.[164–167] An adequate area under the plasma drug concentration–time curve (AUC) is difficult to achieve when the vancomycin MIC exceeds 1 μg/mL.

Despite these observations, vancomycin remains the antibiotic of choice for the treatment of suspected or proven CoNS infection. The need to initiate empiric use of vancomycin prior to receiving blood culture results is disputed. Septicemia from CoNS, even in the NICU population, usually is low grade,[168] and observational studies indicate no adverse effects on survival if vancomycin is withheld until infection has been proved. For example, in a multicenter study involving 348 NICUs that evaluated the need for empiric vancomycin use, the 30-day mortality rate was unaffected by delaying vancomycin therapy, even after the researchers had controlled for multiple potentially confounding variables.[169]

β-Lactam antibiotics should be used for CoNS septicemia when this course is supported by the results of antibiotic susceptibility tests. However, several caveats are noteworthy when considering the results of susceptibility tests. First, penicillin resistance in CoNS frequently is mediated by the production of β-lactamase, which is not always detected by microdilution methods.[170] Therefore all isolates that appear to be susceptible to penicillin or ampicillin should be tested specifically for the presence of β-lactamase.[170] Such testing should be done after exposure to oxacillin, which induces β-lactamase expression. Second, although each organism in a population of CoNS may have the *mecA* genetic determinant for resistance to methicillin (and other penicillinase-resistant β-lactams), only a small fraction express this phenotype under testing conditions.[171] Consequently, resistance to methicillin can be overlooked.[172] In vitro expression of resistance to methicillin is favored by testing a large inoculum and by incubation on a medium containing salt at 30°C to 35°C. Alternatively, PCR testing can be used to identify *mecA* directly in pure colonies. Third, routine susceptibility testing frequently indicates that isolates of CoNS resistant to methicillin are susceptible to cephalosporins; however, cross-resistance is extensive; for clinical purposes, therefore, all staphylococci that are resistant to penicillinase-resistant penicillins also should be considered resistant to cephalosporins.

Assuming rigorous testing, infections caused by penicillin-susceptible, β-lactamase–negative organisms can be treated with penicillin. For isolates resistant to penicillin but truly susceptible to the penicillinase-resistant penicillins, therapy with oxacillin or nafcillin is preferred. Vancomycin is the agent of choice only for CoNS resistant to methicillin and for patients allergic to penicillin. The combination of rifampin and clindamycin (if CoNS are susceptible) might be an alternative regimen for patients allergic to penicillin.[173]

In some situations, such as endocarditis or an infection related to an intraventricular CSF shunt, synergistic antibiotic therapy may be indicated. Synergy has been demonstrated in vitro for vancomycin or β-lactams in combination with rifampin and gentamicin (with isolates susceptible to each). For adults with CoNS, endocarditis involving a prosthesis, therapy with three drugs (a cell wall–active agent plus rifampin and an aminoglycoside) is recommended for the first 2 weeks; the patient then is treated for 4 more weeks with the cell wall–active agent and rifampin.[174] Combination chemotherapy is commonly used for native valve endocarditis caused by CoNS; however, whether the outcome is altered by therapy that includes one or more agents in addition to a β-lactam or vancomycin alone is uncertain.[127]

During the late 1990s and early 2000s, antibiotic alternatives to vancomycin were developed for the treatment of methicillin-resistant CoNS and other multidrug-resistant gram-positive pathogens. Daptomycin, a parenteral lipopeptide, has in vitro activity against most clinical isolates of CoNS,[175–177] but published experience on their use in pediatrics is limited.[178] Linezolid has activity against most isolates of CoNS and other gram-positive bacteria,[179,180] although epidemic clusters of clonally related, linezolid-resistant CoNS infections have been reported.[181,182] Unlike other agents used to treat methicillin-resistant CoNS, linezolid is available in both a parenteral and an oral preparation[183]; the latter allows convenient, effective home therapy in selected patients.

Prevention

Strict handwashing is of primary importance for minimizing the horizontal spread of CoNS. In addition meticulous skin preparation and surgical technique to limit intraoperative bacterial contamination are fundamentally important for minimizing infection related to foreign bodies.

Percutaneously inserted catheters impregnated with broad-spectrum antimicrobial agents (specifically silver sulfadiazine plus chlorhexidine or minocycline plus rifampin) have been tested in adults for their ability to reduce catheter-associated BSIs (CLABSIs) caused by CoNS and other pathogens. Although meta-analyses assessing these devices' ability to prevent catheter infections have been positive,[184] controversy remains about their effectiveness.[185,186] The consensus opinion recommends the use of such catheters only when other prevention measures have failed.[187]

Antibiotic-impregnated CSF shunts also are available.[188–190] Meta-analyses, mostly of single-center studies,[191,192] repeatedly have supported their effectiveness, indicating that they reduce the rate of infection by approximately 50%. Another analysis indicated a favorable cost-benefit ratio for their use under most conditions.[193] However, one of the meta-analyses[192] documented an increased risk of infection caused by methicillin-resistant *S. aureus* and gram-negative bacilli associated with placement of these shunts, even though the study demonstrated an overall reduction in CSF shunt infections.

The use of prophylactic antibiotics during the implantation of a foreign body has not been studied well, and the benefits of this practice remain uncertain. Studies on the addition of vancomycin to hyperalimentation fluid in neonates to reduce the incidence of CoNS CLABSI indicated efficacy,[194,195] but the risk of promoting vancomycin resistance outweighs the risk of CoNS BSI, even in very low birth weight infants. A stronger case has been made for the use of antibiotic lock to reduce the incidence of CLABSI. The advantage of this strategy is that a high concentration of antibiotic can be instilled and allowed to dwell in the catheter, permitting penetration of the biofilm, and then removed. At least two meta-analyses have examined multiple randomized trials that tested the effectiveness of antibiotic lock solutions in reducing infection in a variety of catheter types in adults and children. These studies indicated a significant reduction in CLABSI compared with participants whose catheters were infused only with anticoagulant.[196,197] Several studies have evaluated the effectiveness of a lock solution composed of 70% ethanol, which has broad activity against gram-positive and gram-negative bacteria and fungi, in preventing CLABSI.[198,199] Although mostly retrospective in design, these analyses reported a statistically detectable reduction in the incidence of infection in catheters in place for longer than 1 week.[198–201] Several important aspects of prophylactic antibiotic and ethanol lock strategies remain incompletely defined, including the effects on the catheter's integrity of prolonged exposure to the solutions, and the ideal dwell time; for example, when this strategy is used in infants, dwell time (even if short) can result in frequent episodes of hypoglycemia.[202,203] However, in older children who require life-sustaining CVCs and who have experienced multiple CLABSIs despite other measures, lock strategies may be considered beneficial overall.[187]

During the first decade of the 2000s, several programs successfully promoted “best practices” to reduce CLABSIs, which resulted in a reduction in CoNS infections. “Bundles” of best practices were constructed based on published evidence and expert consensus. Most programs promoted hand hygiene[204] and used two sets of bundles, one for catheter insertion and one for catheter maintenance.[205–207] In many instances the results were dramatic. In the program adopted by 103 adult ICUs in Michigan, catheter-associated BSIs were reduced 82% within 3 months, a level that was sustained over the subsequent year.[208] In the National Children's Hospital Association's collaborative intervention in pediatric ICUs, CLABSIs dropped from 5.4 per 1000 line-days to a sustained rate of 3.1 per 1000 line-days.[207] In the initial Vermont Oxford Network (VON) program implementing best practices in NICUs, the incidence CLABSI fell from 26.3% before intervention to 20.9% after intervention.[209] Subsequently, VON collaborative groups have refined methods to reduce CLABSIs and demonstrated further reductions.[210] In one large U.S. neonatal center, interventions to reduce CLABSIs coupled with the promotion of hand hygiene resulted in the near-eradication of CoNS infection for several consecutive years.[211]

Other Coagulase-Negative Micrococcaceae

The family Micrococcaceae includes the occasional human pathogens *Micrococcus* species and *Rothia mucilaginosa,* among other species.[21] As are CoNS, these organisms are nonmotile, nonspore-forming, gram-positive cocci that grow as irregular clusters. Traditionally, micrococci and staphylococci have been grouped together based on their similar cellular morphology and catalase production. However, the two genera differ considerably in amino acid content, and complete genetic analyses have confirmed only a distant relationship.[21] Organisms formerly belonging to the genus *Micrococcus* have been divided into six separate genera, including *Micrococcus* (which includes the species *M. luteus*), *Kocuria, Kytococcus, Nesterenkonia, Dermacoccus,* and *Arthrobacter*. The micrococci are normal residents of the skin and usually are not considered pathogenic. Occasionally micrococci, particularly those derived from the species *M. luteus,* can cause serious disease. In general, micrococcal infections occur in people who have an indwelling medical device and an associated underlying condition, such as CLABSI in leukemia, peritonitis in CAPD, CSF shunt infection, and endocarditis in patients with prosthetic valves. Micrococci also are common culture contaminants, and assessment of their significance can be difficult. Most isolates are susceptible to a wide range of antibiotics, including penicillin, methicillin, vancomycin, gentamicin, and erythromycin. However, because resistance to a variety of antibiotic classes has been reported, vancomycin is the preferred agent for empiric therapy.

R. mucilaginosa (formerly known as *Staphylococcus salivarius* and later as *Micrococcus mucilaginosus* and then *Stomatococcus mucilaginosus*) is differentiated from organisms in the genera *Micrococcus* and *Staphylococcus* by absent or weak catalase activity and failure to grow in a nutrient medium supplemented with 5% sodium chloride. *R. mucilaginosa* likely is underreported as a human pathogen because it can be mistaken for other microorganisms. When weakly catalase positive *R. mucilaginosa* can be confused with CoNS or micrococci, and when catalase negative with streptococci. Traditionally believed to be an organism with low virulence, *R. mucilaginosa* now is recognized as an opportunistic pathogen that can cause BSI, meningitis, pneumonia, endocarditis, and peritonitis.[212–217] *R. mucilaginosa* also has been implicated in skin and soft tissue infections in children.[216] Most affected children have leukemia or a solid tumor and profound neutropenia.[215,216] Other risk factors for infection include the presence of a CVC, valvular heart disease, CAPD, and intravenous drug abuse. *R. mucilaginosa* is a normal resident of the mouth and upper respiratory tract; oral mucositis, dental surgery, and head and neck surgery have been reported to predispose to infection. The clinical course of *R. mucilaginosa* infection often is characterized by prolonged fever and a slow response to antibiotic therapy. Occasionally, fulminant infection and fatality have occurred.[212,215,216] Based on the limited reported cases, *R. mucilaginosa* appears to be susceptible uniformly to vancomycin, and most isolates also are susceptible to penicillin, ampicillin, oxacillin, cefazolin, imipenem, clindamycin, tetracycline, erythromycin, and rifampin.

Key Points

Staphylococcus epidermidis and Other Coagulase-Negative Staphylococci (CoNS)

Microbiology

- Coagulase-negative gram-positive cocci that grow in irregular clusters
- More than 50 species and subspecies have been identified; 15 are normal human flora.
- Most reside on skin, but also are present on mucosa of the upper respiratory, gastrointestinal, and genitourinary tracts.

Pathogenesis

- Gain entrance through a disruption in the skin or mucosal barrier, such as occurs with a surgical procedure or placement of a device or a prosthesis
- Principal pathogenic characteristics are propensities to adhere to prosthetic surfaces and to form biofilm.
- Do not produce exotoxins; infections usually indolent

Clinical Syndromes

- Bloodstream infection, usually originating from a contaminated intravascular catheter

- Endocarditis, especially in the presence of a prosthetic valve
- Infection related to cerebrospinal fluid shunt
- Infection related to peritoneal dialysis catheter
- Community-associated urinary tract infection caused by *S. saprophyticus*, and healthcare, catheter-associated infection caused by multiple species
- Particularly prevalent in premature infants, in whom infection is less commonly associated with instrumentation than in older children and adults

Treatment

- Some community-associated strains remain susceptible to semisynthetic penicillins and cephalosporins.
- Most hospital-associated strains are methicillin resistant and require use of vancomycin.
- Removal of infected prosthetic material depends on its location, composition, and clinical factors.

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117

Classification of Streptococci

David B. Haslam, Joseph W. St. Geme III

The genus *Streptococcus* is among the most diverse of bacterial genera. It consists of more than 50 species, and classification has been the source of considerable confusion.[1] Until recently, classification was based entirely on external characteristics of the organisms. Some features of the initial classification scheme remain useful to the clinician, such as patterns of hemolysis and serotype. Molecular methods have refined and clarified relationships among the diverse streptococcal species.[2,3] It is noteworthy that a variety of gram-positive catalase-negative cocci belonging to other genera often are erroneously referred to simply as "streptococci" (Box 117.1). The biochemical differentiation and clinical features of these genera are discussed elsewhere (see Chapter 124).

Box 117.1

Clinically Relevant Genera Constituting the Gram-Positive Catalase-Negative Cocci

Streptococcus	*Gemella*
Enterococcus	*Lactococcus*
Leuconostoc	*Abiotrophia*
Pediococcus	*Granulicatella*
Aerococcus	

The earliest subdivision of the genus *Streptococcus* was based on the ability to lyse sheep red blood cells.[4] β-Hemolytic streptococci produce complete hemolysis on sheep blood agar and cause the formation of a transparent ring around each colony. In contrast, α-hemolytic organisms produce partial red cell injury, induced by the release of hydrogen peroxide, which results in a green or grayish zone surrounding the colonies. When α-hemolytic organisms are grown under oxygen-depleted conditions, hydrogen peroxide is not formed, and colonies appear nonhemolytic. Nonhemolytic organisms are classified as γ-hemolytic. In order to avoid confusion in the classification of partially hemolytic streptococci, some investigators prefer that only β-hemolytic organisms be classified as hemolytic and that all others (including the α-hemolytic streptococci) be considered nonhemolytic.

Beyond the broad classification of streptococci based on hemolysis, Lancefield[5] subdivided these organisms on the basis of their reactivity with pools of antisera that now are known to recognize cell surface carbohydrates. Antigenically related strains are grouped alphabetically, A to H and K to V. Although the Lancefield grouping originally was used to differentiate the β-hemolytic streptococci, it should be noted that hemolysis and Lancefield serogrouping are not mutually exclusive. For example, group C streptococci can be α-hemolytic, β-hemolytic, or nonhemolytic.

Colony morphology commonly is used to differentiate streptococci further, and in some circumstances colony size takes precedence over other features in classification. Particularly notable in this regard are the viridans streptococci, an extremely heterogeneous group that includes organisms in most Lancefield groups (excluding A, B, and D) and with all patterns of hemolysis.[6] In general, a strain that produces minute colonies on solid agar is grouped with the viridans streptococci, regardless of its Lancefield reactivity or hemolysis.

When considered together, Lancefield grouping, hemolysis, and colony morphology enable a clinically useful subdivision of the genus (Table 117.1). For the most part the organisms of the Lancefield groups are β-hemolytic and associated with pyogenic infections. Organisms that cannot be assigned to a Lancefield group usually belong with the viridans streptococci; they generally are of lower virulence but may be associated with bloodstream infection, endocarditis, and a variety of diseases in a compromised patient.

Streptococcus pneumoniae is now grouped among the viridans sptreptococci based on its close genetic and phenotypic relatedness to the mitis group of organisms. *S. pneumoniae, S. mitis,* and *S. oralis* are difficult to distinguish using molecular testing methods.[7]

TABLE 117.1

Classification of Streptococci Most Commonly Associated With Human Disease

Lancefield Group[a]	Species	Hemolysis	Most Common Human Diseases
A	*Streptococcus pyogenes*	β	Pharyngitis, skin infection, wound infection, necrotizing pneumonia, conjunctivitis, postinfectious glomerulonephritis and rheumatic fever
B	*Streptococcus agalactiae*	β	Neonatal septicemia, meningitis, osteomyelitis, pneumonia
C[b,c]	*Streptococcus dysgalactiae* subsp. *equisimilis*	β	Wound infection, cellulitis, endocarditis, epidemic pharyngitis, pyogenic arthritis
	Streptococcus equi subsp. *zooepidemicus*	β	Septicemia, nephritis
D	Enterococci *Enterococcus faecalis* *Enterococcus faecium* Nonenterococcal species *Streptococcus bovis*	γ	Neonatal septicemia, intestinal and peritoneal infection, urinary tract infection, opportunistic infection
G[b,c]	*Streptococcus dysgalactiae* subsp. *equisimilis*	β	Puerperal infection, skin and wound infection, endocarditis, pyogenic arthritis
Not groupable[d]	*Streptococcus pneumoniae*	α	Pneumonia, otitis media, sinusitis, meningitis
	Other viridans streptococci *Streptococcus mitis* *Streptococcus salivarius* *Streptococcus anginosus* group *Streptococcus mutans* group *Streptococcus vestibularis* *Streptococcus parasanguis*	α[e]	Endocarditis, septicemia, dental infections, intravascular catheter–related infection

[a] Serogroups E, F, H, and K through V are rarely associated with human infections.

[b] Other group C and group G streptococci are unusual causes of human infections.

[c] *Streptococcus equi subsp. equisimilis* can have other Lancefield antigens, including groups A, G, and L.

[d] Minute, colony-forming organisms of Lancefield groups C, D, and G are included with the viridans streptococci.

[e] Occasional viridans streptococci are nonhemolytic, and others are β-hemolytic.

Other features commonly used to subdivide the streptococci are production of streptolysin-O and streptokinase, susceptibility to bacitracin and optochin, production of acetoin upon metabolism of glucose (Voges-Proskauer test), ability to grow in 6.5% sodium chloride, and ability to metabolize bile esculin or various carbohydrates. (These features are discussed in the other chapters of this section.)

With the advent of molecular techniques, the classification of streptococci underwent reanalysis. On the basis of genomic analysis, the more than 50 species constituting the genus *Streptococcus* have been subdivided into seven species groups that largely parallel the groupings produce by phenotypic methods (Fig. 117.1 and Table 117.2).[2,8] Classification based on genetic relatedness is most useful for the viridans streptococci because phenotypic classification of these organisms is particularly confusing and problematic (see Chapter 121).

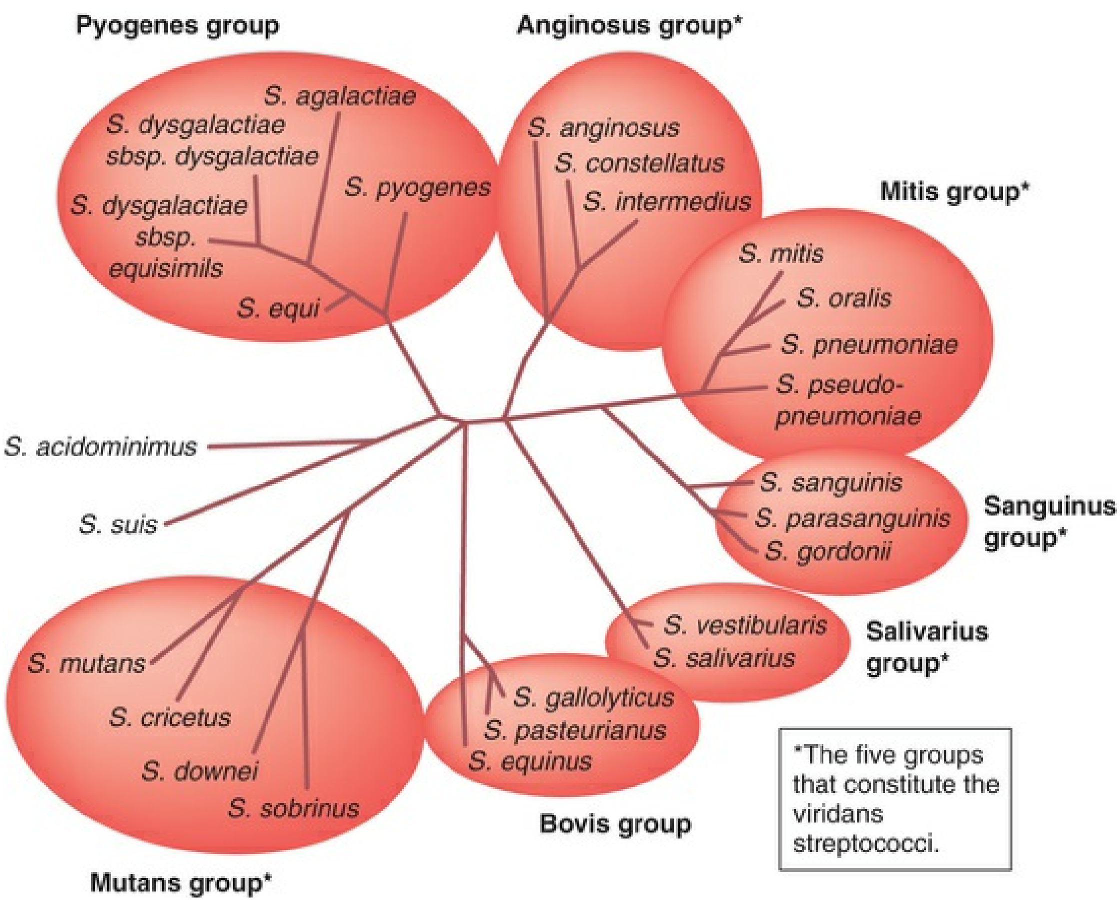

FIGURE 117.1 Schematic diagram of the phylogenetic relationship and classification of *Streptococcus* species. Intraspecis distances are not shown to scale.

TABLE 117.2

Clinically Relevant Organisms Constituting Seven Species Groups in the Genus *Streptococcus*

Group	Species Included
Pyogenes	*Streptococcus pyogenes* *Streptococcus agalactiae* *Streptococcus dysgalactiae subsp. dysgalactiae* *Streptococcus dysgalactiae subsp. equisimilis*
Mitis	*Streptococcus pneumoniae* *Streptococcus mitis* *Streptococcus oralis*
Sanguinis	*Streptococcus sanguinis* *Streptococcus parasanguinis* *Streptococcus gordonii*
Salivarius	*Streptococcus salivarius* *Streptococcus vestibularis*
Anginosus	*Streptococcus anginosus* *Streptococcus constellatus* *Streptococcus intermedius*
Mutans	*Streptococcus mutans*

Bovis	*Streptococcus gallolyticus* *Streptococcus pasteurianus* *Streptococcus equinus*

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Streptococcus pyogenes (Group A *Streptococcus*)

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Group A *Streptococcus* (GAS) is synonymous with *Streptococcus pyogenes*, the only species in this group of β-hemolytic streptococci. GAS is one of the leading pathogenic bacteria that infect children and adolescents, and it is associated with a wide spectrum of infections and diseases. Worldwide more than 600 million cases of GAS pharyngitis ("strep throat") and more than 100 million cases of GAS pyoderma are estimated to occur annually.[1] Although uniformly and exquisitely susceptible to penicillin and many other antimicrobial agents, GAS infections continue to present formidable clinical and public health challenges. The vast majority of GAS infections have a short duration and are relatively benign; however, invasive disease can be fulminant and life threatening. GAS also differs from other pyogenic bacteria in its potential to produce delayed, nonsuppurative sequelae, such as poststreptococcal acute glomerulonephritis (PSAGN) and acute rheumatic fever (ARF), after uncomplicated infections.

The importance of GAS infections in the United States was reinforced at the close of the 20th century by the appearance of severe, invasive GAS infections (e.g., streptococcal toxic shock syndrome [STSS] and necrotizing fasciitis) with high morbidity and mortality.[2] On the global scale, GAS is an important cause of morbidity and mortality primarily in less developed countries, causing more than 500,000 deaths per year.[1]

Description of the Pathogen

Microbiology

GAS is a gram-positive coccoid-shaped bacterium that grows in chains, producing small white to gray colonies with a clear zone of β-hemolysis on blood agar. It is distinguished from other groups of β-hemolytic streptococci by a group-specific polysaccharide (Lancefield antigen) in the cell wall.[3] Serologic grouping by the Lancefield method is precise, but group A organisms can be identified more readily by any one of a number of latex agglutination, coagglutination, or enzyme immunoassay procedures.

GAS can be subdivided into more than 100 immunologic serotypes by the M-protein antigen on the cell surface and by the fimbriae (hairlike fuzz) that project from the outer edge of the cell. Classically, typing of the surface M protein relied on the available polyclonal antisera, but this technique has been supplanted by a contemporary molecular approach that applies the polymerase chain reaction and deoxyribonucleic acid (DNA) sequencing of the 5′ variable region of the *EMM* gene encoding the M protein (http://www.cdc.gov/ncidod/biotech/strep/strepindex.htm). More than 200 distinct M genotypes have been identified using *EMM* typing, and a good correlation has been established between known serotypes and *EMM* types.[4,5]

M serotyping or genotyping has been valuable for epidemiologic studies; particular GAS diseases tend to be associated with certain M types. The M types commonly associated with pharyngitis rarely cause skin infections, and the M types commonly associated with skin infections rarely cause pharyngitis. A few of the “pharyngeal” strains (e.g., M type 12) have been associated with PSAGN, but far more of the “skin” strains (e.g., M types 49, 55, 57, and 60) have been considered nephritogenic. A few pharyngeal serotypes, but no skin strains, have been associated with ARF. However, evidence suggests that rheumatogenic potential does not depend solely on the serotype, but rather is a characteristic of specific strains within several serotypes. Certain GAS M types are more strongly associated with invasive disease, including M1, M3, M6, M12, M18, and M28. A globally disseminated clone of the M1 serotype has been the leading cause of severe invasive GAS infections, such as necrotizing fasciitis and STTS, over the past 3 decades.[6]

The GAS cell is a complex structure. In rapidly dividing strains (e.g., young cultures, epidemic strains), the cell is covered with a hyaluronic acid capsule that gives the colonies a mucoid or water drop appearance. Microscopic fimbriae protrude from the cell surface into the hyaluronic capsular layer, promoting the adherence of GAS to epithelial cells and extracellular matrix proteins. The fimbriae are composed of a surface-anchored, M protein that adopts a coiled-coil structure, which is closely associated with lipoteichoic acid polymers.[7] GAS are now recognized to express surface pili, corresponding to the classic "T antigen" used in earlier serologic typing schemes.[8] Roughly half of GAS strains display the capacity to opacify mammalian serum, through the activity of the surface-anchored serum opacity factor (SOF) protein, which binds to apolipoproteins to displace high-density lipoprotein (HDL) to form lipid droplets.[9]

The group A carbohydrate, encoded by the *gac* operon, comprises 40% to 50% of the dry weight of the GAS cell wall. The carbohydrate, a polymer of rhamnose units with side chains of *N*-acetyl-glucosamine, is responsible for its group (e.g., A) specificity.[3] As with other gram-positive species, a peptidoglycan polymer provides thickness and rigidity for the cell wall, consisting of glycan strands cross-linked by peptide bridges. M protein, pilus antigen, SOF, and other surface proteins are covalently attached to the GAS cell wall by recognition sequences in their C-terminal regions that interact with an anchoring enzyme called sortase.[10]

GAS produces and releases a large number of biologically active extracellular products into the surrounding medium. Some of these are toxic to human and other mammalian cells. Streptolysin S (SLS) is a small, oxygen-stable toxin responsible for β-hemolysis on blood agar; streptolysin O (SLO) is an oxygen-labile, cholesterol-dependent toxin related to staphylococcal α-hemolysin. Both SLS and SLO injure cell membranes, not only lysing red blood cells, but also damaging other eukaryotic cells and membranous subcellular organelles.[11] SLO is antigenic, whereas SLS is not. Streptococcal pyrogenic exotoxins (SPEs) are secreted factors that can act as superantigens and trigger T-lymphocyte proliferation and cytokine release.[12] GAS expresses a broad-spectrum cysteine protease, SpeB, which has multiple host targets; various specific peptidases that cleave host chemokines and complement factors; and several nucleases. GAS also produces bacteriocins, which are low molecular weight proteins that can kill a variety of other gram-positive bacteria, and thus may play a role in the promotion of infection or the persistence of colonization.[13]

GAS quorum sensing and virulence gene expression are controlled by the interplay of several transcriptional regulatory systems.[14–16] These include the two-component control of virulence system (CovR/S), which regulates 10% to 15% of the GAS genome, including its hyaluronic acid capsule synthesis operon, and the stand-alone Mga regulator, which controls expression of M protein and nearby virulence factor genes. Genome sequencing has shown that bacteriophages have played an important role in the evolutionary genetics of GAS, including the transfer of genes that encode antibiotic resistance, SPEs, and other virulence determinants.[17]

Pathogenesis and Virulence

GAS induces serious human disease by at least three mechanisms: suppuration, as in pharyngitis and pyoderma; toxin elaboration, as in STSS; and immune-mediated inflammation, as in ARF and PSAGN.[18] No complete explanation is available for the predilection of certain body sites for GAS infection, nor for the ability of certain M-type strains to produce pharyngitis and of others to produce pyoderma.

The first step in the pathogenesis of GAS disease in humans is successful colonization of the upper respiratory mucosa or skin. A large number of adherence factors for epithelial cells and extracellular GAS have been described, including lipoteichoic acid, M protein, pili, and fibronectin- or laminin-binding proteins, including Sfb1, SOF and Lbp.[19] The formation of a GAS biofilm facilitates persistence in humans.[20] Both M protein and fibronectin-binding proteins are important for subsequent endocytotic uptake of GAS into respiratory epithelial cells.[19] This process of intracellular invasion allows GAS access to a privileged intracellular niche, and it represents a proximal step in the pathogenesis of systemic infection.[21]

The propensity of GAS to produce serious infection in otherwise healthy children and adults defines the pathogen's ability to resist innate immune clearance mechanisms that normally prevent microbial dissemination.[22] For example, when GAS gains access to deeper tissues through cellular invasion or a break in epithelial integrity, it deploys specific peptidases that cleave and inactivate the neutrophil chemoattractants interleukin-8 and complement factor 5a. Likewise, SpeB can degrade the host's immunoglobulins and cationic antimicrobial peptides.

M protein is a multifaceted immune resistance factor that promotes GAS resistance to opsonophagocytosis through multiple mechanisms, including the binding of fibrinogen, complement inhibitory factor H, host antimicrobial peptides, and the Fc region of immunoglobulins.[23,24] M protein is essential to virulence in animal models, and immunization with M protein provides strong protection against infection with a type-specific GAS strain. During invasive infection, significant quantities of M protein are released from the cell surface by proteolysis; these can form a proinflammatory, clotlike complex with human fibrinogen, leading to uncontrolled neutrophil activation, vascular leakage, and toxic shock symptomatology.[25,26] M protein also collaborates with the GAS virulence factor streptokinase to bind host plasminogen to the GAS surface; this generates plasmin activity, effectively coating the bacterial surface with a powerful protease to facilitate tissue spread.[27]

The pore-forming toxins SLS and SLO are toxic to multiple host cell types, including macrophages and neutrophils, and therefore promote GAS tissue damage and resistance to phagocytic clearance. SLO in particular can induce accelerated apoptosis of immune cells[28] and inhibit neutrophil oxidative burst and neutrophil extracellular trap (NET) production.[29] The GAS hyaluronic acid capsule is not immunogenic, mimicking a common human matrix component, and cloaks opsonic targets on the bacterial surface from phagocyte recognition.[30] In the case of the highly invasive, globally disseminated M1T1 GAS clone, hyperinvasive forms bearing mutations in the CovR/S two-component regulator arises in vivo under innate immune selection, leading to upregulation of capsule and other key virulence determinants.[31] Specific virulence determinants present in the hyperinvasive M1T1 clone include the phage-encoded DNAse Sda1, which allows GAS to escape killing in DNA-based NETs, and the serum inhibitor of complement (SIC), which binds and inactivates terminal complement components and host defense peptides.

The SPEs are a family of more than 15 bacterial superantigens, including the bacteriophage-encoded SPE A and SPE C.[32] These superantigens induce antigen-nonspecific T-lymphocyte activation, suppress antibody synthesis, potentiate endotoxic shock, induce fever, promote the release of proinflammatory cytokines, produce reticuloendothelial blockade, and may contribute to the multiorgan failure characteristic of STSS.[33] In the U.S., STSS is commonly associated with infections caused by strains that produce SPE A.[33] Susceptibility to STSS appears to be related to the absence of antibodies to both M protein and superantigens, in addition to the presence of specific human leukocyte antigen (HLA) haplotypes.[34] The SPEs share homology with staphylococcal enterotoxins but not with staphylococcal toxic shock syndrome toxin-1.[12] SPE A and SPE C are responsible for the rash of scarlet fever, stimulating the formation of specific antitoxin antibodies that provide immunity against future scarlatiniform rashes, but not against subsequent GAS infections.

Immunologic Response

Although many GAS constituents and extracellular products are antigenic, protective immunity is type specific, mediated by opsonic anti-M-protein antibodies. These antibodies protect against infection with a homologous M type but confer no immunity against other M types.[35] Therefore, multiple GAS infections attributable to different M types are common during childhood and adolescence. Anti-M antibodies persist for years, perhaps for life, protecting against invasive infection but not against pharyngeal carriage.[36] A type-specific antibody may be transferred across the placenta from mother to fetus.[37] A type-specific antibody against M protein usually is not detectable until 6 to 8 weeks after infection[38];

therefore, its primary role may not be in the limitation or termination of active infection, but rather in the prevention of reinfection by the same serologic type. Opsonic type-specific antibodies do not appear after early and effective antimicrobial therapy.[39]

Humoral antibodies to specific streptococcal extracellular products such as antistreptolysin O (ASO) and anti-DNAse B can be demonstrated readily by neutralization assays. These assays have been particularly useful in allowing a more precise method of defining GAS infection in clinical and epidemiologic studies and in documenting the occurrence of a preceding GAS infection in patients suspected of having a nonsuppurative complication. The ASO assay is the most commonly used streptococcal antibody test. Because SLO is also produced by group C or group G streptococci, the test is not specific for GAS infections, and the response can be feeble in patients with streptococcal impetigo.[40] In contrast, the anti-DNAse B response is demonstrable after both skin and throat infections. Neutralizing antibody titers peak at 3 to 6 weeks for SLO and at 6 to 8 weeks for DNAse B. Antibody titers against GAS extracellular antigens reported by clinical immunology laboratories may vary. The upper limits of normal are higher for children than for adults, and these values, even for the same age group, are higher in some populations than in others.[41]

Epidemiology

GAS has a narrow host range; it is identified almost exclusively in humans and only rarely in other species.[42] GAS is highly communicable and can cause disease in individuals of all ages who do not have type-specific immunity. Disease in neonates is uncommon, probably because of placental transfer of maternal antibody. Significant differences exist between epidemiology of throat and skin infections due to GAS[43] (see chapters 27 and 68).

Severe invasive GAS infections had become uncommon in the U.S. and Western Europe during the second half of the 20th century. However, since the late 1980s a worldwide increase in severe invasive GAS infections has been seen.[44] The incidence of severe invasive GAS disease in industrialized societies (2 to 3 per 100,000 population) is similar in the geographically distinct regions of Europe, North America, and Australia.[45] This rate translates to about 10,000 cases of invasive GAS disease annually in the U.S.[46] However, rates of invasive disease in indigenous populations in Africa, the Asian subcontinent, and the Pacific islands typically are much higher[45]; rates as high as 82.5 per 100,000 have been reported in North Queensland, Australia.[47] Globally it has been estimated that at least 663,000 cases of invasive GAS disease occur each year, resulting in 163,000 deaths.[1]

The stratified squamous epithelium of the oropharynx and skin is the principal barrier against invasive GAS disease. GAS can gain access to sterile sites by means of direct inoculation after an injury that breaches the mucous membranes or skin[46]; however, a substantial number of invasive streptococcal infections have no known site of entry.[48] Epidemiologic data suggest that the oropharynx is the primary site of origin for systemic GAS isolates; therefore, invasive disease is likely to occur as a result of transient bacteremia originating from the oropharynx, possibly as a result of direct tissue penetration by GAS.[48] Varicella is a particularly important risk factor for severe invasive GAS infections in previously healthy children.[49] Other risk factors more common in adults include diabetes mellitus, human immunodeficiency virus infection, intravenous drug use, and chronic pulmonary or cardiac disease.

Clinical Manifestations and Clinical Syndromes

GAS is a common cause of acute pharyngitis (see Chapter 27) (Fig. 118.1) and pyoderma (impetigo) (see Chapter 68) in children and adolescents. GAS also produces a variety of other infections of the respiratory tract, including otitis media, retropharyngeal abscess, peritonsillar abscess, sinusitis, and mastoiditis; infections of the skin and soft tissues (Figs. 118.2, 118.3, and 118.4), which include cellulitis, erysipelas, perianal cellulitis, vaginitis, and blistering distal dactylitis (see chapters 68, 74, and 75), and invasive diseases, including STSS (see Chapter 13), necrotizing fasciitis, septicemia, meningitis, pneumonia, empyema, peritonitis, puerperal sepsis, neonatal sepsis, osteomyelitis, suppurative arthritis, myositis, and surgical wound infections. In addition, GAS is the proven cause of two potentially serious nonsuppurative complications, ARF and PSAGN, and the possible cause of two other potential nonsuppurative complications, poststreptococcal reactive arthritis (PSRA) and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAs) (discussed later in the chapter).

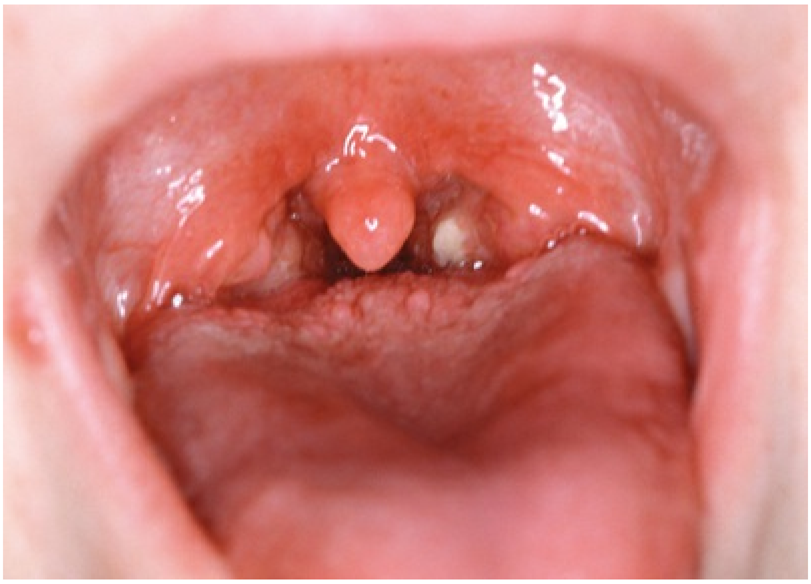
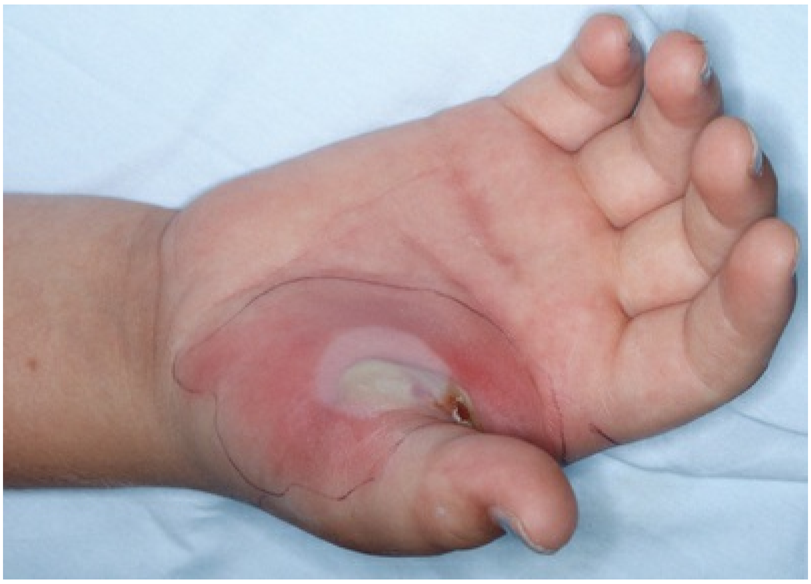


FIGURE 118.1 Typical group A streptococcal pharyngitis showing erythematous soft palate, uvula, and tonsils, with tonsillar exudate. (Courtesy of J.H. Brien©.)



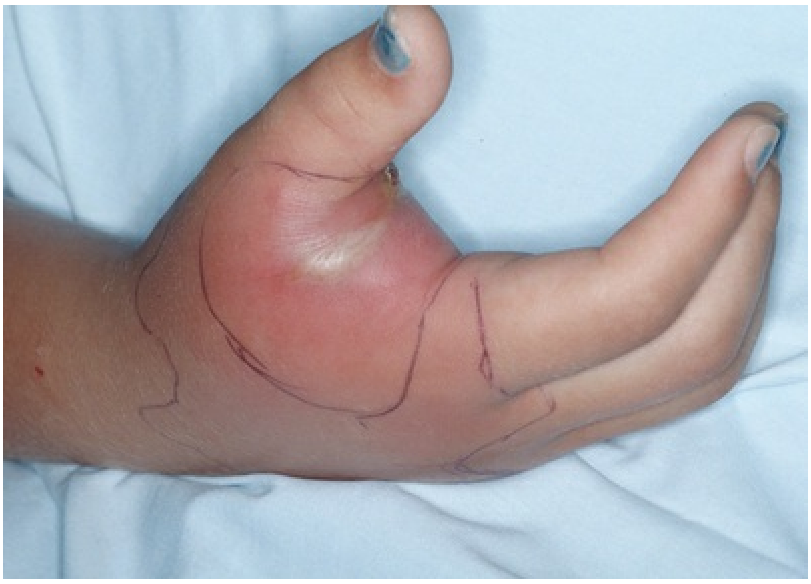
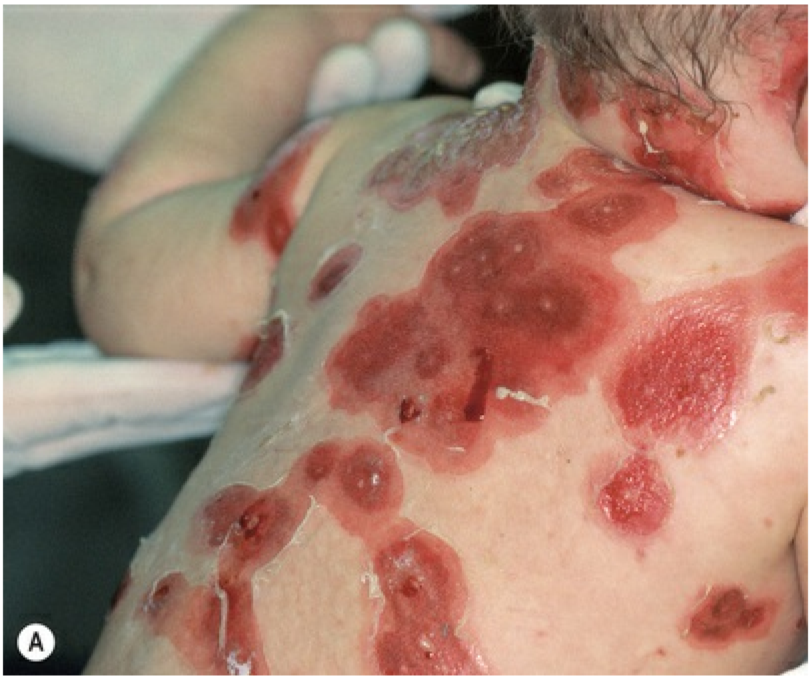


FIGURE 118.2 Young girl with bullous, invasive local infection without trauma or foreign body; the infection was caused by group A streptococcus. (Courtesy of J.H. Brien©.)



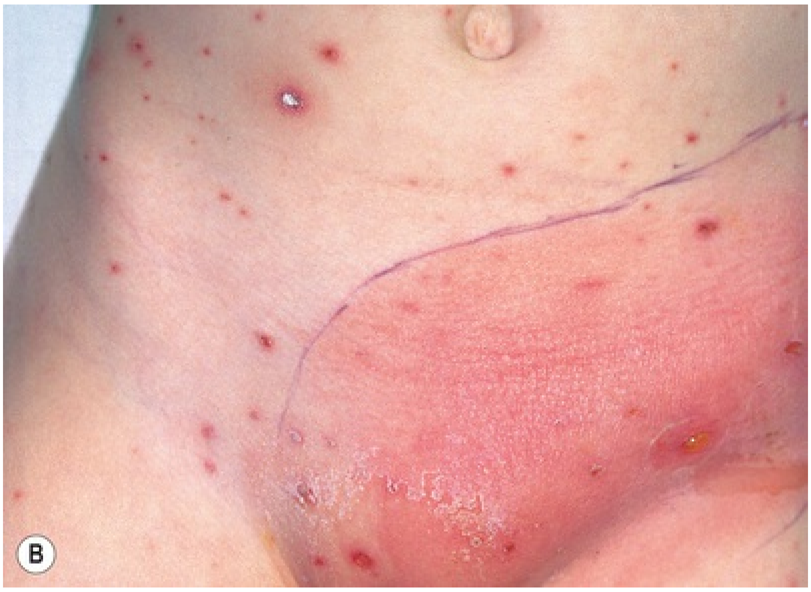


FIGURE 118.3 Toddler with *Staphylococcus aureus* and group A streptococcal infection complicating chickenpox (A). Necrotizing group A streptococcal cellulitis complicating chickenpox (B). (Courtesy of S.S. Long©.)

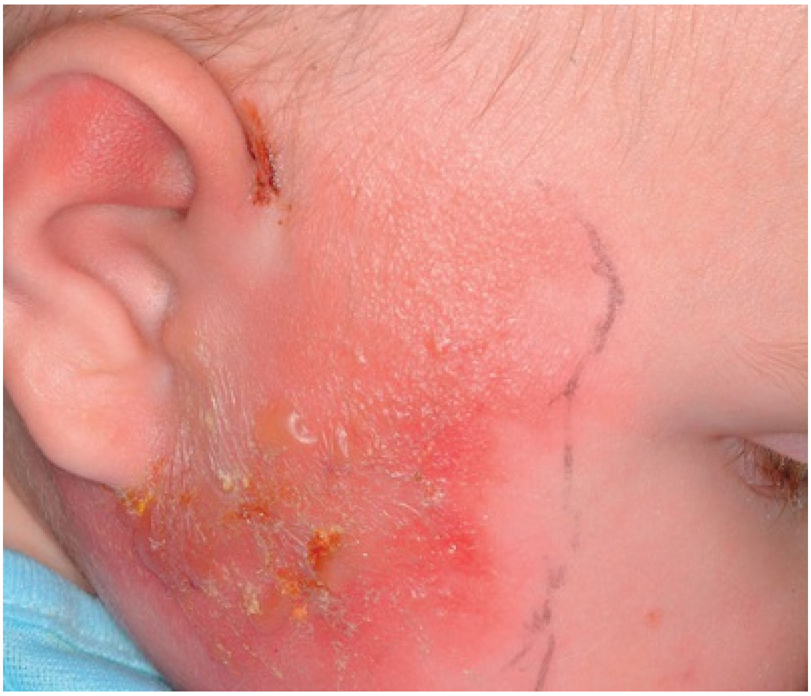


FIGURE 118.4 Toddler with erysipelas caused by group A streptococcus. (Courtesy of J.H. Brien©.)

Severe invasive GAS infection is defined as the isolation of GAS from a normally sterile body site; it includes three overlapping clinical syndromes. Cellulitis and bacteremia are the most common

GAS invasive diseases, each accounting for about 20% to 40% of invasive GAS disease in published epidemiologic reports.[50,51] Clinically, cellulitis is characterized by the acute onset of redness and inflammation of the skin, with associated fever, pain, and swelling. GAS bacteremia often triggers a rapid and robust proinflammatory cytokine response that results in a high fever, nausea, and vomiting. Cellulitis and bacteremia also can be preludes to the more serious invasive disease complications of necrotizing fasciitis and STSS.

The GAS "flesh eating disease," necrotizing fasciitis, is a devastating bacterial infection involving the skin, subcutaneous and deep soft tissues, and muscle. Necrotizing fasciitis involves rapid bacterial growth and spread along the fascial sheaths that separate adjacent muscle groups, breach of the fascial sheaths, and necrosis of adjacent tissues.[52] The pathogenesis of necrotizing fasciitis is complex and incompletely understood at the molecular level. However, the rapid tissue destruction and bacterial spread are thought to involve host and bacterial proteases (plasmin, SpeB), GAS pore-forming cytotoxins (e.g., SLO and SLS), and tissue-damaging enzymes released by host neutrophils in response to GAS cell wall components and superantigens.[52] A major risk factor for the development of necrotizing fasciitis is blunt trauma, which is suggested to result in increased vimentin expression that tethers circulating GAS to the injured muscle.[53] Primary varicella (chickenpox) in unimmunized children also is a well-documented predisposing condition.[49,54]

Invasive GAS infections also can result in STSS, a "cytokine storm" produced in response to GAS superantigens that substantially increases the risk of death.[50,55] GAS superantigens simultaneously engage major histocompatibility complex (MHC) class II molecules and T-cell receptor (TCR) β-chain variable regions, a molecular "bridging" that results in antigen-independent activation of large numbers of T lymphocytes. The resulting cytokine response by T lymphocytes (lymphotoxin-α, interleukin-2 [IL-2], interferon γ) and antigen-presenting cells (tumor necrosis factor [TNF]-α, IL-1β, IL-6) causes widespread organ dysfunction, disseminated intravascular thrombosis, and tissue injury. The result is an acute, rapidly progressive illness typified by high fever, rapid onset hypotension, and accelerated multisystem failure.[56] The magnitude of the STSS inflammatory response is closely linked to the severity of the disease. The sites where superantigens bind to HLA class II molecules are polymorphic, and strong epidemiologic and genetic evidence indicates that the host's MHC class II haplotype influences susceptibility to STSS.[34,57] Specific criteria for the diagnosis of STSS have been established (Box 118.1).[58]

Box 118.1

Definition of Streptococcal Toxic Shock Syndrome

Clinical Criteria

- Hypotension plus two or more of the following:
    - Renal impairment
    - Coagulopathy
    - Hepatic involvement
    - Adult respiratory distress syndrome
    - Generalized erythematous macular rash
    - Soft tissue necrosis

Definite Case

- Clinical criteria plus isolation of group A streptococci from a normally sterile site

Probable Case

- Clinical criteria plus isolation of group A streptococci from a nonsterile site

Working Group on Severe Streptococcal Infections. Defining the group A streptococcal toxic shock syndrome: rationale and consensus definition. JAMA 1993;269(3):390–391.

Laboratory Findings and Diagnosis

The clinical course of severe invasive GAS infections often is precipitous, requiring rapid diagnosis and initiation of the appropriate therapy. Although the initial clinical findings of STSS are nonspecific, a high index of suspicion is required, particularly in patients who have an increased risk (e.g., those with varicella). Pain out of proportion to superficial signs of infection can be a clue to underlying necrotizing fasciitis. Cultures of focal lesions are helpful in patients with skin or soft tissue involvement. Blood culture results can be positive in patients with sepsis without an apparent focus of infection. A complete blood count can show a relatively normal total leukocyte count, with a marked left shift to immature forms. The patient's blood pressure should be evaluated frequently. If necrotizing fasciitis is suspected, magnetic resonance imaging may be helpful in confirming the diagnosis; if the disease is present, histologic examination of excised tissue shows extensive necrosis, inflammation, hemorrhage, and thrombosis of small vessels.

Treatment

The initial management of a child or an adolescent with a severe invasive GAS infection includes hemodynamic stabilization and specific antimicrobial therapy to eradicate the GAS. When necrotizing fasciitis is suspected, prompt surgical drainage, debridement, fasciotomy, or amputation often is required. Patients with necrotizing fasciitis also need careful fluid and nutritional support and may require extensive skin grafting or other reconstructive surgery, as well as physical therapy. Fluid resuscitation is begun urgently and administered frequently; multiple boluses of fluid are required because of severe volume depletion and ongoing capillary leakage. When fluid resuscitation alone is insufficient to maintain adequate tissue perfusion, inotropic agents (e.g., dobutamine, dopamine, norepinephrine) should be considered.

Parenteral antimicrobial therapy should include agents active against GAS and *Staphylococcus aureus* until the results of bacteriologic studies are available. Once GAS has been identified, intravenously administered penicillin G (200,000 to 400,000 U/kg/day in four to six divided doses) is the drug of choice. A mouse model of streptococcal myositis suggests that clindamycin may be more effective than penicillin in eradicating GAS in severe invasive infections.[59] In addition, clindamycin inhibits protein synthesis and the production of important virulence factors (e.g., M protein, SPEs).[33] Therefore, many experts recommend intravenously administered clindamycin (40 mg/kg/day in three or four divided doses) in addition to penicillin.

Several case reports have described the use of intravenous immunoglobulin (IGIV) therapy in patients with severe invasive GAS infections. An observational cohort study conducted in Canada reported significantly reduced mortality among patients treated with IGIV compared with those who were not treated with IGIV.[60] However, this study had confounding factors that could have affected mortality data, including the use of historical controls and increased use of clindamycin among the patients treated with IGIV. A recent comparative observational study in Europe of 67 patients with streptococcal toxic shock syndrome suggested a therapeutic benefit of both IGIV (odds ratio, 5.6; P = .030) and clindamycin (odds ratio, 8.6; P = .007) with 28-day survival as the measured end point.[61]

Prevention

The only specific indication for longterm use of antibiotics to prevent GAS infection is for patients with a history of ARF or rheumatic heart disease (RHD). Mass prophylaxis generally is not feasible except to reduce the number of infections during epidemics of impetigo and to control epidemics of pharyngitis in military populations and in schools.

Measures to prevent the spread of GAS infections have variable effectiveness. The spread of throat or skin infection within a family often occurs before the index case is identified and isolated or treated. In epidemic situations, especially when cases of ARF or PSAGN occur, a culture survey and treatment of all individuals with positive culture results (mass prophylaxis) may be indicated.

Case reports of clusters of invasive GAS infections within a chronic care facility or among members of a single household have been published.[62] However, given the infrequency of these infections and the lack of a clearly effective chemoprophylactic regimen, the available data currently do not support a recommendation for routine testing for GAS colonization or for routine administration of chemoprophylaxis to otherwise healthy household contacts of people with invasive GAS disease. The Centers for Disease Control and Prevention recommend that healthcare providers inform household contacts of a person with invasive GAS disease about the clinical manifestations of pharyngeal and invasive GAS infections and emphasize the importance of seeking immediate medical attention if contacts develop such symptoms.[63]

Unfortunately, an effective vaccine to prevent GAS infection has yet to be developed. A major challenge is the great diversity of unique epitopes (more than 100) presented across GAS strains by the hypervariable N termini of the immunodominant surface M proteins. Another challenge is the data suggesting that GAS components, including the coiled-coil of the M protein and the GlcNAc side chain on the cell wall's group A carbohydrate antigen, could elicit antibodies that cross-react with the host's muscle or neural tissues, thereby triggering ARF. Proteomic and reverse vaccinology approaches have been used to explore conserved, surface-associated GAS protein antigens (e.g., pilus components, C5a peptidase, and fibronectin-binding proteins) as potential universal GAS vaccine candidates.[64] Two approaches have been tested in attempts to use the protective immunity of M protein without incurring the risks of molecular mimicry and autoimmune disease. One approach used a conserved, noncross-reactive, C-repeat region found in the carboxy-terminal of the M protein proximal to the cell wall. In the other approach, molecular techniques have been used to engineer genetically a highly complex multivalent M protein–based vaccine (e.g., 26-valent) containing a minimal B-lymphocyte epitope to optimize functional antibody responses.[65] Because GAS disease is a major cause of health inequality affecting indigenous children in Australia and New Zealand, the governments of the two countries recently formed the Coalition to Advance New Vaccines for group A *Streptococcus* (CANVAS) to assess several candidates and to fast-track development of a vaccine most likely to be safe, efficacious, and cost effective.[66]

Complications

Suppurative complications from the spread of GAS to adjacent structures were common before antibiotics became available. Cervical lymphadenitis, peritonsillar abscess, retropharyngeal abscess, otitis media, mastoiditis, and sinusitis still occur in children in whom the primary illness has gone unnoticed or treatment of pharyngitis has been inadequate. GAS pneumonia occurs occasionally. Nonsuppurative complications are considered in the following sections.

Acute Rheumatic Fever

ARF is an inflammatory disorder that commonly involves the joints and heart (and less commonly the brain and skin). It can develop as a complication of an untreated GAS upper respiratory tract infection. The association of GAS and ARF first was postulated based on parallels in peak age (5 to 15 years) and seasonal (winter/spring) incidence, coupled with the observation that outbreaks of GAS pharyngitis in closed communities (e.g., boarding schools and military bases) could be followed by outbreaks of acute ARF. Subsequent serologic studies documenting anti-GAS antibodies in patients with ARF provided further evidence. Clinical studies showed that the antimicrobial therapy that eliminates GAS from the pharynx also prevents initial attacks of ARF, and that longterm, continuous prophylaxis that prevents GAS pharyngitis also prevents recurrences of ARF.

Epidemiology

The incidence of ARF has declined substantially over the past 8 decades in the U.S. and other developed countries, a decline that began even before the advent of penicillin. However, ARF remains a major public health burden in much of the developing world. Currently at least 15.6 million people worldwide have RHD, and 282,000 new cases and 233,000 deaths annually are directly attributable to ARF or RHD.[1]

The incidence of ARF in some developing countries exceeds 50 per 100,000 children. Some of the highest incidence rates reported are in school-aged Pacific Islander children in New Zealand (80 to 100 per 100,000) and in aboriginal children in central and northern Australia (245 to 351 per 100,000).[67] In contrast, the most recent ARF incidence data for an industrialized country, obtained from the nonindigenous population of New Zealand, shows a rate of less than 10 per 100,000 children.[1] The prevalence of RHD in children aged 5 to 14 years is highest in subSaharan Africa (570 per 100,000), the Pacific Islander and indigenous populations of New Zealand and Australia (350 per 100,000), and south central Asia (220 per 100,000). In contrast, the prevalence in developed countries usually is about 50 per 100,000.[68] A dramatic outbreak of acute ARF occurred in the area of Salt Lake City, Utah, beginning early in 1985; more than 200 cases occurred in the first 4 years.[69] Other, smaller U.S. outbreaks have been reported in various communities and among recruits at military training centers, but these resurgences remained localized and did not lead to a nationwide increase in cases.

The observation that only a few patients with GAS pharyngitis subsequently experience ARF suggests that specific characteristics of the organisms, the host, and the environment contribute to this complication. Although all the risk factors have yet to be identified, certain potential factors have been described.

Experts have long suspected that various strains of GAS differ in the likelihood of subsequent ARF, and a limited number of M serotypes have been linked epidemiologically to outbreaks of ARF. Strains of certain rheumatogenic serotypes (e.g., types 1, 3, 5, 6, and 18), which were isolated infrequently during the 1970s and early 1980s, reappeared dramatically as causes of pharyngitis during the localized outbreaks of ARF in the mid-1980s. The marked decrease in ARF in the U.S. in recent decades has been correlated with replacement of rheumatogenic types by nonrheumatogenic types in childhood acute streptococcal pharyngitis.[70]

A genetic predisposition to ARF appears to be a factor.[71] Studies in twins have shown a higher concordance rate of ARF in monozygotic than in dizygotic twin pairs. Associations between susceptibility to ARF and HLA class II alleles, the B-lymphocyte alloantigen D8/17, or certain single-nucleotide polymorphisms for TNF-α or mannan-binding lectin genes, are under investigation; however, such an association has not been noted consistently in various populations. In one highly defined group with mitral valve disease, the collected data suggested that DRB1*0701, DR6, and DQB1*0201 confer susceptibility to ARF.[72]

Pathogenesis

The pathogenic link between a GAS infection of the upper respiratory tract and an episode of ARF has not yet been established definitively. Most attention has focused on the concept of autoimmunity based on molecular mimicry. This theory is supported by the latent period between GAS infection and ARF and by the observations of antigenic similarity between molecular constituents of GAS and several human tissues, including the heart, synovium, and basal ganglia. The sera of patients with ARF contain heart-reactive or myosin-reactive antibodies, frequently in high titers.[73] Studies of anti-GAS/anti-heart monoclonal antibodies from RHD have revealed that cardiac myosin, and GlcNAc, the immunodominant epitope of the group A carbohydrate antigen, are likely cross-reactive antigens involved in antibody deposition on the valve.[3,72] Early work had demonstrated the persistence of increased levels of anti–group A carbohydrate antibody in RHD and an association with a poor prognosis.[74] More recently, human T-lymphocyte clones also have confirmed cross-reactivity between cardiac myosin sequences and GAS M proteins.[75] Strikingly, immunization with purified recombinant GAS M6 protein is sufficient to induce autoimmune valvular heart disease in rats.[76]

Clinical Features

Because no single clinical or laboratory finding is pathognomonic for ARF, in 1944 T. Duckett Jones proposed guidelines to aid diagnosis of the disease and to limit overdiagnosis. The Jones criteria, as revised in 1992 by the American Heart Association (Box 118.2),[77] provide major criteria and minor criteria, in addition to the requirement for evidence (microbiologic or serologic) of recent GAS infection. The diagnosis of ARF is established according to the Jones criteria when a case fulfills two major criteria or one major plus two minor criteria and meets the absolute requirement of proof of antecedent GAS infection. Nonetheless, ARF can be overdiagnosed even with strict application of the Jones criteria.

Box 118.2

Jones Criteria for Diagnosis of First Episode of Acute Rheumatic Fever

Diagnosis

Diagnosis of acute rheumatic fever requires two major criteria or one major and two minor criteria, plus supporting evidence of antecedent group A streptococcal infection.

Major Criteria

Carditis

Polyarthritis

Chorea

Erythema marginatum

Subcutaneous nodules

Minor Criteria

Clinical findings: Fever; arthralgia

Laboratory finding: Elevated acute phase reactants (erythrocyte sedimentation rate or C-reactive protein); prolonged PR interval

Evidence Supporting an Antecedent Group a Streptococcal Infection

Positive throat culture or rapid antigen test for group A streptococcus
Or

Elevated or rising streptococcal antibody titer (e.g., antistreptolysin O, anti-DNAse B)

Under two circumstances the diagnosis of ARF can be made without strict adherence to the Jones criteria. Chorea may be the only manifestation of ARF. Similarly, indolent carditis may be the only manifestation in patients who first come to medical attention months after onset.

Major Manifestations

Migratory Polyarthritis.

Arthritis occurs in about 75% of patients with ARF and classically involves the larger joints, particularly the knees, ankles, wrists, elbows, or hips. In rare cases the spine or small joints of the fingers or toes can be affected. Inflamed joints and periarticular tissues generally are hot, red, swollen, and exquisitely tender; pain can precede other findings and can appear disproportionate to them. The migratory nature of the disease is most characteristic; a severely involved joint can become normal within 1 to 3 days without treatment, as one or more other large joints become similarly inflamed for up to 2 to 6 weeks. A dramatic response to even small doses of nonsteroidal anti-inflammatory drugs (NSAIDs) is characteristic; lack of a clear response should suggest an alternative diagnosis. Rheumatic arthritis is almost never deforming or associated with chronic changes.

Carditis.

Carditis occurs in about 50% to 60% of people with ARF. Carditis and resultant chronic RHD are the most serious manifestations of ARF, accounting for essentially all associated morbidity and mortality. Rheumatic carditis is a pancarditis, with inflammation of the myocardium, pericardium, and endocardium. Endocarditis (valvulitis), which manifests as one or more cardiac murmurs, is the hallmark of rheumatic carditis; myocarditis or pericarditis without evidence of endocarditis is rarely caused by ARF or RHD. The vast majority of cases consist of isolated mitral valvular or aortic and mitral valvular disease. Valvular insufficiency is characteristic of acute and convalescent stages of ARF, whereas valvular stenosis develops over years or decades. In developing countries, systematic echocardiographic screening suggests that the prevalence of chronic

RHD may be as high as 2% to 3%, 10 times the prevalence previously estimated by clinical screening.[78]

Acute rheumatic carditis usually presents as tachycardia and cardiac murmurs, with or without transient rhythm disturbances (reflecting myocardial involvement) or a friction rub (reflecting pericarditis). The characteristic murmur of mitral regurgitation is a high-pitched, apical, holosystolic murmur that radiates to the axilla. Moderate to severe rheumatic carditis can result in cardiomegaly and congestive heart failure with hepatomegaly and peripheral and pulmonary edema. Currently echocardiographic evidence of carditis without clinical support (i.e. auscultation of a new murmur) is neither a major nor a minor Jones criterion.

Chorea.

Sydenham chorea (St. Vitus dance) is a neurologic disorder that occurs in 10% to 15% of patients with ARF, often much later (up to 6 months) than other manifestations. A frequently subtle disorder of behavior and movement, Sydenham chorea is characterized by uncontrollable movements, emotional lability, hypotonia, poor school performance, and facial grimacing; symptoms often are exacerbated by stress and disappear during sleep.[79] The onset can be insidious, and symptoms can be present for several months before they are recognized. Diagnosis of Sydenham chorea is based on clinical findings, with or without supportive evidence such as high serum levels of antistreptococcal antibodies. Although the acute illness is highly distressing, chorea rarely, if ever, has permanent neurologic sequelae.

Erythema Marginatum.

Erythema marginatum is a rare but distinctive exanthem of ARF that is manifested by nonpuritic, macular lesions that are erythematous, serpiginous and have pale centers. A rash can occur primarily on the trunk and extremities, typically sparing the face; it is seen in less than 3% of patients with ARF.

Subcutaneous Nodules.

Less than 1% of patients with ARF develop firm, painless, subcutaneous nodules approximately 1 cm in diameter. These nodules can be palpated along the extensor surfaces of tendons near bony prominences. Subcutaneous nodules often correlate with significant RHD.

Minor Manifestations

The two minor clinical manifestations included in the 1992 revised Jones criteria are (1) arthralgia in the absence of the major criterion polyarthritis and (2) fever, typically 38.9°C or higher, that occurs early in the course of the illness. Two minor laboratory manifestations are (1) elevations of acute phase reactants, such as C-reactive protein and/or the erythrocyte sedimentation rate (which is usually >50 mm/hour); and (2) a prolonged PR interval on an electrocardiogram (first-degree heart block). Prospective studies have demonstrated that a prolonged PR interval alone does not constitute evidence of carditis nor predict longterm cardiac sequelae.

Evidence of Recent Streptococcal Infection

Supporting evidence of a recent GAS infection is an absolute requirement for the diagnosis of ARF, except with isolated Sydenham chorea. Because ARF develops 2 to 4 weeks after acute GAS pharyngitis, clinical signs of pharyngitis are no longer present, and the throat culture or rapid GAS antigen test result is positive in only 10% to 20% of cases. One third of patients recall no history of previous pharyngitis. Elevated or rising serum antistreptococcal antibody titers are the most reliable basis for diagnosis. If only the ASO level is measured, elevated titers (greater than 500 Todd units) are found in 80% to 85% of patients with ARF; 95% to 100% of such patients are identified if two additional antibody levels (e.g., anti-DNAse B, antistreptokinase or antihyaluronidase) are measured.

Differential Diagnosis

The differential diagnosis of ARF includes many infectious and noninfectious conditions associated with monoarticular or polyarticular arthritis (Table 118.1). Children with juvenile idiopathic arthritis (JIA) tend to be younger and usually have less joint pain relative to their clinical findings that do those with ARF. Spiking fevers, lymphadenopathy, and splenomegaly are more suggestive of JIA. The response to salicylate therapy is much less dramatic in JIA. Systemic lupus erythematosus (SLE) usually can be distinguished by the presence of antinuclear antibodies.

TABLE 118.1

Differential Diagnosis of Acute Rheumatic Fever

Arthritis	Carditis	Chorea
Juvenile idiopathic arthritis Systemic lupus erythematosus Serum sickness Sickle-cell disease Malignancy Gonococcal infection Reactive arthritis (e.g., *Shigella*, *Salmonella*, *Yersinia* spp.) Lyme arthritis	Kawasaki disease Viral myocarditis Viral pericarditis Infective endocarditis Mitral valve prolapse Congenital heart disease Innocent murmur	Huntington chorea Wilson disease Systemic lupus erythematosus Cerebral palsy Tics Hyperactivity Encephalitis

When carditis is the sole major manifestation of ARF, viral myocarditis, viral pericarditis, Kawasaki disease, and infective endocarditis should be considered. In general, the absence of a significant cardiac murmur excludes the diagnosis of ARF. Echocardiography can distinguish functional murmurs from murmurs caused by congenital heart defects. Patients with infective endocarditis can present with both joint and cardiac manifestations; usually positive blood culture results or associated findings (e.g., hematuria, splenomegaly, splinter hemorrhages) distinguish endocarditis.

Treatment

The management of ARF involves antibiotic and anti-inflammatory therapy, symptomatic treatment, and interventions to prevent future GAS infections. When the diagnosis of ARF has been established, a single intramuscular injection of benzathine penicillin or 10 days of orally administered penicillin or amoxicillin (or a macrolide, in penicillin allergy) is administered to eradicate GAS from the upper respiratory tract, regardless of the throat culture results. For patients who have definite arthritis and those who have carditis without cardiomegaly or congestive heart failure, salicylate therapy (50 to 75 mg/kg/day) should be given for 2 to 4 weeks, then tapered over the next 4 to 6 weeks. The response of ARF arthritis to salicylates is characteristically dramatic; no evidence indicates that other NSAIDs are superior. Patients with carditis and cardiomegaly or congestive heart failure often are prescribed corticosteroid therapy (e.g., 2 mg/kg/day for 2 weeks, with slow taper); a recent meta-analysis suggests that compared with aspirin alone, corticosteroids (or IGIV) reduce the risk of heart valve lesions in patients with ARF.[80] Supportive therapies for moderate to severe carditis include oxygen, fluid and salt restriction, diuretics, and angiotensin-converting enzyme inhibitors or digoxin. Bed rest for 2 weeks to 4 months, depending on the degree of carditis, usually is recommended. Because Sydenham chorea often occurs as an isolated manifestation after resolution of the acute phase of ARF, anti-inflammatory agents usually are not indicated. Patients may benefit from rest, limitation of external stimuli, and therapy with phenobarbital, haloperidol or chlorpromazine as guided by a pediatric neurologist.

Secondary Prevention and Prognosis

Because ARF frequently recurs with subsequent GAS infections, secondary prevention is required to avoid recurrences that increase the likelihood and severity of RHD. Secondary prevention requires continuous antibiotic prophylaxis, which should begin immediately after the full course of antibiotic therapy has been completed. Patients with carditis during the initial episode of ARF should receive antibiotic prophylaxis well into adulthood and perhaps for life. Other patients have a relatively low risk of carditis with recurrences, and antibiotic prophylaxis can be discontinued in these patients after 5 years or when they reach the age of 21 (whichever is later). The decision to discontinue antibiotic prophylaxis should be made only after careful consideration of the potential risks and benefits and the epidemiologic factors, such as the risk of exposure to GAS infections.

The regimen of choice for secondary prevention is a single injection of 1.2 million units of benzathine penicillin G every 4 weeks (Table 118.2). Continuous oral antimicrobial prophylaxis can be used in patients likely to adhere to the regimen. Prophylaxis using penicillin given twice daily or sulfadiazine given once daily is equally effective.

TABLE 118.2

Secondary Prevention of Rheumatic Fever (Prevention of Recurrent Attacks)

Agent	Dose
Benzathine penicillin G	1.2 million units IM every 4 weeks[a]
Penicillin V	250 mg PO twice daily
Sulfadiazine	0.5 g PO once daily for patients ≤27 kg; 1 g PO once daily for patients >27 kg
Erythromycin[b]	250 mg PO twice daily

[a] In high-risk situations, administration every 3 weeks is justified and recommended.

[b] For individuals allergic to penicillin and sulfadiazine.

IM, intramuscularly; PO, by mouth; U, units.

Adapted from Dajani A, Taubert Y, Ferrieri P, et al. Treatment of acute streptococcal pharyngitis and prevention of rheumatic fever: a statement for health professionals. Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, the American Heart Association. Pediatrics 1995;96:758. Copyright American Academy of Pediatrics.

The prognosis for patients with ARF depends on the number and severity of clinical manifestations during the initial episode and whether recurrences were allowed to develop. In the absence of recurrent GAS infections, rheumatic fever does not reappear more than 8 weeks after the withdrawal of anti-inflammatory therapy. Approximately 70% of patients with carditis during the initial episode of ARF recover with no residual heart disease if they follow a prophylaxis regimen.

Acute Glomerulonephritis

Epidemiology

PSAGN was described by Richard Bright in 1836 as hematuria after scarlet fever. Unlike ARF, PSAGN occurs as a consequence of either GAS pharyngitis or pyoderma. PSAGN is primarily a disease of preschool and school-aged children; approximately 60% of patients are between 2 and 12 years of age. The actual incidence of PSAGN is difficult to determine because many cases are asymptomatic; however, PSAGN is by far the most common form of glomerulonephritis and acute renal insufficiency in children. Certain M types of GAS associated with pharyngitis (e.g., M1, M2, M3, M4, M12, and M15), in addition to certain M types associated with pyoderma (e.g., M49, M52, M55, M59, M60, and M61), are commonly associated with PSAGN and therefore are considered nephritogenic.[81] However, not all strains of a given M type are nephritogenic. Although PSAGN most often is a sporadic disease, it also can occur in epidemic forms. Concomitant presence of ARF and PSAGN is unusual in a population and rare in a patient.

Pathogenesis and Pathology

Although the pathogenic link between GAS infections and PSAGN has been clearly established, the mechanisms of renal injury have not been completely defined. However, considerable evidence suggests that PSAGN occurs when soluble immunoglobulin G immune complexes are deposited at the glomerular basement membrane, activating complement and the release of chemotactic factors that lead to infiltration by inflammatory cells. Whether the antigen in these complexes is a GAS antigen or a host-derived antigen that cross-reacts with antistreptococcal antibodies is not clear. Candidate GAS antigens for this process include glyceraldehyde-3-phosphatedehydrogenase (also known as "nephritis-associated" streptococcal plasmin receptor) and cysteine protease SpeB.[82,83] Because these proteins are present in virtually all strains of GAS, additional host factors are suspected to influence susceptibility, but studies of HLA antigen distribution have failed to identify a specific association with PSAGN.[84]

Although renal biopsy is rarely indicated for patients with PSAGN, biopsy can be helpful if hypertension, hypocomplementemia, heavy proteinuria, or renal insufficiency persists. The glomerular lesions of PSAGN can be proliferative, exudative, or both; typically glomeruli are involved diffusely. Electron microscopy reveals deposits consisting of immunoglobulin G and complement component C3, which usually are found in a subepithelial location during the first 3 to 6 weeks of the disease; the glomerular basement membrane usually appears normal.

Clinical Features

PSAGN typically occurs about 10 days after the onset of acute GAS pharyngitis or 3 weeks after the onset of GAS pyoderma. Edema (often periorbital) and hematuria are the clinical findings that usually bring patients with PSAGN to medical attention (Box 118.3). Approximately 30% to 50% of children with PSAGN have gross hematuria, which typically is described as "cola-colored" urine. Gross hematuria can persist for as little as a few hours or for as long as 2 weeks.

Box 118.3

Signs and Symptoms of Poststreptococcal Acute Glomerulonephritis (PSAGN)

Common Findings

Hematuria (microscopic or macroscopic)

Edema

Hypertension

Oliguria

Variable Findings

Systemic symptoms (fever, nausea, anorexia, lethargy, abdominal pain)

Uncommon Findings

Hypertensive encephalopathy (vomiting, headache, confusion, somnolence, seizures)

Anuria and renal failure

Congestive heart failure

Approximately 50% to 90% of children with PSAGN have hypertension. The severity of hypertension is highly variable, but systolic pressures greater than 200 mm Hg and diastolic pressures greater than120 mm Hg are not unusual. Most children with PSAGN also have evidence of circulatory congestion from the expansion of the intravascular fluid volume. Dyspnea, orthopnea, cough, or pulmonary rales may be present. Children with PSAGN also can have systemic symptoms, such as lethargy, anorexia, fever, and abdominal pain, but they seldom appear extremely ill. Occasionally a fulminant course can evolve, marked by severe oliguria, congestive heart failure, or hypertensive encephalopathy. Rare occurrences of reversible posterior leukoencephalopathy or autoimmune hemolytic anemia have been described.[85] Renal disease typically is self-limited, and spontaneous diuresis, loss of edema, and improvement in hypertension occur within 1 week.

Laboratory Findings

Virtually all children with PSAGN have microscopic hematuria, and 30% to 50% have gross hematuria. Evaluation of the urine shows pyuria and hyaline, granular, or red blood cell casts. Most children have proteinuria, and approximately 30% are in the nephrotic range, with protein loss greater than 2 g/m^2 per 24 hours.

During the initial 2 weeks of PSAGN, total hemolytic complement activity and C3 levels are depressed in almost all children. About one third of patients have modest elevations of blood urea nitrogen and creatinine. During the first week of PSAGN, elevations of circulating immune complexes are seen in most patients, and the quantity of these immune complexes correlates with the severity of the PSAGN. Patients with moderate to severe impairment of renal function can demonstrate metabolic acidosis, hyperkalemia, hyperchloremia, hyponatremia, hypoalbuminemia, or dilutional anemia. The best evidence of antecedent streptococcal infection is serologic; 90% to 95% of patients have elevations of ASO and/or anti-DNAse B.

Although antibiotic therapy does not affect the clinical course of PSAGN, therapy can eradicate the nephritogenic GAS strain that may still be present and thus reduce the risk of transmission to others. Penicillin is the antibiotic of choice; a macrolide is the preferred agent for patients allergic to penicillin. No immunosuppressant or antiinflammatory therapeutic agent has been shown to accelerate the resolution of renal lesions. Treatment consists primarily of supportive measures directed at complications of the disease. Occasionally the associated hypertension is so severe as to cause encephalopathy. Circulatory congestion can be severe and can lead to pulmonary edema and congestive heart failure. Although oliguria often is seen in children with PSAGN, anuria and renal failure are uncommon. Overall, the prognosis is favorable. More than 95% of children experience spontaneous and complete resolution of symptoms, edema, and renal dysfunction; urinalysis results are abnormal in less than 5% of patients 15 years after the acute episode.[86]

Prevention

In contrast to ARF, which can be prevented with antibiotic therapy of the antecedent GAS infection, no evidence indicates that PSAGN can be prevented once pharyngitis or pyoderma with a nephritogenic strain of GAS has occurred. Antibiotic treatment is given to limit transmission. During outbreaks of GAS pyoderma caused by nephritogenic strains, prophylactic administration of penicillin to children at risk may be beneficial.[87] Because recurrences of PSAGN are rare, longterm antibiotic prophylaxis after an episode is not indicated.

Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections

In 1998 investigators described a series 50 patients with childhood onset obsessive-compulsive disorder (OCD) and/or tics and suggested that these could arise as a result of a poststreptococcal autoimmune process.[88] The investigators coined the acronym PANDAS to denote *p*ediatric *a*utoimmune *n*europsychiatric *di*sorders *a*ssociated with *s*treptococcal infections. They proposed that, in response to GAS infection, this subset of patients with OCD and tic produced autoimmune antibodies that cross-reacted with neuronal tissues in the basal ganglia and associated structures, reminiscent of the autoimmune response implicated in similar clinical manifestations of certain patients with ARF and Sydenham chorea. Recently two prospective, blinded, multicenter cohort studies of matched pairs found no evidence of a temporal association between GAS infection and OCD/tic symptoms in children who met the published diagnostic criteria for PANDAS.[89,90] In another study, no correlation was seen between clinical exacerbations in these patients and serum antibodies cross-reactive with brain tissues.[91] In light of these findings, experts favor a broader concept (i.e., childhood acute neuropsychiatric symptoms [CANS]) and a broader treatment approach.[92]

Inaccurate diagnosis and treatment of PANDAS is widespread in the pediatric medicine community,[93] and new classification schemes can help delineate the risks for this particular subtype of OCD or tic disorder. Current data indicate that although PANDAS remains a hypothesis (perhaps applicable to a very select subset of patients), complicated interventions such as immune globulin or plasmapheresis may not be warranted.[90,94]

Poststreptococcal Reactive Arthritis

PSRA describes an entity in patients who had arthritis after an episode of GAS pharyngitis but lacked other major criteria for ARF. ARF peaks in early childhood (4 to 9 years), but PSRA has a bimodal distribution, with a first peak at 8 to 14 years and a second peak in early adulthood.[95] The arthritis of ARF classically develops 14 to 21 days after an episode of GAS pharyngitis and responds rapidly to NSAID therapy, whereas PSRA occurs about 10 days after GAS pharyngitis and does not respond readily to NSAIDs. In addition, the arthritis of PSRA is cumulative, persistent, and can involve large joints, small joints, or the axial skeleton, whereas the arthritis of ARF is migratory, transient, and usually involves only the large joints. All patients with PSRA have serologic evidence of a recent GAS infection. A few such patients may go on to develop valvular heart disease; therefore, they should be monitored carefully for carditis for several months. In contrast to the arthritis of ARF, PSRA can have a prolonged duration (median, 2 months) and can recur. Some physicians administer secondary prophylaxis to these patients for a period as short as 3 months and as long as 12 months; if carditis is detected, the patient should be classified as having had ARF and should continue to receive secondary prophylaxis. Unfortunately, validated diagnostic criteria for PSRA have yet to be established.[95]

Key Points

Group A *Streptococcus* and Clinical Syndromes

Epidemiology, Pathogenesis, and Immunity

- More than 600 million cases of pharyngitis and more than100 million cases of pyoderma annually worldwide.
- Rheumatic heart disease affects 15.6 million people worldwide
- Infections can be nonsevere and of short duration or rapidly invasive and fulminant.
- Unique among pyogenic bacteria in causing postinfectious, immunologically mediated diseases (acute rheumatic fever, acute glomerulonephritis)
- More than 100 distinct M-protein genotypes identified, which tend to be associated with infectious and nonsuppurative syndromes
- Genome sequencing shows that bacteriophages have been important in organism's evolutionary genetics (e.g., virulence determinants, and toxins).
- Pathogenesis of serious disease can occur by three mechanisms: suppuration, toxin elaboration, and immune-mediated inflammation.
- Expression of multiple specific virulence factors can lead to evasion of the patient's innate clearance response, uncontrollable proinflammatory response, damage to phagocytic cells, accelerated apoptosis of immune cells, inactivation of terminal complement components, superantigen-induced T-lymphocyte activation, and more.
- Opsonic anti-M-protein antibodies rise 6 to 8 weeks after infection and protect against M type-–specific invasive infection.

Clinical Manifestations

- Causes a wide spectrum of simple and complicated oropharyngeal and respiratory tract infections, skin and soft tissue infections, invasive infections, and toxin-mediated syndromes
- Necrotizing cellulitis, myositis, and fasciitis can be suspected when a seemingly minor skin or soft tissue infection is associated with disproportionate pain, hyperesthenia or hypoesthenia, local pallor, tenseness, and a blistering lesion.
- Proven cause of nonsuppurative acute rheumatic fever and acute glomerulonephritis (see text)

Treatment of Suppurative Infections

- Penicillin retains exquisite activity in vitro; no resistance to β-lactam antibiotics has been seen.
- Clindamycin usually is given in addition to a β-lactam for severe invasive or toxin-mediated disease to overcome the "Eagle effect" (loss of bactericidal capacity of β-lactam at a high density of bacteria/stationary growth phase) and to inhibit protein synthesis and virulence factors.
- Immune globulin intravenous (IGIV) therapy is reserved for severely ill patients with toxic shock syndrome.

Prevention

- Vaccine development has been thwarted by the hypervariability and diversity of surface M proteins and by potential immunologic responses that might cross-react with cardiac or neural tissue.
- Novel approaches explore the use of conserved or genetically engineered surface proteins.

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Streptococcus agalactiae (Group B *Streptococcus*)

Morven S. Edwards, Carol J. Baker

The Pathogen and Pathogenicity

Streptococcus agalactiae is the species designation for Lancefield group B *Streptococcus* (GBS). Colonies appear on sheep blood agar as 3- to 4-mm, grey-white colonies with a narrow zone of β-hemolysis; organisms are gram-positive cocci. The group B–specific cell wall carbohydrate antigen is common to all strains, and a surface capsular polysaccharide (CPS) allows classification into types Ia, Ib, II, III, IV, V, VI, VII, VIII, and IX. A surface protein antigen, C protein, with *α* and β components, is common to all Ib strains, to 30% of type Ia strains, to 60% of type II strains, and to some type IV, V, and VI strains. Another surface component is a pilus that facilitates attachment to mucosal surfaces.

Pilus-like protein structures are found in all GBS strains of human origin. Antibodies to pili confer protection in experimental infection, which suggests that they play an important role in mediating attachment and invasion.[1,2] The *α* C surface protein mediates translocation across epithelial barriers; GBS also can use a paracellular route by transiently opening cell junctions.[3,4] The β-hemolysin/cytolysin forms pores that compromise epithelial and endothelial barrier function.[5,6]

High-virulence clones of GBS have emerged.[7] The hypervirulent clonal complex ST-17 of type III has a tropism for meninges and typically is found among invasive but not colonizing neonatal isolates. CPSs allow the organism to evade ingestion by host phagocytic cells. GBS suppresses phagocyte function and promotes bacterial survival by engaging host sialic acid–recognizing immunoglobulin superfamily inhibitory lectins.[8,9] Antibodies to CPSs are protective, and the risk for invasive infection correlates with low concentrations of antibodies to the infecting GBS CPS.[10]

The presence of GBS in the maternal genital tract at delivery is critical to early onset neonatal infection. Early onset infection occurs in 1% to 2% of infants born to mothers with GBS vaginal or rectal colonization at delivery who do not receive intrapartum antibiotic prophylaxis (IAP). Replication of organisms in association with maternal chorioamnionitis further enhances fetal/infant risk. The incidence of early onset disease is influenced by a number of factors (Table 119.1). The higher the genital inoculum, the longer the duration of exposure, and the greater the immaturity of the infant, the greater the risk of invasive neonatal infection.

TABLE 119.1

Pathogenesis of Early Onset Group B *Streptococcus* Infection

Feature	Comment
Strain virulence	Clonal virulence; capsule type (e.g., III), amount of capsule, hemolysin production, and certain surface components (e.g., sialic acid, C protein, hemolysin, pili, among others) enhance virulence by facilitating invasion and downregulating immune responsiveness
Inoculum size	Risk correlates with high density of maternal vaginal colonization
Premature rupture of membranes	Risk of infection increases with rupture of membranes before onset of labor
Preterm delivery	Risk correlates inversely with gestational age
Prolonged rupture of membranes	Risk increases when membranes are ruptured ≥18 hr before delivery
Maternal bacteriuria due to group B *Streptococcus* during pregnancy	Risk increases because bacteriuria correlates with dense maternal genital colonization, premature rupture of placental membranes, and preterm delivery
Serum concentrations of immunoglobulin G (IgG) to colonizing CPS type	Risk correlates inversely with levels of maternal serum IgG to the capsular polysaccharide of colonizing strain

As in early onset infection, low concentrations of antibody to type III CPS are found uniformly in sera obtained during the acute phase of illness from infants with later or very late onset infection. A viral infection preceding development may alter epithelial surfaces in a way that promotes entry of GBS into the bloodstream. Extended hospitalization, as is required by very low birth weight infants, enhances risk of healthcare exposure to GBS, if hand hygiene is not optimal.

Epidemiology

Depending on the culture method used and the population studied, GBS can be isolated from the maternal genital or lower gastrointestinal tract in 15% to 40% of pregnant women. When specimens are obtained from the rectum and lower vagina rather than the cervix, and when a selective antibiotic-containing broth medium is used rather than solid agar, colonization detection rates increase by 30% to 50%. Culture specimens obtained within 5 weeks before term gestation optimize the sensitivity in predicting colonization at delivery.

Neonates acquire colonization with GBS vertically, either in utero by the ascending route or at delivery. Heavy maternal colonization, intrapartum fever, African ethnicity, and lack of intrapartum antibiotic prophylaxis are associated with transmission.[11] Uninterrupted, the rate of vertical transmission of colonization from a mother colonized with GBS to an infant at delivery averages 50%. Infants born to mothers heavily colonized with GBS ($>10^5$ colony-forming units per milliliter [CFUs/mL]) or who have characteristics listed in Table 119.1 are at enhanced risk for invasive infection. Acquisition of colonization by infants can occur from the mother or other household contacts after hospital discharge. Whether late onset disease results from an exogenous source, such as breast milk, or from established colonization or both is unclear. The synchrony of recurrent disease in twins and the detection of GBS DNA in breast milk suggest that an enteral mode of acquisition can occur in some cases.[12]

The incidence of early onset GBS disease (within the first 6 days of life) has declined by 80% compared with the preprevention era baseline rate in 1993. In 2014 the incidence was 0.22 cases per 1000 live births.[13] Attack rates for early onset disease are related inversely to birth weight and can exceed 20 per 1000 live births in infants weighing less than 1000 g. However, because of the much larger number of births at term, most cases of early onset infections (~50%) occur in term infants. The incidence of late onset infection (7 to 89 days of age) has not been reduced through maternal IAP; in 2014 the incidence provisionally was 0.27 per 1000 live births.[13] GBS infections in infants 3 months of age or older occur primarily among those requiring prolonged hospitalization for complications of extreme prematurity.[14,15]

The CPS distribution of isolates causing early onset disease parallels that of organisms colonizing the maternal genital tract.[16] The CPSs that most commonly cause early onset disease, as reported by the Centers for Disease Control and Prevention (CDC), are Ia (30% of cases), III (28%), V (18%), and II (13%).[17] Recent reports indicate that type IV may be emerging as a cause of infant disease.[18] In late onset infections, CPS III accounts for 51% of cases, Ia for 24%, and V for 14%. Infections occur occasionally in epidemic clusters; the associated GBS types are similar to those that cause late onset disease.[19]

Clinical Manifestations

Early Onset Infection

Early onset GBS infection is associated commonly with maternal obstetric complications (Table 119.2).[20] The presenting signs, such as lethargy, apnea or bradycardia, and poor feeding, are indistinguishable from the signs of infections caused by other bacteria. Irritability and hyperthermia are noted more often in term than preterm infants (Table 119.3), and bacteremia without signs of infection occurs almost exclusively in term infants. Regardless of the age of onset and focus of infection, respiratory distress often occurs in infants with early onset infection. Radiographic findings can be consistent with pneumonia, respiratory distress syndrome, transient tachypnea of the neonate, or meconium aspiration.[15]

TABLE 119.2

Comparison of Early, Late, and Very Late Onset Group B

Feature	Early Onset	Late Onset	Very Late Onset
Age range	<7 days	7–89 days	≥3 mo
Median age at onset	1 day	37 days	Unknown
Maternal obstetric complications	Common	Preterm delivery	Varies
Frequency of gestation <37 wk	Frequent (~25%)	Frequent (~50%)	Typical
Usual clinical presentations	Septicemia (80%–85%) Meningitis (5%–10%) Pneumonia (10%–15%)	Meningitis (25%–35%) Bloodstream infection without focus (65%) Soft tissue, bone, joint infection, or pneumonia (5%–10%)	Bloodstream infection without focus (common) Bloodstream infection with a focus (occasional)[a]
Common capsular types	Ia, II, III, V	III (>50%), Ia, V	III, Ia, V
Mortality rate	3%–10%[b]	1%–6%	Low

[a] Includes peritoneum, urinary tract, skin and soft tissue, and central nervous system.

[b] <5% in term infants.

Modified from Edwards MS, Nizet V, Baker CJ. Group B streptococcal infections. In: Wilson CB, Nizet V, Maldonado VY, et al. (eds). Infectious Diseases of the Fetus and Newborn Infant, 8th ed. Philadelphia, Elsevier Saunders, 2016, pp. 411–456.

TABLE 119.3

Clinical Features of Early Onset Group B *Streptococcus* Infection

Features	Term	Preterm
Respiratory distress	+++	++
Lethargy or poor tone	++	+++
Cyanosis	++	++
Poor feeding	++	++
Apnea or bradycardia	+	++
Poor perfusion	+	++
Hypotension	+	++
Irritability	+	–
Hyperthermia	+	–
Healthy appearing	+	–

+++, most common; ++, commonly observed (25%–50%); +, occasionally observed (10%–25%); –, rarely observed.

The clinical syndromes commonly associated with early onset infection are bloodstream infection (BSI) without a focus (with shock in about 25% of cases), pneumonia, and meningitis.[21,22] Payne and colleagues[23] identified 6 features that predict a fatal outcome in early onset disease: (1) birth weight less than 2500 g, (2) absolute neutrophil count less than 1500 cells/mm^3, (3) hypotension, (4) apnea, (5) initial pH less than 7.25, and (6) demonstration of pleural effusion on initial chest radiograph.

Late Onset Infection

The median age of onset for late onset disease is 37 days.[20] Affected term infants usually have an unremarkable early neonatal course. BSI without a focus is the most common presentation, but meningitis occurs in about 30% of cases. Characteristic features are fever, poor feeding, and irritability; infants usually recover uneventfully with antimicrobial and supportive therapy. Infants with meningitis can have similar presenting features, but some have a fulminant onset and rapid progression. In these infants, the presenting features can include poor color, grunting, altered level of consciousness, apnea, or seizures. A number of presenting clinical or laboratory findings are associated with a fatal outcome or abnormal neurologic examination at hospital discharge for infants with GBS meningitis (Table 119.4).[24] Seizures at admission remain a significant risk factor for poor outcome in multivariate analysis.

TABLE 119.4

Features at Admission That Predict an Adverse Early Outcome for Infants With Group B *Streptococcus* Meningitis[a]

Feature	Comment
Need for pressors	Indicates advanced or overwhelming infection
Coma or semicoma	Indicates advanced or overwhelming infection
Seizures	Indicates cerebritis
Pallor	Surrogate for shock
Low cerebrospinal fluid (CSF) glucose	<20 mg/dL
Elevated CSF protein	≥300 mg/dL
High antigen content in CSF	Concentration of III-specific CPS in CSF >3 μg/mL

[a] See reference 24.

Several other foci of infection can occur in late onset disease, including osteomyelitis, arthritis, and cellulitis-adenitis syndrome. Osteomyelitis has an indolent presentation, with diminished mobility of an extremity or pain with motion that has been present for up to a month before diagnosis. Inflammatory signs are present occasionally but not reliably. The proximal humerus is the most frequent site in osteomyelitis; less frequently, the long bones of the lower extremities and flat or small bones are involved.[25]

The mean age at diagnosis of pyogenic arthritis is 20 days. The duration of signs of infection is usually several days, and the hip and knee joints are common sites of involvement. GBS cellulitis-adenitis syndrome usually is unilateral, involving facial or submandibular sites, although inguinal, scrotal, and prepatellar sites have been described.[26] Presenting signs include poor feeding, irritability, and fever. Affected infants typically have a BSI (>90% of cases), and aspiration of the involved soft tissue or lymph node often yields the organism. Abscesses can form, necessitating surgical drainage.

A number of less common or unusual foci of infection have been reported, including urinary tract infection with or without associated structural abnormalities, endocarditis, otitis media, necrotizing fasciitis, and others.[20] Isolation of GBS from a normally sterile body site should be considered indicative of invasive infection.

Very Late Onset Infection

In one report of GBS disease, 20% of the infants were older than 3 months.[15] For these infants, the terms *late onset, later onset,* or *very late onset infection* are applicable. Most of these infections occur among very low birth weight infants who require protracted hospitalization. Immature immune function and continued mucous membrane colonization probably contribute to susceptibility. Among term infants with a very late presentation, immunodeficiency, including human immunodeficiency virus infection, should be considered. BSI, without a focus or with the foci described previously for late onset infection, is the usual presentation (see Table 119.2). Among hospitalized infants, GBS infections associated with indwelling vascular catheters or necrotizing enterocolitis also have been observed.

Laboratory Findings and Diagnostic Tests

The diagnosis of invasive GBS infection is established by isolation of the organism from a sterile body site. Lumbar puncture is critical to diagnosing meningitis because as many as 30% of infants with meningitis have a sterile blood culture.[27] Early onset GBS infection can occur among infants whose mothers have a negative culture for GBS colonization, so a negative maternal GBS screen should not discourage infant evaluation for septicemia.[28] The finding of GBS in gastric or tracheal aspirates or in maternal amniotic fluid contents indicates infant exposure but does not define clinical illness. Abnormalities in the white blood cell (WBC) count, including leukopenia, neutropenia, or an increased ratio of immature-to-total neutrophils, often are found but have poor sensitivity. Sensitivity in predicting early onset GBS septicemia is improved if the WBC count is performed 6 to 12 hours after birth.[29]

Rapid antigen detection methods are not an appropriate substitute for cultures from blood or other normally sterile body fluid specimens. With currently available radiometric blood culture technology, antigen detection is required or indicated uncommonly, and only serum or cerebrospinal fluid (CSF) is recommended for testing.[30] Repeating antigen tests during therapy is not recommended. Diagnostic imaging for infants with meningitis is not useful for diagnosis or for managing the acute course of infection.

Treatment

The initial therapy for suspected GBS infection is ampicillin plus an aminoglycoside, typically gentamicin (Table 119.5). This regimen provides broad coverage for neonatal pathogens, and the combination is synergistic in vitro and in vivo for killing GBS. When GBS has been confirmed as the causative pathogen, a clinical response has been observed, *and* sterility of the bloodstream and CSF has been documented (by re-examination of the CSF, typically 48 to 72 hours after the start of therapy), treatment can be completed with penicillin G alone.

TABLE 119.5

Antibiotic Therapy for Group B Streptococcus Infections

Type of Infection	Antibiotic (Dose)	Expected Duration of Therapy

INITIAL EMPIRIC THERAPY[a]		
Suspected meningitis	Ampicillin (300 mg/kg/day) *plus* Gentamicin[a]	Until cerebrospinal fluid sterility *and* penicillin susceptibility documented
Suspected septicemia	Ampicillin (150 mg/kg/day) *plus* Gentamicin[b]	Until bloodstream sterility documented
DEFINITIVE THERAPY		
Bloodstream infection[c]	Ampicillin (150 mg/kg/day) *or* Penicillin G (200,000 U/kg/day)	Total antibiotic therapy of 10 days
Meningitis	Penicillin G (400,000–500,000 U/kg/day)	Total antibiotic therapy of 14–21 days
Arthritis	Penicillin G (200,000–300,000 U/kg/day)	Total antibiotic therapy of 2–3 wk
Osteomyelitis	Penicillin G (200,000–300,000 U/kg/day)	Total antibiotic therapy of 3–4 wk
Endocarditis	Penicillin G (200,000–300,000 U/kg/day)	Total antibiotic therapy of 4 wk

[a] Empiric therapy is always followed by definitive therapy.

[b] Dose as appropriate for postmenstrual age and days of life.

[c] Assumes that lumbar puncture to exclude meningitis has been performed and that cerebrospinal fluid has no detectable abnormalities.

Penicillin is the drug of choice. The suggested dosages and expected duration of therapy are summarized in Table 119.5. These dosages have proved safe and effective, even in premature infants. The rationale for use of the high doses recommended is that the minimal inhibitory concentration (MIC) of penicillin for GBS ranges from 0.01 to 0.6 μg/mL; the MIC is affected directly by inoculum size, and inoculum at sites of infection can be high. Antibiotic levels achieved in the blood or CSF with the suggested doses will exceed the MIC even when infection is associated with a high inoculum of a strain with an MIC at the upper range of susceptibility.

Reports from the United States and Japan describe point mutations in GBS penicillin-binding proteins that confer reduced susceptibility to penicillin and other β-lactam antibiotics.[31,32] Measured MICs are at the susceptibility threshold, but the clinical implications of these in vitro findings are unclear. In the usual circumstance, it is not necessary to determine the MIC and the minimal bactericidal concentration (MBC) of penicillin for the infecting GBS. Determination of GBS MIC and MBC should be considered when (1) a poor clinical or bacteriologic response to penicillin or ampicillin at the recommended doses occurs; (2) unexplained relapse or recurrence of infection occurs; and (3) infection occurs in an infant with congenital or acquired immunodeficiency.

Supportive care, directed at treating shock, correcting metabolic abnormalities, providing assisted ventilation, and controlling increased intracranial pressure, is paramount for optimizing the outcome of GBS infections. Administration of granulocyte colony-stimulating factor or an immunoglobulin preparation hyperimmune for GBS is clinically unproven.

Lumbar puncture should be considered before therapy for GBS meningitis is discontinued, usually at 14 days in uncomplicated cases. CSF findings that suggest inadequate therapy are a neutrophil value greater than 30% of the total WBCs and a protein level greater than 200 mg/dL. These findings are consistent with cerebritis or parenchymal destruction. It is our practice to continue therapy an additional week if CSF findings suggest inadequate resolution after 14 days of therapy and to reassess the CSF at 21 days of therapy. It is rarely necessary to continue treatment for meningitis longer than 3 weeks.

Contrast-enhanced imaging of the brain should be obtained before antimicrobial therapy is discontinued for infants with GBS meningitis because these findings can lead to prolongation of therapy.[33] Cranial imaging can reveal unresolved cerebritis or ventriculitis and can identify the rare infant with complications of subdural empyema or intracranial abscess. In addition, imaging identifies cerebrovascular complications that also can affect the prognosis.[34] All infants recovering from GBS meningitis should undergo diagnostic auditory brainstem response (ABR) test.

Special Considerations

Prognosis

Case-fatality rates range from 3% to 10% for early onset disease and from 1% to 6% for late onset disease. The risk of death for preterm infants is 8 times that for term infants for early onset and 3 times that for term infants for late onset disease.[17] Premature infants with septic shock who demonstrate periventricular leukomalacia often have neurodevelopmental sequelae. Among 53 term and near-term infants with GBS meningitis in the current era, infection was fatal in 6%, and 22% of survivors had neurologic impairment at hospital discharge, most commonly hypertonicity and persistent seizures.[24] Contemporary data suggest a 19% incidence of severe and a 25% incidence of mild-to-moderate neurologic sequelae among survivors of GBS meningitis.[33]

Recurrent Infection

The recurrence rate for early onset disease is approximately 1%. The mean age is 10 days at first episode and 42 days at recurrence.[35] No common risk factors or underlying conditions predict recurrence. The proposed causes include a persistent focus, inadequate dose or duration of therapy, reinfection with a second strain or type, and recurrent infection with the original strain in a nonimmune patient. Isolates analyzed from first and second GBS episodes often are genotypically identical.[12,36] The following guidance is offered for managing a recurrence: (1) confirm penicillin susceptibility of the isolate by MIC testing; (2) assess serum immunoglobulin and human immunodeficiency virus status; (3) treat empirically for 1 week longer than the usual course; and (4) consider oral rifampin therapy after completion of parenteral therapy in an attempt to eradicate mucosal colonization. The suggested dose for rifampin is 20 mg/kg/day for 4 days; this intervention has a success rate no higher than 50%, probably because the drug is bacteriostatic rather than bactericidal against GBS.[37] Evaluation for proof of eradication of colonization is not recommended because information is lacking for further management if colonization persists.

Prevention

IAP has proved efficacious for early onset disease. In 1986 Boyer and Gotoff[38] demonstrated that IAP administered to high-risk pregnant carriers of GBS reduced vertical transmission to infants, early postpartum febrile morbidity in women, and early onset sepsis. The American Academy of Pediatrics (AAP) published IAP guidelines in 1992.[39] A consensus approach was adopted in 1996 in which selection of women for IAP was based on antenatal cultures for GBS at 35 to 37 weeks' gestation or on the presence of a factor (without culture results) known to increase the risk for neonatal GBS septicemia.[40]

A large, population-based comparison demonstrating that culture-based screening was significantly more effective than risk-based intervention in preventing early onset GBS disease was reflected in the 2002 revised guidelines from the CDC (which were endorsed by the AAP and the American College of Obstetricians and Gynecologists) for prevention of perinatal GBS disease.[41–43] All pregnant women now are screened in each pregnancy for GBS at 35 to 37 weeks' gestation (vaginal and rectal sites are sampled, and specimens are processed in selective broth media). In women who previously delivered an infant with GBS disease or who experienced GBS bacteriuria during the current pregnancy, screening is not needed – IAP should be given. At the time of labor or rupture of membranes, IAP should be given to all pregnant women identified as GBS carriers except those undergoing a planned cesarean delivery before rupture of membranes and the onset of labor (Table 119.6). Prophylaxis with a β-lactam antibiotic (penicillin is preferred), given 4 or more hours before delivery, is highly effective for early onset disease prevention.[44] The risk-based approach should be used only when culture results are not available at the time of delivery.

TABLE 119.6

Indications and Nonindications for Intrapartum Antibiotic Prophylaxis to Prevent Early Onset GBS Disease

Intrapartum GBS Prophylaxis Indicated	Intrapartum GBS Prophylaxis Not Indicated
Previous infant with invasive group B *Streptococcus* (GBS) disease	Colonization with GBS during a previous pregnancy (unless invasive disease in previous infant or an indication for GBS prophylaxis is present for current pregnancy)
GBS bacteriuria during any trimester of the current pregnancy[a]	GBS bacteriuria during previous pregnancy (unless an indication for GBS prophylaxis is present for current pregnancy)
Positive GBS in vaginal-rectal screening culture in late gestation[b] during current pregnancy[a]	Negative GBS in vaginal-rectal screening culture in late gestation[b] during the current pregnancy, regardless of intrapartum risk factors
Unknown GBS status at the onset of labor (culture not done, incomplete, or results unknown) and any of the following:	Cesarean delivery performed in a woman before onset of labor and with intact amniotic membranes, regardless of GBS colonization status or gestational age

• Delivery at <37 wk gestation[c] • Amniotic membrane rupture ≥18 hr • Intrapartum temperature ≥100.4°F (≥38.0°C)[d] • Intrapartum NAAT[e] positive for GBS	

[a] Intrapartum antibiotic prophylaxis is not indicated in this circumstance if a cesarean delivery is performed in a woman before onset of labor and with intact amniotic membranes.

[b] Optimal timing for prenatal GBS screening is at 35–37 weeks' gestation.

[c] Recommendations for the use of intrapartum antibiotics for prevention of early onset GBS disease in the setting of threatened preterm delivery are discussed in reference 44.

[d] If amnionitis is suspected, broad-spectrum antibiotic therapy that includes an agent known to be active against GBS should replace GBS prophylaxis.

[e] NAAT testing for GBS is optional and might not be available in all settings. If intrapartum NAAT is negative for GBS but any other intrapartum risk factor (i.e., delivery at <37 wk gestation, amniotic membrane rupture at ≥18 hours, or maternal temperature ≥100.4°F [≥38.0°C]) is present, intrapartum antibiotic prophylaxis is indicated.

NAAT, nucleic acid amplification tests.

From Fairlie T, Zell ER, Schrag S. Effectiveness of intrapartum antibiotic prophylaxis for prevention of early-onset group B streptococcal disease. Obstet Gynecol 2013;121:570–577.

In 2010 the CDC updated the guidelines to be more comprehensive, but it reaffirmed the major prevention strategy – universal antenatal GBS screening and IAP for culture-positive and high-risk women. It also included new recommendations for (1) laboratory methods for identification of GBS colonization during pregnancy; (2) algorithms for screening and IAP for women with preterm labor and premature rupture of membranes; (3) an updtated prophylaxis regimen for women with a penicillin allergy; and (4) a revised algorithm for the care of newborns.[45] Options for GBS identification from vaginal and rectal swabs now include positive identifications from chromogenic media and identifications directly from antibiotic-containing broth. Nucleic acid amplification tests (NAATs), such as commercially available polymerase chain reaction assays, are allowed for screening after enrichment if laboratories have validated their NAAT performance and use quality controls. Implementation of an algorithm based on the CDC guidelines eliminated 25% of all early onset sepsis evaluations and achieved substantial cost savings at one center.[46]

The maternal IAP regimen should consist of intravenous penicillin G (5 million units initially, then 3 million units every 4 hours) until delivery. Intravenous ampicillin (2 g initially and 1 g every 4 hours until delivery) is an acceptable alternative. Women allergic to penicillin who do *not* have a history of anaphylaxis, angioedema, respiratory distress, or urticaria after administration of penicillin or a cephalosporin should receive cefazolin (2 g initially and 1 g every 8 hours until delivery). The definition of adequate IAP is receipt of an antibiotic (penicillin, ampicillin, or cefazolin) at least 4 hours before delivery.[45] All other agents, doses, or durations are considered inadequate for purposes of neonatal management. For high-risk women allergic to penicillin (anaphylaxis, angioedema, respiratory distress, or urticaria), clindamycin (900 mg every 8 hours until delivery) can be given if the colonizing GBS isolate has been documented to be clindamycin susceptible. Current data estimate that 30% of GBS isolates are clindamycin resistant. Early onset GBS has been documented in an infant with a clindamycin-resistant organism whose mother received IAP with clindamycin.[47] Vancomycin (1 g every 12 hours until delivery) is an alternative agent for women at high risk for penicillin allergy in whom clindamycin-resistant GBS has been isolated from screening cultures. Neither clindamycin IAP nor vancomycin IAP has been evaluated for efficacy in preventing early onset GBS neonatal disease.

The management of infants depends on a number of factors: the infant's clinical status; the presence or absence of maternal chorioamnionitis; the duration of penicillin, ampicillin, or cefazolin IAP before delivery, if indicated; the duration of membrane rupture, and the infant's gestational age. An algorithm of the recommended infant management that applies to all newborns is summarized in Fig. 119.1. If signs of sepsis are noted, a full diagnostic evaluation and empiric antibiotic therapy are indicated. If a healthy-appearing infant is born to a mother with chorioamnionitis, a limited evaluation (blood culture at birth and CBC at birth and/or at age 6 to 12 hours) is recommended, based on the infant's exposure through established maternal infection. Healthy-appearing infants born to a mother who received appropriate doses of intravenous penicillin, ampicillin, or cefazolin 4 hours or longer before delivery are observed in the hospital for at least 48 hours before discharge, unless signs of sepsis develop that prompt a full evaluation and initiation of antibiotic therapy. Infants with a gestational age of 37 weeks or older, and those born to mothers in whom membrane rupture occurred less than 18 hours before deliver and the duration of IAP was less than 4 hours before delivery, should undergo observation for 48 hours. Healthy-appearing infants whose gestational age is less than 37 weeks, and those born to mothers in whom membrane rupture occurred 18 hours or longer before delivery and who received IAP for 4 hours or longer before delivery, require a limited evaluation and observation for 48 hours. Exposure to antibiotics during labor does not change the clinical spectrum of GBS disease or the age of onset of clinical signs of early onset infection, should it occur.[48]

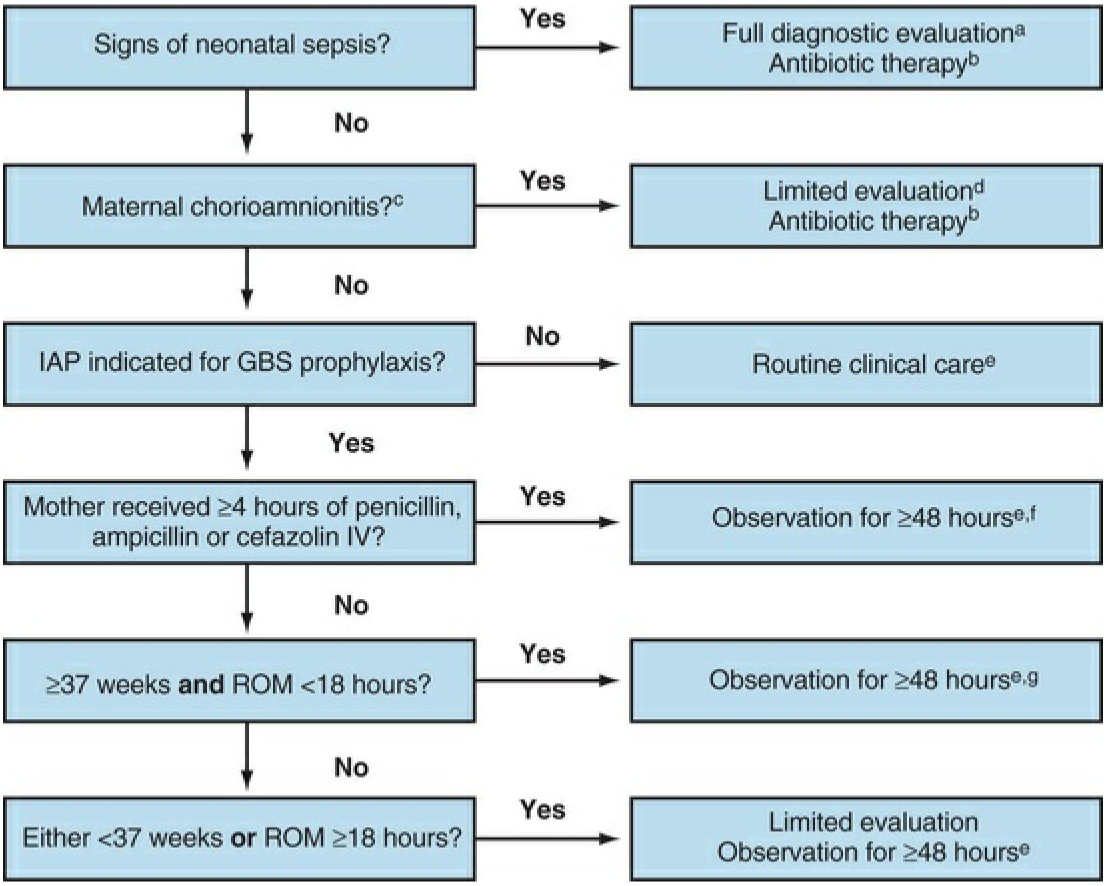
Signs of neonatal sepsis?
Yes
Full diagnostic evaluation[a]
Antibiotic therapy[b]
No
Maternal chorioamnionitis?[c]
Yes
Limited evaluation[d]
Antibiotic therapy[b]
No
IAP indicated for GBS prophylaxis?
No
Routine clinical care[e]
Yes
Mother received ≥4 hours of penicillin, ampicillin or cefazolin IV?
Yes
Observation for ≥48 hours[e,f]
No
≥37 weeks **and** ROM <18 hours?
Yes
Observation for ≥48 hours[e,g]
No
Either <37 weeks **or** ROM ≥18 hours?
Yes
Limited evaluation
Observation for ≥48 hours[e]

FIGURE 119.1 **Algorithm for prevention of early onset group B *Streptococcus* (GBS) disease among newborns. IAP, intrapartum antibiotic prophylaxis; ROM, rupture of membranes. [a]Full diagnostic evaluation includes a blood culture; a complete blood count (CBC), including white blood cell differential and platelet counts; chest radiograph (if respiratory abnormalities are present); and lumbar puncture (if patient is stable enough to tolerate procedure). [b]Antibiotic therapy should be directed toward the most common causes of neonatal sepsis; it should include intravenous ampicillin, with**

consideration of an aminoglycoside for synergy for GBS and coverage for other organisms (including *Escherichia coli* and other gram-negative pathogens) and should take into account local antibiotic resistance patterns. [c]Consultation with obstetrics providers is important to determine the level of clinical suspicion for chorioamnionitis. Chorioamnionitis is diagnosed clinically and some of the signs are nonspecific. [d]Limited evaluation includes a blood culture (at birth) and CBC with differential and platelet counts (at birth and/or at 6 to 12 hours of life). [e]If signs of sepsis develop, a full diagnostic evaluation should be conducted and antibiotic therapy initiated. [f]If ≥37 weeks' gestation, observation may occur at home after 24 hours if other discharge criteria have been met, access to medical care is readily available, and a person who is able to comply fully with instructions for home observation will be present. If any of these conditions is not met, the infant should be observed in the hospital for at least 48 hours and until discharge criteria are achieved. [g]Some experts recommend a CBC with differential and platelets at age 6 to 12 hours. (Adapted from Centers for Disease Control and Prevention. Prevention of perinatal group B streptococcal infection: revised guidelines from CDC 2010. MMWR Morb Mortal Wkly Rep 2010;59[RR-10]:1–31.)

With the substantial reduction in early onset GBS infection achieved through implementation of IAP policies, the current national projection is 990 cases of early onset and 1050 cases of late onset GBS disease annually in the U.S.[13] Black infants remain at higher risk than white infants for GBS disease, possibly because of differences in access to prenatal care and rates of preterm births.[17] A further reduction in early onset disease might be realized by improving implementation of antibiotic prophylaxis and correcting errors in culture screening methods.[49]

Although IAP is a desirable interim approach, it results in the administration of an antibiotic to approximately 30% of women at delivery, and the emergence of antimicrobial resistance remains a concern.[21] Prevention of GBS invasive infections, irrespective of age of onset or presence of maternal risk factors, awaits the development of suitable vaccines. Candidate CPS-protein conjugate vaccines are in development, and maternal immunization to prevent infant disease should be cost-effective.[50] Once a vaccine has demonstrated efficacy, women of childbearing age could be immunized to protect their neonates against GBS. This model has proved successful in the prevention of tetanus, and it holds promise for application to perinatal GBS infection.[51]

Key Points

Diagnosis and Management of Group B *Streptococcus* (GBS) Infection

Microbiology

- Narrow zone of β-hemolysis on blood agar, and gram-positive cocci microscopically
- Grow readily in blood culture media and from normally sterile sites
- Polysaccharide capsule and pilus-like structures enhance virulence.

Epidemiology

- Colonizes lower gastrointestinal and genital tracts of one quarter to one third of men and women
- Major cause of invasive infection in infants <3 months of age
- Early onset infection rates have declined in association with implementation of maternal intrapartum antibiotic prophylaxis, whereas the late onset infection incidence has remained unchanged.
- Three GBS types (Ia, III, and V) account for the most invasive infections.

Diagnosis

- Suspect in young infants with signs of sepsis, meningitis, pneumonia, bone or joint, or skin and soft tissue infection
- Isolation of organism from blood or another normally sterile site is diagnostic.

Treatment

- Penicillin is the drug of choice; isolates are susceptible to β-lactams, vancomycin, and meropenem.
- Usual treatment duration is 10 days for bloodstream infection and 2 to 3 weeks for meningitis.

Prevention

- Intrapartum antibiotic prophylaxis given during labor to GBS-colonized women reduces early onset infection risk.
- Glycoconjugate vaccines in development offer potential for prevention of infection in pregnant women and young infants.

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Enterococcus Species

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Historically enterococci, *Streptococcus bovis,* and *S. equinus* were grouped together as Lancefield group D streptococci. However, DNA hybridization studies have resulted in the reclassification of these organisms, and enterococci now are considered a separate genus (Table 120.1). This chapter focuses on enterococci; the nonenterococcal group D streptococci are discussed in Chapter 121.

TABLE 120.1

Clinical Significance of Enterococci and Group D Streptococci

Species	Association With Infection in Children
***ENTEROCOCCUS* SPECIES**	
Enterococcus faecalis	Relatively frequent
Enterococcus faecium	Infrequent but increasing
OTHER *ENTEROCOCCUS* SPECIES	Infrequent
E. durans, E. avium, *E. casseliflavus, E. dispar,* *E. flavescens, E. gallinarum,* *E. hirae, E. malodoratus,* *E. mundtii, E. pseudoavium,* *E. raffinosus, E. solitorius*	
NON-*ENTEROCOCCUS* SPECIES	Infrequent
Streptococcus bovis	
Streptococcus equinus	

Enterococci were recognized as part of the normal intestinal flora more than a century ago.[1] However, medical science's improved ability to support critically ill patients, including extremely premature infants, and the widespread use of antimicrobial agents have led to the emergence of enterococci as pathogens in human infection.[2]

Description of the Pathogen

Enterococci are gram-positive, facultatively anaerobic bacteria that grow as diplococci or in short chains. Most isolates are nonhemolytic on sheep blood agar, although some have α-hemolytic or β-hemolytic activity. Unlike other gram-positive, catalase-negative bacteria, the group D organisms grow at 45°C and can withstand temperatures up to 60°C. They can grow in bile; in addition, they hydrolyze esculin, a feature not found in other streptococci of the Lancefield groups (5% of viridans streptococci and most lactococci, aerococci, pediococci, and leuconostocs share this property).

Clinical laboratories often distinguish enterococci from nonenterococcal group D organisms on the basis of the enterococci's ability to grow in 6.5% sodium chloride. The PYR reaction (hydrolysis of L-pyrrolidonyl-P-naphthylamide) is also a rapid means of distinguishing enterococci from *S. bovis* and *S. equinus. S. pyogenes,* the only other PYR-positive streptococcus, is easily distinguished from enterococci by its positive reaction with group A antiserum and susceptibility to bacitracin. *Enterococcus faecalis* and *E. faecium* are common human pathogens that are distinguished from each other on the basis of carbohydrate fermentation (Table 120.2).

TABLE 120.2

Biochemical and Growth Characteristics of Clinically Significant Enterococci and Group D Streptococci

	Enterococcus faecalis	*Enterococcus faecium*	*Streptococcus bovis*
Bile esculin	+	+	+
PYR reaction	+	+	−
Growth in 6.5% NaCl	+	+	−
Sorbitol	+	−	+/−
Mannitol	+	+	+/−
Lactose	+	+	+
Starch	−	−	+

+, Most isolates demonstrate the characteristic; +/−, occasional isolates test positive for the characteristic; −, most isolates test negative for the characteristic. NaCl, Sodium chloride; PYR reaction, hydrolysis of L-pyrrolidonyl-P-naphthylamide.

Enterococci have several important virulence factors, including adhesive factors called Esp, aggregation substance, and ACE (a collagen-binding protein). Other virulence determinants include a cytolysin and degradative enzymes, such as gelatinase, hyaluronidase, and a serine protease. Many of these virulence factors are encoded on a pathogenicity island that is more commonly found among virulent than commensal isolates. The propensity of *E. faecalis* to cause endocarditis in adults may be related to surface carbohydrates that permit avid adherence to the endothelium of heart valves.[3] Once established on heart tissue, *E. faecalis* stimulates synthesis of fibrinogen, contributing to vegetation formation. Similarly, infection of the urinary tract may relate to the organism's ability to adhere to renal epithelial cells. The *E. faecalis* cytolysin, which is encoded by the pathogenicity island, has lethal activity against a broad range of eukaryotic and prokaryotic cells. This factor contributes to virulence in experimental models of endocarditis, peritonitis, and endophthalmitis.

Antimicrobial resistance allows the persistence and proliferation of organisms despite treatment with broad-spectrum antibiotics. The enterococci have a remarkable propensity to exchange genetic material, both as donor and recipient. Whole genome sequencing revealed that up to 25% of *Enterococcus* genetic material is composed of mobile or exogenously acquired DNA. The ability to transfer DNA, including vancomycin resistance genes, to other species is a major concern.

Epidemiology

Enterococci are ubiquitous inhabitants of the gastrointestinal tract of humans and animals. *E. faecalis* is the predominant organism and is found in the feces of more than 90% of adults. Nearly 50% of neonates are colonized with *E. faecalis* by 1 week of age. Colonization with *E. faecium* is less common but appears to be increasing in frequency; it is present in approximately 25% of adults. Although the gastrointestinal tract is the predominant habitat of enterococci, organisms also can be found in oral secretions and dental plaque, in the upper respiratory tract, on the skin, and in the vagina.

E. faecalis accounts for most enterococcal infections, which generally are presumed to arise from the patient's indigenous flora. Direct spread from person to person (i.e., by droplet or fecal-oral transmission) has not been considered an important means of transmission, although evidence of nosocomial transmission is growing.[4,5]

Clinical Manifestations

Most enterococcal infections occur in individuals in whom a surface physical barrier breaks down, such as in the gastrointestinal tract, the integument, or the urinary tract. Other factors associated with enterococcal infections in children are prolonged hospitalization, treatment with antibiotics, and a compromised immune system. In neonates, *Enterococcus* organisms commonly are associated with septicemia, whereas in older children and adults they are most commonly associated with bacteremia, intra-abdominal abscess, and urinary tract infection (UTI). Among hospitalized adults, enterococci account for approximately 10% of bloodstream infections (BSIs), and they are associated with mortality in one third of affected patients.[6]

Neonatal Infections

Enterococci account for up to 10% of all cases of neonatal BSI. The rate of enterococcal BSI fluctuates from year to year, but the incidence appears generally to be increasing, concomitant with the longer survival of extremely premature infants. These infections most commonly are caused by *E. faecalis* and much less commonly by *E. faecium*.

Two distinct syndromes of neonatal enterococcal BSI have been described. Early onset BSI (within 7 days of birth) manifests similarly to early onset group B streptococcal septicemia, although the former tends to be milder. Early onset infection most often occurs in full-term infants who are otherwise healthy. Late onset infection (after 7 days of age) is associated with risk factors such as extreme prematurity, presence of an intravascular catheter, necrotizing enterocolitis, or a recent surgical procedure. The symptoms of late onset disease are more severe than those of early onset disease; they include apnea, bradycardia, and deteriorating respiratory function. Focal infections, such as a scalp abscess or a catheter-related infection, also are common. Mortality rates range from 6% in early onset septicemia to 15% in late onset infections associated with necrotizing enterocolitis.[7] Enterococci cause approximately 5% of bacteremic episodes in previously healthy young infants who come to medical attention with a fever.[8]

Enterococcus is an occasional cause of meningitis. In neonates, in particular, meningitis usually occurs as a complication of BSI. Alternatively the organism can gain access to the central nervous system by means of contiguous spread, such as through a neural tube defect, a neurenteric cyst, an intrathecal injection, or a ventricular shunt placed for the management of hydrocephalus.[9] A noteworthy fact is that enterococcal meningitis can be associated with minimal abnormality of the cerebrospinal fluid.

Infections in Older Children

Enterococcal BSI generally is an infection of hospitalized children, and it is not limited to a particular age group.[10] Predisposing factors include an indwelling central venous catheter, gastrointestinal disease, immunodeficiency, cardiovascular abnormalities, and hematologic malignancy. Genitourinary disease is a frequent predisposing factor in adults, although less common in children. Children with community-acquired enterococcal infections generally are younger than 1 year of age. As in adults, BSI caused by *Enterococcus* spp. commonly is polymicrobial, probably reflecting the severity of underlying disease and the bowel as the source.

Enterococci rarely cause UTIs in healthy children, but they account for approximately 15% of nosocomially acquired UTIs in both children and adults. Placement of an indwelling urinary catheter is the major risk factor for a nosocomial UTI, and early removal of urinary catheters reduces the incidence of infection.[11] Enterococci also cause intra-abdominal abscesses after intestinal perforation; however, the significance of enterococci in these polymicrobial infections has been questioned because an antimicrobial regimen with poor activity against enterococci often is an effective treatment. Enterococci frequently are part of polymicrobial chronic infections in patients with neurologic deficits, pressure ischemic osteomyelitis, soft tissue necrosis. Enterococci cause up to 15% of cases of endocarditis in adults, but these organisms rarely infect the heart in children.

Treatment

Antimicrobial Resistance

Enterococci uniformly are resistant to cephalosporins, and they have at least a low resistance to other β-lactam agents. Unfortunately, high resistance to aminoglycosides and vancomycin is becoming increasingly prevalent. The antimicrobial resistance of *Enterococcus* spp. can be divided broadly into intrinsic and acquired forms.[12] In general, intrinsic resistance results from chromosomally encoded factors, whereas acquired resistance is carried on transposable elements (Box 120.1). In most cases of acquired resistance, plasmid-encoded factors are exchanged in a process mediated by sex pheromones. Receptive organisms respond to pheromones by aggregating, which facilitates subsequent conjugation and plasmid transfer. Occasionally, acquired resistance results from mutation of a chromosomal gene. Resistance of *E. faecium* generally is more common and significant than that of *E. faecalis* (Table 120.3).

Box 120.1

Antimicrobial Resistance of Enterococci

Intrinsic Resistance (Chromosomally Encoded)

Aminoglycosides (low-level resistance)

β-Lactams (especially semisynthetic penicillins and cephalosporins)

Clindamycin (low-level resistance)

Acquired Resistance

Aminoglycosides (high-level resistance)

Chloramphenicol

Erythromycin

Clindamycin (high-level resistance)

Fluoroquinolones

Penicillins (β-lactamase)

Tetracycline

Vancomycin

TABLE 120.3

Antimicrobial Susceptibility of *Enterococcus* Species

	Enterococcus faecalis (µg/mL)			*Enterococcus faecium* (µg/mL)		
Agent	**Range**	**MIC$_{50}$**	**MIC$_{90}$**	**Range**	**MIC$_{50}$**	**MIC$_{90}$**
Penicillin	2 to >8	2	8	2 to >8	>8	>8
Ampicillin	0.25 to 8	2	2	0.25 to >128	128	128
Piperacillin	8 to 128	8	16	8 to 128	128	128
Imipenem	1 to >8	4	8	1 to >8	>8	>8
Chloramphenicol	8 to >16	8	16	8 to >16	8	>16
Levofloxacin	1 to >4	2	>4	1 to >4	>4	>4
Vancomycin	2 to >64	2	8	2 to >64	>64	>64
Linezolid	1 to 4	2	4	0.5 to 4	2	4

MIC$_{50}$ and MIC$_{90}$, Minimal inhibitory concentration required to inhibit 50% and 90% of isolates, respectively.

Data from Noskin GA, Siddiqui F, Stosor V, et al. In vitro activities of linezolid against important gram-positive bacterial pathogens including vancomycin-resistant enterococci. Antimicrob Agents Chemother 1999;43:2059.

β-Lactam Resistance.

Enterococci are highly resistant to cephalosporins and semisynthetic penicillins (e.g., nafcillin, oxacillin, and methicillin) and moderately resistant to extended spectrum penicillins (e.g., ticarcillin and carbenicillin). Ampicillin, imipenem, and penicillin are the most active β-lactam agents against enterococci; their minimal inhibitory concentrations (MICs) range from 1 to 8 µg/mL (see Table 120.3). Although the bactericidal activity of active β-lactams always is superior to that of vancomycin, the minimum bactericidal concentration (MBC) often is considerably higher, and tolerance to β-lactam agents (defined as an MBC to MIC ratio >32) is common. Any active drug can be insufficient if used alone for serious infections in which high bactericidal activity is desired. In rare cases, strains of *E. faecalis* produce a plasmid-encoded β-lactamase similar to that found in staphylococci. These isolates are completely resistant to penicillins; consequently, alternative agents or the combination of a penicillin plus a β-lactamase inhibitor is required.

Aminoglycoside Resistance.

All enterococci have an intrinsic low resistance to aminoglycosides (MIC of 8 to 250 μg/mL), which probably reflects poor transport of these antibiotics across the cell wall. Concomitant use of a cell wall–active agent, such as a β-lactam or a glycopeptide antibiotic to which the isolate is susceptible, improves the cell wall's permeability to aminoglycosides, resulting in synergistic killing.[13] High resistance, defined as an MIC greater than 2000 μg/mL, results from the modification of aminoglycosides through adenylation, phosphorylation, or acetylation. Strains that demonstrate high resistance (which usually are acquired nosocomially) are not affected by combination therapy comprising aminoglycosides plus cell wall–active antibiotics. It is noteworthy that some moderately resistant isolates also are not affected synergistically by this therapeutic combination.

Vancomycin Resistance.

Resistance to vancomycin among enterococci emerged during the past 2 decades and spread rapidly. The proportion of enterococcal infections caused by vancomycin-resistant organisms has reached approximately 30%.[14] Both high and moderate resistance have been described for *E. faecalis* and *E. faecium*. High resistance (MIC ≥64 μg/mL) can be transferred by means of conjugation and is usually plasmid mediated. The gene that confers high resistance vancomycin, *vanA*, encodes an inducible protein that creates a D-alanine:D-lactate ester, rather than the normal D-alanine:D-alanine linkage, in the cell wall. Vancomycin binds less avidly to the altered linkage and thus is unable to disrupt cell wall synthesis. Moderate resistance (MIC 8 to 32 μg/mL) results from D-alanine:D-lactate activity expressed from a transposable homologue of *vanA* known as *vanB*. Isolates that harbor the *vanB* gene are only moderately resistant to vancomycin because they have residual D-alanine:D-alanine linkages. Although most *vanB* isolates initially are susceptible to teicoplanin, resistance can emerge during therapy. Other vancomycin phenotypes exist, encoded by *vanC, vanD, vanE,* and *vanG* genetic elements, but these are less prevalent and generally do not result in high resistance.

Other Antibiotics.

Resistance of enterococci to almost all classes of antibiotics, including tetracyclines, macrolides, and chloramphenicol, has been described, and individual susceptibility testing must be performed when use of these antibiotics is considered. Despite the apparent susceptibility of enterococci to trimethoprim-sulfamethoxazole (TMX) in vitro, the drug has poor activity against the organisms in vivo because they efficiently scavenge thymidine and its precursors from blood and urine.

Options for treating vancomycin-resistant enterococci (VRE) infections are limited. Linezolid and daptomycin currently are the most reliable agents. Linezolid, an oxazolidinone, inhibits bacterial protein synthesis and is bacteriostatic against *E. faecium* and *E. faecalis.* Its MIC_{90} (i.e., minimal inhibitory concentration required to inhibit 90% of isolates) is 4 μg/mL or less against both species, including vancomycin-resistant isolates. Treatment with linezolid appears to result in the most favorable outcomes for enterococcal BSI in children.[15] However, resistance to linezolid among VRE isolates has been described and can develop during prolonged therapy. Studies in adults suggest that daptomycin treatment may be associated with improved outcomes.[16]

Daptomycin, the first lipopeptide antibiotic, has been approved for use in complicated skin infections. It disrupts the bacterial membrane through the formation of transmembrane channels, and it has bacteriostatic activity against both *E. faecalis* and *E. faecium.* Resistance to daptomycin has been reported among enterococci but remains rare.

Tigecycline and oritavancin have in vitro activity against VRE. Tigecycline, a tetracycline derivative, has been approved for use in complicated intra-abdominal and skin and soft tissue infections. Although it is bacteriostatic, tigecycline has not yet been approved for use against VRE; however, it has good activity in vitro against both vancomycin-resistant *E. faecalis* and *E. faecium* and likely will become a valuable therapeutic agent.[17]

Quinupristin-dalfopristin (Synercid) is a combination streptogramin antibiotic that inhibits bacterial protein synthesis at two different stages. The drug is active against many *E. faecium* strains, including those with high vancomycin resistance, but notably, it is inactive against *E. faecalis*. Quinupristin-dalfopristin, therefore, should not be used as the sole agent when gram-positive organisms are identified by Gram stain until culture results exclude the presence of *E. faecalis.*

Treatment Strategies

In an otherwise healthy patient, minor localized infections caused by enterococci generally can be treated with ampicillin alone. Antibiotics containing β-lactamase inhibitors (clavulanate or sulbactam) provide an advantage only with rare organisms that have high resistance because they produce β-lactamase. Most species are susceptible to nitrofurantoin and fosfomycin, and these agents are alternatives to penicillins for uncomplicated UTIs.

Severe systemic infections (e.g., BSI, endocarditis, and meningitis) usually are treated with combination therapy. Ampicillin plus an aminoglycoside has been the most common regimen for organisms susceptible to both. However, addition of an aminoglycoside can be associated with nephrotoxicity; this justifies caution in its use for an uncomplicated BSI caused by *E. faecalis*.[18] The combination of ampicillin and ceftriaxone often is used in cases of *E. faecalis* endocarditis, and it has shown equivalent efficacy to ampicillin plus an aminoglycoside in adults.[19] Vancomycin can be substituted for ampicillin for patients with immediate-type hypersensitivity to penicillin, but it should be used with another agent (typically an aminoglycoside) because its action alone is only bacteriostatic.

Infections caused by enterococcal strains with high resistance to aminoglycosides are problematic because bactericidal activity usually cannot be achieved. As a result, endocarditis caused by these strains can relapse even after prolonged therapy. High-dose or continuous-infusion penicillin has been proposed for treatment of these infections in adults.

Linezolid or daptomycin can be used for VRE infection.

Tigecycline has reliable activity against vancomycin-susceptible and vancomycin-resistant enterococci, but it has not been studied in detail for treatment.[20] Generally, in patients with a catheter-associated enterococcal BSI, the catheter should be removed promptly. In one study of neonates, BSI persisted in all patients until the catheter was removed. In patients with endocarditis caused by aminoglycoside-resistant strains, valve replacement may be necessary.

Prevention

Strategies for preventing enterococcal infection include early removal of urinary and intravenous catheters and debridement of necrotic tissue. Contact isolation is suggested for hospitalized patients known to be colonized or infected with organisms highly resistant to aminoglycosides and vancomycin. A number of trials have addressed the use of unabsorbable antibiotics in attempts to eradicate intestinal colonization with VRE; however, decolonization has not gained wide acceptance. The Hospital Infection Control Practices Advisory Committee of the Centers for Disease Control and Prevention, and the Society for Healthcare Epidemiology of America, have published recommendations for education, an infection control policy, and curtailment of the use of vancomycin to prevent the spread of VRE.[21]

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Viridans Streptococci, *Abiotrophia* and *Granulicatella* Species, and *Streptococcus bovis* Group

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The viridans streptococci are genetically diverse organisms that share the propensity to colonize humans and occasionally to penetrate local barriers to cause life-threatening disease. Their importance as the predominant cause of endocarditis in children and adults has been known for years. Improvements in identification and classification led to the recognition that these organisms are a significant cause of other infections, including septicemia and meningitis. In this chapter *Abiotrophia* and

Granulicatella (formerly nutritionally variant streptococci [NVS]) and *Streptococcus bovis* group organisms are considered together with viridans streptococci. *S. bovis* is not uniformly classified within the viridans streptococci but shows significant clinical similarities to this group of organisms.

Description of the Pathogen

As is the case with all streptococci, viridans streptococci are gram positive and do not produce catalase. Most are facultatively anaerobes; however, some (including the *S. anginosus* group) are capnophilic, and others are microaerophilic. Viridans streptococci derive their name from the Latin word *viridis,* meaning green, because most isolates cause α-hemolysis on sheep blood agar, producing a ring of greenish discoloration surrounding the colonies. This pattern of hemolysis is predominantly the result of red blood cell damage mediated by hydrogen peroxide, which is released from the organism when it is grown in the presence of oxygen. Notably, many viridans organisms are nonhemolytic when grown in oxygen, and most are nonhemolytic when grown under anaerobic conditions. Although nucleotide sequence homology places *S. pneumoniae* among the viridans streptococci, this species generally is considered separately because of its unique virulence potential. *S. pneumoniae* is differentiated from other viridans streptococci by its optochin susceptibility and bile solubility. Most viridans streptococci fail to react with the Lancefield antisera, but a number of exceptions exist. For example, the *S. anginosus* group contains minute. colony-forming, β-hemolytic organisms that may react with the antisera of Lancefield groups A, C, F, and G.

Speciation

Speciation of the viridans streptococci has been the subject of considerable confusion. Nucleotide sequencing of the 16S ribosomal RNA (rRNA) genes and whole genome sequencing has helped considerably in the classification of these organisms. The viridans streptococci are now classified into five groups, distinguished from *S. bovis* and the pyogenic streptococci (see Fig. 117.1). In the clinical laboratory, viridans streptococcal species are differentiated on the basis of biochemical reactions and patterns of hemolysis (Table 121.1). (The term viridans streptococci is preferred to *Streptococcus viridans* because it avoids the misconception that these organisms belong to a single species or taxon.)

TABLE 121.1

Biochemical Characteristics That Differentiate Viridans Streptococci and *Streptococcus bovis* Group

Organism	Hemolysis	Voges-Proskauer Test	Hydrolysis Of			Acid Production From			
			Esculin	Arginine	H_2O_2	Mannitol	Sorbitol	Lactose	Tre
S. mutans	α, β, γ	+	+	–	–	+	+	+	+
S. mitis	α	–	–	–	+	–	–	+	v
S. oralis	α	–	–	–	+	–	–	+	v
S. sanguis	α	–	v	+	+	–	v	+	+
S. gordonii	α	–	+	+	+	–	–	+	+
S. cristatus	α	–	–	v	+	–	–	v	+
S. salivarius	α	+	+	–	–	–	–	v	v
S. vestibularis	α	v	v	–	+	–	–	v	v
S. parasanguis	α	–	v	+	+	–	–	+	v
S. anginosus	α, β, γ	+	+	+	v	v/–	–	+	+
S. intermedius	α, γ	+	+	+	v	v/–	–	+	+
S. bovis group	γ	NA	+	–	NA	+	–	+	+
Gemella morbillorum	α, γ	NA	–	–	NA	–	–	–	–

+, 85% of strains or more test positive; –, 85% of strains or more test negative; NA, not available; v, variable; v/–, variable, usually negative.

Adapted from Sinner SW, Tunkel AR. Viridans streptococci and groups C and G streptococci. In: Mandell GL, Bennett JE, Dolin R (eds). Principles and Practice of Infectious Diseases, 7th ed. New York, Churchill Livingstone, 2009, pp. 2349–2361.

Nonviridans streptococci originally were believed to be mutant forms of *S. mitis*. Biochemical testing and genetic sequence analysis dispelled this notion, and these organisms are now classified as either *Abiotrophia* or *Granulicatella* species. They are fastidious organisms that require pyridoxine (vitamin B_6) or thiol supplementation for growth. Because these requirements can be fulfilled by the metabolic byproducts of other bacteria, nonviridans streptococci grow in culture as satellite colonies around other bacterial species, including *Staphylococcus aureus*.

The automated biochemical identification systems commonly used in clinical microbiology laboratories can lead to incorrect species assignment of viridans streptococcal isolates. Advanced techniques, such as 16S rRNA sequencing or matrix-assisted laser desorption ionization time of flight (MALDI-TOF), generally are more accurate but still have difficulty distinguishing *S. pneumoniae* from *S. mitis* and *S. oralis*.[1]

Nonenterococcal group D organisms comprise the *S. bovis* group, and they are an uncommon cause of disease in children. This group previously was classified into two biotypes, I and II, which were subdivided into subtypes II/1 and II/2. The current classification defines distinct species and subspecies: *S. gallolyticus* (also known as *S. gallolyticus* subsp. *gallolyticus* [formerly *S. bovis* biotype I]); *S. pasteurianus* (also known as *S. gallolyticus* subsp. *pasteurianus* [formerly S. bovis biotype II/2]); *S. lutetiensis* (also known as *S. infantarius* subsp. *coli*); and *S. infantarius* (also known as *S. infantarius* subsp. *infantarius*]). The species *S. lutetiensis* and *S. infantarius* formerly were classified as *S. bovis* biotype II/1.

Among the *S. bovis* group, *S. gallolyticus* accounts for the majority of invasive infections in children and *S. pasteurianus* accounts for most of the remainder. Clinical microbiology laboratories might not be capable of identifying these organisms to the species or subspecies level, an undertaking that can require sequencing of the 16S rRNA gene. In addition, in some parts of the literature these organisms still are referred to simply as *S. bovis*, leading to inconsistency and further confusion.

Virulence Properties

Viridans streptococci lack the classic virulence factors that other streptococci have, such as streptolysin O, streptolysin S, deoxyribonuclease B (DNAase B), adhesion-promoting M and F proteins, and pyrogenic exotoxins. The absence of such factors likely accounts for the low pathogenic potential of these organisms in healthy people. However, some viridans species have a notable predilection for causing endocarditis, a characteristic that appears to correlate with the production of extracellular dextran. *S. mutans, S. sanguis, S. mitis,* and to some extent *S. bovis* most often are implicated in endocarditis, and all produce dextran. Dextran exopolysaccharide might play a dual role in the pathogenesis of endocarditis: mediating bacterial adherence to heart valves, and also rendering organisms relatively resistant to penicillin. *S. mutans* plays an important role in dental caries, one that relates at least in part to adherence to dental enamel, which is mediated by glucan exopolysaccharides. *S. anginosus* has an enhanced propensity to cause localized infections, such as dental and intra-abdominal abscesses. In contrast to other viridans streptococci, *S. anginosus* produces hydrolytic enzymes (e.g., hyaluronidase, DNAase, and chondroitin sulfatase) and can produce neuramidase. The role of these enzymes in pathogenesis remains unclear. Many viridans organisms produce an immunoglobulin (Ig) A protease that presumably attenuates the local immune response and enables the organisms to persist in the mouth.

Epidemiology

Viridans streptococci are ubiquitous inhabitants of the mouth in both children and adults. Oral colonization occurs immediately after birth, and viridans streptococci account for more than 30% of oral bacterial isolates by 8 hours of age. Oral viridans streptococci may confer protection in young infants by preventing the overgrowth of more virulent organisms. Other sites of colonization are the upper respiratory, gastrointestinal, and female reproductive tracts.[2]

The niches that oral streptococci occupy are very well defined. For example, *S. mitis* is predominantly localized to the buccal mucosa, whereas *S. mutans* and *S. sanguis* are associated with the teeth, and *S. salivarius* is localized on the tongue. *S. bovis* is an inhabitant of the lower gastrointestinal tract.

Clinical Manifestations

Endocarditis

Viridans streptococci are the most common cause of bacterial endocarditis in children and adults.[3] In contrast, *S. bovis* rarely is isolated from children with endocarditis. Viridans streptococcal endocarditis is insidious in onset, and diagnosis usually is delayed for several weeks. Fever is almost universally present. Malaise, anorexia, and weight loss can be prominent. Other classic signs of bacterial endocarditis, including splenomegaly, altered cardiac examination findings, petechiae, Osler nodes, Roth spots, Janeway lesions, and splinter hemorrhages, are found with varying frequency.

Major factors in the pathogenesis of bacterial endocarditis are turbulent flow within the heart and bacteremia. Most children with viridans streptococcal endocarditis have either a ventricular septal defect or an abnormal heart valve (because of a congenital defect or rheumatic heart disease). Transient bacteremia is common, particularly after dental trauma, which is an important risk factor for endocarditis. Up to 85% of children undergoing dental extraction have bacteremia, and viridans streptococci are the most commonly isolated organisms.[4]

Abiotrophia and *Granulicatella* species (formerly nonviridans streptococci) account for approximately 5% of cases of endocarditis in adults. Although the frequency of endocarditis caused by these organisms appears to be lower in children, several pediatric cases have been described.[5] Historically these fastidious organisms accounted for occasional cases of “culture-negative endocarditis”; however, most of the blood culture media currently available include L-cysteine or vitamin B_6 and therefore support the growth of these fastidious organisms.

Bacteremia and Septicemia

The significance of recovery of viridans streptococci from blood cultures often is difficult to determine. Isolation is more significant if growth is pure and is found in more than one blood culture bottle or set.

Viridans streptococci are a common cause of septicemia in children with cancer[6]; a particularly strong association has been noted between high-dose cytarabine treatment and viridans streptococcal bloodstream infection (BSI). Mucositis and prolonged granulocytopenia are associated risk factors. Viridans streptococci typically are resistant to trimethoprim-sulfamethoxazole (TMP-SMX), and invasion of these organisms may be enhanced by TMP-SMX prophylaxis.[7]

Patients with viridans streptococcal BSI are prone to pulmonary complications, including respiratory distress syndrome, and meningitis. Patients with respiratory distress syndrome can develop septic shock and deteriorate rapidly despite appropriate antimicrobial therapy. These fulminant cases generally are caused by *S. mitis,* tend to occur after bone marrow transplantation, and are more common in children than adults.[8] Notably, a high proportion of causative organisms are resistant to penicillin and cephalosporins; vancomycin usually is added to empiric treatment of neutropenic patients in whom viridans streptococcal infection is suspected.[9]

Approximately 3% to 5% of neonatal BSIs are caused by viridans streptococci.[10] The risk factors, which are similar to those for BSI caused by other organisms, include prematurity, low birth weight, and prolonged rupture of amniotic membranes. The clinical presentation of viridans streptococcal infection resembles that of early onset infection caused by group B streptococci, and the predominant feature is respiratory distress. However, with viridans-type infections, the onset tends to occur later (mean age 3.5 days, compared with <12 hours for group B–type infections), and the incidence is lower for leukopenia, an abnormal immature to total neutrophil ratio, and thrombocytopenia. Associated localized infections are uncommon, although a case report has described an infant with septicemia and meningitis associated with a scalp abscess caused by viridans streptococci.[11]

Among children without an underlying condition, isolation of viridans streptococci from blood cultures generally does not correlate with any disease state. In most cases the patient remains asymptomatic even without specific therapy.[12,13]

Organisms of the *S. bovis* group occasionally are reported as a cause of neonatal BSI, often in association with a primary intestinal disorder.[14] The true incidence of septicemia caused by *S. bovis* group organisms is difficult to determine because some studies might classify the organisms among the enterococci (as a group D *Streptococcus*), and others might assign them to the viridans streptococci. No clinical features distinguish neonatal BSI caused by organisms of the *S. bovis* group from that caused by more typical neonatal pathogens. In rare cases, BSI caused by organisms of the *S. bovis* group is complicated by meningitis, especially when *S. pasteurianus* is the causative organism.[15]

Other Infections

Viridans streptococci can cause pyogenic infections, including brain abscess and localized intra-abdominal infections, such as hepatic and subphrenic abscesses. Organisms of the *S. anginosus* group account for most such infections, reflecting their proclivity for causing localized pyogenic infections, frequently in association with other organisms (Fig. 121.1).

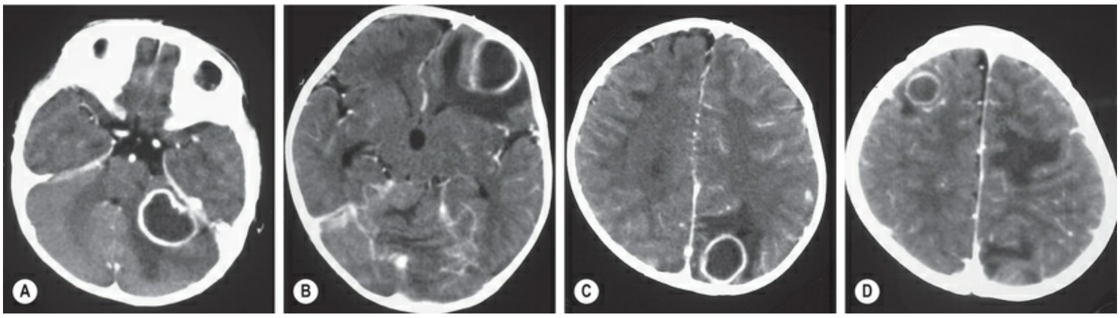

FIGURE 121.1 Multiple brain abscesses caused by *Streptococcus intermedius* and *Eikenella corrodens* in an 11-month-old girl with tricuspid atresia and pulmonary-to-systemic shunting of blood after a hemi-Fontan procedure. She had a 5-day history of fever, irritability, and shaking chills and then a right-sided seizure. She did not have a respiratory illness, exposure to pets, pneumonia, or endocarditis. Axial contrast-enhanced CT shows ring-enhancing brain abscesses with surrounding edema in the left cerebellar hemisphere (A), the frontal (B) and parietal (C) lobes, and the right parietal lobe (D), indicating multifocal vascular territories. Note the additional areas of cerebral edema in contralateral hemispheres (D) related to other abscesses. (Courtesy of E.N. Faerber and S.S. Long, St. Christopher's Hospital for Children, Philadelphia, PA.)

Viridans streptococci are a rare cause of meningitis, accounting for approximately 0.3% to 3% of cases in adults. Few data exist for children, although one study implicated viridans streptococci in approximately 1% of pediatric cases.[16] Most children are younger than 1 year of age and have concomitant BSI. Predisposing factors in older children include endocarditis and trauma or surgery involving the central nervous system.

Dental infections, including dental caries, abscesses, and periodontal disease, often are caused by viridans streptococci, most commonly *S. mutans* and *S. anginosus*. These infections usually are polymicrobial, but viridans streptococci sometimes are isolated as sole pathogens.

Pneumonia, empyema, sinusitis, and otitis media occasionally are ascribed to viridans streptococci. However, because these organisms colonize the mouth in such high numbers, ascribing to them a causative role in respiratory tract infection is difficult except when they are isolated from culture of percutaneously aspirated specimens. Pure growth of a viridans streptococcus has been obtained from bronchoscopy material and from aspirated pleural fluid.[17] In addition, growing evidence indicates a role for *S. anginosus* as a contributor to pulmonary disease in some patients with cystic fibrosis.

Treatment

Historically, more than 80% of viridans streptococci were susceptible to penicillin (minimum inhibitory concentration [MIC] ≤0.1 μg/mL). However, resistance is increasing, perhaps as a consequence of the widespread use of β-lactam antibiotics.[18] Strains with an MIC greater than 0.12 μg/mL and less than 0.5 μg/mL are classified by the American Heart Association (AHA) as relatively resistant; those with an MIC of 0.5 μg/mL or greater are considered resistant. Tolerance (a ratio of minimum bactericidal concentration to MIC greater than 32) is uncommon among viridans streptococci, and its clinical significance is unclear. High penicillin resistance (MIC >4 μg/mL) has been described but remains rare in North America. Viridans streptococci that are resistant to β-lactams appear to have altered penicillin-binding proteins (PBPs). The nucleotide sequence of the *PBP 2B* gene from highly resistant *S. pneumoniae* demonstrates a striking homology with the *PBP 2B* gene from resistant *S. oralis* isolates, which suggests transfer of the mutated gene between the two species.[19]

Viridans streptococci are resistant to aminoglycosides used as single agents. However, aminoglycosides are synergistically bactericidal when combined with β-lactam agents. Cephalosporins (especially ceftriaxone), vancomycin, teicoplanin, meropenem, and chloramphenicol generally have good activity against viridans streptococci. Susceptibility to tetracycline, clindamycin, and erythromycin is variable, and most isolates are resistant to TMP-SMX. Linezolid, tigecycline, and daptomycin are active against the viridans streptococci resistant to β-lactams, but clinical experience in the treatment of viridans-type infections with these drugs is limited.

Approximately one half of the *Abiotrophia* and *Granulicatella* species are at least relatively resistant to penicillin, and occasional isolates demonstrate high resistance.[20] Furthermore, strains that apparently are susceptible to penicillin often are tolerant to bactericidal activity. Relative resistance to aminoglycosides also is common, although high resistance (MIC >500 μg/mL) has not been described. Combination therapy with a cell wall–active agent (e.g., penicillin or vancomycin) and an aminoglycoside results in synergistic bactericidal activity.

The AHA's therapeutic recommendations for viridans streptococcal endocarditis involving native valves can be found in Tables 37.6 and 37.7. Endocarditis caused by isolates susceptible to penicillin (MIC ≤0.12 μg/mL) can be treated with penicillin alone for 4 weeks. As an alternative, the combination of penicillin plus an aminoglycoside can be used for 2 weeks, with or without 2 additional weeks of penicillin alone. Relatively resistant isolates (MIC >0.12 to <0.5 μg/mL) are treated with penicillin plus an aminoglycoside for 2 weeks, followed by 2 weeks of penicillin alone. Patients with penicillin-resistant isolates (MIC >0.5 μg/mL) are treated for 4 to 6 weeks with both penicillin and an aminoglycoside. Vancomycin can be substituted for penicillin in patients who have immediate-type hypersensitivity to penicillin. A 4-week course of vancomycin is recommended if the isolate has a penicillin MIC less than 0.5 μg/mL. If the isolate's MIC is 0.5 μg/mL or greater, the patient should be treated with 4 to 6 weeks of vancomycin plus an aminoglycoside. For the treatment of endocarditis involving prosthetic valves or caused by organisms other than viridans streptococci, the reader is referred to Chapter 37 and the AHA's recommendations.[21]

Some cases of endocarditis in children do not respond to antimicrobial treatment alone and require operative therapy. Relative indications for surgical intervention include persistent infection, embolic phenomena, and worsening of congestive heart failure.

Septicemia, meningitis, and other serious infections caused by viridans streptococci that are fully susceptible to penicillin can be treated with penicillin alone or in combination with an aminoglycoside. Vancomycin is the drug of choice in patients allergic to penicillin or when organisms highly resistant to penicillin have been isolated. Empiric therapy for viridans streptococcal sepsis in children with cancer should include vancomycin, linezolid, or daptomycin because resistance to these agents remains rare among organisms of the *S. mitis* group. If the isolate testing results are favorable, treatment with a β-lactam is superior.

Penicillin is the treatment of choice for infections caused by organisms of the *S. bovis* group because virtually all these isolates are susceptible (MIC <0.1 μg/mL). A single isolate of the *S. bovis* group that demonstrates the *vanB v*ancomycin resistance gene has been described.[22]

Prevention

Measures to prevent viridans streptococcal septicemia in children with cancer include assiduous mouth care and maintenance of oral hygiene, particularly when mucositis is present. Studies suggest that penicillin prophylaxis for neutropenic patients may reduce the incidence of viridans streptococcal septicemia; however, this practice can lead to a greater prevalence of penicillin-resistant organisms and is not currently widespread.

Prevention of endocarditis requires identification of children at risk and stratification of the risk by a cardiologist. The AHA recommends prophylaxis for patients with prosthetic cardiac valves, those who previously have had infectious endocarditis; recipients of a cardiac transplant with cardiac valvulopathy; and certain patients with congenital heart disease.[23] Candidates for prophylaxis are given an antimicrobial agent for tonsillectomy, adenoidectomy, and dental procedures involving manipulation of the gingival tissue or the periapical region of the teeth, or perforation of the oral mucosa.

Ampicillin remains the mainstay of prophylactic therapy. Different recommendations have been established for patients who are allergic to penicillin, unable to take oral medications, or receiving chronic antibiotic prophylaxis, and also for those undergoing procedures such as drainage of focal respiratory infection or manipulation of infected skin or musculoskeletal tissue. The reader is referred to the AHA recommendations[23] and Chapter 7.

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Groups C and G Streptococci

David B. Haslam, Joseph W. St. Geme III

The β-hemolytic streptococci can be subdivided on the basis of whether they form large colonies or minute colonies on solid agar. Most notable among those β-hemolytic streptococci that form large colonies are *Streptococcus pyogenes* (group A) and *Streptococcus agalactiae* (group B). Among the remaining Lancefield-reactive β-hemolytic streptococci, groups C and G organisms are most commonly associated with human disease.[1] In this chapter, groups C and G streptococci refer exclusively to the large-colony–forming "*S. pyogenes*-like" organisms. Minute-colony–forming species belonging to groups C and G are placed in the *S. anginosus* group (formerly *Streptococcus milleri)* (see Chapter 121). In some hospitals, group G streptococci cause more cases of invasive disease than does *S. pyogenes*,[1] perhaps because these organisms are more commonly associated with infection in immunocompromised hosts.

Characteristics of the Pathogens

Groups C and G organisms, like all streptococci, are catalase-negative, gram-positive cocci. Human isolates are almost always β hemolytic on sheep blood agar culture, although rare isolates are α hemolytic or nonhemolytic. Groups C and G organisms resemble *S. pyogenes* on blood agar, thus necessitating biochemical testing and serologic analysis for definitive identification. Latex agglutination typically is used in clinical microbiology laboratories to determine the Lancefield grouping of large-colony β-hemolytic streptococci. Most groups C and G isolates are resistant to bacitracin, but significant fractions are susceptible, thereby making bacitracin susceptibility testing alone unreliable in distinguishing these organisms from *S. pyogenes.* Hydrolysis of L-pyrrolidonyl-P-naphthylamide (PYR reaction) is a useful adjunctive test because the groups C and G organisms are PYR negative and *S. pyogenes* is PYR positive. Colony morphology and lack of acetoin production (negative results of the Voges-Proskauer [VP] test) differentiate large-colony groups C and G streptococci from the *S. anginosus* group (Table 122.1).

TABLE 122.1

Differentiation of β-Hemolytic Group C and G Isolates From *Streptococcus pyogenes* and *Streptococcus anginosus*

Organism	**Lancefield Group**	**Bacitracin**	**PYR Test Result**	**VP Test Result**
Streptococcus pyogenes–like groups C and G, large-colony–forming (*Streptococcus dysgalactiae* subspecies *equisimilis*)	C or G	Resistant[a]	−	−
S. pyogenes	A	Sensitive	+	−
Minute-colony–forming groups C and G (*Streptococcus anginosus* group)	C or G	NA	NA	+

[a] Occasional isolates are susceptible to bacitracin.

+, most isolates produce a positive reaction; −, most isolates produce a negative reaction; NA, data not available; PYR, L-pyrrolidonyl-β-naphthylamide; VP, Voges-Proskauer.

Speciation

Large-colony Group C and G human isolates now are grouped together as *Streptococcus dysgalactiae* subsp. *equisimilis*.[2] The remaining large-colony group C streptococci, predominantly animal pathogens, are grouped as *S. dysgalactiae* subsp. *dysgalactiae*. Nonhuman group G isolates are often considered part of a single species designated as *Streptococcus canis* and are genetically distinct from the *S. dysgalactiae* subsp. *equisimilis* group G organisms.

Virulence Properties

Groups C and G streptococci share several virulence factors with *S. pyogenes*. Both group C and group G isolates produce streptolysin O and can stimulate an increase in the anti–streptolysin O (ASO) titer. In addition, isolates of both groups produce degradative enzymes, including hyaluronidase.

Group G isolates also produce streptolysin S and often produce DNAase that is antigenically similar to *S. pyogenes* DNAase B. Moreover, group G streptococci produce an M protein that is similar immunologically to that of *S. pyogenes* and can be responsible for the occasional association of group G isolates with postinfectious glomerulonephritis. Glomerulonephritis following group C streptococcal infection also is well described. Whereas these isolates fail to produce an M protein, they can produce endostreptosin, which is believed to be involved in the pathogenesis of *S. pyogenes*–induced glomerulonephritis.

A toxic shock–like syndrome associated with group C and G streptococcal infection has been reported. Some of these cases have been associated with a strain that possesses genes homologous to the *S. pyogenes* streptococcal pyogenic exotoxins or that elaborates an unidentified substance with superantigen activity.[3]

Epidemiology

Pharyngeal carriage of groups C and G streptococci is detected in up to 5% of healthy children. In tropical climates, the pharyngeal carriage rate is much higher. The skin, gastrointestinal tract, and vagina also are frequent sites of colonization with groups C and G streptococci. *S. dysgalactiae* subsp. *equisimilis* can be isolated from the umbilicus of healthy neonates but rarely causes invasive disease.

Clinical Manifestations

Groups C and G streptococci are associated with the same spectrum of illnesses caused by *S. pyogenes*. In children, these organisms are implicated most commonly in respiratory tract infections, particularly pharyngitis. The true incidence of pharyngitis caused by groups C and G streptococci is difficult to determine because asymptomatic colonization occurs.[4] Nevertheless, compelling evidence implicates group C and G streptococci as true causes of pharyngitis. For example, several epidemics of group C and group G streptococcal pharyngitis have been reported. Even more convincing support comes from studies of foodborne outbreaks. The clinical presentation of pharyngitis resulting from groups C and G streptococci is indistinguishable from pharyngitis caused by *S. pyogenes*.[5]

Isolated case reports have described group C streptococcal pneumonia in children. Similar to group A streptococcal infection, tissue destruction is considerable. Abscess formation, empyema, and bacteremia are common. Despite effective antimicrobial therapy, these infections typically respond slowly, with persistent fever for >7 days.[6] Other respiratory tract infections reported include epiglottitis[7] and sinusitis.

Groups C and G streptococci also cause skin and soft tissue infections. These organisms can colonize the skin and gain access to subcutaneous tissues after a break in skin integrity. As with *S. pyogenes* infection, lymphangitis can complicate superficial infections caused by groups C and G organisms. Musculoskeletal infections, particularly pyogenic arthritis, occur occasionally, usually in adults with underlying disease.[8] At least 3 well-documented pediatric cases resulting from group C streptococci have been described.[9]

Groups C and G streptococci can cause neonatal septicemia and account for up to 2% of cases in some series. Risk factors include prematurity, prolonged rupture of membranes, and maternal infection. The clinical course may be indistinguishable from early-onset group B *Streptococcus* infection and includes respiratory distress, hypotension, apnea, bradycardia, and disseminated intravascular coagulation. Neonatal streptococcal toxic shock syndrome caused by *S. dysgalactiae* subsp. *equisimilis* has been described.[10]

Endocarditis, bacteremia, central nervous system infections (particularly brain abscess), and toxic shock caused by groups C and G streptococci are described but are uncommon in children. These infections generally occur in children with immune deficits or in adolescents after delayed recognition of sinusitis.

In addition to the postinfectious glomerulonephritis associated with infection with groups C and G streptococci, reactive arthritis has been described after group C streptococcal infection. No convincing evidence of acute rheumatic fever after infection with groups C and G streptococci has been found; therefore, antibiotic treatment is not indicated to prevent rheumatic fever.[11]

Therapy

Groups C and G streptococci are inhibited by low concentrations of penicillin (mean minimum inhibitory concentration <0.2 μg/mL), and penicillin is the drug of choice in most circumstances.[12] However, some isolates demonstrate tolerance to penicillin, with a ratio of minimal bactericidal concentration to minimum inhibitory concentration as high as 512 : 1. Although the clinical significance of tolerance is unclear, one study demonstrated that in adults with endocarditis resulting from tolerant group C streptococci infection, treatment with penicillin and an aminoglycoside resulted in improved outcome.

Other antibiotics with activity against groups C and G streptococci include other β-lactam agents, carbapenems, linezolid, quinupristin-dalfopristin, and vancomycin.[13] Occasional isolates demonstrate tolerance to vancomycin. Chloramphenicol, clindamycin, and erythromycin have poor bactericidal activity, particularly against group G streptococci. Up to 70% of group C streptococci produce a chromosomally encoded factor that mediates resistance to tetracycline.

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Streptococcus pneumoniae

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In the introduction to his classic 1938 monograph *The Biology of the Pneumococcus,* Benjamin White wrote that the "pneumococcus is altogether an amazing cell. Tiny in size, simple in structure, frail in make-up, it possesses physiological functions of great variety, performs biochemical feats of extraordinary intricacy and, attacking man, sets up a stormy disease so often fatal that it must be reckoned as one of the foremost causes of human death."[1] Currently the pneumococcus remains a major cause of respiratory and invasive diseases and contributes significantly to mortality rates in children younger than 5 years of age.[2,3]

Characteristics of the Pathogen

Microbiology

Streptococcus pneumoniae is a gram-positive, catalase-negative, facultatively anaerobic organism that grows as lancet-shaped diplococci and in short chains. Growth is enhanced in 5% carbon dioxide or anaerobic conditions. Autolysis can be responsible for failure of the organism to grow in subculture despite a positive Gram stain reaction. On blood agar, colonies are α hemolytic and can be identified presumptively from their susceptibility to optochin or the latex agglutination test. The specific pneumococcal type based on polysaccharide capsule can be identified using pooled typing sera and microscopic examination or by molecular techniques.

More than 90 immunologically distinct capsular polysaccharide serotypes within 45 serogroups have been identified.[4] In the widely accepted Danish system, serotypes are grouped according to antigenic similarities. For example, serogroup 9 includes types 9A, 9L, 9N, and 9V. Immunologic cross-reactivity among serotypes in the same serogroup can result in some cross-protection, but no cross-reactivity exists among different serogroups.[5]

Nucleic acid amplification tests such as real-time polymerase chain reaction (PCR) have been used for *S. pneumoniae* identification and have improved pneumococcal diagnosis. These assays rely on amplification of several gene sequences such as autolysin (*lytA*), pneumolysin (*ply*), and pneumococcal surface adhesion (*psa A*) to identify *S. pneumoniae*.[6–8] Although they are useful in the rapid identification of *S. pneumoniae* in cultured colonies,[6] these assays also have been used to detect and serotype *S. pneumoniae* in a variety of clinical specimens including blood, middle ear fluid,[6] tissue,[9] cerebrospinal fluid (CSF),[10] and pleural fluid.[11–13] PCR-based techniques interrogate the *S. pneumoniae* gene responsible for capsular polysaccharide synthesis located at the *cps* locus. Serotype is determined by amplification of the entire *cps* locus, followed by restricted fragment length polymorphism analysis[14] or by a sequence-based system using multiplex PCR.[15] The advantage of the PCR-based assay is that the test can be applied to cultivated colonies or to tissue or body fluids in the absence of viable isolates.[10,13]

Before 2000 and the licensure of the 7-valent conjugate pneumococcal vaccine (PCV7) in the United States, most pneumococcal disease was caused by relatively few serotypes. The most frequent types responsible for acute otitis media (AOM) in children were 23F, 19F, 6B, 6A, 14, 19A, 11, 15, 18C, 3, and 9V, although the rank varied by geographic location as exemplified by data from Finland,[5] Alabama,[16] and the Czech Republic and Slovakia.[17] Serotypes responsible for invasive pneumococcal disease (IPD) such as bacteremia, septicemia, or meningitis also were limited, with infection by types 14, 6B, 19F, 18C, 23F, 4, and 9V most common. [18] Shifts in AOM and IPD serotype distribution occurred following PCV7 implementation. Emerging AOM types included the non-PCV7 serotypes 3, 6A, 6C, and 19A.[19–22] By the late PCV7 era (2008–2010), *S. pneumoniae* was isolated from 26% to 36% of 227 children with AOM who underwent tympanocentesis in Rochester, New York. No PCV7 serotypes were found, whereas serotypes 19A and 15 were detected most frequently.[23] Similarly, serotypes responsible for IPD reflected increases in non-PCV7 types including 3, 15, 19A, 22F, and 33F, with serotype 19A the predominant cause of culture-confirmed IPD in US children.[24–27] By 2007, up to 61% of IPD cases in children <5 years of age were caused by non-PCV7 serotypes.[28,29] Strain replacement (in part facilitated by capsular switching[30–32]) in response to the selective pressure exerted by a successful pneumococcal vaccine program that targeted a limited number of serotypes was feared to limit the utility of PCVs. In response, a 13-valent vaccine (13-valent pneumococcal conjugate vaccine [PCV13]) was licensed to replace the use of PCV7 in children in 2010.[33] PCV13 contains the 7 serotypes in PCV7 (4, 6B, 9V, 14, 18C, 19F, and 23F) and 6 additional serotypes (1, 3, 5, 6A, 7F, and 19A). Similarly, with the widespread use of PCV13, IPD caused by PCV7 serotypes as well as the additional 6 serotypes in PCV13 has declined substantially.[34]

Pathogenesis and Virulence

The most important factors in the development of pneumococcal disease are the virulence of the serotype, the absence of type-specific humoral immunity, and the presence of viral respiratory tract disease. *S. pneumoniae* colonizes the nasopharynx of healthy children and can infect the middle ear, sinuses, and lungs by contiguous spread or can invade the bloodstream and establish foci in the meninges and other sites. Pneumococcal AOM is associated with recent nasopharyngeal acquisition of a serotype, rather than the result of prolonged colonization (carriage).[35,36] Recent acquisition also is associated with IPD. Not all pneumococcal types are equally invasive. The composition and quantity of capsular polysaccharide have major roles in virulence and invasive potential. Thus, although certain serotypes are infrequently isolated from the nasopharynx, they can contribute disproportionately to IPD. In large studies from Finland, the United Kingdom, Chile, Israel, Taiwan, and the Czech Republic, serotypes 1, 4, 5, 6B, 9V, 14, 18C, 19A, and 19F were overrepresented in IPD compared with nasopharyngeal colonization in children <5 years of age.[37–42] Similarly, serotypes 1, 3, 5, 18C, 19A, and 19F were overrepresented among AOM isolates compared with nasopharyngeal isolates in children <5 years of age.[43]

Once the pneumococcus enters the bloodstream, encapsulation provides protection from host defense mechanisms by inhibiting neutrophil phagocytosis and classic complement-mediated bactericidal activity. Several protein virulence factors, such as *ply* and *psa A*, have been identified from studies in experimental animals.[44]

In the healthy host, bacteria reaching the lung usually are cleared rapidly by alveolar macrophages or migrating neutrophils. Pneumonia results when disruption of the integrity of the epithelium of the lower respiratory tract is caused by microbiologic (e.g., viral infection), chemical (e.g., alcohol), or mechanical (e.g., aspiration) factors. Bacterial clearance is delayed, resulting in proliferation of *S. pneumoniae*. The role of respiratory viral infection as an antecedent or copathogen with *S. pneumoniae* is suggested by the seasonality of IPD that correlates with respiratory virus activity.[45–47] Further, in pneumococcal vaccine trials, the 9-valent vaccine prevented 31% of cases of pneumonia associated with respiratory viruses in children.[48,49]

Immunity

The polysaccharide capsules of pneumococci are chemically distinct and have immunologically specific features that form the basis of vaccine development. Type-specific protective antibodies against capsular polysaccharide develop after pneumococcal disease or immunization. Children <2 years old require immunization with protein conjugate vaccine to produce type-specific antibody. Antibody facilitates destruction of the pneumococcus by complement-mediated lysis and protects against both local and invasive disease.

Carriage of a particular serotype usually does not produce immunity sufficient to prevent reacquisition of that serotype. Human breast milk can protect infants from pneumococcal infection,[50,51] but specific protective factors have not been identified.

Epidemiology

Initial acquisition of pneumococci occurs in the first months of life, with a mean age of 6 months.[52] In developing countries, cumulative acquisition in several studies has exceeded 90% before 6 months of age. Nasopharyngeal carriage rates have been reported to range from 11% to 93% and vary by age, geographic region, and population.[52–55] In a study of healthy families in Charlottesville, Virginia, carriage rates were as high as 35% in preschool-aged and school-aged children, with lower rates in adolescents (9%). Adults with preschool-aged children have higher rates of carriage (18%) than do adults without children in this age group (9%).[56] Duration of carriage varies with serotype, is inversely correlated with age, and most commonly is 2 to 4 months, but it can be longer.[35,57,58]

Nasopharyngeal carriage of PCV7, PCV10, and PCV13 serotypes decreases in children who have received vaccine, but carriage of nonvaccine serotypes increases.[59,60] In clinical trials comparing PCV13 with PCV7, additional declines in nasopharyngeal carriage of serotypes 1, 6A, 6C, 7F, 19A, and 19F were observed in PCV13 recipients when compared with PCV7 recipients.[61] Factors associated with higher carriage rates include age <2 years, attendance at out-of-home childcare, crowding, winter, and parental smoking.[52,62]

Pneumococci are transmitted from person to person by respiratory droplets. Most disease is episodic, but epidemic disease has occurred in closed populations, such as military recruits,[63] and clusters of cases of IPD have been reported in children attending childcare facilities.[64]

Although type-specific immunity results from previous infection, recurrent infections by the same pneumococcal type can occur in immunocompromised hosts. Recurrent episodes of IPD occur in ~2.5% of patients who survive their initial episode.[65,66] The risk of recurrence is higher in persons with human immunodeficiency virus (HIV) infection and children <5 years of age who have chronic illness. Recurrent pneumococcal meningitis is associated with congenital or acquired disruption of the integrity of the skull, such as fractures of the cribriform plate and nasal, otic, or neurosurgical procedures.

The highest age-specific attack rate of IPD occurs in the first 2 years of life, with a peak between 6 and 11 months of age. This pattern continued during the PCV7 era. Following implementation of PCV13, further declines in IPD occurred in all age groups, especially among children <5 years of age (Fig. 123.1).[27,67] Boys are more commonly affected than girls in most studies. Type-specific antibody is passively transferred from the mother to the newborn and protects infants in the first several months. Accordingly, pneumococcal septicemia is rare in newborns; neonates accounted for only 20 cases in a review of 4428 episodes of IPD from 1993 to 2001.[68] In another series, infants 1 to 90 days of age accounted for 36 of 513 (7%) cases of IPD.[69] In neonatal infection the organism usually is acquired from the maternal genital tract, and both early onset and late onset disease has been reported.[68–70]

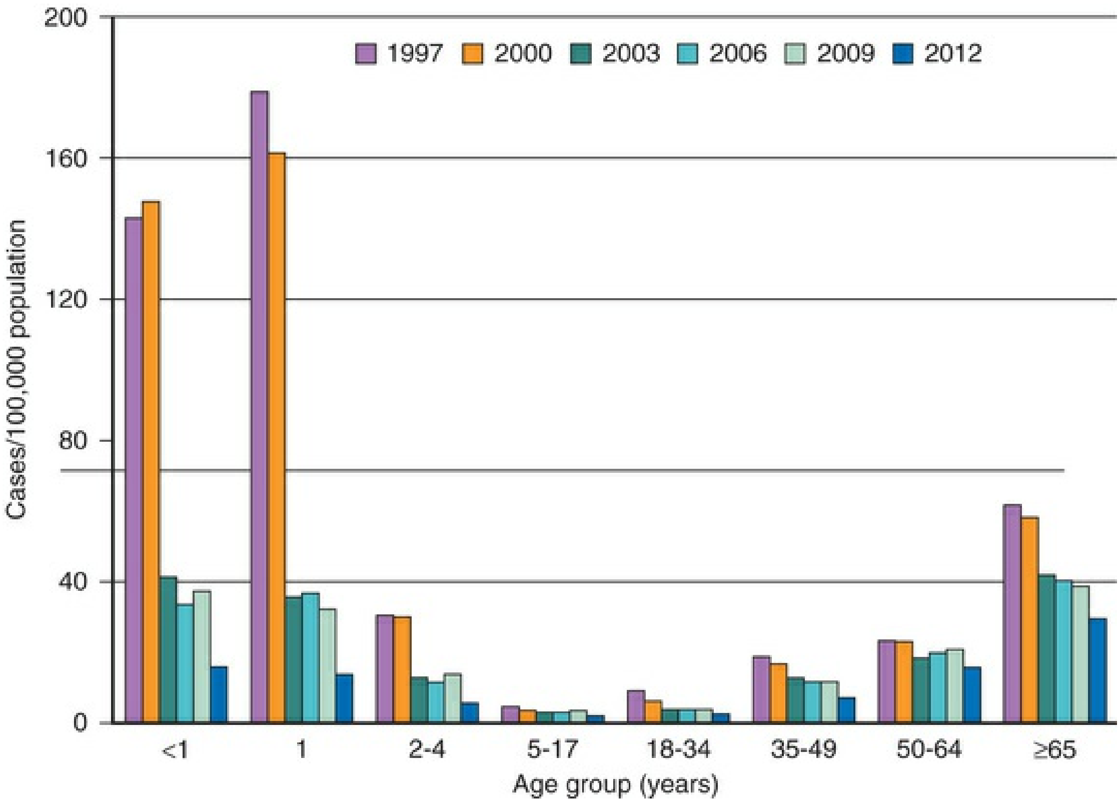

FIGURE 123.1 **Rates of invasive pneumococcal disease by age group in the United States in 1997, 2000, 2003, 2006, 2009, and 2012.** (Redrawn from Centers for Disease Control and Prevention. Active Bacterial Core Surveillance [ABCs]/Emerging Infectious Program [EIP] Network, 2015. www.cdc.gov/abcs/reports-findings/surv-reports.html.)

Children with certain underlying conditions are at high risk of IPD (Table 123.1). In the US before the introduction of PCV7, African Americans, Alaska Natives, and members of specific American Indian groups had higher rates of IPD compared with white people[59,71]; following introduction of PCV7 the racial disparity for IPD compared with whites diminished but has not disappeared.[26,72–75] The extent to which increased risks are attributable to other factors is not clear. The increased risk of race persists despite controlling for income.[59] Some case-control studies have demonstrated the strong association of IPD with underlying disease, larger family size,[51] and attendance at out-of-home childcare in the preceding 3 months.[50] Immunization with PCV7 did not influence the risk for non–vaccine-type IPD.[27] Since the introduction of PCV13, IPD occurs disproportionately in children with high-risk medical conditions that are indications for pneumococcal vaccination.[34,76]

TABLE 123.1

Underlying Medical Conditions That Are Indications for 23-Valent Pneumococcal Polysaccharide Vaccination Among Children ≥2 Years of Age

Risk Group	Condition
Immunocompetent children	Chronic heart disease[a] Chronic lung disease[b] Diabetes mellitus Cerebrospinal fluid leaks Cochlear implant
Children with functional or anatomic asplenia	Sickle cell disease or other hemoglobinopathy Congenital or acquired asplenia or dysfunction
Children with immunocompromising conditions	Human immunodeficiency virus infection Chronic renal failure or nephrotic syndrome Diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemia, and lymphoma, including Hodgkin disease; or solid-organ transplantation Congenital immunodeficiency[c]

[a] Particularly cyanotic congenital heart disease and cardiac failure.

[b] Including asthma if treated with high-dose oral corticosteroid therapy.

[c] Includes B-lymphocyte (humoral) or T-lymphocyte deficiency; complement deficiencies, particularly C1, C2, C3, and C4 deficiency; and phagocytic disorders (excluding chronic granulomatous disease).

From the AAP Committee on Infectious Diseases. Pneumococcal infections. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. Red Book: 2015 Report of the Committee on Infectious Diseases. 30th ed. Elk Groove Village, IL: American Academy of Pediatrics; 2015:626–638.

Children with sickle cell disease (SCD) or with HIV infection, especially those <3 years of age, have a markedly higher incidence of IPD.[59,77] The risk also is increased in children with other hemoglobinopathies, asplenia, nephrotic syndrome, and immunodeficiency other than HIV infection and in children receiving immunosuppressive therapy or who have CSF leaks (see Table 123.1).[33,59,77–79] Children with a cochlear implant, in particular those who received an implant with a positioner, have an increased risk for pneumococcal meningitis.[80]

Clinical Manifestations

The manifestations of pneumococcal infection are not distinct from those caused by other bacteria. The major exception is the classic syndrome of pneumococcal pneumonia described here that occurs in older children and adults.

In the pre-PCV7 era, the most common pneumococcal infections were AOM, pneumonia, and bacteremia with or without a focus, also termed "occult bacteremia."[59] In infants and young children with occult bacteremia, *S. pneumoniae* was the predominant isolate, accounting for 83% and 92% of cases in 2 studies in the post–*Haemophilus influenzae* type b conjugate vaccine and pre-PCV7 era.[81,82] In the PCV era, occult bacteremia in febrile children is uncommon in the United States.[83–89] However, when present, occult pneumococcal bacteremia can be caused by non-PCV7 serotypes.[90–92] Pneumococcal bloodstream infection in patients with SCD or asplenia can have a rapidly progressive course marked by abrupt onset, purpura, disseminated intravascular coagulation, and death within 24 to 48 hours; the course resembles that of Waterhouse-Friderichsen syndrome.

In the US, *S. pneumoniae* remains a leading bacterial cause of community-acquired pneumonia, although ~70% of cases of pneumonia occurring beyond the neonatal period are caused by respiratory viruses.[93] Data from PCV7 trials indicated that *S. pneumoniae* was responsible for approximately one third of radiographically diagnosed cases of pneumonia in infants.[94] However, in the Centers for Disease Control and Prevention (CDC) Etiology of Pneumonia in the Community (EPIC) study of children hospitalized with radiographically confirmed pneumonia in 3 children's hospitals in the US from January 2010 to June 2012, a bacterial pathogen was detected in only 15% of children, with *S. pneumoniae* the second most common bacterial pathogen detected after *Mycoplasma pneumoniae*.[93]

The classic presentation of pneumococcal pneumonia in older children includes a prodrome of viral respiratory tract infection (typically) followed by the abrupt onset of shaking chills, high fever, pleural pain, dyspnea, prostration, rust-colored sputum, and radiographic and physical findings indicating lobar consolidation. The spectrum of manifestations of pneumococcal pneumonia in infants and young children is broad and includes mild, nonspecific respiratory symptoms; cough can be absent, at least initially. In infants and toddlers, fever, vomiting, abdominal distention, and pain can be predominant, even suggesting appendicitis. Patients with right upper lobe pneumonia can have nuchal rigidity suggestive of meningitis.[95]

The characteristic radiographic finding in adolescents and adults is lobar consolidation, but in infants and young children, bronchopneumonia with scattered distribution of alveolar and parenchymal consolidation is common. Other radiographic findings are pleural fluid, lung abscess resulting from necrotizing lobar pneumonia, and, infrequently, pneumatoceles.

Although *S. pneumoniae* continues to be a leading cause of pediatric bacterial pneumonia, the overall rates of pneumonia significantly declined following the introduction of PCV7.[27,94,96–98] Other countries where PCV13 has replaced PCV7 report a further 27% to 64% decline in cases of bacterial pneumonia in hospitalized patients.[34,99–101] In contrast to pneumonia, hospitalizations for complicated pneumonia, effusion, empyema, lung abscess, and necrosis caused by *S. pneumoniae* increased in regions of the world with widespread use of PCV7.[11,102–104] In children with pleural empyema, *S. pneumoniae* continues to be the leading cause in the US and worldwide, although pleural empyema resulting from methicillin-resistant *Staphylococcus aureus* (MRSA) has increased.[13,104,105] An increased incidence of empyema has been associated with *S. pneumoniae* serotypes 1, 3, 7A, and 19A,[13,106–108] and necrotizing pneumonia has been associated with serotype 3.[109] Incidence rates of parapneumonic empyema have decreased by 50% since the introduction of PCV13 in the US.[101]

Among children with pneumococcal meningitis, approximately one half will manifest the classic triad of fever, nuchal rigidity, and change in mental status, and others have at least one of these findings.[110] Common manifestations vary by age in children: seizures, irritability, diarrhea, and a bulging fontanelle at <6 months of age; vomiting, altered mental status, and poor feeding between 6 months and 2 years; neck stiffness, vomiting, and drowsiness between 2 and 10 years; and neck stiffness, focal neurologic sign, headache, and vomiting >10 years of age.[111] CSF often has the following features: typical lancet-shaped, gram-positive cocci in pairs, with accompanying pleocytosis (predominantly neutrophils); a low CSF-to–serum glucose ratio (<0.6); and a high CSF protein concentration. In children with confirmed pneumococcal meningitis, CSF culture results are positive in >90%, and blood culture results are positive in ~75%.[110,112] Common complications associated with pneumococcal meningitis include, shock, respiratory failure, and residual neurologic sequelae, including hearing loss, seizures, and motor and behavioral deficits.[113–117] Neurologic morbidity following pneumococcal meningitis in a contemporary series occurred in 63% of survivors.[117] Features associated with increased morbidity and mortality rates include altered mental status and shock at admission, as well as low CSF white blood cell count and glucose concentration.[110,118]

Pneumococcal diseases also include conjunctivitis,[119–121] sinusitis,[122] soft tissue infections (e.g., buccal and periorbital cellulitis, erysipelas, cystic gingival lesions, and glossitis),[123,124] and invasive infections, including peritonitis,[125] pyogenic arthritis and osteomyelitis,[126] tubo-ovarian abscess and salpingitis,[127] and endocarditis.[128,129] Rare complications of pneumococcal infection include hemorrhage and shock,[130] hemolytic uremic syndrome,[131–134] and rhabdomyolysis.[135]

Laboratory Findings and Diagnosis

Pneumococcal infection can be confirmed by isolation of the organism from culture of blood or another normally sterile site; specimens for culture should be obtained, whenever possible, before antimicrobial therapy is initiated. Specimens should be inoculated into culture media immediately or, if delay in processing is unavoidable, stored in nutrient media at 4°C. Blood culture results usually are positive within 18 hours of inoculation.[82]

Gram stain of infected body fluids also should be performed because the finding of gram-positive diplococci suggests a pneumococcal origin. In patients with fulminant infection, organisms can be seen on microscopic examination of a stained smear of buffy coat of peripheral blood, thus reflecting a high concentration of circulating organisms.

Early in vitro PCR studies demonstrated a lack of sufficient sensitivity or specificity to be useful clinically.[136–138] More recently, sensitive real-time PCR-based assays have been developed that allow for accurate detection of *S. pneumoniae*. In a study of children with community-acquired pneumonia (CAP), PCR was significantly more sensitive than culture in revealing bacteremic pneumonia.[139] In another study of adult CAP, PCR was more sensitive than routine blood culture in identifying pneumococcal pneumonia, and a positive blood PCR result was associated with higher rates of mortality, risk for shock, and the need for mechanical ventilation in adults.[140] Studies also have demonstrated the utility of PCR for identifying pneumococci in pleural fluid.[12,13,141]

In the absence of a positive culture or PCR result, definitive diagnosis of pneumococcal pneumonia is difficult. In adults and older children, culture and Gram stain of expectorated sputum can be useful. Lower respiratory tract secretions can be obtained by tracheal aspiration through a catheter or protected brush or by bronchoalveolar lavage. Bronchoalveolar lavage is warranted in children in whom microbiologic diagnosis is essential for management. The most accurate test is needle aspiration with culture of infected lung parenchyma, but the procedure is not justified in most children with uncomplicated pneumonia.

Rapid antigen tests for pneumococcal capsular polysaccharide have limited value in the diagnosis of pediatric infections. A urine antigen assay used in children demonstrated high sensitivity for pneumococcal bacteremia and focal pneumonia. However, the rate of false-positive test results among febrile children without identified pneumococcal infection was 15%.[142] In children with suspected bacterial meningitis, rapid antigen tests of CSF have approximately the same yield as does Gram stain,[143] but findings with an immunochromatic test demonstrated better performance using CSF.[144] In children with pleural empyema, the confirmation of a pneumococcal origin can be enhanced by use of latex agglutination or PCR assays performed on pleural fluid.[13,145]

Treatment

Antimicrobial Susceptibility

Historically, pneumococci have been susceptible in vitro to penicillins, cephalosporins, macrolides (including erythromycin, clarithromycin, and azithromycin), clindamycin, rifampin, vancomycin, and trimethoprim-sulfamethoxazole. Chloramphenicol and sulfonamides have moderate activity. In the early 1990s, pneumococcal strains resistant to penicillin and other agents emerged and increased. Associated with the introduction of PCV7 in 2000 and a change in definition of nonsusceptibility, antimicrobial resistance decreased during the first decade of the 21st century.

Isolates of *S. pneumoniae* are tested by broth dilution assays or E tests (AB Biodisk NA, Piscataway, NJ), which provide specific susceptibility data. Interpretive definitions are recommended by the Clinical Laboratory Standards Institute.[146] Nonsusceptible isolates are subdivided into intermediate and resistant strains. Most strains of penicillin-nonsusceptible pneumococci have a minimal inhibitory concentration of <2 µg/mL. However, in the late 1990s strains of *S. pneumoniae* with a minimal inhibitory concentration of >8 µg/mL emerged.[147] In 2002, definitions of susceptibility and nonsusceptibility for penicillin, cefotaxime, and ceftriaxone were revised, resulting in a decrease in nonsusceptibility rates (Table 123.2).[146]

TABLE 123.2

Comparison of Former and New Breakpoints of Antimicrobial Agents (Minimum Inhibitory Concentrations) for *Streptococcus pneumoniae*, by Susceptibility Category: Clinical and Laboratory Standards Institute, 2008

Standard	Susceptibility Category MIC (μg/mL)

	Susceptible	Intermediate	Resistant
PENICILLIN			
Former breakpoints (all clinical syndromes and administered route)	≤0.06	0.12–1	≥2
New breakpoints (by clinical syndrome and administered route)			
Meningitis, IV penicillin	≤0.06	—[a]	≥0.12
Nonmeningitis, IV penicillin	≤2	4	≥8
Nonmeningitis, oral penicillin	≤0.06	0.12–1	≥2
CEFOTAXIME OR CEFTRIAXONE			
Former breakpoints (all clinical syndromes and administered route)	<0.5	1.0	≥2.0
New breakpoints (by clinical syndrome and administered route)			
Meningitis	<0.5	1.0	≥2.0
Nonmeningitis	≤1.0	2.0	≥4.0

[a] No intermediate category for meningitis under new penicillin breakpoints.

IV, intravenous; MIC, minimal inhibitory concentration.

From Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing; 18th Informational Supplement. CLSI document M100-S20. Wayne, PA: Clinical and Laboratory Standard Institute; 2008.

The mechanisms of antibiotic resistance of pneumococci are determined genetically and are shown in Table 123.3.[148–155] Most strains of penicillin-resistant pneumococci also are resistant to other antimicrobial agents. Penicillin resistance correlates directly with resistance to broad-spectrum cephalosporins. Strains that are more resistant to cefotaxime or ceftriaxone than to penicillin are rare.[148]

TABLE 123.3

Mechanisms of Antimicrobial Resistance in *Streptococcus pneumoniae*

Agent	Mechanism of Resistance (Proven or Suspected)
Penicillins and cephalosporins	Alterations in penicillin-binding proteins lead to a decreased affinity between penicillin-binding protein and the β-lactam drugs
Macrolides	Acetyltransferase expression of a ribosomal methylase encoded by the *ermAM* gene (MLS_B phenotype) is responsible for high-level macrolide and chloramphenicol resistance and complete cross- resistance with clindamycin
	Efflux of macrolide from cells, encoded by the *mefE* gene (M phenotype) is responsible for low-level resistance and has no effect on susceptibility to clindamycin
Trimethoprim	Affinity of trimethoprim for its target enzyme (dihydrofolate reductase) is reduced
Quinolones	Reduced affinity of DNA gyrase leads to increased drug concentrations needed to obtain the same degree of enzyme inhibition, or active efflux of drug out of the bacterial cell occurs
Linezolid	Mutations and deletions near the linezolid binding pocket within the *rplD* gene lead to decreased affinity[153]
Carbapenems	Stepwise alterations in penicillin-binding proteins lead to a decreased affinity

	of PB1a, PB2x, and PBP26 to carbapenems[154,155]

The more common is the macrolide resistance phenotype. Oxazolidinones (e.g., linezolid) and lipopeptides (e.g., daptomycin) have demonstrated in vitro and clinical efficacy against resistant *S. pneumoniae*.[151,152] Thus far only 2 invasive *S. pneumoniae* isolates nonsusceptible to linezolid have been identified in the US.[153] Although rare, *S. pneumoniae* resistance to the carbapenems has been reported. Unlike with other β-lactam agents, carbapenem resistance is not easily selected for by exposure to carbapenem.[154,155]

The CDC conducts population-based surveillance through the Active Bacterial Core surveillance (ABCs) to monitor drug resistance in the US. Data are available at www.cdc.gov/abcs/index.html. In 1998, 14% to 16%[156,157] of *S. pneumoniae* isolates were nonsusceptible to one or more antimicrobial agents tested; this percentage increased to 22% by 2002 and 2003.[67,158] However, comparing 1998 to 1999 with 2008, penicillin-nonsusceptible IPD rates declined 64% among children <5 years of age (from 12.1 to 4.4 cases per 100,000), and 45% for adults >65 years of age (from 4.8 to 2.6 cases per 100,000).[159] Following the introduction of PCV7 and PCV13 in 2000 and 2010, the proportion of nonsusceptible pneumococci in children to penicillin and third-generation cephalosporins decreased (Fig. 123.2).[67] The reduction in single and multidrug resistance likely reflects both the reduction in pneumococcal colonization following PCV7 and PCV13 and the reduction in use of antimicrobial agents (Table 123.4).[160,161]

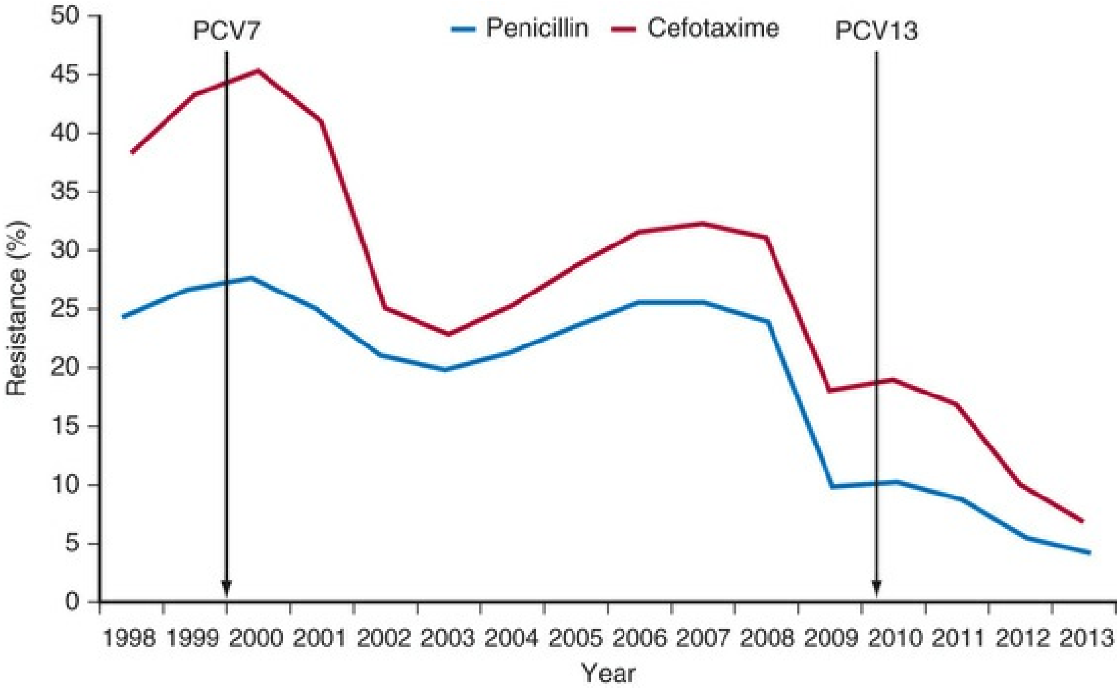

FIGURE 123.2 **Proportion of invasive *Streptococcus pneumoniae* isolates nonsusceptible to penicillin and cefotaxime from 1998 through 2013. PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.** (Redrawn from Centers for Disease Control and Prevention. Active Bacterial Core Surveillance [ABCs]/Emerging Infectious Program [EIP] Network, 2015. www.cdc.gov/abcs/reports-findings/surv-reports.html.)

TABLE 123.4

Antibiotic Susceptibility Patterns for Invasive Pneumococcal Strains in 2000, 2005, 2009 and 2013[a], Based on the Clinical and Laboratory Standards Institute Laboratory Testing Definitions

Agent	Percent Susceptible (%)				Percent Intermediate (%)				Percent Resistant (%)			
	2000	2005	2009	2013	2000	2005	2009	2013	2000	2005	2009	2013
Penicillin	72.6	76.4	89.8	95.4	9.8	13.7	5.2	2.5	17.6	9.9	5	2.1
Cefotaxime	82.3	94.7	91.9	97.5	9.8	4.1	6.2	1.8	8.0	1.2	1.9	0.7
Erythromycin	78.4	79.8	74.9	71.5	0.2	0.1	0.21	0.3	21.5	20.1	24.9	28.2
Trimethoprim-sulfamethoxazole	67.9	78.1	77	81.6	6.1	6.9	7.3	9.8	26.1	15	15.7	8.6
Levofloxacin	99.7	99.4	99.7	99.8	0	0.03	0	0	0.3	0.6	0.35	0.2
Vancomycin	100	100	100	100	0	0	0	0	0	0	0	0

[a] Based on 3691, 3499, 3743, and 2870 isolates in the years 2000, 2005, 2009, and 2013, respectively, using the Clinical and Laboratory Standards Institute definitions.

From the Centers for Disease Control and Prevention. Active Bacterial Core Surveillance Report: Emerging Infections Program Network. *Streptococcus pneumoniae.* www.cdc.gov/abcs/reports-findings/surv-reports.html.

Before PCV7 licensure, risk factors associated with multidrug-resistant pneumococcal nasopharyngeal carriage and disease were age <5 years, white race,[157,162] out-of-home childcare in the previous 3 months,[50] recent antimicrobial treatment,[50,163] and residence in a community with high use of antibiotics.[164] With widespread use of PCV7, antimicrobial resistance of emerging non-PCV7 serotypes to penicillin increased; childcare attendance, upper respiratory tract infection, and the presence of young siblings are important predictors.[160,165,166] Thus far, although widespread use of PCV13 has been associated with an increase in nasopharyngeal colonization with non-PCV13 serotypes in young children, the proportion of resistant *S. pneumoniae* organisms isolated from the nasopharynx of children who have received PCV13 has declined.[167,168]

Antimicrobial Therapy

Acute Otitis Media.

In guidelines published by the American Academy of Pediatrics and the American Academy of Family Physicians in 2004, amoxicillin at a dosage of 80 to 90 mg/kg/day in 2 divided doses is the first choice in uncomplicated AOM.[169] This dosing regimen results in concentrations of drug in the middle ear sufficient to eliminate most penicillin-nonsusceptible (resistant) strains.[170] When amoxicillin fails, alternatives include amoxicillin-clavulanate (14 : 1 formulation) in a dosage of 80 to 90 mg/kg/day of the amoxicillin component in 2 divided doses. This regimen (which has activity against β-lactamase–producing organisms, but not enhanced activity against pneumococcus) was demonstrated to be superior to placebo for children 6 through 23 months of age with AOM.[171] Cefdinir (14 mg/kg/day in 1 or 2 doses), cefuroxime axetil (30 mg/kg per day in 2 divided doses), cefpodoxime (10 mg/kg/day in 2 divided doses), and ceftriaxone (50 mg/kg, administered intramuscularly once) are alternatives.[169] Clindamycin and azithromycin are preferred agents for AOM in children who have severe penicillin allergy. The recommended duration for therapy for children <2 years of age with uncomplicated and mild to moderate AOM is 10 days; children 2 to 5 years of age can be treated for 7 days, and for children >6 years of age, a 5- to 7-day course is adequate.[79,169] Tympanocentesis and myringotomy should be considered in the child whose condition is toxic and in whom AOM has shown poor response to initial therapy, to determine bacteriologic features and antimicrobial susceptibility.

Meningitis.

The preferred empiric regimen for initial therapy of infants and children with suspected bacterial meningitis is vancomycin (60 mg/kg/day in 4 divided doses) in addition to ceftriaxone (100 mg/kg/day in 1 or 2 doses) or cefotaxime (300 mg/kg/day in 3 or 4 divided doses).[79] Specific meningitis susceptibility breakpoints for penicillin for pneumococcal meningitis must be applied (see Table 123.2). If *S. pneumoniae* is identified as the etiologic agent and is susceptible to penicillin, vancomycin should be discontinued, and penicillin G (250,000 to 400,000 U/kg/day in 4 or 6 divided doses), ceftriaxone (100 mg/kg/day in 1 or 2 divided doses), or cefotaxime (300 mg/kg/day in 3 or 4 divided doses) should be given.[172] If the pneumococcal isolate is not susceptible to penicillin (intermediate or resistant) but is susceptible to ceftriaxone and cefotaxime, vancomycin can be discontinued, and ceftriaxone or cefotaxime should be continued. If the isolate is nonsusceptible to penicillin, ceftriaxone, and cefotaxime (intermediate or resistant), vancomycin in addition to ceftriaxone or cefotaxime is continued, and rifampin (20 mg/kg/day in 2 divided doses) can be added.[173] No human data are available to determine the treatment of ceftriaxone-resistant pneumococcal meningitis, but results from a rabbit model indicate more rapid elimination of organisms with vancomycin in addition to ceftriaxone than with vancomycin alone.[174] The duration of therapy in uncomplicated cases of pneumococcal meningitis is 10 days.

Adjunctive therapy with dexamethasone has been demonstrated to decrease the incidence of neurologic and audiologic sequelae in children with meningitis caused by *H. influenzae* type b. Although benefit in patients with pneumococcal meningitis has been debated,[175–177] a meta-analysis of randomized clinical trials indicated that dexamethasone significantly reduces the incidence of severe hearing loss in pneumococcal meningitis and also may possibly be effective in preventing hearing or neurologic deficit, provided that dexamethasone is initiated with or before antibiotic therapy.[178] A Cochrane review concluded that the use of dexamethasone at 0.6

mg/kg daily, given before or with the first dose of antibiotics, in children with acute bacterial meningitis including *S. pneumoniae* infection in high-income countries was beneficial by decreasing mortality rates, although the strength of the evidence was not optimal.[177] As a result, the American Academy of Pediatrics recommended that dexamethasone can be considered in the initial therapeutic regimen for infants and children 6 weeks old and older with possible pneumococcal meningitis.[79] Dexamethasone dosage should be 0.15 mg/kg every 6 hours for 48 hours. A repeat lumbar puncture should be considered at 24 to 48 hours of therapy to help guide further therapy if the organism is penicillin nonsusceptible, dexamethasone has been used, or the clinical response is not optimal.

Pneumonia.

In 2011, the Infectious Diseases Society of America and the Pediatric Infectious Diseases Society issued guidelines for the management of pediatric CAP.[179] *S. pneumoniae* was recognized as a common cause of bacterial CAP in children.[93] The guidelines recommend that amoxicillin be used as first-line therapy for outpatient treatment of previously healthy, appropriately immunized infants and preschool-aged and school-aged children with mild to moderate CAP suspected to be of bacterial origin. A daily dose of amoxicillin of 90 mg/kg divided into 3 equal doses is predicted to achieve clinical and microbiologic cure in 90% of children compared with 65% treated with the same daily dose divided into 2 doses.[179] The guidelines recommend the addition of a macrolide agent primarily in school-aged children and adolescents evaluated in an outpatient setting, with findings compatible with those in CAP caused by atypical pathogens.

For hospitalized children, the guidelines recommend that penicillin G (up to 300,000 U/kg/day divided every 4 hours) or ampicillin (up to 400 mg/kg/day divided every 6 hours) be administered to the fully immunized infant or school-aged child admitted to a general medical unit with CAP when local epidemiologic data document a lack of substantial high-level penicillin resistance for IPD caused by *S. pneumoniae*. Empiric therapy with a third-generation parenteral cephalosporin (ceftriaxone or cefotaxime) should be reserved for the following:

hospitalized infants and children who are not fully immunized or in regions where local epidemiology of invasive pneumococcal strains documents high-level penicillin resistance; or hospitalized infants and children with life-threatening infection, including children with empyema.[180]

Prognosis

Death in pneumococcal infection occurs most commonly in immunocompromised hosts, such as patients with SCD, asplenia, patients with congenital or acquired immunodeficiency, and children from developing countries with limited access to medical facilities. With current therapy, the mortality rate from bacterial meningitis in children beyond the neonatal period is ~10%, but neurologic sequelae, including hearing loss and mild to severe motor and intellectual deficits, remain relatively common. In studies of pneumococcal meningitis, 7% to 13% of children died, 29% to 36% had hearing loss at discharge, and 25% to 63% experienced neurologic sequelae.[115–117,181]

Specific pneumococcal serotypes and age have been associated with increased IPD mortality rates. In a study of nearly 19,000 children with IPD in Denmark, 10% of whom were <5 years of age, the overall 30-day mortality rate was 3% in children <5 years of age and 18% in those ≥5 years of age. Compared with serotype 1, which was the most common serotype isolated in Denmark, serotypes 14, 6A, 7F, and 4 were associated with decreased odds of death among children <5 years of age. In contrast, serotypes 31, 11A, 35F, 17F, 3, 16F, 19F, 15B, and 10A were associated with increased odds of death among children ≥5 years of age.[182]

Children with pneumococcal otitis media uncommonly have suppurative complications, such as chronic suppurative otitis media, mastoiditis, petrositis, labyrinthitis or brain abscess, and meningitis. However, since the introduction of PCV7, one large children's hospital reported an increase in pneumococcal mastoiditis caused by multidrug-resistant serotype 19A.[183]

Prevention

Vaccine

The morbidity and mortality of pneumococcal infection in the antibiotic era led to the development and licensure in 1977 of a polyvalent polysaccharide vaccine in the US. The currently available 23-valent pneumococcal polysaccharide vaccine (PPSV23) is composed of purified capsular polysaccharide antigens of 23 serotypes that offered some protection against ~90% of the serotypes causing IPD in the US between 1998 and 1999, 84% by 2006 and 2007,[27,59] and 68% by 2010 and 2013[34] in children <5 years of age. Whereas PPSV23 elicits type-specific antibody responses in most healthy adults and children >5 years of age, the serologic response to the polysaccharide antigens generally is poor in children <2 years of age.[184] PPSV23 is recommended to be given following receipt of PCVs (which should include ≥1 dose of PCV13) to children ≥2 years of age with underlying conditions (see Table 123.1). The interval between PCV13 and PPSV23 is ≥8 weeks. A second dose of PPSV23 is given once ≥5 years after the first.[79,185]

The conjugate vaccines (PCVs) in which purified capsular polysaccharides of different pneumococcal serotypes are covalently bound to a protein carrier are immunogenic in infants at 2 months of age, induce B-lymphocyte memory cells resulting in an anamnestic response with subsequent doses, and reduce carriage of vaccine serotypes.

The PCV7 (Prevnar-7 Pfizer, New York, New York) vaccine was approved in 2000 for universal infant immunization in a 4-dose schedule in the US.[59,77] PCV7 contains the polysaccharides of serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F; these serotypes accounted for the majority of cases of IPD and AOM cases in US children <6 years of age during the period 1978 to 1994.[59] Infants respond to each PCV type with substantial concentrations of serum antibody believed to be protective against invasive disease.[186] Protective titers are achieved after doses administered at ages 2, 4, and 6 months but wane during the following 6 months, thus requiring a booster dose at 12 to 15 months of age.

Efficacy of PCV7 was demonstrated in prospective, randomized clinical trials in northern California[186] and in Finland.[5] In a large randomized study, PCV7 was somewhat efficacious against placement of tympanostomy tubes, AOM episodes, and related office visits; it was moderately efficacious against pneumonia; and it was highly efficacious in preventing IPD.[186,187] Adverse events were limited to mild erythema, induration, and tenderness at the injection site, and fever (39°C or greater) in approximately 1% to 2% of recipients.[186]

PCV7 was recommended by the American Academy of Pediatrics and CDC in 2000 for all infants in a 4-dose schedule at ages 2, 4, 6, and 12 to 15 months.[59,77] In 2007, the Advisory Committee on Immunization Practices revised recommendations to include routine use in all children 2 through 59 months of age.[188] Studies demonstrated the effectiveness of PCV7 when the vaccine was given in different and abbreviated schedules from that of the 4 doses recommended in the US.[189,190] Surveillance through the Vaccine Adverse Event Reporting System, a US passive database, confirmed the safety of PCV7.[191]

By December 2010, more than 300 million doses of PCV7 had been distributed worldwide; most of the doses were distributed in the US.[192] Following the introduction of PCV7, a significant decline was reported in the burden of IPD, pneumonia, meningitis, and AOM, as well as a decreasing incidence of pneumococcal penicillin resistance.[193–197] The CDC ABCs reported that the incidence of IPD in children <5 years of age decreased from 97.6 cases to 21.8 cases per 100,000 population from 1999 to 2009, a decrease of >80%.[67,198] Indirect effects of PCV7 were demonstrated by declines in IPD in other age groups in whom the PCV7 was not indicated (Table 123.5).[24,27] Comparable decreases in IPD also were reported in other countries using PCV7.[199,200] Decreases in IPD were greatest among children <12 months and 12 to 23 months of age.[27] Further decreases occurred after introduction of PCV13 in 2010. The incidence of IPD decreased by 49%, from 19 cases to 9.6 cases per 100,000 from 2010 to 2013 in children <5 years of age, with the greatest reduction among children <2 years of age (Fig. 123.3).[67]

TABLE 123.5

Changes in Incidence of Invasive Pneumococcal Disease by Age and Serotype, 1998 to 1999 Average (Baseline) Versus 2007

Age Group (Yr)	Serotype	Incidence (Cases Per 100,000 Population)	Change in Rate (2007 vs. Baseline)

		1998–1999 (n = 4,048)	2007 (n= 2,576)	Change (%) (95% CI)
<5	All types	98.7	23.6	−76 (−79 to −73)
	Vaccine	81.9	0.4	−100 (−100 to −99)
	Vaccine-related	7.3	1.7	−77 (−85 to −64)
	Nonvaccine	6.8	10.3	+51 (+20 to +90)
5–17	All types	4.2	2.4	−43 (−55 to −26)
	Vaccine	2.4	0.2	−94 (−97 to −85)
	Vaccine-related	0.2	0.2	+4 (−59 to +164)
	Nonvaccine	1.5	1.4	−2 (−31 to +40)
18–49	All types	13.3	8.0	−40 (−45 to −35)
	Vaccine	7.6	0.7	−91 (−93 to −88)
	Vaccine-related	1.1	1.1	+1 (−22 to +29)
	Nonvaccine	4.2	4.8	+14 (+1 to +29)
50–64	All types	24.0	19.8	−18 (−25 to −9)
	Vaccine	12.8	1.7	−87 (−90 to −83)
	Vaccine-related	1.9	2.6	+35 (+1 to +80)
	Nonvaccine	8.6	12.3	+43 (+25 to +64)
≥65	All types	60.1	37.9	−37 (−42 to −32)
	Vaccine	33.7	2.7	−92 (−94 to −89)
	Vaccine-related	5.8	7.2	+25 (+1 to +54)
	Nonvaccine	18.3	22.5	+23 (+9 to +38)

CI, confidence interval.

From Pilishvili T, Lexau C, Farley MM, et al. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. J Infect Dis 2010;201:32–41

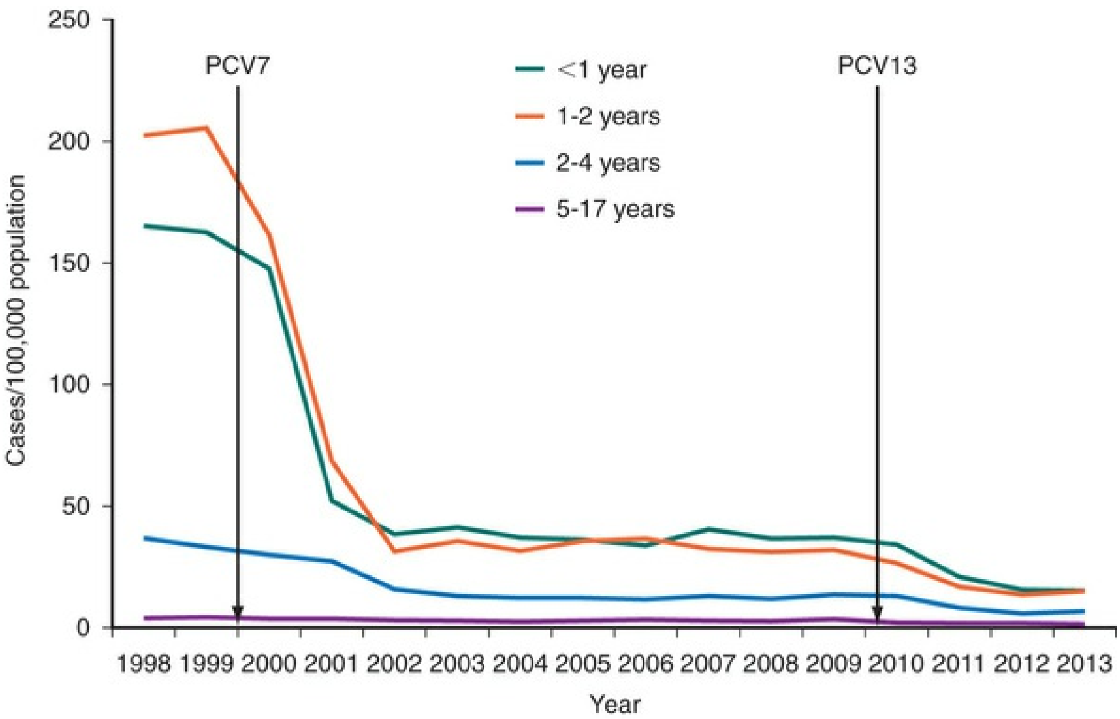

FIGURE 123.3 **Rates of invasive pneumococcal disease among children younger than 18 years old, according to age and year. PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.** (Data from Centers for Disease Control and Prevention. Active Bacterial Core Surveillance From 1998 Through 2013. www.cdc.gov/abcs/reports-findings/surv-reports.html.)

Some regions in the US (including Alaska and Utah) and other regions of the world reported a less dramatic decrease in IPD following the introduction of PCV7 and the early emergence of IPD caused by non-PCV7 serotypes.[25,26,86,105,141] By 2007, non-PCV7 serotypes 19A, 3, 7F, 15B/C, 22F, and 33F were the most common serotypes causing IPD among children <5 years of age in the US.[25,27,201,202] In many regions in the US, serotype 19A emerged as the leading cause of IPD during the PCV7 era; by 2007 to 2008, serotype 19A accounted for 46% of 369 non-PCV7 isolates, whereas serotypes 1, 3, and 7F combined accounted for 22%.[29] In Massachusetts, serotype 19A increased from 10% of IPD cases in 2002 to 41% in 2006.[203] A similar trend also was noted in Texas, where significant increase in infections with serotype 19A were noted between 1999 and 2008.[204]

S. pneumoniae bacteremia without focus, pneumonia, and meningitis decreased significantly following PCV7 licensure.[83,205] Data from the Nationwide Inpatient Sample database demonstrated a sustained 33% decrease in hospitalized children with pneumonia <2 years of age in the PCV7 era (2001–2007) compared with 1996 to

1999.[206] By 2009, a 43% decline in all-cause pneumonia among US children <2 years of age was reported.[207] Similarly, pneumococcal meningitis decreased. Data from the CDC ABCs sites showed a 64% decrease in incidence of pneumococcal meningitis from 4.7 cases to 1.7 cases per 100,000 population between 1998 to 1999 and 2006 to 2007 among children <5 years of age. This decrease was primarily the result of a 97% (from 3.8 to 0.1 cases per 100,000 population) decline in meningitis caused by PCV7seroypes.[27] However, the incidence of pneumococcal meningitis caused by non-PCV7 types, although low, increased 78% (from 0.9 to 1.6 cases per 100,000 population) over the same time period.[27] The largest decline in meningitis occurred in children <2 years of age, and moderate decreases occurred in other age groups not eligible for PCV7.[27,201,208] Similar decreases were noted in national trends in rates of hospitalization for pneumococcal meningitis, by using data from the Nationwide Inpatient Sample and from other countries where PCV7 was used widely.[201,209–212] By 2007, >94% of pneumococcal meningitis cases in the US were caused by non-PCV7 types.[27,201] In a retrospective study of pneumococcal meningitis in 8 children's hospital in the US from 2007 through 2009, 54% of pneumococcal meningitis cases were caused by PCV13 types, with serotypes 19A, 7F, and 3 accounting for >90% of isolates.[116] During the PCV7 era, many sites in the US and Europe reported significant increases in pneumococcal empyema.[11,102–106,213] Li and Tancredi[103] showed a 70% increase in pneumococcal empyema in the US from 2.2 per 100,000 in 1997 to 3.7 per 100,000 children in 2006 in patients <18 years of age. The largest increase was among children <5 years of age. Similarly Grijalva and colleagues[104] noted a twofold increase in hospitalizations for pneumonia complicated by empyema from 3.5 cases per 100,000 children in 1996 to 1998 to 7.0 cases per 100,000 children in 2005 to 2007.

In 2010, the 13-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV13 [Prevnar 13], Pfizer, New York, New York) was approved by the US Food and Drug Administration for prevention of IPD in infants and young children 6 weeks through 71 months of age. PCV13 contains the 7 serotypes included in PCV7 and 6 additional serotypes (1, 3, 5, 6A, 7F, and 19A). PCV13 replaces PCV7.[214,215] PCV13 also is approved for the prevention of AOM caused by the 7 serotypes also covered by PCV7. PCV13 was licensed by the US Food and Drug Administration and elsewhere on the basis of studies demonstrating safety and immunogenicity.[216,217] By 2013, the US national vaccination coverage among children 19 to 35 months of age was 92% for ≥3 PCV13 doses and 82% for ≥4 PCV13 doses.[218]

The epidemiology of IPD since the introduction of PCV13 continues to change. Data from the CDC ABCs sites show a 64% (95% interval estimates, 59%–68%) decrease in the incidence of IPD, when the projected incidence of IPD in 2013 was compared during the period 2004 to 2010. The decline primarily reflects a 93% decrease in IPD caused by the additional 6 serotypes in PCV13. A reduction in IPD in the US has been observed in all age groups.[34] Similar decreases also have been reported in countries where PCV13 has been introduced.[219–222]

A large database of US hospital discharges coded according to the International Classification of Diseases, Ninth Revision (ICD-9) showed a decline in IPD, empyema, all-cause pneumonia, and noninvasive pneumococcal or lobar pneumonia in 2011 to 2012 compared with 2007 to 2009.[101] The declines were among children <2 years of age who were discharged with IPD (64%), empyema (50%), all-cause pneumococcal pneumonia (21%) and noninvasive pneumococcal pneumonia (40%). Similarly, among children 2 to 4 years old, decreases were observed in IPD (55%), empyema (46%), and all-cause pneumococcal pneumonia (17%); as well as empyema (37%) in children 5 to 17 years of age. Among children, the prevalence of pneumonia is reduced compared with that of other IPD syndromes. Potential explanations of differential effects include individual serotypes that could predispose children to specific syndromes and differential effectiveness among children with and without underlying disorders.[101]

Before the introduction of the PCV13 in the US, >95% of cases of IPD in children were caused by serotypes not covered by the PCV7 vaccine, primarily serotypes 19A, 7F, 3, and 1. Three years after the introduction of PCV13, IPD caused by serotypes 19A and 7F declined, significantly with no significant change in infection with serotype 3 (which was associated with reduced immunogenicity in clinical trials of PCV13).[216] By 2013, 69% of cases of IPD in children <5 years of age were caused by non-PCV13 serotypes (Table 123.6). Overall, the most common serotypes currently isolated from patients <18 years old who have IPD are serotypes 22F, 33F, 38, 35B, 15B, 19A, 15C, 3, 23B, and 12F, whereas serotypes 22F, 3, 7F, 19A, 6C, 12F, 33F, 35B, 16F, and 9N are the most common isolates from adults.[34] The impact of PCV13 in groups targeted and not targeted for vaccination also has been observed in France, Denmark, and Norway.[220–222]

TABLE 123.6

Epidemiologic Features of Cases of Invasive Pneumococcal Disease Before Versus After the Introduction of 13-Valent Conjugate Pneumococcal Vaccine[a]

	IPD Before Introduction of PCV13[b] (n = 23,858)	IPD After Introduction of PCV13[c] (n = 9,830)	P Value
AGE (YR)			
<2	1,833 (8%)	426 (4%)	<0.0001
2–4	995 (4%)	285 (3%)	—
5–17	875 (4%)	273 (3%)	—
18–49	6,274 (26%)	2,234 (23%)	—
50–64	6,284 (26%)	2,994 (30%)	—
≥65	7,597 (32%)	3,618 (37%)	—
SEX			
Male	12,513/23,831 (53%)	5,092/9,820 (52%)	0.28
Female	11,318/23,831 (47%)	4,728/9,820 (48%)	—
ANY RISK FACTOR (APART FROM AGE) THAT IS AN INDICATION FOR PPSV23[d]			
<18 yr	61/3,698 (2%)	26/971 (3%)	0.04
≥18 yr	2,383/20 145 (12%)	1,023/8,771 (12%)	0.69
CASES OF IPD CAUSED BY PNEUMOCOCCAL SEROTYPES IN CHILDREN <5 YEARS OLD[e]			
PCV7 types	102/2,438 (4%)	17/638 (3%)	<0.0001
PCV13 minus PCV7 types	1427/2,438 (59%)	179/638 (28%)	—
PPSV23 minus PCV13 types	460/2,438 (19%)	235/638 (37%)	—
Non-PCV13 and non-PPSV23 types	449/2,438 (18%)	207/638 (32%)	—
CASES OF IPD BY CLINICAL SYNDROMES AND AGE			
Age <18 yr			
Bacteremia	1,558/3,283 (47%)	404/844 (48%)	0.005
Pneumonia	1,417/3,283 (43%)	331/844 (39%)	—
Meningitis	308/3,283 (9%)	109/844 (13%)	—
Age ≥18 yr			
Bacteremia	3,446/19,222 (18%)	1,155/8,188 (14%)	<0.0001
Pneumonia	14, 698/19,222 (76%)	6,500/8,188 (79%)	—
Meningitis	1,078/19,222 (6%)	533/8,188 (7%)	—

[a] Data are number (%) or n/N (%). Some percentages do not total 100 because of rounding.

[b] July 2004 through June 2010.

[c] July 2010 through June 2013.

[d] Based on Advisory Committee on Immunization Practices recommendations for children and adults.[33,228–230]

[e] PCV7 types consist of 4, 6B, 9V, 14, 18C, 19F, 23F, and 6A. PCV13 minus PCV7 types consist of 1, 3, 5, 7F, and 19A. PPSV23 minus PCV13 types consist of 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F.

IPD, invasive pneumococcal disease; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

From Moore MR, Link-Gelles R, Schaffner W, et al. Effect of use of 13-valent pneumococcal conjugate vaccine in children on invasive pneumococcal disease in children and adults in the USA: analysis of multisite, population-based surveillance. Lancet Infect Dis 2015;15:301–309.

The safety and adverse reactions after administration of PCV13 in clinical trials were assessed in 3 clinical trials in the US. Injection-site reactions, fever, decreased appetite, irritability, and increased or decreased sleep were solicited adverse reactions reported in ≥20% of subjects. The incidence and severity of solicited local reactions at the injection site (pain, tenderness, erythema, and induration or swelling) and solicited systemic reactions (irritability, drowsiness or increased sleep, decreased appetite, fever, and restless or decreased sleep) were similar in the PCV13 and PCV7 groups.[223]

In the first 3 years following PCV13 introduction in the US, an estimated 10,000 cases of IPD in children and 20,000 cases in adults were prevented. Investigators also estimated that 3000 deaths, 97% in adults, likely were prevented.[34] Ongoing surveillance of pneumococcal diseases, serotypes, clinical syndromes and ages of affected children will be critical to understand the remaining burden and emerging epidemiology of pneumococcal disease and serotypes, to guide national vaccine policy.

Passive Immunoprophylaxis

Immune globulin reduces the incidence of pneumococcal and other bacterial infections in several circumstances. In a placebo-controlled trial in HIV-infected children with clinical or immunologic evidence of disease, children given immune globulin intravenous (400 mg/kg given every 28 days) had a longer time before serious bacterial infection and a smaller number of infections compared with the control group.[224] The benefit primarily was in preventing IPD and clinically diagnosed acute pneumonia. Recommended management includes immune globulin intravenous therapy for HIV-infected children who have both recurrent serious bacterial infections despite appropriate antimicrobial prophylaxis and humoral immunodeficiency.[225]

Chemoprophylaxis

For prevention of IPD in children with functional or anatomic asplenia, particularly SCD, daily antimicrobial prophylaxis with oral penicillin V or G (125 mg twice daily for children <5 years of age; 250 mg twice daily for children >5 years of age) is recommended.[77] A chemoprophylactic regimen of penicillin reduced the incidence of IPD by 84% in a randomized, placebo-controlled trial in children with SCD.[226] These data are the basis of the recommendation to give daily penicillin prophylaxis to these patients beginning before 2 months of age or as soon as the diagnosis is made.[77] Prophylactic penicillin can be discontinued in children with SCD after 5 years if they have not experienced IPD and have received all recommended pneumococcal immunizations.[227] The duration of prophylaxis for children with asplenia from other causes is unknown. Some experts continue prophylaxis throughout childhood.[225]

Prevention of Disease in Contacts

Because secondary cases of IPD are uncommon, chemoprophylaxis is not indicated for contacts of patients with such infections.[225] Universal precautions are recommended for hospitalized patients with IPD, and droplet precautions are recommended for infants and children with presumed bacterial meningitis for the first 24 hours of therapy because of the possibility of infection with pathogens other than *S. pneumoniae* such as *Neisseria meningitidis* or *H. influenzae* type b.

Key Points

Diagnosis and Management of *Streptococcus pneumoniae* Infection

Microbiology

- These catalase-negative, gram-positive cocci appear as lancet-shaped diplococci on Gram stain.
- These facultative anaerobic organisms have enhanced growth in 5% carbon dioxide.
- Organisms exhibit α hemolysis on blood agar and can be identified presumptively from their susceptibility to optochin.
- This capsular polysaccharide results in >90 immunologically distinct serotypes within 45 serogroups.
- Alterations in penicillin-binding enzymes result in penicillin and cephalosporin resistance.

Epidemiology

- It is part of the normal oropharyngeal flora, with the highest prevalence (~35%) in preschool-aged and school-aged children.
- Invasive pneumococcal disease is highest among children <2 years of age.
- History of antecedent upper respiratory tract illness suggests that disruption of mucosal barrier leads to bloodstream invasion.
- *S. pneumoniae* has a predilection for pulmonary or meningeal focus.

Diagnosis

- Recovery from blood culture is enhanced by immediate inoculation of specimen into an automated blood culture system.
- Polymerase chain reaction can detect *Streptococcus pneumoniae* DNA in blood and pleural fluid.
- Gram stain of infected sterile body fluid with findings of lancet-shaped gram-positive diplococci suggests a pneumococcal origin.

Treatment

- Penicillin is drug of choice for penicillin-susceptible *S. pneumoniae* isolates.
- *S. pneumoniae* is susceptible generally to cephalosporins, carbapenems, vancomycin, clindamycin, and levofloxacin.

Duration of Therapy

- Response to therapy is usually rapid.
- Duration of therapy depends on the site of infection.

Prevention

- Widespread use of pneumococcal conjugate vaccines (PCV7, PCV10, and PCV13) have resulted in substantially decreased rates of invasive pneumococcal disease in children and adults.

PCV7, 7-valent pneumococcal conjugate vaccine; PCV10, 10-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.

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124

Other Gram-Positive, Catalase-Negative Cocci

Leuconostoc and *Pediococcus* Species and Other Genera

David B. Haslam, Joseph W. St. Geme III

Characteristics of Pathogens

Among the gram-positive, catalase-negative cocci, streptococci and enterococci cause most human infections. The remaining organisms belong to 5 genera that can be identified according to the criteria proposed by Facklam and colleagues[1] (Table 124.1), and they form colonies that are α hemolytic or nonhemolytic on sheep blood agar and are easily confused with *Streptococcus pneumoniae* or viridans streptococci. These organisms appear to lack typical virulence determinants and consequently are uncommon pathogens.

TABLE 124.1

Biochemical Differentiation of Catalase-Negative Gram-Positive Cocci

Test	*Streptococcus*	*Enterococcus*	*Pediococcus*	*Leuconostoc*	*Aerococcus*	*Gemella*
Arrangement of cells	Chains, pairs	Pairs, chains	Tetrads, some pairs	Pairs, chains	Tetrads, pairs	Pairs, short chains
Gas from glucose	–	–	–	+	–	–
Vancomycin susceptibility	S	S[a]	R	R	S	S
Streptococcal group antigen	v	+	+	+[a]	–	–
Bile esculin	v	+	+	+[a]	v	–
PYRase[b]	–[c]	+	–	–	+	+
Leucine aminopeptidase	+	+	+	–	–	+
Growth in						
65% NaCl	–	+	V	v	+	–
45°C	v	+	+[a]	–	–	–
10°C	–	+[a]	–	+	–	–

[a] Occasional exceptions exist.

[b] Hydrolysis of L-pyrrolidonyl-β-napthlyamide.

[c] Except *Streptococcus pyogenes,* which is pyrrolidonyl peptidase positive.

NaCl, sodium chloride; PYRase, pyrrolidonyl peptidase; R, resistant to vancomycin (absence of a zone of inhibition); S, susceptible to vancomycin; v, variable reaction; −, absent; +, present.

Adapted from Facklam R, Hollis D, Collins D. Identification of gram-positive coccal and coccobacillary vancomycin-resistant bacteria. J Clin Microbiol 1989;27:724–730.

Of these genera, *Leuconostoc* and *Pediococcus* account for most human infections and are notable for their intrinsic high-level resistance to vancomycin. The genus *Leuconostoc* consists of 6 species, of which *L. mesenteroides* and *L. paramesenteroides* are most commonly associated with pediatric infections. The genus *Pediococcus* consists of 8 species, but only *P. acidilactici* and *P. pentosaceus* are recognized as potential pathogens.

Epidemiology

Leuconostocs and pediococci are found on certain foods, including vegetables, dairy products, and processed meats. Occasionally they can be isolated from culture of vaginal and gastrointestinal tract specimens. Leuconostocs can colonize other mucosal surfaces as well, including gastrostomy and tracheostomy sites. Pediococci are components of some probiotic preparations.

Clinical Manifestations

Leuconostoc Species.

Invasive disease caused by *Leuconostoc* spp. is unusual, with approximately 20 cases reported in children. Most infants with systemic infection have an underlying disorder, such as prematurity or a gastrointestinal abnormality.[2] Rarely, however, bloodstream infection can occur in otherwise normal infants.[3] Older children with *Leuconostoc* infection typically have an immunodeficiency. In patients of all ages, previous therapy with vancomycin and the presence of an indwelling catheter appear to be additional risk factors. Contaminated enteral feedings, including infant formula, have been implicated as the source of bloodstream infection in isolated cases. An association exists between *Leuconostoc* infection and enteral feeding in patients with short gut syndrome.[3] In many children with underlying gastrointestinal disease, bloodstream infection is polymicrobial and involves *Leuconostoc* in addition to enteric organisms.

Leuconostoc meningitis and pneumonia have been reported in children, almost always in association with an underlying disease such as gastrointestinal disease or immunodeficiency or with an indwelling central nervous system shunt. Other reported infections include peritonitis in a child with an indwelling peritoneal dialysis catheter.

Pediococcus Species.

Few pediatric cases of invasive *Pediococcus* infection have been described.[4] Reported patients have been <1 year of age and have recently undergone operations for gastrointestinal abnormalities. Antibiotic therapy that included a β-lactam agent and an aminoglycoside were effective.[5]

Gemella Species.

Gemella spp. are uncommon causes of pediatric disease. However, endocarditis resulting from *Gemella* is reported occasionally, in one case following body piercing.[6,7] *Gemella* endocarditis can lead to remote infections such as lung or brain abscess.[8]

Other Genera.

Aerococcus viridans is a rare cause of invasive disease in children, associated with <10 cases of meningitis or bacteremia in medical publications.[9] *Weissella* spp. are newly reclassified organisms that previously were misidentified as lactobacilli. Newer molecular diagnostic methods have identified *Weissella* as an occasional cause of bloodstream, bone, and joint infection.[10]

Therapy

Leuconostocs and pediococci have intrinsic high-level resistance to vancomycin (minimum inhibitory concentration [MIC] ≥64 μg/mL). The mechanism of resistance in both genera is unknown but appears to be chromosomally mediated and is distinct from the mechanism demonstrated by vancomycin-resistant enterococci.

Leuconostocs and pediococci are moderately resistant to penicillin, with MICs ranging from 0.03 to 2 μg/mL; 90% of isolates have an MIC <1 μg/mL.[2] Many isolates are tolerant of penicillin (ratio of minimum bactericidal concentration to MIC >32), although the clinical significance is unclear. Penicillin, either alone or in combination with an aminoglycoside, is the treatment of choice for *Pediococcus* and *Leuconostoc* infections. Chloramphenicol, aminoglycosides, and carbapenems also are active against in vitro, but clindamycin, trimethoprim-sulfamethoxazole, and third-generation cephalosporins have unreliable activity. Daptomycin and linezolid both demonstrate good activity against *Leuconostoc* and *Pediococcus* and may be the preferred treatment for invasive infection in immunocompromised patients.[11] *Aerococcus* and *Gemella* spp. are susceptible to penicillin, cephalosporins, erythromycin, and vancomycin; penicillin alone or in combination with an aminoglycoside is the treatment of choice for invasive infection.

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Gram-Negative Cocci

OUTLINE

125 Neisseria meningitidis

126 Neisseria gonorrhoeae

127 Other Neisseria Species

125

Neisseria meningitidis

Andrew J. Pollard, Adam Finn

Neisseria meningitidis (meningococcus) is a leading cause of serious bacterial infections in children, most commonly manifesting as purulent meningitis or septicemia. Asymptomatic pharyngeal colonization is more common than invasive disease, and humans are the only reservoir.[1] Gaspard Vieusseux provided the first clinical description of meningococcal disease during an outbreak in Geneva, Switzerland, as recently as 1805,[2] which was followed by epidemics across Europe for the next 50 years. The first description in North America was in Medfield, Massachusetts, in 1806.[3] Further cases appeared in New England and Canada during the following decade. In 1887 Anton Weichselbaum described paired cocci inside white blood cells (WBCs) in cerebrospinal fluid (CSF) and named the organism *Diplococcus intracellularis,*[4] and the organism later was reclassified as *Neisseria meningitidis.*

Microbiology

N. meningitidis is a nonmotile, gram-negative coccus, usually appearing in pairs with abutting sides flattened. The genus *Neisseria* also includes *N. gonorrhoeae* and several commensal organisms, including *N. flavescens, N. lactamica, N. mucosa, N. sicca,* and *N. subflava.*

N. meningitidis has complex nutritional requirements but grows well on chocolate, blood, Mueller-Hinton, trypticase soy, and GC agar in a humidified environment at 35°C to 37°C. *N. meningitidis,* like *N. gonorrhoeae,* requires additional carbon dioxide for growth. The organism is highly susceptible to drying, cold, sunlight, and either high or low pH. *Neisseria* species are differentiated initially by biochemical characteristics. *N. meningitidis* can produce acid from glucose and maltose, but *N. gonorrhoeae* uses maltose alone. All neisseriae produce catalase and are oxidase positive.

The cell envelope of *N. meningitidis* has 3 layers (Fig. 125.1): a cytoplasmic membrane, a peptidoglycan cell wall, and an outer membrane that contains lipopolysaccharide (LPS), phospholipid, and outer membrane proteins(OMPs). Invasive meningococci also have a polysaccharide capsule surrounding the cell envelope that confers the capsular group, often termed the "serogroup," and reflecting the main typing method (i.e., serology, used before the availability of molecular typing). The recent appearance of invasive meningococcal disease in 1805 could indicate the acquisition of capsule genes in the last 200 years that have conferred virulence potential on an organism that previously was only a commensal, as well as survival advantages the precise nature of which remains obscure.

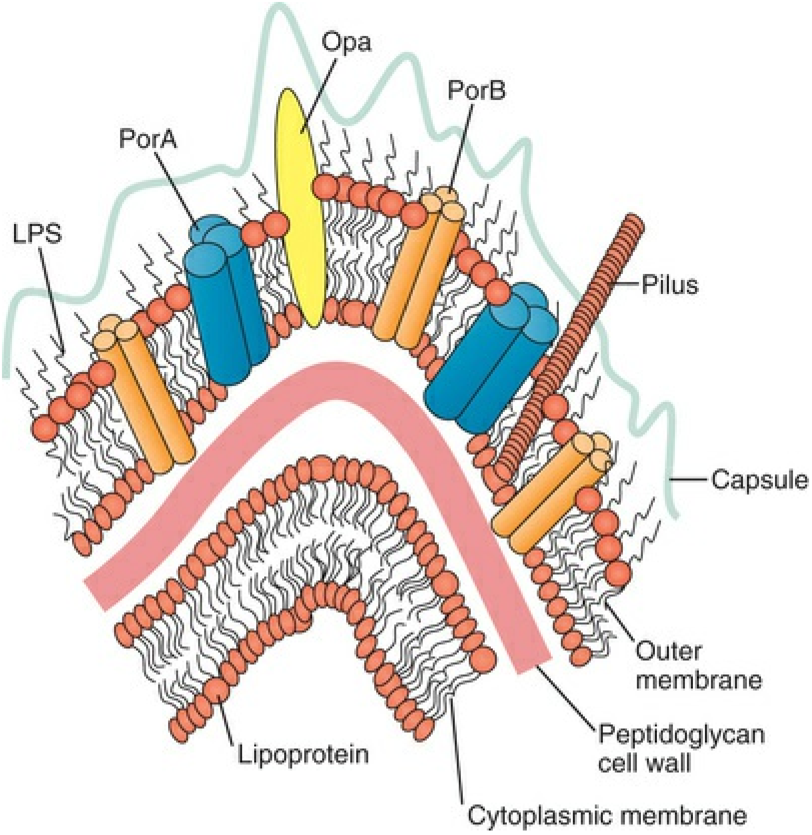

FIGURE 125.1 **Surface structures of *Neisseria meningitidis.* LPS,**

lipopolysaccharide; Opa, PorA, and PorB, outer membrane proteins.

(From Pollard AJ, Levin M. Vaccines for prevention of meningococcal disease. Pediatr Infect Dis J 2000;19:333–345, with permission.)

The antigen responsible for capsular group specificity is the capsular polysaccharide. Twelve different capsular groups of meningococci have been identified (A, B, C, X, Y, Z, 29E, W [formerly designated W135], H, I, J, and L), each with different saccharide subunits, but only 5 are commonly associated with disease: A, B, C, Y, and W (Table 125.1).[5] A sixth, capsular group X, has been associated with epidemics in sub-Saharan Africa. The other capsular groups are responsible for occasional sporadic cases, but these groups are isolated from asymptomatic carriers more commonly than from people with disease.

TABLE 125.1

Chemical Structure of Meningococcal Polysaccharide Capsules

Capsular Group	Chemical Structure
A	*N*-acetyl mannosamine-1 phosphate
B	α2-8 NANA
C	α2-9 NANA
29E	3-deoxy-D-manno-octulosonic acid
X	α1-4 *N*-acetyl-D-glucosamine-1 phosphate
W	Copolymer of NANA with galactose
Y	Copolymer of NANA with glucose

NANA, *N*-acetyl neuraminic acid.

Within each capsular group, serotypes and subtypes can be identified on the basis of differences in 2 OMPs, PorB and PorA, respectively, whereas the immunotype is defined by the LPS structure.[6] More recently, sero(sub)typing has been undertaken by molecular methods in view of the limited availability of serologic reagents.[7] With the advent of novel vaccines based on surface proteins, antigen-gene sequence typing is growing in importance to describe diversity and predict potential vaccine coverage. In addition to serologic and genetic differentiation based on surface antigens, related meningococcal isolates previously were described by differences in the electrophoretic mobility of cytoplasmic enzymes (multilocus enzyme electrophoresis [MLEE]) and more recently have been described by the genetic relatedness of strains using multilocus sequence typing (MLST),[8] which defines meningococci using sequence data from 7 housekeeping genes.

Using this method, 7 hyperinvasive lineages have been described that cause most cases of invasive meningococcal disease worldwide. With the availability of low-cost, high-throughput sequencing, routine whole-genome sequencing is now replacing these other typing methods.

Complete genome sequences were determined for several meningococcal isolates in 2000,[9,10] and these isolates were shown to contain a large number of repeating sequences. In addition, meningococcal genomes contain multiple insertion sequences that are responsible for the uptake of DNA from the microbial environment,[11] thus allowing the addition of new genes. For example, meningococci can acquire the capsular operon from another capsular group and switch to expression of the donor gene product (e.g., switch from capsular group B to capsular group C and vice versa).[11,12] Meningococci also import DNA at high rates from other commensal *Neisseria* spp. during mixed colonization in the nasopharynx.[13] Phase variation of surface structures during colonization and invasion can augment the foregoing mechanisms in helping evade host responses. Variability in the expression of immunogenic proteins may be important for persistence of the organism but has hampered vaccine development. However, sequence data from the meningococcal genome have been used to identify genes encoding potential vaccine candidates that are included in the most recent generation of meningococcal vaccines based on surface-expressed proteins.[14,15]

Virulence and Pathogenesis

The rare episodes of invasive meningococcal disease that occur probably do not provide any survival advantage for the meningococcus. It seems likely that the virulence factors associated with pathogenic meningococci have evolved as a result of a fitness advantage that they confer in the transmission-colonization cycle that describes the organism's normal lifestyle and in the polymicrobial environment of the human nasopharynx. The polysaccharide capsule enhances invasiveness by inhibiting phagocytosis but may also be important, for example, for avoiding desiccation during transmission. Immunoglobulin (Ig) A1 protease, a neutral endopeptidase with specific enzymatic activity against human IgA1, appears to enhance the ability of pathogenic *Neisseria* to colonize mucosal surfaces. The ability of pathogenic *N. meningitidis* to survive and multiply within the human host is facilitated by the organism's ability to extract iron from high-affinity iron-binding proteins by means of a non–energy-requiring cell surface mechanism.

Colonization involves a series of interactions between meningococcal surface structures (including pili and the OMP Opa) and specific ligands on the surface of cells in the nasopharyngeal mucosa of the human,[16–18] and it must precede invasive infection. Invasion of *N. meningitidis* through the nasopharyngeal mucosa into the bloodstream is incompletely understood, but it appears to depend on phase variation of meningococcal surface structures, including the capsule, and it results in the release of endotoxin (LPS) contained in blebs formed from the outer membrane during bacterial growth. A cascade of mediators is triggered in an inflammatory storm with interactions between LPS and CD14 and toll-like receptor 4 and between lipoprotein or peptidoglycan and toll-like receptor 2 at the core. The subsequent cytokine release (rather than direct tissue injury by microbial products) is thought ultimately to produce the features of septic shock in susceptible people. High levels of meningococcal LPS are found in severe meningococcal disease and correlate strongly with death.[19] Many different genes are involved in these responses, and various human gene polymorphisms have been associated with susceptibility to meningococcal infection or severity of disease.[20] Early in meningococcal disease high levels of tumor necrosis factor-α (TNF-α), soluble TNF-α receptor (sTNFR), interleukin-1 (IL-1), IL-1ra, IL-1β, IL-6, IL-8, IL-10, plasminogen activator inhibitor (PAI-1), and leukemia-inhibitory factor are detectable in blood, and elevated levels of many of these cytokines also have been associated with disease severity or fatality.[21] Indeed, the balance between these cytokines and their antagonists may influence the outcome of meningococcal disease.[22]

Although during meningococcal meningitis an inflammatory cascade of cytokines also is released in the subarachnoid space, the levels of these cytokines are not obviously associated with death.[23] Nevertheless, the inflammatory response is thought to mediate neurologic injury in meningococcal meningitis and can be suppressed by use of corticosteroids, although clinical data to support use of this adjunctive treatment for meningococcal meningitis are limited.[24,25]

Immunity

In 1918, Matsunami and Kolmer[26] demonstrated that the bactericidal activity of clotted whole blood from various laboratory animals was related to the resistance of these animals to infection with *N. meningitidis.* These investigators also demonstrated that the bactericidal activity of serum from adults was greater than that from children, thus providing the first link between serum bactericidal activity and the susceptibility of young children to meningococcal disease. Soon afterward, Heist and colleagues[27] found individual variation in the bactericidal activity of sera and individual susceptibility to infection. Unfortunately Heist's own serum contained inadequate bactericidal activity against meningococcus to protect him, and he died of invasive meningococcal disease before the publication of these observations.

Goldschneider and associates[28,29] are credited with firmly establishing the importance of the relationship between serum bactericidal activity (defined as killing of meningococci after mixing with serum and exogenous complement in vitro) and susceptibility to infection. These investigators showed in 1969 that susceptibility to invasion by a newly acquired strain of *N. meningitidis* was associated with the absence of bactericidal antibody against that strain,[28,29] an observation reconfirmed in 2000 during an outbreak in the United Kingdom.[30] This finding is further supported by the age-specific incidence of meningococcal disease caused by capsular groups A, B, and C, which correlates inversely with the age-specific prevalence of protective bactericidal antibody (Fig. 125.2).[29,31,32] Titers of antimeningococcal bactericidal antibody in a newborn infant are similar to those in the mother but decline after birth and reach a nadir at about 6 months of age, which correlates with the peak incidence of meningococcal disease at 5 to 9 months of age.

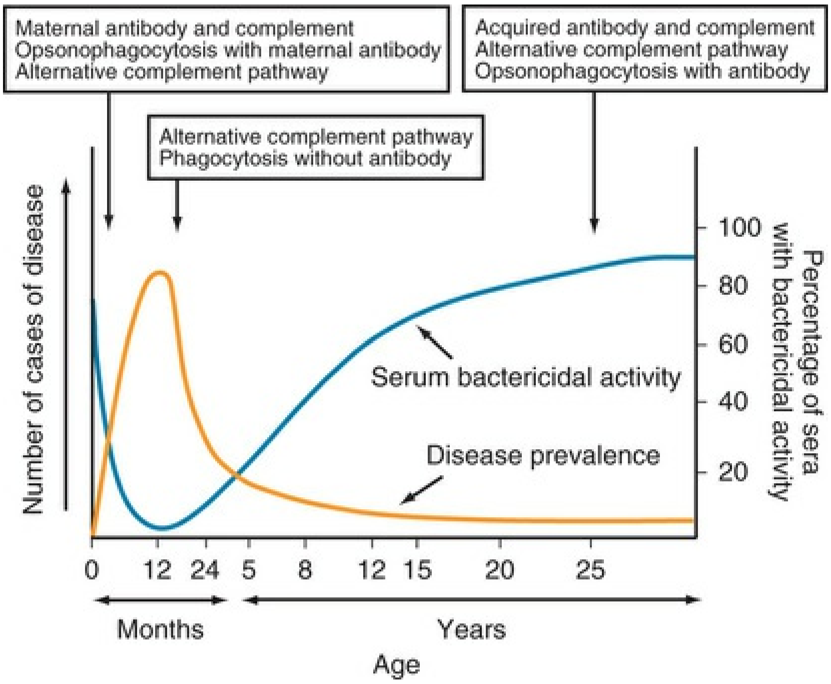

FIGURE 125.2 **Age-specific incidence of meningococcal disease contrasted with serum bactericidal activity.** (Modified from Goldschneider I, Gotschlich E, Artenstein M. Human immunity to the meningococcus. I. The role of humoral antibodies. J Exp Med 1969;129:1307.)

People with hypogammaglobulinemia may have a moderately increased rate of meningococcal infection.[33,34] Conversely, serum therapy was successfully used in the treatment of meningococcal disease before the advent of antibiotics. The mortality rate of untreated meningococcal disease fell from between 60% and 80% following the introduction of therapy using horse serum shortly after 1900 to between 13% and 30% in treated patients, depending on how promptly treatment was initiated.[35]

The bactericidal activity of immune sera requires the presence of both antibody and complement. Approximately 0.3% of patients with meningococcal disease have complement deficiency[36]; 50% of people with a late complement component deficiency (C5–C9) will develop meningococcal disease, and one half of these patients will have recurrent attacks, thus highlighting the importance of complement in defense against meningococcal infection.[37,38] These episodes usually occur in older age groups and often are associated with the less common capsular groups and only rarely with capsular group B disease.[36,39,40] A relative deficiency of late complement components is observed in infancy,[41] and this deficiency may add to the susceptibility to meningococcal infection in this age group. In contrast to people with terminal complement component deficiency, susceptible complement-deficient people who have either properdin or factor D deficiency have a case fatality rate of >50%, although recurrence is rare in survivors.[38,42,43]

In vitro opsonophagocytosis plays a greater role in killing capsular group B meningococci than A, C, Y, or W meningococci despite equivalent C3 binding to the surface of the capsular group B and Y organisms.[44] This finding may explain the relative resistance of complement-deficient people to capsular group B infection and their susceptibility to capsular group Y infection.

Some further data suggest that phagocytic function may be important in immunity against meningococci. Congenital impairment of binding by phagocytes of IgG2 also can predispose to invasive meningococcal disease. In one study, children with fulminant meningococcal disease were more likely than were healthy control subjects to have poor IgG2 binding by the opsonic Fc-γ receptor IIa, which is expressed by phagocytes.[45] The decreased binding results in marked reduction in phagocytosis of meningococci opsonized with IgG2, but not of those opsonized with IgG1.

During the first 2 decades of life, most people develop bactericidal antibody directed against the capsular polysaccharides and subcapsular structures such as OMP and LPS, and these antibodies are thought to mediate naturally acquired immunity.[46] Of the known surface proteins that are important in antimeningococcal immunity, PorA appears to be the dominant immunogen (with short surface exposed segments of loop 1 and 4 of the protein containing the immunogenic epitopes), but bactericidal activity mediated by these antibodies is largely strain specific.[47] Within 2 weeks of asymptomatic acquisition of a meningococcus, the titer of bactericidal antibody against the colonizing strain increases. Cross-reacting (i.e., non–strain-specific) antibodies are directed primarily against OMP and LPS antigens.

Natural immunity can develop as a result of asymptomatic colonization with meningococci or unrelated organisms bearing cross-reactive antigenic structures.[29,48] Carriage of pathogenic meningococci in early childhood is uncommon and therefore unlikely to be responsible for the induction of early natural immunity.[48] However, carriage of *N. lactamica* and of nontypable *N. meningitidis* is common and induces cross-reacting bactericidal antibodies against other strains of meningococci.[49] Enteric bacteria bear many similar surface structures that also can cross-react with meningococci. The *Escherichia coli* K1 capsular polysaccharide cross-reacts antigenically with capsular group B meningococci,[50] and *E. coli* K92 cross-reacts with capsular group C polysaccharide.[51]

The role of cell-mediated immunity in specific host responses to meningococcus is unclear. Lymphoproliferative responses to Opa, Opc, and PorA proteins of the bacterial outer membrane have been described,[52] and age-dependent differences in the cytokine response of peripheral blood mononuclear cells following infection have been observed.[53] Although age-dependent emergence of specific mucosal T-lymphocyte immunity to meningococcus has been demonstrated,[54] evidence also indicates that such responses may be relatively tolerant and therefore poorly protective in the mucosa.[55]

Epidemiology

Meningococcal disease has 2 largely distinct epidemiologic patterns: endemic and epidemic disease.

Endemic disease consists of isolated sporadic cases and occasional small clusters of cases that are associated temporally and geographically. This pattern appears to occur everywhere that disease surveillance performed, although baseline incidence rates vary markedly among different geographic areas within the approximate range 0.1 to 7 cases per 100,000 population per year.[56] In the 1990s disease rates in the United States were at approximately 1 per 100,000,[57] falling considerably since then to <0.2 per 100,000 (Centers for Disease Control and Prevention [CDC], unpublished data, 2013). The exception is in the Pacific Northwest,[58] where higher rates were reported in the late 1990s because of an increase in cases caused by hyperinvasive capsular group B strains. By contrast, during the 1990s in the British Isles, disease rates increased to >5 per 100,000, higher than in other regions of Europe,[59] largely because of a highly virulent clone bearing the capsular group C polysaccharide capsule[60] until the disease was controlled by vaccination from 1999 onward. Most cases of endemic disease occur during the winter season in temperate climates, which may reflect an association with respiratory viral infections.

Capsular group distribution varies with time and place. During the late 1990s a rising incidence of capsular group C disease in Europe and of capsular group Y in North America was reported.[61] Until recently, capsular groups B and C were the most prevalent capsular groups in most industrialized nations, but rates of group C disease fell following introduction of group C meningococcal vaccines in many countries in Europe and in Canada and Australia,[62] and group B meningococci now are the predominant cause of disease in these regions. In the US, serogroup B cases declined in the US to approximately 55 to 65 cases annually in young adults 11 through 24 years of age before the availability of capsular group B vaccines.[63,64] Capsular groups A and W previously caused only a minority of the cases of meningococcal disease in Europe and North America in recent decades, but a sharp rise in group W cases was observed in the UK from 2012.[65] By contrast, capsular group A was the most commonly isolated organism on both sides of the Atlantic during the periods after World Wars I and II and in various parts of Europe, including Finland, and in North America during the 1970s.[66] Capsular group A meningococci caused a significant amount of disease in New Zealand during the 1980s,[67] but these meningococci were replaced by high rates of group B disease from the early 1990s,[68] thus leading to a vaccine intervention program in 2005. Outbreaks of group A meningococcal disease in Russia[69] and Poland[70] highlight the proximity to western Europe of areas with high disease prevalence.

Epidemic meningococcal disease in Africa has occurred predominantly during the dry season in an east-west belt from The Gambia to Ethiopia below the Sahara desert, with cases declining at the onset of the rainy season.[71] Epidemics also have been reported in other developing countries, including China, Nepal, Mongolia, India, and Pakistan. Rates are far higher than endemic disease. For example, in a severe epidemic in Africa in 1996, attack rates of up to 1 in 100 people were recorded. The predominant capsular group is A, although epidemics of capsular groups C, W, and X have been recorded.[72–74] Epidemics of disease also have occurred in conditions of overcrowding,[75] and epidemics of groups A and W have been associated with the Hajj pilgrimage to Saudi Arabia, thus leading to a requirement for immunization before travel.[76]

Factors Influencing Disease Susceptibility and Severity

Susceptibility

Host and pathogen factors that determine susceptibility to and occurrence of meningococcal disease are summarized in Box 125.1. The most important host factor is age. The peak incidence of endemic meningococcal disease occurs in the first year of life, with 35% to 40% of cases occurring in children younger than 5 years of age.[1,57,77] A review of 807 cases of meningococcal disease occurring between 1992 and 1996 in the US found that infants <1 year of age had the highest incidence of disease, when all capsular groups were taken together.[57] The median ages for patients with disease caused by capsular groups B, C, Y, and W in this report were 6, 17, 24, and 33 years, respectively, an observation that may be important for vaccine programs designed for direct effects. Thirty percent of cases of group B meningococcal disease occurred in infants <1 year of age, compared with 14% of cases of disease caused by other capsular groups. Median age increases during epidemics.

Box 125.1

Risk Factors for Invasive Meningococcal Disease

Lack of bactericidal antibody to acquired strain

Age <1 year or 15–24 years of age

Crowded living conditions or close contact (poor housing, military barracks, students in dormitories)

Cigarette smoking, active or passive

Previous viral respiratory infection (especially influenza)

Inherited properdin or factor D deficiency

Inherited or drug-related terminal complement component deficiency (C5–C9)

Family or household contact of person with meningococcal disease

Other factors predisposing to meningococcal disease are overcrowding, poverty, cigarette smoking or exposure to cigarette smoke, previous viral respiratory tract infection, winter or dry season,[78] moving into new communities,[79,80] and certain immunodeficiencies.[81–88] In a case-control study, household smoking had an odds ratio for meningococcal disease of 4.1 (95% confidence interval [CI], 1.6 and 10.7).[82] In a study of military recruits, active or passive smoking raised the risk of carriage of *N. meningitidis*.[89] Coexistent colonization or infection with respiratory viruses and *Mycoplasma* species was associated with meningococcal disease in a study from Chad,[84] and previous studies have implicated influenza A as a predisposing factor.[85] People of low socioeconomic status also are more likely to be carriers and to develop disease.[90]

Deficiency of either antibody or complement increases the risk of meningococcal disease. Compared with the general population, inherited deficiency of properdin or of a terminal component of complement (C5–C8) increases the risk of invasive meningococcal disease by 250-fold and 600-fold, respectively,[91,92] as a result of impaired bacteriolysis even in the presence of specific antibody.[93] However, the proportion of all cases of meningococcal disease that are associated with complement deficiency is small. Patients receiving eculizumab (Soliris, Alexion Pharmaceuticals, New Haven, Conn), a monoclonal antibody used primarily for treatment of atypical hemolytic uremic syndrome, increases the risk of meningococcal disease including serogroup B.[94] Five of 326 subjects (1.5%) in clinical trials of eculizumab developed invasive meningococcal disease despite previous immunization with meningococcal conjugate vaccine.[94]

Indications for screening for complement deficiency by performance of total hemolytic complement activity assay are as follows: recurrence of meningococcal disease; chronic meningococcemia; endemic disease caused by capsular groups other than A, B, and C; and a history of a sibling with recurrent meningococcal disease. Routine screening of all patients with meningococcal disease for complement deficiencies probably is not indicated.[95]

Patients with terminal complement component deficiency should be vaccinated with the conjugated meningococcal vaccine, which reduces the risk of recurrent disease.[96] In addition, both patients and their families should be aware of patients' need for prompt medical care for acute febrile illnesses.

Studies of human single nucleotide polymorphisms have indicated various host factors that may be associated with susceptibility to invasive meningococcal infection, as reviewed by Emonts and coworkers.[20] Polymorphisms in Fc-gamma receptor II and III (CD32 and CD16) are more common in children with meningococcal disease, presumably as a result of reduced binding of IgG2 on the surface of phagocytes.[97] A multinational European study showed an excess of structural variants in mannose-binding lectin exon 1 in cases of meningococcal infection compared with controls,[98] and another study found that single nucleotide polymorphisms in factor H binding protein were associated with increased risk of disease.[99]

Seven families of genetically related *N. meningitidis* have been described (the hyperinvasive lineages) that account for a majority of the invasive infections.[8] These organisms appear to be genetically stable over time and across all geographic regions, a property indicating that they have adapted well to a particular life cycle of colonization and transmission that maintains the persistence of the clonal group. Acquisition of a hyperinvasive *N. meningitidis* increases the risk of disease.

Severity

Severity of meningococcal disease is related to host, pathogen, and other environmental factors. Large numbers of polymorphisms in human genes involved in inflammation, coagulation, and the immune response have been studied, and several associations have been reported (reviewed by Emonts and colleagues[20] and Texereau and associates[100]). Furthermore, some meningococcal clones have been associated with higher case fatality rates and more severe disease.[101]

The delivery of early and optimal medical care compared with late diagnosis and suboptimal medical care was associated with improved outcome in a study of deaths in the UK. Observations on changing case management in the UK suggest that early and rapid cardiovascular resuscitation (particularly volume replacement) may have more impact than early administration of antibiotics, at least in settings within an advanced healthcare system.[102–105]

Transmission and Colonization

Transmission of *N. meningitidis* occurs by means of respiratory droplets and requires close, direct contact. In a meta-analysis, carriage prevalence of *N. meningitidis* increased through childhood from 4.5% in infants to a peak of 23.7% in 19-year-old adults and subsequently decreased to 7.8% in 50-year-old adults.[106] Most strains recovered from carriers younger than 5 years of age are not encapsulated; carriage of encapsulated strains is uncommon until adolescence.[106,107] Capsular group B is the most frequently isolated capsular type in carriage studies from Europe (30%–40%), followed by capsular group Ys (10%–15%), C (5%–7%), W (3%–4%), and A (2%).[108,109] Studies conducted in the UK a decade after a high uptake conjugate vaccine campaign for all children and adults up to the age of 23 years in 2000 to 2001 demonstrated persistently low (although not nonexistent) rates of group C meningococcus carriage[110,111] in young people. Carriage rates of group C meningococcus also were low in the UK before immunization was begun, when group C cases were more frequent.[112]

Asymptomatic carriers are the most common sources of transmission, and evaluation of herd immune effects following introduction of group C meningococcal vaccines suggests that adolescents and young adults are the main vehicles of transmission for this capsular group in the population. Close contacts are the sources of acquisition in most individual cases. Disease is more correctly associated with acquisition than carriage because the incubation period is very short in most cases. Studies in military recruits show that illness often occurs within 48 to 72 hours of colonization.[113] During outbreaks of disease in military recruits, intense transmission occurs, so that 60% to 80% of recruits become carriers of outbreak strains within 6 to 8 weeks of starting basic training. High colonization rates have not been associated with disease outbreaks in semiclosed civilian populations, such as colleges and universities.[114,115] The highest carriage rates are detected at the beginning of the first term in the first year of higher education.[116]

When members of the households of patients with capsular group B or C disease are studied, 20% to 40% of contacts are found to carry the disease strain, and secondary cases of disease occur among close contacts at rates up to 1000 times higher than in the general population.[117]

With the introduction of group C meningococcal conjugate vaccine in the UK, which included a catch-up program in children and young adults as well as a rolling program for infants, carriage rates of groups A, B, W, and Y remained unaffected, whereas carriage rates of group C decreased from 0.45% to 0.15% in 15- to 17-year-old adolescents.[112] This study highlights the finding that colonization rates of disease-associated meningococci in the general population usually are <5%,[118,119] even during outbreaks in a college or school population.[120,121]

Few longitudinal studies have attempted to address duration of carriage. A study of group A stains in Africa suggested that the organism may persist in the nasopharynx for 3 months.[122] By contrast, the median duration of carriage of group B meningococci in another study was 9 months.[123]

Outbreaks

School-related outbreaks have been associated with capsular group B meningococci,[124] but most outbreaks have been caused by group C strains.[125–128] The first described outbreaks occurred in Canada in the late 1980s, but subsequent outbreaks related to schools, colleges, and universities have been reported from the US,[57,86] the UK,[120] Sweden,[129] Germany,[130] Spain,[131] Argentina,[132] and Australia.[133] More recent outbreaks caused by group B strains have occurred in universities in the US, thus prompting mass immunization campaigns and expedited licensure in the US of 2 meningococcal cell wall protein vaccines designed to protect against group B disease. The number of cases in each group B outbreak is small (<10), but in most outbreaks, the proportion of fatal meningococcemia among cases in 15- to 24-year-old patients is high.[86]

Risk factors for college and university outbreaks are summarized in Box 125.2. As in outbreaks among military recruits, the risk of non–group B disease is greatest in first-year college students, especially those living in dormitories.[120,134–136] Meningococcal carrier rates rise rapidly in the first few months after students arrive at college.[88] The highest carriage rates among first-year university students in the UK are during the first week of their first term.[116] These data and the higher age-specific incidence of disease in people 15 to 19 years old,[137] as well as the overrepresentation of people between 12 and 19 years of age in cases occurring in the school-related clusters in Canada and among freshman college dormitory residents in the US, suggest that adolescents transmit meningococci to one another.[86,125] Behaviors such as kissing, smoking, and prolonged duration of close contact in relatively small groups (at dances, parties, and bars, as well as in dormitories) may facilitate transmission of meningococci.[116,138,139] However, for unexplained reasons, no second adolescent peak in incidence is seen in some regions (e.g., Latin America).[140]

Box 125.2

Risk Factors Associated With Meningococcal Disease in College and University Outbreaks

Being a first-year student

Living in a dormitory

Attending a bar, nightclub, disco, or social function within 10 days before onset of the index case

Smoking

Intimate kissing

Although cases arising in college-related outbreaks account for only 3% of all cases in the US, the resulting disruption of college activities and the costs of outbreak management led the American College Health Association to recommend in 1997 that college health services alert students and parents about the risks of meningococcal disease and the benefits of vaccination. Following earlier recommendations concerning polysaccharide vaccine and following vaccine licensure in 2005, the CDC and the American Academy of Pediatrics recommended universal administration of quadrivalent conjugate meningococcal vaccine (MenACWY) to young adolescents (at 11–12 years of age), with catch-up immunization of students entering high school or 15-year-old adolescents and college freshmen who will be living in dormitories.[130] In 2010, the CDC and the AAP recommended a booster dose of MenACWY at 16 years for persons immunized at age 11 or 12 years to ensure persistence of protective levels of bactericidal antibody.[141]

Clinical Manifestations

The spectrum of clinical manifestations of infection with *N. meningitidis* ranges from asymptomatic carriage, the most common form of infection, to death within hours with fulminant meningococcal septicemia (meningococcemia). Meningococcal meningitis and septicemia are the most frequently reported clinical syndromes.

"Benign or unsuspected meningococcemia" has been observed in infants and young adults[142] with a clinical presentation of fever and signs of upper respiratory tract illness without toxicity, meningismus, or rash. Neither clinical features nor laboratory tests reliably distinguish febrile children with unsuspected meningococcemia (i.e., with fever but with no characteristic rash) from those without bacteremia.[143] Although some infants eliminate unsuspected meningococcemia without antibiotic treatment, two thirds of untreated cases progress to meningitis, fulminant meningococcemia, or other complications.[144]

Several clinical algorithms for assisting in the diagnosis and management of the child presenting with a fever and a nonblanching rash have been described,[145–149] but none has been fully, independently validated. These algorithms may enable the clinician to improve the specificity of the diagnosis, although loss of sensitivity for diagnosis of meningococcal disease could obviously have serious consequences.

The rash in all forms of meningococcal disease begins as macules, maculopapules, or urticaria but usually becomes petechial within hours. Large purpuric lesions evolve in severe cases, but some children who die of overwhelming sepsis may have no rash.

The more frequent clinical challenge is the child with fever and a petechial rash (Fig. 125.3). Only 2% to 11% of children with fever and a petechial rash have meningococcal disease; most of the remaining children have a viral illness, predominantly caused by enterovirus. Other viruses associated with petechiae include influenza and other respiratory viruses, parvovirus, Epstein-Barr virus, cytomegalovirus, and measles virus.[150–152] Petechiae or purpura also can occur with coagulation disorders such as congenital or acquired (after varicella infection) proteins S or C deficiencies.[153,154] Other disorders associated with petechial rash include platelet disorders (e.g., idiopathic thrombocytopenic purpura, drug effects, and bone marrow infiltration), Henoch-Schönlein purpura, connective tissue disorders, and trauma (including nonaccidental injury in children). The differential diagnosis of other invasive infection includes septicemia caused by pneumococci, streptococci, staphylococci, gram-negative bacilli, or rickettsia.[155,156] In the case of pneumococcal purpura fulminans, hyposplenism is an important association.

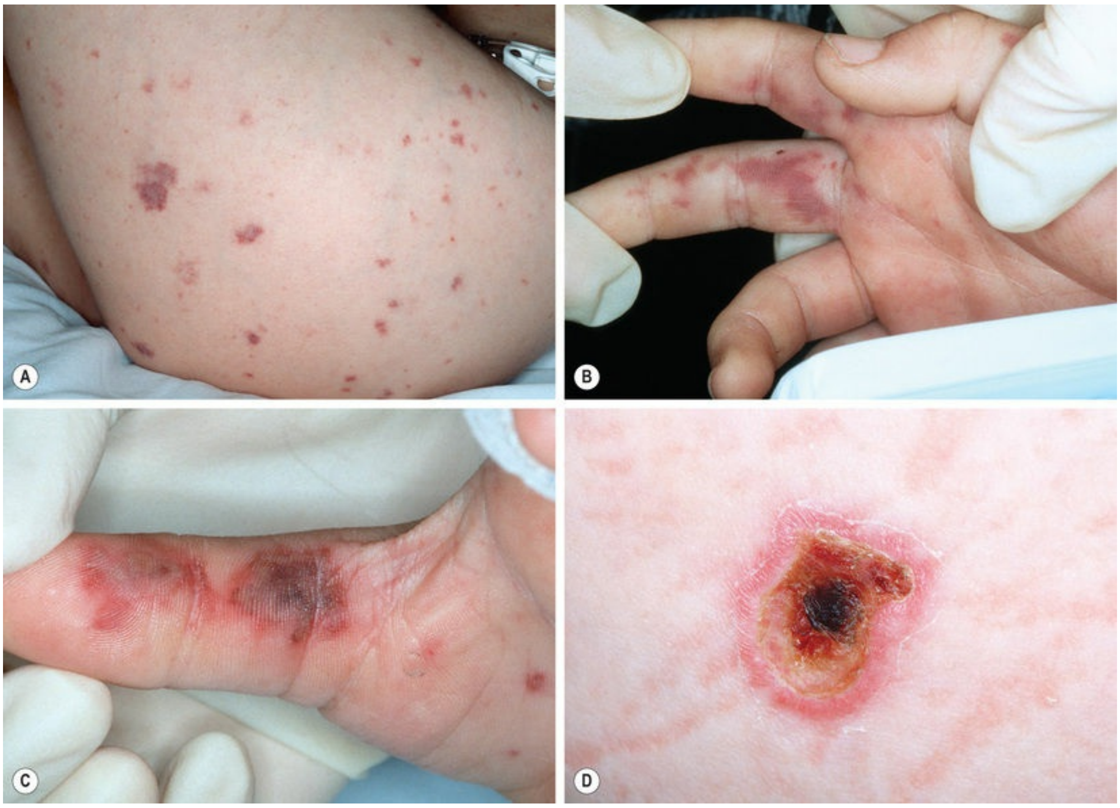

FIGURE 125.3 An 8-year-old boy had acute onset of fever, purpuric rash, and shock. *Neisseria meningitidis* was isolated from blood culture. He recovered. Typically, petechiae and purpura are most dense on (A) buttocks (day 1), lower extremities, and (B)

peripherally (day 1). (C) Tissue damage (day 4) and (D) necrosis (day 10) can ensue. (Copyright by J.H. Brien.)

Histologic analysis of skin lesions shows widespread endothelial necrosis of small veins and capillaries in the dermis and subcutaneous tissue, infiltration of neutrophils, and occlusion of damaged vessels with platelets, WBCs, fibrin thrombi, and hemorrhage.[157] Meningococci are present within the endothelium and thrombi.

Meningitis is the most common form of invasive disease and is associated with a petechial rash in two thirds of patients.[1] Headache, fever, vomiting, irritability, photophobia, lethargy, and neck stiffness can be present, and the Kernig sign can be positive in advanced cases in older children. Seizures occur in as many as 20% of cases, and mental state is altered as disease progresses. Many of the features of meningitis are not reported by younger children, and misery can be the dominant clinical feature. Infants can present with poor feeding, unconsolable irritability, a high-pitched cry, and a bulging fontanelle.

Meningococcal septicemia is a fulminant illness characterized by the onset of a nonspecific febrile illness followed within a few hours by rapid deterioration. Many deaths occur within 12 hours, and almost all occur within 48 hours, of onset. Initial symptoms include fever, headache, myalgia, shivering, cold hands and feet, and influenza-like symptoms and may be associated with vomiting and abdominal pain. Limb pain is a feature in some patients. Features of shock include tachycardia, poor peripheral perfusion, tachypnea, and oliguria. As shock progresses, cerebral perfusion decreases, resulting in alteration in mental status (confusion, agitation, or decreasing consciousness), multiorgan failure, and hypotension as a preterminal event.[126–161] The petechial rash can progress rapidly to purpura and ecchymoses.

Septicemia accounts for 15% to 20% of all cases of invasive meningococcal disease, but some patients also have a mixed picture of meningitis and septicemia. Septicemia is more common in infants and young children.[162,163] The case-fatality rate exceeds 40% in older case series, although more recent reports from specialist pediatric intensive care units in the UK showed improved survival; the mortality rate was less than 5%, with an emphasis on early correction of shock with volume replacement.[103] Many survivors lose extremities or extensive areas of skin as a result of vascular damage and peripheral ischemia and infarction.[164–166] Predictors of death and poor outcome include young age, absence of meningitis, presence of coma, absence of fever, and presence of hypotension, leukopenia, or thrombocytopenia.[167,168]

Less common manifestations of invasive disease are pneumonia, pyogenic arthritis, purulent pericarditis, myocarditis, endophthalmitis, conjunctivitis, primary peritonitis, and osteomyelitis. The incidence of meningococcal pneumonia is not known because the cause is confirmed only if blood or pleural fluid culture results are positive. Compared with patients who have meningitis or bacteremia caused by *N. meningitidis,* patients with pneumonia tend to be older (94.4% are >10 years old) and are more likely to be infected with less common capsular groups, such as W, Y, and Z.[77,169] Meningococcal conjunctivitis should be managed as invasive disease because topical therapy does not prevent invasion, and secondary cases can occur.

Chronic meningococcemia, first described in the early 1900s,[170] is a rare form of meningococcal infection, characterized by recurrent episodes of fever, rash, and arthralgia or arthritis and headache over weeks to months in association with bacteremia that often clears without treatment. The same strain usually is responsible for recurrent episodes, and the patient is well between attacks.[171,172] One study indicated that chronic meningococcemia was associated with the LpxL1 mutant strain that has a less toxic pentacylated LPS molecule.[173] Chronic meningococcemia can mimic acute rheumatic fever, bacterial endocarditis, anaphylactoid (Henoch-Schönlein) purpura, infectious mononucleosis, disseminated gonococcal infection, and immune-mediated vasculitis. The diagnosis is difficult because blood culture results are positive only if the specimen is obtained during a febrile episode. If not recognized and treated, chronic meningococcemia can progress to meningitis or acute meningococcemia. The pathogenesis of chronic meningococcemia is unknown, but inherited deficiencies of terminal components of complement have been found in some cases.[174]

Diagnosis

The diagnosis of meningococcal disease should be made clinically, and appropriate therapy should be instituted immediately. Microbiologic confirmation is important for public health control, to confirm antibiotic sensitivity, and to exclude an alternative diagnosis. Specimens from normally sterile sites (most commonly CSF) are inoculated onto chocolate agar and incubated in 3% to 5% carbon dioxide. Specimens from mucosal sites are inoculated on selective media (e.g., Thayer-Martin chocolate agar) to which vancomycin, colistin, and nystatin have been added to inhibit growth of competing microbes. Visualization of intracellular or extracellular diplococci on Gram staining of CSF, fluid from skin lesions, or the buffy coat of blood can provide positive results immediately. Scrapings or aspirates from skin lesions also can be used for diagnosis (Gram stain and inoculation onto chocolate agar).

Blood culture results may be positive in 40% to 75%, and CSF culture results are positive in 90%, of patients with meningococcal meningitis who have not received antibiotics. Some blood culture media contain sodium polyanethol sulfonate, which can inhibit *Neisseria* spp., and these organisms are very sensitive to a delay in transport to the microbiology laboratory or inoculation of CSF samples onto agar. Results of Gram stain of CSF are positive in 75% to 80% of patients with untreated cases of meningitis, and the test has a specificity of 97%. Combining results of blood and CSF cultures with those of the CSF Gram stain identifies 94% of cases of meningitis. Culture of blood, CSF, and skin lesions improves laboratory confirmation of disease. However, administration of oral or parenteral antibiotics before specimens are obtained reduces the rate of positive results of blood cultures to <10% and of CSF cultures to approximately 50% in patients who have meningitis.[163]

Detection of meningococcal antigen in CSF by latex agglutination can be useful in patients who previously received antibiotics, but the test has poor sensitivity and specificity, particularly for capsular group B, the predominant cause of the disease in most industrialized countries, and it is not recommended routinely if polymerase chain reaction (PCR) is available as an adjunct to culture.[175] PCR assays can detect meningococcal DNA in CSF, plasma, and serum.[176–178] PCR assays may use different amplification methods and gene targets[176,179]; optimal PCR systems are reported to have sensitivity and specificity of >90% and to permit diagnosis within 4 to 8 hours.[179,180] PCR is more sensitive than blood culture, and the proportion of laboratory-confirmed cases of meningococcal disease is increased by 30% to 40% when PCR is included in the investigation of suspected meningococcal disease because the assay is relatively less affected by previous antibiotic therapy.[181]

Lumbar puncture can be associated temporally with deterioration in some patients with meningococcal disease, and in patients with shock the procedure can compromise cardiovascular function.[182–184] Lumbar puncture is contraindicated in patients with cardiorespiratory insufficiency, raised intracranial pressure, coagulopathy, and extensive or spreading purpura and after convulsions until the patient's condition is stabilized. Lumbar puncture can be deferred until the patient's condition is stabilized, when abnormal CSF findings can confirm meningitis, and PCR can be used to confirm the cause.

Some patients come to medical attention in a coma, and computed tomography brain imaging may be helpful to exclude intracranial hemorrhage in patients in whom diagnosis is unclear. However, clinically significant raised intracranial pressure or cerebral edema may not be evident on computed tomography, and the decision to perform a lumbar puncture instead should be based on clinical assessment.[185,186]

Metabolic and Hematologic Abnormalities

In meningococcal meningitis, the CSF WBC count, the peripheral blood WBC count, and inflammatory markers (C-reactive protein, procalcitonin, and erythrocyte sedimentation rate) typically are elevated. Biochemical and coagulation test results usually are normal, but inappropriate antidiuretic hormone secretion can occur and lower the plasma sodium concentration. The CSF shows pleocytosis with raised protein, low glucose, and the presence of gram-negative diplococci.

In meningococcal septicemia, metabolic derangements are common and contribute to depressed myocardial function. Hypoglycemia, hypokalemia, hypocalcemia, hypomagnesemia, hypophosphatemia, and metabolic acidosis are present frequently in severely affected children and should be corrected.[105,187] Renal failure, anemia, and coagulopathy also can occur, and patients may have spontaneous pulmonary, gastric, or cerebral hemorrhage, particularly in the presence of thrombocytopenia. Because onset may be very rapid, normal or depressed WBC and normal C-reactive protein values are common initially. Protein C, fibrinogen, prothrombin, coagulation factors (V, VII, and X), and antithrombin levels typically are depressed. Tissue factor pathway inhibitor is raised. Coagulopathy can be corrected with fresh frozen plasma, platelets, and, in severe cases, cryoprecipitate, to prevent life-threatening hemorrhage.

Treatment

Antimicrobial Agents

Use of a third-generation cephalosporin, such as ceftriaxone or cefotaxime, for initial therapy of suspected meningococcal disease seems prudent because meningococcal strains that are relatively resistant to penicillin appear to be susceptible to these antibiotics (discussed later) and because third-generation cephalosporins also provide coverage for *Haemophilus influenzae* and most cases of *Streptococcus pneumoniae*. In geographic locations where penicillin-resistant cephalosporin-resistant pneumococci are prevalent, addition of vancomycin is recommended.

Prehospital antibiotic therapy is recommended in some countries, especially when any delay in transfer to hospital is likely. No high-quality studies, however, address the benefit of such an approach, and available observational data are conflicting. Urgent transfer to a hospital may improve outcome among patients with septicemia because fluid resuscitation appears to be the clinical priority.

For confirmed disease, ceftriaxone (80 mg/kg/day, maximum 4 g/day, in 1–2 divided doses, intravenously), cefotaxime (200 mg/kg/day, maximum 12 g/day, in 3–4 divided doses [50 mg/kg/dose], intravenously), penicillin G (50 mg/kg every 4–6 hours, maximum 2.4 g every 4 hours), or chloramphenicol (100 mg/kg/day, maximum 2 g/day, 4 divided doses orally or intravenously) is effective.[188] Ceftriaxone sterilizes the CSF more rapidly than does cefotaxime, ampicillin, or chloramphenicol ($P < 0.01$), although the clinical importance is unknown.[189] Many countries recommend penicillin for confirmed disease in view of its low cost and narrow spectrum, although penicillin, unlike the third-generation cephalosporins, does not clear nasopharyngeal colonization. Chloramphenicol is widely used and effective in resource-poor settings, and it is used elsewhere in patients with severe β-lactam allergy. One randomized controlled trial in Turkey found that necrotic skin lesions occurred more frequently with penicillin G therapy than with ceftriaxone ($P < 0.05$).[190] In the UK, ceftriaxone is recommended as definitive therapy for penicillin-susceptible organisms because it appears to be less expensive when administration costs are considered, and the long half-life and dose interval also make it easier for children who can complete treatment as outpatients.[36]

Emergence of strains with increased resistance to penicillin (i.e., with a minimum inhibitory concentration between 0.12 and 1.0 µg/mL) has been reported from Africa, the UK, Spain, Argentina, the US, and Canada.[191] Failure of penicillin therapy for meningitis caused by such strains is reported, but these strains remain susceptible to third-generation cephalosporins.[192] Resistance results from a genetic mutation that appears to have been acquired from avirulent *N. lactamica* or other *Neisseria* spp. through DNA transformation and causes alteration in penicillin-binding protein 2. The highest prevalence of penicillin resistance has been reported from Spain, where rates exceed 40%.[193] Although the frequency of penicillin-resistant *N. meningitidis* has increased in many parts of the world, the prevalence in the US remained unchanged at 3% between 1991 and 1997,[194] and it remained unreported in the Netherlands in 2012.[195]

Although the recommended duration of therapy for meningitis and meningococcemia is 7 days, no high-quality studies are available to support any specific duration of therapy. In some studies, treatment with penicillin, chloramphenicol, or ceftriaxone for 4 to 5 days appeared to be effective. Treatment with 1 or 2 doses of ceftriaxone or a long-acting oily suspension of chloramphenicol, in a developing country, was shown to be as effective as more prolonged therapy.[196–203]

The appropriate duration of therapy for meningococcal infections at other sites (bone, joint, heart, lung) has not been established, although descriptive evidence supports short-course treatment of arthritis[204]; nevertheless, patients with such infections should be treated at least until all clinical and laboratory signs of infection have resolved.

Adjunctive Therapy

The use of corticosteroid therapy for presumed meningococcal meningitis is controversial because no pediatric studies have had an adequate sample size to assess benefit, although benefit has been shown for other bacterial causes of meningitis.[205] Studies in developing countries do not show benefit from corticosteroid therapy in bacterial meningitis.[206] However, studies in adults in industrialized countries have shown benefit in all-cause meningitis and a trend toward benefit in meningococcal meningitis.[207] If used, dexamethasone can be administered in a dose of 0.15 mg/kg 4 times daily for 4 days.

No studies of high-dose corticosteroid treatment in children with meningococcemia or other types of shock have been conducted, but data from adult studies showed no benefit and the potential for harm. Studies of low (“physiologic”) doses in adults showed conflicting results, but some authorities believe that replacement doses (25 mg/m^2 hydrocortisone 4 times daily) may be useful in children who have refractory shock in association with impaired adrenal gland responsiveness; investigation in Europe is ongoing.[208,209]

Reduced concentrations of protein C have been found in the plasma of patients with meningococcal sepsis, and low levels are associated with an increased risk of death. Activated protein C inhibits both inflammatory and procoagulant pathways that are activated by the proinflammatory cytokines released in response to sepsis and reduces mortality rates in adults with sepsis.[210] Although small controlled trials showed increased survival in treated patients,[211–213] a randomized, placebo-controlled study of the use of activated protein C in children with severe sepsis failed to demonstrate apparent benefit in children with septic shock, and serious bleeding was a complication.[214] Protein C is therefore not recommended.

Recombinant bactericidal permeability-increasing protein (rBPI), which binds to endotoxin and blocks the inflammatory cascade, was studied in a randomized, multicenter, placebo-controlled trial, but the study was not sufficiently powered to assess a reduction in mortality rates adequately.[215,216] However, children who received rBPI had fewer amputations, decreased blood product transfusions, and improved functional outcome, and fewer children died who received a full 24-hour infusion of rBPI (2% rBPI vs. 6% placebo; P = 0.07).

Various other agents and other adjunctive therapies have been used or considered in the management of septicemia including fibrinolysis, extracorporeal membrane oxygenation, plasmapheresis, and antimediator therapy, but only the antiendotoxin antibody, HA1A, has been subjected to rigorous clinical trials and did not show benefit.[217] None of these adjunctive therapies currently are recommended.

Emergency Management

Pulmonary edema or poor pulmonary perfusion and hypoxia can be present in patients with meningococcal septicemia and requires elective endotracheal intubation during volume resuscitation. Intubation also is recommended if the patient is still in shock after 40 to 60 mL/kg of volume resuscitation because pulmonary edema is common during ongoing resuscitation. After securing the airway, the 2 clinical management priorities in children with meningococcal disease are correction of cardiovascular shock and control of raised intracranial pressure. Most patients die of decompensated shock, and a few die of raised intracranial pressure. Aggressive volume resuscitation and inotropic support to maintain tissue perfusion are critical to improving survival and minimizing sequelae in patients with fulminant disease and shock. Children with meningococcal septicemia may require fluid replacement volumes equivalent to or several times greater than their circulating blood volume. Fluid replacement should be administered initially as 0.9% sodium chloride solution in a volume of 20 mL/kg over 5 to 10 minutes and repeated until shock improves (reduction in heart rate and increased tissue perfusion). Human albumin solution (4.5%) is recommended as an alternative by many intensivists, but currently no data are available to guide the type of fluid to be used. If the child is still in shock after receiving 40 to 60 mL/kg of fluid, vasoactive therapy is required. Metabolic derangements, anemia, and coagulopathy should be monitored and corrected as appropriate. Renal support may be necessary. For the child with raised intracranial pressure, management should be directed at ensuring adequate cerebral perfusion by correcting coexistent shock and by providing neurointensive care. In patients with meningococcal meningitis without raised intracranial pressure or inappropriate secretion of antidiuretic hormone, volume resuscitation should be aggressive. No evidence supports the historical practice of fluid restriction in such cases, and one study found increased rates of neurologic sequelae among patients who had fluid restriction.[218] Analysis of the mechanisms of excess 48-hour mortality rates reported in children with severe febrile illnesses who were given fluid boluses in a randomized trial in Africa[219] indicates that death was not primarily caused by respiratory or neurologic events associated with fluid overload but by cardiovascular collapse.[220] Accordingly, fluid resuscitation and inotropic support remain the standard approaches to meningococcal shock in settings where close observation and intensive support are available.

An algorithm has been developed to assist direction of early management in both children and adults,[106,221] and updated versions are available from the Meningitis Research Foundation website (www.meningitis.org).

Outcome

Mortality

The overall case-fatality rate for invasive meningococcal disease is approximately 10%.[57,179,222,223] In a case series from the Netherlands,[224] the risk of death was higher in infants <6 months of age, adolescents, and adults >50 years of age (odds ratio, 5.1, 3.4, and 9.8, respectively) than in children 1 to 9 years old. The risk of death was greater among female patients (odds ratio, 2.3; 95% CI, 1.2 and 4.7).

Death or severe ischemic damage with extremity loss or extensive skin gangrene occurs much more commonly in fulminant meningococcemia than in meningitis. Optimized initial management and aggressive supportive care in the pediatric intensive care unit of the most severely affected patients have been associated with a reduction in mortality rates in this group of patients from a predicted risk of death of 25% to less than 5%.[136] With prompt and appropriate antibiotic and supportive therapy, patients with uncomplicated cases of meningococcal disease improve rapidly. Most patients with meningitis return to a normal state of consciousness within 2 days, are afebrile within 3 to 4 days, and show resolution of meningismus within 4 to 5 days.

Prognostic scoring systems have been developed that use presenting clinical signs and laboratory findings.[225–227] The first of these systems demonstrated that the combination of 3 or more of the following features was associated with a poor prognosis: (1) petechiae for less than 12 hours before presentation, (2) hypotension, (3) absence of meningismus, and (4) peripheral blood WBC lower than 10,000 cells/mm^3 and an erythrocyte sedimentation rate less than 10 mm/hr.[228] The Glasgow meningococcal septicemia prognostic score[229] has been widely used as a research tool but tends to overestimate mortality. The clinical utility of scoring systems has not been fully established.

Postinfectious Inflammatory Syndromes

Various immunologic or reactive complications, such as arthritis, cutaneous vasculitis, iritis, and pericarditis, can occur in patients with meningococcal disease from 4 days after the onset of invasive disease (after bacteriologic eradication). The mechanism is focal deposition of immune complexes containing meningococcal polysaccharide antigen, IgG, and C3 that results in acute inflammation.[230] All forms of reactive disease resolve spontaneously. Symptoms usually can be relieved by administration of acetylsalicylic acid or nonsteroidal anti-inflammatory agents.

The rate of reactive arthritis is 5% to 8%; reactive arthritis more often is reported in adults than in children, and it affects medium-sized joints preferentially.[231] Fever occurs at the time of onset of joint pain, and arthritis resolves within 6 to 10 days without residual damage. The onset of arthritis is associated with the disappearance of meningococcal antigen from the serum, a rise in antibody titer, and a drop in serum C3 concentration.[232]

Cutaneous vasculitis occurs in approximately 2% of patients, with onset 5 to 9 days after appearance of disease.[213] Small numbers of warm, red papules appear, mainly on the extremities, and they often progress to form bullae that rupture, leaving a shallow ulcer. Several crops of papules can appear over 2 to 3 days. Healing occurs without scarring in 4 to 8 days.

Inflammation of the iris or sclera occurs in approximately 1% of patients, often in association with reactive arthritis or vasculitis.[231] Reactive pericarditis, characterized by chest pain, pericardial friction rub, recurrence of fever, and sterile, nonpurulent pericardial exudate, also can occur.[233] Concurrent presence of polyarthritis and polyserositis is common. Pericardial effusion rarely leads to tamponade or requires drainage.

Sequelae

Rates of severe and moderate neurologic sequelae after 5 years are lower after meningitis caused by *N. meningitidis* (2.9% and 6.5%, respectively) than following meningitis caused by *H. influenzae* (3.4% and 7.3%, respectively) or *S. pneumoniae* (9.7% and 13.9%, respectively).[234] In 562 cases of meningococcal disease in the Netherlands, 8.5% of survivors had one or more sequelae, including deafness in 3.1%, motor dysfunction in 1.2%, and other neurologic deficits in 1.2%.[225] The frequency of sequelae did not vary significantly with the serogroup or serotype of the pathogen or with the sex or age of the patient. A review of 471 cases of invasive meningococcal disease in Quebec, Canada, between 1990 and 1994 demonstrated significantly higher rates of death (13.8% vs. 7.2%) and major complications such as skin scars and amputations (15.3% vs. 3.2%) in patients infected with group C than in those with group B meningococcal infection, respectively.[222]

Psychological problems are frequently reported, and neurologic deficits are found in 7% of patients.[36] It is important to perform follow-up auditory testing in all patients with meningococcal disease to identify hearing loss (rate of occurrence 2% to 15% of cases in various studies),[235] as well as to provide hearing aids and plan cochlear implantation as necessary in a timely manner.

Perfusion of the skin and muscle can be severely compromised in meningococcal shock, and areas affected by purpura and pressure areas can be necrotic and at risk of secondary infection. In one study, ischemic infarction of skin and soft tissues resulted in significant scarring or extremity loss in 3.9% of survivors, most often after fulminant meningococcemia.[225] Multiple areas are involved in most patients. The limbs are the predominant sites of damage. In a study of 21 patients with skin infarction, the lower limbs were involved in 20, the arms in 9, the trunk in 8, the face in 4, and the scalp and ear in 1 each.[236] The mean area of skin necrosis was 13% of total body surface area. Across several studies, skin damage or scarring was noted in 13% of cases.[36]

Limb compartment syndromes often are observed during the course of disease, and fasciotomy has been used in management in some circumstances, but its role is not established clearly.[237] Except in the presence of infection, amputations of ischemic limbs should be undertaken late to allow maximum limb recovery before lines of viability are finalized. Amputations are necessary in approximately 3% of cases, and a further 3% of patients have other orthopedic complications. With effective surgical treatment, rehabilitation, and support such patients can achieve a high quality of life; clinicians therefore should not be deterred from active management in the acute phase of the disease.[238]

Impaired organ perfusion results from hypovolemia, vasoconstriction, and myocardial depression resulting in prerenal failure in some patients, with oliguria or anuria or acute tubular necrosis. Most patients recover without any renal support, some require hemofiltration, and rarely permanent renal failure ensures.

Prevention

Management of Contacts

Household and kissing contacts of a patient with meningococcal disease are at significantly increased risk of meningococcal disease

(Box 125.3).[86,239,240] The incidence of disease in household contacts, although still low, is 500 to 1000 times that in the general population.[241] In sporadic cases of disease, 1% to 3% of households have 1 or more secondary cases of disease within 30 days of onset of the index case if no intervention occurs.[242] Approximately 20% of secondary cases are coprimary infections (i.e., occurring on the same day as the index case); 30% of secondary cases occur in the first week, 20% in the second week, and 30% in weeks 3 to 8 after the index case. Because of the rapid onset in 50% of related cases, early antibiotic prophylaxis when indicated, education, and close follow-up of contacts to ensure rapid intervention if they experience febrile illness are important. Culture of specimens from contacts usefully does not inform management.

Box 125.3

Contacts of a Patient With Meningococcal Disease Who Are at Increased Risk of Disease

Household members

Childcare center and nursery school contacts

School or college contacts during outbreak

Anyone directly exposed to a patient's oral secretions through mouth kissing or the sharing of food, drinks, utensils, glasses, water bottles, or anything that has been in the mouth of the patient

Healthcare personnel exposed directly to the patient's oral secretions through mouth-to-mouth resuscitation, or endotracheal intubation or tube management in the first 2 days of therapy without wearing a surgical mask[a]

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[a] Healthcare workers without such exposure are not at increased risk.

Adapted from Advisory Committee on Immunization Practices. Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2000;49:1; and Pollard A, Begg N. Meningococcal disease and healthcare workers. BMJ 1999;319:1147.

Trials of mass prophylaxis with sulfadiazine in military recruit camps during World War II suggested efficacy for eradication of carriage and interruption of epidemics. However, mass prophylaxis has not been effective in other situations,[243] and usually it is avoided. The emergence of worldwide resistance of capsular groups A, B, and C to sulfonamide drugs after 1963 led to the investigation of other agents for use in eradication of meningococcal carriage as a means of prophylaxis. Efficacy against all capsular groups has been noted for rifampin, minocycline, ceftriaxone, ciprofloxacin, and ofloxacin. Minocycline rarely is used for prophylaxis because of its high rate of adverse effects (dizziness, nausea, and vomiting).

Rifampin is the only agent that has been studied widely, but it has the following disadvantages: (1) the eradication rate is only 80% to 85%; (2) adverse effects occur in 25% of patients; (3) 4 doses are required; (4) rifampin is expensive and not readily available; and (5) a liquid suspension is not always available for children.[241] Moreover, emergence of resistance to rifampin can occur rapidly. Ceftriaxone, administered as a single intramuscular injection, has been shown to be >97% effective in eradicating carriage.[244] Additional advantages are single-dose therapy and safety during pregnancy. Disadvantages are the pain associated with intramuscular injection and potential adverse effects on mucosal flora related to broad-spectrum activity. Ciprofloxacin and ofloxacin effectively eradicate meningococcal carriage after a single oral dose.[245–248] However, fluoroquinolones are not approved for use in pregnant women, and the use of these drugs is restricted in children in some countries.

All contacts must be treated immediately and concurrently for maximal impact on secondary cases. Otherwise, untreated carriers could infect contacts who have already completed prophylaxis. Treatment of patients with index cases with ceftriaxone also eradicates carriage. Patients who are treated with antibiotics not known to eradicate carriage should receive appropriate prophylaxis before hospital discharge to prevent reintroduction of the pathogen into the household or community.

Details of prophylactic regimens are given in Table 125.2. Prophylaxis is not routinely recommended for the following: (1) school, church, or community contacts; or (2) medical personnel caring for the patient, except for those who have unusual, direct exposure to respiratory secretions through mouth-to-mouth resuscitation, or intubation or suctioning without wearing a mask.[249] Prophylaxis is recommended for infants and young children who have been in close contact with affected people in daycare centers.

TABLE 125.2

Chemoprophylaxis Regimens for Contacts of Patients of Meningococcal Disease

Antibiotic	Dose
Rifampin	10 mg/kg per dose (maximum dose 600 mg) PO every 12 hours for 4 doses (for infants <1 month of age, 5 mg/kg per dose)
Ceftriaxone	Single injection of 125 mg for <15 years and 250 mg for ≥15 years[a]
Ciprofloxacin	20 mg/kg (max 500 mg) >1 month of age[a]

[a] From American Academy of Pediatrics Committee on Infectious Diseases.

IM, intramuscularly; PO, by mouth.

Red Book: 2015 Report of the Committee on Infectious Diseases, 30th ed. Elk Grove, IL, American Academy of Pediatrics, 2015.

Immunization

Polysaccharide Vaccines

Vaccines composed of purified capsular polysaccharide of large molecular size have been developed against capsular groups A, C, W, and Y and have been formulated as monovalent A and C, bivalent A/C, and quadrivalent A,C,W,Y vaccines (PsACWY). The major vaccine-related determinants of immunogenicity are the molecular size and dose of the vaccine, and the major host factor is age.[250,251] Currently licensed vaccines contain 50 µg of each capsular group polysaccharide per dose. Vaccines are safe, with rare reports of serious systemic events.[251–254] Benign febrile seizures have been reported rarely in young children who have undergone vaccination with bivalent group A and group C vaccine.[255] Transient local reactions, such as erythema and tenderness, can occur at the site of injection. These reactions are more common after quadrivalent vaccine (30% to 40%) than after monovalent group A or C vaccines (8% to 10%).

In US adults vaccinated with PsACWY, bactericidal antibodies directed at group A and C polysaccharides peaked at 1 month, declined after 2 years, but remained higher than baseline for 10 years after vaccination.[256] In rural Nigeria, however, increases in antibody to group A polysaccharide were not sustained 2 years after vaccination.[257]

Protection induced by meningococcal vaccine is capsular group specific. Group A vaccine is effective in preventing disease in all age groups (Box 125.4). Two doses administered 2 to 3 months apart in infants 3 to 18 months of age (or 1 dose in older children and adults) have a protective efficacy >95%.[66,67] Group A vaccine appears to be effective in terminating epidemics of group A disease, although logistical challenges limit the impact of this approach. However, because duration of protection against invasive disease in adults does not appear to last more than 3 to 5 years, PsA vaccine is not recommended for routine use.

Box 125.4

Recommended Uses of Meningococcal Vaccines

Recommended Uses

Routine immunization of infants or toddlers with monovalent capsular group C meningococcal conjugate vaccine (MenC) recommended in some countries (currently not available in the United States) with booster doses increasingly advised in adolescence to maintain individual protection and herd immunity

Routine immunization of children at 11 or 12 years of age and with catch-up immunization of those through 18 years of age, using a quadrivalent conjugate capsular group ACYW vaccine (MenACYW), recommended in the US. Booster doses of MenACYW for adolescents advised in some countries with established MenC programs in early childhood.

Routine immunization of infants with MenB vaccine recommended in the United Kingdom (2-, 4-, and 12-month schedule) and some subcountry regions of Europe and Canada (2-, 4-, 6-, and 12-month schedule) (2 MenB are licensed currently in the US)

Immunization of at-risk populations for control of outbreaks caused by capsular groups contained in vaccine

Immunization with relevant meningococcal vaccines of travelers to an epidemic area (see Table 125.3 for US recommendations)

Routine immunization in high-risk setting with MenACWY or MenB vaccines, or both (see Table 125.3 for US recommendations)

Immunization of children with special high-risk conditions:

- UK recommendations: **Persistent complement deficiencies** at 9 months of age and children with **other high-risk conditions such as asplenia** at 2 years of age, with MenACWY in a 2-dose series 3 months apart. MenB vaccine also advised for these populations in some countries

- US recommendations: **Persistent complement deficiencies, functional or anatomic asplenia, HIV infection, or risk during a community outbreak attributable to vaccine serogroup** (beginning at 2 months of age for HibMenCY-TT [MenHibRix, GlaxoSmithKline, Philadelphia, Pa] or MenACWY-CRM [GlaxoSmithKline]; beginning at 9 months after primary pneumococcal conjugate vaccines for MenACWY-D [Menactra, Sanofi Pasteur, Swiftwater, Pa])

- **Travel to or residence in country where meningococcal disease is hyperendemic or epidemic** (beginning at 2 months of age for MenACWY-CRM and 9 months of age for MenACWY-D) (see Table 125.3 for US MenB recommendations)

Revaccination

Routine booster immunization of adolescents at 16 years of age who received MenACYW at 11 or 12 years of age or at 18 years of age for those who received MenACYW at 13 or 14 years of age. No booster recommended routinely for persons who received MenACYW at ≥15 years of age

Booster immunization of persons in high-risk groups every 5 years (with first booster after 3 years in those immunized at <2 years of age who continue to be at high risk of disease)

Recommendations for boosters of MenB vaccine pending

Contraindications

Severe reaction (anaphylaxis) to previous dose of vaccine

Immunization with the PsC vaccine has been >90% effective in preventing disease in young adults, and its routine use in the military eliminated outbreaks of group C disease.[258,259] However, PsC vaccine is poorly immunogenic in infants. Repeated doses of group C vaccine, unlike group A vaccine, do not cause an anamnestic response at any age. Indeed, 1 dose of PsC vaccine was shown to induce immunologic hyporesponsiveness to subsequent doses in infants, toddlers, and adults.[251,260–262] The duration and clinical relevance of such hyporesponsiveness are uncertain, but the phenomenon can last several years in recipients.[249,263]

Group Y and group W polysaccharide vaccines are immunogenic in children older than 12 to 24 months of age. Proof of efficacy has not been obtained, mainly because of the absence of epidemics caused by groups W or Y until more recent W outbreaks.[65,264,265]

The polysaccharide vaccines largely have been superseded by the glycoconjugate vaccines.

Conjugate Vaccines

Conjugation of group A, C, W, and Y polysaccharides to proteins such as CRM197 (CRM), tetanus toxoid (TT), or diphtheria toxoid (D) achieves similar or greater immunogenicity and duration of protection in infants, children, adolescents, and adults without increases in reactogenicity, compared with the much larger doses in plain polysaccharide vaccines.[260–268] Moreover, the conjugated vaccines induce immunologic memory,[261,263] unlike polysaccharide vaccines, and can overcome the hyporesponsiveness induced by previous doses of some polysaccharide vaccines.[262,269] Conjugated group C vaccines also have been shown to induce salivary IgG and IgA antibodies in infants vaccinated at 2, 3, and 4 months of age,[270] adolescents,[271] and young adults,[272] and general use of the vaccine is associated with reduction in carriage rates.[112]

Because of a significant rise in the incidence of group C disease, a mass immunization program was started in November 1999 in the UK with meningococcal conjugate C (MenC) vaccines from 3 manufacturers.[273] Vaccination was offered first to infants <1 year of age and adolescents 15 to 17 years of age, the age groups at highest risk. Subsequently, vaccine was offered to all children and young adults <24 years of age. The campaign was highly effective both as a result of direct protection of individual people and perhaps more as a result of community (herd) protection through reduction in transmission of the organism.[112,274,275]

MenC vaccines have been licensed and used in many other countries on the basis of the efficacy demonstrated in the UK, by using either a 2- or 3-dose infant schedule or a single-dose toddler schedule with a catch-up campaign.[62,276] Data from the UK show that persistence of antibody after primary infant immunization is poor, and effectiveness data indicate that protection wanes to 0 by 1 year after completion of the 3-dose infant schedule.[274] In response to this finding, the UK Department of Health announced the addition of a booster dose of MenC vaccine in 2006 to be administered in the second year of life. However, more recent studies suggest that persistence of functional antibody is poor even after this booster dose given at 1 year of age.[277] By contrast, persistence of antibody is more sustained after primary immunization of children who are older than 10 years of age.[278] Furthermore, a marked response to a booster and persistence of antibody occur for at least 1 year if the booster is administered beyond 6 years of age.[279] Booster doses in adolescents now have been implemented or are being considered in several countries with an infant MenC program. Vaccination of this age group appears likely to interrupt transmission of MenC bacteria, and thus introduction of boosters should maintain the community protection induced following the mass campaigns at the time of vaccine introduction. In a study of 53 people who developed invasive group C meningococcal disease despite receipt of MenC vaccine, antibody response to disease was consistent with an anamnestic response, a finding indicating that persistence of antibody may be a better correlate of long-term protection than priming for immune memory.[280]

In 2005, MenACYW-D (Menactra, Sanofi Pasteur, Swiftwater, PA) was licensed and recommended for universal use in the US in children at the age of 11 years.[139] Preliminary data from the CDC in 2010 indicated a vaccine effectiveness of 75% (95% CI, 17 to 93).[281] Cases of Guillain-Barré syndrome (GBS) occurring within 6 weeks of receipt were reported soon after implementation of MenACYW-D for adolescents. Ongoing investigations since then in the US, as well as surveillance in Canada, describe no excess cases or rare excess cases over that predicted, and most experts no longer consider GBS to be a risk of the vaccine.[282,283] MenACYW-CRM (GSK vaccines, Rixsensart, Belgium) was launched in 2010 in Europe and North America, and MenACYW-TT (Pfizer Vaccines, Pearl River, NY) is also available in some regions. In view of their immunologic advantages, the MenACYW conjugate vaccines should replace the plain polysaccharide vaccines for all indications in children and adults. MenACYW vaccines are recommended universally at 11 years and from 2 months of age for those at increased risk of meningococcal disease.[141]

Waning of bactericidal antibody following MenACWY immunization given at 11 or 12 years of age led to the US recommendation in 2010 for a second dose at 16 years of age, or at 18 years of age if the primary dose was given at 13 through 15 years of age.[141] In countries with established monovalent C conjugate vaccination programs in early childhood the quadrivalent MenACWY vaccine or the monovalent MenC vaccine is being introduced to overcome waning population immunity among adolescents, as described earlier. The former approach has the advantage of maintaining control of capsular group C disease and protecting the vaccinated teenagers from A, Y, and W infection while also inducing community protection to prevent disease caused by all 4 groups across ages.

Prospects for control of epidemic group A meningococcal disease in the meningitis belt of Africa have been enhanced by an alliance between the World Health Organization (WHO) and the Program for Appropriate Technology in Health (PATH) to develop a monovalent capsular group A meningococcal vaccine for Africa, funded by the Bill & Melinda Gates Foundation. Vaccine program implementation began across the meningitis belt of Africa during 2010, and results indicate a decline in disease among vaccinated populations.[284]

Development of a polysaccharide vaccine against group B meningococci, the major cause of endemic disease, is thwarted by the relative lack of immunogenicity of the B polysaccharide in humans.[285] Because B polysaccharide has structural and immunologic identity with sugars decorating the neural cell adhesion molecule, a membrane glycoprotein on human neurons in the developing brain, such antibodies have the potential to be autoreactive and thus harmful.[286] Field trials of a vaccine containing outer membrane vesicles (OMVs) (blebs of bacterial outer membrane containing OMPs, lipid, and LPS) derived from a Norwegian outbreak strain reduced the incidence of group B disease among schoolchildren aged 14 to 16 years by 53%.[287] A Cuban OMV vaccine from a local outbreak strain may have had somewhat greater efficacy in Cuba,[288] but it did not perform so well when tested in other settings against heterologous strains. OMV vaccines may have limited utility for endemic disease because the bactericidal antibody elicited appears to be limited largely to the immunodominant strain-specific PorA proteins. However, this property makes OMV vaccine ideal for control of an outbreak caused by a single clone, such as in New Zealand, in which a single group B clone caused a prolonged epidemic starting in the early 1990s. An OMV vaccine based on the outbreak strain was first used in 2004 with high apparent effectiveness,[289] and the program was discontinued in 2008. Since the vaccine campaign, most cases caused by the outbreak strain have been among unvaccinated people, a finding suggesting that the vaccine may still be providing some protection in the population.[290]

Development of a more comprehensive capsular group B vaccine has been an important public health goal, and many vaccine candidates have been considered over the past 3 decades, as reviewed by Sadarangani and Pollard.[291] Data from the genome-sequencing projects have provided information about novel vaccine candidates,[14] and 2 vaccines have been licensed by various regulatory authorities: a 4-component vaccine containing meningococcal factor H binding protein, neisserial adhesion A, neisserial heparin binding antigen, and the New Zealand outbreak strain OMV (MenB-4C); and a 2-component vaccine containing 2 variants of meningococcal factor H binding protein (2fHbp) (MenB-FHbp). Data from studies of these vaccines in adults and children indicate that the vaccines induce bactericidal antibody against strains bearing the antigens contained in the vaccine and provide in vitro evidence of potential cross-protection to other endemic strains of meningococci that contain and express variants of the vaccine antigens.[292–296] MenB-4C has been developed both for infants and adolescents (as with other meningococcal vaccines) and has waning of antibody after vaccination in early childhood, although this characteristic is variable among the vaccine components,[297–300] and persistence of immunity is better among adolescents. Some evidence indicated an impact of MenB-4C vaccine on carriage of the organism in the oropharynx in a study of university students, but uncertainty remains about whether this effect is sufficient to induce community protection.[110] MenB-4C (GSK) was introduced into the UK infant immunization program for all infants at 2, 4, and 12 months of age in September 2015, and it has been used for university and community outbreaks of disease in the US and Canada, respectively. Early data from the UK program indicate vaccine effectiveness (VE) of 82.9% (95%, CI 24.1–95.2) against all capsular group B disease in infants, which is presumed to be an underestimate of true VE since the vaccine is not expected to cover all circulating strains. Two group B meningococcal vaccines (MenB-FHbp [Trumenba, Pfizer, New York, NY] for a 3-dose series and MenB-4C [Bexsero, GlaxoSmithKline] for a 2-dose series) were licensed by the US Food and Drug Administration by an accelerated pathway in 2014 and 2015 for children and adults 10 through 25 years of age. The AAP and the CDC recommend use of MenB vaccine for high-risk groups (Table 125.3). The current low number of *N. meningitidis* B cases in the US makes universal recommendation of MenB vaccines cost prohibitive. Despite outbreaks of group B on US college campuses, the incidence of disease in college students (0.09 per 100,000) is similar to or lower than the incidence in all 18 through 23 year olds (0.14 per 100,000) (CDC, unpublished data), thus precluding a recommendation of MenB vaccine for college students alone.[94] Approval was based on clinical trial immunogenicity data rather than clinical efficacy.

TABLE 125.3

Increased Risk Groups Recommended for the Different Meningococcal Vaccine

MenACWY	MenB
Complement deficiency[a]	Complement deficiency[a]
Anatomic or functional asplenia[b]	Anatomic or functional asplenia[b]
HIV infection	
Outbreak caused by MenACWY[c]	Outbreak caused by MenB[c]
Microbiologists[d]	Microbiologists[d]
Travelers[e]	—
First-year college students[f]	—
Military recruits	—

[a] Inherited or chronic deficiencies of C3, C5-9, properdin, factor D, or factor H or eculizumab (Soliris) use.

[b] Includes sickle cell disease.

[c] The Centers for Disease Control and Prevention defines outbreaks and those at risk: http://www.cdc.gov/meningococcal/downloads/interim-guidance.pdf.

[d] Only microbiologists who routinely work with *Neisseria meningitidis.*

[e] To areas with hyperendemic or epidemic meningococcal disease.

[f] Unvaccinated or inadequately vaccinated first-year college students who live in residence halls.

MenACWY, quadrivalent meningococcal A, C, Y, W conjugate vaccine; MenB, meningococcal B vaccine.

Key Points

Diagnosis, Management, and Prevention of *Neisseria meningitidis* Infection

Microbiology

- Catalase-positive, oxidase-positive, piliated Gram-negative coccus that oxidizes glucose and maltose

- Outer phospholipid membrane contains endotoxin and various outer membrane proteins that are subject to phase variation.

- Can be surrounded by a polysaccharide capsule or acapsulate; 5 capsule “capsular groups” associated with most global disease: A, B, C, Y, and W

- Grows well on chocolate or blood agar; enhanced growth in humidified carbon dioxide environment

Epidemiology

- Highest rate of colonization (up to 40%) in adolescents and young adults; colonization rare in children <10 years of age

- Respiratory route of transmission

- Peak of disease in children <2 years of age and smaller peak in adolescence

- Risk of disease increased by smoking (active and passive), overcrowding, previous viral respiratory tract infection, winter or dry season, moving into new communities, complement deficiency, and various human single nucleotide polymorphisms.

- Capsular group distribution varies over time and with geographic location: B and C (where vaccine has not been introduced) account for most disease in Europe; B, C, and Y in North America; and capsular group A in Africa and Asia.

- In developed countries most cases are sporadic but small clusters can occur (mostly capsular group C strains). Epidemics of disease can occur (mainly capsular group A, with some X or W) in developing countries, especially the meningitis belt of Africa.

Clinical Features

- Four presentations, all of which are most often associated with a nonblanching (petechial or purpuric) rash:

- Meningitis with a mortality rate <5%
- Septic shock (meningococcemia or meningococcal septicemia) with a high mortality rate
- A mixed picture of meningitis and shock
- Bloodstream infection without shock or meningitis

- Death usually is caused by cardiovascular collapse in patients with septic shock or, rarely, by raised intracranial pressure in patients with meningitis.
- Complications include the following: a self-limiting inflammatory reactive syndrome; neurologic sequelae (including deafness). following meningitis; and limb, digit, and skin scarring or loss after septic shock

Diagnosis

- Microbiologic diagnosis usually is made by Gram stain of CSF or culture of blood (automated culture system) or CSF
- PCR of blood or CSF can yield higher rate of identification (especially with receipt of antibiotic before sampling)

Treatment

- Ceftriaxone is recommended as empiric therapy for suspected cases
- Urgent management of shock includes volume replacement therapy and supportive care (mechanical ventilation and inotropic drugs)
- Meningococcal meningitis should be managed with antibiotics and maintenance fluids with careful assessment for coexistent shock or raised intracranial pressure

Duration of Therapy

- Duration of therapy should be 5 to 7 days, but some studies suggest that as little as 1 dose of an appropriate antibiotic may be sufficient

- Response to therapy usually is rapid

Vaccine Prevention

- Monovalent capsular group C meningococcal conjugate vaccines (MenC) are widely used in Europe, Australia, and Canada for routine immunization of infants or toddlers and are highly effective, although more recent data suggest that an adolescent booster is required to maintain population immunity

- Quadrivalent meningococcal A, C, Y, W conjugate vaccines (MenACYW) are used routinely in North America for adolescent immunization and are now recommended in many countries for high-risk groups and travelers (as young as 2 months of age) and are being adopted to replace MenC as an adolescent booster outside the US

- Booster doses of MenACYW are recommended in the US for high-risk children and persons immunized at <15 years of age

- Capsular group B outer membrane vesicle (OMV) vaccines have been used successfully for outbreaks involving single clones but are not suitable for endemic, polyclonal disease

- Two novel capsular group B vaccines (MenB-4C, 2-dose series; MenB-FHbp, 3-dose series) aimed at broad capsular group B coverage have been licensed for people ≥10 years of age. Recommendations in the US are limited to at-risk patients and outbreak settings, and the vaccines can be given at 16 through 23 years of age at “clinical discretion”

CSF, cerebrospinal fluid; PCR, polymerase chain reaction.

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Neisseria gonorrhoeae

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Neisseria gonorrhoeae is a pathogen only of humans. Gonorrhea, one of the oldest known human illnesses, continues to result in significant morbidity; an estimated 106 million cases occur worldwide each year.[1] In the United States, gonorrhea is the second most frequently reported communicable disease after *Chlamydia trachomatis*.[2] The reader is referred to organism- or syndrome-specific chapters for the overall approach to genital tract infections. The major public health impact of the sexually transmitted infection (STI) gonorrhea is acute salpingitis, which is one of the leading causes of infertility in women around the world. Gonorrhea also is a potent amplifier of the spread of human immunodeficiency virus (HIV), by increasing rates of HIV sexual transmission up to fivefold.[3]

Microbiology, Virulence, Immunity, and Pathogenesis

N. gonorrhoeae, an oxidase-positive, gram-negative diplococcus, primarily infects columnar or transitional epithelial cells in the human genital tract. Transmission results almost exclusively from intimate contact, such as sexual activity or parturition. Adherence to mucosal epithelium is mediated by numerous gonococcal surface structures, including pili, opacity-associated outer membrane (Opa) proteins, and lipo-oligosaccharides (LOSs), and is followed by penetration of organisms between and through epithelial cells to submucosal tissue.[4] Cytokine release, which usually occurs in the process of invasion of male urethral cells, contributes to the symptomatic nature of gonococcal disease in men.[5] A neutrophil response follows, with subsequent sloughing of the epithelium, pus formation, and development of submucosal microabscesses. If infection is untreated, macrophages and lymphocytes eventually replace neutrophils, and hematogenous extension can occur. In contrast, subversion of host immune function can occur in women with uncomplicated cervical infection, resulting in a lack of antibody and interleukin production.[5] However, in a model of upper genital disease that uses organ explant culture of fallopian tubes, gonococcal endotoxin (lipopolysaccharide) impairs ciliary motility and contributes to the destruction of surrounding ciliated cells.[6]

N. gonorrhoeae has evolved multiple mechanisms to evade host immune responses, with resulting successful adaptation to variable microenvironments (e.g., the male urogenital tract, the female lower and upper genital tracts that also vary throughout the menstrual cycle, and the human bloodstream).[5] Although both humoral and local secretory antibodies to *N. gonorrhoeae* are induced during some uncomplicated infections, specific antibodies are rendered ineffective by antigenic variation of gonococcal surface molecules.[7] For example, the organism can perform the following functions: (1) turn on or off the synthesis or shift the expression of pili, Opa proteins, and LOS; (2) vary surface immunoaccessibility of porin (Por) and LOS antigens; (3) elicit antibody responses that are not protective (e.g., antibodies to the reduction-modifiable protein [Rmp] that block bactericidal activity of other antibodies against Por and LOS); and (4) alter LOS enzymatically by sialylation, thereby causing a loss of serum bactericidal activity.[8] The organism also resists clearance by neutrophil oxidative and nonoxidative killing mechanisms.[9] The exact role of host defense mechanisms in modulating infection or conferring immunity to reinfection is unclear because repeated infections are common.

Epidemiology

Approximately 820,000 new *N. gonorrhoeae* infections occur annually in the US.[10] In 2014, 350,062 US cases were reported; the incidence of reported disease rose from 98 cases per 100,000 population in 2009 (a historic low) to 111 cases per 100,000 population in 2014.[2] During 2010 to 2014, the rate among men increased 28%, whereas the rate among women decreased 4%. The magnitude of increase among men compared with the decrease among women suggests either increased transmission or increased case ascertainment (e.g., through increased extragenital screening) among gay, bisexual, and other men who have sex with men (collectively referred to as MSM). However, most jurisdictions do not routinely report the sex of the patient's sex partner or the site of infection for gonorrhea cases, so trends in gonorrhea rates among MSM over time cannot be assessed.[2] The highest incidence overall is among women and men 20 to 24 years of age (Fig. 126.1).[2] When data are examined by single-year age groups, in California, rates of infection are much higher in women 18 and 19 years of age than in women 15, 16, or 17 years of age; these findings indicate the potential for more targeted prevention and treatment efforts in settings serving older adolescents and young adults.[11] Prevalence continues to be highest in girls and women, in the 14- to 19-year-old age group, in non-Hispanic blacks, and in the residents of inner cities.[12,13] The risk of gonorrhea in adolescents and young adults is multifactorial, including an increased likelihood of multiple sex partners, unprotected sex, and susceptibility to infection as a result of cervical ectopy (in adolescent women), as well as less access to STI prevention services (lack of insurance or other ability to pay, lack of transportation, discomfort with facilities designed for adults, and concerns about confidentiality).[2,14] Additional risk factors include older sexual partners and substance abuse, particularly of alcohol and marijuana.[15,16]

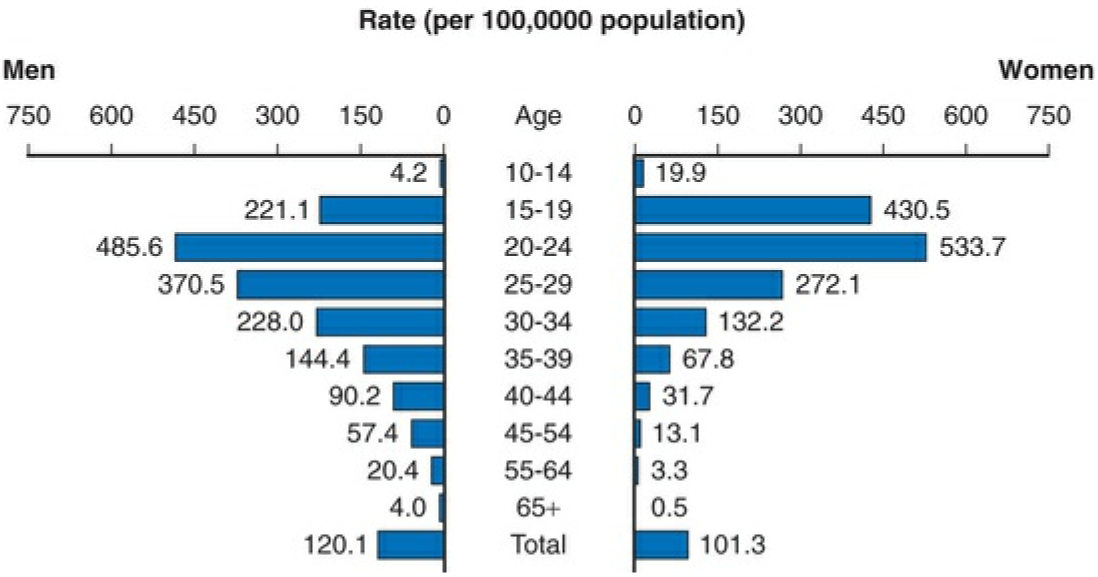

FIGURE 126.1 **Age- and sex-specific rates for gonorrhea, United States, 2014.** (From Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance. Atlanta, GA, United States Department of Health and Human Services, 2015.)

The likelihood of transmission of *N. gonorrhoeae* depends on the anatomic site exposed and the number of exposures. A man's risk of acquiring urethral infection after a single episode of vaginal intercourse with an infected woman is approximately 20%; the risk increases to 60% to 80% after 4 exposures.[17–19] The risk of male-to-female transmission has not been evaluated as thoroughly but is probably ~50% to 70% after a single contact, with little evidence that risk increases with multiple exposures.[19,20] The risk of transmission by rectal or oral contact is less well defined but is thought to be relatively efficient for insertive or receptive rectal intercourse. Pharyngeal gonorrhea can be acquired easily through fellatio, which may account for 26% of cases of urethral gonorrhea in MSM.[19] Oral sex is a highly prevalent practice among heterosexual young people, regardless of whether they have engaged in penetrative intercourse. As a result, pharyngeal gonorrhea has become increasingly prevalent, particularly among adolescents. In 2 Los Angeles STI clinics, 65% of patients between 15 and 24 years of age reported having oral sex; in this group, the prevalence of pharyngeal gonorrhea was 6% compared with 7% for urogenital gonorrhea.[21]

Prevalence in a community is sustained through continued transmission by asymptomatically infected people and also by a “core group” of transmitters who are more likely than the general population to become infected and to transmit *N. gonorrhoeae* to their sex partners.[22] Characteristics of core groups include demography (e.g., low socioeconomic status, geographic clustering in inner cities) and unique behavior (e.g., history of repeated gonococcal infections, drug use, multiple sex partners, prostitution, and failure to abstain from sex despite symptoms or knowledge of recent exposure).[23–26] Effective control efforts for gonorrhea must target both asymptomatically infected people and infected core group members.

Antibiotic Resistance

N. gonorrhoeae is facile at developing resistance to commonly used antimicrobial agents. The epidemiology, genetics, and mechanisms of resistance have been described.[19,27] Risk factors for antibiotic resistance include travel outside the community, high-risk behaviors, and recent antibiotic use, but these risk factors are not always identified in patients infected with resistant *N. gonorrhoeae*.[23–26,28,29]

The history of recommended antimicrobial therapy and development of resistance is well known. The organism has evolved to resist each single agent used formerly as first-line therapy. The emergence of cephalosporin resistance and the accompanying cephalosporin treatment failures worldwide[30–32] (though not yet in the US), prompted designation of *N. gonorrhoeae* as antibiotic resistance threat level "Urgent" by the US Centers for Disease Control and Prevention (CDC) because of the potential clinical impact, economic impact, incidence, 10-year projection of incidence, transmissibility, availability of effective antibiotics, and barriers to prevention.[33] The percentage of isolates with elevated cefixime mean inhibitory concentrations (MICs; ≥0.25 μg/mL) has varied between 0.8% and 1.4% in recent years of surveillance in the US Gonococcal Isolate Surveillance Project; elevated ceftriaxone mean MICs (≥0.125 μg/mL) have occurred in 0.1% to 0.4% of isolates, but no treatment failures have yet been identified in the US.[2] Although most definitions of cephalosporin resistance are based on ceftriaxone, important differences in susceptibility can exist across cephalosporins, thus precluding generalizability of cephalosporin susceptibility monikers. Resistance mechanisms include altered penicillin binding proteins, reduction of antimicrobial entry into cells, and active efflux. β-Lactamase has not been found in strains of *N. gonorrhoeae* that express relative cephalosporin resistance. Currently the only reliable method for detecting resistance to cephalosporins consists of isolation and susceptibility testing. Limitations of direct specimen testing using nucleic acid amplification tests (NAATs) are incomplete correlations among identification of specific mutations, MICs, and clinical outcomes.[27]

Clinical Manifestations

N. gonorrhoeae typically infects susceptible columnar or transitional epithelial cells (e.g., mucous membranes of the conjunctiva, pharynx, urethra, endocervix, and rectum). Infection often remains localized to the site of inoculation but can disseminate.

Perinatal Infections

Perinatal infection generally is acquired during passage through an infected birth canal, although transmission can occur after cesarean delivery, especially following premature rupture of membranes. Infant risks for infection include lack of appropriate ophthalmic prophylaxis, lack of maternal prenatal care, and maternal history of STI or substance abuse. An infant born to a woman with cervical gonococcal infection has an approximately 30% risk of acquiring ophthalmic infection,[34] versus a <5% risk if ocular prophylaxis is given.[35]

Ophthalmia Neonatorum

The usual incubation period for gonococcal ophthalmia neonatorum is 2 to 5 days, but onset can be as early as several hours after birth (following prolonged rupture of membranes) or as late as several weeks.[36] Prematurity and premature rupture of membranes are significant risk factors for gonococcal ophthalmia. The time of onset and clinical findings do not reliably distinguish *N. gonorrhoeae* conjunctivitis from *C. trachomatis* conjunctivitis.

Typical findings of gonococcal conjunctivitis are marked bilateral eyelid edema, chemosis, and copious purulent discharge. Asymptomatic infection or mild chronic infection with intermittent symptoms lasting for several months also has been reported.[37] Although gonococcal conjunctivitis generally is less severe in neonates than in adults, corneal complications, such as ulceration and perforation of the globe (rarely), panophthalmitis, and blindness, can occur.[38]

Other Perinatal Infections Including Systemic Infection

N. gonorrhoeae can be isolated from culture of pharyngeal swabs or orogastric fluid in approximately one third of infants with ophthalmia neonatorum.[39,40] Examples of neonatal mucosal infections include vaginitis (uncommon because neonatal vaginal mucosa is well estrogenized by circulating maternal hormone), urethritis, rhinitis, anorectal infection, and funisitis. *N. gonorrhoeae* scalp abscess can follow fetal electrode monitoring.[41,42]

Disseminated disease is rare in neonates; pyogenic arthritis is the most common manifestation.[43,44] Clinical symptoms typically develop at 1 to 4 weeks of age; pseudoparalysis is characteristic. Multiple joint involvement is common.[43] Most affected infants do not have concurrent or previous conjunctivitis or other mucosal infections. Skin lesions representing septic emboli of bloodstream infection (BSI), commonly seen in adults, are not described in neonates. Rarely, neonatal infection results in meningitis[45] or endocarditis.

Mucosal Infections in Children, Adolescents, and Adults

N. gonorrhoeae causes a variety of mucosal infections in sexually active adolescents and adults, as well as in sexually abused children. Transmission by fomites or through nonsexual contact is extremely rare.

In prepubertal children, gonococcal infection usually occurs in the genital tract, and vaginitis is the most common manifestation (the nonestrogenized alkaline vaginal mucosa permits colonization). *N. gonorrhoeae* infection should be considered in any girl with vaginal discharge, even when sexual abuse is not suspected. In a study of 43 girls <12 years of age with vaginal discharge, 9% had gonorrhea.[46] Sexual abuse must be considered strongly when gonococcal infection is diagnosed in prepubertal children (beyond the newborn period).[47] Among sexually abused children, pharyngeal and anorectal gonococcal infections are common and are often asymptomatic.[47,48] Gonococcal urethritis, perihepatitis, and pelvic inflammatory disease (PID) are uncommon but possible in prepubertal children.

Most men who come to medical attention with *N. gonorrhoeae* infection are symptomatic; asymptomatic or minimally symptomatic infections may be more common than appreciated but usually are recognized only through screening programs or after symptomatic infection in a contact.[49] In a cohort of men whose time of acquisition of the infection was defined, only 2.5% remained asymptomatic for 2 weeks.[19] However, certain phenotypes of gonococci have been more frequently associated with asymptomatic infection.[50] Acute urethritis is the major clinical manifestation in men, who complain of dysuria or note a mucoid or mucopurulent discharge 2 to 5 days after infection. The discharge often becomes profuse and purulent within 24 to 48 hours of onset.

Women are more likely than men to have asymptomatic infection or mild, sometimes unappreciated, symptoms. The endocervical canal is the predominant site of urogenital infection; urethral colonization also occurs in most cases in which the cervix is involved. The incubation period for urogenital infections in women is less certain and more variable, but in most symptomatic women, the symptoms develop within 10 days of infection.[51,52] Symptomatic female patients can have vaginal discharge, dysuria, abdominal pain, and intermenstrual bleeding; symptoms and signs range from mild to severe. The cervix can appear normal or can exhibit edema, erythema, or friability, as well as purulent or mucopurulent discharge.[53]

Pharyngeal infection occurs in approximately 3% to 7% of *N. gonorrhoeae* infections in heterosexual men and in approximately 10% to 20% of infections in heterosexual women or MSM.[54–56] Most pharyngeal infections are asymptomatic; rarely, acute tonsillopharyngitis or cervical lymphadenopathy occurs.[54,55]Pharyngeal infections can progress to disseminated gonococcal infection (DGI) if untreated.[57–60] Oral sex also has a role in sustaining gonorrhea in a population of MSM by providing a pool of untreated asymptomatic infections,[61] and it may account for as much as 34% of the population attributable risk for symptomatic gonococcal urethritis in MSM.[62]

Asymptomatic rectal infection is present in 26% to 68% of women with gonococcal cervicitis; translocation of infected secretions is thought to be the mechanism because rectal infection positivity correlates with duration of infection.[63,64] In MSM, rectal mucosa can become infected after receptive anal intercourse.[63] In contrast to MSM who experience a high proportion of rectal-only *N. gonorrhoeae* infections (≤86%), the rectum is the sole site of infection in a minority of women (≤44%).[65] Anorectal infection often is asymptomatic. If present, symptoms range from painless mucopurulent discharge and scant rectal bleeding to overt proctitis with associated rectal pain and tenesmus.[63,64]

Gonococcal conjunctivitis is rare in adults, usually results from autoinoculation, and occurs most often in people with anogenital infection. Untreated gonococcal conjunctivitis can progress rapidly to ulcerative keratitis and corneal perforation; however, mild or asymptomatic conjunctival infection also occurs. The outcome correlates closely with the severity of disease at the initiation of therapy.[66] Gonococcal conjunctivitis also has been described in prepubertal children without laboratory evidence or a suggestive history of sexual abuse.[67]

Disseminated Gonococcal Infection

Disseminated gonococcal infection (DGI), also known as the arthritis-dermatitis syndrome, is the most common manifestation of acute systemic gonococcal infection beyond the neonatal period. In the 1970s when gonococcal strains with a propensity to disseminate were common, DGI occurred in up to 3% of people with untreated mucosal gonorrhea[68–70]; DGI is much less common currently. DGI was described more commonly in women, with an onset within 7 days of the start of menstruation in approximately one half of cases[68–70]; however, more recent case series describe more male than female cases.[71,72] Certain strains of *N. gonorrhoeae* (uncommon in the US currently) are associated with disseminated infection. DGI strains often cause asymptomatic urogenital infection and typically, although not always, are penicillin G susceptible and resistant to the complement-mediated bactericidal activity of human serum.[69,70] Complement deficiency, which predisposes to gonococcal or meningococcal BSI, is found in up to 13% of patients with DGI.[73,74]

The characteristic findings of acute arthritis, tenosynovitis, and dermatitis, alone or in combination, result from intermittent BSI. Less than one half of patients with DGI have *N. gonorrhoeae* isolated from blood, joint fluid, skin lesions, or other sterile sites, but *N. gonorrhoeae* can be isolated from a mucosal site or from a sex partner in approximately 80% of cases.[68–70,75] Dermatitis occurs in approximately 75% of patients with DGI. The classic skin lesions are discrete, tender necrotic pustules on erythematous bases located distally on an upper extremity; macules, papules, petechiae, bullae, or ecchymoses also have been described. Results of culture or Gram stain of lesions are positive for *N. gonorrhoeae* in only approximately 10% to 15% of cases. Migratory polyarthralgia or tenosynovitis (especially in the flexor and extensor tendon sheaths) affecting smaller joints is an early finding. Pyogenic monoarticular or polyarticular arthritis develops later in approximately one third of patients; the wrist, metacarpophalangeal, ankle, and knee joints are involved most commonly.[68,69,70,75]

Gonococcal endocarditis is a rare complication, occurring in approximately 1% to 3% of patients with DGI.[68,69,76] The aortic valve is affected most often; valvular damage can progress rapidly if the disease is untreated. Hepatitis and meningitis are uncommon complications of DGI.

Laboratory Findings and Diagnosis

Laboratory confirmation of *N. gonorrhoeae* infection is essential in children because of the legal implications of potential sexual abuse. Confirmation also is critical in adolescents and adults to improve adherence to therapy and referral of sex partners.

Gram Stain

Gram-stained smears of exudate from the conjunctivae, endocervix of postpubertal girls and women, vagina of prepubertal girls, male urethra, skin lesions, synovial fluid, and cerebrospinal fluid can be useful, if results are positive, in the initial evaluation of patients with suspected gonococcal infection. Visualization of intracellular gram-negative diplococci (most often as multiple, kidney bean–

shaped diplococci within a relatively few neutrophils in the specimen) is presumptive evidence of *N. gonorrhoeae* infection; identifying only extracellular organisms is less specific in mucosal specimens. Compared with culture, Gram stain is 90% to 95% sensitive in urethral specimens from men with symptomatic urethritis but only 50% to 70% sensitive in endocervical specimens from women with uncomplicated gonorrhea.[19,77–79] Gram stain of pharyngeal or rectal specimens is not recommended because of a lack of specificity.

Culture

Isolation of *N. gonorrhoeae* by culture is critical to monitoring development of resistance to current antimicrobial treatment regimens.[80] *N. gonorrhoeae* does not tolerate drying; clinical specimens should be inoculated immediately onto appropriate culture media and incubated at 35°C to 37°C in an atmosphere of high humidity and 4% to 6% carbon dioxide. "Bedside" inoculation in a nutritive transport system (e.g., a polystyrene dish containing selective gonococcal media and an inner well containing a carbon dioxide–generating tablet) is helpful. *N. gonorrhoeae* grows well only on chocolate agar or similarly enriched media; media used for specimens from the urogenital tract or pharynx should contain antimicrobial agents (e.g., vancomycin, colistin, plus an antifungal agent) to inhibit growth of saprophytic organisms. Thayer-Martin and Martin-Lewis are the most commonly used enriched antimicrobial media. Sterile body fluids (e.g., blood, synovial fluid, cerebrospinal fluid) should be inoculated onto antibiotic-free, enriched media such as chocolate agar.

N. gonorrhoeae are oxidase-positive, gram-negative diplococci that use glucose but not maltose, sucrose, fructose, or lactose. *N. gonorrhoeae* can be distinguished from other *Neisseria* spp. and from *Moraxella catarrhalis* by carbohydrate use or by a nucleic acid confirmation test. Although specimens from urogenital infections generally give straightforward results, confirmation at a reference laboratory occasionally is necessary. Presumptive identification of *N. gonorrhoeae* from extragenital mucosal sites such as the pharynx should be interpreted with caution because of the expected presence of nonpathogenic *Neisseria* species; at least 2 confirmatory bacteriologic tests using different methodologies (e.g., biochemical and enzyme substrate) should be performed.[81,82]

The sensitivity of a single, properly obtained specimen inoculated onto selective media is >95% for male patients with symptomatic urethritis and 80% to 90% for women with endocervical infections. Obtaining a second endocervical specimen improves culture sensitivity in women.

Advantages of culture include low cost and availability of an isolate for further studies (e.g., antibiotic susceptibility testing or subtyping). Disadvantages include transport and growth requirements and a time delay of 24 to 72 hours from specimen collection to presumptive result.[80]

Nonculture Tests

The sensitivity of NAATs for the detection of *N. gonorrhoeae* at genital and nongenital anatomic sites is superior to culture but varies by NAAT and specimen type.[80] Product information inserts for each NAAT test must be read carefully because specimen types approved by the Food and Drug Administration (FDA) vary by test. NAATs are not FDA approved for use on specimens from the rectum, pharynx, conjunctiva, joint fluid, blood, or cerebrospinal fluid. Despite the lack of FDA approval, and to facilitate clinical management, many commercial and public health laboratories have established performance specifications to satisfy Centers for Medicare and Medicaid Services (CMS) regulations for FDA Clinical Laboratory Improvement Amendment (CLIA) compliance in testing and reporting results for nongenital specimens. Specificity is the key factor for performance because of cross-reaction with nongonococcal *Neisseria* spp. Advantages of NAATs include rapid turnaround time, flexibility in sampling source, and utility when transport problems preclude the use of culture.[80,83]

Use of NAATs performed on urine or other easily obtained genital specimens offers several advantages for detection of reproductive tract infection. Advantages include patients' preference (compared with speculum examinations of women and urethral swabs of men), the option of self-collection, and the feasibility of testing in settings where traditional genitourinary examinations are not performed, such as schools. For men, urine is the preferred sample for testing or screening because testing specimen of urine is more sensitive than urethral swab and has equivalent specificity.[80] However, NAATs can be less sensitive in women when the tests are performed on urine compared with genital (vaginal or endocervical) swab samples.[80] For women, vaginal swab samples are preferable to endocervical swabs for screening for *N. gonorrhoeae* by NAATs because of convenience and equivalent sensitivity and specificity. Endocervical swabs are acceptable when pelvic examinations are performed, but vaginal swab specimens are an appropriate sample type even when a full pelvic examination is being performed.[80]

For detection of rectal and pharyngeal infections, NAATs are superior to culture.[83–85] However, not all commercially available NAATs are equivalently specific (particularly polymerase chain reaction tests) for pharyngeal specimens or FDA approved, and results must be interpreted cautiously (see earlier).[80,83,84]

Data on the use of NAATs are limited in children, and performance depends on both sample site and the specific test. In a multicenter study of testing using strand displacement amplification or transcription-mediated amplification in children being evaluated for sexual abuse, sufficient data were collected from prepubertal girls to conclude that testing of urine samples using these 2 commercially available NAATs is a reliable alternative to vaginal culture for detection of *N. gonorrhoeae*.[86] However, culture still remains the recommended method for detection of *N. gonorrhoeae* in urethral specimens from boys and for extragenital specimens (conjunctiva, pharynx and rectum) from all children because NAATs have not yet been sufficiently evaluated for these populations and sample sites.[80]

Because accurate diagnosis is the goal, no justification exists for the routine use of less sensitive nonamplified test technologies such as nucleic acid genetic transformation, enzyme immunoassays, or nucleic acid hybridization probe assays.[80] Serologic assays for diagnosis or screening for gonococcal infection are neither recommended nor available.

Treatment

Management Considerations

The goals of antibiotic therapy are to relieve symptoms, reduce the risk of sequelae, eradicate infection, and halt transmission. Persons with suspected gonococcal infections should be treated empirically, before susceptibility test results of the isolate are known. Selection of an appropriate regimen requires consideration of local and national resistance patterns, anatomic sites of infection, likelihood of concurrent infections with *C. trachomatis* or another STI, side effects, and relative cost. Generally, ceftriaxone is the drug of choice for all gonococcal infections in the US, with dosing dependent on age and weight, and length of therapy varying by site and severity of infection (Table 126.1). On the theoretical basis that combination antimicrobial therapy using 2 agents with different mechanisms of action may enhance treatment efficacy and potentially slow the emergence and spread of resistance to cephalosporins, dual treatment with ceftriaxone combined with azithromycin is now recommended; this approach has added benefit for patients coinfected with *C. trachomatis*.[87] Further support for azithromycin as opposed to doxycycline as the second drug comes from the higher prevalence of tetracycline resistance (a proxy marker for doxycycline resistance) and the convenience and compliance of single-dose therapy. All persons diagnosed with gonorrhea also should be tested for *Chlamydia* infection, syphilis, HIV infection, and other STIs.[38]

TABLE 126.1

Recommended Treatment of Gonococcal Infections

Age Group	Infection	Treatment Regimen	Length of Therapy
Neonates	Ophthalmia neonatorum	Ceftriaxone[a] 25–50 mg/kg IV or IM once (max 250 mg) plus lavage of infected eye frequently until discharge eliminated	Once
	Disseminated infection Scalp abscess Septic arthritis	Ceftriaxone 25–50 mg/kg IV or IM every day *OR* Cefotaxime 25–50 mg/kg IV or IM q8–12h[b]	7 days
	Meningitis	Ceftriaxone 25–50 mg/kg IV or IM every day *OR* Cefotaxime 25–50 mg/kg IV or IM q8–12h	10–14 days
	Endocarditis	Ceftriaxone 25–50 mg/kg IV or IM every day *OR*	Minimum 28 days

		Cefotaxime 25–50 mg/kg IV or IM q8–12h	
Children ≤45 kg	Pharyngeal infection Anorectal infection Urogenital infection	Ceftriaxone 25–50 mg/kg IV or IM once (max 250 mg)	Once
	Conjunctivitis	Ceftriaxone 50 mg/kg IM once (max 1 g) plus lavage infected eye with saline solution	Once
	Disseminated infection Septic arthritis	Ceftriaxone 50 mg/kg IV or IM every day (max 1 g daily)	7 days
	Meningitis	Ceftriaxone 50 mg/kg IV or IM q12–24h (max 4 g daily)	10–14 days
	Endocarditis	Ceftriaxone 50 mg/kg IV or IM q12–24h (max 4 g daily)	Minimum 28 days
Adults, adolescents, and children >45 kg	Pharyngeal infection Anorectal infection Urogenital infection	Ceftriaxone 250 mg IM once *PLUS* Azithromycin 1 g PO once	Once
	Conjunctivitis	Ceftriaxone 1 g IM once *PLUS* Azithromycin 1 g PO once plus lavage infected eye with saline solution	Once
	Disseminated infection Septic arthritis	Ceftriaxone 1 g IV or IM every day	7 days
		PLUS	
		Azithromycin 1 g PO once	Once
	Meningitis	Ceftriaxone 1–2 g IV q12–24h	10–14 days
		PLUS	
		Azithromycin 1 g PO once	Once
	Endocarditis	Ceftriaxone 1–2 g IV q12–24h	Minimum 28 days
		PLUS	
		Azithromycin 1 g PO once	Once

[a] Cefotaxime should be substituted for ceftriaxone in neonates with hyperbilirubinemia (particularly neonates who are premature) and in infants <28 days of age if receiving calcium-containing intravenous fluids. Consult neonatal dosing references.

[b] Dose or dosing frequency change after postnatal age >7 days of life: consult neonatal dosing references.

IM, intramuscularly; IV, intravenously; max, maximum; PO, orally.

Return visits for test-of-cure cultures are not recommended for patients with uncomplicated urogenital gonorrhea who become or remain asymptomatic following treatment with a recommended or alternative regimen. However, anyone with pharyngeal gonorrhea who is treated with an alternative regimen should return 14 days after treatment for a test of cure using either culture or NAAT. If the

NAAT result is positive, effort should be made to perform a confirmatory culture before retreatment, with antimicrobial susceptibility testing of isolates.[88]

If symptoms persist after therapy, culture for *N. gonorrhoeae* should be obtained, and antimicrobial susceptibility testing should be performed. Symptoms of persistent urethritis, cervicitis, or proctitis also can be caused by *C. trachomatis, Mycoplasma hominis, Ureaplasma urealyticum,* and other organisms. Gonococcal infection detected after an appropriate course of therapy usually represents reinfection rather than treatment failure. Because infection occurs most commonly in patients who have been diagnosed and treated for gonorrhea in the preceding several months, patients with gonorrhea should be retested 3 months after treatment or whenever they seek medical care within the following 12 months.[38]

Gonorrhea is a reportable disease, and partner notification for evaluation and treatment is imperative to prevent reinfection of the index case patient, to eradicate large numbers of asymptomatic infections, and to interrupt transmission of the disease. In heterosexual adolescents and adults, expedited partner therapy (detailed later) should be considered.

Perinatal Infections

Infants born to mothers who have untreated gonorrhea are at high risk for infection and should be given a single dose of ceftriaxone intravenously (IV) or intramuscularly (IM), even in the absence of signs or symptoms.[38] Neither ocular silver nitrate nor topical antibiotic ointment (e.g., erythromycin, tetracycline) is adequate therapy for established gonococcal ophthalmia.[36] Infants with gonococcal ophthalmia should be hospitalized and disseminated infection should be excluded[82]; considering the rarity of gonococcal meningitis, most experts would not perform lumbar puncture in a well-appearing, afebrile infant.

Infants with uncomplicated ophthalmia neonatorum should be treated with ceftriaxone; additional topical therapy is unnecessary, but frequent saline irrigations are important.[82] Some physicians elect to continue ceftriaxone once daily until blood, joint, and cerebrospinal fluid (if obtained) culture results are negative at 48 to 72 hours. Ceftriaxone should be administered cautiously to infants with hyperbilirubinemia, especially preterm infants; cefotaxime is an alternative in these cases.[82] If DGI or gonococcal scalp infection is identified, ceftriaxone IM or IV daily or cefotaxime twice daily should be administered for 7 days. If meningitis is documented, the treatment course should be 10 to 14 days. No data are available regarding dual therapy for neonatal infection.[38,39]

The mother of an infant diagnosed with a gonococcal infection (and her sex partner) also should receive appropriate evaluation and treatment, and the infant should be evaluated for *Chlamydia* infection, syphilis, and HIV infection.

Mucosal Infections in Adolescents and Adults

Single-dose ceftriaxone 250 mg IM cures >99% of uncomplicated anorectal and urogenital infections and 99% of pharyngeal infections. Gonococci are eradicated from the urine, urethra, and semen of symptomatic men within 24 hours of therapy.[89] Azithromycin 1 g given orally in a single dose, as mentioned earlier, should be administered simultaneously with ceftriaxone for dual therapy for gonococcal infection, preferably under direct observation.

Gonococcal conjunctivitis should be treated with a single dose of ceftriaxone 1 g IM in combination with azithromycin 1 g orally; lavage with saline solution (once) should be considered.[38]

Alternative Regimens

If ceftriaxone is not available, alternative cephalosporins for uncomplicated anorectal and urogenital infection include oral cefixime or other single-dose injectable regimens (ceftizoxime 500 mg IM, cefoxitin 2 g IM administered with probenecid 1 g orally, or cefotaxime 500 mg IM). Although oral therapy avoids the cost and inconvenience of injections and decreases the risk of accidental needlestick injuries to medical personnel who may be treating a population at high risk of HIV infection,[89] the recommended 400 mg oral dose of cefixime does not provide as high or as sustained a bactericidal level as that provided by the ceftriaxone 250 mg IM. In published clinical trials, cefixime 400 mg orally cured 98% of uncomplicated anorectal and urogenital infections, but only 92% of pharyngeal infections.

As part of dual therapy, doxycycline should be given instead of azithromycin *only* if a contraindication to azithromycin (e.g., known immunoglobulin E–mediated allergy) exists, considering that gonococcal strains in the US with elevated MICs to cefixime are also likely to be tetracycline resistant but not macrolide resistant.[38]

A clinical trial of dual treatment of uncomplicated urogenital gonorrhea demonstrated that single doses of oral gemifloxacin 320 mg plus oral azithromycin 2 g were associated with cure rates of >99%, and dual treatment with single doses of intramuscular gentamicin 240 mg plus oral azithromycin 2 g cured 100% of cases. This trial was not powered to provide reliable estimates of the efficacy of these regimens for treatment of rectal or pharyngeal infection, but both regimens cured the few extragenital infections among study participants. Either of these regimens could be considered as alternative treatment options in the presence of cephalosporin allergy. However, gastrointestinal adverse events can limit their use: approximately 8% of patients treated with gemifloxacin plus azithromycin and 3% of patients treated with gentamicin plus azithromycin vomited within 1 hour of medication administration, thus necessitating retreatment with ceftriaxone and azithromycin.[90]

None of the other injectable cephalosporins offers any advantage over ceftriaxone for urogenital infection, and efficacy for pharyngeal infection is less certain. Other oral cephalosporins are similarly not recommended because of inferior efficacy and less favorable pharmacodynamics. Although cefpodoxime 400 mg orally, cefpodoxime proxetil 200 mg orally, and cefuroxime axetil 1 g orally all meet minimum efficacy criteria for alternative regimens for urogenital infections, efficacy in treating pharyngeal infections is unsatisfactory (estimated to be 70%, 79%, and 57%, respectively), and concerns exist about the pharmacodynamics of both the lower dose of cefpodoxime and the 1-g dose of cefuroxime axetil.[38]

Spectinomycin in a single 2-g dose IM may possibly be useful in persons who cannot tolerate cephalosporins (estimated efficacy 98% for uncomplicated urogenital and anorectal infections), but the drug is relatively expensive, must be injected, is not effective against pharyngeal gonococcal infection (estimated efficacy 52%) or incubating syphilis, and is not available currently in the US.[38,91,92]

Monotherapy with azithromycin 2 g orally as a single dose has been demonstrated to be 99% effective against uncomplicated urogenital gonorrhea.[93] However, monotherapy is no longer recommended because of concerns over the ease with which *N. gonorrhoeae* can develop resistance to macrolides and because several studies documented azithromycin treatment failures. The high rate of gastrointestinal symptoms associated with the 2-g dose also limits its usefulness. Azithromycin 1 g orally, the dose used for gonorrhea dual therapy, is not an appropriate alternative for monotherapy of gonococcal infection.[88]

Disseminated Infection Including Meningitis and Endocarditis in Adolescents and Adults

Hospitalization usually is recommended for initial therapy of DGI to establish the correct diagnosis and especially when purulent synovitis or another major complication is present. Azithromycin 1 g by mouth should be given as a single dose, and daily parenteral ceftriaxone should be administered until at least 24 to 48 hours after clinical improvement begins. Alternative agents include cefotaxime 1 g IV every 8 hours or ceftizoxime 1 g IV every 8 hours in addition to single-dose azithromycin. Switching to an oral agent (e.g., cefixime) can occur, once organism susceptibility is confirmed and if clinical improvement is substantial, for a total treatment course of at least 7 days. Patients with gonococcal meningitis or endocarditis should be treated with single-dose azithromycin plus parenteral ceftriaxone *twice daily*, for at least 10 to 14 days (see Table 126.1).[38]

Childhood Infections

Treatment regimens for children weighing >45 kg are the same as for adolescents and adults. In children weighing ≤45 kg, single-dose ceftriaxone (25–50 mg/kg IV or IM with a maximum dose of 250 mg IM) is recommended for treatment of uncomplicated vulvovaginitis, cervicitis, urethritis, pharyngitis, or proctitis; higher weight-based dosing (50 mg/kg) is used to treat conjunctivitis (as a single dose), as well as disseminated infections including bacteremia, arthritis, meningitis, and endocarditis (minimum 7 days; see Table 126.1).[38,82] No data exist regarding the use of dual therapy for treating children ≤45 kg with gonococcal infection.

Special Considerations

PID, a spectrum of inflammatory disorders of the female upper genital tract, can comprise any combination of endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis. Women who have gonococcal versus nongonococcal salpingitis are more likely to be febrile, to appear acutely ill, and to seek medical attention during the first 3 days of symptoms, although laparoscopic studies have shown that the severity of tubal disease is similar in gonococcal versus nongonococcal disease.[94] In PID, isolation of *N. gonorrhoeae* from the cervix does not necessarily mean that it is the sole pathogen. Acute perihepatitis (Fitz-Hugh–Curtis syndrome) can occur with gonococcal or chlamydial infections. PID is the most common complication of gonorrhea in women, and it occurs in approximately 10% to 20% of women with infection.[95,96] Even asymptomatic infections can progress to PID. Prevention of PID is critical because of potential long-term consequences: tubal infertility, ectopic pregnancy, and chronic pelvic pain.

Without treatment, gonococcal urethritis usually resolves spontaneously over several weeks, and >95% of untreated patients become asymptomatic within 6 months.[19] Most men with gonococcal epididymitis also have overt urethritis.[19] Epididymitis currently is an uncommon complication, and acute or chronic gonococcal prostatitis occurs rarely. Other unusual local complications of gonococcal urethritis include edema of the penis secondary to dorsal lymphangitis or thrombophlebitis, periurethral abscess or fistulas, seminal vesiculitis, and balanitis in uncircumcised men.

The manifestations of gonorrhea during pregnancy are not distinctive, except that pharyngeal infections appear to be more prevalent and PID probably is less common.[19,97] Reported complications in pregnancy include spontaneous abortion, premature rupture of membranes, premature delivery, intrauterine growth retardation, and acute chorioamnionitis, in addition to infection in the neonate.[19,97]

In immunocompromised people such as HIV-infected patients, the manifestations and sequelae of gonococcal infections are not different from or more common than in HIV-uninfected patients. However, nonulcerative STIs enhance HIV transmission by three- to fivefold, in part because of increased viral shedding by people with urethritis or cervicitis. Gonococcal infection also can increase the risk for acquisition of HIV, with the presence of significantly increased numbers of HIV-susceptible CD4$^+$ T lymphocytes and dendritic cells the hypothesized mechanism.[98]

Complement deficiencies, particularly of components involved in the assembly of the membrane attack complex (C5–C9), predispose to *Neisseria* BSI generally and are found in up to 13% of patients with DGI.[73,74]

Prevention and Control

Ocular Prophylaxis

Ocular prophylaxis with topical silver nitrate (1% aqueous solution), erythromycin (0.5%), or tetracycline (1%) ophthalmic ointment reduces the incidence of gonococcal ophthalmia neonatorum with equivalent efficacy.[82,99] Insufficient data exist to recommend 2.5% povidone-iodine for standard prophylaxis in the US.[38,100] Topically applied antibiotics are less irritating than silver nitrate but are slightly more expensive, and they have been associated with emergence of gonococcal resistance.[101] Silver nitrate and tetracycline ophthalmic ointment are no longer manufactured in the US, thus leaving erythromycin ophthalmic ointment as the only recommended agent for ocular prophylaxis.[10] Single-use tubes or ampules are recommended, and prophylaxis should be administered as soon as possible to all newborn infants after delivery.[38,82] If erythromycin ointment is not available, infants at risk for *N. gonorrhoeae* (especially those born to a mother with untreated gonococcal infection or who has not received prenatal care) can be given ceftriaxone 25 to 50 mg/kg IV or IM, not to exceed 250 mg, in a single dose. Properly administered ocular prophylaxis can fail to prevent infection acquired before delivery as a result of prolonged rupture of membranes or infection acquired after administration of prophylaxis. Prophylaxis does not eliminate neonatal nasopharyngeal colonization by *C. trachomatis*, and its efficacy for prevention of chlamydial ophthalmia is unclear.[38]

Partner and Expedited Partner Therapy

All sex partners within the 60 days preceding symptom onset or gonorrhea diagnosis (or, if none, the most recent sex partner) should be examined and treated presumptively.[38] For heterosexual patients whose providers are concerned about partners' access to prompt clinical evaluation and treatment, extended partner therapy (EPT) with cefixime 400 mg and azithromycin 1 g can be delivered to partners by the patient, a disease investigation specialist, or a collaborating pharmacy as permitted by law.[102] Randomized controlled trials demonstrated the safety and noninferiority of EPT versus traditional care in heterosexual patients.[103] The American Medical Association,[104] the American Academy of Pediatrics, the American Academy of Family Physicians,[105] the American College of Obstetricians and Gynecologists,[106] and the Society of Adolescent Health and Medicine[107] endorse EPT for heterosexual patients when in-person evaluation and treatment are impractical or unsuccessful. Partners, however, should be encouraged to seek clinical evaluation to optimize management of STIs. Because of the high risk for coexisting undiagnosed STIs including HIV infection in MSM, EPT is not considered a routine partner management strategy for this patient group.[38]

Screening as Prevention

Because gonococcal infections may not be associated with overt symptoms, particularly in women, annual screening of sexually active women <25 years of age and older women at increased risk for infection is important to prevent disease and sequelae.[38,108] These groups include the following: women who have a new sex partner, more than 1 sex partner, a sex partner with concurrent sex partners, or a sex partner who has an STI; use condoms inconsistently and are not in mutually monogamous relationships; have previous or coexisting STI; exchange sex for money or drugs; are members of a higher-prevalence population or living in an area of higher prevalence. Active gonococcal screening programs decrease the prevalence of *N. gonorrhoeae* infections. Although the US Preventive

Services Task Force has not defined high-prevalence area, a threshold of 4.75% has been cited as a level for cost-effectiveness for screening of women <25 years old who have risk factors (previous gonococcal infection, other STIs, new or multiple sex partners, inconsistent condom use, commercial sex work, and drug use).[109] Frequent rescreening in previously infected people is important; reinfection rate is high (median, 7% in male patients and 12% in female patients).[110,111] Sexually active MSM should be screened at least annually, preferably using NAAT on specimens (urine, rectal swab, or pharyngeal swab) from all sites involved in intercourse. More frequent STI screening at 3- to 6-month intervals is indicated for MSM if risk behaviors persist or if they or their sexual partners have multiple partners.[38] Screening only for urethral infections in MSM would miss up to 95% of gonococcal infections in asymptomatic MSM.[112] Pregnant women at risk or living in an area with high prevalence should be screened for *N. gonorrhoeae* infection at the initial antenatal visit. Those pregnant women found to have gonococcal infection should be treated immediately and retested within 3 months. At-risk patients (including those found to have gonococcal infection) should be screened again during the third trimester.[38]

Vaccination

Although understanding of the pathobiology and immunology of gonorrhea has advanced, limits to knowledge about what constitutes protective immunity, lack of a suitable animal model that mirrors human disease, and previous gonococcal vaccine trial failures have hampered vaccine development.[8,113] Multiple immunogens or adjuvants will likely be required in any *N. gonorrhoeae* vaccine to protect against diverse strains.[8,113,114]

Key Points

Diagnosis and Management of *Neisseria gonorrhoeae* Infections

Microbiology

- *Neisseria gonorrhoeae* is an oxidase-positive, gram-negative diplococcus.

- It requires chocolate agar or other enriched media and carbon dioxide for initial growth in vitro.

- Penicillin, tetracycline, and fluoroquinolone resistance is well described.

- Emerging cephalosporin resistance is identified worldwide.

Epidemiology

- Highest prevalence is in adolescents and young adults 15 to 24 years of age.

- Prevalence of gonorrhea in a community is sustained by continued transmission by asymptomatically infected people and by “core group” transmitters.

- Transmission is primarily sexual (oral, rectal, genital contact) or perinatal during deliver.

- Infection often is localized to the site of inoculation but can disseminate.

Diagnosis

- Most diagnoses are made by nucleic acid amplification testing of urine, or urethral, vaginal, cervical, rectal, or pharyngeal swabs.

- Maintaining culture capability to isolate *N. gonorrhoeae* remains critical as the only method to monitor development of resistance to current antimicrobial treatment regimens.

- Screening and rescreening of at-risk people (e.g., sexually active women <25 years, and men who have sex with men) is strongly recommended.

Treatment

- Ceftriaxone plus azithromycin is recommended therapy for most gonococcal infections because of enhanced treatment efficacy and potential slowing of the emergence and spread of resistance to cephalosporins.

- Susceptibility to other cephalosporins is variable (heterogeneous mechanisms of resistance).
- Sex partners within 60 days of onset of patient's symptoms should be examined and *treated presumptively*.

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Other *Neisseria* Species

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Currently 25 known *Neisseria* species have been isolated in humans and animals. *Neisseria gonorrhoeae* and *N. meningitidis* are the 2 pathogenic *Neisseria* species. Other *Neisseria* species are common commensal inhabitants of the upper respiratory tract and oral cavity of humans and other animals, but they have been implicated in clinical disease in occasional cases, particularly in immunocompromised patients.[1–3] The focus of this chapter is these *Neisseria* species, as well as species that previously have been misidentified as either of the pathogenic *Neisseria* species.

Microbiology and Laboratory Diagnosis

Neisseria species are gram-negative, oxidase-positive bacteria. All are catalase positive, except some strains of *N. bacilliformis* and *N. elongata*. All are diplococci, except *N. bacilliformis* and *N. elongata*. Whereas meningococci and gonococci require additional carbon dioxide for optimal growth and grow only at temperatures of 30°C to 37°C, the other species are less fastidious, growing without added carbon dioxide and at 22°C to 25°C. Unlike *N. gonorrhoeae* and *N. meningitidis,* the other *Neisseria* species (except *N. lactamica*) generally do not grow on selective media such as Thayer-Martin agar; LBVT.SNR medium is used to isolate commensal species.[4] Commensal and pathogenic species usually can be distinguished by biochemical and serologic tests. Carbohydrate use reactions, production of polysaccharide from sucrose, and reduction of nitrate are commonly used for identification (Table 127.1).[2–6] Difficulties in accurate identification of certain species resulted in some confusion and incorrect identifications in earlier published reports.[2]

TABLE 127.1

Selected Characteristics of *Neisseria* Species

Species	Morphology	Pigment	Polysaccharide Synthesis	Acid Produced From				Re of
				Glucose	Maltose	Sucrose	Lactose	
Neisseria gonorrhoeae	Diplococci	−	−	+[a]	−	−	−	−
Neisseria meningitidis	Diplococci	−	−	+	+	−	−	−
Neisseria bacilliformis	Bacilli	+	−	−	−	−	−	+/
Neisseria cinerea	Cocci in pairs or clusters	+/−	−	−	−	−	−	−
Neisseria elongata	Bacilli	+	−	+/−	−	−	−	−
Neisseria flavescens	Cocci in pairs or tetrads	+	+	−	−	−	−	−
Neisseria lactamica	Diplococci	+	−	+	+	−	+	−
Neisseria mucosa	Diplococci	+/−	+	+	+	+	−	+
Neisseria oralis	Cocci in chains	+	?	+/−	+/−	+/−	+/−	+
Neisseria polysaccharea	Diplococci	−	+	+	+	−	−	−
Neisseria sicca	Cocci in pairs or tetrads	+/−	+	+	+	+	−	−
Neisseria skkuensis	Cocci	+	?	+	−	+	−	−
Neisseria subflava	Cocci in pairs or tetrads	+	+/−	+	+	+/−	−	−

[a] Some *N. gonorrhoeae* strains are weak acid producers and may appear to be glucose negative.

+, strains typically are positive, but mutations lacking the specific enzyme activity are found occasionally; −, most strains are negative; +/−, strains are variable.

Epidemiology

Neisseria species commonly colonize the upper respiratory tract and occasionally the genital tract. In a study evaluating carriage rates of 2 *Neisseria* species in healthy infants and children, the prevalence of *N. lactamica* carriage was 3.8% at 3 months of age, peaked at 21% at 18 months of age, and declined to 1.8% by early adolescence.[7] In contrast, the rate of *N. meningitidis* carriage was 0.7% in the first 4 years of life and increased to 5.4% by early adolescence. Similarly, among 1400 healthy children 0 to 10 years of age in Turkey, 17.7% of these children were colonized with *N. lactamica,* whereas only 1.2% were colonized with *N. meningitidis.*[8] Similar results were found in a study of 1- to 29-year-old male and female study subjects in Burkina Faso.[9] Carriage of nonpathogenic strains can be important because *N. meningitidis* and *N. lactamica* share cross-reactive carbohydrate antigens; carriage of *N. lactamica* is likely associated with the development of "natural" immunity against *N. meningitidis*.[10] Cross-reacting antibodies to *N. meningitidis* were found in 66% of children who had asymptomatic colonization with *N. lactamica,* compared with 5% of children who were not colonized.[7] Moreover, inhibition of meningococcal carriage of multiple sequence types was demonstrated following nasal inoculation of *N. lactamica* into university students.[11] *N. lactamica*–based vaccines are being evaluated as a potential strategy to prevent meningococcal disease.[11–14]

Most adults are colonized, either densely or sparsely, by 2 or 3 *Neisseria* strains. For example, oropharyngeal cultures from patients in a clinic for sexually transmitted infections revealed *N. subflava* (biovar *perflava*) in >95%; *N. cinerea, N. mucosa,* and *N. subflava* (biovar *flava*) were found in 25%; and *N. lactamica* in 1%.[15]

Clinical Manifestations

Information on clinical disease caused by commensal *Neisseria* species is accrued primarily through case reports. Characteristics of various species of human origin and some infections caused by the organisms are briefly described here; species of animal origin causing human disease (e.g., *N. animaloris*, *N. canis*, *N. weaver,* and *N. zoodegmatis*) are not discussed. Antibiotic susceptibility testing should be performed on all clinically relevant isolates because some organisms are penicillin resistant secondary to β-lactamase production or altered penicillin binding proteins.

Neisseria bacilliformis.

Strains of *N. bacilliformis* grow as light grey colonies that resemble *N. elongata* on sheep blood agar or chocolate agar at 35°C with 5% carbon dioxide. *N. bacilliformis* is one of a few bacillary *Neisseria* species isolated from humans. *N. bacilliformis* does not produce indole, and reactions in catalase, nitrate reduction, and tributilin tests vary by strain. Sequencing of the 16S ribosomal RNA (rRNA) gene is the most reliable way to identify *N. bacilliformis*.[6]

N. bacilliformis predominantly causes infections of the oral cavity and respiratory tract in immunocompromised people, but cases of native valve endocarditis have been reported in previously healthy men.[16,17]

Neisseria cinerea.

N. cinerea grows as translucent yellow colonies that closely resemble *N. gonorrhoeae*. Misidentification as *N. gonorrhoeae* also can occur when these strains are grown on gonococcus-selective media (e.g., Martin-Lewis medium)[18] or when the Bactec (Becton, Dickinson, Franklin Lakes, NJ) radiometric system is used for detection of glucose use.[19] However, susceptibility to colistin and the ability to grow in trypticase soy broth or Mueller-Hinton agar are characteristics of *N. cinerea* and not *N. gonorrhoeae.*

N. cinerea has been isolated from the oropharynx and nasopharynx and, rarely, from the genital tract. Infections attributed to this species includes hospital-associated pneumonia, cavitary pneumonia and chronic cervical lymphadenitis in immunocompromised patients,[20–22] dialysis-associated peritonitis,[23] bloodstream infection, endocarditis, proctitis, orbital cellulitis, and conjunctivitis.[24–27] In some cases, the isolate was initially misidentified as *N. gonorrhoeae.*

Neisseria elongata.

N. elongata is rod shaped and elongates into filaments when exposed to sublethal concentrations of penicillin. Currently identified subspecies include *N. elongata* subsp. *elongata*, *glycolytica*, and *nitroreducens*, all of which have been reported to cause human disease. Multiple reports exist of *N. elongata,* particularly subsp. *nitroreducens*, as a cause of endocarditis,[28–35] and 1 case was associated with septic emboli and brain abscess.[36] Many of these infections followed dental procedures and occurred in people with preexisting heart disease; the infection frequently caused valvular damage that required surgical intervention. Other infections associated with *N. elongata* include bloodstream infection, osteomyelitis, and dialysis-related peritonitis.[29,37]

Neisseria flavescens.

N. flavescens, a yellow-green-pigmented strain, does not use carbohydrates. This species has been recovered in patients with meningitis, endocarditis, and necrotizing pneumonia with empyema.[38–40]

Neisseria lactamica.

N. lactamica resembles *N. meningitidis* in the following ways: colony morphology; growth on selective media containing vancomycin, colistin, and trimethoprim; and production of acid from glucose and maltose. *N. lactamica* is differentiated by its ability to produce β-galactosidase, which can cleave lactose to glucose; this process causes a color change when *o*-nitrophenyl-β-D-galactopyranoside medium is used.

N. lactamica colonizes the nasopharynx, especially of infants and children,[7–9] and rarely the genital tract.[41] *N. lactamica* has caused meningitis in infants and children, as well as in adults including 1 patient with cerebrospinal fluid leak secondary to fracture of the cribriform plate,[42–44] cavitary lung disease in an organ transplant recipient,[45] bacteremic pneumonia in a patient with cirrhosis,[46] and arthritis and septicemia with myeloma in a patient receiving corticosteroids.[47]

Neisseria mucosa.

N. mucosa is an encapsulated organism that forms large, colorless, moist, mucoid colonies on blood and chocolate agar. It can be differentiated from other species (except *N. oralis*) by its ability to reduce nitrate to nitrite and gaseous nitrogen. Reports of infection include postpneumonectomy empyema, endocarditis, purulent pericarditis, meningitis, peritonitis, and neonatal conjunctivitis.[48–56] In patients with chronic granulomatous disease, *N. mucosa* has caused pneumonia (a pulmonary coin lesion[57]) and visceral botryomycosis.[58]

***Neisseria oralis*.**

Seven strains of a novel *Neisseria* species were reported in 2013.[59] Colonies are small, circular, raised, moist, and yellow, and they are weakly α hemolytic on trypticase soy agar supplemented with 5% sheep blood. Cocci sometimes form chains. All strains reduce nitrate, produce acid from carbohydrates; some strains variably produce β-galactosidase and ferment lactose, characteristics formerly considered unique to *N. lactamica*.

N. oralis has been isolated from blood, subgingival biofilm, urine, and paracentesis fluid. 16S rRNA gene sequencing and DNA-DNA hybridization show similarity to *N. lactamica* but identify *N. oralis* as a novel species.[59] Additional analysis, including whole genome sequencing, indicate that *N. oralis*, although phylogenetically distinct, is most closely related to *N. mucosa*.[4]

***Neisseria polysaccharea*.**

Neisseria polysaccharea, a nonencapsulated *Neisseria* species, produces polysaccharide from sucrose and acid from glucose and maltose. Although its biochemical reactions are similar to those of *N. lactamica* and *N. meningitidis, N. polysaccharea* is distinguished by its unique production of polysaccharide. Some *N. polysaccharea* strains can grow on colistin-containing selective media (i.e., Thayer-Martin).[60] By matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS), *N. polysaccharea* can be misidentified as *N. meningitides*; verification should use biochemical methods.[61] The organism has not been implicated in disease, although its *absence* has been shown to be a risk indicator for periodontal disease.[62]

***Neisseria sicca*.**

N. sicca, a variably pigmented species, grows on agar in dry, wrinkled colonies but rarely grows on gonococcus-specific media because of its susceptibility to colistin. *N. sicca* colonizes the upper respiratory tract and can be responsible for inflammation of oral mucous membranes.[63] Ascribed infections include meningitis,[52] meningitis as a complication of ventriculostomy, or shunt endocarditis, endocarditis with spondylodiscitis, pneumonia, peritonitis, liver abscess complicating transcatheter arterial embolization, and vertebral osteomyelitis.[64–78]

Neisseria skkuensis.

N. skkuensis grows in light grey colonies on sheep blood agar and can be distinguished from most other *Neisseria* species by its ability to produce acid from glucose and sucrose only; it does not reduce nitrate. *N. skkuensis* has been associated with bacteremic diabetic foot infection[79,80] as well as with prosthetic valve endocarditis in an adult with cirrhosis who was undergoing hemodialysis.[81]

Neisseria subflava.

N. subflava, a yellow-pigmented species, grows in smooth and opaque colonies on selective (modified Thayer-Martin) agar. Common inhabitants of the respiratory and genitourinary tracts, the former species *N. subflava, N. flava,* and *N. perflava* have been reclassified as a single species, *N. subflava.*[2] *N. subflava* and *N. sicca* have identical patterns of acid production and similar pigmentation and can be misidentified.[82,83] *N. subflava* has been the cause of bacteremia with cutaneous nodules in an immunocompromised adolescent,[82] meningitis after intrathecal contrast injection,[83] and other rare cases of bloodstream infection, meningitis, endocarditis, epidural abscess-diskitis-vertebral osteomyelitis, and endophthalmitis.[84–91] In children, *N. subflava* can cause fulminant infection that is associated with a petechial or purpuric rash and results in death in approximately one third of cases. Thus, infection with *N. subflava* can be clinically indistinguishable from infection with *N. meningitidis,* and because the strains have similar fermentative patterns, identity can be confused without additional testing.[84]

Special Considerations and Prevention

Misidentification of “other” *Neisseria* species as *N. meningitidis* can result in the unnecessary administration of antibiotic prophylaxis and unwarranted concern in the community regarding potential spread of meningococcal infection. The misidentification of these species as *N. gonorrhoeae* can have important social and medicolegal ramifications, particularly in children.

Several studies have examined the potential role of commensal *Neisseria* as a reservoir for transferring β-lactam antibiotic resistance to pathogenic *Neisseria* strains.[92,93] A 25.2-md conjugative plasmid, similar to that isolated from *N. gonorrhoeae,* has been found in some tetracycline-resistant isolates of *N. meningitidis.* By contrast, some tetracycline-resistant strains of *N. subflava* and *N. mucosa* appear to carry the *TetM* determinant in the chromosome.[94] In addition, *N. subflava* isolates have shown broader resistance to penicillin, cephalosporins, or ciprofloxacin and may be involved in the emergence of resistant *N. gonorrhoeae* strains through horizontal genetic exchange of the *penA* gene.[95] Further studies and surveillance for changes in resistance patterns are important.

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Gram-Positive Bacilli

OUTLINE

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Arcanobacterium haemolyticum

Denise F. Bratcher

Arcanobacterium haemolyticum was first identified as *Corynebacterium haemolyticum* in 1946 in pharyngeal cultures of World War II soldiers and Pacific Islanders with pharyngitis that was indistinguishable clinically from infection caused by group A *Streptococcus*.

Epidemiology

Humans are the primary reservoir of *A. haemolyticum*, where the organism is found in the pharynx and on the skin. Although many studies reporting an association of *A. haemolyticum* with pharyngitis failed to exclude viral pathogens and *Mycoplasma pneumoniae, A. haemolyticum* has been implicated increasingly in association with pharyngitis (reported incidence of 0.3%–9.3%) and rash in older children and young adults, with an increased incidence reported among adolescents 15 to 18 years of age.[1] Multiple case reports document infection at pulmonary and extrapulmonary sites. A slight predominance in girls and women is noted among reported pharyngitis series, but a male predilection is noted in systemic *A. haemolyticum* infections.[2,3] Transmission occurs from person to person purportedly by droplet transfer[4]; the incubation period is uncertain.

Microbiology

A. haemolyticum is a gram-positive or gram-variable, pleomorphic, nonmotile, nonsporulating bacillus. It appears strongly gram positive in young cultures and becomes gram variable after 24 hours. Optimum growth occurs on human or rabbit blood agar and is enhanced in carbon dioxide; after 48 hours of incubation, colonies on horse or sheep blood agar (the preferred medium for throat cultures) are small (0.1–0.5 mm), with a narrow zone (1 mm) of hemolysis. A black, opaque dot appears at the center of each colony, and a tiny, dark pit remains if the colony is scraped aside. In clinical isolates, smooth and rough colonies have been noted.[5] *A. haemolyticum* resembles *Corynebacterium diphtheriae* on Löffler medium, whereas poor growth on tellurite medium and lack of catalase distinguish *A. haemolyticum*. The organism also ferments glucose and maltose, usually within 4 days. Production of a dermonecrotic toxin has been demonstrated.

Many cases of *A. haemolyticum* pharyngitis can go undetected because of the slow growth (≥72 hours) in culture and if streptococcal antigen testing is performed without a backup throat culture.

Clinical Manifestations

A. haemolyticum is reported most frequently in association with pharyngitis in people 10 to 30 years old. Most patients complain of mild fever and sore throat. Some have persistent or recurrent pharyngeal symptoms for weeks before diagnosis. Pharyngeal erythema is present universally, and tonsillar exudate is common, occurring in up to 70% of cases. Membranous pharyngitis mimics diphtheria.[6] Lymphadenopathy occurs in 26% to 81% of reported patients, primarily involving the anterior cervical or submandibular lymph nodes bilaterally.

An associated rash (only in patients with pharyngitis) was noted in 23% to 75% of cases reported, most frequently involving the extensor surfaces of the extremities, the neck, and trunk; face, palms, and soles typically are spared, although a single case report of vesicular lesions of the palms and soles exists.[4] The exanthem, commonly described as a scarlatiniform rash (erythematous, blanching fine papules), usually develops 1 to 4 days after the onset of sore throat, although rash has been noted before the development of pharyngitis.[6] Pruritus occurs in approximately 50% of patients, and urticaria and erythema multiforme have been described.[6] Mild desquamation of the skin on the hands and feet follows illness.

In both healthy and immunocompromised hosts, *A. haemolyticum* is the cause of sporadic invasive infections, including septicemia, endocarditis, septic emboli, jugular vein thrombosis (Lemierre syndrome), peritonsillar abscess, meningitis, brain abscess, pneumonia, pleural effusion, sinusitis, urinary tract infections, pelvic abscess, spontaneous bacterial peritonitis, and bone and joint infections.[7–28] Cellulitis, cutaneous abscesses, skin ulcers, wound infections, a paravertebral abscess, and paronychia also have been reported.[7,24,29–35] Chorioamnionitis caused by *A. haemolyticum* was reported in a 19-year-old mother who delivered a healthy infant.[36]

Most invasive *A. haemolyticum* infections that are reported among children also occur in adolescents. These infections include septicemia, brain abscess, pneumonia, empyema, peritonsillar abscess, thyroid abscess, sinusitis associated with orbital cellulitis, and membranous pharyngitis.[a] Endocarditis complicated by cerebral emboli was described in a young woman with congenital heart disease.[41] Septicemia has been reported rarely in adolescents with Epstein-Barr virus infections.[8,42] Coinfection of *A. haemolyticum* with *Fusobacterium necrophorum, Streptococcus agalactiae, Streptococcus milleri, Staphylococcus aureus, Bacteroides* species, *Veillonella* species, *Mycobacterium tuberculosis*, and *Mycoplasma pneumoniae* has been reported.[b]

Diagnosis

The diagnosis is made when *A. haemolyticum* is isolated from a clinical specimen. Pharyngeal isolates of *A. haemolyticum* can be confused with streptococci or *C. diphtheriae* or may be disregarded because colonies are confused with those of normal oral flora. Group A *Streptococcus* and other streptococci have been isolated concomitantly with *A. haemolyticum* from pharyngeal specimens. If *A. haemolyticum* infection is suspected, particularly in an adolescent or young adult with pharyngitis and exanthem, consideration should be given to inoculating agar containing human or rabbit blood or to holding cultures on sheep blood agar for ≥72 hours, in an effort to identify the small hemolytic colonies of *A. haemolyticum.* Use of trypticase soy agar with 5% horse blood in 5% carbon dioxide detected *A. haemolyticum* at 48 hours consistently in 1 study.[45] Modern techniques such as 16S ribosomal RNA (rRNA) amplification and gene sequencing, denaturing high-performance liquid chromatography (DHPLC), and matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) can provide more specific methods of identification.[3,34,41,46] Mild leukocytosis with neutrophilia is common. Biopsy of skin lesions shows only a mild lymphohistiocytic perivascular infiltrate.

Treatment

Neither the benefit of antimicrobial treatment of *A. haemolyticum* pharyngitis nor the comparative efficacy of therapeutic agents has been established in prospective, randomized clinical trials. In case reports, *A. haemolyticum* isolates are susceptible in vitro to penicillin, erythromycin, cefotaxime, cephalothin, chloramphenicol, clindamycin, and tetracycline.[47,48] Bacteriologic failure has been reported after penicillin treatment of pharyngitis and sinusitis,[49] although the significance of persistent colonization is uncertain. *A. haemolyticum* can invade respiratory epithelial cells, thereby potentially creating an intracellular reservoir; in the laboratory, erythromycin kills intracellular bacteria more efficiently than does penicillin.[50] Empiric therapy for pharyngitis with erythromycin or other macrolides is effective against *A. haemolyticum*.[51]

Anecdotal experiences with extrapharyngeal infections with *A. haemolyticum* typically report resolution with intravenous therapy with penicillin G. Tolerance of *A. haemolyticum* to bactericidal effect of penicillin is described among pharyngeal isolates in vitro.[47] Clinical significance of tolerance has been described in an *A. haemolyticum* strain causing endocarditis.[12] Minimum inhibitory concentrations by Etest (Biodisk, Sweden) of 10 invasive *A. haemolyticum* strains determined that all isolates were susceptible to penicillin, cephalosporins, macrolides, clindamycin, ciprofloxacin, and vancomycin but resistant to trimethoprim-sulfamethoxazole.[52] Resistance to ciprofloxacin, tetracycline, and vancomycin has been reported.[3,20,50] Suggested treatment options for pharyngitis include high-dose penicillin plus an aminoglycoside,[12] broad-spectrum β-lactam antibiotics, clindamycin, and macrolides.[9] Antimicrobial treatment of extrapharyngeal infections caused by *A. haemolyticum* is based on the susceptibility pattern of a specific isolate and testing for penicillin tolerance (or avoidance of β-lactam antibiotics).

Key Points

Diagnosis and Management of *Arcanobacterium haemolyticum* Infection

Microbiology

Gram-positive or gram-variable, pleomorphic, nonmotile bacillus

Grows best on human or rabbit blood; enhanced growth in carbon dioxide

Requires ≥72 hours to grow in culture on sheep blood agar and can be missed in routine handling of throat cultures

Epidemiology

Implicated increasingly in association with pharyngitis and rash

Increased incidence reported among adolescents compared with young children

Clinical Manifestations

Typical presentation: sore throat, mild fever, and an erythematous papular rash

Examination reveals: pharyngeal erythema (often with exudate), cervical lymphadenopathy, (frequent) and scarlatiniform rash (frequent)

Causes occasional sporadic invasive infection in healthy and immunocompromised hosts

Coinfection with other respiratory pathogens reported

Diagnosis

Recovery in culture from clinical specimens

Consider holding cultures on sheep blood agar for 72 hours or inoculating onto agar containing human or rabbit blood

Treatment

Suggested treatment for pharyngitis includes penicillin, other ß-lactam agents, clindamycin, and macrolides.

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Bacillus Species (Anthrax)

Denise F. Bratcher

Bacillus species, ubiquitous in the environment, are found in soil, water, dust, and air. With the exception of *B. anthracis,* which causes anthrax, *Bacillus* spp. previously have been considered nonpathogenic when isolated from clinical specimens. However, nonanthrax species are increasingly recognized as pathogens in immunosuppressed people and in patients with indwelling devices. Isolates are more likely to be significant if the organism is present on a direct smear of the original specimen or is isolated repeatedly from blood cultures.[1]

In addition, *B. anthracis* has long been recognized as a potential biologic weapon.[2] In the fall of 2001, the deliberate release of *B. anthracis* through the US Postal System provided experience in the clinical presentation, diagnosis, prophylaxis, and treatment of anthrax disease following a bioterrorism-related outbreak.

Immediate notification of the local hospital epidemiologist, the local or state health department, and local or state health laboratories should occur at the first suspicion of an anthrax illness. When bioterrorism alleging the use of anthrax or other agents occurs, the local emergency response system should be activated or local law enforcement agents should be notified.[3] Comprehensive clinical guidance for the unique decisions surrounding prophylaxis and treatment of children following deliberate *B. anthracis* release is provided by the American Academy of Pediatrics (AAP) and the

Centers for Disease Control and Prevention (CDC) Pediatric Anthrax Writing Group.[4]

Microbiology

Bacillus spp. are aerobic or facultatively anaerobic, gram-positive or gram-variable, encapsulated, spore-forming rods that usually are motile. *Bacillus* spp. produce several toxins (including enterotoxin, emetic toxin, phospholipases, proteases, and hemolysins[5]) responsible for much of the morbidity and mortality associated with *B. anthracis*.[4] The species are differentiated by a variety of laboratory observations involving colony morphology, growth on selective media, agglutination reactions, and penicillin susceptibility. *B. anthracis* grows well on blood agar as large, opaque, irregular, “curled-hair” colonies.[6]

Bacillus Anthracis

Epidemiology

B. anthracis, a large, gram-positive, encapsulated, spore-forming, nonmotile rod, is the cause of anthrax. Anthrax, a disease of herbivores that acquire *B. anthracis* while grazing in areas where soil is contaminated by spores, is a zoonotic disease of worldwide occurrence. Disease tends to occur in animals in summer and fall[7]; insects can serve as vectors.[8] Humans typically become infected as they contact infected domestic or wild animals or their products.[7] *B. anthracis* spores can survive for prolonged periods, thus permitting relapsing infection. Human infections have resulted from contact with contaminated products, such as hides, wool, bone meal, and imported dolls, drums, and toys.[9–12] Injection anthrax, associated with use of contaminated heroin, has also been described.[13] Discharge from cutaneous lesions potentially is infectious, and person-to-person transmission is possible. The incubation period is 1 to 7 days but can be up to 60 days depending on host factors, exposure dose, and chemoprophylaxis.

Naturally occurring human disease is rarely reported in the United States.[14] Before the bioterrorism-related anthrax outbreak of 2001, only 18 cases of inhalational anthrax had been reported in the

US in the 20th century.[14] A series of US cases involved exposure to imported animal hides associated with drumming or drum making.[10,11,15]

Clinical Manifestations

Three forms of human disease occur:

1. *Cutaneous anthrax*[16] accounts for most anthrax seen in the US and worldwide; infection follows inoculation of existing skin lesions with *B. anthracis* spores. A painless lesion evolves from a pruritic papule (malignant papule) to a vesicular lesion over 2 to 6 days and eventually forms an eschar (see Fig. 68.7). Striking local edema occurs as a result of release of extracellular toxin, and regional lymphadenopathy and lymphangitis also are noted. Although antibiotic treatment does not alter the progression of an anthrax lesion itself, the mortality rate approaches 20% in patients with untreated cases.

2. *Inhalational anthrax* (wool sorters' disease) results from inhalation of aerosolized spores. A biphasic disease, when it occurs naturally, begins with mild upper respiratory tract symptoms that progress to dyspnea, cyanosis, tachycardia, fever, hypoxemia, shock, and usually death. Bacteremia and hemorrhagic meningitis are common.[17] The chest radiograph typically shows a widened mediastinum consistent with massive lymphadenopathy. This finding in a previously healthy patient with evidence of overwhelming flu-like illness essentially is pathognomonic of advanced inhalation anthrax; pleural effusions also are common. The mortality rate is reported to approach 90%[2]; the case-fatality rate among people who received intensive care in the 2001 attacks was 45%.[18] The first case of naturally acquired inhalation anthrax in the US since 1976 was reported in 2006 in a man who made African drums from imported animal hides.[11] A 2011 inhalational anthrax case with an undefined source involved a 61-year-old man following a vacation and represented only the third naturally acquired case reported in the US since 1976.[19]

3. *Gastrointestinal disease* is a result of ingestion of contaminated, undercooked meat, with deposition of spores in the lower

gastrointestinal tract. Disease manifests as abdominal pain and distention, with vomiting and diarrhea, followed by ascites, hemorrhagic lymphadenitis, and septicemia. An anthrax case involving the gastrointestinal form of disease was reported following animal-hide drum exposure.[9] The mortality rate is 40% or less.[20] *Laryngopharyngeal anthrax* can follow upper gastrointestinal mucous membrane infection acquired from consumption of contaminated meat and manifests as lesions at the base of the tongue or tonsils, dysphagia, profound swelling of the neck, lymphadenopathy, and systemic symptoms.[21,22]

All forms of anthrax can progress to septicemia and meningitis, poor prognostic indicators.[1] Intentional delivery of *B. anthracis* spores through the US mail in 2011 led to 22 cases of anthrax: 11 cases of inhalational and 11 cases of cutaneous anthrax. The patients with inhalational cases likely had direct exposure to a *B. anthracis*–containing envelope. Five patients exhibiting fulminant signs of inhalational illness at presentation died; 6 who came to medical attention less ill received combination antibiotic therapy active against *B. anthracis* and aggressive supportive care and survived. This ~55% overall survival rate is higher than that in previous reports.[24] Fever, chills, fatigue, malaise, and lethargy with minimal or nonproductive cough and nausea or vomiting were common symptoms. Profuse, drenching sweating was a prominent feature. No initial chest radiograph was normal, and pleural effusions were common.

Multiple cases of anthrax have been reported in children, including meningitis, hemorrhagic meningoencephalitis, periorbital cellulitis, neonatal septicemia and meningitis, laryngopharyngeal anthrax, intestinal anthrax, and cutaneous anthrax.[7,12,15,22,25–35] Clinical signs and symptoms in children are nonspecific and variable; the mortality rate is high.[4,22] During the 2001 US Postal Service anthrax outbreak, a 7-month-old infant developed cutaneous anthrax with microangiopathic hemolytic anemia; anthrax spores were identified at his mother's out-of-home office.[36]

Diagnosis

B. anthracis can be isolated from ordinary nutrient broth and on blood agar.[7] Gram stain and culture of vesicular fluid confirm the diagnosis of cutaneous anthrax. Peripheral blood smears can show large, gram-positive bacilli with a "jointed bamboo-rod" appearance; growth in blood culture is positive within 24 hours in inhalational and gastrointestinal anthrax.[4] A direct fluorescent antibody test is available for analysis of a smear of vesicular fluid. Automated blood culture systems readily identify *B. anthracis.* Enzyme immunoassay, immunohistochemistry, and polymerase chain reaction tests are available at state and national reference laboratories (www.cdc.gov/anthrax/labs/labresearch.html). Samples of blood, skin, respiratory secretions, stool, vesicular, pleural, cerebrospinal, or ascitic fluid should be obtained when feasible.[4] The microbiology laboratory should be alerted if anthrax is suspected.

Treatment

Successful management depends on a high index of suspicion and early administration of effective antibiotics. High-dose intravenous penicillin therapy historically has been the drug of choice for all forms of anthrax. Based on more recent data indicating the presence of constitutive and inducible β-lactamases in *B. anthracis* isolates, the use of a penicillin alone for treatment of systemic *B. anthracis* infection is not recommended.[4,37] *B. anthracis* also produces a cephalosporinase, thus inhibiting the use of cephalosporins in treatment.[4,24] Because of concerns regarding genetically engineered *B. anthracis,* the Working Group on Civilian Biodefense recommends that antibiotic resistance to penicillin and tetracycline antibiotics be assumed after a terrorist attack until laboratory testing demonstrates otherwise.[2] Extensive clinical guidance for antimicrobial selection, dosing, supportive care, and prophylaxis of children is provided in the 2014 AAP Clinical Report,[4] and it is summarized in the *Red Book: 2015 Report of the Committee on Infectious Diseases*.[38] Similar comprehensive guidance for adults is provided by the CDC (https://wwwnc.cdc.gov/eid/article/20/2/13-0687_intro).[39]

For cutaneous anthrax, oral ciprofloxacin or doxycycline is considered first-line therapy. If signs of systemic involvement, extensive edema, or head and neck lesions are noted, a multidrug intravenous therapy regimen is recommended. When disease is thought to result from aerosol exposure, antimicrobial therapy is continued for 60 days because of the potential persistence of spores in the respiratory tract. Oral antimicrobial agents can be used for completion of therapy.

Because of the high mortality rate associated with severe systemic anthrax, triple antibiotic therapy given intravenously is recommended for children >1 month of age: 2 bactericidal agents (a fluoroquinolone [ciprofloxacin] *plus* a ß-lactam [meropenem] or glycopeptide [vancomycin]) *plus* a protein synthesis inhibitor (linezolid or clindamycin) to reduce exotoxin production.[4] Alternative regimens are prescribed if meningitis is ruled out or penicillin susceptibility is confirmed. Dosing adjustments are available for infants <1 month of age. Transition to oral combination regimens to complete 2 weeks or more of therapy, based on clinical improvement, is acceptable except for meningitis, which requires 2 to 6 weeks of intravenous therapy. Oral postexposure prophylaxis (PEP) should continue after the initial antimicrobial course to complete a total of 60 days if anthrax resulted from a bioterrorism event.

Other agents with in vitro activity against *B. anthracis* that are suggested for use in multidrug regimens include levofloxacin, moxifloxacin, imipenem, doripenem, vancomycin, penicillin, ampicillin, rifampin, and chloramphenicol. If meningitis is suspected, doxycycline should be avoided because of poor central nervous system penetration. Use of anthrax immune globulin (AIG) was associated with decreased mortality rates in older reports and has been used in more recent inhalational and gastrointestinal anthrax cases.[19,22,40,41] A human monoclonal antibody, raxibacumab, directed against a component of the anthrax toxin has shown improved survival in animal studies of inhalational anthrax.[42] The AAP Clinical Report recommends the addition of an antitoxin product (either AIG or raxibacumab) to combination antimicrobial therapy to treat systemic or progressive disease.[4] Corticosteroid therapy has been suggested for patients with the following: extensive edema, respiratory compromise, and meningitis associated with systemic anthrax; extensive edema of the head and neck region associated with cutaneous anthrax; and adrenal failure.[4,37]

Postexposure Prophylaxis and Prevention

Prevention of naturally occurring human disease depends on control of animal disease and industrial contamination. Contact precautions to prevent transmission from draining wounds and secretions are advised for medical personnel during the first 24 hours of treatment[38] of patients with cutaneous or inhalational anthrax. Contaminated linens should be incinerated or steam sterilized to destroy spores. Autopsies on patients with systemic anthrax require special precautions.

Following a confirmed or suspected aerosol exposure, PEP is indicated for 60 days to prevent inhalational anthrax.[4,43] Initial therapy with ciprofloxacin (30 mg/kg/day divided every 12 hours, maximum 500 mg/dose) or doxycycline (4.4 mg/kg/day divided every 12 hours, maximum 1 g/dose) is recommended for adults and children until antimicrobial susceptibilities of the implicated *B. anthracis* isolate are known. Clindamycin and levofloxacin are alternatives. If penicillin susceptibility is confirmed, oral amoxicillin is appropriate prophylactic therapy for children (75 mg/kg/day divided every 8 hours; maximum dose, 1 g/dose).[44,45] Decisions regarding PEP for pregnant or breastfeeding mothers should be made independent of considerations for the infant.[46] The most current information related to the treatment and PEP is available through the CDC website at www.cdc.gov.

Vaccine for Pre-exposure and Postexposure Prophylaxis

Animal and human vaccines are available.[10,47] The only licensed human anthrax vaccine available in the US is made from the cell-free filtrate of a nonencapsulated, attenuated strain of *B. anthracis* (BioThrax, Emergent BioSolutions, Lansing, Mich).[14] Anthrax vaccine is indicated for workers who contact imported animal hides, hair, or textiles in the workplace and for those involved with military, diagnostic, or investigational work. The current pre-exposure vaccine series consists of 2 intramuscular injections administered 4 weeks apart, followed by 3 subsequent injections at 6, 12, and 18 months, in addition to annual booster doses; administration in the deltoid muscle is recommended.[18] AVA (anthrax vaccine adsorbed) is not currently licensed for use in children but would be available under an Investigational New Drug application if indicated for postexposure administration.[4,14] Postexposure administration includes 3 doses of AVA at 0, 2, and 4 weeks after exposure in the midst of 60 days of antimicrobial chemoprophylaxis for children ≥6 weeks; vaccine is delayed until infants reach 6 weeks of age while antimicrobial chemoprophylaxis is instituted. Local reactions, including edema, erythema, warmth, tenderness, and pruritus, are substantially reduced by intramuscular versus subcutaneous injections. Systemic reactions are rare.

Newer vaccine technologies offer the potential for improved anthrax vaccines, and alternate treatment and prophylactic modalities are under investigation.

Bacillus Cereus

Epidemiology

Bacillus cereus is a significant cause of toxin-induced food poisoning characterized by emesis and diarrhea.[48] From 1998 to 2008, 235 outbreaks of foodborne disease caused by *B. cereus* were reported in the US.[49] Although various foods have been implicated, including infant cereal, contaminated fried rice most frequently is associated with the emetic form of disease, which is caused by heat-resistant, preformed toxin, cereulide, or *B. cereus* spores that germinate when boiled rice is left unrefrigerated[49–52] Nausea, vomiting, and diarrhea with abdominal cramping can occur within 1 to 6 hours of ingestion of contaminated food. The isolated diarrheal form, which is associated with profuse diarrhea produced by an enterotoxin similar to that of *Clostridium perfringens,* has a longer incubation period of 6 to 24 hours. *B. cereus* can be isolated from stools of asymptomatic people, but person-to-person transmission does not occur.[48] Confirmation of food poisoning requires isolation of *B. cereus* from stool or emesis in addition to isolation of *B. cereus* (10^5 colony-forming units/g) in contaminated food.

Clinical Manifestations

B. cereus food poisoning typically is brief and self-limited, requiring no antimicrobial therapy. A few fatal cases caused by *B. cereus* emetic toxin have been reported, including the following: fulminant hepatic failure and rhabdomyolysis in an adolescent after consumption of contaminated pasta[53]; hepatic failure and pulmonary hemorrhage in a 7-year old after consumption of contaminated pasta salad[54]; and acute encephalopathy in a 1-year-old 6 hours after eating reheated fried rice.[55] This last patient and his 2-year old sibling had cereulide detected in serum at presentation; the sibling recovered after plasma exchange and hemodialysis. One child developed fulminant hepatitis, shock, and prolonged seizures associated with *B. cereus* food poisoning,[56] and another presented with acute encephalopathy and features consistent with Reye syndrome.[57]

Multiple other human infections with *B. cereus* have been reported.[4] *B. cereus* ranks as the second most common pathogen of posttraumatic ophthalmitis, after *Staphylococcus epidermidis*.[58,59] The organism typically is introduced by a projectile foreign body or open globe injury, producing a rapidly severe infection that frequently results in enucleation or poor visual outcome. A postsurgical endophthalmitis outbreak has been described, but *B. cereus* is an uncommon cause of postoperative endophthalmitis.[60] Management is aggressive, including surgical intervention and parenteral, intravitreal, and topical antimicrobial treatment.

B. cereus is a cause of clinically significant bloodstream infection and, occasionally, fulminant septicemia in neonates, intravenous drug abusers, and immunocompromised patients, including children with cancer and those with an indwelling catheter or prosthetic device.[4,61–75] Septicemia has followed transfusion of *B. cereus*–contaminated platelets and dietary tea consumption in children with cancer.[76,77] A mortality rate of 31% is reported for *B. cereus* septicemia in patients with hematologic disease. Endocarditis, typically involving a prosthetic valve or the tricuspid valve in intravenous drug abusers, also has been described.[78–81] Pneumonia was reported in immunosuppressed patients and neonates,[4,80,82] and it was associated with fulminant septicemia in 2 previously healthy welders.[83] Hepatic abscess caused by *B. cereus* in a previously healthy teen was noted.[84] Meningitis, hemorrhagic meningoencephalitis, and brain abscess caused by *B. cereus* have been reported, often affecting neonates, immunocompromised children, or children with ventriculoperitoneal shunts.[5,64,80,85–95] Case reports describe the following: hemorrhagic and early, cavitating, selective white matter destruction as typical of neonatal *B. cereus* meningoencephalitis[96]; local infection after burns, trauma, or surgical procedures[97,98]; primary cutaneous infections in neutropenic children[99]; necrotizing cellulitis[100]; osteomyelitis associated with accidental or surgical trauma or intravenous drug abuse[101]; urinary tract infection in a patient with invasive bladder cancer; peritonitis associated with peritoneal dialysis[102–104]; and intestinal diseases in neonates.[105,106] Nosocomial transmission of *B. cereus* is reported,[105,107–112] and 2 children developed *B. cereus* central line–associated bacteremia possibly associated with contaminated alcohol pledgets.[113]

Antibiotic therapy is indicated in invasive *B. cereus* infections, but optimal therapy is not defined. Vancomycin, clindamycin, fluoroquinolones, and carbapenems are used commonly. Antimicrobial susceptibility testing is essential; clindamycin and carbapenem resistance is reported.[72,114] Removal of prosthetic devices usually is necessary for cure and is associated with a significantly lower recurrence rate.[63,72,104,115] Surgical intervention typically is required in ophthalmic infection, brain abscess, and soft tissue infection. Endophthalmitis typically is treated with intravitreal vancomycin, vitrectomy, and topical and systemic fluoroquinolone therapy.

Bacillus Subtilis and Other *Bacillus* Species

Other *Bacillus* spp. implicated in human infections include *B. alvei, B. brevis, B. circulans, B. coagulans, B. infantis, B. idriensis, B. laterosporus, B. licheniformis, B. macerans, B. pumilus, B. sphaericus, B. subtilis,* and *B. thuringiensis*.[a] Nonanthrax *Bacillus* species have been associated with bloodstream infection (including catheter-related infection), brain abscess, meningitis, pneumonia, pleuritis, endocarditis, pericarditis, urinary tract infection, peritonitis, periorbital cellulitis, and ocular infections. *B. thuringiensis* has been associated with foodborne gastrointestinal illnesses.[48] Case reports of infections with *Bacillus* species are sometimes difficult to interpret because the species frequently is identified incorrectly or can represent a contaminant of the culture.

B. subtilis specifically is described in association with bloodstream infection, cholangitis, meningitis, chronic osteomyelitis, panophthalmitis, pneumonia, and ventriculoperitoneal shunt infections.[5,80,124] Unlike *B. cereus, B. subtilis* is susceptible to penicillins in addition to vancomycin, clindamycin, aminoglycosides, and third-generation cephalosporin agents.

Key Points

Bacillus Species

- Nonanthrax *Bacillus* species are increasingly recognized as pathogens in immunocompromised people, especially if the organisms are isolated repeatedly from blood culture or if they appear on a direct smear of the original specimen.

- Naturally occurring anthrax infections usually result from contact with infected domestic or wild animals or their products (e.g., hides, hair).

- Three forms of anthrax disease occur in humans: (1) cutaneous, (2) inhalational, and (3) gastrointestinal. All 3 forms can progress to septicemia and meningitis, and pediatric patients have been reported with all forms of the disease.

- *Bacillus anthracis* grows in standard nutrient broth and on blood agar from blood and clinical specimens.

- Triple antimicrobial therapy is recommended for treatment of systemic anthrax, anchored by bactericidal agents (ciprofloxacin) plus a ß-lactam agent (meropenem) plus a protein synthesis inhibitor (clindamycin).

- Oral ciprofloxacin is considered first-line therapy for cutaneous anthrax.

- Anthrax is recognized as a potential biologic weapon. Guidance for clinical decisions for treatment and postexposure prophylaxis following presumed deliberate *B. anthracis* release is available for adult, pediatric, and pregnant or postpartum patients.

- Anthrax vaccine adsorbed is not currently licensed for use in children but can be a component of postexposure prophylaxis under an Investigational New Drug application, if indicated.

- *B. cereus* is a significant cause of toxin-mediated food poisoning and has been implicated in several other clinically significant human infections, particularly among immunocompromised hosts.

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[a] References 5, 59, 63, 68, 80, 116 to 123.

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Corynebacterium diphtheriae

Irini Daskalaki

Diphtheria is a toxicosis caused by infection with *Corynebacterium diphtheriae*. The genus and species names are derived from Greek roots: *korynee* ("club") after the microscopic appearance of the organisms and *diphtheria* ("leather hide") for the pseudomembrane that is the hallmark of respiratory tract infection. Once a major cause of childhood death, diphtheria was among the first infectious diseases to be controlled through the use of modern principles of microbiology, immunology, and public health. Increased immunization rates, rare circulation of toxigenic strains, and improved living conditions have controlled diphtheria in developed countries. However, the rare importation of diphtheria into the United States from developing countries and recent outbreaks in developed countries, with significant morbidity and mortality, have underscored the continuing need for diphtheria immunization.

Etiology

Corynebacterium species are aerobic, nonencapsulated, nonspore-forming, mostly nonmotile, pleomorphic gram-positive bacilli. Isolation is enhanced by the use of selective media (e.g., cystine-tellurite blood agar) that inhibit the growth of competing organisms and, when reduced by *C. diphtheriae,* produce colonies that appear grey to black. Modified Tinsdale medium and Löffler or Pai slants are additional effective enrichment media. Growth occurs within 48 hours; Gram staining of typical colonies from Löffler or Pai media can confirm a presumptive identification. Three phenotypes (*mitis, gravis,* and *intermedius*), each capable of causing diphtheria, are distinguished by colonial morphology, hemolysis, and fermentation reactions. A lysogenic bacteriophage that encodes for production of exotoxin confers no essential protein to the bacterium, but factors other than toxin production can cause virulence and facilitate the spread of infection.[1]

Production of diphtheria toxin can be demonstrated in vitro by use of an agar well or antitoxin membrane immunoprecipitin technique (Elek test) or by in vivo toxin neutralization tests in the guinea pig.[2,3] Investigational polymerase chain reaction (PCR) tests detect the presence of genes for both A and B toxin subunits but do not prove toxin production directly.[4] Toxigenic strains are indistinguishable by colony type, microscopy, or biochemical tests. Expression of toxin is enhanced in vitro by nutrient or iron depletion or exposure to ultraviolet light. Nontoxigenic *C. diphtheriae* can be converted to toxigenic strains by lysogenic infection. Studies of outbreaks in which molecular techniques were used suggest that indigenous nontoxigenic *C. diphtheriae* strains can be rendered toxigenic, producing clinical diphtheria, after importation of single cases of toxigenic *C. diphtheriae.*[5] Nondiphtheria strains of *Corynebacterium* (e.g., *C. ulcerans*) can produce diphtheria toxin and cause a respiratory diphtheria-like illness.[6,7]

Epidemiology

Coryneform bacteria ("diphtheroids") are ubiquitous in nature. They are found on human skin and mucous membranes, on plants, in soil, and in freshwater and saltwater. Humans are the only known reservoir of *C. diphtheriae,* although a novel strain was isolated from cats in West Virginia.[8] The primary modes of spread are by airborne respiratory droplets and by direct contact with respiratory secretions or exudate from skin lesions. Asymptomatic or convalescent respiratory carriers are important reservoirs for transmission. In endemic areas 3% to 5% of healthy people harbor toxigenic organisms, but pharyngeal carriage of these strains is uncommon if clinical diphtheria is rare. Skin infection, or carriage, can be the silent reservoir of toxigenic diphtheria. Viability in dust and on fomites for up to 6 months has unknown epidemiologic significance. Transmission by means of animals, contaminated milk, and an infected food handler has been proved or suspected.[9]

Diphtheria occurs worldwide. In temperate climates the incidence is higher during the colder months. The disease remains endemic in many developing countries with inadequate immunization rates, occurring predominantly in poor socioeconomic conditions. In industrialized countries the main risk factor for acquisition of toxigenic *C. diphtheriae* is travel to endemic areas (Asia, South Pacific, Eastern Europe) or laboratory acquisition.[10] A complete list of areas in which diphtheria is endemic is available from the Centers for Disease Control and Prevention (CDC).[11]

Before 1930 more than 125,000 cases and 10,000 deaths caused by diphtheria were reported annually in the United States (incidence, 100 to 200 cases per 100,000). The highest fatality rates occurred among people younger than 5 years of age and those older than 40 years. The widespread use of diphtheria toxoid vaccine in the U.S. after World War II produced a steady decline in the incidence of diphtheria, to 0.001 per 100,000 population; between 2004 and 2015 only 2 cases of diphtheria were reported in the U.S., and since 1988 all cases have been imported.[12]

Although immunization does not prevent respiratory or cutaneous carriage or infection with toxigenic *C. diphtheriae,* neutralization of toxin diminishes local tissue spread, necrosis, multiplication, and transmission, thereby providing herd immunity. It is estimated that 70% to 80% of a population must be immunized to prevent epidemic spread.[13] Even with the low rate of circulating toxigenic *C. diphtheriae* in most industrialized countries, subgroups have been identified that would be at risk if the organism were introduced as a consequence of underimmunization. In a multicenter European study, screening of upper respiratory specimen cultures revealed both toxigenic and nontoxigenic strains of *C. diphtheriae,* indicating carriage in highly vaccinated populations.[14] The National Immunization Survey in the

U.S. has demonstrated that coverage with at least three doses of diphtheria toxoid among children 19 to 35 months old has been approximately 95% for about a decade.[15] However, in serosurveys in the U.S. and western European countries, where childhood immunization is universal, 20% to more than 60% of the people were found to lack protective antitoxin levels (antitoxin level >0.01 IU/mL). The elderly had particularly low levels.[13,16–19]

Low levels of antitoxin in some populations may reflect relatively poor rates of administration of booster diphtheria vaccines after primary immunization in childhood. The recent epidemiology of diphtheria demonstrates a shift from endemic disease in childhood to outbreaks in adults. In 27 sporadic cases of respiratory tract diphtheria in the U.S. in the 1980s, 70% occurred in people older than 25 years.[18] A similar shift of the epidemiology of diphtheria to adult cases has been identified in Europe.[20]

In the 1990s a massive outbreak of diphtheria occurred in the Newly Independent States of the former Soviet Union; more than 150,000 cases occurred within 6 years in 14 of the 15 states.[21] Case-fatality rates ranged from 3% to 23% by state, and more than 60% of cases occurred among people older than 14 years. Factors contributing to the epidemic included a large population of susceptible (i.e., underimmunized) adults, decreased childhood immunization, population migration, crowding, and a failure to respond aggressively during early phases of the epidemic. Attempts to control the epidemic with childhood immunization alone failed, whereas mass immunization of both children and adults was successful. Cases of diphtheria among travelers were transported to many countries in Europe. Molecular characterization of the Russian *C. diphtheriae* isolates by ribotyping and multilocus enzyme electrophoresis demonstrated that the outbreak was caused by a distinct clonal group that emerged in Russia in 1990.[22]

Cutaneous diphtheria may be central to the changing epidemiology of diphtheria. Cutaneous diphtheria has accounted for more than 50% of *C. diphtheriae* isolates reported in the U.S. since 1975. Cutaneous infection is infrequently associated with toxic complications, and it is caused by toxigenic and nontoxigenic strains, often in association with other bacteria. In contrast to respiratory tract infection, cutaneous diphtheria is associated with prolonged bacterial shedding, increased environmental contamination, and increased transmission to close contacts. Outbreaks of cutaneous diphtheria have been associated with homelessness, crowding, poverty, alcoholism, poor hygiene, contaminated fomites, underlying dermatosis, and introduction of new strains from exogenous sources. From 1971 through 1982, a total of 1100 *C. diphtheriae* infections were documented in Seattle; 86% were cutaneous, and 40% involved toxigenic strains.[23] A more recent review from Vancouver found associations with injection drug use and poverty.[24]

Currently cutaneous diphtheria is a reservoir for toxigenic *C. diphtheriae* in the U.S. and has been a frequent mode of importation of source cases for sporadic respiratory tract diphtheria. However, attention has been focused on respiratory tract diphtheria, which is much more likely to cause complications and toxic manifestations, and cutaneous diphtheria has not been a nationally reportable disease since 1980.

Pathogenesis

Both toxigenic and nontoxigenic *C. diphtheriae* organisms cause skin and mucosal infection, in addition to rare distant infection after bacteremia. The organisms remain confined to superficial layers of skin lesions or respiratory mucosa and induce a local inflammatory reaction. The major virulence factor is a potent 62-kd polypeptide exotoxin that consists of a binding segment A and an active segment B which, when cleaved, is internalized and inactivates transfer RNA translocase, preventing the addition of amino acids during protein synthesis. Within the first few days of respiratory tract infection, a dense, necrotic “pseudomembrane” forms, consisting of organisms, epithelial cells, fibrin, leukocytes, and erythrocytes. The pseudomembrane advances and becomes adherent. Removal is difficult and reveals a bleeding, edematous submucosa. Early local effects of the toxin include paralysis of the palate and hypopharynx. Absorption and hematogenous dissemination of the toxin can lead to necrosis of the kidney tubules and hepatic parenchyma, amegakaryocytic thrombocytopenia, myocardiopathy, and demyelinating neuropathy. Cardiomyopathy and neuropathy occur 2 to 10 weeks after the initial mucocutaneous infection and may involve an immune-mediated pathophysiology in addition to delayed appearance of toxic tissue damage.

Clinical Manifestations

Respiratory Tract Diphtheria

In a classic description of 1400 cases of diphtheria, infection involved the tonsils or pharynx in 94%; the nose and larynx were the next two most common sites.[25] After an average incubation period of 2 to 4 days, local signs and symptoms of inflammation develop. Fever is low grade or absent. Infection of the anterior nares (more common in infants) causes serosanguineous, erosive rhinitis with membrane formation. Shallow ulceration of the external nares and upper lip is characteristic. Sore throat is a universal early symptom of tonsillar or pharyngeal diphtheria, but only 50% of patients have fever, and fewer than 50% of patients have dysphagia, hoarseness, malaise, or headache. Mild pharyngeal injection is followed by unilateral or bilateral tonsillar membrane formation, which extends off tonsillar tissues to variably affect the uvula, soft palate, posterior oropharynx, hypopharynx, and glottic areas (Fig. 130.1). Underlying soft tissue edema and enlarged lymph nodes can cause cervical swelling (e.g., bullneck), characterized by obliteration of the borders of the mandible, sternocleidomastoid muscle, and clavicle by brawny, pitting, warm, tender, but nonerythematous edema. The degree of toxin extension correlates directly with symptoms of prostration, bullneck, airway compromise, and subsequent toxin-mediated complications of distant organs. A patient with laryngeal diphtheria is highly prone to acute airway compromise as a result of local edema and the formation of the pseudomembrane. Establishment of an artificial airway and resection of pseudomembrane may be lifesaving.

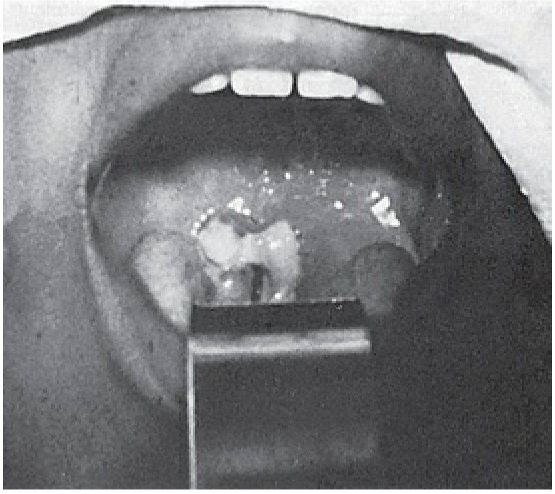

FIGURE 130.1 Four-year-old girl with faucial diphtheria.

The appearance of the leatherlike, adherent pseudomembrane, which extends beyond the faucial tonsillar area, and a relative lack of fever and dysphagia help distinguish diphtheria from the exudative pharyngitis caused by *Streptococcus pyogenes,* adenovirus, and Epstein-Barr virus. The absence of exanthem or ulcers elsewhere on the oral mucosa and tongue distinguishes diphtheria from infections arising from other viral causes. Vincent angina and Lemierre disease, phlebitis and thrombosis of the jugular veins, mucositis in patients undergoing cancer chemotherapy, and a faucial membrane after tonsillectomy usually are distinguished by the clinical setting. Diphtheritic infection of the larynx, trachea, or bronchi can be primary or can occur from secondary extension after pharyngeal infection; hoarseness, stridor, dyspnea, and a croupy cough are clues to infection of these sites. Differentiation from bacterial epiglottitis, severe viral laryngotracheobronchitis, and staphylococcal or streptococcal tracheitis hinges partially on the relative paucity of other signs and symptoms in a patient with diphtheria and primarily on visualization of an adherent pseudomembrane at the time of laryngobronchoscopy and intubation.

Cutaneous Diphtheria

Cutaneous diphtheria usually is an indolent, nonprogressive infection characterized by a superficial, ecthymic, nonhealing ulcer with a grey-brown membrane. Diphtheritic skin infection often cannot be distinguished from streptococcal or staphylococcal impetigo, and the conditions frequently coexist. In the Seattle outbreak,[23] *S. pyogenes* was isolated in 73% of diphtheritic skin lesions. The role of *C. diphtheriae* as the cause of localized findings is not clear. Ulcers do not respond to antitoxin therapy, but infection elicits high antitoxin levels. In most cases, underlying dermatoses, lacerations, burns, bites, or impetigo have become secondarily contaminated. The extremities are affected more often than the trunk or head. Pain, tenderness, erythema, and exudate are typical. Local hyperesthesia or hypoesthesia can occur. Respiratory tract colonization or symptomatic infection, in addition to toxic complications, occur in a minority of patients with cutaneous diphtheria. Of the infected adults in Seattle, 3% of those with cutaneous infections – compared with 21% of those with symptomatic nasopharyngeal infection with or without skin involvement – had toxic myocarditis, neuropathy, or obstructive respiratory tract complications.[23] All had received at least 20,000 units of equine antitoxin at the time of hospitalization.

Infection at Other Sites

C. diphtheriae occasionally causes infections at other mucocutaneous sites, such as the ear (otitis externa), eye (purulent and ulcerative conjunctivitis involving primarily palpebral areas), and genital tract (purulent and ulcerative vulvovaginitis). The clinical setting, ulceration, pseudomembrane formation, and submucosal bleeding help differentiate diphtheritic infection from other bacterial and viral causes.

Rare cases of septicemia caused by *C. diphtheriae* have been described, and such cases often are fatal. Sporadic cases of endocarditis occur, and clusters among intravenous drug users have been reported,[26,27] as have occasional cases in children living in endemic areas.[28,29] Notable clinical features are aggressive valvular destruction with associated pyogenic arthritis and major vascular complications (emboli and aneurysms) caused by the large size of vegetations; most complications have been caused by nontoxigenic strains. Most patients did not have respiratory tract symptoms. Although skin lesions were not described, skin is likely to have been the portal of entry. Sporadic cases of pyogenic arthritis, mainly caused by nontoxigenic strains, have been reported in adults and children.[30] Diphtheroids isolated from sterile body sites should not be dismissed as contaminants without careful consideration of the clinical setting, and they should be identified to the species level if validly associated with invasive disease. If *C. diphtheriae* is isolated, toxigenicity studies of the isolate should be completed and prophylaxis for contacts should be considered.

Toxic Myocardiopathy

Toxic myocardiopathy occurs in approximately 10% to 25% of patients with diphtheria and is responsible for 50% to 60% of deaths. Subtle signs of myocarditis may be detectable in many patients, especially in the elderly, but the risk of significant complications for an individual correlates directly with the extent and severity of exudative oropharyngeal disease and delays in administration of antitoxin.[23,25,26]

Most often the first evidence of cardiomyopathy is recognized in the second to third week of illness, as pharyngeal disease improves. However, cardiomyopathy can appear as early as the first week (the likelihood of a fatal outcome is high) or insidiously, as late as the sixth week of illness. Tachycardia out of proportion to fever is common evidence of cardiac toxicity or autonomic nervous system dysfunction. A prolonged PR interval or ST-segment and T-wave changes are relatively frequent findings on an electrocardiogram, and dilated or hypertrophic cardiomyopathy frequently is observed on an echocardiogram. Single or progressive cardiac arrhythmias can occur, such as first-, second-, and third-degree heart block, atrioventricular dissociation, and ventricular tachycardia. Clinical congestive heart failure can have an insidious or acute onset. Elevation of the serum aspartate aminotransferase concentration closely parallels the severity of cardiac myonecrosis. Severe arrhythmia portends death.[16,25,31] Histologic postmortem findings can show a minor abnormality or diffuse myonecrosis with an acute inflammatory response. Except for survivors of more severe arrhythmias, who may have permanent conduction defects, patients usually recover completely from toxic myocardiopathy.

Toxic Neuropathy

Neurologic complications parallel the extent of primary infection and are multiphasic in onset.[23,25,31] Two to 3 weeks after the onset of oropharyngeal inflammation, hypoesthesia and local paralysis of the soft palate commonly occur. Weakness of posterior pharyngeal, laryngeal, and facial nerves may follow, causing a nasal quality in the voice, difficulty swallowing, and the risk of death from aspiration. Cranial neuropathies usually occur in the fifth week, leading to oculomotor and ciliary paralyses; these manifest as strabismus, blurred vision, or difficulty with accommodation. Symmetric polyneuropathy can have its onset 10 days to 3 months after onset of oropharyngeal infection and principally causes motor defect and diminished deep tendon reflexes.

Both proximal muscle weakness of the extremities that progresses distally, and more commonly, distal weakness that progresses proximally, have been described. The clinical and cerebrospinal fluid findings are indistinguishable from those seen with the polyneuropathy of Guillain-Barré syndrome. Paralysis of the diaphragm can occur, but complete recovery is likely. In rare cases 2 or 3 weeks after the onset of illness, dysfunction of vasomotor centers can cause hypotension or cardiac failure.

Management of Symptomatic Patients

Diagnostic Tests

Specimens for culture should be obtained from the nose and throat and from any affected mucocutaneous site. A portion of the pseudomembrane and the underlying exudate should be removed and submitted for testing. Growth from slants are stained with Neisser stain or Löffler methylene blue and examined for metachromatic granules. When the specimens are submitted, the laboratory must be notified to use selective media for isolation. *C. diphtheriae* survives drying, but if transport to a laboratory will require more than 24 hours, a transport medium should be used. In remote areas a swab specimen can be placed in a silica gel pack and sent to a reference laboratory.

Evaluation of direct smears using Gram stain or specific fluorescent antibody is unreliable. When coryneform bacteria are isolated from sterile body sites or from mucocutaneous sites in suspected cases or contacts, the organisms should be identified to the species level and toxigenicity and antimicrobial susceptibility tests should be performed on *C. diphtheriae* isolates. Although the only commercially available methods to diagnose *C. diphtheriae* infection are culture and toxigenicity tests, the CDC performs a PCR assay that allows detection of the regulatory gene for toxin production *(DTXR)* and the diphtheria toxin gene *(TOX).* This assay provides supportive evidence for the diagnosis; it is not sufficient for confirmation but can be particularly useful if nonviable organisms are present in clinical specimens.[32] Few laboratories measure serum antibodies to the toxin; however, if this is done before antitoxin is administered, it could be helpful in assessing the probability of the diagnosis.

Antitoxin

Specific antitoxin neutralizes only free toxin; therefore, if the clinical findings and epidemiology support the diagnosis, antitoxin should be administered promptly, before culture confirmation. The mortality rate is less than 1% if antitoxin is administered on the first day of disease, but it increases 20-fold if treatment is delayed until the fourth day.

Antitoxin of human origin might be available in some countries, but in the U.S. only an equine preparation is available. Equine diphtheria antitoxin (DAT) is available only from the CDC through an investigational new drug protocol (CDC Emergency Operations Center; 24-hour telephone: 770-488-7100).[33] Antitoxin is administered once at an empiric dosage based on the degree of toxicity, site and size of the pseudomembrane, and duration of illness.[33] The intravenous route is preferred. Antitoxin is probably of no value for local manifestations of cutaneous diphtheria but can be recommended if signs of systemic toxicity are present. Prophylactic treatment with antitoxin for exposed individuals should be considered only in special circumstances. Antitoxin is not recommended for asymptomatic carriers.

The frequency of anaphylaxis and serum sickness is considered to be low in the current era because it is partially influenced by the previous administration of animal serums in the population. However, even patients who are very ill must be tested before infusion of antitoxin, and those who show immediate reactions should undergo a desensitization protocol.[33]

Commercially available immune globulin preparations for intravenous use (IGIVs) contain antibodies to diphtheria toxin, but the amounts likely vary from lot to lot. Their use for therapy of diphtheria has neither been proved nor recommended. Identification of a human monoclonal antibody as a safer and efficacious alternative to antitoxin is under investigation.[34]

Antimicrobial Therapy

Antimicrobial therapy is indicated to limit presumed continuing toxin production, to treat localized infection, and to prevent the transmission of organism to contacts; however, antibiotic therapy is not a substitute for antitoxin therapy. *C. diphtheriae* usually is susceptible in vitro to penicillins, erythromycin, newer macrolides (clarithromycin, azithromycin), clindamycin, rifampin, fluoroquinolones, and tetracycline. Resistance to erythromycin has been documented in cutaneous diphtheria outbreaks in the U.S.[23] Only penicillin and erythromycin have been evaluated in prospective trials, and they are the sole agents recommended. Erythromycin is marginally superior to penicillin for eradication of nasopharyngeal carriage. Appropriate therapy is erythromycin given orally or parenterally (40 to 50 mg/kg/day, maximum 2 g/day); or aqueous crystalline penicillin G intramuscularly or intravenously (100,000 to 150,000 units/kg/day divided into 4 doses) or procaine penicillin intramuscularly (25,000 to 50,000 units/kg/day divided into 2 doses). Therapy is given for 14 days. Some patients with cutaneous diphtheria have been treated for 7 to 10 days. Elimination of the organism should be documented by two successive cultures from the nose, throat, and skin (when appropriate) at least 24 hours apart after completion of therapy. Treatment with erythromycin is repeated if the culture result is positive.

Other Measures

Droplet isolation is recommended for patients with pharyngeal diphtheria; contact isolation is sufficient for patients with cutaneous diphtheria. Isolation is continued until at least two culture results from the nose and throat (and skin lesions, if present) taken after cessation of therapy are negative. Cutaneous wounds should be cleansed thoroughly with soap and water. Bed rest is recommended during the acute phase of the disease. The return to physical activity should be guided by the degree of toxicity and cardiac involvement. Patients with oropharyngeal or laryngeal diphtheria should be observed closely for signs of airway obstruction and aspiration. Congestive heart failure and malnutrition should be anticipated and prevented when possible.

Corticosteroid therapy is not recommended. In a study of 66 children with respiratory tract diphtheria who were alternately treated with or without prednisone for 14 days from the time of diagnosis, toxic myocarditis occurred in 26%, neuritis in 17%, and bullneck diphtheria in 10%, with no difference in occurrence or death in those who received steroids.[31] The use of digitalis for treatment of myocarditis is associated with an excess occurrence of arrhythmia.

The prognosis for diphtheria depends on the virulence of the organism, the patient's age and immunization status, the site of infection, the presence and severity of complications, and the speed of antitoxin administration. Mechanical obstruction from laryngeal or bullneck diphtheria and complications of myocarditis account for most deaths.[35] Ventricular ectopy with or without evident clinical myocarditis at the time of initiation of therapy predicted a fatal outcome with 100% sensitivity and specificity in children with severe diphtheria. A minimum case-fatality rate of 10% for respiratory tract diphtheria has not changed in 50 years, and the mortality rate was 18% and 23% in outbreaks that occurred in the 1980s and 1990s in Sweden[1] and states of the former Soviet Union,[21] respectively. The rate was 33% in a retrospective study from the United Kingdom, where deaths were observed only in people who had not been immunized.[10]

Because sustained immunity does not develop in all patients after infection, administration of diphtheria toxoid is indicated at recovery to complete the primary series or booster doses of immunization.

Management of Others

Exposed People

Public health officials should be notified promptly when a diagnosis of diphtheria is suspected or proved. Investigation is aimed at preventing secondary cases in exposed people and at determining the source case and carriers to halt spread to unexposed individuals. Reported rates of carriage in household contacts of case-patients have ranged from 0% to 25%.[9,16,36] The risk of developing diphtheria after household exposure to a case is approximately 2%; it is 0.3% after similar exposure to a carrier.

The highest priorities are prompt identification and investigation of close contacts (defined as all household contacts and those who have had intimate respiratory or habitual physical contact with the patient). The following steps should be taken for these people:

- Monitor closely for illness through the 7-day incubation period.
- Perform cultures of the nose, throat, and any cutaneous lesion.
- Give antimicrobial prophylaxis, regardless of immunization status, with oral erythromycin (40 to 50 mg/kg/day for 7 to 10 days, maximum 1 g/day). If the individual is intolerant to erythromycin or if complete adherence is not assured, intramuscular benzathine penicillin should be administered (600,000 units for those weighing <30 kg or 1,200,000 units for those weighing ≥30 kg). The efficacy of antimicrobial prophylaxis is presumed but not proved, and the newer macrolides (e.g., clarithromycin and azithromycin) have not been evaluated for their ability to eliminate carriage of *C. diphtheriae.*
- Give diphtheria toxoid vaccine doses or other suitable combination vaccine, such as – pediatric diphtheria and tetanus toxoid vaccine (DT); pediatric diphtheria and tetanus toxoids, and acellular pertussis vaccine (DTaP); tetanus toxoid, reduced diphtheria toxoid and reduced acellular pertussis vaccine (Tdap); or tetanus toxoid and reduced diphtheria toxoid vaccine (Td) – appropriate for age and prior receipt (i.e., Tdap) to immunized individuals who have not received a booster dose within 5 years. Tdap vaccine has not been evaluated in the control of outbreaks, but it should be reliable based on the immune responses elicited when it is given to people who received a primary series of DTaP.

Those who have received fewer than three doses of diphtheria toxoid or whose immunization status is unknown should be immunized with an age-appropriate preparation on a primary schedule. The use of the Schick test (intradermal injection of diphtheria toxin) to determine immunity in contacts is no longer recommended, and the reagents for testing are generally no longer available.

Asymptomatic Carriers

When an asymptomatic carrier is identified, the following steps should be taken:

- Give antimicrobial prophylaxis for 7 to 10 days.
- Give an age-appropriate preparation of diphtheria toxoid immediately if the individual has not received a booster within 5 years.[37]
- Place the individual in droplet isolation (respiratory tract colonization) or contact isolation (cutaneous colonization only) until the results of at least two subsequent cultures taken at least 24 hours apart after cessation of therapy are negative for *C. diphtheriae.*
- Perform repeat cultures at a minimum of 2 weeks after completion of therapy in cases and carriers; if the culture result is positive, an additional 10-day course of oral erythromycin should be given and follow-up cultures performed.

Neither penicillin nor erythromycin eradicates carriage in 100% of carriers. In one report[38] eradication failed in 21% of carriers after a single course of therapy. Antitoxin is not recommended for close contacts or asymptomatic carriers, even if they are inadequately immunized, because of the adverse effects of horse serum and the lack of demonstrable evidence of benefit above antimicrobial prophylaxis. Booster immunization elicits a rapid rise in antitoxin levels.

Transmission of diphtheria in modern hospitals is rare.[39] Meticulous handwashing and handling of secretions are mandatory. Only those who have had unusual contact with respiratory or oral secretions should be managed as contacts. Investigation of casual contacts of patients and carriers and of people in the community without known exposure has generally yielded extremely low carriage rates and is not recommended routinely.

Prevention

Universal immunization with vaccines containing diphtheria toxoid to provide constant protective antitoxin levels and to reduce indigenous *C. diphtheriae* is the only effective control measure. This requires multiple injections in childhood and adulthood. Serum antitoxin levels, measured by toxin neutralization tests in Vero cell culture or rabbit skin or by hemagglutination, are roughly equivalent. A concentration of 0.01 to 0.1 IU/mL is conventionally accepted as the minimum protective level, although the protective limit of antibody has not been precisely defined.[32] In outbreaks 90% of people with clinical disease have had antitoxin levels less than 0.01 IU/mL, and 92% of asymptomatic carriers have had titers greater than 0.1 IU/mL.

Vaccine Preparations

Diphtheria toxoid is prepared by formaldehyde treatment of toxin and is standardized for potency according to the specifications of the U.S. Food and Drug Administration. Toxoid is adsorbed to aluminum salts, which enhances immunogenicity. Two preparations of diphtheria toxoids are formulated according to limit of flocculation (Lf) content, a measure of quantity of toxoid. Pediatric preparations (DTP, DT, DTaP) contain 6.7 Lf units or more of diphtheria toxoid per 0.5 mL dose, whereas adolescent and adult preparations of combination vaccines of diphtheria-tetanus (Td) or tetanus–diphtheria–acellular pertussis (Tdap) contain no more than 2 Lf units of toxoid per 0.5 mL dose. The higher potency (D) formulation of toxoid is used for the primary series and for booster doses for children through 6 years of age because of superior immunogenicity and minimal reactogenicity. For individuals 7 years of age or older, Td or Tdap (for one dose only) is recommended for the primary series and booster doses because the lower concentration of diphtheria toxoid is adequately immunogenic and because increasing the content of diphtheria toxoid heightens reactogenicity with advancing age.

Schedules

For children 6 weeks through 6 years of age, five 0.5-mL doses of diphtheria-containing (D) vaccine should be given. The adult preparations (d) should not be used in children younger than 7 years because of these vaccines' reduced immunogenicity. The primary series includes doses at approximately 2, 4, and 6 months of age. The fourth dose is an integral part of the primary series and is given approximately 6 to 12 months after the third dose to maintain adequate immunity during the preschool years. A booster dose is given at 4 to 6 years (unless the fourth primary dose was administered after the fourth birthday).

For people 7 years of age or older, three 0.5-mL doses of diphtheria-containing vaccine (Td, or Tdap for one dose) are recommended as a primary series; this primary series includes two doses 4 to 8 weeks apart and a third dose 6 to 12 months after the second dose; the preferred schedule is Tdap followed by Td, but Tdap can replace any single dose of Td. The only contraindication to diphtheria toxoid is a history of neurologic or severe hypersensitivity reaction after a previous dose.

For children in whom vaccination was delayed, D or d toxoids (DT or Td) are used as follows: those who began with either diphtheria-tetanus-pertussis or DT at younger than 1 year of age should have a total of five 0.5-mL doses of D-containing vaccine by 6 years. For those beginning at or after 1 year of age, the primary series is two 0.5-mL doses of D vaccine, with a third dose 6 to 12 months later and a booster given at 4 to 6 years unless the third dose was given after the fourth birthday.[37]

A further reduction in the number of cases of diphtheria in industrialized countries will require universal booster immunization throughout life. Booster doses of 0.5 mL Td should be given every 10 years (these are conveniently given to most people at 15 years, 25 years, 35 years of age, and so forth). Tdap should be given to replace one dose of Td for routine administration. Vaccination with diphtheria toxoid should be used whenever tetanus toxoid is indicated to ensure continuing diphtheria immunity. There is no known association of DT or Td with an increased risk of convulsions. Local side effects alone do not preclude continued use. Arthus-type hypersensitivity reactions after a dose of Td have been described in adults who have received excessive doses over a short period; these reactions usually are associated with high serum levels of tetanus antitoxin. An Arthus reaction is rare in children and adolescents. DT or Td can be given concurrently with other vaccines. *Haemophilus influenzae* conjugate vaccines containing diphtheria toxoid (PRP-D) and the variant of diphtheria toxin, CRM1$_{97}$ protein (HbOC) as a carrier protein, are not substitutes for diphtheria toxoid immunization.

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Key Points

Diagnosis and Management of *Corynebacterium diphtheriae* Infection

Microbiology

- Pleomorphic gram-positive bacilli
- Selective or enrichment media are required for growth.
- Infection of the bacteria with a lysogenic bacteriophage is responsible for exotoxin production.

Epidemiology

- Humans are the only reservoir.
- Infection spreads by respiratory droplets or direct contact with respiratory or skin secretions.
- As a result of universal childhood immunization, diphtheria cases in the U.S. are imported; however, diphtheria is still endemic in many developing countries.
- Classic presentations include pharyngitis and cutaneous

diphtheria, but endocarditis and arthritis have been documented.

- Complications include toxic cardiomyopathy and neuropathy.

Diagnosis

- Isolation from the nasopharynx or from skin lesions
- Coryneform bacteria isolated from the blood of patients suspected of having diphtheria should not be discounted as contaminants before identification to the species level.
- PCR (not commercially available) allows detection of regulatory gene for toxin production.

Treatment

- Specific antitoxin is lifesaving if administered within 24 hours of symptom onset.
- Equine antitoxin is available in the U.S. only through the CDC Emergency Operations Center.
- Antimicrobial therapy is indicated to limit toxin production and prevent transmission.
- Strains usually are susceptible to penicillins and macrolides.
- Administration of diphtheria toxoid vaccine is indicated upon recovery because not all patients develop sustained immunity after infection.

Infection Control/Prevention

- Droplet isolation is indicated for pharyngeal and contact isolation for cutaneous diphtheria cases.
- The only effective control measure is universal immunization with vaccines containing diphtheria toxoid and booster doses throughout life.

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Other Corynebacteria

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Corynebacterium species, which are recognized as members of the normal human flora, are isolated from the skin, mucous membranes, and gastrointestinal tract. Although frequently dismissed as contaminants in clinical specimens, corynebacteria are recognized more often as pathogens, particularly in immunocompromised people.[1,2] Infections caused by *Corynebacterium* species have occurred predominantly among patients with prosthetic and other medical devices. Currently, 88 valid studies have been published on *Corynebacterium* species, and further definition of the pathogenic role of these species in human infections and of the mechanisms of pathogenesis continues to be elucidated. Many case reports have questionable validity because of the limitations of commercial identification systems, use of inappropriate identification methods, significant changes in taxonomy, and lack of distinction between colonization and infection.[1]

Identification of significant clinical isolates of *Corynebacterium* spp. and antimicrobial susceptibility and synergy testing are warranted; identification is enhanced by the combination of biochemical testing using commercially available panels, sequence-based methods using 16S (small subunit) ribosomal RNA (rRNA) gene sequencing, and matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry.[3] Characteristics of reported infections caused by *Corynebacterium* species are outlined in Table 131.1. *Corynebacterium* infections among children rarely cause severe symptoms or mortality.[4]

TABLE 131.1

Characteristics of Infection and Habitats of Frequently Reported *Corynebacterium* Species

	Infection			
Species	**Normal Flora**	**Normal Host**	**Compromised Host**[a]	**Children**
C. afermentans	Human Animal	Brain abscess Hepatic abscess	BSI Endocarditis Pulmonary infections	
C. amycolatum		Septic arthritis Endocarditis	BSI Endocarditis Peritonitis	BSI
C. bovis	Animal	Skin infection Meningitis Mastoiditis	BSI Endocarditis Glomerulonephritis Meningitis Septic arthritis	
C. coyleae			Ascites Sepsis Skin/soft tissue infection	BSI
C. glucuronolyticum	Human Animal		Prostatitis Genitourinary infections	
C. jeikeium	Human	BSI Cardiac device infections Otitis media Septic arthritis	Abscess BSI Endocarditis Enteritis Meningitis Osteomyelitis Peritonitis Pneumonia Pyelonephritis Septic arthritis Skin infections Transverse myelitis Urinary tract infection Ventriculitis	Abscess BSI Endocarditis Meningitis Pulmonary infection
C. macginleyi			Catheter-related infection Conjunctivitis Endocarditis Endophthalmitis Keratitis Sepsis Urinary tract infection	S: Multiple V: FQ R: Ery

C. minutissimum[d]	Human	BSI Cellulitis Erythrasma (polymicrobial) Meningitis	BSI Abscess Endocarditis Erythrasma Peritonitis	Erythrasma Pyelonephritis
C. propinquum	Human	Endocarditis	Pulmonary infection	Endocarditis
C. pseudodiphtheriticum (Corynebacterium hofmannii)	Human	Conjunctivitis/keratitis Discitis Endocarditis Lymphadenitis Pharyngitis (membranous) Pulmonary infections Skin infections	BSI Endocarditis Peritonitis Pulmonary infections Septic arthritis Surgical site infection Urinary tract infection[d]	BSI Endocarditis Lymphadenitis Otitis media Pharyngitis (membranous) Pulmonary infections Surgical site infection Urinary tract infection
C. pseudotuberculosis (Corynebacterium ovis)	Animal	Lymphadenitis Pneumonia	Abscess Lymphadenitis Pneumonia	Lymphadenitis Septic arthritis
C. striatum[d]	Human		Endocarditis BSI Central line infection Chorioamnionitis Meningitis Osteomyelitis Peritonitis Pulmonary infections Septic arthritis Skin/soft tissue infection	BSI Ventriculitis
C. ulcerans	Animal	Pharyngitis (membranous) Sinusitis Skin ulcers	Pharyngitis Pneumonia Pulmonary nodules	Pharyngitis (membranous) Otitis media
***C. urealyticum* (group D2)**	Human		BSI Endocarditis Osteomyelitis Pericarditis Pneumonia Urinary tract infection (encrusted) Wound infection	Soft tissue infection Urinary tract infection
C. xerosis[d]	Human	Endocarditis	BSI Central nervous system infections	BSI Endocarditis Meningitis

			Endocarditis Keratitis (postoperative) Osteomyelitis Peritonitis Pulmonary infections Septic arthritis	Pericarditis Ventriculitis

[a] Compromised hosts include immunodeficient patients, neutropenic patients, those with indwelling devices, and postsurgery and trauma patients.

[b] There are no reports of controlled clinical trials using different antimicrobial agents in the treatment of infections with *Corynebacterium* species. Notation is based on antimicrobial susceptibilities reported in cases and laboratory evaluations.

[c] MDR: Multidrug resistance has been reported; the only drugs active against these strains are glycopeptides, linezolid, quinupristin/dalfopristin, daptomycin, and tigecycline.

[d] Some reports likely represent misidentification of *Corynebacterium amycolatum* or another *Corynebacterium* strain.[1]

[e] Surgical excision after parenteral antibiotic therapy is necessary for cure.

BSI, bloodstream infection; Amg, aminoglycosides; Ceph, cephalosporins; 1G Ceph, first-generation cephalosporins; 2G Ceph, second-generation cephalosporins; 3G Ceph, third-generation cephalosporins; Chloro, chloramphenicol; Clin, clindamycin; Dapto, daptomycin; Ery, erythromycin; Imip, imipenem; Lin, linezolid; Pcn, penicillin; FQ, fluoroquinolones; R, resistant; Rif, rifampin; S, susceptible; Teico, teicoplanin; Tet, tetracyclines; Tig, tigecycline; T/S, trimethoprim-sulfamethoxazole; V, variable; Vanc, vancomycin.

Corynebacterium Jeikeium

Corynebacterium jeikeium, formerly known as Centers for Disease Control and Prevention (CDC) group JK, was identified as a distinct group in 1976, and a pathogenic role in endocarditis after cardiovascular surgery has been noted since 1963. *C. jeikeium* increasingly has been identified in association with a variety of clinical entities, predominantly in immunocompromised people, and it is recognized as a significant nosocomial pathogen. *C. jeikeium* is the most frequently recovered medically significant corynebacterial species in patients in intensive care units.[5]

Only pathogenic for humans, *C. jeikeium* is found in soil and water and is part of normal human skin flora. The colonization rate increases with hospitalization; it has been reported in hospital personnel and in up to 40% of hospitalized patients, especially on the skin of the perirectal area, groin, and axilla.[6] Infection is thought to occur when *C. jeikeium* invades through mucosal breaks and colonizes prosthetic devices. Risk factors for *C. jeikeium* infection include prolonged hospitalization; profound, extended granulocytopenia; multiple or prolonged courses of antibiotic therapy; disruption of mucocutaneous barriers; and presence of a medical device.

In one study *C. jeikeium* was recognized as the most frequent cause of bloodstream infection (BSI) among patients who had received a bone marrow transplant[6]; BSI also has been reported among immunocompetent and immunosuppressed patients. *C. jeikeium* is the most common cause of diphtheroid endocarditis of prosthetic valves,[7] and it also can infect native valves. *C. jeikeium* infection is the corynebacteria infection most likely to require valve replacement.[8] Other infections attributed to *C. jeikeium* include skin and wound infections, catheter-related infection, enteritis, meningitis, osteomyelitis, peritonitis, pneumonia, prosthetic joint infection, pyelonephritis, and liver abscess in a patient with AIDS.[9–17] Several infections caused by *C. jeikeium* have been reported in children, including meningitis associated with a ventriculoperitoneal shunt, BSI, endocarditis, and a localized skin abscess at a puncture site.[18–20] Most cases were associated with immunosuppression, a medical device, or trauma.

C. jeikeium is a nonmotile, gram-positive bacillus that can appear to be coccobacillary. Growth appears as discrete, pinpoint, smooth white colonies that take on a characteristic metallic sheen after 24 to 48 hours of incubation. The bacterium ferments glucose but does not produce urease or reduce nitrate. Identification frequently is confirmed on the basis of resistance to many antibiotics, including β-lactams, aminoglycosides, erythromycin, and tetracycline. Vancomycin generally is the most active antibiotic against *C. jeikeium* and is the drug of choice for the treatment of these infections, although vancomycin resistance has been reported.[21] Telithromycin, linezolid, and quinupristin/dalfopristin have good in vitro activity.[22] Although some have suggested that removal of a central venous catheter may not always be necessary, removal of involved prosthetic devices usually is required for cure. *Corynebacterium* species form biofilms that are refractory to vancomycin therapy.[6,23] Prevention of nosocomial transmission of *C. jeikeium* depends on meticulous handwashing and aseptic technique. Further elucidation of the modes of transfer of *C. jeikeium* in healthcare settings may suggest additional methods of infection control.

Other *Corynebacterium* Species

The frequency of corynebacteria infections has been increasing over the past 20 years; in addition, many new *Corynebacterium* species have been established, and more new identifications are expected.[1] Corynebacteria are diverse morphologically, metabolically, and structurally. Multiple changes and improvements in the taxonomic framework for coryneform bacteria have facilitated clinical associations.

C. amycolatum, a species established in 1988, probably accounted for many previously reported infections that had been misidentified as *C. kutscheri, C. minutissimum, C. striatum,* and *C. xerosis.*[1] *C. amycolatum,* one of the species most commonly isolated from clinical specimens,[1] has been reported as a cause of septicemia in a patient with diabetes[24] and a premature infant,[25] and also as a cause of pyogenic arthritis.[26] *C. amycolatum* typically is resistant to multiple antibiotics but is susceptible to vancomycin and teicoplanin.

Other newly identified *Corynebacterium* spp. have been reported in association with human disease in rare cases; these include *C. accolens, C. afermentans, C. argentoratense, C. auris, C. falsenii, C. glucuronolyticum, C. kroppenstedtii, C. lipophiloflavum, C. macginleyi, C. propinquum, C. resistens, C. riegelli, C. simulans, C. tuberculostearicum,* and *C. ureicelerivorans.*[27–30]

Current methods of identification of *Corynebacterium* species, especially those relying on commercial identification systems, may be inadequate because a limited number of species are represented. Similarly, numerous differences within reference strains of *Corynebacterium* species have been noted.[1] Referral of isolates to a reference laboratory may be necessary. Standardized guidelines for susceptibility testing of *Corynebacterium* species were updated in 2010 and 2012.[31,32] Variable susceptibility to antimicrobial agents mandates specific testing of each clinical isolate. In general, *Corynebacterium* species are susceptible to vancomycin and linezolid.[3] Vancomycin is recommended for empiric therapy of suspected *Corynebacterium* infections. Multidrug-resistant strains have been identified, primarily *C. jeikeium*, *C. striatum*, and *C. urealyticum*.

Key Points

Corynebacterium Species

- *Corynebacterium* species often are dismissed as contaminants in clinical specimens; however, they increasingly are recognized as pathogens, especially in immunocompromised people.

- Newer molecular and protein fingerprinting methods of identification have led to clarification of the taxonomy of *Corynebacterium* species and have corrected some previous, misleading reports.

- *Corynebacterium* species have been associated with a variety of infections; the propensity for certain infections varies by species.

- Variable susceptibility of corynebacteria to antimicrobial agents, including some multidrug-resistant strains, requires specific susceptibility testing of each isolate.

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Listeria monocytogenes

Monica M. Farley

The bacterium *Listeria monocytogenes* is a rare but important cause of severe illness in neonates, pregnant women, older adults, and people with impaired cell-mediated immunity. It often presents as a life-threatening bloodstream infection (BSI) and meningoencephalitis or as less severe febrile gastroenteritis.[1,2] It has been established as a foodborne pathogen associated with both sporadic and outbreak-related disease, raising concerns about food safety and earning *L. monocytogenes* infection recognition as one of the most lethal foodborne diseases.[3]

Description of the Pathogen

L. monocytogenes is a facultatively anaerobic, nonsporulating, catalase-positive, oxidase-negative, short, nonbranching gram-positive bacillus that grows readily on blood agar, producing incomplete β-hemolysis.[4,5] The bacterium has polar flagellae and exhibits a characteristic tumbling motility at 25°C. Unlike most bacteria, *L. monocytogenes* grows well at refrigerator temperature (4°C to 10°C), and by so-called cold enrichment, it can be separated from other contaminating bacteria by long incubation in this temperature range. Selective media have been developed to isolate the organism from specimens containing multiple species (food, stool) that appear to be superior to cold enrichment.[4,6]

In clinical specimens the organisms can be gram variable and can resemble diphtheroids, cocci, or diplococci. The media typically used to isolate bacteria that cause diarrhea from stool cultures inhibit listerial growth. Laboratory misidentification of the organisms as diphtheroids, streptococci, or enterococci is not uncommon; therefore, isolation of a "diphtheroid" from blood or cerebrospinal fluid (CSF) should always alert the clinician to the possibility that the organism actually is *L. monocytogenes.*[7,8]

Of the six *Listeria* species (*L. monocytogenes, L. seeligeri, L. welshimeri, L. innocua, L. ivanovii,* and *L. grayi*), only *L. monocytogenes* is pathogenic for humans. *L. monocytogenes* has at least 13 serovars, but almost all disease is caused by types 4b, 1/2a, and 1/2b.[3,9] A number of molecular techniques, including pulsed-field gel electrophoresis, ribotyping, multilocus enzyme electrophoresis and, most recently, whole-genome sequencing (WGS) analysis by whole-genome multilocus sequence typing, have been used to categorize isolates into distinct groups and have proved useful for investigating epidemics.[10–15]

Epidemiology

L. monocytogenes is an important cause of zoonoses, especially in herd animals. Widespread in nature, it commonly is found in soil, decaying vegetation, and as part of the fecal flora of many mammals.[4,9] The organism also has been isolated from the stool of approximately 5% of adults,[9,16] and higher rates of recovery have been reported from household contacts of patients with clinical infection.[17] In three healthy, asymptomatic adults who were followed for 1 year, *L. monocytogenes* was present transiently in 3.5% of stool specimens.[18]

Many foods are contaminated with *L. monocytogenes,* and recovery rates of 15% to 70% and higher are common from raw fruits and vegetables, raw milk, fish, poultry, and meat, including fresh or processed chicken and beef available as ready-to-eat products at supermarkets and delicatessen (deli) counters.[5] Although disease is rare, ingestion of *L. monocytogenes* must be a common occurrence.

Two active surveillance studies performed in the 1980s by the

Centers for Disease Control and Prevention (CDC) indicated annual infection rates of 0.74 cases per 100,000 population, accounting for approximately 1850 cases a year in the United States and 425 deaths.[19] Listeriosis declined significantly over the next two decades, after food industry regulations were instituted to minimize the risk of foodborne listeriosis. Surveillance reports from 2009 to 2011 showed a low but stable incidence rate of 0.29 cases per 100,000 population.[20–22] The highest infection rates are seen among older adults, people who are immunocompromised, pregnant women, and newborns (Fig. 132.1).[12,19,21] In a report that summarized data from U.S. listeriosis cases and outbreaks between 2009 to 2011, pregnancy-associated disease (maternal and fetal/newborn) accounted for 14% of all cases, and the risk was highest among pregnant women of Hispanic ethnicity.[21] Compared with the general population, the rate was 4-fold higher for adults 65 years or older, 10-fold higher for pregnant women, and 24-fold higher for pregnant Hispanic women.[21]

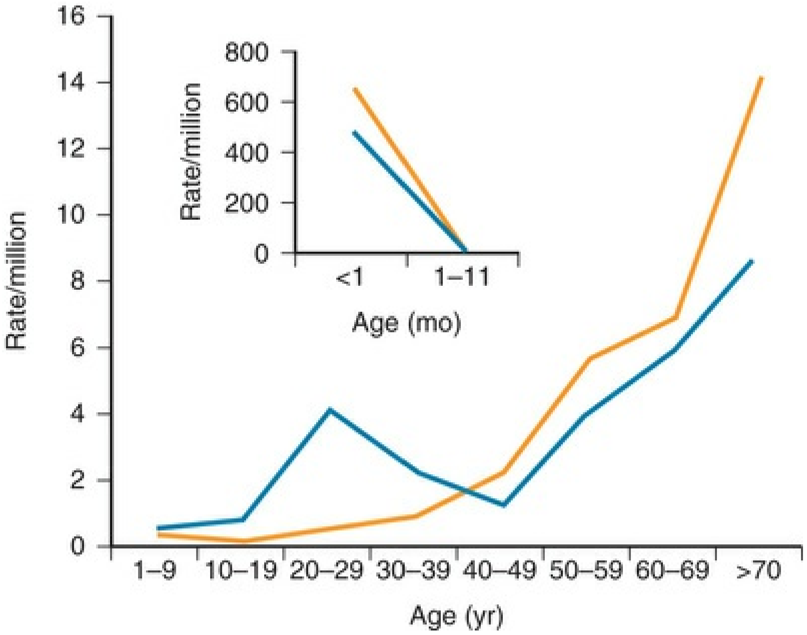

FIGURE 132.1 Age-specific incidence of listeriosis by gender. The *orange line* indicates male patients; the *blue line* indicates female patients. (Redrawn from Ciesielski CA, Hightower AW, Parsons SK, et al. Listeriosis in the United States: 1980–1982. Arch Intern Med 1988;148:1416–1419.)

Most cases that are not associated with pregnancy (≥70%) occur in individuals with one or more underlying conditions, including malignancy, diabetes mellitus, renal failure, AIDS, organ transplantation, and cirrhosis, and in patients receiving immunosuppressive agents, including corticosteroids and biologic immune modulators used in immunologic or inflammatory diseases.[23]

Listeria was recognized as a foodborne pathogen after a 1983 report described a foodborne outbreak of human listerial infection in Canada that was linked convincingly to contaminated coleslaw.[16] Many subsequent foodborne outbreaks resulting in invasive disease (BSI, meningitis) have been documented[12,24]; vehicles have included milk,[25] soft cheeses,[26,27] ice cream,[28] cantaloupes,[21] stone fruit,[14] prepackaged caramel apples,[29] sprouts, ready-to-eat seafood, pork products,[30] hot dogs, and deli-ready turkey.[31,32] *L. monocytogenes* can persist in food processing environments and contribute to ongoing food contamination.[33] Substantial economic losses have occurred from major food recalls prompted by outbreaks and/or detection of *Listeria* in food commodities. The importance of food as a source of sporadic listeriosis was illustrated by two CDC studies, which showed that 11% of all refrigerator food samples were contaminated with *Listeria*; 64% of infected patients had at least one food item in their refrigerator that was contaminated; and in 33% of cases, isolates from the patient and from a contaminated food were identical strains.[34,35]

Although most cases of human listeriosis appear to be foodborne, other modes of transmission are possible, such as transmission from mother to child transplacentally or through an infected birth canal, and cross infection in neonatal nurseries.[36,37] A common-source outbreak was traced to contaminated mineral oil used for bathing infants.[38] Localized cutaneous infections have occurred in veterinarians and farmers after direct contact with aborted calves and infected poultry. *L. monocytogenes* has been isolated from units of donated apheresis platelets on multiple occasions, but no contaminated units have been transfused.[39,40]

In 1998 the CDC added *L. monocytogenes* to PulseNet (http://www.cdc.gov/pulsenet/), a network of public health and food regulatory laboratories that use pulsed-field gel electrophoresis to subtype foodborne pathogens so as to speed detection of disease clusters that may have a common source.[41] This system has been used effectively for the early detection of outbreaks of listeriosis.[12,42] Future monitoring may rely on methods involving whole-genome sequencing.[14,15]

Pathogenesis

Except for vertical transmission from mother to fetus and rare instances of cross contamination in the delivery suite or neonatal nursery, human-to-human infection has not been documented.

Most often, listeriae are acquired through ingestion of contaminated food.[2,5,12] The oral inoculum required to produce clinical infection has not been not well established yet, but infectious doses in animal experiments have ranged from 10^4 to 10^9 organisms.[43,44] The infectious dose may be lower in people who are immunocompromised and in those with reduced gastric acid production because of the use of antacids, histamine-2 (H_2) blocking agents, proton pump inhibitors, or ulcer surgery.[45,46] The incubation period appears to be shorter than the previously accepted 31 days[26] and varies by clinical syndrome. A careful analysis of 37 *Listeria* cases with precise incubation periods, reported over a 32-year period, demonstrated the following incubation periods: overall incubation period for all invasive listeriosis, 8 days (range, 1 to 67 days); pregnancy-associated disease, 27 days (range, 17 to 67 days); BSI, 2 days (range, 1 to 12 days); and central nervous system (CNS) infection, 9 days (range, 1 to 14 days). The median incubation period for gastroenteritis was much shorter (mean, 24 hours; range, 6 to 240 hours).[47] Although not required for *L. monocytogenes* infection, intercurrent gastrointestinal infection with another pathogen may enhance invasion in people colonized with *L. monocytogenes*.[48,49] Both meningitis and BSIs caused by *Listeria* have occurred shortly after colonoscopy and sigmoidoscopy.[50,51]

After ingestion of *L. monocytogenes,* bacteria can colonize the intestine or cross the intestinal epithelium via transcytosis and invade mesenteric lymph nodes and the blood.[5,52,53] The liver and spleen are target organs that may serve as reservoirs of persistent organisms.[53] Once the bacteria are in the bloodstream, dissemination can occur to any site; *L. monocytogenes* has a particular predilection for the CNS and the placenta. It is generally believed that listeriae reach the CNS by a bacteremic route, but animal experiments suggest that rhombencephalitis can develop by intra-axonal spread of bacteria from peripheral sites to the CNS.[54] The intracellular, molecular pathogenesis of listeriosis has been reviewed in detail.[53,55–57] Several virulence factors enable *L. monocytogenes* to thrive as an intracellular organism. The listerial surface proteins internalin A and internalin B (InlA and InlB) aid adherence to cell surface receptors, including[58] E-cadherin, a receptor on macrophages and intestinal epithelial cells, to promote entry of the organism into the host cell.[52,53,59,60] A major virulence factor, pore-forming listeriolysin O, along with phospholipases, enables listeriae to escape from the phagosome and avoid intracellular killing.[61] Once free in the cytoplasm, the bacterium can divide and, by inducing host cell actin polymerization, propel itself to the cell membrane,[53,62] where pseudopod-like projections enable invasion of adjacent host cells (Fig. 132.2). The bacterial surface protein ActA is necessary to induce actin filament assembly into a cometlike tail that promotes cell-to-cell spread, thus maintaining an intracellular life cycle to evade the host immune response. *Listeria* organisms have a variety of mechanisms that facilitate iron acquisition, transport, and metabolism.[5,63] In vitro, iron enhances organism growth; in animal models of listerial infection, iron overload is associated with enhanced susceptibility to infection and iron supplementation with enhanced lethality, whereas iron depletion results in prolonged survival.[64] The clinical associations of listerial infection with hemochromatosis[8] and of outbreaks in dialysis patients with transfusion-induced iron overload[65] attest to the importance of iron in the pathogenesis of listeriosis.

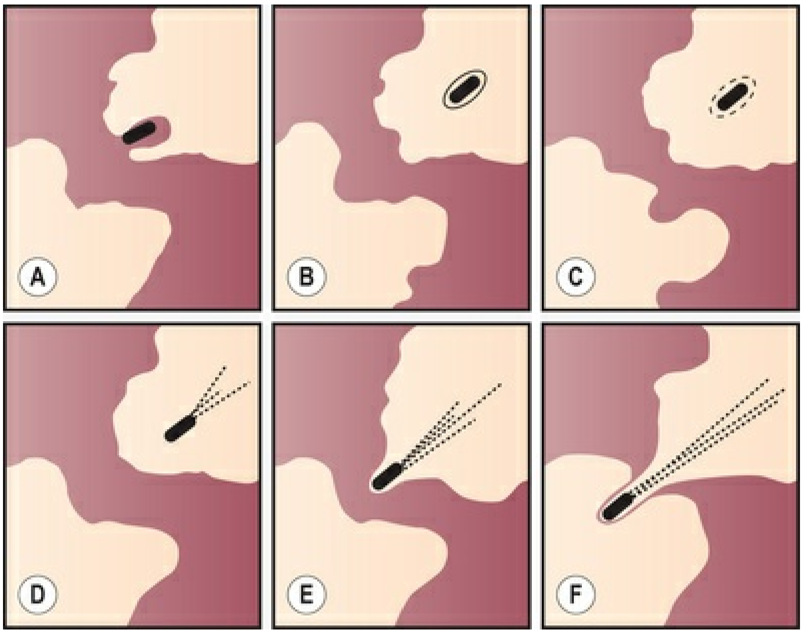

FIGURE 132.2 Steps in the engulfment of *Listeria monocytogenes* and subsequent transfer of the bacterium from one macrophage to another. (A) Adjacent macrophages, one of which has been induced to phagocytose *L. monocytogenes*. (B) After ingestion the organism is held in a single membrane phagosome. (C) Through the action of listeriolysin O, the bacterium escapes from the phagocytic vacuole before it is damaged and replication occurs. (D) Host cell actin is induced by the organism, now free in the cytoplasm. (E) Polymerized actin forms an elongating lattice that propels the bacterium to the host cell membrane, forming a pseudopod-like extension. (F) The pseudopod-like extension containing a bacterium is engulfed by an adjacent macrophage, resulting in a double-membrane vacuole. (Drawing by B. Lorber.)

Immunity

Resistance to listerial infection involves both innate and adaptive immune responses.[66] The adaptive response primarily is cell mediated, as evidenced by experiments showing that immunity can be transferred by sensitized lymphocytes but not by antibodies.[67] Further evidence is provided by the overwhelming clinical association between listerial infection and conditions of impaired cellular immunity, including lymphoma, pregnancy, AIDS, and corticosteroid immunosuppression.[1,2,7,8,68–70] Invasive listeriosis has complicated the use of agents that neutralize tumor necrosis factor-α (e.g., infliximab) in a variety of conditions.[71–75] In a murine model, tumor necrosis factor was found to play a critical role in the intracerebral control of *L. monocytogenes* infection.[76] Toll-like receptor 2 contributes to the recognition and control of listeriosis.[77] The role of humoral immunity is unknown, although both immunoglobulin M (absent at birth) and classical complement activity (low in neonates) have been shown to be necessary for efficient opsonization of *L. monocytogenes.*[78]

Listeriosis has been reported to be 100 to 1000 times more common in patients with AIDS compared with the general population.[79–82] However, listerial infection rates have declined as a result of effective antiretroviral therapy with immune reconstitution and the use of trimethoprim-sulfamethoxazole (TMP-SMX) for prophylaxis against *Pneumocystis jirovecii* pneumonia.[22,83] The frequency of listeriosis is not increased in people with neutrophil deficiencies in number or function, splenectomy, persistent complement deficiency, or immunoglobulin disorders; the latter finding is not surprising because of the cell-to-cell spread of *L. monocytogenes* and the predominant intracellular location.

Clinical Syndromes

The species name derives from the fact that an extract of the *L. monocytogenes* cell membrane has potent monocytosis-producing activity in rabbits; however, monocytosis is an uncommon feature of human infection.[84,85]

Infection in Pregnancy.

During gestation, mild impairment of cell-mediated immunity occurs, and pregnant women have at least a 10-fold increased risk of developing listerial BSI.[21,86,87] Listeriae can proliferate in the placenta, which serves as a sanctuary site that is not subject to the usual defense mechanisms, and cell-to-cell spread facilitates maternal-fetal transmission.[88,89] Listeriosis in pregnant women can be asymptomatic; can result in mild symptoms, including gastroenteritis or flulike symptoms; or can result in overt sepsis. CNS infection, the most commonly recognized form of listeriosis in other groups, is rare during pregnancy in the absence of other risk factors.[1,16,19] BSI manifests clinically as an acute febrile illness, often accompanied by myalgia, arthralgia, headache, and backache. Maternal mortality is uncommon. Infection can occur at any time during pregnancy but is most common in the third trimester, probably because of the major decline in cell-mediated immunity seen at 26 to 30 weeks of gestation.[86]

Neonatal Infection.

Despite relatively mild and often self-limited maternal disease manifestations, the impact on the fetus can be devastating. Between 20% and 33% of pregnancy-related infections result in fetal loss from stillbirth or spontaneous abortion. The risk of fetal/neonatal loss is significantly greater with earlier gestational age at the time of onset of listeriosis; when *Listeria* is isolated from the mother's blood; and with a history of symptomatic maternal infection.[90–92] Prompt diagnosis and antimicrobial therapy can result in the birth of a healthy infant.[93,94] The fetus can be stillborn or can die within hours as a result of a disseminated form of listerial infection known as granulomatosis infantiseptica, which is characterized by widespread microabscesses and granulomas that are particularly prevalent in the liver and spleen. With this infection, abundant bacteria often are visible on a Gram stain of the meconium.[95–97]

Most pregnancy-associated *Listeria* cases result in live births. Neonatal infection manifests similarly to group B streptococcal disease in one of two forms[2]: (1) early onset sepsis syndrome, most often occurring in the first 48 hours after birth, usually associated with prematurity, and probably acquired in utero; or (2) late onset meningitis, occurring at about 2 weeks of age in term infants, who most likely acquired organisms from the maternal vagina at parturition.[38]

In early onset disease, *L. monocytogenes* can be isolated from the conjunctivae, external ear, nose, throat, meconium, amniotic fluid, placenta, and blood and sometimes from the CSF. A Gram stain of meconium may show gram-positive rods, allowing early diagnosis. The highest concentrations of bacteria are found in the neonatal lung and gut, which suggests that infection may be acquired in utero from infected amniotic fluid rather than by a hematogenous route.[98] In rare cases, purulent conjunctivitis and a disseminated papular rash have been described in neonates with early onset disease, but clinical infection is otherwise similar to infections caused by other bacterial pathogens.

Bloodstream Infection.

Bacteremia without an evident focus is the most common manifestation of listeriosis after the neonatal period.[1,2,12] Clinical manifestations typically include fever and myalgias; a prodromal illness with nausea and diarrhea can occur.

Meningitis.

An active surveillance study of bacterial meningitis from 2003 to 2007 showed that *L. monocytogenes* accounted for 5% of cases in neonates and 9% of those in people 65 years of age or older; this represented an overall decline of 46% and 36%, respectively, compared with earlier meningitis surveillance studies.[83,99] Worldwide, *L. monocytogenes* is one of the three major causes of neonatal meningitis, and it remains an important cause of bacterial meningitis in older adults, particularly those with malignancies or organ transplants, and those receiving immunosuppressive therapy for any reason.[2,83,100–102]

Clinically, meningitis caused by *L. monocytogenes* generally is similar to meningitis from more common causes.[103] However, *L. monocytogenes* has tropism for the brain parenchyma (particularly the brainstem) and the meninges.[2,8] Many patients with meningitis experience altered consciousness, seizures, or movement disorders and actually have meningoencephalitis. Features particular to listerial meningitis are summarized in Table 132.1.

TABLE 132.1

Distinctive Features of Listerial Meningitis Compared with Those of More Common Bacterial Etiologies

Feature	Rate of Occurrence (%)
CLINICAL AND LABORATORY	
Subacute presentation (>24 hr) is more common	~60
Unimpaired neck movement is more common	25
Movement disorders (ataxia, tremors, myoclonus) are more common	15–20
Seizures are more common	~25
Fluctuating mental status is common	~75
Focal neurologic findings are more common	35–40
Positive blood culture result is more common	63–75
CEREBROSPINAL FLUID (CSF)	

Positive Gram stain result is less common	30–40
Normal CSF glucose level is more common	>60
Mononuclear cell predominance is more common	~30

In several studies of *L. monocytogenes* meningitis in adults,[104,105] notable clinical features included headache (67% to 88%), nausea or vomiting (46% to 83%), and fever (90% to 91%); however, only 70% to 75% of patients had a stiff neck at the time of presentation. A focal neurologic deficit was present in 32% to 37% (likely reflecting the organism's propensity for brain parenchymal involvement). Just under one half (43% to 49%) had the classic meningitis triad of fever, neck stiffness, and change in mental status. In one study[104] 19 of 30 patients had experienced symptoms for longer than 24 hours at presentation, and 8 had symptoms for 4 days or longer. In another study, the median duration of symptoms at the time of presentation was 70 hours.[105] Remarkable CSF findings included a median white blood cell count of 550 to 620 cells/mL (range, 24 to 16,003 cells/mL) and a protein level of 252 mg/dL. Gram stain of CSF revealed a gram-positive rod in only 28% to 30% of patients, and blood cultures were positive in 46% to 63% of patients. Sixteen percent of survivors had sequelae at discharge, including hemiparesis and cranial nerve palsies; the mortality rate was 15% to 28%.[104,105]

Brainstem Encephalitis (Rhombencephalitis).

An unusual form of listerial encephalitis involves the brainstem[106] and is similar to the unique zoonotic listerial infection known as circling disease of sheep.[107] In contrast to other listerial CNS infections, this illness usually occurs in healthy older children and adults; neonatal cases have not been reported. The typical clinical picture is a biphasic illness with a prodrome of fever, headache, nausea, and vomiting lasting about 4 days, followed by the abrupt onset of asymmetric cranial nerve deficit, cerebellar signs, and hemiparesis or hemisensory deficit, or both. Respiratory failure develops in about 40% of cases, and nuchal rigidity is present in about 50%. The CSF is only mildly abnormal, and the CSF culture result is positive in about one third of cases; almost two thirds are bacteremic. Magnetic resonance imaging is superior to computed tomography for demonstrating rhombencephalitis.[106,108] Mortality is high, and serious sequelae are common in survivors.

Brain Abscess.

Macroscopic brain abscesses account for about 10% of CNS listerial infections. Bacteremia is almost always present, and concomitant meningitis, with isolation of *L. monocytogenes* from the CSF, is found in 25% of cases; both of these features are rare in other forms of bacterial brain abscess.[109] About 50% of cases occur in groups known to be at risk for listerial infection. Subcortical abscesses in the thalamus, pons, and medulla are common; localization in these sites is exceedingly rare when abscesses are caused by other bacteria. Mortality is high, and survivors usually have serious sequelae.[110]

Endocarditis.

Listerial endocarditis accounts for about 6% to 7.5% of adult listerial infections.[8,111] It affects the population at risk for viridans streptococcal endocarditis, produces both native valve and prosthetic valve disease, and has a high rate of septic complications; the mortality rate is 48%.[112,113] Cases in children are rare.

Localized Infection.

Rare reports of focal infections from which *L. monocytogenes* has been isolated include direct inoculation resulting in conjunctivitis,[114] skin infection,[115] and lymphadenitis.[8] BSI can lead to hepatic infection,[116,117] cholecystitis,[118,119] peritonitis,[120,121] splenic abscess,[9] pleuropulmonary infection,[122–124] septic arthritis (and often prosthetic joint infections later),[125,126] osteomyelitis,[127] pericarditis,[128] myocarditis,[129] infected aortic aneurysm,[130,131] and endophthalmitis/panophthalmitis.[8,132] Complications, including disseminated intravascular coagulation,[133] adult respiratory distress syndrome,[134] and rhabdomyolysis with acute renal failure,[135] have been documented. Nothing clinically unique distinguishes these localized infections; many, but not all, have occurred in people known to be at risk for listeriosis.

Febrile Gastroenteritis.

Patients with invasive listeriosis can have a history of antecedent gastrointestinal illness, often accompanied by fever. Although sporadic cases of gastrointestinal illness caused by *L. monocytogenes* appear to be rare,[136] multiple outbreaks of foodborne gastroenteritis caused by the organism have been documented.[137] In a particularly large outbreak involving two schools, 1566 individuals, most of them children between the ages of 6 and 10, became ill after eating cafeteria food provided by caterers; 19% were hospitalized.[138] Illness typically occurs 24 hours (range, 6 hours to 10 days) after ingestion of a large inoculum of bacteria and usually lasts 1 to 3 days (range, 1 to 7 days); attack rates are high (52% to 100%) and often involve healthy individuals. Common symptoms include fever, watery diarrhea, nausea, headache, and pains in joints and muscles. Vehicles of infection have included chocolate milk, cold corn and tuna salad, cold smoked trout, jellied pork, and deli meat. *L. monocytogenes* should be considered a possible etiology in outbreaks of febrile gastroenteritis when routine cultures fail to yield a pathogen.

Diagnosis

Diagnosis requires isolation of *L. monocytogenes* from clinical specimens (e.g., CSF, blood) and identification of the organism through standard microbiologic techniques. Antibodies to listeriolysin O have not proved useful in invasive disease,[139] nor have polymerase chain reaction probes.[140] Antibodies to listeriolysin O may be useful during investigations of outbreaks of febrile gastroenteritis.[141] Selective media are required to isolate *Listeria* from stool specimens, and use of such media should be considered in an outbreak of febrile gastroenteritis when the results of routine stool cultures are negative.[142] MRI is superior to CT for demonstrating parenchymal brain involvement, especially in the brainstem.[106,108]

Treatment

No controlled trials have established a drug of choice or duration of therapy for listerial infection. Ampicillin generally is considered the preferred agent.[8,143–146] Based on the synergy seen in vitro and in animal models,[147] many authorities suggest adding gentamicin to ampicillin for treatment of BSI in patients with significant immunocompromising conditions, particularly in cases of meningitis and endocarditis.[144] However, clinical evidence for an improved outcome with the addition of aminoglycosides, gathered from observational studies of listeriosis in adults who were not pregnant, is inconclusive.[148] In one nonrandomized study,[149] the combination of TMP-SMX plus ampicillin was associated with a lower failure rate and fewer neurologic sequelae than ampicillin combined with an aminoglycoside.

TMP-SMX is the best alternative for patients intolerant of penicillins.[144,150–152] In rare cases, oral TMP-SMX has been used effectively.[153] Meropenem has been suggested as an alternative treatment for *Listeria* meningitis.[154] No currently available cephalosporin should be used because none has adequate activity,[144,155] and meningitis has developed in patients receiving cephalosporins.[156] For this reason, ampicillin always is included in empiric therapy for septicemia or meningitis in infants younger than 2 months of age, and it is recommended for empiric coverage of bacterial meningitis in pregnant women, adults with immunocompromising conditions, and people older than 50 years of age.[154]

Vancomycin has been used successfully in a few patients with penicillin allergy,[157,158] but other patients have developed listerial meningitis while receiving vancomycin.[159] Rifampin is active in vitro; however, clinical experience is minimal, and in animal models the addition of rifampin to ampicillin was not more effective than was ampicillin used alone.[145] Although fluoroquinolones and linezolid show good in vitro activity, clinical experience is mixed,[160–162] and to date too limited to support recommending these agents for therapy.

With listerial infections, initial dosing of antibiotics as for meningitis is prudent for all patients, even in the absence of CNS or CSF abnormalities, because of the high affinity of *L. monocytogenes* for the CNS. Patients with listerial meningitis should be treated for no fewer than 3 weeks; bacteremic patients without CSF abnormalities can be treated for 2 weeks.

No data are available on antimicrobial efficacy in listerial gastroenteritis. The illness generally is self-limited, but secondary meningitis that developed 19 days after febrile gastroenteritis has been reported in a 72-year-old adult[163]; this suggests that treatment may be prudent in a patient at high risk for invasive listeriosis.

Extracorporeal membrane oxygenation has been used with some success in neonates with severe *L. monocytogenes* disease.[164]

Prevention

Recommendations for prevention of listeriosis from a foodborne source are presented in Box 132.1.[165–167]

Box 132.1

Dietary Recommendations for Preventing Foodborne Listeriosis

For All People

1. Rinse raw produce (e.g., fruits and vegetables) thoroughly under tap water before preparing
2. Scrub firm produce (e.g., melons and cucumbers) with a clean brush
3. Keep uncooked meats separate from vegetables, cooked foods, and ready-to-eat foods
4. Cook raw food from animal sources (e.g., beef, pork, and poultry) thoroughly
5. Avoid consumption of raw (unpasteurized) milk or foods made from raw milk
6. Wash hands, knives, and cutting boards after handling uncooked foods
7. Use precooked or ready-to-eat foods as soon as possible; do not use them after the use-by date

Additional Recommendations for People at High Risk[a]

1. Avoid soft cheeses (e.g., queso, feta, Brie, Camembert) and blue-veined cheese; hard cheeses, cream cheese, cottage cheese, and yogurt need not be avoided

2. Heat leftover foods or ready-to-eat foods (e.g., hot dogs, deli meats) until steaming hot before eating

3. Consider avoiding foods from delicatessen counters[b]

4. Avoid refrigerated seafood products unless canned or shelf stable

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[a] People immunocompromised by illness or medications, pregnant women, and the elderly.

[b] Although the risk of listeriosis associated with foods from delicatessen counters is relatively low, pregnant women and immunosuppressed people may choose to avoid these foods or to reheat cold cuts thoroughly before consumption.

Complication of successive pregnancies by a neonatal listerial infection is virtually unknown; therefore, intrapartum antibiotic therapy is not recommended for mothers with a history of perinatal listeriosis. No vaccine is available for listeriosis. Effective prevention of listerial infections can be achieved by administration of TMP-SMX, given as prophylaxis for *P. jirovecii* pneumonia, to recipients of organ transplants or to people with HIV.[168,169]

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Key Points

Listeria monocytogenes

Microbiology

- *L. monocytogenes* is a gram-positive rod; these organisms often are mistaken for diphtheroids, streptococci, or enterococci.

- Isolation of a "diphtheroid" from a normally sterile body fluid, particularly cerebrospinal fluid, should alert the clinician to the possibility of listeriosis.

Epidemiology

- Illness is primarily zoonotic, particularly in herd animals.
- Transmission occurs from mother to fetus/neonate in utero; in humans it occurs at birth.
- After the neonatal period the infection typically is a foodborne illness; highest risk foods are deli-style, ready-to-eat meats and unpasteurized cheeses.
- At-risk populations include neonates, older adults, pregnant women, and people with impaired cell-mediated immunity as a result of disease (e.g., malignancy, cirrhosis, diabetes, renal failure) or immunosuppressive therapy (e.g., corticosteroids, anti–tumor necrosis factor agents).

Clinical Features

- Bloodstream infection and meningoencephalitis are the most common invasive infections.
- Meningitis can be subacute.
- Neonatal infection occurs as both early and late onset disease, similar to *Streptococcus* group B infection.
- Acute febrile gastroenteritis occurs more often in outbreaks than sporadically; consider especially in a foodborne outbreak with negative results on routine stool cultures.

Diagnosis

- Consider especially in the following:

▪ Sepsis or meningitis in infants younger than 2 months of age

▪ Meningitis or parenchymal brain infection in people with impaired cell-mediated immunity

- Fever during pregnancy
- Subcortical brain abscess or brainstem infection

Treatment

- Ampicillin plus consideration of gentamicin is recommended for central nervous system infections.
- Cephalosporins are not adequate therapy.
- Trimethoprim-sulfamethoxazole is recommended for patients allergic to penicillin.

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133

Other Gram-Positive Bacilli

Denise F. Bratcher

A number of pleomorphic, nonsporulating, gram-positive bacilli have long been identified as “diphtheroids” and dismissed as contaminants. However, many of these organisms can cause endocarditis and other serious diseases, especially in immunosuppressed patients. For this reason, coryneform bacteria isolated from clinical specimens should be identified as a matter of routine, particularly if they are found in pure culture, are from multiple specimens, or are found in immunocompromised patients.

Erysipelothrix rhusiopathiae

Erysipelothrix rhusiopathiae first was isolated in 1878 from mice by Koch. It later was identified as the cause of swine erysipelas and as a human pathogen. In recent years *E. rhusiopathiae* has become recognized as a cause of serious human diseases.[1]

Microbiology.

E. rhusiopathiae is a gram-positive, pleomorphic, non–spore-forming, nonmotile, encapsulated, aerobic or facultatively anaerobic bacillus. Older colonies can lose cell wall integrity, making them appear to be gram negative or gram variable. The organism grows readily on standard media and in conventional blood culture systems. Both rough and smooth colonies are noted on blood agar. Smears from rough colonies can show granular, nonbranching filaments. Some strains can cause α-hemolysis in 48 to 72 hours. *E. rhusiopathiae* is distinguished readily from other morphologically similar, gram-positive bacteria (*Listeria* species and diphtheroids) by an absence of motility, a negative catalase reaction, and hydrogen sulfide (H_2S) production. *E. rhusiopathiae* is oxidase and urease negative; it produces acid from glucose and lactose. A growth pattern in gelatin stab cultures that resembles a test-tube brush or a pipe cleaner is highly characteristic.

Epidemiology.

E. rhusiopathiae, a ubiquitous organism, is primarily a pathogen of animals. It has been isolated from wild mammals; various fowl, fish, and shellfish; and from domestic animals, such as pigs, sheep, cattle, and horses.[1,2] Contaminated soil is thought to be a source. Human infections often are to the result of occupational exposure to infected animals or contaminated animal products. People at risk include slaughterhouse workers, butchers, poultry workers, fishermen, fish marketers, veterinarians, farmers, and housewives.[2] The incidence of human infection is higher in the summer months. A 4 : 1 male preponderance may reflect male occupational exposure.

Clinical Manifestations.

The three major types of clinical disease are (1) the most common form, a localized, recurring but usually self-limited, cutaneous form, known as erysipeloid, which resembles streptococcal erysipelas; (2) a diffuse cutaneous form, which manifests with multiple skin lesions and systemic symptoms; and (3) a systemic form, which is marked by septicemia and endocarditis. Erysipeloid is a painful, inflammatory lesion of the skin that usually involves the hands and fingers and commonly occurs at the site of a scratch contaminated through contact with animals or other infectious material. The incubation period is 1 to 7 days (usually <4 days) after inoculation. The lesion appears with a characteristic purplish red hue and irregular, raised borders that spread peripherally as central clearing occurs. The lesion can spread proximally to involve an adjacent joint. Erysipeloid lesions usually recover in 1 to 4 weeks.

The diffuse cutaneous form of *E. rhusiopathiae* infection, with progression of violaceous lesions remote from the initial site, is rarely reported; it is associated more frequently with systemic symptoms, such as fever, malaise, arthralgia, myalgia, and severe headache. Although this form of the infection is not accompanied by bacteremia, its clinical course is more protracted and often complicated by recurrences.[2–4]

Septicemia and endocarditis are rare complications of *E. rhusiopathiae* infections, including occupationally acquired diseases.[1] Of more than 50 reported cases of bloodstream infection (BSI) caused by *E. rhusiopathiae,* approximately 90% were associated with endocarditis, which manifests as an acute or subacute process and is preceded by erysipeloid lesions in only one third of cases. The infection commonly affects people of normal health. It also affects native heart valves, involving the aortic valve in 70% of reported cases. Approximately 40% of patients have had previous heart disease. Valvular degeneration and abscess are common,[5] and intracranial complications have been reported.[6–9] Some experts have questioned whether *E. rhusiopathiae* bacteremia has a predilection for association with endocarditis.[10]

A variety of other infections associated with *E. rhusiopathiae* have been reported, such as BSI resulting from colonic perforation by a toothpick, and BSI in patients with lupus nephritis, HIV infection, and Crohn disease. Conditions associated with *E. rhusiopathiae* infection have included chronic meningitis, vertebral osteomyelitis, pyogenic arthritis, infected arthroplasty, pneumonia, peritonitis associated with peritoneal dialysis, intra-abdominal abscess, spinal abscess, necrotizing fasciitis, and infection from cat bite.[4,11–24]

Reported pediatric infections include endocarditis; BSI with acute leukemia, systemic lupus erythematosus, and HIV infection; systemic disease and pleural effusions; empyema, septic arthritis, pyomyositis, osteomyelitis, and localized infection of the knee.[3,6,25–30]

Diagnosis.

The diagnosis of erysipeloid relies on clinical recognition and an epidemiologic link to animal exposure. The organism is located deep in the reticular layer of the dermis; successful isolation from a skin lesion requires a full-thickness biopsy obtained from the peripheral quadrant of the lesion.[4] *E. rhusiopathiae* is isolated from blood in patients with septicemia or endocarditis. A high index of suspicion is necessary because these isolates occasionally are misidentified as streptococci or considered insignificant diphtheroids.[2,13] Serologic diagnostic methods are unreliable; however, polymerase chain reaction (PCR) methods may improve diagnostic accuracy in the future.[3]

Treatment.

Penicillin is considered the drug of choice for *E. rhusiopathiae* infections, based on exquisite susceptibility in vitro and limited clinical experience. Imipenem also has excellent activity against *E. rhusiopathiae* in vitro, followed by cefotaxime, clindamycin, tetracycline, and chloramphenicol. The organism is resistant to aminoglycosides, vancomycin, teicoplanin, and trimethoprim-sulfamethoxazole.[24] *E. rhusiopathiae's* resistance to vancomycin is noteworthy because this drug frequently is used as empiric therapy for endocarditis, especially in patients allergic to penicillin. Oral penicillin therapy usually is adequate for erysipeloid. *E. rhusiopathiae* BSI and endocarditis are best treated with aqueous penicillin G, 12 to 20 million units intravenously daily, in divided doses every 4 hours for 4 to 6 weeks.[1,2] No data are available to evaluate in vitro synergy with an aminoglycoside. Surgical intervention often is indicated for endocarditis.[31] Alternative drugs for patients allergic to penicillin include cephalosporins, imipenem, and fluoroquinolones.[10,32–34]

Rothia dentocariosa

Microbiology.

Rothia dentocariosa is a nonmotile, non–spore-forming, non–acid-fast, gram-positive bacillus with a variable morphology that includes coccoid and branching filamentous forms. Preferring aerobic conditions, *R. dentocariosa* grows less well in microaerophilic environments. The organism is slow growing and occasionally is isolated from anaerobic cultures that have been held longer than aerobic cultures. Colonies are either smooth and convex or rough with a "spoke-wheel" surface with scalloped edges.[35] *R. dentocariosa* produces acid from glucose, sucrose, maltose, and glycerol; it is catalase positive and oxidase, indole, and urease negative (although urease-positive and catalase-negative strains have been identified). *R. dentocariosa* hydrolyzes esculin, reduces nitrate, produces hydrogen sulfide, and typically is identified correctly by commercial identification systems. Microbial identification also has been confirmed by 16S (small subunit) ribosomal RNA (rRNA) gene sequencing.[36]

Epidemiology.

R. dentocariosa, part of the normal flora of the human mouth, first was isolated from dental caries in 1949 and remains a constituent of carious teeth.[37] This organism's pathogenic potential has been confirmed by a growing body of case reports, predominantly of infective endocarditis.

Clinical Manifestations.

The first human infection involving *R. dentocariosa,* a periappendiceal abscess, was reported in 1975. Since then, rare *R. dentocariosa* infections in people of normal health have been reported: BSI, periodontitis, pericoronitis, maxillary cyst, pilonidal cyst, and endocarditis.[38–48] Endocarditis associated with *R. dentocariosa* is reported most commonly. It typically involves native valves with preexisting cardiac abnormalities in patients with carious dentition or periodontitis, or who have undergone dental manipulation; occasionally prosthetic valves are involved.[41–51] Complications of endocarditis include brain abscess, multiple intracranial hemorrhages, mycotic aneurysms, and subarachnoid hemorrhages and aneurysm.[42–46,52] A few patients also had an underlying malignancy.[41,49] Additionally, *R. dentocariosa* has caused pneumonia and BSI in patients with underlying lung cancer and leukemia; peritonitis associated with peritoneal dialysis; septic arthritis in an immunosuppressed patient with rheumatoid arthritis; and arteriovenous fistula infection in a diabetic patient undergoing hemodialysis.[53–59] A proposed etiologic association with cat-scratch disease has not been verified.

Few *R. dentocariosa* infections have involved children.[47] Reported cases include BSI without endocarditis (in a neonate) and complicating lymphoproliferative disease after renal transplantation, congenital heart disease, and herpangina. Case reports also include severe exudative tonsillitis in a healthy 4-year-old child and corneal abscess in an 11-year-old boy who licked his fingertip before rubbing his eye.[60–64] Fetal blood cultures grew *R. dentocariosa* in an intrauterine fetal death.[65]

Treatment.

Penicillin appears to be the drug of choice for *R. dentocariosa* infections, based on clinical experience of cure in patients with endocarditis.[41–44,46,48–51] Most treatments also included an aminoglycoside. Although data are limited, the organism consistently is susceptible in vitro to penicillin, ampicillin, cephalothin, third-generation cephalosporins, erythromycin, rifampin, and vancomycin; it is variably susceptible to clindamycin, aminoglycosides, tetracycline, and trimethoprim-sulfamethoxazole. Determination of in vitro susceptibility is advisable because individual instances of β-lactam resistance and other variable resistance patterns have been described. Treatment failure has been observed in a few patients with endocarditis who initially were treated with vancomycin.

Rhodococcus (Corynebacterium) equi

Microbiology.

Rhodococcus equi (formerly *Corynebacterium equi*) is a gram-positive, encapsulated, intracellular bacillus that varies in shape from coccoid to long and club shaped. *R. equi* initially produces small, white, mucoid colonies, which become large, salmon-colored colonies on standard media in approximately 4 days. The bacilli can demonstrate a weak acid-fast reaction (often leading to their misidentification as mycobacteria) because of the presence of mycolic acids in their cell walls.[66] *R. equi* does not ferment carbohydrates or liquefy gelatin, and it is catalase positive and oxidase negative. *R. equi* strains have been categorized as virulent, intermediately virulent, and avirulent on the basis of virulence-associated antigens and plasmids.[67]

Epidemiology.

R. equi is a well-established pathogen in animals. The first human infection, a lung abscess, was described in 1967. Reports of *R. equi* infection are increasing, predominantly among immunocompromised patients, especially those with defects in cell-mediated immunity.[68] The natural habitat of *R. equi* is soil; infections are believed to be acquired by the respiratory route. *R. equi* is an intracellular organism that survives and replicates in macrophages by preventing fusion of phagolysosomes.[69] *R. equi* infections occur in patients with and without animal contact.

Clinical Manifestations.

Most reports of *R. equi* infection involve patients infected with HIV. (The associated mortality rate in patients with HIV is greater than 50%, compared with 20% in patients without HIV.)[70] The lung is the most commonly noted site in both immunocompetent and immunocompromised patients, and reports of infection in recipients of solid organ transplants are increasing.[71] The clinical course of pneumonia mimics mycobacterial disease (i.e., necrotizing, cavitary lesions and, commonly, upper lobe involvement). Endobronchial granulomas also have been reported.[66,72,73] Empyema, lung abscess, mediastinitis, malakoplakia, and other pulmonary manifestations have been described.[72,74–78]

Other reported clinical associations in immunocompetent and immunocompromised patients include BSI; diarrhea; meningitis; abscesses of the brain, thyroid, lung, adrenal glands, liver, spleen, and paravertebral area; skin and soft tissue infections; lymphadenitis; mastoiditis; peritonitis; granulomatous hepatitis; colonic polyps; pericarditis; osteomyelitis; mandibular osteitis; foot mycetoma and disseminated infection; endophthalmitis; keratitis after ocular surgery; orbital implant infection; and peritonitis complicating chronic ambulatory peritoneal dialysis.[79–108]

R. equi infections occasionally have been reported in children, often involving extrapulmonary sites. Such infections include pneumonia (complicated by brain abscesses, and cavitary lesions) in patients with AIDS, BSI (alone or associated with pneumonia, and lymphadenitis), malakoplakia, eye infections, meningitis resulting from orbital trauma, osteomyelitis following trauma, and wound infection resulting in pyogenic arthritis.[73,89,98,109–119] *R. equi* infections are reported less commonly among immunocompromised children than among immunocompromised adults. Infections have been reported in children with HIV, leukemia, chronic granulomatous disease, interferon γ–receptor deficiency, and ependymoma; other conditions that have been noted include toxic epidermal necrolysis and congenital hepatic fibrosis with polycystic kidney disease.[99,109–116,120–122] Neonatal infections include BSI, and meningitis following ventriculoperitoneal shunt insertion.[118,123,124]

Treatment.

The optimal treatment and duration of treatment for *R. equi* infections are unknown, and many different methods of susceptibility testing have been applied in case reports. *R. equi* generally shows in vitro susceptibility to erythromycin, rifampin, vancomycin, fluoroquinolones, aminoglycosides, and carbapenems. *R. equi* typically is resistant to penicillins, and susceptibility to clindamycin, tetracycline, chloramphenicol, and cephalosporins is variable.[86] *R. equi* resists intracellular killing by macrophages; treatment requires use of an antibiotic with intracellular activity. The choice of treatment is based on antimicrobial susceptibility testing, and combinations of antibiotics with bactericidal and intracellular activity are recommended strongly. Antibiotic-resistant mutants can easily be selected using monotherapy, and monotherapy has been ineffective in a number of cases.[78] Some experts suggest initial treatment with vancomycin plus a carbapenem, rifampin, macrolide, teicoplanin, fluoroquinolone, or an aminoglycoside, followed by oral therapy with a combination of erythromycin plus rifampin, or erythromycin plus ciprofloxacin, or rifampin plus ciprofloxacin. Others suggest an initial intravenous combination that includes imipenem as optimal. Azithromycin in combination with other antimicrobials appears to be an appropriate choice because it achieves high tissue levels.[125] Levofloxacin has been used with rifampin.[126,127] Because of the high incidence of relapse among immunocompromised patients, especially those with HIV infection, treatment is recommended for at least 2 months and possibly up to 6 months.[66,75,128] Surgical drainage or resection of lesions often is required.

Gardnerella vaginalis

Gardnerella vaginalis (formerly known as *Haemophilus vaginalis* and *Corynebacterium vaginale*) has been implicated as the cause of bacterial vaginosis (BV) since 1955. *G. vaginalis* is consistently isolated as the predominant organism in women with BV, but its role in the pathogenesis of this syndrome is confounded by isolation rates of up to 69% in vaginal specimens from healthy women.[129]

Microbiology and Pathogenesis.

G. vaginalis is a facultatively anaerobic, nonmotile, pleomorphic, gram-negative or gram-variable bacillus that is oxidase and catalase negative. Electron microscopic studies demonstrate a cell wall consistent with gram-positive and gram-negative organisms and a laminated cell wall typical of neither. *G. vaginalis* ferments a wide variety of carbohydrates, producing acetic acid as an end product. *G. vaginalis* does not reduce nitrate or hydrolyze urea. Colonies on blood agar are 0.3 to 0.5 mm in diameter after 48 hours of incubation; a distinct β-hemolysis is demonstrated on human and rabbit blood agar but not on sheep agar.

The ability of *G. vaginalis* to adhere to vaginal and urinary epithelial cells at a pH of 5 to 6 is thought to contribute to its role in the pathogenesis of BV and urinary tract infections.[130] Some experts hypothesize that other, undefined factors disturb the ecologic balance between *G. vaginalis* and *Lactobacillus* species in the female genital tract, allowing *G. vaginalis* and anaerobic organisms to proliferate, leading to BV.[131]

G. vaginalis also produces phospholipase, which breaks down phospholipids to arachidonic acid, producing a cascade of prostaglandins that may explain the relationship between BV and the onset of preterm labor.[132]

Epidemiology.

The incidence of bacterial vaginosis caused by *G. vaginalis* is difficult to define. Sexual transmission has been proposed as the main mode of transmission, which is supported by isolation of *G. vaginalis* of the same biotype from urethral cultures of men and their partners with BV.[133] Colonization of the genital tract also may result from transfer from an endogenous intestinal site.[134]

G. vaginalis is rare among prepubertal females.[135–139] In a study of prepubertal males with no history of suspected or known sexual abuse, *G. vaginalis* colonization of the urethra, glans, or rectum was not found.[140] The presence of *G. vaginalis* in a vaginal specimen from a prepubertal female or isolation from a symptomatic prepubertal boy should heighten suspicion of sexual abuse, but it is not incontrovertible evidence of it (see Chapter 54).[137,140]

Clinical Manifestations.

The clinical features of BV are addressed in Chapter 51. *G. vaginalis* also is a cause of postpartum or postabortion septicemia, and it is associated with fever, vaginal discharge, abdominal tenderness, and leukocytosis.[141] In rare cases BSI has been described in women undergoing gynecologic procedures and in men after urologic surgery or with urolithiasis.[142–144] *G. vaginalis* infection has been associated with endometritis, chorioamnionitis, episiotomy and hysterectomy wound infections, intrauterine infections, and vaginal abscess.[141–143,145] Urinary tract infections (UTIs) have occurred in both males and females, especially in pregnant women and renal transplant recipients.[146] Balanoposthitis, nonspecific urethritis, cystitis, and prostatitis in males have been associated with *G. vaginalis*.[145,147] Lung abscess, empyema, and BSI from inhalation pneumonia were reported in an individual with alcoholism.[148] In one report *G. vaginalis* also was associated with retinal vasculitis.[149]

Neonates with *G. vaginalis* septicemia, meningitis, cellulitis, conjunctivitis, and pneumonia have been reported.[150–154] *G. vaginalis* has been the presumed cause of osteomyelitis that complicated a cephalhematoma after use of an internal scalp electrode, and also of early onset infection of a scalp hematoma.[155,156] *G. vaginalis* was grown from the purulent exudate of a 20-month-old boy with balanitis without evidence of sexual abuse.[140] Other reports of pediatric *G. vaginalis* infection include UTIs.[157]

Diagnosis.

Culture of vaginal secretions is not recommended for diagnosis of BV.[158] Direct smear, especially Gram stain, is the preferred diagnostic test (to assess relative numbers of *G. vaginalis* and *Lactobacillus* species). Clue cells (epithelial cells coated peripherally with *G. vaginalis*) are observed on direct examination of vaginal secretions from patients with BV (see Fig. 52.1).[158] The addition of

10% potassium hydroxide to specimens results in a fishy, aminelike odor (known as the amine, or whiff, test). The clinical criteria for the diagnosis of BV are (1) a vaginal pH above 4.5; (2) positive results on the whiff test; (3) the presence of clue cells; and (4) a homogeneous, white, adherent vaginal discharge. The indirect fluorescent antibody method also detects *G. vaginalis* in specimens of vaginal secretions. Identification of the organism from culture is based on the demonstration of thin, gram-variable, catalase-negative rods that grow with a narrow zone of β-hemolysis after 48 hours of incubation.

Treatment.

Metronidazole (1 g/day orally in 2 divided doses for 7 days) is the drug of choice for treatment of BV, and initial cure rates are 90% or greater.[145] Other options include orally administered clindamycin (600 mg/day in 2 divided doses for 7 days), intravaginally applied metronidazole gel (0.75%, 5 g or one applicator once daily for 5 days) or clindamycin cream (2%, 5 g or one applicator at bedtime for 7 days). Treatment of sexual partners has not been shown to alter the clinical course of BV or to prevent relapsing or recurrent infections,[159,160] and the development of metronidazole resistance after treatment has been noted.[161] *G. vaginalis* isolates are susceptible in vitro to penicillin, ampicillin, erythromycin, clindamycin, chloramphenicol, trimethoprim, and vancomycin, providing options for treatment of extragenital infections.[162]

Lactobacillus Species

Epidemiology and Microbiology.

Lactobacillus species are normal flora of the human mouth, gastrointestinal tract, and female genital tract, where they produce lactic acid (resulting in a low vaginal pH) and competitively inhibit pathogenic organisms. *Lactobacillus* species are associated with dental caries.[163,164] Some species of *Lactobacillus* are used commonly as probiotics.

Lactobacilli are small, slender, nonmotile, gram-positive bacilli in chains. Immature colonies appear smooth, convex, and translucent. Organisms are microaerophilic or anaerobic and oxidase and catalase negative; they hydrolyze esculin and ferment carbohydrates. *Lactobacillus* can be difficult to identify correctly using most commercial identification systems. PCR assay, 16S rRNA gene sequencing, and matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry offer improved microbial identification.[165–167]

Clinical Manifestations.

Usually regarded as commensals or contaminants in clinical specimens, lactobacilli increasingly are identified as pathogens, although true *Lactobacillus* bacteremia accounts for only 0.1% of all positive blood cultures.[167] Endocarditis, the most common infection, frequently is associated with a structural heart defect or an immunocompromised state, including cardiac transplant.[168–170] Previous dental manipulation or parturition is a common factor in the affected patient's history. Endocarditis usually affects the left side of the heart and rarely involves prosthetic valves; involvement of the pulmonic and tricuspid valves has been reported.[171,172] Species associated with endocarditis include *L. acidophilus, L. casei* (subspecies *alactosus, casei,* and *rhamnosus*), *L. fermentum, L. jensenii, L. plantarian,* and *L. salivarius*. Failure of antibiotic treatment for endocarditis typically is associated with the use of single-drug regimens.

Cases of *Lactobacillus* endocarditis have occurred in children.[173] Species reported in children include *L. acidophilus* BSI in an infant[174]; *L. casei* BSI in a child with a congenital HIV infection[175]; *L. iners* pericarditis in an infant[176]; *L. rhamnosus* BSI and pericarditis and BSI and subsequent meningitis in recipients of bone marrow transplants[177,178]; and fatal pneumonia caused by *L. rhamnosus* in a child with aplastic anemia.[179] In one series, four cases of *Lactobacillus* BSI in children were reported: *L. rhamnosus* in an infant with necrotic bowel, *L. sakei* ssp. *carnosus* in a neutropenic patient with an ependymoma, *L. curvatus* after trauma, and *L. paracasei* ssp. *paracasei* after a burn.[180] A retrospective review of clinical isolates identified 41 *Lactobacillus* species isolated from 40 children, including *L. acidophilus, L. fermentum, L. jensenii, L. catenaforme,* and others.[181] Sources for these isolates included abscesses (dental, subcutaneous, vulvovaginal, abdominal, subdiaphragmatic, lung, and tonsillar), pneumonia, ear infection, catheter-related BSI, and conjunctivitis. Infections were polymicrobial in 90% of patients.

Clinical infections caused by *Lactobacillus* species typically occur among immunocompromised patients; they include BSI, pneumonia, empyema, abscesses (liver, spleen, pelvic, peritonsillar and retropharyngeal, and abdominal wall), meningitis, peritonitis, endometritis, endophthalmitis, UTI, cholecystitis, empyema of the gallbladder, and septic arthritis.[178,182–204] Little is known about the pathogenesis of infection. The most common *Lactobacillus* species reported as pathogenic are *L. casei, L. fermentum,* and *L. acidophilus*, although species often are not identified completely.

In rare cases, probiotic-associated invasive disease attributable to *L. rhamnosus* GG has been reported in children. Short bowel syndrome appears to be the most common clinical association in children presenting with *L. rhamnosus* GG BSI after enteral *L. rhamnosus* GG therapy.[205] Other pediatric cases associated with *L. rhamnosus* GG include a patient with congenital heart disease who had BSI and an atrial wall thrombus; an infant with trisomy 21 and probiotic-associated aspiration pneumonia after respiratory viral infection; a teen with ulcerative colitis and BSI; and a newborn with intrauterine growth retardation.[206–211] Three reports found no significant change in the rate of *L. rhamnosus* BSI after introduction of probiotics clinically in Finland and Sweden.[208,212,213] A review of the safety of probiotics suggests they are safe for clinical use despite these rare infections.[214,215] The U.S. Food and Drug Administration has defined groups potentially at risk for adverse events in probiotic clinical trials; these include immunocompromised people, premature infants, and people with short bowel syndrome, central venous catheters, or cardiac valve disease.[215]

Treatment.

Antimicrobial susceptibility seems to be species dependent. Susceptibility data are scarce, and neither standards for susceptibility testing nor guidelines for interpretation have been established. Salminen et al.[216] found low minimum inhibitory concentrations (MICs) among blood isolates for imipenem, piperacillin-tazobactam, erythromycin, and clindamycin. Vancomycin MICs were high for all species except *L. gasseri* and *L. jensenii.* Susceptibility to penicillin and cephalosporins was variable.

High-dose penicillin or ampicillin plus gentamicin are synergistic, and combination therapy typically has been considered the standard of care in endocarditis and other serious or deep-seated infections. Optimal antibiotic therapy is best guided by the clinical presentation, susceptibility testing of the isolate, and consideration of companion isolates.

Tsukamurella Species

Epidemiology and Microbiology.

Tsukamurella species first were isolated from the ovaries of bed bugs in 1941; they are also found in soil and sludge. The first human isolate, then known as *Gordona aurantiaca,* was described in 1971 from sputum samples of patients with chronic pulmonary disorders.[217] On the basis of gene sequences analysis, *Tsukamurella* was proposed as a genus in 1988. Seven species have been identified, and six have been reported to cause infections in humans: *T. inchonensis, T. paurometabola, T. pulmonis, T. spurrae*, *T. strandjordae,* and *T. tyrosinoslovens.*[218,219]

Tsukamurella are gram-positive, aerobic, nonmotile, non–spore-forming bacilli. They are partially acid fast because of the mycolic acid in the cell envelope. They grow rapidly on MacConkey agar and appear as yellow, rough, irregular, flat, dry colonies, often with a suedelike appearance.[217] *Tsukamurella* can be misidentified because it has characteristics similar to those of *Rhodococcus, Nocardia, Corynebacterium,* and rapidly growing mycobacteria.[217] Advanced molecular methods (e.g., PCR and 16s rRNA gene sequencing) can distinguish *Tsukamurella* from other genera but may not discriminate among *Tsukamurella* species.[219,220]

Clinical Manifestations.

Tsukamurella infections in humans are rare and usually are related to medical devices. The most commonly seen type is catheter-related BSI; other types include dialysis catheter–related peritonitis, infections related to an implantable cardioverter-defibrillator and to a knee prosthesis, keratitis after trauma, corneal grafting, or ocular abnormalities.[217–230] *Tsukamurella* pulmonary infections have occurred in patients with underlying pulmonary disease, in an AIDS patient (with a cavitary lesion), and as a cause of community-acquired pneumonia.[231–235] Septic pulmonary emboli were noted to complicate a catheter-related BSI caused by *T. tyrosinosolvens*.[236] Local skin infection, subcutaneous abscess with necrotizing fasciitis, conjunctivitis, cerebellar abscess complicating chronic otitis media, and fatal meningitis in a patient with leukemia have been associated with *Tsukamurella* species.[217,218,237–239]

Among children three cases of *Tsukamurella* BSI have been reported in immunosuppressed patients with central venous catheters: *T. strandjordae* infection in a patient with acute myelogenous leukemia[240]; *T. pulmonis* infection in a patient who had received a bone marrow transplant for severe combined immunodeficiency; and infection by an untyped *Tsukamurella* species in an infant with myelodysplastic syndrome.[217]

Two *Tsukamurella* pseudo-outbreaks caused by laboratory contamination of clinical specimens and an outbreak of BSI among oncology patients as a result of improper preparation of a saline flush have been reported.[241–243]

Treatment.

Limited data are available on antimicrobial susceptibility testing of *Tsukamurella* isolates; reported susceptibility patterns are similar across *Tsukamurella* species. *Tsukamurella* typically is resistant to penicillins and cephalosporins but susceptible to amikacin, ciprofloxacin, clarithromycin, imipenem, and sulfamethoxazole.[217] *T. paurometabola* demonstrates high-level resistance to imipenem.[244] Combination therapy typically has been used to treat *Tsukamurella* infections.[217,233] Catheter removal is indicated in catheter-related infections.

Cellulosimicrobium (Formerly *Oerskovia*) Species

Epidemiology and Microbiology.

Human infections caused by *Nocardia*-like, diphtheroid-like organisms of the *Cellulosimicrobium* (formerly *Oerskovia*) genus have been described rarely. The genus consists of three species, *C. cellulans* and *C. funkei* (formerly *O. xanthineolytica* and *O. turbata*, respectively), and *C. terreum,* which are found in grass cuttings, aluminum hydroxide gel, and soil in many parts of the world. *Cellulosimicrobium* organisms are gram-positive, branched, filamentous, non–acid-fast bacilli that fragment into motile rods. The bright yellow pigment of colonies is characteristic. Organisms produce acid from glucose, lactose, maltose, sucrose, and xylose. They hydrolyze esculin and reduce nitrate, and they are catalase positive and oxidase and urease negative. *Cellulosimicrobium* organisms can be identified by 16s rRNA sequencing and MALDI-TOF mass spectrometry.[245,246]

Clinical Manifestations.

Cellulosimicrobium infections are rare in humans and usually occur in immunocompromised patients with indwelling foreign devices. Case reports of *C. cellulans* BSI have involved patients with alcoholic cirrhosis, short bowel syndrome, colon cancer, and breast cancer.[247–250] Endocarditis has been reported in recipients of bone marrow and renal transplants.[251,252] *C. cellulans* has caused dialysis-related peritonitis[253–256] (including in a 13-year-old with recurrent and culture-negative peritonitis),[255] meningitis associated with a ventriculoperitoneal shunt,[257] a prosthetic knee joint infection,[258] septic arthritis after a penetrating thorn injury, endophthalmitis after penetration by a foreign body and after ophthalmologic surgery,[259,260] flexor sheath tenosynovitis in a patient with multiple splinters,[261] keratitis in a contact lens wearer,[262] and chronic tongue ulcerations in a patient with HIV infection.[263] A case of early onset neonatal sepsis also has been reported.[264]

C. funkei has caused two cases of BSI (in a patient with AIDS[265] and in a 3-year-old with leukemia[266]); endocarditis in a patient with Crohn disease associated with ankylosing spondylitis and aortic insufficiency[267] and in another patient after aortic valve replacement complicated by cerebral abscesses[268]; dialysis-related peritonitis[245]; and an axillary abscess in a patient with AIDS.[269] Individual cases of pyonephrosis[270] and BSI related to a contaminated parenteral nutrition solution[271] were caused by unspecified *Cellulosimicrobium* species.

Treatment.

Antimicrobial susceptibility varies among the isolates reported.

However, using the interpretive guidelines for corynebacteria, *Cellulosimicrobium* species consistently are susceptible to vancomycin (considered the therapy of choice) and imipenem. They are variably susceptible to amikacin, ampicillin, cephalosporins, ciprofloxacin, levofloxacin, penicillin, tetracyclines, and trimethoprim-sulfamethoxazole, and they are resistant to clindamycin, erythromycin, gentamicin, and tobramycin. Susceptibility to linezolid has been reported, and therapy with rifampin combined with other agents has been described.[246] Optimal therapy generally involves removal of hardware or foreign bodies.[246,256]

Kurthia Species

Microbiology.

Kurthia species are coryneform organisms identified as short, plump, non–spore-forming, aerobic, gram-positive bacilli. These organisms grow poorly in anaerobic environments; demonstrate motility at 36°C but not at 21°C; are catalase positive, oxidase negative, and urease positive after 24 hours incubation; and do not ferment carbohydrates or reduce nitrate.

Clinical Manifestations.

Kurthia species have been isolated from clinical specimens, including feces, sputum, and those obtained from a pilonidal cyst and from the conjunctiva, although these isolates were not considered significant clinically. *K. zopfii* was isolated from the blood of an infant with septicemia.[272] A sexually transmitted zoonotic infection (urethritis) caused by *K. gibsonii* was reported in an adult male.[273] The course of a 31-year-old narcotic user who had endocarditis of native aortic valves caused by *K. bessonii* was complicated by a cusp abscess and fistula.[274]

Treatment.

Kurthia species typically are susceptible to penicillin, ampicillin, carbenicillin, cephalothin, gentamicin, amikacin, erythromycin, chloramphenicol, and trimethoprim-sulfamethoxazole. They are resistant to oxacillin, clindamycin, and kanamycin.

Key Points

Gram-Positive Bacilli (Other Than *Listeria monocytogenes*)

- A number of gram-positive bacilli previously identified as diphtheroids increasingly have been implicated as human pathogens, especially among immunocompromised patients.

- *Erysipelothrix rhusiopathiae* causes three forms of clinical disease: localized cutaneous, diffuse cutaneous, and systemic. Septicemia and endocarditis occur in rare cases.

- *Rothia dentocariosa* is associated with endocarditis.

- *Rhodococcus equi,* typically seen in patients infected with HIV, can cause pulmonary infections that mimic mycobacterial disease.

- *Gardnerella vaginalis* commonly is associated with bacterial vaginosis and can cause urologic and gynecologic infections.

- *Lactobacillus* endocarditis is associated with probiotic-associated invasive disease attributable to *L. rhamnosus* GG has bee reported in rare cases.

- *Tsukamurella, Cellulosimicrobium,* and *Kurthia* species can cause infection in humans in rare cases.

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134

Mycobacterium tuberculosis

Silvia S. Chiang, Jeffrey R. Starke

The genus *Mycobacterium* consists of a diverse group of acid-fast bacilli (AFB) with a lipid-rich cell wall. The bacilli are aerobic, non–spore-forming, nonmotile, and slightly curved or straight organisms. Mycobacteria take up stain poorly but retain specific dyes despite treatment with acid-alcohol solutions. This acid-fast property is demonstrated with fuchsin stain techniques, such as the Ziehl-Neelsen and Kinyoun methods, or the fluorochrome method using auramine and rhodamine stains.

Tuberculosis (TB) disease results from infection with any member of the *Mycobacterium tuberculosis* complex: *M. tuberculosis* (which accounts for most human TB), *M. bovis, M. africanum* (which causes one half of pulmonary TB in West Africa), and *M. canetti* (which may be an ancestral strain of *M. tuberculosis*). The complex also includes several species that cause TB primarily in animals, and occasionally through animal exposure, in humans: *M. microti* (i.e., rodents), *M. pinnipedii* (i.e., aquatic mammals), and *M. capral* (i.e., animals in Europe).

M. bovis, the primary cause of TB in cattle, causes a small but significant portion of human TB cases, which are acquired primarily through unpasteurized dairy products, although person-to-person transmission has been documented. The incidence of *M. bovis* likely is underestimated because most diagnostic tests cannot differentiate between *M. bovis* and *M. tuberculosis*. Disease caused by *M. bovis* is similar to that caused by *M. tuberculosis*, but *M. bovis* enteritis and other forms of extrapulmonary disease are more common among children and immunocompromised adults. *M. bovis* usually is identified by its intrinsic pyrazinamide resistance. Isolated pyrazinamide resistance occurs rarely in *M. tuberculosis* infection.

Immunology and Pathogenesis

Exposure to *M. tuberculosis* can result in elimination of the bacteria, TB infection (an asymptomatic state evidenced only by a positive test of infection), or clinically significant TB disease (Box 134.1). TB diseases mirror a continuum of immunologic responses. At one end of the spectrum, severe disseminated disease represents a failure of T-lymphocyte proliferation in response to *M. tuberculosis* and often is associated with a negative tuberculin skin test (TST) result.[1–5] In contrast, patients with TB pleuritis have an effective immune response. Few bacilli are found in the pleural fluid and tissue, and resolution without therapy is common.[4]

Box 134.1

Terminology Related to *Mycobacterium tuberculosis* Exposure, Infection, and Disease

Exposure occurs when the child has had significant contact ("shared the air") with an adult or adolescent with infectious tuberculosis. Not all children after exposure progress to infection.

Infection indicates that *M. tuberculosis* has invaded the lung, draining lymphatics, as evidenced by a reactive TST or positive IGRA result, but has not resulted in any signs, symptoms, or chest radiograph abnormalities (except for calcifications in the lung parenchyma and/or regional lymph nodes). Not all children with tuberculosis infection progress to disease.

Disease occurs when intrathoracic or extrathoracic signs or symptoms or radiographic manifestations (other than calcifications in the lung parenchyma and/or regional lymph nodes) caused by *M. tuberculosis* are apparent.

IGRA, interferon γ release assay; TST; tuberculin skin test;

M. tuberculosis typically enters the body through the respiratory tract, where mucociliary transport and cough serve as the first line of defense. After *M. tuberculosis* reaches the alveolus, the Ghon focus develops. Bacilli drain from this granulomatous focus along local lymphatics to regional lymph nodes. Together, the Ghon focus, lymphangitis, and regional lymphadenopathy form the Ghon complex. Most immunocompetent persons contain the infection within the Ghon complex and never develop TB disease. However, failure to achieve initial control of the infection leads to early disease. In reactivation disease, tubercle bacilli are disseminated by bacteremia to lung fields and distant body sites. The host may successfully contain the infection but develop reactivation disease years later if there is disruption of the host-pathogen balance.

Immunologic defenses against *M. tuberculosis* primarily are mediated by $CD4^+$ T lymphocytes and macrophages. *M. tuberculosis*–specific $CD4^+$ lymphocytes primarily produce type 1 helper T-lymphocyte (Th1) cytokines, which include interferon γ (IFNγ) and tumor necrosis factor-α (TNF-α). The protective roles of these cytokines against *M. tuberculosis* are demonstrated by the increased TB risk among patients treated with anti-TNF monoclonal antibodies and those with inherited defects in IFNγ pathways.[6–9] Although $CD8^+$ lymphocytes, neutrophils, and natural killer cells manifest mycobacteriostatic effects in vitro, their clinical significance remains unclear. The role of B lymphocytes also is undefined, although they are found in substantial numbers in granulomas. Several in-depth reviews describe the immune response to *M. tuberculosis*.[1–5]

Epidemiology

Transmission

Transmission of *M. tuberculosis* usually occurs person to person through mucous droplets that become airborne when an individual with pulmonary TB coughs or sneezes.[10] Droplets containing tubercle bacilli dry and become droplet nuclei, which can remain suspended in air for hours. Only droplet nuclei less than 10 μm in diameter can reach the alveoli. In rare cases, transmission occurs by direct contact with infected body fluids (e.g., urine, wound drainage), fomites (e.g., syringes, gastric lavage tubes), or improperly cleaned bronchoscopes.

The most important marker of contagiousness is the visualization of AFB in a sputum smear.[11–14] Young children with pulmonary TB have paucibacillary endobronchial secretions and diminished force of cough, and they therefore rarely infect others.[15,16] Because adolescents with reactivation pulmonary TB have a greater bacillary burden and stronger cough, they can be contagious and should be treated with the same infection control measures used for adults.[17–19] Most TB outbreaks in pediatric healthcare facilities have been linked to adult or adolescent visitors.[20,21] Adult and adolescent hospital visitors to children with suspected TB should be screened for cough, and coughing visitors should undergo chest radiography to exclude them as sources of transmissible infection.[15,16,20,21]

A patient is deemed no longer contagious on the basis of symptom improvement, decreased number of AFB in the sputum smear, radiographic improvement, and adherence to an effective treatment regimen.[17] Epidemiologic and animal transmission studies indicate that most patients with drug-susceptible TB become noncontagious within 2 weeks of starting effective treatment. Many patients become noncontagious within several days, although some patients, especially those with multidrug-resistant organisms remain infectious for weeks to months.

Routes of Infection

An estimated one third of the world's population is infected with *M. tuberculosis*, including 66 million children younger than 15 years of age.[22] In recent surveys from five Asian and African countries, the prevalence of childhood TB infection ranged from 7% (Nepal) to 23% (Somalia).[23–27] In crowded parts of Cape Town, South Africa, which has one of the world's highest TB rates, TB infection was documented among 28% of 5- to 10-year-old children and 42% of 11- to 15-year-old children.[28]

The overall prevalence of TB infection among US children is 1.1%; prevalence among foreign-born children is 12%, compared with 0.3% for US-born children.[29] From 2007 to 2012, 13% of US immigrant and refugee children tested positive for TB infection.[30]

Most children acquire TB infection from close contact with a contagious adult or adolescent living in the same household. Consequently, the most efficient method of finding children infected with *M. tuberculosis* is household contact investigation of adults with contagious pulmonary TB.[31] On average, 30% to 50% of household contacts of a case have a reactive TST result. The infectiousness of the source case and the degree and duration of contact mediate the likelihood of transmission. For instance, a child has a higher risk of infection if the source case is the primary caregiver or sleeps in the same room.[32,33] Although children are less frequently infected from casual, nonhousehold contacts, outbreaks have occurred in schools, childcare facilities, churches, and on school buses. In most cases, a highly contagious adult working in the area was the source case. During a 1994 elementary school outbreak traced to a teacher with longstanding, unrecognized pulmonary TB, almost 50% of the students had *M. tuberculosis* infection, and 11% had radiographic evidence of disease.[34]

Disease Incidence and Epidemiology

The World Health Organization (WHO) estimates about 10 million incident TB cases and 3 million TB-related deaths in the world every year. According to the WHO, approximately 550,000 of these cases occurred among children younger than 15 years of age.[35–37] However, modeling studies have concluded that the true pediatric disease incidence is 800,000 to 1,000,000 cases per year.[22,38]

Epidemiology of childhood TB requires thorough knowledge of disease epidemiology for adults. From 1953 to 1984, the US TB (i.e., TB disease in this chapter unless stated otherwise) incidence declined by an average of 6% per year. However, from 1985 to 1993, the number of TB cases reported in the United States increased by 18%.[39] The most important factors underlying the resurgence of TB were the human immunodeficiency virus (HIV) epidemic, influx of immigrants from high-prevalence countries, and inadequate implementation of public health policy. Fortunately, increased TB control efforts in the United States starting in the 1990s led to a steady decrease in TB incidence resulting in an all-time low of 9,582 cases in 2013 (Fig. 134.1).[39]

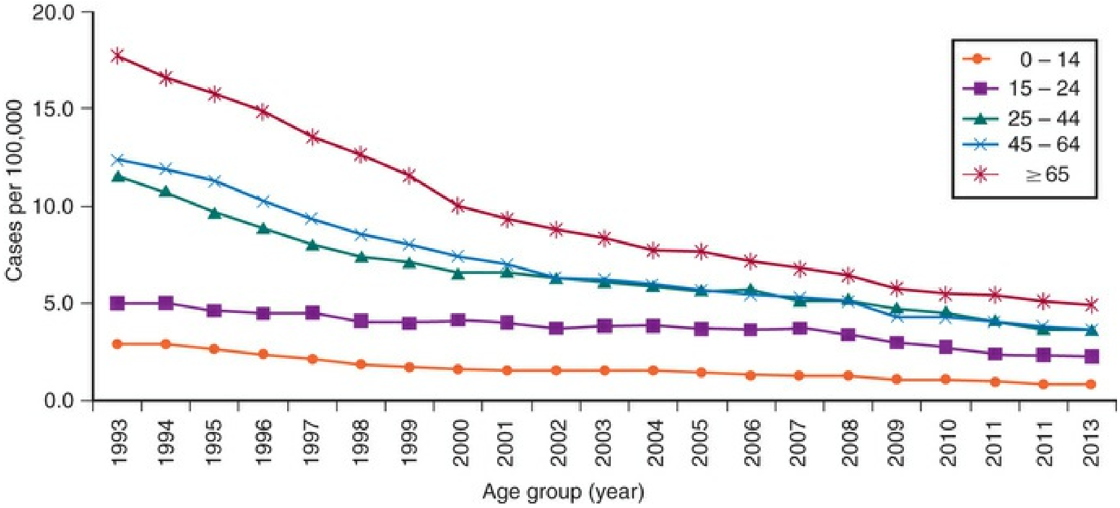


FIGURE 134.1 Reported tuberculosis cases per 100,000 people by age group in the United States, 1993 to 2013. (Data from the Centers for Disease Control and Prevention. Reported Tuberculosis in the United States, 2013. Atlanta, GA, CDC, 2014.)

When TB was more prevalent in the United States, risk of exposure to a contagious adult was uniformly high throughout the population. With the currently low TB incidence, exposure to *M. tuberculosis* is more confined to well-defined populations. The proportion of patients with TB disease who are foreign born has risen steadily since 1993 and reached an all-time high of 65% in 2013. Five countries of origin (i.e., Mexico, Philippines, Vietnam, India, and China) accounted for 54% of the cases.[39] Increased risk of TB infection historically has been associated with intravenous drug use and residence in jails, prisons, and homeless shelters, especially in large urban sites. Metropolitan areas with at least 500,000 people accounted for 67% of the US population and 80% of TB cases in 2013.[39]

The incidence of childhood TB in the United States declined by approximately 6% per year between 1953 and 1980. From 1980 through 1987, rates stabilized and then began a steady rise in 1988. In 1993, 1721 TB cases were reported in children younger than 15 years of age, a 40% increase over 1987. By 2013, the number of TB cases in children younger than 15 years had declined to 483, a 72% reduction since 1993.[39] Of these 483 cases, 61% occurred in children younger than 5 years of age, reflecting this age group's high risk of disease progression, and 20% occurred among foreign-born children.[39] Hispanics and Asians had the highest percentage of cases among US-born children and foreign-born children, respectively.[39] Fifty-seven percent of reported cases among children younger than 15 years occurred in seven states (i.e., California, Florida, Georgia, Illinois, Nevada, New York, and Texas), with 34% in California and Texas alone.[39]

The risk of progression from *M. tuberculosis* infection to disease is age dependent and is highest among children younger than 2 years of age, likely due to a suboptimal immunologic response.[1] Disease risk is low between 5 and 10 years of age, rising again during early adolescence (Table 134.1).[40] Age also affects disease phenotype. Infants and young children are more likely to have pulmonary, meningeal, disseminated, and lymphatic TB, whereas older children and adolescents more commonly have reactivation pulmonary, pleural, genitourinary, or peritoneal disease.[41–44] Among younger children, the sex ratio for TB disease is approximately 1 : 1, but girls have a higher incidence during early adolescence.[42,45–49]

TABLE 134.1

Age-Specific Risk of Progression to Tuberculosis in Immunocompetent Children

Age at Primary Infection (yr)	Percentage (%) of Children Who Do Not Develop Disease	Percentage (%) of Children Who Develop Pulmonary Disease	Percentage (%) of Children Who Develop Meningitis or Disseminated Disease
<1	50	30–40	10–20
1–2	85–90	10	2–5
2–5	95	5	0.5
5–10	98	2	<0.5
>10	80–90	10–20	<0.5

Data from Marais BJ, Gie RP, Schaaf HS, et al. The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. Int J Tuberc Lung Dis 2004;8:392–402.

Drug-Resistant Tuberculosis

Drug-resistant TB poses a significant threat to global TB control. The spread of drug resistance stems from many factors: poor public health infrastructure (e.g., delays in the diagnosis of drug resistance, inconsistencies in TB medication supply), inadequate treatment (e.g., unmonitored therapy, nonadherence, incorrect use of anti-TB agents), inefficient infection control, and the HIV epidemic.[50,51] India, China, and the former Soviet republics account for more than one half of the world's cases of multidrug-resistant TB (MDR-TB) defined as resistance at least to isoniazid and rifampin (Fig. 134.2).[37]

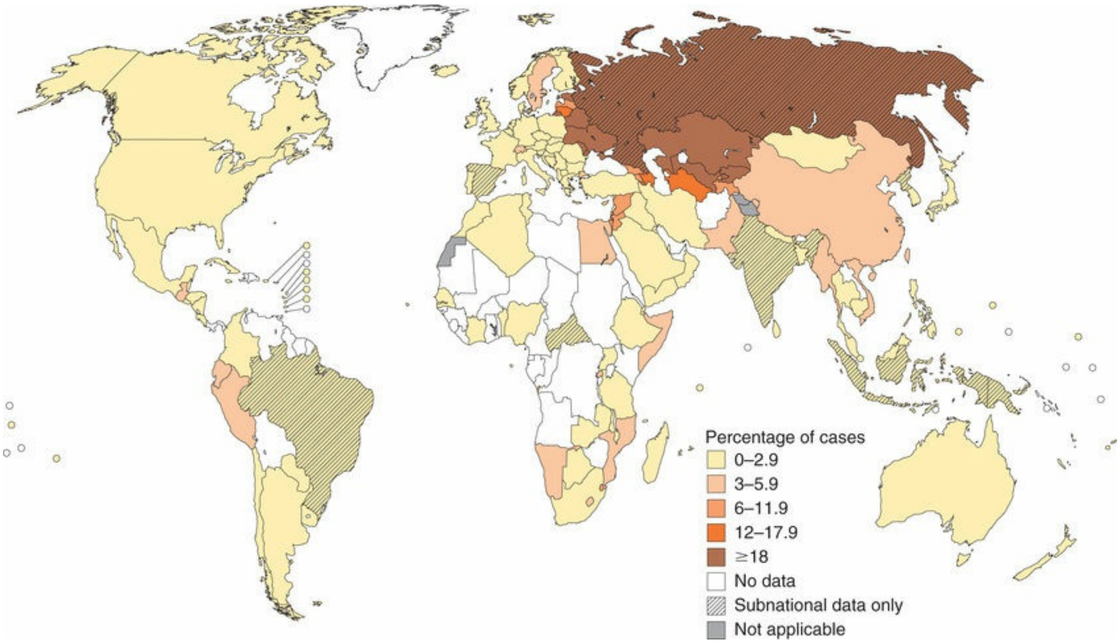


FIGURE 134.2 Percentage of multidrug-resistant tuberculosis cases estimated to occur among notified pulmonary tuberculosis cases. (Data from the World Health Organization. Global Tuberculosis Report, 2015. Geneva, Switzerland, WHO, 2015.)

In 2013, the WHO estimated that 8% of new TB cases and 14% of previously treated cases had isoniazid resistance without concurrent rifampicin resistance, and an additional 4% of new cases and 21% of previously treated cases had MDR-TB. Of greater concern, 30% of MDR-TB cases met criteria for pre-extensively drug-resistant TB (i.e., resistant to at least isoniazid, rifampin, and a fluoroquinolone or a second-line injectable agent) or extensively drug-resistant TB (XDR-TB) (i.e., resistant to at least isoniazid, rifampin, a fluoroquinolone, and a second-line injectable agent).[37] Surveillance gaps, caused in large part by insufficient resources for drug susceptibility testing, limit the quality of drug-resistant TB epidemiology. Underdetection of resistant TB is greater for children, who frequently have culture-negative disease.

Although the WHO has not published estimates of childhood drug-resistant TB, modeling work estimated an annual incidence of 88,000 cases of isoniazid-resistant TB without concurrent rifampin resistance and 32,000 MDR-TB cases among children younger than 15 years of age. Southeast Asia and the Western Pacific regions bear the brunt of these cases.[38,52]

In the United States, isolated strains demonstrating multidrug resistance and isolated isoniazid resistance have hovered around 1% and 9%, respectively, for the past several years. Among children younger than 15 years of age with culture-confirmed disease, approximately 2% have MDR-TB.[39,52,53] Patients with any of the following characteristics have a higher risk of drug-resistant TB: previous treatment for TB disease, birth in a country with a high drug-resistant TB prevalence (see Fig. 134.2), or contact with a source case previously treated for TB disease or born in a country with a high drug-resistant TB burden.

Tuberculosis in Immunocompromised Children

The HIV epidemic has affected profoundly the epidemiology of childhood TB.[54–56] HIV-infected adults are more likely to have TB infection, pulmonary disease, and lack of classic features allowing prompt diagnosis. Children with HIV infection have a higher risk of progressing from TB infection to disease.

For adults and children, pulmonary TB is a defining condition for acquired immunodeficiency syndrome (AIDS). Studies have suggested that HIV-seronegative and HIV-seropositive adults with smear-positive pulmonary TB are equally infectious. However, HIV-infected adults with pulmonary TB may be less likely to have a positive acid-fast sputum smear than HIV-seronegative adults. A retrospective study in Florida observed a rise in childhood TB after an increase in pulmonary TB among HIV-infected adults in the community.[57]

Clinical and autopsy studies in countries with a high TB burden demonstrate excessive risk of TB disease among HIV-infected cohorts of children.[58–61] In economically developing nations, the underdiagnosis of childhood TB likely is greater among HIV-infected children because of similarities in clinical presentation to other opportunistic infections, frequent skin test anergy, and elusive culture confirmation. All children with suspected TB disease should be tested for HIV infection.

Other causes of immune suppression—including malignancies and their therapy and use of high-dose corticosteroids—have been associated with higher rates of TB disease. Anti-TNF drugs used to control inflammatory bowel and rheumatologic diseases greatly increase the risk of rapid progression from TB infection to disease in adults.[62,63]

Clinical Manifestations

Intrathoracic Disease

Pulmonary Disease

Most children infected with *M. tuberculosis* do not develop signs, symptoms, or radiographic abnormality.[40] However, the occasional child may experience several days of low-grade fever and mild cough at the start of infection. Other children may have fever and mild systemic symptoms at 3 to 12 weeks after acquisition of infection; these symptoms resolve over 1 to 3 weeks.

The Ghon complex affects lobes of the lung equally, and 25% of cases have multiple parenchymal foci.[64] Initial inflammatory response is not usually visible radiographically, but a localized, nonspecific infiltrate can appear. Within days, infection spreads to regional lymph nodes. As tissue sensitivity develops, inflammation in lung and lymph nodes intensifies. The hallmark of childhood pulmonary TB is disproportionately enlarged regional lymph nodes compared with a relatively minor parenchymal focus (Fig. 134.3). Because approximately 70% of Ghon foci are subpleural, the initial presentation commonly includes localized pleural reaction.

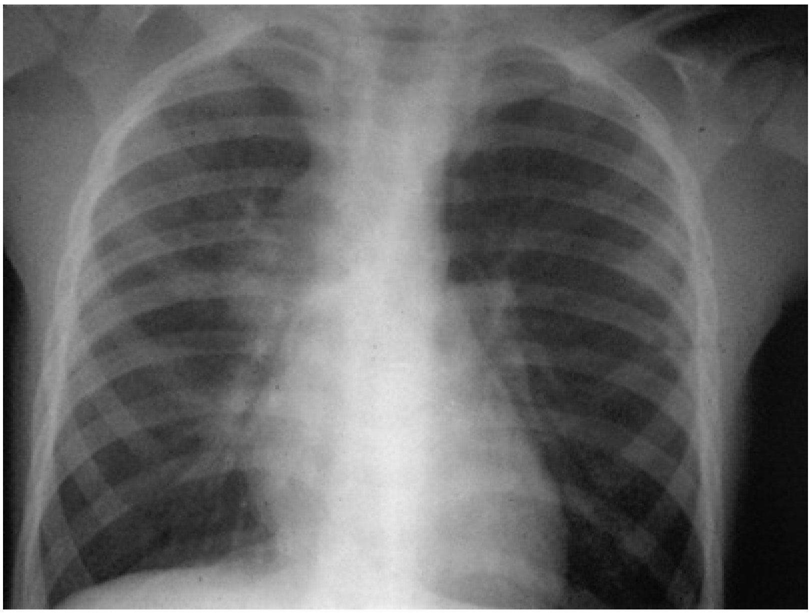


FIGURE 134.3 Right-sided hilar lymphadenopathy with minor parenchymal infiltrate in a 3-year-old boy with pulmonary tuberculosis. (Courtesy S. S. Long, St. Christopher's Hospital for Children, Philadelphia, PA.)

In most children, lung inflammation and adenopathy resolve spontaneously and quickly, often by the time the chest radiograph is obtained. These children have successfully contained the tubercle bacilli but can develop reactivation disease in the future. Other children, particularly infants, progress to disease. Lymph nodes continue to enlarge and can compress airways, causing partial or complete bronchial obstruction.[64] The inflammatory response can erode the bronchial wall, leading to luminal infection. This process also can lead to partial or complete bronchial obstruction. A common radiographic sequence is adenopathy followed by localized hyperinflation and then atelectasis of contiguous parenchyma, referred to as segmental lesions (Fig. 134.4). This radiographic picture is different from other bacterial pneumonias and mimics foreign body aspiration and other obstructive disorders.

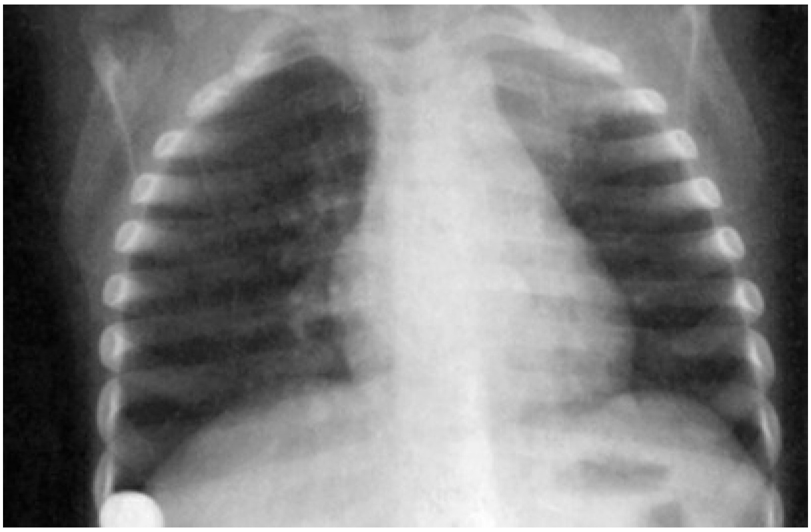


FIGURE 134.4 Mediastinal adenopathy and left upper-lobe segmental lesion in a child with pulmonary tuberculosis.

Although rare, obstructive emphysema of a lobar segment occurs most often in children younger than 2 years. Obstruction usually resolves spontaneously, but corticosteroids may hasten the process; complete resolution often takes several months. Up to 40% of children younger than 1 year of age with *M. tuberculosis* infection develop a segmental lesion, compared with 15% of children 11 to 15 years of age. Occasionally, the radiographic abnormality is lobar pneumonia, which is indistinguishable from acute bacterial pneumonia (Fig. 134.5). Enlarged subcarinal nodes can impinge on the esophagus, causing swallowing difficulty or the development of a bronchoesophageal fistula. Other enlarged nodes can compress the subclavian vein, causing upper extremity edema. Nodes can rupture into the mediastinum and lead to supraclavicular adenitis (Fig. 134.6).

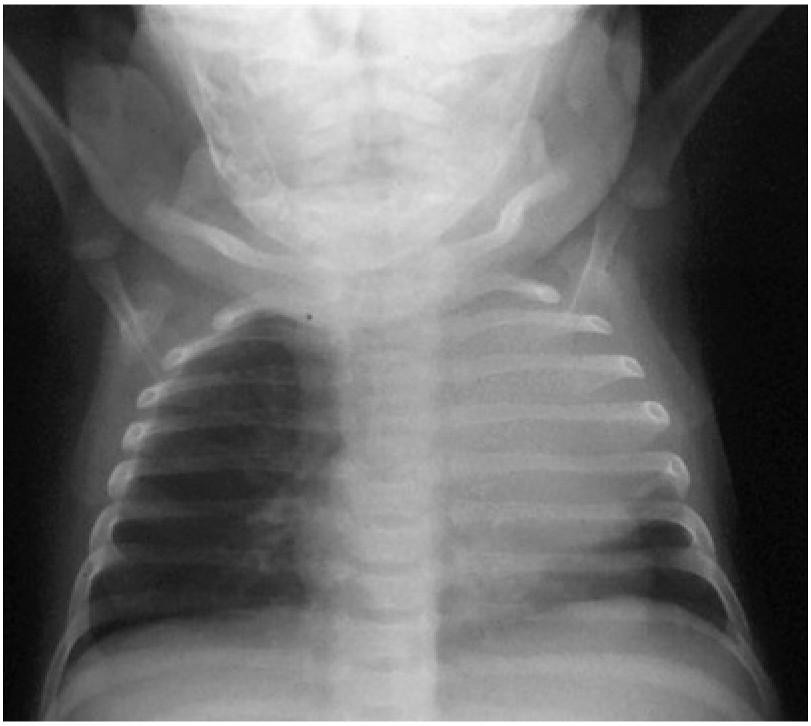
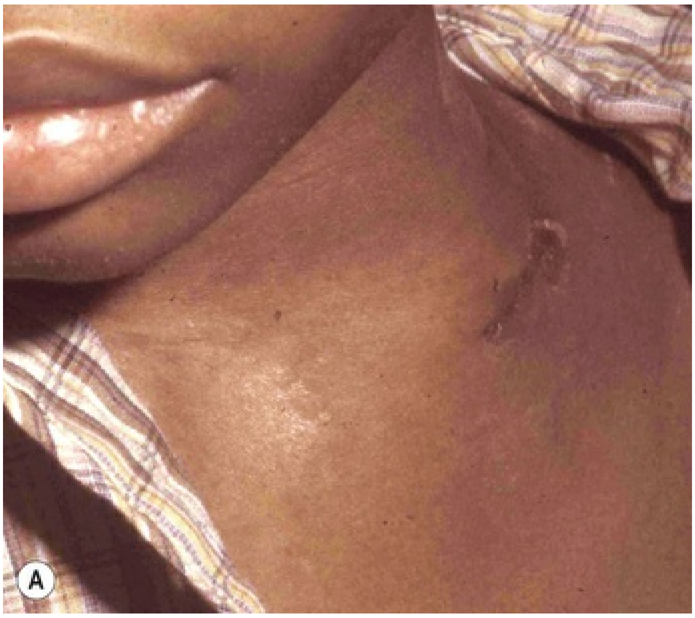


FIGURE 134.5 Left upper-lobe consolidation in a 16-month-old child with pulmonary tuberculosis. (Courtesy S. S. Long, St. Christopher's Hospital for Children, Philadelphia, PA.)



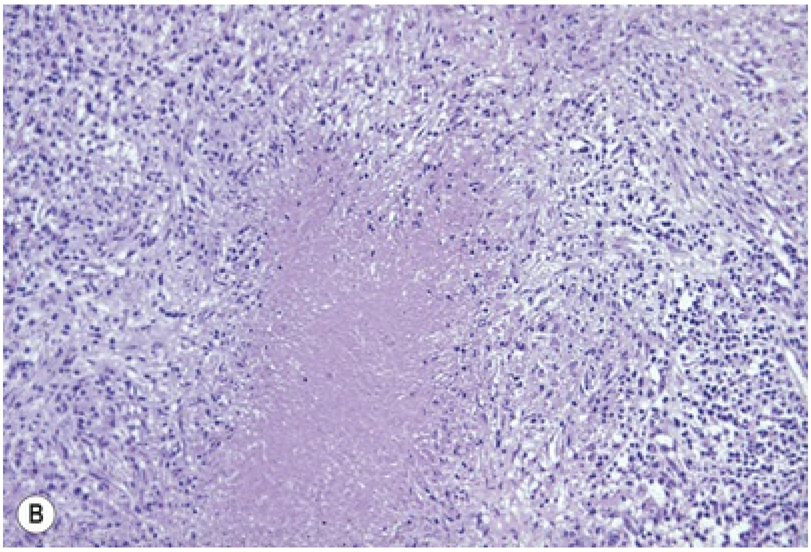


FIGURE 134.6 An adolescent girl had biopsy performed of a supraclavicular mass (A) to exclude lymphoma because of a 1-month history of fever and weight loss and a chest radiograph showing a mediastinal mass. Histology (B) revealed caseous necrosis and granulomatous reaction (400×, hematoxylin and eosin stain). (Courtesy S. S. Long, St. Christopher's Hospital for Children, Philadelphia, PA.)

The signs and symptoms of pulmonary TB in children usually are minor and occur more commonly in children younger than 5 years of age.[65,66] Infants most frequently manifest nonproductive cough and mild dyspnea. Fever, night sweats, anorexia, and irritability are less common. Some infants have failure to thrive, which may not improve until months after initiation of appropriate chemotherapy. Tachypnea, localized wheezing, or decreased breath sounds can occur with bronchial obstruction, but respiratory distress is rare.[67,68] Nonspecific signs and symptoms occasionally resolve after antibiotic therapy for more common bacterial pneumonias; this occurrence suggests superinfection distal to nodal obstruction.

Progressive pulmonary TB, a rare but serious complication, occurs when the parenchymal focus enlarges and develops a large caseous center. The clinical course and radiographic appearance can resemble those of acute bacterial pneumonia (Fig. 134.7).[69–71] Common findings include hyperpyrexia, moderate to severe cough, night sweats, dullness on chest percussion, rales, and decreased breath sounds over the affected area. Central liquefaction can produce a thin-walled cavity, which can cause rupture into the pleural space (i.e., causing a bronchopleural fistula or pyopneumothorax) or the pericardium (i.e., causing acute pericarditis with or without constriction). Before the advent of chemotherapy, 30% to 50% of children with progressive pulmonary TB died. With current treatment, the prognosis is excellent for full recovery.

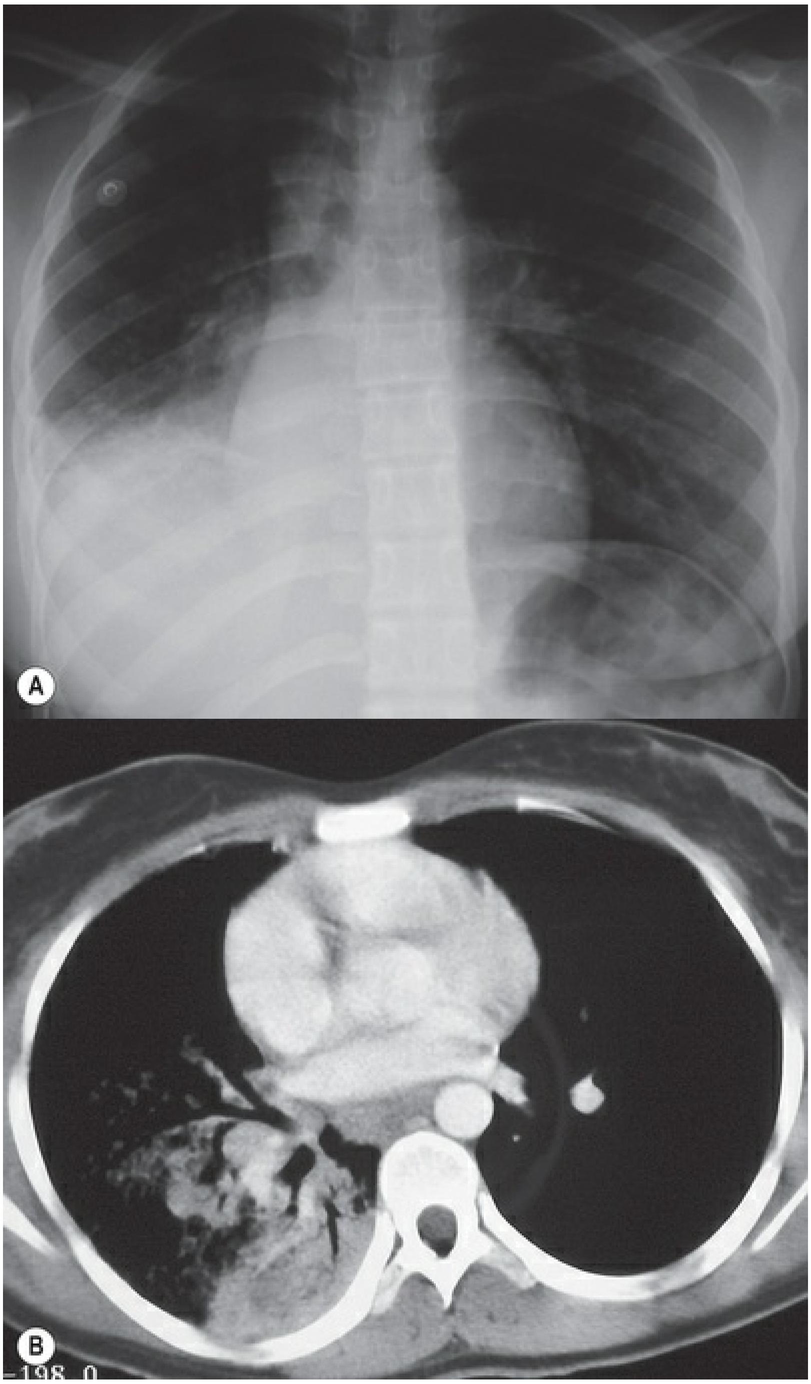


FIGURE 134.7 Pulmonary tuberculosis with hemoptysis. (A) Chest radiograph shows right lower-lobe consolidation. Bronchoscopy revealed hemorrhage and a large clot obscuring lumen to the

right lower lobe. Computed tomography showed multiple nodes abutting airways and consolidation and atelectasis of the right lower lobe. A hilar node and the most rostral lower lobe infiltrate are shown (B). Bronchoalveolar lavage was smear negative but culture positive for *Mycobacterium tuberculosis.* (Courtesy S. S. Long, St. Christopher's Hospital for Children, Philadelphia, PA.)

Older children can have reactivation (adult-type) pulmonary TB.[41,72–76] This occurs more frequently when infection is acquired after 7 years of age, especially at the onset of puberty.[40,72] Common symptoms include fever, anorexia, weight loss, night sweats, productive cough, chest pain, and hemoptysis. Physical examination findings usually are minor or absent, but the radiographic appearance is disproportionately abnormal (e.g., extensive upper lobe infiltrates, upper lobe cavities with or without calcification) (Fig. 134.8). Reactivation infection usually remains localized to the lungs. Most signs and symptoms improve within several weeks of the start of effective treatment, although cough can linger for several months.

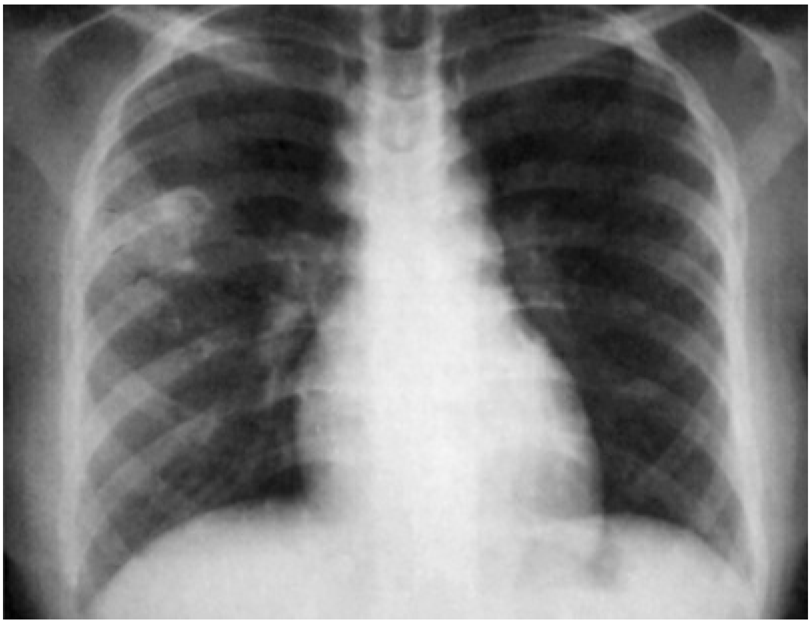


FIGURE 134.8 Multiloculated cavity with calcification in right upper lobe due to adult-type tuberculosis.

Pleural Disease

Pleural TB is caused by the hypersensitivity response to the discharge of a few bacilli from a subpleural focus into the pleural space.[77] Occasionally, a larger discharge causes a unilateral generalized pleural effusion, which usually occurs within 6 to 9 months of initial infection.[78] Pleural TB is not associated with segmental pulmonary lesions and only rarely is associated with miliary TB. Symptoms usually begin abruptly and consist of fever, chest pain, and shortness of breath. Examination reveals dullness to percussion and diminished breath sounds on the affected side. Fever often is high and persists for several weeks despite effective treatment.[79]

Pleural membrane biopsy is the most valuable diagnostic procedure because histopathologic examination demonstrates caseating granulomas in up to 90% of cases and tissue culture is positive in up to 70% of cases. Acid-fast smear of pleural fluid usually is negative; pleural fluid culture is positive in 30% to 50% of cases. Pleural fluid typically is yellow and occasionally is blood tinged, with a specific gravity of 1.012 to 1.025, protein level of 2 to 4 g/dL, glucose level of 20 to 40 mg/dL, and white blood cell count of 100 to 1000 cells/mm^3. Cells classically are predominantly neutrophils early, followed by a high proportion of lymphocytes.

Cardiac Disease

Occurring in 1% to 4% of childhood TB cases, pericarditis is the most common form of cardiac TB.[80] In approximately 10% to 20% of cases, fibrosis leads to constrictive pericarditis over a period of months to years. Early symptoms of serofibrinous pericarditis are nonspecific and usually consist of low-grade fever, malaise, weight loss, and cough; in children, chest pain is unusual. Examination can reveal a pericardial friction rub, distant heart sounds, and pulsus paradoxus. Initially, pericardial fluid is serofibrinous or slightly hemorrhagic; it rarely stains positive for AFB but yields a positive culture in 30% to 70% of cases. Pericardial biopsy shows caseating granulomas in 50% to 75% of cases, and culture usually is positive. The detection of stranding on echocardiography can suggest the diagnosis of TB.[81] The TST result is positive in 75% of cases.

Extrathoracic Disease

Disseminated (Lymphohematogenous) Disease

Clinical manifestations of early bacteremic spread, which occurs in all asymptomatic and symptomatic *M. tuberculosis* infections of the lung, depend on the continual balance between the pathogen and host's immunologic containment. Infants and children with immunosuppression are more likely to have severe forms of disseminated disease.[40,82]

There are three forms of lymphohematogenous TB. The first and most common form is occult dissemination that remains clinically silent or manifests months to years later with metastatic, extrapulmonary TB. The second form is protracted bloodstream infection (rarely seen today), which arises from the intermittent release of bacilli from erosion of a caseous focus into a pulmonary vessel. Protracted bloodstream infection manifests more frequently with indolent, prolonged, intermittent fevers than with acute, spiking fevers. Initial mild pulmonary involvement becomes diffuse after several weeks. Multiorgan involvement is common and often includes hepatosplenomegaly, lymphadenitis of superficial or deep nodes, and appearance of papulonecrotic tuberculids in crops on the skin. Meningitis, which occurs late in the disease course, often was the cause of death in the prechemotherapy era. Gastric aspirate culture often is negative; blood or urine culture can be positive. Bone marrow or liver biopsy yields a high rate of positive stain and culture results.

The third and most common clinically significant form of disseminated TB is miliary disease, which occurs when massive bloodstream infection causes disease in two or more organs.[83–85] Miliary TB most often occurs as an early complication of *M. tuberculosis* infection (i.e., within 2 to 6 months) during infancy or early childhood. However, breakdown of a healed Ghon lesion can lead to miliary spread in older individuals. Clinical manifestations are protean and depend on the number and final location of disseminated organisms.[83] Lesions usually are largest and most numerous in the lungs, spleen, liver, and bone marrow.

The clinical onset of miliary TB usually is indolent, but it can be explosive over several days. Early manifestations consist of malaise, anorexia, listlessness, weight loss, and low-grade fever with normal physical findings. Higher fever, hepatosplenomegaly, and generalized lymphadenopathy develop within several weeks in approximately 50% of children. During this time, the patient has few respiratory symptoms and can have normal chest radiographic findings. A few weeks later, respiratory distress, cough, rales, or wheezing occurs as lungs often become filled with tubercles, and the classic radiographic finding appears (i.e., diffuse lung tubercles resembling millet seeds).[83] If pulmonary disease progresses, alveolar-capillary block can result in respiratory distress, hypoxia, and pneumothorax.

Timely diagnosis of miliary TB requires a high index of suspicion because premortem microbiologic confirmation is achieved in only one third of cases.[85] The highest-yield tests of microbiologic confirmation are acid-fast smear and culture of bone marrow or liver tissue. Gastric aspirate culture usually is negative; blood or urine culture sometimes is positive. Ophthalmologic examination reveals choroid tubercles in 13% to 87% of children.[84–86] Because more than 30% of children with miliary TB have a negative pretreatment TST result, eliciting a history of exposure to an adult with contagious TB is crucial.

The differential diagnosis of miliary parenchymal disease includes lymphocytic interstitial pneumonia in HIV-infected children, histoplasmosis, disseminated neuroblastoma or thyroid carcinoma, and histiocytosis. Headache usually indicates TB meningitis, whereas abdominal pain or tenderness often heralds TB peritonitis.[84,86]

With timely treatment, children with miliary TB have an excellent prognosis. The general sense of well-being improves within 2 weeks of beginning therapy, but resolution of other signs and symptoms lags. For instance, weight gain may not occur for weeks to months, and chest radiograph abnormalities often persist for months.

Lymphatic Disease

TB of the superficial lymph nodes (i.e., scrofula) is the most common form of childhood extrapulmonary TB, accounting for approximately 67% of cases. Historically, scrofula often resulted from drinking unpasteurized cow's milk laden with *M. bovis.* Currently, most cases arise from *M. tuberculosis* acquired by aerosol or droplet nuclei. Supraclavicular, anterior cervical, tonsillar, and submandibular nodes most often are involved due to extension of a

Ghon lesion of the upper lung fields or abdomen. Tuberculous inguinal, epitrochlear, or axillary lymphadenopathy usually results from cutaneous or skeletal TB and rarely occurs in children.

Infected lymph nodes, which enlarge gradually in the early stages, are discrete and firm but not hard or tender. Nodes often feel fixed to underlying or overlying tissues.[87,88] Involvement usually is unilateral but can be bilateral because of crossover drainage of lymphatic vessels in the chest and lower neck. Infection can involve several nodes, resulting in a matted mass. Other than low-grade fever, systemic signs and symptoms typically are absent. The TST result usually is reactive. Although usually present, a Ghon focus is visible radiographically in only 30% to 70% of cases and usually does not cause symptoms. Occasionally, lymphadenitis can progress more acutely, with rapid enlargement associated with high fever, tenderness, and fluctuation. Scrofula rarely manifests as a fluctuant mass with overlying cellulitis.

Distinguishing scrofula from nontuberculous mycobacteria (NTM) lymphadenitis is challenging.[87] Both conditions cause chronic, nontender adenopathy with tissue breakdown or sinus tracts. Chest radiographic findings usually are normal for both infections. If the lymphadenitis is caused by *M. tuberculosis*, the TST induration usually is more than 15 mm; in contrast, NTM usually produce a less intense reaction or no reaction. Two epidemiologic clues—history of exposure to a contagious TB case and the patient's age—can help with the diagnosis. Whereas scrofula occurs in children of all ages, approximately 80% to 90% of NTM lymphadenitis occurs in children younger than 5 years of age.[89,90] Excisional biopsy with culture of the lymph nodes often is required to establish the cause.

Untreated lymphadenitis can resolve but more often progresses to caseating necrosis, capsular rupture, and spread to adjacent nodes and overlying skin, which becomes effaced, shiny, and erythematous (see Fig. 134.6A). Rupture through the skin creates a draining sinus tract, which may require surgical removal.[88]

Central Nervous System Disease

Central nervous system (CNS) TB most commonly manifests as TB meningitis or tuberculoma. TB meningitis complicates 0.5% to 3% of untreated *M. tuberculosis* infection in children and occurs most frequently between the ages of 6 months and 4 years.[91] Occurring 2 to 6 months after initial infection, TB meningitis is rare in infants younger than 4 months of age.

TB meningitis arises from direct invasion during uncontrolled dissemination or from the renewed activity in a caseous lesion in the cerebral cortex or meninges that was established during early, occult lymphohematogenous dissemination.[92–94] Lesions enlarge and discharge small numbers of bacilli into the subarachnoid space. The resulting exudate infiltrates the cortical or meningeal blood vessels, producing inflammation, obstruction, and subsequent infarction of the cerebral cortex. The base of the brain is affected most commonly, accounting for frequent involvement of cranial nerves III, VI, and VII. Exudate can interfere with cerebrospinal fluid (CSF) flow at basilar cisterns, leading to communicating hydrocephalus.[95] The combination of vasculitis, infarction, cerebral edema, and hydrocephalus causes severe brain injury. Hyponatremia and volume expansion due to the inappropriate secretion of antidiuretic hormone commonly occur and contribute to the pathophysiology.[96]

The clinical onset of TB meningitis can be rapid or gradual.[97–103] The disease progresses more quickly among infants and young children, who may have symptoms only for several days before the onset of hydrocephalus, seizures, or cerebral edema. More often, the disease course progresses over several weeks and can be divided into three stages.[104,105] Stage I typically lasts 1 to 2 weeks and is characterized by nonspecific symptoms such as fever, headache, irritability, and drowsiness. Focal neurologic signs are absent, but infants can lose developmental milestones. This stage usually can be recognized as early TB meningitis only in retrospect. Stage II often begins abruptly with lethargy and apathy, nuchal rigidity, a Kernig or Brudzinski sign, seizures, hypertonia, vomiting, cranial nerve abnormalities, and other focal neurologic signs. Some children have signs only of encephalitis, such as disorientation, abnormal movements, and speech impairment. If significant hydrocephalus occurs, early placement of a ventriculoperitoneal shunt or extraventricular device can relieve the symptoms.[106] Stage III is marked by coma, hemiplegia or paraplegia, hypertension, decerebrate or decorticate posturing, progressive vital sign abnormalities, and eventual death.

Microbiologic confirmation of TB meningitis can be difficult. Ideally, CSF should be sampled by lumbar puncture; ventricular CSF often is normal because the pathology occurs distal to the lateral ventricles. The likelihood of microbiologic confirmation directly correlates with the quantity of CSF sampled. Overall rates of positivity for acid-fast stain and culture are 9% and 35%, respectively.[97] In contrast, with at least 10 mL of lumbar CSF, acid-fast stain and culture are positive in up to 30% and 70% of cases, respectively. Other CSF studies, such as nucleic acid amplification tests (NAATs), provide important diagnostic clues, as does microbiologic confirmation of pulmonary TB. The lumbar CSF leukocyte cell count ranges from 10 to 500 cells/mm^3. Neutrophils can predominate early, but lymphocytic predominance is more typical. The CSF glucose level is usually between 20 and 40 mg/dL, but can be less than 10 mg/dL; CSF protein concentration is elevated, sometimes markedly (>400 mg/dL).

Cranial computed tomography (CT) and especially magnetic resonance imaging help establish the diagnosis. Although CT findings can be normal early in the disease, basilar enhancement with communicating hydrocephalus and signs of cerebral edema or focal ischemia can occur later. Magnetic resonance imaging (MRI) is more sensitive and can show widespread areas of focal necrosis, ring enhancement, and edema (Fig. 134.9). Approximately 70% of cases have an abnormal chest radiograph. The TST result is less helpful because it can be nonreactive in up to 45% of cases.[97] History of exposure to or newly identifying a contagious source case is a key diagnostic clue.

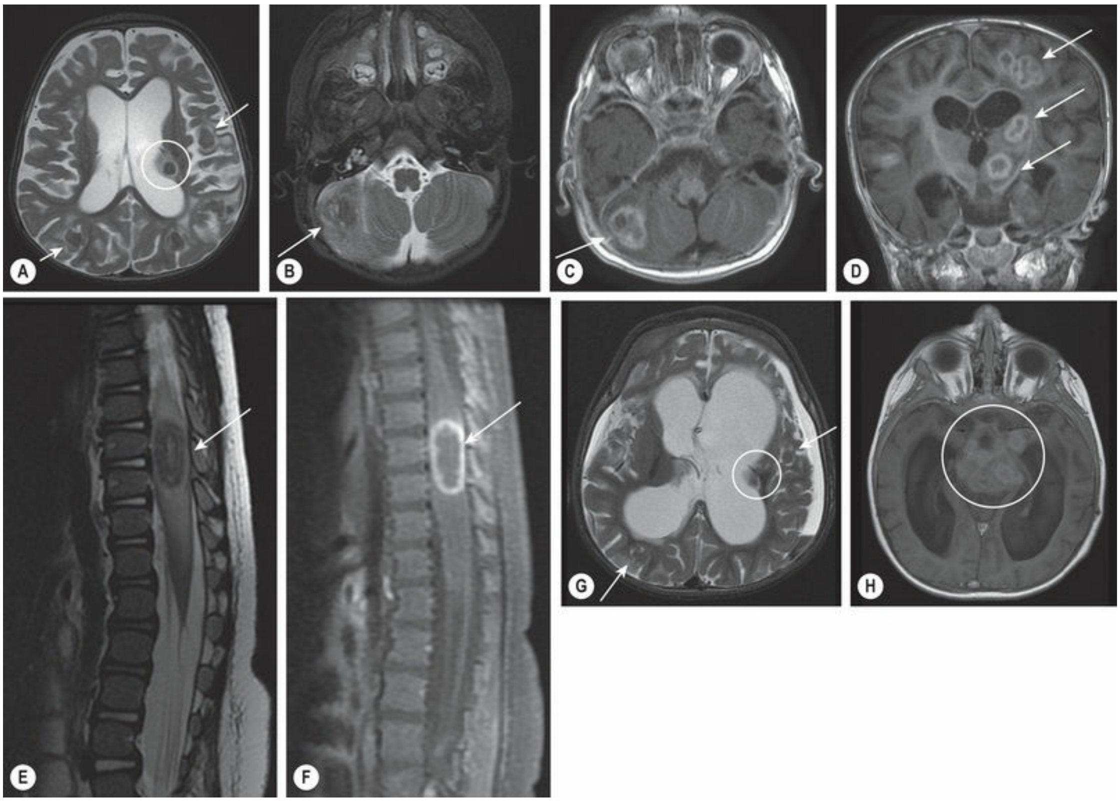


FIGURE 134.9 Tuberculous meningitis in a 6-month-old infant with a 2-week history of lethargy and acute onset of seizures, right facial paralysis, and right-sided hemiparesis. Some representative magnetic resonance images obtained at admission are shown. Axial short tau inversion recovery (STIR) sequence (A) shows ventriculomegaly and multiple bilateral supratentorial T2 hypointense lesions (*arrows* and *circle*). (B) Infratentorial T2 hypointense lesion with surrounding vasogenic edema. Axial postcontrast T1 sequence (C) shows corresponding ring enhancement of lesion in B. Coronal postcontrast T1 sequence (D) shows multiple supratentorial ring enhancing lesions (*arrows*). Sagittal image shows T2 hypointense intramedullary lesion with surrounding vasogenic edema that expands the spinal cord (E). Postcontrast T1 sequence image demonstrates the ring enhancement (F). The patient was given anti-tuberculosis drugs plus corticosteroids and improved. Neurosurgical spinal decompression was performed. Six weeks later, axial STIR sequence shows (G) regression of initial lesions (*arrows* and *circle*) but (H) new nodular lesions within the suprasellar cistern (*circle*). The corticosteroid dose was increased. Drug-susceptible *Mycobacterium tuberculosis* was isolated from gastric aspirates. (Courtesy A. Malik and S. S. Long, St.

Christopher's Hospital for Children, Philadelphia, PA.)

Before the availability of anti-TB drugs, TB meningitis invariably caused death, usually within 3 weeks.[107] Even with current treatment regimens and advanced life-support measures, the disease kills approximately 19% of the children it affects and leaves 54% of survivors with permanent neurologic complications, which include blindness, deafness, paraplegia, and behavioral and intellectual disabilities.[97]

The prognosis for TB meningitis correlates with the clinical stage of illness at the time effective treatment is begun.[97] Patients whose treatment begins in stage I have a 1% risk of death. For patients whose treatment begins in stage II or III, the risks of death increase to 10% and 34%, respectively. The risks of neurologic sequelae are 27%, 41%, and 71% for survivors whose treatment began in stage I, II, and III, respectively.[97]

Because of the diagnostic challenges and poor prognosis associated with TB meningitis, anti-TB treatment should be instituted empirically (while the diagnosis is being established) at least for any child with basilar meningitis accompanied by hydrocephalus, infarction, or cranial nerve involvement with no other apparent cause.

Tuberculoma, another form of CNS infection, usually manifests as a space-occupying lesion and occurs most often in children younger than 10 years of age. The lesion typically is singular and infratentorial and is located at the base of the brain near the cerebellum.[108] Tuberculoma and TB meningitis were once considered distinct entities, but neuroimaging has demonstrated that many young children have both (see Fig. 134.9). Tuberculoma most commonly manifests with headache, fever, and convulsions. The TST result usually is positive, and chest radiographic findings are normal. Although surgical excision is unnecessary, biopsy often is performed for diagnosis.

Paradoxical appearance of tuberculomas during effective therapy for TB meningitis can occur[109,110] (see Fig. 134.9). The pathogenesis of tuberculoma is similar to that of immune reconstitution inflammatory syndrome (IRIS), and the finding does not signify treatment failure. Tuberculoma should be suspected if focal neurologic abnormalities arise or change during treatment of TB meningitis. After consideration of optimized treatment and the possibility of drug-resistant infection, corticosteroid therapy is appropriate, although optimal duration is unclear. Tuberculomas resolve slowly, typically over months to years.

Osteoarticular Disease

Skeletal TB arises from direct lymphohematogenous seeding or extension of a caseous regional lymph node. The interval between infection and clinical manifestations can range from 1 month (i.e., TB dactylitis) to years (i.e., osteoarthritis of the hip). Infection usually begins in the metaphysis. The formation of granulation tissue and caseation can lead to bone necrosis. The bone infection may extend into adjacent soft tissue, leading to abscess formation, or a nearby joint, resulting in articular TB. Often, the infection becomes clinically apparent when the joint becomes involved.

TB most commonly affects weight-bearing bones and joints, especially vertebrae. Spinal TB (i.e., Pott disease) can involve any or multiple vertebral bodies but has a predilection for the lower thoracic or upper lumbar spine. Affected vertebrae usually are contiguous, but there can be skip areas between lesions.[111–113] Vertebral body infection leads to bone destruction and collapse, spondylitis of one or more disk spaces, collapse and wedging of the vertebral body with subsequent angulation of the spine (i.e., gibbus spine), or kyphosis. Infection can rupture into soft tissue, causing paraspinal, psoas, or retropharyngeal abscesses. In children, Pott disease most commonly manifests with low-grade fever, irritability, and restlessness; back pain (usually without significant tenderness); and abnormal positioning or refusal to walk. Rigidity of the spine results from involuntary immobilization and muscle spasm.

Other common sites of skeletal TB include the knee, hip, elbow, and ankle.[114,115] The extent of involvement ranges from mild joint effusion without bone destruction to frank bone destruction and joint restriction due to chronic fibrosis of the synovial membrane. Evolving over months to years, the process most commonly causes mild pain, stiffness, limping, and restrictive movement. The TST result is reactive in 80% to 90% of cases. Culture of joint fluid or bone biopsy usually yields the organism.

TB dactylitis, one form of bony disease, is peculiar to infants. Affected children have distal endarteritis followed by painless swelling of hands or feet and cystic bone lesions. Abscesses are rare. The TST result usually is positive.

Abdominal and Gastrointestinal Disease

TB enteritis, caused by hematogenous dissemination or swallowing of tubercle bacilli discharged from the patient's lungs, most commonly involves the jejunum and ileum near Peyer patches and the appendix.[116–118] Painful shallow ulcers, diarrhea or constipation, and weight loss are typical findings. Mesenteric lymphadenitis usually is prominent. Inflamed nodes can obstruct the intestines or erode through the omentum to cause generalized peritonitis. TB enteritis should be considered as a diagnosis for any child with chronic gastrointestinal complaints and a positive TST result.[119] Diagnosis usually requires biopsy, stain, and culture of lesions.

TB peritonitis is uncommon in adolescents and rare in young children. Generalized peritonitis can result from subclinical or miliary hematogenous dissemination. Localized peritonitis arises from direct extension from an infected intra-abdominal lymph node, an intestinal focus, or TB salpingitis.[120] TB peritonitis typically manifests mild pain and tenderness, ascites, and low-grade fever. The TST result almost always is positive. Rarely, lymph nodes, omentum, and peritoneum become matted and manifest as a palpable, doughy, irregular, nontender mass. Diagnosis is confirmed by paracentesis or biopsy with stains and cultures, but the procedure must be performed with caution to avoid entering fixed bowel intertwined with matted omentum.

Genitourinary Disease

Renal TB rarely occurs in children because the incubation period is at least several years.[121] The disease process begins when tubercle bacilli reach the kidney during lymphohematogenous dissemination, as documented by recovery from urine in disseminated or pulmonary TB. Small caseous tubercles develop in the renal parenchyma and release *M. tuberculosis* into the tubules. A large mass can develop near the renal cortex; this focus of infection discharges large numbers of bacteria through a fistula into the renal pelvis. Infection spreads locally to the ureters, prostate, or epididymis. In early stages, renal TB often is clinically silent except for sterile pyuria and microscopic hematuria.[122] As disease progresses, dysuria, flank or abdominal pain, and gross hematuria can develop. Superinfection frequently occurs and can delay recognition of underlying TB. Ureteral stricture or hydronephrosis complicates the disease.[123] Urine mycobacterial culture results are positive in 80% to 90% of cases, but acid-fast stains of large volumes of sedimented urine are frequently less positive. The TST result usually is positive.

TB of the genital tract is uncommon in both sexes before puberty. Infection usually originates from lymphohematogenous seeding, although it can spread contiguously from the intestinal tract or bone. Adolescent girls can develop hematogenous genital tract TB during the primary infection. Female genital tract TB most often involves the fallopian tubes, followed by the endometrium, ovaries, and cervix. Usual symptoms include lower abdominal pain and dysmenorrhea or amenorrhea. Male genital tract TB typically causes epididymitis or orchitis—manifesting as a unilateral, nodular, painless swelling of the scrotum—and rarely involves the glans penis. Both sexes have a positive TST result, absence of systemic manifestations, and normal chest radiographs. Because unrecognized female genital tract TB can lead to infertility and in vitro fertilization has been associated with congenital tuberculosis, women from endemic regions should have a TST before in vitro fertilization.[124] Suspicion of congenital tuberculosis should rise when mother is from a country with high endemic TB prevalence and she was not tested during infertility evaluation.

Cutaneous Disease

Cutaneous TB, more common decades ago, has four presentations: scrofuloderma, a lesion from direct inoculation, a site of hematogenous dissemination, or a hypersensitivity reaction to the tubercle bacillus.[125] Scrofuloderma occurs when a caseous lymph node ruptures through the skin and leaves an ulcer or sinus tract. Direct inoculation of the skin through an abrasion, cut, or insect bite can cause a small, painless nodule, sometimes with tiny satellite lesions that soon turn into indolent ulcers without surrounding inflammation. Regional lymphadenitis is striking, but systemic symptoms usually are lacking. Direct inoculation also results in verrucosa cutis, a wart-like lesion that appears most commonly on the arms or legs in a person already sensitized to the organism.[126]

Hematogenous dissemination can lead to verrucosa cutis and papulonecrotic tuberculids, which are miliary tubercles in the skin that usually appear as tiny papules appearing most often on the trunk, thighs, and face. The characteristic apple-jelly center of papulonecrotic tuberculids is best demonstrated by covering it with a glass slide. The most common hypersensitivity reaction is erythema nodosum, characterized by large, painful, purple-brown nodules on the shins and extensor forearms.

Congenital Disease

Congenital TB is rare, with fewer than 400 cases reported in the English language literature.[127] The affected infant's mother can have an existing diagnosis of TB, but the mother's disease often is not diagnosed until delivery or later.[128]

Congenital infection depends on the presence and intensity of hematogenous dissemination of *M. tuberculosis* during pregnancy. Placental infection facilitates transmission to the fetus by blood or aspiration of amniotic fluid. However, even massive TB placentitis does not always lead to congenital infection. Congenital infection has been associated with maternal infertility (likely related to fibrosing TB salpingitis) and fetal infection after in vitro fertilization.[124]

In hematogenous congenital TB, *M. tuberculosis* reaches the fetus through the umbilical vein and disseminates widely. If bacilli infect the liver, a primary focus develops with involvement of periportal lymph nodes.[129] Hematogenous primary focus in the fetal lung usually remains dormant until after birth, when oxygenation and circulation increase significantly. Congenital infection of the infant also occurs by aspiration or ingestion of infected amniotic fluid.[130]

Symptoms of hematogenous congenital TB can be present at birth but typically appear by the second or third week of life.[127,128] The most common manifestations are respiratory distress, fever, hepatosplenomegaly, poor feeding, lethargy or irritability, lymphadenopathy, abdominal distention, ear drainage, and skin lesions. Clinical manifestations vary with lesion size and location. Some infants have a normal chest radiograph early in the course, but most have diffuse radiographic abnormalities as disease progresses. More common early radiographic findings are hilar lymphadenopathy and parenchymal infiltrates; approximately 50% of patients have a miliary pattern.

Congenital TB should be suspected in any infant who has sepsis syndrome or other findings compatible with congenital infection with no response to antibiotic therapy and negative evaluation for another congenital infection. Suspicion is high if the mother is at risk for, has, or has had TB.

Timely diagnosis of congenital or neonatal TB is difficult and often is delayed. The initial TST result usually is negative, frequently becoming reactive after 1 to 3 months of therapy. Positive results of acid-fast stains and cultures of body fluids and tissues (e.g., middle ear fluid, tracheal aspirate, bone marrow, lymph node) are needed to confirm the diagnosis.[127] AFB in gastric or tracheal aspirates in a neonate is almost diagnostic because false-positive smear results are rare. Although only 20% of affected children have meningeal involvement, CSF examination and culture should be performed because a diagnosis of TB meningitis would change management. Endometrial specimens from the mother should be obtained because they usually yield positive culture results.

Diagnosis

Tests of Infection

Diagnostic tests for TB detect *M. tuberculosis* in a clinical sample or the host's immune response to the organism. TB diagnosis is complicated by the need to distinguish between asymptomatic infection and clinically significant disease. Current tests of infection, the TST and interferon γ release assays (IGRAs), are immune based and cannot discriminate between infection and disease.

Tuberculin Skin Test

The definitive TST uses 5 tuberculin units of purified protein derivative (PPD) stabilized in Tween 80. A 26- or 27-gauge needle and a graduated syringe are used to inject 0.1 mL of PPD intradermally into the volar surface of the forearm; the immediate appearance of a wheal indicates correct technique.[131] The delayed hypersensitivity reaction to the TST usually peaks at 48 to 72 hours.

In some people, reaction occurs after 72 hours and should be measured. It may take up to 10 weeks after infection occurs for an immunocompetent individual to react to the TST.

For accuracy, the TST result should be interpreted by trained healthcare providers. The diameter of induration—not erythema—is measured perpendicular to the axis of administration and recorded in millimeters. TST result should not be recorded as simply positive or negative. An allergic or Arthus-like reaction to TST components can cause erythema and induration within hours after application, peaking as late as 24 hours (for the Arthus reaction) and beginning to wane at 48 hours; these findings do not indicate *M. tuberculosis* infection.

A nonreactive TST result does not exclude *M. tuberculosis* infection or disease because a variety of factors can lower tuberculin reactivity (Box 134.2).[132] Approximately 10% of immunocompetent children with culture-confirmed TB disease do not react at first to the TST.[133] Most of these children have a positive test result after several months of treatment, suggesting that TB was acquired recently or that untreated disease depressed specific immune responses. Patients with immunocompromise due to a variety of causes, including disseminated TB and age younger than 6 months, often are anergic (i.e., have diminished cellular response to multiple stimuli).[134] The measles vaccine can suppress TST response transiently. This suppression does not occur when the TST is done on the same day as measles vaccination. However, if the vaccine has already been administered, the TST should be delayed until 4 to 6 weeks after immunization unless the clinician is evaluating the child for recent exposure or TB disease. Due to theoretic concerns, this recommendation extends to other live viral vaccines.[135] Improper storage, dilution, placement, and interpretation of the TST can cause false-negative results.

Box 134.2

Factors That Cause Decreased Response to Tuberculin Skin Test

Host-Related Factors

Infection

- Viral (rubella, rubeola, varicella, influenza)

- Bacterial (typhoid fever, brucellosis, leprosy, pertussis, overwhelming tuberculosis)

- Fungal (blastomycosis)

Live virus vaccines

Chronic renal failure

Malnutrition

Diseases affecting lymphoid organs (leukemia, lymphoma, human immunodeficiency virus infection)

Immunosuppressive drugs (corticosteroids, antineoplastic agents)

Age (infants <6 months of age and elderly)

Stress (surgery, burns, mental illness)

Tuberculin-Related Factors

Improper storage (exposure to light or heat)

Improper dilution

Chemical denaturation

Contamination

Adsorption to glass or plastic

Administration-Related Factors

Incomplete injection of test dose

Delayed administration after loading syringe

Injection given subcutaneously

Reading-Related Factors

Inexperienced reader (should measure induration only)

Conscious or unconscious bias

Error in recording

The most significant causes of false-positive TST reactions are recent NTM infection and prior bacille Calmette-Guérin (BCG) vaccination.[136–138] NTM infection, which occurs more frequently near the equator, usually causes a cross-reaction of 10 mm or less (but can be larger); cross-reactivity can last for several months. In studies of BCG-vaccinated newborns, only 50% have a positive TST result, and 80% to 90% lose the reactivity within 5 years. Children or adults who receive BCG have higher initial and longer responses to TST, but most lose tuberculin reactivity within 10 years of vaccination.[139] The degree of reactivity also is affected by BCG product and nutritional status.[136,138] TST reactivity after BCG vaccination is expected to measure less than 10 mm of induration at 48 to 72 hours, although reactions of 10 to 15 mm can occur.

Prior BCG vaccination is not a contraindication to tuberculin testing. In the United States, the TST result usually is interpreted similarly for persons with or without a history of vaccination.[18] Countries that use BCG vaccine frequently have high rates of endemic TB, and studies have demonstrated that a positive TST result for a previously BCG-vaccinated child who is a close contact with an active TB case likely represents *M. tuberculosis* infection.[137,140]

Three cutoff values are used to interpret TST reactivity. The cutoff values represent a statistical attempt to minimize false-positive or false-negative readings and vary according to individual and epidemiologic factors, of which exposure to *M. tuberculosis* is the most heavily weighted (Box 134.3). For children at highest risk for infection progressing to disease, an induration diameter of ≥5 mm is classified as a positive result. For other high-risk groups, an induration diameter ≥10 mm is a positive result. For low-risk children, an induration diameter ≥15 mm is a positive result.

Box 134.3

Interpretation of Tuberculin Skin Test as Positive by Diameter of Induration and Risk

Category[a]
Induration ≥5 mm in Diameter
Contact with an infectious case
Abnormal chest radiograph
Human immunodeficiency virus infection
Immunosuppression from any cause
Induration ≥10 mm in Diameter
Birth in a tuberculosis high-prevalence country
Frequent exposure to high-risk adults[b]
Illicit intravenous drug use
Other medical risk factors[c]
Work in healthcare field
Member of a locally identified high-risk population
Age ≤4 years
Induration ≥15 mm in Diameter
Regardless of age or risk factors

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[a] Single risk factor in a category is sufficient.

[b] Such as individuals who are HIV-infected, homeless, users of illicit drugs, residents of nursing homes, incarcerated or institutionalized, or migrant farm workers.

[c] Such as Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure, and malnutrition.

In the United States, it is preferable to screen children for *M. tuberculosis* infection risk factors with a questionnaire. The test of infection is performed only if there are risk factors.[141]

Interferon γ Release Assays

QuantiFERON-TB Gold (QFT, Cellestis/Qiagen, Carnegie, Australia) and T-SPOT-TB (T-SPOT, Oxford Immunotec, Abingdon, UK) are the two commercially available IGRAs. In terms of performance, neither test is preferred.[132] IGRAs measure IFNγ secreted by the patient's T lymphocytes (QFT) or the number of IFNγ-secreting lymphocytes (T-SPOT) on ex vivo stimulation with *M. tuberculosis*-specific antigens that are not found in BCG vaccines or most NTM species (except *M. marinum*, *M. kansasii*, *M. szulgai*, and *M. flavescens*). Both IGRAs use positive and negative controls; if either control fails, the result is deemed indeterminate (QFT) or invalid (T-SPOT).

Like the TST, IGRAs produce continuous results, and cutoff values are used to interpret results as positive or negative. For T-SPOT only, an intermediate result is classified as borderline. Unlike the TST, each IGRA has only one cutoff value regardless of the patient's exposure history or immune status. However, multiple studies have questioned this lack of risk stratification and suggest a need for further refinement of IGRA cutoff values.[142–148]

Pediatric studies have demonstrated that IGRAs have a higher specificity than the TST for TB infection, particularly in settings of low TB burden and among BCG-vaccinated children.[149–152] One meta-analysis estimated a specificity of 90% to 100% for IGRAs, compared with 56% for the TST.[152] IGRAs and the TST have comparable sensitivities of 75% to 90% in immunocompetent individuals.[149–152] However, like the TST, IGRAs have poor sensitivity among immunocompromised hosts and cannot differentiate TB infection from disease.[153–157] A lack of data on IGRA performance in children younger than 5 years of age has prompted hesitancy to use these assays in this age group.[132] In contrast, the TST is routinely used in children as young as 6 months of age.

Recommendations for Tests to Diagnose Tuberculosis Infection

In high-income countries, a TST or IGRA may be used to diagnose TB infection in children at least 5 years of age. For children younger than 5 years of age, TSTs are preferred, although some experts use an IGRA for children 2 years or older, particularly if they have received BCG and have no significant TB risk factors.

An IGRA can be used to confirm TB infection in a BCG-vaccinated child who has a positive TST result. Alternatively, an IGRA can be used in lieu of the TST for the initial evaluation. However, exposure to a contagious TB patient is the most important consideration in the interpretation of tests of infection. A positive TST result in a BCG-vaccinated child recently exposed to a person with contagious tuberculosis is most likely a true positive, and confirmation with an IGRA is not recommended.

Because of their imperfect sensitivities, negative tests of infection cannot rule out TB disease and must be interpreted in concert with epidemiologic, clinical, and radiographic data.[132] Some experts may use the TST and both IGRAs to maximize sensitivity in an immunocompromised child suspected of having TB disease. The WHO recommends against IGRA use in high-burden, resource-limited settings because IGRAs are more expensive than the TST, require greater laboratory infrastructure, and do not substantially improve diagnostic sensitivity.[158]

Microbiologic Confirmation and Drug Susceptibility Testing

Methods of Specimen Collection

Expectoration is the preferred specimen collection method for children who can produce sputum. However, for young children who cannot expectorate, other approaches are used to collect respiratory specimens. While a child sleeps, mucociliary transport sweeps respiratory secretions up the airways into the throat. The child swallows these secretions into the stomach.

Gastric aspiration attempts to collect these swallowed respiratory secretions. To minimize the chance of stomach emptying, the procedure should be performed as early in the morning as possible, and the child should abstain from eating or drinking for the preceding 8 hours. The procedure begins with nasogastric tube insertion. If lubrication is required, sterile water or the patient's own saliva should be used; commercially available lubricants can be bactericidal. The stomach contents should then be aspirated. If less than 10 mL of material is aspirated, 5 to 10 mL of normal saline should be injected through the tube, left for 2 to 3 minutes, and then aspirated and added to the first collection. Because the tubercle bacilli do not tolerate gastric acidity, the sample should be neutralized immediately. Concentration, decontamination, and culture also should be performed as soon as possible after collection. To optimize diagnostic yield, gastric aspirates should be performed on 3 consecutive mornings.[159,160]

Sputum induction, an alternative to gastric aspiration, works by increasing the child's tussive force. Sputum induction requires the child to fast for 3 hours before the procedure. A 5-mL solution of 3% hypertonic saline is administered by nebulization with a flow of 6 to 8 L/min. Children with a history of airway reactivity may benefit from premedication with a β-agonist, which decreases the risk of bronchospasm. For infants and young children who cannot expel the resulting sputum, trained personnel must suction out the oropharynx to collect the specimen; two or three samples are recommended to increase diagnostic yield.[160] Most studies demonstrate a lower yield of *M. tuberculosis* from bronchoalveolar lavage specimens compared with properly obtained gastric aspirates.[161–163]

Methods of Microbiologic Confirmation and Drug Susceptibility Testing

Tests of microbiologic confirmation are divided into genotypic tests, which detect nucleic acid fragments from *M. tuberculosis*, and phenotypic tests, which detect whole microbes or their components. The sensitivity of both methods depends on bacterial burden and is therefore low for children due to the paucibacillary nature of childhood disease. Drug susceptibility testing (DST) methods also are characterized as phenotypic or genotypic. Phenotypic DST evaluates the strain's growth or metabolic activity in the drug's presence, and genotypic DST detects resistance-conferring mutations.

Conventional Approach.

The conventional approach consists of acid-fast stain and microscopy, mycobacterial culture, and the proportion method for DST. Acid-fast microscopy and mycobacterial culture have low sensitivity for detecting *M. tuberculosis*. Even with optimal specimen collection and laboratory processing, only 10% to 15% of children with clinically suspected pulmonary TB have smear-positive samples, and only 30% to 40% have culture-positive samples.[160,164,165] Microbiologic confirmation of extrapulmonary TB also is elusive.[44,97,166,167] For example, the proportions of smear-positive and culture-positive CSF samples for children treated for TB meningitis are approximately 9% and 35%, respectively.[97]

The proportion method for DST, which is the gold standard, can be performed only if *M. tuberculosis* has been isolated in culture. To perform the test, a critical concentration of each drug is placed in media with standardized inoculum. Resistance is diagnosed if the proportion of resistant bacilli exceeds 1%. The proportion method is performed routinely with more than one critical concentration of isoniazid—a clinically significant practice because higher concentrations (doses) of the drug may overcome low-level resistance. Different levels of isoniazid resistance correlate with specific genetic mutations; genotypic DSTs assess for different levels of isoniazid resistance by detecting the corresponding mutations. The proportion method lacks standardized techniques and interpretations for ethambutol, pyrazinamide, and second-line drugs.[168]

Obtaining a positive culture on solid media, such as Löwenstein-Jensen or Middlebrook agar, often requires 4 to 6 weeks, followed by an additional 2 to 4 weeks for DST. Automated liquid media systems have shortened the time to positivity to 1 to 3 weeks but have not increased culture sensitivity. Use of an automated liquid media system for the proportion method shortens time to result to 1 week.

Nucleic Acid Amplification.

Several NAATs for mycobacteria have been developed with various target sequences, assay formats, and specimen-processing procedures.[169–177] Most NAATs use the insertion element IS6110 to detect *M. tuberculosis*.[174]

Xpert MTB/RIF (Xpert), the most widely used NAAT, uses an automated, cartridge-based polymerase chain reaction (PCR) platform and probes to detect in 2 hours the presence of *M. tuberculosis* and mutation of *rpoB*, the gene responsible for most rifampin resistance. Because rifampin resistance rarely occurs in the absence of isoniazid resistance, detection of a *rpoB* mutation serves as a proxy for the diagnosis of MDR-TB. Compared with culture, a meta-analysis showed that the Xpert overall sensitivity was only 66% for respiratory samples from 2600 children.[178] In stratified analyses, Xpert had a sensitivity of 95% for AFB smear-positive samples but only 55% to 62% sensitivity for AFB smear-negative, culture-positive samples.[178] HIV status and specimen type (i.e., sputum or gastric lavage) did not affect assay performance.[178] Taken together, Xpert appears to be more sensitive than sputum smear microscopy but less sensitive than culture for confirming childhood pulmonary TB.

Few reports have described Xpert's diagnostic utility for childhood extrapulmonary TB. In a large cohort study that used culture as the reference standard, Xpert demonstrated sensitivities of 100% and 75% for lymph node tissue and CSF, respectively.[179] In other studies that included children but did not disaggregate pediatric results, sensitivities ranged between 50% and 100% for both CSF and lymph node tissue.[178,180–182] Xpert has demonstrated 95% or higher sensitivity and specificity for rifampin resistance, but false-positive results can result from the detection of silent *rpoB* mutations that do not affect phenotypic susceptibility.[178,183,184]

The line probe assay (LiPA), another NAAT, uses PCR to isolate and amplify genes with resistance mutations. LiPAs, which can be performed on patient samples or culture isolates, produce results in 1 to 2 days. Numerous LiPA models are commercially available and vary in the mutations detected. The newest models detect resistance to ethambutol and drugs used to treat MDR-TB. LiPAs have 98% or higher sensitivity and specificity for rifampin resistance. Although specificity for isoniazid resistance is consistently high, sensitivity varies with the LiPA model and ranges from 57% to 100%.[185,186]

Genetic Sequencing.

DNA sequencing, which has been used to identify *M. tuberculosis* strains for epidemiologic purposes, has been adapted for DST. Unlike NAATs, which use probes to detect a set number of resistance-conferring mutations fixed a priori into the product design, sequencing platforms can identify all possible mutations in target genes and be rapidly modified to add more genes. Sequencing can also distinguish between silent and phenotypically significant mutations. Studies have shown more than 90% sensitivity and specificity for isoniazid resistance and more than 95% sensitivity and specificity for rifampin resistance.[184,187–189]

Recommendations for Diagnosing Tuberculosis Disease and Drug Resistance

The diagnostic approach for TB disease in children varies according to the patient's clinical presentation and the available technology. Guiding principles include the following:

1. Although microbiologic confirmation of childhood TB disease is difficult, most cases can be diagnosed clinically. All children suspected of having TB should undergo a careful history, including identification of possible source cases, physical examination (including growth assessment), test of infection (i.e., TST or IGRA), and relevant radiologic exams (e.g., chest radiography for pulmonary disease, neuroimaging for TB meningitis). Each of these elements may provide important diagnostic clues.

2. In most cases of suspected childhood TB, microbiologic confirmation should be pursued with culture, which remains the most sensitive diagnostic tool. For children with a known source case, a positive test result for infection, and classic radiographic findings, microbiologic testing may not be necessary as long as the source case has a DST result that can guide treatment.

3. Although less sensitive than culture, molecular methods may shorten the time to microbiologic confirmation and diagnosis of drug resistance. Diagnostic speed is particularly important in instances of severe, life-threatening disease or in areas with high drug-resistant TB prevalence, particularly when no source case DST is available to guide therapy. When available, both culture and molecular testing should be obtained to increase diagnostic yield.[190] Molecular methods also should be applied to known source cases to ensure timely initiation of appropriate therapy for themselves and

their child contacts.

4. In the United States and other countries with a low prevalence of rifampin resistance, the detection of rifampin resistance by Xpert should be confirmed with phenotypic DST or sequencing.[191] The diagnosis of MDR-TB should trigger testing for resistance to second-line drugs. In the United States, the Centers for Disease Control and Prevention (CDC) offers expanded DST through its Molecular Detection of Drug Resistance service, which employs sequencing methods.[192]

Therapy

Antituberculosis Agents

Anti-TB drugs are bacteriostatic or bactericidal (Table 134.2). Isoniazid, rifampin, pyrazinamide, and ethambutol are the first-line agents for adults and children.

TABLE 134.2

Antituberculous Drugs Used for Children

Drug	Dosage Forms	Daily Dosage for Treatment of Infection or Disease (mg/kg/day)	Twice- or Thrice-Weekly Dosage for Treatment of Infection or Disease (mg/kg/dose)	Maximum Dose
Isoniazid[a]	Scored tablets • 100 mg • 300 mg Syrup • 50 mg/5 mL[b] • 100 mg/5 mL[b]	10–20 (PO)	20–30	Daily: 300 mg Intermittent: 900 mg/dose
Rifampin[a]	Capsules • 150 mg • 300 mg Syrup formulated from capsules[c] Aqueous solution for IV injection	10–20 (PO or IV)	10–20	Daily: 600 mg Intermittent: 600 mg/dose

Pyrazinamide	Scored tablets • 500 mg	20–40 (PO)	50–70	2 g
Streptomycin	Vials • 1 g • 4 g	20–40 (IM or IV)	20–40 (IM or IV)	1 g
Ethambutol	Scored tablets • 100 mg • 400 mg	20 (PO)	50	2.5 g
Ethionamide	Tablets • 250 mg • 1 g	10–20 (PO)	No data to support intermittent dosing	1 g
Amikacin	Vials • 500 mg • 1 g	15 (IM or IV)	15–25 (IM or IV)	1 g
Kanamycin	Vials • 75 mg/2 mL • 500 mg/2 mL • 1 g/3 mL	15 (IM or IV)	15–25 (IM or IV)	1 g
Capreomycin	Vials • 1 g	15–30 (IM or IV)	15–30 (IM or IV)	1 g
Cycloserine	Capsules • 250 mg	10–20 (PO)	No data to support intermittent dosing	1 g
***p*-Aminosalicylic acid**	Granule packets • 3 g	200–300 divided bid (PO)	No data to support intermittent dosing	10 g
Levofloxacin	Tablets • 250 mg • 500 mg • 750 mg Vials • 25 mg/mL	15–20 (PO or IV)	No data to support intermittent dosing	1 g
Linezolid[e]	Tablets • 400 mg • 600 mg IV solution	10 mg (once daily ≥12 yr; divided bid <12 yr of age)	No data to support intermittent dosing	300 mg

[a] Rifamate is a capsule containing 150 mg of isoniazid and 300 mg of rifampin. Two capsules provide the usual adult (≥50 kg) daily dose of each drug. Rifater is a tablet containing 50 mg of isoniazid, 120 mg of rifampin, and 300 mg of pyrazinamide. Neither combination has been studied in children, and neither is available in a pediatric formulation.

[b] Many experts recommend avoidance of isoniazid syrup because it is unstable and is associated with frequent gastrointestinal complaints, especially diarrhea.

[c] Merrell Dow Pharmaceuticals (Cincinnati, OH) issues directions for preparation of this extemporaneous syrup.

[e] Dosing recommendations from Garcia-Prats AJ, Rose PC, Hesseling AC, Schaaf S. Linezolid for the treatment of drug-resistant tuberculosis in children: a review and

recommendations. Tuberculosis (Edinb) 2014;94:93–104.

[d] Total adult daily dosage. Fluoroquinolones can cause gastrointestinal disturbance, rash, and headache. In theory, they damage growing cartilage, but in practice, this reaction is rarely observed.

Isoniazid.

Isoniazid, the most widely used anti-TB medication, is bactericidal, easily administered, inexpensive, and relatively nontoxic in children. Isoniazid is almost completely absorbed from the gastrointestinal tract, and the recommended dose achieves therapeutic levels in all body tissues and fluids, including the CSF. In adults, isoniazid has been associated with symptomatic deficiency of pyridoxine, which is mainly found in milk and meat. However, in pediatrics, this effect occurs almost exclusively in malnourished or HIV-infected children.[193] Pyridoxine supplementation (25 to 50 mg/day) is not usually necessary in otherwise healthy, well-nourished children but is recommended for exclusively breastfed infants, HIV-infected children, pregnant adolescents, and children and adolescents with meat- and milk-deficient diets.

The major toxicity of isoniazid is hepatitis. Almost 10% of children develop transiently elevated serum alanine aminotransferase (ALT) levels while taking isoniazid, but clinical toxicity is rare. Most children are followed clinically without serum biochemical monitoring, and ALT levels usually return spontaneously to normal without interruption of treatment.[194] Isoniazid can interact with several other drugs and can increase serum phenytoin levels by blocking its metabolism in the liver, leading to toxicity.[195,196] A dose of isoniazid exceeding 15 mg/kg/day or in combination with rifampin enhances toxicity.[197]

Rifampin.

Rifampin is bactericidal for *M. tuberculosis* and generally well tolerated at a dose of 15 mg/kg/day. Rifampin belongs to the rifamycin class of antibiotics. This class also includes rifabutin and rifapentene; the latter has a long half-life that allows for weekly administration. Although 75% of rifampin is protein bound, it penetrates well into most tissues and fluids except the CSF. Despite rifampin's only modest CSF penetration—which improves in the setting of inflammation—its use has been associated with improved outcomes of childhood TB meningitis.[198]

Gastrointestinal upset is rifampin's most common side effect. Other adverse events include skin eruptions, hepatitis, and occasional thrombocytopenia or cholestatic jaundice.[193] Rifampin is excreted in bodily fluids and causes urine and stool to turn orange. Discoloration of tears may cause orange staining of contact lenses. This body fluid discoloration serves as a useful indicator of treatment adherence. Rifampin lowers the effectiveness of oral contraceptives and accelerates excretion of some hepatically metabolized drugs including HIV protease inhibitors.

Pyrazinamide.

Pyrazinamide is bactericidal for *M. tuberculosis*, particularly when bacilli are found inside macrophages or other similarly acidic environments. Pyrazinamide exerts maximal effect during the first 2 months of therapy, and its use allows treatment duration to be shortened to 6 months.[199] Pyrazinamide is well absorbed from the gastrointestinal tract and penetrates most tissues, including CSF.[200,201]

The optimal dose in children has not been established because of a lack of pharmacokinetic data. In children, hepatotoxicity occurs infrequently at the standard daily dose of 30 to 40 mg/kg but is more common with higher doses.[202] Nonetheless, pyrazinamide causes hepatitis more often in children than does isoniazid or rifampin, particularly when given with rifampin. Adults taking pyrazinamide can experience symptomatic hyperuricemia with arthralgia, arthritis, and overt gout; children rarely experience these symptoms. Other adverse events include gastrointestinal upset, rashes, and intense pruritis.[193]

Ethambutol.

Ethambutol is administered, easily absorbed well, and bacteriostatic against *M. tuberculosis*. Ethambutol has poor CSF penetration, even in the setting of inflammation.[198,203,204] Ethambutol primarily is used as the fourth drug when there is a possibility of resistance to other first-line drugs.

The most serious adverse effect is retrobulbar neuritis, which appears to be dose related and manifests with blurred vision, central scotoma, and red-green color blindness.[193] At the standard daily dose of 20 mg/kg, neuritis is rare in children and all patients with normal renal function.[205] A child's inability to cooperate with vision testing or report visual changes should not preclude ethambutol use.

Second-Line Agents.

Mostly used to treat MDR-TB, second-line agents may be useful for drug-susceptible disease in patients with CNS TB, a contraindication to first-line drugs, or a decreased ability to tolerate or absorb enteral medications (Table 134.3). Ethionamide and fluoroquinolones cross the blood-brain barrier well and appear to be effective for CNS TB.[103,198,206] Amikacin, kanamycin, and streptomycin have some ability to penetrate the CNS and may be used as the fourth drug, but dose-dependent ototoxicity and nephrotoxicity may limit their use. For patients who cannot tolerate or absorb enteral drugs, rifampin, amikacin, kanamycin, streptomycin, capreomycin, fluoroquinolones, and linezolid have parenteral formulations.

TABLE 134.3

Regimens for Treatment of Tuberculosis Infection

Drugs	Duration (mo)	Pediatric Dose	Frequency	Total Doses	Contraindications
Isoniazid	9	10–15 mg/kg; 300 mg maximum	Daily	270	Source case with isoniazid resistance
		20–30 mg/kg; 900 mg maximum	Twice or thrice weekly[a]	76	
Isoniazid *plus* rifapentine	3	Children ≥2 yr old: Isoniazid[b]: 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum Rifapentine[b]: 10.0–14.0 kg, 300 mg 14.1–25.0 kg, 450 mg 25.1–32.0 kg, 600 mg 32.1–49.9 kg, 750 mg ≥50.0 kg, 900 mg maximum	Once weekly[a]	12	Source case with isoniazid or rifampin resistance; child with HIV infection receiving antiretroviral therapy; pregnancy; age <2 yr
Rifampin	4[c]	10–20 mg/kg; 600 mg maximum	Daily	120	Source case with rifampin resistance; child with HIV infection receiving antiretroviral therapy

Isoniazid *plus* rifampin	3	Isoniazid: 10–20 mg/kg; 300 mg maximum Rifampin: 10–20 mg/kg; 600 mg maximum	Daily	90	Source case with isoniazid or rifampin resistance; child with HIV infection receiving antiretroviral therapy

[a] Intermittent regimens must be provided by directly observed therapy (DOT).

[b] Isoniazid is formulated as 100-mg and 300-mg tablets. Rifapentine is formulated as 150-mg tablets in blister packs that should be kept sealed until use.

[c] Some experts recommend 6 months of daily rifampin (180 doses); the American Academy of Pediatrics endorses both the 6-month and the 4-month regimens.

Optimal doses and dosing intervals for second-line agents have not been established for the treatment of childhood TB. Moreover, child-friendly formulations do not exist for most second-line agents. Second-line agents usually have less efficacy and greater toxicity, and they should be used only in consultation with a TB expert.

Principles of Approach to Antimicrobial Regimens

Success of antimicrobial therapy against *M. tuberculosis* depends on antimicrobial susceptibility, bacillary number and activity level, and location of the organisms (e.g., open cavities, closed caseous lesions, within macrophages). The high oxygen tension and low pH in open cavities allows *M. tuberculosis* to grow to a density of more than 10^9 organisms. Reactivation TB is associated with a high density of organisms at all three sites. Most young children with pulmonary TB are infected with a smaller number of organisms because they do not have cavitary lesions.

Any large population of a single *M. tuberculosis* strain has individual bacilli resistant to a particular antibiotic, even if the strain responds clinically to that drug.[207] This phenomenon occurs because *M. tuberculosis* drug resistance mutations occur at predictable frequencies: for streptomycin, mutations per organism occur at a density of 10^{-6}; for ethambutol, 10^{-7}; for isoniazid, 10^{-6} to 10^{-7}; and for rifampin, 10^{-8}. A cavity containing 10^9 tubercle bacilli has thousands of drug-resistant organisms, and a closed caseous lesion with 10^6 bacilli has few or none. Fortunately, because the genetic loci for resistance are unlinked on the mycobacterial chromosome, the chance occurrence of resistance to one drug is unrelated to that of any other drug. For a single bacillus to have primary drug resistance to two drugs, it would require a density of 10^{11} to 10^{16}, which rarely occurs clinically.

In adults and children with TB disease, high bacterial density assumes presence of many bacilli that are resistant to a single drug, and therapy requires two or more anti-TB drugs. A single effective drug would select for emergence of a dominantly resistant population and produce secondary drug-resistant TB. Conversely, in persons with *M. tuberculosis* infection, the low bacterial density allows the use of a single drug.

Treatment of Mycobacterium tuberculosis Infection

The number of childhood TB cases occurring in even the poorest countries can be reduced drastically with timely evaluation and treatment of child contacts of pulmonary TB patients.[208–210] Because most childhood disease occurs 2 to 9 months after infection, early intervention is highly beneficial and cost-effective.[40,211]

The decision to administer treatment should consider several aspects of the natural history of childhood TB. First, children younger than 5 years of age with TB infection were infected recently. Second, infants with untreated TB infection have up to a 40% chance of developing TB disease. Third, the risk for disease progression decreases gradually throughout childhood and then increases slightly in adolescence. Fourth, infants and young children are more likely to have life-threatening forms of TB, including meningitis and disseminated disease. Fifth, unlike adults, children with TB infection remain at risk for disease progression over many years.

Treatment of TB infection significantly reduces the risk of TB disease. Treatment options are daily or twice-weekly isoniazid for 9 months, daily rifampin for 4 or 6 months, daily isoniazid plus rifampin for 2 to 3 months, or once-weekly isoniazid and rifapentine for 12 doses (see Table 134.3).

The efficacy of isoniazid has been demonstrated by placebo-controlled trials involving more than 125,000 subjects. These studies showed a 60% median risk reduction for TB in adults after 1 year of treatment and follow-up. Among the subgroup of adults with good medication adherence, effectiveness approached 90%.[212] Because infants, children, and adolescents tolerate isoniazid better than adults and have a minimal risk of isoniazid-related hepatitis, the risk-benefit ratio for treatment of TB infection is especially favorable.[197,213] One study of 2750 children with *M. tuberculosis* infection showed a 94% reduction in TB disease during the first year after treatment and a 70% reduction over the subsequent 9-year period.[214] Other large clinical trials also demonstrated risk reductions of 70% to 90%.[215,216]

In the United States, most children receive a 9-month course of isoniazid as self-administered daily therapy or twice-weekly directly observed therapy (DOT).[141] Twice-weekly isoniazid has been used extensively to treat TB infection in children, especially school children and close contacts of cases.[217,218] Although no controlled clinical trials of intermittent treatment of childhood TB infection have been performed, an observational study of approximately 400 children younger than 18 years of age demonstrated high rates of efficacy and safety, despite the higher dose per day (see Table 134.3).[219] Although a 6-month course of treatment is recommended by the WHO to lower cost, data from large placebo-controlled trials have shown that a 9-month course confers a greater risk reduction for developing TB disease.[217]

The 4-month rifampin regimen is an alternative to isoniazid for children who cannot tolerate isoniazid or have a source case with isoniazid-resistant but rifampin-susceptible disease. Adult and pediatric studies have shown 4 months of rifampin to be *less* toxic than 9 months of isoniazid; moreover, the shorter regimen has been associated with *higher completion rates* among adults and children.[220–228] Some experts treat children younger than 12 years of age with rifampin for 6 months instead of 4 months.

A randomized, controlled trial of 1058 children between 2 and 17 years of age showed a 12-week regimen of once-weekly isoniazid and rifapentine given under DOT was as efficacious as 9 months of daily self-administered isoniazid.[229,230] No hepatotoxicity or other severe adverse treatment events were reported for children in either arm. The rifapentine group had significantly lower rates of treatment discontinuation; however, the DOT may partly explain this finding.[229]

In randomized, controlled trials of treatment of adults, 3 months of daily isoniazid plus rifampin demonstrated equivalency to 9 months of isoniazid in efficacy, adverse events, and adherence.[220,231,232] The WHO and CDC have not endorsed this regimen, but it is used in several European countries.

Guidelines do not exist for treating MDR-TB exposure or infection. A TB expert should be consulted about the management of children with either condition.[233]

No controlled studies have been published regarding the efficacy of any form of treatment of TB infection in HIV-infected children. The recommended regimen is a 9-month course of daily isoniazid.[141] Most experts recommend pyridoxine supplementation and routine monitoring of serum hepatic enzymes for HIV-infected children treated with isoniazid.

Window Prophylaxis

Isoniazid should be given to children younger than 5 years of age who have negative TST results but known or suspected exposure to a contagious source case. The rationale for this therapy—known as *window prophylaxis*—is that an untreated child may develop severe TB disease before TST reactivity develops (8–10 weeks). Children receiving window prophylaxis should have a repeat TST at 8 to 10 weeks after contact with the source case has been broken by physical separation or adequate initial treatment of the source case. If the second TST result is positive, isoniazid therapy is continued for the full 9 months, but if it is negative, treatment can be stopped.

Treatment Regimens for Tuberculosis Disease

Drug-Susceptible Pulmonary Tuberculosis

Early regimens for pulmonary TB lasted 12 to 18 months. Although they were effective, poor adherence led to high failure rates. Extensive adult and pediatric studies have shown that short-course chemotherapy—6-month regimens that typically consist of a 2-month intensive phase using 3 or 4 drugs followed by a 4-month continuation phase using 2 drugs—cures most forms of TB.[199,234–238] The efficacy of short-course chemotherapy depends on the use of multiple bactericidal drugs in the intensive phase and monitored adherence with DOT.[239]

To treat pulmonary TB, the American Academy of Pediatrics and the American Thoracic Society endorse standard RIPE therapy: 6 months of isoniazid plus rifampin supplemented during the first 2 months by pyrazinamide plus ethambutol (see Table 34.3).[240,241] Ethambutol is safe in children and helps prevent the emergence of rifampin or isoniazid resistance.[242] If the isolate from the child or the likely source case is susceptible to isoniazid and rifampin, ethambutol can be stopped. The WHO endorses decreasing the frequency of medication administration from daily to thrice-weekly at the start of the continuation phase for non-HIV–infected children in settings with strong DOT programs.[190] Although not recommended by the WHO, daily therapy for the first 2 weeks followed by twice-weekly therapy under DOT has been shown to be as safe and effective (>95% cure rate) as longer durations of daily therapy.[234,237]

Treatment regimens for pulmonary TB depend on the extent of disease, medication adherence, adverse drug reactions, and clinical and bacteriologic response. Some experts consider a 6-month regimen of only isoniazid and rifampin adequate therapy for children with hilar adenopathy, no other radiographic abnormalities, and minimal risk of drug-resistant TB. If the chest radiograph shows pulmonary cavitation or slow improvement or sputum culture remains positive after 2 months of therapy, treatment duration should be extended to 9 months.

Extrapulmonary Tuberculosis

No clinical trials comparing treatment regimens for childhood extrapulmonary TB have been conducted. Several pediatric trials of 6-month, three-drug regimens included cases of lymph node and disseminated TB; both disease types responded favorably to short-course chemotherapy.[235,243] Most treatment data for extrapulmonary TB come from case series of adult patients; according to these reports, most non–life-threatening forms respond well to the 6-month RIPE therapy used for pulmonary TB.[244,245] One exception is bone and joint TB, for which 9 to 12 months of treatment is recommended because 6-month regimens (especially without surgical intervention) have been associated with a higher failure rate.[246,247]

Similarly, most experts treat childhood TB meningitis for 9 to 12 months. For a patient with a low likelihood of drug-resistant TB, isoniazid, rifampin, and pyrazinamide constitute the first three drugs. A study from Thailand demonstrated better survival and lower morbidity when pyrazinamide was added to the initial 2 months of treatment.[248] Ethionamide, levofloxacin, amikacin, kanamycin, or streptomycin serves as the fourth drug. The fourth drug may be stopped after confirmation of susceptibility to isoniazid and rifampin. After the 2-month intensive phase, pyrazinamide may be discontinued if the patient has demonstrated good clinical response. An alternative regimen used extensively in South Africa is four drugs (i.e., isoniazid, rifampin, pyrazinamide, and ethionamide) given daily for 6 months (or 9 months for HIV-infected patients).[98,103]

Regimen recommendations for childhood TB meningitis derive from observational studies and clinician experience.[97] The only component of therapy that has been supported by randomized, controlled trials is the administration of daily corticosteroids (1 to 2 mg/kg/day of prednisone or its equivalent) during the first month of therapy.[249,250]

Special Circumstances

Treatment of Tuberculosis Infection in HIV-Infected Children.

The optimal therapy for TB in HIV-infected children has not been established; the only treatment outcome data are from small case series.[55,251,252] Children and adults with HIV-TB coinfection usually achieve cure with RIPE therapy if total treatment duration is extended to 9 months (i.e., isoniazid plus rifampin for 9 months supplemented by pyrazinamide plus ethambutol for the first 2 months) or to 6 months after sputum smears and cultures become negative, whichever is longer.[55,252,253] Intermittent, including thrice-weekly, therapy is not recommended for HIV-infected patients. Rifabutin can replace rifampin in patients receiving protease inhibitors; however, experience in children is limited.[254–256]

Infants of Mothers With Tuberculosis.

An infant whose mother or other household contact may have TB is at high risk for infection and disease. If possible, separation of the mother or contact and infant should be minimized. Recommendations for various clinical scenarios follow.[141]

Infected Household Contact With No Evidence of Disease.

Other household and extended family members to whom the infant may be exposed should undergo evaluation for TB. If no other household or family members show evidence of disease, the infant does not need further assessment. Treatment for TB infection should be considered for the contact and any other household or family members with TB infection.

Mother With Disease Who Is Noncontagious at Delivery.

Contact investigation of household and extended family members is mandatory. The neonate should have a chest radiograph and complete physical examination to evaluate for congenital TB. If the chest radiograph and examination are unremarkable, the infant should receive isoniazid. Separation of the mother and infant is unnecessary if treatment and follow-up are ensured. The infant can breastfeed safely.

The infant should have a TST at 3 to 4 months. Isoniazid can be discontinued if the TST result and physical examination are normal, the mother adheres to therapy and shows satisfactory response, and no other close contacts have infectious TB. If the infant has a positive TST result, isoniazid should be continued for the full 9-month course.

Mother With Disease Who Is Suspected to Be Contagious at Delivery.

Management is the same as for the infant of a mother who is noncontagious at delivery, with the exception that while the mother remains contagious, contact between mother and infant should be limited to short periods, during which the mother must wear a mask.

Drug-Resistant Tuberculosis

The drug susceptibility pattern of the likely source case should guide empiric therapy while the child's own DST results are pending. Most cases of childhood pulmonary TB that are isoniazid-resistant but rifampin- and pyrazinamide-susceptible can be treated with a 6-month regimen of rifampin plus pyrazinamide plus ethambutol given daily or thrice weekly. Because of its inherent pyrazinamide resistance, *M. bovis*, barring additional drug resistance, should be treated with isoniazid and rifampin for 9 months, accompanied by ethambutol for the first 2 months.

MDR-TB regimens usually involve four or more drugs to which the patient's strain is susceptible and last 12 to 24 months. The use of an injectable drug, such as amikacin, for the first 6 months has been associated with improved outcomes but also with ototoxicity.[257–259] Intermittent administration of medications is not recommended for resistant TB, and daily DOT is critical to prevent emergence of additional resistance. Several resources provide a more comprehensive overview of the management of childhood drug-resistant TB.[260–262] A TB expert should be involved in designing the treatment regimen for all drug-resistant cases.

MDR-TB treatment guidelines for children are based on adult studies.[258,263,264] Pediatric data are scarce, but clinical experience and observational reports support several generalizations. First, children tolerate second-line therapy well, despite the lack of pediatric dosages. Second, children with intrathoracic TB respond favorably when the regimen includes three or more drugs to which the isolate is susceptible. Third, children with TB meningitis, HIV infection, or poor access to health resources have worse outcomes. Fourth, outpatient therapy for most or all of the treatment course is not associated with worse outcomes.[257,260,265]

The US Food and Drug Administration has approved bedaquiline for adults with MDR-TB. No pediatric data exist for the drug's safety, tolerability, efficacy, or pharmacokinetics.[266]

Adjunctive Measures and Monitoring

Corticosteroid Therapy

Corticosteroids are beneficial in the management of childhood TB when host inflammatory response contributes significantly to tissue damage or impaired function.[267] Corticosteroids decrease mortality rates and long-term neurologic sequelae for patients with TB meningitis by reducing vasculitis, inflammation, and increased intracranial pressure.[249,250,268] Corticosteroids also are used for a CNS inflammatory mass that arises during therapy for TB meningitis; enlarged hilar lymph nodes that compress the tracheobronchial tree, causing respiratory distress, localized emphysema, collapse, or consolidation[269]; and miliary disease associated with alveolar-capillary block, pleural effusion, or pericardial effusion. The most commonly used agent is prednisone at 1 to 2 mg/kg/day for 4 to 6 weeks followed by a taper.

Follow-Up During Antituberculosis Therapy and Directly Observed Therapy

The primary goals of treatment monitoring consist of ensuring adherence, watching for adverse drug reactions, and assessing clinical response. In the United States, TB cases must be reported to the local public health department, which assists with treatment monitoring, compiles statistics, and performs necessary contact investigations. Moreover, public health officials should be promptly alerted about nonadherence and missed appointments because they may be able to help patients overcome barriers to adherence to therapy and clinic visits. The use of DOT in adult populations with increased risk factors for nonadherence (e.g., homelessness, intravenous drug use, HIV infection, lower socioeconomic status) demonstrated reductions in drug resistance, overall relapse rates, and relapses with MDR organisms.[270] Children and adolescents with TB should be managed with DOT whenever possible.[190,218]

Children have low rates of adverse reactions to anti-TB medications.[141,193] Asymptomatic mild elevations (i.e., more than three times the normal level) of serum ALT occur frequently during isoniazid or rifampin therapy, do not predict hepatotoxicity, and are not indications for discontinuing drugs. With the exception of pregnant or postpartum adolescents, who may have an elevated risk of hepatotoxicity, pediatric TB patients do not usually require routine biochemical monitoring. Rather, their caregivers should receive education regarding signs and symptoms of adverse events (e.g., anorexia, vomiting, abdominal pain, jaundice), which should prompt discontinuation of all medications and evaluation by a physician. Children taking ethambutol require regular monitoring of visual acuity and color discrimination if they can cooperate with testing.

While receiving chemotherapy, the patient should be seen periodically to encourage regular intake of the prescribed drugs and to assess treatment response and possible adverse drug effects. Because radiographic improvement of intrathoracic TB occurs slowly, routine chest radiographs typically need to be obtained only at diagnosis, 1 or 2 months into treatment, and at the conclusion of therapy. Normal chest radiograph appearance is not a necessary criterion for treatment completion. Hilar lymphadenopathy commonly persists for 2 to 3 years after therapy.

Adults and children with HIV infection and tuberculosis may develop IRIS if antiretroviral drugs are started with or shortly after the initiation of anti-TB therapy.[271,272] As the HIV load drops and the $CD4^+$ lymphocyte count rises, TB disease appears to worsen, or new foci of infection (e.g., tuberculoma of the brain, abdominal lesions) appear despite effective chemotherapy. IRIS is an immunologically mediated phenomenon and does not indicate inadequate anti-TB treatment. The addition of corticosteroids to the treatment regimen usually hastens resolution of new lesions.

Bacillus Calmette–Guérin Vaccine

Despite decades of routine use of BCG vaccines in every country except the Netherlands and the United States, TB remains a major cause of morbidity and mortality worldwide.[273] The lack of known in vitro correlates for immunity to *M. tuberculosis* poses a major obstacle to TB vaccination. However, increased understanding of TB immunity has led to efforts to produce a more effective vaccine, and several vaccine candidates are in various stages of development.[274]

Studies suggest that BCG vaccination can confer some protection against infection with *M. tuberculosis*.[275] Meta-analyses of published trials and case-control series suggest that BCG vaccination of children prevents about 50% of all cases of TB disease, 60% to 80% of severe cases (especially meningitis and miliary disease), and 60% to 80% of deaths from TB.[91,276–278] Strong evidence supports the use of BCG vaccines in TB high-burden countries to prevent meningitis and disseminated disease in young children, but in 2011, vaccination rates in high-burden countries were only 47% to 85%.[279]

In the United States, the low risk of *M. tuberculosis* infection in the general population and the vaccine's limited efficacy render universal BCG vaccination inappropriate. However, BCG vaccination is recommended for infants and children with negative TST results who have a high risk of intimate and prolonged exposure to persistently untreated or ineffectively treated people with infectious pulmonary TB, cannot be removed from the source of exposure, and cannot be given appropriate preventive therapy.

BCG vaccine is contraindicated in some patients: those whose immunologic responses are impaired because of HIV infection, congenital immunodeficiency, or generalized malignancy (e.g., leukemia, lymphoma); persons receiving corticosteroids, alkylating agents, antimetabolites, or irradiation; and pregnant women.[280] Patients who are undergoing TB treatment or who receive BCG vaccine can be given measles or other live virus vaccines unless they are taking corticosteroids, are severely ill, or have specific vaccine contraindications.

Complications of BCG vaccine include BCG lymphadenitis and abscesses. Immunosuppressed individuals and occasionally young children can develop infection at disseminated sites (e.g., bone, brain, liver, lung).[281–289] Standard anti-TB therapy is recommended to treat osteitis and disseminated disease caused by BCG and can be considered for treatment of chronic suppurative lymphadenitis when surgical excision cannot be performed.

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135

Mycobacterium Nontuberculosis Species

Marc Tebruegge, Nigel Curtis

The growing importance of nontuberculous mycobacteria (NTM) in the past 2 decades prompted development of sophisticated microbiologic techniques that enable more rapid and accurate identification of older species and identification of species that are emerging as human pathogens.[1–3] More than 160 species of mycobacteria are currently recognized.

Epidemiology

NTM species are ubiquitous in soil, water, foodstuffs, and domestic and wild animals.[4,5] Human strains of *Mycobacterium avium* and *M. intracellulare* (collectively called *M. avium* complex [MAC]) are found in fresh and brackish waters in warm climates and in some animals, particularly swine. Bird strains of *M. avium* are molecularly different from human strains.[6] Tap water has emerged as the major reservoir for several NTM species, including *M. kansasii, M. xenopi, M. gordonae, M. simiae,* and *M. mucogenicum,*[7] *M. fortuitum, M. chelonae,* and *M. abscessus.*[4] Fish and fish tank water are a major reservoir for *M. marinum.*[8–12] Rapidly growing mycobacteria (i.e., *M. fortuitum, M. mucogenicum, M. immunogenum,* and *M. abscessus)* are associated with healthcare-associated infections, most likely from environmental sources.[13–17] When identical methods are used, isolation rates of NTM are remarkably similar in diverse geographic areas.[18]

There are particular geographic regions in which pathogenic species are found more commonly in the local environment and as etiologic agents of disease.[19] These include *M. simiae* (e.g., southwestern United States, Europe, Israel), *M. malmoense* (e.g., northern and central Europe), *M. xenopi* (e.g., Canada, United States, Europe), *M. ulcerans* (e.g., Africa, Australia), and *M. kansasii* (e.g., Europe, areas of the central and southern United States).[18–36]

The incidence of human disease due to NTM increased significantly in the 1980s and 1990s in parallel with increasing numbers of AIDS cases.[37] Epidemiologic data suggest that the incidence of infections due to NTM among immunocompetent individuals has also risen in the past few decades.[19,20,34,35,38–40] The changes in incidence may be real or may reflect increased awareness and enhanced laboratory detection.[19,35]

One study of children found seasonal variation in the incidence of NTM disease in temperate climates. Peaks occurred in late winter and spring, and troughs occurred in autumn,[41] analogous to the reported seasonality for tuberculosis.[42]

Pathogenesis

The pathogenesis of NTM infection in humans is not well understood. Humans are thought to acquire these organisms primarily from environmental sources. Although it was previously thought that there is no human-to-human transmission,[18,40,43–46] data from cases with cystic fibrosis (CF) suggest that *M. abscessus* can be transmitted between patients.[47] Pulmonary NTM infection results from inhalation of airborne organisms, whereas skin and soft tissue infections result from direct inoculation. Ingestion of NTM can result in gastrointestinal disease or cervical lymphadenitis. Although the pathogenesis of disseminated disease, especially for rapidly growing mycobacteria, is not understood completely,[48] colonization of central venous catheters (CVCs) may be important.

Many host factors that increase the risk of NTM infection have been identified.[18] Each species has a characteristic level of virulence and propensity to cause infection in particular organs or settings (Table 135.1). This includes contaminated wounds and open fractures (e.g., *M. fortuitum, M. goodii*), prosthetic devices such as indwelling CVCs (e.g., *M. fortuitum, M. mucogenicum*) and prosthetic heart valves (e.g., *M. fortuitum, M. abscessus),*[48–50] tympanostomy tubes (e.g., *M. abscessus*, MAC),[14,17] immune suppression with organ transplantation (e.g., *M. chelonae, M. abscessus*),[51] and bronchiectasis in the setting of CF (e.g., MAC, *M. abscessus*).[52–54] Another iatrogenic factor predisposing to mycobacterial disease is treatment with tumor necrosis factor-α (TNF-α)–inhibiting agents (e.g., infliximab, etanercept), usually in the context of rheumatoid arthritis or inflammatory bowel disease[55–58] (see Chapter 107).

TABLE 135.1

Clinical Manifestations of Infection Caused by Nontuberculous Mycobacteria

Site	Predominant *Mycobacterium* Species	Typical Lesions	Setting
Skin and soft tissue	*M. marinum*	Papular, nodular, or plaque-like; less commonly ulcerative	Usually associated with aquatic trauma (aquarium granuloma, swimmer's granuloma)
	M. fortuitum	Granuloma	Postoperative, central venous catheter associated, after trauma or penetrating injury
	M. abscessus	Granuloma	
	M. chelonae	Granuloma	
	M. ulcerans	Ulcer	Mode of transmission is uncertain
Lymphadenitis	*M. avium* complex	Submandibular or anterior cervical mass	Typically unilateral; subacute; 1–5 yr olds
	M. haemophilum		
	M. malmoense[a]		
Otitis media and mastoiditis	*M. abscessus*	Chronic otorrhea; unresponsive to conventional antibiotics	Almost exclusively in patients with tympanostomy tubes in situ
	M. avium complex		
Pulmonary infection	*M. avium* complex	Cavitation or nodular disease and bronchiectasis	Typically in patients with preexisting lung disease; cystic fibrosis and bronchiectasis in children and adolescents; chronic obstructive pulmonary disease in adults
	M. kansasii		
	M. abscessus		
	M. fortuitum		
	M. simiae[a]		
Disseminated infection	*M. avium* complex	Organism recovered from	Immunocompromised host (malignancy, impaired cell-mediated immunity, HIV

	M. kansasii *M. abscessus* *M. chelonae* *M. haemophilum*	blood, bone marrow, liver, and lymph nodes	infection, immunosuppressive treatment or chemotherapy)

[a] Common only in certain geographic areas.

Investigation of genetic polymorphisms that increase host susceptibility to NTM is ongoing. The interferon γ (IFNγ), TNF-α, and interleukin-12 (IL-12) pathways play an important role in the host immune response to mycobacterial infections. Isolated immune defects identified in patients with disseminated mycobacterial infections include mutations in the IFNγ receptor gene and IL-12 receptor deficiency.[59–65]

Virulence factors that enhance the invasiveness of NTM species largely are unknown, in part because comparatively few NTM species have undergone genomic sequencing. The complete genome of *M. ulcerans* was published in 2007, followed by the genomes of *M. avium, M. marinum,* and *M. abscessus*.[66–71] Additional NTM species have been sequenced since then.[72–74] *M. ulcerans* produces mycolactone, a polyketide toxin that induces tissue necrosis and has immunosuppressive properties.[75] The genes required for mycolactone production are plasmid encoded.[76]

Laboratory Diagnosis

The mycobacterial species, the site of specimen origin, and quantity of growth in culture are important factors in assessing the potential pathogenic role of an NTM isolate.[18] Heavy growth of a single organism usually indicates infection, whereas light growth in a single sputum sample may indicate colonization or contamination.[18] This does not apply to normally sterile body fluids or bronchoalveolar lavage (BAL) fluid, in which NTM isolation confirms infection.[18] Recommendations for isolation and interpretation of culture results are published.[18] Because some NTM have unusual requirements for nutrition and incubation (e.g., *M. haemophilum, M. ulcerans, M. genavense, M. marinum*),[2,9,18,77] laboratory staff should be consulted to optimize specimen collection and culture conditions.

Conventional methods used for *M. tuberculosis* remain useful for processing and staining of specimens for NTM before culture.

Typically, *N*-acetyl-L-cysteine is used as a mucolytic agent to free acid-fast bacilli from proteinaceous material, followed by 2% sodium hydroxide to kill non–acid-fast organisms. However, some NTM species, especially rapidly growing mycobacteria such as *M. abscessus*, are highly susceptible to sodium hydroxide and lose viability.[78] Chlorhexidine decontamination may be preferable when *M. abscessus* is suspected.[78] For tissue samples and fluids from normally sterile sites, decontamination procedures are not required.[18]

Fluorochrome, Kinyoun, and Ziehl-Neelsen stains are used for direct staining.[3,18] Because the appearance of mycobacteria in stained specimens varies, experience is required for accurate interpretation. Colony morphology, growth rates, and pigmentation are superior to microscopic morphology as an indication of mycobacterial group; however, neither should be used to identify species.

Standard culture methods involve a combination of broth and solid media. Although most NTM species grow well with standard incubation at 37°C, some species, including *M. ulcerans* and *M. marinum*, grow poorly or not at all at 37°C. If these organisms are suspected, additional cultures should be incubated in parallel at 30°C to 32°C.[9,79,80]

Historically, isolation on solid media required 2 to 4 weeks, and identification based on biochemical tests took another 4 to 6 weeks. However, the use of broth culture incubation systems, such as the BioFM (Bio-Rad) and the Bactec MGIT 960 (Becton Dickinson), has reduced the time for detection of growth to an average of 1 to 2 weeks, depending on species and positivity of direct smear.[3,81–83] A more rapid method for mycobacterial species identification is cell wall mycolic acid analysis by thin-layer chromatography, gas-liquid chromatography, or high-performance liquid chromatography (HPLC).[1,84–87]

Use of matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) mass spectrometry has been explored for NTM species identification.[88,89] A variety of molecular methods also can be used for species identification, including commercial DNA probes (e.g., *M. tuberculosis* complex, MAC, *M. gordonae, M. kansasii*) (AccuProbe, Gen-Probe) and commercial hybridization strips (i.e., line probe assays) for multiple species (INNO-LiPA Mycobacteria v2, Fuji-Rebio; GenoType Mycobacterium CM/AS, Hain Lifescience; MolecuTech REBA Myco-ID, YD Diagnostics).[18,90–94] Other methods include a commercial 16S rRNA gene sequencing kit (MicroSeq, Applied Biosystems),[95,96] noncommercial (in-house) sequencing and polymerase chain reaction (PCR) plus restriction fragment length polymorphism (RFLP) analysis (PRA) of the *hsp*65 gene.[97–100]

Methods to detect and identify NTM directly from clinical specimens are being studied, including DNA probes, target amplification methods (e.g., PCR), signal amplification methods, and gene amplification.[3,101] The most effective of these has been amplification, followed by identification of the 16S rRNA or *hsp65* gene.[3,101] None of the PCR-based methods are available commercially, and both gene targets suffer from the fact that they are single-copy genes, which greatly reduces detection sensitivity.

NTM have been identified by means of pyrosequencing of the hypervariable regions of the 16S rRNA gene.[102–104] This method allows higher throughput, is usually less expensive than traditional chain-termination (Sanger) sequencing, and has a high level of accuracy for differentiating among mycobacterial species. The automated, PCR-based GeneXpert system (Cepheid) allows rapid detection of *M. tuberculosis* combined with testing for rifampicin resistance genes with the Xpert MTB/RIF assay. Although this system is useful for *M. tuberculosis* and has become widely available across North America and Europe,[105–108] it has not yet been developed to test for NTM. The Xpert MTB/RIF assay and most other PCR-based assays target genes within the MTB complex and therefore detect all eight species within the MTB complex, including *M. africanum* and *M. bovis* (including BCG).[109] Most assays, including the Xpert MTB/RIF, target the 1610 gene, which is shared also by *M. smegmatis*.[110]

Standardized procedures for susceptibility testing of NTM in broth systems have been published.[111] Susceptibility or resistance of NTM species in vitro often does not correlate well with clinical efficacy, with the exception of clarithromycin resistance for treatment of disseminated or pulmonary MAC, clarithromycin resistance for *M. chelonae* and *M. abscessus* infections, and rifampin resistance for pulmonary *M. kansasii*.[112–115]

Immunoassays for the Diagnosis of

Nontuberculous Mycobacterial Infections

IFNγ release assays (IGRAs) have emerged as a tool for the diagnosis of tuberculosis.[116,117] Both available commercial assays, the QuantiFERON-TB Gold in-Tube (QFT-GIT) assay (Cellestis/Qiagen) and the T-SPOT.*TB* assay (Oxford Immunotec), incorporate early secretory antigenic target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10) as stimulatory antigens, which are absent from most NTM, with the notable exceptions of *M. kansasii*, *M. marinum,* and *M. szulgai*.[116–118] IGRAs overall have greater specificity for tuberculous infections compared with the Mantoux tuberculin skin test (TST).[119] However, IGRAs have several limitations, particularly in children: (1) less robust performance in young children,[120–124] (2) high proportions of indeterminate (i.e., uninterpretable) results in some pediatric studies,[120,123,125,126] and (3) incomplete understanding of the mechanisms underlying discordance with TST results, which is frequently attributed (without definitive evidence) to prior BCG vaccination or exposure to NTM.[120,127–130]

In one study of children with mycobacterial lymphadenitis (mainly caused by *M. avium*), the QuantiFERON-TB Gold assay and the T-SPOT.TB assay showed a greater ability to discriminate between tuberculous and NTM lymphadenitis than the tuberculin skin test (TST).[131] Other reports support their usefulness to differentiate pulmonary infections due to MTB from certain NTM infections, including MAC, *M. malmoense*, *M. genavense,* and *M. gordonae*.[132–137] A negative IGRA result does not exclude MTB.[138] The pooled sensitivity of the QFT-GIT assay and T-SPOT.*TB* assay for patients with active tuberculosis in a meta-analysis was only 81% and 88%, respectively.[139] A positive IGRA result does not prove *M. tuberculosis* infection because most patients with NTM disease caused by *M. kansasii*, *M. marinum,* or *M. szulgai* have positive IGRA results.[133,134,137,140,141] Case reports suggest that IGRAs can be useful to support a suspected diagnosis of *M. marinum* skin infection when PCR and culture results are pending.[142,143]

Clinical Manifestations

Localized Skin, Soft Tissue, and Bone

Infections

The NTM responsible for most posttraumatic or postsurgical skin and soft tissue infections are *M. marinum, M. ulcerans, M. fortuitum, M. chelonae,* and *M. goodii.*[18,48,144–147] Diagnosis requires demonstration of the organism in a biopsy specimen or culture of aspirated fluid from a skin nodule, wound, or abscess. In immunocompetent hosts, cutaneous NTM infection usually represents the primary site of infection after local trauma.[48] In immunocompromised hosts, cutaneous lesions can be a manifestation of disseminated disease.[18,148–150]

Infection with *M. marinum* usually follows cutaneous trauma in nonchlorinated swimming pools, aquariums, or natural bodies of water,[8,9,142,151,152] most commonly after exposure in home aquariums.[8,9,12] *M. marinum* infection also can follow injuries inflicted by marine life (i.e., fish spines or bite injuries). Lesions may be singular but typically are clusters of nontender papules or nodules; erythematous plaques have also been reported. Lesions usually occur on the elbows, legs, and feet in pool-related cases and on the hands and arms of aquarium owners; truncal lesions are rare. A sporotrichoid distribution (i.e., linear distribution along lymphatic vessels) of multiple lesions is seen in about one fourth to one third of cases.[12,153–155]

Regional lymphadenitis or systemic symptoms are rare.[12] Locally invasive disease, including tenosynovitis, arthritis, and osteomyelitis, is uncommon.[156] Disseminated infection is rare and occurs almost exclusively in immunocompromised hosts.[8,150,157,158]

M. ulcerans infection mainly occurs in sub-Saharan Africa and Australia, where it is referred to as Buruli ulcer or Bairnsdale ulcer, respectively.[18,24,25,29,144,159–162] Cases also are reported from some Asian countries and Latin America.[159,160,163–167] The infection is most commonly acquired in riverine and coastal areas, and aquatic insects or mosquitos may play a role.[160,168,169] The initial lesion is a single, subcutaneous nodule, which evolves into a painless, undermined ulcer that is typically located on the extensor surface of the lower extremities. Local necrosis and occasionally widespread secondary necrosis occur with or without satellite lesions. The infection can spread to deep tissue planes. Healing proceeds slowly over 6 to 9 months, often resulting in severe limb deformity.[161]

Lymph node enlargement and systemic symptoms are rare.

M. fortuitum, M. abscessus, and *M. chelonae* are rapidly growing mycobacteria that cause a spectrum of cutaneous infections.[48] Primary cutaneous disease often follows penetrating injury and usually manifests as localized cellulitis, a draining abscess, or an individual nodule with minimal tenderness.[18,36,48,145,151] Outbreaks of cutaneous abscesses after injections have been associated with use of contaminated multiple-dose vials.[15,16] Outbreaks of postoperative wound infections have been reported after median sternotomy,[48,170,171] plastic surgery using contaminated gentian violet,[172] and plastic surgery procedures such as liposuction and mammaplasty.[13,48] Sporadic infections have been associated with a wide variety of surgical procedures. Unlike other bacterial infections, there often is a considerable gap between the surgical procedure and the onset of symptoms (1–5 weeks).[170] Patients have poor wound healing or breakdown of a healed wound, with drainage of serous fluid. *M. fortuitum* has been associated with infections of the foot after puncture wound, which can be indistinguishable clinically from pseudomonal or staphylococcal infection.[36,48,147] The most common healthcare-associated NTM infection is CVC infection due to *M. fortuitum*.[18,49,50]

MAC can cause synovial infection, usually manifesting as tenosynovitis of the hands or upper extremity. Infection usually is localized and results from local trauma. Skin lesions due to MAC are rare and usually are a manifestation of disseminated disease (Fig. 135.1).[149]

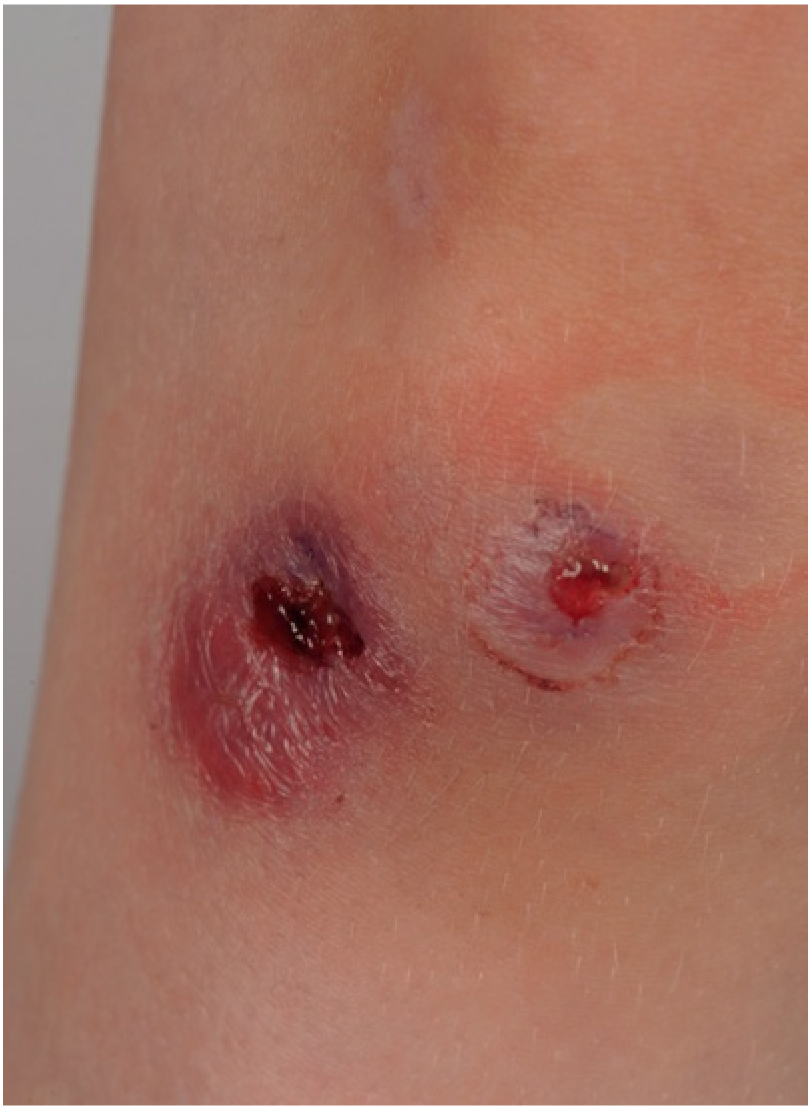

FIGURE 135.1 The lesion on the right knee of a previously well 5-year-old girl developed over a 1- to 2-month period and did not respond to conventional antibiotics. Biopsy of the lesion showed granulomatous inflammation and acid-fast bacilli. *Mycobacterium avium* complex (MAC) was identified by culture. Skin infection due to MAC is rare and occurs almost exclusively in immunocompromised hosts, but in this case, immunologic investigations, including testing of the IFNγ/IL-12 pathway, did not reveal evidence of immunodeficiency. The lesion resolved almost completely within 3 months of starting a combination of rifampin and clarithromycin.

Infection of bones, bursa, and tendon sheaths can follow penetrating trauma or surgical procedures. The most common causative agent in these situations is *M. fortuitum.* Less commonly, *M. terrae* complex, MAC, and *M. goodii* are implicated.[18] Rare cases of osteomyelitis in children have been reported. The clinical presentation of skeletal NTM infection (especially vertebral osteomyelitis) resembles that of tuberculosis and has an indolent, chronic course.[173]

Lymphadenitis

Lymphadenitis is the most common manifestation of NTM infection in children, usually occurring in otherwise healthy children younger than 12 years of age (peak incidence, 1–5 years).[18,20,36,38,41,151,173–179] Children older than 12 years with mycobacterial adenitis usually have MTB infection.[175,178] In industrialized nations with a low prevalence of tuberculosis, NTM infections account for most cases of chronic cervical or submandibular lymphadenitis.[176] MAC accounts for 70% to 90% of cases of culture-positive NTM lymphadenitis, although *M. scrofulaceum* (now rare) was the predominant etiologic agent when the disease was first recognized.[18,20,21,36,38,41,151,173–180]

In northern and central Europe, a significant proportion of NTM lymphadenitis is caused by *M. malmoense*.[20,180] The importance of *M. haemophilum* as a cause of cervical lymphadenitis was previously underestimated because of its unusual growth requirements (i.e., iron supplementation and optimal incubation temperature of 30°C).[77,179,181,182] The proportion of *M. haemophilum* in some series approaches 25%.[176] Other uncommon causative agents are *M. kansasii, M. simiae, M. chelonae,* and *M. fortuitum.* [21,22,36,174,176–178,183]

Lymphadenitis due to NTM usually is unilateral and most commonly involves the anterior cervical or submandibular lymph nodes (Fig. 135.2); the preauricular lymph nodes are affected less often.[38,174–177,179,180,183,184] In about 5% of patients, lymphadenitis involves intrathoracic (paratracheal or mediastinal) nodes.[175,185]

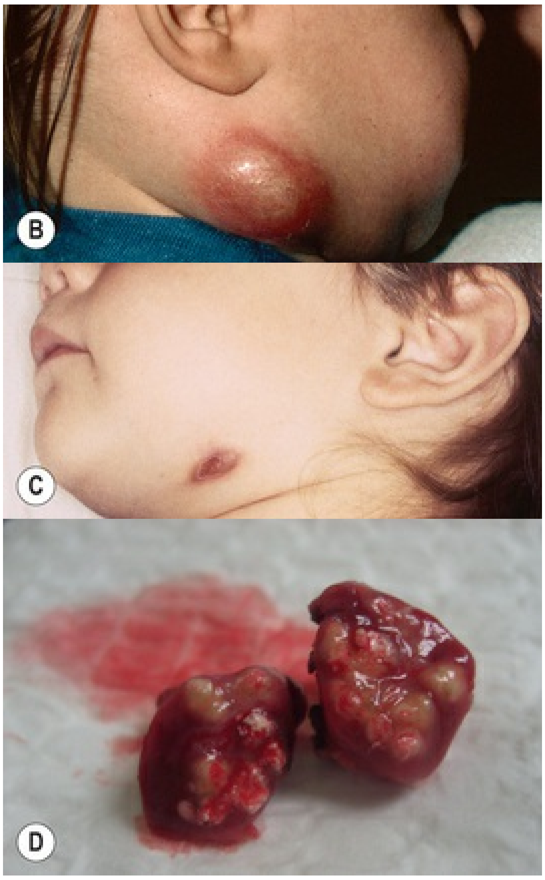

FIGURE 135.2 Three toddlers with characteristic ages, sites, appearances, and courses of nontuberculous lymphadenitis. (A) The patient had a 9-mm reactive tuberculin skin test result and was treated with clarithromycin. The node regressed without suppuration. (B) The patient had typical erythematous, effaced skin overlying an abscess caused by *Mycobacterium avium* complex. Management included aspiration, antimycobacterial therapy, and surgical excision. (C) Photograph of the patient was taken 7 months after incision and drainage were performed because of misdiagnosis of acute lymphadenitis and 6 months after starting clarithromycin and rifampin therapy. Eventually, intermittent drainage ceased, and the scar lightened. (D) Nine years after treatment of the patient (C), a mass recurred at the edge of the surgical scar. Two noncaseating granulomas measuring 0.7 and 1 cm in diameter were excised and confirmed by histology. (Courtesy of S.S. Long, MD, and B. Burkey, MD.)

Patients usually are well, without constitutional signs or symptoms, and have no or only mild local tenderness.[180] The lesion can be fluctuant or nonfluctuant on palpation.[175–177] If left untreated, the overlying skin often becomes violaceous and effaced as the lymph nodes enlarge and soften.[176,186] Nodes can then rupture and drain through a sinus tract to the skin for a prolonged period (see Fig. 135.2C). Infection sometimes resolves spontaneously, or lymph nodes do not rupture but heal, leading to fibrosis and calcification that can be disfiguring.[175,187] Remote recrudescence also can occur (see Fig. 135.2D).

The complete blood cell count usually is unremarkable; only a small proportion of patients have leukocytosis.[41,175,176,180] The erythrocyte sedimentation rate may be elevated.[41,175,176,180] Chest radiography is unremarkable in approximately 90% to 95% of cases.[174,175,180] Some studies reported a negative TST result for most patients[38,180]; two others found that approximately one half of cases had an induration of ≥6 mm or ≥10 mm, respectively.[177,178] Skin testing with mycobacterial sensitins (i.e., purified proteins) derived from NTM (e.g., *M. avium, M. scrofulaceum, M. kansasii*) was more sensitive than with the TST.[188] However, sensitins are currently not available for clinical use, and even in experimental settings, their usefulness is restricted by their limited ability to differentiate between TB and NTM infections.[128]

The differential diagnosis for NTM lymphadenitis is extensive and includes infection with *M. tuberculosis, Bartonella henselae,* Epstein-Barr virus, or *Toxoplasma gondii;* malignancy; and cystic hygroma (see Chapter 17). The diagnosis of NTM lymphadenitis is supported by the histopathologic appearance of the lymph node showing caseating or noncaseating granulomas.[151,175,180,182] Acid-fast bacilli are detected in approximately one half to two thirds of cases.[174,175,180] Although the TST result frequently is reactive, a negative result does not exclude NTM infection. A definitive diagnosis of NTM lymphadenitis is made by isolating NTM from a lymph node or by molecular detection. In most series (using older, conventional culture media), organisms were isolated from only about 50% of infected lymph nodes.[174,175] Later data suggest that PCR-based detection in nodal specimens has a higher sensitivity than isolation in mycobacterial culture media.[41]

Bilateral lymphadenitis and involvement of posterior cervical, supraclavicular, axillary, and inguinal nodes are features more frequently associated with tuberculosis than with NTM infections (see Fig. 134.6 in Chapter 134). Lymph nodes in cases of acute bacterial lymphadenitis often are larger, evolve more rapidly, and are more tender and erythematous. Fever is a prominent symptom, and the white blood cell count and C-reactive protein level typically are elevated.[175,187–189]

Pulmonary Infection

Previously thought to be rare in children,[5,145] NTM lung infections are recognized increasingly in the setting of bronchiectasis and especially in patients with CF.[52–54,190–192] NTM lung infection in patients with CF typically occurs in adolescents or young adults with relatively mild disease. Some infections are difficult to distinguish from the symptoms of CF, whereas other patients have fever, weight loss, and fatigue that do not respond to antipseudomonal therapy.[192] The disease appears to be more common in the south and southeastern United States, where up to 20% of adolescent CF patients are infected. The most common reported species affecting the lung in CF patients are MAC, *M. abscessus, M. chelonae, and M. fortuitum.*[53,192–194] NTM organisms should be considered as possible pathogens when recovered repeatedly from the sputum of patients with CF who have severe lung disease or pulmonary exacerbations unresponsive to broad-spectrum antibiotics.[187,191,192]

Most children with non–CF-associated, isolated pulmonary infection due to NTM are immunocompetent and have no underlying pulmonary disease.[173,195] Reported pediatric cases have been caused by MAC, *M. kansasii, M. abscessus, M. chelonae,* or *M. fortuitum.*[36,41,195–199] Signs and symptoms vary and are nonspecific, including fever, cough, dyspnea, hemoptysis, malaise, and fatigue. Weight loss and night sweats are uncommon.[27,197] Enlargement of mediastinal and hilar lymph nodes is common.[195,197] Endobronchial obstruction due to external compression or endobronchial granulation tissue can manifest as reduced air entry and persistent wheezing, mimicking foreign body aspiration.[195,197]

The diagnosis of pulmonary NTM infection should be considered for any child who has a pulmonary illness that is consistent with tuberculosis but is not responding well to usual antituberculous medications. NTM infections are increasingly recognized as a cause of graft dysfunction in lung transplant recipients.[200]

Physical examination and routine laboratory tests seldom provide etiologic clues. Chest radiographic findings are nonspecific and cannot be differentiated easily from those of tuberculosis or fungal infection. However, cavitating lesions are less common in pulmonary NTM disease compared with tuberculosis.[27] Involvement of multiple pulmonary segments is common.[201] Chest computed tomography, including high-resolution studies, is used increasingly for diagnosis and follow-up.[202] Imaging features depend on whether lung disease is primarily fibrocavitary (similar to tuberculosis) or is characterized by nodules and bronchiectasis.[18,201,202]

Isolation of NTM is essential for diagnosis. The interpretation of a positive sputum or gastric aspirate culture is confounded by the ubiquity of NTM in the environment. A single positive culture result does not establish the diagnosis of NTM disease.[18] Diagnosis requires growth of the same NTM organism from multiple sputum samples or a BAL specimen after the exclusion of other causes for the clinical symptoms. Certain NTM that are usually nonpathogenic, including *M. gordonae*, *M. terrae* complex, and *M. mucogenicum,* are more likely to be contaminants if isolated from respiratory specimens.[18]

The American Thoracic Society (ATS) has established diagnostic criteria for NTM pulmonary infection in adults, but their validity for children has not been established.[18] The role and importance of BAL cultures in diagnosing CF have not been established, nor have the sensitivity and specificity of sputum cultures compared with BAL cultures been confirmed. When the underlying cause remains uncertain, lung biopsy should be considered to exclude other causes, to demonstrate histopathologic changes consistent with mycobacterial disease (e.g., granulomatous inflammation with or without acid-fast bacilli), and to obtain specimens for culture.[18]

Otitis Media

Otitis media with or without mastoiditis due to NTM occurs almost exclusively in children with tympanostomy tubes.[203–211] Outbreaks[17] and sporadic[14] disease have been described. The most commonly implicated NTM are *M. abscessus*, although cases caused by MAC also have been reported. Patients usually have persistent drainage unresponsive to standard antibiotic therapy.

Disseminated Infection

Disseminated disease due to NTM is rare in healthy people but can occur in immunocompromised hosts, such as patients with underlying malignancy or congenital or acquired defects of cell-mediated immunity,[8,18,48,51,150,157,158,212] patients with isolated defects in the IFNγ/IL-12 pathway,[41,63,65] solid organ and stem cell transplant recipients,[212–218] and patients on long-term corticosteroid therapy or cytotoxic chemotherapy.[212,219] These patients often exhibit skin lesions as the earliest manifestation of disseminated disease, but lesions sometimes are related to an indwelling CVC. The most common pathogens in these settings are *M. chelonae* and *M. abscessus*.[48,219] Other pathogens include MAC, *M. haemophilum*, *M. kansasii, M. fortuitum, and M. simiae*.[18,48,212,216,220]

Skin or soft tissue manifestations of *M. kansasii* infection are rare compared with rapidly growing mycobacteria and include verrucous or granulomatous papules, cellulitis, sporotrichoid eruptions, ulcers, and necrotic papulopustules.[148,212] Multiple skin nodules occurring in clusters or without a definite pattern can be associated with *M. haemophilum* infection, usually in an immunocompromised host.[18]

Disseminated disease with NTM (primarily MAC) has long been recognized in patients with AIDS and in patients with congential immunodeficiencies, including severe combined immunodeficiency (SCID).[20,221–223] MAC infection occurs in 6% to 14% of children infected with human immunodeficiency virus (HIV), with the incidence increasing to 24% among those with severe depletion of CD4$^+$ T lymphocytes (<100 cells/mm^3).[224–226] As in the adult population,[37] disseminated MAC infection usually occurs late in the course of symptomatic HIV infection in children.

Disseminated MAC infection in children with AIDS is associated with systemic symptoms, including fever, weight loss, night sweats, and gastrointestinal complaints, which often are accompanied by neutropenia or anemia, or both. Although the mortality directly attributable to disseminated MAC infection is difficult to establish, morbidity can be significant.[225,226] Early autopsy studies suggested that MAC infection is rarely a cause of death; later studies have found disseminated MAC infection to be associated with shortened survival.[37]

Clinicians should have a high index of suspicion for disseminated MAC infection in HIV-infected children with low CD4$^+$ T lymphocyte counts. Definitive diagnosis rests on recovery of MAC from blood, bone marrow, liver, visceral lymph nodes, or other normally sterile body sites.[221] MAC bacteremia can be intermittent and low grade; multiple blood specimens must be collected to detect infection.[226] A positive stool culture result can occur in the absence of symptoms and most likely represents gastrointestinal colonization or localized disease.

Immune reconstitution inflammatory syndrome (IRIS) related to NTM infection has been repeatedly described in HIV-infected patients with a good response (i.e., increasing CD4$^+$ lymphocyte counts) to antiretroviral therapy.[227–230] IRIS manifests typically as localized disease that becomes apparent as peripheral lymphadenitis, pulmonary disease, or abdominal disease. Morbidity and mortality rates for HIV-infected children with IRIS related to mycobacterial infections are high.[231] The role of corticosteroid therapy in this context has not been established firmly.[227,231]

Treatment

Many NTM species are resistant to traditional or first-line drugs used to treat *M. tuberculosis.* Antimicrobial susceptibility testing is essential for appropriate selection of an effective treatment regimen.

Localized Skin, Soft Tissue, and Bone Infections

The optimal treatment for *M. marinum* infection remains uncertain due to the absence of controlled trials. The latest ATS and Infectious Diseases Society of America (IDSA) guidelines recommend combination therapy comprising clarithromycin plus ethambutol or rifampin (international nonproprietary name is rifampicin).[18] However, the largest published study on *M. marinum* infections reported that 18% of the patients receiving clarithromycin (alone or in combination with other antimycobacterial antibiotics) failed to respond or relapsed.[12] Some experts suggest adding rifampin as a third agent in patients with bone or joint involvement.[8,9,18,232] Cases with extensive locally invasive disease may require surgical debridement. Antibiotic treatment should be continued for 1 to 2 months after resolution of all lesions.[8,9,232,233]

Traditionally, lesions due to *M. ulcerans* were universally treated by surgical excision with or without skin grafting.[159] Circumstantial evidence suggests that radical excision with a wide safety margin is more effective than more limited surgery.[234] However, incomplete cure and recurrence are not uncommon with surgery alone, even with radical excision.[161,234–236] Systemic therapy with trimethoprim-sulfamethoxazole, minocycline, dapsone, or clofazimine has been used, but clinical response in longstanding ulcerative lesions often is poor.[25,159,160,237] However, antibiotic treatment may limit the need for surgical management. Anecdotal reports and data from observational studies suggest that treatment with rifampin-containing combination therapy can be curative without surgery.[238,239] Data from a randomized, controlled trial of treatment of patients with early, limited *M. ulcerans* infection also suggest that these cases can be effectively managed with antimycobacterial treatment alone.[240] Patients in this study received rifampin plus streptomycin for 8 weeks or the same combination for 4 weeks, followed by 4 weeks of rifampin plus clarithromycin; cure rates were greater than 90% in both groups. In a pilot study that included 15 patients, an 8-week course of oral rifampin plus clarithromycin was curative without surgery.[241]

Primary cutaneous lesions due to *M. fortuitum, M. chelonae,* and *M. abscessus* require drainage of localized abscesses and removal of any foreign bodies.[18] With available antimicrobial agents, surgical excision of infected tissue is not required routinely. Because of different drug susceptibilities between and within species, susceptibility testing is essential.[18,111] *M. fortuitum* isolates usually are susceptible to several oral antibiotics, including clarithromycin, doxycycline, minocycline, sulfonamides, and fluoroquinolones.[18] However, all isolates of *M. fortuitum* contain an inducible *erm* gene that confers resistance to macrolides[242]; macrolides should therefore be used with caution.[18]

Limited data suggest that clarithromycin monotherapy is usually effective for *M. chelonae* skin infections.[18,219] Serious skin and soft tissue infections with *M. abscessus* should be treated empirically with a macrolide (i.e., clarithromycin or azithromycin) plus a parenteral agent (i.e., amikacin, cefoxitin, or imipenem).[18] The duration of therapy must be individualized according to host factors, clinical response to treatment, and extent of infection. However, the standard recommended duration of therapy for severe disease, including osteomyelitis, is 6 months.[18]

Lymphadenitis

Surgical excision with removal of all visibly affected lymph nodes has been considered to be the standard therapy for NTM lymphadenitis.[18,145,174,187,189] However, only one randomized, controlled trial investigated the efficacy of surgery compared with antimycobacterial antibiotics in children.[179] The cure rate was significantly higher for the group allocated to surgery (96%) than for the group receiving conservative treatment with clarithromycin and rifabutin (66%). However, 6 patients (12%) in the surgery group developed postoperative wound infections, and 7 (14%) had facial nerve dysfunction postoperatively, which was permanent in 1 patient (2%). Adverse events in the antibiotic group were mild and transient. Importantly, outcome is dependent on surgical expertise, and these data can therefore not be generalized. Further limitations of the study are discussed elsewhere.[41,183]

Subsequently, published data from the same study suggested that the aesthetic outcome might be better with primary surgery than with antimycobacterial treatment.[186] When complete excision is not possible, as in the case of lymphadenitis with extensive facial nerve involvement, partial excision, thorough curettage, or conservative treatment with antimycobacterial antibiotics alone are options. Because MAC is by far the most common causative agent of NTM lymphadenitis, empiric treatment with clarithromycin plus rifabutin with or without ethambutol is a suitable choice.[18,179,189,243–246] Watchful waiting (i.e., no intervention) is another option because NTM lymphadenitis is usually self-limiting.[183,247,248] However, spontaneous resolution often takes 9 to 12 months, and the child and the parents must be prepared to tolerate the physical appearance during that period.

Incisional drainage is not advisable because many patients develop a draining sinus tract as a result, and disease often recurs (see Fig. 135.2C).[174,175,184] Drainage by needle aspiration remains controversial, and sinus tract formation occurs more than infrequently with this approach.[180,183]

Pulmonary Infection

Treatment regimens for NTM pulmonary disease in children are not well established. Patients with minimal symptoms can be observed without treatment, although recognition of the pathogenicity of NTM makes this approach increasingly uncertain.

Patients with more severe clinical symptoms, radiographic findings, or persistently positive culture results require treatment.[18] The ATS/IDSA guidelines suggest using a three-drug regimen comprising clarithromycin or azithromycin, ethambutol, and rifampin or rifabutin for adults with MAC lung disease, with the addition of an intravenous aminoglycoside for severe disease.[18] The same guidelines recommend a combination of rifampin, isoniazid, and ethambutol for pulmonary *M. kansasii* infection. A study of adults with *M. kansasii* lung disease showed a regimen of clarithromycin, rifampin, and ethambutol to be effective.[249]

For adults, the guidelines recommend a duration of therapy for MAC or *M. kansasii* disease of 12 months after the sputum culture result is negative.[18] Some adults with disease confined to one lobe of the lung have benefited from surgical lobectomy, particularly if response to medical therapy was poor.[18] However, there are no uniform criteria for the selection of patients with NTM lung disease for surgical therapy.[18]

Doses, drugs, and end points of therapy have not been established for CF patients with MAC or *M. abscessus. M. abscessus* lung disease in the setting of CF usually is treatable but incurable. Long-term intravenous therapy with amikacin combined with cefoxitin or imipenem is suggested in the ATS/IDSA guidelines.[18]

The clinical and microbiologic responses of *M. abscessus* lung disease to clarithromycin have been poor despite susceptibility in vitro.[18] The *M. abscessus* species recently was divided into three new subspecies based on *rpoB* gene sequences: *M. abscessus* subsp. *abscessus [sensu stricto], M. abscessus* subsp. *massiliense,* and *M.*

abscessus subsp. *bolletii*.[250,251] Response to treatment appears to depend on the subspecies, with patients with *M. massiliense* responding better than those with *M. abscessus sensu stricto* pulmonary disease.[252] In one clinical study, inducible resistance to clarithromycin was found in all *M. abscessus sensu stricto* isolates but was not found in any *M. massiliense* isolate.[252]

Published data on newer antibiotics, including linezolid and tigecycline, for the treatment of *M. abscessus* are limited.[253–255] Adolescents with CF who are being considered for macrolide monotherapy or immunotherapy for CF should have sputum cultures for NTM before therapy and periodically thereafter. Those with repeated isolation of NTM should not receive macrolide monotherapy.[18]

Disseminated Infection

Empiric treatment of disseminated NTM infection in patients with AIDS involves a multidrug regimen comprising at least two agents: clarithromycin or azithromycin plus ethambutol. A third drug, such as rifabutin or amikacin, often is added.[18] In vitro drug susceptibilities to drugs other than the macrolides do not predict clinical outcome and should not be used to direct drug therapy.[18,111] Symptomatic improvement may take 2 or 3 weeks to 2 months, and repeated blood cultures are useful to assess reduction of the bacterial load. Neither a durable response nor an extension of survival in the absence of immune reconstitution has been demonstrated definitively in prospective clinical trials. However, when clinical improvement is observed, therapy should be continued for the lifetime of the patient or until sufficient immune reconstitution has occurred.

For patients with CVC-related infection or infection related to prosthetic devices (e.g., ventriculoperitoneal shunts, peritoneal dialysis catheters), removal of the device is essential. Choice of agents for and duration of antimicrobial therapy are based on causative species, results of in vitro susceptibility tests, and the degree of immunocompromise. It is not unusual for new skin lesions to appear during successful therapy of disseminated disease; they may be immunologically mediated. After 4 to 6 weeks of therapy for *M. chelonae*, culture of a biopsy specimen from a newly appearing lesion is expected to be sterile.[219] Treatment for *M. abscessus* infection often requires 3 to 4 months to achieve culture negativity.

In children with cancer, *M. chelonae* and *M. fortuitum* have caused infections related to venous or implanted catheters for which blood culture results were transiently positive and disseminated skin lesions persisted despite removal of the device and therapy. Treatment of bone infections, especially with open fractures and foreign material, often requires surgical debridement and prolonged multidrug therapy.[18]

Prophylaxis against disseminated MAC in adults with AIDS has been studied extensively in trials. Clarithromycin or azithromycin prophylaxis is recommended by the US Public Health Service for HIV-infected adults and adolescents whose CD4$^+$ T lymphocyte counts are less than 50 cells/mm.[3,256] Before the initiation of prophylaxis, patients must be evaluated to exclude active disease due to disseminated MAC, *M. tuberculosis,* or other mycobacterial species. Robust data do not exist for children, but prophylaxis consisting of daily clarithromycin (15 mg/kg/day divided into two doses, maximum of 500 mg/day) or once-weekly azithromycin (20 mg/kg, maximum of 1200 mg) is recommended in the US guidelines for HIV-infected children with profound CD4$^+$ lymphocytopenia.[257,258]

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Nocardia Species

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Since the first reported case of human nocardiosis in 1890, *Nocardia* spp. increasingly have been recognized as serious human pathogens. Molecular analysis identified 80 species in the *Nocardia* genus, with ongoing evolution in the understanding of *Nocardia* taxonomy.[1,2] Although challenging, identification of *Nocardia* isolates to the species level is important to determine pathogenicity and predict antimicrobial susceptibility.[1]

The more common clinical isolates reported by laboratories in past decades as *Nocardia asteroides* have been divided into six groups based on unique antimicrobial susceptibility patterns. Initially referred to as *N. asteroides* complex groups I to VI, all six groups are valid taxonomic clusters by gene sequencing and are given species or complex names. Although not a recognized taxonomic designation, *N. asteroides* complex is used for convenience to refer to all six groups. The term *complex*, when used with one of the six species groups, refers to a cluster of multiple but similar strains that have not been studied adequately to name all as individual species (Table 136.1).

TABLE 136.1

Changing Classification of Medically Relevant *Nocardia* Species

Current Classification	Classification Circa 1990–2000	Classification Before 1990
***Nocardia abscessus* complex**[a]	*Nocardia asteroides* complex group I	*Nocardia asteroides*
Nocardia brevicatena-paucivorans	*Nocardia asteroides* complex	*Nocardia asteroides*

complex[a]	group II	
***Nocardia nova* complex**[a]	*Nocardia nova* (group III)	*Nocardia asteroides*
***Nocardia transvalensis* complex**[a,b]	*Nocardia asteroides* complex group IV	*Nocardia asteroides*
Nocardia farcinica	*Nocardia farcinica* (group V)	*Nocardia asteroides*
Nocardia cyriacigeorgica	*Nocardia asteroides* complex group VI	*Nocardia asteroides*
***Nocardia otitidiscaviarum* complex**[a]	*Nocardia otitidiscaviarum*	*Nocardia caviae*
Nocardia brasiliensis	*Nocardia brasiliensis*	*Nocardia brasiliensis*
Nocardia pseudobrasiliensis	*Nocardia pseudobrasiliensis*	*Nocardia brasiliensis*

[a] These taxa include diverse strains within the species groups. It is recommended that the term *complex* be used with the species names to indicate their heterogeneity and that the taxonomy eventually be more clearly defined.[2]

[b] *N. wallacei* is the most common species encountered in the *N. transvalensis* complex and is frequently referred to by *N. wallacei* rather than *N. transvalensis* complex.

Data from References 1, 2, 43, 64.

Current designations for the *N. asteroides* complex are *N. abscessus* complex, *N. brevicatena-N. paucivorans* complex, *N. nova* complex, *N. transvalensis* complex, *N. farcinica,* and *N. cyriacigeorgica.*[2–4] The *N. farcinica* and *N. cyriacigeorgica* groups each contain closely related strains that represent a single species. Using the new taxonomy, most clinically significant isolates are *N. cyriacigeorgica, N. farcinica, N. abscessus* complex, or *N. nova* complex.[2,5] Human non–*N. asteroids* complex pathogens usually are *N. brasiliensis* or *N. otitidiscaviarum* complex (formerly *N. caviae*). *N. brasiliensis* has been subdivided into *N. brasiliensis* and *N. pseudobrasiliensis.* Whereas *N. brasiliensis* infections often are limited to skin and subcutaneous tissue in healthy individuals, all species have been reported in pulmonary and systemic infections.[3,6–10]

Microbiology

The family Nocardiaceae is composed of aerobic actinomycetes and characterized by filamentous growth with true branching. *Nocardia* spp. are catalase- and urease-positive organisms that grow on multiple media, including Sabouraud dextrose agar, Löwenstein–Jensen medium, brain-heart infusion agar, and simple blood agar. Although growth occurs over a wide temperature range, human pathogenic *Nocardia* spp. grow best at 37°C in the presence of 10% carbon dioxide. Unlike most other *Nocardia* spp., *N. farcinica* grows as well at 45°C as it does at 35°C, and this property can be used to differentiate this species.[11]

Many selective (i.e., inhibitory) media used for isolation of pathogenic fungi do not support the growth of *Nocardia* spp. Colonies can appear within 48 hours when present in pure culture; in mixed culture from clinical specimens such as sputum, other organisms often obscure small *Nocardia* colonies, making it difficult to recognize the typical morphologic characteristics before 2 to 4 weeks of incubation. Laboratory personnel should be notified to observe cultures for 4 weeks when nocardiosis is being considered. Colonies can be smooth and moist or waxy; with further incubation, development of aerial hyphae causes a velvety or chalky appearance. Primary isolates usually are light orange, but the color can vary from cream to brick red.

Microscopically, *Nocardia* spp. often are detected first on Gram stain, and they appear as delicately branched, weakly gram-positive organisms that tend to fragment into coccoid and bacillary elements (Fig. 136.1). Filaments show true branching, with irregular staining that creates a beaded appearance. Many *Nocardia* spp. are acid fast but retain fuchsin less avidly than *Mycobacterium* spp. Organisms from initial isolation are most reliably acid fast but become progressively less so on repeated subculture. A modified Ziehl-Neelsen or Kinyoun stain with the use of 1% sulfuric acid instead of acid alcohol for decoloration optimizes demonstration of acid-fast *Nocardia* in clinical specimens (Fig. 136.2).

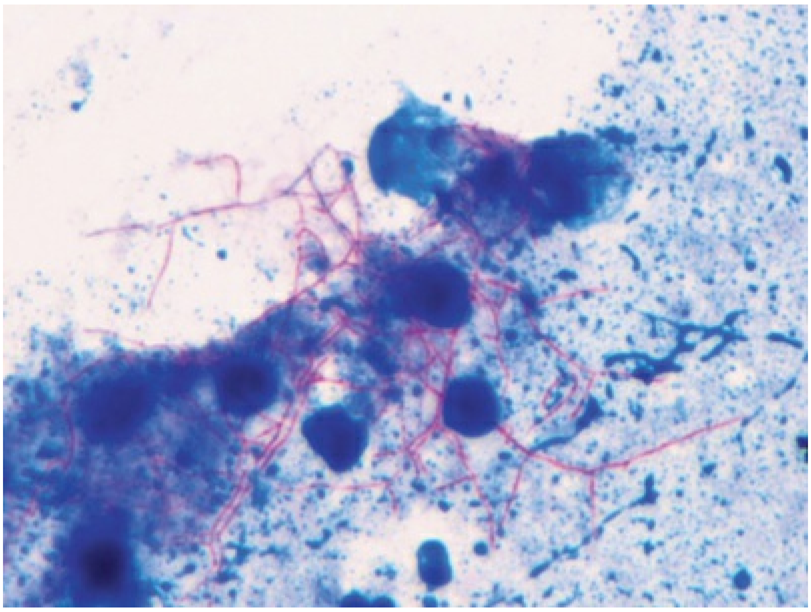

FIGURE 136.1 Gram-stained smear (oil immersion objective, ×1000) of *Nocardia* sp. in purulent sputum specimen. Notice the filamentous, branching, beaded, or stippled gram-positive rods.

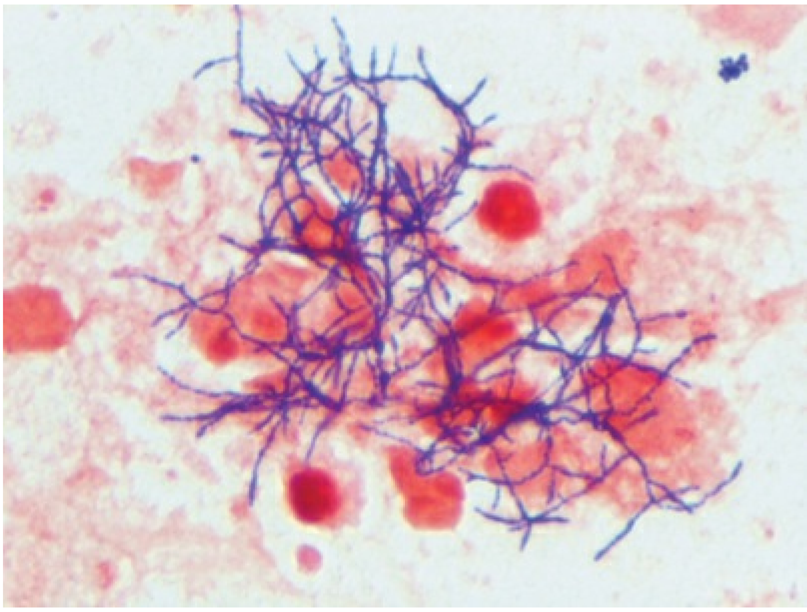

FIGURE 136.2 Modified acid-fast–stained smear (oil immersion objective, ×1000) of *Nocardia* sp. in the same purulent sputum specimen shown in Fig. 136.1.

Epidemiology

Nocardia are ubiquitous, saprophytic soil organisms that are easily aerosolized and found in house dust, garden soil, decaying vegetation, beach sand, fresh and salt water, and swimming pools. The lung is the primary portal of entry, and underlying pulmonary dysfunction with decreased bronchociliary clearance mechanisms (e.g., cystic fibrosis, asthma, bronchiectasis) predisposes to sporadic colonization, although infection rarely occurs in the absence of immunosuppression in patients with such dysfunction.[5,12,13]

Pathogenesis

Inhalation of *Nocardia* spp. can lead to primary pulmonary disease that resolves spontaneously or progresses to pneumonia.

Disseminated infection occurs by hematogenous spread from the respiratory tract, especially in immunocompromised hosts. Primary cutaneous infections usually are the result of trauma with soil contamination of the wound, resulting in infection localized to the skin and subcutaneous tissue. Keratitis that is posttraumatic or associated with contact lens use and endophthalmitis have been reported.[14–16] A few case clusters have been described, and person-to-person transmission has been documented on rare occasions.[17,18]

Patients with deficient host defenses, such as those with lymphoreticular malignancy, chronic obstructive pulmonary disease, chronic granulomatous disease, dysgammaglobulinemia, human immunodeficiency virus infection, or receiving corticosteroid therapy, are at high risk for invasive nocardiosis.[5,7,9,13,19–21] Recipients of bone marrow or solid-organ transplants have a particularly high risk. In the latter group, high-dose corticosteroid therapy, a history of cytomegalovirus disease, and high levels of calcineurin inhibitors are independent risk factors for *Nocardia* infections.[22] There are many reports of *Nocardia* infections developing in adults treated with tumor necrosis factor inhibitors, especially infliximab.[23,24]

The host response to *Nocardia* consists of early neutrophil mobilization to localize infection; cell-mediated immunologic mechanisms then supervene, followed by killing of the organism by activated macrophages and cytotoxic T lymphocytes.[25] As a facultative intracellular pathogen, the virulence of *Nocardia* is associated with the ability to inhibit phagosome-lysosome fusion in macrophages and to neutralize phagosomal acidification.[9]

Nocardia causes suppurative necrosis and abscess formation similar to that seen in pyogenic infection. Although tuberculoid granulomas and giant cells have been reported, lesions usually do not demonstrate granulomatous inflammation or tissue fibrosis. Confluent abscesses without capsules are characteristic, which may explain the frequency of dissemination from the primary pulmonary focus. *Nocardia* granules or grains, which are similar to the sulfur granules characteristic of actinomycosis, occasionally are found in superficial *Nocardia* infections but are absent in visceral infections.

Clinical Manifestations

The most common clinical manifestation is pulmonary disease, occurring in more than two thirds of cases. Infection causes acute, subacute, or chronic suppurative disease, which tends to remit and relapse. Acute onset with fever and systemic symptoms is uncommon. Pulmonary infection can manifest with cough or dyspnea and with nonspecific symptoms such as anorexia and weight loss. Hemoptysis occasionally occurs in the setting of cavitary disease.

Untreated pulmonary nocardiosis mimics tuberculosis, with a chronic course that can resolve spontaneously, obscuring the source of subsequent metastatic infection. Chest radiographic findings vary and include bronchopneumonia, alveolar infiltrates, single or scattered nodules or abscesses, and interstitial reticular infiltrates. Cavitation or pleural involvement, or both, can occur.

Widespread dissemination can occur, especially in solid-organ transplant recipients and other immunocompromised hosts. The central nervous system is the most common secondary site, where disease manifests as single or multiple brain abscesses. *N. farcinica* and *N. otitidiscaviarum* have been reported in brain abscesses with increasing frequency, which may have implications for treatment due to their antibiotic resistance patterns.[26–28] *Nocardia* also has been recognized as a cause of persistent neutrophilic meningitis despite negative routine cultures. Neurologic symptoms range from headache to coma with subacute or acute presentations.

Neurotropism is so prominent a feature of nocardiosis that cranial imaging should be performed for patients with pulmonary infection even without the symptoms of central nervous system disease. Computed tomography (CT) or magnetic resonance imaging (MRI) typically shows a necrotic cavity surrounded by a contrast-enhancing smooth capsule of uniform thickness and surrounding edema, in contrast to the more irregular capsule seen in malignant tumors.[26] T2-weighted MRI scans can show multiple concentric rings with various signal intensities.[29]

Skin manifestations of disseminated disease can be indistinguishable from primary cutaneous nocardiosis. Cutaneous lesions include cellulitis, pustules, ulcerations, pyoderma, subcutaneous abscesses, and mycetoma, which is a slowly progressive, often painless granulomatous mass associated with nodules, sinuses, and granules, usually involving the foot. Patients with skin involvement should be evaluated thoroughly to exclude disseminated disease. Subcutaneous abscesses, which are more nodular than fluctuant, do not have the same propensity for fistulous drainage as those caused by *Actinomyces*.[8,30] A cervicofacial syndrome with cervical adenitis due to *Nocardia* has been described in children.[31]

Lymphocutaneous infection caused by *N. brasiliensis* can be indistinguishable from sporotrichosis manifesting as a primary ulcerative lesion at the site of injury, often on the lower extremity, with nodular lymphangitis, and it sometimes is associated with regional adenopathy and mild systemic symptoms.[6,8,30] This syndrome also has been described at the site of a cat scratch.[32]

Nocardia can disseminate to most organs, including kidneys, intestine, pancreas, heart, spleen, liver, joints, bones, eye, spinal cord, thyroid, and adrenal glands.[7,16,20,33,34] Organ infection with *Nocardia* spp. consists of single or multiple nodules or abscesses. Renal infection can cause dysuria, hematuria, or pyuria. *N. brasiliensis* arthritis in a healthy child without a history of penetrating injury was initially treated as juvenile idiopathic arthritis.[35] Nocardia bacteremia is rare, but infections associated with central venous catheters (CVCs) and peritoneal dialysis catheters have been reported. Removal of the CVC followed by 3 months of antibiotic treatment has been successful in these cases.[19,36,37] Limited case reports of nocardiosis in children suggest that clinical presentations are similar to those in adults.

Laboratory Findings and Diagnosis

Nocardia spp. in tissue appear as branching, beaded, gram-positive filaments when stained by the Brown-Brenn modification of the Gram stain or other standard tissue Gram stain and Gomori methenamine-silver stain. *Nocardia* are not visible when stained with hematoxylin and eosin or periodic acid–Schiff stain. Identification in tissue can be confirmed using a modified acid-fast stain because *Nocardia* spp. are acid fast, but other branching, gram-positive rods are not.

Although *Nocardia* grow best on antibiotic-free media, the rate of recovery can be enhanced using selective techniques to suppress rapidly growing organisms in specimens from skin or mucosal sites. Pretreatment with an acid wash and inoculation onto selective buffered charcoal-yeast extract agar (as formulated for the detection of *Legionella* spp.) can increase the recovery of *Nocardia* from respiratory specimens.[38] Although uncommon, *N. asteroides* complex strains can be isolated in automated blood culture systems, especially if patients are receiving immunosuppressive therapy. Performing blind subcultures on day 5 of incubation on negative specimens can increase recovery.[39] When *Nocardia* infection is not suspected, cultures usually are discarded without terminal subculture or too early to allow growth of the organism.

Usual laboratory biochemical methods can be used to differentiate *N. asteroides* complex, *N. otitidiscaviarum* complex, and *N. brasiliensis*; however, phenotypic testing does not identify the many species within the *N. asteroides* complex or the less common human pathogens within the genus.[4,11,40] Definitive identification requires analysis of gene sequences by molecular methods (i.e., 16s rRNA gene and multilocus sequence analysis of 5–7 housekeeping genes have been most successful) and may be necessary for some patients with serious disease.[1,2,4,41–43]

Presumptive identification of a limited number of *N. asteroides* complex isolates can be provided using an abbreviated battery of tests. For example, *N. farcinica* is resistant to ceftriaxone, grows at 45°C, and opacifies Middlebrook agar, whereas *N. cyriacigeorgica* is susceptible to ceftriaxone, imipenem, and amikacin but resistant to ampicillin and erythromycin.[1,44,45] Matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) mass spectrometry is an emerging method for the identification of species.[46] As the databases expand, full species identifications will be readily and accurately available.

Performance of bronchoalveolar lavage in pulmonary disease or biopsy of an affected tissue site may be necessary when other clinical specimens are nondiagnostic, especially in immunocompromised hosts.

Treatment

Clinical laboratory methods for the susceptibility testing of *Nocardia* spp. are standardized, with breakpoints established for interpretation.[47–48] Although initial selection of antimicrobial therapy must be empiric, primary drug resistance exists. All clinical isolates should be tested.[45,48] In a multisite reproducibility study, end-point determinations were especially difficult for ceftriaxone, imipenem, tigecycline, and sulfonamide. Specific caution for interpreting in vitro testing of *N. cyriacigeorgica* and *N. transvalensis* with ceftriaxone is warranted.[49] Laboratories with little experience should consider sending isolates to reference laboratories for testing.[3]

A retrospective study of more than 750 *Nocardia* isolates sent to the Centers for Disease Control and Prevention from 1995 to 2004 found increasing resistance over time.[50] Among the four most prevalent *Nocardia* species, TMP-SMX resistance ranged from 20% for *N. brasiliensis* to 80% for *N. farcinica*. Linezolid was the only antibiotic to which 100% of the isolates were susceptible. Resistance among all strains tested was lowest for amikacin (5%), imipenem (30%), and ceftriaxone (52%), although *N. farcinica* typically is resistant to the cephalosporins.[3,51] In vitro studies have shown that meropenem is more active than imipenem against most *Nocardia* spp. but less active against *N. farcinica* and *N. nova;* in contrast, most *Nocardia* spp. are resistant to ertapenem.[5,13,52,53]

Amoxicillin-clavulanate is active against many strains of *Nocardia,* except *N. nova, N otitidiscaviarum,* and *N. cyriacigeorgica,* which are resistant.[50–52] Moxifloxacin usually is more active than ciprofloxacin and was shown in one report to be successful in treating a *N. farcinica* brain abscess in an immunosuppressed patient.[54] Data for 1299 clinical isolates confirm the excellent activity of amikacin and linezolid, document increasing resistance to imipenem (51% resistance), and report only 2% of all strains are resistant to TMP-SMX (0.5% resistance for *N. farcinica*).[55]

A sulfonamide always has been the treatment of choice for nocardiosis when used in conjunction with appropriate surgical drainage or excision of empyema or large abscesses. Trimethoprim-sulfamethoxazole (TMP-SMX) is reportedly effective in many clinical series, supplanting sulfonamides as the treatment of choice of many experts.[56] Reports of sulfonamide resistance or lack of effectiveness in immunosuppressed patients led most clinicians to use additional agents in combination with a sulfonamide, at least initially. Nephrotoxic interaction between TMP-SMX and cyclosporine may necessitate the use of alternative agents in organ transplant recipients.[20] Thrice-weekly TMP-SMX used for prophylaxis against *Pneumocystis jirovecii* infections frequently is ineffective in preventing nocardiosis.[19,22]

Because of linezolid's excellent in vitro activity (i.e., minimal inhibitory concentration [MIC] <8 μg/mL for all strains of *Nocardia*) linezolid may be useful as initial therapy until speciation or susceptibility of the isolate is available.[57] Although linezolid is approved only for short courses and is expensive, it has been used for longer-term therapy (with caution that long-term use can have adverse effects). Although clinical improvement can occur with single-drug therapy, two or three drugs with in vitro activity (preferably a combination demonstrating synergy, such as TMP-SMX with amikacin or a carbapenem) should be used for progressive disease, especially in immunocompromised hosts.

Duration of therapy for nocardial infection depends on the site of infection and the immune status of the host. For primary cutaneous nocardiosis, a course of 6 to 12 weeks of sulfonamide therapy is appropriate, although spontaneous resolution of disease without therapy has been reported.[58,59] For patients with isolated pulmonary disease, 6 to 12 months of therapy is preferred.[60] Brain abscess or meningitis requires longer therapy, at least 12 months in most cases. A second or third drug with proven activity in vitro, such as amikacin and ceftriaxone, usually is given for the first 4 to 12 weeks of treatment or until clinical and radiographic improvement is observed.[5,13,60] Parenteral therapy should be used for the first 3 to 6 weeks, until a response to therapy has been documented and the species and its antibiotic susceptibilities have been determined; thereafter, oral therapy can be used to complete the course of treatment.

Relapses after prolonged therapy occur but are uncommon. Lifelong suppressive therapy for nocardiosis is probably prudent in patients with acquired immunodeficiency syndrome and persistent, severe $CD4^+$ T-lymphocyte depletion.[51] Delayed appearance of metastatic abscesses, even during effective therapy, often represents the evolution of a previously seeded focus. Because infection by *Nocardia* can manifest concurrently with infection due to other opportunistic pathogens in immunocompromised patients, poor response to therapy or the development of new lesions should raise the possibility of a concomitant pathogen, such as *Mycobacterium tuberculosis, P. jirovecii,* or *Aspergillus.*

Although older series report mortality rates of 44% to 85%, later published mortality rates range from 15% to 26%.[5,12,20,61–63] Mortality rates for patients with cancer may be as high as 60%. Factors that increase mortality rates include concurrent corticosteroid or antineoplastic therapy and coinfection with cytomegalovirus.[19] Consideration of nocardial infection in the differential diagnosis of immunocompromised or debilitated patients and aggressive diagnostic pursuit can lead to an earlier diagnosis and improved outcome.

Key Points

Epidemiology, Clinical Syndromes, Diagnosis and Treatment of *Nocardia* Infections

Epidemiology

- Ubiquitous soil organisms
- Lung is the primary portal of entry into the body.
- Most infections occur in children with immunodeficiency (e.g., chronic granulomatous disease, HIV infection, chronic high-dose corticosteroid therapy, lymphoreticular malignancies, bone marrow and solid-organ transplantation, and dysgammaglobulinemia).

Clinical Syndromes

- Pulmonary infiltrates or abscesses with or without pleural effusion
- Disseminated disease usually includes pulmonary and central nervous system infection, but any organ can be affected.
- Primary cutaneous or lymphocutaneous infection results from direct inoculation.

Diagnosis

- Tissue diagnosis (e.g., bronchoalveolar lavage, tissue biopsy) often is necessary.
- Branching, beaded, gram-positive filaments using standard Gram staining procedures for tissue or smears
- Modified acid-fast stain confirms identification because *Nocardia* spp. are weakly or partially acid fast, but other branching, gram-positive rods are not.
- Selective media (e.g., selective buffered charcoal-yeast extract agar) may be necessary to prevent overgrowth of more rapidly growing contaminants in specimens from skin or mucosal sites.
- Laboratory personnel should be notified to hold cultures for at least 2 weeks to allow for slow growth of *Nocardia.*
- Definitive species identification requires gene sequencing, although MALDI-TOF mass spectrometry is emerging as a rapid and accurate alternative.
- Standardized methods for in vitro antimicrobial testing are available.

Treatment

- Trimethoprim-sulfamethoxazole (TMP-SMX) has been the historical treatment of choice, but emergence of resistant strains dictates broader coverage.
- Empiric combination therapy is used for pulmonary or disseminated disease, especially in immunocompromised hosts.
  - Two or three active agents are used, including TMP-SMX, linezolid, amikacin, carbapenem, and ceftriaxone.
  - Definitive therapy is guided by in vitro susceptibility tests.

- Surgical debridement as adjunctive therapy is often required
- Duration of therapy for invasive disease is 6 to 12 months or longer.

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Enterobacteriaceae: Gram-Negative Bacilli

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Escherichia coli

Edwin J. Asturias

Escherichia coli is a genetically diverse species comprising nonpathogenic gut commensals and strains responsible for intestinal and extraintestinal infections in humans.[1] Commensal *E. coli* is the predominant facultative anaerobe of the human gut microbiota, and it colonizes the gastrointestinal tract within hours after birth. *E. coli* is a gram-negative bacillus and oxidase-negative organism of the family Enterobacteriaceae. It grows well aerobically and anaerobically, preferably at 37°C. Approximately 90% of strains ferment lactose and produce indole and cadaverine by means of lysine decarboxylase.

Classic and molecular serotyping is based on the Kauffman classification scheme using the O (somatic) polysaccharides and H (flagellar) surface antigens. Currently, 174 *E. coli* somatic and 53 flagellar antigens are recognized, but only a small subgroup produce disease in humans.[2,3] Pathogenic *E. coli* have evolved various pathotypes (i.e., group of strains of the same species causing a common disease), and multilocus sequence typing (MLST) is a common method for strain typing and establishing relatedness. Before 2011, only few reports of Shiga toxin–producing enteroaggregative *E. coli* (EAEC) causing bloody diarrhea and hemolytic uremic syndrome (HUS) existed, but the outbreak of *E. coli* O104:H4 in Germany proved the plasticity of EAEC and enterohemorrhagic *E. coli* (EHEC) to form a hybrid (EAHEC). Pathogenic *E. coli* virulence factors usually are encoded by large plasmids or chromosomal pathogenicity islands. *E. coli* lacking specific virulence factors also can be opportunistic pathogens of compromised hosts.

Pathogenesis

Enteric Infections

Based on the types of virulence factors and host clinical symptoms, *E. coli* strains are classified as seven major pathotypes for enteric infections: enterotoxigenic *E. coli* (ETEC), enteropathogenic *E. coli* (EPEC), enterohemorrhagic *E. coli* (EHEC), enteroinvasive *E. coli* (EIEC, including *Shigella* sp), enteroaggregative *E. coli* (EAEC), and diffusely adherent *E. coli* (DAEC).

ETEC adheres to the small bowel mucosa using one of the fimbrial colonization factor antigens (CFAs), of which more than 25 have been identified, but seven (i.e., CFA/I and CS1–CS6) are considered important. After colonization, ETEC produces one or both of two enterotoxins: heat-labile enterotoxin (LT) and heat-stable enterotoxin (ST).[4–6] Most ETEC express LT alone (27%) or in combination with ST (33%), with variations across regions and populations. LT, a strong immunogen in humans, possesses one A subunit and five identical B subunits. It belongs to the family of AB5 enterotoxins, and they act as adenylate cyclase inducers.

ST shares structural similarity with heat-stable toxins from *V. cholerae* O1/non-O1 and *Yersinia enterocolitica*, and it acts by binding the age-dependent surface membrane receptor guanylyl cyclase type C (GC-C). GC-C stimulation is followed by an increase in intracellular cGMP concentrations, activation of protein kinase A (PKA) or cGMP-dependent protein kinase type II (cGKII) and increased chloride secretion through apical cystic fibrosis transmembrane conductance regulator (CFTR) channels, leading to diarrhea. ST also can induce bicarbonate secretion in a non–cGMP-, non–GC-C-, and non–CFTR-dependent manner.

The phenotypic hallmark of EPEC is its ability to produce attaching and effacing (AE) lesions (Fig. 137.1).[7–9] AE lesions are characterized by actin remodeling of the host cell cytoskeleton and development of a bundle-forming pilus, allowing EPEC to inject intimin (i.e., virulence factor) into the cytosol of enterocytes, causing extensive effacement of the microvilli. Like EPEC, EHEC also adheres to luminal enterocytes and produces AE lesions.[10,11]

EHEC contains a pathogenicity island called the locus of enterocyte effacement (LEE), which is crucial for development of AE lesions. After colonic colonization, EHEC releases one or more toxins related to the Shiga toxin of *Shigella dysenteriae* (i.e., Shiga-like toxin [Stx]) that are cytotoxic to vascular endothelium.

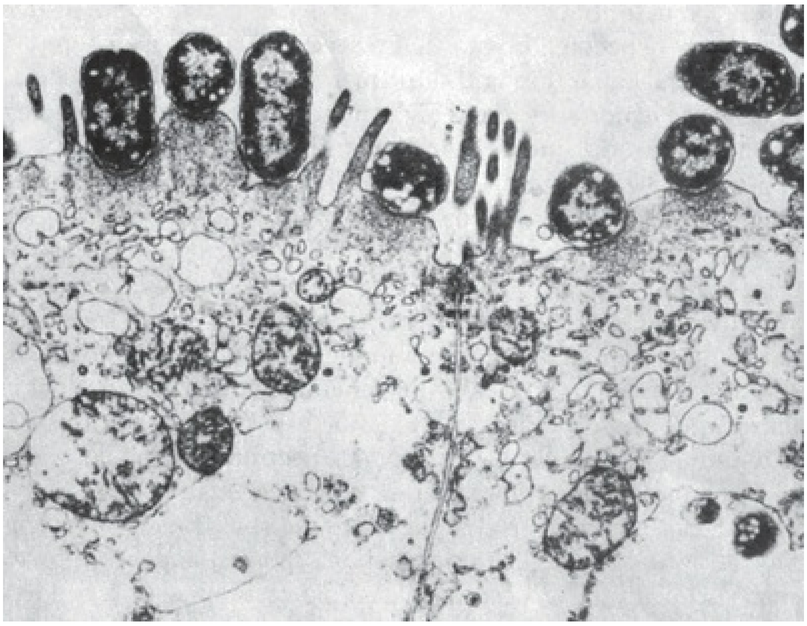

FIGURE 137.1 Electron photomicrograph of the attaching and effacing lesion induced in the gnotobiotic piglet ileum after oral administration of a human enteropathogenic *E. coli* (EPEC) strain. Bacteria are seen intimately attached to the epithelial cells, which respond by forming cup-like pedestals composed of cytoskeletal protein. An identical lesion can be induced by human EHEC strains. (From Baldini MM, Kaper JB, Levine MM, et al. Plasmid-mediated adhesion in enteropathogenic *Escherichia coli*. J Pediatr Gastroenterol Nutr 1983;2:543.)

Similar to EHEC, EIEC can invade colonic enterocytes and spread laterally through the mucosa and lamina propria. EIEC produces secretogenic enterotoxins responsible for the watery diarrhea manifested in most cases. EAEC adheres tenaciously to the intestinal mucosa in a characteristic biofilm. Adherence is mediated by fimbrial organelles called aggregative adherence fimbriae (AAFs). After colonization is achieved, EAEC secretes a series of cytotoxic, secretogenic, and proinflammatory proteins.[12]

Extraintestinal and Disseminated Infections

Extraintestinal infections are primarily urinary tract infections (UTIs) caused by uropathogenic *E. coli* (UPEC) and sepsis or meningitis caused by neonatal meningitis *E. coli* (NMEC).

Uropathogenic *E. coli*

Colonization and adherence are key preceding events in UTI pathogenesis.[13] A typical UTI begins with periurethral contamination by intestinal *E. coli*, followed by urethral colonization and migration to the bladder, which requires appendages such as flagella and pili. UPEC survives by invading the bladder epithelium, producing toxins and proteases to release nutrients from the host cells, and synthesizing siderophores to obtain iron. UPEC binds to uroplakins, the major protein that forms a crystalline array of umbrella cell apical plasma membranes, which protects the bladder. Expressed at the surface of uroepithelial cells, $\alpha_3\beta_1$ integrins also can serve as receptors for UPEC. *E. coli* can then ascend to the kidneys, attaching by adhesins or pili to colonize the renal epithelium and produce tissue-damaging toxins.

The pathogenesis of renal damage by *E. coli* is not fully understood, but direct cellular damage by UPEC hemolysin or direct invasion may be important. By crossing the tubular epithelial barrier, UPEC can access the bloodstream, resulting in bacteremia. UPEC also can form intracellular biofilms called pods, which may promote persistence and relative antibiotic resistance.

Neonatal Meningitis *E. coli*

A distinct extraintestinal pathotype known as NMEC has the ability to survive in blood and invade the meninges of infants.[14] Typical NMEC strains carry the K1 capsular polysaccharide and *sitA* genes with at least two of three other genes: *vat*, *neuC,* and *iucC*. NMEC strains that carry more virulence genes are more invasive to cerebral microvascular endothelial cells. NMEC strains also have a greater ability to produce biofilms.

Epidemiology

Children are especially susceptible to intestinal infection due to *E. coli*. ETEC causes an estimated 280 million cases of diarrhea each year in children younger than 5 years of age and approximately 380,000 deaths mainly due to dehydration. ETEC infection also accounts for 50% to 60% of traveler's diarrhea cases or approximately 60 million cases per year.[15]

For many years, EPEC was considered only second to rotavirus as the most common cause of diarrhea in hospitalized children and responsible for 8% to 10% of outpatient cases of acute gastroenteritis, with important regional and temporal variations. The recent demonstration that EPEC can colonize children asymptomatically, especially those who are breastfeeding, suggests that EPEC requires the interplay of multiple factors to cause diarrhea.

Shiga toxin–producing *E. coli* (STEC) is a foodborne zoonotic agent associated with outbreaks worldwide since it was first identified in 1982. STEC causes hemorrhagic colitis through ingestion of contaminated food or water, including contaminated ground beef, steak, salami, dairy products (e.g., raw milk, cheese, butter, cookie dough), and vegetables (e.g., spinach, lettuce, sprouts). A low infectious dose (i.e., 50–100 colony-forming units) is sufficient to cause disease in humans.

The incidence of STEC infections in the United States in 2012 reported by the Foodborne Diseases Active Surveillance Network (FoodNet) was 0.92 cases per 100,000 people for O157:H7 and 1.43 cases per 100,000 people for non-O157 STEC. In 2013, 87 cases of postdiarrheal HUS were reported among children younger than 18 years of age (0.79 cases/100,000), with half occurring in children younger than 5 years of age (1.55 cases/100,000). The incidence of STEC in other high-income countries varies from 0.4 cases per 100,000 people in Australia to 5.33 cases per 100,000 people in Ireland. Much higher incidences are reported in other middle- and low-income countries such as Argentina and India.

Each year, UTIs affect 150 million people worldwide. In the United States, the cumulative incidence data for UTIs indicate that 3% to 7% of girls and 1% to 2% of boys are diagnosed with a UTI by 6 years of age. UPEC is the most common causative agent for uncomplicated (75%) and complicated (65%) UTIs.[16,17]

NMEC is the main cause of bacterial meningitis in preterm infants and is second to group B streptococci in term neonates. NMEC is sevenfold more frequent among preterm than term infants. Two peaks of infection are recognized: 0 to 3 days, mostly in preterm neonates, and 11 to 15 days in term neonates. Infection rates increase with decreasing birth weight. Most infants with NMEC infections are preterm, and the mortality rate is as high as 33%. A significant increase in multidrug-resistant NMEC strains has been observed recently.[18]

Clinical Manifestations

E. coli remains one of the most common bacterial infections in children. It can manifest as acute gastroenteritis, UTI, bloodstream infection (BSI), and meningitis.

Acute Gastroenteritis

Clinical manifestations of acute gastroenteritis depend on the *E. coli* pathotype. ETEC causes profuse, watery diarrhea and abdominal cramping. Fever, nausea with or without vomiting, chills, loss of appetite, headache, and muscle aches also can occur. The incubation period is 1 to 3 days after exposure and lasts for 3 or 4 days up to 1 week. The severity of ETEC infection usually is less than that of cholera. ETEC is the most common cause of travelers' diarrhea in people of all ages, with onset occurring an average of 7 to 9 days after the start of travel.

EPEC and EAEC usually cause a self-limited, watery diarrhea with a short incubation period of 6 to 48 hours. Nausea, abdominal cramps, and mild fever also can occur. EPEC strains cause diarrhea primarily in nonbreastfeeding children. Persistent diarrhea (>14 days) has been reported with EPEC and especially with EAEC. EAEC is the second leading cause of travelers' diarrhea worldwide. EIEC causes diarrhea that usually is watery, but dysentery develops in a few cases.

EHEC infection characteristically causes hemorrhagic colitis without fever, and it often can be confused with intussusception, inflammatory bowel disease, or ischemic colitis. EHEC infections can evolve to HUS. DAEC causes diarrhea particularly in children. AIEC is the most recently recognized diarrheal pathotype that later was associated with Crohn disease.

Urinary Tract Infection

UPEC is the most common cause of UTIs in children, and risk factors include very young age, no circumcision, constipation, urinary tract anomalies, spinal disorders, and immunodeficiency. In young children, UTI can manifest as fever alone, accompanied by irritability, poor feeding, vomiting, failure to thrive, or jaundice. A UTI should be considered in any infant or child younger than 24 months of age with fever without an apparent source of infection. In older children and adolescents, cystitis typically manifests with dysuria, urgency, and frequency or sometimes with enuresis.

Pyelonephritis often is associated with more severe or systemic symptoms, including fever, back and flank pain, nausea, and vomiting. Ascending infection can result in BSI and systemic inflammatory response syndrome or septic shock (i.e., urosepsis).

Other Extraintestinal Manifestations

Extraintestinal *E. coli* infections can be community-acquired or healthcare-associated infections. NMEC is a major cause of gram-negative neonatal bacterial meningitis in high- and low-income countries. Many of the survivors have neurologic sequelae.

Postdiarrheal Manifestations

Hemolytic Uremic Syndrome

After the characteristic self-limited hemorrhagic colitis, 5% to 7% of EHEC cases develop HUS, which is characterized by the triad of hemolytic anemia, thrombocytopenia, and acute renal failure. HUS is the direct result of the release of Stx, a potent toxin that can enter the systemic circulation through absorption across the epithelium.

Shiga toxin 1 (Stx1) and Shiga toxin 2 (Stx2) are structurally and enzymatically similar but distinct immunologically. Stx1 mimics Stx from *Shigella*, whereas Stx2 shares only 55% of the amino acid sequence, is more potent than Stx1 in humans, and is more commonly associated with hemorrhagic colitis and HUS. Stx binds to the globotriaosylceramide (Gb3) receptor in endothelial cells of the microvasculature of the intestine, kidney, and brain. Formation of a biofilm by some STEC strains (e.g., highly virulent EAEC serotype O104:H4) caused 34 deaths and 908 HUS cases in Germany in 2011.[19]

HUS most commonly occurs in children between 1 and 5 years of age. Oliguria and hypertension are the most common signs of renal injury; seizures, coma, and hemiparesis signal neurologic complications that occur in up to one third of cases.[20] HUS is a nonconsumptive coagulopathy with thrombocytopenia but minimal decrease of clotting factors. Other complications include transient hepatocellular injury in 40% and pancreatitis leading to diabetes mellitus.

Management of HUS requires careful fluid and electrolyte balance and prompt recognition of acute renal failure to prevent fluid overload and lessen hypertension. Antimotility agents should not be administered to anyone with inflammatory or bloody stools or to any child with diarrhea exposed to a person with HUS or hemorrhagic colitis because these drugs are a risk factor for progression of STEC diarrhea. Antibiotics for the treatment of STEC infection are controversial due to induction of the phage lytic cycle and the potential for increased production of Stx. Although some studies have identified an increased risk of HUS with use of trimethoprim-sulfamethoxazole or β-lactam antibiotics, a meta-analysis of all available studies did not reveal a consistent association of antibiotic administration with HUS risk.[21–23]

HUS is a life-threatening disease with a 5% mortality rate. Among survivors, 5% to 10% develop end-stage renal disease or permanent neurologic damage. The duration of *E. coli* O157:H7 shedding seems to be age dependent, with children younger than 5 years carrying the organism for longer periods after the resolution of symptoms.[24] A nondiarrheal form of HUS not associated with Stx of EHEC or *Shigella dysenteriae* type 1 has is caused by the neuraminidase produced by *Streptococcus pneumoniae* infections, which also causes complicated pneumonia.

Inflammatory Bowel Disease

Inflammatory bowel diseases, primarily Crohn disease and ulcerative colitis, are chronic inflammatory disorders of the gastrointestinal tract due to dysfunction of the epithelial barrier with deregulation of the mucosal immune system and the gut microbiota. Some studies postulate a role for AIEC and intestinal dysbiosis in inflammatory bowel disease.[25]

E. coli has been recovered from 65% of chronic lesions in resected ileums of patients with Crohn disease, with strains capable of adherence to buccal cells in vitro. High *E. coli* antigen and antibody concentrations are found in the blood and resected intestinal specimens of Crohn disease patients. The AIEC genome, similar to that of UPEC, encodes type 1 pili. AIEC binding depends on expression of pili on the bacterial surface and on expression of carcinoembryonic antigen–related cell adhesion molecule 6 (CEACAM6) receptors on the apical surface of ileal epithelial cells. CEACAM6 receptors are increased in the ileal mucosa of Crohn disease patients.

AIEC infection also induces the release of tumor necrosis factor-α by macrophages, a key cytokine in bowel inflammation and granuloma formation.[26] In a genetically susceptible host, AIEC may result in permanent changes in the microbiota that can lead to chronic inflammation and inflammatory bowel disease.[27]

Laboratory Findings and Diagnosis

Although the diagnosis of *E. coli* gastroenteritis begins with a routine stool culture, identification of strains belonging to different pathotypes requires proof of expression of one or more group-specific virulence factors. One exception is EHEC O157:H7, which can be distinguished by its inability to ferment sorbitol, yielding colorless colonies on MacConkey agar with added sorbitol. The yield of O157:H7 is substantially higher when stool culture is performed within the first 6 days of diarrheal illness. EHEC (STEC) is now routinely identified by most clinical and public health laboratories by a *stx1* or *stx2* gene using antigen or nucleic acid amplification.

MALDI-TOF mass spectrometry can detect extracted proteins from bacterial cells from growth on primary stool culture and identify all *E. coli* pathotypes to the species level. The FilmArray gastrointestinal panel can simultaneously detect 22 enteric pathogens directly from stool specimens, such as EAEC, EPEC, ETEC, EIEC, and EHEC (i.e., Stx1 and Stx2), including O157:H7 strains. Although more sensitive (95% to 100%), the FilmArray panel has a specificity between 35% and 80% because many *E. coli* detected are associated with copathogens.

UTI diagnosis requires a urinalysis demonstrating evidence of pyuria and a urine culture growing more than 50,000 colony-forming units/mL of *E. coli*.[28,29] Transurethral bladder catheterization or a suprapubic aspirate are the preferred urine collection methods for children. Midstream clean voiding can be used in older children and adolescents.

Treatment

Most *E. coli* diarrheal infections are self-limited and may not require antibiotic therapy. Support of fluid and electrolyte status is the therapeutic priority. If indicated, oral trimethoprim-sulfamethoxazole, azithromycin, or cefixime for 5 days is considered adequate therapy for ETEC, EIEC, EAEC, and EPEC infections.[30–32] Fluoroquinolones are preferable in adolescents and adults. Antimicrobial therapy for ETEC disease is limited by frequent resistance to commonly used antibiotics. Multidrug-resistant *E. coli* strains, a consequence of widespread use of antibiotics in animal and food products, result primarily from β-lactamase production (3% to 36%) and have complicated the therapy of these infections. Extended-spectrum β-lactamases are reported in 15% of cases, and strains can also exhibit chromosomal or plasmid-encoded fluoroquinolone resistance (8% to 40%).

Treatment of UTI should be initiated only when the diagnosis is confirmed. For the febrile young child, empiric therapy may be indicated before urine culture results are final. The goals of treatment of acute UTI are to eliminate the acute infection, to prevent complications, and to reduce the likelihood of renal damage. Oral antibiotic therapy is effective in most children with UTIs. A narrow-spectrum cephalosporin, amoxicillin–clavulanic acid, or trimethoprim-sulfamethoxazole is an appropriate choice, depending on local resistance patterns.

Nitrofurantoin, which is excreted in the urine but has a low therapeutic concentration in the bloodstream, should not be used to treat febrile infants with UTI because it may be insufficient to treat pyelonephritis or urosepsis. Data on short 1- to 3-day courses for febrile UTIs show inferiority to courses of 7 to 14 days; the minimal duration of therapy therefore should be 7 days. UTIs can lead to renal scarring and kidney failure. Since 2011, the American Academy of Pediatrics guidelines for management of a first UTI in children between 2 and 24 months of age recommend performance of a voiding cystourethrogram (VCUG) only for patients with an abnormal renal or bladder ultrasound result.[28,29]

Definitive therapy for septicemia or meningitis due to *E. coli* should be based on in vitro susceptibility tests and the use of bactericidal agents with penetration into the central nervous system. Repeat lumbar puncture is recommended to document eradication of the infecting pathogen. Duration of therapy is based on response and usually is 10 to 14 days for neonates with uncomplicated septicemia and a minimum of 21 days (and at least 14 days after sterilization of cerebrospinal fluid) for meningitis.

Special Considerations

E. coli is on the Centers for Disease Control and Prevention (CDC) list of biologic agents potentially threatening to public health and safety. The *E. coli* O157:H7 strain is recognized as a category B agent because of its food safety hazard and ease of production.

Prevention

Strategies for the prevention and control of the spread of *E. coli* include access to safe water, handwashing and hygiene, decreasing the risk of food contamination, sanitation measures, public education, and vaccination. Exclusive breastfeeding exerts a protective effect against acute gastroenteritis in the first 4 to 6 months of life. Travelers should consume only cooked food and boiled or bottled beverages when visiting developing areas. Prevention of EPEC and EIEC in indigenous populations is best accomplished by improvements in sanitation, food storage, and personal hygiene.

Prevention of EHEC infection has centered on protection of the food supply, especially beef products. Animal carriage of STEC can be diminished by vaccination and improved farm practices. All commercially prepared hamburgers are required to reach an internal temperature of 68°C (155°F), which kills *E. coli*. Hamburgers should be cooked until no pink remains and until juices are clear. Treatment of STEC with antibiotics or toxin-binding agents does not prevent HUS.

Vaccination may be an important primary prevention strategy for humans against the most harmful strains, such as ETEC, UPEC, and NMEC. Despite being a global priority, no effective vaccine is available for the prevention of these infections.[33,34] A patch LT antigen vaccine tested in adult travelers did not fully protect them against ETEC diarrhea in Mexico and Guatemala due to a mismatch in prevalent strains.[35] A vaccine intended to target 80% of ETEC strains globally would require seven or eight colonization factors (i.e., CFA/I, CS1–3, CS4–6, and CS21), assuming the use of an LT toxin component, and it must ensure high levels of mucosal and systemic protection. Vaccines against the K1 capsule on the surface of UPEC and NMEC have not been protective, and the capsular antigen match to host sialic acid has raised concerns about autoimmune reactions similar to previous meningococcal B vaccine candidates.

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Klebsiella and *Raoultella* Species

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Microbiology and Epidemiology

The genus *Klebsiella*, family Enterobacteriaceae, contains at least five *Klebsiella* species and three *Raoultella* species: *K. pneumoniae*, *K. oxytoca*, *K. granulomatis*, *K. variicola*, *K. singaporensis*, *R. terrigena*, *R. ornithinolytica*, and *R. planticola*.[1–6] The two most important human pathogens in terms of frequency and disease severity are *K. pneumoniae* and *K. oxytoca*. *K. pneumoniae* is divided further into subspecies *pneumoniae*, *ozaenae*, and *rhinoscleromatis*. The latter two *K. pneumoniae* subspecies are associated with chronic respiratory tract infections with unusual clinical presentations: ozena, a chronic atrophic rhinitis, and rhinoscleroma, a chronic granulomatous infection of the nose, respectively. These diseases occur most frequently in the tropics.

Subspecies may be difficult to separate from each other and from biochemically inactive strains of *K. pneumoniae* subsp. *pneumoniae*. *K. granulomatis*, formerly known as *Calymmatobacterium granulomatis*, is the agent of granuloma inguinale or donovanosis, a sexually transmitted ulcerative disease of skin and subcutaneous tissues of the genital region (see Chapter 139).

Most *Klebsiella* and *Raoultella* spp. are ubiquitous in nature. They are found in environmental sources such as surface and drinking waters, soil, vegetation, sewage, and industrial waste, and they are associated with mucosal surfaces and diseases of humans, other mammals, birds, and reptiles.[5,7] *K. variicola* is a recently described species that has been isolated from plants and human sources, including the bloodstream. *K. ozanae, K. rhinoscleromatis,* and *K. granulomatis* have been recovered only from human clinical specimens. *Raoultella* spp. are isolated infrequently from human sources. *R. ornithinolytica* and *R. planticola* produce histidine decarboxylase and have been implicated in causing scombroid fish poisoning.[8]

Members of the genera *Klebsiella* and *Raoultella* have properties similar to other Enterobacteriaceae with some distinctive features (see Key Points). Only *R. ornithinolytica* produces ornithine decarboxylase. *Klebsiella* spp. typically use citrate as a sole carbon source, often produce urease, and are positive on the Voges-Proskauer test.[1–6] They are hydrogen sulfide and indole negative, except for *K. oxytoca,* which is indole positive.

K. pneumoniae subsp. *pneumoniae* and *K. oxytoca* usually grow as large, mucoid, lactose-fermenting colonies on MacConkey agar. Commercial and conventional biochemical identification systems can differentiate these two species; the lack of indole production by *K. pneumoniae* is the main identifying feature.

K. pneumoniae is difficult to differentiate from *R. planticola* and *R. terrigena* using basic biochemical tests and commercial identification systems. Studies conducted in Europe have suggested that a significant percentage of organisms identified as *Klebsiella* spp. may be *R. planticola,* but similar studies conducted in the United States suggest that recovery of *R. planticola* is rare.[9,10] Prevalence of these organisms in human disease may vary by geographic location.

Matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) mass spectrometry has been used for identification of bacterial isolates, has demonstrated overall good performance in the identification of gram-negative bacilli,[11] and can correctly identify and differentiate *Klebsiella* from *Raoultella* spp. Early reports revealed some misidentifications, but supplementation of databases should improve performance.[12,13]

The role of specific virulence factors in the pathogenesis of infection due to *Klebsiella* spp. is unclear, and the importance of different factors may vary by site of infection. Identified virulence factors include cell surface adhesins that may mediate attachment to mucosal surfaces, cell surface capsular polysaccharides and lipopolysaccharide that may inhibit phagocytosis and serum bactericidal activity, and other factors such as siderophores (i.e., iron-chelating compounds), cytotoxins, enterotoxins, and hemolysins.[4,5] Strains of *K. pneumoniae* and *K. oxytoca* that produce enterotoxins and cytotoxins have biologic effects in various animal models of gastrointestinal pathology. Overgrowth of these organisms in the gut of patients receiving antibiotics may lead to gastrointestinal syndromes, including antibiotic-associated colitis.[14]

K. pneumoniae subsp. *pneumoniae* and *K. oxytoca* may be carried in the nasopharynx (1%–6%) and in the intestinal tract (5%–40%) of the general population.[4] Carriage in hospitalized patients and healthcare personnel can be dramatically higher, particularly in the respiratory tract. Airway colonization with *Klebsiella* spp. and other gram-negative bacilli in the mechanically ventilated neonate is a moderate risk factor for bloodstream infections (BSIs) and is associated with severe bronchopulmonary dysplasia.[15]

Clinical Manifestations

Klebsiella spp. are important opportunistic pathogens of children that cause a wide variety of infections, including healthcare- and community-associated BSIs; infections of the central nervous system (CNS), respiratory tract, urinary tract, musculoskeletal system, and peritoneal cavity; and deep abscesses and postsurgical, trauma, and burn wound infections. Approximately 75% of BSIs are healthcare associated.[16–24] Outbreaks in neonatal units are a major concern.[25] Neonatal infections include BSI, meningitis, brain abscess, conjunctivitis, hepatic abscess, endocarditis, pneumonia, necrotizing fasciitis, arthritis, osteomyelitis, urinary tract infection (UTI), and necrotizing enterocolitis (NEC).[26–32] The clinical manifestations of infection are no different from those of other gram-negative bacilli. Although *Escherichia coli* is the most frequent cause of UTI, *Klebsiella* and *Proteus* spp. are also common Enterobacteriaceae organisms associated with UTI.[33]

Gram-negative organisms account for more than 50% of BSIs in children. During a 6-year prospective study of gram-negative BSIs in a pediatric tertiary care medical center in Israel, *K. pneumoniae* was the most commonly identified pathogen, comprising 26% (109 of 419) of isolates.[19] In a review of 57 cases of pediatric BSI caused by *K. pneumoniae*, 67% were younger than 12 months of age, and most had at least one underlying condition, including gastrointestinal tract abnormality in 56%, central venous catheter in 35%, neutropenia in 25%, and urinary tract abnormality in 16%.[34]

The Surveillance and Control of Pathogens of Epidemiologic Importance project based at Virginia Commonwealth University in Richmond has provided important data for identifying the predominant pathogens responsible for healthcare-associated BSIs in children.[35] Although gram-positive organisms, especially coagulase-negative *Staphylococcus* spp., accounted for more than 50% of isolates, *Candida* spp. accounted for 9.3%, and *Klebsiella* spp., *Enterobacter* spp., and *Escherichia coli* accounted for 5.8%, 5%, and 5% of isolates, respectively.

Other conditions associated with *Klebsiella* spp. BSI in childhood include prematurity, prior antibiotic exposure, preceding rotavirus gastroenteritis, Kasai procedure for biliary atresia, malignancy, postoperative status, burns, multiple trauma, acquired immunodeficiency syndrome, granulocyte disorders, homozygous sickle cell disease, solid-organ transplantation, the postoperative period after splenectomy, systemic lupus erythematosus, and interleukin-12 receptor β1 chain deficiency.[19,35–41] Contaminated intravenous solutions also have been identified as a source of *Klebsiella* spp. BSI.[42]

The overall mortality rate for *Klebsiella* spp. BSI is approximately 11%, with a mortality rate of 14.5% for healthcare-associated BSI.[19,35] An increased mortality rate is significantly associated with acute leukemia, neutropenia, healthcare-associated infections (HAIs), and previous corticosteroid therapy.

Cytotoxin-producing strains of *K. oxytoca* have been implicated in antibiotic-associated hemorrhagic colitis.[14,43,44] The clinical manifestations of abdominal pain and bloody diarrhea usually are preceded by antibiotic treatment with a β-lactam agent. Colitis usually is segmental and located predominantly in the right colon. Cessation of the offending antimicrobial agent and supportive care typically result in clinical resolution. Enterotoxigenic and enteroaggregative strains of *K. pneumoniae* also have been implicated as causes of childhood gastroenteritis.[45]

Raoultella spp. have been reported inconsistently as colonizing bacteria of the gastrointestinal tract of hospitalized neonates and as agents of BSI and adult pneumonia.[46,47] *R. planticola* has been isolated from adult urine; wounds, including an intra-abdominal abscess associated with pancreatitis; and contaminated infant formulas.[48–50] *R. ornithinolytica* has been recovered from the blood of a neonate with visceral heterotaxy, functional asplenia, and complex congenital heart disease who had NEC; from one adult with a giant renal cyst; and from another with an enteric fever–like syndrome.[51–53]

R. ornithinolytica and *R. planticola* appear to cause scombroid (histamine) fish poisoning.[8] This condition follows ingestion of improperly stored (>20°C) scombroid fish (e.g., tuna, mahi-mahi, bonito, mackerel, sardine) and results from the breakdown of high concentrations of histidine into histamine by the action of bacterial histidine decarboxylase.[51,53] The incubation period can be 1 minute to 3 hours. Clinical manifestations can include marked skin flushing (especially of the face, upper trunk, and arms), headache, dizziness, abdominal cramps, vomiting, diarrhea, burning of the mouth, urticaria, generalized pruritus, and (rarely) hypotension and bronchospasm.

Therapy

K. pneumoniae and *K oxytoca* frequently are susceptible to the aminoglycosides, carbapenems, third- and fourth-generation cephalosporins, extended-spectrum penicillin/β-lactamase inhibitor combinations, trimethoprim-sulfamethoxazole, and fluoroquinolones; *K. pneumoniae* commonly is susceptible to cefazolin.[54] Both organisms are routinely resistant to ampicillin due to plasmid-mediated β-lactamases such as TEM-1, TEM-2, and SHV-1.[33]

HAIs due to extended-spectrum β-lactamase (ESBL)–producing isolates of *K. pneumoniae* and *K. oxytoca* have emerged.[22,34,35,55–57] The ESBLs are a group of diverse enzymes derived primarily from genes coding for TEM- or SHV-type enzymes by single or multiple amino acid substitutions near the active site of the enzyme.[4,58,59] ESBLs can hydrolyze third-, fourth-, and fifth-generation cephalosporins and monobactams, rendering organisms harboring the enzymes clinically resistant to these agents. However, in vitro

ESBL activity against different β-lactam agents varies, and resistance is not always detected.

β-Lactamase inhibitor combination antibiotics (e.g., piperacillin-tazobactam) can retain some activity in vitro due to inhibition of ESBL by the β-lactamase inhibitor, but reduced susceptibility is typical. Cefepime, a fourth-generation cephalosporin, and piperacillin-tazobactam demonstrate an inoculum effect in vitro, with diminished susceptibility as the inoculum increase from 10^5 to 10^7 organisms. Susceptibility to the cephamycins (i.e., cefoxitin and cefotetan) and carbapenems is maintained.

Genes coding for ESBLs usually are located on transferable plasmids that also can harbor resistance determinants to other antimicrobial agents, including the fluoroquinolones and aminoglycosides.[58,59] In 1998, the incidence of ESBL-producing isolates of *K. pneumoniae* in the United States was about 5% in the National Nosocomial Infection Study system.[4] In another US surveillance network study conducted from 1996 to 2000, the ESBL rates for *K. pneumoniae* and *K. oxytoca* rose from 7% to 9% and 3% to 6%, respectively.[60] Fortunately, ESBL prevalence among organisms isolated from children is considerably lower. The SENTRY Antimicrobial Surveillance Program reported that 1.9% of *E. coli* and 1.1% to 3.2% of *Klebsiella* spp. produced ESBLs.[61] Although TEM-type ESBLs have been prevalent in the United States, CTX-M-type ESBLs have emerged as the predominant ESBL type in many regions of the world and are common in the United States.[62,63] These enzymes preferentially hydrolyze cefotaxime over ceftazidime.

The incidence of ESBLs in *Klebsiella* spp. in the United States varies by institution, mainly because of the isolation of ESBL-positive *K. pneumoniae* in intensive care units and in immunocompromised hosts in tertiary care institutions.[33,55–57] Among 296 pediatric BSI isolates of *E. coli* and *Klebsiella* spp. from hospitalized US children in 1999 to 2003, 35 (12%) produced ESBLs: 17 *K. pneumoniae,* 10 *K. oxytoca,* and 8 *E. coli* isolates. ESBL-producing *Klebsiella* spp. represented 18% of all BSI isolates of *Klebsiella* spp.[64] In this population, risk factors for BSI due to these ESBL-producing organisms were exposure to third-generation cephalosporins in the 30 days before infection, female sex, infection with a *Klebsiella* sp., and corticosteroid use in the 2 weeks before infection. Children with BSI due to these organisms tended to have higher mortality rates and longer lengths of hospitalization compared with children with non–ESBL-producing isolates.

Bacterial strains producing ESBLs may be underdetected because they usually do not demonstrate overt resistance to the third- and fourth-generation cephalosporins and monobactams by standard in vitro laboratory test methods. Detection can be optimized by using screening and confirmatory tests recommended by the Clinical Laboratory and Standards Institute (CLSI).[65] CLSI also established lower breakpoints for the cephalosporins (rather than phenotypic screening among the Enterobacteriaceae) as the primary method for detecting and reporting possible ESBL-producing organisms.[65] For several antibiotics (e.g., cefotaxime, ceftriaxone, ceftazidime, cefepime, aztreonam), the revised or lower minimal inhibitory concentrations (MICs) and larger disk diffusion breakpoints required to categorize an isolate as susceptible allow reporting of susceptibility test results for these agents, obviating the need for screening and confirmatory tests for ESBLs. An additional advantage of the revised breakpoint approach is that it is applicable for detection of ESBLs in all Enterobacteriaceae organisms compared with the traditional screening and confirmation test approach, which is applicable only to *Klebsiella* spp., *E. coli*, and *Proteus mirabilis*.

One of the difficulties in adopting the newer approach is that US Food and Drug Administration (FDA)–cleared commercial antimicrobial test systems currently use the traditional breakpoints. Laboratories desiring to adopt the newer breakpoints must verify the newer breakpoints and devise approaches to reinterpret MIC results from the test systems before reporting. Some commercial systems do not have adequate low-end antimicrobial concentrations to allow interpretation with the revised lower-susceptibility breakpoints. Whatever system is used, it is imperative that laboratories communicate clearly and that physicians interpret susceptibility test results as reported.

In vitro screening tests are no longer recommended for routine use by CLSI, but they may be appropriate for epidemiologic purposes.[65] The phenotypic testing is designed to detect possible ESBL-producing strains of *K. pneumoniae, K. oxytoca, E. coli,* and *P. mirabilis* based on an elevated MIC or a reduced zone of inhibition by disk diffusion testing to select cephalosporins while still falling within traditional interpretative categories of susceptibility. Multiple antimicrobial agents are used in screening tests because in vitro activities of ESBL enzymes vary among β-lactam agents. Failure to identify these strains may lead to a report of false susceptibility to third- and fourth-generation cephalosporins, selection of inappropriate therapy, and treatment failure.

If a screening test suggests the presence of an ESBL, confirmation depends on demonstrating that the activity of one or more antimicrobial agents (commonly ceftazidime and cefotaxime) is enhanced by the addition of clavulanic acid. At least an eightfold decrease in the MIC or a minimum of a 5-mm increase in the zone diameter of inhibition by disk diffusion confirms the presence of an ESBL. If confirmed, the isolate is reported as resistant to all penicillin, cephalosporin, and monobactam agents, with a comment that the organism has been confirmed to produce an ESBL. Although the fourth-generation cephalosporins have greater in vitro activity against these isolates, their clinical efficacy is unclear, and the compounds also should be reported as having resistant organisms.[54–56,58,59] Although the CLSI recommendation is to report the activity of extended-spectrum penicillin/β-lactamase inhibitor combination agents, some consider the use of these agents in treatment of ESBL-positive organisms as ill advised. Until these controversies are resolved, it is prudent not to use these agents as monotherapy for serious infections due to ESBL-producing organisms.

Aminoglycosides, fluoroquinolones, cephamycins, and carbapenems usually maintain activity against ESBL-producing Enterobacteriaceae organisms.[64–68] Amikacin may be the most active aminoglycoside, with susceptibility of 89% of ESBL-producing *E. coli* and *Klebsiella* spp.[64] Fluoroquinolone resistance among *Klebsiella* spp. causing UTI ranges from 4.2% to 7.8%, with 80% of ESBL-producing *E. coli* and *Klebsiella* spp. susceptible to ciprofloxacin.[64,68] Resistance has developed after the use of cephamycins due to loss of porin channels that are responsible for cephamycin entry into the cell, and there is little clinical experience demonstrating their efficacy. The carbapenems retain full activity against ESBL-producing isolates and should be used for treatment of serious infections.[66,67]

Klebsiella spp. can harbor other plasmid-mediated β-lactamases, including AmpC β-lactamases, similar to the chromosomal enzymes commonly found in *Enterobacter* spp., inhibitor-resistant TEMs, and carbapenemases. The AmpC β-lactamases are not inhibited by clavulanic acid and other β-lactamase inhibitors, and extended-spectrum penicillin/β-lactamase inhibitor combination antibiotics and the cephamycins usually are ineffective. The fourth-generation cephalosporins and carbapenems retain activity.[4,58–61,69]

Perhaps most alarming is the emergence among Enterobacteriaceae organisms of carbapenem resistance due to carbapenemases. Organisms harboring these enzymes have been responsible for many HAIs worldwide.[70–73] The most common carbapenemases among Enterobacteriaceae are the *K. pneumoniae* carbapenemases (KPCs), first identified in the United States in a *K. pneumoniae* isolate in North Carolina.[74] Most reports of infections due to KPC-positive organisms are from metropolitan centers in the northeast, but they increasingly are reported throughout the United States. The KPCs constitute a group of similar enzymes (i.e., serine carbapenemases) that can be found in *K. pneumoniae, K. oxytoca, E. coli, Citrobacter freundii, Enterobacter* spp., and other gram-negative bacilli, but the enzymes occur most frequently in isolates of *K. pneumoniae*. The KPCs confer resistance to all of the carbapenems and to all generations of cephalosporins.

Although β-lactamase inhibitors such as clavulanic acid and tazobactam demonstrate some inhibition of KPCs, inhibition usually is not sufficient to render extended-spectrum penicillin/β-lactamase inhibitor combination antibiotics active against these organisms. However, a novel β-lactamase inhibitor, avibactam, with increased potency and an expanded spectrum of inhibition of ESBLs, Amp C β-lactamases, and KPCs is promising.[75]

CLSI published updated susceptibility test interpretive criteria for the Enterobacteriaceae, with lower MIC and higher disk diffusion breakpoints to define isolates susceptible to the carbapenem antibiotics, including ertapenem, meropenem, imipenem-cilastatin, and doripenem.[76] The revised breakpoints are designed to better identify organisms that may be harboring carbapenemases but would not be reported as intermediate or resistant with use of older breakpoints. Laboratories may choose to continue to use screening and confirmatory tests with the older breakpoints to identify carbapenemase-producing

Enterobacteriaceae in much the same way as using screening and confirmatory tests for detection of ESBLs. *Raoultella* spp. exhibit antibiotic susceptibility patterns similar to those of *Klebsiella* spp.[48]

The recommended confirmatory test for carbapenemase production is the modified Hodge test.[76] The test is performed on an agar plate, and carbapenemase activity in a test organism is demonstrated by the ability of the enzyme to inactivate a carbapenem antibiotic, allowing a carbapenem-susceptible indicator *E. coli* organism to show enhanced growth in the presence of the antibiotic. Biochemical-based detection kits are available to screen bacterial isolates for resistance, and the use of MALDI-TOF has been investigated as a possible method for detection of carbapenemases.[77–79]

Empiric treatment for the seriously ill patient with suspected HAI due to a *Klebsiella* spp. or other gram-negative bacilli should include the combination of meropenem and amikacin. For patients with BSI (including those with granulocytopenia or hypotension) or other serious infections due to these organisms, combination therapy with a β-lactam antibiotic plus an aminoglycoside to which the organism is susceptible is reasonable.[80,81] Fluoroquinolones and piperacillin-tazobactam have been used to treat serious infections caused by *Klebsiella* spp. that were resistant to the aminoglycosides and cephalosporins.[82,83] Unfortunately, resistance to these agents also is reported, and definitive antimicrobial therapy must be guided by the results of susceptibility testing.

For meningitis due to antibiotic-susceptible *Klebsiella* spp., a third-generation cephalosporin and aminoglycoside administered intravenously is the regimen of choice. In one study of children 4 days to 7 months old who were receiving cefotaxime and amikacin parenterally, the mean duration of positive cerebrospinal fluid (CSF) cultures was 5.8 ± 4.7 days (range, 2–15 days).[80] Five of these patients also received 1 to 25 doses of intraventricular amikacin; however, intraventricular instillation is not recommended in children who do not have a central nervous system device in place. The efficacy of treatment for children with gram-negative bacillary meningitis should be monitored by repeated examinations and CSF cultures. Patients with prolonged positive cultures may be candidates for meropenem if supported by susceptibility testing. Therapy should be continued for at least 2 weeks after the first sterile CSF culture or for a total course of at least 21 days, whichever is longer.

Management recommendations for infections associated with intravascular devices due to *Klebsiella* spp. and other members of the Enterobacteriaceae family usually have included the removal of the foreign body. For device-associated BSI due to gram-negative bacilli, an attempt to treat with antibiotics without device removal is reasonable if the patient is clinically stable and the bloodstream is sterilized quickly (<72 hours).[84] Duration of therapy is 10 to 14 days after blood stream sterilization, if the device is retained. If the device is removed, 10 days should be adequate. Oral cephalosporins, trimethoprim-sulfamethoxazole, or fluoroquinolones can be considered for treatment of UTIs due to susceptible organisms.

Treatment of infections due to carbapenem-resistant Enterobacteriaceae organisms may be problematic because they are resistant to all β-lactam antibiotics and can be resistant to the aminoglycosides (50% to gentamicin and amikacin) and fluoroquinolones (98%).[85] Additional antibiotic susceptibility testing should be performed for tigecycline, colistin or polymyxin B, aztreonam, ceftazidime-avibactam, and fosfomycin (for urinary tract isolates). The newer agent tigecycline, the revived agent colistin, and the investigated ceftazidime-avibactam may offer therapeutic options.[75,86,87] Combination therapy with two or more agents is recommended for the treatment of infections due to carbapenem-resistant members of the Enterobacteriaceae family because of the associated high mortality rate, concern about emergence of resistance during monotherapy, and lack of clearly effective monotherapy.[87]

Prevention

A 24-valent *K. pneumoniae* capsular polysaccharide vaccine is immunogenic in patients who have sustained trauma, a group known to be at risk for serious infection with gram-negative bacteria.[88] Prevention of *Klebsiella spp.* infection predominately correlates with prevention of HAIs (see Key Points Box in Chapter 139). In the future, active immunoprophylaxis may be a consideration for people at risk for infections caused by *Klebsiella* spp. and other gram-negative bacilli.

Key Points

Diagnosis and Management of *Klebsiella* and *Raoultella* Infection

Microbiology

- Members of the Enterobacteriaceae family, the catalase-positive, oxidase-negative, gram-negative bacilli are facultative anaerobes that reduce nitrate to nitrite and ferment glucose and other carbohydrates. They are nonmotile, usually encapsulated, and usually produce lysine but not ornithine decarboxylase.

- They grow well on blood, chocolate, and usually MacConkey agar, often producing a large, mucoid, lactose-fermenting colony on the latter.

- *Klebsiella* spp. can produce extended-spectrum β-lactamases (ESBLs) and AmpC-type β-lactamases, and *K. pneumoniae* carbapenemases (KPCs) have emerged.

- Organisms are identified by biochemical methods or MALDI-TOF mass spectrometry. Susceptibility testing performed by automated and manual methods is standard. Revised Clinical and Laboratory Standards Institute breakpoints optimize screening for enzyme-resistance mechanisms.

Epidemiology

- The organisms are ubiquitous in nature (i.e., soil and water), contaminate healthcare environments and personnel, and colonize mucosal surfaces.

Clinical Importance

- *Klebsiella spp*. are important pathogens in a wide variety of infections, including healthcare- and community-associated bloodstream infections (BSIs); central nervous system (CNS), respiratory tract, and urinary tract infections (UTIs); and postoperative, trauma, and burn wound infections in neonates and children.

- Cytotoxin-producing *K. oxytoca* is implicated in antibiotic-associated hemorrhagic colitis; enterotoxigenic and enteroaggregative *K. pneumoniae* are potential causes of childhood gastroenteritis.

- *Raoultella ornithinolytica* and *R. planticola* are associated with scombroid fish poisoning and rarely cause BSIs.

- Organisms are recovered in culture using standard laboratory procedures.

Treatment

- Organisms are susceptible in vitro to and usually treatable with aminoglycosides, carbapenems, first-generation and extended-spectrum cephalosporins. and penicillin/β-lactamase inhibitor combinations.

- ESBL-producing strain infections can be treated with a carbapenem; amikacin is added for serious infections.

- Infections with AmpC-type β-lactamase–producing strains can be treated with a carbapenem or a fourth-generation cephalosporin; an aminoglycoside is added for serious infections.

- Infections with carbapenemase-producing strains can be treated with combination therapy of two or more drugs based on the results of susceptibility testing for tigecycline, colistin, aztreonam, and ceftazidime-avibactam; fosfomycin can be tested for urine isolates.

Duration of Therapy

- Uncomplicated UTI: 7- to 10-day course usually is adequate; removal of a catheter hastens eradication.

- Infection of CNS: minimum of 2 weeks after documented sterilization.

- Intravascular device–associated BSI: removal of the device (attempt to treat without removal is possible if the patient is clinically stable and the bloodstream is sterilized <72 hours); minimum of 10- to 14-day course of antibiotics after documented sterilization if the device is retained; shorter duration if device removed.

Special Considerations

- Multidrug-resistant infections should be managed in consultation with an infectious diseases specialist.

- Patients colonized or infected with a multidrug-resistant pathogen should be cared for under contact isolation conditions.

- Hospital-associated infections can be minimized by strict attention to hand hygiene, limiting the use of invasive devices, antimicrobial stewardship, and use of infection control bundles during placement of invasive devices. Use of ethanol locks in certain populations requiring long-term venous access can decrease the incidence of recurrent central line–associated BSIs.

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Klebsiella granulomatis: Granuloma Inguinale

Bradley P. Stoner

Granuloma inguinale, or donovanosis, is a chronic, slowly destructive, ulcerative disease of skin and subcutaneous tissues caused by *Klebsiella* (formerly *Calymmatobacterium*) *granulomatis*.[1,2] Uncommon in industrialized countries, donovanosis historically has been seen among adolescents and adults in some tropical and developing regions, including Papua New Guinea, central Australia, South Africa, Brazil, and regions of India.[3–7] Sporadic cases also have been reported in the West Indies, South America, and other areas of southern Africa. Children rarely are diagnosed with donovanosis.[8,9]

In recent years, several endemic regions have reported substantial declines in prevalence,[10–12] and case reports from developed countries often involve people who have migrated from endemic areas.[13–15] The published literature on donovanosis represents few geographic locations, reflects limited microbiologic testing, and relies on syndromic genital ulcer disease surveillance in areas where donovanosis is thought to be most common.[16] Increased awareness of the role of genital ulcer disease in human immunodeficiency virus (HIV) transmission may raise public health interest in donovanosis.[17,18]

The sexual transmission of donovanosis has been controversial, but there is substantial evidence that *K. granulomatis* is transmitted sexually.[16,19] Transmission rates of up to 52% have been reported among steady sexual partners of those with donovanosis.[8] Although rare, vertical transmission of donovanosis has been reported.[20] There also is evidence that transmission can occur through fecal contamination.[21]

Clinical Manifestations

Donovanosis lesions involve the genitalia (typically the prepuce or glans in men and the vagina or labia minora in women) in 80% to 90% of cases but also can involve the inguinal and anal regions (Fig. 139.1A and B). Beginning as a small papule or multiple papules at the site of inoculation, donovanosis typically manifests with painless, easily bleeding ulcers or vegetative lesions (see Fig. 139.1C), which can be ulcerogranulomatous, hypertrophic, necrotic, or sclerotic.[22] Ulcerative lesions expand slowly and become clean, shallow, well-demarcated ulcers with a beefy red granular base (see Fig. 139.1D). Prominent lymphadenopathy often develops, leading to further ulceration of overlying skin.[23] In most cases, clinical findings suggest donovanosis but are not highly specific.[8,19,24]

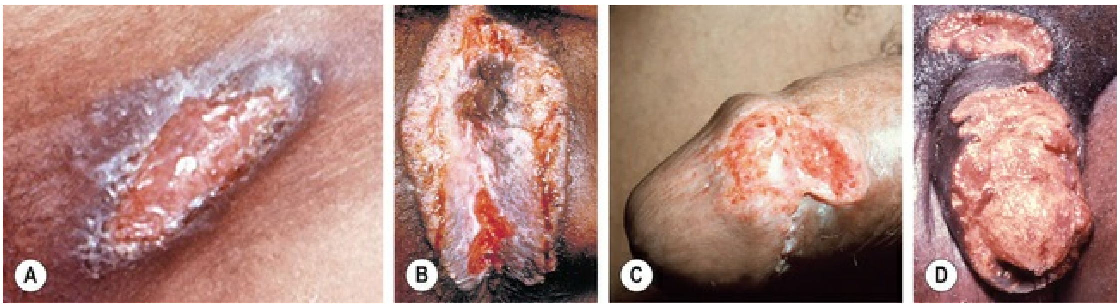

FIGURE 139.1 Lesions in patients with donovanosis. (A) Healing inguinal ulcer. (B) Perianal skin ulcer. (C) penile ulcer. (D) Penile ulcer with extensive tissue damage. (From Centers for Disease Control and Prevention's Public Health Image Library. http://phil.cdc.gov/phil/home.asp.)

Untreated lesions can cause extensive local tissue damage, including pelvic and perianal fistulas, urethral obstruction, and lymphedema.[19] Although uncommon, lesions can develop secondary bacterial infection and cellulitis. Systemic infections can cause fever, weight loss, and anemia. Involvement of the bone, joint, and liver occurs infrequently and is likely more common in pregnant women. Involvement of the head and neck also has been described.[25] Unusual manifestations in HIV-infected patients have also been reported, including penile autoamputation and malignant transformation to squamous cell carcinoma.[26,27]

The differential diagnosis of donovanosis includes syphilis, lymphogranuloma venereum, chancroid, lymphoma, carcinoma, tuberculosis, blastomycosis, and other granulomatous diseases. People suspected of having donovanosis should have a thorough examination and should be tested for syphilis and other sexually transmitted infections, including HIV, which can coexist with donovanosis.[19,26–28] The increased risk of HIV transmission associated with genital ulcer disease (e.g., syphilis, herpes simplex virus infection, donovanosis) underscores the importance of prompt recognition and treatment.[17]

Laboratory Diagnosis

K. granulomatis is a pleomorphic, intracellular, gram-negative bacterium. Although difficult to grow on artificial media, *K. granulomatis* can be identified using tissue crush or biopsy specimens. For tissue crush specimens, granulation tissue is collected from a lesion and crushed between two microscopic slides. After excess material has been removed from the ulcer base with a cotton swab, the first swab collection is most sensitive.[16,22]

Donovan bodies, which look like safety pins clustered in macrophages when stained with Wright or Giemsa stain, are diagnostic of *K. granulomatis.* A polymerase chain reaction test for *K. granulomatis* is available for use in some research settings but is not available commercially.[29,30] Light microscopy is a less reliable diagnostic technique for donovanosis.[8,24,31]

Treatment and Management

Prompt identification and treatment are important for optimal management.[32] However, in most donovanosis-endemic areas, diagnostic testing is limited, and treatment is determined by syndromic algorithm. The syndromic algorithm should be evaluated routinely to determine whether donovanosis therapy should be included in the genital ulcer disease treatment provided.

Initiation of antibiotic therapy slows progression of lesions, but prolonged therapy usually is required for effective treatment. Several antimicrobial regimens are effective, but few controlled trials have been published. Although doxycycline has historically been the treatment of choice for donovanosis, accumulating evidence supports the use of azithromycin as the preferred first-line agent.[33,34] European treatment guidelines recommend azithromycin given orally as 1 g weekly or 500 mg daily for adults and as 20 mg/kg once daily for children.[22] Updated treatment guidelines from the US Centers for Disease Control and Prevention (CDC) also recommend azithromycin administered as 1 g weekly or 500 mg daily.[35] Alternative regimens include doxycycline (100 mg PO twice daily), ciprofloxacin (750 mg PO twice daily), erythromycin base (500 mg PO four times daily), and trimethoprim-sulfamethoxazole (one double-strength (160 mg/800 mg) tablet PO twice daily).

Recommendations for the duration of antimicrobial therapy vary. The CDC recommends treatment for at least 3 weeks and until all lesions have healed completely. Some specialists recommend the addition of an aminoglycoside (e.g., 1 mg/kg of gentamicin IV every 8 hours) if clinical improvement is not evident within the first few days of antibiotic therapy.[35]

Clinical studies suggest an incubation period for donovanosis of 1 to 8 weeks or longer.[8,22] Contact intervals are not standardized. The CDC treatment guidelines recommend that sex partners within 60 days before the onset of the patient's symptoms be examined and offered therapy. However, the value of empiric therapy in the absence of clinical signs and symptoms has not been established.[22,35]

Because doxycycline and ciprofloxacin are contraindicated in pregnant women (and pregnancy is a relative contraindication to the use of sulfonamides), pregnant and lactating women should be treated with a macrolide regimen (i.e., azithromycin or erythromycin). Judicious addition of an aminoglycoside may also be considered.

Few data exist regarding preferred treatment regimens and clinical outcomes of HIV-infected patients. One study found no difference in the duration of ulcer healing and rate of recurrence between HIV-infected and uninfected pregnant women.[36] The CDC treatment guidelines recommend that people with granuloma inguinale and HIV infection should receive the same regimens as those who are HIV uninfected. However, patients should be monitored closely for relapse or treatment failure, and if failing the initial antimicrobial therapy, an aminoglycoside (e.g., gentamicin) can be added.[35]

The risk of complications, such as complete genital erosion and urethral obstruction, can be minimized with early therapy. If extensive tissue destruction has occurred, surgery may be required.[37] Relapse is common, especially if the duration of treatment is inadequate, and can occur 6 to 18 months after apparently effective therapy.

Prevention and Control

Few data exist regarding effective prevention and control. Prevention should be part of a broad sexually transmitted infection prevention and control program, with emphasis on providing information about risks and complications of sexually transmitted infections (including HIV), safer sex practices, early recognition and treatment of sexually transmitted infections, and sex partner evaluation and treatment.[6,23,35]

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Enterobacter, *Cronobacter*, and *Pantoea* Species

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Microbiology and Epidemiology

The genera *Enterobacter, Cronobacter,* and *Pantoea* are all members of the Enterobacteriaceae family. The genus *Enterobacter* has undergone significant taxonomic revision. Although there are more than 15 named species, molecular techniques likely will identify additional species.[1–9] Many former members of this genus have been transferred to other genera in the family Enterobacteriaceae, including to *Klebsiella, Serratia, Hafnia,* and *Pantoea* genera. Some have been transferred to new genera, including to *Lelliottia, Pluralibacter,* and *Kosakonia*.[2]

The genus *Pantoea* has been proposed to accommodate several isolates with significant biochemical and nucleic acid diversity that formerly were included in the heterogeneous taxon called the *Enterobacter agglomerans* group.[10] There are more than 20 species, with *P. agglomerans* and *P. ananatis* most associated with human infections. Some commercial biochemical identification systems include *P. agglomerans* or *P. agglomerans* group in their databases, but they may not differentiate correctly among *Pantoea* species.

The *Enterobacter* spp. most commonly recovered from human sources include *E. cloacae, E. aerogenes,* and to a lesser extent, *Pantoea* (formerly *Enterobacter*) *agglomerans* group, *Cronobacter* spp., *E. gergoviae,* and *E. asburiae*. *E. cloacae* is by far the most common clinical isolate. A number of newly named species (formerly included in the *E. cloacae* group) are difficult to differentiate by biochemical test methods.[1–5] Organisms formerly classified as *E. sakazakii* comprised a diverse group and are renamed as *Cronobacter* spp., which comprise at least seven named species, of which *C. sakazakii* and *C. malonaticus* are most frequently isolated from human infections. Some commercial biochemical identification systems use the terms *E. cloacae* group and *C. sakazakii* group to describe these closely related and difficult to distinguish organisms.

Improved identification methods are needed. Matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) mass spectrometry demonstrates overall good performance in the identification of gram-negative bacilli.[11] It shows promise for differentiating among *Enterobacter, Cronobacter,* and *Pantoea* species.[12–14]

Enterobacter, Cronobacter, and *Pantoea* spp. are nonfastidious in nature and grow on blood and chocolate agar and selective media for enteric bacteria. On MacConkey agar, *E. cloacae* and *E. aerogenes* commonly appear as pink, lactose-fermenting, mucoid colonies similar in appearance to *Klebsiella pneumoniae* and *K. oxytoca.* Most isolates of *Cronobacter* spp. and *P. agglomerans* group organisms produce a nondiffusible, yellow pigment, which often is more intense when grown on enriched media at 25°C versus 35°C. Colonies of *Cronobacter* can appear dry, wrinkled, and leathery on some media.

Most isolates of *Enterobacter* spp. are motile, use citrate as a sole carbon source, and give a positive Voges-Proskauer test result but do not produce indole or hydrogen sulfide. With the exception of the *P. agglomerans* group organisms, most isolates have ornithine decarboxylase activity. Motility and ornithine reactions help to differentiate *Enterobacter* spp. from the common human isolates of *Klebsiella* spp.

Commercial or conventional biochemical identification systems usually perform well for identifying and differentiating *E. cloacae, E. aerogenes, P. agglomerans,* and *Cronobacter* spp., but the other species present a greater challenge and are not all represented in the databases of commercial systems. A report of *Enterobacter* spp. or *Cronobacter* spp. may be sufficient for most clinical purposes, although knowledge of the specific species is important in the setting of a potential nosocomial outbreak or when the clinical significance of the isolate is questioned.

Enterobacter spp. and *Pantoea* spp. are common inhabitants of the gastrointestinal tract of humans and other mammals, and they can be found in water, sewage, soil, plant material, and foods. Even the more common human isolates, *E. cloacae* and *E. aerogenes,* have been described as having a ubiquitous animal and environmental distribution. *Pantoea* spp. are commonly associated with plants or are well-known agents of disease in plants.

In humans, *Enterobacter* spp. and *Pantoea* spp. are opportunistic pathogens and are among the most common causes of nosocomial pneumonia, urinary tract infection, surgical wound infection, and catheter-related bloodstream infection (BSI). These organisms frequently colonize the skin and respiratory, urinary, and gastrointestinal tracts of hospitalized patients. These sites act as portals of entry for localized or invasive disease.[1–5] *Enterobacter* spp. and *Pantoea* spp. also cause community-acquired urinary tract, skin, soft tissue, and other infections, although at much lower rates than other gram-negative bacilli such as *E. coli, Proteus* spp., and *Klebsiella* spp. Community-acquired infections due to *P. agglomerans* have been associated with foreign bodies and with plant thorn and wood splinter injuries.

Enterobacter spp. accounted for 5% of all bacterial pathogens and 9% of gram-negative bacilli in more than 4000 episodes of nosocomial or community-acquired BSIs in North America and Latin America in 1997.[15] Of almost 75,000 gram-negative bacilli recovered from BSIs in patients in intensive care units (ICUs) in the United States between 1993 and 2004, *Enterobacter* spp. accounted for 14% of isolates.[16]

Two US studies indicate that *Enterobacter* spp. represent the fourth and seventh most common pathogens causing BSI in pediatric ICUs (PICUs) and neonatal ICUs (NICUs), respectively.[17,18] A 2003 US study of ICU nosocomial bacterial infections reported that *Enterobacter* spp. accounted for 10%, 4%, 9%, and 7% of pneumonia, BSI, surgical site, and urinary tract infections, respectively, due to gram-negative bacilli.[19] *Enterobacter* spp. also accounted for 15% of all gram-negative BSIs in children in Israel.[20] An outbreak of *E. gergoviae* among adult kidney transplant recipients was associated with a common source of contamination, which was presumed to be urinary catheters or stents.[21]

An endogenous source of *Enterobacter* spp. is most common in nosocomial infections. Approximately 40% of infants are fecal carriers of *Klebsiella* or *Enterobacter* spp. on discharge from NICUs. Colonization in nursery settings has been associated with overcrowding, inadequate handwashing, low birth weight, prematurity, endotracheal intubation, prolonged hospitalization, contaminated infant formula or parenteral nutrition fluid, and the use of antibiotics or central venous catheters (CVCs). Risk factors for infection include immunosuppression from any cause, prematurity, use of devices (e.g., CVC, endotracheal tube, urinary catheter), and prior use of antibiotics. The role of microbial virulence factors in the pathogenicity of these organisms has been reviewed.[5]

Clinical Manifestations

BSI is the most common form of invasive infection due to *Enterobacter* spp.[6–9,22,23] Signs and symptoms in children are similar to those due to other gram-negative enteric bacteria. Fever occurs in 83% to 87% and hypotension or shock in 8% to 28% of patients. Leukocytosis or leukopenia can develop, and mortality rates for children range from 6% to 24%.

Lower respiratory tract infection, including pneumonia with BSI, is the second most common pediatric infection due to *Enterobacter* spp. In pediatric national nosocomial surveillance studies, *Enterobacter* spp. were the third and fourth leading causes of nosocomial pneumonia in PICUs and NICUs, respectively, rising from 7.4% in 1992 to 13% in 1997.[17,18] Pneumonia due to *Enterobacter* spp. occurs more often in infants younger than 2 months of age than in older infants and children.

Other *Enterobacter* spp. infections in infants and children include meningitis, brain abscess, endocarditis, pyogenic arthritis, and peritonitis. *Klebsiella* or *Enterobacter* spp. accounted for 16% of meningitis cases due to gram-negative enteric bacteria during a 21-year period in Dallas.[24] *Enterobacter* spp. also are associated with nosocomial gastrointestinal, urinary tract, surgical site, eye, ear, nose, and throat infections (Table 140.1).[17,18]

TABLE 140.1

Pediatric *Enterobacter* spp. Infections Reported by the National Nosocomial Infections Surveillance System

Infection	Percentage of Cases	
	Neonatal ICU	Pediatric ICU
Bloodstream	2.9	6.2
Gastrointestinal tract	5.5	ND
Pneumonia	8.2	9.3
Lower respiratory tract other than pneumonia	ND	12.2
Urinary tract	ND	10.3
Surgical site	7.6	8.1
Eye, ear, nose, throat	4.5	ND

ICU, intensive care unit; ND, no data.

Data from Andresen J, Asmar BI, Dajani AS. Increasing *Enterobacter* bacteremia in pediatric patients. Pediatr Infect Dis J 1994;13:787–792; Delétoile A, Decré D, Courant S, et al. Phylogeny and identification of *Pantoea* species and typing of *Pantoea agglomerans* strains by multilocus gene sequencing. J Clin Microbiol 2009;47:300–310.

Cronobacter spp. have particular importance in young infants because of an association with powdered infant formula feeding[25] and because of a propensity for causing necrotizing enterocolitis and meningitis in a fashion similar to *Citrobacter koseri* (see Chapter 141). *C. sakazakii* is the only member of the genus that can use sialic acid, and this may contribute to its association with neonatal infections because sialic acid is found in breast milk, infant formula, the gastrointestinal tract, and the brain.[26]

Neonatal meningitis due to *Cronobacter* is associated with a high prevalence of brain abscess or cyst formation, high mortality rate (40% to 80%), and long-term neurologic sequelae in survivors. There is controversy about whether the intracerebral cystic lesions visualized on computed tomography (CT) in neonates with *Cronobacter* meningitis result from infarction leading to sterile liquefaction cysts or from abscess formation. *Cronobacter* has been isolated from brain cysts, suggesting a need to obtain cyst aspirates for Gram stain and culture if possible. When *Cronobacter* is recovered from neonatal blood or cerebrospinal fluid (CSF) culture, serial CT or magnetic resonance imaging studies should be performed to evaluate brain cyst or abscess formation to guide optimal management.[27] The World Health Organization has recommended preparation guidelines and continued improvement of powdered infant formula manufacturing processes to reduce this mode of acquisition of *Cronobacter* spp.[25]

Pantoea agglomerans is an uncommon human pathogen. It has been reported to cause BSIs, including neonatal BSI related to administration of contaminated intravenous solutions, and has been associated with contamination of indwelling catheters. Septic shock, respiratory failure, and death occurred in 7 of 8 patients in one outbreak related to contaminated parenteral fluid.[28] Another study reported 5 sporadic cases of *Pantoea agglomerans* BSI in preterm neonates over a 2-year period at one hospital; no source was identified.[29]

Inflections can be polymicrobial, making the role of *Pantoea* difficult to determine.[30] Other reported infections include peritonitis during chronic ambulatory peritoneal dialysis, suppurative arthritis, skin and soft tissue infections presumably resulting from medical devices, a foreign body, and a plant thorn injury during rose gardening[31,32] *Pantoea* spp. endophthalmitis developed in a patient after ocular trauma while using a lawn mower; a metal fragment was found lodged in the lens of the eye.[33]

Treatment

Antibiotic susceptibility patterns for *Enterobacter* spp. vary between centers and among species, making monitoring of antimicrobial susceptibility patterns critical. *Cronobacter* spp. and *E. gergoviae* may be susceptible to ampicillin, cefazolin, and other narrow-spectrum cephalosporins, but *E. cloacae, E. aerogenes,* and several other *Enterobacter* spp. are uniformly resistant to these agents.[34]

E. cloacae, E. aerogenes, and other selected Enterobacteriaceae, including *Citrobacter freundii, Proteus vulgaris, Morganella morganii, Serratia* spp., and *Providencia* spp., harbor a chromosomal gene (*ampC*) coding for AmpC-type β-lactamase production.[35] Frequently produced at low levels on initial laboratory isolation, high-level production is induced after in vitro or in vivo exposure to selected β-lactam antibiotics, particularly compounds such as ampicillin, first- or second-generation cephalosporins, and clavulanic acid.

Initial isolates can appear susceptible to extended spectrum β-lactam agents by in vitro test methods, particularly rapid susceptibility test methods. AmpC β-lactamase production can be stably de-repressed in these organisms due to a chromosomal mutation of the *ampD* gene that normally plays a role in repressing *ampC* gene transcription. These strains, referred to as *stably de-repressed mutants*, can emerge during selective antimicrobial pressure within days of starting a course of β-lactam therapy and produce high levels of AmpC β-lactamase constitutively.[34–36]

Emergence of resistance appears to occur more often in *Enterobacter* spp. than in other enteric bacteria known to harbor *ampC* genes.[36] High-level AmpC production renders the organism resistant to many β-lactam antibiotics, including third-generation cephalosporins and extended-spectrum β-lactam/β-lactamase inhibitor combination drugs. Susceptibility to fourth-generation cephalosporins and carbapenems is retained.

No routine procedures are recommended by the Clinical Laboratory and Standards Institute (CLSI) for laboratory detection of inducible AmpC-mediated resistance in *Enterobacter* spp. and related organisms. A double-disk approximation test can be used, in which a known AmpC inducer antibiotic disk and an indicator antibiotic disk are placed in adjacent positions on a lawn of a test organism. A measurable reduction (i.e., flattening) in the zone of inhibition on the side of the indicator antibiotic disk adjacent to the inducer antibiotic disk suggests AmpC production.[37] An alternative approach is a disk diffusion test format similar to the CLSI confirmation disk test for the presence of extended-spectrum β-lactamases (ESBLs). (see Chapter 138).[38]

In areas where inducible AmpC resistance is common, it seems prudent to report *E. cloacae* and other known AmpC producers as resistant to third-generation cephalosporins and extended-spectrum β-lactam/β-lactamase inhibitor combination drugs or at least to caution against their use as monotherapy for serious infections.[39] It is equally important to repeat testing of secondary isolates of *Enterobacter* spp. and other gram-negative bacilli recovered from normally sterile body sites when recovered 24 to 48 hours after commencing appropriate antibiotic therapy.

Enterobacter spp. can contain plasmids encoding for ESBLs and other genes coding resistance to other classes of antibiotics.[3] In a

North American and Latin American survey of gram-negative BSIs in which 399 *Enterobacter* spp. isolates were tested, meropenem, imipenem, and cefepime were the most active agents; more than 99% of isolates were susceptible. The fluoroquinolones and aminoglycosides also had good activity; 90% to 96% of isolates were susceptible. No other antibiotic demonstrated activity for more than 78% of isolates.[15]

Optimal antibiotic therapy for infections due to *Enterobacter* spp. is unclear. For serious infections, it may be prudent to avoid the use of a single-agent, extended-spectrum cephalosporin or a β- lactam/β-lactamase inhibitor combination other than a fourth-generation cephalosporin because of possible rapid selection of resistance. Addition of an aminoglycoside is reasonable for a serious infection outside the central nervous system (CNS). For treatment of meningitis, meropenem is the optimal choice, and many experts add an aminoglycoside in this setting.[40–42] For patients with type I hypersensitivity reactions to β-lactams, use of a fluoroquinolone plus an aminoglycoside may be effective.

Careful monitoring of the patient's clinical course, particularly for occurrence of CNS complications, is essential, especially with *Cronobacter* infection. Appropriate specimens must be obtained sequentially to demonstrate a sustained bacteriologic response. Prompt removal of contaminated prosthetic devices is essential to eradicate the organism and effect a cure. Failure to remove these devices compromises a rapid bacteriologic response and increases the likelihood that resistant organisms will emerge.

Good handwashing technique and assiduous application of other infection control practices are essential to prevent nosocomial transfer of organisms. The use of broad-spectrum antimicrobial agents should be strictly limited; unnecessary antimicrobial therapy should be avoided.

Key Points

Diagnosis and Management of *Enterobacter* Species Infections

Microbiology

- Members of Enterobacteriaceae: facultative, gram-negative bacilli that are catalase positive and oxidase negative, reduce nitrate to nitrite, and ferment glucose and other carbohydrates

- Indole negative; most species are motile and usually are encapsulated.

- Good growth on blood, chocolate, and MacConkey agar (usually); often produce large, mucoid colonies that are pink, indicating lactose fermentation

Epidemiology

- Common inhabitants of the gastrointestinal tract of humans and other mammals; found in water, sewage, soil, plant material, and foods

- *Enterobacter aerogenes* and *E. cloacae* are the most common clinically encountered species.

- Important pathogen in a wide variety of infections, including the bloodstream, central nervous system, and respiratory and urinary tracts; substantial cause of nosocomial infections

- Risk factors include foreign bodies and medical devices, neutropenia, and immunosuppression.

Diagnosis

- Recovery in culture using standard laboratory procedures

- Identification by biochemical methods or MALDI-TOF; susceptibility testing by automated or manual methods

Treatment

- Many species have intrinsic low-level resistance to third-generation cephalosporins and β-lactam–β-lactamase inhibitor combination drugs.

- An infectious diseases consultation is prudent when treating patients with *Enterobacter*, *Cronobacter*, or *Pantoea* infection. When selecting antimicrobial agents for empiric therapy, local antibiograms can help to guide the decision.

- Therapy with third-generation cephalosporins or β-lactam/β-lactamase inhibitor combinations should be avoided because these agents can induce *ampC* resistance.

- Meropenem is the drug of choice for meningitis. Some experts add an aminoglycoside.

- Cefepime plus an aminoglycoside is an effective combination therapy for serious infections outside the central nervous system.

- In patients allergic to cefepime, a fluoroquinolone plus gentamicin may be reasonable therapy.

Duration of Therapy

- For patients with meningitis, treatment is 4 to 6 weeks after cerebral spinal fluid sterilization is documented.

- For patients with bacteremia and no foreign body, treatment is 2 to 3 weeks after sterilization of the blood is documented.

- For patients with persistent bacteremia or when a foreign body is not removed, the duration of therapy is 4 to 6 weeks after sterilization of the blood is documented, but it may not be curative.

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Citrobacter Species

Stella Antonara, Monica I. Ardura

Microbiology and Epidemiology

The genus *Citrobacter* has undergone significant taxonomic revision through the use of newer techniques based on DNA relatedness. The genus contains 11 named species: *Citrobacter freundii, C. koseri* (formerly *C. diversus*), *C. amalonaticus, C. youngae, C. farmeri, C. braakii, C. werkmanii, C. sedlakii, C. gillenii, C. murliniae,* and *C. rodentium.*[1–5] All species except *C. rodentium* (pathogenic for mice) have been recovered from human clinical specimens. However, *C. freundii* and *C. koseri* and *C. braakii* are the most important human pathogens. *C. freundii*, *C. koseri*, and *C. amalonaticus* appear to be distinct organisms, but only *C. koseri* appears to be genetically homogeneous. Several other named species form a closely related group and are difficult to differentiate biochemically; they are sometimes referred to as *C. freundii* complex organisms.

Citrobacter spp. are gram-negative bacilli in the family Enterobacteriaceae. They ferment glucose and other carbohydrates, are catalase and oxidase positive, and reduce nitrate. Most isolates are motile and use citrate as a sole carbon source, but they lack urease and lysine decarboxylase activity. Production of hydrogen sulfide varies, occurring in *C. freundii* and a few other species. On *Salmonella-Shigella* agar, lactose-negative and hydrogen sulfide–positive isolates of *Citrobacter* spp. produce black colonies resembling those of *Salmonella* spp. The lysine decarboxylase reaction allows separation of the hydrogen sulfide–producing isolates of *Citrobacter* spp. from *Salmonella* spp.[1–5]

Selected isolates of *C. freundii* have O (somatic) cell wall antigens closely related to the O antigens of *Salmonella* spp. and therefore cross-react with *Salmonella* typing antisera.[1] Rare isolates of *C. freundii* and *C. braakii* cross-react with some commercial *Escherichia coli* O157 typing antisera. For this reason, it is always prudent to confirm the identification of suspected *Salmonella* spp. and *E. coli* O157 by the use of biochemical and serologic methods. Identification of *Citrobacter* species also can be successfully achieved by the use of proteomic methods such as matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) mass spectrometry.[6,7] Any limitation in the identification of rarely encountered species depends on the inclusion of those species in the system's database.

Citrobacter spp. primarily are inhabitants of the intestinal tract of mammals and other vertebrates. Their isolation from environmental sources such as water and soil likely is the result of fecal excretion. *Citrobacter* spp. are not common agents of human disease, and most often are recovered from stool as colonizing flora of the gastrointestinal tract. When associated with significant human infection, *Citrobacter* can be recovered from blood, cerebrospinal fluid (CSF), urine, respiratory tract secretions, and wounds. The most common *Citrobacter* spp. isolated from human sources are *C. freundii* (all sites previously listed), *C. koseri* (all sites but most commonly the CSF and brain), *C. amalonaticus* (all sites except CSF), *C. braakii* (primarily stool), and *C. youngae* (primarily stool).[2]

The pathogenesis of infection has not been fully characterized. Most *C. koseri* isolates produce hemolysins, are piliated, and are resistant to killing by pooled human sera. The proclivity to cause central nervous system (CNS) infection and particularly brain abscesses is not well understood. Tropism for the CNS may be associated with specific outer membrane proteins. In one study, 79% of strains of *C. koseri* isolated from CSF had a unique 32-kd outer membrane protein, which was found in only 9% of isolates from other kinds of specimens.[8] *C. freundii* invades and replicates within brain microvascular endothelial cells in vitro.[9] *C. koseri* can enter macrophages, survive phagolysosomal fusion, and replicate intracellularly in the neonatal rat model; infected macrophages can then infiltrate blood vessels in the brain, starting the process leading to brain abscess formation.[1,10] Myeloid differentiation primary response gene 88 *(MYD88)*–dependent pathways in primary astrocytes are crucial for the induction of an inflammatory response and containment of *C. koseri* in CNS infection.[11]

In the pediatric population, infections occur most commonly in neonates.[12,13] Organisms can be transmitted by vertical transmission from mothers or by nosocomial spread, although most are considered sporadic cases from an unknown source. Direct mother-to-infant transmission has been confirmed by ribotyping and DNA fingerprinting.[14,15] It is likely that individual strains circulating in the community periodically gain access to a hospital nursery from the hands of nursery personnel and visitors.[14,16,17] One nursery outbreak of *C. freundii* was traced to contaminated infant formula.[18]

Clinical Manifestations

Citrobacter spp. are opportunistic pathogens in humans that can lead to invasive disease, including infections of the urinary tract, respiratory tract, CNS, skin, and soft tissue. The bacteria can cause osteomyelitis, suppurative arthritis, bacteremia, endocarditis, endophthalmitis, and intra-abdominal infections, particularly in neonates and immunocompromised hosts.

In infants, sepsis and meningitis are the most common clinical manifestations of infection.[12,13] Bacterial sepsis is associated with meningitis in about one half of cases. From 1969 to 1989 in Dallas, TX, *Citrobacter* spp. accounted for 9% of 91 cases of gram-negative enteric meningitis in infants 1 day to 2 years of age.[19] *C. koseri* was responsible for 90% of cases, and *C. freundii* caused most of the remaining cases. Neonatal sepsis and meningitis can manifest as early-onset (<1 week of life) or late-onset (>1 week of life) disease and can be fulminant or insidious. In 2002 and 2003, *Citrobacter* spp. caused 2.9% of early-onset sepsis in very low birth weight infants.[20]

No early features distinguish meningitis due to *Citrobacter* spp. from meningitis due to other gram-negative rods. Approximately 80% of infants with meningitis due to *Citrobacter* spp. develop one or more intracerebral abscesses (Fig. 141.1). In contrast, less than 10% of cases of infants with meningitis due to other gram-negative organisms have associated abscesses.[12,13] Neonatal brain abscesses also can occur with infections caused by *Cronobacter* (formerly

Enterobacter) *sakazakii, Proteus mirabilis,* and *Serratia marcescens*. In a contemporary review of brain abscesses in children, intracranial abscesses caused by *Citrobacter* spp. were more frequent compared with historical cohorts and occurred solely in neonates.[21] Brain abscesses can evolve any time during the acute course, including several weeks after commencement of treatment.

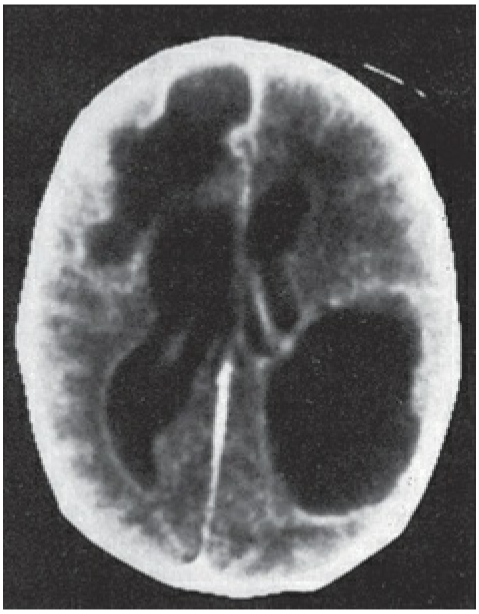

FIGURE 141.1 Computed tomography of a neonate with multiple brain abscesses caused by *Citrobacter koseri*.

The prognosis for meningitis due to *Citrobacter* spp. in neonates is poor. Approximately 30% to 35% of infected infants die, and only 15% to 20% survive with a structurally normal brain at completion of therapy; however, data on long-term prognosis are limited.[12] Although at least 40% of survivors show some form of developmental delay or physical impairment, or both, there are reports of infants with brain abscesses due to *Citrobacter* spp. who develop normally.[22]

Other *Citrobacter* spp. infections in infants occur rarely. Gastroenteritis, osteomyelitis, pyogenic arthritis, pulmonary infections, and pneumatosis intestinalis have been described.[13] In older children, adults, and immunocompromised hosts, *Citrobacter* spp. is associated most commonly with urinary tract, bloodstream, intra-abdominal, skin, soft tissue, and respiratory tract infections.[23]

Citrobacter spp. are the cause of urinary tract infection (UTI) in less than 3% of adults and children.[24,25] In a review of 37 pediatric cases, the mean age was 6.9 years, with a range of 1 month to 18 years.[24] Females predominated, and 56% of patients had underlying urinary tract or renal anomalies or neurologic impairment. Presenting symptoms were similar to those of UTI from other causes, including dysuria, fever, incontinence, frequency, flank pain, and hematuria. *C. freundii* accounted for 71% of cases, and *C. koseri* for the remainder. UTIs involving *Citrobacter* spp. and other enteric bacilli occurred in about 25% of patients.

In immunocompromised patients, *Citrobacter* spp. causes bacteremia but rarely leads to CNS disease. *C. freundii* caused 2.3% of bloodstream infections in the first year after lung transplantation in 190 pediatric patients.[26] Infections in immunocompromised patients more frequently are caused by multidrug-resistant strains.[23,27–29] Eye infections, including keratitis and endogenous and traumatic endopthalmitis caused by *Citrobacter* spp., have been reported.[30–32] An outbreak of severe gastroenteritis associated with several cases of hemolytic uremic syndrome occurred in a nursery school.[33] The source of this outbreak was sandwiches prepared with green butter containing a toxigenic strain of *C. freundii*. The butter had been made with contaminated parsley grown in an organically fertilized garden.

Treatment

Most data on in vitro antimicrobial susceptibility and therapeutic management are for infections due to *C. freundii* and *C. koseri*. These organisms can harbor a wide variety of β-lactamases. Both species are resistant uniformly to ampicillin, and *C. freundii* is also resistant to first-generation cephalosporins. *C. freundii* and some other *Citrobacter* spp. harbor chromosomal AmpC-type β-lactamases that can inactivate third-generation cephalosporins (see Chapter 140).[34] This enzyme is not inhibited by β-lactamase inhibitors such as tazobactam or clavulanate. A US national surveillance study of hospital-associated bloodstream infections reported resistance patterns for 23 *C. freundii* isolates.[35] Resistance to piperacillin, piperacillin/tazobactam, ceftriaxone, and ceftazidime occurred commonly (39%–48%); 96% of the ceftazidime-resistant isolates were susceptible to cefepime.

Some strains of *C. freundii* also harbor extended-spectrum β-lactamases and *Klebsiella pneumoniae*–type carbapenemases (KPCs) that are found more commonly in *Klebsiella* spp. (see Chapter 138). These plasmid-mediated enzymes are problematic because they are readily transferred from one strain to another in a healthcare environment.[36,37]

Citrobacter spp. usually are susceptible to fourth-generation cephalosporins such as cefepime (compared with third-generation cephalosporins such as ceftriaxone or ceftazidime) due to relative stability to inactivation by AmpC enzymes. Emergence of cefepime resistance in a clinical C. *freundii* strain due to a novel plasmid-mediated AmpC-type β-lactamase has been reported.[38] The carbapenems typically are active. *C. koseri* susceptibility to trimethoprim-sulfamethoxazole and the aminoglycosides varies. Among 117 *Citrobacter* spp. from US hospitals in 2007, the rates of susceptibility to the agents listed were 100% for meropenem and imipenem, 98% for cefepime, 95% for ceftriaxone, 86% for ceftazidime, 94% for piperacillin/tazobactam, 96% for gentamicin, 95% for tobramycin, and 97% for ciprofloxacin and levofloxacin.[39] In an antimicrobial surveillance study examining 776 *Citrobacter* species collected between 2008 and 2012 using the revised Clinical and Laboratory Standards Institute (CLSI) breakpoints for carbapenems, there was no significant change in the sensitivity of imipenem (97.1%), ertapenem (97.7%), meropenem (98.8%), and doripenem (98.9%).[40] Multidrug-resistant isolates may be susceptible to colistin, polymyxin B, and tigecycline.[41]

Optimal antimicrobial therapy for *C. koseri* meningitis has not been established, but a combination of a third- or fourth-generation cephalosporin plus an aminoglycoside to which the organism is susceptible is reasonable.[13] Monotherapy with high-dose cefotaxime or ceftriaxone or with imipenem-cilastatin has been successful.[42,43] Meropenem seems a logical carbapenem choice due to less potential for neurotoxicity. With recognition of the possible role of intracellular *C. koseri* in the pathogenesis of cerebral abscesses and possible poor CNS penetration of aminoglycosides, treatment with a third-generation cephalosporin in combination with ciprofloxacin has been used successfully.[44]

In infants with meningitis, a repeat lumbar puncture after 24 to 48 hours of antibiotic therapy should be performed to ensure CSF sterility. Neuroimaging should be obtained for all neonates with invasive *Citrobacter* infections. Neurosurgical drainage of abscesses has been used with various degrees of success. For patients with an accessible brain abscess, neurosurgical drainage is recommended if clinically feasible. For children who have progressive hydrocephalus and fibrous compartmentalization of the ventricular space, instillation of intraventricular urokinase also has been performed.[45] In the presence of CNS abscesses, cultures of CSF should be performed regularly until sterility is documented. Meningitis without abscess formation usually is treated for a minimum of 21 days after the first sterile CSF culture. For intracranial abscesses, a 4- to 6-week course from initial sterile CSF cultures is the minimal duration usually recommended, depending on clinical and radiologic improvement.[12,13] Testing for hearing loss and neurologic and developmental delays should be performed in all infants with *Citrobacter* spp. CNS infection.

Prevention of infections due to *Citrobacter* spp. is related predominantly to preventing healthcare-associated infections. Strict cohorting of infected or colonized neonates is prudent but may not effectively control nursery outbreaks. Meticulous handwashing is mandatory.

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Key Points

Diagnosis and Management of Infections With Citrobacter Species

Microbiology

- Catalase-positive, oxidase-negative, gram-negative rod
- Lactose fermenting on MacConkey media
- Chromosomal AmpC-producing; resistant to ampicillin and first-generation cephalosporins

Epidemiology

- Normal enteric flora; also found in the environment
- In infants <2 months, proclivity for CNS disease, including meningitis and brain abscesses
- Most cases are sporadic; vertical and horizontal transmission are described.
- Outbreaks support person-to-person transmission.

Diagnosis

- *C. koseri* is recovered easily in cultures from CSF samples, without use of specialized media.
- Use of PYR disk can differentiate atypical *Citrobacter* species (positive) from *Salmonella* species (negative).
- MALDI-TOF can differentiate *Citrobacter* spp. from other Enterobacteriaceae.

Treatment

- A combination of surgical and antimicrobial therapy typically is used.
- Empiric therapy with a third- or fourth-generation cephalosporin plus an aminoglycoside is common but depends on local antimicrobial susceptibility data.
- Targeted therapy should be guided by antimicrobial susceptibilities of the clinical isolate.

Duration of Therapy

- Duration of therapy for meningitis is similar to that for other enteric gram-negative neonatal pathogens.
- Prolonged therapy (4–6 weeks after documented CSF

sterilization) is required for brain abscesses and is guided by clinical and imaging improvement.

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Less Commonly Encountered Enterobacteriaceae

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Microbiology, Epidemiology, Clinical Manifestations, and Treatment

More than 99% of the Enterobacteriaceae family of bacteria recovered in clinical laboratories belong to a few dozen species. Three species—*Escherichia coli, Proteus mirabilis,* and *Klebsiella pneumoniae*—make up more than 90% of isolates, and several other well-recognized species account for most of the remaining clinical isolates.[1] Some less common genera have well-described, clinically important member species, whereas others are newly described genera with species that have rarely been reported to cause human infections.[1–6]

Many newly described species were formerly classified as atypical members of recognized species or by various group designations, such as enteric group organisms, with a numeric designation. DNA relatedness and 16S ribosomal RNA gene sequencing studies have allowed the placement of these organisms into new genera. No single commercial identification system includes all of these species in its database. It may be appropriate for laboratories to report such organisms with questionable identities as *Escherichia coli*-like or *Enterobacter*-like and to refer the isolate to a reference laboratory for definitive identification when clinically warranted.

Antibiotic susceptibility testing should produce reliable in vitro results because the organisms are members of the family Enterobacteriaceae, for which standardized test methods are available.[7] The taxonomic classification of newly described organisms will evolve as additional genetic relationships are discovered. Similarly, our understanding of their true clinical significance will improve as better laboratory identification methods become available.[7]

Buttiauxella species.

Buttiauxella encompasses at least seven species—*B. agrestis*, *B. ferragutiae*, *B. gaviniae*, *B. brennerae*, *B. izardii*, *B. noackiae*, and *B. warmboldiae*—which include environmental, nonhuman strains and opportunistic human pathogens.[2,4,8] Identification can be performed with biochemical methods, 16S rDNA sequencing, and proteomic methods such as matrix-assisted laser desorption ionization (MALDI).[9]

Case reports describe wound infection and urinary tract infection (UTI) with *Buttiauxella*.[9,10] A new class of chromosomal inducible β-lactamases was reported in a clinical *Buttiauxella* isolate from a skull wound infection.[11]

Cedecea species.

The genus *Cedecea* includes *C. davisae*, *C. lapagei*, *C. neteri*, and several unnamed species.[2] *Cedecea* was first discovered at the Centers for Disease Control and Prevention (CDC), and its name is derived from the letters CDC. Strains of *Cedecea* spp. have biochemical reactions similar to those of *Serratia*, including lipase positivity and resistance to polymyxin B, but they lack deoxyribonuclease and gelatinase activity.

Cedecea spp. are rare human pathogens, with most infections reported for adults with underlying conditions, including diabetes mellitus, malignancy, heart disease, and chronic renal disease. *Cedecea* has been isolated primarily from the bloodstream, respiratory tract, peritoneal fluid, or associated with soft tissue infections. There are at least 8 reported cases of bloodstream infection (BSI) due to *Cedecea* spp.: *C. davisae* (5), *C. neteri* (2), and *C. lapagei* (1) in a patient with a cement-related chemical burn wound.[6,12–14] Although *Cedecea* spp. have been isolated from the feces of hospitalized children, there are no reported cases of pediatric infection.[15]

Treatment of *Cedecea* infections can be challenging due to antibiotic resistance. Isolates resistant to extended-spectrum cephalosporins, aminoglycosides, and carbapenems have been reported due to AmpC β-lactamases (i.e., class C or group 1) combined with porin deficiency.[6,12,16,17]

Edwardsiella species.

Organisms of the genus *Edwardsiella* are found in freshwater environments and cold-blooded animals, including fish, reptiles, and amphibians, but they occasionally are found in birds and mammals. *E. tarda*, *E. hoshinae*, *E. ictaluri*, and *E. piscicida* are the four recognized species of this genus, but only *E. tarda* has been associated with human disease.[1–6] *Edwardsiella* spp. usually are positive for lysine and ornithine decarboxylase activity, but they yield a negative Voges-Proskauer test result and do not use citrate as a sole carbon source. Most clinical isolates of *E. tarda* produce hydrogen sulfide on *Salmonella-Shigella* agar plates and do not ferment lactose. Further testing is required to exclude *Salmonella* spp.[1–6]

E. tarda is not considered to be part of the normal human intestinal flora because it is recovered in less than 1% of stool samples in colonization studies. Human infections usually result from exposure to the organism in its natural environments.

A variety of human infections due to *E. tarda* are described, but none has been associated with outbreaks or epidemics of disease.[18–26] Infections can be divided into intestinal and extraintestinal forms. Multiple clinical and epidemiologic investigations suggest that *E. tarda* is a true enteropathogen because it is isolated from stool cultures significantly more frequently in people with diarrhea than those who are asymptomatic.[1,2] Intestinal infections due to *E. tarda* usually manifest as acute secretory enteritis associated with consumption of raw seafood or snake flesh or with other aquatic exposures. Although gastroenteritis typically is self-limited, intestinal infections in immunocompromised patients can be severe, and fatal cases of *E. tarda* diarrhea have been described.[26]

Extraintestinal infections include septicemia and meningitis; wound infections such as cellulitis, myonecrosis, and gas gangrene; cholecystitis; peritonitis; intra-abdominal, hepatic, and tubo-ovarian abscesses; prosthetic valve endocarditis; pyogenic arthritis; and osteomyelitis.[1,18–22,27–29] Wound infections are the most important *E. tarda* infections and usually occur after local trauma, such as abrasion, laceration, or penetrating injury. Wound infections also have been associated with aquatic injuries and often represent combined infection with *Aeromonas hydrophila*,[1] although *E. tarda* has been isolated as the sole pathogen in many cases.[27] Invasive infection most commonly occurs in adults with underlying conditions, including hepatobiliary disease, malignancy, and diabetes mellitus. In children, sickle cell anemia has been linked to serious infections due to *E. tarda,* as it has been with *Salmonella* spp.[11,18,28] Osteomyelitis and meningitis have occurred in individuals with hemoglobinopathies and chronic granulomatous disease, and myonecrosis has been reported in an immunocompetent host.[27,30]

Although the precise pathogenesis is unknown, the gastrointestinal tract is presumably the site of *E. tarda* colonization, with invasion leading to BSI and subsequent focal infection. Case reports suggest that *E. tarda* in neonates may be acquired from the mother.[20,29]

E. tarda is commonly resistant to colistin and polymyxin B. In serious invasive infections, combination therapy with an extended-spectrum cephalosporin and an aminoglycoside has been successful. Antibiotic therapy for gastroenteritis due to *E. tarda* usually is not indicated in immunocompetent hosts.

Ewingella americana.

Ewingella americana is the only species in the genus *Ewingella*. Biochemically, this organism is similar to *Pantoea agglomerans*, but it does not use arabinose.[2] Infrequent reports of *E. americana* infections include bacteremia, peritonitis, pneumonia, exacerbation of chronic obstructive pulmonary disease, conjunctivitis, and Waterhouse-Friderichsen syndrome in adults with underlying medical conditions.[6,31] A case of conjunctivitis due to *E. americana* was reported for a 3-year-old immunocompetent child.[32] *E. americana* caused a number of cases of pseudo-BSI due to contamination of blood culture bottles by the use of nonsterile citrated blood collection tubes in a children's hospital.[33] Multidrug resistance has been reported.[31,34]

***Hafnia* species.**

Hafnia alvei was the only named species of the genus *Hafnia*, although organisms currently classified as *H. alvei* can be separated into three distinct genospecies.[35] A new species, *Hafnia paralvei,* was created for the former members of *H. alvei* genogroup.[2] Both species can be isolated from clinical specimens, but *H. alvei* is likely more toxigenic.[1,36] Unlike *E. tarda, H. alvei* is found commonly in feces of humans and animals, in sewage, and in soil. Several reports suggest that *H. alvei* is one of the most frequently recovered members of the family Enterobacteriaceae in the human gastrointestinal tract. Organisms can be recovered on routine enteric media such as MacConkey agar and appear as colorless colonies similar to *Salmonella* or *Shigella* spp.[2] *H. alvei* also appears similar to *E. coli* O157 on sorbitol-MacConkey agar because both organisms commonly are D-sorbitol negative and appear as colorless colonies. *H. alvei* is lysine decarboxylase and ornithine decarboxylase positive and is positive in the Voges-Proskauer test.[3]

H. alvei is an uncommon cause of human infection, and its role remains unclear in many cases because it is often recovered concomitantly with more virulent organisms. It has been implicated as a cause of gastroenteritis in adults and children, but the evidence is not convincing.[35] Extraintestinal infections include BSI, meningitis, UTI, keratitis, endogenous endophthalmitis, wound infection, intra-abdominal abscess, and empyema in immunocompromised patients, although infection has been reported in immunocompetent hosts.[37–42] In a case of chorioamnionitis and preterm birth, *H. alvei* was detected by 16S rDNA sequencing from a vaginal specimen.[43]

Most infections in adults are healthcare related and associated with underlying medical conditions. Reports of extraintestinal infections in children between 7 days and 13 years of age include bacteremia, meningitis, UTI, and hepatic abscess after liver transplantation.[41,42,44] In contrast to adults, many children with *H. alvei* infections did not have identifiable comorbidities.[42] *H. alvei* can harbor chromosomal AmpC β-lactamases.

Kluyvera **species.**

The genus *Kluyvera* includes four species: *K. cryocrescens, K. ascorbata, K. georgiana,* and *K. cochleae. Kluyvera* spp. are phenotypically similar to *E. coli* but are citrate positive.[2] Found in water, soil, sewage, and healthcare environments, most human infections result from *K. ascorbata*.[45] Reports of *Kluyvera* infections in children describe a range of clinical presentations, including UTI, BSI (including catheter-associated infections), diarrhea, peritonitis, neonatal meningitis and sepsis, skin and soft tissue infection, pneumonia, and emphysematous gastritis.[45–47] *Kluyvera* spp. also have been implicated in opportunistic infections of immunocompromised patients, specifically diarrheal disease in adults with neutropenia.[45]

Chromosome-encoded genes in *Kluyvera* spp. are thought to be the progenitors of CTX-M enzymes, which are plasmid-mediated, extended-spectrum β-lactamases of growing concern for infections caused by Enterobacteriaceae.[48] A multidrug-resistant *K. ascorbata* causing septicemia and a *Klebsiella pneumoniae* carbapenemase (KPC)–producing *K. georgiana* causing pneumonia have been described.[49,50]

Leclercia adecarboxylata**.**

L. adecarboxylata was previously known as *Escherichia adecarboxylata* on the basis of its similarity to *E. coli* but with negative decarboxylase reactions.[2] *Leclercia* has been isolated from environmental sources, including food and water.[51] In immunocompetent and immunocompromised adults, *Leclercia* has been recovered from various sites, including blood, wounds, peritoneal fluid, synovial fluid, and a dental and parapharyngeal abscess.[52,53] In many cases, *Leclercia* was a component of mixed bacterial growth.[53] A few reports of skin and soft tissue infections were water related, including fresh and salt water.[54]

Reports of *Leclercia* infections in children are rare and include BSI, neonatal sepsis, cellulitis, and a peritoneal dialysis-related infection.[55,56] BSI with an extended-spectrum β-lactamase–

producing *L. adecarboxylata* was reported.[57]

Leminorella species.

The genus *Leminorella* contains *L. grimontii*, *L. richardii*, and possibly a third unnamed species.[2] Most human isolates have been recovered from feces and urine. The role of these organisms as primary human pathogens is unclear, but several healthcare-associated infections have been reported, including urinary tract, skin and soft tissue, and surgical site infections, as well as bacteremia and peritonitis.[6,58,59] In one study, *Leminorella* isolates were variably susceptible to antibiotics, including the extended-spectrum cephalosporins and β-lactam/β-lactamase inhibitor combinations; imipenem and amikacin showed the most activity.[58] *Leminorella* isolates harboring extended-spectrum β-lactamases also have been described.[60]

Moellerella wisconsensis.

The genus *Moellerella* contains one species: *M. wisconsensis*.[2] Isolates have been recovered primarily from stool and mainly from people in the state of Wisconsin, including patients with diarrhea, but the enteropathogenicity of *Moellerella* is not clear.[61] Of the few reports of *Moellerella* infections, most were isolated from patients with acute cholecystitis.[61,62] Additional isolates were recovered from blood, bronchial aspirates, and wounds.

Photorhabdus species.

The genus *Photorhabdus* consists of at least three species, but only *P. asymbiotica* has been isolated from humans.[2] *Photorhabdus* spp. live symbiotically in the intestinal lumen of various nematodes and can infect insects. Colonies can have a yellow pigment and are bioluminescent when viewed in a darkened room.

Human infection with *P. asymbiotica* typically involves a primary skin focus (e.g., subcutaneous nodule, ulcer, wound) .[63] *Photorhabdus* organisms have been isolated from soft tissue abscesses, skin biopsies, blood, and sputum. Some infections have relapsed and required prolonged antimicrobial therapy.[63,64]

Rahnella species.

The genus *Rahnella* consists of one primary species, *R. aquatilis*, and at least two additional genospecies.[65] *R. aquatilis* is found in the environment primarily in water.[66] In humans, *R. aquatilis* has been isolated from blood, urine, a burn wound, and a bronchoalveolar lavage specimen. Most infections occur in patients with immunocompromising or other chronic medical conditions.[66] *R. aquatilis* septicemia in a premature infant has been reported.[67] Rahnellae produce β-lactamases but usually are susceptible to extended-spectrum cephalosporins and other antibiotic classes active against Enterobacteriaceae.[66]

Tatumella species.

The genus *Tatumella* is closely related to *Pantoea*.[68] Until recently, only *T. ptyseos* was described in human specimens, but a new species isolated from a patient with cystic fibrosis was reported with the proposed name *T. saanichensis* sp. nov.[69] Most human isolates are from the respiratory tract, but a few have been from BSIs.[70,71] A *T. ptyseos* isolate resistant to imipenem was recovered from an intravenous central line in an adult.[70]

Trabulsiella species.

The genus *Trabulsiella* contains *T. guamensis* and *T odontotermitis*.[72,73] *Trabulsiella* resembles *Salmonella* spp. biochemically because it is positive for hydrogen sulfide production and lysine and ornithine decarboxylase activity (arginine varies). *T. guamensis* has been recovered from soil and human stool, but its clinical significance is unknown.[73]

Yokenella regensburgei.

Y. regensburgei, formerly called *Koserella trabulsii*, is biochemically similar to *H. alvei* but is citrate positive.[74] In the environment, *Y. regensburgei* has been isolated from well water, salads, insects, and reptiles.[75] Rare reports of *Y. regensburgei* infections in adults include BSI, suppurative arthritis, and skin and soft tissue infection.[75,76] *Y. regensburgei* also has been isolated from sputum, urine, and feces.[77]

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Key Points

Less Commonly Encountered Enterobacteriaceae

Microbiology

- Advances in molecular diagnostic techniques have identified new species of Enterobacteriaceae that were previously classified as atypical members of other recognized species.

- Susceptibility testing should produce reliable in vitro results for these strains when standardized methods are used.

Epidemiology

- Some organisms are known to cause human infections (e.g., *Edwardsiella*), whereas the roles of other organisms are unclear (e.g., *Trabulsiella*).

- Many published reports have described infections in those with immunocompromising or chronic medical conditions, although infections can occur in previously healthy people individuals.

Clinical Manifestations

- A wide range of clinical manifestations for these species has been described, often limited to case reports.

Treatment

- Optimal treatment varies by species and should be based on susceptibility testing and clinical considerations, including agents and regimens typically used against Enterobacteriaceae.

- Isolates of some species harbor resistance genes such as *ampC* (e.g., *Cedecea*), extended-spectrum β-lactamases (e.g., *Leclercia*), and carbapenemases (e.g., *Kluyvera*).

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Plesiomonas shigelloides

Shai Ashkenazi

Plesiomonas shigelloides is a common inhabitant of surface water and fish. It causes acute gastroenteritis, mainly in travelers to tropical regions, and uncommonly severe extraintestinal infections in children.[1–6]

Description of the Pathogen

P. shigelloides is the only species in the genus *Plesiomonas*. Based on phenotypic characteristics, *P. shigelloides* was classified in the Vibrionaceae family.[4] However, sequence analysis indicates its phylogenetic ancestry is more closely aligned with the tribe Proteaceae in the Enterobacteriaceae family.[7]

P. shigelloides are facultative anaerobic, gram-negative rods, which are motile using a polar flagellum. Some isolates of *P. shigelloides* share the capsular O antigen with that of *Shigella sonnei*. *P. shigelloides* are oxidase, indole, and catalase positive. They also are ornithine, lysine, and arginine decarboxylase positive.

P. shigelloides grow well on traditional enteric media, including MacConkey, Hektoen enteric deoxycholate citrate (Leifson), and *Salmonella-Shigella* agars. Growth is enhanced when inoculated on selective media, such as trypticase soy broth with ampicillin.[3] *P. shigelloides* produces gray, nonhemolytic colonies after 18 to 24 hours of incubation at 37°C; optimal growth occurs at temperatures of 40°C to 44°C.[3]

Pathogenesis

P. shigelloides is epidemiologically associated with gastroenteritis, particularly in the first 2 years of life. However, when fed to adult human volunteers, the bacteria does not cause diarrhea.[8,9] In vitro and in vivo studies suggest low pathogenicity.[10] Clinical manifestations of gastroenteritis suggest enteroinvasion as a possible mechanism of disease. However, *P. shigelloides* yields negative or variable results by most standard assays of invasiveness.[3,9–11] DNA probes for virulence genes of *Shigella* spp. and enteroinvasive *Escherichia coli* also are negative.[9,11]

Mutant studies have documented a crucial role of the lipopolysaccharide in pathogenicity through resistance to complement and adhesion to and invasion of some eukaryotic cells.[12] *Plesiomonas* does not produce an enterotoxin; cytotoxin production has been demonstrated in some strains.[9,11,13] A high-molecular-weight plasmid has been identified in most strains of *P. shigelloides,* but its role in the pathogenesis of diarrhea has not been determined.[10] Investigations have demonstrated pronounced cell adhesion of *P. shigelloides* clinical isolates, a characteristic not observed in environmental isolates.[14]

It is unclear whether some strains are virulent but others are nonpathogenic or whether there is age- and immunity-related susceptibility. In a case-control study of childhood diarrhea in Bangladesh, *P. shigelloides* was isolated with similar frequency from stool specimens in cases and controls, but it was not isolated in nondiarrheal patients in China.[1,15]

Epidemiology

P. shigelloides was isolated from 3% of outpatients with acute diarrhea in China and was the only pathogen isolated from 2%.[1] Its natural reservoirs are water and fish in temperate and tropical regions. Humans are infected with *P. shigelloides* after ingestion of contaminated food or water or through contact with colonized animals.[16] *Plesiomonas* colonizes the gut of various animals and has been isolated from cats, dogs, pigs, cows, snakes, newts, fish, shellfish, monkeys, and vultures; molecular studies suggest that *P. shigelloides* can be zoonotic.[17] Although *Plesiomonas* has been identified in about 1% of tropical fish tanks, aquarium-associated illness is rare.

Occupations associated with an increased risk of *P. shigelloides* infection include veterinarians, aqua culturists, fish handlers, and zoo keepers.[3] *P. shigelloides* can be isolated from stools of patients with gastroenteritis who reside in tropical and subtropical regions of Africa, Asia, and Australia.[3] Asymptomatic carriage of *P. shigelloides* in humans living in developed countries is uncommon. The organism has been isolated from coastal waters of the Gulf of Mexico and has been implicated as a cause of diarrhea in travelers to Mexico and the Caribbean. In the United States and Europe, most cases of gastroenteritis are associated with travel to tropical areas or with consumption of raw oysters or shellfish.[3]

Clinical Manifestations

After an incubation of 1 to 4 days, acute gastroenteritis is the most common clinical presentation.[1–3] About 70% of gastroenteritis due to *P. shigelloides* is associated with an underlying illness or identifiable risk factor, such as travel or consumption of raw seafood.[1,3,4] The clinical presentation varies; symptoms include abdominal cramps, dehydration, fever, headache, vomiting, and diarrhea, which usually last for a few days.[1,2] A study from Bangladesh suggests that diarrhea primarily occurs in the first 2 years of life. Most illness (84%) manifests with acute watery diarrhea, although dysenteric disease (16%) and persistent diarrhea (13%) lasting more than 2 weeks also occur. A Canadian study documented persistent symptoms (>2 weeks in 76%, >4 weeks in 32%), mostly in people who recently had traveled, been exposed to seafood, or had contact with contaminated water. However, the high frequency of persistent symptoms may reflect selection biases.

Extraintestinal manifestations are rare but include bacteremia, meningitis, osteomyelitis, septic arthritis, cellulitis, endophthalmitis, proctitis, peritonitis, pseudoappendicitis, pancreatitis, and cholecystitis.[1,2,5,6,18–23] Underlying illnesses associated with extraintestinal infections include immunodeficiency, sickle cell disease, and cirrhosis and other hepatic diseases.[1,2] *P. shigelloides* keratitis due to a laceration has been reported.[24] There are cases of early-onset neonatal septicemia and meningitis.[4,15,17] The mortality rate is high when extraintestinal infection occurs. For neonates with meningitis, the mortality rate can be greater than 80%.

Diagnosis

Isolation of the organism after growth in appropriate medium is essential for the diagnosis of *P. shigelloides.* Clinical laboratories sometimes underrecognize the organism because up to 30% of clinically significant isolates ferment lactose. If an oxidase test is not performed, these lactose-fermenting isolates can be misidentified as normal enteric flora. When *P. shigelloides* is being considered on the basis of foreign travel or ingestion of raw seafood or untreated water, an oxidase test should be performed. Selective media also can be used. *P. shigelloides* is isolated readily from normally sterile body fluids in cases of extraintestinal infection.

Treatment

Acute Gastroenteritis

Because *P. shigelloides*–associated gastroenteritis is usually self-limited, replacement of fluid and electrolyte losses is the main treatment. The need for antimicrobial therapy is controversial because the disease is usually self-limited. In some studies, antimicrobial therapy appears to shorten the duration of illness, but a case-control study of Thai children found no difference in the duration of diarrhea in treated and untreated groups.[25] Antimicrobial therapy is recommended for gastroenteritis in children with underlying conditions. *P. shigelloides* are usually resistant to penicillins (by β-lactamase production) and sometimes to trimethoprim-sulfamethoxazole, but they are usually susceptible to cephalosporins, amoxicillin-clavulanate, carbapenems, and fluoroquinolones.[1,4,26,27] When antimicrobial therapy for *Plesiomonas*-gastroenteritis is indicated, the recommended empiric agent is ceftriaxone (50 mg/kg once daily for 5 days).

Extraintestinal Infections

Intravenous antibiotic therapy is recommended for children with extraintestinal infections. It should be guided by local susceptibility data and then by the individual isolate because there is considerable variation in antimicrobial susceptibility. Empiric therapy with an extended-spectrum cephalosporin is reasonable because isolates typically are susceptible in vitro and because of good penetration into the cerebrospinal fluid.[1,4,26,27]

Key Points

Epidemiology, Clinical Manifestations, and Management of *Plesiomonas shigelloides* Infection

Epidemiology

- Natural reservoirs are fresh water and fish in temperate and tropical regions.
- Infections usually are associated with travel to tropical areas or consumption of raw seafood.

Clinical Features

- Incubation period: 1 to 4 days
- Typical illness: acute onset of diarrhea (sometimes with blood or mucus), with nausea, vomiting, abdominal cramps, and sometimes fever
- Extraintestinal manifestations: bloodstream and focal infections (rare, occurring mainly in neonates or children with chronic underlying conditions)

Management

- Mainstay is replacement of fluid and electrolyte losses, preferably by oral rehydration.

- Antimicrobial therapy is recommended for extraintestinal infections and for acute gastroenteritis in children with underlying conditions.
- Most strains produce β-lactamase, but they are susceptible to cephalosporins, amoxicillin-clavulanate, carbapenems, and fluoroquinolones.
- Recommended empiric antibiotic therapy usually is a third-generation cephalosporin.

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Proteus, Providencia, and *Morganella* Species

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Microbiology and Epidemiology

Organisms belonging to the genera *Proteus, Providencia,* and *Morganella* are phylogenetically related members of the family Enterobacteriaceae and often referred to as the Proteeae. All members of these genera have phenylalanine deaminase activity, and most have urease activity and motility. Organisms can be isolated readily in the laboratory on enriched media, such as blood and chocolate agars, and on gram-negative selective media, such as MacConkey agar, on which they appear as colorless colonies because they do not use lactose.[1–5] Identification of these species can be successfully achieved by the use of proteomic methods such as matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) mass spectrometric analysis.[6]

There are at least five named *Proteus* species and several unnamed genospecies. The named species include *P. mirabilis, P. vulgaris, P. penneri, P. hauseri,* and *P. myxofaciens.* The two species of primary human clinical significance are *P. mirabilis* and *P. vulgaris.* Both species produce hydrogen sulfide and swarm on noninhibitory agar medium. *P. mirabilis* is positive for ornithine and negative for indole production, whereas *P. vulgaris* is negative for ornithine but positive for indole. *P. penneri* is a species that accommodates indole-negative, genetically distinct variants of *P. vulgaris.*

There are five named *Providencia* species, including four that produce indole: *P. stuartii, P. rettgeri, P. alcalifaciens,* and *P. rustigianii. P. stuartii* and to a lesser extent *P. rettgeri* are the two species of primary human significance. *Providencia* species can be differentiated from *Proteus* species and *M. morganii* based on their ability to use citrate as the sole carbon source and to ferment D-mannitol. *M. morganii* is the only *Morganella* species, which has subspecies *morganii* and *sibonii. M. morganii* usually is positive for indole, urea, and ornithine.[1–5]

Proteus, Providencia, and *M. morganii* are found in the natural environment in soil and water and in environmental sources in healthcare facilities. They are normal flora in the gastrointestinal tract of humans, other mammals, and birds.[1,5] These organisms can colonize the skin and respiratory mucosa of hospitalized patients and healthcare personnel and can be transmitted to other patients. Members of all three genera also commonly colonize reptiles and fish.

Investigations of pathogenic mechanisms of these organisms have focused on *P. mirabilis* as an agent of urinary tract infection (UTI). Virulence factors that appear to contribute to pathogenicity include motility, production of fimbrial proteins, and other factors that facilitate attachment to uroepithelial cells.[5] Other studies have demonstrated the ability of *Providencia* spp. to attach to and invade human cells in tissue culture and implicated these organisms as agents of gastroenteritis, including travelers' diarrhea.[5]

P. mirabilis causes most cases of infection due to members of the *Proteus, Providencia,* and *Morganella* genera and is considered primarily a community-associated pathogen. Other members of these genera often are isolated in healthcare-associated infections (HAIs), such as UTIs, burn wounds, and bloodstream infections (BSIs). *P. mirabilis* was the cause in 4% of HAIs at major centers in the National Nosocomial Infections Surveillance System from 1986 to 1989. *Proteus* spp. accounted for 3% of healthcare-associated UTI in children and frequently was associated with indwelling bladder catheters.[7] Wound infections due to *Proteus* spp. have occurred after surgical procedures (e.g., spinal fusions, myocutaneous flap surgery in patients with spinal injury), animal bites, burns, and with decubitus ulcers.[5,8–11]

Clinical Manifestations

P. mirabilis is the third most frequent agent of UTI in childhood after *Escherichia coli* and *Klebsiella* spp.[12,13] In one series of primary UTI in males, *P. mirabilis* replaced *E. coli* as the most prevalent pathogen.[14] *Proteus* spp. also frequently cause recurrent UTIs. The urease enzyme produced by *P. mirabilis* and related bacteria hydrolyzes urea in the urine, forming ammonium hydroxide. This reaction increases urinary pH, which is toxic to renal cells and promotes precipitation of inorganic and organic compounds, leading to the formation of struvite stones.[15] These stones can act as foreign bodies, rendering infections difficult to eradicate and promoting reinfection. Recovery of *Proteus* spp. from urine should alert the physician to the possibility of urolithiasis.

Toxic encephalopathy due to a high serum concentration of ammonia has been reported as a complication of *P. mirabilis* and *P. rettgeri* UTI in children with prune belly syndrome.[16,17] Xanthogranulomatous pyelonephritis, most commonly due to *E. coli* and *P. mirabilis,* is a rare type of chronic pyelonephritis that can be mistaken for Wilms tumor.[18] This diagnosis should be considered for a child with a renal mass, hematuria, anemia, and leukocytosis, and it can be associated with urinary tract obstruction and nephrolithiasis.

Proteus, Providencia, and *Morganella* spp. have been recovered from children with a variety of infections other than UTIs, including chronic suppurative otitis media.[19] *P. mirabilis* is the third most common organism recovered from cultures of ear drainage in children with tympanostomy tubes; *Pseudomonas aeruginosa* and *Staphylococcus aureus* are recovered more commonly.[20] Intracranial and extracranial complications due to *P. mirabilis* have been associated with mastoiditis and chronic otitis media.[21,22] *Proteus* spp. have been reported as a cause of folliculitis, pneumonia, BSI, sacroiliitis, and meningitis; hepatic, pulmonary, renal, and splenic abscesses; osteomyelitis in patients with sickle cell anemia; sinusitis in neurologically impaired children; soft tissue or wound infections complicating trauma, burns, surgical procedures, and skin lesions associated with Buruli ulcers, cutaneous leishmaniasis, and hidradenitis suppurativa; necrotizing fasciitis associated with omphalitis; spinal cord abscess complicating a dermal sinus; and brain abscess as a complication of neonatal meningitis and after neurosurgical procedures.[5] Many of these infections occur in neonates and immunocompromised hosts.

In a 21-year review by Unhanand and colleagues, *P. mirabilis* was the cause of gram-negative meningitis in 3 (6%) of 49 term infants and in 1 (6%) of 18 infants who were 1 to 3 months old.[23] *Proteus* spp. also have been associated with pump pocket infections in patients receiving intrathecal baclofen for spasticity.[24] Neonatal infections, including early- and late-onset septicemia, meningitis, and brain abscess, have been attributed to *M. morganii*.[5,25,26] *Proteus* spp. and *M. morganii* can secrete the enzyme L-histidine decarboxylase, which can convert the free amino acid histidine, found in muscle tissue of certain fish (e.g., tuna, mahi-mahi, bonito, mackerel, sardine), into histamine. This occurs in improperly stored fish and can lead to scombroid poisoning with an anaphylactic-like syndrome after human consumption.[5]

In Brazil, Jorge and coworkers described the microbiology of abscesses due to *Bothrops* spp. snake bites and found *M. morganii* in 23 (58%) of 40 and *P. rettgeri* in 7 (18%) of 40 abscesses; 16 (40%) of 40 cases were polymycrobial.[27] *Providencia* spp. are recovered occasionally from patients with chronic otitis media or infected burn wounds and rarely from patients with meningitis. It also can be responsible for diarrhea (especially *P. alcalifaciens*).[28–30] When recovered from the urinary tract, *Providencia* spp. typically are found in the setting of an underlying structural, physiologic, or neurologic abnormality (e.g., neurogenic bladder).[5]

Treatment

Treatment of infections due to these organisms can be difficult because of frequent antimicrobial resistance. Although most isolates of *P. mirabilis* remain susceptible to ampicillin, first-generation cephalosporins, and trimethoprim-sulfamethoxazole (TMP-SMX), plasmid-mediated resistance to penicillins and cephalosporins due to β-lactamases is becoming more common.[31,32] *P. mirabilis* is resistant intrinsically to nitrofurantoin, a characteristic useful for identification.

The indole-producing members of the Proteeae, including *Proteus vulgaris, Providencia* spp., and *M. morganii,* typically are resistant to ampicillin and cefazolin, as is the indole-negative species *Proteus penneri*. Historically, third- and fourth-generation cephalosporins, aztreonam, piperacillin-tazobactam, carbapenems, fluoroquinolones, and TMP-SMX usually were active.[5,33–35]

Worldwide, there are increasing reports of resistance to TMP-SMX and fluoroquinolones among *P. mirabilis* and *M. morganii* recovered from hospitalized patients, with resistance rates for *P. mirabilis* of 16% and 15% and for *M. morganii* of 25% and 22% to TMP-SMX and fluoroquinolones, respectively; higher resistance rates were associated with overuse of these agents.[5,35] *P. mirabilis* urine isolates from pediatric outpatients and inpatients retain similar susceptibility patterns for ampicillin, first-generation cephalosporins, and TMP-SMX.[36]

Extended-spectrum β-lactamase (ESBL)–producing strains of *P. mirabilis* and other species of the Proteeae can cause infections in children.[37–39] Healthcare-associated outbreaks have occurred due to strains of *P. mirabilis* that have acquired plasmid AmpC-type β-lactamases similar to the chromosomal AmpC enzymes found in *Enterobacter cloacae* and other Enterobacteriaceae.[40] Most isolates of *M. morganii* carry genes coding for AmpC-type β-lactamase enzymes. A neonate with early-onset *M. morganii* sepsis developed persistent ventriculitis due to emergence of a cefotaxime-resistant variant as a result of derepression of its AmpC β-lactamase.[41] Combination therapy with meropenem, ciprofloxacin, and gentamicin resulted in a microbiologic cure. Use of third-generation cephalosporins as monotherapy should be reconsidered when treating serious infections due to organisms known to harbor AmpC β-lactamases (see Chapters 138 and 140).

The activity of aminoglycosides against the Proteeae varies, with amikacin tending to have the most reliable activity. When infection with one of these organisms is suspected, initial empiric treatment regimen for serious infection should include meropenem and amikacin. For infection of the central nervous system, a minimum of 2 weeks of antibiotic therapy is recommended after documented cerebrospinal fluid (CSF) sterilization. Drainage of brain abscesses may be required, but resolution of smaller abscesses after antibiotic therapy alone has been reported. Specific therapy should be guided by the results of definitive identification and susceptibility testing (see Chapter 46).

Gram-negative bacillary otitis externa can be treated effectively with topical ofloxacin otic solution.[42,43] A 7- to 10-day course of antibiotics usually is adequate for treatment of uncomplicated UTI; removal of an indwelling urinary catheter hastens eradication. Otherwise, failure to eradicate the bacteria should alert the physician to the possibility of urolithiasis or a structural anomaly. Stone removal or surgical correction of an obstruction often is required for a cure.

Key Points

Diagnosis and Management of *Proteus, Providencia,* and *Morganella* Infections

Microbiology

- Members of the Enterobacteriaceae family; these catalase-positive, oxidase-negative, gram-negative bacilli are non–lactose fermenting on MacConkey agar.
- Grow well on blood, chocolate, and MacConkey agars
- *Proteus spp.* swarm on blood agar media.
- *Proteus mirabilis, Proteus vulgaris, Providencia stuartii, Providencia rettgeri,* and *Morganella morganii* are the species. Susceptibility testing performed by automated and manual methods is standard. Most commonly associated with human infection.

Epidemiology

- Normal enteric flora but also found in environmental soil and water
- Can be found in environmental sources of healthcare facilities

Clinical Importance

- Urinary tract infections and occasional cause of chronic ear drainage
- Secondary infections of traumatic wounds, burns, and operative sites
- Neonatal sepsis or meningitis
- *Proteus* spp. and *M. morganii* associated with scombroid fish poisoning

Treatment

- *Proteus mirabilis*: usually susceptible to ampicillin, first-generation cephalosporins, fluoroquinolones, and trimethoprim-sulfamethoxazole; resistant to nitrofurantoin
- Indole-positive Proteeae, including *P. vulgaris, Providencia spp.,* and *M. morganii* are resistant to ampicillin and first-generation cephalosporins but usually susceptible to piperacillin-tazobactam, third- and fourth-generation cephalosporins, and carbapenems.
- Empiric therapy for serious infections with carbapenem and amikacin is considered effective against extended-spectrum β-lactamase (ESBL)– and AmpC β-lactamase–producing *Proteus*; fourth-generation cephalosporin can be used to treat infection due to AmpC β-lactamase–producing organisms.
- Otitis externa usually can be treated with a topical fluoroquinolone.

Duration of Therapy

- Uncomplicated urinary tract infection (UTI): 7- to 10-day course usually adequate; removal of a catheter hastens eradication
- Central nervous system infection: minimum of 2 weeks after documented cerebrospinal fluid bacteriologic sterilization

Special Considerations

- Recovery of *P. mirabilis* from urine should alert to the possibility of urolithiasis (i.e., struvite stones).

- Hyperammonemia with encephalopathy has been reported in prune belly syndrome with *P. mirabilis* and *P. rettgeri* UTI.

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Serratia Species

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Microbiology

The genus *Serratia,* family Enterobacteriaceae, contains at least 15 species. *Serratia marcescens* is the primary pathogenic species in humans, but a few cases of human infections are caused by *S. liquefaciens*, *S. rubidaea*, *S. plymuthica*, *S. odorifera*, *S. ficaria*, and *S. fonticola*, which are diverse groups containing several biogroups based on DNA hybridization analyses.[1–4]

The facultatively anaerobic, motile, gram-negative bacilli are recovered readily in the laboratory on enriched, nonselective and selective enteric agar. Strains of *S. rubidaea*, *S. plymuthica,* and *S. marcescens* (more frequent in environmental than in hospital-acquired samples) commonly produce the red pigment prodigiosin and are red colored. Most human isolates of *Serratia* spp. do not ferment lactose (and therefore appear as colorless colonies on the enteric agars), but they reduce nitrate to nitrite, are catalase positive and cytochrome oxidase negative, and ferment glucose and a number of other sugars.[5]

S. marcescens and the other *Serratia* spp. do not produce many virulence factors. Hydrolytic enzymes, including gelatinase, lipase, and DNAse, are commonly produced, an uncommon property somewhat among the Enterobacteriaceae. These and other extracellular enzymes may be virulence factors that promote tissue invasion. The most important biochemical tests for differentiating among *Serratia* spp. are the finding of lysine and ornithine decarboxylase and acid production from several sugars.[1–4]

Epidemiology

Because *Serratia* spp. are not a common component of human fecal flora, human infections are thought to result from environmental contamination. *Serratia* [6] can survive in harsh settings, including disinfectants, which can serve as the initial source for an outbreak.[6] Most infections have been associated with hospital outbreaks.[5] In neonatal intensive care units (NICUs) or pediatric intensive care units (PICUs), outbreaks have been associated with contaminated milk[7], parenteral nutrition or medication,[8] liquid soap,[12] tap water, or hospital equipment, and further dissemination has occurred through the hands of healthcare personnel.[3,6–14] Additional risk factors include the use of intravenous or urinary catheters, ventilator treatment, long duration of hospitalization, previous antibiotic therapy, and underlying conditions such as birth weight less than 1500g, prematurity, diabetes mellitus, and altered host immunity.[15–17]

In a national point-prevalence survey of PICU-acquired infections, *S. marcescens* was the 10th ranked organism, accounting for 2% of all PICU-acquired infections.[18] In a review of 276 NICU outbreaks that occurred in different parts of the world, *Serratia* spp. accounted for 12% of outbreaks, was the third most common pathogen, and had a mortality rate up to 7.7%.[19] In an outbreak setting, genotyping of the isolates by pulse field electrophoresis or polymerase chain reaction (PCR)–based methods should be performed.[5,15] Consecutive outbreaks occurring over 3 to 10 years in the NICU have been associated with different clones that were circulating for long periods.[5,20,21]

The most common sites for colonization are the respiratory and gastrointestinal tract in infants and the respiratory tract in adults.[25] Prolonged colonization can occur, particularly in immunocompromised hosts.[22]

Clinical Manifestations

Nosocomial Infections.

In neonates, the symptoms and signs of sepsis or meningitis due to *S. marcescens* are indistinguishable from those caused by other pathogens, but the mortality rate can be as high as 44%.[16,23,24] Neonatal meningitis can occur in 11% to 25% of infants with *S. marcescens* bloodstream infections (BSIs), and up to 50% of cerebrospinal fluid (CSF) specimens can have a normal cell count and glucose level, whereas the protein concentration usually is elevated.[16,25] In a study involving almost 9000 infants discharged from 333 NICUs, isolation of *S. marcescens* (and *S. pneumoniae*) from CSF showed the highest concordance with blood compared with other pathogens in infants with (22%) or without (10%) ventriculoperitoneal shunt infections.[25]

Meningitis can develop while on therapy for sepsis and can be associated with ventriculitis, hydrocephalus, or brain parenchyma destruction. These processes can lead to loculated areas of infection or cyst formation, similar to infections caused by *Enterobacter sakazakii* and *Citrobacter* spp. Serial neuroimaging studies should be performed during therapy.[26] Most survivors are neurologically impaired.[25]

In children, *S. marcescens* is associated with BSI, pneumonia, urinary tract infection (UTI), meningitis with or without brain abscess, bone and joint infection,[27] ocular infection, intra-abdominal infection (including peritonitis in patients undergoing dialysis),[28] and wound infection (including surgical site infection).[15,16,27,28] Although uncommon, necrotizing fasciitis due to *S. marcescens* in previously healthy children has been reported.[29,30] In older children and adults, isolation of *Serratia* spp. invariably is associated with an indwelling catheter and instrumentation (e.g., tracheostomy, ventilator use, bronchoscopy), causing UTIs and nosocomial pneumonia.[5,31] Endocarditis is mainly diagnosed in intravenous drug users. *S. marcescens* and *Serratia* spp. also are responsible for a large proportion of eye infections, including keratitis, corneal ulcers, conjunctivitis, and endophthalmitis.[32,33] The latter is associated with poor outcomes and can lead to complete visual loss.[34]

Community-Acquired Infections.

Serratia infections acquired in the community can occur in children with chronic granulomatous disease (CGD) and may represent the sentinel infection that leads to the diagnosis of this disorder. The estimated incidence of *Serratia* infections in CGD patients is up to

0.98 cases per 100 patient-years, with a recurrence rate of 18%. Lymphadenitis and skin abscesses are the most common infections (44%), followed by pulmonary infections (36%) and osteomyelitis (8%).[35] Any child with a community-acquired infection due to a *Serratia* spp., particularly infection of bone or lymph nodes, should be evaluated for CGD.

Treatment

Serratia spp. are intrinsically resistant to ampicillin and amoxicillin with or without β-lactamase inhibitors, first-generation cephalosporins, macrolides, nitrofurantoin, and colistin, but they can be resistant to broader-spectrum antimicrobial agents through different mechanisms of resistance.[5] Treatment of *Serratia* spp. infections can be challenging, and every effort should be made to identify the source in an outbreak setting to limit the spread of the organism by stringent cohorting of cases and aggressive education regarding handwashing by healthcare personnel.[15,36] Infected patients should be monitored for clinical responses during treatment, and if suboptimal or cultures remain positive, susceptibility testing should be repeated and therapy adjusted accordingly.

There are several mechanisms of resistance. First, inducible chromosomal AmpC-type β-lactamases (see Chapter 140) can be expressed at a low level and may not be detected in standard laboratory susceptibility tests. However, the genes coding for these enzymes can be induced or derepressed, leading to high-level enzyme production as early as 3 to 4 days into therapy.[37] Treatment failures using monotherapy with a third-generation β-lactam antibiotic can occur. In the laboratory, resistance to cefoxitin is a good indicator for the detection of AmpC production. Second, *Serratia* spp. less frequently also carries extended-spectrum β-lactamases (ESBLs), which are plasmid encoded.[38,39] Resistance to third-generation cephalosporins can be an indicator of ESBLs in a *Serratia* isolate. Third, carbapenemases have been found to a lesser extent in *S. marcescens,* including serine carbapenemases such as plasmid-borne KPC-type and chromosomal SME-type enzymes and plasmid-borne metallocarbapenemases, including IMP-, VIM-, and NDM-type enzymes.[40–43] Fourth, carbapenem resistance in *S.*

marcescens can be mediated by hyperproduction of AmpC-type β-lactamases along with mutations of outer membrane porin proteins.[44]

The Clinical and Laboratory Standards Institute (CLSI) recommendations for the screening and confirmation of AmpC and ESBL enzymes in *Serratia* spp. are not standard. However, in 2014, CLSI recommended the adoption of the revised susceptibility test breakpoints for the Enterobacteriaceae to more accurately categorize the susceptibility of β-lactamase-producing isolates.[37] Using the revised CLSI breakpoints for carbapenems, 1119 *Serratia* spp. were analyzed. The greatest effect was in the drop in susceptibility to imipenem to 92.9%, but there was no significant change in susceptibility to other carbapenems: ertapenem (98%), meropenem (98.8%), and doripenem (98.8%).[37,38,45]

Antibiotic selection depends on the severity of the infection, ability of the drug to penetrate into the infected areas (especially in the setting of retained material), in vitro susceptibility, and the likelihood of emerging drug resistance during the course of treatment. *Serratia* spp. are susceptible to fluoroquinolones, aminoglycosides, thrimethoprim-sulfamethoxazole, piperacillin-tazobactam, ticarcillin-clavulanate, third- and four-generation cephalosporins, and carbapenems.[46] Nevertheless, source control is the key and may include removal of prosthetic material or invasive devices, and adequate drainage and debridement of infected tissue. For uncomplicated infections (i.e., UTI) in the setting of susceptible isolates, antibiotic monotherapy is warranted. For the treatment of severe infections, empiric treatment should include a carbapenem, an extended-spectrum cephalosporin, or absent central nervous system involvement, an extended-spectrum β-lactam/β-lactamase inhibitor combination plus an aminoglycoside.

A study of hospitalized patients with invasive infections caused by AmpC β-lactamase–producing Enterobacteriaceae showed no differences in the 30-day mortality rate or length of hospital stay for patients who received cefepime versus meropenem.[47] In this study, *Serratia* spp. represented 22% of all isolates, and 15% of them were phenotypically confirmed as Amp-C β-lactamase producers. Cefepime may be a reasonable option for the treatment of invasive *Serratia* infections as long as adequate source control is achieved.[47] For infections with *Serratia* spp. that produce ESBL, a carbapenem remains the drug of choice.

For neonatal meningitis caused by *Serratia* spp., CSF cultures should be performed repeatedly until sterility is confirmed.[24] Therapy should be continued for a minimum of 21 days or for 10 to 14 days after CSF sterility has been documented, whichever is longer. Imaging studies should guide medical and surgical management. Between 4 and 8 weeks of antibiotic therapy may be required for infants with ventriculitis, abscesses, encephalitis, or infarction.

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Key Points

Diagnosis and Management of *Serratia* Infections

Microbiology

- Facultative anaerobic, catalase-positive, gram-negative bacillus
- Of all *Serratia* spp, *Serratia marcescens* is most commonly isolated in human infections.

Epidemiology

- Environmental organism, rarely causes infections in healthy hosts.
- Nosocomial pathogen is mainly associated with outbreaks in neonatal or pediatric intensive care units.
- Children with community-acquired infection should be evaluated for chronic granulomatous disease.

Clinical Manifestations

- Can involve various organ systems
- Urinary tract infection common in older children

Diagnosis

- Organism can be recovered from all sample types using standard culture.
- Genotyping of the isolates should be performed in the setting of an outbreak.

Treatment

- Can harbor various mechanisms of resistance, primarily intrinsic chromosomal AmpC-type β-lactamase, followed by extended-spectrum β-lactamase (ESBL) or carbapenemase.
- For severe infections, empiric treatment should include a carbapenem, an extended-spectrum cephalosporin, or an extended-spectrum β-lactam/β-lactamase inhibitor combination plus an aminoglycoside.

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Salmonella Species

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Nontyphoidal *Salmonella* species are found widely in animals and cause a broad spectrum of clinical infections that include asymptomatic carriage, gastroenteritis, bacteremia, and metastatic focal infections. In contrast, *Salmonella* serotypes Typhi and Paratyphi A are human-specific pathogens that cause typhoid or enteric fever, a protracted febrile illness with myriad manifestations.

Description of the Pathogen

Salmonella species are gram-negative bacilli that belong to the family Enterobacteriaceae. They ferment glucose, reduce nitrate to nitrite, and are oxidase negative. *Salmonella* are indole negative and, with rare exceptions, are motile and lactose negative.

All *Salmonella* organisms are closely related by DNA-DNA hybridization studies. Clinically important *Salmonella* consist principally of a single species, *Salmonella enterica.*[1] Although more than 2500 serotypes of *Salmonella* have been described, fewer than 100 serotypes cause most human infections. Reactions of *Salmonella* with antisera to specific O (somatic) antigens determine the serogroups A, B, C_1, C_2, D, and E; O, H (flagellar), and Vi (capsular) antigenic characterization results in a unique serotype that traditionally has served as a surrogate species designation. The Centers for Disease Control and Prevention (CDC) published guidelines to clarify *Salmonella* nomenclature (Table 146.1).[1]

TABLE 146.1

Salmonella Nomenclature

Complete Name	CDC Designation	Common Clinical Usage (Recommended)
***Salmonella enterica* subsp. *enterica* ser. Typhi**	*Salmonella* ser. Typhi	*Salmonella typhi* (Typhi)
***Salmonella enterica* subsp. *enterica* ser. Paratyphi A**	*Salmonella* ser. Paratyphi A	*Salmonella paratyphi* A (Paratyphi A)
***Salmonella enterica* subsp. *enterica* ser. Typhimurium**	*Salmonella* ser. Typhimurium	*Salmonella typhimurium* (Typhimurium)
***Salmonella enterica* subsp. *enterica* ser. Enteritidis**	*Salmonella* ser. Enteritidis	*Salmonella enteritidis* (Enteritidis)
***Salmonella enterica* subsp. *enterica* ser. Dublin**	*Salmonella* ser. Dublin	*Salmonella dublin* (Dublin)

CDC, Centers for Disease Control and Prevention; ser., serotype; subsp., subspecies.

Modified from Brenner FW, Villar RG, Angulo FJ, et al. *Salmonella* nomenclature. J Clin Microbiol 2000;38:2465.

The pathogenesis of *Salmonella* infections is complex, but it is being unraveled because genome sequencing has provided a complete blueprint of the genetic repertoire for several serotypes of *S. enterica,* including *S.* Typhimurium, *S.* Typhi, and *S.* Paratyphi.[2] Examination of the *S.* Typhi genome has identified up to 10 pathogenicity islands, and comparisons with the *S.* Typhimurium genome have disclosed other smaller *S.* Typhi–specific gene clusters or individual genes. Further studies of virulence genes should enable an understanding, for example, of why *S.* Typhi infects only humans and why the rare animal serotype *S.* Dublin is almost 80-fold more likely to invade the bloodstream than is *S.* Typhimurium.[3]

Most nontyphoidal *Salmonella* do not extend beyond the lamina propria and local lymphatics of the gut, whereas *S.* Choleraesuis and *S.* Dublin rapidly cause bacteremia with little or no intestinal involvement. The quintessential invasive serotype is *S.* Typhi, which can cause intestinal perforation.[2,4–6] On reaching the small intestine, *S.* Typhi adheres to the specialized epithelial M cells overlying Peyer patches. Penetration of the mucosa includes cytokine secretion (e.g., interleukin-8, interleukin-6), uptake by macrophages, and translocation to lymphoid follicles in the gut and the draining lymph nodes. An asymptomatic bacteremia disseminates *S.* Typhi throughout the body, where the bacteria survive and multiply within mononuclear cells of the liver, spleen, and bone marrow. After an incubation period of 7 to 14 days, a sustained secondary bacteremia heralds the onset of symptoms.

Many factors predispose to *Salmonella* infection (Table 146.2). The incubation period, symptoms, and clinical severity vary with the number of organisms ingested. Relative hypochlorhydria and rapid gastric emptying help explain the relative vulnerability of neonates and young infants to symptomatic salmonellosis.[6,7]

TABLE 146.2

Factors Predisposing to *Salmonella* Infection or Dissemination

Site of Defect	Mechanism and Clinical Setting
Gastric acid barrier	Achlorhydria
	Anatomic: gastrectomy, gastroenterostomy
	Functional: ingestion of buffers, vagotomy
	Rapid emptying (neonates, postgastrectomy)
Intestinal mucosal barrier	Inflammatory bowel disease
	Tissue ischemia or infarction (sickle cell anemia, trauma)
Gut flora	Prior antimicrobial therapy (results in increased infection and prolonged carriage)
Opsonins	Sickle cell anemia (defect in alternative complement pathway)
Neutrophils	Chronic granulomatous disease
Cell-mediated immunity	After organ transplantation or with defects associated with acquired immunodeficiency syndrome, infancy, malnutrition, or corticosteroid therapy
	Defects in type 1 helper T-lymphocyte (Th1) functions (interleukin-12 and interferon γ axis), including mutations in the genes for interleukin-12Rβ1 and interleukin-12
Sequestered organisms	Schistosomiasis
	Reticuloendothelial cells (typhoid fever)
	Solid tumors
	Gallbladder disease
Reticuloendothelial system	Overload with hemoglobin or iron (hemolytic anemia as in sickle cell disease, thalassemia, bartonellosis, and malaria) or impaired function due to malignancy such as leukemia or lymphoma

Impaired reticuloendothelial or cellular immune response raises the risk for severe, complicated infection.[7,8] Children with sickle cell disease are prone to septicemia and osteomyelitis when infected with nontyphoidal *Salmonella.* Decreases in phagocytic and opsonizing capacity of patients with sickle cell disease, along with infarcts in the gastrointestinal tract, bones, and reticuloendothelial system, contribute to the high infection rate.

Epidemiology

Nontyphoidal *Salmonella*

Since 2005, between 45,000 and 51,000 cases of culture-proven nontyphoidal salmonellosis have been reported each year in the United States; however, an estimated 1.4 million diarrheal illnesses and 600 deaths annually are attributed to *Salmonella*.[8–12] About one third of cases occur in children younger than 4 years of age, and children in the first few months of life have the highest incidence.

Nontyphoidal *Salmonella* infections have worldwide distribution, with a prevalence that varies according to public health standards, water treatment, sewage disposal, animal exposures, and food-handling practices. More *Salmonella* infections occur during warm summer months in temperate climates. Nontyphoidal *Salmonella* are the most common cause of culture-confirmed foodborne infection in the United States.[12] *S*. Enteritidis and *S*. Typhimurium have been the most commonly identified serotypes in the United States since 1996 (www.cdc.gov/narms).

The Foodborne Surveillance Network (i.e., FoodNet), a collaborative program among state health departments, the US Department of Agriculture, the US Food and Drug Administration (FDA), and CDC, was established in 1996 and has enhanced outbreak recognition by adding pulsed-field gel electrophoresis analyses to traditional serotyping.[9–12]

The major reservoir of nontyphoidal *Salmonella* is the gastrointestinal tract of infected, often asymptomatic birds, mammals, and reptiles. Chickens, turkeys, ducks, sheep, cows, pigs, and various pets, especially turtles, snakes, lizards, iguanas, chicks, ducklings, and hedgehogs, commonly are infected.[13–17] Some serotypes can be isolated from a variety of cold- and warm-blooded animals; others are relatively restricted (Table 146.3). Isolation of an uncommon serotype can suggest a likely source of infection. Illness can result from exposure to pets and animals in public settings and from environmental contamination even without direct contact with an infected animal.[18,19] Handling pet food treats containing dried beef and chicken has caused infections.[20,21] Handwashing after exposure to pets and animals, their food, and environments is essential.

TABLE 146.3

Examples of *Salmonella* Serotypes Associated With Cold-Blooded and Warm-Blooded Animals

Animal Reservoir	Serotypes Isolated
Snake	Arizonae, Montevideo, Eingedi
Iguana	Marina, Montevideo, Poona
Lizard	Poona
Komodo dragon	Enteritidis
Terrapin	Tel-el-kebir
Turtle	Pomona, Chester, Typhimurium, Muenchen, Java
Gecko	Weltevreden, Typhimurium, Enteritidis, Saintpaul, Agama
Crocodile	Typhimurium, Tsevie, Duval, Schwerin, Tinda, Tallahassee
Chicken	Typhimurium, Enteritidis, Heidelberg, Hadar, Montevideo, Thompson, Berta, Livingstone, Virchow
Turkey	Kentucky, Anatum, Heidelberg, Reading, Senftenberg, Saintpaul
Pig	Infantis, Choleraesuis, Typhimurium
Cattle	Dublin, Typhimurium
Hedgehog	Tilene

Salmonella are the leading cause of foodborne outbreaks and outbreak-related hospitalization, and infections are especially common and severe in young children.[12] *Salmonella* serotypes have been isolated from 20% to 75% of fresh or thawed retail poultry samples, and they are found in pork, beef, and frozen egg products. Foods containing raw or undercooked eggs (e.g., Caesar salad, egg-dipped bread, homemade eggnog) can be contaminated. Eggs become contaminated by *Salmonella* that penetrate the egg from the shell surface or from direct transovarian inoculation to the egg yolk. Dairy products also have been incriminated as sources of human infection. *Salmonella* can be killed by heating to 54.4°C for 1 hour or 60°C for 15 minutes, but the organisms remain viable at ambient or reduced temperatures for days to weeks.

The number of bacteria that must be ingested to cause symptomatic disease in healthy adults is 10^6 to 10^8 nontyphoidal *Salmonella* organisms.[22] A smaller inoculum can produce disease in infants and toddlers and when ingested with foods rich in fat (e.g., cheese, chocolate, peanut butter). Nursery outbreaks are a result of several factors, including neonatal susceptibility to low numbers of *Salmonella.* Transplacental infection and perinatal transmission during vaginal delivery have been reported.[23] Healthcare-associated infections have been related to contaminated medical equipment (e.g., endoscopes) and diagnostic or pharmacologic preparations, particularly those of animal origin (e.g., pituitary extracts, bile salts, pancreatic extracts, pepsin, vitamins).

After infection, nontyphoidal salmonellae are excreted in feces for a median of 5 weeks. In infected children younger than 5 years of age, excretion is prolonged. Approximately 40% of these children excrete organisms for 20 weeks after illness. In older children and adults, *Salmonella* excretion lasting more than 8 weeks after infection is uncommon, but antimicrobial therapy may prolong excretion.

Emerging antimicrobial resistance of animal-associated serotypes of *Salmonella* has become an international public health problem, especially in industrialized countries.[24] A zoonotic strain of *S.* Enteritidis known as definitive phage type 104 (DT104) with chromosomal resistance to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline was recognized in the 1990s in the United States and several countries in Europe.[8] Subsequently, clonal spread of fluoroquinolone-resistant DT104 strains from food animals to humans was documented in Denmark.[24] In the United States in 2000 and Canada in 2002, cattle-associated multidrug-resistant strains of *S.* Newport with plasmid-encoded AmpC β-lactamase were isolated from ill children.[25] These ceftriaxone-resistant Newport-MDR AmpC strains were estimated by the CDC to cause more than 20,000 *Salmonella* infections in 2001 alone.[25]

Although most extended-spectrum cephalosporin resistance is attributed to plasmid-encoded AmpC β-lactamases, extended-spectrum β-lactamases have been reported.[26] Fluoroquinolone-resistant, invasive *S.* Choleraesuis strains in Taiwan have spread to humans from pigs, and life-threatening infantile diarrhea has resulted from highly resistant *S.* Typhimurium with mutations in the *gyrA* and *parC* genes.[27,28] These events led to the restriction or prohibition in food animals of fluoroquinolones and other antimicrobial agents used for treating human disease.[24–28]

In the United States, resistance among nontyphoidal *Salmonella* isolates submitted to the National Antimicrobial Resistance Monitoring System (NARMS) has decreased over the past decade. Approximately 3% of nontyphoidal isolates in the United States are resistant to ceftriaxone, and 5% are resistant to more than four antimicrobial agents (http://www.cdc.gov/narms/pdf/2012-annual-report-narms-508c.pdf). Patients with resistant organisms were more likely to have bacteremia and to be hospitalized compared with those with fully susceptible isolates.[29]

The scourge of multidrug-resistant nontyphoidal *Salmonella* has not spared Africa, where unregulated over-the-counter sale of antimicrobial agents rather than use in animals has fueled resistance.[30] Over the past decade, increasing resistance encoded on large, self-transferable plasmids has been documented in 30% to 80% of *S.* Typhimurium and *S.* Enteritidis cases, which account for almost 80% of the nontyphoidal *Salmonella* isolated from blood, feces and cerebrospinal fluid in Kenyan studies.[30]

Salmonella Typhi

The worldwide disease burden of typhoid and paratyphoid fever is estimated to approach 27 million illnesses, with up to 600,000 deaths yearly.[6,31] The impoverished and children suffer disproportionately, especially in south central and southeast Asia and southern Africa.[32] About 300 cases of typhoid fever are reported annually in the United States; almost 80% occur in travelers to or visitors from highly endemic areas, especially the Indian subcontinent, and children account for about 40% of cases.[33]

Because *S.* Typhi and Paratyphi A have no animal reservoir, fecal contamination of food or drink by ill, convalescing, or asymptomatically infected people accounts for most cases of enteric fever. Infection by person-to-person contact is thought to be rare, but sexual transmission has been documented.[34] The inoculum required for *S.* Typhi varies between 1000 and 1 million organisms, which is about 1000-fold lower than that customarily associated with other *Salmonella* infections.[6,22] Systemic and local humoral and cellular immune responses result from typhoid infection, but immunity is not robust and confers incomplete protection from relapse and reinfection.[6]

Antimicrobial resistance of *S.* Typhi to chloramphenicol became widely recognized in the 1970s, and plasmid-mediated multidrug resistance emerged in the 1990s. These multidrug-resistant strains commonly were resistant to all drugs used for initial treatment of enteric fever (i.e., ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole).[6] Resistance to fluoroquinolones has become widespread, and ceftriaxone resistance is emerging. Reports buttressed by elegant molecular studies have documented multidrug-resistant clones of *S*. Typhi in Africa and Asia, which now account for 85% to 100% of outbreak strains in Kenya.[35,36] These patterns of resistance appear to be shifting with changing pressures in antimicrobial use. Fluoroquinolone-resistant *S*. Typhi and *S*. Paratyphi A is an emerging problem in India, Korea, and Nepal as fluoroquinolone use increases.[37–40] In some studies, 10% of *S*. Typhi and 14% of *S*. Paratyphi A isolates are fluoroquinolone resistant. Despite this steady rise in fluoroquinolone resistance, strains susceptible to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole are re-emerging.[38,40] Because high cost has restricted use, ceftriaxone resistance remains low in these areas.[38]

Clinical Manifestations

Several clinical syndromes can develop in children infected with *Salmonella,* depending on host factors and the specific serotype involved.

Gastroenteritis

Gastroenteritis is the most common clinical presentation of nontyphoidal *Salmonella* infection. After an incubation period of 6 to 72 hours (mean, 24 hours), abrupt onset of nausea, vomiting, and cramping abdominal pain is followed by watery or dysenteric (i.e., containing blood and mucus) diarrhea. Fever (38.5°C–39°C) occurs in approximately 70% of cases, and the abdomen can be tender. Feces may contain neutrophils and occult blood. Patients commonly have mild peripheral blood leukocytosis with a left shift.

Symptoms subside in less than 1 week in most healthy children. In neonates, young infants, and children with immunodeficiency, symptoms can persist for weeks. In patients with AIDS, the infection can disseminate, with multisystem involvement, shock, and death. In patients with inflammatory bowel disease, especially active ulcerative colitis, *Salmonella* gastroenteritis can be associated with invasion of the bowel wall and rapid development of toxic megacolon, systemic toxicity, and death. Reactive arthritis without clinical joint infection follows *Salmonella* gastroenteritis in 2% of cases, usually in adolescents or adults with the human leukocyte antigen B27 (HLA-B27) antigen. The duration of fecal shedding (median, 7 weeks) after symptoms subside can be prolonged in children younger than 5 years of age.[6]

Bloodstream Infection

Nontyphoidal *Salmonella* gastroenteritis is complicated by transient bacteremia that is usually associated with fever, chills, and toxicity in 1% to 5% of patients overall and more frequently in infants and malnourished children.[41,42] *S.* Typhimurium and *S.* Enteritidis are the most common serotypes associated with bloodstream infections (BSIs) in the United States.[7,30,42,43] Certain serotypes (e.g., Choleraesuis, Dublin) cause bacteremia more often than they cause gastroenteritis.[5,27] Children, especially neonates, may be afebrile and nontoxic.

The occurrence, morbidity, and mortality of nontyphoidal *Salmonella* BSIs are related to age and underlying conditions. Infants with BSI (~20% of cases) uncommonly are immunocompromised apart from age, whereas older children usually have a predisposing condition.[44] Death is more common if the patient has an underlying condition. Metastatic foci of infection and death are more common in the first year of life.[7,45]

Nontyphoidal *Salmonella* BSI commonly persists when treated with oral antibiotics or single-dose parenteral antibiotics. Laboratory and clinical findings do not predict adequately which children will experience persistent bacteremia. Approximately 35% of immunocompromised children develop serious focal infections (e.g., meningitis, osteomyelitis, pyogenic arthritis, pneumonia) after *Salmonella* bacteremia, whereas previously healthy children are at relatively low risk (3%).[46–48]

Recurrent *Salmonella* septicemia without an obvious focus sometimes complicates infection in people with AIDS and occurs despite antibiotic therapy.[7,8] Prolonged or recurrent bacteremia also occurs in patients with schistosomiasis, who exhibit persistence of infection unless the schistosomiasis also is treated. *Salmonella* organisms can multiply within the schistosomes, where they are protected from antimicrobial agents. Hemolytic anemia, such as that occurring with sickle cell disease, malaria, and *Bartonella* *bacilliformis* infection, is associated with a higher risk of bacteremia, presumably because of blockade of the reticuloendothelial system. Invasive nontyphoidal salmonellosis during pregnancy in otherwise healthy women is rare, and prognosis for the mother is favorable, but transplacental infection usually is lethal for the fetus.[23]

Extraintestinal Focal Infections

Salmonella can cause metastatic infection in almost any organ. Sites with preexisting anatomic abnormalities typically are involved (e.g., polycystic kidney or liver, hyperplastic lymph nodes, tumor). Bone infections due to *Salmonella* occur in infarcted bone of children with sickle cell disease. Osteomyelitis and suppurative arthritis can develop at sites of previous trauma, in skeletal prostheses, and occasionally without any predisposing factor.[8] Infants younger than 2 months of age with *Salmonella* gastroenteritis have an increased risk of bacteremia, meningitis, and other foci of infection. Meningitis is primarily a disease of infants; neonates may have little or no fever initially but have rapid deterioration, high mortality rates (~50%), and neurologic sequelae among survivors.[7,30,49–52] Rarely, other focal infections such as urinary tract infection, pericarditis, peritonitis, pneumonia, and empyema complicate *Salmonella* bacteremia.[53]

Enteric Fever

Although enteric fever (i.e., typhoid fever) classically is associated with *S.* Typhi and *S.* Paratyphi, other *Salmonella* strains occasionally cause disease mimicking this syndrome.[6,31,54–57] The clinical features of enteric fever with *S.* Typhi or *S.* Paratyphi are indistinguishable. During the first week of illness, there is a stepwise, insidious increase in fever, which eventually becomes unremitting and is associated with systemic symptoms such as headache, lethargy, malaise, myalgia, and abdominal pain. In the second week, hepatosplenomegaly occurs, and rose spots may be seen; headache is replaced by stupor. Relative bradycardia is not a feature of typhoid fever in children.[58] During the third to fourth week of fever, intestinal hemorrhage and perforation are common; fever begins to show morning remissions, and there is a gradual decline in fever spikes. Myocarditis, shock, meningitis, and pneumonia can complicate the course.[59]

During the first several weeks of illness, children often have diarrhea with blood and fecal leukocytes, although in a few patients, diarrhea does not begin until the third week. Occasionally, resolution does not occur until 6 weeks after onset. Even in the preantibiotic era, recurrences were sometimes seen after apparent resolution. Death related to central nervous system involvement, intestinal hemorrhage, or perforation usually does not occur until after the first week of illness. In infants and young children, *S.* Typhi can cause less impressive fever and toxicity, and the resultant nonspecific syndrome can be misinterpreted as a viral infection.

Asymptomatic Infection

After clinical recovery from nontyphoidal *Salmonella* gastroenteritis, asymptomatic fecal excretion of *Salmonella* continues for weeks and can be a source for contamination of food or drink and transmission to others.[8] Excretion of *Salmonella* for several months is typical in infants infected very early in life. Asymptomatic fecal excretion for weeks is also seen after typhoid fever in all ages. The role of convalescing excreters of *S.* Typhi among children in endemic areas is more important than chronic carriage in perpetuating transmission. Convalescent (≤1 year) and chronic (>1 year) carriage in adults is a consequence of biliary tract disease, especially gallstones, which usually are asymptomatic.[33]

Laboratory Findings and Diagnostic Tests

Gastroenteritis is best diagnosed by cultures of stool specimens rather than rectal swab specimens. Selective media that inhibit the growth of normal flora, such as MacConkey, Hektoen enteric, or xylose-lysine-deoxycholate (XLD) agar, should be used. Enrichment broth (e.g., selenite F) can be used to enhance isolation when low numbers of *Salmonella* are present in stools. Rare lactose-fermenting *Salmonella* may pose a diagnostic problem, but other biochemical features enable accurate identification.[60]

Blood cultures are the best method for diagnosing typhoid fever and BSIs that can complicate other *Salmonella* infections.[6,31,55–59] The sensitivity of blood cultures (60% to 80%) depends principally on the volume of blood sampled in children and adults.[6] Quantitative studies have shown a median of 0.3 organisms/mL (interquartile range, 0.1 to 10 organisms/mL) in blood compared with 9 organisms/mL (interquartile range, 1.0 to 85 organisms/mL) in bone marrow.[61] A minimum of 1 to 15 mL of blood, depending on the age and weight of the child, should be cultured.[6]

Culture of bone marrow is more sensitive (80% to 95%), but it is done less often because most children in endemic areas are treated outside the hospital. Bone marrow cultures may be useful when the diagnosis is elusive for persistently febrile patients. Metastatic focal infections that can complicate infection due to many *Salmonella* serotypes are best diagnosed by cultures of aspirates of pus, biopsy specimens, or cerebrospinal fluid.[8,31]

Given the worldwide prevalence of multidrug-resistant *Salmonella,* accurate antimicrobial susceptibility testing in accord with Clinical Laboratory Standards Institute (CSLI) methods and interpretive criteria is imperative, and results should guide or refine therapy.[62] For fecal isolates of *Salmonella,* only ampicillin, a fluoroquinolone, and trimethoprim-sulfamethoxazole should be tested and reported routinely. Chloramphenicol and an extended-spectrum cephalosporin should be tested for extraintestinal isolates. Resistance to nalidixic acid is a practical but imperfect surrogate test for gyrase (i.e., *gyrA* and *gyrB*) and topoisomerase IV (i.e., *parA* and *parC*) mutations that render isolates less responsive or refractory to fluoroquinolone therapy. Additional resistance mechanisms for fluoroquinolones include plasmid-mediated resistance encoded on *qnr* or *aac*(6′)-*Ib-cr*.[40] Although resistance to extended-spectrum β-lactams and carbapenems have been found in nontyphoidal *Salmonella*, few cases in *S*. Typhi have been reported.[31,40] Investigational interpretive criteria for susceptibility testing of *S*. Typhi to azithromycin were published by CLSI in 2015.

Clinically, *Salmonella* gastroenteritis cannot be distinguished easily from other bacterial causes of bloody diarrhea, although age, exposures, fever, associated enteritis symptoms, and various epidemiologic features sometimes suggest an etiologic agent.

Inflammatory diarrhea with fever also is consistent with *Shigella,* enteroinvasive *Escherichia coli,* enterohemorrhagic *E. coli, Campylobacter jejuni, Yersinia enterocolitica,* and *Clostridium difficile* infections. *Trichuris trichiura, Balantidium coli,* and *Entamoeba histolytica* are important possible parasitic causes of bloody mucoid diarrhea. When abdominal pain and tenderness are severe, alternative diagnoses such as appendicitis, perforated viscus, and ulcerative colitis merit consideration. Typhoid fever can mimic other infections of the reticuloendothelial system, including Epstein-Barr virus infection, disseminated tuberculosis, histoplasmosis, ehrlichiosis, anaplasmosis, brucellosis, tularemia, plague, and murine typhus.

Treatment

For people with gastroenteritis, initial therapy focuses on rehydration, correction of electrolyte disturbances, and general supportive care. Antimicrobial agents usually are not indicated for uncomplicated gastroenteritis because they do not speed resolution of symptoms. Rather than eliminating fecal excretion, antimicrobial agents can prolong colonization. Antimicrobial therapy may be appropriate for patients with gastroenteritis who are at high risk for complications, although the efficacy of this measure is unproved.

Suspected or proven BSIs and extraintestinal focal *Salmonella* infections should be treated with a third-generation cephalosporin unless susceptibility data demonstrate that the organism is susceptible to ampicillin, trimethoprim-sulfamethoxazole, or chloramphenicol; usual doses are listed in Table 146.4. Considering the intracellular site of *Salmonella* in the reticuloendothelial system, trimethoprim-sulfamethoxazole or fluoroquinolones may have a theoretical advantage over ampicillin for treatment of enteric fever. About 40% of nontyphoidal *Salmonella* isolates in the United States are resistant to one or more antimicrobial agents; worldwide multidrug resistance of all *Salmonella* serotypes is increasing.[3,6,20,24–30,35–40] Fluoroquinolones are best avoided in children younger than 18 years of age unless alternative agents are not available.[6]

TABLE 146.4

Antimicrobial Agents for Extraintestinal *Salmonella* Infections[a]

Drug	Dosage
Ampicillin	200 mg/kg/day in 4 divided doses daily
Azithromycin	10 mg/kg once daily for 7 days
Trimethoprim-sulfamethoxazole	10 mg/kg/day of trimethoprim in 2 divided doses daily
Ceftriaxone	100 mg/kg/day in 1 or 2 divided doses daily
Chloramphenicol	50–75 mg/kg/day in 4 divided doses daily

[a] Serotype, site infected, and susceptibility determine optimal agent and duration of therapy.

Duration of therapy depends on the serotype and site of infection. Therapy usually is continued for 10 to 14 days for children with BSI, for 4 to 6 weeks for acute osteomyelitis, and for 4 weeks for meningitis.[8,59] Meningitis can recur even after 4 weeks of therapy, although most patients who have relapses have received less than 3 weeks of antimicrobial therapy. Surgical drainage of focal purulent collections is indicated.[59] In the developing world, *Salmonella* infection associated with schistosomiasis requires treatment of both infections to achieve resolution.

S. Typhi infection usually is treated with a minimum of 10 to 14 days of therapy. Ceftriaxone is the best initial parenteral choice because of widespread resistance to other agents. For susceptible strains, ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol have been used successfully, and fluoroquinolones have been used extensively, even in children in endemic areas.[6,31] Defervescence in typhoid fever usually requires at least 36 hours of therapy, and fever can persist for 5 to 7 days, even with ultimately effective therapy.

Azithromycin has been effective in children with strains resistant to first-line agents.[63,64] Corticosteroids are used as adjunctive therapy for delirium, obtundation, stupor, coma, or shock in children with typhoid fever. A dose of 3 mg/kg of dexamethasone initially, followed by 1 mg/kg every 6 hours for 48 hours, was associated with reduction of the mortality rate from between 35% and 55% to 10%.[65] For patients in whom intestinal perforation develops, surgery coupled with broad-spectrum antimicrobial therapy directed at anaerobic and gram-negative enteric bacteria is indicated. The mortality rate after perforation can be as high as 10% to 30%.[6]

Special Considerations

Immunocompetent children with *Salmonella* gastroenteritis usually have an uneventful recovery without antimicrobial therapy. Young infants and immunocompromised patients, particularly patients with focal infection, can have prolonged, complicated courses. *Salmonella* meningitis has a poor prognosis and high relapse rate, particularly if treated with too short a course of therapy. Antimicrobial-resistant nontyphoidal *Salmonella* is associated with excess BSIs, hospitalizations, and deaths.[5,66]

Even with appropriate therapy, patients can have recurrence of typhoid fever after completion of therapy (i.e., 5% to 20% relapse rate). Relapses of *Salmonella* infections presumably reflect the difficulty in killing intracellular organisms. Because relapse sometimes results from resistant bacteria, an agent different from the initial drug should be used empirically while awaiting culture and susceptibility test results. Antibiotic-resistant strains of *S.* Typhi are independently associated with increased virulence and adverse outcomes.[67,68]

Prevention

Chlorination of water, proper sewage disposal, and appropriate food-handling practices are necessary to prevent salmonellosis. Hand hygiene is critical to prevent transmission by food. People who excrete *S.* Typhi should be excluded from occupations in food preparation and childcare until results of repeated stool cultures are negative; infected children younger than 5 years of age also are excluded until repeated stool cultures are negative. For nontyphi salmonellosis, recovery from symptomatic disease but not stool culture negativity is required for return to group childcare.[69] For hospitalized infants and children, enteric precautions are recommended because low inocula levels can cause infection in children. Prolonged breastfeeding reduces the infection rate.[70]

No vaccine against nontyphoidal *Salmonella* or *S.* Paratyphi infections is available, although two vaccines are available for *S.* Typhi (Table 146.5).[71–74] The vaccines have similar efficacy, typically in the range of 50% to 75% for reducing the number of laboratory-confirmed cases in 2 to 3 years. Seven-year follow-up data for enteric-coated capsules containing Ty21a live vaccine suggest greater than 60% long-term protection. The live, attenuated vaccine should not be used in immunocompromised hosts or in people receiving antimicrobial agents at the time of immunization. Pediatric use of typhoid vaccines has been limited to children who will travel in areas where prolonged exposure to *S.* Typhi is likely, live where multidrug-resistant strains are prevalent, or are members of households with documented carriers.

TABLE 146.5

Vaccines for Prevention of *Salmonella* Typhi

Vaccine	Age Indicated	Dose and Route	Adverse Reactions
Oral live, attenuated Ty21a vaccine (Vivotif)	≥6 years		0–5% fever or headache
Primary series		1 enteric-coated capsule every 2 days for 4 doses	
Booster (every 5 years)		1 enteric-coated capsule every 2 days for 4 doses	
Vi capsular polysaccharide vaccine (Typhim Vi)	>2 years		0–1% fever, 2–3% headache, 7% redness or induration at injection site
Primary series		Single dose of 0.5 mL (25 μg) IM	
Booster (every 2 years)		Single dose of 0.5 mL (25 μg) IM	

IM, intramuscular.

Mass vaccination of children to prevent typhoid fever in endemic areas is desirable. A substantial proportion of typhoid occurs in children younger than 5 years of age, for whom the oral vaccine is not approved.[54] The World Health Organization (WHO) has recommended widespread use of the Vi vaccine in developing countries in which typhoid fever is endemic, and a recent cluster-randomized trial suggests efficacy in preschool children.[54,74] The *S.* Typhi Vi conjugate vaccine (Vi-rEPA) appears to be effective.[75] Neither of the two FDA-licensed vaccines is effective against *S.* Paratyphi A, which is an emerging, often antibiotic-resistant cause of enteric fever.[37,38]

Key Points

Diagnosis, Management, and Prevention of *Salmonella* Infection

Microbiology

- Gram-negative bacillus, oxidase negative and usually not lactose fermenting
- Characterization based on O (somatic), H (flagellar), and Vi (capsular) antigens
- Chromosomal and plasmid-mediated antimicrobial resistance to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole; emerging resistance to fluoroquinolones and extended-spectrum cephalosporins

Epidemiology

- Flora of birds, mammals, and reptiles, except *S.* Typhi and *S.* Paratyphi, which are uniquely human pathogens
- Highest prevalence in children <5 years of age, in whom excretion is prolonged
- Person-to-person transmission is rare, especially for *S.* Typhi and *S.* Paratyphi.
- Host factors and serotype contribute to clinical manifestations.
- Classic enteric fever is common with *S.* Typhi and *S.* Paratyphi; gastroenteritis is more common with *S.* Enteritidis and *S.* Typhimurium.
- Immunocompromised children (including those with sickle cell disease) have increased risk of serious focal infections.

Diagnosis

- Recovery from blood (typhoidal disease; infants and malnourished) or stool (nontyphoidal > typhoidal)
- Culture of stool requires selective and inhibitory media to suppress normal flora; enrichment broth enhances isolation.

- Antimicrobial susceptibility testing is imperative, with extended testing for extraintestinal isolates.

Treatment

- Third-generation cephalosporin is empiric choice for bloodstream infection and extraintestinal focal infections.
- Azithromycin has been effective for typhoidal strains resistant to first-line agents.

Duration of Therapy

- Length of therapy depends on serotype, site of infection, and agent used.
- Usual treatment is 10 to 14 days for bloodstream infection, 4 to 6 weeks for acute osteomyelitis, and 4 weeks for meningitis.

Prevention

- Hand hygiene and enteric precautions
- Vaccines for *S.* Typhi

References

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Shigella Species

Shai Ashkenazi

Shigella species cause acute gastrointestinal tract infections, sometimes with extraintestinal manifestations. Shigellosis has substantial public health importance, especially in developing countries, with an estimated 164.7 million annual cases and 1.1 million deaths worldwide.[1] The term *dysentery* denotes colitis manifested as frequent, painful passage of stools containing blood or mucus. Bacillary dysentery is caused by bacteria, including shigellae and enteroinvasive *Escherichia coli* that possess *Shigella* virulence genes.[2,3]

Description of the Pathogen

Shigella organisms are human-adapted *E. coli* that have acquired the ability to invade human intestinal mucosa and cause disease.[3] They are nonmotile, nonencapsulated, gram-negative bacilli in the family Enterobacteriaceae. They do not ferment lactose and lack urease activity. About 50 serotypes, belonging to four serogroups (or species), have been identified: group A *(S. dysenteriae),* group B *(S. flexneri),* group C *(S. boydii),* and group D *(S. sonnei).*

Pathogenesis and Immunity

Shigellosis is one of the most communicable forms of bacterial diarrhea, with as few as 10 organisms causing diarrhea in adult volunteers. The low dose required to cause disease explains the efficiency of person-to-person spread.

The central event in pathogenesis is invasion of colonic mucosa.[4,5] Ingested *Shigella* bacteria cross the colonic epithelium by transcytosis through M cells, the specialized cells that cover the lymphoid follicles of the intestinal mucosa. At the dome area of the lymphoid follicle, the bacteria are phagocytosed by macrophages, which the bacteria kill by inducing apoptosis, dampening the innate immune recognition and evading inflammasome activation.[5,6] With this strategy, shigellae reach the subepithelial tissue and invade colonic epithelial cells through their basolateral surface. During the initial step of cellular entry, shigellae induce actin polymerization in epithelial cells, with formation of filopodes.

After entry, the bacteria free themselves from membrane-bound vacuoles, proliferate in cytoplasm, and spread by actin-based motility. This enables infection of neighboring cells by formation of finger-like protrusions. Intracellular shigellae also reprogram host cells to express proinflammatory cytokines, such as interleukin-1 (IL-1), IL-6, and IL-8, which augment local inflammation and attract neutrophils. Leukocytes transmigrate the epithelium into the lumen of the colon. *Shigella* kills neutrophils by inducing necrosis, and release of granular proteins contributes to further epithelial disruption.[5]

Plasmid and chromosomal virulence genes have been defined in *Shigella* and invasive *E. coli.* Specific chromosomal genes enhance replication (e.g., the siderophore aerobactin facilitates multiplication of *Shigella* within tissues), increase bacterial resistance to nonspecific defense mechanisms (e.g., somatic antigens), or prevent killing by phagocytic cells (e.g., superoxide dismutase).[5] *S. dysenteriae* serotype 1 can increase severity of illness through expression of Shiga toxin, which contains an enzymatically active (A) subunit and five cell-binding (B) subunits.[7] The A subunit irreversibly inhibits mammalian protein synthesis by cleaving an *N*-glycosidic bond at adenine 4324 in the 28S ribosomal RNA, blocking elongation factor 1–dependent binding of aminoacyl transfer RNA to the ribosome. Five identical copies of subunit B bind to globotriaosylceramide, the cell receptor glycolipid.

Chromosomal genes also act by regulating expression of genes on the *Shigella* virulence plasmid. The *malA* gene product functions in the inner membrane as a sensor for the high osmolarity of the colonic contents in the primate intestine, inducing expression of plasmid invasion genes. The chromosomal keratoconjunctivitis provocation gene *(kcpA)* is responsible for movement of *Shigella* in the cytoplasm. The *virR* regulatory loop gene responds to conditions outside the bacteria by inhibiting expression of the invasive phenotype at 30°C.

All virulent *Shigella* species contain a 120- to 140-megadalton (i.e., 200- to 220-kilobase) plasmid.[3,8] As with the chromosomal genes, plasmid genes are involved in regulatory functions, invasion, or intercellular spread; *virF* governs the plasmid virulence regulon by directly activating transcription of two other gene loci, *virG* and *virB*. The latter locus then activates invasion plasmid antigens ipaABCD. The *ipaABCD* genes are highly conserved in *Shigella* invasion plasmids.[2,3] These proteins are the dominant virulence plasmid antigens recognized during the humoral immune response to *Shigella*. Intracellular and intercellular bacterial spread is encoded by *virG*, which has a sequence of repeating motifs in its amino terminus that is involved in polymerization of actin monomers to provide the force to propel *Shigella* within the cytoplasm and into adjacent cells.

This model explains the histologic observations of early neutrophil efflux in colonic crypts and bacterial invasion. The desquamation, ulceration, and formation of microabscesses in the colonic mucosa inhibit absorption of water, with production of stools that are frequent and scanty and that contain blood, inflammatory cells, and mucus. Invasion beyond the mucosa to the bloodstream seldom occurs.

Although mucosal secretory immunoglobulin (Ig) A antibodies develop against the virulence plasmid invasion antigens (ipaABCD) after natural infection, immunity is serotype specific. It is unclear why some people infected with *Shigella* remain asymptomatic.[9] Cellular immunity and cytokine production develop during acute illness. IL-1α, IL-1β, tumor necrosis factors (i.e., TNF-α and TNF-β), IL-4, IL-8, IL-6, and transforming growth factor-β are induced, whereas interferon γ is suppressed.[10,11]

Pathology

Shigella primarily affects the colon.[12] Macroscopically, the affected mucosal surface is edematous and erythematous, covered by a layer of gray mucopurulent exudate with various degrees of ulceration and hemorrhage. Microscopic examination typically reveals hyperemia, edema, and neutrophil infiltration of the colonic mucosa. In early stages, the surface epithelium can be reduced in height and infiltrated with neutrophils. As disease progresses, epithelial cells detach from the edematous lamina propria, leaving microulcerations. With advanced disease, large numbers of lymphocytes and plasma cells can be seen in the lamina propria. At the base of deep necrotic, ulcerated mucosa, a thick pseudomembrane forms, composed of neutrophils, erythrocytes, fibrin, and desquamated epithelial cells. Crypt abnormalities include a marked reduction of goblet cells and hyperplasia of epithelial cells, crypt abscesses, and distention due to exudates. Aphthoid ulcers form over lymphoid aggregates.

In small blood vessels near the lamina propria, pathologic changes include hyperemia, edema, focal hemorrhage, and swelling of endothelial cells. In some cases, thrombosis of blood vessels in the lamina propria and submucosa is associated with widespread necrosis of colonic mucosa. The pathophysiologic basis for the initial watery diarrheal presentation may be related to enterotoxin production, but it has not been fully elucidated.

Epidemiology

The number of annual cases of shigellosis in the United States reported to the Centers for Disease Control and Prevention (CDC) varied from 7746 in 2012 to 22,625 in 2008, with an incidence of 3 to 13 cases per 100,000 people in the general population.[13–15] However, there is substantial underreporting, and the numbers are estimated to be 20 times higher. The highest risk is for children between the ages of 1 and 4 years (particularly children 12 to 36 months), followed by children 5 to 9 years of age.[13,15] Large childcare-associated outbreaks are common and are difficult to control (see Chapter 3).

In the United States, the seasonality of shigellosis has changed from a peak in summer to a high incidence in the late summer and fall.[13] In developing countries with tropical climates, *Shigella* infection is common throughout the year, but higher isolation rates occur during the summer and rainy seasons.

The prevalence of *Shigella* serotypes varies over time and geography. *S. sonnei* is the predominant serotype (~80% of *Shigella* isolates) in developed countries and is increasing in prevalence in developed and developing countries.[3,13,15] In developing countries, *S. flexneri* is still most common, with occasional outbreaks caused by *S. dysenteriae* serotype 1.[16,17]

Shigella are hardy organisms that can be recovered for up to 6 months from contaminated water samples maintained at room temperature.[18] Organisms can survive for up to 30 days in foods such as milk, whole eggs, oysters, shrimp, and flour. *Shigella* can be isolated from toilet surfaces in homes of patients with dysentery and from the fingers of patients who use toilet paper. The ability to survive coupled with a low infectious dose explains contagion. Most cases of shigellosis probably result from person-to-person transmission of small inocula through the fecal-oral route. There is a high risk of spread within families, in childcare centers, in custodial care institutions, in internment camps, and among men who have sex with men.

Water and food are responsible for outbreaks of shigellosis in military camps, cruise ships, community gatherings, and restaurants. In the United States, 58% of the reported *Shigella* outbreaks were restaurant-associated, including large outbreaks with commercially prepared foods distributed in multiple states.[19] Foods usually consumed raw were implicated in 24% of the outbreaks and infected food handlers in 23%.[19] Water plays a major role in transmission in developing countries, as does overcrowding and unsanitary conditions.

Healthy people who become infected with *Shigella* can shed organisms for up to 1 month; appropriate antibiotic treatment reduces the period of excretion to a few days.[18] Malnourished children shed the organism for prolonged periods as a result of their inability to eliminate the organism or to prevent reinfection. In patients with acquired immunodeficiency syndrome (AIDS), prolonged, relapsing, symptomatic shigellosis and lengthy carrier states have been described despite proper treatment.

Clinical Manifestations

Uncomplicated Shigellosis

In adult volunteers, the first symptoms of shigellosis usually occur within 12 to 48 hours of exposure, but symptoms can be delayed for up to 1 week. In mild infections, the only complaints may be watery or loose stools for a few days, with minimal or no constitutional symptoms.[18] In contrast, typical disease in children includes acute onset of high fever, malaise, abdominal cramps, and copious watery diarrhea followed by resolution or heightened toxicity, nausea and vomiting, and passage of frequent, scanty, mucoid, bloody stools associated with abdominal pain and tenesmus.[18,20] Some children have bloody mucoid diarrhea from the onset of illness. Physical findings usually include fever (≥38.5°C), general toxicity, mild dehydration, lower abdomen tenderness, and increased bowel sounds. Rectal examination elicits severe pain. In most cases, symptoms resolve without antimicrobial therapy within 1 week; however, therapy shortens clinical illness and fecal excretion of organisms.

Complications of Shigellosis

The main complications of shigellosis include dehydration due to fluid loss through diarrhea and vomiting, electrolyte imbalance (including hyponatremia and hypokalemia, commonly observed with *S. dysenteriae*), and less commonly, hypoglycemia due to failure of glycogenolysis and gluconeogenesis, especially in young infants.[18,20] Hypoglycemia and hyponatremia have been associated with a higher risk of death.[20] Protein-losing enteropathy can contribute to poor nutrition. In malnourished children with chronic diarrhea or frequent relapses, rectal prolapse can be observed.[20] Hemolytic uremic syndrome is a major complication of infections due to *S. dysenteriae* serotype 1, caused by Shiga toxin production and damage to vascular endothelium.[20]

Bacteremia.

Severe colitis and ulceration can result in loss of the mucosal protective barrier and resulting bacteremia.[21,22] Although *Shigella* bacteremia is rare in developed countries, a study in Bangladesh found that 4% of patients with shigellosis were bacteremic.[21] In this setting, bacteremia was more common in malnourished infants and was associated with significant mortality. *S. dysenteriae* is more commonly associated with bacteremia, disseminated intravascular coagulation, endotoxic shock, and death than other *Shigella* species. However, in one case series of 15 children with *Shigella* bacteremia in Israel, most of the patients were infants with failure to thrive, 87% of the isolates were *S. flexneri,* and there were no isolates of *S. dysenteriae* serotype 1 and no deaths.[23] In patients with AIDS, shigellosis is more common, more severe, and more often associated with bacteremia. After *Shigella* infections, other enteric gram-negative bacilli can cross the damaged mucosa and cause bacteremia.[24,25]

Surgical Complications.

A review of 57 published cases of surgical complications of shigellosis in children over a 40-year period categorized the complications in four groups: intestinal obstruction (53%), appendicitis with or without perforation (28%), colonic perforation (17%), and intra-abdominal abscesses (2%). Thirteen children (23%) died, often despite antimicrobial therapy.[26]

Extraintestinal Infections

Extraintestinal infections caused by *Shigella* spp. are rare. Vulvovaginitis and urinary tract infections are well documented and often result in delayed diagnosis and inappropriate treatment.[27,28,29] Eye infections include keratitis, conjunctivitis, iritis, and iridocyclitis.[26]

Neurologic Symptoms.

In series of hospitalized children with *Shigella* infections, 10% to 45% have neurologic symptoms, including seizures, lethargy, confusion, hallucinations, and headache.[20,30,31] However, neurologic symptoms are overrepresented in hospitalized patients because seizures often are the indication for admission, and in outpatient-based studies, seizures are uncommon. Neurologic symptoms can precede the onset of diarrhea and can suggest a central nervous system intoxication or infection. Cerebrospinal fluid usually is normal; mild lymphocytic pleocytosis (≤12 cells/mm^3) has been observed.[30]

The pathogenesis of *Shigella*-induced neurologic symptoms is not understood fully. Clinical and complementary studies in a murine model documented the role of bacterial components, host inflammatory mediators (e.g., TNF-α, IL-1β, nitric oxide), and brain edema.[32,33] Most children recover completely with no residual neurologic deficit, although studies conducted in Bangladesh found altered consciousness, seizures, and dehydration to be unfavorable prognostic signs.[20,34,35] Fatalities sometimes occur early in the course of illness among children who lack significant dehydration or septicemia but demonstrate stupor, coma, hyperpyrexia, shock, convulsions, and decorticate or decerebrate posturing due to cerebral edema. This Reye-like syndrome may be the most common cause of death from shigellosis in developed countries.[36] *S. flexneri* and *S. sonnei* are the most frequently associated species. This fulminant toxic encephalopathy (called Ekiri syndrome in Japan) has a poor prognosis.[31,36,37] Hypocalcemia may play a role in pathogenesis.[20,36]

Musculoskeletal Symptoms.

A study of 278 patients with shigellosis and 597 controls found that 7% of the patients had reactive arthritis.[38] An additional 2% had other musculoskeletal symptoms, including tendinitis, enthesopathy, or bursitis. Only a single control subject had reactive arthritis. Human leukocyte antigen (HLA) B27 was positive in 36% of the patients with reactive arthritis.[38] Reiter syndrome (i.e., arthritis, urethritis, and conjunctivitis) was reported mainly in adults.

Neonatal Shigellosis.

Shigellosis in neonates and young infants has several unique features. Neonatal shigellosis is uncommon, accounting for only 0.6% of cases in children younger than 10 years of age.[39] This finding may be explained by maternal protective factors that pass through the placenta or by breastfeeding. Conversely, complications, including dehydration, hypothermia, septicemia, meningitis, rectal prolapse, toxic megacolon, and colonic perforation, are more common in infants than in older children; paradoxically neonates often have a shorter duration of diarrhea.[40–43] The mortality rate for infants younger than 3 months of age who were hospitalized with shigellosis was at least double that of older children. Risk factors associated with poor outcome include ileus, hypoproteinemia, gram-negative bacteremia, and hyponatremia.[43]

Laboratory Findings and Diagnosis

The differential diagnosis for watery diarrhea associated with fever due to *Shigella* includes viruses and other bacteria (e.g., *Salmonella, Campylobacter, Yersinia enterocolitica, Clostridium difficile, E. coli, Aeromonas, Plesiomonas*). For patients with clinical dysentery, *Entamoeba histolytica, Balantidium coli,* and noninfectious diseases (e.g., inflammatory bowel disease, allergic proctitis in infancy) also should be considered.

The peripheral white blood cell count in bacillary dysentery can show a dramatic left shift, but this is not consistently found. Microscopic or macroscopic fecal blood and fecal leukocytes are each detected in approximately 70% of cases of *Shigella* infection; both occur in 50% of cases.[44] Although seen more commonly in shigellosis than in other types of bacterial enteritis, findings of fecal blood and leukocytes are signs of colitis due to any cause.

Stool culture to isolate *Shigella* is the basis for diagnosis. However, culture requires several days of incubation, the sensitivity is only 72% to 80%, the organism may not survive transport to the laboratory, and the culture result can be negative for children who have received antimicrobial therapy. Matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) can shorten the time of *Shigella* identification.[45] Studies showed that polymerase chain reaction (PCR) testing of stool specimens increased diagnosis by 50% compared with culture, with possible simultaneous identification of other enteric pathogens.[46–49] Immune assay with monoclonal antibodies to the IpaC protein detected *Shigella* spp. and enteroinvasive *E. coli* with high sensitivity and specificity.[18] Serology has little value in the diagnosis of acute infection.

Treatment

Rapid correction of fluid and electrolyte deficits, early reinstitution of feeding, and continual replacement of ongoing losses are key elements of therapy.[50] Oral rehydration is the treatment of choice, although patients in shock or coma and those with ileus should be treated with intravenous replacement of fluids and electrolytes.

Appropriate antimicrobial therapy of shigellosis shortens the duration of fever, diarrhea, and fecal excretion of the pathogen (thereby reducing infectivity) and reduces the risk of complications.[18,50,51] Empiric antimicrobial treatment is recommended for patients with colitis or dysentery until culture results are available. Lack of response to therapy or an inability to confirm infection should prompt collection of stool specimens for a second culture and consideration of other possible diagnoses.

Antimicrobial resistance of *Shigella* spp. is increasing worldwide and susceptibility testing of all isolates is recommended.[16,52,53] According to the US National Antimicrobial Resistance Monitoring System for Enteric Bacteria, 67% of *Shigella* isolates were resistant to trimethoprim-sulfamethoxazole, 34% to ampicillin, and 6% to nalidixic acid; resistance was very low to ceftriaxone and ciprofloxacin.[54] Most resistance is plasmid mediated and easily transferable among bacteria. Reduced susceptibility or resistance to azithromycin (i.e., minimal inhibitory concentration [MIC] of 16–32 and ≥32 μg/mL, respectively) has been reported in the United States, Europe, and Asia.[54–57] During 2010–2012, the resistance rate in Asia and Africa to ceftriaxone, cefotaxime, and ceftazidime were 14%, 23%, and 6%, respectively; the rates in Europe and America were less than 1%.[58]

The empiric antimicrobial regimen is determined by host factors, severity of illness, local resistance patterns, and history of travel to an area of frequent resistance. Parenteral antibiotic therapy is recommended for children with proven or suspected shigellosis who have underlying immune deficiency or suspected bacteremia and for those who are unable to take oral medications. A third-generation cephalosporin, preferably ceftriaxone, typically is used empirically because of the excellent clinical and microbiologic response and unlikely resistance (Table 147.1).[50,59,60] Susceptibility results should be used to tailor therapy. In one study, a single dose of ceftriaxone showed bacteriologic failures, but a 2-day course was as effective as a 5-day course, and it can be used when there is a good clinical response, no extraintestinal infection, and no underlying immune deficiency.[60]

TABLE 147.1

Antibiotic Therapy for Children With Suspected or Proven Shigellosis[a]

Drug[b]	Dosage
Cefixime	8 mg/kg/day PO once daily
Ceftriaxone	50 mg/kg/day IV or IM in one dose daily (maximum 1.5 g/day)
Trimethoprim-sulfamethoxazole[c]	10 mg/kg/day (TMP) PO in two divided doses (maximum 320 mg TMP/day)
Ampicillin[c]	100 mg/kg/day IV or PO in four divided doses
Azithromycin	12 mg/kg (maximum 500 mg) on the first day, then 6 mg/kg (maximum 250 mg) for 4 days

[a] Therapy is given for a total of 5 days. Susceptibility test results are used to tailor therapy.

[b] Ciprofloxacin or other fluoroquinolones may be appropriate.

[c] Resistance is common.

IM, intramuscular; IV, intravenous; PO, by mouth; TMP, trimethoprim.

Oral trimethoprim-sulfamethoxazole should be used only for patients who are infected with a susceptible organism or people who have acquired infection in a locale with low resistance. For patients infected with an ampicillin-susceptible, trimethoprim-sulfamethoxazole–resistant organism, ampicillin can be given (see Table 147.1). Cefixime was clinically effective in children infected mostly with *S. sonnei* but showed a relatively high bacteriologic failure rate and was less effective in adults with severe shigellosis caused mostly by *S. dysenteriae* and *S. flexneri*.[61,62] A 2-day course of cefixime was less effective than 5 days.[63] Azithromycin was effective in adults with shigellosis.[64]

In an open, randomized study of children, azithromycin and cefixime had similar clinical efficacy, but azithromycin had a better bacteriologic response.[65] Azithromycin was superior clinically and microbiologically to nalidixic acid in an outbreak of shigellosis in children.[66] Azithromycin is usually recommended as the first-line oral empiric antibiotics for suspected or proven shigellosis in children.

In some settings, antimicrobial resistance patterns leave only fluoroquinolones as a feasible option.[67] Ciprofloxacin (10 mg/kg every 12 hours for 5 days, maximum single dose of 500 mg) is effective treatment, as are ofloxacin and gatifloxacin, although experience in children is limited, and resistance, related mainly to international travel, is well documented.[68]

With appropriate antibiotic therapy, clinical improvement is expected within 1 or 2 days. If there is no improvement by 72 hours of therapy, antimicrobial resistance, extraintestinal complications, or other diagnoses should be suspected.[18,69] Antimicrobial therapy for children with mild disease or children who have recovered by the time the result of a positive *Shigella* culture becomes available is unlikely to affect the clinical course and is therefore controversial. However, antibiotics do shorten fecal excretion and reduce the spread of this highly contagious bacterium, and treatment is recommended for children who are hospitalized, live in institutions, attend childcare centers, or are immunologically compromised.

Antimotility agents should be avoided in cases of shigellosis and other infectious causes of colitis.[70] Data suggest that these drugs prolong symptoms and shedding of the organism. In countries where vitamin A deficiency is common, a single oral dose of vitamin A (200,000 IU) in addition to antimicrobial therapy reduces severity of the illness.[71] Zinc supplementation (20 mg/day, elemental) in Bangladeshi children shortened the duration of the acute disease, promoted weight gain, and improved the immune response.[72,73] A diet rich in animal proteins given for 21 days after completion of antimicrobial therapy for shigellosis resulted in significantly greater height gains in Bangladeshi children.[74]

Prevention

The best strategy to prevent shigellosis in young children is prolonged breastfeeding.[75,76] Specific protective antibodies in the milk of women living in endemic areas decrease the severity of infection in infants.[77,78] Clean running water and appropriate sanitation are crucial. For toddlers and older children, good hygiene practices are helpful but are difficult to implement. Adults involved in food preparation should be instructed in proper hand hygiene technique.[79,80]

Symptomatic children with stool cultures positive for *Shigella* should be excluded from group childcare until treatment is initiated, the diarrhea has resolved, and depending on local regulations, until stool cultures are negative for *Shigella*. In addition to standard precautions, contact isolation is recommended for children hospitalized with shigellosis. Fly control also has been suggested to aid control of spread.

Despite continuing efforts and substantial progress, a *Shigella* vaccine is not available commercially. Several strategies for vaccine development are under study.[81] Lipopolysaccharide-based conjugate vaccines showed minor adverse reactions, a good immune response, and promising efficacy in children.[82–84] Antibiotic prophylaxis against shigellosis usually is not recommended, although for certain brief, high-risk exposures (e.g., travel of immunocompromised child to endemic region), prophylaxis may be reasonable. Appropriate antibiotic treatment of shigellae shortens the duration of excretion and thereby decreases secondary spread to close contacts, especially in settings such as group childcare.

Key Points

Epidemiology, Clinical Manifestations, and Management of Shigella Infections

Epidemiology

- Peak incidence is in children 1 to 4 years of age.
- Because of the low infectious dose, direct person-to-person transmission through the fecal-oral route is most common, especially among young children and in childcare settings.
- Transmission can occur by contact with contaminated environmental surfaces and by consumption of contaminated food or water.

Clinical Features

- Incubation period is 24 to 48 hours but can be as long as 1 week.
- Acute onset of diarrhea (often with blood or mucus) manifests with fever, nausea, vomiting, and abdominal cramps.

- Dehydration and electrolyte imbalance are the most common complications, especially in very young children.
- Extraintestinal complications are uncommon and occur more frequently in neonates or immunocompromised children.

Management

- Mainstay is replacement of fluid and electrolyte losses, preferably by oral rehydration solutions.
- Appropriate antimicrobial therapy shortens the duration of diarrhea, fever, and fecal shedding (thereby reducing infectivity) and apparently reduces the risk of complications.
- Empiric antibiotic therapy should be based on local resistance patterns.
- In most locations, the preferred empiric oral and parenteral antimicrobial agents are azithromycin and a third-generation cephalosporin, respectively.
- No vaccine is available.

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Yersinia Species

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Yersinia species are bacteria in the family Enterobacteriaceae. Of 15 species of *Yersinia*, only *Yersinia enterocolitica*, *Y. pseudotuberculosis*, and *Y. pestis* are human pathogens. *Y. enterocolitica* and *Y. pseudotuberculosis* are enteropathogens transmitted by consumption of contaminated food or water and cause gastrointestinal syndromes that can develop into fatal septicemia in immunocompromised people. *Y. pestis* is the cause of plague that most commonly manifests in the bubonic or primary septicemic forms after the bite of an infected flea or direct contact with infected animal tissues.

Description of the Pathogens

Yersinia are pleomorphic, bipolar-staining, gram-negative coccobacilli. They are aerobic or facultatively anaerobic, non–spore-forming bacteria that ferment glucose, are oxidase negative, and reduce nitrates to nitrites. Species are differentiated by a variety of traits, such as production of urease (*Y. pestis* is negative), motility (*Y. pestis* is nonmotile at 25°C and 37°C), ornithine decarboxylase (*Y. enterocolitica* is positive), and rhamnose (*Y. pseudotuberculosis* is positive) and by several carbohydrate fermentation reactions (*Y. enterocolitica* is positive).

Pathogenesis

Yersinia can survive in a large variety of environmental reservoirs (e.g., soil, plants, insects) and in warm-blooded animals (e.g., rodents, pigs, humans). Despite differences in their mode of entry into the host, clinical manifestations, and disease severity, all three pathogenic *Yersinia* species have a common tropism for lymphoid tissue.

Virulence factors shared by the three species include factors that promote serum resistance, coordinate gene expression, and facilitate iron acquisition. All have a virulence plasmid (pYV) encoding for a type III secretion system (TTSS), which translocates a set of Yop effector proteins into the host cell and are essential for sustained bacterial replication in host tissue. The pYV plasmid differentiates pathogenic from nonpathogenic strains. Adhesins (i.e., Ail, YadA, YadB, YadC, Pla, and pH6 antigen) mediate pathogen-host interactions. Although most bacterial multiplication occurs in the extracellular space, there is evidence that the three pathogenic *Yersinia* species survive and multiply within macrophages, especially during the early stages of colonization.[1–5]

Some virulence genes are unique to a single species. For example, *Y. enterocolitica* has a chromosomal gene that encodes for a guanylate cyclase–stimulating enterotoxin structurally related to the heat-stable enterotoxin produced by enterotoxigenic *Escherichia coli*. *Y. pseudotuberculosis* produces a superantigenic toxin (YPM) that plays a role in systemic infections and a chromosomally encoded PhoP/Q system that regulates survival and growth in macrophages. Highly pathogenic *Y. enterocolitica* and *Y. pseudotuberculosis* harbor the chromosomal high-pathogenicity island, which encodes the siderophore yersiniabactin for iron capture.[5] *Y. pestis* has three main virulence plasmids: pYV, which encodes the TTSS and toxins; pFra, which codes for a capsule that confers resistance to macrophages; and pPla, whose main product (Pla) has protease and plasminogen activator effects.[6–8]

Yersinia Enterocolitica

Epidemiology

Yersiniosis due to infection with *Y. enterocolitica* is a zoonotic gastrointestinal disease in humans. *Y. enterocolitica* can be isolated from a variety of domestic and wild animals (e.g., pigs, cattle, sheep, goat, rabbits, dogs, cats, wild boars, small rodents). Pigs are considered to be the main reservoir of human pathogenic strains. People who eat or handle pork are at risk for illness, and pork intestines (i.e., chitterlings) are a documented source of infection.[9] Eating food prepared from raw products or treated sausage and contact with domestic animals are the main risk factors for sporadic yersiniosis in children.[10]

Milk and other dairy products, even if pasteurized, can sometimes be the source of outbreaks because organisms proliferate at refrigerator temperatures, and low levels of contamination can lead to substantial risk. Refrigerated stored blood is a source of transfusion-acquired illness.[11] Contaminated water can also be a source of infection. Familial and nosocomial spread of *Y. enterocolitica* suggest that person-to-person transmission occurs.

Human infections are more common in cooler climates and tend to occur in winter months. Most reported cases have been from Canada, Europe, and the United States. From 1996 through 2009, the average annual incidence of *Y. enterocolitica* infection in the United States was 0.5 cases per 100,000 people. The rate was highest among African Americans (0.9 per 100,000) but decreased over time from 3.9 to 0.4 cases per 100,000 people. The largest decline occurred in African American children younger than 5 years of age, from 41.5 cases per 100,000 children in 1996 to 3.5 cases per 100,000 children in 2009.[12]

In the European Union, yersiniosis ranks third among reported bacterial zoonoses after campylobacteriosis and salmonellosis. Germany accounts for more than one half of yersiniosis cases reported in Europe.[13] From 2001 through 2008, the average annual incidence of *Y. enterocolitica* infection in Germany was 7.2 cases per 100,000 people, with an incidence of 58 cases per 100,000 children younger than 5 years of age and 108 cases per 100,000 infants.

Clinical Manifestations

Enteric Disease

Y. enterocolitica most commonly causes enterocolitis associated with fever, abdominal pain, vomiting, and diarrhea that contains mucus and gross blood. This presentation occurs most frequently for children younger than 5 years of age. During the first 3 months of life, enteritis can be complicated by bacteremia in up to 28% of cases.[14–16] The relative frequency of specific symptoms may vary by strain biotype/serotype.[13,17] Acute infections cause considerable burden of illness; more than one fourth of patients require hospitalization, and diarrhea commonly persists for more than 2 weeks and occasionally for several months.[18] Untreated people shed organisms for several weeks.

Between 20% and 50% of children with *Y. enterocolitica* infection have bloody diarrhea compared with less than 10% of adolescents and adults. Older children can have mesenteric lymphadenitis (i.e., pseudoappendicitis) or terminal ileitis with fever, abdominal pain, right lower quadrant tenderness, and leukocytosis. Abdominal complications of *Y. enterocolitica* enteric infection include intestinal perforation, peritonitis, intussusception, toxic megacolon, mesenteric vein thrombosis, chronic ileitis, and gangrene of the bowel wall.

Extraintestinal Manifestations

Bacteremia is the major complication of *Yersinia*-associated enteric infection in young children and people with iron overload syndromes, including those undergoing frequent transfusions and chelation therapy, due to sickle cell anemia, β-thalassemia, aplastic anemia, cirrhosis with hemochromatosis, or malignancy and those undergoing long-term hemodialysis and receiving oral iron supplementation.[9,19–23] Less common extraintestinal manifestations include chronic infection with prolonged fever, granulomatous hepatitis, multiple liver and spleen abscesses, acute and chronic pancreatitis, acute pharyngitis, meningitis, osteomyelitis, pyomyositis, myocarditis, endocarditis, conjunctivitis, pneumonia and pleural empyema, urinary tract infection, and renal abscess.

Dermatologic manifestations include cellulitis, abscess, erythema nodosum, erythema multiforme, and cutaneous vasculitis. In adults, the most common complications of enteric infection are postinfectious sequelae, such as erythema nodosum, arthralgia, arthritis, and uveitis.[18] Polyarthritis occurs primarily in people with major histocompatibility class 1 antigen HLA-B27. Although joint swelling can persist for several months, the long-term prognosis is usually benign.[24,25] Chronic inflammatory bowel disease also has been associated with *Y. enterocolitica* infection.[26]

Laboratory Findings and Diagnosis

Fecal leukocytes are common in patients with colitis. *Y. enterocolitica* can be isolated from stool and sometimes from mesenteric lymph nodes or peritoneal fluid specimens from children who have undergone appendectomy. *Y. enterocolitica* grows on all commonly used enteric media. Cold enrichment in phosphate-buffered saline or other selective enrichment media are useful for recovery of *Y. enterocolitica.* Cefsulodin–irgasan–novobiocin (CIN) agar, which is selective for the growth of *Yersinia,* is preferred for isolation from fecal samples. Growth of pathogenic *Yersinia* can require up to 4 weeks of incubation.[27]

Yersinia organisms are coccobacillary and exhibit bipolar staining in blood agar. Stored samples or cultures grown on more restrictive media show morphologic variation with Gram stain. Avirulent strains are pyrazinamidase positive and fail to autoagglutinate; virulent strains stain with crystal violet and Congo red binding assays.

Y. enterocolitica species are divided into six biotypes (i.e., 1A, 1B, and 2–5), which include several serotypes. Most human pathogenic *Y. enterocolitica* strains are biotype 4, serotype O:3. Serotypes most commonly associated with disease in North America are different from those identified in Europe. Serologic responses can be used as evidence of infection when culture results are negative and a compatible syndrome is identified.

Titer determinations are available through commercial laboratories for the most common serotypes, but results should be interpreted with caution. Children younger than 1 year of age are less likely to develop a serologic response than older children. Cross-reactions with *Brucella abortus, Morganella morganii, Salmonella* species, *Bartonella henselae, Chlamydophila pneumoniae, Rickettsia rickettsii,* and *Borrelia burgdorferi* and persistence of titers for several years after *Y. enterocolitica* infection limit the usefulness of serodiagnosis. Using antibodies raised against the recombinant attachment-invasion locus (Ail) protein, detected by indirect enzyme immunoassay and Western blot immunoassay, can aid in identifying pathogenic *Y. enterocolitica* strains.

Several molecular techniques have been developed to identify *Y. enterocolitica* DNA in clinical, food, and environmental samples.[28–30] The detection rate of pathogenic *Y. enterocolitica* in clinical specimens is higher using polymerase chain reaction (PCR) than culture, but results must be interpreted with caution when the sample is from a nonsterile site.

Treatment

The benefit of antibiotics for management of immunocompetent people with *Yersinia* enterocolitis has not been established conclusively. Infected patients with abdominal pain and mesenteric adenitis usually are treated. Patients who are immunocompromised and patients with extraintestinal dissemination should be treated with antibiotics. *Y. enterocolitica* usually is susceptible in vitro to trimethoprim-sulfamethoxazole, chloramphenicol, fluoroquinolones, aminoglycosides, tetracycline, piperacillin, and extended-spectrum cephalosporins and resistant to most penicillins and first-generation cephalosporins.

If septicemia develops during desferrioxamine treatment in patients with iron overload states, chelation should be stopped temporarily. Antibiotic therapy has no beneficial effect on postinfectious syndromes.

Prevention

Outbreaks of illness due to *Y. enterocolitica* often are foodborne and should receive prompt and thorough investigation. Recall of suspected contaminated items can abort an outbreak. Careful attention to appropriate cooking practices in handling of pig products, especially intestines, should decrease the risk associated with these food products. Consumption of uncooked meats should be avoided, and meat should not be refrigerated for prolonged periods before consumption because *Y. enterocolitica* growth can be enhanced at refrigerator temperatures. No vaccine against *Y. enterocolitica* is available, although several candidates are under evaluation.

Key Points

Epidemiology, Clinical Manifestations, Diagnosis, and

Management of *Yersinia enterocolitica* and *Yersinia pseudotuberculosis* Infections

Epidemiology

- Yersiniosis is a zoonotic gastrointestinal disease.
- Contact with pork is a risk factor.
- Infections tend to cluster during winter months.
- Highest incidence
  - *Y. enterocolitica*: children <5 years of age
  - *Y. pseudotuberculosis*: children 5 to 15 years of age

Clinical Manifestations

- Most commonly
  - *Y. enterocolitica:* febrile enterocolitis with or without blood in stools
  - *Y. pseudotuberculosis:* pseudoappendicitis and less commonly Kawasaki-like illness
- Most serious complication: bacteremia mainly in infants and immunocompromised children

Diagnosis

- Stool culture using selective enrichment media
- Mesenteric lymph node or peritoneal fluid culture in children undergoing surgery
- PCR assays are available for clinical samples, food products, and

environmental samples.

Treatment

- Benefit of antimicrobial treatment is not established conclusively for immunocompetent children.
- Antimicrobial therapy should be used for immunocompromised patients with enterocolitis and patients with extraintestinal infection.
- Trimethoprim-sulfamethoxazole, chloramphenicol, fluoroquinolones, aminoglycosides, tetracycline, piperacillin, and extended-spectrum cephalosporins are usually active in vitro.
- Mortality rate for *Y. pseudotuberculosis* septicemia is 75%, irrespective of antimicrobial use.

Yersinia Pseudotuberculosis

Epidemiology

Y. pseudotuberculosis is distributed worldwide in animals, including rodents, birds (e.g., turkey, duck, geese, pigeons, canaries), rabbits, deer, and farm animals. Infection can follow exposure to well and mountain water. The organism was originally described as causing tuberculosis-like lesions in guinea pigs. Household pets often are the source of infection for children. *Y. pseudotuberculosis* also can be transmitted through food products, and outbreaks have been linked to pasteurized milk, lettuce, and carrots.[31,32]

As with *Y. enterocolitica,* infections in humans cluster in colder months. Human infections are most common among children between 5 and 15 years of age, with a threefold male predominance. Although the organism has a worldwide distribution, most cases have been reported from Europe. From 1996 through 2007, the average annual incidence of *Y. pseudotuberculosis* infection in the United States was 0.04 cases per 1 million people.[33] Compared with *Y. enterocolitica, Y. pseudotuberculosis* infects older individuals, who are more likely to require hospitalization for invasive infection. Patients with iron overload are at increased risk for infection, although this seems to be a less common risk factor than for *Y. enterocolitica* infections.

Clinical Manifestations

Y. pseudotuberculosis causes acute gastroenteritis and mesenteric lymphadenitis, often accompanied by fever and abdominal pain. The most common clinical syndrome is pseudoappendicitis, which is characterized by abdominal pain, right lower quadrant tenderness, fever, and leukocytosis. Less commonly, *Y. pseudotuberculosis* can mimic Kawasaki disease and has been implicated as a possible cause.[34–37] Yersinia has also been associated with intussusception, mainly in children.[38] Septicemia or extraintestinal spread of *Y. pseudotuberculosis* is uncommon and primarily has been reported in patients with underlying conditions such as cirrhosis, malignancy, diabetes, aplastic anemia, thalassemia, iron overload, and human immunodeficiency virus (HIV) infection.

Acute renal failure with interstitial nephritis is a complication in up to 14% of patients with *Y. pseudotuberculosis*, although prognosis is usually good.[39,40] *Y. pseudotuberculosis* infection occasionally leads to postinfectious sequelae such as reactive arthritis and erythema nodosum. Reactive arthritis and severe clinical outcome have been particularly associated with *Y. pseudotuberculosis* serotype O:3.[40]

Laboratory Findings and Diagnosis

Stool cultures of individuals with *Y. pseudotuberculosis*–associated pseudoappendicitis commonly are negative even though intestinal infection must have preceded spread to mesenteric nodes. Culture of mesenteric nodes removed at appendectomy can be positive. Cold enrichment of stool cultures and use of CIN agar appears to enhance recovery of *Y. pseudotuberculosis*. Identification of *Y. pseudotuberculosis* from food products and environmental sources using biochemical reactions can be misleading, and serotyping or molecular methods for virulence determinants should be used.[41]

Although 21 serotypes of *Y. pseudotuberculosis* have been identified, 80% of human cases are caused by serotype O:1. Several PCR assays have been developed to identify *Y. pseudotuberculosis*

DNA in clinical, food, and environmental samples, alone or in conjunction with genes for *Y. enterocolitica* or *Y. pestis*.

Treatment

Recovery from *Y. pseudotuberculosis* infection can occur without specific therapy. *Y. pseudotuberculosis* is usually susceptible to ampicillin, aminoglycosides, cephalosporins, trimethoprim-sulfamethoxazole, tetracycline, and chloramphenicol. Optimal antibiotic treatment of the rare patient with septicemia is unclear. The mortality rate for *Y. pseudotuberculosis* septicemia is 75% despite the use of an antimicrobial agent effective in vitro.

Prevention

There is no practical way to prevent sporadic cases of this rare disease. Outbreaks can be managed through careful epidemiologic investigation and intervention. Case contacts are usually at low risk and should not receive prophylactic antibiotics. Several candidate vaccines are under evaluation.

Yersinia Pestis

Y. pestis evolved from *Y. pseudotuberculosis* sometime during the past 20,000 years. Documented plague pandemics occurred during the 6th century (i.e., Justinian Plague) and the 14th century (i.e., Black Death). A third, ongoing pandemic began in the mid-19th century in China. India suffered an estimated 6 million deaths between 1900 and 1909, and Vietnam accounted for approximately 80% of the world's cases between 1965 and 1975. Since the 1990s, African countries (i.e., Madagascar, Congo, and Tanzania) have accounted for more than 90% of cases worldwide.[42–44] Although the severity of these pandemics has decreased due to improved sanitation and use of antibiotics, cases still occur, although mainly in underdeveloped regions.

Epidemiology

Plague is a zoonotic infection that is primarily maintained in rodents and their fleas. Animal reservoirs include rats, rabbits, prairie dogs, bobcats, coyotes, ground squirrels, rock squirrels, and wild mice.[45] Humans are incidental hosts primarily infected through a flea bite or direct contact with animal tissues.

The oriental rat flea *(Xenopsylla cheopis)* is the most efficient vector among many fleas capable of transmitting plague. A blood meal containing the bacillus clots in the flea's gut and causes intestinal obstruction. When the flea continues to feed, it regurgitates organisms into the victim's skin. Cases of human infection often occur after large numbers of infected rats have died, forcing fleas to seek other hosts. Primary pneumonic plague occurs after inhalation of respiratory droplets from a human or animal with pulmonary infection. Although primary pneumonic plague is rare, *Y. pestis* is a category A bioterrorism agent because of its potential to be spread by aerosol.

Plague occurs worldwide with enzootic foci in parts of Africa, Asia, and the Americas. Since 2000, approximately 22,000 cases of plague and 1600 deaths have been reported to the World Health Organization, with more than 95% occurring in countries in sub-Saharan Africa.[46] An upward trend in the incidence was observed starting in 2005, with a global average of 2083 cases reported annually.[47]

In the United States, a total of 1006 human plague cases were reported from 1900 through 2012, including 468 cases since 1965, with a median of 8 cases per year.[48] Since 1965, 88% of US cases have been reported from four states: New Mexico, Arizona, Colorado, and California. The median age of patients was 28 years (range, <1–94 years), and 268 (57%) were male. Although 54% (198 of 370) of patients were white, 33% (123 of 370) were Native American. The route of infection was unknown in 238 (51%) of cases, but 101 (22%) had a known flea bite, and 120 (33%) had contact with an infected animal. The peak onset was in July.

Plague has been associated with occupations and outdoor activities likely to bring people into contact with animals and fleas.[48,49] Occasionally, fleas of a pet dog or cat are the source of infection. Cats can develop symptomatic plague and spread infection through biting, scratching, or coughing. Similarly, dogs can develop moderate to severe illness or die as a result of infection; 62 confirmed cases of canine plague were identified from 2003 to

2011 in New Mexico.[50] An outbreak of four human pneumonic plague cases with dog-to-human transmission was reported in Colorado in 2014.[51]

Clinical Manifestations

Clinical syndromes associated with *Y. pestis* infection are bubonic, septicemic, pneumonic, and meningeal plague. Asymptomatic infections also occur.

Bubonic Plague.

Bubonic plague is the most common form of plague. Symptoms appear 2 to 10 days after a flea bite and are characterized by exquisitely tender, nonfluctuating lymphadenitis (i.e., bubo) in regional lymph nodes draining the bite area. A papule, vesicle, or ulcer at the inoculation site develops in approximately 25% of cases. The skin may show insect bites and scratch marks, but there is no associated ascending lymphangitis. Localized cellulitis or abscess at the flea bite site is rare. In 90% of cases, the bubo is unilateral and can reach up to 10 cm in diameter; suppuration, sometimes with drainage, occurs in approximately 20%.

Although the onset of fever usually coincides with lymphadenitis, it can precede the bubo by several days. Bacteremia usually is associated with high fever accompanied by chills, headache, malaise, anorexia, vomiting, myalgia, and prostration. Complications include endotoxic shock and purpura or gangrene of the extremities due to disseminated intravascular coagulopathy. Bubonic plague was referred to as the Black Death due to the appearance of these lesions. Untreated, it has a mortality rate of approximately 50%.

Septicemia.

Between 10% and 25% of plague cases manifest as primary septicemia with endotoxemia, hypotension, shock, and multiorgan failure without obvious lymph node involvement.[42,49] These patients have a mortality rate that exceeds 30% despite appropriate antimicrobial treatment. Abdominal pain, nausea, vomiting, and diarrhea can occur and confuse the initial diagnostic approach.

Pneumonia.

Pneumonia occurs in less than 16% of cases due to inhalation (i.e., primary plague pneumonia) or hematogenous seeding associated with bubonic or septicemic plague (i.e., secondary pneumonia). Symptoms include chest pain, progressive tachypnea, dyspnea, hypoxia, and productive cough. Sputum can be watery, frothy, blood tinged, hemorrhagic, or purulent. The chest radiograph characteristically shows alveolar infiltrations and extensive bronchopneumonia; cavitation can be seen.

Primary plague pneumonia is characterized by a short incubation period lasting from a few hours to 3 days, with death occurring as early as the first day of symptoms. Secondary pneumonia occurs in 57% of septicemic plague cases and 6% of bubonic cases. Untreated pneumonic plague has a fatality rate of 93%. However, an outbreak in Colorado in 2014 highlighted the potential for milder pneumonic plague in patients taking antimicrobial agents.[51] Pneumonia is the only form of plague with the potential for human-to-human transmission. The possibility of aerosol transmission and the severe disease of pneumonic plague are the basis for considering *Y. pestis* a potential biologic weapon.[42] Rarely, pharyngeal plague can follow direct contact with infectious materials.

Meningitis.

Altered mental status, including lethargy, stupor, and delirium, is common in bubonic plague, but true meningitis tends to be a late complication in patients receiving inadequate treatment. Meningitis is more common in children than in adults and occurs in about 10% of children with plague in the United States[49,52]

Pediatric Considerations.

Among 183 US pediatric plague cases from 1947 to 2001, the primary clinical presentations were bubonic (91%) and septicemic (7%).[49] One third of the bubonic cases developed secondary complications, including bacteremia, pneumonia, or meningitis. Children were more likely than adults to have bubonic plague (91% vs. 79%), develop complications (32% vs. 27%), and die (17% vs. 14%).

Laboratory Findings and Diagnosis

The diagnosis of plague usually is confirmed by culture of *Y. pestis* from blood, bubo aspirate, sputum, or cerebrospinal fluid. *Y. pestis* grows in routine culture media, including blood agar, within 48 hours. Blood cultures are positive for approximately 60% of children with bubonic plague and 100% with septicemic plague. Quantitative blood culture data suggest that a bacterial density greater than 10^2 organisms/mL is associated with an increased risk of hypotension and death. Automated blood culture identification systems can misidentify *Y. pestis*. Isolation of *Yersinia* species from an automated system should be evaluated to determine whether the clinical presentation is consistent with plague.

A positive Wright-Giemsa, Wayson, or fluorescent antibody stain on direct smear or cultures of clinical specimens provides presumptive evidence of *Y. pestis* infection.[53] A single positive serologic test result for *Y. pestis* F1 antibodies by passive hemagglutination or enzyme immunoassay in an unimmunized patient also provides presumptive evidence of plague. A fourfold or greater rise in antibody titers in paired specimens confirms the diagnosis.[42] PCR tests that use structural genes for F1 antigen, plasminogen activator, or murine toxin have been developed and are available in some reference or public health laboratories. Use of a bioluminescent reporter phage that allows rapid detection and antibiotic susceptibility analysis of *Y. pestis* directly from clinical specimens also has been evaluated.[54]

Suspected plague cases should be reported immediately to state and local public health departments. Laboratory personnel should be notified that they will be receiving specimens for evaluation.

Differential Diagnosis

The differential diagnosis of bubonic plague includes streptococcal and staphylococcal lymphadenitis, tularemia, and cat-scratch disease.[49] Septicemic plague, especially in patients with purpura and peripheral gangrene, can be confused with meningococcemia or with sepsis due to other gram-negative pathogens. Common causes of community-acquired pneumonia, tularemia, and hantavirus infection should be considered in the differential diagnosis of pneumonic plague.

Treatment

Y. pestis from human cases have been susceptible universally to β-lactam agents, cephalosporins, carbapenems, tetracycline, aminoglycosides, chloramphenicol, and quinolones.[55] Most isolates are resistant to colistin, polymyxin B, and macrolides, including clarithromycin. Plasmid-mediated multidrug resistance has been described.[56] In many countries, intramuscular streptomycin (20 to 30 mg/kg/day in 2 doses for 7 to 10 days) is the drug of choice for treating plague. Gentamicin, alone or in combination with tetracycline or doxycycline, appears to be equally effective and is an alternative choice.[57]

In a randomized, controlled trial of bubonic plague, gentamicin and oral doxycycline were equivalent; however, it is unclear whether these results can be extrapolated to pneumonic plague.[58] Trimethoprim-sulfamethoxazole is approved by the US Food and Drug Administration (FDA) for the treatment of plague but has higher failure rates and should not be used as first-line therapy for bubonic plague or as monotherapy for septicemic or pneumonic plague.

Fluoroquinolones have been shown to be highly effective in animal and in vitro studies, and the FDA has approved levofloxacin for the treatment of plague. Streptomycin and ciprofloxacin have superior efficacy in vitro against intracellular *Y. pestis*, which is important for the initial phase of infection.[55] In a murine model, the combination of ciprofloxacin and gentamicin was more effective than gentamicin monotherapy to eradicate *Y. pestis* from the lymph node.[59] Chloramphenicol (75 to 100 mg/kg/day) is the drug of choice for plague meningitis, but levofloxacin and other fluoroquinolones with good cerebrospinal fluid penetration should be considered as an alternative therapy.

Fever typically resolves an average of 6 days (range, 1–15 days) after initiation of effective antimicrobial therapy. Relapse after completion of therapy is rare despite the fact that organisms occasionally can be recovered from buboes late in therapy. Intravenous fluids for correction of shock and dehydration usually are required as part of initial management of plague. Corticosteroid therapy is not indicated, and heparin has no proven value for treating associated disseminated intravascular coagulation.

The case-fatality rate ranges from 50% to 90% for untreated bubonic plague and approaches 100% for untreated septicemic and pneumonic plague. With effective antibiotic therapy, the case-fatality rate can be as low as 5% for bubonic plague but remains at 30% or higher for septicemic plague.[60] Patients with pneumonic plague who do not receive therapy within 18 hours of onset of respiratory symptoms are unlikely to survive.

Y. pestis is considered a category A bioterrorism agent.[61,62] Doxycycline or ciprofloxacin is recommended for mass treatment or prophylaxis after a potential bioterrorism event. Children exposed to patients with pneumonic plague or aerosolized *Y. pestis* can receive prophylaxis with doxycycline (2 mg/kg twice daily), trimethoprim-sulfamethoxazole (4 to 6 mg/kg of the trimethoprim component twice daily), ciprofloxacin (15 to 20 mg/kg twice daily), or chloramphenicol (25 mg/kg every 6 hours) for 7 days.[63,64]

Prevention

People living in plague-endemic areas should take measures to decrease rat and flea exposures. Use of an insect repellent containing *N,N*-diethylmethyltoluamide (DEET) applied to the legs and ankles is helpful if exposure is likely. Care in handling of dead animals is important. Insecticides and rat control are useful in the prevention of murine plague. Flea control for pet dogs and cats also is important. Public health officials should be notified when a case of plague is diagnosed to assist in managing environmental reservoirs and vectors.

Spread of pneumonic plague is best prevented by early diagnosis, initiation of appropriate therapy, and strict isolation (including droplet precautions) for patients in whom plague is suspected for several days after initiation of appropriate therapy. Contacts of individuals with plague pneumonia should receive tetracycline, doxycycline, or ciprofloxacin prophylactically for 7 days. Animal studies suggests that imipenem may be used for prophylaxis of *Y. pestis* aerosol exposure.[65] Microbiology laboratory personnel should be alerted when receiving samples possibly containing plague bacillus to exercise extreme caution in handling.

In experimental mouse models, maternal antibodies induced by the plague vaccine can be transferred to the newborn through the placenta and lactation. This suggests that passive immunization could be an effective countermeasure against plague during an epidemic.[66]

Live, attenuated and killed whole-cell vaccines against *Y. pestis* have been available for many years, but they have several shortcomings, including unproven effectiveness, and they are not licensed for use in the United States. Several other vaccines are under development, including live, attenuated; DNA; and subunit vaccines (i.e., F1 and LcrV antigens).[67,68] The potential use of *Y. pestis* for bioterrorism emphasizes the need to develop more effective vaccines against airborne infection.

Key Points

Epidemiology, Clinical Manifestations, Diagnosis, and Management of *Yersinia pestis* Infection

Epidemiology

- *Y. pestis* causes *bubonic or septicemic plague* when acquired through a flea bite.

- Plague occurs largely in poor populations in contact with rodents, particularly in endemic countries of Africa, Asia, and the Americas.

Clinical Manifestations

- Bubonic plague
  - Most common form of plague: symptoms appear 2 to 10 days after a flea bite
  - Symptoms: bubo (exquisitely tender, nonfluctuating lymphadenitis), high fever, headache, malaise, anorexia, vomiting, myalgia, and prostration
  - Complications: endotoxic shock and purpura or gangrene of extremities

- Septicemic plague
  - Sole clinical manifestation in 10% of plague cases
  - Septicemia symptoms: abdominal pain, nausea, vomiting, hypotension, shock, and multiorgan system failure
  - Pneumonia symptoms: chest pain, progressive tachypnea, dyspnea, hypoxia and productive cough (sputum can be watery, frothy, blood tinged, hemorrhagic, or purulent)
  - Chest radiograph: alveolar infiltrates and extensive bronchopneumonia with or without cavities
  - Aerosol transmission and a high potential for severe disease make *Y. pestis* a potential biologic weapon
  - High lethality if not treated promptly
- Meningitic plague
  - Late complication in patients receiving inadequate treatment for bubonic plague
  - More common in children than adults
  - Symptoms: altered mental status, including lethargy, stupor, and delirium

Diagnosis

- Characteristic bipolar-staining coccobacilli in bubo aspirate, cerebrospinal fluid, or sputum using Wright-Giemsa or Wayson stain

- Routine culture media

- Rapid diagnosis: antigen detection tests and PCR

- Fourfold serum antibody rise is diagnostic

Treatment

- Most strains are susceptible in vitro to β-lactam agents, tetracycline, aminoglycosides, chloramphenicol, and fluoroquinolones.

- Drugs of choice include intramuscular streptomycin and gentamicin alone or in combination with tetracycline or doxycycline or ciprofloxacin.

- Doxycycline or ciprofloxacin is recommended for prophylaxis of contacts.

- Mortality rate is 50% to 100% for untreated plague, 5% for treated bubonic plague, and ≥30% for treated septicemic plague.

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Nonenterobacteriaceae Gram-Negative Bacilli

OUTLINE

149 Acinetobacter Species
150 Aeromonas Species
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Acinetobacter Species

Guliz Erdem, Amy Leber

Microbiology

Acinetobacter species are nonmotile, oxidase-negative, catalase-positive, strictly aerobic, gram-negative coccobacilli. Their inability to ferment glucose or to reduce nitrate distinguishes *Acinetobacter* from the family Enterobacteriaceae. *Acinetobacter* is a genus of opportunistic pathogens within the Gammaproteobacteria class in the family Moraxellaceae along with the *Moraxella*, *Psychrobacter*, and other genera.[1–5]

The more than 40 genospecies in the genus *Acinetobacter* include *Acinetobacter calcoaceticus* (genospecies 1), *A. baumannii* (genospecies 2), *A. haemolyticus* (genospecies 4), *A. junii* (genospecies 5), *A. johnsonii* (genospecies 7), *A. lwoffii* (genospecies 8), and *A. radioresistens* (genospecies 12) (http://www.bacterio.net/acinetobacter.html).[6] Most other genospecies cannot be separated easily with conventional biochemical tests or commercial identification systems. Isolates of *A. calcoaceticus, A. baumannii, A. pitti* (formerly genospecies 3), and *A. nosocomialis* (formerly genospecies 13TU) strains can use glucose oxidatively and often are identified as *A. baumannii* by conventional identification systems.[4,7] These organisms can be reported collectively as *Acinetobacter calcoaceticus–A. baumannii* group organisms, but this classification is suboptimal because of the increased clinical significance of *A. baumannii* in human infections. The use of *A. baumannii* group to refer to *A. baumannii*, *A. pitti,* and *A. nosocomialis* may be the limit of differential identification for most laboratories.

Similarly, non–glucose-oxidizing isolates of *A. lwoffii, A. johnsonii,* and *A. junii* may be reported as nonsaccharolytic *Acinetobacter* spp. Most nonhemolytic, glucose-oxidizing clinical isolates are *A. baumannii*, and most nonhemolytic, non–glucose-oxidizing clinical isolates are *A. lwoffii*. Most hemolytic isolates of *Acinetobacter* spp. are *A. haemolyticus*.[1,2,4,5]

Acinetobacter spp. can be isolated readily from clinical material on blood, on chocolate, and usually on MacConkey agar; some fastidious strains grow poorly or not at all on the latter medium. Colonies first appear as small and nonpigmented on blood and chocolate agars and as colorless, light pink, or purplish growths on MacConkey agar. On Gram stain, *Acinetobacter* spp. are short, plump coccobacilli or rods (sometimes resembling *Moraxella* or *Neisseria* spp.) but distinguished easily by their lack of cytochrome oxidase activity. Some cells from direct staining of clinical specimens or from culture can hold the crystal violet of Gram staining and appear as gram-positive, staphylococcal-like cocci.

Additional nutritional and physiologic tests beyond standard identification systems may be necessary.[4] Matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) mass spectrometry has good performance for identification of gram-negative bacilli. However, with current databases, identification of *Acinetobacter* species other than *A. baumannii* does not appear to be reliable.[8–10]

For definitive identification of the *A. baumannii* group, genotypic methods such as amplified ribosomal DNA restriction analysis (ARDRA) of the 16S rRNA gene and amplified fragment length polymorphism (AFLP) are recommended.[6] Whole genome sequencing can be used for accurate genotyping and for investigation of the emergence of antibiotic-resistant strains[11,12] (http://www.ncbi.nlm.nih.gov/genome/browse/). Genotypic identification may further clarify roles of the *Acinetobacter* spp. in human disease.

A. baumanii survives for prolonged periods in healthcare environments, resists inactivation by disinfectants, and acquires resistance to a wide variety of antibiotics. The plasticity of the genome appears to play a major role in the organism's ability to gain and rearrange genes associated with pathogenicity. Data on virulence factors associated with *A. baumannii* and other *Acinetobacter* spp. are limited. Factors include capsular polysaccharides, protein adhesins, proteolytic and lipolytic enzymes, aspects of boil formation, and gram-negative lipopolysaccharide.[2,7] OmpA, an outer membrane porin, has been associated with virulence by several mechanisms, including host cell death through apoptosis and biofilm formation.[13] Reports suggest that ethanol can play a regulatory function in the organism, which is a concern because of the common use of ethanol in clinical care settings.[7]

Acinetobacter strains display a twitching motility, particularly in response to light. Regulation of motility is thought to contribute to the organism's spread over surfaces and may facilitate biofilm formation.[7,14] In addition to OmpA liposaccharide, capsular polysaccharide, phospholipase, penicillin-binding protein 7/8, outer membrane vesicles, and acinetobactin-mediated iron acquisition system have been identified as possible virulence factors.[7]

Epidemiology

Acinetobacter spp. are found in many environmental sources, including water, soil, foods, and arthropods, and they can survive on dry surfaces much longer than other bacteria causing with healthcare-associated infections (HAIs).[15,16] Unlike most other gram-negative bacilli, *Acinetobacter* bacteria can colonize dry and moist areas of healthy human skin. In one study of skin and mucous membranes, up to 43% of nonhospitalized patients were colonized with *Acinetobacter* spp.; *A. lwoffii*, *A. johnsonii*, and *A. junii* were the most common species detected.[17] *A. baumannii* uncommonly colonizes healthy human skin and is recovered infrequently from environmental sources outside the hospital. Its natural habitat has not been determined.[5]

Acinetobacter spp. are opportunists in healthcare and home care settings. In a US and European study, *Acinetobacter* spp. were the eighth most common organism isolated from patients hospitalized with pneumonia between 2009 and 2012.[18] Genospecies of *Acinetobacter* may show geographic variations.[19,20] In one US study conducted between 1995 and 2003, approximately one third of *Acinetobacte*r bloodstream infections (BSIs) were caused by *A.*

nosocomialis or *A. pitti*, and 63% were caused by *A. baumannii*.[21] In a study of *Acinetobacter* spp. BSIs in a children's hospital, the most common species recovered were *A. baumannii* (44%) and *A. lwoffii* (39%).[22] Although *Acinetobacter* spp. frequently are acquired nosocomially, BSIs in children were substantially acquired in the home setting in one study.[22] Most patients had an indwelling central venous catheter, and exposure to water or soil was considered a major risk factor.

The rate of colonization with *Acinetobacter* spp. of the skin, oral mucosa, and gastrointestinal tract increases rapidly after admission to the hospital and particularly to intensive care units (ICUs). Nosocomial outbreaks have been associated with reservoirs such as tap water, sinks, room humidifiers, water baths, air conditioners, tap water aerators, respiratory care equipment, dusty filters, and the skin of healthcare personnel.[23–25] Contaminated parenteral solutions can be a source.[26] Patient-to-patient transmission of *A. baumannii* probably occurs by transient colonization and spread by the hands of healthcare personnel.

Acinetobacter spp. are considered pathogens of low virulence. They cause opportunistic infections only in people with compromised immune status or with an indwelling device, or both. Of the top 10 organisms causing hospital-acquired BSIs in US hospitals from 1995 to 2002, *Acinetobacter* spp. ranked 10th in incidence (0.6 of 10,000 admissions) but second in crude mortality rates (34%).[27]

In two reports from the SENTRY Antimicrobial Surveillance Program on pediatric blood, urine, pulmonary, or wound infections for 1998 to 2003 and for 2004, *Acinetobacter* spp. accounted for 1.8% of all pathogenic isolates.[28,29] Risk factors for *Acinetobacter* infection included the use of intravenous devices and urinary tract catheters, immunosuppression, admission to an ICU or burn unit, respiratory failure at ICU admission, previous antimicrobial therapy, diabetes mellitus, and chronic lung disease.[30–32] In a report of the National Nosocomial Infections Surveillance System of the Centers for Disease Control and Prevention (CDC) for 1992 to 1997, the contribution of *Acinetobacter* spp. to pediatric ICU HAIs was 2% of BSIs, 3% of pneumonia cases, 3% of lower respiratory infections other than pneumonia, and less than 1% of urinary tract or surgical site infections.[33] Other infections included endocarditis, meningitis after neurosurgical infections, and peritonitis.

Acinetobacter spp. can be recovered from cultures of blood or other clinical specimen as contaminating or colonizing organisms. This complicates the interpretation of positive cultures.

Clinical Manifestations

Clinical manifestations of *Acinetobacter* BSIs are not unique. Temperature instability, central apnea, and thrombocytopenia can occur in infants.[26] In a study of 29 episodes of *Acinetobacter* spp. BSIs in children with cancer, 11 episodes were polymicrobial, and only 3 occurred in children with an absolute neutrophil count less than 500/mm^3. Risk of infection was associated with solid tumors, indwelling intravascular catheter, recent chemotherapy treatments, and prior receipt of antimicrobial agents. There were few manifestations of gram-negative septicemia other than fever and malaise, and no child developed septic shock.[34,35]

Although *A. baumannii* was the most prevalent species among nosocomial BSIs in two US studies, *A. pitti* and *A. nosocomialis* accounted for more catheter-related BSIs.[21,36] BSI due to *A. baumannii* is associated with a higher mortality rate than BSIs due to *A. pitti* or *A. nosocomialis*.[37] Crude mortality rates for *A. baumannii* BSIs are 28% to 68%.[7,27] In a pediatric case review, the attributable mortality rate was 14.5%.[38]

In a review of 25 patients, including 5 children with nosocomial meningitis due to *Acinetobacter* spp. after neurosurgery, most patients had fever and signs or symptoms of central nervous system infection.[39] The average cerebrospinal fluid white blood cell count was 5700 cells/mm^3 with 90% neutrophils. *A. lwoffii* was more commonly associated with meningitis than other *Acinetobacter* spp. Risk factors for meningitis in infants included a ventriculoperitoneal shunt, previous neurosurgery, and central nervous system abnormalities.[40] *Acinetobacter* spp. have been associated with pediatric outbreaks, predominantly in neonatal ICUs, involving BSI and meningitis.[38]

Most cases of suspected or confirmed pneumonia due to *Acinetobacter* spp. are HAIs in intubated children. Clinical manifestations are not distinctive. Determining a precise pathologic role is challenging because *Acinetobacter* spp. can be isolated from intubated patients, colonizing the upper respiratory tract and contaminating tracheal aspirates. Quantified recovery of *Acinetobacter* spp. from specimens collected by bronchoalveolar lavage is more meaningful in defining infection. The mortality rate for pneumonia due to *Acinetobacter* spp. in ventilated patients can be as high as 23% to 73%.[41]

Urinary tract and wound infections are relatively uncommon in children and usually occur in patients with hematologic malignancies, neonates, or those with neurologic disorders and bladder dysfunction.[42] The incidence of soft tissue infections appears to be increasing.[2] *A. baumannii* is also an important cause of burn infections.[7] Trauma-associated osteomyelitis has been reported among military personnel.[7] *Acinetobacter junii* is reported as a rare cause of BSI and ocular infection in pediatric patients.[24,43]

Treatment

Antimicrobial susceptibility of *Acinetobacter* spp. varies widely across institutions and countries; however, the emergence of multidrug-resistant strains of *A. baumannii* due to selective antimicrobial pressure and intrinsic resistance mechanisms is a worldwide problem.[44–47] Mechanisms of resistance include production of inactivating enzymes, including broad-spectrum β-lactamases class A, B, C, and D and aminoglycoside-modifying enzymes; alteration of penicillin-binding proteins; alterations of DNA gyrase and topoisomerase IV, the target sites for quinolone antibiotics; ribosomal RNA methylation; decreased permeability of the outer membrane to β-lactam antibiotics; and overexpression of efflux pumps and biofilm formation.[2,45]

All strains of *A. baumannii* harbor chromosomally encoded AmpC-type enzymes, referred to as *Acinetobacter*-derived cephalosporinases, somewhat analogous to the AmpC enzymes found in *Enterobacter* spp. and other Enterobacteriaceae.[1] Overexpression of these enzymes results in resistance to extended-spectrum cephalosporins, but cefepime and carbapenem antibiotics retain activity. A wide variety of extended-spectrum β-lactamases (ESBLs) can be found in *Acinetobacter* spp., and these enzymes appear to be similar to ESBLs found in other Enterobacteriaceae and *Pseudomonas aeruginosa*. Horizontal transfer of resistance islands with many resistance genes and rearrangement of preexisting genes permit *Acinetobacter* spp. to adapt to hospital environments.[48]

In a retrospective UK study, *A. baumannii* carbapenem resistance rates rose from 0% in 1998 to 55% in 2006 among bacteremic patients.[49] In the United States, carbapenem resistance rates of *Acinetobacter* spp. rose from 6% in 1999 to 28% in 2006,[21] which are higher than for other gram-negative bacteria.[50] In a US report on ICU patients in 2011, in vitro susceptibility of *Acinetobacter* spp. was 39% to ceftazidime, 43% to meropenem, 48% to tobramycin, and 37% to ciprofloxacin.[18]

Healthcare-related outbreaks due to carbapenem-resistant strains of *Acinetobacter* spp. are reported increasingly.[45,51] In two pediatric ICUs in Thailand and Greece, 64% and 62% of *Acinetobacter* spp. were carbapenem resistant, respcctively.[52,53]

The β-lactamase inhibitor agent sulbactam and the polymyxin antibiotic colistin have been used with some success in a limited number of nonrandomized clinical trials.[54–59] Sulbactam has both β-lactamase inhibitor activity and direct antibacterial activity against *Acinetobacter* spp. by binding irreversibly to penicillin-binding protein 2. Sulbactam has excellent in vitro activity and is effective in treating *Acinetobacter* infections. In vitro synergy with meropenem also has been demonstrated.[56] Ampicillin-sulbactam is more active than ticarcillin-clavulanate or piperacillin-tazobactam and was more effective than polymyxins for the treatment of infections due to multidrug-resistant (including carbapenem-resistant) *Acinetobacter* spp.[54,55] When active, carbapenems have excellent bactericidal activity. Several uncontrolled studies of intravenous colistin for the treatment of multidrug-resistant *Acinetobacter* spp. infections appear to demonstrate effectiveness and safety.[58,60] Minocycline and tigecycline have in vitro activity against *A. baumannii*, but clinical efficacy data are limited, particularly in pediatrics.[61]

Case reports and small studies suggest that combination antimicrobial therapies such as colistin plus rifampicin and tigecycline plus colistin were effective[62,63] and may be preferred for severely ill patients.[64] Aminoglycosides can be used in combination.[59] Eravacycline is being evaluated as an agent with in vitro activity against *A. baumannii*.[65]

Although disk diffusion and dilution minimum inhibitory concentration (MIC) methods of susceptibility testing are recommended for *Acinetobacter* spp. by the Clinical and Laboratory Standards Institute (CLSI), differences in the categorical interpretations of these two methods against selected β-lactam agents have been reported.[66,67] There also are differences between gradient agar diffusion E-test MIC and broth microdilution MIC for *Acinetobacter* spp. against the polymyxins. There are no CLSI disk diffusion or MIC breakpoints for tigecycline against *Acinetobacter* spp., and only MIC breakpoints are provided for colistin.[66] Discordance in the susceptibilities of carbapenems is increasingly described for imipenem, meropenem, and doripenem.[59]

The available data preclude a firm recommendation for combination treatment or monotherapy for children with resistant infections. Most experts prefer combination treatment for severely ill patients. The use of prolonged infusion β-lactam agents, increased drug doses, and altered routes of administration such as nebulized therapy for pulmonary infections may help treatment of infections due to strains resistant to all available antibiotics.[45,67]

Contaminated indwelling devices should be removed. Prevention of *Acinetobacter* spp. infections requires judicious use of medical devices and antimicrobial agents and meticulous adherence of healthcare personnel to infection control practices.

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Key Points

Diagnosis and Management of *Acinetobacter* Spp. Infections

Microbiology

- Nonmotile, oxidase-negative, catalase-positive, strictly aerobic, gram-negative coccobacilli

- Good growth on blood, chocolate, and usually on MacConkey agar; *A. calcoaceticus*

- *A. baumannii, A. pitti,* and *A. nosocomialis* use glucose oxidatively and often are identified as *A. baumannii* by conventional systems.

Epidemiology

- Wide variety of environmental sources (e.g., water, soil, foods)

- Survives for prolonged periods in the healthcare environment, resists inactivation by disinfectants, and can acquire multidrug resistance

- Risk factors for infection include the use of intravenous devices and urinary tract catheters, immunosuppression, admission to an intensive care unit (ICU) or burn unit, respiratory failure at ICU admission, previous antimicrobial therapy, diabetes mellitus, and chronic lung disease.

- Bloodstream infection, pneumonia, and meningitis are common.

Diagnosis

- Recovery in culture uses standard laboratory procedures.

- Amplified ribosomal DNA restriction analysis (ARDRA) of the 16S rRNA gene and amplified fragment length polymorphism (AFLP) are techniques used for definitive identification but are not available widely.

- Whole genome sequencing can be used for genotyping and investigation of emergence of antibiotic-resistant strains.

Treatment

- Emergence of multidrug-resistant strains is a worldwide problem.

- Ampicillin-sulbactam and carbapenems can be used if strains are susceptible.

- Combination antimicrobial therapies (e.g., colistin plus rifampicin, tigecycline plus colistin) may be preferred for severely ill patients with resistant strains.

- Duration of therapy for systemic and osteoarticular infections or endocarditis is similar to that for other infectious agents.

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Aeromonas Species

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Description of the Pathogen

The genus *Aeromonas* consists of environmental, facultatively anaerobic, gram-negative bacilli that are predominantly motile as a result of a single polar flagellum. Although at least 25 species have been described in this genus, only *A. hydrophila, A. caviae, A. veronii* biovar *sobria, A. dhakensis,* and *A. trota* are relevant human pathogens.[1–6] *Aeromonas* spp. produce oxidase, catalase, nitrate reductase, and an array of exoenzymes. They can display a variety of virulence factors, including heat-stable and heat-labile enterotoxins, lipopolysaccharides, hemolysins, proteases, leukocidin, elastase, fibrinolysin, DNase, lecithinase, lipases, amylase, adhesins, agglutinins, pili, and an array of outer membrane proteins.[1,3] The motility of these species is essential for survival in liquid environments and for colonization of surfaces. Subsequently, other outer membrane proteins, including fimbrial systems, mediate human cell adherence. Some strains are also capable of cell invasion and immune system evasion, thereby favoring invasive disease.[3]

Epidemiology

Aeromonas spp. are ubiquitous and can be isolated from almost any environment. Most environmental isolates come from fresh or brackish water sources; contamination of chlorinated tap water also has been reported.[1,3] *Aeromonas* spp. colonize and can cause disease in cold-blooded animals, including fish, amphibians, and reptiles, which can act as reservoirs.[1,5]

The first report of human *Aeromonas* infection occurred in 1954 in a woman with myositis. In 1961, *Aeromonas* spp. were first isolated from human feces. Since then, *Aeromonas* spp. have been incriminated as agents of gastroenteritis, skin and soft tissue infections, and sepsis and other invasive infections mainly in immunocompromised patients. Infection is most common during warmer months and is acquired through ingestion of contaminated water or food, especially fish, seafood, and vegetables, or by swimming or bathing in contaminated water.[1,5,7,8] Skin and soft tissue infections caused by wild animal bites and leech therapy also have been described.[9,10]

Disease burden is difficult to determine as a result of underreporting and lack of routine diagnosis. Specific diagnostic tests are required to differentiate pathogenic species from normal flora and other pathogenic gram-negative bacilli such as *Vibrio* and *Plesiomonas* spp.[1,7] Asymptomatic fecal carriage is observed in approximately 1% to 2% of healthy people residing in nontropical regions and in up to 27% of healthy adults residing in tropical areas.[11–13] *Aeromonas* spp. have been implicated in 1% to 13% of cases of endemic diarrhea in children and in 2% to 7% of cases of diarrhea in adults.[13] These pathogens also have been associated with approximately 2% of dysentery episodes in developed countries and in 7% to 22% of dysentery episodes in developing countries.[14] Among travelers, 1% to 4% of cases of diarrhea have been attributed to *Aeromonas* species, with a higher incidence in travelers to Southeast Asia.[1,2,13]

A prospective study in 70 hospitals in France identified 78 *Aeromonas* spp. infections over 6 months in 2006; of these infections, 44% were skin and soft tissue infections, 26% bacteremia, 19% gastroenteritis, 6% respiratory tract infection, and 5% miscellaneous.[5]

Clinical Manifestations

Gastroenteritis.

Gastroenteritis is the most common clinical illness attributed to *Aeromonas* infection in humans.[13] Both the small intestine and large intestine can be infected. Self-limited watery diarrhea is the most common presentation, although cholera-like illness has been reported.[1] Fever and vomiting are common in children. One third of patients have dysentery associated with colitis[14,15]; fever and malaise are more common in patients with this presentation. In contrast to other causes of dysenteric bacterial gastroenteritis, stool leukocytes are uncommon. Chronic or intermittent diarrhea lasting for weeks has been described in one third of patients infected by *A. caviae*.[1,15] Reported complications include bacteremia, intussusception, failure to thrive, hemolytic uremic syndrome, and strangulated hernia.[1,16]

Skin and Soft Tissue Infections.

Skin and soft tissue infections comprise the second most common presentation of *Aeromonas* infections; *A. hydrophila* is the predominant species.[5] Major predisposing factors are local trauma occurring in people during recreational swimming, exposure to contaminated water in occupational or recreational activities, and shark or reptile bites. Soft tissue infection also has been reported in patients immersed in water immediately after being burned and, more rarely, after leech therapy or standard medical procedures such as gastrointestinal tract operations.[1,5,9] Cellulitis develops 8 to 48 hours after trauma, eventually followed by rapid spread to deep tissues. The clinical spectrum includes localized skin nodules, soft tissue abscess, furunculosis, ecthyma gangrenosum, bullous cellulitis with crepitance, synergistic necrotizing cellulitis, and myonecrosis.[17] *Aeromonas* soft tissue infection can mimic cellulitis caused by group A streptococcus, *Clostridium* species, and ecthyma gangrenosum caused by *Pseudomonas aeruginosa*.[1,17,18] Immunocompromised patients are at increased risk for bacteremia and sepsis.[19]

Sepsis.

Septicemia is the most serious and life-threatening complication of *Aeromonas* infection. Septicemia occurs primarily in immunocompromised patients, especially people with hematologic malignant diseases, hepatobiliary conditions, and malnutrition.[5,6,20–23] Cases in immunocompetent hosts increasingly are reported, associated with burns, penetrating trauma, and recreational or professional activities with exposure to contaminated water.[1,5] Although most cases are community acquired, nosocomial bloodstream infection (BSI) has been described in oncologic patients.[6] Clinical presentation is similar to that caused by other gram-negative bacilli, including fever (74%–89%), jaundice (57%), abdominal pain (16%–45%), septic shock (40%–45%), and dyspnea (12%–24%). Diarrhea immediately preceding or concurrent with the onset of bacteremia is uncommon (9%–14%). In 60% to 70% of these BSIs, *Aeromonas* is the only bacterium isolated, but the remaining infections occur in association with other organisms such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Staphylococcus aureus*. A secondary focus of infection in ascitic fluid, bile, wounds, or urine can be found in up to 25% of patients.[1,5–7,20,22,24] BSI-associated mortality rates range from 5% to 60%, depending on the underlying condition. Poor prognosis has been associated with altered consciousness, septic shock, underlying liver cirrhosis and cancer, community-acquired focal infection, and persistent or secondary bacteremia.[6,24]

Uncommon Clinical Presentations.

Aeromonas spp. have been rarely associated with a variety of other systemic and local infections including intra-abdominal infections (peritonitis, pancreatitis, cholangitis, hepatic abscesses), pneumonia (aspiration associated with near-drowning episodes), lung abscess, endophthalmitis, tonsillitis, otitis media, urinary tract infection, endocarditis, meningitis, osteomyelitis, pyogenic arthritis, and suppurative thrombophlebitis.[1,5,25–27]

Laboratory Findings and Diagnosis

No pathognomonic clinical laboratory findings are present in *Aeromonas* spp. infections. Gastroenteritis can be associated with abnormalities of acid-base and renal function; white blood cell count and serum C-reactive protein level can be mildly elevated.[1,5] In skin and soft tissue infection, BSI, and other invasive infection, moderate leukocytosis (up to 16,000 cells/mm^3) and a high serum C-reactive protein level are common.[5,22]

Bacterial isolation is essential to support the diagnosis. Stool samples should be transported at room temperature in transport media such as Cary-Blair. Blood and other fluids should be transported and incubated in blood culture bottles. *Aeromonas* spp. grow easily in routine enteric isolation media such as MacConkey, xylose lysine deoxycholate (XLD), Hektoen enteric (HE), *Salmonella Shigella* (SS), and deoxycholate citrate (DC) agar. Because *Aeromonas* are nonlactose fermenting, colonies can be misclassified as normal enteric flora. Use of selective media, such as sheep blood agar containing ampicillin, is recommended. DNase-toluidine blue agar can be used to detect nonhemolytic and ampicillin-susceptible strains, which represent <10% of pathogenic strains. Cefsulodin-irgasan-novobiocin (CIN) agar is more cost-effective because it allows concomitant isolation of *Yersinia* and *Plesiomonas* species. *Aeromonas* agar is a highly selective media that contains irgasan and D-xylose.[1,2] Aeromonads can be differentiated from other gram-negative bacilli by biochemical testing. *Aeromonas* spp. are oxidase positive, indole positive, and urease negative. Oxidase activity helps differentiate *Aeromonas* spp. from Enterobacteriaceae.[1,2] Biochemical tests have limitation for taxonomic classification of aeromonads.

Gene amplification assays have been developed and validated for *Aeromonas* spp. detection, both in clinical and environmental samples, as single pathogen assays or in multiplex tests.[6,28–33] Genotyping by partial sequence analysis of housekeeping genes such as *gyrB, rpoB,* and *rpoD* can be useful for epidemiologic purposes.[6,28,30]

Treatment

Most cases of *Aeromonas*-associated gastroenteritis are self-limited, but appropriate rehydration is important. Data from uncontrolled studies suggest a possible benefit of antimicrobial therapy in shortening the duration of disease.[34] Antibiotics are recommended in patients with dysentery or prolonged diarrhea (>7 days) and for immunocompromised patients. A 3-day course of azithromycin (10 mg/kg/day), ciprofloxacin (15 mg/kg twice a day), or ceftriaxone (50–75 mg/kg/day) is a treatment option for children. In adults, azithromycin (500 mg once a day), ciprofloxacin (750 mg once a day), or levofloxacin (500 mg once a day) can be used.[14]

For skin and soft tissue infections, early diagnosis, aggressive surgical debridement, and parenteral antibiotics are important.[17,19,35,36] BSI should be managed with parenteral antimicrobial therapy and a thorough search for focal infection. Aminoglycosides, fluoroquinolones, trimethoprim-sulfamethoxazole, third-generation cephalosporins, and carbapenems are reasonable empiric therapies for skin and soft tissue infections, BSIs, and other invasive infections.[37,38] However, in vitro susceptibility testing of clinical isolates is important because resistance to multiple agents is described,[6] including penicillin, first- and second-generation cephalosporins, vancomycin, clarithromycin, clindamycin, and carbenicillin.[1,34,39] At least 4 different types of β-lactamases have been reported in *Aeromonas* spp., of which an inducible chromosomal β-lactamase is predominant. Isolates producing extended-spectrum β-lactamases occur sporadically.[37] Although induction of β-lactamases in the clinical setting is rare, clinicians should monitor the patient for potential relapse when using cephalosporins for a serious *Aeromonas* infection.[5,6,19]

Prevention

Aeromonas spp. are present in fresh and brackish nonprocessed water, fish, shellfish, meat, and fresh vegetables. Avoiding ingestion of natural source water and contaminated food, especially by infants and immunocompromised patients, is important. Cooking food products eliminates these organisms. Cross-contamination after processing should be avoided. Food products should be handled appropriately (e.g., storing raw and processed products separately and chilling until consumption). *Aeromonas* infections also should be considered in the management of traumatic wounds sustained in or exposed to aquatic natural environments and in near-drowning events.[1]

Key Points

Diagnosis and Management of *Aeromonas* Species Infection

Microbiology

- Environmental, facultatively anaerobic, gram-negative bacilli
- Display a variety of virulence factors including a single polar flagellum, adhesins, enterotoxins, and exoenzymes
- Motility, cell invasion, and immune system evasion relevant pathogenic mechanisms

Epidemiology

- *Aeromonas* spp. colonize and can cause disease in cold-blooded animals (fish, amphibians, and reptiles), which can act as reservoirs.
- Transmission to humans is most common during warmer months, through ingestion of contaminated water or food, or by swimming or bathing in contaminated water.
- Can cause gastroenteritis, skin and soft tissue infections, and sepsis and other invasive infections predominantly in immunocompromised patients

Diagnosis

- Grow easily in routine enteric isolation and blood culture media (can be missed or misclassified as normal enteric flora nonlactose fermenting; selective media, biochemical tests, and PCR assays are useful for their identification)
- Identification from a clinically relevant sample essential for diagnosis and susceptibility tests
- PCR techniques for single-pathogen or multiplex assays available for *Aeromonas* spp. detection in clinical and environmental samples

Treatment

- Most cases of gastroenteritis are self-limited, and hydration is the priority in management.

- Antimicrobial therapy (azithromycin, fluorquinolone or ceftriaxone) is recommended in patients with dysentery or prolonged diarrhea (>7 days) and for immunocompromised patients.

- Skin and soft tissue infections, bloodstream infections, and other invasive infections require parenteral antibiotics (aminoglycoside, fluoroquinolone, trimethoprim-sulfamethoxazole, third-generation cephalosporin, or carbapenem). Skin and soft tissue infections require aggressive surgical debridement.

Prevention

- Appropriate handling and processing of potentially contaminated food and water

- Avoidance of contamination of traumatic wounds or burns with nonprocessed water

PCR, polymerase chain reaction.

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Less Commonly Encountered Nonenteric Gram-Negative Bacilli

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Microbiology and Epidemiology

Several genera of nonglucose-fermenting gram-negative rods are infrequent opportunistic human pathogens. As a group, most are nonfastidious, aerobic, catalase-positive organisms; motility, oxidase activity, and growth on MacConkey agar are variable. Those organisms that grow on MacConkey agar typically produce colorless colonies. Identification of organisms has depended on phenotypic and biochemical characteristics. Matrix-assisted laser-desorption ionization–time of flight (MALDI-TOF) mass spectrometry has been used more recently.[1–3] The utility of MALDI-TOF mass spectrometry improves as databases are expanded. Taxonomy continues to undergo significant changes based on DNA homology studies and 16S ribosomal RNA (rRNA) gene sequencing. The organisms are widely distributed in natural environments including plant material, soil, and water, as well as in the environment in healthcare facilities. Some species can colonize mammalian mucosal surfaces.[1,2,4] In many ways, these organisms resemble *Pseudomonas* spp. including *Pseudomonas aeruginosa.* This chapter focuses on select taxonomic family groups not discussed in other chapters.

Pseudomonadaceae.

Certain organisms in the family Pseudomonadaceae have been reclassified. An earlier classification scheme grouped the pseudomonads into 5 homology groups based on similarities in 16S rRNA gene sequence. At present, only the former members of rRNA homology group I are retained in the amended genus *Pseudomonas.* The most common *Pseudomonas* spp. isolated from human clinical specimens are the fluorescent pseudomonad group organisms, *P. aeruginosa, P. putida,* and *P. fluorescens*. *P. stutzeri, P. mendocina, P. alcaligenes, P. pseudoalcaligenes, P. luteola,* and *P. oryzihabitans* are isolated less frequently (see Chapter 154). Both *P. luteola* (formerly *Chryseomonas luteola*) and *P. oryzihabitans* (formerly *Flavimonas oryzihabitans*) are catalase-positive, oxidase-negative, motile, gram-negative bacilli that form yellow-pigmented, often wrinkled colonies on blood and MacConkey agar. The negative oxidase reaction of these organisms is unique among *Pseudomonas* spp. *P. luteola* can be differentiated from *P. oryzihabitans* on the basis of its ability to hydrolyze esculin and orthonitrophenyl-β-D-galactopyranoside.[4]

rRNA homology group II organisms now are designated *Burkholderia* spp., *Ralstonia* spp., *Cupriavidus* spp., *Pandoraea* spp., and related organisms in the family Burkholderiaceae; rRNA homology group III contains *Comamonas* spp., *Delftia* spp., and *Acidovorax* spp. in the family Comamonadaceae; rRNA homology group IV pseudomonads are now classified as *Brevundimonas* spp. in the family Caulobacteraceae; and rRNA homology group V pseudomonads are now *Stenotrophomonas* spp.[1]

Alcaligenaceae.

Both *Achromobacter* and *Alcaligenes* spp., along with the closely related *Bordetella* spp., currently are grouped together within the family Alcaligenaceae. The clinically relevant *Achromobacter* and *Alcaligenes* spp. include *Alcaligenes faecalis, Achromobacter piechaudii, Achromobacter denitrificans,* and *Achromobacter xylosoxidans.*[2,5] The first 3 organisms listed are asaccharolytic and biochemically are similar to *Bordetella* spp. and *Oligella ureolytica,* also members of this family.[6] *Achromobacter xylosoxidans* is saccharolytic and biochemically is similar to several organisms of uncertain taxonomic position, including *Achromobacter* groups B, E, and F and *Ochrobactrum anthropi*; the former *Achromobacter* groups A, C, and D are biovars of *O. anthropi*.[7] *Ochrobactrum* spp. have been placed in the family Brucellaceae. The genus *Oligella* contains 2 species of clinical significance, *O. urethralis* and *O. ureolytica*.[6] *O. urethralis* (formerly *Moraxella urethralis*) is nonmotile, shares several characteristics with *Moraxella* spp., and is thought to be a commensal of the genitourinary tract. *O. ureolytica* is motile and biochemically is similar to *Bordetella bronchiseptica,* including the property of rapid hydrolysis of urea.

Caulobacteraceae.

Several *Brevundimonas* spp. have been named, but only *B. diminuta* and *B. vesicularis* are of human clinical significance. These species currently are placed in the family Caulobacteraceae. All these organisms are aerobic, oxidase-positive, motile, gram-negative bacilli that can be isolated in the laboratory on blood or chocolate agar; most but not all strains also grow on MacConkey agar. Some isolates produce a yellow or tan-brown pigment.

Comamonadaceae.

Current members of the family Comamonadaceae include the following: *Comamonas testosteroni* and *C. terrigena; Delftia acidovorans* (formerly *Comamonas acidovorans*) and *D. tsuruhatensis;* and 3 *Acidovorax* spp.—*A. facilis, A. delafieldii,* and *A. temperans.*

Flavobacteriaceae.

The family Flavobacteriaceae has undergone extensive revision and now contains many genera including *Chryseobacterium, Elizabethkingia, Flavobacterium, Weeksella, Bergeyella, Empedobacter,* and *Myroides. Elizabethkingia meningoseptica* (formerly *Chryseobacterium meningosepticum* and *Flavobacterium meningosepticum*) and *Chryseobacterium indologenes* are the most common human isolates of this group.[1,2,5,6] *E. meningosepticum* produces large, smooth colonies on blood and chocolate agar within

24 hours, but most isolates do not grow on MacConkey agar. Gram stain of agar isolates reveals long, thin rods that can be filamentous. Isolates are encapsulated and produce proteolytic enzymes including elastase, a potential virulence factor. Ribotyping demonstrates heterogenicity among strains of *E. meningoseptica.*[4] Other *Chryseobacterium* spp. produce colonies of similar appearance; some produce yellow-pigmented colonies on blood agar, but pigment production may be negative or weak, except for the deep-yellow pigment produced by *C. indologenes.*[1]

Flavobacterium breve has been reclassified as *Empedobacter brevis.* Organisms formerly classified as *F. odoratum* are now classified as 2 distinct species, *Myroides odoratus* and *M. odoratimimus*. *Weeksella zoohelcum* has been reclassified as *Bergeyella zoohelcum,* and *Weeksella virosa* remains as the single species in the genus. Unlike the other flavobacteria that are environmental organisms, *W. virosa* and *B. zoohelcum* are found on mucosal surfaces of humans and other mammals.[1,2,4,5] Colonies of *W. virosa* are mucoid, adherent to agar, and can develop a tan appearance, whereas colonies of *B. zoohelcum* can be sticky and tan in appearance. Useful tests to differentiate these organisms include the following: hydrolysis of gelatin, starch, and esculin; DNase and urease production; nitrate reduction; and susceptibility to penicillin and polymyxin B.[1,2,4,5]

Methylobacteriaceae.

Methylobacterium spp. and *Roseomonas* spp., members of the family Methylobacteriaceae, are oxidase positive and produce characteristic pink- or coral-pigmented colonies on a variety of media, including blood, Sabouraud, Thayer-Martin, and buffered charcoal–yeast extract agar. These are environmental organisms that also can be found in the healthcare environment. Colonies of *Methylobacterium* spp. generally appear dry, and Gram stain shows large, highly vacuolated, pleomorphic bacilli; growth on MacConkey agar at temperatures higher than 40°C usually is negative. In contrast, colonies of *Roseomonas* spp. are mucoid in culture and show nonvacuolated, coccoid bacilli on Gram stain; these organisms usually grow on MacConkey agar at temperatures up to 42°C.[4]

Rhizobiaceae.

Rhizobium spp. *and Agrobacterium* spp. are members of the family Rhizobiaceae and are natural inhabitants of soil and well-known pathogens of plants. *Rhizobium radiobacter* (formerly *Agrobacterium radiobacter* and *A. tumefaciens*) is the only medically important species in the family.[8] Colonies of the organism can appear mucoid and pink on MacConkey agar, resembling colonies of *Klebsiella* spp.

Sphingomonadaceae.

The family Sphingomonadaceae contains numerous species, but only 2 species are considered to be of human clinical significance, *Sphingomonas paucimobilis* (formerly *Pseudomonas paucimobilis*) and *S. parapaucimobilis. S. paucimobilis* grows slowly and produces yellow colonies; however, in contrast to *Sphingobacterium* spp., most isolates of *S. paucimobilis* are urease negative and susceptible to polymyxin B.[2]

Sphingobacteriaceae.

The family Sphingobacteriaceae contains several former *Flavobacterium* spp., but only 2 species are considered of human clinical significance, *Sphingobacterium multivorum* and *S. spiritivorum. Sphingobacterium* spp. generally are yellow pigmented, urease positive, and resistant to polymyxin B; this last property is shared with *Burkholderia* spp., *Chryseobacterium* spp., and a few other genera of nonfermentative gram-negative bacilli.[2]

Shewanellaceae.

The genus *Shewanella*, family Shewanellaceae, has more than 20 species, but only *S. putrefaciens* and *S. algae* are thought to be of clinical importance. *S. algae* is a halophilic and asaccharolytic organism and thought to be the more common human isolate, whereas *S. putrefaciens* is nonhalophilic and saccharolytic and more commonly isolated from the environment. Among nonfermentative gram-negative bacilli, these organisms have the unique property of producing hydrogen sulfide in Kligler or triple sugar iron agar.[2]

Acetobacteraceae.

Acetic acid bacteria belonging to the family Acetobacteraceae have been associated with human infection relatively recently. Relevant clinical genera in this family include *Asaia, Gluconobacter,* and *Granulibacter*.[2] These organisms oxidize alcohols or sugars, thus producing acetic acid. They are found in soil or associated with plants and have been used to convert wine to vinegar. *Asaia* spp. include a group of pink-pigmented gram-negative rods. Colonies are pale pink with scant to moderate growth on sheep blood agar, and they are oxidase negative. Relevant clinical species include *A. bogorensis, A. lannensis* and *A. siamensis*. *Gluconobacter* are gram-negative, catalase-positive, oxidase-negative rods. *Granulibacter* are oxidase-negative, coccobacillary, gram-negative rods.

Clinical Manifestations and Treatment

As a group, these organisms are opportunistic pathogens that cause relatively few human infections. Most infections occur in people with underlying medical conditions or indwelling medical devices. For many organisms, no standardized methods are available for in vitro antimicrobial susceptibility testing or interpretation of results. Empiric management rests on clinical experience and published reports. In vitro testing should establish antimicrobial minimum inhibitory concentrations to guide definitive therapy. Disk diffusion testing can be unreliable. An in vitro test result of “resistant” indicates a likely treatment failure, but a result of “susceptible” may not predict treatment success. Device removal and surgical debridement when relevant are primary treatments.

Acidovorax, Brevundimonas, Comamonas, and *Delftia* Species

Single cases of *Acidovorax* spp. bloodstream infection (BSI) and implanted port- or catheter-related infections have been reported.[9,10] *Brevundimonas vesicularis* infections in children have included septic arthritis in a healthy toddler,[11] as well as BSIs in a patient undergoing hemodialysis, in a child with sickle cell disease,[12] and in 2 premature neonates.[13,14] Infections with *B. vesicularis* in adults have included infective endocarditis,[15] keratitis after laser surgical procedures,[16] and BSIs following bone marrow transplantation,[17] open heart surgery,[18] and ambulatory peritoneal dialysis.[19] *B. vesicularis* typically is susceptible to meropenem, piperacillin-tazobactam, and aminoglysosides.[20] Susceptibility is less common for ceftazidime and trimethoprim-sulfamethoxazole.[20] *B. diminuta* has been associated with BSI and vascular catheter infections primarily in patients with cancer, peritonitis associated with chronic ambulatory peritoneal dialysis, and cutaneous infections in immunocompetent people.[19,21–22] *Comomonas testosteroni* and *C. kerstersii* infections commonly are polymicrobial and occur most often in the abdomen including following perforation of the appendix.[23,24] *C. testosteroni* was reported to cause catheter-associated BSI, endocarditis, and meningitis in a patient with recurrent cholesteatoma.[25–30] *Delftia acidovorans* has caused catheter-associated BSI, endocarditis associated with intravenous drug use, conjunctivitis, and otitis externa.[31–34] *Delftia tsuruhatensis* has caused catheter-associated BSI.[35] Antibiotic susceptibility of this group of organisms is variable, but most isolates are susceptible to broad-spectrum cephalosporins, carbapenems, and fluoroquinolones. *B. diminuta*, however, is intrinsically resistant to fluoroquinolones,[21] and susceptibility to aminoglycosides is variable.

Achromobacter and *Alcaligenes* Species

Achromobacter and *Alcaligenes* spp. are opportunistic human pathogens causing sporadic cases of pneumonia, septicemia, peritonitis, and urinary tract and other infections.[36–39] *Achromobacter xylosoxidans* and *Alcaligenes faecalis* are the most common isolates and agents of disease, but little is known about factors promoting virulence. Whereas BSI, meningitis, and pneumonia are reported most commonly, sites of isolation also include peritoneal fluid in chronic ambulatory peritoneal dialysis, joint fluid, bone, and urine.[36–40] Infections have been associated with contaminated medical supplies and devices, such as transducers, topical medications, nuclear medicine tracers, deionized water used for hemodialysis, and fluids from incubators and humidifiers.[38,41,42] In patients with cancer, the gastrointestinal tract can be the source of infection.[37] *A. xylosoxidans* has been recovered from blood and cerebrospinal fluid (CSF) of neonates with nosocomial infection, in maternal BSI, and from bone after penetrating nail injury in older children.[36,38,42] Clinical illness resulting from *A. xylosoxidans* BSI is indistinguishable from that of other gram-negative bacilli.[43]

Intravascular catheters frequently are predisposing factors to infection, but neutropenia is not a major risk factor.[37]

A. xylosoxidans and A. faecalis can colonize the respiratory tract of intubated children and patients with cystic fibrosis.[40,44] *A. xylosoxidans* is a "late colonizer" in up to 8.7% of patients with cystic fibrosis and can contribute to exacerbation of pulmonary disease.[45,46] *A. xylosoxidans* has been reported to cause lymphadenitis in patients with chronic granulomatous disease and hyperimmunoglobulin M syndrome.[47,48]

The antimicrobial susceptibility pattern of these organisms is variable.[37,49] Isolates of *A. xylosoxidans* and *A. faecalis* produce several types of β-lactamases that hydrolyze a variety of the penicillins and cephalosporins. Ceftazidime generally retains good in vitro activity against *A. xylosoxidans;* meropenem and trimethoprim-sulfamethoxazole typically also are active. Resistance to aminoglycosides and aztreonam is expected; activity of ureidopenicillins, ticarcillin−clavulanic acid, and the fluoroquinolones is variable. Monotherapy is probably sufficient in most cases of infection, but 2 agents may be required to eradicate the organism in patients with severe, deep-seated infections such as endocarditis. Removal of a contaminated venous catheter or other device often is necessary to clear infections.

Rhizobium radiobacter

Virtually all reported cases of human infections with members of the Rhizobiaceae family are caused by *Rhizobium radiobacter* and have occurred in immunocompromised hosts or in patients with medical devices, especially central venous catheters (CVCs), chronic ambulatory peritoneal dialysis catheters, or implanted biomedical prostheses.[50–58] The ability of this organism to adhere to silicone and other inert surfaces may explain these associations. Approximately 20% of cases of human infections have occurred in people ≤16 years of age. More than 50% of infections required antibiotic therapy and removal of the device for resolution. *R. radiobacter* also has caused native valve endocarditis and urinary tract infection.[50–58]

The antimicrobial susceptibility is variable, and many isolates are multiply resistant because of production of antibiotic-inactivating enzymes. Most strains are inhibited by ceftriaxone (but not ceftazidime), gentamicin (but not tobramycin), trimethoprim-sulfamethoxazole, piperacillin-tazobactam, ciprofloxacin, and carbapenems. Although *R. radiobacter* infections typically are of low virulence, variable antibiotic susceptibility and lack of optimal therapeutic regimens make them difficult to treat.[50–52]

Chryseobacterium, Elizabethkingia, Bergeyella, Weeksella, Myroides, and *Empedobacter* Species

Members of the genera *Chryseobacterium, Elizabethkingia, Bergeyella, Weeksella, Myroides,* and *Empedobacter* spp., all once classified as *Flavobacterium* spp., are responsible for infrequent infections. *Elizabethkingia* (formerly *Flavobacterium*) *meningoseptica* is of greatest medical importance. Although recovered from patients with community-acquired infections, *E. meningoseptica* is most frequently an opportunistic nosocomial pathogen of infants ≤3 months of age, who account for >75% of reported cases.[59,60] *E. meningoseptica* has caused numerous nursery outbreaks of infection, especially BSI and meningitis.[61] Approximately one half of reported cases of meningitis caused by *E. meningoseptica* in neonates have occurred during nursery outbreaks.[62] Outbreaks have been associated with contamination of solutions and equipment in the hospital environment, including containers of antiseptic solutions, vials of intravenous drugs, chlorinated water sources, and respiratory care equipment.[62]

Infants become colonized with *E. meningoseptica* in the nose, throat, or gastrointestinal tract before development of invasive infection. The clinical course of BSI or meningitis is similar to that of infection with other gram-negative bacilli; meningitis can have either an early or a late onset. The onset of disease can be insidious, and CSF evaluation can be unremarkable initially.[61] The mortality rate of neonatal meningitis caused by *E. meningoseptica* is >50%, and survivors frequently have severe neurologic sequelae, including hydrocephalus. Development of hydrocephalus is significantly associated with administration of intrathecal antibiotics or positive CSF cultures for >10 days.[61]

E. meningoseptica rarely causes infection in immunocompetent children beyond the neonatal period, but infections in immunocompromised people occur as outbreaks in intensive care units or as isolated cases; >90% of cases are nosocomially acquired.[60] Pneumonia is the most common infection, accounting for 40% of reported cases. The mortality rate in immunocompromised patients is >60%. Other reported *E. meningoseptica* infections include endocarditis, ophthalmologic infections, cellulitis, pyogenic arthritis related to an elbow joint prosthesis, abdominal abscesses, and burn wound sepsis.[63,64] Prolonged antibiotic therapy may predispose patients to infection.

Although *Chryseobacterium indologenes* is the most common human isolate within this group, recovery of the organism is not always associated with infection. *C. indologenes* primarily causes BSI in immunocompromised patients and in patients with indwelling intravascular devices, but it also has been implicated in cellulitis, bacteremia, pneumonia, meningitis, pyomyositis, and keratitis.[65–69]

Weeksella virosa is recovered primarily from urine and urogenital tract specimens, but its clinical significance is questioned. *Bergeyella zoohelcum* is an inhabitant of the oropharynx of dogs and cats and has been recovered in bite wound infections and in a case of meningitis that followed multiple bites.[70–73] *Bergeyella* sp. was recovered from amniotic fluid of a mother delivering a preterm infant, but its significance was unclear.[74] The 2 current *Myroides* spp., *M. odoratus* and *M. odoratimimus*, are uncommon human isolates from urine, respiratory tract, and rarely blood. *Empedobacter brevis* also is reported rarely as an agent of human disease.

E. meningoseptica and other related species can be resistant to antimicrobial agents routinely prescribed for gram-negative infections including third- and fourth-generation cephalosporins, carbapenems, aztreonam, and the aminoglycosides. *E. meningoseptica*, however, may be susceptible in vitro to agents generally active against gram-positive organisms including rifampin, vancomycin, and clindamycin. Antibiotics with the most consistent in vitro activity against both *E. meningoseptica* and *C. indologenes* are minocycline, rifampin, and levofloxacin. Ciprofloxacin, trimethoprim-sulfamethoxazole, and piperacillin-tazobactam are less active.[60,61,75–78] In vitro test results may not correlate with clinical efficacy. Both *W. virosa* and *B. zoohelcum* are susceptible to a wide variety of antimicrobial agents. Disk diffusion susceptibility testing of *Chryseobacterium* spp. and related agents can be unreliable.[76,77]

Optimal therapy for serious infections, including meningitis, caused by *E. meningoseptica* is not well established. Minimum inhibitory concentrations of vancomycin are high for almost all isolates. A study of 4 *E. meningoseptica* isolates recovered from neonatal CSF demonstrated synergy in vitro between vancomycin and rifampin in 3 of 4 isolates, as well as additive interaction between vancomycin and ciprofloxacin and antagonism between vancomycin and meropenem in all 4 isolates.[79] High-dose vancomycin and rifampin may be the optimal therapy for management of central nervous system infections.[79] Minocycline for patients ≥8 years of age, trimethoprim-sulfamethoxazole, or a fluoroquinolone is a treatment option, based on susceptibility testing, for infections outside the central nervous system.

Methylobacterium and *Roseomonas* Species

Methylobacterium mesophilica and *Roseomonas gilardii* are the most frequently isolated species. Both organisms have been reported as agents of BSI, primarily in association with an indwelling CVC, hemodialysis catheter, and contaminated endoscope. Other reported infections include peritonitis related to chronic ambulatory peritoneal dialysis, septic arthritis, endophthalmitis, cellulitis, bacteremia, keratitis, ventilator-associated pneumonia, and urinary tract infection.[80–90] These organisms generally are susceptible to carbapenems, aminoglycosides, tetracycline, and fluoroquinolones.[91–93] *Roseomonas mucosa* strains typically are more resistant than are strains of *R. gilardii*.

Ochrobactrum Species

Ochrobactrum anthropi is the most common *Ochrobactrum* sp. causing disease. *O. anthropi* colonizes the respiratory tract and wounds and subsequently can cause a variety of opportunistic infections including CVC-associated BSI, prosthetic valve endocarditis, septic arthritis, osteomyelitis, peritonitis, BSI, and meningitis.[52,94–110] Other *Ochrobactrum* spp. including *O. haematophilum* and *O. pseudogrignonense* have been isolated rarely from human clinical specimens.[111] The closely related *Achromobacter*-like groups B, E, and F organisms have been recovered most commonly from blood cultures of patients with CVCs.[112] Most isolates of these *Achromobacter*-like groups and *O. anthropi* are susceptible to aminoglycosides, carbapenems, fluoroquinolones, and trimethoprim-sulfamethoxazole.[113]

Oligella Species

The 2 *Oligella* spp. of clinical significance, *O. urethralis* and *O. ureolytica,* have been recovered primarily from the urogenital tract and rarely as agents of urosepsis or pyogenic arthritis.[114,115] *O. urethralis* has an antibiotic susceptibility pattern similar to that of *Moraxella* spp. Antibiotic susceptibility of *O. ureolytica* is variable.

Pseudomonas luteola and *Pseudomonas oryzihabitans*

Both *P. luteola* and *P. oryzihabitans* are found in natural environments such as soil, water, and damp environments including rice paddies, as well as in the hospital environment in sinks and respiratory therapy equipment. Infections with both organisms are found most commonly in patients with medical devices or immunosuppressive conditions,[116–121] and they include osteomyelitis, peritonitis, endocarditis, meningitis after a neurologic procedure, leg ulcer in a patient with sickle cell disease, endophthalmitis following cataract operation, polymicrobial BSI, cellulitis, abscesses, and wound infections.[122–129]

Published data are insufficient to recommend treatment regimens. *P. luteola* and *P. oryzihabitans* are susceptible to most extended-spectrum penicillins, third-generation cephalosporins, fluoroquinolones, and aminoglycosides, but they usually are resistant to ampicillin and first- and second-generation cephalosporins.[116–119] Because of the low virulence of *P. oryzihabitans,* patients can recover spontaneously from infection after removal of foreign material.[121]

Sphingobacterium, Sphingomonas, and

Shewanella Species

Sphingobacterium multivorum and *S. spiritivorum* are the most commonly recovered species from clinical specimens, usually from blood and urine. Isolates generally are resistant to the aminoglycosides and polymyxins, are susceptible to fluoroquinolones and trimethoprim-sulfamethoxazole, and have variable susceptibility to β-lactam agents.[130–132]

Sphingomonas paucimobilis and other *Sphingomonas* spp. have been recovered from blood, CSF, urine and urogenital sites, and wounds; these organisms have caused sporadic or community-acquired infections including BSI, osteomyelitis, pyogenic arthritis, meningitis, urinary tract infection, and wound infection.[133–139] Infections follow acquisition from the environment or nosocomially from contaminated fluids or equipment.[129–131] A single case of BSI caused by *S. mucosissima* in a patient with sickle cell disease was reported.[139] Most isolates are susceptible to aminoglycosides, fluoroquinolones, and trimethoprim-sulfamethoxazole; susceptibility to β-lactam agents is variable.[134]

Shewanella algae and *S. putrefaciens* have clinical importance. *Shewanella* spp. have been recovered in association with BSI, CVC-associated BSI, ventilator-associated pneumonia, tonsillitis, cerebellar abscess, ventriculoperitoneal shunt infection, peritonitis, osteomyelitis, pyogenic arthritis, and external ear and skin and soft tissue infections following trauma.[140–151] These organisms generally are susceptible to a wide variety of antimicrobial agents, except for first-generation penicillins and cephalosporins.[140–151]

Granulibacter, *Asaia*, and *Gluconobacter* Species

A few acetic acid bacteria have been reported to cause human infections. *Granulibacter bethesdensis* can cause fever and necrotizing lymphadenitis in patients with chronic granulomatous disease.[152,153] Biopsy can reveal necrotizing granulomatous inflammation, negative Gram stain but growth within 3 weeks on Middlebrook 7HII, buffered charcoal–yeast extract, or fungal media. These reported infections required surgical treatment and prolonged antimicrobial therapy for resolution,[152] and recurrence or relapse is possible. *Granulibacter* organisms typically are multiresistant. Susceptibility testing is difficult because of poor growth. Ceftriaxone, aminoglycosides, doxycycline, and trimethoprim-sulfamethoxazole can be active against these organisms in vitro. Ceftriaxone may be the preferred agent.[152] *G. bethesdensis* has been shown to persist in monocytes in patients with chronic granulomatous disease as a result of resistance to oxygen-independent microbicides in monocytes; this organism requires intact reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase for clearance.[154]

Infections with *Asaia* spp. primarily have consisted of catheter-associated BSI, peritonitis related to peritoneal dialysis, and BSI in an intravenous drug user.[155–158] Identification in clinical specimens usually requires 165 rRNA gene sequence analysis. Antimicrobial therapy and catheter removal have been successful as treatment. *Asaia* spp. are multidrug resistant, with susceptibility in reported cases limited to tobramycin and tetracyclines.

Acetic acid bacteria such as *Gluconobacter*, *Acetobacter*, and *Asaia* spp. have been isolated from sputum of patients with cystic fibrosis, in whom a liquid acidic environment likely is relevant.[99,159] The role of these bacteria in clinical symptoms is unclear. Association with intravenous drug abuse may reflect the use of acidic substances (vinegar or lemon juice) to dilute heroin and the possible contamination of compounds used.[158–162]

Key Points

Diagnosis and Management of Less Commonly Encountered Nonenteric Gram-Negative Bacilli

Microbiology

- Nonglucose-fermenting nonenteric gram-negative rods
- Nonfastidious, aerobic, and catalase-positive organisms
- Motility, oxidase activity, and growth on MacConkey agar variable

Epidemiology

- Environmental organisms (plant material, soil, water, and healthcare facilities) that rarely cause infections in normal hosts

- Some species able to colonize mammalian mucosal surfaces

Clinical Manifestations

- Commonly associated with indwelling devices

- May be present in respiratory samples taken from patients with cystic fibrosis during respiratory exacerbations; but role frequently is unclear

Diagnosis

- Organisms recoverable by standard culture methods

- Antibiotic resistance testing required because of the considerable strain susceptibility variation

Treatment

- Empiric antimicrobial treatment should include agents with broad spectrum activity against gram-negative bacilli.

- Definitive therapy is based on antimicrobial susceptibility test results.

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152

Eikenella, Pasteurella, and *Chromobacterium* Species

Guliz Erdem, Amy Leber

Microbiology

Eikenella, Pasteurella, and *Chromobacterium* species display both common and contrasting characteristics of laboratory properties, epidemiology, and clinical presentations. *Eikenella* and *Pasteurella* spp. are nonmotile, whereas *C. violaceum* is motile and less fastidious than the others.

The genus *Eikenella* contains only 1 species, *E. corrodens,* which belongs to the family Neisseriaceae along with the genera *Neisseria* and *Kingella.*[1–4] *E. corrodens* is a small, straight rod that can appear coccobacillary. The organism is oxidase positive and ornithine decarboxylase positive and reduces nitrates to nitrites, but it does not produce catalase, urease, or indole.[1–3] *E. corrodens* originally was thought to be related to the strictly anaerobic bacterium *Bacteroides ureolyticus* (formerly *Bacteroides corrodens*) because of the characteristic "corroding" or "pitting" of the surface of blood or chocolate agar by some isolates, suggesting a preference for anaerobic growth.

The genus *Pasteurella* contains several species of clinical significance and belongs to the family Pasteurellaceae along with the genera *Aggregatibacter, Actinobacillus, Haemophilus,* and *Mannheimia*. Most *Pasteurella* spp. are oxidase and catalase positive, reduce nitrates, and use glucose and a variety of other carbohydrates. The taxonomy of the genus is in flux; currently *P. multocida*, the most important species of human significance, can be separated into the subspecies *multocida, septica,* and *gallicida*. *P. canis*, *P dagmatis,* and *P stomatis* are other species isolated from humans.[1,5–7] Several other *Pasteurella* spp. are rarely if at all associated with human disease.[1,2,6–8] The classification of *Pasteurella* spp. is undergoing revision based on DNA-DNA hybridization studies and ribosomal RNA sequence analysis, and several species, including *P. pneumotropica, P. aerogenes,* and *P. bettyae,* may be reclassified as members of the genus *Actinobacillus* or other genera in the family Pasteurallaceae.[9,10] Organisms formerly classified as *P. gallinarum* now are named *Avibacterium gallinarum,* and some formerly classified as *P. haemolytica* now are named *Mannheimia haemolytica.*

The genus *Chromobacterium* currently contains only 1 species of human significance, *C. violaceum,* and also is placed in the family Neisseriaceae; certain other *Chromobacterium* spp. recovered from environmental sources have been proposed. Most of these organisms are microaerophilic, facultatively anaerobic, somewhat fastidious, gram-negative bacilli that can appear pleomorphic or coccobacillary in direct smears or smears prepared from culture. *C. violaceum* is a long, gram-negative, slightly curved bacillus. *C. violaceum* is positive for catalase, nitrate reductase, and arginine dihydrolase; it grows on sheep blood, MacConkey, chocolate, and Mueller-Hinton agar; and it produces a deep purple pigment (violacein) that can result in black-appearing colonies. The pigment also can be produced during infection, thus resulting in violaceous cellulitis.

Pathophysiology and Epidemiology

E. corrodens is part of the normal flora of the oral cavity, upper respiratory tract, and mucosal surfaces of the gastrointestinal and genitourinary tracts of humans and some mammals.[11,12] From both a clinical and a laboratory diagnostic perspective, it is useful to discuss *E. corrodens* in the context of the so-called HACEK group organisms. This mnemonic stands for *Haemophilus parainfluenzae, Aggregatibacter aphrophilus* (formerly *Haemophilus aphrophilus* and *H. paraphrophilus*), *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans, Cardiobacterium hominis, E. corrodens,* and *Kingella kingae* and other *Kingella* spp. As a group, these are slow-growing organisms that often require elevated carbon dioxide concentrations and hemin in the culture medium for optimum growth.[11] HACEK organisms are clinically important in specific disease syndromes, including disseminated diseases, such as subacute bacterial endocarditis and pyogenic arthritis, as well as localized pyogenic diseases of the oral cavity, head, and neck.[12] Compared with the other organisms in the HACEK group, *E. corrodens* is less fastidious and generally is recoverable within 24 to 48 hours on routine blood and chocolate agar media. Because of improvements in composition of broth media and detection techniques, blood cultures from patients with endocarditis suspected to be caused by *E. corrodens* or other HACEK group organisms generally need not be incubated beyond the routine 5 days used in most laboratories.[1–3,13] *E. corrodens* has a lectin-like protein and multiple pilus proteins on the cell surface that may contribute to adherence to mucosal epithelial cells. Some genes coding for pilus proteins share nucleotide homology, and the pilus proteins show amino acid sequence homology with pilin genes and proteins from *Moraxella* spp. and *Neisseria gonorrhoeae.* Other cell surface proteins have the ability to agglutinate red blood cells. The cell wall possesses lipopolysaccharide, and *E. corrodens* can synthesize an extracellular polysaccharide or slime layer. The organism can trigger inflammation in periodontal tissue that can promote periodontitis.[14] Such virulence factors also may play a role in inhibiting phagocytosis or modulating macrophage activity.[2]

Pasteurella spp. are commensals of the upper respiratory tract, with oropharyngeal carriage found in most dogs and cats, including large cats (lions, tigers, panthers), as well as in swine, rats, opossums, rabbits, fowl, and possibly humans.[15] *Pasteurella* spp. are primary pathogens of a variety of animals, and several species can cause various human infections, most commonly associated with animal bites or scratches. In a study of 159 human isolates of *Pasteurella* spp. recovered from dog or cat bites, *P. multocida* subsp. *multocida* accounted for 60% of isolates, *P. canis* for

18%, *P. multocida* subsp. *septica* for 13%, *P. stomatis* for 5%, and *P. dagmatis* for 3%.[7] *Pasteurella* also can be acquired through aerosol inhalation, and differences in the propensity of the 2 *P. multocida* subspecies to cause respiratory tract disease may be present.[16] Although a known animal exposure is present in most human *P. multocida* infections, 5% to 15% of cases of these infections have none. *Pasteurella* spp. generally can be isolated from culture on blood or chocolate agar within 24 to 48 hours of incubation; most strains do not grow on MacConkey agar. Gram stain smears of growth on agar reveal small gram-negative coccobacilli. Biochemical identification of *P. multocida* is straightforward; however, identification of some other *Pasteurella* species can be difficult.[5,8–10] Use of conventional biochemical systems such as Vitek (bioMérieux, Inc., Durham, NC) and also matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry are able to identify *Pasteurella* to the genus level accurately, with MALDI-TOF mass spectrometry better able to give accurate species identification.[17]

Studies of virulence factors of *Pasteurella* spp. have been focused on *P. multocida*, in which virulence can be associated with production of neuraminidase and lipopolysaccharide endotoxin. A dermonecrotic toxin, a known virulence factor in animals, can be detected more commonly in strains isolated from adults with chronic bronchitis than from other sources. The best characterized potential virulence factor is *P. multocida* toxin (PMT), a highly potent mitogen that blocks apoptosis. PMT is thought to be a potential carcinogen, but little evidence exists for its role in human cancer.[18,19]

C. violaceum is a common saprophyte of soil and water, especially in tropical and subtropical areas.[20,21] The organism usually gains entry through the skin to cause localized wound infection, but bloodstream and disseminated infection can occur in patients with select immune dysfunction. *C. violaceum* can be isolated readily from blood, abscess fluid, or purulent drainage, and identification is achievable using commercial systems. *C. violaceum* is included in MALDI-TOF mass spectrometry databases and in the VITEK 2 ID-GNB card.[1,22] Pigmented and nonpigmented strains can have similar pathogenicity and disease severity.[23,24] Several virulence factors have been identified including endotoxin, adhesins, invasins, and cytolytic proteins.[25]

Clinical Manifestations

Most infections caused by *E. corrodens* involve the head, neck, or respiratory tract or are related to human bites or fist-to-mouth injuries.[12,26–29] Localized infections generally are indolent and follow a slowly progressing course, often becoming manifest no earlier than 1 week after injury. *E. corrodens* is a cause in approximately 25% of infections resulting from clenched fist injuries. These slowly evolving infections can lead to complications such as a stiff joint or, rarely, even amputation.[27] Oral contamination can lead to infection of surgical wounds, such as after craniofacial or esophageal reconstruction. *E. corrodens* is prevalent in subgingival plaque of adults with periodontitis.[30] Pleuropulmonary infections also can occur, presumably as a result of aspiration of oral contents or leakage of oral secretions into the pleural space after surgical procedures. In these cases, pneumonia, empyema, or pulmonary cavitation can result.[29–31] *E. corrodens* often is part of a polymicrobial infection, especially with viridans or β-hemolytic streptococci, staphylococci, and oral anaerobic bacteria in human bites, head and neck infections, respiratory tract infections, and hepatic abscesses.[1–3,32–34] *E. corrodens* infections occur in immunocompromised people as well as in people with normal immune function.[35] *E. corrodens* can be found concurrently with *Actinomyces* spp. and may contribute to the pathogenesis of actinomycosis,[1,36] and it has also been implicated with *Actinomyces* spp. in a distinctive clinical infection known as chronic diffuse sclerosing osteomyelitis of the mandible.[36]

E. corrodens also can be recovered from peritoneal cultures after ruptured appendix, gastric operations, traumatic duodenal rupture, gastric cancer, and abscesses of the spleen, liver, and pancreas.[37–39] Other serious *E. corrodens* infections include bloodstream infection (BSI), endocarditis, pyogenic arthritis, spondyloarthritis, chorioamnionitis, neonatal sepsis, neonatal conjunctivitis, orbital infections, meningitis, sinusitis, submandibular abscess, thyroiditis, thyroid abscess, renal abscess, and brain abscess.[28,40–51] Invasion of the central nervous system can occur by extension from periodontal, middle ear, or sinus infections (Fig. 152.1). BSI and endocarditis most often occur in immunocompromised hosts, intravenous drug abusers, and patients with previous cardiac valve damage. Osteomyelitis of the calcaneus has been reported subsequent to penetration of the heel by a toothpick.[27] Injection and fingerstick site abscesses caused by *E. corrodens* have been reported in adolescents with insulin-dependent diabetes mellitus; licking or biting skin or nails could provide an opportunity for the organism to contaminate traumatized skin.[52]

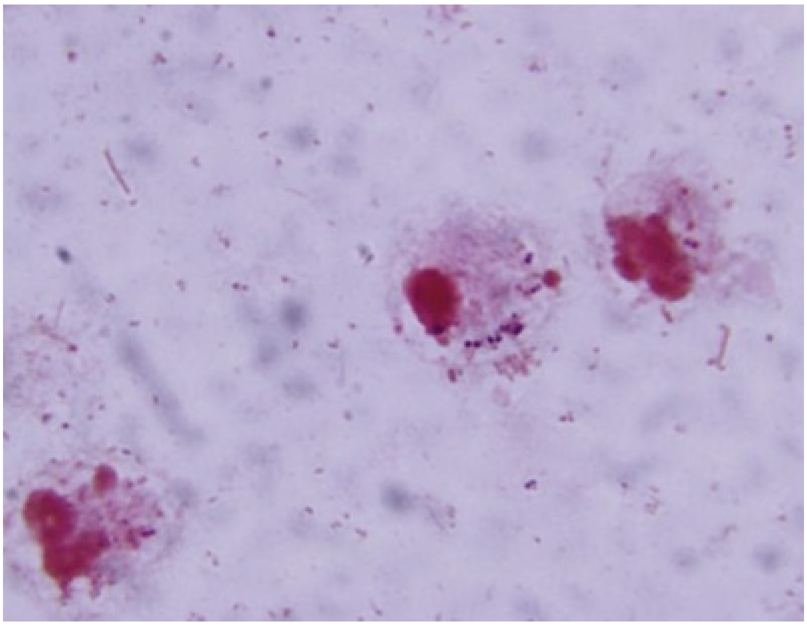

FIGURE 152.1 **Gram stain of epidural fluid from a 6-year-old boy with acute onset of fever, sinusitis, mental status change, and hemiparesis. *Eikenella corrodens* and group C streptococcus were isolated.** (Courtesy of E.D. Thompson and K.D. Herzog, St. Christopher's Hospital for Children, Philadelphia.)

Infection with *Pasteurella* spp., most commonly *P. multocida,* generally occurs after an animal bite.[53–55] *P. multocida* is the pathogen in >50% to 75% of infections following a cat bite and in up to 50% of infections following a dog bite[54] (Fig. 152.2). Cat scratches also can be complicated by *P. multocida* infection. Infection can occur after bite injuries from lions, tigers, or other large cats, as well as rats, rabbits, and other animals. Wound infections caused by *P. multocida* typically develop rapidly, within 12 to 24 hours after injury, and manifest with warmth, swelling, redness, and tenderness and with serosanguineous-to-purulent discharge at the site.[53] Regional lymphadenopathy, chills, and fever are common. In a review spanning 10 years, the highest rate of infection occurred in children <5 years of age and in adults >55 years of age.[53] Tenosynovitis and tendon sheath abscess formation, osteomyelitis, and pyogenic arthritis are complications related to deep penetration by the teeth or claws of the animal.[54,56] Preexisting joint disease can predispose patients to pyogenic arthritis.

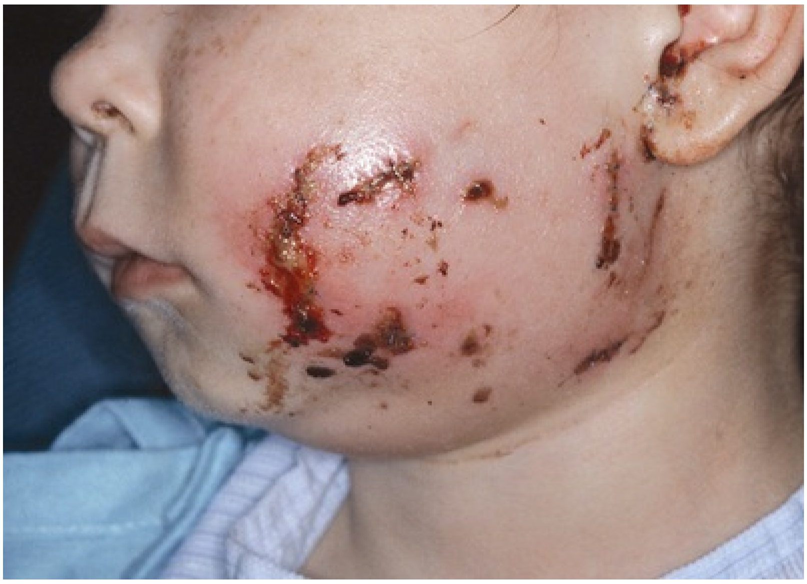

FIGURE 152.2 **A toddler with facial cellulitis caused by *Pasteurella multocida* following a dog bite.** (Copyright by J.H. Brien.)

Some cases of infection with *Pasteurella* spp. occur in people with frequent animal exposure but without a bite or scratch injury. These cases include infections of the upper respiratory tract, soft tissue infection secondary to accidental injury, intra-abdominal infections, meningitis, and bone and joint infections.[54] Pneumonia with or without empyema is rare and occurs chiefly in adults with underlying chronic bronchopulmonary disease. *P. multocida* can cause BSI and meningitis in infants and children, with most cases occurring in infants <12 months of age.[57–60] Exposure to animals was frequently nontraumatic and typically subsequent to a pet dog or cat licking the infant's face. The symptoms of central nervous system infection and abnormalities of cerebrospinal fluid in infected children are typical of bacterial meningitis; however, a mononuclear cell predominance in cerebrospinal fluid has been reported.[58,59,61,62] BSI is documented in approximately 50% of patients with meningitis. Neurologic sequelae are uncommon. Other *P. multocida* central nervous system infections include brain abscess secondary to direct penetration of the brain parenchyma after a dog bite, subdural empyema, and ventriculoperitoneal shunt infections.[61,63]

P. multocida is a rare cause of fetal infection secondary to maternal BSI and invasion through the placenta,[64] although ascending infection also has been postulated.[65,66] This situation is in contrast to fetal infections in animals, in which *Pasteurella* spp. are well-documented causes of septic abortion. Neonatal systemic infection with *P. multocida* has been reported only rarely. The presentation is similar to that of early onset group B streptococcal disease and is characterized by fulminant septicemia with or without meningitis. Neonatal infection usually occurs in the setting of a maternal obstetric complication, including chorioamnionitis, premature onset of labor, prolonged rupture of membranes, postpartum fever, or premature delivery.[67,68] The mortality rate is high, particularly in infants who acquire infection in utero and who are symptomatic at birth. The maternal genital tract is the source of the infection for both infant and mother. Genital colonization is thought to occur as a result of hand inoculation after animal contact.[67,69] Late onset meningitis and cervical spine osteomyelitis were reported in a 20-day-old infant from a household with 2 pet cats.[70] The infection occurred without an obvious history of cat bites, scratches, or licks. Systemic infections are rare in older children and adults.[71,72]

People with underlying abnormalities of host defense, especially liver disease, are predisposed to BSI caused by *P. multocida* infection.[53] Direct trauma from an animal bite or scratch has occurred in some patients, but oropharyngeal colonization secondary to contact with secretions of a pet also can be the source of invasive infection. Septic shock develops in approximately 50% of patients, and the mortality rate approaches 40%. Contiguous spread of infection from liver to lung with involvement of the diaphragm has been reported.[73] *P. multocida* also has been associated with peritonitis secondary to a ruptured appendix or peritoneal dialysis, endophthalmitis after a cat scratch, prosthetic vascular graft infection, and granulomatous hepatitis.[74–76] Urinary tract infection caused by *P. multocida* is rare but has been reported in children with underlying renal disease.[77,78] Repeated catheterization and skin contamination with *P. multocida* can contribute to introduction of the organism into the urinary tract.[77]

Possible horizontal transmission has been reported.[71] A case of *P. multocida* BSI in a patient with Kikuchi disease has been reported, but the relationship between Kikuchi disease and *P. multocida* infection could not be established.[79] Several other *Pasteurella* spp. have been reported as human pathogens. *P. canis, P. dagmatis,* and *P. stomatis* have been associated with wound infections and osteomyelitis after cat or dog bites, as well as with endocarditis, peritonitis, and sepsis in a patient with cirrhosis and with septicemia in a diabetic patient.[80–83] The reservoir of *P. canis* is the oral cavity of dogs, whereas the latter 2 species have been recovered from the oral cavity of both dogs and cats. *P. aerogenes* has been associated with animal bite wounds, urinary tract infection, and peritonitis in humans.[10,84] *P. bettyae* has been recovered from amniotic fluid, blood (usually in the neonatal period), finger lesions, abscesses, wounds following rectal surgical procedures, and genitourinary lesions, particularly Bartholin gland abscesses.[10,85] Peritonitis caused by *P. aerogenes* and *P. pneumotropica* was reported in a patient undergoing peritoneal dialysis following bites by hamsters.[80,86]

C. violaceum is a rare human pathogen but is a common soil and water inhabitant in tropical and subtropical areas; most infections are reported from Southeast Asia.[1,20,21] All cases of infection reported in the United States have been in the southeast, especially Florida, Georgia, Louisiana, and South Carolina. A review of 106 reported cases between 1952 and 2009 showed that 42% of the patients were younger than 10 years of age, and most patients did not have any predisposing factors.[24] Infections occur primarily in boys or men during the summer months and usually involve injury to the skin in association with exposure to soil or water. Most infections have a short incubation time, but symptoms can occur 60 days after a specific exposure.[24] The initial symptom typically is pain at the wound site. Infection can be limited to the wound, or it can disseminate rapidly, causing overwhelming septicemia with a high mortality rate.[20,87,88] Rapid progression to sepsis with metastatic abscesses to liver, lung, and spleen is striking.[24] Fever, nausea, vomiting, abdominal pain, and diarrhea frequently are noted. Septic shock, pneumonia, osteomyelitis, lymphadenitis, diarrhea, urinary tract infection, conjunctivitis, orbital cellulitis, and abscesses of spleen, lung, brain, and liver have been described.[20,89–95]

Pneumonia after aspiration of fresh warm water was reported in 2 cases of near drowning.[91] Multiple sites of abscesses tend to occur, especially in the liver, spleen, and lungs. Healthcare-associated infections and pneumonia have been reported.[96] Infections can recur.[88] Although most infections have occurred in people presumed to be immunologically competent, chronic granulomatous disease predisposes to *C. violaceum* infection.[95] One review suggested that patients with chronic granulomatous disease may have lower rates of bacteremia and death than patients without chronic granulomatous disease.[88] Similarities have been observed in clinical presentations of *C. violaceum* infection and the septicemic form of melioidosis caused by *Burkholderia pseudomalleii*.[89] Diagnosis is made by culture of wound exudate, biopsy specimen, blood, or abscess fluid.

Treatment and Prevention

Eikenella corrodens.

E. corrodens generally is susceptible in vitro to the following: penicillin, ampicillin, or amoxicillin; amoxicillin-clavulanate and ampicillin-sulbactam; most second- and third-generation cephalosporins; carbapenems; ureidopenicillins; tetracyclines; and newer fluoroquinolones.[34,97,98] Clindamycin, antistaphylococcal penicillins, macrolides, metronidazole, and aminoglycosides generally are inactive, and first-generation cephalosporins have variable activity. First-generation cephalosporins should not be given to patients with suspected *E. corrodens* infections.[35] β-Lactamase-producing strains have been reported rarely; these strains were highly susceptible to amoxicillin-clavulanate and ampicillin-sulbactam.[99] Because many infections involving *E. corrodens* are polymicrobial and can include anaerobic bacteria, selection of therapy should take into account other potential pathogens. Parenteral therapy is appropriate for initial therapy of severe infection, whereas amoxicillin or amoxicillin-clavulanate administered orally can be used to complete treatment in most instances. Surgical drainage of abscesses can be required. Standardized methods for in vitro antimicrobial susceptibility testing have been published.[100]

Pasteurella multocida.

P. multocida is susceptible to penicillin, which is the drug of choice for treatment of infections. Other active agents include ampicillin, amoxicillin-clavulanate, cefuroxime, cefoxitin, fluoroquinolones, tetracyclines, and trimethoprim-sulfamethoxazole.[97,101] Erythromycin, clindamycin, cephalexin, cefadroxil, cefaclor, and dicloxacillin have poor activity against *P. multocida* and should not be used to treat infection.[57,101,102] β-Lactamase–producing strains of *P. multocida* have been isolated from human infections.[69] One report noted that the addition of any of the β-lactamase–inhibiting compounds reduced the minimal inhibitory concentration of this organism at least 64-fold.[102] Testing for β-lactamase using a chromogenic cephalosporin (nitrocefin test) is recommended for isolates from normally sterile body sites. Standardized methods for in vitro testing of *Pasteurella* spp. have been published.[100,103]

Although most wound infections caused by *P. multocida* typically respond well to appropriate oral antibiotic therapy, worsening of disease during the first 24 hours of treatment is not unusual. When polymicrobial wound infection is suspected, amoxicillin-clavulanate or cefuroxime is recommended. The duration of oral antibiotic therapy for localized infections typically is 7 to 10 days.

Hospitalization should be considered for patients with certain *P. multocida* infections: systemic infections; infections in people with diabetes mellitus or immunocompromising conditions; and serious infections of the head, hands, joint spaces, or tendons. Parenteral antimicrobial agents active against *Pasteurella* spp. include penicillin, ampicillin, ampicillin-sulbactam, piperacillin, cefuroxime, and cefotaxime.[57,101] The duration of parenteral therapy for severe or disseminated infections should be 10 to 14 days. When mixed infection is considered, ticarcillin-clavulanate, cefuroxime, ampicillin-sulbactam, or meropenem should be effective.

Parents should be discouraged from allowing pets to lick infants and children on the face or on wounds. Handwashing after pet contact is prudent. Limiting contact with wild and domestic animals probably is the only way to prevent human infections with *Pasteurella* spp. Animal bites and scratches should be vigorously cleaned, irrigated, and debrided promptly. The use of antibiotic prophylaxis to prevent wound infection secondary to animal bites is controversial. Some experts recommend prophylactic antibiotic therapy in persons with the following: (1) cat bite; (2) severe bite wound accompanied by edema, crush injury, or involvement of bone, joint, or tendon sheath; (3) immunocompromising condition, asplenia, or diabetes mellitus; (4) injury sustained ≥8 hours before medical assistance is sought; and (5) bite on the hands, feet, or genital area.[57] Amoxicillin-clavulanate is a good choice when antimicrobial prophylaxis or preemptive therapy of a bite wound is indicated. For the penicillin-allergic child, trimethoprim–sulfamethoxazole or cefuroxime axetil can be considered. Minimal data exist about the role of suturing bite wounds and risk of infection.[57]

Chromobacterium violaceum.

C. violaceum usually is susceptible to chloramphenicol, aminoglycosides, tetracyclines, meropenem, fluoroquinolones, and trimethoprim-sulfamethoxazole but is resistant to penicillin, ampicillin, and first-generation cephalosporins.[20,21,89] Initial empiric therapy based on penicillins and cephalosporins can result in increased mortality rates.[63] Trimethoprim-sulfamethoxazole in combination with ciprofloxacin is the treatment of choice for initial therapy, but chloramphenicol in combination with an aminoglycoside, or a carbapenem, can be an effective alternate therapy.[98] Erythromycin is not effective for treatment, regardless of susceptibility test results, and resistance to the aminoglycosides and broad-spectrum β-lactam agents has been documented.[91,103] Antimicrobial susceptibility testing can be helpful in guiding management; however, currently no standardized methods exist for in vitro testing of *C. violaceum,* and test results should be interpreted cautiously. Antimicrobial therapy for infections with *C. violaceum* should be initiated with parenteral antibiotics until the patient is stable and improving, followed by oral therapy (trimethoprim-sulfamethoxazole, tetracycline, or a fluoroquinolone) for at least an additional 2 to 3 months, to prevent relapse.[24] Necrotizing skin lesions should be debrided and abscesses drained aggressively at initiation of antimicrobial therapy. Disseminated infection requires aggressive supportive care. Relapse of BSI is a documented complication, usually occurring approximately 2 weeks after completion of therapy. *C. violaceum,* along with the more common *Aeromonas hydrophila,* should be considered when choosing empiric antibiotic therapy for cellulitis or rapidly progressive illness following exposure to soil or water, particularly stagnant water in the southeastern United States.[20]

Key Points

Diagnosis and Management of *Eikenella corrodens* Infections

Microbiology

- Catalase-negative, oxidase-positive, small gram-negative, straight bacilli
- Good growth on blood and chocolate agars but not MacConkey agar; enhanced growth in carbon dioxide
- Colonies often showing a fringe of spreading growth and ability to pit the agar
- Generally susceptible to penicillin, but β-lactamase-producing strains reported (susceptible to penicillin or β-lactamase inhibitor compounds)

Epidemiology

- Normal oropharyngeal and transient gastrointestinal tract flora
- Associated with juvenile and adult periodontitis
- Oral, pleuropneumonic, and abdominal infections; often polymicrobial
- Wound infection associated with human bites and fist-to-mouth injuries
- Can cause bone and joint infection
- Agent of subacute bacterial endocarditis, especially subsequent to dental manipulation or intravenous drug abuse

Diagnosis

- Recovery in culture uses standard laboratory procedures.
- Polymerase chain reaction and 16S ribosomal RNA gene sequencing have been used for diagnosis but are not available widely.
- *Eikenella corrodens*–specific DNA probes have been used to analyze the microbial flora associated with periodontal disease.

Treatment

- Penicillin the drug of choice for infection because the organism is β-lactamase negative
- Susceptible generally to ampicillin and amoxicillin (if β-lactamase negative), amoxicillin-clavulanate, extended-spectrum cephalosporins, ciprofloxacin, and doxycycline; generally resistant to clindamycin and the macrolides

Duration of Therapy

- Response to therapy usually is rapid.
- Duration of therapy for systemic infection including osteoarticular infections or endocarditis is similar to that for other infectious agents.

Key Points

Diagnosis and Management of *Pasteurella multocida* Infections

Microbiology

- Catalase- and oxidase-positive, small gram-negative, coccoid to short bacilli
- Good growth on blood and chocolate agar but not MacConkey agar; does not require carbon dioxide

- Colonies can be mucoid, particularly those recovered from the respiratory tract.

- Generally susceptible to penicillin, but β-lactamase-positive strains causing penicillin and ampicillin resistance reported (susceptible to penicillin or β-lactamase inhibitor compounds)

Epidemiology

- Normal inhabitants of the nasopharynx, gingival, and oral cavity of a wide variety of wild and domestic mammals including cats and dogs; also found in the respiratory tract of birds

- Associated with wound infections following animal bites, scratches, or other exposures (licking of open skin lesions)

- Infected cat bites more likely than infected dog bites to contain *Pasteurella multocida*

- Causes respiratory tract infection including sinusitis and bronchitis, pneumonia, and empyema, primarily in people with underlying disease

- Two subspecies, *P. multocida* subsp. *multocida* and *P. multocida* subsp. *Septica,* the former responsible for the majority of infections

- Can cause bloodstream and disseminated infection, including meningitis, endocarditis, peritonitis, and bone and joint infection

Diagnosis

- Recovery in culture from most body sites uses standard laboratory procedures.

- Polymerase chain reaction and 16S ribosomal RNA gene sequencing have been used for diagnosis but are not available widely.

Treatment

- Penicillin the drug of choice for β-lactamase-negative infections
- Susceptible generally to ampicillin and amoxicillin (if β-lactamase negative), amoxicillin-clavulanate, extended-spectrum cephalosporins, ciprofloxacin, and trimethoprim-sulfamethoxazole; generally resistant to clindamycin, whereas macrolides and aminoglycosides have reduced activity

Duration of Therapy

- Response to therapy usually is rapid, particularly with administration of antibiotic parenterally; however, disease can progress initially after commencing an appropriate antibiotic, particularly an oral agent.
- Duration of therapy for systemic infection including osteoarticular infections or endocarditis is similar to that for other infectious agents.

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Moraxella Species

Eugene Leibovitz, David Greenberg

Microbiology

Discovered at the end of the 19th century, *Moraxella catarrhalis* (formerly *Micrococcus catarrhalis*, *Neisseria catarrhalis,* and *Branhamella catarrhalis*) has undergone several changes of nomenclature and changes in status as either a commensal of the upper respiratory tract or a true pathogenic organism of both the upper and lower respiratory tract.[1–4] The morphologic and phenotypical similarity to *Neisseria* spp. led to the previous misidentification of *M. catarrhalis* as a species of *Neisseria, N. cinerea* (a commensal of the adult pharynx).[3,4] DNA-DNA and ribosomal RNA (rRNA)–DNA hybridization techniques have shown *M. catarrhalis* to be more closely related to *Moraxella* than to *Branhamella* spp.[3–7]

Currently, *M. catarrhalis* is responsible for up to 20% of cases of acute otitis media (AOM), (the third most common etiologic agent after nontypable *Haemophilus influenzae* and *Streptococcus pneumoniae*).[8–13] *M. catarrhalis* is the second (after *H. influenzae*) most common cause of exacerbations of chronic obstructive pulmonary disease in adults and is responsible for 2 to 4 million episodes in the United States.[14]

Members of the genus *Moraxella* are nonmotile, oxidase-positive, catalase-positive, aerobic, asaccharolytic, gram-negative coccobacilli or diplococci that tend to resist decolorization on Gram stain.[1] *M. catarrhalis, M. osloensis, M. nonliquefaciens,* and *M. lincolnii* are part of the normal flora of the respiratory tract, whereas *M. canis* is recovered from the upper respiratory tract of cats and dogs. Other pathogens include *Psychrobacter phenylpyruvicus;* the differentiation of *P. phenylpyruvicus* from *Brucella* spp. is important and requires microscopy and fermentation tests. Most laboratories do not perform species identification except for *M. catarrhalis*. Colonies of *M. catarrhalis* grow well on both blood and chocolate agar, and some strains also grow well on modified Thayer-Martin and other selective media. Colonies are grey white, opaque, and smooth. A useful observation for *M. catarrhalis* is the ability to push colonies over the surface of blood agar similar to a hockey puck on ice.[1] *M. catarrhalis* is distinguished easily from *Neisseria* spp. by the former's ability to hydrolyze ester-linked butyrate groups. Almost all contemporary *M. catarrhalis* isolates produce β-lactamase.[15,16]

M. catarrhalis colonizes the mucosal surfaces of the upper and lower respiratory tract by expression of adhesins and activation of metabolic pathways to overcome specific nutrient limitations. Several adhesins and receptors have been identified and characterized.[17] The family of ubiquitous surface proteins (Usps), consisting of at least 3 proteins (UspA1, UspA2, and UspA2H), consists of highly conserved and extensively studied outer membrane proteins (OMPs) with major roles in adhesion, invasion, and resistance to classic and alternative complement systems. The whole genomic sequence of *Moraxella catarrhalis* strain RH4 (16S rRNA subtype 1strain) has been reported.[18] The *Moraxella* immunoglobulin D (IgD)–binding protein (MID, also named hemagglutinin) is another extensively studied and highly conserved OMP that has a unique ability to bind IgD and also type II alveolar epithelial cells.[17,19] Fifty-seven proteins carried by outer membrane vesicles (OMVs) have been identified, including UspA1, UspA2, MID, lipo-oligosaccharide, and DNA.[20] UspAs are the most important complement-resisting OMPs, as demonstrated in clinical isolates from patients with otitis media or chronic obstructive pulmonary disease.[17,20–22] Strains resistant to complement-mediated killing are more virulent and adherent to epithelial cells.[17,23,24] The membrane lipo-oligosaccharides also are considered important for *M. catarrhalis* adhesion and virulence.[17,25]

M. catarrhalis can form biofilms in vitro and has been detected in biofilms in the middle ear of patients with chronic otitis media.[26–28] Biofilm production by *S. pneumoniae* and *M. catarrhalis* is proposed to enhance the roles of these pathogens in recurrent AOM and otitis media with effusion.[29]

At the respiratory tract mucosal level, *M. catarrhalis* activates an proinflammatory response that is mainly dependent on toll-like receptor 2 (TLR2),[17,30] and it also can inhibit the inflammatory cascade, thereby leading to evasion and persistent mucosal surface colonization.[31]

The importance of *M. catarrhalis* in the post–pneumococcal conjugate vaccine 13 (PCV13) era and its increasing resistance to antimicrobial agents foster consideration of a vaccine for *M. catarrhalis*.[16,17,32,33] UspA1, UspA2, and MID/hemagglutinin are considered important OMP adhesin candidates for development of a vaccine.[34,35] The chinchilla model has promise as a relevant animal model for human vaccine development.[36,37]

Epidemiology

Colonization rates with *M. catarrhalis* in the upper respiratory tract vary with age, with rates highest in the first year of life (28% −100%).[38,39] *M. catarrhalis* can persist for several months, and earlier colonization in the first year is associated with higher risks of AOM and recurrent disease.[39] Seasonal peaks of *M. catarrhalis* colonization and disease (winter and spring) are similar to several viral respiratory viruses.[40,41] In the chinchilla, coinfection of respiratory syncytial virus and *M. catarrhalis* facilitated ascension of *M. catarrhalis* from the nasopharynx into the middle ear.[42] Physiologic cold shock[43,44] of *M. catarrhalis* is associated with expression of important virulence factors, such as genes involved in adherence to epithelial cells, iron acquisition, serum resistance and immune evasion.[44] The risk of repeated *M. catarrhalis* colonization was reported to be increased in children with TLR4 Asp299Gly polymorphism.[45] Conversely, the pili (fimbriae), cell surface organelles found on the surface of *M. catarrhalis,* enhance pathogen clearance from the middle ear, probably mediated through neutrophil-dependent TLR5 signaling.[46]

Five percent to 32% of older adults with chronic obstructive pulmonary disease may have, at any time, *M. catarrhalis* colonizing the respiratory tract, with a median carriage duration of 30 to 40 days.[47]

The development of mature specific IgG antibodies against *M. catarrhalis* is slow, and children <4 years of age have low titers of IgG antibodies.[48] In a study analyzing the humoral immune responses to potential *M. catarrhalis* vaccine candidates from birth to 2 years of age, the level of antigen-specific IgG was lower than that obtained from umbilical cord blood.[49]

The most frequent infections caused by *M. catarrhalis* are AOM, sinusitis, bronchitis, and pneumonia. Most cases of *M. catarrhalis* AOM resolve spontaneously. Compared with AOM caused by other pathogens, *M. catarrhalis* AOM is more often a mixed-infection AOM, and it is less often associated with spontaneous perforation and mastoiditis.[50] *M. catarrhalis* hardly ever causes suppurative complications of AOM, such as osteomyelitis, meningitis, or brain abscess. Although major decreases in pneumococcal AOM, with near elimination of PCV13 serotype disease in the post-PCV13 era, are well documented,[51] the dynamics of *M. catarrhalis* AOM are unknown. No change in the nasopharyngeal carriage of *M. catarrhalis* was observed in children <2 years of age following PCV7.[52]

Establishing a causative role for *M. catarrhalis* in children with community-acquired pneumonia is challenging because of poor diagnostic tests and frequent colonization of the upper respiratory tract.[53,54] *M. catarrhalis* bacteremia is infrequently reported; it occurs in children <2 years of age, usually in association with community-acquired pneumonia, and is characterized by low grade fever and a lack of leukocytosis but prolonged hospitalizations.[55]

M. catarrhalis can cause purulent conjunctivitis, periorbital cellulitis, endophthalmitis, pyogenic arthritis, pancreatitis, pericarditis, endocarditis, prosthetic vascular graft infections, pleural effusion, or localized abscesses.[56–66] In immunocompromised patients, *M. catarrhalis* septicemia is reported in patients with leukemia, acquired immunodeficiency syndrome, and agammaglobulinemia.[67–69]

Septicemia associated with diarrhea in children that is caused by *M. osloensis, M. nonliquefaciens,* and *M. lacunata* has been reported.[70] Septicemia, endocarditis, and pyogenic arthritis caused by *M. liquefaciens* and *M. nonliquefaciens* has also been reported.[70–74] *M. osloensis* has been associated with osteomyelitis, peritonitis, catheter-related bloodstream infection, and other deep-seated infections.[75] *M. canis,* an inhabitant of the upper respiratory tract of dogs and cats, has been associated with rare cases of bloodstream infection, wound infections following dog bites, and ulcerated metastatic lymph node infection.[76,77]

Treatment

Most *Moraxella* spp. other than *M. catarrhalis* are susceptible to penicillin and ampicillin, cephalosporins, tetracyclines, macrolides, aminoglycosides, and quinolones; however, β-lactamase–producing strains have been identified in some species, including strains of *M. osloensis* and *P. phenylpyruvicus.*[1,78,79] The prudent approach is to test clinically significant isolates for β-lactamase production. All 117 *M. catarrhalis* isolates tested during 2012 in British Columbia were sensitive to amoxicillin-clavulanate, doxycycline, clarithromycin, levofloxacin, and trimethoprim-sulfamethoxazole, and only 1 isolate was intermediately resistant to cefuroxime.[80]

M. catarrhalis is almost uniformly resistant to penicillin, ampicillin, and amoxicillin because of the production of a *Branhamella/Moraxella* (BRO)-1 or BRO-2 β-lactamase.[1,81,82] The drug of choice to treat *M. catarrhalis* infections is amoxicillin-clavulanate. Second- or third-generation cephalosporin drugs are alternative therapeutic agents. With a wide variety of antimicrobial agents (including fluoroquinolones and carbapenems) uniformly active against *M. catarrhalis*, the need rarely exists for susceptibility testing except for β-lactamase, which also aids identification.[1,82] Strains of *M. catarrhalis* with low-level fluoroquinolone resistance and resistance to both macrolides and quinolones have been reported.[83,84]

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Pseudomonas Species and Related Organisms

Jane L. Burns

Pseudomonas spp. are water and soil organisms of relatively low virulence that are catalase-producing, nonglucose-fermenting, gram-negative bacilli that grow well on routine microbiologic culture media at 37°C. Pseudomonads are motile and both indophenol and oxidase positive; many produce pyoverdins or other visible or fluorescent pigments. Speciation is based primarily on physical characteristics (pigment production, odor, colonial morphology, and flagellar structure) and biochemical profiles (including carbohydrate fermentation patterns and production of arginine dihydrolase and lysine decarboxylase). Several related genera are recognized, many of which used to be species within the genus *Pseudomonas* (Box 154.1). Still remaining within the genus are *P. aeruginosa, P. stutzeri, P. putida,* and *P. fluorescens. P. oryzihabitans* (formerly *Flavimonas*) and *P. luteola* (formerly *Chryseomonas*) have been returned to the genus (Table 154.1).[1,2]

Box 154.1

Closely Related Genera Formerly Included With *Pseudomonas*

Acidovorax

Brevundimonas

Burkholderia

Comamonas

Delftia

Methylobacterium

Ralstonia

Shewanella

Sphingomonas

Stenotrophomonas

TABLE 154.1

Human Pathogens Included Within the Genus *Pseudomonas* (Non-*aeruginosa*)

Species	Subspecies
Pseudomonas fluorescens species complex	23 species
Pseudomonas luteola	(Formerly *Chryseomonas luteola*)
Pseudomonas monteilii	(Closely related to *Pseudomonas putida*)
Pseudomonas oryzihabitans	(Formerly *Flavimonas oryzihabitans*)
Pseudomonas putida	2 biovars
Pseudomonas stutzeri	18 genomovars

Pseudomonads and closely related species are nutritionally diverse; many are used in industry because of their unique ability to catabolize toxins. Although *P. aeruginosa* is the most important human pathogen within this group, other species have been reported to cause nosocomial infections in immunocompromised and postoperative patients and in patients with indwelling catheters and to cause sporadic infections in previously healthy people. In addition, some organisms occupy specific environmental niches. Several species, including *P. fluorescens* and *Ralstonia* spp., are isolated commonly from the sputum of patients with cystic fibrosis but are of unknown clinical significance. *R. mannitolilytica* is the most commonly isolated *Ralstonia* species from patients with cystic fibrosis (46% of *Ralstonia*-positive patients), followed by *R.*

respiraculi and *R. pickettii* (19% and 18%, respectively).[3] Other pediatric isolates of *Ralstonia* occur mainly in patients with nosocomial infections and among patients with infections and malignant disease.[4] In 2011, *R. paucula* was reported in an outbreak of pseudobacteremia within a pediatric emergency department that was associated with a skin antiseptic.[5] *Sphingomonas paucimobilis* can cause nosocomial infections, most commonly in immunocompromised people; contaminated solutions often are the cause.[6] Bloodstream infection in the presence of a central venous catheter has been reported in children with neonatal sepsis, malignant disease, and aplastic anemia; patients undergoing continuous peritoneal dialysis also are at risk for catheter-associated peritonitis.[7]

The fluorescent group of *Pseudomonas* includes *P. aeruginosa, P. fluorescens, P. putida, P. veronii*, and *P. monteilii*. DNA sequence analysis has resulted in reclassification of strains previously identified as *P. fluorescens* into the *P. fluorescens* species complex (23 species, including *P. fluorescens* and *P. veronii*).[8] These organisms have been described in both nosocomial and community-associated infections in children, including bloodstream infection, pneumonia, urinary tract infection, and postoperative wound infection.[9] In 2008, a multistate outbreak of *P. fluorescens* bloodstream infection was reported, associated with exposure to contaminated heparinized saline flushes.[10] A case series from 2007 reported an outbreak of *P. aeruginosa* and *P. putida* catheter-associated infections associated with contaminated tap water on a pediatric oncology unit.[11] Because these organisms are uncommon human pathogens, few studies of susceptibility of these organisms have been conducted; in vitro susceptibility testing should guide therapy.

P. oryzihabitans, P. luteola, and *P. stutzeri* are members of the nonfluorescent group. Although they are rare human pathogens, these organisms are reported occasionally as nosocomial pathogens in both previously healthy and immunocompromised people. *P. oryzihabitans* has been described as an etiologic agent of bloodstream infection in premature neonates and in children with malignant disease, postoperative infections, and catheter-associated infections.[12,13] Case reports of *P. luteola* causing brain abscess, meningitis, and endocarditis and a case series of 7 pediatric patients with bacteremia have been published.[14–16] *P. stutzeri* has been reported to cause posttraumatic pyogenic arthritis and postoperative brain abscess.[17,18] Other pseudomonads, including *Brevundimonas vesicularis, Delftia acidovorans, Comamonas testosteroni, Acidovorax avenae,* and *Shewanella putrefaciens,* can cause sporadic infections or nosocomial outbreaks in immunocompromised people but have not been identified as significant human pathogens.[19–23]

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Pseudomonas aeruginosa

Paul J. Planet

Microbiology

Pseudomonas aeruginosa is a gram-negative bacillus found widely in nature, in soil and water. Classified as an opportunistic pathogen, *P. aeruginosa* causes disease infrequently in normal hosts but is a major cause of infection in patients with underlying or immunocompromising conditions. The genome of *P. aeruginosa*, which is especially large for a prokaryote, has provided an understanding of the metabolic and pathogenic mechanisms that underlie the success of this versatile pathogen, and it has become a model for understanding microbial genomic variation and evolution in chronic disease. *P. aeruginosa* has few nutritional requirements and can adapt to conditions not tolerated by other organisms. It does not ferment lactose or other carbohydrates but oxidizes glucose and xylose. Organisms grow aerobically or anaerobically if nitrate is available as an inorganic electron acceptor, as is the case in the lungs of patients with cystic fibrosis (CF).[1] *P. aeruginosa* gene expression responds to environmental conditions with discrete patterns typical of environmental isolates: motility, piliation, and expression of numerous exoproducts. In subacute and chronic infections, the accumulation of intracellular dinucleotides (cyclic diguanidine monophosphate) favors a biofilm mode of growth with the formation of an extracellular polysaccharide matrix,[2] thus enabling the organisms to avoid innate immune clearance mechanisms and persist in human airways.[3]

The organism produces the fluorescent siderophores pyoverdin and pyochelin, which function to scavenge iron. Redox-active phenazines such as pyocyanin, the pigment that gives *P. aeruginosa* its characteristic blue color, play an important role in electron transport especially under microaerophilic conditions, increase the bioavailability of iron, and enhance virulence through oxidative stress.[4,5] *P. aeruginosa* can be identified biochemically as having indophenol oxidase-positive, citrate-positive, and L-arginine dehydrolase-positive activity. Differentiation of *P. aeruginosa* from other pseudomonads or organisms such as *Burkholderia* species, *Stenotrophomonas maltophilia,* and *Achromobacter* spp. occasionally can require testing for DNAse activity, growth at 42°C, and differential carbohydrate metabolism or using molecular methods.

Virulence Factors and Pathogenesis

Multiple virulence factors and their purported roles in pathogenesis are shown in Table 155.1. *P. aeruginosa* thrives under conditions that would be adverse to many other bacteria with only a minimal carbon source and a moist environment. *P. aeruginosa* is intrinsically resistant to many classes of antimicrobial agents and can acquire additional resistance genes from other organisms, thus flourishing under selective pressures that eliminate competing flora. Depending on specific environmental conditions (e.g., availability of nutrients, especially iron) and immune responses, specific virulence factors are expressed in a highly regulated manner. Hosts without underlying conditions occasionally experience serious *P. aeruginosa* infections if a break in normal barrier defenses occurs through puncture wounds,[6] skin trauma, or burns.[7] More commonly, *P. aeruginosa* acts as an opportunist, infecting patients who have defective mucosal immunity, impaired pulmonary clearance as in CF, or disease-induced or iatrogenic neutropenia.[8,9]

TABLE 155.1

Virulence Factors of *Pseudomonas aeruginosa*

Component	Mechanism	Role in Pathogenesis

Type IV pilus	Adhesin: recognizes the GaINAcbeta1-4Gal receptor in asialoglycolipids	Mediates attachment to epithelial surfaces, provides twitching motility essential for biofilm formation, activates inflammation
Flagella	Motility, chemotaxis, mucin-binding, major immunostimulant through toll-like receptor 5 recognition	Facilitates tissue invasion, activates inflammation
Alginate mucoexopolysaccharide	Antiphagocytic	Characterizes chronic infections in cystic fibrosis
Elastase	Cleaves elastin, proteins including IgA	Destroys extracellular matrix components
Alkaline protease	Cleaves proteins	Causes tissue destruction
Phospholipase C (hemolytic and nonhemolytic)	Cleaves phosphatidylcholine and sphingomyelin	Degrades pulmonary surfactant, facilitates infection in the lung
Phospholipase D (PldA and PldB; type VI secretion)	Activates PI3K/Akt pathway	Facilitates intracellular invasion through actin rearrangement
Neuraminidase	Releases sialic acid from glycoconjugates	Facilitates colonization
Cytotoxin	Forms pores in membranes	Causes tissue destruction
Pseudomonas **autoinducer (PAI)**	Homoserine lactone derivative, a secreted cofactor necessary for the expression of elastase, alkaline protease, neuraminidase, and biofilm formation	Coordinates gene expression within a population of organisms
Exotoxin A	ADP ribosylating enzyme, which inactivates EF-2, inhibiting protein synthesis	Causes tissue destruction
Exoenzyme S, T, U (type III secreted toxins)	ADP ribosylating enzymes (S and T) and toxins with specific eukaryotic targets, including GTPases; phospholipase A_2	Facilitates invasion, cytotoxicity, interferes with cytoskeletal integrity
Siderophores (pyochelin, pyoverdin)	High-affinity iron-binding capacity	Facilitates iron acquisition for bacterial metabolism
Phenazines (pyocyanin)	Blue-green pigment: oxidant activity	Destroys ciliary activity, toxic to airway cells, oxidative stress

ADP, adenosine diphosphate; EF-2, elongation factor-2; GTPases, guanosine triphosphatases; IgA, immunoglobulin A.

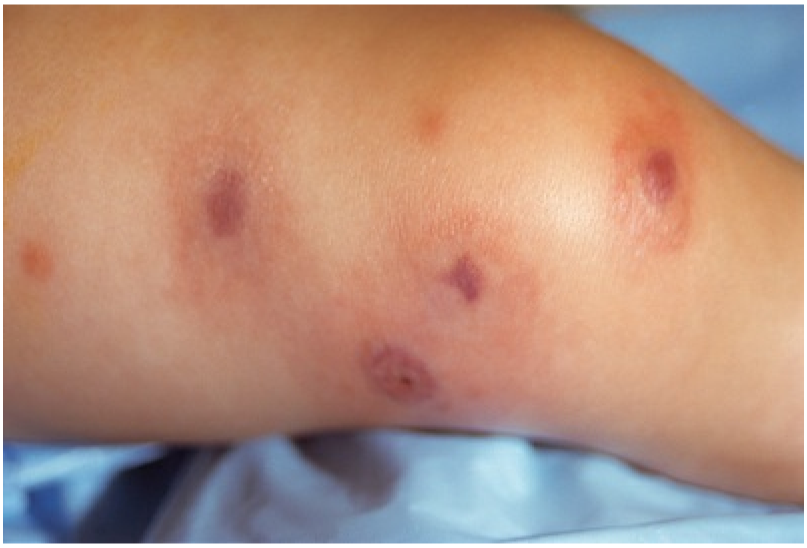

FIGURE 155.1 Multiple early skin lesions of *Pseudomonas aeruginosa* septicemia in an infant as the initial manifestation of congenital neutropenia. (Courtesy of S.S. Long.)

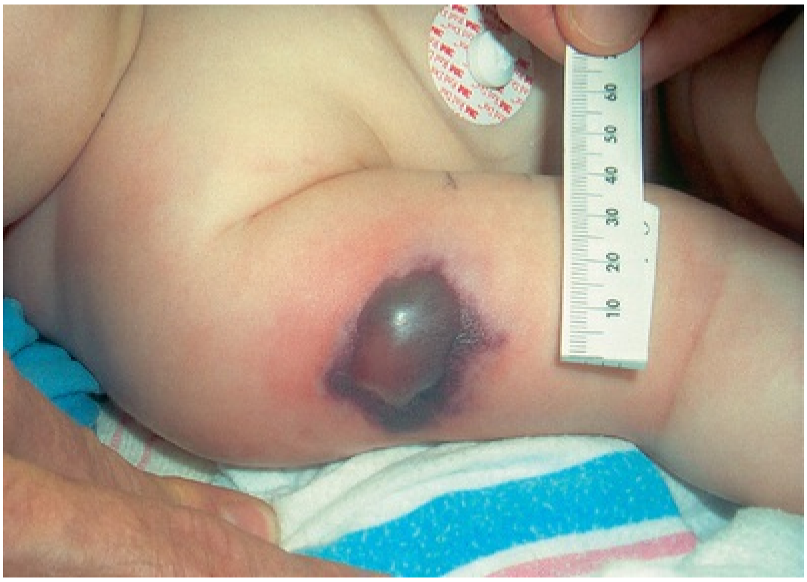

FIGURE 155.2 Ecthyma gangrenosum lesion as the initial manifestation of chronic granulomatous disease in an infant boy. (Courtesy of S.S. Long.)

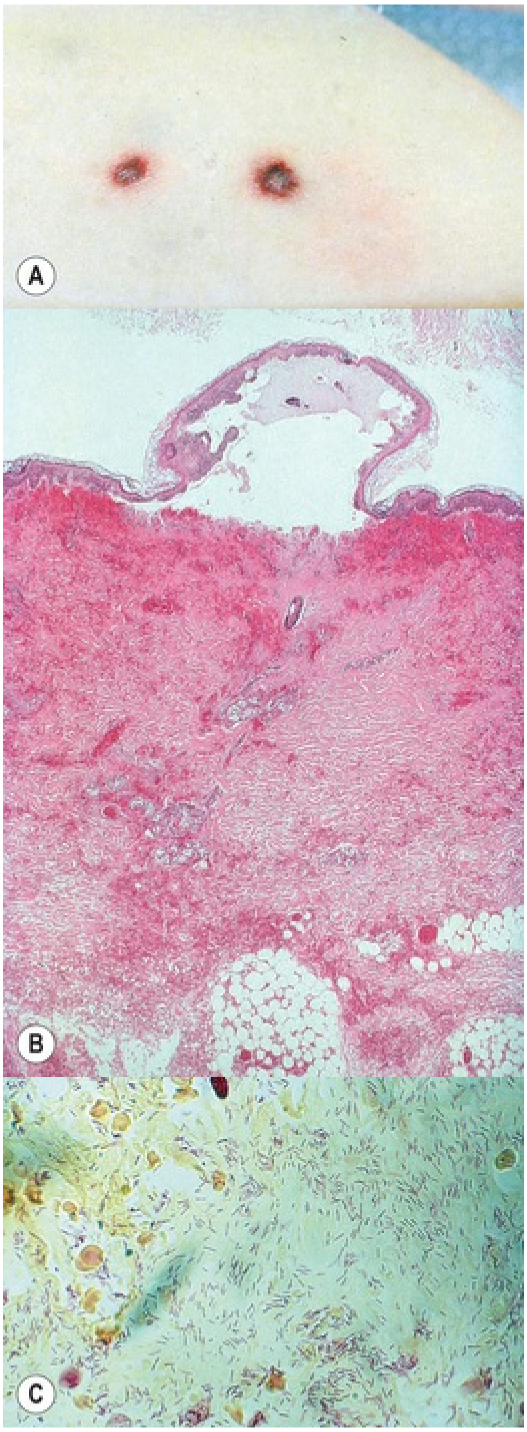

FIGURE 155.3 (A) Early skin lesions of *Pseudomonas aeruginosa* septicemia in an infant with leukemia. (B) Hematoxylin and eosin stain of a biopsy specimen of the lesion (200×) showing characteristic ischemic necrosis and vesicle formation. (C) Tissue Gram stain of fluid from the biopsy specimen (1000×). (Copyright by J.H. Brien.)

P. aeruginosa expresses numerous virulence factors that stimulate both airway epithelial cells and professional immune cells to produce proinflammatory cytokines and chemokines, such as interleukin-8 (IL-8),[10] IL-17A/F,[11] granulocyte-macrophage colony-stimulating factor,[12] and mucin.[13] Secreted exoenzymes interact with specific eukaryotic targets to affect cytoskeletal components and thereby disrupt the integrity of the epithelial tight junctions and induce inflammation.[13] Products of type III secretion systems (T3SS) are expressed commonly in acute infection, often in the setting of hospital-acquired pneumonia, by causing cytotoxicity and facilitating invasion.[14] The T3SS effector proteins include exoenzyme U (ExoU), a potent phospholipase A_2 that requires host superoxide dismutase for activation and often is associated with severe pneumonia[15]; ExoS or ExoT, closely related toxins with both adenosine diphosphate (ADP) ribosyltransferase activity and Rho GTPase activating protein activity,[14] are expressed commonly in clinical isolates from acute infections. The T3SS virulence factors have been associated with severe *P. aeruginosa* pneumonia in hospitalized patients,[16] and they have been targeted as potential antigens in *Pseudomonas* vaccines and immunotherapy.

The more recently discovered type VI secretion systems (T6SS) export toxins for interbacterial competition, but the secreted effectors also enhance invasion of host cells through activation of the PI3K/Akt pathway to cause actin rearrangement.[17] Other bacterial products such as phenazines (e.g., pyocyanin), initially considered to be metabolic waste products, have strong effects on other microorganisms and also are toxic to host cells through oxidative stress.[18]

Whereas lipopolysaccharide often is considered to be the major immunostimulatory factor in gram-negative bacteria, *P. aeruginosa* lipopolysaccharide does not activate proinflammatory signaling as potently as does lipopolysaccharide of other organisms.[19] *P. aeruginosa* flagella are important in pathogenesis signaling through toll-like receptor 5 (TLR5) and the inflammasome leading to proinflammatory responses to the organisms.[20–22] Indeed, the inflammasome plays a central role in the immune response to *P. aeruginosa* by being activated by bacterial products including flagellins,[21,22] type IV pilins,[23] T3SS components,[22,24] and the toxin RhsT.[25] Inflammasome activation also appears to be dampened by several of the T3SS effectors.[26,27] Whether the inflammasome response to *P. aeruginosa* is beneficial or detrimental to the host, either by aiding to clear bacterial infection or by causing increased tissue destruction, is likely to depend on the specific clinical circumstances.

During infection of patients with CF, shedding of bacterial immunostimulants activates cytokine and chemokine production by airway epithelial cells and recruited immune cells. After the initial steps of colonization, *P. aeruginosa* undergoes gene regulatory changes that aid in the establishment of persistent infection. The milieu within the CF-affected airways is relatively anaerobic, a property that affects both bacterial gene expression and antimicrobial susceptibility.[28] Once a sufficient density of organisms is resident in the airways, bacterial gene expression is regulated by a quorum sensing system, which involves the secretion of freely diffusible homoserine lactones that act along with transcriptional activators to coordinate the gene expression of the entire population of bacteria. Quorum sensing facilitates a biofilm mode of growth, by turning off expression of the more immunostimulatory gene products such as exoenzymes and flagella while favoring secretion of exopolysaccharides.[29] Although few organisms are directly adherent to the epithelial surface, high density of organisms persists in biofilm-like aggregates in the airways as a result of reduced mucociliary clearance and loss of airway surface hydration.[30] Because organisms within biofilms are relatively less susceptible to antimicrobial agents and phagocytosis, the ability to persist in biofilms provides a major selective advantage to the species.[31]

In chronic CF infections, *P. aeruginosa* strains tend to accumulate genetic changes that diminish or eliminate expression of proinflammatory bacterial products such as flagella or pili with the appearance of *muc* mutants with copious production of the extracellular alginate,[32] a phenotype that is virtually pathognomonic for CF isolates.[33] Although resistant to phagocytosis, these organisms are not invasive, but they chronically infect the airways. Together these changes have a profound impact on host inflammation.[34] Longterm infections also lead to high levels of phenotypic and genomic diversity that likely have an impact on the overall fitness of the infecting bacterial population.[35] This reproducible evolutionary tendency has been studied in detail using whole genomes,[36,37] and it may be enhanced by higher rates of mutation in these strains.[38] The tendency to adapt in specific ways suggests that chronic inflammation may not be beneficial for the bacterium.

Epidemiology and Clinical Manifestations

P. aeruginosa is associated with a wide variety of infections, depending on the nature of the host and the severity of underlying disease, ranging from self-limited folliculitis[39] to overwhelming septic shock.[40] Because of its exceptional genetic plasticity, *P. aeruginosa* adapts readily to healthcare settings and is a major cause of healthcare-associated infections,[41] including ventilator-associated pneumonia and infections of indwelling catheters.[42] Genomic sequencing studies suggest that a relatively limited number of clones may be responsible for these infections, but with extensive phenotypic diversity within clones.[43] Patients with CF generally have a phase of intermittent colonization with a variety of distinct *P. aeruginosa* strains, followed by chronic infection with single clones with adapted virulence profiles.[44] Although most strains appear to be acquired from the environment,[45] several transmissible strains (e.g., Liverpool Epidemic Strain) have been identified.[46,47] Tables 155.2 and 155.3 show the epidemiology and clinical manifestations of *P. aeruginosa* infection in normal and special hosts, respectively.

TABLE 155.2

Epidemiology and Clinical Manifestations of Community-Acquired and Nosocomial *Pseudomonas aeruginosa* Infection in the Normal Host

Infection	Clinical Characteristics
COMMUNITY-ACQUIRED	
Ocular infection	Keratitis is common after minor eye trauma (as in wearers of contact lenses) or penetrating eye trauma; treatment often involves subtenon or intravitreal injections
Otitis externa	“Swimmer's ear” is associated with excessive moisture, or otitis externa results from chronic suppurative otitis media; topical treatment is sufficient; malignant otitis externa is a severe systemic infection usually limited to diabetic patients and other compromised hosts; parenteral therapy and debridement are required
Endocarditis	Intravenous drug abusers can develop *Pseudomonas aeruginosa* endocarditis,

	usually of the tricuspid valve; injected foreign materials can damage endothelium and create a niche for injected organisms to adhere; septic emboli cause pneumonia; therapy can require surgical intervention
Bone and soft tissue infection	Puncture wounds of the foot are complicated especially by *P. aeruginosa* infection because the organisms are found in the moist environment within the soles of sneakers; biopsy of bone can be necessary to differentiate osteomyelitis from a contaminated drainage tract, and exploration can be necessary to remove a retained foreign object
Folliculitis	Immersion in contaminated bathtubs, hot tubs, and pools has been associated with superficial, self-limited infection, commonly confined to abraded areas and those areas covered by bathing suits; infants or patients who experience cellulitis can have severe systemic signs of infection and require anti-*Pseudomonas* treatments
NOSOCOMIAL	
Respiratory tract infection	Ventilator-associated pneumonia, intubation, and use of broad-spectrum antibiotics predispose to pneumonia; *P. aeruginosa* pneumonia (fever, purulent secretions, necrotizing pneumonia, and respiratory deterioration) must be differentiated from colonization; outbreaks of *P. aeruginosa* respiratory infection in intensive care units suggest contamination of a common source (e.g., respiratory equipment, sinks, blood pressure transducers, or common intravenous flush vials)
Urinary tract infection	Use of prophylactic or broad-spectrum antibiotics, indwelling urinary catheters, another foreign body, and obstruction are predisposing factors; successful treatment almost always requires removal of the foreign body
Surgical infection	Wound infection can follow neurosurgical, urologic surgical, or orthopedic surgical procedures; osteomyelitis is an infrequent complication that often requires debridement to effect a cure; antimicrobial therapy is prolonged, with few clinical end points; neurosurgical infections involving shunts require removal of the foreign material

TABLE 155.3

Epidemiology and Clinical Manifestations of *Pseudomonas aeruginosa* Infections in Special Hosts

Infection	Clinical Characteristics
NEUTROPENIA OR NEUTROPHIL DYSFUNCTION	
Septicemia	This healthcare-associated infection and complication of chemotherapy causes profound neutropenia, associated with higher mortality and morbidity rates than infection with other pathogens; successful outcomes are associated with recovery or engraftment of bone marrow, recovery of neutrophils; it affects immunodeficient patients and extremely low birth weight infants
	Central venous access devices are a source
Ecthyma gangrenosum	These erythematous tender lesions with an area of central necrosis are usually manifestations of or are associated with septicemia; perianal lesions portend poor outcome (Figs. 155.1–155.3)
CNS infection	Infection occurs by direct extension from sinuses, bacteremic spread, or secondary to contamination of shunts or reservoirs; in immunosuppressed patients, CNS infections can be insidious
HIV INFECTION	
Pneumonia or bacteremia	*Pseudomonas aeruginosa* is a rare cause of community-acquired pneumonia in HIV-infected adults and children, usually those *not* receiving effective antiretroviral therapy
Burns	Burn wound sepsis is a complication accompanied by high mortality rates; meticulous debridement, grafting, and judicious use of antibiotics can help to

	decrease the incidence of most such infections
Cystic fibrosis	Infection usually occurs early in infancy and childhood and leads to neutrophil-dominated inflammation of the airway, chronic inflammation, fibrosis, and loss of pulmonary function; aggressive anti-*Pseudomonas* therapy and control of inflammatory response are mainstays of therapy

CNS, central nervous system; HIV, human immunodeficiency virus.

Antibiotic Resistance

Epidemiologic Trends

Intrinsic virulence factors and facile acquisition of antimicrobial resistance in response to immune and chemotherapeutic pressure make *P. aeruginosa* a formidable pathogen in healthcare settings. Numerous reports of human clinical isolates document resistance to all available antimicrobial agents including polymyxins.[48] Moreover, particularly in patients harboring large numbers of organisms, as in CF, hypermutable strains are recovered that have increased rates of spontaneous mutations resulting from alterations in the DNA mismatch repair systems.[49] Such hypermutable strains rapidly acquire resistance to multiple antimicrobial agents. National surveillance of antimicrobial resistance rates for *P. aeruginosa* suggests relatively stable resistance trends,[50] but with important geographic differences in resistance patterns across the United States.

Mechanisms of Antibiotic Resistance

Permeability Factors and Efflux Systems.

Analysis of the *P. aeruginosa* genome demonstrates that multiple redundant mechanisms survive potential threats from antimicrobial agents, a likely consequence of the origin of this organism in the soil commensurate with fungi that produce common antimicrobial agents. The organism's ability to limit permeability through several efflux pumps is paramount. These efflux pumps are important in export of quorum sensors (that regulate biofilm production), invasiveness, and antimicrobial resistance.[51] The *mexAB* operon likely accounts for “intrinsic” resistance of *P. aeruginosa* to many classes of antibiotics, including tetracyclines, fluoroquinolones, chloramphenicol, macrolides, and trimethoprim, as well as β-lactam agents and β-lactamase inhibitors. Genome analysis reveals at least

20 homologues of the mexAB system in *P. aeruginosa.* The combination of limited permeability (increased efflux) and strategically placed enzymes such as β-lactamases within the periplasmic space accounts for much of the antimicrobial resistance of the species.

β-Lactamase Production.

P. aeruginosa expresses both chromosomally mediated and plasmid-associated enzymes that degrade β-lactam antibiotics. Chromosomal expression of *ampC* induces an enzyme that preferentially cleaves the 6-membered nucleus of the cephalosporin family and is a conserved gene in this species. Although normally repressed, this chromosomally encoded enzyme can be induced, particularly by cephalosporin compounds. This enzyme is not inhibited by the β-lactamase inhibitors currently in clinical use, tazobactam and clavulanate.[52] In addition, *P. aeruginosa* proficiently accepts plasmid-mediated β-lactamases of many different types. These constitutively expressed enzymes readily cleave most penicillins. β-Lactamase enzymes with inhibition of extended-spectrum β-lactam agents are increasingly common and have significant activity against a variety of β-lactam and carbapenem structures. Whereas the most common TEM-type plasmid-mediated β-lactamases are susceptible to clavulanate and tazobactam, many more recently identified extended-spectrum β-lactam agents are resistant. Large numbers of bacteria, frequently associated with pulmonary infections such as in patients with CF or in burn wounds, facilitate the selection of mutants resistant to entire classes of antimicrobial agents.

Aminoglycoside-Modifying Enzymes.

Plasmid-encoded or transposon-associated enzymes that can acetylate, phosphorylate, or adenylate specific sites on aminoglycosides can be associated with clinically significant aminoglycoside resistance. The prevalence of these genes varies widely among healthcare facilities. In general, amikacin is less susceptible to modification by these enzymes than is tobramycin or gentamicin, and rates of resistance to amikacin are lower compared with other aminoglycosides. Most aminoglycoside resistance, however, stems from efflux systems resulting in limited uptake of the drug, either alone or in combination with these enzymes.

Treatment

Uncomplicated Infections in a Normal Host.

The major clinical considerations in treating *P. aeruginosa* infections involve the health of the host, immunocompetence, the site of infection, the size of the bacterial inoculum, and the potential for antimicrobial resistance. Thus, in a healthy adolescent with *P. aeruginosa* osteomyelitis associated with a puncture wound, or folliculitis acquired in a hot tub, a single drug with high activity against the isolate would be sufficient, and the patient could be treated orally. Similarly, otitis externa (swimmer's ear) in a healthy child, commonly caused by *P. aeruginosa,* often can be treated topically, whereas otitis externa in a patient with diabetes requires systemic and usually parenteral therapy. Systemic illness caused by *P. aeruginosa* usually is treated with 2 drugs likely to have synergistic activity against the organism. The outcome of *P. aeruginosa* bloodstream infection is improved significantly if the empiric regimen includes at least 1 antibiotic with activity against the *P. aeruginosa* organism isolated.[53] Surveys across the US indicate the following rates of *P. aeruginosa* susceptibility: piperacillin-tazobactam, 86%; ceftazidime, 80%; ciprofloxacin, 67%; and levofloxacin, 67%.[50] Isolates from patients with CF generally are more resistant than isolates from people without CF.

Infection in Immunocompromised Hosts.

Despite the lack of well-controlled, blinded studies, most clinicians would treat a “serious” *P. aeruginosa* infection (e,g., a bloodstream infection in a neutropenic host or sepsis in a premature infant) with 2 antipseudomonal agents likely to have synergistic activity. Because oncology patients and particularly patients who undergo stem cell transplantation often have prolonged periods of neutropenia and frequent febrile episodes, empiric antimicrobial regimens in such patients always include agents with activity against *P. aeruginosa.* Fluoroquinolones or β-lactam agents are commonly combined with an aminoglycoside despite the potential for renal toxicity (especially in this patient population). The frequency of *P. aeruginosa* infection in these patients has decreased substantially, whereas the isolation of gram-positive pathogens and fungi has increased. Most patients with CF are managed with longterm inhaled tobramycin and several other antimicrobial agents (e.g., aztreonam and amikacin), which also can be delivered by inhaled aerosol. Exacerbations in CF often are treated in the outpatient setting, and this treatment can include parenteral therapy.

Renal Infection.

Because extremely high concentrations of most of the antipseudomonal antibiotics are achieved in the urine of patients with normal renal function, most urinary tract infections can be treated with a single agent. In patients with urinary tract obstruction, renal stones, or foreign bodies, antimicrobial therapy alone often fails or a relapse of the infection occurs because the organisms commonly form biofilms in this setting and are substantially less susceptible to antimicrobial agents.

Central Nervous System Infections.

P. aeruginosa shunt infections generally are treated with removal of the contaminated shunt. Agents that cross the blood-brain barrier and have high anti-*P. aeruginosa* activity, such as the carbapenems[54] or fluoroquinolones,[55] usually are effective. Because aminoglycosides do not accumulate in the central nervous system, these drugs are of questionable value.

Ocular Infections.

Usually associated with accidental or surgical trauma, ocular infection requires urgent and careful ophthalmologic examination to define the extent of the infection and guide the aggressiveness of antipseudomonal therapy. Superficial infections may respond to topical therapy; superfortified aminoglycoside and fluoroquinolone preparations for ocular administration are available. More invasive infections require intraocular treatment to achieve high local levels of drug. Ciprofloxacin and imipenem have some ocular penetration.[56] Infection of the vitreous or anterior chamber usually requires intravitreal or subtenon administration of the antibiotic, chosen according to results of specific susceptibility tests, and vitrectomy can be required.

Pulmonary Infections.

Because pneumonia usually involves a high inoculum, treatment conventionally includes 2 antipseudomonal agents that are likely to be synergistic. This regimen usually includes a β-lactam agent such as piperacillin-tazobactam, a fluoroquinolone, or an aminoglycoside. Antipseudomonal cephalosporins (ceftazidime or cefepime) also are effective, although these drugs can select for mutants with constitutive expression of the *ampC* chromosomal enzyme. Carbapenems (imipenem, meropenem, and ertapenem) often are chosen when the isolate is resistant to other agents, particularly when it expresses extended-spectrum β-lactamase. In patients with CF who require parenteral therapy, an aminoglycoside (often inhaled tobramycin) is used with a β-lactam agent or a fluoroquinolone. Fluoroquinolones (ciprofloxacin and levofloxacin) are used widely, both as single agents and in combination with other classes of drugs. Aminoglycosides can be given in large doses by the aerosol route for these pulmonary infections without systemic side effects (see Chapter 106).

Single daily dosing of aminoglycosides is used frequently and appears effective on the basis of studies performed in neonates, children with CF, and neutropenic hosts.[57] The carbapenems and monobactam-aztreonam regimens generally are reserved for patients with infections caused by organisms resistant to the other β-lactam agents or for patients with renal disease who are at risk of aminoglycoside-related nephrotoxicity. Patients with multidrug-resistant isolates have been treated successfully with colistin (polymyxin),[58] as well as with polymyxins that can be delivered by aerosol.[59]

Prevention

Nosocomial acquisition of the organism is prevented through careful hand hygiene practices, prevention of exposure to high-density organisms from water sources, and adherence to general principles of infection control. Avoidance of uncooked foods, including raw fruits and vegetables, in neutropenic patients can decrease ingestion of *P. aeruginosa*. Despite decades of interest in the development of an antipseudomonal vaccine for patients known to be at high risk, no vaccine is currently available. A flagellin-based vaccine has been developed for use in patients with CF, but it has been difficult to evaluate because of the efficacy of routine prophylactic antimicrobial therapy for *P. aeruginosa.*[60]

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Burkholderia cepacia Complex and Other *Burkholderia* Species

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The genus *Burkholderia* was proposed in 1992 for 7 species that previously were included in *Pseudomonas* homology group II.[1] All are animal or plant pathogens but are not significant pathogens in healthy humans. *Burkholderia* spp. are nutritionally diverse water and soil organisms that are catalase producing and nonglucose fermenting. Species are distinguished primarily on the basis of phenotype and biochemical characteristics (including carbohydrate fermentation patterns and production of indophenol oxidase).

Infections associated with *Burkholderia* spp. are shown in Table 156.1. *B. cepacia* complex has been associated with severe pulmonary infections in patients with cystic fibrosis (CF) and with fatal bloodstream infection (BSI) in patients with chronic granulomatous disease (CGD). *B. pseudomallei* is the cause of melioidosis, an endemic disease in Southeast Asia and northern Australia, and *B. mallei* is the organism that causes glanders, an equine infection seen in Asia and Africa that can be transmitted to humans. *B. gladioli* has been isolated from patients with CF, from immunocompromised people, and from high-risk neonates.[2] Other *Burkholderia* spp. can cause sporadic infections or nosocomial outbreaks in immunocompromised people but have not been associated with specific syndromes.

TABLE 156.1

Infections Caused by *Burkholderia* Species

Organism	Underlying Disease	Disease Caused	Site or Type of Infection
***Burkholderia cepacia* complex**	Cystic fibrosis Chronic granulomatous disease	Pneumonia and others	Lungs Lungs and pleura Lymph nodes Skin and soft tissue Bloodstream Septicemia
Burkholderia pseudomallei	Immunocompromised state Diabetes mellitus Renal insufficiency	Melioidosis	Septicemia Lungs Skin and soft tissue Bone
Burkholderia mallei		Glanders	Septicemia Skin Peritoneum Lymph nodes
Burkholderia gladioli	Cystic fibrosis Chronic granulomatous disease	Pneumonia and others	Lungs Lungs and pleura Lymph nodes Skin and soft tissue Bloodstream Septicemia

Burkholderia Cepacia Complex

B. cepacia is recognized as a complex of at least 20 named species, some of which can be distinguished phenotypically and others that require genotypic identification[3–7] (Box 156.1). *B. cepacia* complex primarily is a nosocomial pathogen and is relatively avirulent in the healthy host. In fact, multiple outbreaks of *B. cepacia* complex infection associated with contamination of intravenous solutions, intravascular devices, bronchoscopy equipment, and urinary catheters have resulted in minimal morbidity.[8–12] Because *B. cepacia* complex is able to grow in many commonly used disinfectants, such outbreaks are frequently associated with contaminated cleaning solutions.[13–16] Endemic *B. cepacia* complex infections in a large pediatric hospital were associated with contamination of ultrasound gel.[17] *B. cepacia* complex BSI also has been reported in children with hemoglobinopathies,[18] as well as cancer.[19] Patients with CF[20–22] and CGD[23,24] appear to be susceptible specifically to infection by *B. cepacia* complex; such infections can be fatal.

Box 156.1

Named Species Within *Burkholderia cepacia* Complex

Burkholderia ambifaria

Burkholderia anthina

Burkholderia arboris

Burkholderia cenocepacia

Burkholderia cepacia

Burkholderia contaminans

Burkholderia diffusa

Burkholderia dolosa

Burkholderia lata

Burkholderia latens

Burkholderia metallica

Burkholderia multivorans

Burkholderia pseudomultivorans

Burkholderia pyrrocinia

Burkholderia seminalis

Burkholderia stabilis

Burkholderia stagnalis sp. nov.

Burkholderia territorii sp. nov.

Burkholderia ubonensis

Virulence and Pathogenesis

Despite the virulence of *B. cepacia* complex in certain subpopulations of patients, specific mechanisms of pathogenesis have been difficult to elucidate, and they may depend on the underlying disease process.[25,26] Intracellular growth within professional phagocytes and epithelial cells and the proinflammatory activity of *B. cenocepacia* lipopolysaccharide likely contribute to pathogenesis.[27,28] Genomic, transcriptomic, and proteomic analyses have identified potential pathways involved in virulence including osmotic tolerance,[29] iron acquisition, drug efflux, adherence,[30,31] and motility.[32] These findings are supported by studies examining *B. cenocepacia* gene expression during growth in CF-affected sputum.[33]

Epidemiology

B. cepacia complex consists of ubiquitous organisms found in soil and water and is both a plant pathogen and an important organism for biologic control and bioremediation.[34] Nosocomial spread of *B. cepacia* complex most frequently occurs because of the contamination of disinfectant solutions used to clean reusable patient equipment, such as bronchoscopes and pressure transducers, or to disinfect skin.[13–16]

The molecular epidemiology of *B. cepacia* complex in CF has been well characterized; a predominant *B. cepacia* complex strain appears to occur at each CF center, and person-to-person transmission has been demonstrated.[3,35] A pathogenicity island in *B. cenocepacia* encodes the *B. cepacia* epidemic strain marker (BCESM), a transcriptional activator that has been associated with transmissibility as well as virulence.[36] The surface cable (Cbl) pilus, which binds CF mucin and is expressed by many *B. cenocepacia* strains, also has been associated with transmission in CF.[37]

Investigation of the epidemiology of *Burkholderia* in CGD found that, unlike in CF, patients are infected repeatedly with distinct strains. *B. cepacia* complex infections in CGD also involve multiple species including *B. ambifaria* and *B. metallica*.[23]

Clinical Manifestations

Nosocomial *B. cepacia* complex infections are most commonly BSIs,[38] although wound infections, urinary tract infections, and pneumonia can occur when those sites are contaminated.[17] BSI is also the most frequent infection in immunocompromised patients.[18,19] However, even in this population, patients rarely die of *B. cepacia* complex BSI.

Pulmonary infection in patients with CF usually does not have a discrete onset. Patients become culture positive for the organism late in the course of their disease, virtually always after infection with *P. aeruginosa* has been established. Patients with positive culture results for *B. cepacia* complex have 1 of the following 3 clinical patterns: (1) transient colonization and no change in the rate of pulmonary decompensation, (2) chronic colonization and a more rapid pulmonary deterioration, or (3) an unexpectedly rapid decline in clinical status that results in death.[20] Epidemiologic studies suggest that some species, including *B. cenocepacia* and *B. dolosa,* can cause more severe disease in patients with CF,[21,39] although other species are not considered nonpathogenic.

In CGD, pneumonia is the most common manifestation of *Burkholderia* infection[21,39]; lymphadenitis and bacteremic soft tissue infections have also occurred. In addition, macrophage activation syndrome with secondary hemophagocytic syndrome has been reported.[40,41] The onset of disease is insidious, with low-grade fever and malaise early in the course of disease and signs of systemic toxicity 3 to 4 weeks later. Pleural effusion has been seen in 50% of reported cases, and several patients with cavitary lesions have been described.[41,42] The organism is rarely isolated from sputum in these patients. Rather, cultures of blood, pleural fluid, and bronchoscopy and lung biopsy specimens have yielded *B. cepacia* complex.

Treatment

B. cepacia complex infections are difficult to treat because these organisms are highly resistant to antibiotics. Resistance is primarily related to limited entry of antimicrobial agents into the bacterial cell. Organisms are resistant uniformly to the aminoglycosides and polymyxin because of the intrinsic structure of the bacterial cell wall.[43] Limited outer membrane impermeability,[44] combined with induction of chromosomal β-lactamases,[45] results in frequent resistance to β-lactam antibiotics. Multiple antibiotic efflux mechanisms also have been reported in *B. cepacia* complex organisms and likely affect susceptibility to multiple unrelated agents.[46] The agents with the greatest in vitro activity against *B. cepacia* complex include minocycline, meropenem, ceftazidime, and doxycycline; however, in vitro synergy studies find very few synergistic 2-drug combinations.[47] Multiple-combination-drug bactericidal testing suggests that 2- and 3-drug combinations that include meropenem have the best in vitro activity against *B. cepacia* complex isolates,[48] although clinical correlation has not been demonstrated.[49] A placebo-controlled trial evaluated the efficacy of inhaled aztreonam for *Burkholderia* infection in CF and found that 24 weeks of continuous therapy did not improve lung function significantly.[50] Attempts at eradication of early *B. cepacia* complex infection in CF have been unsuccessful.[51]

Burkholderia Pseudomallei

B. pseudomallei is a major cause of melioidosis, an endemic infection in Southeast Asia and northern Australia. Melioidosis has also been reported sporadically from other tropical and subtropical areas including the Indian subcontinent, Central and South America, and central Africa, as well as in travelers returning from endemic areas.[52,53] Melioidosis occurs in rural populations, most commonly infecting people who have regular contact with soil and water. Infection can result from direct subcutaneous inoculation, inhalation, or ingestion through the skin. Underlying risk factors, which are rare in pediatric patients, include diabetes, heavy alcohol use, chronic pulmonary disease, renal insufficiency and thalassemia.[52] Clinical melioidosis is much less common in children than in adults.[54] However, the rate of seroconversion between the ages of 6 and 42 months has been estimated to be 24% of the population per year, and symptomatic infection can occur in children as young as 12 months of age.[55]

Melioidosis can manifest as a localized infection or as fulminant septicemia. In pediatric melioidosis, localized infection is the most common presentation (46.2%), followed by septic shock (38.4%) with or without lung involvement.[54] Localized infection in children most commonly consists of skin and soft tissue infection of the head and neck, including cervical and submandibular abscesses, suppurative parotitis, and necrotizing fasciitis.[56] Neurologic melioidosis has been reported in adults and children and is characterized by fever, headache, and ataxia.[57] Children with melioidosis and septic shock frequently have pneumonia. Multiorgan failure can occur, and in a small pediatric study, the mortality rate in patients with melioidosis and septic shock was 80%.[54] In adults, the mortality rate in septicemic melioidosis ranges from 17% to 40%, even with appropriate antimicrobial therapy.[58,59] A review of neonatal melioidosis in Thailand reported 22 cases presenting with BSI or meningitis and found a crude mortality rate of 73%.[60]

Definitive diagnosis of melioidosis is made by isolation of *B. pseudomallei* from the blood or infected site. Culture remains the gold standard for diagnosis in the absence of other commercially available tests. Serologic testing is more specific in young children than in older children and adults because of the low seroprevalence in young age groups.[55] The indirect hemagglutination antibody assay is the most commonly used serologic test, but immunochromatographic immunoglobulin M (IgM) and IgG assays have a sensitivity and specificity of 95% when both tests are used, and results can be available in <10 minutes.[61] Polymerase chain reaction detection of the *B. pseudomallei* type III secretion system in DNA extracted from clinical samples, including blood, sputum, urine, body fluids, and swabs of affected areas, has been reported to have a sensitivity of 65% and a specificity of 100%, with no polymerase chain reaction–positive results in specimens from patients without melioidosis.[62]

Treatment of melioidosis is difficult, and relapse is common.[63] *B. pseudomallei* is intrinsically resistant to the aminoglycosides and polymyxins. Agents demonstrating in vitro activity include ceftazidime, meropenem, imipenem, piperacillin-tazobactam, doxycycline, chloramphenicol, amoxicillin-clavulanate, and trimethoprim-sulfamethoxazole.[64] Treatment has 2 phases: (1) an intensive phase with 2 weeks of intravenous administration of ceftazidime, meropenem, or imipenem, followed by (2) 3 to 6 months of an oral eradication phase using trimethoprim-sulfamethoxazole to prevent relapse.[53]

Burkholderia Mallei

B. mallei is the cause of glanders, an equine infection seen primarily in the Far East and only rarely spread to humans. In the United States, a single laboratory-acquired case has been reported since 1945.[65] The organism is present in the nasal secretions and pustular drainage of infected horses and can be spread by skin or mucous membrane contact with these infected materials. The disease in humans is a severe systemic infection with ulcerative necrosis of the upper respiratory tract, cervical and mediastinal lymphadenopathy, pustular skin lesions, and pneumonia, with subsequent septicemia.[66] Without treatment, BSI caused by *B. mallei* usually is fatal within 1 to 2 weeks. Localized infection can be acute or chronic. *B. mallei* infections have been treated successfully with sulfadiazine in both humans and animals. Tetracyclines, aminoglycosides, ceftazidime, combinations of β-lactam agents and β-lactamase inhibitors, carbapenems, sulfonamides, and fluoroquinolones demonstrate activity in vitro.[64]

Burkholderia Gladioli

Because of its pigmentation and ability to grow on selective agars, *B. gladioli* frequently is misidentified as *B. cepacia* complex. *B. gladioli* can be distinguished biochemically because it is usually indophenol oxidase negative and does not produce an acid reaction on lactose- and maltose-containing media. *B. gladioli* has been isolated from the sputum of patients with CF with variable clinical impact,[67] but sometimes it is associated with severe lung disease. *B. gladioli* infections in immunocompromised children and adults also have been reported.[2,68]

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Stenotrophomonas maltophilia

Jane L. Burns

Stenotrophomonas maltophilia originally was classified as *Pseudomonas* but was transferred to the genus *Xanthomonas* and subsequently to its own genus, *Stenotrophomonas,* because of its pattern of biochemical reactions and its role as a human pathogen.[1–3] *S. maltophilia* exhibits a negative indophenol oxidase reaction, and many strains require methionine for growth. A unique feature of *S. maltophilia* that can aid in its identification is a positive reaction on deoxyribonuclease (DNase) test agar.

Virulence Factors

Many potential virulence factors have been identified in *S. maltophilia*, and the organism is able to grow in biofilms; however, clinical correlation of these factors with disease has not been reported.[3] Comparative genomic analysis using a pathogenic isolate of *S. maltophilia* and a plant-associated *S. rhizophila* found that the plant pathogen was missing pathways encoding adhesins, hemolysins, exopolysaccharide synthetic proteins, heat shock protein chaperones, and antibiotic resistance mechanisms,[4] findings suggesting a possible role for these factors in human virulence.

Epidemiology

S. maltophilia is found in water sources in home and hospital environments and is associated with healthcare-related infections in patients with comorbidities.[5] *S. maltophilia* can persist in commonly used disinfectant solutions, resulting in both true infections and pseudoinfections.[3,6,7] Bloodstream infection (BSI) and pneumonia are most commonly reported, but *S. maltophilia* also causes central BSI and peritoneal dialysis catheter-associated infections, endocarditis, skin and soft tissue infections, and other nosocomial infections.[5,8–11] In a study of pediatric BSI caused by glucose nonfermenting gram-negative bacilli other than *Pseudomonas aeruginosa, S. maltophilia* was the most common pathogen, occurring in 67% of patients.[12] Risk factors associated with pediatric *S. maltophilia* BSI are listed in Box 157.1.[10] Unlike with many other gram-negative pathogens, community-associated infections are not uncommon,[5] and polymicrobial infections are typical in children.[10] In children with human immunodeficiency virus infection or malignant disease, *S. maltophilia* has been reported as an important cause of central venous catheter-associated BSIs.[13] Risk factors associated with *S. maltophilia* BSI in oncology patients include severe mucositis, diarrhea, and use of metronidazole. Several reports of cross-infections in neonatal nurseries have been published.[14,15]

Box 157.1

Risk Factors Associated With *Stenotrophomonas Maltophilia* Bloodstream Infections in Children

Malignant disease

Acquisition of infection in the community

Trimethoprim-sulfamethoxazole exposure in previous 30 days

Receipt of corticosteroids or other immunosuppressive therapy

African American race

S. maltophilia is an evolving pathogen in cystic fibrosis (CF). The prevalence of isolation of *S. maltophilia* from respiratory tract specimens in patients with CF has increased steadily since 1991; more recent data found up to a 30% prevalence among teenage and young adult patients in the US.[16] In a large cohort of children and adults with CF, an increased risk of acquisition of *S. maltophilia* was associated with younger age and greater lung function decline.[17] *S. maltophilia* is also reported to be an independent risk factor for CF pulmonary exacerbations.[18] Despite uncertainty about the impact of *S. maltophilia* on longterm pulmonary function in CF,[19,20] a significant decline in forced expiratory volume in 1 second following pulmonary exacerbation has been demonstrated.[21]

Clinical Manifestations and Treatment

Infections caused by *S. maltophilia* are not distinct from nosocomial infections caused by other gram-negative organisms, with the possible exception of hemorrhagic manifestations including ecthyma gangrenosum and pulmonary hemorrhage, which may be associated with protease activity.[22–24]

S. maltophilia is highly antibiotic resistant, making treatment difficult. The organism is intrinsically resistant to the carbapenems and aminoglycosides, and resistance to most cephalosporins and penicillins is common, with many mechanisms contributing to resistance.[3,25,26] Although trimethoprim-sulfamethoxazole has long been considered first-line therapy, resistance is increasing; surveys have reported in vitro resistance as high as 10% among European isolates.[14,26,27] Despite emerging antibiotic resistance, moxifloxacin and the tetracyclines including tigecycline remain highly active in vitro.[13,25–29] Newer therapeutic approaches include combination therapy and, for pulmonary infections, inhaled agents.[3] With the exception of trimethoprim-sulfamethoxazole, isolates from patients with CF are more resistant than are isolates from people without CF.[25]

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Vibrio cholerae (Cholera)

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Cholera is an acute diarrheal disease with great potential for epidemic spread. For centuries cholera has caused considerable morbidity and mortality, particularly in the most impoverished areas of the world, where it remains a major public health challenge. Epidemic cholera is caused by 2 toxin-producing serogroups of the bacterium *Vibrio cholerae,* O1 or O139. When severe, cholera causes rapid loss of fluid and electrolytes, and unless volume resuscitation is prompt, death can quickly result.

Description of the Pathogen

V. cholerae is a gram-negative bacterium of the family Vibrionaceae. Somatic (O) antigens differentiate the serogroups. Epidemic cholera is caused by toxin-producing strains of serogroups O1 or O139. The horizontal acquisition of genes and expression of the transcriptional coregulated pilus (located on the *Vibrio* pathogenicity island 1) and cholera toxin carried on a bacteriophage are the primary virulence factors. Nontoxigenic and non-O1, non-O139 *Vibrio cholerae* strains can cause diarrhea and septicemia, but only toxigenic O1 and O139 have caused epidemics (see Chapter 159). *V. cholerae* O1 is further divided into 2 serotypes (Inaba and Ogawa) and 2 biotypes, classical and El Tor. During epidemics, a shift from 1 serotype to another can occur.[1,2] *V. cholerae* O139 closely resembles the El Tor biotype but, unlike *V. cholerae* O1, possesses both a capsule and a distinct lipopolysaccharide and does not agglutinate with O1 antisera.[3,4]

Microbiology

Measuring 1.4 to 2.6 μm in length, *V. cholerae i*s a curved, gram-negative bacillus with a single polar flagellum. It can be grown on a selective medium such as thiosulfate citrate bile salts sucrose (TCBS) agar that facilitates isolation. After 24 hours of incubation at 37°C, *V. cholerae* colonies grown on TCBS agar are large (2–4 mm in diameter) and yellow with opaque centers and translucent edges. The organism ferments glucose and sucrose and is oxidase positive. Presumptive identification is based on slide agglutination with O1 or O139 antiserum. Two biotypes of *V. cholerae* serogroup O1, classical and El Tor, have been defined on a genetic level. The classical biotype was predominant until the 1960s, when the El Tor biotype spread around the world, started the seventh pandemic, and gradually displaced the classical biotype. Serogroup O1 isolates react with Inaba or Ogawa antiserum; both these serotypes are found among classical and El Tor biotype strains. Confirmation of O1 and O139 isolates involves demonstration of either cholera toxin production or the presence of cholera toxin gene sequences.[5]

Virulence and Pathogenesis

Infection with toxigenic strains of *V. cholerae* O1 and O139 causes a spectrum of illness. A study in Bangladesh found that 59% of people infected with the classical biotype of *V. cholerae* O1 were asymptomatic compared with 75% of those infected with the El Tor biotype. Among people with symptomatic infection, 11% of those infected with the classical biotype compared with only 2% to 5% of those with El Tor infections were hospitalized for severe cholera. The remainder had mild or moderate illness.[6,7] Mortality rates in severe cases can reach 50% in remote regions or among populations for whom treatment is not readily available. However, with prompt and appropriate volume resuscitation, the mortality rate should be

<1%. More recently, "altered" or "atypical" strains that possess an integrated El Tor biotype phage but express the classical cholera toxin allele were described.[8,9] The classical cholera toxin genes increase toxin secretion and can lead to a more severe clinical presentation.[10]

V. cholerae O1 and O139 remain in the gastrointestinal tract and typically do not invade the bloodstream; however, some reports have been published of cholera bacteremia resulting from *V. cholerae* O139.[11,12] The voluminous secretory diarrhea of cholera results from the concerted actions of two major virulence factors: cholera toxin and the toxin coregulated pilus (TCP). Cholera toxin, a protein, is composed of an A subunit and five B subunits arranged in circular form. Once the B subunit of CT phage has bound to intestinal cells, the A subunit activates adenylate cyclase, resulting in increased intracellular concentrations of cyclic adenosine monophosphate (cAMP), which fuels secretion of sodium and chloride into the gut lumen; water follows passively. Isotonic fluid is secreted at a rate that exceeds the absorptive capacity of the colon. TCP serves as the receptor for the cholera toxin phage, mediates colonization in the intestinal tract, and mediates bacterial interactions. Three additional enterotoxins, the zona occludens toxin (ZOT),[13] accessory cholera enterotoxin (ACE),[14] and WO7 toxin15 produced by *V. cholerae* O1, have been described. Cholera toxin, a protein, is composed of an A subunit and 5 B subunits arranged in a circular form. Once the B subunit of cholera toxin phage has bound to intestinal cells, the A subunit activates adenylate cyclase, thus resulting in increased intracellular concentrations of cyclic adenosine monophosphate, which fuels secretion of sodium and chloride into the gut lumen; water follows passively. Isotonic fluid is secreted at a rate that exceeds the absorptive capacity of the colon.[16,17]

Immunity

Immunity to cholera is incompletely understood. Nonspecific defense mechanisms include gastric acidity and intestinal peristalsis. People with blood group O are particularly likely to have severe cholera, although the reason is unknown.[18,19] A study in Bangladesh found that although people with blood group O were more likely to develop severe disease once they were infected, they were less likely to become infected with *V. cholerae* O1 in the first place, a finding consistent with the hypothesis of adaptive immunity.[20] The incubation period varies with the ingested dose and gastric pH but averages 1 to 3 days, with a range of a few hours to 5 days.

Antimicrobial therapy decreases the volume and duration of diarrhea and shortens the time when *V. cholerae* is detectable in stool.[21,22] Without antimicrobial therapy, *V. cholerae* is detectable in stools for approximately 1 to 2 weeks. Prolonged carriage is rare but does occur.[23] Infection with *V. cholerae* O1 induces development of serum antibacterial (vibriocidal) and antitoxin antibodies. As with other noninvasive enteric infections, specific immunity is provided primarily by secretory immunoglobulin (immunoglobulin A), which, in the case of cholera, lasts only a few months. Cholera infection can induce long-lasting immunologic memory, but reinfection with the same or a different serogroup, biotype, or serotype is possible.[24] However, repeated infections with the same or different serogroups, biotypes, or serotypes can confer longterm immunity.[25] A study comparing the immune response of patients infected with *V. cholerae* O1 and O139 revealed that both serogroups elicit vibriocidal and cholera toxin–specific responses. However, previous infection with serogroup O1 does not offer protection against infection with serogroup O139.[26,27] Where cholera is prevalent, children who are not breastfed are infected more often than are breastfed children.[28] A mother who breastfeeds not only protects her infant from unsafe alternative food sources,[28] but also, if previously exposed to *V. cholerae,* can transfer specific immunoglobulin A antibodies in her milk.[29]

Epidemiology

Cholera can be endemic, epidemic, or pandemic. For centuries, cholera has remained endemic in countries bordering the Bay of Bengal and has spread in periodic pandemic waves. Worldwide, epidemics tend to occur during warm seasons.

The modern era of cholera comprises 7 pandemics; the first 6 occurred between 1817 and 1923. Most of these pandemics originated in Asia, usually the Indian subcontinent, and subsequently extended to Europe, the Americas, and sometimes Africa.[30] During the third pandemic, the English physician John Snow traced cholera in London to the Broad Street pump and documented waterborne disease transmission before the etiology of the disease was known. During the fifth pandemic, Robert Koch isolated *V. cholerae* from patients with diarrhea, thereby establishing the etiologic agent. Strains of the fifth and sixth pandemics were of the classical biotype.

The ongoing seventh pandemic, already the longest and most widespread, began in 1961, when *V. cholerae* O1, biotype El Tor, spread from a focus in Sulawesi (formerly Celebes), Indonesia. In 1971, it reached both East and West Africa, where it remains endemic. After more than 100 years without epidemic cholera, the pandemic reached the Americas, in January 1991, when *V. cholerae* O1 appeared in Peru and spread swiftly through much of South and Central America.[31,32] Compared with epidemics of the 19th century, attack rates were higher, but mortality rates were lower.[33,34] From 1991 through 1996, more than 1.3 million cases of cholera, and nearly 12,000 associated deaths, were reported from 20 countries in Latin America, sparing the Caribbean.[35] In stark contrast to the situation in Africa, cholera was nearly eliminated from Latin America within a decade because of investments in water and sanitation infrastructure that brought additional benefits, such as decreased infant mortality.[36,37] Cholera incidence during the Latin American epidemic correlated with infant mortality, a finding suggesting that they share a common denominator of unsafe drinking water and poor sanitation.[38] Cholera remains endemic in sub-Saharan Africa, the region with the lowest population coverage for improved water sources and sanitation, with recurrent outbreaks in several countries.[39–43]

In 2010, cholera was identified in Haiti approximately 10 months after the devastating earthquake. Haiti had no documented history of epidemic cholera.[44,45] Within 1 month of the first diagnosed cases in October 2010, cholera had reached all 10 departments in Haiti, and cases had been confirmed in the Dominican Republic and the United States.[46,47] Since the introduction of cholera to Haiti, smaller outbreaks have been reported in other Latin American countries whose isolates matched the Haiti strain. Cholera occurred in Cuba in 2012 and Mexico in 2013; both outbreaks were linked by molecular epidemiology to the Haitian epidemic. As of January 1, 2016, Haiti had reported a cumulative total of nearly 806,000 cases, nearly 477,000 hospitalizations, and nearly 9,600 deaths resulting from cholera (case-fatality rate, 1.2%). From 2011 through 2014, case counts dropped dramatically each year, with small increases in 2015 and 2016; the annual fatality rate has remained close to 1%. The decreased case counts have resulted from an international collaboration with the Haitian government to improve access to safe water and sanitation, increase clinicians' awareness and knowledge of cholera treatment, and educate the public about cholera prevention.

In the US, 111 cases of cholera were reported to the Centers for Disease Control and Prevention (CDC) from 2001 through 2011. Cholera was associated with international travel in 90 (81%) patients and was domestically acquired in 20 (18%). From October 2010 to December 2011, 40 (83%) of the 48 travel-associated cases were associated with travel to Hispaniola. Of 20 patients who acquired cholera domestically, 17 (85%) reported seafood consumption; 10 (59%) ate seafood from the US Gulf Coast.[48]

In 2015, the latest year for which data were available, 42 countries notified the World Health Organization (WHO) of a total of 172,454 cholera cases and 1034 deaths (case-fatality rate, 0.8%).[43] Of the 26 countries reporting deaths from cholera, 17 (65%) were in Africa and 8 (30%) were in the Americas. The ongoing outbreak in Hispaniola contributed 36,591 (21%) of all reported cholera cases in 2015, with another 71,176 (41%) reported from Africa. Underreporting because of concerns about the political and economic ramifications of reporting cholera cases and deaths remains a problem. However, although differences in reporting account for some of the disparity in reported cases, issues regarding water, sanitation and hygiene infrastructure, and access to basic medical care clearly play a role.[49]

In 1992, a new strain of *V. cholerae* was identified in Chennai, India. The strain did not agglutinate with O1 antiserum or with antisera to any of the other 137 previously known serogroups, and it spread rapidly to 11 countries in South Asia.[11,50] Designated *V. cholerae* O139 Bengal, it was the first non-O1 *Vibrio* to cause epidemic disease. Because immunity to *V. cholerae* O1 was not protective against this new serogroup, the proportion of adults affected was unusually high. Given the potential immunologic advantage of this relatively new serogroup, concern was expressed that the advent of *V. cholerae* serogroup O139 marked the beginning of the eighth pandemic of cholera.[38] Thus far, however, O139 has remained confined to South and Southeast Asia and only transiently displaced O1 as the dominant serogroup.[51]

Brackish aquatic environments are the natural reservoirs of both O1 and non-O1 strains of *V. cholerae.* When conditions are favorable, *V. cholerae* multiplies and can survive for years, independent of human fecal contamination, in brackish water and associated invertebrates (e.g., copepods, crabs, shrimp, and oysters). Endemic foci of *V. cholerae* O1 persist in several areas of the developed world, including the US Gulf Coast, where a unique O1 strain was first identified in 1973.[52] In the developed world, rare sporadic human cases can follow ingestion of water or undercooked shellfish.[53] However, these cases occur more commonly in travelers returning from areas where disease is epidemic.[54]

Introduction of cholera into a developing area, where the drinking water supply is not protected from human fecal contamination, can cause explosive epidemics. Infection typically follows drinking of contaminated water or consumption of food washed with, or seafood harvested from, contaminated water or food prepared by someone who is excreting *V. cholerae*.[55] Waterborne transmission of *V. cholerae* was identified in multiple investigations during the epidemics in Latin America, from contamination of municipal source water and of stored water in the home.[56] Foodborne transmission can occur through foods and beverages held at ambient temperatures for long periods of time or prepared with unsafe water or ice. Drinking water from uncovered household storage containers into which hands or objects can be introduced increases the risk of illness.[38,57] Direct person-to-person spread of cholera can occur, especially in healthcare settings[58]; however, this is not thought to be a major mode of transmission.[59]

Clinical Manifestations

The hallmark of cholera is watery diarrhea leading to varying severity of volume depletion and dehydration. Mild or moderate disease can be difficult to distinguish from disease caused by several other enteric pathogens, including enterotoxigenic *Escherichia coli* (ETEC) or rotavirus; however, severe cholera is distinctive. No other diarrheal illness produces volume depletion as rapidly as cholera. Cholera usually begins with watery, colorless diarrhea flecked with mucus (“rice-water stools”) without abdominal cramps or fever. Stools can have a mild, fishy odor. Vomiting is common, can be severe, and can precede or follow diarrhea. Patients with cholera typically do not have a fever.

In untreated severe cholera, diarrhea and vomiting usually result in volume depletion with shock in 4 to 12 hours and death in 18 hours to several days. When the disease is most severe, patients lose ≥1 L of fluid per hour and die within hours. The early signs of dehydration (thirst, tachycardia, dry mucous membranes, loss of skin turgor, and sunken eyes) are followed quickly by hypotension and anuria. Renal failure secondary to hypovolemia is reversible with volume resuscitation. Altered mental status is common but usually is mild and can consist of somnolence, restlessness, or lethargy. Very rarely, patients have abdominal distention and ileus without diarrhea; this has been called “cholera sicca,” or dry cholera.[60]

Other clinical manifestations result from electrolyte imbalances. Profuse watery diarrhea rich in potassium and bicarbonate (Table 158.1) leads to hypokalemia with arm and leg cramps and metabolic acidosis, which can increase the frequency of vomiting. Hyperglycemia, resulting from high concentrations of epinephrine, glucagon, and cortisol, is more common overall than hypoglycemia, which can occur when glycogen stores are depleted and gluconeogenesis is impaired.[61] However, children with cholera are especially prone to hypoglycemia, which can lead to convulsions and poor outcomes.[62] Fever and obtundation also are more common in children.[63] Sequelae related to fluid and electrolyte derangements, followed by hypoglycemia, are the most important life-threatening consequences of cholera. During pregnancy, cholera can be particularly severe and subsequently increases the risk for fetal and neonatal death.[64]

TABLE 158.1

Electrolyte Composition of Diarrheal Stools From People With Cholera and Composition of Rehydration Solutions

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	Sodium (mEq/L)	Potassium (mEq/L)	Chloride (mEq/L)	Base[a] (mEq/L)	Carbohydrate
CHOLERA STOOLS					
Adults	135	15	100	45	—
Children	105	25	90	30	—
ORAL SOLUTIONS					
WHO-ORS	90	20	80	30	111 mmol/L
WHO-ORS (reduced osmolarity)	75	20	65	10	75 mmol/L
Ceralyte 70 (rice based)	70	20	60	30	40 g/L
Ceralyte 90 (rice based)	90	20	80	30	40 g/L
RINGER LACTATE	130	4	109	28	—

[a] Consists of bicarbonate or citrate.

WHO-ORS, World Health Organization oral rehydration solution.

Modified from Swerdlow DL, Ries A. Cholera in the Americas: guidelines for the clinician. JAMA 1992;267:1495–1499.

Laboratory Findings and Diagnosis

Cholera is a clinical diagnosis. Once cholera is suspected, treatment must be begun before laboratory confirmation is obtained. Cholera should be considered in any patient with profuse watery diarrhea and vomiting. Clinical suspicion should increase if these symptoms are severe in any patient who has returned from an area with epidemic cholera or who has eaten undercooked shellfish in the 5 days before the onset of illness.

Cholera is diagnosed definitively by isolation of toxigenic *V. cholerae* O1 or O139 from a stool specimen or rectal swab, which should be collected before antibiotics are given.[65] Rectal swabs should be placed in a transport medium such as Cary-Blair medium warmed to room temperature; buffered glycerol saline is not acceptable. Because *V. cholerae* rarely is isolated routinely by laboratories in the US, clinicians should alert the laboratory if cholera is suspected so that specimens can be inoculated on TCBS agar or other appropriate selective media. Isolates of *V. cholerae* should be sent to the state public health laboratory for testing with O1 and O139 antisera and then to the CDC for confirmation of serogroup and serotype and detection of the cholera toxin gene.

Antimicrobial susceptibility can be determined by disk diffusion or broth microdilution testing. Interpretive criteria have been established for ampicillin, chloramphenicol, sulfonamides, tetracycline, and trimethoprim-sulfamethoxazole.[66] Susceptibility results for tetracycline by disk diffusion are used as markers for predicting susceptibility to doxycycline. No available breakpoint values exist for disk diffusion testing for ciprofloxacin or azithromycin. Specific Clinical and Laboratory Standards Institute (CLSI) criteria should be used for interpretation of results.[66] If paired acute and convalescent phase serum samples are available, rises in vibriocidal antibody titers can confirm infection retrospectively in clinically compatible cases; however, this test is not used routinely for diagnosis of cholera. Rapid immunoassays for presumptive detection of *V. cholerae* O1 or O139 from stool for field settings and during outbreaks have been marketed,[67–70] but they do not replace culture for definitive diagnosis and do not provide an isolate for antimicrobial susceptibility testing.[71]

Nonspecific abnormalities in laboratory test results include hypoglycemia or hyperglycemia, hypercalcemia, hypermagnesemia, and hyperphosphatemia. Potassium deficit may not become apparent until the patient's metabolic acidosis is corrected. Serum sodium and chloride concentrations usually are normal or slightly decreased. The white blood cell count can be elevated. Volume depletion often results in increases in hematocrit and total serum protein concentration and can cause elevated blood urea nitrogen and serum creatinine values.

Treatment

Volume Replacement

Steps in management of children with suspected cholera are listed in Box 158.1. Rapid volume resuscitation is the cornerstone of therapy. Treatment options depend on available resources and training of healthcare providers. A simple scheme can be used to determine the severity of volume depletion and guide fluid resuscitation after acute diarrhea of any cause (Table 158.2).

Box 158.1

Management of People With Suspected Cholera

- Assess for volume depletion.

- Rehydrate with oral or intravenous fluids, or both, and monitor frequently.
- Maintain hydration: replace continuing fluid losses until diarrhea and vomiting cease.
- Consider zinc supplementation in addition to rehydration.
- Give oral antibiotics to patients with moderate but progressive volume depletion and those with severe volume depletion.
- Resume feeding with a normal diet; continue breastfeeding for infants and young children.

Modified from World Health Organization. Guidelines for Cholera Control. Geneva, World Health Organization, 1993.

TABLE 158.2

Signs and Symptoms of Dehydration in Children With Watery Diarrhea

	Degree of Dehydration		
	Mild (3%–5%)	**Moderate (6%–9%)**	**Severe (≥10%)**
OBSERVATIONS			
Mental status	Alert	Restless, irritable	Lethargic or unconscious
Thirst	Slightly increased	Moderately increased	Very thirsty or too lethargic to drink
Mucous membranes	Slightly dry	Dry	Very dry
Tears	Present	Absent	Absent
Eyes	Normal	Sunken	Very sunken and dry
EXAMINATION			
Pulse	Normal	Faster than normal	Very fast, weak, or nonpalpable
Pinched skin	Retracts rapidly	Retracts slowly	Retracts very slowly
Extremities	Warm; normal capillary refill	Delayed capillary refill	Cool, mottled
Fontanelle	Normal	Sunken	Very sunken
THERAPY	Oral rehydration	Oral or intravenous rehydration	Intravenous rehydration

Modified from World Health Organization. Guidelines for Cholera Control. Geneva, World Health Organization, 1993; and Centers for Disease Control and Prevention. The management of acute diarrhea in children: oral rehydration, maintenance, and nutritional therapy. MMWR Morb Mortal Wkly Rep 1992;41:1–20.

Theoretically, children without signs of volume depletion can be treated at home with oral rehydration solution (ORS), by using small volumes of fluid initially and then gradually increasing the amount as tolerated.[72] However, this situation is very rare because most patients with clinically recognized cases have rapid volume depletion. For patients with mild volume depletion (loss of 3%–5% of body weight), 50 mL/kg of ORS should be given in the first 2 to 4 hours of therapy. For patients with moderate volume depletion (loss of 6%–9% of body weight), 100 mL/kg of ORS should be given in the first 2 to 4 hours. In both cases, volume status is reassessed at 4 hours. If volume depletion is corrected, treatment enters the maintenance phase. If losses continue, fluid deficit is estimated again, and fluid administration is resumed.[72] ORS can be administered through the nasogastric route if the patient has mild to moderate volume depletion and cannot drink.

If volume depletion is severe (loss of ≥10% of body weight) or if patients are unable to tolerate oral rehydration because of mental status changes or intractable vomiting, intravenous therapy should be started immediately. Rapid volume resuscitation can save even patients whose pulse is not initially detectable. Ringer's lactate is the appropriate fluid in the US (see Table 158.1); normal saline is far less effective because it lacks potassium and bicarbonate. Dextrose-water solutions should not be used because they do not effectively replete volume. Ringer's lactate is infused rapidly until pulse, perfusion, and mental status return to normal. Volume status is reassessed frequently. ORS (≈5 mL/kg/hr) should be added as soon as the patient is able to drink and should replace intravenous fluids as early as is practical.

During both initial volume resuscitation and maintenance, ongoing fluid losses from stool and vomit should be replaced, initially by 10 mL/kg of ORS for each watery stool passed and 2 mL/kg for each episode of emesis. Ongoing fluid losses during maintenance therapy can be replaced with either low-sodium ORS or ORS containing 75 to 90 mEq/L of sodium accompanied by another source of low-sodium fluid (e.g., human milk, formula, or water) (see Table 158.1).[72] Urine output usually resumes within 6 to 8 hours, and ≥1 mL/kg/hr every 3 to 4 hours signifies adequate fluid administration. Additional ORS always can be administered coincident with thirst. Infants and young children should continue breastfeeding, and older children should resume a normal diet as soon as they are able.

Oral rehydration therapy is as effective as intravenous rehydration[73,74]; patients with mild to moderate volume depletion can be treated with oral solutions alone, administered in small sips to patients who are vomiting.[72] In the US, WHO ORS is available in salt packets by the case or carton (Jianas Brothers, Kansas City, Mo; 816-421-2880; http://rehydrate.org/resources/jianas.htm). When mixed with 1 L of clean water per packet, the resulting solution can be used to restore fluid and electrolyte balance in patients with cholera (see Table 158.1). A systematic review of ORS among a pediatric population found that a solution with 75 mEq/L of sodium compared with the standard solution of 90 mEq/L of sodium was associated with reduction in stool output, vomiting, and intravenous fluid use.[75] Based in part on these findings, the WHO has advocated for a solution with reduced osmolarity since 2002. The current recommended solution contains 75 mEq/L of sodium with an osmolarity of 245 mOsm/L. Ceralyte (Cera Products, Columbia, Md; 888-237-2598; http://www.ceraproductsinc.com/collections/ceralyte), and a rice-based product also is available. This glucose polymer-based ORS has been shown to result in a greater reduction of stool output than glucose-based ORS.[76] Oral solutions with sodium concentrations <75 mEq/L should not be used in the treatment of cholera. Beverages high in simple sugars such as fruit juices and energy drinks should also be avoided and can actually worsen diarrhea because of their high osmotic load.[72] For patients with altered mental status who are unable to drink sufficient quantities of ORS, use of an orogastric or nasogastric tube should be considered.[77] If ORS is not available or the patient has severe dehydration, volume resuscitation should be started immediately with intravenous fluids.

Antimicrobial Agents

Although the cornerstone of treatment for cholera is replacement of fluid volume and electrolytes, treatment with antimicrobial agents decreases the duration of illness, the volume of stool output, and the period of excretion of *V. cholerae.* In conjunction with hydration, treatment with antibiotics is recommended for moderately and severely dehydrated patients, particularly for those patients who continue to pass a large volume of stool during rehydration treatment, and for all hospitalized patients.

Single-dose doxycycline orally is recommended as the first-line treatment in adults[78]; single-dose azithromycin or ciprofloxacin can be used as effective alternatives (Table 158.3).[79] Azithromycin, as a single dose, is recommended as the first-line treatment in children and pregnant women.[80] Emerging resistance to azithromycin has been noted in Vietnam.[81] Antibiotic susceptibility patterns should be determined, particularly in outbreak settings, because antibiotic-resistant strains of *V. cholerae* are common, and antibiotic choices should be informed by susceptibility patterns in the area from which the infection was most likely obtained. Antibiotics should not be used routinely for prophylaxis, but they can be considered for outbreaks occurring in institutionalized populations.[82,83] Antidiarrheal and antispasmodic agents should not be used. Zinc supplementation, in addition to rehydration, can reduce duration and severity of cholera diarrhea, particularly in children.[84]

TABLE 158.3

Antibiotics for Treatment of Cholera[a]

Antibiotic	Dose	
	Children (mg/kg)	**Adults (mg)**
DRUG OF CHOICE		
Doxycycline (a single dose)	6	300
ALTERNATIVE FOR CHILDREN <8 YR OF AGE		
Azithromycin (single dose)	20	1000
ALTERNATIVE FOR PREGNANT WOMEN		
Azithromycin (single dose)	N/A	1000

[a] See text.

Prevention

Public Health Measures

In the developed world, water and sewage treatment makes the epidemic spread of cholera extremely unlikely, although some underserved populations may be at risk.[85] In the developing world, however, contaminated drinking water and food set the stage for epidemic cholera. Chemoprophylaxis is not recommended in the US, but in the developing world, it should be considered during outbreaks that occur in institutionalized settings, such as prisons, where antimicrobials can be administered quickly and easily to potentially exposed persons. Chemoprophylaxis of household contacts in the developing world has also been suggested.[86] However, this measure can promote development of antibiotic resistance; absent convincing evidence of benefit, it is not recommended.[87–89] Quarantine of patients and mass chemoprophylaxis have not halted epidemic cholera, and they have had harmful social, economic, and microbiologic consequences; they are not recommended as epidemic control measures. Education regarding protecting drinking water and washing hands with soap and water after defecation and before preparation or eating of food can help control a cholera epidemic, particularly if education is conducted in conjunction with distribution of household water treatment supplies and soap to populations affected and those at risk. A strategy that empowers families to disinfect drinking water with chlorine and to store this water safely in closed, narrow-mouth vessels to prevent recontamination was developed in the course of the cholera epidemic in Latin America (www.cdc.gov/safewater/).[90] This approach can reduce the introduction and spread of cholera in households and has been used widely in Africa.[91,92] Breastfeeding protects infants, whether or not the mother has immunity to *V. cholerae*.[28,29]

Vaccination

Historically, parenteral cholera vaccines have not been favored because of low efficacy and a high rate of side effects. Considerable progress has been made in development of both live and killed oral cholera vaccines since the 1980s.

Currently 2 types of oral vaccines are available in some countries, although none is licensed in the US. These vaccines include the following: (1) Dukoral (manufactured by Crucell/SBL Vaccines, Sweden) contains a mixture of heat- and formalin-killed classical and El Tor *V. cholerae* strains and a recombinant B subunit of cholera toxin (WC/rBS), which can be given to adults and children ≥2 years of age; and (2) Shanchol (manufactured by Shantha

Biotechnics, Hyderabad, India) and mORCVAX (manufactured by VABIOTECH, Hanoi, Vietnam), a modified, killed, whole-cell vaccine that contains different mixtures of strains without a cholera toxin subunit and can be administered to adults and children ≥1 year old.[93,94] Both Dukoral and Shanchol are WHO prequalified. A previously marketed oral live, attenuated single-dose vaccine, Orochol (CVD 103-HgR), was discontinued, but it may be available again in the future.[94]

When Dukoral was tested extensively in the 1980s in a field trial in Bangladesh where both El Tor and classical strains were present, it yielded a protective efficacy of 62% in the first year of the trial.[95] Efficacy waned after 2 years and was substantially lower among people of blood group O,[96] among children, and against infection with El Tor biotype as opposed to classical biotype.[97] In this cluster randomized trial in an endemic area, although vaccine coverage rates varied, herd protection was observed.[98] In a large, cluster-randomized, double-blind, placebo-controlled trial conducted in India from 2006 to 2008, Shanchol was safe and effective against clinically significant cholera with a vaccine efficacy of 65% for up to 5 years.[99–101] Shanchol is less expensive and easier to administer than Dukoral.

Given concerns about the effectiveness of cholera vaccines in areas with a high prevalence of human immunodeficiency virus (HIV) infection, a case-control study using Dukoral was conducted in a city in Mozambique with an HIV seroprevalence of >20%. Although the vaccine was found to be effective, providing 78% protection, data on HIV status were not collected from study participants.[102] Neither cholera vaccine has been approved for use in pregnant women; however, a retrospective report of women who received at least 1 dose of Dukoral during pregnancy during a mass vaccination campaign in Zanzibar found no statistically significant evidence of a harmful effect of gestational exposure. This study had insufficient power to detect infrequent events.[103]

Cholera vaccines are not recommended for the general population. Given the extremely low risk of cholera for typical US and European travelers in areas with epidemic or endemic disease, counseling about risk avoidance is more cost-effective than vaccination. However, a new vaccine, Vaxchora, was recently approved by the U.S. Food and Drug Administration and the

Advisory Committee on Immunization Practices for nonpregnant, nonbreastfeeding adults 18 to 64 years old who are traveling to an area of active cholera transmission.[104]

Vaccination should be considered in areas where cholera is endemic.[94] However, it should always be done in conjunction with the implementation of safe water, sanitation, and hygiene promotion programs. In resource-poor areas, vaccination should be targeted at children ≥2 years old. After taking into account herd immunity, cholera vaccination can be a cost-effective measure in some endemic middle- to low-resource settings.[94] The WHO endorses cholera vaccination for outbreak settings where appropriate and recommends consideration of preemptive vaccination to help prevent potential outbreaks, for example, in complex humanitarian emergencies, such as in refugee settlements.[94] However, even in stable refugee populations at risk for epidemic cholera, vaccination generally is a less cost-effective intervention than improvements in water sanitation and treatment.

Epidemiologic Investigations

Because of the potential for epidemic spread in the developing world, even a single case of cholera has important public health implications. Because many *V. cholerae* infections are mild or asymptomatic, a single recognized case often portends a larger outbreak. If a case is suspected, local public health authorities should be notified, and a search should be begun immediately to identify the source. The CDC can assist state and local health departments and other countries with these epidemiologic investigations.

Advice for Travelers

Travelers to areas where epidemic cholera occurs can prevent infection by following the precautions described for prevention of traveler's diarrhea[105,106] (Box 158.2). Additionally, a new vaccine, Vaxchora, is approved for use in nonpregnant, nonbreastfeeding adults 18 to 64 years old who are traveling to an area of active cholera transmission.[104] When simple precautions are followed, the risk of cholera is low. Nonetheless, travelers to areas with cholera who experience profuse watery diarrhea, especially if it is accompanied by vomiting, should seek medical attention immediately because prompt volume resuscitation can be lifesaving.

Box 158.2

Advice for Travelers to Areas Affected by Epidemic Cholera

Usually Safe

Cooked foods that are still hot

Fruits peeled by the traveler

Carbonated bottled water without ice

Other carbonated beverages

Beverages made with boiled water

Unsafe/Avoid

Cooked food stored at ambient temperature

Salads and raw vegetables

Raw or undercooked fish and shellfish

Food and beverages from street vendors

Unboiled or untreated water or ice

Modified from Swerdlow DL, Ries A. Cholera in the Americas: guidelines for the clinician. JAMA 1992;267:1495–1499.

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Other *Vibrio* Species

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In addition to organisms that cause cholera (see Chapter 158), several other *Vibrio* species cause vibriosis. These can be divided into invasive species primarily associated with bloodstream and wound infections (e.g., *V. vulnificus*) and species that typically cause gastroenteritis (e.g., *V. parahaemolyticus*). With the exception of *V. parahaemolyticus* and *V. vulnificus* biogroup 3, these organisms rarely cause outbreaks.

Description of the Pathogens

Vibrios are bacteria of the family Vibrionaceae. They are fermentative, facultatively anaerobic, gram-negative bacilli with a single polar flagellum. Except for *V. cholerae* and *V. mimicus,* all *Vibrio* species are halophilic (salt requiring).

Possible virulence factors have been described for the nontoxigenic *Vibrio* species, including cell-associated adhesins, extracellular toxins, and proteases[1]; the actual role of these factors in disease is unknown. Some *V. cholerae* non-O1, non-O139 strains[2] and *V. mimicus* strains produce cholera toxin. Little is known about immunity against nontoxigenic vibrios.

Vibrios are free-living inhabitants of marine coastal waters and, occasionally, brackish inland lakes and streams; their presence does not indicate fecal contamination. Water surface temperatures and salinity affect concentrations of most *Vibrio* species. Most *Vibrio* infections occur during summer and fall when surface waters are relatively warm. *V. vulnificus* uses iron for growth; people with elevated iron levels are at higher risk for infection.

Epidemiology

An estimated 80,000 cases of vibriosis, including 500 hospitalizations and 100 deaths, occur in the United States yearly, with most infections in men.[3,4] The incidence of vibriosis has been increasing in the US.[5] *V. parahaemolyticus* is the most frequently identified nontoxigenic *Vibrio* species in the US, and it accounts for approximately one half of human infections; *V. alginolyticus* and *V. vulnificus* are the next most commonly identified species (Table 159.1). Vibriosis is reported more commonly from coastal than inland states.[6] Estuarine filter feeders (e.g., oysters, clams, mussels, shrimp, and crabs) can sequester and concentrate vibrios. Vibriosis often occurs in people who have consumed raw or undercooked seafood, especially shellfish.[7–9] It also can occur after exposure of a wound to seawater.[8,10] Not all cases are detected because many laboratories do not routinely use media selective for vibrios.[11,12] For decades, infections with toxigenic *V. cholerae* serogroups O1 and O139 were notifiable nationally; in 2007, infection caused by any *Vibrio* species became notifiable nationally.[13]

TABLE 159.1

Vibrio Species Most Commonly Associated With Vibriosis in the United States, 2010 to 2013

Vibrio Species	Site of Isolation			
	Blood	Stool	Wound	Percentage of Reported *Vibrio* Isolates[a] (%)
Vibrio parahaemolyticus	+	+++	+	46
Vibrio alginolyticus	+	+	+++	18
Vibrio vulnificus	+++	+	++	13
Vibrio cholerae, nontoxigenic	++	+++	++	8
Vibrio fluvialis	+	+++	++	5
Vibrio mimicus	+	+++	+	2
Grimontia (Vibrio) hollisae	+/−	+++	+	1

[a] Based on 3912 vibriosis infections reported to the Centers for Disease Control and Prevention's Cholera and Other Vibrio Illness Surveillance System, 2010 to 2013. Species constituting ≥1% of reported isolates are listed.

+++, common (51%–100% of isolates); ++, occasional (10%–50% of isolates); +, infrequent (1%–9% of isolates); +/−, rare (<1% of isolates).

Vibrio vulnificus

V. vulnificus was first described by the Centers for Disease Control and Prevention (CDC) in 1979.[14] It is the *Vibrio* species most commonly associated with life-threatening illness in the US.[6] The CDC receives reports of approximately 125 illnesses, 100 hospitalizations, and 35 deaths from *V. vulnificus* yearly.[15] It is the most lethal infection associated with raw oyster consumption.[16] *V. vulnificus* has been isolated from all coastal regions of the US.[8] The organism causes 2 major syndromes: primary bacteremia and wound infection.

Infections are classified as primary bacteremia when *V. vulnificus* is isolated from a normally sterile site and the patient has no preceding wound infection. Of patients with *V. vulnificus* primary bacteremia in the US between 1988 and 1996, 96% consumed raw oysters in the 7 days before symptoms began.[17] Almost all patients with primary bacteremia have an underlying condition, such as liver disease, malignant disease, hemochromatosis, or immunocompromise.[18,19] The CDC has issued guidance regarding the risks of consuming raw or undercooked seafood, particularly in people with underlying conditions (Box 159.1).[19a]

Box 159.1

Centers for Disease Control and Prevention Guidance Regarding *Vibrio* Infection

People should be informed that consumption of raw or undercooked seafood and open wound contact with warm seawater increase the risk of *Vibrio* infection.

People who are immunocompromised, especially those with chronic liver disease, are at highest risk for severe *Vibrio* infection.

To ensure appropriate diagnosis of infection, clinicians should request microbiologic culture with selective media when *Vibrio* is suspected.

Clinical laboratories should send all *Vibrio* isolates to their state public health laboratory for confirmation and species identification. (If a positive result of a culture-independent test was used to diagnose *Vibrio* infections, a specimen should be obtained for culture.[52])

Data from Centers for Disease Control and Prevention. *Vibrio* species causing vibriosis. 2016. https://www.cdc.gov/vibrio/index.html.

Wound infection with *V. vulnificus* typically occurs through exposure of a wound to warm seawater in adults with an underlying condition,[8,20] but it can occur rarely in healthy children. Severe wound infections with *V. vulnificus* biogroup 3 have been reported from Israel among previously healthy people handling live tilapia.[21]

Vibrio parahaemolyticus

V. parahaemolyticus is the most frequently reported cause of *Vibrio* illness in the US,[6] where it produces sporadic cases and outbreaks of gastroenteritis.[22,23] Patients frequently report eating raw oysters in the week before the onset of illness. Serogroup O4 (including O4:K12 and O4:K unknown), historically linked to shellfish in the Pacific Northwest, caused outbreaks linked to consumption of raw Atlantic Coast shellfish in 2012 and 2013.[4,24] Soft tissue infections with *V. parahaemolyticus* are rare.[25,26]

Other *Vibrio* Species

Non-O1, non-O139 *V. cholerae* strains are common inhabitants of coastal and estuarine saltwater areas, although infections have also occurred after exposure to freshwater inland lakes.[27] These organisms are isolated commonly from oysters and other shellfish, especially during warmer months. Gastroenteritis is the most common presentation; bacteremia and wound infections also occur. Non-O1 strains of *V. cholerae* can produce a polysaccharide capsule, which may explain their ability to cause invasive disease.

V. alginolyticus has become the leading cause of non–foodborne *Vibrio* infections in the US. It can cause infections of the ear, eye, nose, and sinuses, especially in younger children.[8,15] *V. mimicus*, which causes primarily gastroenteritis, is associated with raw seafood consumption.[28] *V. fluvialis* has been isolated from stool of infants, children, and young adults in Bangladesh with diarrhea.[29] *V. furnissii* has been identified in patients with gastroenteritis who consumed raw seafood or came in contact with seawater, although it is also frequently isolated from asymptomatic people.[30]

Clinical Manifestations

Vibrio vulnificus

Primary bacteremia caused by *V. vulnificus* is often fulminant, with a 61% case-fatality rate.[9] One third of patients present in shock; of these patients, 90% die, usually within 48 hours of hospitalization.[31] Most have characteristic bullous skin lesions. Necrotic ulcers can progress to necrotizing fasciitis. Thrombocytopenia is common, and disseminated intravascular coagulation can occur. Initial hypotension, hemorrhagic bullous skin lesions, leukopenia, thrombocytopenia, and low serum albumin levels predict fatal outcomes.[31–36]

Patients with *V. vulnificus* wound infections typically have fever, cellulitis with ecchymosis and bullae, swelling, and intense pain at the wound site. In severe cases, fasciitis, myositis, or secondary bacteremia can ensue. In 1 series, 17% of patients presenting with *V. vulnificus* wound infection died, with higher fatality rates in patients with underlying liver disease.[8] *V. vulnificus* has been isolated from stool of patients with gastroenteritis who consumed raw oysters.[37] The typical incubation period for any *V. vulnificus* syndrome is approximately 18 hours; incubation periods up to 10 days have been reported.[38] No long-term sequelae are expected for survivors.[39]

Vibrio parahaemolyticus

V. parahaemolyticus causes gastroenteritis characterized by diarrhea that can contain mucus or blood, abdominal cramps, nausea, and vomiting.[22] The median incubation period is 17 hours (range, 4–90 hours); symptoms typically resolve after 2 days (range, 8 hours–12 days).[22] *V. parahaemolyticus* can cause wound infections when wounds are exposed to warm seawater; these infections are less likely to cause shock, amputation, or death than are *V. vulnificus* infections.[8] Primary bacteremia comprises only 5% of *V. parahaemolyticus* cases reported.[22]

Other *Vibrio* Species

Only toxigenic *V. cholerae* O1 and O139 strains, which cause cholera epidemics, are defined by the World Health Organization as causes of cholera. Some *V. cholerae* non-O1, non-O139 strains also produce cholera toxin. *V. cholerae* non-O1, non-O139 infection can be associated with diarrhea, which ranges from mild to profuse and can be bloody, as well as abdominal cramps, fever, and vomiting.[40] These strains have been isolated from wounds exposed to seawater,[8] and they can cause primary bacteremia, usually in patients with underlying immunodeficiency, hematologic malignant disease, or cirrhosis.[40,41] Symptoms resemble those of *V. vulnificus* bacteremia but usually without bullous skin lesions. The case-fatality rate of bloodstream infections is >50%.[42]

Nontoxigenic vibrios, which include *V. cholerae* O1 and O139 strains that do not produce cholera toxin, occasionally are isolated from other body sites; infections attributed to *Vibrio* species include otitis media, otitis externa, meningitis, pneumonia, peritonitis, cholecystitis, conjunctivitis, and panophthalmitis.[8,43,44] *V. alginolyticus* and *Photobacterium (Vibrio) damselae* usually are associated with external ear and wound infections, respectively, in people exposed to saltwater. *Grimontia (Vibrio) hollisae, V. fluvialis, V. mimicus,* and nontoxigenic strains of *V. cholerae* O1 typically cause gastrointestinal tract infection.[1] Isolation of an uncommon *Vibrio* species does not prove that it is the cause of clinical symptoms; the pathogenicity of some vibrios is not clearly established.

Laboratory Findings and Diagnosis

Vibrio infection should be suspected in any patient with bacteremia, wound infection, or gastroenteritis with a history of raw shellfish consumption or exposure to saltwater or brackish water. *Vibrio* species are isolated readily from blood on sheep blood agar. Isolation from stool or wounds is best accomplished using selective media, such as thiosulfate citrate bile salts sucrose (TCBS) agar,[45] which are often not included in routine microbiologic testing of stool.[11] All pathogenic *Vibrio* species (except *Grimontia [Vibrio] hollisae*) grow on TCBS agar. Final identification is made by standard biochemical tests.[46]

Treatment

Patients with primary bacteremia require prompt supportive care, including monitoring of hemodynamic status and fluid management. Early antimicrobial therapy for *V. vulnificus* bacteremia can decrease the case-fatality rate.[31,14] Recommended therapy has consisted of trimethoprim-sulfamethoxazole in combination with an aminoglycoside for children (although organisms are not susceptible uniformly to either agent) and doxycycline in combination with a third-generation cephalosporin or fluoroquinolone for adults.[47] A single-agent regimen with a fluoroquinolone such as levofloxacin, ciprofloxacin, or gatifloxacin has been reported to be at least as effective in an animal model as combination drug regimens with doxycycline and a cephalosporin.[48] This would be an appropriate use for a fluoroquinolone in children. Patients with wound infections or necrotizing fasciitis often require prompt debridement.[49,50] Most *Vibrio* gastrointestinal infections, such as those caused by *V. parahaemolyticus*, are mild and self-limited and do not require treatment other than oral rehydration (see Chapter 158). Antibiotics such as tetracycline or ciprofloxacin can be used in patients with severe or prolonged gastrointestinal illnesses; antibiotic choice should be based on antimicrobial susceptibilities.[51]

Prevention

Although the risk of vibriosis in consumers of raw oysters is greatest during summer and fall, cases occur year round. Prevention strategies are appropriate for everyone, especially for people with certain medical conditions, including liver disease, diabetes, and immunocompromising conditions, who are at higher risk for complications and death. Effective preventive measures are as follows: (1) thoroughly cooking shellfish; (2) refrigerating cooked seafood if it is not eaten immediately; (3) preventing cross-contamination of other foods with raw seafood; and (4) avoiding exposure of open wounds or broken skin to warm saltwater, brackish water, or raw shellfish harvested from such waters.

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Gram-Negative Coccobacilli

OUTLINE

160 Bartonella Species (Cat-Scratch Disease)
161 Brucella Species (Brucellosis)
162 Bordetella pertussis (Pertussis) and Other Bordetella Species
163 Campylobacter jejuni and Campylobacter coli
164 Other Campylobacter Species
165 Capnocytophaga Species
166 Chlamydophila (Chlamydia) pneumoniae
167 Chlamydia trachomatis
168 Chlamydia (Chlamydophila) psittaci (Psittacosis)
169 Coxiella burnetii (Q Fever)
170 Family Anaplasmataceae (Anaplasmosis, Ehrlichiosis, Neorickettsiosis, and Neoehrlichiosis)
171 Francisella tularensis (Tularemia)
172 Haemophilus influenzae
173 Other Haemophilus Species and Aggregatibacter Species
174 Helicobacter pylori
175 Other Gastric and Enterohepatic Helicobacter Species
176 Kingella Species
177 Legionella Species
178 Rickettsia rickettsii (Rocky Mountain Spotted Fever)
179 Other Rickettsia Species
180 Streptobacillus moniliformis (Rat-Bite Fever)
181 Other Gram-Negative Coccobacilli

160

Bartonella Species (Cat-Scratch Disease)

Jin-Young Han, Richard F. Jacobs

The genus *Bartonella* consists of more than 20 species, of which the best known is *B. henselae.* The role of *B. henselae* in most cases of cat-scratch disease has been established through serologic analysis of patients and their cats, polymerase chain reaction tests on lymph nodes and skin test antigen, and isolation of the organism from human lymph nodes and cats.[1–6] *B. quintana,* the cause of louse-borne trench fever, and *B. henselae* both have been identified as the causes of bacillary angiomatosis, bacillary peliosis, bacteremia, and endocarditis. *B. bacilliformis* is the cause of Carrión disease, and other *Bartonella* species (e.g., *B. elizabethae, B. alsatica*) have been causes of endocarditis.

Description of the Pathogen and Epidemiology

Bartonella spp. are pleomorphic, gram-negative bacilli with fastidious growth requirements. Routine cultures have low yield and typically require at least 7 days before growth can be detected. Recovery on solid agar is best achieved through inoculation onto fresh chocolate agar or heart infusion agar with 5% rabbit blood. Inoculated agar is incubated in 5% carbon dioxide at 35°C for 2 to 6 weeks. Increasingly, molecular methods are used for diagnosis.

The true incidence of cat-scratch disease in the United States is unknown, although the diagnosis is made in an estimated 22,000 ambulatory patients annually, with a national incidence of hospitalization of 0.42 in 100,000 to 0.86 in 100,000.[7,8] A slightly larger proportion of cases occurs in male patients than in female patients. Although children are more likely to be affected than adults, the disease is rare in infancy.[9] The incidence is highest in southern states and lowest in arid, western states.

The domestic cat is a major reservoir for *B. henselae* and the major vector for transmission to humans. *B. henselae* bacteremia in otherwise well-appearing cats is common and can be prolonged.[10] Studies have demonstrated that 41% of pet and impounded cats have bacteremia with *B. henselae*,[6] whereas 93% of feral cats and 75% of pet cats have been found to be seropositive.[11] Although flea-borne *(Ctenocephalides felis)* transmission of *B. henselae* from cat to cat appears to be efficient, epidemiologic data do not support the efficient transmission from cats to humans by cat fleas.[12]

A cat scratch can result in cat-scratch disease. The incubation time from the cat scratch until the appearance of lymphadenopathy is 5 to 50 days (median, 12 days). Other animals, such as dogs and monkeys, as well as inanimate objects such as pins and splinters, occasionally are associated with human infection.[13]

Cat-scratch disease is a sporadic illness with no evidence of person-to-person transmission. Even if asymptomatic, members of households in which a case has been diagnosed are more likely to be seropositive than the general population.[2] Multiple cases have occurred in families, presumably resulting from direct contact with the same animal. Several widespread outbreaks also have been described. A survey of 33 geographic regions throughout North America showed that increasing prevalence of antibody to *B. henselae* in cats paralleled increasing climatic warmth and annual precipitation.[14] Seroprevalence was highest in regions with warm, humid climates, which also have a higher incidence and severity of flea infestation of cats.

Most cases of cat-scratch disease occur in fall and winter; 71% to 93% of cases are reported from August through January.[2,7,9] Seasonality may be related to feline reproductive cycles, in combination with flea activity; that is, a cohort of kittens is born in midsummer (while flea activity is high) and is weaned in early fall.

Kittens are more commonly implicated as sources of infection than adult cats, possibly because kittens are more likely to scratch. A survey of cats indicated that seroconversion occurred during the first year of life, a finding suggesting that young cats are more likely to have active infection than older ones.[15]

Humans are the only known vertebrate hosts for *B. quintana* and *B. bacilliformis*.[16,17] The arthropod vector for *B. bacilliformis* is the sandfly.[17] The vector involved in transmission of *B. quintana* is the body louse, and the association of body lice with trench fever was recognized during World War I. Both these *Bartonella* species can produce prolonged periods of asymptomatic bacteremia, thus providing a reservoir from which the body louse and sandfly can transmit the organisms to human hosts sequentially.

Bacillary angiomatosis is a rare vasoproliferative disorder that occurs almost exclusively in severely immunocompromised people.[18,19] It also has been reported in a few apparently immunocompetent people. In patients with bacillary angiomatosis, those infected with *B. henselae* often have a history of cat exposure, but those infected with *B. quintana* do not. Bacillary peliosis occurs primarily in terminally ill patients with acquired immunodeficiency syndrome, but it also has occurred in patients with other chronic debilitating diseases, such as tuberculosis and malignant disease. Persistent or relapsing fever with bacteremia caused by *B. henselae* or *B. quintana* occurs primarily in immunocompromised people but also has been reported in immunocompetent people.[20]

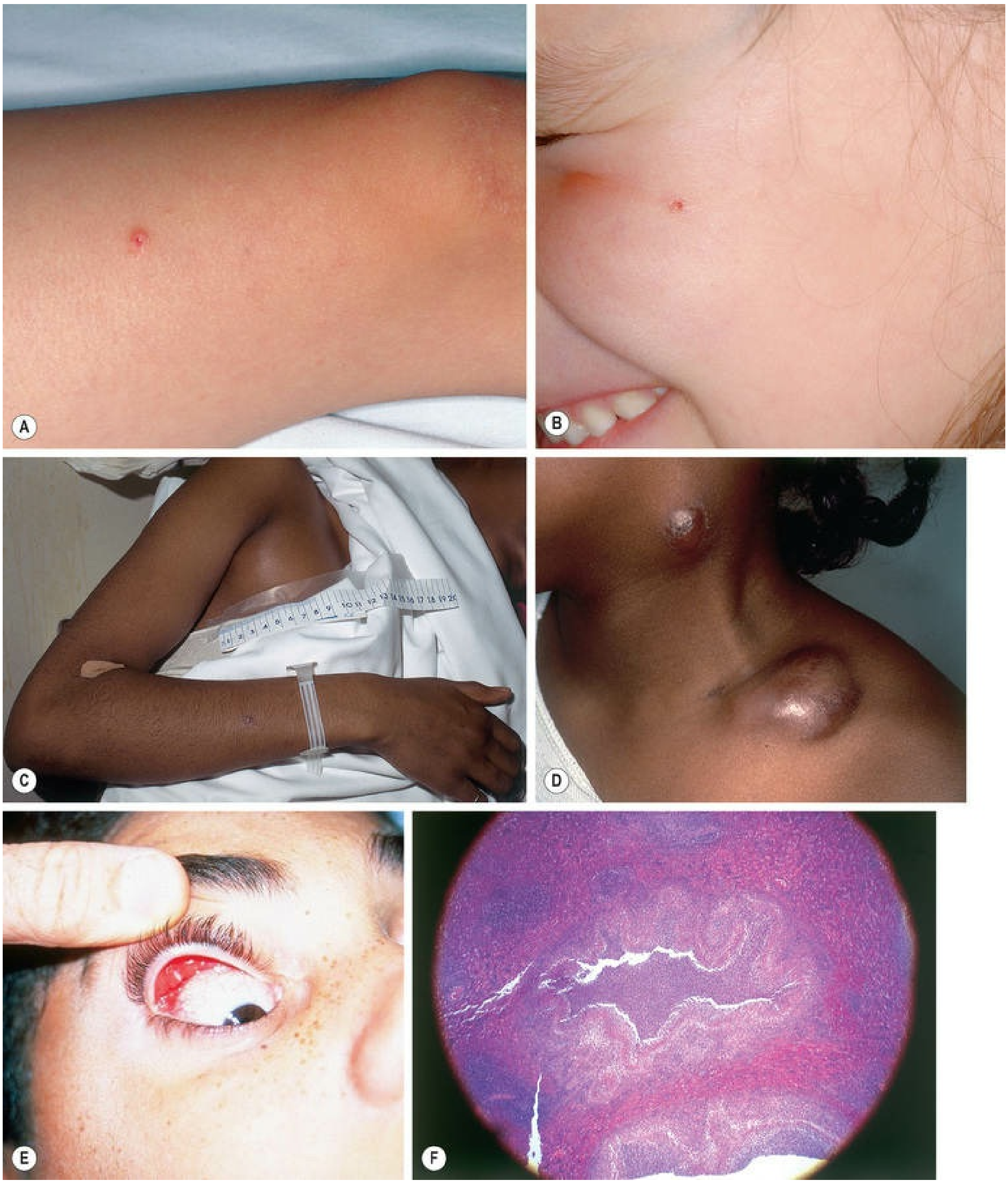
Bartonella now is recognized as a significant cause of culture-negative endocarditis.[21] Cases are most often reported in adults, and >95% of cases are caused by *B. quintana* or *B. henselae*.

B. bacilliformis infection (Carrión disease) is not reported outside a restricted geographic region in the Andes mountains in western South America. Two forms of this disease are recognized: (1) the acute form, known as Oroya fever, which is a severe febrile illness with a high mortality rate; and (2) the chronic phase, known as verruca peruana, which is characterized by red, warty, vascular cutaneous lesions that resemble bacillary angiomatosis.[17]

Clinical Manifestations

Cat-Scratch Disease

Human infections with *B. henselae* can be asymptomatic or symptomatic (Fig. 160.1A to J). For symptomatic patients, regional lymphadenopathy, fever, and mild constitutional symptoms are common. Cat-scratch disease is the most common cause of chronic unilateral regional lymphadenitis in children in the US.[9,22–24] After an incubation period of 7 to 12 days, 1 or more erythematous papules 2 to 5 mm in diameter will appear at the inoculation site. This primary lesion persists for ≥1 week and then regresses spontaneously. Lymphadenitis, the hallmark of cat-scratch disease, appears at 2 to 4 weeks. A hypersensitivity-type of reaction can cause the appearance of reactivation of the primary lesion at this time.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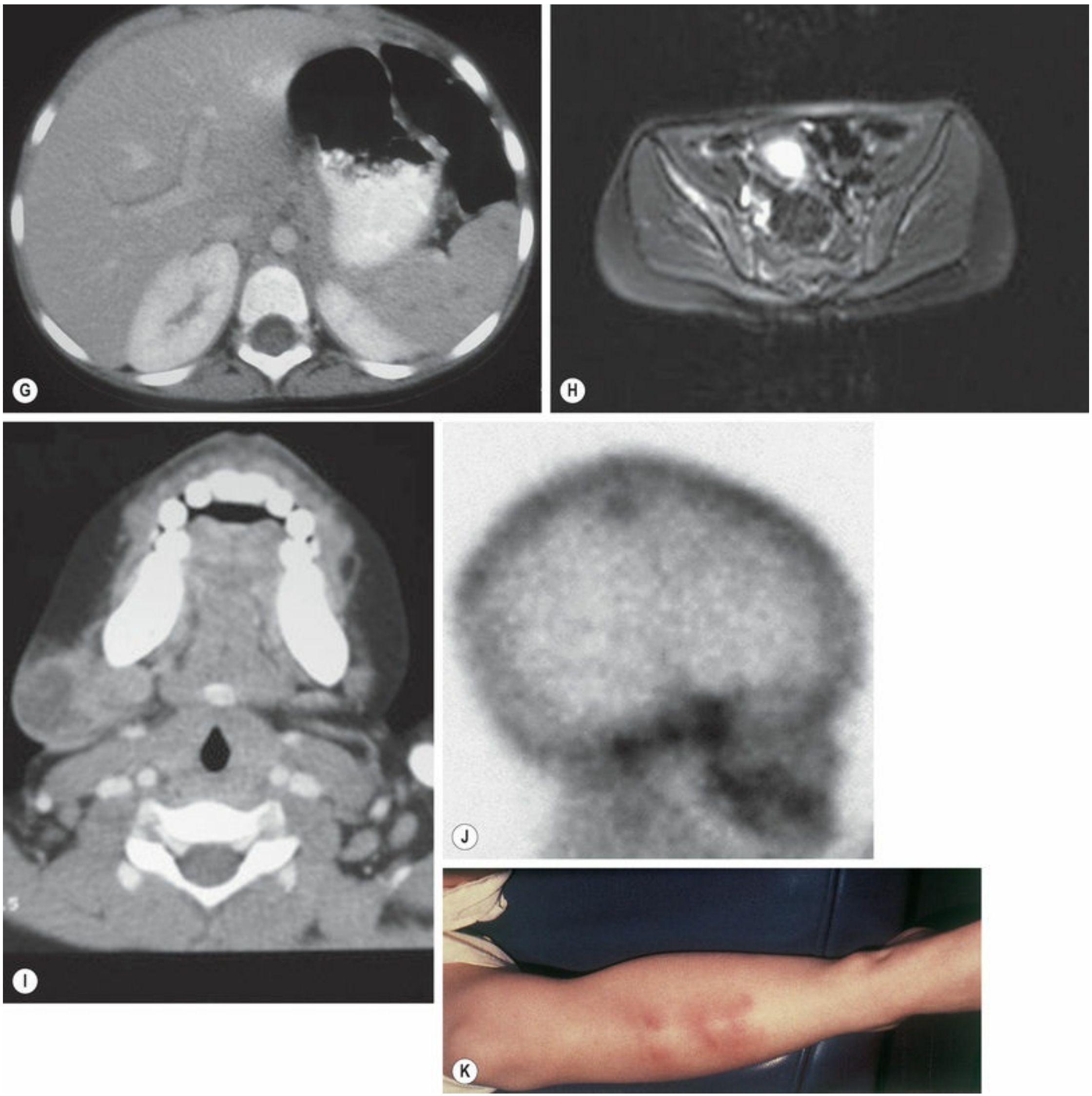

FIGURE 160.1 Typical clinical findings of *Bartonella henselae* infection (cat-scratch disease). Simple papule at the scratch site on (A) the leg of a young boy and (B) the face of a young girl. (C) Papular lesion on the arm and axillary lymphadenopathy in an adolescent. (D) Papular lesion and fluctuant, enlarged lymph nodes in the supraclavicular and neck areas of an adolescent girl who frequently cuddled her kitten over her chest and shoulder. (E) Granulomatous conjunctivitis and preauricular lymphadenopathy in a 12-year-old boy. (F) Histologic specimen of an excised neck mass showing a lymph node with granuloma and stellate microabscess (hematoxylin and eosin, 200×). (G) Computed tomography of the abdomen without contrast in a young girl with fever of unknown origin showing multiple hypodense areas in the spleen that changed minimally following administration of contrast. (H) Gadolinium-enhanced axial magnetic resonance imaging showing bone marrow enhancement of the ilium in a 6-year-old girl who came to attention for fever of unknown origin and right hip pain; no osteolytic lesion was evident on plain film. (I) Computed tomography of the neck showing a superficial necrotizing mass and (J) delayed phase of technetium-99m bone scan showing increased uptake in the skull (and ilium: not shown) in a 5-year-old girl with persistent fever and hip pain while being treated with amoxicillin for lymphadenitis; she had no signs or symptoms referable to the skull finding. (K) Erythema nodosum in a 7-year-old girl with axillary lymphadenopathy. (A, B, E, H, Copyright J.H. Brien, Scott and White Memorial Hospital,

Temple, Tex; C, D, F, K, Courtesy of S.S. Long, St. Christopher's Hospital for Children, Philadelphia, Pa; G, I, J, Courtesy of E.D. Thompson, St. Christopher's Hospital for Children, Philadelphia, Pa.)

Lymphadenitis usually involves nodes that drain the site of inoculation; however, in as many as 20% of cases, additional lymph node groups are affected. At any site of lymphadenitis, a single lymph node is involved in approximately one half of cases, and multiple nodes are involved in the remainder. The site most commonly involved is the axilla, followed by the cervical, submandibular, and inguinal areas. The area around an affected lymph node typically is tender, warm, erythematous, and indurated. In as many as 30% of cases, the affected lymph node suppurates spontaneously. Untreated, lymphadenitis usually regresses over 4 to 6 weeks.

Most patients with cat-scratch disease are afebrile and lack constitutional symptoms. When present, constitutional symptoms typically are low-grade fever, malaise, anorexia, fatigue, and headache. Parinaud oculoglandular syndrome is a distinctive presentation of cat-scratch disease in which the site of inoculation is the eyelid or conjunctiva, and a papular lesion and conjunctivitis develop at the inoculation site accompanied by ipsilateral preauricular lymphadenitis (see Fig. 160.1).

Systemic cat-scratch disease occurs in a small proportion of cases.[25] Patients with systemic cat-scratch disease typically come to medical attention for prolonged fever (1–3 weeks), malaise, listlessness, myalgia, and arthralgia; some have skin eruptions, weight loss, abdominal pain (which can be severe), peripheral lymphadenopathy, hepatomegaly, and splenomegaly. In a case series in which the presentation was fever of unknown origin, abdominal pain was present in more than one half of patients and lymphadenopathy in less than one half.[26] Using ultrasonography and computed tomography imaging, multiple microabscesses or granulomas of the liver or spleen can be identified in some cases. Other less common manifestations include encephalopathy or encephalitis, aseptic meningitis, neuroretinitis, osteolytic lesions, bone marrow granulomas, granulomatous hepatitis, pneumonia, thrombocytopenic purpura, and erythema nodosum. Patients in anecdotal cases have had demonstrable bony involvement by magnetic resonance imaging or technetium-99m bone scan, without osteolytic lesions on plain radiographs.

Other *Bartonella henselae* and *Bartonella quintana* Infections

Bacillary angiomatosis is characterized by the gradual appearance of vascular proliferative lesions of the skin and subcutaneous tissues.[18,22] These lesions can be verrucous, papular, or pedunculated, and although they usually have an erythematous base and a vascular appearance, the lesions are occasionally dry, scaly, hyperkeratotic, or plaque-like. The lesions can occur singly or in large numbers, to cover the entire body; lesions usually enlarge if untreated. Bacillary angiomatosis also can manifest either as subcutaneous nodules with or without overlying tenderness and erythema or as deep soft tissue masses.

Bacillary peliosis is characterized by the appearance of reticuloendothelial lesions in visceral organs, primarily the liver (peliosis hepatis); however, the spleen, abdominal lymph nodes, and bone marrow also can be involved. The visceral lesions of bacillary peliosis can be accompanied by the cutaneous lesions seen in bacillary angiomatosis.

Immunocompromised patients who are infected with *B. henselae* or *B. quintana* can have persistent or relapsing fever with bacteremia, frequently accompanied by weight loss and other constitutional symptoms. Patients with *Bartonella* endocarditis have clinical manifestations similar to those of other patients with subacute endocarditis.

Laboratory Findings and Diagnosis

Results of routine laboratory evaluation of patients with cat-scratch disease usually are unremarkable. The most consistently reported abnormality is an elevated erythrocyte sedimentation rate and C-reactive protein.[20,23] In disseminated disease, serum hepatic transaminase concentrations can be elevated if the liver is involved (but not in all cases of hepatic infection), and occasionally, a biliary obstructive pattern of abnormalities can be seen. Computed tomography (and, less sensitively, ultrasound) can reveal multiple round, oval, or irregular lesions 3 to 30 mm in diameter.

Several serologic tests for cat-scratch disease have been developed. Using strict clinical case criteria, immunoglobulin M

(IgM) and IgG indirect immunofluorescence antibody assays show a sensitivity of 88% and a specificity of 98%.[3,27] An enzyme immunoassay has excellent specificity (IgM, 99%; IgG, 98%).[1,2,20,28] Rates of background seropositivity (titer ≥ 1 : 64) with the immunofluorescence antibody test are low (2%–6%) but can be higher in cat owners. Demonstration of a rising IgG titer provides the best evidence of infection; however, most patients with cat-scratch disease already have high titers at the time of presentation, and titers may not fall for 2 to 6 months. In a prospective trial of antibody kinetics, enzyme immunoassay (IgM) results remained positive for 3 months and indicated acute infection. Enzyme immunoassay (IgG) antibody decreased over time, with 25% of patients remaining positive for 1 year after the onset of cat-scratch disease. No association was found between height of antibody titers or their kinetics and the clinical manifestations or duration of disease.[28] Cross-reactivity among *Bartonella* spp. is common, and serologic tests do not yet accurately distinguish among species. Western blot with cross-adsorption enables identification of specific species,[21] but the test is not readily available in the US.

If tissue specimens are obtained from patients with cat-scratch disease, attempts to isolate *Bartonella* species usually are not helpful because incubation in vitro requires 2 to 4 weeks, and for poorly understood reasons, viable organisms are rarely isolated from such patients. The histologic findings of lymph nodes or other affected tissues are characteristic but not pathognomonic. Early histologic changes consist of lymphocytic infiltrates with epithelioid granuloma formation. Later histologic changes consist of neutrophilic infiltrates within granulomas that have begun to fuse and become necrotic (stellate microabscesses) (see Fig. 160.1), followed by large, pus-filled sinuses that eventually rupture through the node capsule into surrounding tissue. Organisms can be visualized using a Warthin-Starry silver impregnation stain; however, this test is not specific for *B. henselae.*

In cases of bacillary angiomatosis and bacillary peliosis, the diagnosis usually is made by biopsy. The histologic appearance of each of these lesions is characteristic, and clusters of organisms can be demonstrated with Warthin-Starry staining. Attempts to culture *Bartonella* have been more successful in specimens collected from patients with these manifestations than in specimens collected from patients with typical cat-scratch disease.[29] Serologic tests are useful, although results are not always positive in patients with human immunodeficiency virus infection. Several procedures have been developed that are accurate and can discriminate among different *Bartonella* species in clinical tissue specimens.[30–33]

The most sensitive method of diagnosing a *B. henselae* or *B. quintana* infection is by polymerase chain reaction testing performed on various clinical specimens such as valvular tissue for endocarditis. Polymerase chain reaction results from blood samples are sometimes positive in patients with bacteremia or endocarditis.

Treatment

The management of typical cat-scratch disease primarily is supportive; the disease usually is self-limited, resolving spontaneously in 2 to 4 months. Painful suppurative lymph nodes can be treated with needle aspiration for relief of symptoms; surgical excision generally is unnecessary. *B. henselae* is susceptible in vitro to a wide range of antimicrobial agents, including penicillins, tetracyclines, macrolides, trimethoprim-sulfamethoxazole, rifampin, fluoroquinolones, aminoglycosides, and later-generation but not first-generation cephalosporins. Anecdotal reports of treatment of patients with systemic infection[25,29,34] and typical cat-scratch disease[35,36] suggest a clinical response to several antimicrobial agents, including trimethoprim-sulfamethoxazole, rifampin, ciprofloxacin, and gentamicin. A prospective, randomized, double-blind, placebo-controlled investigation of 5 days of oral azithromycin therapy for patients with serologically confirmed, typical cat-scratch lymphadenitis demonstrated a modest clinical benefit in decrease in lymph node volume as noted by ultrasound examination in the first month of therapy.[37] The value of antimicrobial therapy for patients with any form of cat-scratch disease remains uncertain.

Although the benefit of antimicrobial therapy for patients with bacillary angiomatosis or bacillary peliosis has not been studied systematically, experience suggests that such therapy is beneficial and clearly is indicated. The lesions and symptoms of these diseases respond rapidly to erythromycin or doxycycline therapy.[38] Tetracycline, minocycline, and azithromycin also have been effective.[39] Rifampin also may be effective but usually is recommended as a second drug in combination with either erythromycin or doxycycline. Patients who have only cutaneous lesions should be treated for at least 2 weeks, and those who have visceral lesions should be treated for at least 4 weeks.

Optimal therapy for *Bartonella* endocarditis is unknown; however, an aminoglycoside and doxycycline often are used.

As a systematic review demonstrated, current treatment recommendations for human bartonellosis rely mostly on personal experiences and expert opinions because of the lack of high-quality efficacy data.[40]

Complications, Sequelae, and Prognosis

Complications of cat-scratch disease are unusual. Encephalopathy is the most serious complication of cat-scratch disease, and it occurs in up to 5% of patients.[2,41] Typically, 1 to 3 weeks after the onset of lymphadenopathy (but occasionally in the absence of lymphadenopathy), the patient experiences the sudden appearance of neurologic symptoms, which can include seizures, combative or bizarre behavior, lethargy, and coma. Focal neurologic findings are unexpected. Neurologic imaging findings generally are normal, and lumbar puncture results are normal or show only slight lymphocytic pleocytosis or elevation of protein. Fever usually is absent or low grade, and systemic symptoms are minimal. The patient usually improves rapidly and spontaneously, sometimes returning to normal after a few days. In a series of 61 patients with cat-scratch encephalopathy, two thirds had fully recovered by 4 weeks, and none showed any residual encephalopathy after 1 year.[42] Cat-scratch encephalopathy should be included in the differential diagnosis of new onset status epilepticus in previously healthy school-aged children.[43]

Optic neuritis or neuroretinitis, with painless unilateral visual loss, can occur as a complication of cat-scratch disease several weeks after the onset of lymphadenopathy. Although visual loss can be profound, patients usually recover completely over a period of months. A case series of neuroretinitis documented only 3 (6%)

of 53 patients with a visual acuity of 20/200 or worse at final follow-up.[44] Peripheral neuralgia and paresthesia, as well as facial nerve palsies, also have been reported.[38] Other complications of cat-scratch disease are erythema nodosum (see Fig. 160.1K), osteolytic lesions, thrombocytopenic and nonthrombocytopenic purpura, nonimmune hemolytic anemia, atypical pneumonia, and glomerulonephritis.[45–49] Osteolytic lesions frequently are associated with a soft tissue phlegmon, can be multiple, and frequently involve unusual sites such as the spine, cranium, sternum, or fibula[47] (see Fig. 160.1).

Although acute illness caused by cat-scratch disease can be dramatic, the prognosis for all forms of this illness is excellent. Even in the absence of treatment, almost all immunocompetent patients recover fully. Reinfection appears to be extremely rare.

Bacillary angiomatosis and bacillary peliosis, even in severely immunocompromised patients, usually respond to antimicrobial therapy. However, relapses are common.

Prevention

Avoiding cats is a simple although unpopular method of preventing infections with *B. henselae*. Removing a family pet to which a case of cat-scratch disease has been attributed is unnecessary because the capacity for disease transmission appears to be transient. People with immunodeficiency should avoid contact with cats that scratch or bite, and, if obtaining a new pet, they should avoid cats younger than 1 year of age. People should wash sites of cat scratches or bites immediately, and they should not allow a cat to lick their open cuts or wounds. Control of flea infestation has the potential for limiting transmission of *B. henselae* among cats. At present, recommendations for prevention of *B. quintana* infection are limited to avoiding contact with lice and promptly eradicating lice infestation.

Key Points

Diagnosis and Management of *Bartonella henselae* Infection

Microbiology

- Slow growing, pleomorphic, gram-negative bacilli
- Fastidious growth requirements

Epidemiology

- The true incidence of human disease is unknown.
- Sporadic and asymptomatic human disease is common.
- No person-to-person transmission occurs.
- Domestic cats are the natural reservoir.
- Incidence of disease is highest in fall and winter of each year.

Diagnosis

- Routine laboratory tests usually are not helpful.
- Serologic testing is used to establish most diagnoses.
- Polymerase chain reaction performed on a clinical sample can establish the diagnosis.

Treatment

- The management of most infections is supportive.
- *Bartonella henselae* is susceptible in vitro to penicillins, tetracyclines, macrolides, trimethoprim-sulfamethoxazole, rifampin, fluoroquinolones, and aminoglycosides.
- Only azithromycin has been evaluated in a prospective, randomized, double-blind, placebo-controlled investigation; modest clinical benefit was shown for reduction in size of lymph node.
- Azithromycin therapy for cat-scratch lymphadenitis typically is 5 days.

- Only anecdotal guidance exists for treatment of systemic *B. henselae* infections.

- Optimal agents and duration of therapy for systemic infections are unknown.

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161

Brucella Species (Brucellosis)

Edward J. Young

Brucellosis is a disease of animals that can be transmitted to humans (zoonosis).[1] The genus *Brucella* belongs to the alpha-2-subgroup of *Protobacteria* phylogenetically related to plant and other intracellular animal pathogens (e.g., *Bartonella* and *Rickettsia*).[2] Based on phenotypic analysis, 6 named (nomen) species initially were identified relating to their preferred natural hosts. Subsequently, genotypic analysis indicated a high degree of relatedness suggesting a single species with multiple biovars.[3] For epidemiologic purposes, the original nomen species classification has been retained (Table 161.1). More recently, the use of molecular techniques has expanded the number of *Brucella* spp., and more are likely to be found. Among them is a unique isolate (*B. inopinata*) from a breast implant and blood of a 71-year-old woman with no known exposure to other sources of brucellosis.[4]

TABLE 161.1

Genus *Brucella*

Nomen Species	Biovars	Preferred Hosts	Human Pathogen
Brucella abortus	1–6, 9	Cattle	Yes
Brucella melitensis	1–3	Goats, sheep	Yes
Brucella suis	1–3	Swine	Yes
	4	Caribou, reindeer	Yes
	5	Rodents	Yes
Brucella canis[a]	None	Dogs	Yes

Brucella ovis[a]	None	Sheep	No
Brucella neotomae	None	Desert wood rats	No
Brucella ceti	None	Porpoises, dolphins, whales	Yes
Brucella pinnipedialis	None	Seals	Yes
Brucella microti	None	Voles	No
Brucella inopinata	None	Unknown	Yes

[a] Signifies naturally rough strains (lacking O-polysaccharide).

Pathogen and Pathogenesis

Brucellae are small, gram-negative coccobacilli that lack endospores, capsules, or native plasmids. Their metabolism is oxidative, and all strains are aerobic, although some strains can require added carbon dioxide for primary isolation. Various media support the growth of brucellae in vitro; however, prolonged incubation (≥21 days) may be required. Rapid isolation techniques such as Bactec (Becton, Dickinson, Franklin Lakes, NJ) systems have shortened the time for primary isolation. Culture of bone marrow may have a higher yield than routine cultures of blood. *Brucella* strains are always catalase positive, but production of oxidase, urease, and hydrogen sulfide is variable. Rapid identification systems have misidentified *Brucella* as *Moraxella* spp., *Haemophilus* spp. and *Ochrobactrum* spp.[5] Because of the risk of laboratory-acquired infection, biosafety level 3 practices, containment equipment, and facilities are recommended for the handling of suspected *Brucella* cultures.[6,7]

Brucella spp. contain an unconventional cell wall lipopolysaccharide that differs from classical enterobacterial endotoxin such as *Escherichia coli*. For example, *B. abortus* lipopolysaccharide possesses a diaminoglucose backbone (rather than glucosamine); acyl groups are longer (C18–C19, C28 rather than C12 and C14) and are linked to the core by amide bonds (rather than ester and amide bonds).[8] These properties result in a lipid A with low endotoxic activity, resistance to degradation within macrophages, and protection against the host's toll-like receptor 4–mediated innate immune response.[9,10]

Brucella spp. are facultative intracellular pathogens that can survive and replicate within host phagocytic cells. Innate and acquired humoral immunity plays some role in resistance to infection; however, cell-mediated immunity is the major mechanism of recovery from brucellosis. Coincident with acquired cellular resistance, hypersensitivity to brucella antigens develops, and this may contribute to some of the clinical manifestations of the disease.

Epidemiology

Brucellosis exists worldwide but is especially prevalent in the Mediterranean basin, the Arabian peninsula, the Indian subcontinent, and in parts of Mexico, Central America, and South America. It has also reemerged in Eastern Europe, where the collapse of the former Soviet Union led to social and economic upheaval with a decline in veterinary and human health services.[11,12] Although brucellosis was once common in the United States, eradication of bovine brucellosis has reduced the incidence of human infection to <0.5 cases per 100,000 population. In states bordering Mexico, where *B. melitensis* remains enzootic in goats, brucellosis is 8 times more prevalent than elsewhere in the country, and childhood brucellosis has become an imported disease.[13]

Humans are accidental hosts, contracting the disease by direct contact with infected animals, their carcasses, or their milk. Farmers, veterinarians, abattoir workers, and laboratory personnel are at increased risk of infection. Increasingly, cases of brucellosis are linked to ingestion of fresh goat milk cheese imported from countries where the disease is enzootic. In some countries, brucellosis has been linked to the ingestion of raw camel milk or cheese[14]; consequently, people of all ages can be infected, and they may have no history of direct animal contact. In the evaluation of patients with unexplained fever, clinicians should obtain a thorough history of travel, food consumption, occupation, and avocations.[15]

The usual routes of transmission of brucellosis from animals to humans are listed in Table 161.2. Human-to-human transmission is rare, but cases of apparent venereal transfer have been reported.[16,17] Brucellosis during pregnancy poses a risk of spontaneous abortion,[18,19] and it rarely may even present a risk to hospital personnel involved in delivery.[20,21] Although rare, neonatal brucellosis has been reported, and transmission could occur through the placenta of an infected mother or by breast milk following delivery.[22,23] Once considered rare in children, brucellosis now is recognized commonly in countries where *B. melitensis* is enzootic. In such areas, fresh milk from goats and camels is fed to children, and newborn animals often share family living space, thus providing conditions favorable to transmission.[24] In countries where brucellosis is no longer common, failure of physicians to consider the diagnosis may contribute to the low reported incidence of childhood infection.[25]

TABLE 161.2

Routes of Acquisition of Brucellosis

Nomen Species	Route	Common Settings
Brucella abortus	Intracutaneous	Delivering aborting cattle or slaughtering infected animals
	Oral	Ingestion of unpasteurized milk
Brucella abortus (strain 19)	Intracutaneous	Accidental needlestick with vaccine
	Conjunctival	Accidental splash with vaccine
Brucella melitensis	Oral	Ingestion of unpasteurized milk or cheese
Brucella melitensis (strain Rev-1)	Intracutaneous	Accidental needlestick with vaccine
	Conjunctival	Accidental splash with vaccine
Brucella suis	Respiratory	Inhalation of aerosol in abattoir
	Conjunctival	Inoculation of infected blood
	Oral	Ingestion of undercooked meat, blood, or bone marrow (traditional foods)
	Intracutaneous	Slaughtering and dressing feral swine
Brucella canis	Intracutaneous	Attending aborting dogs Accidental needlestick in laboratory
	Oral	Accidental ingestion while pipetting blood or serum in laboratory

Clinical Manifestations

Brucellosis is a systemic illness characterized by nonspecific complaints with a paucity of abnormal physical findings. The onset can be insidious or acute, with symptoms generally beginning 2 to 4 weeks after exposure. Series of childhood brucellosis from countries where *B.* melitensis is endemic indicate that fever, malaise, lethargy, and joint pains are the most common complaints (Table 161.3),[26–29] and a typical presentation is a child with fever who refuses to bear weight on an extremity. Compared with adults, the lower proportion of reported general symptoms (e.g., sweats, chills, headache) in children could reflect the difficulty in obtaining accurate histories from this age group.[30]

TABLE 161.3

Clinical Findings in Childhood Brucellosis From Selected Case Series

Signs and Symptoms	Israel, 1987–1992 (N = 88)	Saudi Arabia, 1984–1995 (N = 115)	Greece, 1979–1993 (N = 52)	Turkey, 1993–2006 (N = 90)
Fever	91%	88%	88%	64%
Arthralgia	83%	73%	62%	86%
Arthritis	22%	73%	NR	7%
Headache	8%	7%	21%	NR
Sweats	5%	9%	19%	NR
Rash	7%	2%	12%	NR
Weakness or fatigue	NR	18%	29%	NR
Hepatomegaly	43%	13%	33%	16%
Splenomegaly	42%	12%	52%	11%
Lymphadenopathy	NR	2%	23%	NR

NR, not reported.

Organ Systems of Involvement

Skeletal System.

Osteoarticular involvement is common and often is the predominant manifestation of brucellosis in children.[31,32] In contrast to adults, in whom sacroiliitis predominates, childhood brucellosis most often affects large peripheral joints (knees, hips, ankles), and spondylitis is rare. Arthritis usually is accompanied by fever, malaise, weight loss, and other systemic symptoms and must be distinguished from juvenile rheumatoid arthritis. Limitation of movement with swelling and tenderness of the affected joints is prominent, similar to other forms of pyogenic arthritis.[33] Plain radiography generally is unhelpful, but ultrasound, radionuclide bone scans, and magnetic resonance imaging are useful for disclosing hip and vertebral involvement.[34,35] Synovial fluid aspiration rarely is needed unless the joint effusion is large. The fluid is exudative, and brucellae are isolated in more than one half of the cases.[36,37] In addition to pyogenic arthritis, reactive arthropathy can develop shortly after antibiotic therapy has begun, thereby raising the possibility of a Herxheimer-like reaction.[38] Most experts agree that treatment of brucellosis involving the spine should be continued for at least 3 months.[39]

Central Nervous System.

Although headache, mental inattention, and depression are common complaints in human brucellosis, invasion of the nervous system occurs in only 2% to 6% of cases.[40,41] Meningitis is the most common neurologic manifestation, and fever, headache, confusion, and cranial nerve disorders are frequent. Examination of cerebrospinal fluid reveals lymphocytic pleocytosis, elevated protein, and often hypoglycorrhachia that must be differentiated from central nervous system tuberculosis. Results of cerebrospinal fluid cultures are positive for brucellae in <50% of cases, but confirmation of neurobrucellosis can be made by demonstrating *Brucella* antibodies or antigen by agglutination, enzyme-linked immunosorbent assay, or polymerase chain reaction.[42,43] Neuroimaging in pediatric neurobrucellosis varies from normal to a variety of imaging abnormalities including inflammatory and vascular changes.[41,44] Other neurologic complications include encephalitis, myelitis, neuritis, radiculopathy, mycotic aneurysms, and brain abscess.[45] In addition to standard therapy for brucellosis, many experts recommend the addition of ceftriaxone because of its ability to achieve high concentrations in cerebrospinal fluid.[46]

Alimentary Tract.

Nausea, vomiting, anorexia, weight loss, and abdominal discomfort occur in two thirds of cases of acute brucellosis.[47] Rare cases of cholecystitis, ileitis, colitis, and pancreatitis have been reported in patients infected with *B. melitensis*.

Reticuloendothelial System.

As the largest organ of the reticuloendothelial system, the liver likely is involved in all cases; however, serum hepatic enzyme levels are elevated only mildly and can be normal. Histologically, infection with *B. abortus* has been characterized by noncaseating granulomas, whereas *B. suis* often causes suppurative abscesses. Infection with *B. melitensis* can result in a variety of hepatic lesions, most often nonspecific reactive hepatitis.[48] Rarely, chronic hepatosplenic abscesses caused by *B. melitensis* or *B. suis* can require surgical intervention for cure.[49]

Cardiovascular System.

The most common cardiovascular complication of brucellosis is endocarditis; however, this is rare in children (0.5%). Other complications include arterial and venous thrombosis, cutaneous vasculitis, and endarteritis leading to peripheral and cerebrovascular aneurysms.[50] Endocarditis most often involves the aortic valve and can occur on both native and prosthetic valves. Endocarditis was once the principal cause of death in brucellosis, but advances in diagnosis and combined medical and surgical treatments have dramatically improved the prognosis.[51] Myocarditis and pericarditis can occur with or without endocarditis.[52]

Genitourinary Tract.

Orchitis or epididymitis is relatively common in adults with brucellosis but rare in children.[53] Although *Brucella* can be recovered from urine with appropriate techniques, it generally does not compromise renal function. Nephritis or glomerulonephritis usually occurs in conjunction with endocarditis.[54]

Respiratory Tract.

Although cough is common in brucellosis, respiratory tract lesions are documented in <5% of cases in most series. Only rarely are brucellae seen on stains or grown from expectorated sputum; therefore, a definitive diagnosis depends on isolating the organism from other sites. The spectrum of pulmonary involvement is wide, including pneumonia, pulmonary nodules, and empyema.[55,56]

Hematologic System.

Mild hematologic abnormalities such as anemia, lymphocytosis, and thrombocytopenia can occur in the course of brucellosis, but they generally resolve promptly with antimicrobial therapy. Rarely, complications, such as pancytopenia, thrombocytopenic purpura, and mucosal bleeding can be life-threatening.[57,58]

Laboratory Findings and Diagnosis

A definitive diagnosis is made by recovering *Brucella* organisms from blood, bone marrow, or other tissues. In the absence of bacteriologic confirmation, a presumptive diagnosis is made by demonstrating high or rising titers of specific antibodies in serum. Various serologic methods are available, but the serum agglutination test is the standard.[59] This test measures the total quantity of *Brucella* antibodies directed against smooth lipopolysaccharide with sufficient cross-reaction to detect the major nomen species. It does not, however, differentiate among immunoglobulin classes; for this, the serum agglutination test is run in the presence of 2-mercaptoethanol, which inhibits the agglutinating activity of immunoglobulin M (IgM) without affecting IgG agglutination.[60] To detect antibodies to *B. canis*, a rough lipopolysaccharide antigen is required.[61] The immune response in brucellosis is characterized by an initial rise in IgM antibodies followed by a gradual switch to IgG synthesis. With treatment, both antibody isotypes decline over time with <5% remaining elevated after 2 years; persistent elevation of IgG antibodies presages a relapse or chronic infection.[60,62]

More recently, serologic tests based on enzyme immunoassay technology have found wide use for the detection of IgM and IgG antibodies to *Brucella* spp.[63] However, commercial enzyme immunoassays have been shown to have poor specificity for *Brucella* compared with agglutination tests, and the Centers for Disease Control and Prevention recommends that any positive result on enzyme immunoassay should be confirmed by an agglutination method.[64,65]

Among rapid point-of-care tests for *Brucella* antibodies, an immunochromatographic IgM-IgG lateral flow assay offers simplicity (a drop of blood), ease of interpretation (formation of a band), and convenience (does not require refrigeration).[66]

Polymerase chain reaction technology is advancing rapidly, but acceptance of molecular diagnostics has been slow.[67] Various primers and techniques are available to detect *Brucella* by genus, species, or biovar.[68] By using polymerase chain reaction, *Brucella* DNA has been detected in the blood of patients after the completion of apparently successful treatment, an observation that needs to be explored fully.[69]

Treatment and Outcome

Several drugs have activity in vitro against *Brucella* spp., but clinical efficacy is not always predicted by in vitro results. General recommendations for the treatment of brucellosis are listed in Table 161.4. The tetracyclines (especially doxycycline) remain the most useful drugs, and when combined with an aminoglycoside they are associated with the fewest relapses. In an attempt to find a completely oral treatment regimen, in 1986 the World Health Organization recommended the combination of doxycycline *and* rifampin administered for 45 days. Although this combination has been used successfully for uncomplicated brucellosis, it is less effective than doxycycline in combination with an aminoglycoside for focal complications such as spondylitis.[39,70] One meta-analysis (based on the results of 2 trials) recommended doxycycline *and* aminoglycoside *and* rifampin, with the aminoglycoside given for the first 7 to 14 days and with doxycycline *and* rifampin given for 6 to 8 weeks.[71]

TABLE 161.4

Recommended Therapies for Human Brucellosis

Condition	Antimicrobial Agents	Adult Dose	Route	Duration of Therapy
ADULTS				
Acute brucellosis or relapse	Doxycycline	200 mg/day	PO	6 wk
	Plus			
	Streptomycin	1 g/day	IM	2 wk
	Or			
	Gentamicin	3–5 mg/kg/day	IM or IV	1 wk
Alternative	Doxycycline	200 mg/day	PO	6 wk
	Plus			
	Rifampin	15–20 mg/kg per day	PO	6 wk
CHILDREN				
>8 years	Same as adults			
<8 years	TMP-SMX[a]	2 DS tablets/day	PO	45 days
	Plus			
	Rifampin	15–20 mg/kg/day	PO	45 days
COMPLICATIONS[b]				
Meningitis	Doxycycline	200 mg/day	PO	4–6 mo

	Plus			
	Rifampin;	900 mg/day	PO	4–6 mo
	Or			
	TMP-SMX[a]	2 DS tablets/day	PO	4–6 mo
	Plus			
	Rifampin	900 mg/day	PO	4–6 mo
Endocarditis	Same as meningitis[c]			
Pregnancy	Rifampin	900 mg/day	PO	6 wk

[a] TMP-SMX standard formulation (80 mg trimethoprim/400 mg sulfamethoxazole) is given as 4 standard tablets or 2 double-strength tablets per day.

[b] See text.

[c] Valve replacement surgery may be necessary.

DS, double-strength; IM, intramuscular; IV, intravenous; PO, by mouth; TMP-SMX, trimethoprim-sulfamethoxazole.

In the search for drugs that can be used without adverse effects in children <8 years of age, trimethoprim-sulfamethoxazole (80 mg trimethoprim/400 mg sulfamethoxazole) was initially considered satisfactory. However, subsequent controlled trials indicated a high rate of relapse when the drug was used alone. Consequently, trimethoprim-sulfamethoxazole is used in combination with rifampin for childhood brucellosis.[72,73] In addition, many fluoroquinolone antibiotics have activity in vitro against *Brucella* and are most effective when used in combination with other drugs such as rifampin.[74,75]

Osteoarticular complications rarely present special problems in treatment; however, spondylitis can require a longer course of antibiotics depending on the clinical evolution.[76] Surgical intervention may be necessary to drain pyogenic joint effusions, rare paraspinal abscesses, or chronic hepatic or splenic abscesses.

A prolonged course of therapy also may be necessary for treatment of neurobrucellosis. Multiple anti-*Brucella* agents usually are required. Although extended-spectrum cephalosporins have proved disappointing when used as monotherapy for brucellosis, some experts recommend the addition of ceftriaxone to doxycycline *in addition to* rifampin therapy despite the lack of objective evidence of benefit.[46,77,78] The use of corticosteroids as an adjunct to antibiotics may be of benefit in children with confirmed *Brucella* meningitis.[79]

Brucella endocarditis is a complication with no recognized optimal therapy; however, combinations of drugs including bactericidal agents (e.g., trimethoprim-sulfamethoxazole) have been used with success. Given the difficulties in establishing the diagnosis, surgical valve replacement often is required in addition to prolonged antibiotic therapy.

Brucellosis occurring during pregnancy can result in spontaneous abortion and in congenital and neonatal infections; however, early recognition and treatment can result in a successful outcome for mother and child.[80,81] Rifampin (900 mg once daily for 6 weeks) is the treatment of choice, whereas trimethoprim-sulfamethoxazole is an alternative after 13 weeks of gestation.

Prevention

Currently, the only licensed vaccines are veterinary products for use in domestic and semidomestic animals. Live, attenuated vaccine strains of *B. abortus* (strain 19) and *B. melitensis* (strain Rev-1) provide protection in animals but are too virulent for use in humans.[82] Another live, attenuated rough strain of *B. abortus* (strain RB51) largely has replaced strain 19 for use in cattle in the US, and although it is less virulent for humans, it is licensed only for animal use. No vaccines exist for *B. suis*, *B. canis*, or other nomen species. Children can be protected from foodborne brucellosis by ensuring pasteurization of milk and cheese and by thorough cooking of meat from susceptible animals.

Key Points

Diagnosis and Management of Brucellosis

Microbiology

- For epidemiologic purposes, pathogenic species are classified according to their preferred natural hosts: *Brucella abortus* (cattle), *B. melitensis* (goats, sheep), *B. suis* (swine), *B. canis* (dogs).

Epidemiology

- It occurs worldwide but is locally enzootic in the Mediterranean basin, Arabian peninsula, Indian subcontinent, Eastern Europe, and parts of Mexico and Central and South America.

- In the United States, the incidence of human infection is <0.5 per 100,000 population.

- Most infections result from ingestion of raw milk products from infected animals including fresh goat milk cheese.

Clinical Features

- Onset can be insidious or acute.

- Symptoms are nonspecific including fever, fatigue, and back pain.

- Any organ or system can be involved, but osteoarticular manifestations predominate.

Diagnosis

- Definitive: isolation of *Brucella* spp. from blood, bone marrow, cerebrospinal fluid, or other tissues

- Presumptive: specific antibody titer (generally >1 : 160) by standard tube agglutination test

- Detection of *Brucella* DNA in a clinical specimen by polymerase chain reaction assay

Treatment

- See Table 161.4

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162

Bordetella pertussis (Pertussis) and Other *Bordetella* Species

Sarah S. Long, Kathryn M. Edwards, Jussi Mertsola

Pertussis is an acute respiratory tract infection that was well described in the 1500s and endemic in Europe by the 1600s; its current worldwide prevalence is dampened only by continuous use of active immunization. Sydenham first used the term *pertussis* (intense cough) in 1670. Inexorable spasms of coughing and a protracted course characterize pertussis, as attested to by names given to the disease in many languages: *tos ferina* and *tosse canina* (dog's bark) in Spanish and Italian, respectively, *chincough* (gasping cough) in old English, *coqueluche* (cock's crow) in French, and the "cough of 100 days" in Chinese.

Etiology

Bordetella pertussis is the sole cause of epidemic pertussis and the usual cause of sporadic pertussis. *B. parapertussis* contributes substantially to total cases of pertussis in Europe and accounted for approximately 5% of isolates of *Bordetella* spp. through the 1990s in the United States.[1] Using species-discriminating polymerase chain reaction (PCR) testing of respiratory samples from suspect pertussis cases from 9 states in 2008–2010,[2] and from Wisconsin in 2011–2012,[3] 14% and 6% of *Bordetella*-positive tests revealed *B. parapertussis*, respectively, sometimes found dually with *B. pertussis. B. parapertussis* typically causes milder pertussis.[4] *B. pertussis* is exclusively a human pathogen. *B. parapertussis* also has been found in lambs, but ovine and human strains are genetically distinct. *Bordetella bronchiseptica* is a common animal pathogen causing kennel cough in dogs and cats, snuffles in rabbits, and atrophic rhinitis in swine. Occasionally, *B. bronchiseptica* infects humans causing upper and lower respiratory tract infections, but endocarditis, septicemia, posttraumatic and postsurgical meningitis, and peritonitis have been reported. Typically, cases of *B. bronchiseptica* occur in immunocompromised people, patients with cystic fibrosis, or young children with exposure to infected farm animals or pets.[5–7] *Bordetella hinzii* has been recovered from blood of patients with immunodeficiency states without a respiratory illness and from sputum of patients with cystic fibrosis.[7] *Bordetella holmesii* and *B. holmesii*–like organisms have been associated with cases of bronchitis and suspected pertussis as well as septicemia, endocarditis, pericarditis, and meningitis,[8] predominantly in asplenic or immunosuppressed individuals and possibly acquired from dogs.[9–11] Of 22 patients with *B. holmesii* identified from sterile body sites in patients from 6 US states in 2010–2011, their median age was 17.1 years (youngest 1.5 years), and 64% had anatomic or functional asplenia (79% due to sickle cell disease).[12] These cases occurred during pertussis outbreaks, in which *B. holmesii* also was isolated in >10% of suspect pertussis cases. Patients with invasive *B. holmesii* did not have pertussis-like illnesses. *Bordetella petrii* caused pyogenic arthritis and osteomyelitis of the elbow in an adult after a dirt bike accident in Hawaii.[13]

Protracted coughing can be caused by *Mycoplasma* spp., adenoviruses, parainfluenza or influenza viruses, enteroviruses, and respiratory syncytial virus and *Chlamydophila pneumoniae*.[14,15]

Epidemiology

Worldwide, there are an estimated 15 million cases of pertussis annually. The World Health Organization estimates that in 2008 there were 89,000 deaths due to pertussis. During the prevaccine era in the US, pertussis was the leading cause of death from communicable disease among children younger than 14 years. During 1934–1943, an average of 200,752 cases and 4034 pertussis-related deaths were reported annually.[16] Widespread use of diphtheria and tetanus toxoid and whole cell pertussis vaccine (DTP) in the US since the late 1940s was responsible for a >100-fold decline in incidence from 110 (1922–1948) to 0.5 cases per 100,000 (1981). The 1010 cases and 7 deaths reported in 1976 in the US are the all-time lowest recorded. Incidence increased in developed countries in the 1980s related to low DTP coverage,[17,18] use of less potent vaccines,[19] or interruption of universal DTP vaccination.[20] Despite high DTP immunization rates in children younger than 7 years in the US, pertussis was increasingly recognized in 3- to 5-year cycles in the mid-1980s to 1990s, and disproportionately in adolescents and adults. By 2004, the 25,827 cases reported in the US represented the highest number since 1959 (Fig. 162.1),[21] and 34% of all US-reported cases occurred in adolescents 11 to 18 years of age (incidence ~30 per 100,000).[22] In two prospective studies using comprehensive laboratory methods, the annual incidences of prolonged undifferentiated cough illness due to pertussis in adolescents and adults were estimated to be 370 and 450 per 100,000 population, respectively.[23,24] In other studies, 12% to 32% of adolescents and young adults with prolonged cough illnesses were confirmed to have pertussis.[25,26] With development and licensure of tetanus toxoid, reduced-content diphtheria toxoid and acellular pertussis antigen vaccine (Tdap), Tdap was recommended universally in 2006 in the US at 11 to 12 years of age.[27] With 53% of US adolescents 13–18 years vaccinated by 2009, there was an approximately 50% reduction in pertussis in the age group of 11 to 19 years.[28]

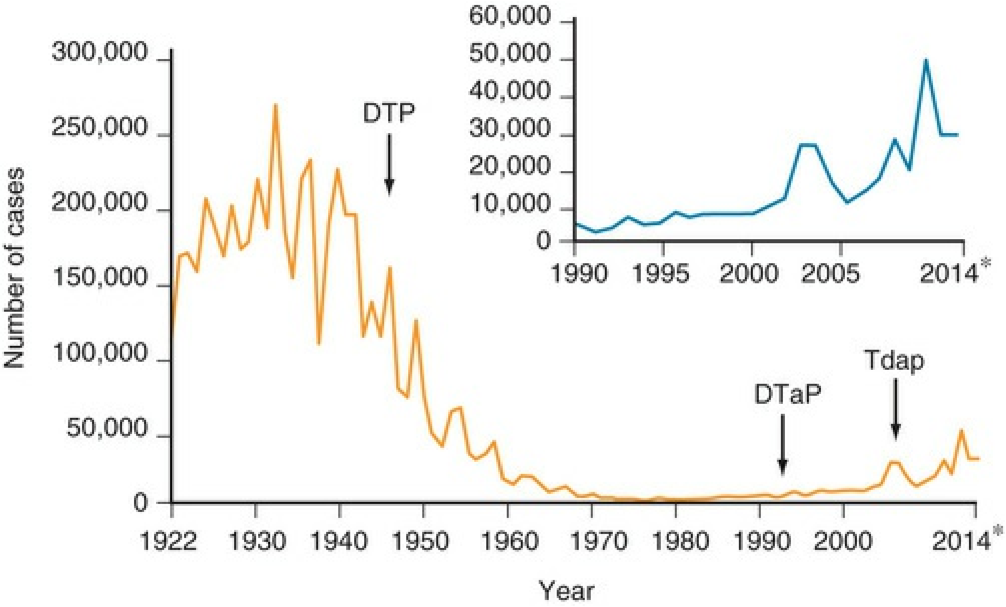


FIGURE 162.1 Annual reported cases of pertussis in the United States, 1922 through 2014. *Case numbers for 2014 are provisional. (Data from National Notifiable Diseases Surveillance System [NNDSS] for 1950 to 2014, and from passive reports to the Public Health Service for 1922 to 1949. Redrawn from Centers for Disease Control and Prevention data.)

During the prevaccine era in the US, the peak incidence of pertussis was in children 1 to 5 years of age, with infants younger than 1 year and individuals older than 10 years each accounting for less than 15% of cases.[19,20] Subclinical "boosting" reinfections and higher transplacental protection likely were responsible. However, by 1993, 44% of pertussis cases reported to the Centers for Disease Control and Prevention (CDC) occurred in children younger than 1 year. The incidence, morbidity and mortality in young infants has continued to rise (Fig. 162.2).[29] Currently, infants younger than 2 months have the highest age-related risk for pertussis (incidence ~200 per 100,000). From 2001 through 2010, 189 US deaths occurred among 27,995 reported infant cases, a case fatality ratio of 6.8/1000 infant cases.[21]

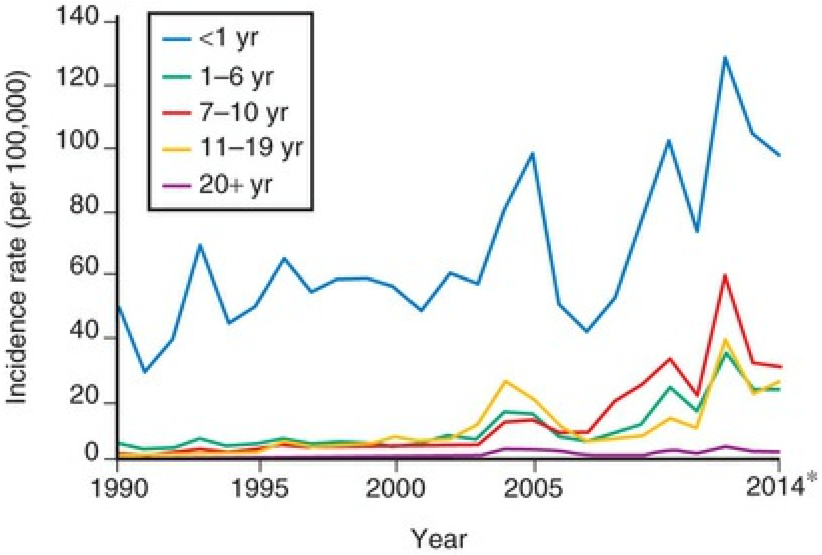


FIGURE 162.2 Age-related incidence of pertussis per 100,000 in the United States, 1990 through 2014. *Case numbers for 2014 are provisional. (Data from National Notifiable Diseases Surveillance System. Redrawn from Centers for Disease Control and Prevention data.)

Because of local and systemic reactogenicity of DTP, acellular antigen vaccines (DTaP) were developed and tested clinically, and licensed DTaP replaced DTP in the US for the reinforcing fourth and fifth doses in 1992, and for all doses in 1997. The epidemiology of pertussis has changed again in the US since 2006, likely related to use of acellular pertussis vaccines. Despite six doses of pertussis vaccine recommended between 2 months of age and adolescence, pertussis is the least well-controlled vaccine-preventable disease for which recommendations have been highly implemented.[30] More than 27,000 cases were reported in 2010, 2012, and 2014. Between 2011 and 2012, every state in the US except California reported an increase in pertussis, and the case count of 48,277 nationally in 2012 was higher than had been reported since the early 1950s.[21] After the high case rates in infants, an unusually large burden of disease was observed in age groups 7 to 10 years in 2010,[31] 13 to 14 years in 2012,[32] and 14 to 16 years in 2014, and most often in children who were fully immunized, solely with acellular pertussis vaccines.[33]

Role of Waning Immunity in Current Epidemiology

The increased incidence of pertussis in the past several decades likely is related to several overlapping factors (Fig. 162.3). Considerable evidence suggests that lack of durable protection after acellular pertussis vaccines—both DTaP and Tdap—is responsible predominantly.[34–36] Vaccine effectiveness immediately after 5 doses of DTaP is 75% to 89%[35,36] but declines each year thereafter, associated with rapidly falling antibody levels to pertussis toxin,[34–37] with odds of acquiring pertussis increasing 42% per year in one study.[37] After the last receipt of DTaP at 4 to 6 years of age, vaccine effectiveness in 8- to 12-year-olds has been estimated to be only 24%,[38] and one modeling study, assuming 85% initial protection following DTaP, estimated that only 10% of children would be protected 8.5 years later.[39] In Australia, where the fourth dose of DTaP at 18 months was discontinued in 2003, 3-year-olds currently have a greater risk for pertussis than infants.[21] Similarly, there is rapid waning of protection after Tdap, with vaccine effectiveness within the first year of >70% but only 34% 2 to 4 years after vaccination.[39,40] The abrupt return to susceptibility of immunized children aged 7 to 10 years since the mid-2000s, then of 13- to 14-year-olds in 2012 and 14- to 16-year-olds in 2014, in the US likely is due to the aging cohort of children who received acellular pertussis vaccines exclusively.[31–33,37,38,40] Observational data from Australia and the US suggest that even a distant priming effect from a single dose of DTP appears to increase durability of subsequent boosting effects of acellular vaccines[31,38,41] (Fig. 162.4).

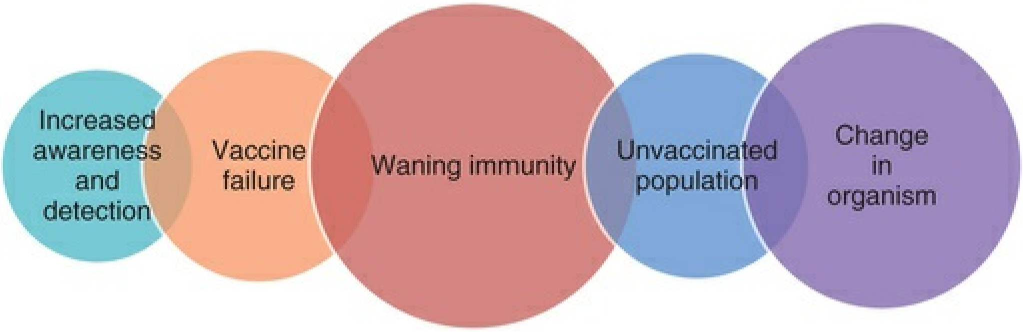


FIGURE 162.3 Schematic showing multiple factors contributing to increased incidence of pertussis.

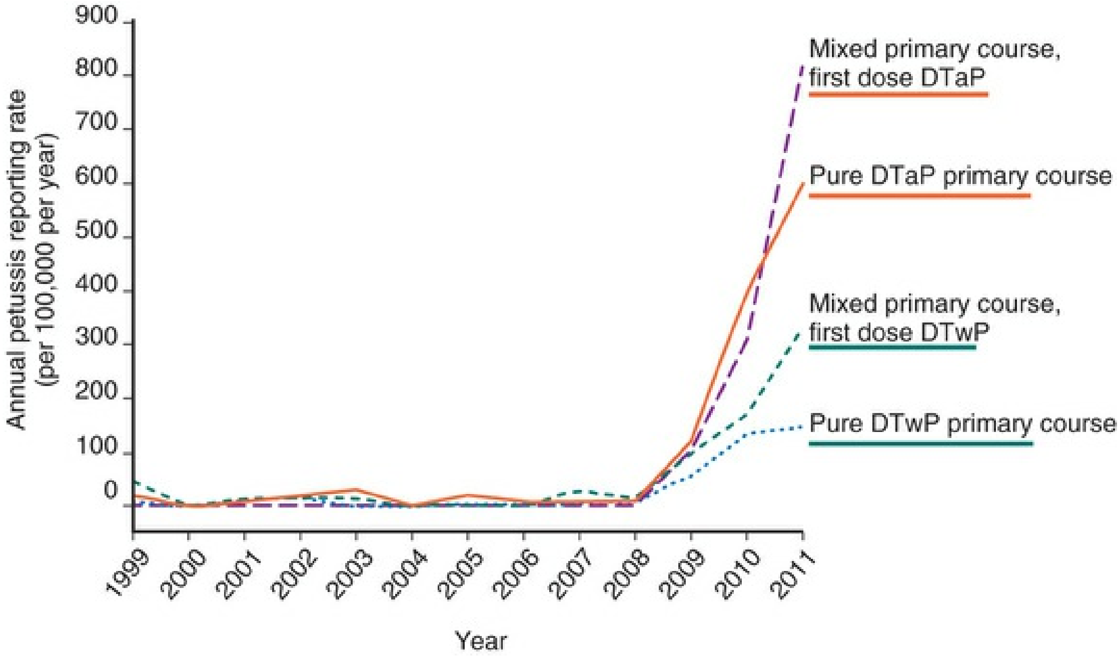
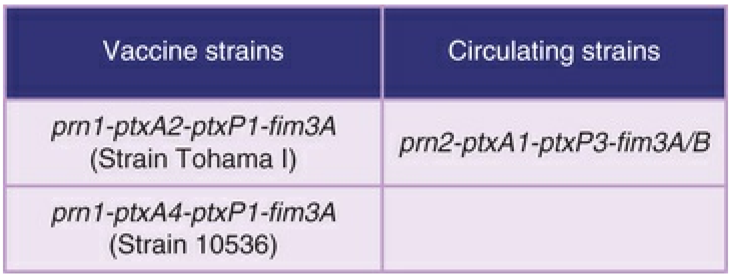


FIGURE 162.4 Reported cases of pertussis in outbreak years 2009−2011 in Queensland, Australia by receipt of primary course of DTP (whole cell pertussis vaccine) versus DTaP (acellular vaccine) for children born in 1998. Because of staggered introduction of DTaP, infants born in 1998 could have received all DTP, DTaP, or mixed vaccine primary series. (Modified from Sheridan SL, Ware RS, Grimwood K, et al. Number and order of whole cell pertussis vaccines in infancy and disease protection (letter to the editor). JAMA 2012;308:454−456.)

The predominant immunologic response to acellular pertussis vaccines is a type 2 helper T-lymphocyte (Th2) (antibody) response with diminished type 1 helper T-lymphocyte (Th1) (cellular) response, in contrast to a mixed Th1 and Th2 response after whole cell vaccines. Antibody titers to pertussis antigens, particularly pertussis toxin, wane quickly.[42–45] Animal studies suggest that Th17 cells are likely important in protection against pertussis, and studies in humans to assess such responses are needed.[46]

Role of Organism Adaptation in Current Epidemiology

The limited overall effect of pertussis vaccination on *B. pertussis* circulation permits pathogen adaptation, under selective pressure. Acellular vaccines licensed in the US were developed to mirror alleles of presumed virulence factors of predominant *B. pertussis* strains of previous decades as well as those included in DTPs. Divergence of circulating *B. pertussis* strains from vaccine strains began during the DTP era, with genetic adaptations occurring through allelic changes of surface proteins, including pertussis toxin, pertactin, and fimbriae, and regulation of toxin expression through the toxin promotor gene (*ptxP*).[47–53] Allelic changes were not associated with increased notification of pertussis in the US, but in the Netherlands increased cases were temporally associated with upregulation of pertussis toxin through the *ptxP3* promotor mutation.[44] Pertussis toxin is a complex bacterial toxin with an A protomer responsible for biologic activities and a B pentamer directing binding and entry of the A subunit into the cytoplasm. The *ptxA* subunit has the most potent toxic activity and is the most immunologic of the group, but allelic variants exist. Most vaccines in the US and Europe were derived from strains expressing *ptxA2* and *ptxA4*; most current circulating strains globally have the *ptxA1* allele.[45,48,50] Multiple alleles are described for *ptxP*; *ptxP1*, *ptxP2,* and *ptxP3* are predominant. The *ptxP3* largely has replaced the *ptxP1* allele worldwide and is associated with 1.6 times greater pertussis toxin production compared with *ptxP1* strains.[45,48] The *ptxP3* allele also may confer selective advantage of enhanced transmission by delaying an effective immune response and by evading complement-associated opsonophagocytosis through an autotransporter protein Vag8.[54] The two currently licensed US vaccines are *ptx1* derived (Fig. 162.5).[47–49] There has been adaptation of *B. pertussis* globally, in countries using whole cell vaccine exclusively and where acellular vaccines are used, although vaccine and circulating strains vary by country. *B. pertussis* circulating in European countries using acellular vaccines during 1998–2012 and in the US show molecular typing profiles of vaccine-divergent alleles *prn2-ptxA1-ptxP3* almost exclusively.[47,48,50,51] Fimbrial alleles show more variability, with *fim3* predominating and, in the US, transitioning from *fim3A* to *fim3B* only in the past decade during exclusive use of acellular vaccines.[48]



Vaccine strains	Circulating strains
prn1-ptxA2-ptxP1-fim3A (Strain Tohama I)	*prn2-ptxA1-ptxP3-fim3A/B*
prn1-ptxA4-ptxP1-fim3A (Strain 10536)	

FIGURE 162.5 Schematic showing allelic composition of US vaccine-derived and circulating strains of *Bordetella pertussis*. (Data from Schmidtke AJ, Boney KO, Martin SW, et al. Population diversity among *Bordetella pertussis* isolates, United States, 1935–2009. Emerg Infect Dis 2012;18:1248–1255.)

Since the exclusive use of acellular pertussis vaccines beginning in the late 1990s, pertactin-deficient strains have emerged, representing a small proportion of *B. pertussis* isolates in many countries, such as Japan, France, Finland, Australia, and Canada, and a large proportion of the strains in the US.[52,55–58] Pertactin-deficient strains increased rapidly in Australia from 2008–2012.[57] Pertactin-deficient *B. pertussis* strains were first reported in the US among 11 of 12 isolates from infants cases in Philadelphia in 2011 and 2012[59]; the earliest pertactin-deficient isolate in the Philadelphia collection (2007 onward) was from 2008.[60] A CDC study of isolates since 1935 showed first archived isolate of a pertactin-deficient strain from 1994, with reappearance only in 2010 and rapid increase since.[47] Pertactin-deficient *B. pertussis* strains have become predominant in outbreaks, such as in Washington State in 2012,[49] and in sporadic cases. In a retrospective study of 753 pertussis cases with isolates studied from 8 states in the US during 2011 and 2013, patients who had received at least one dose of pertussis vaccine had an adjusted odds ratio (aOR) of 2.2 (95% confidence interval [CI], 1.3–4) for having a pertactin-deficient isolate, suggesting possible selective advantage.[30] Unlike other allelic changes, pertactin-deficient strains have emerged only in countries using acellular vaccines and demonstrate multiple different gene mutations, suggesting that a number of recombinant events have occurred independently rather than that a single clone has expanded globally.[43,48,51,57]

Although pertactin is a *B. pertussis* virulence factor,[61] deficient organisms retain virulence in the mouse[45,61,62] and primate models.[63] In a mouse model, Hegerle found that pertactin-deficient isolates resist antibody-mediated cytotoxicity in vitro[45,64] and that acellular pertussis immunization provides a "fitness" advantage of sustained infection.[45] Infants with pertussis due to pertactin-deficient and pertactin-sufficient *B. pertussis* strains manifest similar illnesses.[49,60,65]

Pathogen and Pathophysiology

Pathogen

Bordetella are tiny, gram-negative coccobacilli that grow aerobically on starch-blood agar or completely synthetic media with nicotinamide supplemented for growth, amino acids for energy, and charcoal or cyclodextrin resin to absorb fatty acids and other inhibitory substances. All *Bordetella* spp. share a high degree of DNA homology among virulence genes. However, only *B. pertussis* expresses pertussis toxin.

Speciation of *Bordetella* can be based on specifically targeted PCR testing, or phenotypic characterization and direct fluorescent antibody (DFA) testing of isolates using specific antisera. Pulsed-field gel electrophoresis (PFGE) of chromosomal DNA, multilocus variable number tandem repeat analysis, multiantigen sequence typing, and whole genome sequencing of *B. pertussis* isolates from epidemiologic studies show dominance of certain strains and relatedness of epidemiologically linked cases, but diversity of strains over time and location with little evidence of geographic clustering.[54] Whole genome sequencing is the gold standard for strain differentiation but is expensive. New methodology using a single nucleotide primer extension to detect polymorphisms offers a simpler highly discriminatory alternative.[66]

Bordetella organisms elaborate a number of biologically active substances; their role in pathogenesis and protection has been reviewed by Hewlett.[67] (Table 162.1). *B. pertussis* is acquired by inhalation and has strict tropism (related to several surface molecules) for ciliated epithelium of the respiratory tract, to which infection is limited. Pertussis toxin appears to play several major roles in the pathogenesis of pertussis: facilitating attachment of *B. pertussis* to ciliated respiratory cells, contributing to cell toxicity, enhancing respiratory tract colonization by inhibiting neutrophil and monocyte migration, and delaying the induction of specific immune responses.[67] Tracheal cytotoxin, adenylate cyclase and pertactin also contribute to ciliostasis and epithelial damage.

TABLE 162.1

Components of *Bordetella pertussis* and Possible Roles in Pathogenesis and Immunity

Component	Cellular Site	Biologic Activity
Pertussis toxin (PT)	Extracellular	Facilitates attachment to ciliated respiratory epithelium
		Produces cell cytotoxicity
		Elicits lymphocytosis
		Delays induction of specific immunity
		Stimulates production of interleukin-4 and immunoglobulin E
		Inhibits migration of neutrophils and monocytes
		Causes cytopathic effect in Chinese hamster ovary cell
Filamentous hemagglutinin (FHA)	Cell surface	Facilitates attachment to ciliary respiratory epithelium
		Agglutinates erythrocytes in vivo
Pertactin (PRN)	Cell outer membrane	Facilitates attachment to ciliary respiratory epithelium
		Resists clearance by neutrophils
Agglutinogen (FIM)	Cell surface Fimbriae associated	Facilitates attachment to ciliary respiratory epithelium
Adenylate cyclase (AC) toxin	Extracytoplasmic	Inhibits phagocytic function of leukocytes
		Induces apoptosis in macrophages; catalyzes supraphysiologic production of cyclic adenosine monophosphate
		Causes hemolysis in vitro
Tracheal cytotoxin (TCT)	Extracellular	Elicits interleukin-1 and nitric oxide synthase
	Peptidoglycan-like	Causes ciliary stasis, cytopathic effect on tracheal mucosa in mice, necrosis of mouse tracheal explants

Pertussis toxin causes lymphocytosis in experimental animals by preventing their migration from the circulating blood pool. The injection of pertussis toxin intravenously into adult humans, however, was reported not to be associated with lymphocytosis.[68] Severe or fatal pertussis has been correlated with degree of lymphocytosis, a likely manifestation of pertussis toxin activity. There is no evidence of neurotoxic effects of *B. pertussis*. Although a hydrogen peroxide–detoxified pertussis toxin vaccine protects children in the short term against severe disease,[69] multiple lines of evidence support a central but not singular role for pertussis toxin.

Transmission

Pertussis is highly contagious, with attack rates of >90% in susceptible individuals exposed to aerosol droplets at close range. Chronic carriage by humans is not documented. After intense exposure, as in households and childcare facilities, the rate of subclinical infection or mild disease exceeds 50% in fully DTP immunized or naturally immune individuals.[70,71] When carefully sought, a symptomatic source case can be found for most infants.[70,71] Vaccination reduces transmissibility of *B. pertussis* even when vaccinated individuals develop symptomatic infection.[72] Although acellular pertussis vaccines protect against disease in the baboon model, they fail to prevent infection and transmission.[46]

Immunity

Neither disease, DTP, DTaP, or Tdap provides complete or lifelong immunity against reinfection or disease. There is no generally accepted laboratory correlate of protective immunity. Taken together, data suggest that high levels of antibody against pertussis toxin (PT), combinations of antibodies against multiple *B. pertussis* antigens, and cell-mediated immunity all have a role in immunity, but their precise roles remain to be determined.[69,73] Cell-mediated immune response induced by infection and whole cell vaccines can last beyond 5 years, and antibodies elicited undoubtedly include responses to many unknown antigens.[73] Acellular pertussis vaccines induce little cellular response, and antibodies elicited are against a narrow range of antigens. Antibodies begin to wane immediately after DTaP or Tdap but not immediately after whole cell vaccines or natural pertussis.[74]

Clinical Manifestations

Cadence of Symptoms

Pertussis is a prolonged disease, classically divided into catarrhal, paroxysmal, and convalescent stages, each lasting 2 weeks, but cough can persist for several months (Fig. 162.6). These stages provide useful markers for progression of disease and timing of potential complications; the duration of each, however, depends on the patient's age and immunization status, classic pertussis being seen only in unimmunized toddlers and children. In infants younger than 3 months, the catarrhal phase usually lasts a few days or is unrecognized, the paroxysmal phase is protracted, and convalescence with episodes of spasmodic cough occur throughout the first year of life. In immunized children, all stages of pertussis are foreshortened. Adults with pertussis have indistinct stages.

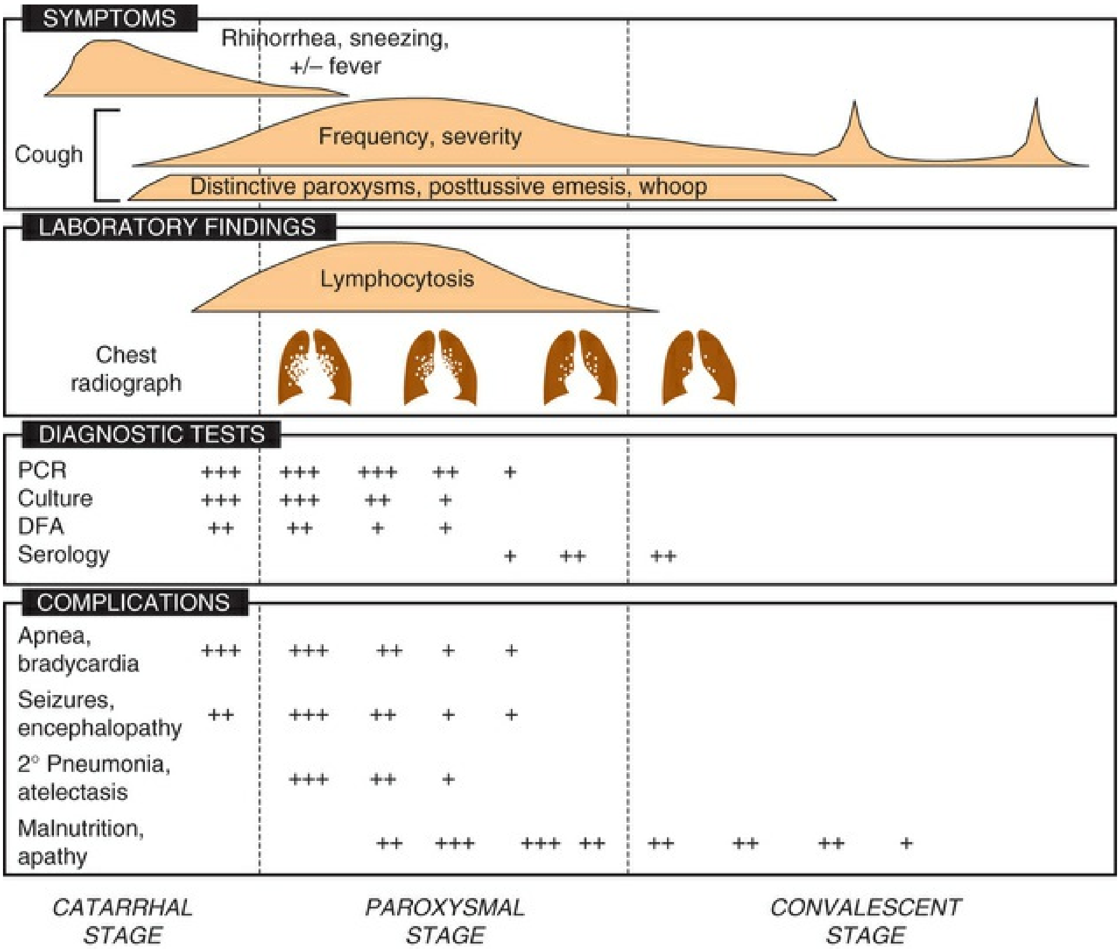

SYMPTOMS
Rhinorrhea, sneezing, +/– fever
Cough
Frequency, severity
Distinctive paroxysms, posttussive emesis, whoop
LABORATORY FINDINGS
Lymphocytosis
Chest radiograph
DIAGNOSTIC TESTS
PCR +++ +++ +++ ++ +
Culture +++ +++ ++ +
DFA ++ ++ + +
Serology + ++ ++
COMPLICATIONS
Apnea, bradycardia +++ +++ ++ + +
Seizures, encephalopathy ++ +++ ++ + +
2° Pneumonia, atelectasis +++ ++ +
Malnutrition, apathy ++ +++ +++ ++ ++ ++ ++ +
CATARRHAL STAGE
PAROXYSMAL STAGE
CONVALESCENT STAGE

FIGURE 162.6 Manifestations and complications of pertussis. Duration of stages depends on patient's age and immunization status. +++, Most likely to be positive or to occur; ++, can be positive or can occur; +, occasionally positive or occurring; *DFA,* direct fluorescent antibody; *PCR,* polymerase chain reaction.

The incubation period usually is 7 to 10 (range, 5–21) days. Nondistinctive catarrhal symptoms are followed by coughing, which begins as a dry, intermittent, irritative hack and evolves into paroxysms that are the hallmark of pertussis. With insignificant provocation, the well-appearing playful toddler suddenly expresses an anxious aura and commences a machine-gun burst of uninterrupted coughs (tongue protruding, eyes bulging and watering, face reddened) on a single breath, followed by a loud whoop as inspired air traverses the still partially closed glottis. The episode may end with expulsion of a thick mucus plug. Infants younger than 3 months have heralding episodic gagging, gasping, choking, cyanosis, apnea, or a brief resolved unexplained event (BRUE) rather than paroxysmal cough; whoop generally is absent.[29,75–77] Adults describe a sudden feeling of strangulating suffocation as spasms of coughing begin. Posttussive emesis is common in pertussis at all ages and is a clue to the diagnosis in adolescents and adults.

Paroxysms progress in number and severity over days to a week and remain at peak for days to weeks, sometimes with multiple episodes hourly, before fading into convalescence when the number, severity, and duration of episodes diminish. In young infants, whoop may become louder and more classic in convalescence. Paroxysmal coughing can recur with subsequent viral respiratory illnesses over several months and is not due to reactivation of *B. pertussis*.

The physical examination between paroxysms is normal; this finding supports the diagnosis of pertussis. Fever and signs of lower respiratory tract disease generally are not seen. Conjunctival hemorrhages and petechiae on the upper body are common.

Spectrum of Symptoms

Pertussis should be suspected in any individual who has a pure or predominant complaint of paroxysmal cough that is escalating in the second week of illness. In prospective studies, nonspecific, protracted cough illness is the most frequent manifestation in adolescents and adults. In four care series in adolescents,[78–81] the following symptoms were reported: cough for >28 days, 41% to 76%; paroxysms, 82% to 100%; vomiting, 45% to 71%; whoop, 30% to 67%; cyanosis, 6% to 15%; and “apnea,” 19% to 86%. Findings with predictive value are listed in Table 162.2. Clinical case definitions for pertussis have been developed by the Council for State and Territorial Epidemiologists. A sporadic clinical case, defined as a cough illness lasting 14 or more days with at least one associated symptom of paroxysms, whoop, or posttussive vomiting with no other apparent cause, had a sensitivity of 81% and specificity of 58% using culture confirmation as the gold standard.[82] In Canadian adolescents and adults, prolonged duration of violent cough (median, 43 days) and posttussive vomiting distinguished those with pertussis from others.[83]

TABLE 162.2

Predictive Factors for Pertussis

Positive Factors	Negative Factors
Coughing contact	Fever
Incomplete immunization	Diarrhea
Years since immunization ≥3	Exanthem
Pure or predominant cough	Enanthem
Paroxysmal cough	Tachypnea
Well between paroxysms	Wheezes
Whoop	Rales
Posttussive vomiting	Lymphadenopathy
Apnea, bradycardia (infant)	Neutrophilia
Choking, gasping spells	Neutropenia
Petechiae above the clavicles	Lymphocytosis (atypical cells)
Lymphocytosis (normal cells)	

Sudden infant or unexpected death syndrome (SIDS/SUDS) is one manifestation of pertussis in young infants. Postmortem evidence of *B. pertussis* was found in 3 of 12 infants with SIDS studied in Syracuse, New York.[84] During pertussis outbreaks in the United Kingdom in the 1980s and Norway and Sweden in 1997, 3% to 5% of SIDS was associated with *B. pertussis* infection.[85,86] In a prospective study of 254 German infants with SIDS, respiratory tract specimen was positive by PCR testing for *B. pertussis* in 5% of cases.[87]

Differential Diagnosis

Other respiratory pathogens can cause pertussis-like symptoms. Adenovirus infections frequently can be distinguished from pertussis on the basis of associated features, such as fever, sore throat, and conjunctivitis, not commonly seen in pertussis. In one study, median days of cough was 18 for adenovirus infection compared with 35 days for pertussis. However, almost 50% of children with adenovirus had paroxysmal cough for >21 days, and 53% had posttussive vomiting; fewer (20%) had whooping.[14] *Mycoplasma* infection is difficult to distinguish from pertussis clinically[14,15]; if present, a history of fever, headache, and systemic symptoms at the onset of disease, and rales on auscultation, differentiate *Mycoplasma. Chlamydia trachomatis* in young infants can be distinguished by the typical staccato cough (breath with every cough), purulent conjunctivitis, tachypnea, and rales. Respiratory syncytial virus (RSV) is distinguished by wheezing and seasonal presentation. In >2000 children hospitalized with bronchiolitis whose nasal secretions were tested by PCR for *B. pertussis*, 0.2% were positive.[88] Unless the infant with pertussis has developed a secondary bacterial pneumonia, or has a dual infection with a virus, such as RSV, the physical findings between paroxysms are normal. A young infant who is being evaluated because of a history of paroxysmal cough and who appears completely well should have a paroxysm witnessed by medical personnel before disposition is planned.

Laboratory Findings and Diagnosis

Lymphocytosis (15,000 to 100,000 cells/mm^3) is characteristic in late catarrhal and paroxysmal stages of pertussis, being present in at least 75% of unvaccinated children.[89] Lymphocytes are both T and B cells and are normal small cells rather than the large atypical lymphocytes classically found in some viral infections. Lymphocytosis is uncommon in previously immunized people with pertussis.[90] Absolute increase in neutrophils or shift to immature forms suggests a secondary bacterial infection. Eosinophilia is not a feature of pertussis, even in young infants.

Lymphocytosis and thrombocytosis in young infants parallel the severity of illness. Lymphocytic leukemoid reaction or extreme thrombocytosis in infants is associated with fatal outcome.[91,92] Hypoglycemia (a PT effect) is reported only occasionally. The chest radiograph is abnormal in most hospitalized infants, showing perihilar infiltrate or interstitial edema (sometimes with a butterfly appearance) and variable atelectasis. Parenchymal consolidation suggests secondary bacterial infection. Pneumothorax, pneumomediastinum, and soft tissue air can be seen occasionally.

Culture usually is positive during the catarrhal stage and escalating paroxysmal stage in unimmunized children when proper specimen collection, transport, and methodology are used.[82] Culture is positive in <10% of immunized individuals at recognition of pertussis, those who have received macrolides or trimethoprim-sulfamethoxazole, and those who come to attention late in illness. Optimal specimen for culture is obtained by deep nasopharyngeal aspiration, nasal wash, or placing a flexible (calcium alginate– or Dacron-tipped) swab in the posterior nasopharynx for 30 seconds. Throat swab provides an inadequate specimen.[93] For short delay before inoculation, 1% casamino acid liquid medium is an acceptable transport media. Otherwise, Stainer-Scholte broth with cyclodextrin or Regan-Lowe semisolid transport medium should be used, allowing adequate recovery of organisms for up to 4 days.[82] Regan-Lowe charcoal agar with 10% horse blood and 5 to 40 μg/mL cephalexin, and Stainer-Scholte medium with cyclodextrin resins, are the preferred media for culture. Cultures are incubated at 35°C to 37°C in a humid environment (with or without 5% carbon dioxide) and should be examined with a stereoscopic microscope daily for 7 days to detect tiny glistening colonies. Culture detection is optimized by DFA testing of colonies using specific antibody for *B. pertussis* to *B. parapertussis.*

PCR testing usually is more sensitive than culture[94,95] and is the predominant method of laboratory confirmation of pertussis. In one study, only 20% of PCR-positive samples were positive by culture; culture positivity correlated with bacterial load as measured by quantitative PCR testing.[96] In adolescents and adults with pertussis, however, culture or PCR test results are positive in <10% of cases that are confirmed by serology, and especially when tests are performed >2 weeks after onset of cough.[94,95] PCR assays targeting only a single insertion sequence (IS)*481* identify *B. pertussis*, *B. holmesii,* and some strains of *B. bronchiseptica* but cannot differentiate among species and do not detect *B. parapertussis*. A *multitarget* reverse transcriptase PCR assay can detect and differentiate *B. pertussis* (including pertactin-deficient strains), *B. parapertussis,* and *B. holmesii* by targeting IS*481* and IS*1001* in *B. parapertussis* (pIS*1001*) and the IS*1001*-like element in *B. holmesii* (hIS*1001*). To confirm *B. pertussis*, a monoplex PCR for *ptxS1,* the first subunit of pertussis toxin, is used.[97]

Serologic tests using enzyme immunoassay (EIA) for detection of antibodies to components of *B. pertussis* are the most sensitive tests for diagnosis in distantly immunized individuals and those evaluated after the second week of cough, particularly adolescents and adults.[93] Serologic testing for anti-PT immunoglobulin G (IgG) antibody is the most reliable. An anti-PT IgG level of >94 EU/mL in a standardized assay has been proposed as a diagnostic cutoff point (with sensitivity of 80% and specificity of 93% using culture as the gold standard).[98] Resting anti-PT IgG level of >50 EU/mL ≥3 years after immunization is highly unusual and is supportive of pertussis disease when the clinical illness is suggestive. Antibody to PT is specific for *B. pertussis,* whereas other antibodies (e.g., pertactin and hemagglutinin) can cross-react with organisms such as *B. parapertussis, B. bronchiseptica,* and nontypable *Haemophilus influenzae.*[79,94,98] Tests for IgA and IgM antibodies to pertussis toxin lack sensitivity, specificity, and reproducibility.

Complications and Outcome

The principal complications of pertussis are apnea, secondary bacterial infections (e.g., pneumonia and otitis media), respiratory failure (from apnea, pneumonia, or pulmonary hypertension), and physical sequelae of forceful coughing. Reported rates of complications of pertussis are affected by age, immunization status, and completeness of diagnosis and reporting. Infants younger than 6 months have high morbidity and mortality, especially those younger than 3 months,[22,28,75,76] with the highest reported rates of pertussis-associated hospitalization (>90%), pneumonia (13%–25%), seizures (2%–4%), encephalopathy (0.4%–1%), and death (0.5% –1%).[22,28,99] Of 23 infants with fatal pertussis in the US reported during 1992 and 1993, 96% had pneumonia, 17% had seizures, and 13% had encephalopathy.[28] Infants intubated because of respiratory failure have a worse prognosis than those intubated because of apnea.[92]

Pertussis-related deaths are increasingly clustered among very young infants and represented 64% of deaths reported to the CDC during the 1980s and 82% in the 1990s; by 2000, all 17 pertussis-related deaths were in infants younger than 4 months.[75,100,101] With striking similarity, 94% to 100% of pertussis-related deaths reported from the United Kingdom,[101] Canada,[92] and Australia[102] since the mid-2000s were in children younger than 2 months. Other risk factors associated with death include Hispanic ethnicity in the US, multiple births, premature birth, and household source of infection.[75,91,92,100,101] Pulmonary hypertension is an increasingly recognized complication of pertussis in young infants leading to dilation of the right ventricle and respiratory failure, and usually is fatal.[76,103] Pulmonary hypertension can be misdiagnosed as pneumonia. Infants with pulmonary hypertension generally are younger than 4 weeks and frequently were born before 39 weeks of gestation. Pathologic findings identified in the respiratory tract of fatal cases, and the known physiologic responses of the infant's lung to hypoxia, suggest that *B. pertussis* triggers a cascade of events that includes pulmonary vasoconstriction, luminal aggregation of abundant leukocytes in pulmonary vessels, and compromised pulmonary blood flow; hypoxemia is exacerbated, and refractory pulmonary hypertension ensues.[98] Progression toward respiratory failure in young infants should prompt urgent evaluation, including an echocardiogram for pulmonary hypertension. High median white blood cell count was associated with pulmonary hypertension and nonsurvival in a collaborative intensive care unit study of 127 patients.[104] Only 1% to 7% of older children and adolescents are hospitalized, and complications occur in only 5%, with pneumonia and otitis media most common.[78–81,83] Individuals with underlying cardiac, pulmonary, muscular, or neurologic disorders have high risk for severe disease.

Fever, tachypnea, and respiratory distress between paroxysms, as well as absolute neutrophilia, are clues to secondary bacterial pneumonia. Expected pathogens include *Staphylococcus aureus, Streptococcus pneumoniae,* and bacteria of oropharyngeal flora.

Increased intrathoracic and intra-abdominal pressure during coughing can result in conjunctival and scleral hemorrhages (Fig. 162.7), petechiae on the upper body, epistaxis, central nervous system and retinal hemorrhages, pneumothorax and subcutaneous emphysema, umbilical and inguinal hernias, rib fracture, and urinary incontinence. Laceration of the lingual frenulum is not uncommon.

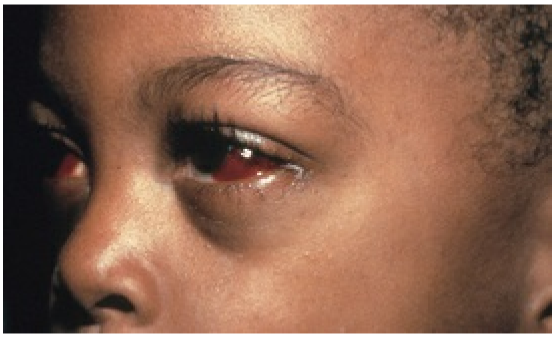


FIGURE 162.7 Bilateral scleral hemorrhages and periorbital edema in a young boy with pertussis.

Central nervous system abnormalities are almost always the result of hypoxemia or hemorrhage associated with coughing or apnea in young infants. Apnea or bradycardia or both can occur from apparent vagal stimulation or laryngospasm just before a coughing episode, from obstruction during an episode, or from hypoxemia after an episode. Occasionally, apnea or bradycardia occurs without coughing. Seizures usually are the result of hypoxemia, but hyponatremia from inappropriate secretion of antidiuretic hormone in the setting of pneumonia also should be considered.

Management

Assessment and Supportive Care

The goals of management are to limit the number of paroxysms, to observe the severity of cough and provide assistance when necessary, and to maximize nutrition, rest, and recovery. Infants younger than 3 months are admitted to the hospital almost without exception, as are many infants between 3 and 6 months of age unless witnessed paroxysms are not severe.

The specific, limited goals of hospitalization are to (1) assess progression of disease and likelihood of life-threatening events, particularly the development of pulmonary hypertension; (2) prevent or treat complications; and (3) educate parents about the natural history of the disease and the care that will be needed at home. For most infants older than 2 months without complications, goals are accomplished within a 48- to 72-hour hospitalization. Continuous electronic monitoring is performed, with alarm settings so that each paroxysm is witnessed by healthcare personnel. A detailed cough record is constructed to quantify episodes, to interpret risks and trajectory of the clinical course, and to assess safety and timing of discharge (Table 162.3). Infants whose paroxysms repeatedly lead to life-threatening events require intubation, paralysis, and ventilation. Subsequent management is challenging and should anticipate interventions because of airway obstruction, bradycardia, or cardiopulmonary complications.

TABLE 162.3

Assessment of Severity of Paroxysms During Pertussis

Clinical Assessments	Expected	Worrisome
Duration of paroxysm	<45 sec	>60 sec
Demeanor during paroxysm	Anxious, unconsolable, nondistractable; rigid; eyes bulging; tearing	Limp
Character of cough	Loud, forceful uninterrupted bursts until all air expelled	Gagging/choking/gasping > coughing
Color change	Red	Blue
Tachycardia	Resolves <30 sec after end of paroxysm	Persists
Bradycardia (<60 in infant <3 mo)	Resolves at end of paroxysm without stimulation	Persists, requires stimulation
Oxygen desaturation	Resolves <30 sec after end of paroxysm	Persists
Mucus plug	Self-expectorated	Obstructive, requires suctioning
Self-rescue breath	Immediate, large volume	Apnea or feeble attempt
Whoop	Strong	None
Posttussive state	Exhausted	Unresponsive

Mist by tent is useful for some infants with thick tenacious secretions and irritable airways. The benefit of a quiet, low-lit, undisturbed, and comforting environment cannot be overestimated or forfeited by the desire to monitor and intervene. Feeding children with pertussis is challenging. The risk for precipitating cough by nipple feeding does not warrant the use of nasoenteral or parenteral alimentation in most infants. However, large-volume feedings should be avoided.

Therapeutic Agents

Antimicrobial Agents

In vitro, *B. pertussis* is susceptible to erythromycin, newer macrolides, fluorquinolones, third-generation cephalosporins, and meropenem.[105] Ampicillin, rifampin, and trimethoprim-sulfamethoxazole are modestly active, but first- and second-generation cephalosporins are not. Rare isolates of erythromycin-resistant *B. pertussis* have been identified in children who had prolonged symptoms despite erythromycin therapy.[106–108] A few macrolide-resistant *B. pertussis* strains were found in China in 2012.[109] Recent strains, including pertactin-producing and pertactin-deficient isolates, have retained macrolide susceptibility.[110] In vitro, *B. parapertussis* is less susceptible to all agents except macrolides. *B. bronchiseptica* is most susceptible to antipseudomonal penicillins, aminoglycosides, fluoroquinolones, and tetracycline (with antagonism demonstrated between the last two drugs); erythromycin resistance is not uncommon.[5] *B. holmesii* is most susceptible to fluoroquinolones and carbapenems.[11] Use of agents with proven activity in vitro does not necessarily correlate with observable clinical benefit.

An antimicrobial agent always should be given when pertussis is suspected or confirmed in infants within 6 weeks after cough onset and in persons older than 1 year within 21 days after cough onset[111,112] (Table 162.4). There is excess risk for infantile hypertrophic pyloric stenosis (IHPS) associated with macrolide use in infants 42 days or younger,[113,114] which is highest at 14 days or younger in term infants and with erythromycin (aOR, 13.3; 95% CI, 6.8–25.9) compared with azithromycin (aOR, 8.3; 95% CI, 2.6–26).[115] In one reported experience of azithromycin use in 58 neonates, IHPS did not occur.[116] In another report, 2 of 3 triplets born at 32 weeks of gestation who were given azithromycin for 5 days at 7 weeks of age developed IHPS at 12 and 13 weeks of age, respectively.[117] Despite risk, neonates always should be given azithromycin for pertussis disease or exposure, with vigilance for IHPS.

TABLE 162.4

Recommended Antimicrobial Agents for Treatment and Postexposure Prophylaxis of Pertussis

	Age Group			
Agents	**<1 mo**	**1–5 mo**	**≥6 mo and Children**	**Adults**
PRIMARY AGENTS				

Azithromycin	Recommended agent 10 mg/kg, once daily × 5 days	10 mg/kg once daily × 5 days	10 mg/kg (max 500 mg) once on day 1; then 5 mg/kg (max 250 mg) once on days 2–5	500 mg once on day 1; then 250 mg once on days 2–5
Clarithromycin	Not recommended	15 mg/kg/day divided twice daily × 7 days	15 mg/kg/day (max 1 g/day) divided twice daily × 7 days	1 g/day divided twice daily × 7 days
Erythromycin	Not preferred	40–50 mg/kg/day divided 4 times daily × 14 days	40–50 mg/kg/day (max 2 g/day) divided 4 times daily × 14 days	2 g/day divided 4 times daily × 14 days
ALTERNATE AGENT				
TMP-SMX	Contraindicated	Contraindicated at age <2 months. At ≥2 months, TMP 8 mg/kg/day + SMX 40 mg/kg/day divided twice daily × 14 days	TMP 8 mg/kg/day + SMX 40 mg/kg/day (max TMP 320 mg/day) divided twice daily × 14 days	TMP 320 mg/day + SMX 1600 mg/day divided twice daily × 14 days

TMP-SMX, trimethoprim-sulfamethoxazole.

Modified from Tiwari T, Murphy TV, Moran J, et al. National Immunization Program. Centers for Disease Control and Prevention. Recommended antimicrobial agents for treatment and postexposure prophylaxis of pertussis. MMWR Recomm Rep 2005;54(RR-14):1–13.

Clinical efficacy of antimicrobial therapy is most evident in young infants and others who come to medical attention quickly[118]; otherwise the purpose of therapy is to eliminate contagiousness. Infants younger than 6 months (and other incompletely immunized children) have higher density and duration of colonization. Azithromycin dose is 10 mg/kg per day for 5 days.[111,112] In clinical studies, macrolides are superior to amoxicillin for eradication of *B. pertussis.* In those 2 months and older who are intolerant of macrolides, trimethroprim-sulfamethoxazole is the alternative agent.[111] Alternative therapies are not well studied. Patients with pertussis and pneumonia should be treated with one or more antibiotics in addition to a macrolide, such as ampicillin-sulbactam or cefotaxime (with additional consideration of methicillin-resistant *S. aureus* where prevalent).

Other Therapies

No randomized, blinded clinical trial of sufficient size has been performed to evaluate corticosteroids for pertussis, and their use is not warranted. A handful of small clinical trials suggest a modest reduction in symptoms with the use of aerosolized albuterol. However, one small study showed no effect,[119] and its use can trigger paroxysms of coughing. Hyperimmune serum (raised by immunization of adults with acellular pertussis vaccines) given intramuscularly reduced whooping significantly in infants treated in the first week of disease in a double-blind study in Sweden.[120] Pertussis immune globulin intravenous (P-IGIV), prepared from plasma of adults immunized with pertussis toxoid was evaluated in a prospective, placebo-controlled clinical trial in the US and Canada but was terminated prematurely because of expiration of P-IGIV lots. No benefit was noted in these studies,[121] and P-IGIV product is no longer available. Commercial IGIV is not indicated.

Several reports show that infants with pertussis who fail mechanical ventilation and are managed using extracorporeal membrane oxygenation have extremely high death rates (>80% in infants <6 weeks of age).[76,92,99] Several single cases and small series of young infants with extreme leukocytosis, respiratory insufficiency despite ventilator therapy, and pulmonary hypertension have been reported to survive after rapid leukoreduction by leukopheresis or exchange transfusion.[122–127] In a collaborative intensive care unit study of 127 cases, however, there was no apparent survival benefit of leukoreduction.[104] In a single case report, an infant with severe pulmonary hypertension treated with sildenafil and inhaled nitric oxide survived.[128]

Control Measures

Isolation

In addition to standard precautions, droplet precautions are recommended for at least 5 days after initiation of macrolide therapy. For infants who require longer hospitalization, isolation frequently is continued to avoid any possibility of spread, to reduce noxious stimuli, and to avoid the protective concern of other families.

Care of Household and Other Close Contacts

Postexposure prophylaxis (PEP) with a macrolide agent should be given promptly to all household contacts, other close contacts (such as those in childcare facilities), and closely exposed healthcare personnel (HCP) regardless of age, history of immunization, or symptoms.[111,112,129,130] PEP may not be necessary for all out-of-home exposures in adolescents. Choice of agent, dosage, and duration for PEP is the same as for treatment (see Table 162.4). Repeatedly, studies have shown high transmission rates and efficacy of macrolide chemoprophylaxis for maternal-neonatal exposure,[131] as well as in households[132,133] when prophylaxis is given before onset of a secondary case,[134] in residential facilities, and hospitals.[135] Visitation of coughing family members to the hospital must be controlled until they have taken a macrolide for 5 days. For outbreaks in childcare facilities and schools, all children, students, and staff who have cough illness compatible with pertussis should be excluded for 5 days after beginning therapy or for 21 days after onset of cough if not treated.

Immunization status of close contacts also should be considered. Children younger than 7 years who have received fewer than four doses of DTaP should be given further dose(s) to complete the recommended series; children who received a third dose 6 months or more before exposure, or a fourth dose 3 years or more before exposure, should be given a booster DTaP dose. Adolescents 10 years of age or older and adults who have not received Tdap, and DTaP-underimmunized children 7 through 10 years of age, should be given a single dose of Tdap.

Several outbreaks of pertussis have been described in a variety of inpatient and ambulatory healthcare settings, affecting HCP, with subsequent transmission from HCP to patients.[77,135–137] Guidance for management should be sought from infection preventionists and health departments.[138] Postexposure strategies are resource intensive and include contact identification, PEP, surveillance, and furlough of coughing HCP.[77,139] Pre-exposure vaccination and cough precautions should be stressed. Brisk response (by 2 weeks) of adults to Tdap also supports a role for vaccination of Tdap unvaccinated individuals in outbreak control.[140]

Even when *B. pertussis* infection is documented, the individual should complete the recommended immunization series: DTaP for those younger than 7 years, and Tdap for adolescents and adults.[22,27]

Prevention

Current Vaccines and Strategies

DTaP is given universally in the US in a 5-dose series in children 6 weeks through 6 years of age. In 2006, a single dose of Tdap was recommended universally for 11- or 12-year-olds, with catch-up for older adolescents[22,27]; for all HCP; for all adults younger than 65 years to replace one decennial dose of Td, and for wound prophylaxis. In 2010–2011, a single dose of Tdap was recommended for children 7 through 10 years of age who previously were not fully immunized with DTaP.[141,142] The CDC expanded Tdap recommendation to all adults 19 years and older (i.e., including >64 years of age) who previously did not receive Tdap. In 2011, one Tdap product (Boostrix) was FDA licensed for use in people 65 years of age and older; Boostrix is preferred over Adacel when available (see Chapter 6 and reference 29).

DTaP and Tdap vaccines available in the US are composed of varying amounts of PT, FHA, and pertactin; Sanofi Pasteur vaccines also contain *fim2* and *fim3*. Vaccine effectiveness for DTaP ranges from 75% to 90% immediately after the primary series.[143,144] Short-term effectiveness of adolescent Tdap observed in field studies is approximately 70%.[145] There is rapid waning of antibody and protection after the DTaP series and Tdap in people who never received DTP (see earlier sections “Epidemiology” and “Immunity”). Because of short duration of Tdap protection, routine boosting is not cost effective or recommended currently for the general population or for HCP. Active research facilitated by the primate model of pertussis seeks better understanding of infection and immunologic responses as well as optimized antigens, adjuvants, and toxoiding methods for novel vaccines.[146]

Many studies have shown that household contacts (currently siblings more commonly than parents) are sources for pertussis in neonates.[70,71,147,148] The American Academy of Pediatrics (AAP), the CDC, the American College of Obstetricians and Gynecologists, and many European countries recommend a cocoon strategy (immunization of women, families, and other contacts) to increase protection of young infants. In 2012, the CDC and the UK Department of Health recommended universal administration of Tdap during *each* pregnancy, optimally between 27 and 36 weeks (US, Tdap) or 28 and 38 weeks (UK, DTaP/IPV) of gestation, as the cornerstone of reduction of pertussis-related deaths.[149,150]

Uptake in the UK has been much higher than in the US. Safety data in an observational study of >20,000 vaccinated pregnant women in the UK[151] were reassuring, as was a small prospective placebo-controlled trial in the US.[152] Observational and case-control studies in England and Wales demonstrate approximately 90% effectiveness of vaccination during pregnancy in preventing pertussis in infants younger than 2 months.[153,154]

If not given during pregnancy, Tdap should be administered immediately postpartum to women who never received Tdap. Catch-up immunization should be performed for underimmunized siblings (DTaP for those <7 years of age and Tdap for those 7−10 years of age) and for previously Tdap unimmunized adolescents and adults of all ages.[141,142]

Pertussis vaccination in the neonatal period using DTaP has been studied and is associated with interference with responses to other infant vaccines.[155–158] Tdap immunization during pregnancy has not appeared to adversely affect subsequent infant or toddler responses to DTaP and other vaccines, although additional studies are in progress.[152,159] The standard DTaP series can be begun at 6 weeks of age. Studies from the CDC and Sweden showed protective effect against pertussis death in infants 42 days or older who had received 1 dose or more of vaccine (aOR, 0.28; 95% CI, 0.11−0.74).[160,161]

Rates of local and systemic adverse reactions after vaccination are lower following DTaP than DTP vaccine, as are hypotonic-hyporesponsive episodes and febrile seizures. In a study of 14 children who developed encephalopathy with seizure onset within 72 hours of whole cell DTP vaccination, 11 patients were found to have genetic epileptic encephalopathy due to mutations in a neuronal sodium channel gene, *SCN1A*,[162] with vaccine-associated fever likely unmasking the condition. Rates of local reactions are increased with the fourth and fifth doses of DTaP. Tdap vaccination does not appear to be more reactive after all-acellular primary series.[163] Tdap should be administered when indicated regardless of interval since receipt of diphtheria- or tetanus-toxoid containing vaccines.[141–142] Local and systemic events following administration of Tdap are similar to those following Td,[163–165] with no increase with a short interval (1 month to 2 years) between receipt of DT- or Td-containing vaccines and Tdap.[166–170]

Extensive limb swelling (ELS) of the injected extremity has been reported in 2% to 6% of children receiving the fourth or fifth doses of DTaP.[171–174] ELS is self-limited; the pathogenesis is not fully understood, and the reaction is not consistently related to diphtheria or tetanus content, pertussis proteins, or aluminum content of vaccines.[175,176] ELS has been reported almost as frequently after Td and hepatitis B vaccinations in adolescents.[168] In a study of 20 children who had ELS after dose 4 of DTaP, 5 children had ELS and 7 had swelling >5 cm after dose 5, but all events were well tolerated and resolved rapidly.[177] ELS is not a contraindication to further recommended doses of DTaP, or to Tdap.[22,27,112]

New Vaccine Approaches

The increase in pertussis disease in developed countries such as Europe and the US suggests the need for new vaccine approaches. The findings from baboon studies also suggest that immunization with acellular vaccine does not prevent infection and transmission. New vaccine strategies being evaluated include development of live, attenuated *B. pertussis* vaccine[178]; reintroducing less reactogenic whole cell vaccines for at least the first vaccine dose; use of adjuvants in combination with the acellular vaccines; and addition of other pertussis antigens to vaccines used currently.[179] Human challenge models, like the baboon model, could be employed to evaluate transmission as well. Finally, better understanding of the role of Th17 in immunity to pertussis should be pursued.[179]

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Campylobacter jejuni and *Campylobacter coli*

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Campylobacter spp. are one of the most common causes of culture-proven bacterial gastroenteritis in developed and developing countries.[1–3] In the United States, the annual incidence is about 13.5 per 100,000 persons and is highest in children younger than 5 years.[4–6] Although diarrhea is the most common clinical manifestation, *Campylobacter* infections can be asymptomatic or can result in bacteremia, localized extraintestinal findings, or inflammatory and autoimmune manifestations such as reactive arthritis and Guillain-Barré syndrome (GBS).

Description of the Pathogen

The genus *Campylobacter* (from the Greek and Latin meaning "curved rod") comprises gram-negative, mostly microaerophilic bacteria. These curved, spiral, or S-shaped bacteria are 0.2 to 0.5 µm wide and 1 to 5 µm long and possess rapid and darting motility in corkscrew fashion by means of a single, unsheathed flagellum in one (monotrichous) or both (amphitrichous) ends. Campylobacters are commensal organisms living in the gastrointestinal tract of birds and mammals. *Campylobacter* genomes are relatively small (approximately 1600–1900 genes). The complete genomes of several *Campylobacter* spp. have been sequenced and include a variety of genes involved in biosynthesis and modification of carbohydrate surface structures that may be involved in antigenic variation and molecular mimicry.[7–10]

As of 2014, the genus *Campylobacter* included 26 species, two provisional species, and nine subspecies.[4,11] About one half of these are known human pathogens, although human illness is mostly due to *C. jejuni* and *C. coli* and less frequently to *C. upsaliensis, C. lari,* and *C. fetus* (Table 163.1; see also Chapter 164). *C. jejuni* is reported in about 90% of diarrheal illnesses caused by *Campylobacter*.[4] *C. coli* is not common in the United States but may cause up to 25% of *Campylobacter*-related illness in certain regions.[1] In addition, *C. jejuni* can lead to autoimmune manifestations such as GBS.[1] *C. jejuni* and *C. coli* have similar epidemiology and clinical features, and belong to the same cluster phylogenetically.

TABLE 163.1

Taxonomy, Clinical Syndromes, and Common Sources of *Campylobacteria* That Are Pathogenic to Humans

Organism	Associated Illness	Reservoir
CAMPYLOBACTER SPECIES		
C. jejuni subsp. *jejuni*	Diarrhea, bacteremia, meningitis, Guillain-Barré syndrome, reactive arthritis	Poultry, cattle, dog, cat, sheep, monkey
C. jejuni subsp. *doylei*	Diarrhea, bacteremia	Pig
C. coli	Diarrhea, bacteremia, meningitis	Pig, poultry
C. upsaliensis	Diarrhea, bacteremia	Dog, cat
C. lari	Diarrhea, bacteremia	Wild birds, poultry, dogs, cats
C. fetus subsp. *fetus*	Bacteremia, endocarditis, abscess, meningitis	Cattle, sheep, reptiles
C. hyointestinalis	Diarrhea	Pig, cattle, hamster
C. concisus	Periodontal diseases, diarrhea, abscesses	Humans, domestic pets
C. sputorum subsp. *sputorum*	Abscesses, diarrhea	Cattle, pigs
C. curvus	Alveolar abscess, diarrhea	Human oral cavity
C. rectus	Periodontitis, abscesses	Human oral cavity

Epidemiology

Enteric *Campylobacter* infections are common worldwide. *C. jejuni* is the most common species of *Campylobacter* isolated from patients with diarrhea in both developed and developing countries.[1,3,12,13] In developed countries, illness occurs across all age groups but predominates in infants and young children and young adults.[1,2,14] *Campylobacter* can cause outbreaks.[1,2,6] *C. jejuni* rate doubles in the summertime, which might be explained by poultry contamination during the hotter months of the year and increased consumption of more barbecued and undercooked poultry.[15] In the US, *Campylobacter* is estimated to cause about 845,000 illnesses, 8500 hospitalizations, and 76 deaths annually.[16] Outbreaks of *Campylobacter* occur typically in the setting of contaminated poultry products, dairy, or water exposure.[1,16] Preliminary data from the Foodborne Diseases Active Surveillance Network (FoodNet) showed that *Campylobacter* infection rates increased by 13% in 2014 (13.5 per 100,000) compared with 2006–2008.[6] In comparison, rates of Shiga toxin−producing *Escherichia coli* O157 and *Yersinia* decreased, and *Listeria* and *Salmonella* exhibited no change.[6] *Campylobacter* fluctuates with *Salmonella* as the most common bacterial cause of foodborne illness in the US and was second to *Salmonella* in 2014.[6] *Campylobacter* also was the leading cause of travel-associated diarrhea in the US during 2004–2009, accounting for 42% (3445/8270) of cases, followed by *Salmonella* (32%) and *Shigella* (13%).[17]

In resource-limited settings, *Campylobacter* is detected year-round and is the most common bacteria isolated from infants with diarrhea due to continuous exposure to contaminated water and food.[13] Seasonality is usually less pronounced or absent, asymptomatic infections are common, and diarrhea typically occurs in children but not adults.[3] However, epidemiologic data are lacking in these settings owing to poor surveillance and insensitive methods of detection.[3] A multinational population-based surveillance study of more than 9000 children younger than 60 months with moderate to severe diarrhea (and controls) in resource-limited settings detected *C. jejuni* as a significant pathogen in children younger than 1 year in Bangladesh and Pakistan and in children 2 to 5 years of age in Pakistan and India.[18] *Campylobacter* was not associated with significant burden of diarrhea in the African countries in this study (Mali, Kenya, The Gambia, and Mozambique).[18] Additional data are needed to better understand the burden of *Campylobacter* in resource-limited settings.

Enteric *Campylobacter* infection has several well-defined modes of transmission. The most important is the ingestion of contaminated food such as undercooked poultry and meat and unpasteurized milk.[2,6,19–21] Ingestion of contaminated water and direct contact with animals, including pets and animals on farms and in slaughterhouses, has also been documented.[21–24] Person-to-person transmission is rare but does occur in childcare centers and in families,[25,26] as does perinatal transmission through contact with a contaminated birth canal[27] and through sexual contact among men who have sex with men.[28–30]

Pathogenesis

In susceptible individuals, as few as 360 colony-forming units are required to induce diarrhea.[31] Although *C. jejuni* is killed by hydrochloric acid at pH 2.3, it can survive in milk or water for several weeks.[32] The mechanisms by which *C. jejuni* induces disease are not well understood, but the process involves bacterial virulence and colonization factors involved in surviving passage through the stomach and small intestine, and subsequent colonization and growth in the distal ileum and colon.[32–34] Several proposed mechanisms of virulence and survival are listed in Table 163.2.

TABLE 163.2

Proposed *Campylobacter* Virulence and Survival Factors

Virulence/Survival Factor	Target/Effect
Flagella/chemotaxis	Navigation to favorable colonization sites (e.g., mucus-filled crypts of chick ceca) Facilitate invasion of host cell
Adherence	Binds to fibronectin on gastrointestinal epithelial cells Induces internalization of organisms
Cytolethal distending toxin	Blocks host cell progression to mitosis Causes cell death
Lipo-oligosaccharide	Facilitates colonization Enhances immune evasion Affects molecular mimicry resulting in immune-mediated manifestations such as Guillain-Barré syndrome
Iron uptake	Enhances survival and colonization in poultry
Multidrug efflux pump	Permits drug, bile, and heavy metal resistance

Stress response	Causes downregulation of cellular responses that favor growth in times of limited amino acid availability Increases amino acid synthesis that enhances survival Has high frequency of intragenomic recombination leading to ability to survive in unfavorable conditions Expresses antioxidants to resist host immune response Enters a viable but nonculturable state in response to reduced pH or during starvation

Three general stages during *Campylobacter* infection have been postulated to lead to different clinical syndromes: (1) colonization and adherence to the epithelium of the distal ileum and colon may result in noninflammatory diarrhea through unknown mechanisms; (2) invasion and proliferation within the intestinal epithelium causes cell damage and an inflammatory response clinically manifest as dysentery with fecal leukocytes; and (3) translocation across the intestinal epithelium with spread to mesenteric lymph nodes causes mesenteric adenitis, and also causes spread to extraintestinal sites (e.g., bacteremia, meningitis).[1,32,35]

Immunity

Immunity to *C. jejuni* develops after one or more infections.[36–39] Children living in endemic areas have a progressive decrease in the illness-to-infection ratio with increasing age.[40] Cohort studies also demonstrate that *Campylobacter* diarrhea occurring in young children protects against subsequent reinfections; however, no protection occurs after asymptomatic infection.[40] Serum antibodies to specific antigens of *Campylobacter* increase after natural infection.[36,38,41] Experimental challenge studies in volunteers show that rechallenge with the same strain of *C. jejuni* is associated with protection at 1–2 months after the initial challenge and partial protection at 1 year after the initial challenge, resulting in milder illness.[39,42] Immunocompromised patients can develop prolonged, severe, and recurrent *C. jejuni* infections and fail to respond to therapy or mount a humoral response.[43–45]

A rapid and intense serum response involving both monomeric and polymeric immunoglobulin A (IgA) occurs in the first week, reaches a peak after the second week, and declines to low levels within 30 days after the onset of symptoms.[46] A local secretory IgA response also occurs after *Campylobacter* enteritis.[46] Patients infected with *C. jejuni* O:19, the serotype most frequently associated with

GBS, had a significantly higher IgA antibody response than did patients infected with other serotypes.[38] Isotype-specific IgG and IgM antibodies peak on days 15 to 21 and decrease to low levels within 3 months after onset of symptoms.[36,38] In persons who are chronically exposed in hyperendemic areas, serum-specific IgA antibodies increase progressively through life.[36] *Campylobacter* antibody levels in populations in developed compared with developing countries are significantly lower.[47] Studies in breastfed Mexican children have demonstrated protection against *Campylobacter* diarrhea conferred by specific secretory IgA antibodies present in human milk.[41,48] Human and mouse experimental infections also suggest that cell-mediated immune responses are important and correlate with protection against *Campylobacter* enteric infections.[39,49]

Clinical Manifestations

Campylobacter infections produce clinical manifestations that are particular to the species involved as well as characteristics of the host, such as age, immunosuppression, and underlying chronic and debilitating illnesses (see Table 163.1). The most common clinical finding is enteritis, of which >90% of cases are caused by *C. jejuni*.[2–4] Bloodstream infections (BSIs), extraintestinal infections, and perinatal infections are rare and are caused by other *Campylobacter* spp.

Enteritis

Campylobacter enteritis in children typically is mild but also can manifest as inflammatory diarrhea.[1,4,40,50] Symptoms usually start 24–72 hours after ingestion, and the peak of symptoms typically lasts 24 to 48 hours.[1]

Substantial differences in the clinical characteristics of diarrhea occur in children in developed and developing countries. Inflammatory diarrhea is more common in developed countries, whereas secretory diarrhea seems to prevail in resource-limited settings and in younger children. Vomiting and dehydration may also occur.[3,4,13,40] In general, episodes are mild and self-limited; 60% to 70% subside within 1 week, 20% to 30% subside in 2 weeks, and

5% to 10% persist for several weeks. Relapses can occur. In one third to one half of patients, the onset of diarrhea is preceded by intense abdominal pain, malaise, myalgia, and headache.[50] Pain generally lasts a week and is periumbilical and cramping and when present can be severe in 20% of patients, sometimes mimicking appendicitis.[51] When laparotomy is performed, mesenteric lymphadenitis or signs of ileocolitis are found. In patients who have undergone proctoscopy or colonoscopy because of a protracted course of illness, 50% show evidence of mucosal edema, congestion, friability, and granularity. The spectrum of histologic changes ranges from minimal edema with acute and chronic inflammatory cells without vascular congestion, to moderate inflammation with cryptitis and crypt abscess formation.[52]

The clinical features of inflammatory diarrhea are indistinguishable from those caused by *Shigella* and are characterized by generalized malaise, fever, abdominal cramps, tenesmus, and bloody stools. Severe cases, which are rare, can occur in adolescents and young adults and can be mistaken for ulcerative colitis, Crohn disease, or pseudomembranous colitis; occasionally, disease progresses to toxic megacolon, massive bleeding, or colonic perforation.[53–55] In neonates, blood streaking of formed stool has been associated with *C. jejuni*.[56,57] Abdominal examination can reveal tenderness to deep palpation, especially in the right lower quadrant. Splenomegaly has been reported rarely.

If specific treatment is not given, fecal shedding of *Campylobacter* persists for a median of 2 to 3 weeks, with a range of 3 days to several months.[40,56,58] Younger children tend to shed the organism for longer periods.[59] Severe, persistent, and recurrent *C. jejuni* infections have been reported in patients with immunodeficiencies, including congenital or acquired hypogammaglobulinemia and AIDS.[40,43–45]

Bloodstream Infection

BSI due to *C. jejuni* is relatively rare and occurs in <1% of children with enteritis and mostly in malnourished children, patients with chronic debilitating illnesses or immunocompromising conditions, and elderly patients.[40,60] *C. jejuni* or *C. coli* organisms account for 60% to 90% of blood isolates, followed by *C. fetus* in 8% to 15%. BSI can be transient and asymptomatic in normal hosts but severe in hosts who are immunosuppressed, with mortality of 10% to 15%.[43,61–63] Most episodes of BSI occur in patients with diarrhea.

Three clinical manifestations of BSI are described: (1) cryptogenic BSI, which occurs as an isolated event that is self-limited or readily responds to antibiotics; (2) secondary BSI associated with focal infections such as meningitis, pneumonia, endocarditis, and thrombophlebitis; and (3) chronic BSI with relapses that can persist for several months (mostly in immunosuppressed patients).

Localized Extraintestinal Infections

A localized infection can be the first manifestation of *C. jejuni* infection or can occur after or simultaneously with BSI. Extraintestinal infections caused by *C. jejuni* include cholecystitis, urinary tract infection, pancreatitis, septic arthritis, and meningitis.[64–69] These manifestations are uncommon and generally occur in patients who are immunosuppressed or at the extremes of age.[70]

Perinatal Infections

Perinatal infections rarely have been associated with *C. jejuni*. Three clinical manifestations of perinatal infection have been described: abortion and stillbirth, premature labor, and neonatal septicemia and meningitis.[68,69,71–73] Symptomatic gastroenteritis and bloody diarrhea attributable to *C. jejuni* are reported in neonates, with the mother (who can be symptomatic or asymptomatic at the time of delivery) usually being the source.[56] In general, perinatal infections caused by *C. jejuni* are less severe than those caused by *C. fetus*.

Immune-Mediated Complications

Immune-mediated complications such as GBS, reactive arthritis (formerly Reiter syndrome), erythema nodosum, and inflammatory bowel disease occur occasionally after *C. jejuni* diarrhea.[67,74–80] *Campylobacter* is the single most common cause of GBS, and annual rates of campylobacteriosis correlate directly with rates of GBS.[81,82] The risk for GBS within 2 months of a symptomatic *Campylobacter* infection is 100-fold that of the general population, and about 30%

to 40% of patients with GBS are infected with *Campylobacter* in the preceding 2 weeks. People 60 years and older are at highest risk for GBS (248 cases per 100,000 *Campylobacter* infections), whereas GBS is rare in children.[83,84] The pathogenesis of *Campylobacter*-induced GBS is thought to be cross-reactivity between antibodies produced against *C. jejuni* lipo-oligosaccharide and human ganglioside (e.g., GM_1) resulting in nerve damage. T-lymphocyte response to lipo-oligosaccharide also is thought to contribute to GBS.[1] Patients with *C. jejuni*–associated GBS are more likely than other patients with GBS to have neurophysiologic features of axonal neuropathy, antibodies to ganglioside GM_1, pure motor GBS, and poor outcome.[74,75,85] Cranial nerve involvement occurs in one third of cases, and recovery is complete in most patients.[85] Miller Fisher syndrome, a polyneuritis variant characterized by ophthalmoplegia, areflexia, ataxia, and high levels of IgG antibodies to ganglioside GQ_{1b}, also has been associated with preceding *Campylobacter* infection.[86–89] A third variant is acute motor axonal neuropathy, or Chinese paralytic syndrome, which is characterized by an explosive onset with rapid progression to tetraplegia and respiratory failure.[90–93] The illness is due to a reversible lesion of the motor nerve terminal or anterior horn cell. Epidemics of acute motor axonal neuropathy have occurred in northern China for >20 years, taking place in the summer and fall in rural areas and involving mainly children.[92]

Reactive arthritis can be associated with *Campylobacter* enteritis as well as with *Salmonella, Shigella,* and *Yersinia* enteritis.[67,78,79] It is relatively more common in young male adults. Arthritis begins 3 to 40 days (mean, 11 days) after the onset of diarrhea, usually is oligoarticular and asymmetric (affecting mainly the knees), is of short duration (range, 1–21 days), and has no sequelae. Arthralgia is reported in up to 20% of infected patients. Synovial fluid is sterile, and fever and leukocytosis are absent, but the sedimentation rate is elevated. The histocompatibility antigen HLA-B27 has been associated with more severe or prolonged illness in some studies.[94]

Some studies also suggest an association between *Campylobacter* infection and postinfectious irritable bowel syndrome, especially in those having diarrhea for >7 days.[95] Other potential host predisposing factors for postinfectious irritable bowel syndrome include younger age, female sex, prior anxiety or depression, and fever and weight loss during the acute enteric illness.[96,97]

Diagnosis

Several methods of *Campylobacter* diagnosis are available clinically. Isolation from stool culture is the gold standard in enteritis. Several methods are available for isolation of campylobacters from stool, food, and environmental samples that take advantage of their innate antibiotic resistance, slender morphology, and tolerance to high temperatures.[98–100] Use of blood or charcoal agar containing selective antibiotics that suppress the growth of the normal human colonic microflora permit growth as nonpigmented colonies that have oxidase activity.[101] Many *Campylobacter* spp., other than *C. jejuni* and *C. coli,* can be susceptible to the selective antibiotics. To circumvent this issue, some have used cellulose membranes filtration enrichment that traps most colonic organisms but allows slender campylobacters to pass through.[102] All species associated with human diseases grow better in a microaerophilic atmosphere containing 5% to 10% oxygen, and 3% to 5% CO_2, and can grow at 37°C. *C. jejuni* and *C. coli* grow best at 42°C, likely an adaptation for inhabitation of the intestine of birds, the natural hosts of thermophilic campylobacters; normal avian body temperature is 38°C to 42°C.

Biochemical techniques then can be used to identify the genus and species. Molecular techniques of matrix-assisted laser desorption ionization−time of flight (MALDI-TOF) spectrophotometry and multiplex polymerase chain reaction (PCR) also can be used to identify *Campylobacter*.[103–105] Multiplex PCR is anticipated to change diagnostics over the next several years. PCR is highly sensitive, detecting *C. jejuni* and *C. coli*, but is not species specific. PCR can detect asymptomatic shedding (the duration of which has not been established in children); results should be interpreted in the context of clinical findings.[105] Sensitivity of rapid enzyme immunoassay antigen testing of stool may approach that of culture, but false-positive results can occur (possibly related to blood) that can misdirect management.[106,107] Isolation of an organism from culture can be characterized further (e.g., subtyping) and is important for public health purposes.[108]

Campylobacteriosis is a nationally notifiable disease through the

Centers for Disease Control and Prevention (CDC) National Notifiable Diseases Surveillance System and should be reported to the appropriate state health department. Although culture is the preferred method of diagnosis, the National Notifiable Diseases Surveillance System recognizes that this method of detection is not consistently used in all clinical laboratories. Information can be found at http://wwwn.cdc.gov/nndss/conditions/campylobacteriosis.

Treatment

Rehydration and correction of electrolyte abnormalities are the mainstay of treatment for enteritis. Need for antibiotic treatment is debated but should be considered for *C. jejuni*–infected patients who have bloody or severe diarrhea, fever, or worsening of symptoms and for immunosuppressed patients. Antimotility agents have been associated with prolongation of symptoms and fatalities and should not be used.[109,110]

Campylobacter spp. often are resistant to penicillin, ampicillin, and cephalosporins. Most strains of *C. jejuni* and *C. coli* are susceptible to erythromycin, azithromycin, gentamicin, carbapenems, and chloramphenicol.[111–114] When antibiotic therapy is indicated for gastroenteritis, erythromycin or azithromycin is the drug of choice.[115,116] Erythromycin shows little propensity to select for plasmid-mediated resistance, which mainly is selected by point mutations. Although erythromycin resistance currently is low, it is an emerging health concern, especially in countries that use erythromycin in food-producing animals.[117,118] *C. coli* harbors higher rates of erythromycin resistance than *C. jejuni*.[6,119] Macrolide-resistant isolates tend to be multidrug resistant.[120,121] Studies have shown no clinical benefit of erythromycin therapy over placebo if given late in the course of disease.[111,115,122] If antibiotic therapy is initiated within the first 4 days of illness, fecal excretion might be reduced; results are conflicting regarding resolution of symptoms.[118,123,124]

There has been an increase in fluoroquinolone resistance in the past decades.[125,126] Rise in resistance coincides with the licensure of fluoroquinolones for use in poultry and veterinary medicine.[126,127] Basic mechanisms of resistance are outlined in Table 163.3. The most widely studied mechanism of resistance is the cmeABC efflux pump, which results in resistance to multiple drugs including fluoroquinolones and macrolides.[128,129] In countries such as Spain, Thailand, Taiwan, and Hong Kong, fluoroquinolone resistance is ≥80%.[119,130] In one study from China, the rate of fluoroquinolone resistance in *C. jejuni* increased from 44% in 1994–1998 to 98% in 2005–2010.[131]

TABLE 163.3

Mechanisms of Resistance

Mechanisms of Resistance	**Examples**	**Antibiotic Class Affected**
Modification of antibiotic target	DNA gyrase mutation	Fluoroquinolone
	23S rRNA mutation	Macrolide
	TetO binding to target ribosomal A site	Tetracycline
Efflux pump	cmeABC (multidrug efflux pump)	Macrolide, fluoroquinolone, β-lactam
Inability of antibiotic to reach target	Expression of major outer membrane protein leading to decreased membrane permeability	β-lactam antibiotics, macrolide
Modification or inactivation of antibiotic	β-lactamase	β-lactam antibiotics
	Aminoglycoside-modifying enzymes	Aminoglycosides

The CDC National Antimicrobial Resistance Monitoring System monitors antibiotic resistance for select enteric bacteria (http://www.cdc.gov/narms/reports/index.html). As of 2013, ciprofloxacin resistance in *C. jejuni* in the US remained stable at 22%, but macrolide resistance doubled in *C. coli* from 9% in 2012 to 18% in 2013.[132]

Prevention

Pasteurization and chlorination of water kill *C. jejuni*, but organisms survive in milk or other foods kept at 4°C. Because campylobacters have relatively high temperature requirements, they tend not to multiply in foods (in contrast to *Salmonella*), and therefore most cases are sporadic rather than occurring in large outbreaks. Milkborne outbreaks have been reported as a result of the consumption of unpasteurized or ineffectively pasteurized milk,[133,134] and a few waterborne outbreaks have been described.[135,136] About 50% to 80% of all human campylobacteriosis is related to chickens.[137] Strategies to decrease *Campylobacter* infections in humans are being explored and include removing *Campylobacter* from colonized chickens, reducing environmental exposures, and increasing the resistance of chickens to *Campylobacter*.[6,137]

Key Points

Campylobacter jejuni and *Campylobacter coli*

Epidemiology

- A major cause of bacterial gastroenteritis worldwide
- Highest incidence occurs in infants and young children.
- Well-defined modes of transmission are undercooked poultry, undercooked meat, and unpasteurized milk.

Clinical Features

- Generally a mild illness, but inflammatory diarrhea and hospitalization can occur; extraintestinal infections and death are rare.
- Most common cause of Guillain–Barré syndrome
- Most perinatal infections are caused by *C. fetus*.

Diagnosis

- Stool samples cultured on selective media are the gold standard.

Treatment and Prevention

- Rehydration and correction of electrolyte abnormalities are the mainstays of therapy.
- Consider antimicrobial therapy in patients with bloody or severe diarrhea, fever, worsening of symptoms, or patients who are immunosuppressed.
- Drug of choice for enteritis is azithromycin or erythromycin.

- Antibiotic therapy for enteritis may be beneficial when given within the first 4 days of illness.
- Fluoroquinolone resistance occurs in about 22% of US isolates but is higher in some other countries.
- Antimotility agents are contraindicated.
- Pasteurization and chlorination of water kill *C. jejuni*.

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Other *Campylobacter* Species

Bethany K. Sederdahl, Evan J. Anderson

The genus *Campylobacter* includes approximately 26 species and 9 subspecies.[1] Of the *Campylobacter* species that are associated with human disease, *C. jejuni* is the prototype for enteric infections, and *C. fetus* is the prototype for extraintestinal infections. *Campylobacter* spp. other than *C. jejuni* and *C. coli* isolated from stool are estimated to comprise 3% of *Campylobacter* isolates.[2] Refinement of microbiologic techniques for isolation of *Campylobacter* spp. and use of molecular assays have expanded our knowledge about the diversity of *Campylobacter* spp. and the spectrum of human infections associated with these organisms.[3–6] However, *Campylobacter* spp. other than *C. jejuni* and *C. coli* may be significantly underdiagnosed as causes of gastrointestinal tract disease because selective *Campylobacter* media and incubation conditions may inhibit their growth, and similarities between their biochemical characteristics may make species identification difficult.[7]

Phylogenetic trees have been established for *Campylobacter* on the basis of 16S ribosomal DNA sequences. These trees contain three distinct clades or species groups (Table 164.1).[8] The first clade includes *C. fetus* and *C. hyointestinalis,* which are generally associated with disease in farm animals. The second clade includes *C. coli, C. jejuni, C. lari,* and *C. upsaliensis,* which are associated with gastroenteritis in humans. The third includes *C. curvus, C. concisus,* *C. gracilis, C. rectus, C. showae,* and *C. sputorum,* which are associated with the periodontal cavity of humans and animals. *C. jejuni* and *C. coli* are described in Chapter 163.

TABLE 164.1

Location of and Disease Associated With *Campylobacter* Species

Association or Disease	*Campylobacter* Species
Disease in farm animals	*C. fetus*[a]
	C. hyointestinalis[a]
Gastroenteritis and rarely bacteremia	*C. coli*[a]
	C. jejuni[a]
	C. helveticus
	C. lari[a]
	C. upsaliensis[a]
Periodontal cavities of humans and animals	*C. curvus*
	C. concisus
	C. gracilis
	C. rectus
	C. showae
	C. sputorum

[a] Clearly associated with human disease.

Campylobacter fetus

In 1913, McFadyean and Stockman found a *Vibrio*-like organism in aborted ovine fetuses and proposed the name *Vibrio fetus ovis*.[9] The same organism later was implicated as a cause of abortion and infertility in other domestic animals, and the name was shortened to *V. fetus*.[10] A second type of infection in cattle and sheep, causing sporadic abortion but not infertility, was recognized; the causal agent was named *V. fetus* subsp. *venerealis*.[11] In 1947, Vincent and colleagues reported the first human infection by *C. fetus* in a pregnant woman with bloodstream infection (BSI) who aborted at 6 months of gestation.[12] Currently, three subspecies of *C. fetus* have been recognized: *C. fetus* subsp. *fetus*, *C. fetus* subsp. *venerealis*, and *C. fetus* subsp. *testudinum*.[1,13] *C. fetus* subsp. *fetus* and *venerealis* cause infection of the genitourinary tract of sheep and cattle. *C. fetus* subsp. *testudinum* is newly identified organism that has been associated with bacteremia and diarrhea in adult men, most of whom had reptile exposure.[13] It appears to be an opportunistic pathogen, affecting immunocompromised or elderly individuals.

Only *C. fetus* subsp. *fetus* and *testudinum* have been identified as causing disease in humans.

Microbiology and Epidemiology

C. fetus subsp. *fetus* are curved, gram-negative, microaerophilic bacteria that are oxidase, catalase, and nitrate positive; they grow at 25°C and 37°C, but not at 42°C. It is estimated that at least 20% of *C. fetus* infections are undetected since isolation is typically performed at 42°C.[14] A paracrystalline protein structure composed of S-layer proteins surrounding the bacterial outer membrane is a unique virulence factor of *C. fetus* and *C. rectus*. This structure is implicated in invasion, resistance to phagocytosis and complement-mediated killing, and immune evasion by antigenic variation.[15–19]

Although *C. fetus* accounts for 0.3% to 3.9% of all *Campylobacter* isolates, it is identified in 19% to 53% of *Campylobacter* bacteremia.[20–24] A source of *C. fetus* infection seldom is identified, although cases have been reported with cattle or sheep exposure, after ingestion of raw milk or contaminated food or water, by sexual and transplacental transmission, and in neonates after vaginal delivery.[25–30]

In adults, nearly 75% of reported *C. fetus* infections are in men, and 62% to 74% of systemic cases occur in patients with underlying conditions such as alcohol abuse, liver disease, diabetes mellitus, human immunodeficiency virus (HIV) infection, or malignancies.[22,23,31–36] There also is an increased risk for infection among healthy elderly individuals and pregnant women.[14,37] Although uncommon, *C. fetus* infection during pregnancy can result in birth complications and systemic infection of the neonate.[30,38] *C. fetus* infections in children are usually confined to the neonatal period in association with maternal infection, but case reports of infection in children with underlying disease describe *C. fetus* septicemia, hepatitis, and pericarditis.[30,39–41]

Clinical Manifestations and Management

In humans, *C. fetus* infection generally causes a systemic illness manifesting as fever and can be associated with translocation of the organism through a relatively intact intestinal mucosa to the reticuloendothelial system and the bloodstream.[24] BSI is the most common manifestation of *C. fetus* infection; this organism appears to have a predilection for vascular endothelium, with manifestations such as thrombophlebitis, pericarditis, mycotic aneurysms, and endocarditis.[41–46] Patients with BSI due to *C. fetus* should be evaluated for localized vascular infection. Confusion and lethargy are common, although focal neurologic signs are unusual except when meningitis or cerebral abscesses are present. The following three clinical presentations of BSI have been described: (1) cryptogenic BSI occurring as an isolated event that is self-limited or readily responds to antimicrobial therapy; (2) secondary BSI, the most common presentation, associated with focal infections such as meningitis, pneumonia, endocarditis, and thrombophlebitis; and (3) chronic BSI with relapses that can persist for several months, occurring mostly in immunosuppressed patients.

A focal lesion can be the first manifestation of *C. fetus* infection or can occur after or simultaneously with BSI. Meningitis, cholecystitis, pancreatitis, cellulitis, urinary tract infection, lung and gluteal abscesses, pericarditis, endocarditis, thrombophlebitis, septic arthritis, and salpingitis have been reported.[47–54]

Mortality from *C. fetus* BSI has been estimated at 14%, with higher rates among patients who have secondary BSI with a distant focal infection.[36] Infections with *C. fetus* usually are systemic and therefore require parenteral antibiotic therapy. *C. fetus* organisms often are susceptible to ampicillin and gentamicin, but imipenem or meropenem is preferred for treatment pending results of in vitro susceptibility tests.[30,55,56] Duration of therapy depends on the site of infection.

Three clinical manifestations of perinatal infection have been described: abortion and stillbirth, premature labor, and neonatal septicemia and meningitis.[38,57–62] The pathology of perinatal *C. fetus* infection consists of placental necrosis, and widespread endothelial proliferation, intravascular fibrin deposition, perivascular inflammation, and hemorrhagic necrosis in the brain of the neonate.[63] An infected woman can harbor *C. fetus* with or without symptoms, having recurrent abortions or premature deliveries as a result.[29,38,62,64–68] In cases of neonatal septicemia and meningitis, *C. fetus* has been isolated from the maternal cervix or vagina.[47,62,68] Cervical cultures remained positive in women who had recurrent abortions and whose husbands had high antibody titers to the organism.[69] In general, perinatal infections caused by *C. fetus* are more severe than those caused by *C. jejuni*.[38]

Campylobacter upsaliensis

Microbiology

A species of thermotolerant, catalase-negative or weakly catalase-positive, cephalothin-susceptible *Campylobacter* was isolated from dogs with diarrhea in 1982.[70] DNA hybridization and phylogenetic studies with comparison of the 16S rRNA sequence demonstrated that this organism belongs to a new species, *C. upsaliensis*, named after the Swedish city in which it was first isolated.[71,72] *C. upsaliensis* now is considered a relatively common enteric pathogen of humans and can cause BSI in malnourished children and immunocompromised adults.[73–77]

C. upsaliensis can be differentiated from other *Campylobacter* species on the basis of several phenotypic characteristics.[72] Most strains are thermotolerant, which means that they grow well at 42°C, but not at 25°C. *C. upsaliensis* is weakly positive or negative for catalase production and does not produce hydrogen sulfide in triple sugar medium or hydrolyze hippurate. A high proportion of isolates possess multiple plasmids. All strains are susceptible to cephalothin and nalidixic acid. Because *C. upsaliensis* is susceptible to the antimicrobial agents used in *Campylobacter*-selective media, it is not detected in cultures using these media.[73]

Epidemiology, Clinical Manifestations, and Treatment

C. upsaliensis is underidentified in routine clinical laboratories, making the true prevalence of infection with this pathogen difficult to estimate.[78,79] *C. upsaliensis* is isolated more frequently from populations with poor sanitation and overcrowded conditions and frequently is isolated from dogs and cats with or without symptoms of infection.[78,80,81] Infections in humans sometimes are associated with close contact with infected dogs.[80,82–85] *C. upsaliensis* detection in dogs increases in the summer and fall, and *C. upsaliensis* is isolated more commonly in humans from May through November.[74,86,87] *C. upsaliensis* is reported as a gastrointestinal pathogen in children more often than adults.[74,88,89] Diarrhea of short duration is the most common clinical presentation; 25% of patients have gross or occult blood in stools, 20% have fecal leukocytes, and vomiting occurs occasionally, but the disease appears to be milder than that caused by *C. jejuni*.[74,87] In South Africa, testing for *Campylobacter* in stool from children with diarrhea identified *C. upsaliensis* in 24% of samples.[89] An outbreak of *C. upsaliensis* in childcare centers in Brussels described chronic or relapsing diarrhea that was likely related to fecal-oral transmission.[88] Serum antibodies to *C. upsaliensis* were found in most children with *C. upsaliensis*, indicating that the organism is not commensal.[88] In immunocompromised or malnourished children with diarrhea, the infection can progress to septicemia.[75–77,90] *C. upsaliensis* infection has been associated with abortion, and BSI was described in a patient with ruptured ectopic pregnancy.[91]

Experience with antimicrobial treatment of *C. upsaliensis* is limited. Resistance to streptomycin, vancomycin, methicillin, trimethoprim, and piperacillin has been observed, but isolates have been found to be susceptible to gentamicin, azithromycin, erythromycin, meropenem, cephalosporins, fluoroquinolones, tetracycline, and aminoglycosides.[72,86,92–95] Diarrhea generally can be treated with macrolide, but no controlled trials have been conducted, and in some studies up to 13% to 15% of *C. upsaliensis* strains are resistant to macrolides in vitro.[93]

Campylobacter lari

In the early 1980s, Skirrow and Benjamin isolated nalidixic acid –resistant, thermophilic campylobacters in seagulls and in feces of domestic animals, seals, and ducks.[96] Although *C. lari* has been isolated in up to 10% of cloacal swabs from chickens, transmission to humans is rare. *C. lari* accounts for 1% of all diarrhea-associated *Campylobacter* isolates.[97] *C. lari* BSI has been described in immunocompromised patients and neonates.[98–100] An outbreak of diarrhea occurred among construction workers who drank water contaminated by surface water from Lake Ontario.[101]

Other *Campylobacter* Species

C. curvus, C. concisus, C. gracilis, C. rectus, C. showae, and *C. sputorum* generally are associated with the periodontal cavities of humans and animals and have no definitive association with human gastroenteritis. However, *C. curvus* has been isolated from patients with bloody and chronic diarrhea, and *C. curvus* and *C. rectus* have been reported as the cause of extraoral abscesses in humans.[102–104] Reports of the isolation of *C. concisus* from nonoral human clinical specimens (from blood and stool of patients with diarrhea, and from the foot of a diabetic patient with osteomyelitis) suggest that this organism can be a human pathogen.[105] *C. concisus* has been identified in 0.7% to 9% of stool samples from individuals with diarrhea.[106] However, whether *C. concisus* is a cause of diarrhea remains uncertain because it has been found in stools from healthy controls (children and adults) as often as in those with diarrhea.[6,106] It may be an opportunistic pathogen causing diarrhea in immunocompromised patients.[107] *C. concisus* has been identified in adults and children with Crohn disease and ulcerative colitis. It is unclear whether the organism plays a causative or opportunistic role in inflammatory bowel disease.[106,108–110]

C. hyointestinalis has been associated with human disease. In two studies, the rates of diarrhea due to *C. hyointestinalis* were 0.01% and 0.08% of all *Campylobacter*-associated episodes.[4,87] Other reports have described this organism as an uncommon cause of diarrhea or BSI.[111–114]

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Capnocytophaga Species

Lorry G. Rubin

Capnocytophaga is a genus in the family Flavobacteriaceae encompassing a group of slow-growing, capnophilic (carbon dioxide–loving), facultative anaerobic, gram-negative fusiform bacilli. The 9 species are divided into two groups, with 7 in the "human" group (formerly classified as Centers for Disease Control and Prevention [CDC] biogroup dysgenic fermenter [DF]-1), which colonize the oral cavity of humans and 2 species in the zoonotic group (CDC biogroup DF-2), which are distinguishable from human *Capnocytophaga* because they are oxidase and catalase positive and colonize the oral cavity of dogs and cats.[1] Recovery in culture requires incubation in an environment with enhanced carbon dioxide concentration under aerobic or anaerobic conditions. Colonies are detectable after 2 to 4 days or longer incubation on several media, including blood agar; growth does not occur on MacConkey agar. Generally, species in this genus ferment carbohydrates, except mannitol and xylose.[1] Species can be distinguished by means of DNA hybridization, 16S rRNA analysis, or matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) spectrometry.[2–4] These two groups are considered separately because the patient population, epidemiology, and clinical features of infection are distinct.

Human *Capnocytophaga*

Microbiology and Epidemiology

The human *Capnocytophaga* spp.—*C. ochracea, C. gingivalis, C. sputigena, C. haemolytica, C. granulosa, C. leadbetteri,* and genospecies AHN8471—are normal flora of the gingival sulci of humans.[1,3,5] Identification by conventional tests frequently is not successful. 16S rRNA polymerase chain reaction (PCR)–restriction fragment length polymorphism or sequencing is used to identify species,[2] but MALDI-TOF may be useful for rapid identification.[3] Human *Capnocytophaga* spp., most commonly *C. ochracea*, cause invasive infection in the presence of neutropenia and oral mucosal ulceration, which often is cancer chemotherapy induced. This implicates the neutrophil specifically as important in host defense. Possible virulence factors include a serum-resistant phenotype, production of immunoglobulin A protease, and bacterial factors that interfere with host responses to infection, such as neutrophil migration.[6]

Clinical Manifestations and Treatment

The most significant infections are bloodstream infections (BSIs) (occasionally polymicrobial) in immunosuppressed children or adults, especially those with malignancies or recipients of stem cell transplantation.[6] These patients generally are neutropenic and have oral lesions such as mucositis or aphthous stomatitis.[7] Based on series of cases reported from France[7] and Spain,[8] the mortality rate associated with BSI is <2%. *Capnocytophaga* spp. have been recovered from other infected sites such as the lung, pleural space, eye, brain, wounds, heart, bone, and joints in immunocompetent patients, commonly in association with other bacteria.[9] *Capnocytophaga* spp. have been documented as a cause of chorioamnionitis[10] and early-onset sepsis in premature neonates[10–12] and are important pathogens in juvenile periodontitis.

Although many isolates are susceptible to penicillin, strains resistant to penicillin and cephalosporins due to production of β-lactamase are common. Some strains produce extended-spectrum β-lactamases that inactivate third-generation cephalosporins.[13] Resistance to multiple other antimicrobial agents has been reported.[7,10,14] Imipenem or a β-lactam–β-lactamase inhibitor combination is highly active against *Capnocytophaga;* either can be considered a drug of first choice until results of antibiotic susceptibility testing, including a test for β-lactamase production, is available.[15] Clindamycin, chloramphenicol, and tetracycline show good activity, and linezolid has been used successfully.[16,17] Ciprofloxacin and trimethoprim-sulfamethoxazole have variable activity and aminoglycosides, metronidazole, and vancomycin generally lack activity.

Zoonotic *Capnocytophaga*

Microbiology and Epidemiology

Both *C. canimorsus* (originally called CDC bigroup DF-2) and *C. cynodegmi* (CDC biogroup "DF-2 like")[18] are found commonly in the oral flora of dogs[19–21] and cats.[20,21] *C. canimorsus,* the predominant pathogen, resists phagocytic killing by human polymorphonuclear leukocytes[20,22] and causes invasive disease in asplenic hosts and patients with alcoholic cirrhosis, implicating the spleen as important for protection against invasive infection. Infections with *C. canimorsus* are zoonotic; infected patients report a dog bite or scratch or at least dog exposure (or much less commonly, cat exposure) before the onset of infection.[20,23,24] Most cases have occurred in adults, although infections have been reported in children, including neonates.

Clinical Manifestations and Treatment

Septicemia, in some cases with associated cellulitis, is the most common clinical infection due to *C. canimorsus,* occurring about 5 days (range, 1–8 days) after a dog (or rarely cat) bite or exposure to saliva.[20,23,24] Disseminated intravascular coagulopathy, purpura fulminans, and peripheral gangrene resulting in amputations can accompany sepsis. A mortality rate of 24% has been estimated.[20] Meningitis also occurs and has a lower case-fatality rate than septicemia.[20,25] Localized cellulitis without sepsis after a dog-bite wound occasionally occurs, and endocarditis, pneumonia, vertebral osteomyelitis, and brain abscess are reported. *C. cynodegmi* causes localized wound infection but rarely causes BSI. Although septicemia due to *C. canimorsus* can occur in immunologically normal hosts, many patients have an underlying condition, specifically asplenia or alcohol abuse or have received corticosteroid therapy.[20,24] Infection is fulminant in more than one half of asplenic patients.[18] Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome have been reported in adults with *C. canimorsus* septicemia.[26]

Diagnosis is confirmed by culture of blood or cerebrospinal fluid. High-grade bacteremia can occur in asplenic patients particularly, and Gram stain of a buffy coat smear of blood may reveal organisms. In blood cultures, growth may be detected first in the anaerobic bottle, and blind subculture on enriched media may be needed because of inhibition of growth in the presence of sodium polyanethol sulfonate.[1] Isolates can be identified rapidly using MALDI-TOF.[4] Strains are susceptible to penicillin, except for 2 reports of resistance,[20] as well as to some cephalosporins, chloramphenicol, clindamycin, erythromycin, and tetracycline.[15] Susceptibility to aminoglycosides and trimethoprim-sulfamethoxazole is variable, and strains are resistant to aztreonam. Asplenic patients should be given penicillin prophylactically after a dog bite in an attempt to prevent this life-threatening infection (see Chapter 88).

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Chlamydophila (Chlamydia) pneumoniae

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The Pathogen

Chlamydiae are obligate intracellular pathogens, which former genus *Chlamydia pneumoniae* has been reclassified (somewhat controversially[1]) through genome sequencing and comparative analysis of the ribosomal operon to *Chlamydophila pneumoniae,* with three biovars—human (TWAR), koala, and equine.[2] In this chapter, the term *C. pneumoniae* will refer to *Chlamydophila pneumoniae,* biovar TWAR, the agent causing infection in humans.

C. pneumoniae was first described as a human respiratory tract pathogen in the mid-1980s.[3,4] This obligate intracellular pathogen causes atypical pneumonia and upper respiratory tract disease and has been associated with a number of nonrespiratory conditions. *Chlamydia* spp. are classified as bacteria because of the ability to reproduce by binary division. Like *Chlamydia trachomatis* and *Chlamydophila psittaci, C. pneumoniae* has a biphasic developmental cycle of replication. The infectious bacterial form, known as the elementary body, enters the eukaryotic cell by endocytosis, resides within a cytoplasmic inclusion, and then transforms into a vegetative form (the reticulate body) to replicate by binary fission.

As the inclusion fills with progeny, chlamydiae transform back into the metabolically inactive but infectious elementary body and are released through host cell rupture or fusion of the inclusion with the host cell plasma membrane.

Epidemiology

C. pneumoniae is a common infection worldwide.[5–10] Variable quality of diagnostic assays and lack of standardization remain important challenges to a precise description of the epidemiology, but many retrospective serologic studies, as well as prospective studies using culture and polymerase chain reaction (PCR) testing, have identified the mode of transmission, incidence of disease, and clinical characteristics of infection.[3,5,11–15]

Infection occurs most commonly in late winter or early spring.[16] The age at which primary infection apparently occurs differs according to the testing tools used. Population-based serologic studies indicate that acquisition of specific antibody occurs most often in children between 5 and 15 years of age[17]; the seroprevalence in this age group is approximately 30%.[18] New or repeat infections continue through adolescence and adulthood, culminating in 70% to 80% seropositivity in elderly patients.[19] Acute infections (either primary infection or reinfection) are most common in school-aged children. In a prospective population-based study in Seattle, the incidence of acute infection by age groups per 100 person-years was as follows: 0 to 4 years (no cases); 5 to 9 (9.2); 10 to 14 years (6.2); 15 to 19 years (2.2); and ≥20 years (1.5).[17] In contrast, a population-based study in Thailand identified rates of *C. pneumoniae* pneumonia of 2–20 per 100,000 population, with the highest rates occurring in those younger than 1 year and older than 65 years.[20] If culture or PCR testing is used for such studies, colonization (or possibly infection) in younger children is identified commonly in the absence of a detectable antibody response.[12,15,21,22] Whether the absence of a serologic response in young children results from an insensitive test or from the absence of tissue invasion remains unresolved. *C. pneumoniae* was isolated from the nasopharynx or throat of 1% to 10% of healthy children and can be identified by PCR testing in 5% to 25% of children who attend childcare centers; those with respiratory tract symptoms and those from large families had the highest rates of identification of *C. pneumoniae*.[11,12,14,23–26]

C. pneumoniae is shed from the respiratory tract during the acute clinical illness and for up to 1 year later.[24] Subclinical infection with antibody response also is common.[17,23,24,27–29] It is not known whether the presence of symptoms increases the likelihood of transmission. Animal experiments suggest that aerosolized particles are an inefficient means of spreading *C. pneumoniae.* Although the organism remains viable only briefly on skin, it survives for 20 to 30 hours on environmental surfaces, suggesting that direct inoculation may be the predominant mode of transmission in clinical settings.[13]

Among military trainees in Finland, attack rates during a *C. pneumoniae* epidemic ranged from 60 to 84 per 1000 exposed men.[29] Attack rates during an outbreak of *C. pneumoniae* respiratory infections among Air Force cadets ranged from 1.5%–3.4%, and rates were highest among freshman military recruits, who tend to spend more time in close proximity to one another.[30] The outbreak ended after 8 months, possibly related to the movement of cadets off base after senior graduation. Attack rates were higher during institutional outbreaks, ranging from 44%–68% among nursing home residents and 22%–34% among nursing home staff.[31,32] The incubation period is 2–4 weeks as determined by the temporal clustering of cases during institutional[32] and military[29] outbreaks. Protracted epidemics of *C. pneumoniae* infection can occur in some settings. Epidemics among military trainees in Finland lasted approximately 6 months.[29] Some evidence points to epidemic periods occurring every 6 months to 3 years, superimposed on low levels of endemic *C. pneumoniae* infection.[4,27,29]

Clinical Manifestations

C. pneumoniae infects the upper respiratory tract epithelium of young children, where it occasionally causes or contributes to acute otitis media and sinusitis, as well as prolonged cough illness and community-acquired pneumonia. *C. pneumoniae* has been identified by culture and PCR testing in middle-ear fluid specimens from approximately 5% of children with acute otitis media.[11,12,33] Most often, another bacterial pathogen is found concurrently, and infection resolves in the absence of therapy directed at *C.*

pneumoniae. The organism has not been detected in individuals with chronic middle-ear effusions.[34] *C. pneumoniae* can be a cause of prolonged cough illness. The organism has been detected in 5% to 17% of individuals with prolonged cough; the clinical features resemble pertussis.[14,35,36] In patients with prolonged cough during outbreaks of pertussis-like illness, the mean duration of cough associated with *C. pneumoniae* infection has been 25 to 30 days, compared with 50 days for cough associated with *Bordetella pertussis*.[14,37,38] *C. pneumoniae*–associated fever and upper respiratory tract symptoms, including sore throat and hoarseness, can be self-limited or can progress to coughing and lower respiratory tract involvement.[15,21,39]

C. pneumoniae is a relatively uncommon cause of severe pneumonia in children. Earlier studies implicated *C. pneumoniae* in 5% to 14% of cases of pediatric community-acquired pneumonia.[5,10,15,25,40–47] However, *C. pneumoniae* was identified using a nasophyarngeal swab PCR test in only 0.5% of 2222 children hospitalized with radiographically confirmed community-acquired pneumonia at 3 US hospitals in 2011–2012.[48] In India, *C. pneumoniae* infection was identified by serologic testing in 1.1% of 2345 children younger than 12 years who met the World Health Organization definition of pneumonia in 2011–2013.[49] The illness tends to have a subacute onset, indistinguishable from that due to *Mycoplasma pneumoniae* or influenza. More than one half of infected patients have fever, cough, shortness of breath, chills, nausea, headache, and myalgia.[39,50] Crackles, wheezing, and rhonchi often are detected on physical examination. Chest auscultation and radiograph can indicate pneumonia even when respiratory tract symptoms are mild. Because of the prolonged and relatively mild nature of initial symptoms, the patient may seek medical attention >1 week after onset of illness, at which time fever and symptoms of systemic illness may have resolved.[39] *C. pneumoniae* infections cannot be differentiated reliably from other causes of pneumonia in children. Among adults requiring hospitalization for community-acquired pneumonia, patients with *C. pneumoniae* etiology were more likely than those with bacterial etiology to have a duration of illness >7 days (odds ratio, 3.5; 95% confidence interval, 1.3–9.4) and less likely to have a productive cough (odds ratio, 0.3; 95% confidence interval, 0.1–0.7).

C. pneumoniae has been associated with severe illness in sporadic case reports. *C. pneumoniae* was isolated from culture of the respiratory tract and pleural fluid of a previously healthy adolescent boy with severe pneumonia complicated by respiratory failure and parapneumonic effusions.[51] A 13-year-old girl developed pneumonia and hemorrhagic pericarditis; *C. pneumoniae* was detected in the pericardial fluid by PCR.[52] Encephalitis has been associated with *C. pneumoniae* in pediatric reports.[53–55] A 12-year-old girl developed concomitant lower respiratory tract infection and encephalitis; *C. pneumoniae* DNA was detected by multiplex PCR in endotracheal secretions, and immunoglobulin M (IgM) and IgG antibodies were detected in serum, but not cerebrospinal fluid specimens.[53]

Most studies that include appropriate control groups fail to demonstrate an association between asthma and acute or chronic *C. pneumoniae* infection.[56–60] For example, *C. pneumoniae* was identified in 3.4% of children during an asthma exacerbation, in 6% of children during an initial episode of wheezing, and in 2.5% of patients with stable asthma or allergic rhinitis.[56] However, Teig and colleagues detected *C. pneumoniae* by PCR from 24% of children with stable asthma but from 0% of healthy nonasthmatic children[61]; it is unclear why *C. pneumoniae* was detected less frequently in the control population in this study compared with previous studies.

Nonstandardized laboratory testing has resulted in widely varying and often unconfirmed reports of new clinical associations of *C. pneumoniae,* including Alzheimer disease, atherosclerotic cardiovascular disease, multiple sclerosis, meningoencephalitis,[62–64] pyoderma gangrenosum,[65] and a variety of other diseases in children and adults (Table 166.1). *C. pneumoniae* was identified by immunohistochemistry in cardiovascular tissue of sporadic cases of Kawasaki disease.[66] This association was not confirmed in a case-control study.[67]

TABLE 166.1

Diseases Associated With *Chlamydia pneumoniae* Infection

Pathologic Role Established	Association Supported by Several Lines of Evidence
Pneumonia	Otitis media
Prolonged cough illness	Cardiovascular disease
Acute bronchitis	Asthma

SPECULATIVE ASSOCIATIONS	
Meningoencephalitis	Multiple sclerosis
Alzheimer disease	Myalgia
Kawasaki disease	Conjunctivitis
Lung cancer	Arthritis
Hypertension	Adult respiratory distress syndrome
Erythema nodosum	Chronic fatigue syndrome
Chronic bronchitis	Ischemic stroke

Modified from Sanchez F, Dowell S. *Chlamydia pneumoniae* infection in children: a pediatric infection with possible consequences in adults? Pediatr Infect Dis J 1999;19:367–373.

Laboratory Diagnosis

Recommendations for standardized approaches to culture, PCR testing, serology, and immunohistochemistry were published by the US Centers for Disease Control and Prevention (CDC) and the Canadian Laboratory Centres for Disease Control (LCDC).[68] However, only one of the many diagnostic assays used worldwide to identify *C. pneumoniae* has been approved by the US Food and Drug Administration (FDA) for clinical use.[69] This lack of standardization has resulted in substantial variation in interlaboratory test performance, even when using the same test and diagnostic criteria.[70]

Serologic testing has been the primary means of clinical diagnosis because of its widespread availability and relative simplicity. However, many of the available assays, including complement fixation, whole-inclusion fluorescence, and various enzyme immunoassays, perform poorly or have not been adequately validated; microimmunofluorescence testing remains the only endorsed serologic approach, despite limitations.[68] During primary infection, IgM antibody appears 2 to 3 weeks after illness onset. IgG antibody may not reach high titer until 6 to 8 weeks after illness onset. Confirmation of primary acute infection requires an IgM titer of 1 : 16 or higher, or a fourfold rise in IgG titer between acute and convalescent serum specimens. During reinfection IgM antibody may not appear, and IgG antibody titer can rise within 1 to 2 weeks of infection.[68] Criteria proposed in the past, including a single IgG titer >1 : 512 or elevated IgA antibody, are no longer endorsed because of low specificity. IgG titers ≥1 : 16 are consistent with previous exposure and are found in approximately one-half of adults. A single elevated IgG titer does not confirm the diagnosis *C. pneumoniae* infection.

The organism or its DNA can be identified by culture or PCR testing from specimens from nasopharyngeal or throat swabs, sputum, blood, or tissue. Culture has been considered the reference-standard diagnostic method. A specimen for culture can be collected on a Dacron-tipped, wire-shafted, or plastic-shafted swab. The specimen, transported in appropriate media at 4°C, is then centrifuged onto HEp-2 (human epithelial cell line type 2) or HL (heteroploid line with a slow life cycle) cell lines, passaged twice, and examined at 3 to 7 days after staining with monoclonal antibodies to identify the *C. pneumoniae* inclusions. Observation of inclusions constitutes a presumptive positive result; confirmation requires either successful passage of the isolate or confirmation with PCR. Swabs with calcium alginate or cotton tips and wooden shafts can inhibit the growth of the organisms, depending on the adhesive used. Specimens that cannot be processed within 24 hours should be frozen and held at −70°C.

Only 4 of >30 published PCR assays met validation criteria proposed by the CDC and LCDC.[68,70] Validation in these 4 studies was primarily analytical; extensive validation on clinical specimens has not yet been performed. Only the FilmArray Respiratory Panel, a multiplex PCR panel that also detects multiple viruses, has received approval by the FDA for detection of *C. pneumoniae* in respiratory or other specimens.[69,71] Reports of PCR detection in clinical specimens, as well as in research studies on atherosclerotic plaques, peripheral blood mononuclear cells, brain, lung, and other tissues, should be interpreted in the context of other confirmatory information. Identification of *C. pneumoniae* in the respiratory tract by culture or PCR testing does not establish causation of disease because of prolonged shedding.[24,28,72] Despite CDC recommendations, there remains a high degree of heterogeneity in serologic methods and diagnostic criteria used in studies purporting *C. pneumoniae* respiratory tract infections.[70]

C. pneumoniae can be detected in tissue by PCR testing or in situ hybridization, but immunohistochemical techniques have been used most commonly. The prevalence of the organism in arterial plaques has varied by report from 0% to >50%, highlighting the importance of appropriate selection of the monoclonal antibody, use of appropriate controls in the staining procedures, and careful interpretation to exclude false-positive staining results.[68,73]

Routine laboratory studies do not distinguish *C. pneumoniae* from other causes of acute respiratory tract infection.[15,21,39] The erythrocyte sedimentation rate typically is elevated (range, 21–75 mm/hr). Peripheral white blood cell count can be elevated or normal, usually with neutrophil predominance.[50] Radiographic appearance of pneumonia usually is bilateral ground-glass or nodular infiltrates, although unilateral alveolar infiltrate and pleural effusion have been reported in more than one fourth of cases.[50,51,72,74]

Treatment

Standards for in vitro susceptibility testing have not been established, but *C. pneumoniae* appears to be susceptible to most antibiotics that inhibit protein or DNA synthesis, including tetracyclines, macrolides, ketolides, and most fluoroquinolones (e.g., levofloxacin and moxifloxacin, but not ciprofloxacin); *C. pneumoniae* is resistant to sulfa drugs.[72,75–78] Microbiologic eradication of the organism from the nasopharynx occurs in 70% to 90% of children with *C. pneumoniae* pneumonia after a 10-day course of erythromycin or clarithromycin, or a 5-day course of azithromycin.[21,79,80] Clinical resolution occurs in a high percentage of children who are not treated[81] or who are given a β-lactam agent predicted to be ineffective.[11,79] Typical treatment regimens, when prescribed, are 14–21 days for tetracycline or doxycycline, 14 days for erythromycin, 7–14 days for fluoroquinolones or clarithromycin, and 5 days for azithromycin. In some patients, clinical symptoms and persistent isolation of the organism occur despite 10- to 30-day courses of appropriate therapy.[28,82] The role of prolonged therapy in patients with persistent or relapsing symptoms is not clear.

Complications

Complications of acute *C. pneumoniae* infection are rare. The possibility that *C. pneumoniae* can establish a state of persistent infection has lent plausibility to a number of associations with chronic diseases. The association between *C. pneumoniae* and atherosclerotic cardiovascular disease is based on higher prevalence of serum antibodies in patients with coronary heart disease than in controls,[73] detection and culture of the organism in atheromatous plaques,[73,83,84] and animal studies and small human trials suggesting a benefit of treatment with macrolides.[85–87] A meta-analysis has failed to support a significant serologic association,[88] and large, prospective, randomized trials have thus far not found evidence of treatment benefit of the magnitude suggested by the earlier studies.[89] A longitudinal study of children found no association between repeated anti-*Chlamydophila* treatments in childhood and early vascular changes, suggesting that antimicrobial therapy does not prevent atherogenicity potentially associated with repeated infectious insults.[90] Although studied less extensively, evidence is conflicting for *C. pneumoniae* as a causative agent in Alzheimer disease,[91–93] ischemic stroke,[94,95] asthma,[58,59,96,97] multiple sclerosis,[98–101] Kawasaki disease,[66,67] and other conditions (see Table 166.1).[62,65,102]

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Chlamydia trachomatis

Toni Darville, G. Ingrid J.G. Rours

The Pathogen

Chlamydiae are obligate, intracellular, nonmotile, gram-negative bacteria with a unique biphasic developmental cycle consisting of extra- and intracellular forms. Chlamydiae have an outer membrane that contains lipopolysaccharide (LPS) and membrane proteins. Peptidoglycan is present in the septum of dividing bacteria.[1] Although chlamydiae contain DNA, RNA, and ribosomes, they obtain high-energy phosphate compounds from the host cell. *Chlamydia trachomatis* encodes an abundant protein called the major outer membrane protein (MOMP or OmpA) that is surface exposed and is the major determinant of serologic classification.

Life Cycle

The biphasic developmental cycle of chlamydiae is unique among microorganisms and involves two highly specialized characteristic morphologic forms, as shown in Fig. 167.1. The extracellular form or *elementary body* (EB) has a rigid, thick outer membrane that contains extensive disulfide cross-links both within and between outer membrane proteins and is stable outside of the cell. The small (350 nm in diameter) EB is infectious but inactive metabolically.

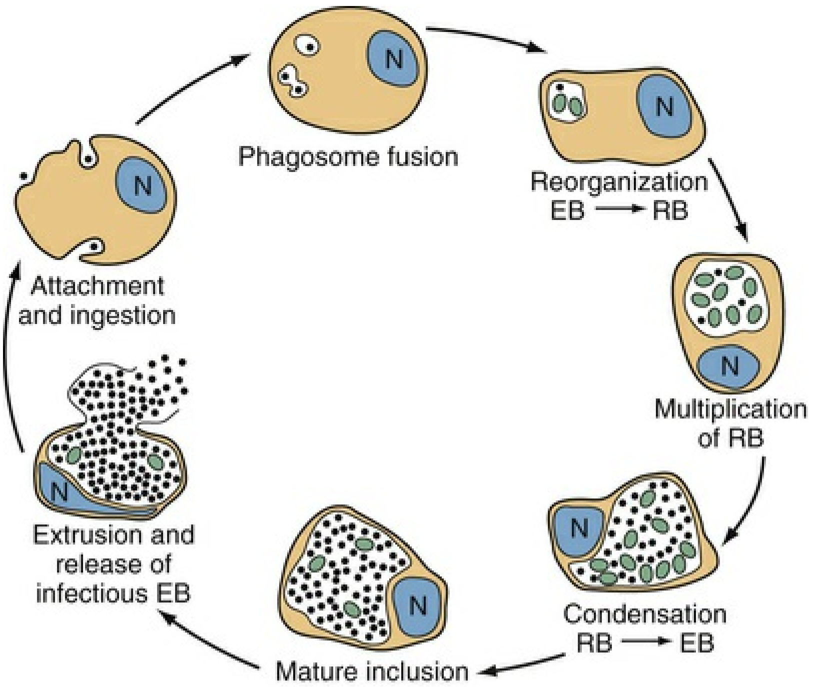


FIGURE 167.1 Life cycle of *C. trachomatis* in tissue culture. *EB,* elementary bodies; *N,* nucleus; *RB,* reticulate bodies. (Redrawn from Jones RB. *Chlamydia trachomatis* (trachoma, perinatal infections, lymphogranuloma venereum, and other genital infections). In: Mandell GL, Bennett JE, Dolin R [eds]. Principles and Practice of Infectious Diseases, 5th ed. New York, Churchill Livingstone, 2000, p. 1990.)

The developmental cycle is initiated when an EB attaches to a mucosal epithelial cell. A number of candidate adhesins have been proposed, but their identity and that of associated epithelial cell receptors remain uncertain. When inside the cell, the EB resides within a membrane-limited endosome and prevents fusion of the endosome with lysosomes, protecting itself from enzymatic destruction. Escaping from host attack by antibody or cell-mediated defenses, the EB enlarges and reorganizes into the replicative and metabolically active form, the *reticulate body* (RB). Chlamydiae hijack certain host cell signaling pathways to protect the cell from recognition and attack while preventing apoptosis and maintaining integrity of their host cells.[2]

RBs remain strictly intracellular, successfully parasitizing the host cell, synthesizing messenger RNA, dividing, and multiplying. As the RB divides by binary fission, it fills the endosome, now a cytoplasmic *inclusion,* with its progeny. After 48 to 72 hours, multiplication ceases and nucleoid condensation occurs as the RBs reorganize and transform again to new infectious EBs. Eventually, the host cell's nutrients are expended, and EBs are released from the cell by cytolysis,[3] exocytosis, or extrusion of the whole inclusion,[4] leaving the host cell intact. The last fact may explain the frequency of asymptomatic or subclinical chlamydial infections. The release of the infectious EBs allows infection of new host cells to occur.

Classification

The family Chlamydiaceae contains a single genus, *Chlamydia,* and 11 pathogenic species, which infect humans and a wide variety of animals; for example, *C. pneumoniae* infects humans, horses, koala, amphibians, and reptiles; *C. psittaci* 6BC infects birds and mammals; and *C. abortus* infects sheep, goats, cattle, and swine.[5] Humans are the natural host for the more than 18 serovars of *C. trachomatis*, divided into subgroups based on antigenic variation in the major outer membrane proteins (serovars) and clinical patterns of disease.[6,7] Trachoma is caused by serovars A, B, Ba, and C; oculogenital and neonatal disease by serovars B, Da, Ga, Ia, and D-K; and lymphogranuloma venereum (LGV) by serovars L1, L2, L2a, and L3.

Pathogenesis

LGV serovars can replicate in lymph nodes and macrophages, whereas replication of the other serovars of *C. trachomatis* is confined to mucosal epithelial cells. After an incubation period of 10 days (between 7 and 21 days) a variety of clinical manifestations can result from the host inflammatory response and tissue destruction. Primary infection is characterized by marked influx of neutrophils, especially early in infection.[8–11] Lymphocytes and plasma cells also participate in the primary response, but they appear later, concurrently with resolution of infection. In adult ocular and genital infections, plasma cells can be present in large numbers,[12–14] whereas in neonates and infants with ocular or respiratory tract infection, eosinophils and neutrophils predominate.[15]

The host is assumed to develop a protective immune response since chlamydial infections can be self-limited.[16,17] However, asymptomatic infection can be chronic, lasting for months or even years.[18,19] Although repeated infections are common, especially among high-risk adolescent women,[20] resistance to reinfection can develop. A recent study revealed that rates of reinfection over a 1-year follow-up period were lower (4.5%) in women who spontaneously cleared their infection compared with women who had persisting infection (16.5%).[17] Early detection and treatment may attenuate protective immunity in some patients.[21]

Epidemiology

C. trachomatis strains exhibit tissue tropism, with different strains infecting either the mucosa of the genital tract or the eye. *C. trachomatis* is the leading cause of bacterial sexually transmitted infection (STI) in the world. However, in endemic areas, mostly in Africa and the Middle East, *C. trachomatis* causes trachoma, the leading cause of preventable blindness worldwide.

The World Health Organization estimated that 92 million new cases of *C. trachomatis* infection occur annually worldwide.[22] It is estimated that >3 million chlamydial infections occur annually in sexually active adolescents and adults in the United States. Most infected men and women are either asymptomatic or minimally symptomatic, and diagnosis is a result of screening or because a contact is symptomatic. The rate of chlamydial infection reported to the Centers for Disease Control and Prevention (CDC) from 1993 through 2011 increased from 178 to 453.4 cases per 100,000 population.[23] Possible reasons for the increase are increased awareness and screening, increased use of nucleic acid amplification tests (NAATs), and improved reporting, as well as continuing high burden of disease. In 2013, 1,401,906 chlamydial infections were reported to the CDC. This is the first time since national reporting began that the rate of reported cases decreased. The reported number of cases of chlamydial infection was >4 times that of reported cases of gonorrhea. Table 167.1 outlines prevalence estimates reported for selected conditions and patient groups.[24–30]

TABLE 167.1

Prevalence of Chlamydial Genital Infection in Selected Patient Groups and Conditions

Subject Group or Condition	Females (%)	Males (%)
Adolescents	8–37	13–15
Adults (asymptomatic)	4–8	3–5
Adults (STD clinic)	>20	15–20
Gonorrhea	25–50	5–30
Mucopurulent cervicitis or nongonococcal urethritis	9–15	30–40
Pelvic inflammatory disease or epididymitis	8–54	50

STD, sexually transmitted disease.

Data collated from Centers for Disease Control and Prevention. Prevalence of *Chlamydia trachomatis* genital infection among persons aged 14−39 years—United States, 2007−2012. MMWR Morb Mortal Wkly Rep 2014;63:834−838.

Young age (<20 years) is the sociodemographic factor most strongly associated with chlamydial infection. A study in Louisiana public high schools revealed an overall prevalence of *C. trachomatis* of 6.5%, with rates among girls more than twice that of boys (9.7% vs. 4%).[31] In a study of more than 3000 sexually active adolescent girls attending middle school health centers in Baltimore, chlamydial infection was found in ~24% at the first visit and 14% at repeat visits; 14-year-old girls had the highest age-specific prevalence rate (28%).[26] Independent predictors of chlamydial infection failed to identify a subset of adolescent females with most infections.

Substantial racial and ethnic differences exist in the prevalence of chlamydial infections. In the United States a cross-sectional analysis in a prospective cohort study of a nationally representative sample of 14,322 young adults aged 18 to 26 years revealed the overall prevalence of chlamydial infection to be 4.2%.[32] Women (4.7%) were more likely to be infected than men (3.7%). Prevalence was highest among black women (14%) and black men (11%) and lowest among white women (2.5%), white men (1.4%), and Asian men (1.1%). Prevalence was highest in the South (5.4%) and lowest in the Northeast US. (2.4%). Significant geographic variation in prevalence rates occur in other countries as well; for example, in the Netherlands, rates as high as 16.2% occur among Antillean women compared with 1.8% among Dutch women.[33] Other predictors of incident chlamydial infection in young women include single marital status, having a new sex partner, smoking, having gonorrhea or bacterial vaginosis, and presence of high-risk carcinogenic human papillomavirus.[20,29,30] Use of progestin-only or combined estrogen and progestin contraceptives did not alter risk for incident infection in a study of young women at low to moderate risk (4% baseline infection rate).[29] Oral contraceptives had no effect on risk for chlamydial infection in a study of adolescents, but use of depot medroxyprogesterone acetate injections increased the risk for infection fivefold compared with nonhormone users.[34] In a prospective study in 948 Kenyan sex industry workers, users of oral contraceptives had increased risk for acquisition of *Chlamydia* (hazard ratio, 1.8; 95% confidence interval [CI], 1.1–2.9). Those using depot medroxyprogesterone acetate had significantly increased risk for *Chlamydia* infection (hazard ratio, 1.6; 95% CI, 1.1–2.4) but significantly decreased risk for pelvic inflammatory disease (PID) (hazard ratio, 0.4; 95% CI, 0.2–0.7).[35]

Partner transmission rates are approximately 65% and appear to be similar for female-to-male and male-to-female transmission.[36,37] The number of exposures or coinfection with *Neisseria gonorrhoeae* did not affect the transmission rate.

Clinical Manifestations

C. trachomatis infects susceptible squamocolumnar or transitional epithelial cells (e.g., mucous membranes of the conjunctivae, posterior nasopharynx, urethra, endocervix, and rectum).

Perinatal Infection

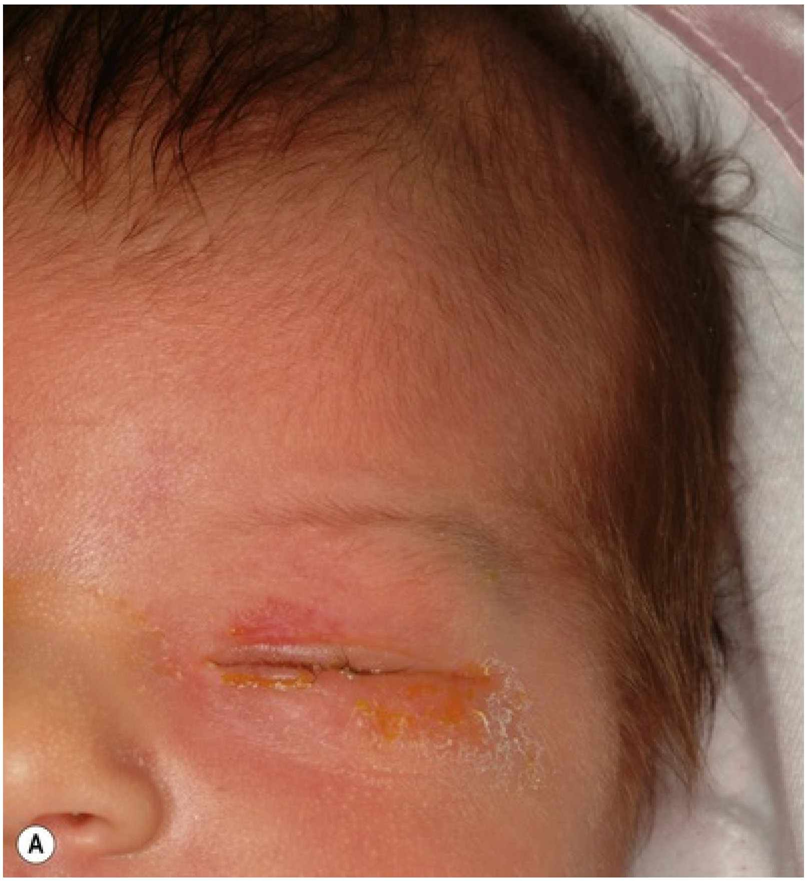
Neonatal infection generally is acquired during passage through an infected birth canal. In a recent Chinese study, the vertical transmission rate was 67% after vaginal delivery and 8% after cesarean delivery.[38] Prospective studies of infants born to women with chlamydial infection of the cervix show 50% to 75% risk that the infant will acquire *C. trachomatis* at one or more anatomic sites.[39–43] In infants exposed to *C. trachomatis,* risk for conjunctivitis is 20% to 50%, and risk for pneumonia is 5% to 20%.

In ~14% of infants born to women with chlamydial infection, asymptomatic rectal or vaginal *C. trachomatis* can be detected, which can persist for ≥18 months.[44] Persistence of *C. trachomatis* in the genital tract can confound evaluation for possible sexual abuse and requires thorough and appropriate investigation.[45]

Inclusion Conjunctivitis

C. trachomatis is the most common cause of ophthalmia neonatorum, the major clinical manifestation of neonatal chlamydial infection.[46] The usual incubation period is 5 to 14 days after birth, but symptoms can occur earlier after premature rupture of membranes or as late as 6 weeks after birth.[39] At least 50% of infants with chlamydial conjunctivitis have concurrent infection in the nasopharynx.

The most common symptom is watery ocular discharge that progressively becomes more purulent (95%), followed by swelling of the eyelids (73%) and conjunctival erythema (65%)[46] (Fig. 167.2). Most cases resolve spontaneously during the first few months of life. However, if the condition is untreated, chronic conjunctivitis can develop. Although conjunctivitis can be quite severe, corneal ulceration, scars, and pannus formation are rare, and recovery is expected without visual impairment.[47]



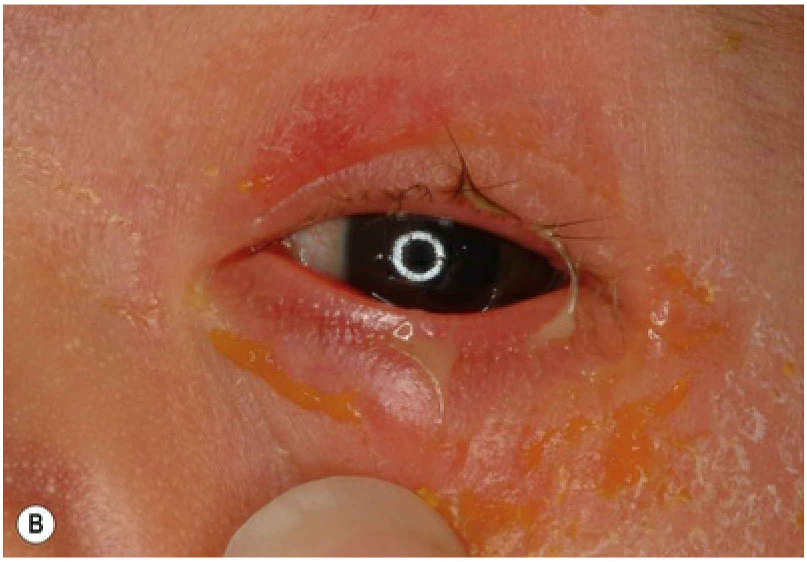


FIGURE 167.2 (A and B) A neonate with chlamydial conjunctivitis. (Courtesy of J. H. Brien ©.)

Chlamydial conjunctivitis must be distinguished from that produced by pyogenic bacteria, particularly *N. gonorrhoeae.* Gonococcal ophthalmia usually occurs earlier (around 2–5 days after birth) and usually progresses more rapidly. Clinical findings of neonatal conjunctivitis caused by *C. trachomatis, N. gonorrhoeae,* or other pathogens can be indistinguishable.

Pneumonia in Infancy

Pneumonia caused by *C. trachomatis* in infancy occurs characteristically between 3 and 12 weeks of age but sometimes can manifest later.[48–52] Characteristically, the infant has been symptomatic for 3 or more weeks before coming to medical attention. Most infants are only modestly ill and are afebrile. Symptoms of nasal obstruction and a pertussis-like (but nonproductive, staccato) cough gradually worsen over ≥1 week. Physical findings include tachypnea and rales but not wheezing. About 50% of the affected infants have a history or evidence of conjunctivitis. Laboratory findings include hyperinflation with symmetric interstitial infiltrates on chest radiography, peripheral eosinophilia (>400 cells/mm^3), and increased levels of serum immunoglobulins. *C. trachomatis* pneumonia in preterm neonates has been reported to manifest as early as 48 hours after birth, with idiopathic respiratory distress that improved initially but was complicated by apneic spells and feeding problems.[53–56]

Genital and Ocular Infections

C. trachomatis causes a variety of oculogenital infections in sexually active adolescents and adults, as well as in children who have been sexually abused (see Table 167.1).[57] Most infected persons are asymptomatic. In the National Longitudinal Study of Adolescent Health, 95% of *C. trachomatis*–infected people did not report symptoms in the 24 hours preceding specimen collection.[32] Among infected men, urethral discharge and dysuria were present only in 3% and 2%, respectively. Among infected women, vaginal discharge and dysuria were present only in 0.3% and 4%, respectively. Among patients reporting urethral discharge, the prevalence of chlamydial infection was high (38%) in men, but low (1%) in women. Of note, 6% of women reporting dysuria had chlamydial infection.

The incubation period for symptomatic males is 7 to 14 days. They may complain of dysuria, a slight, clear or mucopurulent urethral discharge, or stained underwear in the morning; or discharge may be detected only after penile stripping during genital examination by a healthcare provider.[58] The primary complications of chlamydial urethritis in men are epididymitis, reactive arthritis (including Reiter syndrome), and transmission to women. *C. trachomatis* and *N. gonorrhoeae* are the most frequent causes of epididymitis in men <35 years of age; urethritis also usually is present.

Although asymptomatic rectal carriage of *C. trachomatis* occurs in both infants[59] and adults,[60] *C. trachomatis* is a frequent cause of proctitis and proctocolitis in men who have sex with men.[61] Approximately 1% of men with nongonococcal urethritis develop acute aseptic arthritis of presumed immune-mediated etiology. One third of patients have the full complex of Reiter syndrome (arthritis, nonbacterial urethritis, and conjunctivitis); most such patients carry the histocompatibility antigen HLA-B27.[62]

The natural course of *C. trachomatis* infection in women was described in a study of Colombian women followed for a 5-year period using serotyping and polymerase chain reaction (PCR) on cervical-scrape samples.[18] Approximately 46% of infections, if not treated, were persistent at 1 year, 18% at 2 years, and 6% at 4 years of follow-up. Symptoms of *C. trachomatis* infection in women include a dysuria-pyuria syndrome, vaginal discharge, intermittent bleeding, and mild abdominal pain. The cervix can appear normal or can exhibit edema, erythema, friability, or mucopurulent discharge. In prepubertal girls, vaginitis can occur secondary to *C. trachomatis* infection of transitional cell epithelium. In contrast, the squamous epithelium of the adult vagina is not susceptible, and vaginal discharge generally reflects endocervical infection.

In some women, ascending infection of the genital tract develops, resulting in endometritis and salpingitis (Fig. 167.3). Eighteen (16%) of the infected asymptomatic adolescent women in one study who were monitored for ≥2 months became symptomatic, but <2% developed clinical PID.[63] A review of 24 studies examined PID diagnosis and sequelae after untreated chlamydial infection.[64] On average in high-risk settings, 2% to 5% of untreated females developed PID within the approximately 2-week period between testing positive for *C. trachomatis* and returning for treatment.[65,66] In several studies, repeated chlamydial infection was associated with PID and other reproductive sequelae, although it was difficult to determine whether there was stepwise increase with each recurrent episode.[65,67,68] No prospective study has directly assessed the risk for infertility after untreated *C. trachomatis* infection. However, according to the largest studies, after symptomatic PID of any cause has occurred, up to 18% of women can develop infertility.[69]

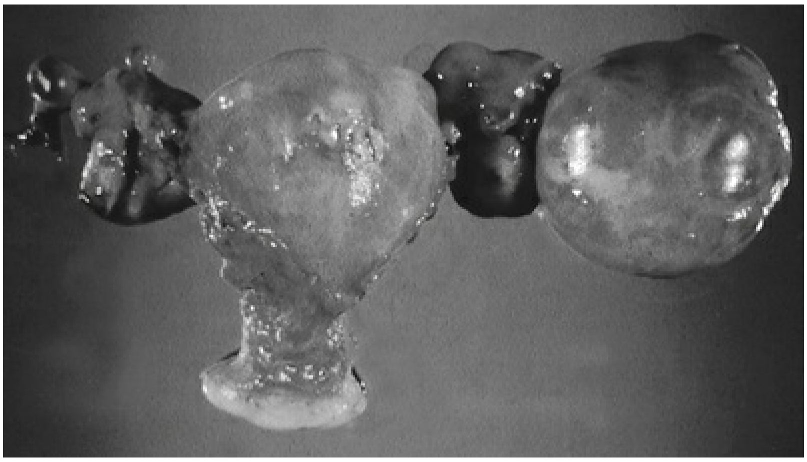


FIGURE 167.3 Pathologic specimen of uterus and salpinx from a patient with involuntary infertility and a history of repeated chlamydial infections.

C. trachomatis and *N. gonorrhoeae* are the most common causes of

PID, with more than one half of cases due to one or both organisms. The spectrum of PID associated with *C. trachomatis* infection ranges from asymptomatic to acute, severe disease with perihepatitis and ascites (Fitz-Hugh–Curtis syndrome). Compared with women who have gonococcal or nongonococcal-nonchlamydial salpingitis, women with chlamydial salpingitis are more likely to experience a chronic, subacute course with a longer duration of abdominal pain before they seek medical care.[70] Yet, they have as much or more tubal inflammation at laparoscopy.[71] Chronic infections, even if subclinical, can lead to infertility and ectopic pregnancy.

Adolescents and adults with genital tract disease presumably can autoinoculate their eyes, leading to inclusion conjunctivitis.[72,73] Additionally, infection can follow exposure to infected eye secretions without sexual contact or can occur in conjunction with unrecognized genital infection that has resolved. Acute follicular conjunctivitis is typical. Symptoms are those of a foreign body sensation in the eye. The infection usually resolves without complications but, if untreated, can persist for months and can result in scarring.

Infection and Pregnancy

C. trachomatis infection can negatively influence pregnancy.[74] Previous chlamydial infection has been associated with increased risk for ectopic pregnancy, as evidenced by serologic studies, isolation of *C. trachomatis* from fallopian tubes, and chlamydial DNA detection from cervical, endometrial, or salpingectomy tissues.[75,76] In addition, *C. trachomatis* infection has been associated with spontaneous abortion, stillbirth, and preterm delivery.[77–79] In a nationwide study in New South Wales of first-time mothers having singleton births, prior history of infection with chlamydia was associated with a 40% increased rate of stillbirth and a 17% increased risk for preterm birth.[77] Another study revealed a threefold increased risk for preterm delivery in women with cervical infection at 24 weeks of gestation.[79] Evidence that preterm delivery is associated with *C. trachomatis* infection has increased with the use of NAAT.[80] In a Dutch noninterventional prospective cohort study among pregnant women, chlamydial infection was associated with preterm delivery before 32 weeks (odds ratio [OR], 4.35; 95% CI, 1.3, 15.2) and 35 weeks (OR, 2.66; 95% CI, 1.1, 6.5) of gestation.[33] Infection of the placenta may lead to preterm delivery. Among 304 pregnant women with delivery before 32 weeks of gestation, *C. trachomatis* was detected in 25% of placentas. Histologic evidence of inflammation was present in 54% of placentas with *C. trachomatis* versus 36% without.[81] Chlamydial infection correlated with the progression and intensity ($P = 0.007$) of maternofetal placental inflammation.

Lymphogranuloma Venereum

LGV is an STI caused by the L1 to L3 serovars of *C. trachomatis.* The bubonic form is endemic in tropical and subtropical areas but is reported rarely in the US. Classically, LGV is a disease of the lymphatic tissue with acute and chronic manifestations.[82] The primary lesion is a small, inconspicuous, asymptomatic genital papule or ulcer that heals without a scar. Days to weeks later, unilateral acute lymphadenitis with bubo formation occurs at the site of lymphatic drainage of the primary lesion; acute hemorrhagic proctitis develops after a rectal lesion. Systemic symptoms can include fever, myalgia, or headache. About one third of inguinal buboes become fluctuant and rupture; the remainder involute slowly. Although most patients recover from LGV after this secondary stage, a small number develop a chronic inflammatory response with fibrosis (owing to the persistence of chlamydiae in anogenital tissues) that can result in chronic genital ulcers or fistulas, rectal strictures, or genital elephantiasis.

Rare in the Western world before 2003, outbreaks of LGV proctitis have been reported in the Netherlands,[83] Europe, North America, and Australia among men who have sex with men.[84] Most were HIV infected with high-risk sexual behavior and a high rate of concomitant STIs, including hepatitis C.[85]

Ocular Trachoma

Trachoma still is one of the world's leading causes of blindness; approximately 30% of the children in a holoendemic area are at risk for blindness due to severe trachoma.[86] Extensive studies in Taiwan revealed the importance of reinfection in the pathogenesis of trachoma.[87] Both pannus formation (the superficial vascularization that is pathognomonic of trachoma) and progressive disease with scarring are believed to be due to cycles of active infection and resolution repeated over many years.

In areas that are endemic for trachoma, infections occur early in life, and active disease persists for several years. Poor hygiene and presence of eye-seeking flies enhance transmission. Initially, chronic follicular conjunctivitis typical of inclusion conjunctivitis develops, followed by more intense inflammation of the conjunctivae and then scarring of the tarsal conjunctiva. After severe scarring of the inner surface of the lids, trichiasis (in-turning of the eyelashes) often develops, resulting in further corneal ulceration, scarring, opacification, and loss of vision. *C. trachomatis* can be isolated from conjunctival scrapings and nasopharyngeal cultures obtained from young children with active trachoma. The clinical spectrum of trachoma can vary from mild to severe; a simplified World Health Organization grading scheme can be used for standardized clinical assessment.[88,89] Young preschool children who have persistent or severe disease and chronically shed *C. trachomatis* act as an important reservoir of infection within a family unit.[90]

Laboratory Diagnosis

The diagnosis of trachoma in endemic areas can be based on clinical findings. Other chlamydial infections generally require laboratory confirmation to distinguish them from other conditions. A positive laboratory test for *C. trachomatis* can be used for patient education and to improve adherence to treatment regimens and increase the likelihood of referral of sexual partners. The development of tissue cell culture methods in the 1960s was a major advance, but they have been replaced by NAATs as methods of choice for diagnosis.

Definitive diagnosis of chlamydial infection, as would be required in a medicolegal setting (i.e., suspected sexual abuse or rape), requires isolation of *C. trachomatis* in cell culture or a positive NAAT confirmed by a second NAAT that targets a different gene sequence.[91]

Diagnostic Specimens

Many screening tests for *C. trachomatis* require appropriately handled samples containing columnar epithelium from mucosal sites rather than exudate.

The discomfort caused by obtaining a urethral swab in males has precluded its widespread use in asymptomatic men. A dipstick test for leukocyte esterase performed on the first portion of voided urine is a cost-effective and relatively sensitive screen (72%–95%) in asymptomatic young men.[92] Sediment from leukocyte esterase −positive urine then is used for a nonculture diagnostic test and, in members of low-risk populations, as a second confirmatory test. When feasible, urine NAAT provides a more sensitive and equally noninvasive method of detection.

Diagnostic Methods

Cell Culture.

Use of chlamydial transport media containing antibiotics maximizes recovery. Swabs used to obtain a specimen should have plastic or metal shaft and a tip made of cotton or Dacron because this causes less inhibition than nylon or alginate. Storage at 4°C or maintenance at –70°C is required if inoculation within 24 hours is not possible. Cycloheximide-treated McCoy or HeLa cell lines are used most frequently for isolation. Centrifugation techniques enhance absorption of chlamydiae to cells. Intracytoplasmic inclusions can be detected at 48 to 72 hours with species-specific immunofluorescent monoclonal antibodies or Giemsa or iodine staining.

Nonculture Tests.

NAATs have a higher sensitivity than all other tests, while retaining high specificity when cross-contamination is avoided.[93] NAATs have US Food and Drug Administration approval for testing cervical swabs from women, urethral swabs from men, and urine from men and women. NAATs detect *C. trachomatis* in urine or in self-administered vaginal swab specimens with sensitivity comparable with clinician-obtained urogenital swab specimens, which makes noninvasive testing possible.[94,95] Data suggest that NAATs are equivalent to or better than culture for the detection of

C. trachomatis in the conjunctiva and nasopharynx of infants[96] and are used currently in evaluation of newborns with conjunctivitis or pneumonia.

Direct fluorescent antibody (DFA) assays use fluorescein-conjugated monoclonal antibodies to stain chlamydial antigens in smears. DFA assays are cleared by the US Food and Drug Administration for use with pharyngeal specimens and potentially have high specificity if a *C. trachomatis*–specific stain is used. The tests also perform well on conjunctival specimens, with sensitivities >90% and specificities ≥95% compared with culture.[97,98] DFA assays that use antibodies specific for chlamydial MOMP are highly specific, but certain commercial kits using anti-LPS antibodies can lead to false-positive results.

Enzyme immunoassays detect chlamydial LPS but are less sensitive than culture and NAATs, and there is a potential for false-positive results caused by cross-reaction with LPS of other microorganisms, including other *Chlamydia* species.[99]

Serologic tests are of limited value in individual cases and are used primarily for population studies. However, serology can be used to detect *C. trachomatis* in women with tubal-factor infertility and in newborns. The detection of specific serum immunoglobulin M (IgM) or tear IgA antibodies in an individual is suggestive of current infection. In infants IgM levels often are elevated with neonatal pneumonia, but not with conjunctivitis.[100] Cytology is used mainly to diagnose conjunctivitis. Characteristic glycogen-containing intracytoplasmic inclusions can be identified in Giemsa-stained conjunctival scrapings from up to 90% of infants and 50% of adults who have inclusion conjunctivitis but from only 10% to 30% of patients who have active trachoma.[101] This method allows for visualization of *C. trachomatis* and other bacteria, such as gonococci, and of cytologic findings suggesting viral infection. Glycogen staining does not exclude other pathogens, is not helpful in patients with mild disease, and is not recommended for evaluation of endocervical specimens.

Treatment

Antibiotics against *C. trachomatis* act by inhibiting protein synthesis, growth and division of RBs, DNA-gyrase activity, or cell wall biosynthesis. Antibiotics used should be able to gain access to and exhibit activity in intracellular sites. The 72-hour life cycle and the asynchronous nature of chlamydial infection further require the maintenance of adequate antibiotic concentration in tissues. Table 167.2 summarizes treatment regimens for chlamydial infections. Antibiotic resistance has been described only rarely.

TABLE 167.2

Recommended Oral Treatment Regimens for *Chlamydia trachomatis* Infections

Condition	Treatment
PERINATAL INFECTIONS	
Inclusion conjunctivitis *or*	Erythromycin (50 mg/kg/day in 4 doses) for 14 days *or*
Pneumonia of infancy	Azithromycin (20 mg/kg/day in one dose) for 3 days
OCULOGENITAL INFECTIONS	
Children: <45 kg	Erythromycin (50 mg/kg/day in 4 doses) for 14 days
Children: ≥45 kg but <8 years old	Azithromycin (1 g in a single dose)
Children: ≥8 years old	Azithromycin (1 g) single dose Doxycycline (100 mg twice daily) for 7 days
Nonpregnant adolescents or adults	Doxycycline (100 mg twice daily) for 7 days *or*
	Azithromycin (1 g) single dose *or*
	Alternative regimen:
	Levofloxacin (500 mg 2 times daily) for 7 days *or*
	Ofloxacin (300 mg 2 times daily) for 7 days *or* Erythromycin base (500 mg 4 times daily) for 7 days *or*
	Erythromycin ethylsuccinate (800 mg 4 times daily) for 7 days
Pregnant adolescents or adults	Azithromycin (1 g) single dose *or* amoxicillin (500 mg 3 times daily) for 7 days
	Alternative regimen:
	Amoxicillin (500 mg 3 times daily for 7 days) *or* Erythromycin base (500 mg 4 times a day) for 7 days *or* Erythromycin base (250 mg 4 times daily) for 14 days *or*
	Erythromycin ethylsuccinate (800 mg 4 times daily) for 7 days *or*
	Erythromycin ethylsuccinate (400 mg 4 times daily) for 14 days
LYMPHOGRANULOMA VENEREUM	Aspiration of fluctuant buboes plus doxycycline (100 mg twice daily) for 21 days *plus* erythromycin base (500 mg 4 times daily) for 21 days
TRACHOMA	Azithromycin (20 mg/kg to max of 1 g) as a single dose to the case and all contacts

Data from Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep 2015; 64(RR-03):1-137.

Perinatal Infection

Topical treatment of inclusion conjunctivitis is not recommended because local therapy does not eliminate nasopharyngeal carriage and subsequent risk for pneumonia or recurrent conjunctivitis. Conjunctivitis or pneumonia is treated with a macrolide orally. The efficacy of erythromycin therapy is approximately 80%; a second course may be required in some cases.[102] Erythromycin can have gastrointestinal side effects and interact with other drugs and has been associated with infantile hypertrophic pyloric stenosis (IHPS) in infants <6 weeks of age.[103] Azithromycin suspension was shown to be safe and effective for neonatal chlamydial conjunctivitis in one study.[104,105] The recommended dosage was 20 mg/kg/day for 3 days. A recent retrospective cohort study using the military health system database demonstrated an increased risk for IHPS after drug exposure in the first 14 days of life: after erythromycin (OR, 13.3; 95% CI, 6.80–25.9) and azithromycin (OR, 8.26; 95% CI, 2.62–26); and after exposure between 15 and 42 days of life: erythromycin (OR, 4.10; 95% CI, 1.69–9.91) and azithromycin (OR, 2.98; 95% CI, 1.24–7.20).[106] The risk for IHPS after treatment with other macrolides is unknown.

Prophylactic therapy of infants born to women known to have untreated chlamydial infection is not indicated because the efficacy of such prophylaxis is limited. Such infants should be monitored for signs of infection and to then ensure appropriate treatment.

Oculogenital Infection

Treatment for uncomplicated oculogenital infections in nonpregnant adolescents and adults is doxycycline for 7 days or azithromycin in a single dose.[107,108] Erythromycin is less efficacious than both azithromycin and doxycycline, and gastrointestinal side effects discourage adherence to treatment.

Sex partners should be evaluated, tested, and treated if they had sexual contact with the patient during the 60 days preceding either onset of the patient's symptoms or diagnosis of *Chlamydia*. The most recent sex partner should be treated even if the time of the last sexual contact was >60 days before diagnosis of the index case. Patients do not need to be retested for eradication after completing treatment with doxycycline or azithromycin unless symptoms persist or reinfection is suspected. A test of cure may be considered 3 weeks after completion of treatment with erythromycin. Testing at <3 weeks after completion of therapy to identify cases that did not respond to therapy may not be valid.[109]

Azithromycin is the recommended first choice for treatment of pregnant women, with amoxicillin as the alternative.[107] Doxycycline and ofloxacin are contraindicated in pregnant women. Azithromycin is prescribed widely during pregnancy and lactation and is excreted minimally in breast milk. The benefits of human milk feeding outweigh the risks associated with infant exposure to small amounts of azithromycin.

Lymphogranuloma Venereum

Recommended oral treatment for LGV is doxycycline for 21 days or erythromycin base for 21 days.[107] Fluctuant buboes should be aspirated through intact skin to prevent bubo rupture with formation of sinus tracts.

Trachoma

Trachoma control programs including screening and antibiotic treatment are conducted on a population level. However, on the occasion that an individual comes to attention with symptoms indicating trachoma, the individual should be examined and tested, and if trachoma is diagnosed the case and contacts should be treated with a single dose of azithromycin. Results of trials of mass treatment with single doses of azithromycin at the village level indicate that both infection and clinical disease are decreased markedly at 6 and 12 months later.[110–112]

Complications and Sequelae

Chlamydiae can persist in host cells in a quiescent state for extended periods. *C. trachomatis* has been implicated as a pathogen in 8% to 54% of women who have PID and has been associated with the long-term consequences of tubal infertility (17%), ectopic pregnancy (10%), or chronic pelvic pain (17%).[113] Pregnant women with untreated chlamydial infection are at risk for endometritis after delivery or induced abortions[114] and can experience adverse pregnancy outcomes such as premature rupture of membranes, prematurity,[33] and stillbirth.[77]

C. trachomatis infection and its complications account for serious morbidity and economic cost. In males, epididymitis, prostatitis, and reactive arthritis are the most common sequelae. Furthermore, untreated or incorrectly treated chlamydial conjunctivitis can result in chronic conjunctivitis that can develop alone or as part of Reiter syndrome, which includes urethritis, conjunctivitis, mucosal lesions, and reactive arthritis.

Prevention

Screening of high-risk patients for subclinical *C. trachomatis* infection is the most effective means of preventing disease and sequelae. Behavioral interventions (e.g., delaying intercourse, decreasing the number of sex partners, and using barrier method of contraception) should be pursued aggressively. Women with any of the following risk factors should be tested routinely for *Chlamydia*: mucopurulent cervicitis, sexually active and <20 years of age, >1 sex partner during the last 3 months, or inconsistent use of barrier contraception while in a nonmonogamous relationship.[107] Because of the frequency of repeated chlamydial infections within the first several months after treatment of an initial infection, more frequent (e.g., every 6 months) screening of asymptomatic sexually active adolescents may be necessary.[20] A cost-effectiveness study published in 1998 in women attending family planning clinics revealed that a strategy that combined use of PCR on cervical specimens in women receiving pelvic examinations and use of PCR testing of urine of women with no medical indication for a pelvic examination prevented the most cases of PID and provided the highest cost savings.[115]

Pregnant women should be screened and treated for *C. trachomatis* to prevent adverse pregnancy outcomes, chlamydial infection among infants, and maternal postnatal complications.[107] Mothers of infants who have *Chlamydia* and the male partners of these women should be evaluated, tested, and treated presumptively.

In neonates, ocular prophylaxis with topical erythromycin or tetracycline has reduced the incidence of gonococcal ophthalmia but does not appear to be effective against *C. trachomatis* and can mask infection at other sites.[116]

To combat trachoma, the World Health Organization has endorsed an integrated strategy known as SAFE: *S*urgery for people at immediate risk of blindness, *A*ntibiotic therapy to treat individual active cases and reduce the community reservoir of infection, *F*acial cleanliness and improved hygiene to reduce transmission, and *E*nvironmental improvements to elimination of living conditions that facilitate the maintenance and transmission of trachoma. This strategy has successfully eliminated trachoma in several countries, and global efforts are underway to eliminate blinding trachoma worldwide by 2020.[117]

Chlamydial EBs are extremely efficient invaders of mucosal epithelial cells, and because the replicating RB form resides within an intracellular inclusion, bacterial killing at this stage requires a cell-mediated immune response, with the primary effectors being interferon γ−secreting Th1 cells. Novel delivery methods and Th1-inducing adjuvants that induce strong mucosal T-lymphocyte immunity likely will be necessary for any effective chlamydial vaccine.[118] Attenuated *C. trachomatis* ocular strains devoid of plasmid have shown promise as a vaccine against trachoma in macaques.[119] Incorporation of molecular technology and increasing understanding of the host response to chlamydiae will aid development of vaccine candidates.

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168

Chlamydia (Chlamydophila) psittaci (Psittacosis)

Preeta Krishnan Kutty

The Pathogen

Chlamydia psittaci (also known as *Chlamydophila psittaci*) is a gram-negative obligate intracellular zoonotic bacterium that causes both systemic infection and pneumonia, often referred to as *psittacosis* or *ornithosis* (Fig. 168.1).[1] Originally named *parrot fever* because of its association with psittacines (e.g., parrots, parakeets), psittacosis can be transmitted by virtually all domestic and wild birds.[2,3]

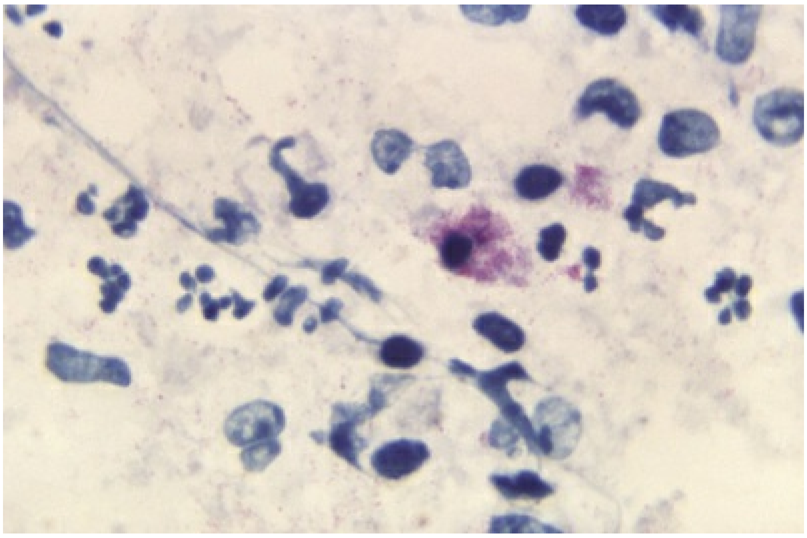

FIGURE 168.1 Photomicrograph of *Chlamydia psittaci*.
(Courtesy of D. Reese, Centers for Disease Control and Prevention.)

Epidemiology

Psittacosis was first described in 1879.[4] It became a nationally notifiable disease in the United States in 1944.[5] From 1992 through 2012, the Centers for Disease Control and Prevention (CDC) received 757 reports of psittacosis, with a decrease in reported incidence over the 20 years (Fig. 168.2). Overall, 9% of cases occurred in people younger than 20 years.[6] The low number of reported cases, especially pediatric cases, is likely an underestimate of the actual number of cases because of (1) lack of recognition by clinicians, (2) difficulties in diagnosis of infection, and (3) underreporting. As of 2008, psittacosis was reportable in all states except Connecticut and Texas.[7] Disease incidence does not vary by season.

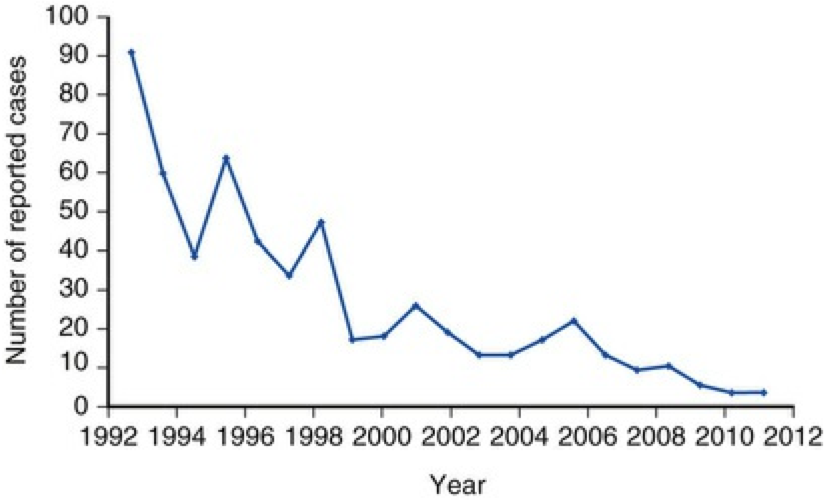

FIGURE 168.2 Cases of psittacosis reported to the Centers for Disease Control and Prevention, 1992 to 2012.

C. psittaci is transmitted through inhaled aerosols from the respiratory tract secretions, eye secretions, urine, or feces of infected birds.[1] Mouth-to-beak contact, handling of plumage, and lawn-mowing have been reported modes of exposure.[8] Illness can occur after even brief exposure to infected birds or their droppings. Most reported psittacosis cases have a known exposure to pet birds. However, outbreaks associated with domiciliary birds, wild birds, poultry processing, veterinary clinics, and aviaries have been described.[9–14] Infected birds can be asymptomatic or only mildly ill and can shed the organism for prolonged periods after recovery.[15] Because *C. psittaci* resists drying and can remain infectious in the environment for months, bird exposure may not be reported in some cases. Although biologically plausible, reports of person-to-person transmission are rare.[16–18] Confirmed and probable cases of psittacosis should be reported to the local or state health department to prevent further transmission.[7]

Clinical Manifestations

Psittacosis classically causes an "atypical" pneumonia. However, the acute disease manifestations can range from a mild, influenza-like illness to severe systemic disease[12,19] (Box 168.1), rarely fatal in humans if treated properly.[20,21] Symptoms generally develop after an incubation period of approximately 5 to 14 days but can occur up to 1 month after exposure.[12] Because signs and symptoms of C.

psittaci infection are similar to those caused by other community-acquired pneumonia pathogens (including *Mycoplasma pneumoniae, Chlamydophila pneumoniae, Coxiella burnetii,* and influenza virus), psittacosis should be considered in any child with pneumonia who has had close exposure to birds.[22,23]

Box 168.1

Clinical Manifestations of *Chlamydia (Chlamydophila) psittaci* Infection

Common

Fever

Chills

Weakness

Fatigue

Myalgia

Headache

Cough

Less Common

Temperature-pulse dissociation (fever without elevated pulse)

Splenomegaly

Rash

Rare

Myocarditis

Hepatitis

Arthritis

Keratoconjunctivitis

Encephalitis

Placental infection and fetal compromise (gestational psittacosis)

Laboratory Findings and Diagnostic Tests

Culture and isolation of *C. psittaci* rarely is undertaken outside research laboratories, largely owing to technical difficulties. Diagnosis usually is made by observing a fourfold or greater increase in antibody in a paired sera (acute and convalescent sera). In the absence of a clear exposure to birds, serologic testing should be interpreted cautiously because of the potential for cross-reactivity with other *Chlamydia* spp. Use of complement fixation is discouraged owing to its poor specificity. Microimmunofluorescence is generally more sensitive and specific than complement fixation; however, there is still some cross-reactivity with other chlamydiae.[1] Acute serum collection should occur as soon as possible after onset of clinical illness, with convalescent serum collection 2 to 4 weeks later. A real-time polymerase chain reaction assay for *C. psittaci* has been developed using respiratory specimens but is available only in specialized laboratories.[24–28] Information on availability of laboratory testing can be obtained from most state public health laboratories.[1]

Treatment

Tetracyclines are the drugs of choice for treating *C. psittaci* infections. In groups for whom tetracyclines are contraindicated (i.e., pregnant women and children younger than 8 years), macrolide antibiotics are considered the best alternative, although in vivo efficacy has not been determined.[29] Clinical response to therapy usually occurs within 48 to 72 hours; however, treatment should continue for 10 to 14 days after fever ceases in order to avoid relapse.[1] Tetracycline resistance has not been reported in *C. psittaci* but has been documented in other *Chlamydophila* spp.[30]

Key Points

Diagnosis and Management of *Chlamydia*

(Chlamydophila) psittaci Infection

Microbiology

- Obligate, intracellular, gram-negative coccobacilli
- Biphasic life cycle; includes two forms: elementary body (infective) and reticulate body (reproductive)

Epidemiology

- Reportable disease in the United States, with decline in incidence since 1990s
- Occurs sporadically and in outbreaks
- Transmitted through inhaled aerosols from the respiratory tract secretions, eye secretions, urine, or feces of infected birds
- Human-to-human transmission documented rarely

Diagnosis

- Clinical presentation and history of exposure to birds
- Paired serum showing more than fourfold increase in antibody titer using microimmunofluorescence
- Serologic cross-reactivity can occur; titer <1 : 128 should be interpreted with caution.
- Real-time polymerase chain reaction assay on respiratory specimens is available within specialized laboratories.

Treatment

- Tetracyclines are the drugs of choice.
- Macrolide antibiotics are considered the best alternative in patients for whom tetracyclines are contraindicated (e.g., pregnant women).

- Clinical response usually occurs within 48 to 72 hours.
- Treatment should continue for 10 to 14 days after fever ceases to avoid relapse.

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Coxiella burnetii (Q Fever)

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The Pathogen

Q fever (or "query" fever) is caused by the intracellular bacterium *Coxiella burnetii*, which belongs to the order Legionellaceae, family Coxiellaceae. *C. burnetii* primarily is a zoonotic pathogen. The organism can be present in high concentrations in the placenta and amniotic fluid of parturient animals and can be transmitted to humans through inhalation or direct contact.[1,2] *C. burnetii* is highly infectious to humans, with infection possible by inhalation of <10 organisms.[3,4] The organism survives and replicates in eukaryotic cells but also is remarkably long-lived in the environment, where it is resistant to environmental extremes and desiccation.[1,2] The organism is thus classified as a Category B bioterrorism agent. Human Q fever was made nationally reportable in 1999.[5]

Variation in the outer lipopolysaccharide of *C. burnetii* causes two antigenic phases: phase I is the pathogenic phase, and phase II is derived after laboratory passage and has low virulence. Persons with acute infection show primarily antibodies directed against phase II antigen, whereas people with chronic Q fever infections predominantly show a phase I antibody response.[6]

Epidemiology

Q fever is enzootic in domestic ruminants throughout the world, and human cases have a similar worldwide distribution.[1] Large outbreaks of Q fever have been reported from numerous geographic locations, including the United States, Australia, and Europe.[1] A particularly large series of outbreaks occurred in the Netherlands in 2007–2010, with >4000 Q fever cases documented.[7] Classically, outbreaks are linked to occupational exposure (farm or slaughterhouse workers) or research institutions that use pregnant livestock in research. Several outbreaks of Q fever have been documented among persons living downwind from infected livestock, strongly implicating windborne transmission.[8,9] Although sheep, cattle, and goats are most commonly implicated in the transmission of Q fever to humans, outbreaks also have been associated with other parturient animal species, including dogs and cats.[10,11] Ticks are known to harbor *C. burnetii* and can transmit infection in rare circumstances.[12,13] Consumption of unpasteurized dairy products also has been suggested as a possible means of transmission.[14]

In the United States, Q fever is widespread in cattle, sheep, and goats, with seroprevalence rates of antibodies to *C. burnetii* of 3%, 16%, and 42% in these animals, respectively.[15] In disease-endemic areas, contact with infected animals can result in sporadic cases or localized outbreaks of Q fever in humans. From 2008 through 2012, the average US annual reported incidence rate was 0.42 per million persons.[16] Because of difficulties in recognizing infection and establishing a diagnosis, the true incidence of infection likely is much higher. Seroprevalence surveys suggest that 3% of the general US population have antibodies to *C. burnetii*.[17] Seroprevalence is likely to be higher among persons with livestock contact; a survey of veterinarians found a seroprevalence of 22%.[18]

Q fever is considered to be a disease primarily of middle-aged adults rather than children, probably because of its strong occupational associations. The reported annual incidence of Q fever in children in the US is less than 0.05 cases per million persons (Fig. 169.1). From 2000 through 2012, a total of 47 cases of Q fever were reported in persons younger than 20 years in the US.[16] Studies examining age distribution in large outbreaks have shown that children less frequently develop symptomatic illness, even when exposures and seroconversion rates are similar to those observed in adults.[19] However, pediatric Q fever cases are recognized, especially in countries where Q fever is reported frequently.[20,21] A report of Q fever infections among children in Greece suggests that specific pediatric age groups (11–14 years of age) and risk factors (livestock contact, consumption of unpasteurized dairy products) may be associated with infection.[21]

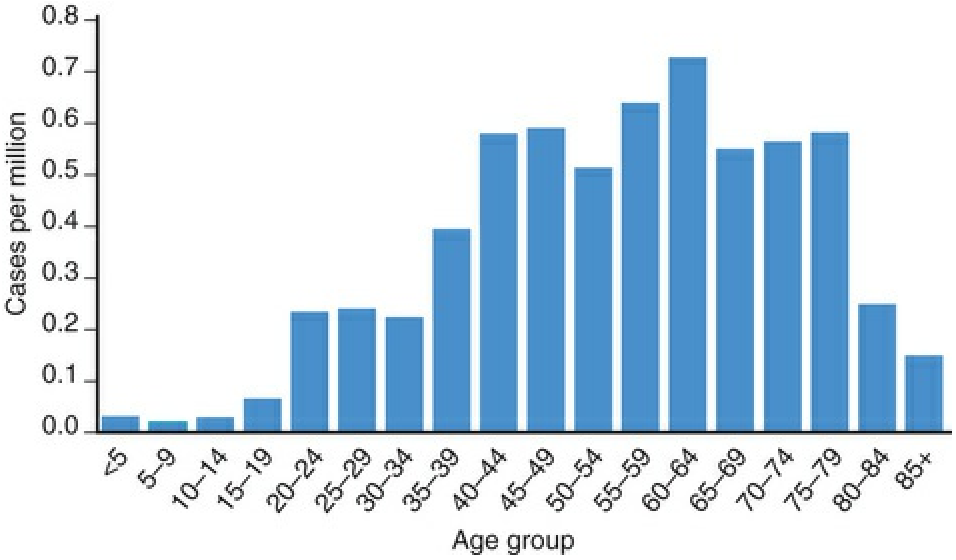

FIGURE 169.1 Cases of acute Q fever per million persons in the United States in specific age groups. The data cover the years 2008–2012. (From Dahlgren FS, McQuiston JH, Massung RF, et al. Q fever in the United States: summary of case reports from two national surveillance systems, 2000–2012. Am J Trop Med Hyg 2015;92:247–255.)

Clinical Manifestations

Outbreak investigations have suggested that >50% of adults and >80% of children exposed to *C. burnetii* can have asymptomatic infection.[19,22] Apparent infections can result in signs and symptoms ranging from mild to severe. Although acute infection may be self-limited, all recognized cases should be treated. Chronic forms of infection are more severe, can be life-threatening, and require long-term treatment.[1,2] Classic symptoms of acute respiratory Q fever in North America include sudden onset with fever, headache (often frontal), chills, general malaise, cough, anorexia, and myalgia. These symptoms should prompt the inclusion of Q fever in the differential diagnosis particularly in patients with a history of exposure to ruminants. However, the lack of direct animal contact should not preclude a clinical suspicion because airborne transmission of *C. burnetii* is possible.

Acute Q fever manifests 1 to 3 weeks after exposure, and symptoms in children usually are similar to those recognized in adults. Acute infection typically is a self-limited febrile illness or pneumonia.[1,2,23] In children, Q fever pneumonia may be characterized by a cough (up to 90% of cases) and radiographic changes that include bilateral infiltrates, atelectasis, and pleural effusion.[23] Respiratory failure and death are uncommon but can occur in patients with underlying conditions.[24] A review of 18 cases of Q fever in infancy listed fever of unknown origin as the most frequent clinical manifestation; pneumonia, convulsions, and malaise also were reported.[25] Common clinical signs among infants in the series included anorexia, cough, and diarrhea.[25] In a review of hospitalized children with Q fever in Spain, common symptoms included fever (92%), gastrointestinal tract symptoms (83%), hepatomegaly (67%), fatigue (50%), cough (50%), headache (42%), splenomegaly (25%), arthralgia (17%), and nuchal rigidity (8%).[19,26] In a review of pediatric Q fever cases in Australia, most experienced a clinical illness similar to illness observed in adults, and 14% reportedly experienced protracted symptoms of fatigue >3 months after acute infection.[20] More severe manifestations of acute disease include severe atypical pneumonia, hepatitis, myocarditis, pericarditis, rhabdomyolysis, or meningoencephalitis.[1,2,19,21,26–29] A case of hemolytic uremic syndrome has been reported.[30]

Chronic Q fever occurs months or years after the initial acute infection and can be difficult to diagnose because of its lack of a temporal association with specific exposures. Chronic infection is characterized by development of chronic hepatitis, osteomyelitis, infective endocarditis, or vascular infection.[1,2,19,27,31,32] Children with Q fever osteomyelitis may not show systemic illness but often experience recurrent episodes at multiple sites, which are poorly responsive to traditional treatment.[31] Children with a history of underlying heart valve disease or immunocompromising conditions may be at increased risk for developing chronic Q fever endocarditis, which manifests as culture-negative endocarditis.[19] Chronic Q fever endocarditis can be fatal, especially if it is not recognized and treated.

Laboratory Findings and Diagnosis

Abnormal laboratory findings in children with Q fever include elevation of serum hepatic enzymes, leukopenia or leukocytosis, and thrombocytopenia.[2,26] Because of the vague clinical signs associated with Q fever, most physicians rely on serologic tests for confirmation. Indirect immunofluorescent antibody assays are used most commonly. These tests can detect either phase I or phase II antibodies, which can help differentiate between acute and chronic infection.[6] In general, chronic infections are associated with a higher ratio of phase I to phase II antibodies than acute infections.[6]

Although considered the gold standard for diagnosis, serologic confirmation of Q fever infection can be difficult. Most serologic tests are based on detection of immunoglobulin G (IgG), which usually appears 9 to 14 days after onset of clinical signs.[6] Laboratory confirmation is complicated further by the persistence of elevated IgG titers for years after infection[33]; a single elevated IgG titer may not be strong evidence of recent infection. The presence of IgM antibodies is stronger evidence of recent infection; IgM antibodies appear as early as 4 days after symptom onset.

The most reliable method for diagnosis of Q fever is the laboratory testing of acute- and convalescent-phase serum samples. Paired serum samples that show a fourfold change in phase II IgM or IgG titer should be considered indicative of confirmed cases of Q fever for reporting purposes.[5] Patients with a clinically compatible illness who show a single elevated titer should be considered probable cases.[34] Chronic Q fever is confirmed in patients with a compatible clinical illness (e.g., endocarditis, vascular infection), whose phase I IgG titer is ≥1 : 1024.[34]

Demonstration of *C. burnetii* in blood or tissue samples through polymerase chain reaction (PCR), immunohistochemistry, or culture also can be used for diagnosis.[34] PCR on blood or serum is essential for diagnosis in the early stages of infection before antibody titers are detectable.[35] Immunohistochemistry and culture are useful on excised heart valve tissue for patients with endocarditis undergoing valve replacement surgery. Only biosafety-level 3 laboratories should attempt isolation and culture of the organism.[1]

Treatment

Because a definitive diagnosis of Q fever can be delayed, clinicians should provide empiric treatment based on a suspicion of Q fever. Although most cases of acute Q fever infection resolve without treatment, antibiotic treatment may shorten the length of clinical illness.[1,2,19] For treatment of acute Q fever in children of any age, doxycycline (2.2 mg/kg twice daily, with a maximum of 200 mg/day) should be administered for 14 days.[34] Studies suggest that this dosage and duration of doxycycline will have no appreciable effect on tooth color.[36,37] Alternative antibiotics that might be considered in milder cases include trimethoprim-sulfamethoxazole or rifampin.[19]

Treatment of chronic Q fever requires aggressive, long-term antibiotic therapy. In adults, combination therapy consisting of oral doxycycline and hydroxychloroquine for at least 18 months usually is required.[19,38] Even with long-term therapy, relapse can occur after cessation of antibiotic treatment. An infectious diseases specialist should be consulted regarding treatment and serologic follow-up of chronic Q fever in children.

Special Considerations

Children with chronic immunosuppressive conditions may be at increased risk for Q fever infection. A fatal case of Q fever pneumonia is reported in a child with chronic granulomatous disease,[24] and patients with congenital heart defects or chronic immunosuppressive conditions may be predisposed to develop Q fever endocarditis.[19] Patients with preexisting valvular heart disease should have careful consideration and serologic monitoring to optimize early detection and rapid treatment of chronic *C. burnetii* infection.

Case reports have associated *C. burnetii* infection during pregnancy with abortion or premature delivery, and *C. burnetii* has been isolated from the placenta and milk of infected mothers.[19,39,40] Infected women may pose a risk for infection to healthcare providers during delivery because of aerosolization of infectious material.[40] Pregnant women who are diagnosed with Q fever should be treated with trimethoprim-sulfamethoxazole up to 32 weeks' gestation, and followed serologically to evaluate possible progression to chronic infection.[19,41]

Prevention

Children can be protected by minimizing contact with parturient and newborn animals, especially livestock, including sheep, goats, and cattle. Adults who come in contact with parturient or newborn animals should take care to minimize their own contact with children until they can shower and wash potentially contaminated clothing.[11] Because dairy products sometimes have been implicated as a means of transmission, children should be allowed to consume only milk and dairy products that have been boiled or pasteurized. A Q fever vaccine is not currently licensed for use in the US, but a licensed vaccine is available in Australia. Its use generally is limited to persons with high-risk occupations, such as abattoir workers and laboratory scientists who work with *C. burnetti*.[1,2,42]

Key Points

Diagnosis and Management of *Coxiella burnetii* Infection (Q Fever)

Microbiology

- Obligate intracellular, gram-negative γ-proteobacterium
- Grows in embryonated eggs, mice, guinea pigs, or tissue culture of host cells

Epidemiology

- Zoonotic pathogen with worldwide distribution
- Cases and outbreaks usually are associated with exposure to domestic ruminants.
- Occupational exposure to infected animals is a significant risk

factor.

- Seroprevalence in US persons is 3%.

- Disease likely is underreported owing to nonspecific flu-like symptoms.

Clinical Manifestations and Diagnosis

- Acute form Q fever usually manifests 1 to 3 weeks after exposure with flu-like symptoms, sometimes also with pneumonia and/or hepatitis.

- Chronic Q fever can develop many months after infection.

- Chronic infection can result in culture-negative endocarditis (possibly requiring valve replacement) or osteomyelitis.

- Detection of fourfold rise in phase II immunoglobulin G serum antibody titer is the most common method of diagnosis.

- Antibody titer usually does not increase until at least 2 weeks after symptom onset.

- Polymerase chain reaction assay can detect *Coxiella burnetii* in blood or serum samples during first 2 weeks of symptoms.

Treatment

- Doxycycline (2.2 mg/kg twice a day, maximum of 200 mg/day) is the optimal treatment.

- No significant drug resistance is reported.

- Acute infection: 14-day course of antibiotic

- Chronic infection: ≥18 months of therapy may be needed; relapse is not uncommon.

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Family Anaplasmataceae (*Anaplasmosis, Ehrlichiosis, Neorickettsiosis,* and *Neoehrlichiosis*)

William L. Nicholson

Description of the Pathogens

The family Anaplasmataceae is classified in the order Rickettsiales and currently contains five genera and two candidate genera of obligate intracellular bacteria. Four of the genera contain members that are known to infect humans: *Anaplasma, Ehrlichia, Neorickettsia,* and "*Candidatus* Neoehrlichia." These zoonotic bacteria are transmitted by invertebrate vectors and can cause potentially life-threatening diseases in humans and animals. Their natural cycles are maintained through vector transmission among wildlife or domestic animals. Five species in the genus *Ehrlichia* and four species in the genus *Anaplasma* are documented as causes of human disease, and multiple species have been reported from children and adolescent patients worldwide (Table 170.1). Globally, thousands of human cases due to Anaplasmataceae are reported each year, particularly in the United States. The dominant species responsible for disease in the US are *Ehrlichia chaffeensis, E. ewingii*, *E. muris eauclairensis*, and *Anaplasma phagocytophilum*. As new species are characterized, it is likely that additional Anaplasmataceae capable of causing human disease may be discovered in the future.

TABLE 170.1

Characteristics of Bacterial Species in the Family *Anaplasmataceae* That May Infect Humans

Species[a]	Geographic Distribution	Primary Target Host Cell	Primary Invertebrate Vector
Ehrlichia chaffeensis	North America (some evidence for infection in S. America, Africa, and Asia)	Monocytes, macrophages	*Amblyomma americanum*
Ehrlichia ewingii	North America (some evidence for infection in Africa and Asia)	Granulocytes	*Amblyomma americanum*
Ehrlichia muris muris	Asia (PCR-positive cases from Far East Russia)	Undetermined (perhaps monocytes)	*Ixodes persulcatus*
Ehrlichia muris eauclairensis[b]	North America (found only in Minnesota and Wisconsin)	Undetermined (may be found in endothelial cells of infected mice)	*Ixodes scapularis*
Ehrlichia canis	Worldwide (limited human cases in Venezuela)	Monocytes, macrophages	*Rhipicephalus sanguineus*
Ehrlichia ruminantium	Africa, North America (Panola Mountain strain in US) (uncommon)	Endothelial cells	Several *Amblyomma* spp. (*A. americanum* in US)
Anaplasma phagocytophilum	Worldwide	Granulocytes	*Ixodes scapularis, I. pacificus* (North America), *Ixodes ricinus* (Europe), *Ixodes persulcatus* (Asia)
Anaplasma platys	Worldwide (limited human cases reported from Venezuela, US)	Platelets	*Rhipicephalus sanguineus* (suspected)
Anaplasma ovis	Europe, Asia, Africa, North America (human cases in	Erythrocytes	*Rhipicephalus bursa, R. sanguineus* (suspected); *Dermacentor andersoni* (US)

	Cyprus and Iran)		
"Anaplasma capra"[c]	China (multiple human cases)	Undetermined (bone marrow precursor cells or endothelial cells suspected)	*Ixodes persulcatus*
Neorickettsia sennetsu	South-East Asia (uncommon)	Monocytes, macrophages	Trematodes (transmission is by ingestion of fish infested with flukes infected with neorickettsiae)
"*Candidatus* Neoehrlichia mikurensis"[d]	Europe, Asia (multiple human cases), Africa (one human case)	Endothelial cells (seen in infected animals, but not yet shown in humans)	*Ixodes ricinus* (Europe), *Ixodes persulcatus* (Asia)

[a] Bold indicates documented cases in the pediatric population.

[b] Formerly designated the *Ehrlichia muris*–like agent, but has now been recognized as a subspecies of *E. muris*.

[c] This species name has been proposed for the agent cultured from humans and animals, but a published description following the rules of the International Code of Nomenclature of Bacteria will be required to formally name the species.

[d] This taxon is biologically and genetically distinct. Although the candidate genus and species have been proposed and used in the literature, a formal description published according to the rules of the International Code of Nomenclature of Bacteria will be required for recognition of these designations as valid names.

Data from References 7, 19–33.

Ehrlichia and *Anaplasma* species are small (0.5–1.5 μm) gram-negative cocci.[1] The genomes of these organisms are relatively small, with a size of 1.18 Mb for *E. chaffeensis* and 1.47 Mb for *A. phagocytophilum*.[2] After attachment to membrane receptors on the surface of target cells and subsequent induction of phagocytosis, the organisms multiply in endosomes that fail to develop into mature phagocytic or lysosomal vacuoles. Organisms reside within the cell cytoplasm of infected cells (monocytes, granulocytes, macrophages, erythrocytes, platelets, and endothelial cells, depending on the species). Organisms replicate within membrane-bound vesicles to form microcolonies known as morulae.[3] The morphologic features of morulae vary among the species in size, number of individual organisms, and presence of a fibrillar matrix (Fig. 170.1). Individual morulae can contain few to many bacteria, which are released into the extracellular space after cell lysis or by exocytosis after fusion of the vacuole membrane with the plasma membrane. *Ehrlichia* spp. can spread to uninfected cells by concentration in filopodia in early infection and by host cell membrane rupture in late infection. *Anaplasma* are released by host cell lysis without loss of host cell cytoplasm.[3,4] *Neorickettsia sennetsu* is found in monocytic cells of blood and lymph nodes, whereas the target cell of "*Candidatus* Neoehrlichia mikurensis" is not yet known for humans. It has been found in endothelial cells of infected rodents.

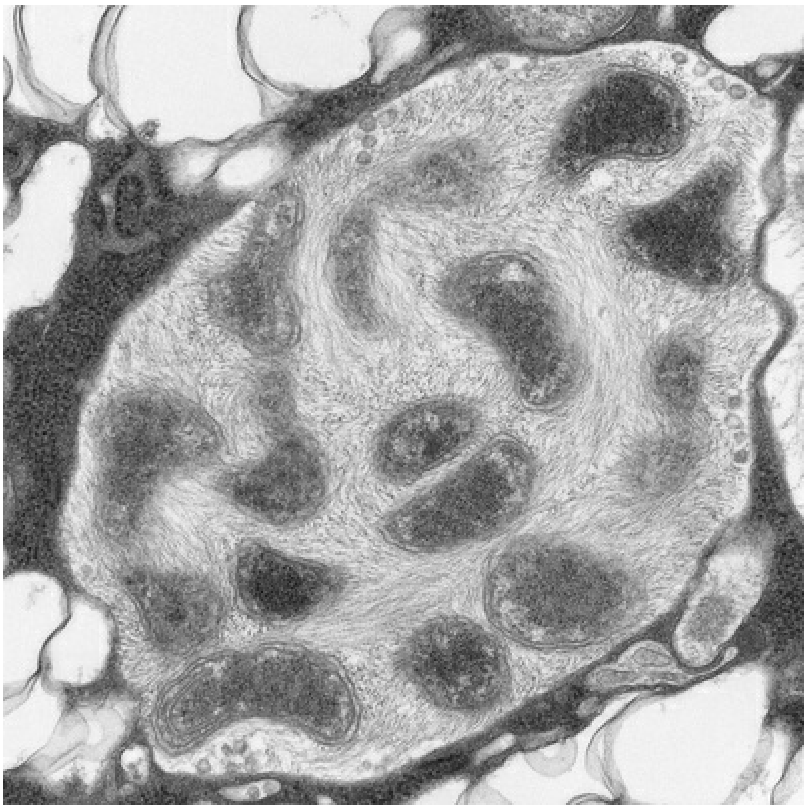

FIGURE 170.1 Electron micrograph of *Ehrlichia muris eauclairensis* morula within an infected endothelial cell (RF/6A). Note the fibrillar material among the pleomorphic organisms contained in the vacuole.

Ehrlichia and *Anaplasma* spp. have developed adaptive mechanisms to subvert the host cell response and increase their survival.[3,5] Immune response of the host appears to be responsible for the pathology seen in infected patients, and cytokine and chemokine production by infected tissues may lead to more severe damage. Perivascular inflammatory infiltrates become apparent in many organs, and morulae can be visualized within the leukocyte populations present in these infiltrates. Mechanisms of many of the hematologic and biochemical perturbations (e.g., cytopenia and abnormal serum hepatic enzyme levels) are not completely clear.[6] It is noteworthy that these infections do not usually cause the vasculitis or endothelial damage characteristic of other rickettsial diseases, such as Rocky Mountain spotted fever.

Epidemiology

Ecologically, the species of Anaplasmataceae are usually maintained in wild or domestic mammalian species and are transmitted within that system and to humans though invertebrate vectors, most often through the bite of a hard tick (Acari: Ixodidae).[7,8] The pathogens are distributed within the geographic ranges of their primary tick vectors.

The members of the Anaplasmataceae can infect persons of all ages but are more frequently recognized in older adults. More than half of patients are hospitalized, and infections can result in life-threatening illness.[9] The epidemiology of infections in children is derived from case reports and case series in the literature.[10–15] *E. chaffeensis* accounts for most Anaplasmataceae infections seen in the pediatric population. In the most recent surveillance summary, the case fatality rate was highest in children younger than 5 years and in adults 70 years and older.[16] Active surveillance for *A. phagocytophilum* (also called human granulocytic anaplasmosis) indicates that the age-specific incidence is notably low in persons younger than 18 years and is highest in adults older than 50 years. Reasons for low case numbers in younger patients remain unclear, and the frequency of asymptomatic infection in children is unknown. Seroprevalence studies using generally accepted cutoff titers suggest that about 5.3% of children 19 years or younger in an endemic area of New York had antibodies to *A. phagocytophilum*,[17] and another study indicated that 13% of children aged 17 years or younger in the south-central and southeastern US had antibodies to *E. chaffeensis*.[18]

Infections by the Anaplasmataceae occur throughout the world, yet specific pathogens occur in certain regions or countries[7,19–33] (see Table 170.1). *A. phagocytophilum* has been documented in many countries, whereas *E. chaffeensis* is thought to occur primarily in the US. *E. chaffeensis* or antigenically similar organisms (some supported by molecular evidence) have been detected in other countries, suggesting a wider range than appreciated currently.[34] *N. sennetsu* generally is limited to South East Asia and has more recently re-emerged in Laos.[22] Despite the fact that "*Candidatus* Neoehrlichia mikurensis" is widespread in rodents and ticks in Europe and Asia, human cases have not been numerous, and childhood infection has not been documented.[33,34] Further study utilizing culture and multiple molecular targets for Anaplasmataceae infections will enhance our knowledge of emerging pathogens and help determine their threat to public health.

In the US, national passive surveillance found a fourfold increase in the number of ehrlichiosis cases reported from 2008–2012 compared with 2000.[16] From 2008–2012, 4613 cases of *E. chaffeensis* were recorded. The incidence rate was 3.2 cases/million person-years, with a 57% hospitalization rate and 1% case fatality rate. The highest case fatality rate (4%) was seen in children younger than 5 years. During this same period, 55 cases of *E. ewingii* were reported to national surveillance. The incidence rate was 0.04 cases/million person-years, with a 77% hospitalization rate. No death was recorded. Cases occurred across the southeastern and south-central US and in New Jersey and Indiana.[16,35] Although in previous studies infection primarily affected patients with altered immune status, cases reported more recently have occurred in previously healthy persons.

The US cases of anaplasmosis also increased in national surveillance system reports.[36] From 2008–2012, a total of 8896 cases of *A. phagocytophilum* infection were reported, with an overall incidence of 6.3 cases/million person-years. Cases were reported from 38 states, and the highest incidence was seen in Minnesota (97 cases/million person-years), Wisconsin (79), and Rhode Island (51). The hospitalization rate was 31%, with a case fatality rate of 0.3%. Increasing age was associated with incidence, hospitalization, and case fatality rates.

From 2008–2012, a total of 726 cases of ehrlichiosis or anaplasmosis for which the specific etiology could not be determined based on available test results also were reported through national passive surveillance.[37] When active case finding is conducted, both ehrlichiosis and anaplasmosis show incidences a magnitude higher than national passive surveillance.

Human ehrlichioses and anaplasmosis share certain epidemiologic features. In addition to being reported most commonly in adults, cases are reported most frequently in males.[6] Approximately 60% of the recorded pediatric cases have occurred in boys.[10–12] Although cases can occur throughout the year, the peak seasonal incidence of disease is in May through August.[9,38–40] Although generally a sporadic disease, clusters of cases have occurred during recreational activities and occupational exposure. Certain populations may be disproportionately affected by rickettsial diseases. It has been shown that American Indians in the US had a higher incidence rate of infection than other races.[41] Although ehrlichiosis and anaplasmosis generally increase with age, American Indian cases had more cases in the lower age groups. Most American Indian cases were reported from geographic regions endemic for ehrlichiosis, which may reflect increased exposure.

The endemic region for specific diseases can be reasonably approximated by the geographic distribution of each agent's primary tick vector.[34,42] The pathogens are maintained in a variety of domestic and wildlife animal hosts by tick bite transmission. Infections caused by *E. chaffeensis* and *E. ewingii* are associated with the bite of the lone star tick, *Amblyomma americanum*.[34,40,42] This tick is primarily distributed across central Texas and eastern Oklahoma, eastward throughout the southeastern US, and northerly along the Atlantic coastal plain into New England. The greatest number of cases of *E. chaffeensis* ehrlichiosis and those caused by *E. ewingii* have been reported from the southeastern and south central US.[16] The recognized geographic range of *A. americanum* is expanding, suggesting that the area of risk for ehrlichial pathogens transmitted by this vector should be considered dynamic.[42,43] Most anaplasmosis cases have occurred in the north central and northeastern states, particularly New York, Connecticut, Minnesota, and Wisconsin.[36,39,44] The principal tick vector is the blacklegged tick, *Ixodes scapularis,* the same tick that transmits *Borrelia burgdorferi*.[42] This tick also is expanding its range, and more states reported anaplasmosis cases from 2008–2012 compared with previous years.[36,45] In the western US, *Ixodes pacificus* is the main vector of *A. phagocytophilum* to humans and animals.[42,44] In Europe, *Ixodes ricinus* has been incriminated in Europe, while *Ixodes persulcatus* is the primary vector in Asia.[44]

Ticks in the genus *Ixodes* can transmit several other pathogens, including *Babesia* spp., flaviviruses, and *B. burgdorferi.* Dual infections with *A. phagocytophilum* and *B. burgdorferi* have been reported.[46] In some children, the concurrent presence of anaplasmosis and Lyme disease has resulted in more severe disease.[47]

Other Anaplasmataceae.

E. muris eauclairensis recently has been recognized in Minnesota and Wisconsin.[25] More than 70 cases have been reported from residents or travelers to these two states. The epidemiology is not fully understood, but evidence suggests that *E. muris eauclairensis* can be found in white-footed mice and *I. scapularis* ticks at low levels. There are at least two polymerase chain reaction (PCR)-confirmed and 84 serologically diagnosed cases attributed to *E. muris muris* infection in the Perm region of Russia, whereas Japanese investigators reported a 1.1% seroprevalence of antibodies against *E. muris muris* among Tokyo residents.[26,29]

"*Candidatus* Neoehrlichia mikurensis" has been reported in elderly patients in Europe and Asia, yet pediatric cases have not been reported. Most patients were immunocompromised, and a majority were asplenic.[33,34] *Neorickettsia sennetsu* infection, also known as sennetus or glandular fever, is not common, with <100 reported cases in Southeast Asia since its first description in 1954.[22] The pathogen is thought to be transmitted by ingestion of raw or improperly cooked fish. The fish are infested with digenean trematodes (flatworms) that are, in turn, infected by the neorickettsiae. Other species (see Table 170.1) have been associated with human disease, but further investigation is needed to learn more about these emerging pathogens.

Clinical Manifestations

Children and adults come to attention with fever, malaise, headache, and myalgia. Laboratory abnormalities include leukopenia, thrombocytopenia, and increased serum hepatic transaminase levels. These early clinical features may resemble other infectious and noninfectious diseases. A high level of suspicion is important, particularly when obtaining a complete epidemiologic and travel history. Outdoor activities (occupational or recreational) can increase the risk for tick bite. Patients may not recall tick bites because of the small size of ticks and the fact that the tick is not often attached at presentation. Clusters of ehrlichiosis or anaplasmosis can occur geographically or temporally; asking about illness in associates or family can be helpful. History of travel within the US or to other countries will provide valuable clues to the possible etiology of suspected imported Anaplasmataceae infection (see Table 170.1).

The incubation period typically is between 5 to 21 days after a recognized tick bite.[39] Many parents and children (55% to 85%) recall a tick bite several days to weeks before the illness.[10,12,13] Common symptoms in children include fever, myalgia, and headache. Additional clinical features include anorexia, nausea or vomiting, and less frequently, hepatomegaly or spenomegaly.[12,42,46,48] In adults with *E. chaffeensis* infections, rash is seen in only about 25%, yet rash occurs in about 66% of children.[6,12,42] Fewer than 10% of patients infected by *A. phagocytophilum* exhibit a rash.[39,42] When present, rash typically involves the trunk (sparing the hands and feet) and can appear macular, papular, maculopapular, or occasionally petechial. Gastrointestinal tract symptoms, including nausea, vomiting, anorexia, and diarrhea, are observed in approximately 60% of children with ehrlichiosis, slightly greater than that reported in adults with *E. chaffeensis* infection.[12,42] Adults with anaplasmosis have gastrointestinal tract symptoms less frequently (<40%).[42,44]

Moderate to severe headache is a common feature regardless of etiologic agent; however, encephalitis or meningitis is most commonly reported with *E. chaffeensis*.[6] Long-term neurologic sequelae, including bilateral footdrop, speech impairment, and diminished reading and fine motor ability, have been described in children after severe disease.[6,12,13]

Infections can result in severe pulmonary disease and may be a cause of acute respiratory distress syndrome in adults or children.[6,13] Intubation and mechanical ventilation have been required for severe cases of *E. chaffeensis* ehrlichiosis.[12,13,49] As in adults, the most severe disease in children is associated with infection by *E. chaffeensis.* Immunosuppressive conditions, including chemotherapy and organ transplantation, may predispose children to more severe disease by *E. chaffeensis.*[13,50]

Presumably, the same or similar conditions predispose children to infection by *E. ewingii*. The first report of *E. ewingii* disease was in an 11-year-old boy receiving immunosuppressive therapy after kidney transplantation, and there have been recent case reports of severe *E. ewingii* infections in children with acute lymphoblastic leukemia and sickle cell disease.[13,14,51,52]

Opportunistic infections may occur in patients as a result of alterations in neutrophil and $CD4^+$ lymphocyte function.[7] Disseminated candidiasis, invasive pulmonary aspergillosis, *Cryptococcus neoformans* pneumonia, herpes simplex, and cytomegalovirus infections have been noted.[39,42,53] Reinfection of the same patient with *E. chaffeensis* has been reported and reinfection with *A. phagocytophilum* has been documented.[54,55]

Other Anaplasmataceae.

Frequent symptoms of neoehrlichiosis included fever, localized pain afflicting muscles or joints, vascular and thromboembolic events, transitory ischemic attacks, pulmonary embolism, and arterial aneurysm.[33] *Neorickettsia sennetsu* infection is characterized by fever, weakness, anorexia, and lymphadenopathy.[22]

Laboratory Findings and Diagnostic Tests

Differential diagnosis for Anaplasmataceae infections can be difficult because of the broad spectrum of clinical features. Early in the illness, the nonspecific findings of fever, headache, myalgia, nausea, and malaise can be mistaken for various viral syndromes, upper respiratory tract illness, septicemia, urinary tract infection, or gastroenteritis. A history of a tick bite is helpful in diagnosis of tick-borne illness, but clinical features may be similar to other tick-transmitted pathogens.[42]

Leukopenia (<4000 white blood cells/mm^3), thrombocytopenia (<150,000 platelets/mm^3), and elevations in liver transaminase levels (aspartate aminotransferase >55 U/L) characteristically develop in patients of all ages early in the course of the illness. These laboratory findings provide early presumptive clues to the diagnosis of Anaplasmataceae infection regardless of the specific agent.[12,13,42] Leukopenia occurs with both *E. chaffeensis* and *A. phagocytophilum* infection, with the nadir typically between 1000 and 4000/mm^3. Lymphopenia is common in patients with ehrlichiosis and anaplasmosis, and neutropenia is reported in adults with anaplasmosis.[42] Thrombocytopenia is reported in >70% of patients, with platelet counts generally between 50,000 and 150,000/mm^3. Anemia is reported in about one third of children with *E. chaffeensis* infection. The bone marrow of cytopenic patients usually is normocellular or hypercellular, suggesting that the leukopenia and thrombocytopenia could be due to peripheral sequestration or destruction.[6]

Mildly or moderately elevated levels of serum transaminases occur in most children infected by *E. chaffeensis*.[12,13,39,42] Alkaline phosphatase levels are less affected. Electrolyte abnormalities, particularly mild to moderate hyponatremia, are noted frequently in children and adults with severe disease.[11,12,42]

Cerebrospinal fluid (CSF) pleocytosis, elevated protein levels, or both most often are reported in patients with *E. chaffeensis* ehrlichiosis, as are episodes of confusion, disorientation, or delirium.[6] Morulae of *E. chaffeensis* have been identified in mononuclear cells in the CSF, and the organism has been isolated from the CSF of patients with ehrlichiosis.[42,56]

Other Anaplasmataceae.

General laboratory findings for neoehrlichiosis showed leukocytosis with neutrophilia, anemia, and elevated C-reactive protein levels. Peripheral blood smears can show atypical lymphocytes.

Diagnostic Testing

Targeted serologic and molecular laboratory methods can be used to confirm the diagnosis of ehrlichiosis or anaplasmosis, and many tests are available from commercial laboratories. More specialized testing may be available through state and national public health laboratories, specialized reference laboratories, or academic research centers. Diagnostic methods include serologic tests to measure specific antibody titers, detection of DNA by PCR assays of blood or CSF, detection of morulae in peripheral blood or CSF leukocytes, direct detection of ehrlichiae in tissue samples by immunohistochemistry, and isolation of the bacteria from clinical specimens.[9,42,57]

Indirect immunofluorescence can be used to detect *E. chaffeensis* or *A. phagocytophilum* immunoglobulin M (IgM) or IgG antibodies in serum or plasma. There are no serologic tests for *E. ewingii*. Specific serologic testing for the less common Anaplasmataceae affecting humans is limited to several commercial or research laboratories. A fourfold rise in IgG antibody titer between acute-phase (at healthcare presentation) and convalescent-phase (2–4 weeks later) serum samples can confirm the diagnosis in a patient with acute illness. Immunofluorescence assay tests to detect IgG and IgM antibodies frequently are negative in the first week of illness, providing limited diagnostic assistance, and do not exclude Anaplasmataceae infections. IgM titers can remain elevated for lengthy periods after treatment and resolution of disease. Antibodies reactive with other species can be seen in 10% to 30% of patients' sera and may be due to cross-reactive epitopes or with separate exposure events. However, antibodies cross-reactive with *E. chaffeensis* antigens can be useful in diagnosing some cases of *E. ewingii* infection.[42,51]

Identification of intraleukocytic morulae in peripheral blood, CSF, or bone marrow aspirate preparations stained with an eosin azure–type stain (e.g., Wright-Giemsa, Diff-Quik) may be used for presumptive diagnosis (Fig. 170.2).[56] Artifacts, toxic granules, and overlying platelets can sometimes be misinterpreted as morulae. Morulae are identified in leukocytes from patients with anaplasmosis (25%–75%) more often than from those with ehrlichiosis (~25%).[42,58]

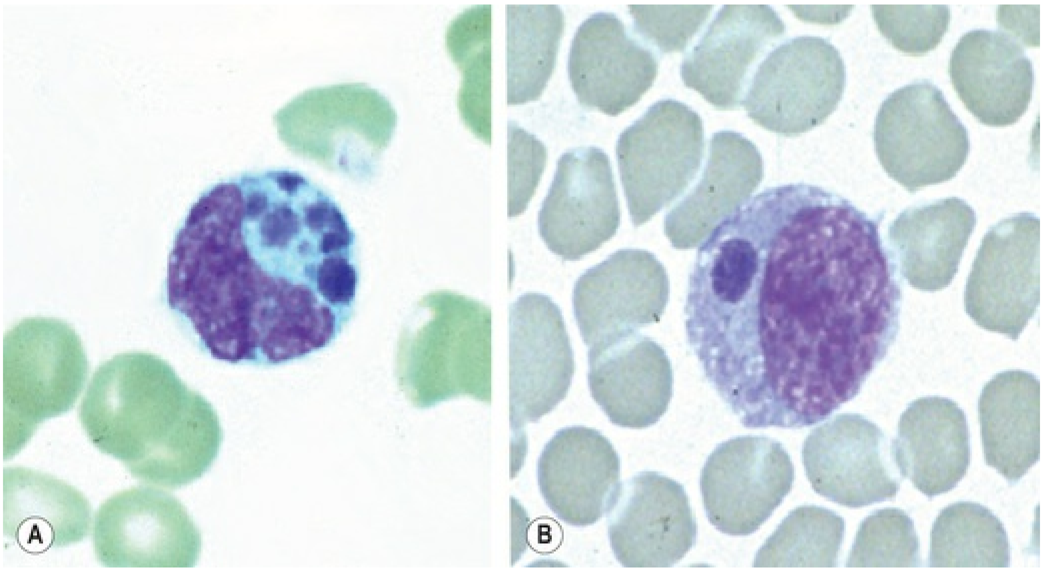

FIGURE 170.2 (A and B) Morulae of *Ehrlichia chaffeensis* as seen on Wright stain of mononuclear cells in the peripheral blood of patients with ehrlichiosis.

Molecular methods of laboratory diagnosis have greatly enhanced the detection and specific identification of rickettsial pathogens.[42,57,59] Although proven very useful for Anaplasmataceae infections, PCR also is the primary means by which *E. muris eauclairensis* and *E. ewingii* infections are identified in the US.[16,25,37] Positive results can be obtained from acute-phase whole blood samples before specific antibodies are detectable.[58] PCR is most sensitive during early infection (0–4 days) and is significantly less sensitive as the disease progresses.[60] Detectability by PCR declines rapidly after the first 24–48 hours of doxycycline treatment.

Cultivation of the microorganisms in a variety of susceptible cell lines provides a valuable means of diagnosis; however, this approach requires appropriate laboratory facilities and trained staff. Appropriate samples include blood, buffy coat, separated leukocytes, CSF, or other autopsy tissue samples, and primary isolation can take several days up to several weeks.[61,62] The sensitivity of other laboratory procedures compared with isolation has been investigated in only a few circumstances because isolation of these organisms is seldom attempted in clinical laboratories.[42] Cultivation has not yet been accomplished for *E. ewingii* or “*Candidatus* Neoehrlichia” infections.

Treatment

Anaplasmataceae infections respond well to appropriate antibiotic treatment.[9,42,63] When any rickettsial disease is suspected, appropriate antibiotic treatment should be initiated before laboratory results are available. Delayed treatment can increase rate of transfer into intensive care, increase duration of hospitalization, and increase length of illness.[64] Doxycycline is the drug of choice for adults and children of *all ages* infected with any Anaplasmataceae species.[13,39] For children, 2.2 mg/kg administered orally or intravenously every 12 hours is recommended. For older children and adults, the maximal (adult) dose is 100 mg administered orally or intravenously every 12 hours. Most patients can be treated with oral therapy, but severely ill patients or patients unable to tolerate oral medications are given doxycycline parenterally. Treatment length is variable, but typically is 7 to 14 days (at least 3 days after defervescence). Doxycycline therapy for 2 weeks may be required in patients coinfected with *A. phagocytophilum* and *B. burgdorferi* (Lyme disease).[42] The reluctance to treat children younger than 8 years with doxycycline generally is unfounded. Multiple studies have shown that short-term use of doxycycline, as is used for rickettsial infections, is safe and does not cause discoloration of teeth.[9,63,65]

With appropriate therapy, most patients defervesce within 24 to 48 hours. Indeed, failure to respond to a tetracycline antibiotic within the first 3 days should suggest possible infection with a nonrickettsial agent. Other clinical manifestations generally subside over the next 2 weeks, and patients recover completely. Occasionally, headaches, generalized weakness, and malaise can persist for several weeks after recovery from the acute febrile illness.

Special Considerations

Alternative treatment or prolonged treatment of infections is warranted only in rare circumstances. Alternate drugs have been used with limited numbers of patients. Chloramphenicol appears ineffective against *E. chaffeensis* when tested in cell culture systems, and treatment failure has been reported with this drug in some patients, including death in one child.[9,11,42]

Antibiotics used frequently for empiric treatment of bacterial infections in febrile patients (e.g., β-lactams, macrolides, aminoglycosides, and fluoroquinolones) are ineffective in treating Anaplasmataceae infection. Although levofloxacin has in vitro activity, it appears only to inhibit organisms, and infection recrudesces when drug is discontinued. Additionally, anecdotal evidence suggests that sulfa-containing antimicrobial agents may increase the severity of the disease. Descriptions of pediatric patients with severe or fatal infections include reports of children to whom sulfonamides were administered for a week or longer before the disease was diagnosed correctly.[49,53,66] It remains unclear whether use of sulfa drugs resulted in delayed diagnosis or exacerbation of infection.

Rifampin may be a suitable drug for use in patients with allergies, gastric intolerance, or phototoxic hypersensitivity to doxycycline. Limited numbers of *A. phagocytophilum* infections have been successfully treated with rifampin during pregnancy.[9,67–70] Healthy uninfected infants were delivered after treatment of the pregnant mothers at 17, 25, and 39 weeks' gestation. Rifampin has been used at a dose of 10 mg/kg given twice daily as single-agent therapy in two children with acute human granulocytic anaplasmosis.[68] Rifampin has been successfully used for treatment of *E. chaffeensis* infection in one adult patient.[69]

Prevention

No vaccine for any member of the Anaplasmataceae is available currently for humans, thus prevention of exposure through tick bite prevention is essential. Prevention of tick bites and avoidance of tick-infested habitats are key to preventing ehrlichiosis, anaplasmosis, and other tick-borne infections. Children returning from outdoor activities in tick-infested habitats should be inspected carefully for crawling or attached ticks. Appropriate use of approved tick repellents on skin or clothing is safe and effective in preventing tick bite, but adherence to the product label is important to reduce possible adverse effects in children. Daily body examinations for attached ticks (tick checks) are useful as prompt discovery and removal of recently attached ticks lessen the risk of infection; ticks may require 24 to 48 hours of attachment to a host before the bacteria can be transmitted.[42] Prophylactic administration of doxycycline after a tick bite is not indicated because the overall risk for infection is low, even when tick infection is documented.

Key Points

Diagnosis and Management of Anaplasmosis and Ehrlichiosis

Microbiology and Vectors of *Anaplasma* and *Ehrlichia* Species in the United States

- Anaplasmosis worldwide is caused by the bacterium *Anaplasma phagocytophilum*.

- The blacklegged tick (*Ixodes scapularis)* is the vector to humans in New England and the north central US; the western blacklegged tick (*Ixodes pacificus)* is the vector in northern California.

- Ehrlichiosis is caused by three bacteria in the US: *Ehrlichia chaffeensis, E. ewingii,* and *E. muris eauclairensis*.

- The principal vector of *E. chaffeensis* and *E. ewingii* is the lone star tick *(Amblyomma americanum);* the tick vector of *E. muris eauclairensis* is thought to be *Ixodes scapularis*.

Anaplasmataceae Outside the United States

- Various species of both *Anaplasma* and *Ehrlichia* cause infection in humans globally, but their public health impact is unclear.

- Neoehrlichiosis is an emerging pathogen of humans in Europe and Asia, is caused by "*Candidatus* Neoehrlichia mikurensis," and is transmitted by various *Ixodes* spp. of ticks.

- Neorickettsiosis is a re-emerging illness of Asia caused by *Neorickettsia sennetsu*. This pathogen is transmitted by ingestion of an infected helminth found in fish.

Diagnosis

- Doxycycline treatment should be initiated as soon as the disease is clinically suspected, and not postponed while awaiting laboratory confirmation.

- PCR of whole blood is commercially available, is highly specific, and is highly sensitive when performed during the early acute phase of illness; sensitivity decreases sharply after 48 hours of appropriate treatment.

- Immunofluorescence assay serology for immunogloblulin G antibodies to demonstrate a fourfold increase in titers between acute and convalescent samples is the gold standard for serodiagnosis.

- Visualization of morulae in white blood cells in a peripheral blood smear during the first week of illness is possible in some patients; however, this requires an astute microscopist to differentiate various structures and artifacts from morulae.

Treatment

- Doxycycline is the treatment of choice for adults and children *of all ages* and is most effective if started within the first 5 days of symptoms; alternative antibiotics may not be as effective at preventing severe complications or death.

- Recommended doxycycline dosage

- Children <45 kg: 2.2 mg/kg administered orally or intravenously every 12 hours

- Adults: 100 mg administered orally or intravenously every 12 hours

- Treatment is continued for at least 3 days after fever subsides and clinical improvement is documented (7–14 days total).

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Francisella tularensis (Tularemia)

Lorry G. Rubin

Description of Pathogen and Epidemiology

Francisella tularensis, the etiologic agent of tularemia, is a small, fastidious, non–spore-forming, strictly aerobic gram-negative coccobacillus, which is nonmotile and nonpiliated and has a thin capsule composed mostly of lipid.[1] Tularemia is a zoonotic disease; in addition to humans, who are accidental hosts, more than 100 animal species are affected, particularly ground squirrels, rabbits, hares, voles, and muskrat.[2] Organisms most frequently are transmitted by ticks and biting flies,[3,4] but infections can be transmitted by direct contact with rabbits (other than domesticated rabbits) or other infected animals or their aerosols, especially related to skinning, dressing, or eating infected animals.[5] Domestic animals, especially cats but also sheep, hamsters,[6] and prairie dogs,[7] occasionally have been implicated.[1,8] Infections also can be transmitted through contaminated food or water[9] (possibly facilitated by the organism's survival within amebas) and by other biting vectors such as mosquitoes, fleas, and mites.[2–4] Fomites have been involved rarely, but person-to-person spread through contact with infected ulcers is not an important mode of transmission. There is a potential use of *F. tularensis* as a biologic weapon by intentional aerosol release of organisms, and *F. tularensis* is classified as a Category A agent of biologic threat by the Centers for Disease Control and Prevention (CDC).[10]

Although there are three subspecies, human disease is due primarily to two subspecies: *F. tularensis* subsp. *tularensis* (type A) and *F. tularensis* subsp. *holarctica* (formerly *palaearctica;* type B), both found only in the Northern Hemisphere.[1,11] Type A strains are more virulent than type B strains and are almost exclusively found in North America, with subclades A1a and A1b predominating in the eastern half of the United States, California, and Oregon and subclade A2 in the western US, whereas type B strains are found throughout the northern hemisphere but primarily in Europe and Asia. Cottontail rabbits, three ticks, *Amblyomma americanum* (Lone Star tick), *Dermacentor andersoni* (wood tick), and *Dermacentor variabilis* (dog tick), and biting flies are the main source of the type A subspecies.[1] In the US, most cases occur from June through September, the season correlating with increased tick activity. Approximately 100 to 200 cases of tularemia are reported annually. In 2012, 149 cases of tularemia were reported to the CDC from 26 states; the highest numbers of cases were in the contiguous states of Kansas, Missouri, Arkansas, and Oklahoma.[12] Approximately one fourth of cases occurred in children, and among all ages, children 1 through 4 years of age had the highest attack rate.[12]

Subspecies B is less virulent and often results in self-limited or subclinical infection, but it can cause typhoidal infection in immunocompromised patients[13] and pneumonia.[14] Subspecies B undergoes a waterborne cycle predominantly, with aquatic rodents such as muskrats, beavers, and ground voles as reservoirs. Transmission occurs through these rodents and mosquitoes. Subspecies B has a worldwide distribution in the northern hemisphere between latitudes 30°N and 71°N, which includes the continents of Europe, Asia, and North America.[11]

Pathogenesis and Immunity

The portal of entry most commonly is the skin through a tick or fly bite, crushing of a tick found on an animal, or a wound,[3,15] but entry also can occur through the conjunctivae, respiratory tract through aerosols, or oropharynx or rarely other parts of the gastrointestinal tract. *F. tularensis* is highly contagious; an inoculum size as small as 10 organisms through the skin is sufficient to induce tularemia in experimental infection of humans.[16] Regardless of the route of inoculation, bacteria usually invade regional lymph nodes and are disseminated to other organs and lymph nodes through bacteremia. *F. tularensis* is a facultative intracellular pathogen that survives and multiplies within macrophages. Infection generally results in humoral and cellular immune responses and protection against reinfection.[1] Protection chiefly is mediated by a cellular immune process in which bacteria are killed by macrophages activated by specifically committed T lymphocytes, but humoral immunity also has been demonstrated to contribute to immunity.[17] Protective immunity develops approximately 2 weeks after infection and is long lasting.

Clinical Manifestations

Important clues to the diagnosis of tularemia are a history of a tick or fly bite, exposure to live or dead rabbits or squirrels (or other wild or domestic animals, including other rodents), or consumption of poorly cooked game meat. Clinical manifestations appear after an incubation period of 2 to 10 days (ranging up to 21 days). The most common clinical syndromes include lymphadenopathy and are termed *ulceroglandular* and *glandular tularemia*, which account for 80% of reported cases. Other manifestations include oropharyngeal (the second most common finding in children in some series,[18]) oculoglandular, typhoidal, gastrointestinal, and pleuropulmonary syndromes (Table 171.1). Regional lymphadenopathy was present in 76% of 250 patients from Arkansas with tularemia.[4] Children with tularemia have constitutional symptoms (e.g., fever, chills, malaise, and fatigue) and gastrointestinal symptoms more frequently than do adults.[8]

TABLE 171.1

Clinical Forms of Tularemia

Clinical Form	Features
Glandular	Most common form; painful lymphadenitis with or without a papule that becomes an ulcer distal to the lymphadenitis; several lymph nodes or groups of lymph nodes can be involved; late suppuration common

Oculoglandular	Nodular conjunctivitis; painful preauricular lymphadenopathy
Oropharyngeal	Can simulate diphtheria; fever common; may have oral ulcers; associated with ingestion of contaminated meat or water
Typhoidal tularemia	Caused by ingestion of contaminated food; can have gastrointestinal tract ulceration; “sepsis” manifestation; high, prolonged fever usual
Gastrointestinal	Caused by ingestion of contaminated food; diarrhea and abdominal or back pain
Pneumonia	Rare in children; caused by aerosol exposure or hematogenous dissemination to lung; can be rapidly fatal

Ulceroglandular and Glandular Disease.

Ulceroglandular disease is manifest as swollen tender lymph nodes in the inguinal, cervical, or axillary regions, usually from the bite of a bloodsucking arthropod. Lymphadenopathy can be accompanied by systemic symptoms and typically is preceded by a painful, swollen papule or at times a vesicle distal to the involved lymph nodes that can evolve into an ulcer with raised edges. In young children, disease commonly manifests as lymphadenopathy without an ulcer.[19] Ulcers on the upper extremities usually result from exposure to infected mammals and occur in hunters and ranchers. Ulcerated lesions can persist for weeks if untreated. Lymphadenopathy in the inguinal region develops more frequently in patients with tick-associated infection than in those with rabbit-associated infection.[4] Frequently, multiple enlarged lymph nodes can be observed. In one pediatric series, most children had enlarged nodes in more than one cervical location or in a cervical chain and another regional location.[8,18] With mosquito-borne infection by type B strains in northern Finland, children had high fever and lymphadenopathy for 2 to 4 days, followed by low-grade fever and, commonly, a draining skin ulcer at the site of the mosquito bite.[11] Symptoms lasted a median of 26 days.

Oculoglandular Infection.

Oculoglandular disease results from conjunctival infection, usually acquired from contaminated fingers. Multiple, small, well-demarcated nodules and ulcers can be seen on the conjunctiva in association with inflammation and edema. Pain is a major symptom, causing the patient to seek medical care early in the course of infection, and sometimes before the development of preauricular lymphadenopathy. The associated enlarged preauricular lymph node is painful, a feature unique to oculoglandular infection due to *F. tularensis* and *Coccidioides,* which distinguishes it from the oculoglandular syndrome of cat-scratch disease, sporotrichosis, tuberculosis, and syphilis.[20]

Oropharyngeal Infection.

In the oropharyngeal form of tularemia, organisms enter the oropharyngeal mucosa from ingestion of inadequately cooked infected meat or contaminated milk or water. The clinical presentation is tonsillitis with throat pain out of proportion to the visible lesions and cervical lymphadenitis. Oral ulceration can develop, and there can be an oropharyngeal pseudomembrane similar to infection with *Corynebacterium diphtheriae.* Fever and other systemic symptoms can occur, and affected lymph nodes can suppurate. In the US, this form occurs most commonly in children.

Typhoidal Tularemia.

The signs and symptoms of typhoidal tularemia are similar to those of acute septicemia of any etiology and include high fever, chills, malaise, headache, vomiting, myalgia, and on occasion, photophobia. Hepatosplenomegaly is frequent, and diarrhea occurs occasionally. When typhoidal tularemia results from the ingestion of contaminated food, necrotic lesions can occur in the bowel.[4] Patients generally do not have cutaneous ulcers or lymphadenopathy. Untreated cases can have a fatal outcome or resolve after persistent fever for 2 to 3 weeks or longer. Patients also can have persistent diarrhea and abdominal or low-back pain from gastrointestinal tract tularemia without septicemic symptoms.

Pneumonia.

The pneumonic form of tularemia occurs almost exclusively in adults but has been reported in children exposed to an aerosol from an infected rabbit carcass run over by a lawn mower.[21] Intentional aerosol release as a biologic weapon would most commonly cause pneumonia (or typhoidal tularemia).[10] Pneumonia is the most common manifestation of tularemia acquired by laboratory workers. The usual radiographic finding is a unilateral lower lobe infiltrate, sometimes with associated pleural effusion or hilar adenopathy, or both. This form of infection can be severe or fatal. Pneumonia also can result from hematogenous dissemination to the lungs from typhoidal (30%–80% of cases) or ulceroglandular (10% –15% of cases) infections. *F. tularensis* infection causing fever and a pulmonary nodule has been reported in a stem cell transplant recipient.

Occasional Sites.

Rare manifestations of infection have included subcutaneous nodules resembling sporotrichosis, meningitis with a mononuclear cell predominance and hypoglycorrhachia,[22] encephalitis, pericarditis, endocarditis, peritonitis, and osteomyelitis. A variety of rashes can be seen, including maculopapular, pustular, and erythema nodosum.

Laboratory Findings and Diagnosis

Gram-stain smears prepared from exudate or tissue sections rarely can show weakly staining gram-negative coccobacilli in an extracellular or intracellular location. Organisms can be identified using an indirect immunofluorescent antibody test. The histopathology of affected lymph nodes shows follicular hyperplasia with mixed cellular inflammatory infiltrates, stellate and caseous necrosis with central suppuration, and epithelioid cell granulomas, findings similar to those seen in tuberculosis or *Bartonella henselae* infection.[23] A polymerase chain reaction assay to detect bacterial DNA in clinical specimens such as swabs of ulcers shows good sensitivity and excellent specificity.[24–26]

Culture of *F. tularensis* is not performed routinely in clinical laboratories because of the potential for aerosol inhalation and infection of laboratory personnel. Specimens should be collected cautiously and laboratory personnel notified when specimens suspected of harboring *F. tularensis* are submitted. Biosafety level 2 is recommended for clinical laboratory work and transfer of cultures to biosafety level 3 as soon as *F. tularensis* is suspected.[27] An enriched medium such as cysteine heart blood agar supplemented with 9% chocolatized sheep blood, chocolate agar enriched with cysteine, or buffered charcoal yeast extract agar (used for culture of *Legionella*) incubated aerobically is required for isolation of *F. tularensis* from clinical specimens.[1] Colonies are 1 to 2 mm in diameter, blue-grey, round, smooth, and slightly mucoid. Direct isolation can be achieved from ulcer scrapings, lymph node biopsy specimens, gastric washings, sputum, and occasionally, culture of blood using a radiometric or nonradiometric technique.[1,28] Identification of colonies can be made using biochemical tests complemented by immunologic and molecular methods.[1] Inoculation of laboratory animals such as mice or rabbits is a sensitive means of isolation of *F. tularensis* but is not used commonly for diagnosis.

The laboratory diagnosis of tularemia most often is confirmed by serologic testing using a tube agglutination or microagglutination assay. Antibodies generally are detectable at the end of the second or during the third week of illness. A fourfold increase or decrease in titer using a serum agglutination test is diagnostic; a single titer of >1 : 160 by tube agglutination or >1 : 128 by microagglutination is a presumptive positive result but also could reflect past infection.[1] Infected patients can have convalescent titers >1 : 1000, and a prozone phenomenon can be observed. Nonspecific cross-reactions can occur in patients infected with bacteria from the genus *Brucella* and certain other gram-negative bacteria.[1,27] The microagglutination assay is more sensitive than the tube agglutination test. An enzyme immunoassay using lipopolysaccharide antigens with immunoblot confirmation as a two-step procedure is more sensitive and specific than agglutination assays.[2,29] An immunochromatographic test has similar sensitivity and specificity to the microagglutination assay.[30] Assay for immunoglobulin M (IgM) antibodies is not useful because IgM antibodies are not present earlier than IgG antibodies and can persist for years.[1]

Treatment

Empiric antimicrobial therapy often must be initiated before serologic confirmation of infection is possible. A 7-day course of streptomycin or gentamicin,[31] or possibly amikacin, is the treatment of choice for tularemia, and defervescence is expected within a few days. Treatment is associated with a low relapse rate.[4] A 10-day or longer course may be administered in cases of severe disease and slow response. Streptomycin is given intramuscularly twice daily at a dose of 30 to 40 mg/kg per day with a maximum of 2 g/day. Gentamicin is given to children at a dose of 5-7.5 mg/kg/day as 2 or

3 doses, either intramuscularly or intravenously[10]; gentamicen has been administered once daily in adults.[32] A Jarisch-Herxheimer reaction can occur early during aminoglycoside treatment. Ciprofloxacin (or possibly levofloxacin) given for 10 to 14 days is the best alternative to aminoglycosides and may be used for treatment of mild infection and after relapse following aminoglycoside therapy.[33–37] Treatment with tetracycline or chloramphenicol often results in a prompt clinical response, but these agents are not bactericidal, and relapse occurs in at least one half of patients after cessation of therapy. In vitro susceptibility does not necessarily predict clinical efficacy. For example, *F. tularensis* is susceptible to third-generation cephalosporins in vitro, but all of 8 children treated with ceftriaxone failed to improve, indicating that this therapy is ineffective.[38] In a series of adult and pediatric patients from Missouri, 52% of 121 patients were hospitalized.[37] Suppurative lymph nodes that require surgical drainage occur in 14% to 33% of cases.[19] In one pediatric series, late suppuration after antibiotic therapy developed in 33% of children. In these cases, the aspirated or excised material was sterile.[8] The mortality rate for tularemia is <1%.[37]

In Finnish patients infected with *F. tularensis* subsp. *holarctica* (type B) organisms, the impact of antibiotics on the clinical course was uncertain, given the relatively mild course of infection.[11] By in vitro susceptibility testing, strains are susceptible to tetracyclines, aminoglycosides, fluoroquinolones, chloramphenicol, and rifampin. Strains generally are resistant to β-lactam antibiotics, carbapenems, aztreonam, and macrolide antibiotics.[39,40]

Prevention

The key to preventing tularemia is interruption of transmission, which can be achieved by prevention or timely detection of tick bites, avoidance of handling sick or dead rabbits or rodents, use of rubber gloves to handle game meat, and thorough cooking of meat. An investigational live, attenuated vaccine given pre-exposure using a multiple puncture technique was used in the US for research personnel with exposure to *F. tularensis* but is no longer available. This vaccine prevents respiratory tract infection in laboratory personnel but does not prevent ulceroglandular infection.[41,42] A new generation of live, attenuated vaccines is under development.[41] A 14-day course of doxycycline or ciprofloxacin has been recommended for prophylaxis of exposed persons following an intentional aerosol release of organisms or exposure in a laboratory.[10]

Key Points

Diagnosis and Management of Tularemia

Microbiology

- Small, aerobic gram-negative coccobacillus
- Nutritionally fastidious, requires enriched medium

Epidemiology

- Zoonotic infection
- Transmitted primarily by ticks, biting flies, or direct contact with rabbits or other infected animals or their aerosols
- Summer occurrence
- Potential for bioterrorism through intentional aerosol release of organisms

Clinical Features

- Incubation period: 2–10 days (up to 21 days)
- Most common presentation is lymphadenitis (“glandular”) with or without painful papule or ulcer at inoculation site; often lymphadenitis occurs at more than one site.
- Other presentations: oropharyngeal, oculoglandular, typhoidal, gastrointestinal, pleuropulmonary
- Fever is common.

Diagnosis

- Fourfold rise in serum immunoglobulin G antibody titer is confirmatory.
- Organism can be isolated from ulcers using enriched medium but is a biohazard for laboratory personnel.

Treatment

- Gentamicin or streptomycin for 7 days
- Alternative: ciprofloxacin for 10–14 days
- Ceftriaxone is ineffective; relapses occur after tetracycline.

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172

Haemophilus influenzae

Joseph W. St. Geme III, Katherine A. Rempe

Haemophilus influenzae was first isolated by Pfieffer during the 1889 influenza pandemic.[1] For a time, *H. influenzae* was believed to be the causative agent of influenza and originally was called the *influenza bacillus.* However, subsequent studies demonstrated the fallacy of this notion, and the organism ultimately was given the genus name *Haemophilus,* meaning *blood loving.* The species name was chosen to reflect the historical association with influenza.

In 1995, the nucleotide sequence of the entire genome of *H. influenzae* strain Rd KW20 was published, representing the first organism to be sequenced completely. The annotated sequences of this strain and many others can be found at http://www.ncbi.nlm.nih.gov/genomeprj.

The Pathogen

H. influenzae is a nonmotile, non–spore-forming, gram-negative bacterium and typically appears as small coccobacilli, roughly 1 × 0.3 µm in size, although some isolates grow as long filaments. *H. influenzae* can grow aerobically or anaerobically. Aerobic growth requires two supplements known as factors X and V, whereas anaerobic growth requires only factor X. Factor X can be supplied by heat-stable iron-containing pigments, including hemin and hemoglobin, both of which represent a source of protoporphyrin IX. Factor V can be supplied by nicotinamide adenine dinucleotide, nicotinamide adenine dinucleotide phosphate, or nicotinamide nucleoside. Factor V is present in erythrocytes but must be released to sustain growth; as a consequence, standard blood agar is an unsatisfactory medium for propagating *H. influenzae*. Optimal growth is achieved on media enriched with erythrocytes that have been disrupted by heating (e.g., chocolate agar) or by peptic digestion (e.g., Fildes medium). Incubation in the presence of 5% to 10% carbon dioxide has a beneficial effect on the growth of some strains and is recommended for primary isolation.

Isolates of *H. influenzae* are classified according to their polysaccharide capsule.[2] As detailed in Table 172.1, six structurally and antigenically distinct capsular types (serotypes) exist and are designated as serotypes a through f. In addition, strains can be nonencapsulated; these strains are defined on the basis of their failure to react with typing antisera against capsular serotypes a through f and are referred to as *nontypable*. Worldwide, most clinical isolates are either type b or nontypable.[3,4]

TABLE 172.1

Chemical Composition of the Capsule of *Haemophilus influenzae*

Type	Sugar	*N*-Acetyl	Phosphate
a	Glucose, ribitol	–	+
b	Ribose, ribitol	–	+
c	Galactose, glucosamine	–	+
d	Glucosamine, mannosamine	–	+
e	Glucosamine, mannosamine	+	+
f	Galactosamine	+	+

Isolates also can be separated into subgroups called *biotypes* by using biochemical tests that determine the production of indole and the presence of ornithine decarboxylase and urease.[5] These reactions define eight biotypes designated I through VIII (Table 172.2). Data generated from biotyping studies indicate that type b isolates are predominantly biotype I.[6] Nontypable strains also can be biotype I, but in most collections they more often are biotype II or III.[7] Clinical isolates that are biotypes IV, V, VI, VII, or VIII are relatively uncommon and are almost always nontypable.

TABLE 172.2

***Haemophilus influenzae* Biotypes**

Biotype	Indole	Urease	Ornithine Decarboxylase
I	+	+	+
II	+	+	–
III	–	+	–
IV	–	+	+
V	+	–	+
VI	–	–	+
VII	+	–	–
VIII	–	–	–

Multilocus enzyme electrophoresis and a variety of other molecular techniques have been used to examine relatedness of isolates of *H. influenzae.* Studies using multilocus enzyme electrophoresis and other molecular techniques demonstrate that the population structure of encapsulated *H. influenzae* is clonal, with most isolates falling into a few common clonal groups.[8] Nontypable strains are genetically distinct and more heterogeneous than encapsulated *H. influenzae* and appear to lack clonality.[9]

Epidemiology

In the past, *H. influenzae* type b (Hib) strains were found in the upper respiratory tract of 3% to 5% of children and a small percentage of adults. In general, colonization rates with type b strains are even lower now because of routine immunization of infants with conjugate Hib vaccines, although exceptions exist.[10] Non–type b encapsulated *H. influenzae* stains are present in the nasopharynx of <2% of individuals, whereas nontypable strains colonize the respiratory tract of 40% to 80% of children and adults.[11–13]

Until approximately 1990, Hib was the leading cause of bacterial meningitis in children younger than 5 years in the United States, accounting for 8000 to 10,000 cases per year.[14] Hib also was the predominant cause of epiglottitis and a major cause of pyogenic arthritis, pneumonia, pericarditis, and facial cellulitis in young children. Approximately 1 in 200 children in the US experienced invasive (bacteremic) disease with this organism before the age of 5 years, with a peak incidence at 6 to 7 months of age. Invasive disease was more frequent in boys, African Americans, Alaskan

Eskimos, Apache and Navajo Indians, childcare center attendees, and children living in overcrowded conditions.[15–19] Medical conditions predisposing to invasive Hib disease included sickle cell disease, asplenia, human immunodeficiency virus (HIV) infection, certain immunodeficiency syndromes, and malignancies. Since 1990, the incidence of invasive Hib disease in the US has fallen by >99%, with only 30 cases reported in children younger than 5 years in 2013.[20–24] However, occasional shortages of vaccine have resulted in small clusters of cases in underimmunized young children.[25] In addition, there has been a modest resurgence of cases in recent years in parts of the US and in other developed countries.[26,27] Some children fail to respond to Hib vaccination and develop invasive Hib diseases, in most cases reflecting underlying immunodeficiency.[27,28]

Despite the overall successful reduction in invasive Hib disease in the US and other industrialized countries, Hib remains a common pathogen in many developing countries, where routine vaccines still are not available to most of the population. In these countries, Hib remains the leading cause of bacterial meningitis and the second leading cause of bacterial pneumonia.[29,30] Based on data from the World Health Organization, in 2012 vaccines against Hib were unavailable in 10 countries, most notably populous nations in Asia and parts of Africa (http://www.who.int/immunization/topics/hib/en/). As of 2013 only 52% of infants worldwide had received three doses of Hib vaccine by age 1 year (http://www.who.int/immunization/topics/hib/en/).

Nontypable strains of *H. influenzae* are a common cause of localized respiratory tract infections in children and adults.[31,32] In children, these organisms are the most common cause of purulent conjunctivitis, the most common or second most common cause of acute otitis media, and a frequent cause of sinusitis. In children in developing countries, nontypable *H. influenzae* is a frequent cause of pneumonia and an important source of mortality. In adults, nontypable *H. influenzae* is an especially common cause of community-associated pneumonia and exacerbations of underlying lower airway and lung disease and also accounts for a substantial proportion of cases of otitis media and sinusitis. Beyond producing localized disease, nontypable *H. influenzae* is an occasional cause of serious systemic disease such as septicemia, meningitis, and pyogenic arthritis, especially in neonates, pregnant women, and individuals with compromised immune function.[33,34]

Disease due to *H. influenzae* non−type b encapsulated strains occurs occasionally, in both developed and underdeveloped countries. For example, a 2010 study in Canada found that approximately 20% of invasive *H. influenzae* infections were caused by encapsulated non−type b strains.[35] Based on recent reports in the US, Canada, and Europe, cases of *H. influenzae* type a, type e, and type f invasive disease are increasing in frequency and are fatal in up to 20% of children and 30% of adults.[36–42]

Pathogenesis

Generally, *H. influenzae* is transmitted by airborne droplets or by direct contact with respiratory tract secretions. Colonization with a particular strain can persist for weeks to months, and most individuals remain asymptomatic throughout this period.[43] A variety of bacterial factors appear to influence the process of respiratory tract colonization. For example, the lipid A component of *H. influenzae* lipopolysaccharide (LPS), peptidoglycan fragments, protein kinase C_ε, and a surface-associated glycerophosphodiester phosphodiesterase called *protein D* or *GlpQ* (which allows choline to be transferred from the host to the bacterial surface) cause ciliostasis and thereby interfere with mucociliary clearance.[44–48] In addition, both pilus and nonpilus adherence factors exist and are known to mediate binding to mucus and to respiratory epithelium.[49–53] Like other mucosal pathogens, *H. influenzae* produces immunoglobulin A_1 (IgA_1) protease, an enzyme that cleaves human IgA_1 and presumably facilitates evasion of the local immune response.[54,55] Bacterial antigenic variation, entry into host cells, penetration between host cells (paracytosis), changes in LPS, and biofilm formation also may promote evasion of local immunity and persistence on mucosal surfaces.[56–66]

In certain circumstances, colonization is followed by contiguous spread within the respiratory tract, resulting in local disease in the middle ear, sinuses, conjunctiva, or lungs (Fig. 172.1). Anatomic factors, deficiencies in local immune function, concurrent viral respiratory infection, exposure to cigarette smoke, and allergies predispose to localized respiratory tract disease.[67] On occasion, bacteria penetrate the nasopharyngeal epithelial barrier and enter the bloodstream (see Fig. 172.1). The determinants of this event remain poorly defined but may include bacterial LPS.[68] Of note, penetration of the epithelial barrier appears to involve the separation of tight junctions, which allows bacteria to migrate between cells and into the subepithelial space.[69] In most cases, bacteremia probably is transient. However, in nonimmune hosts, intravascular bacteria that express the type b capsule sometimes are able to survive, replicate, and disseminate to distant sites. In the absence of specific antibody, the type b polysaccharide capsule promotes resistance to serum bactericidal activity and to phagocytosis. A variety of other factors also have been implicated in resistance to serum killing, including binding of factor H and vitronectin by bacterial surface proteins.[65,70–73]

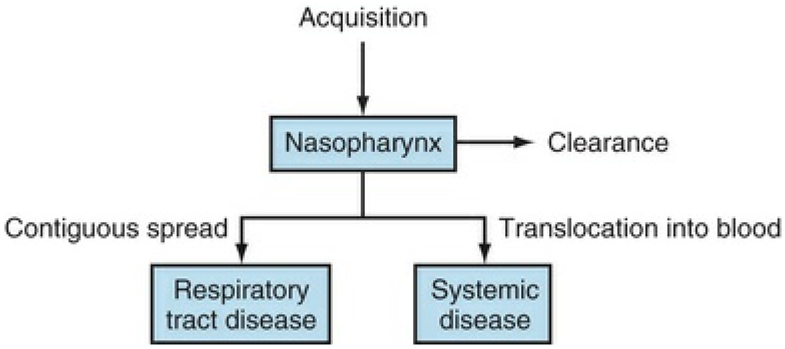


FIGURE 172.1 Pathogenic sequence for disease caused by *Haemophilus influenzae.*

Immunity

The age-associated susceptibility to Hib disease is inversely related to the presence of serum bactericidal antibody, much of which is directed against the type b polysaccharide capsule.[74,75] Antibody against the type b capsule activates complement-mediated bacterial killing and facilitates phagocytosis by opsonization.[76] Based on studies performed in the pre-Hib vaccine era, during the first 3 to 6 months of life, most infants have protective levels of maternally acquired anticapsular antibody. These levels gradually decline, reach a nadir by 6 to 12 months of age, and remain low for the next few years. By the age of 5 years, virtually all individuals have acquired anticapsular antibody, in some cases as a result of colonization with Hib or probably more frequently from exposure to commensals (e.g., *Escherichia coli* K100) or ingested food possessing cross-reactive epitopes.[77–79] Antibodies to noncapsular antigens such as LPS and outer membrane proteins also contribute to serum bactericidal and opsonic activity.[80,81]

At the time of infection, serum antibodies against the serotype b capsule are low or absent. In children younger than 2 years, levels remain low during convalescence because of an age-related deficiency in the ability to respond to polysaccharide antigens (T-lymphocyte–independent antigens).[82] In older children, infection stimulates a brisk increase in the level of anticapsular antibody. Natural infection also is associated with the formation of antibodies to LPS and surface-associated proteins, and these antibodies contribute to protection against recurrent Hib disease.

The complement system is critical in host defense against Hib disease, and patients with congenital deficiencies of certain complement components, including C2, C3, and C4, have increased susceptibility to Hib disease.[83] Hib is capable of activating both the classic and the alternate complement pathways.[83,84] Early in the course of infection in nonimmune hosts, the alternate pathway probably is more important, whereas at later stages, the antibody-dependent classic pathway is more likely to predominate. Clearance of bacteremia with type b organisms also requires an intact mononuclear phagocytic system, thus explaining the higher incidence of Hib bloodstream infection in patients with splenic dysfunction.

Immunity to nontypable organisms involves both systemic and local antibody responses. Moreover, evidence suggests that systemic priming functions to enhance the local response. Based on studies of patients with otitis media and bronchitis, it appears that the immune response to nontypable *H. influenzae* often is strain specific. For example, Faden and colleagues observed a population of children prospectively for 2 years and identified 8 subjects who experienced two separate episodes of acute otitis media from nontypable *H. influenzae*.[85] In all 8 patients, the second episode was caused by a different strain. Serum was collected from 6 of these patients at the time of the second episode and was found uniformly to contain bactericidal antibody against the first strain. However, only 3 of these 6 samples possessed measurable bactericidal antibody against the second strain, thus indicating the absence of cross-reacting bactericidal activity. Consistent with these findings, Musher and associates found that adsorption of normal human serum with nontypable *H. influenzae* removed bactericidal activity against the adsorbing isolate but not necessarily against other nontypable strains.[86] Major targets of the antibody response to infection include the P2 major outer membrane protein, the HMW1/HMW2 and Hia adhesins, protein D, and LPS.[87]

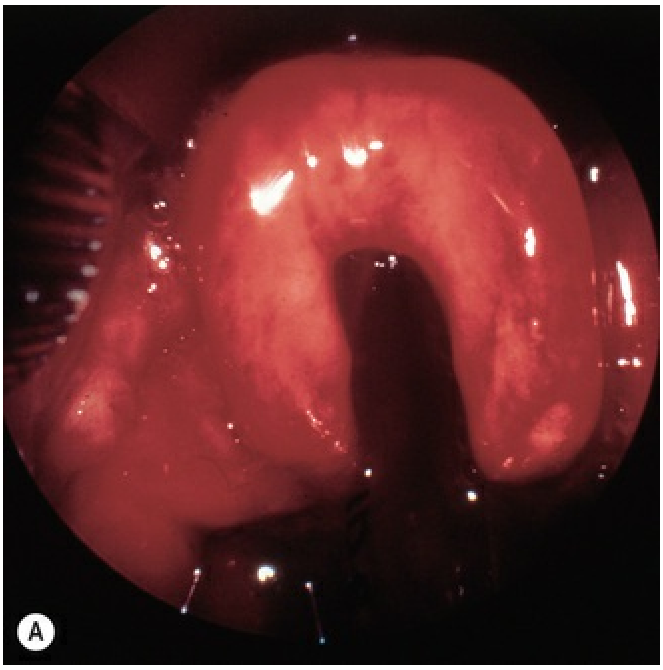
Clinical Manifestations of *Haemophilus influenzae* Type b Infection

Meningitis

Meningitis is the most common and most serious form of Hib disease. Symptoms typically include fever, irritability, lethargy, and vomiting. Antecedent symptoms of an upper respiratory tract infection are common. Occasionally, the course is fulminant, with rapid neurologic deterioration leading to respiratory arrest.[88] Shock is present in 20% of cases of meningitis and can be associated with coagulopathy and purpura.[89] An association of Hib meningitis and anemia is clear and appears to be related, at least partly, to adsorption of capsular antigen to the red cell surface with secondary immune-mediated hemolysis.[90] Complications of Hib meningitis include subdural effusion or empyema, ischemic or hemorrhagic cortical infarction, cerebritis, ventriculitis, intracerebral abscess, and hydrocephalus. The overall mortality rate is approximately 5%. Among survivors, between 5% and 10% have permanent sensorineural hearing loss, and about 30% have some other significant handicap. If subtle neurologic deficits are sought, up to one half of survivors have sequelae.[91–93]

Epiglottitis

Epiglottitis is a life-threatening infection involving cellulitis of the epiglottis and the aryepiglottic folds. Complete obliteration of the vallecular and piriform sinuses is typical, and acute airway obstruction can occur. Most affected children are between 2 and 7 years of age. Symptoms often are sudden in onset and classically include high fever, sore throat, stridor, and dyspnea progressing rapidly to dysphagia, pooling of oral secretions, and drooling. In children younger than 2 years, fever can be low grade, a croup-like cough can be present, and dysphagia and drooling sometimes are absent. Regardless of age, the patient usually is restless and anxious and adopts a sitting position with the neck extended and the chin protruding to reduce airway obstruction. Abrupt deterioration can occur within a few hours and result in death unless an artificial airway is established. Direct laryngoscopy at the time of controlled placement of an endotracheal tube reveals a red and swollen epiglottis and swollen aryepiglottic folds (Fig. 172.2A, B). On a lateral neck radiograph, the swollen epiglottis produces the *thumb sign* (Fig. 172.2C).



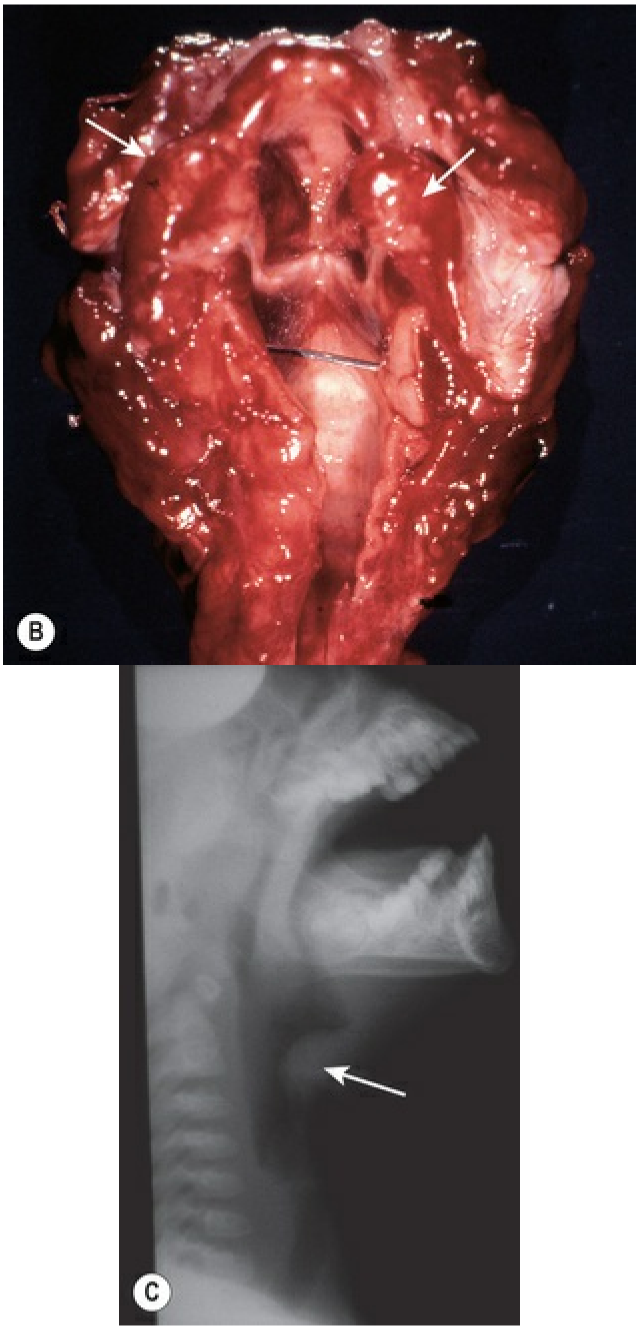


FIGURE 172.2 Clinical findings in confirmed cases of *Haemophilus influenzae* type b epiglottitis. Direct laryngoscopic findings of erythema and edema of the epiglottis in a 4-year-old child (A). Gross specimen from a fatal case shows erythema and edema predominantly of arytenoids structures *(arrows)* and aryepiglottic folds (B). Lateral neck examination. Lateral neck radiograph in another case shows thumbprint appearance *(arrow)* of the swollen epiglottis (C). (Courtesy of S. S. Long.)

Pneumonia

Patients with Hib pneumonia typically have a consolidative pulmonary infiltrate. In 50% of cases, evidence of pleural involvement can be seen on the initial chest radiograph, and up to 90% of these patients have pleural fluid recoverable by thoracentesis. Generally, Hib pneumonia is more insidious in onset than is pneumonia from *Staphylococcus aureus* or *Streptococcus pneumoniae.* Nearly one fourth of patients have concomitant meningitis or epiglottitis. An important complication is contiguous spread to the pericardium and subsequent purulent pericarditis, which is manifest as severe dyspnea (grunting in infants), tachycardia, and cardiac failure. Although patients with Hib pneumonia often have a persistent pleural reaction with secondary restrictive lung function at the time of hospital discharge, long-term abnormalities are rare.

Osteoarticular Infection

Historically, Hib was the most common cause of pyogenic arthritis in children younger than 2 years, usually of a single large weight-bearing joint (hip, knee, or ankle).[94] In 10% to 20% of cases, contiguous osteomyelitis is present. Osteomyelitis alone is unusual. The response to systemic antibiotics combined with prompt drainage of the joint is dramatic, but long-term follow up is important because residual joint dysfunction can occur. On occasion, culture-negative arthritis develops during treatment of *H. influenzae* meningitis, presumably as a result of immune complex deposition in the joint.[95] In 75% of patients with reactive arthritis, signs of joint inflammation begin 1 week or more after therapy is begun.

Bacteremic Cellulitis

Cellulitis is the result of a metastatic focus of bacteremia and is seen predominantly in young children. Typically, the patient is febrile and has a warm, tender area of erythema or violaceous discoloration on the cheek or in the periorbital area. Facial (buccal) cellulitis almost invariably occurs in children younger than 1 year. The age of the child, the location of the cellulitis, and the occasional distinctive violaceous color should suggest the etiology (Fig. 172.3). Aspirate cultures, either from the center of the lesion or the leading edge, usually yield the organism. Concomitant bacteremia is present in most patients, and another focus of infection such as meningitis develops in approximately 10% of cases.[96,97] Cellulitis that occurs as a complication of trauma to the skin is not caused by *H. influenzae.*

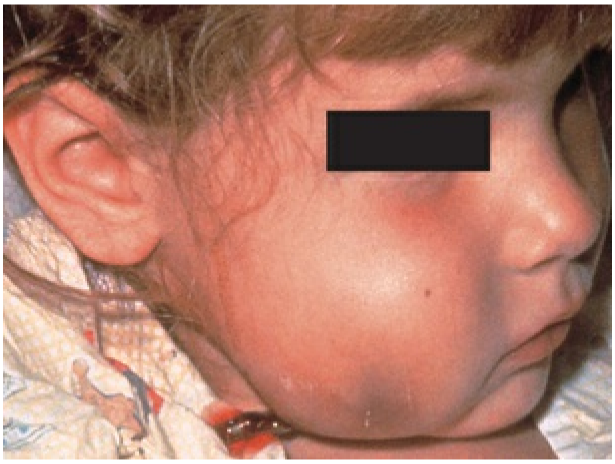


FIGURE 172.3 Buccal cellulitis in a 14-month-old girl whose blood culture yielded *Haemophilus influenzae* type b. Note distinctive site of cellulitis on the lower cheek and violaceous color. (Courtesy of S. S. Long.)

Other Infections

Other manifestations of Hib disease include occult bacteremia (which rarely is self-limited), otitis media, orbital cellulitis, septicemia, endophthalmitis, urinary tract infection, and peritonitis. In addition, purulent pericarditis can result from direct seeding from bacteremia.

Infection Due to Nontypable *Haemophilus influenzae*

Respiratory Tract Infection

Contemporary studies examining the bacteriology of acute otitis media consistently demonstrate *H. influenzae* as the most common pathogen.[98–101] Among *H. influenzae* isolates, almost all are nontypable. According to studies reported from the US and Scandinavia, the peak age-specific incidence of *H. influenzae* acute otitis media occurs between 6 and 15 months of age.[102,103] Characteristic manifestations include ear pain, fever, irritability, sleep disturbance, and otorrhea. On examination, the tympanic membrane usually is red or yellow and bulging, with distorted landmarks, and pneumatic otoscopy reveals decreased mobility. Additionally, nontypable *H. influenzae* is the pathogen implicated most commonly in otitis media with effusion and accounts for >40% of cases with positive tympanocentesis cultures.[104,105] Nontypable *H. influenzae* also has been associated with dual infection of the conjunctiva and the middle ear.[106] These infections occur primarily during the winter months and have been termed the *conjunctivitis-otitis syndrome*. Nontypable strains also are an important cause of isolated conjunctivitis (see Chapter 173).

Among children with acute sinusitis, *S. pneumoniae, H. influenzae,* and *Moraxella catarrhalis* account for nearly three fourths of recoverable isolates, with most *H. influenzae* strains being nontypable.[107,108] Most patients with sinusitis have persistent nasal discharge or cough that lasts longer than 10 days without improvement. Others present acutely with high fever and purulent nasal discharge. Physical examination often reveals tenderness over the involved paranasal sinuses. Data on the microbiology of chronic sinusitis are limited but suggest that nontypable *H. influenzae* is a prominent pathogen.[109] Several studies have examined the predictive value of surface cultures of the nose, throat, or nasopharynx in patients with acute or chronic sinusitis. Although the organisms isolated from direct aspiration of infected sinuses generally are recovered from surface cultures, they are not consistently the predominant organisms. Surface cultures are of minimal value in establishing an etiologic agent.

Because sputum frequently is contaminated by pharyngeal bacterial flora, interpretation of the growth of *H. influenzae* from sputum culture is difficult. However, there is substantial evidence that nontypable *H. influenzae* causes bacterial pneumonia, especially in children in developing countries, elderly people, and patients with frequent aspiration or underlying lung disease. Among children in developing countries with clinical evidence of pneumonia, lung aspiration studies demonstrate that bacteria can be recovered >60% of the time; up to half of these isolates are nontypable *H. influenzae.*[110,111]

Meningitis

Nontypable *H. influenzae* is an occasional cause of meningitis and, unlike Hib, usually occurs by direct extension from a contiguous focus of infection. Most individuals with nontypable *H. influenzae* meningitis have a predisposing factor, such as sinusitis, otitis media, head trauma, or another anomaly resulting in cerebrospinal fluid leak. In patients with recurrent bacterial meningitis, nontypable *H. influenzae* is the second most common cause (after *S. pneumoniae*) and generally enters the central nervous system through a communication between a parameningeal site and the subarachnoid space.[112]

Neonatal Infection

Nontypable *H. influenzae* is a well-recognized neonatal pathogen.[113–117] (Non−type b encapsulated strains occasionally also have been implicated in this setting.) In most cases, *H. influenzae* produces an early-onset neonatal syndrome similar to that caused by group B streptococci. Disease occurs primarily in premature neonates and is associated with a mortality rate of nearly 50%. Symptoms develop in most infants within the first few hours of life, with pneumonia and respiratory distress dominating the clinical picture. Meningitis occurs infrequently. *H. influenzae* usually can be isolated from the genitourinary tract of mothers of infected infants, often in association with maternal postpartum endometritis. Paired maternal-infant isolates have been confirmed to be the same strain by a variety of methods.[118,119] A substantial percentage of these isolates are biotype IV, a subgroup of nontypable *H. influenzae* found uncommonly at other sites of infection.[115] Analysis of these biotype IV strains by multilocus enzyme electrophoresis indicates divergence from other *H. influenzae,* and chromosomal DNA hybridization studies and 16S rRNA gene sequencing suggest that these strains represent a distinct *Haemophilus* species most similar to

H. haemolyticus, leading to the designation *Haemophilus* cryptic genospecies.[120,121]

Other Infections

Nontypable *H. influenzae* has been reported rarely as a cause of endocarditis, pericarditis, pyogenic arthritis, osteomyelitis, epiglottitis, cellulitis, urinary tract infection, intra-abdominal infection, and occult bacteremia.[67]

Diagnosis

In most cases of invasive Hib disease, blood cultures are positive. When meningitis is present, bacteria almost always can be recovered from CSF. In patients with epiglottitis, culture of the epiglottis usually is positive, but specimens should be obtained only after establishment of an artificial airway. *H. influenzae* is often cultivated from samples of pleural fluid, joint fluid, or pericardial fluid in affected patients. In roughly 70% of patients with *H. influenzae* meningitis, Gram stain of centrifuged CSF is positive for gram-negative coccobacilli. The sensitivity of CSF Gram stain correlates with bacterial density and ranges from 0% in the presence of $<10^3$ colony-forming units per milliliter to nearly 100% when the density is $\geq 10^5$ colony-forming units per milliliter.[122]

Type b capsular polysaccharide is secreted during bacterial growth, and detection of capsular antigen can aid in diagnosis. Methods available for this purpose include latex particle agglutination, coagglutination, countercurrent immunoelectrophoresis, and enzyme immunoassay. Serum, CSF, urine, and other normally sterile body fluids are suitable for examination for capsular antigen. Antigen detection techniques are most valuable in patients who have previously received antibiotic therapy and have sterile cultures, or to facilitate early chemoprophylaxis of contacts. In cases of culture-proven meningitis, capsular antigen is detected roughly 90% of the time in CSF and even more frequently in concentrated urine. False-positive reactions occur occasionally as a result of cross-reactivity with *E. coli, S. pneumoniae,* staphylococci, or meningococci. Of note, Hib conjugate vaccines can produce positive reactions in urine and CSF for days to weeks after vaccination.[123–127]

Because *H. influenzae* is a common commensal organism in the upper respiratory tract, establishing *H. influenzae* as an etiology of localized respiratory tract disease is challenging. Procedures such as tympanocentesis, sinus aspiration, tracheal or lung aspiration, bronchoscopy, and bronchoalveolar lavage can provide a definitive diagnosis when required, as in patients with persistent or recurrent infection or underlying immunodeficiency.

Treatment

Resistance to ampicillin now is common among isolates of *H. influenzae,* with the incidence in the range of 40% in some communities.[128,129] Ampicillin should never be used alone as empiric therapy of invasive disease. Ampicillin resistance usually is related to plasmid-mediated production of β-lactamase but occasionally is due to decreased affinity of certain penicillin binding proteins (in particular PBP3).[130] To detect both forms of resistance, a β-lactamase assay should be performed along with disk or broth-dilution susceptibility tests. The third-generation cephalosporins are the therapy of choice for *H. influenzae* meningitis. Both cefotaxime and ceftriaxone have potent activity against *H. influenzae* (including isolates that produce β-lactamase and isolates with an altered penicillin-binding protein) and achieve high levels in CSF. For infections outside the central nervous system, cefuroxime and ampicillin-sulbactam are suitable alternatives.

For patients with meningitis, dexamethasone therapy in a dose of 0.15 mg/kg every 6 hours for the first 2 or 4 days of treatment appears to decrease the likelihood of neurologic sequelae, including hearing deficit.[131–133] Dexamethasone should be initiated before the first dose of antibiotic whenever possible. Patients with epiglottitis require placement of an artificial airway, and children with pneumonia often need treatment with supplemental oxygen. When pleural empyema, purulent pericarditis, or pyogenic arthritis is present, prompt drainage is essential for a good outcome.

Otitis media and sinusitis are treated effectively with oral agents to which the causative strain is susceptible. Table 172.3 shows comparative minimal inhibitory concentrations inhibitory to 90% of isolates (MIC_{90}) for selected oral antibiotics.

TABLE 172.3

In Vitro Activity of Selected Oral Agents Against *Haemophilus influenzae*

Antibiotic	MIC_{90} (μg/mL)
Cephalexin	8
Cefaclor	8
Cefprozil	8
Cefdinir	1
Cefuroxime	0.5
Cefpodoxime	0.06
Cefixime	0.06
Cefditoren	0.03
Amoxicillin-clavulanate	16
Trimethoprim-sulfamethoxazole	0.5
Clarithromycin	8
Azithromycin	1

MIC_{90}, minimal inhibitory concentration required to inhibit the growth of 90% of strains.

Prevention

Vaccination

First-generation vaccines against Hib were purified type b capsular material, polyribosylribitol phosphate (PRP). These vaccines were not effective in children younger than 24 months and had variable efficacy in children 24 months and older.[134,135] Second-generation vaccines contain PRP or a derivative of PRP conjugated to an immunogenic carrier protein, are effective in infants, and have replaced the earlier vaccines. Currently, three conjugate vaccines are licensed, all differing to some extent in the size of the polysaccharide, chemical linkage between the polysaccharide and the carrier, and the type of protein carrier (Table 172.4).[136] Among these three vaccines, PRP-T (PRP-tetanus toxoid) and PRP-OMP (PRP–*Neisseria meningitidis* outer membrane protein) are available in the US. As a result of differences in immunogenicity, the primary series in infancy consists of three doses (at 2, 4, and 6 months of age) for PRP-T and two doses (at 2 and 4 months) for PRP-OMP. Regardless of the particular vaccine used during the first year of life, a booster dose should be administered between 12 and 15 months of age. Combination vaccines that contain an Hib conjugate formulation licensed and available in the US are MenCY/PRP-T (MenHibRix) and DTaP-IPV/PRP-T (Pentacel).

TABLE 172.4

Haemophilus influenzae Type b Conjugate Vaccines

Vaccine	Trade Name	Polysaccharide	Linkage	Protein Carrier
PRP-OMP[a]	PedvaxHIB	Medium	Thioether	*Neisseria meningitidis* outer membrane protein
PRP-T[a]	ActHIB	Large	6-Carbon	Tetanus toxoid
PRP-T	Hiberix	Large	6-Carbon	Tetanus toxoid

[a] Additional combination vaccines have been licensed that include these conjugate vaccines. DTaP/PRP-T (TriHIBit) contains DTaP vaccine and PRP-T; DTaP-IPV/PRP-T (Pentacel) contains DTaP vaccine, inactivated poliovirus vaccine, and PRP-T.

OMP, outer membrane protein; PRP, polyribosylribitol phosphate; PRP-T, PRP-tetanus toxoid.

Children with sickle cell disease, anatomic or functional asplenia, HIV infection, or IgG2 subclass deficiency, patients receiving chemotherapy for malignancies, and patients who have undergone bone marrow transplantation have an increased risk of invasive Hib disease. Conjugate vaccine should be considered for those who are unvaccinated. Two doses (at least 1 month apart) are recommended for children 12 to 59 months of age and one dose for those 60 months or older. (For further consideration, see the *2015 Red Book* by the American Academy of Pediatrics Committee on Infectious Diseases and Section 1, Active and Passive Immunization.).[136]

All of the conjugate vaccines are well tolerated, with the most common adverse effect being short-lived redness and swelling at the site of injection. Postlicensing studies indicate that the existing conjugate vaccines are highly effective against Hib disease and reduce rates of nasopharyngeal colonization. These vaccines confer no protection against non–type b or nontypable strains.

A 10-valent pneumococcal nontypable *H. influenzae* protein D –conjugate vaccine was examined in a randomized, double-blind efficacy trial and was found to be associated with an efficacy against nontypable *H. influenzae* otitis media of 35·3% [95% confidence interval, 1.8%–57.4%].[87] This vaccine has been licensed in more than 40 countries but is not yet licensed in the US. A variety of other nontypable *H. influenzae* surface proteins also are under study as candidate vaccine antigens.[137]

Chemoprophylaxis

Chemoprophylaxis is an important intervention for preventing invasive Hib disease.[125] The intent is to eradicate nasopharyngeal colonization and thereby interrupt transmission. In households with one or more infants younger than 12 months who have not received the complete Hib primary vaccine series, all household contacts should receive rifampin prophylaxis. The same applies in households with children younger than 4 years who are incompletely vaccinated and in families with a fully vaccinated but immunocompromised child even if the child is older than 48 months. In addition, when two or more cases of invasive disease occur within a 60-day period in attendees of a group childcare facility and incompletely vaccinated children attend the facility, rifampin is recommended for all attendees and supervisory personnel. Management after a single case at a childcare facility is controversial and depends on the age and immunization status of the attendees and the duration of daily contact between attendees and the index patient. In-home group childcare settings are managed like families. For prophylaxis, rifampin is given once a day for 4 days (20 mg/kg; maximal dose, 600 mg; some would administer a dose of 10 mg/kg daily for infants younger than 1 month).

Treatment of the index case with cefotaxime or ceftriaxone eradicates Hib colonization, eliminating the need for prophylaxis in this individual. However, index patients who are treated with other agents (e.g., ampicillin or meropenem) and who are younger than 2 years or have a susceptible household contact should receive rifampin prophylaxis at the end of systemic treatment for invasive disease.

Chemoprophylaxis for recurrent otitis media from nontypable *H. influenzae* (or other typical pathogens) is not recommended due to increasing concerns over antibiotic resistance.[138]

Key Points

Diagnosis and Management of *Haemophilus influenzae* Infection

Microbiology

- Nonmotile, non–spore-forming, gram-negative coccobacillus
- Grows aerobically and anaerobically; requires factor X and factor V for aerobic growth and factor X for anaerobic growth
- Optimal growth is achieved on media enriched with erythrocytes that have been disrupted by heating (e.g., chocolate agar) or by peptic digestion (e.g., Fildes medium).
- Isolates are classified according to polysaccharide capsule (encapsulated forms are designated serotypes a–f; nonencapsulated forms are designated nontypable).

Epidemiology

- Normal nasopharyngeal flora; type b and non–type b encapsulated stains generally colonize nasopharynx of <3% of individuals, whereas nontypable strains colonize the nasopharynx of 40% to 80% of children and adults.
- Hib was leading cause of bacterial meningitis and other invasive diseases in children younger than 5 years in the United States until routine infant immunization in 1990; remains a common pathogen in young children in countries without routine immunization.
- Type a, type e, and type f invasive disease appears to be increasing in frequency in the US, Canada, and Europe.
- Nontypable strains are a common cause of localized respiratory tract disease in both children and adults.

Diagnosis

- Culture from a normally sterile site (blood, cerebrospinal fluid, joint fluid, pleural fluid, pericardial fluid, epiglottis)
- Culture of fluid obtained by tympanocentesis, sinus aspiration, tracheal or lung aspiration, bronchoscopy, and bronchoalveolar

lavage when specific microbiologic diagnosis is required

Treatment

- About 40% of isolates are ampicillin resistant, in most cases because of β-lactamase production.
- Ampicillin should never be used alone as empiric therapy of invasive disease but can be used as definitive therapy for ampicillin-susceptible isolates.
- A third-generation cephalosporin is the therapy of choice for meningitis.
- A variety of β-lactam and other oral agents are suitable for otitis media, sinusitis, and most other respiratory tract infections.

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Other *Haemophilus* Species and *Aggregatibacter* Species

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Of the *Haemophilus* species, *H. influenzae* causes by far the most human disease. Several other members of this genus, however, are capable of causing clinical illness. These include *H. influenzae* biogroup *aegyptius, H. ducreyi, H. parainfluenzae, H. pittmaniae, H. sputorum, H. haemolyticus, H. parahaemolyticus,* and the ill-defined species *H. paraphrohaemolyticus*.[1] Three former *Haemophilus* spp. known to cause human disease have been reclassified into the genus *Aggregatibacter,* as follows: *H. aphrophilus* and *H. paraphrophilus* are now the single species *A. aphrophilus*, and *H. segnis* now is *A. segnis*.[2,3] Reclassification is based on phenotypic properties and molecular analyses (16S rRNA analysis and DNA-DNA hybridization studies). The genus name *Aggregatibacter* refers to "rod-shaped bacteria that aggregate with others," and aptly describes their tendency to adhere to test tube walls (see also Chapter 181).

The genus *Haemophilus* is classified in the family Pasteurellaceae. Members of this genus are small, pleomorphic, facultatively anaerobic, gram-negative coccobacilli. *Haemophilus* spp. can be distinguished based on need for X factor (hemin) or V factor (nicotinamide) for in vitro growth, ability to lyse horse erythrocytes, and production of catalase (Table 173.1). With the exception of *H. ducreyi*, all *Haemophilus* spp. ferment glucose. *H. ducreyi* grows optimally at 33°C, whereas other species grow optimally at 35°C–37°C. In general, haemophili grow best in a humid environment enriched with 5%–10% carbon dioxide.[1] Both *A. aphrophilus* and *A. segnis* are small gram-negative bacilli that do not require X factor, have variable dependence on V factor, and ferment glucose.[2]

TABLE 173.1

Some Differential Characteristics of *Haemophilus* Species

	Growth Factor Requirement		Hemolysis	Catalase	CO$_2$ Enhances Growth
	X	V			
***HAEMOPHILUS* SPP.**					
H. influenzae	+	+	–	+	–
H. aegyptius	+	+	–	+	–
H. parainfluenzae	–	+	–	D	–
H. ducreyi	+	–	–	–	+
H. haemolyticus	+	+	+	+	–
H. parahaemolyticus	–	+	+	+	–
***AGGREGATIBACTER* SPP.**					
A. aphrophilus[a]	–	D	–	–	+
A. segnis[b]	–	+	–	D	D

[a] Previously *H. aphrophilus* and *H. paraphrophilus.*

[b] Previously *H. segnis.*

D, differences are encountered; V, nicotinamide; X, hemin.

Haemophilus influenzae Biogroup Aegyptius

The Koch-Weeks bacillus, originally observed in Egyptian children with conjunctivitis by Koch in 1883 and further characterized by Weeks in 1886, was designated *Haemophilus aegyptius* in 1950.[4] Controversy over whether *H. aegyptius* merited classification as a separate species from *H. influenzae,* already extant at that time, persisted. Although there are phenotypic and pathogenetic differences between *H. aegyptius* and *H. influenza,*[4–8] no single characteristic distinguishes the two organisms unequivocally, and DNA hybridization studies indicate high relatedness.[9,10] The Koch-Weeks bacillus, therefore, presently is considered as a distinct subgroup of *H. influenzae* biotype III and termed *H. influenzae* biogroup *aegyptius*.[8]

In the United States, *H. influenzae* biogroup *aegyptius* has been a cause of seasonal acute conjunctivitis in southern states during warmer months. Studies performed in Texas[11] and Georgia[12] found this organism to be the leading cause of acute purulent conjunctivitis among children in the 1930s to 1950s. Some studies have suggested that the eye gnat (*Hippelates pusio*) might serve as a transmission vector (hence the lay term, "gnat sore eyes"), although this role has not been proved.

H. influenzae biogroup *aegyptius* also can cause severe infection, Brazilian purpuric fever (BPF). The first known cases of BPF occurred in 1984 in rural Brazil, when 10 children died from a rapidly progressive illness characterized by fever, abdominal pain, vomiting, purpura, and vascular collapse.[13] Epidemiologic investigations noted strong association with recent history of purulent conjunctivitis. When another outbreak occurred in Brazil in 1986, the etiology of BPF was established.[14] *H. influenzae* biogroup *aegyptius* was isolated from 9 blood cultures and 1 hemorrhagic cerebrospinal fluid culture from 10 clinically affected children.

The age range of reported cases of BPF is 3 months to 10 years, with peak incidence between 1 and 4 years. About 90% of patients have a recent history of conjunctivitis, and about 70% of identified cases have been fatal.[15,16] In Brazil, epidemic and sporadic cases have been reported from the states of São Paulo, Paraná, and Mato Grosso.[13–16] Single cases of BPF with bloodstream infection due to *H. influenzae* biogroup *aegyptius* have been reported from Australia[17] and the United States.[18] Molecular studies demonstrated isolates were unique clones.[18,19] Extensive analyses, including examination of protein profiles, ribotyping, plasmid restriction patterns, seroagglutination, and multilocus sequencing,[20] indicate that the isolates causing BPF in Brazil belong to a single clone that is distinct from other strains of *H. influenzae* biogroup *aegyptius* in Brazil and other countries.[10]

Interestingly, there were no reports of BPF from the mid-1990s until 2007 when 7 suspected cases of BPF occurred in children in

Anajas, Brazil, including 5 deaths within 24 hours.[21] Speculation about the apparent “disappearance” of this illness includes natural history of a bacterial species, underrecognition or underreporting of the disease (given clinical similarity to meningococcemia), and potential rapid acquisition of immunity in a previously nonimmune population.[22] No explanation completely accounts for the unusual disease pattern, and investigations into the pathogenesis of BPF continue.

Potential virulence factors of BPF strains include lipooligosaccharides, capsular polysaccharides, pilus proteins, immunoglobulin A proteases, membrane-associated proteins, and extracellular proteins.[23] BPF strains express both pilus and nonpilus adhesins that presumably facilitate mucosal colonization.[24] Compared with non-BPF strains, BPF strains resist lysis after incubation with normal adult human serum[25] and are cytotoxic for microvascular endothelial cells.[26] Additionally, BPF strains produce an extracellular hemagglutinating protein purported to be responsible for the hemorrhagic manifestations of BPF.[27] Horizontal transfer of virulent genes from *Neisseria meningitidis* to *H. influenzae* recently has been described, and this type of genetic acquisition also may play a role in pathogenic potential of *H. influenzae* biogroup *aegyptius*.[28]

Early systemic antibiotic therapy can improve clinical outcome in patients with BPF. Appropriate therapeutic options include ampicillin, chloramphenicol, cefotaxime, or ceftriaxone; most isolates of the BPF clone are resistant to trimethoprim-sulfamethoxazole.[10] In a randomized trial of children with *H. influenzae* biogroup *aegyptius* conjunctivitis, systemic therapy with rifampin (20 mg/kg orally once daily for 4 days) eradicated the organism in 12 of 12 children, compared with only 7 of 16 children treated with topical chloramphenicol 0.5%.[29] This finding led to speculation that oral rifampin might prevent development of BPF.

Haemophilus ducreyi

H. ducreyi is the causative agent of chancroid, a sexually transmitted infection characterized by genital ulceration and inguinal adenitis.[30] Described by Ducrey in 1889, *H. ducreyi* is a fastidious coccobacillary gram-negative bacterium that requires X factor for growth. Studies of DNA homology and ribosomal RNA gene sequences indicate that, although *H. ducreyi* is correctly assigned to the family Pasteurellaceae, classification in the genus *Haemophilus* should be reconsidered.[31,32]

Chancroid occurs sporadically in developed countries but is a major cause of genital ulcer disease in developing countries.[30] In the U.S., chancroid usually occurs in discrete outbreaks, and reported cases increased markedly during the 1980s to a high of 5001 cases in 1988. Since then, reported cases have declined steadily, with only about 300 reported cases from 2000 to 2007, <50 cases per year since 2004, and only 8 cases reported in 6 states in 2011.[33] Poverty, sex for money or drugs, and illicit drug use are well-recognized risk factors. Chancroid is an important cofactor in the transmission of human immunodeficiency virus (HIV). In addition, as many as 10% of patients with chancroid have syphilis or herpes simplex virus (HSV) infection.[34]

Transmission of *H. ducreyi* occurs through sexual contact, putatively gaining tissue entry through epithelial microabrasions. After an incubation period of 3 to 10 days, a papule develops. Papules, typically surrounded by erythema, evolve over 2–3 days into pustules that ultimately rupture to form tender, friable, sharply circumscribed ulcers with grey or yellow purulent exudates. Without therapy, ulcers usually resolve only after several weeks or months. In advanced cases, however, scarring can occur despite appropriate therapy.[35] Chancroid occurs more frequently in men than women. Depending on the locations of ulcers, women can have subtle symptoms such as dysuria, dyspareunia, vaginal discharge, dyschezia, or rectal bleeding. Rarely, extragenital lesions occur. About 50% of patients develop painful, tender enlarged inguinal lymph nodes, which can become fluctuant and, if not aspirated or drained surgically, rupture spontaneously. Occasionally, ulcers can appear and resolve, with development of suppurative inguinal adenitis 1–3 weeks later.[30]

Recently, *H. ducreyi* was newly recognized as a cause of chronic skin ulcers in children. Two studies, primarily of children with nongenital skin ulcers in Papua New Guinea, identified *H. ducreyi* as the causative agent for a large proportion of these lesions.[36–38] Compared with yaws, *H. ducreyi* ulcers tended to be more shallow and painful and more commonly are found on the lower extremities.[38]

Although the pathogenesis of *H. ducreyi* infection is incompletely understood, several potential virulence factors have been described.[39–45] These include lipooligosaccharide,[42–45] pili,[46] soluble cytolethal distending toxin,[47–49] hemoglobin-binding outer membrane protein,[50,51] cytotoxic hemolysin,[52,53] copper-zinc superoxide dismutase,[54,55] filamentous hemagglutinin-like protein,[56] and zinc-binding periplasmic protein.[57] In addition, two proteins that likely facilitate *H. ducreyi* persistence within genital epithelium are HgbA, which mediates hemoglobin binding,[58] and Dsr, which mediates serum resistance.[59–61]

In the US, the most common causes of genital ulcer disease in sexually active patients are HSV infection, syphilis, and chancroid. In developing countries, the differential diagnosis also includes granuloma inguinale and lymphogranuloma venereum.[62] Definitive diagnosis of chancroid requires recovery of *H. ducreyi* on special culture media, which often is not available readily. Even under optimal conditions, culture sensitivity is <80% compared with polymerase chain reaction testing; however, no US Food and Drug Administration–approved polymerase chain reaction test for *H. ducreyi* exists currently.[62] Direct Gram stain examination of clinical material can be misleading and is not recommended as a diagnostic test.[30,63] The diagnosis of chancroid, therefore, is based on clinical findings and the exclusion of other causes of genital ulcers.[34] Current guidelines from the Centers for Disease Control and Prevention indicate that diagnosis of a probable chancroid can be made in a patient with all of the following features: (1) one or more painful genital ulcers; (2) no evidence of syphilis (i.e., by darkfield examination of ulcer exudate *or* serologic testing performed ≥7 days after onset of ulcers); (3) clinical presentation, appearance of genital ulcers and, if present, regional lymphadenopathy; and (4) a negative test for HSV performed on the ulcer exudate.[62]

Effective antibiotic regimens in the treatment of chancroid include ceftriaxone (250 mg) as a single dose intramuscularly, azithromycin (1 g) as a single dose orally, ciprofloxacin (500 mg) twice daily for 3 days orally, and erythromycin base (500 mg) thrice daily for 7 days orally.[62] Worldwide, intermediate resistance has been noted to either ciprofloxacin or erythromycin.[62] HIV-infected patients who receive single-dose ceftriaxone or azithromycin therapy should be monitored closely because data are limited regarding efficacy of these regimens in this population.[62] Patients should be re-examined 3 to 7 days after initiation of therapy. If therapy is successful, symptoms improve within 3 days and ulcers begin to resolve objectively after 7 days. Possible reasons for therapeutic failures include incorrect diagnosis, coinfection with another sexually transmitted infection, coinfection with HIV, nonadherence to therapy, and infection with an *H. ducreyi* strain resistant to the prescribed antimicrobial agent. Large ulcers may not heal completely for >2 weeks. Fluctuant lymph nodes may require needle aspiration or incision and drainage despite otherwise successful medical therapy. Uncircumcised men and patients with HIV infection do not respond as well to treatment as do those who are circumcised or not infected with HIV.[62] Patients with chancroid should be evaluated for other sexually transmitted infections at the time of diagnosis and should be retested for syphilis and HIV infection 3 months later if initial test results are negative. Sex partners (i.e., contact within 10 days before symptom onset) of patients with chancroid should be examined and treated even if symptom free.[34,62]

Oral and Pharyngeal *Haemophilus* Species

Haemophilus spp. (including those reclassified as *Aggregatibacter* spp.) account for about 10% of the cultivable flora of the oral cavity and upper respiratory tract of healthy children. *H. parainfluenzae* comprises about three fourths of pharyngeal *Haemophilus* isolates. A recent study of children undergoing adenoidectomy found that 97% were colonized with *H. parainfluenzae* in the adenoid core; biofilm formation was identified as having a potential role in chronic adenoiditis.[64] Nonencapsulated *H. influenzae,* although present in 80% of healthy children, makes up <2% of total pharyngeal flora.[65] *Aggregatibacter* spp. (formerly *H. aphrophilus, H. paraphrophilus,* and *H. segnis*) are found especially in dental plaque specimens in adults, and *H. haemolyticus* is recovered primarily from gingival crevices.[1,65] Additionally, *H. parainfluenzae* and *H. influenzae* occasionally are isolated from urethral and vaginal specimens from adults and children.[66,67] On rare occasions, these commensals can cause disease. Infections most consistently associated with *H. parainfluenzae* in children are endocarditis and meningitis[68,69]; however, it is possible that *H. influenzae* isolates that were misidentified as *H. parainfluenzae* account for many of the reported meningitis cases.[1,69] Other pediatric infections reportedly caused by *H. parainfluenzae* include bacteremia; septic arthritis; urinary tract infection; peritonitis; abscesses of the liver, brain, and soft tissue; and head and neck infections.[68–72] Historically, *A. aphrophilus* (formerly *H. aphrophilus*) was associated with a similar spectrum of diseases in children, along with rare cases of cervical lymphadenitis[73–77] Bacteremia and secondary brain abscesses have been associated with recent dental work, including one pediatric case after manipulation of dental braces.[78] *A. aphrophilus* (formerly *H. paraphrophilus*) has been reported in children to cause epiglottitis,[79] fatal pneumonia,[80] septic arthritis,[81] and intracerebral abscess.[82] *H. parahaemolyticus* was reported to cause periorbital cellulitis in a toddler.[83] *H. haemolyticus* frequently colonizes the oropharynx of children with bronchiectasis, the significance of which is unclear.[84] Recently, using multilocus sequence analysis, *H. haemolyticus* (misidentified as *H. influenzae*) was found to cause bacteremia in a 1-year-old child, suggesting a possible role in invasive infections more frequently than recognized previously.[85] *A. segnis* (formerly *H. segnis*) has not been described as a pediatric pathogen.

Haemophilus spp. (now including *Aggregatibacter* spp.) cause approximately 3% to 5% of cases of infective endocarditis in adults[86] and children.[87,88] A literature review of cases reported between 1965 and 2001 identified 17 pediatric cases of *Haemophilus* spp. endocarditis; etiologic agents were *H. parainfluenzae* in 13 cases and *A. aphrophilus* in 4 cases. Of these cases, 10 had underlying cardiac abnormalities, 8 suffered embolic complications, 6 required cardiac surgery, and 2 died.[72] *A. aphrophilus* endocarditis is more common in patients with congenital heart disease but can occur in structurally normal hearts.[89] *A. paraphrophilus*, which is a rare cause of endocarditis in adults, has not been reported in children.

Ampicillin remains the drug of choice for infections caused by ampicillin-susceptible *Haemophilus* spp. Ampicillin resistance due to β-lactamase production or alterations in penicillin binding proteins can occur.[1] In studies from southern Europe, 10%–57% of respiratory *H. parainfluenzae* isolates produced β-lactamase; moreover, 40% were resistant to trimethoprim-sulfamethoxazole, and 40% were resistant to clarithromycin. Additionally, there are isolated reports of extended-spectrum β-lactamases–mediated resistance, as well as high-level fluoroquinolone–resistant *Haemophilus* spp.[90,91] A case report from Switzerland in 2013 described the first cases of extensively drug-resistant *H. parainfluenzae*.[92] Because antimicrobial susceptibility testing has not been well standardized for *A. aphrophilus,* rates of resistance are unknown. For treatment of serious infections caused by *Haemophilus* spp. and *A. aphrophilus*, cefotaxime or ceftriaxone should be administered intravenously until antibiotic susceptibility test results are available. For uncomplicated native valve endocarditis, the minimal duration of antimicrobial therapy is 4 weeks.

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Helicobacter pylori

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Helicobacter pylori infection is ubiquitous among humans. Moodley and colleagues estimated that *H. pylori* has infected humans for >80,000 years.[1,2] Despite declining prevalence in developed countries, *H. pylori* continues to be one of the most common human infections worldwide.[3] Different sources of infection have been suggested, including contaminated water and contact with soil, but person-to-person transmission seems to be the primary mechanism through fecal-oral, oral-oral, and gastro-oral routes during early childhood.[4–7] Although a number of zoonotic mechanisms for transmission have been postulated, nonhuman reservoirs have not been demonstrated definitively. *H. pylori* infection causes gastritis, duodenal and gastric ulcers, as well as gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma. *H. pylori* also has been associated with extragastric conditions, including growth failure, iron deficiency anemia, cardiovascular diseases, and chronic idiopathic thrombocytopenia purpura (ITP). Bacterial virulence, host factors, and potentially environmental exposures play a role in determining the type of gastroduodenal inflammation that occurs and in *H. pylori* disease outcome.[8,9] Evidence-based clinical practice guidelines published in 2011 recommend eradication of *H. pylori* in infected children if there are primary family members with gastric cancer or in patients with peptic ulcer disease, but discourages the “test and treat” approach.[10]

The Pathogen

H. pylori is a gram-negative, motile, flagellated spiral-shaped bacillus that resides in the human gastric mucosa. It is S shaped in vivo and measures up to 5 μm long. Numerous studies provide evidence of colonization of the oral cavity, and a meta-analysis demonstrated a close relationship between the presence of *H. pylori* in the oral cavity and stomach and suggested the oral cavity may be a source of reinfection.[11–14]

The pattern of gastric mucosal colonization by *H. pylori* and resultant gastric inflammation appears to play a major role in influencing disease phenotype.[15–17] In 2005, the Nobel Prize in Medicine was awarded for the 1982 discovery of *H. pylori* (then called *Campylobacter pyloridis*) and its association with duodenal and gastric ulcer disease.[18] *Helicobacter* constitutes group III of the rRNA superfamily VI, which also includes *Campylobacter* (group I) and *Arcobacter* (group II).[19–22] A number of *Helicobacter* species have been identified, with *H. pylori* being the most common and the primary pathogen associated with human disease.[23–25] *H. pylori* has been isolated from primates (previously called *Helicobacter nemestrinae*), but no conclusive evidence exists of animal-to-human transmission.[26]

H. pylori is a microaerophilic bacterium able to successfully overcome the adversity of the acidic gastric mucosa owing to its unique properties, including spiral shape, motility, and production of significant quantities of urease. Other virulence factors include the production of catalase, oxidase, mucinase, and a vacuolating cytotoxin (VacA), but the role of these on disease severity or progression is unclear. *H. pylori* urease is a potent stimulus for memory CD8$^+$ T lymphocytes, which show a 15-fold greater response to urease in infected compared with uninfected subjects, and might have important implications for development of more severe disease.[27,28] Much attention has been focused on a portion of the *H. pylori* bacterial genome called the *cytotoxin-associated gene pathogenicity island*, which contains genes responsible for disease outcomes in the infected host.[19,29–32] Genetic variability is the rule with *H. pylori,* and these genetic modifications have led investigators to label variant strains a type of "quasi-species."[33–35]

H. pylori infection elicits a variety of phenotypic responses in cultured gastric epithelial cells, including the expression of proinflammatory genes and changes in the actin cytoskeleton. Both responses are mediated by the type IV secretion system (TFSS) encoded by the *cag* pathogenicity island (*cag* PAI) that contains more than 31 genes.[21,28,36] TFSS is unique among bacteria species and is postulated to be a key mechanism in *H. pylori*–associated carcinogenesis.[32] In addition, blood group antigen-binding adhesin BabA-mediated binding of *H. pylori* to Lewis blood group b antigen (Le^b) on the epithelial surface augments TFSS-dependent *H. pylori* pathogenicity by triggering the production of proinflammatory cytokines and precancer-related factors.[37] *H. pylori* adheres intimately to epithelial cells in the gastric mucosa and expresses several surface proteins, including a blood group antigen-binding adhesin, BabA.[38–40] Lewis-associated antigens, carbohydrates related biochemically to the ABO blood groups, also are thought to play a role in *H. pylori* adhesion to gastric mucosa. *H. pylori* is one of the few known microbes to be able to use its host glycoproteins (i.e., Le^x and Le^y antigens) within its outer membrane to facilitate immune evasion. Moreover, *H. pylori* contains a fucosyltransferase gene (*α1,3,4-FUT*) expressed in the bacterial outer membrane as lipopolysaccharide moieties strikingly similar to Le^x and Le^y epitopes, which facilitates the persistence in colonization and immune cell evasion.[37,38,41,42]

Epidemiology

H. pylori resides in the stomach of more than 50% of the world's population, making it the most common chronic infection worldwide. Prevalence varies by geographic area, age, race, and socioeconomic status. In developed countries, <40% of the population might be infected.[3] However, in developing countries or populations with poor water and sanitation conditions (e.g., Native Canadians and Native Alaskans), up to 90% of the population is infected.[43,44] Socioeconomic status has an inverse relation with the prevalence of infection and is one of the most important risk factors for acquisition.[45] In poor populations, infection usually is acquired early in children <10 years of age.[43–47]

A large study in Amazonian natives found an overall *H. pylori* seroprevalence of 92%, with >80% of children positive by 3 years of age; interestingly, infection did not correlate with the length of contact with the outside world, suggesting that *H. pylori* was indigenous.[48] In contrast, several studies suggest *H. pylori* seroprevalence has decreased worldwide since the 1960s, with greater declines in developed countries and overall seroprevalence of <15% by 10 years of age (Fig. 174.1).[45,49–54] The reasons for declining prevalence is unknown, although better living conditions, less crowding, smaller family size, clean and chlorinated water, and the widespread use of antibiotics might have contributed.[55,56] Some researchers have speculated that (1) not all *H. pylori* strains are pathogenic, (2) at some point *H. pylori* may have been part of the human gastrointestinal microbiome, and (3) changes in the prevalence of *H. pylori* infection might have implications for human health.[57–63]

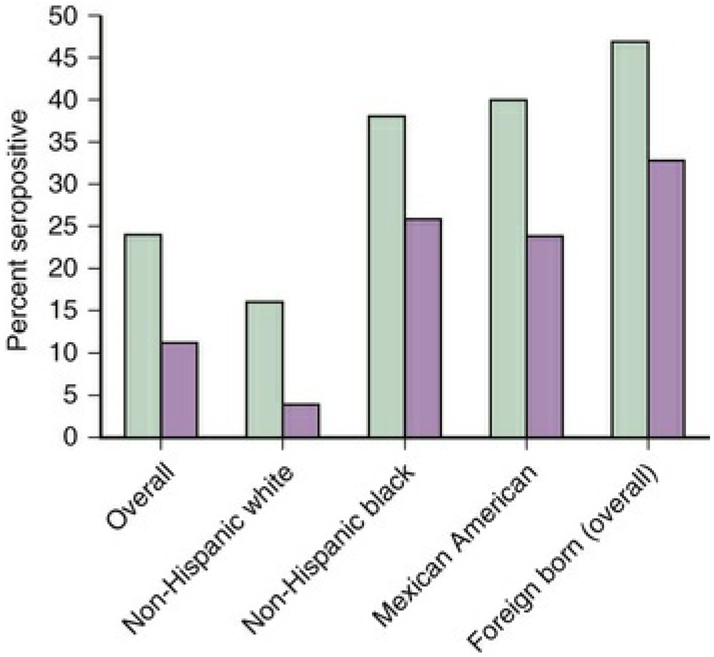

FIGURE 174.1 Declining seroprevalence of *Helicobacter pylori* in US children, using sera from NHANES III (1988–1991) (*pale blue bars*, 2795 subjects) and NHANES (1999–2000) *(purple bars,* 2898 subjects). Change in seroprevalence over time periods has P < 0.001. (Redrawn from Gold BD, Kruszon-Moran D, Sobel J, et al. Decreasing seroprevalence of *Helicobacter pylori* infection in U.S. children ages 6–19 years. J Pediatric Gastroenterol Nutr 2003;37:360.)

Most new *H. pylori* infections are acquired during childhood, especially in developing countries.[56,64–67] Up to half of all children in Chile, Portugal, Nigeria, and Bangladesh are infected during their first 5 years of life.[68–71] Turkish children acquire *H. pylori* infection 2.5 times more often than they discard infection[72]; after eradication of infection, children, particularly adolescents, become reinfected more frequently than adults. Close contact with children, especially siblings <5 years of age, could be a more important risk factor for recurrent infection than age at initiation of treatment.[73]

In the United States, ethnic differences are notable in the prevalence of *H. pylori* infection. African American and Hispanic populations, as well as immigrant populations, have a twofold to sixfold increased risk for seropositivity compared with white people of higher socioeconomic status.[48,52,53] Data from the National Health and Nutrition Evaluation Survey (NHANES) demonstrated that as many as 42% of Mexican Americans aged 6–19 years are infected compared with 40% of non-Hispanic blacks and 17% of non-Hispanic whites.[74] Overall, gender is not associated with prevalence of *H. pylori* infection but may play a role in the disease outcome.[75] Lower socioeconomic status and poor hygiene in the living environment, particularly during childhood, correlate with higher *H. pylori* prevalence.[44,46,76–79] A study of twins raised separately who were discordant for *H. pylori* infection found that affected twins were raised under poorer conditions compared with their unaffected cotwins.[80] Most data infer that the mother more than the father plays the predominant role in infection owing to overall higher contact with their infants and young children in whom acquisition primarily occurs.[44,81–83] Increased consumption of fruits and vegetables and vitamin C supplements reduces the probability of acquisition of *H. pylori* infection and the severity of disease outcomes.[84,85] Breastfeeding during infancy has not been found to be protective against *H. pylori* infection.[86,87]

H. pylori transmission occurs primarily from person to person, but waterborne and iatrogenic spread through contaminated medical equipment also have been described.[88–91] Person-to-person transmission includes fecal-oral, gastro-oral and oral-oral routes, with much higher risks associated with neurologically impaired persons residing in an institutionalized setting where close personal contact and exposure to feces and vomitus is frequent.[92–95] Multiple studies of families, some multigenerational, show increased risk for intrafamilial transmission, especially mother to offspring, younger to older sibling, and between spouses.[93,96–100] The risk for transmission to young children is estimated to be eightfold higher if the mother is infected and fourfold higher if the father is infected.[101] A number of studies demonstrated that *H. pylori* isolates from family members are homologous by DNA fingerprinting.[102–106]

The fecal-oral route is the predominant mode of transmission, and *H. pylori* DNA is detected in the stool of infected individuals by a variety of molecular methods.[106–108] DNA purification followed by *H. pylori* polymerase chain reaction (PCR) analysis is an effective tool for harvesting *H. pylori* DNA isolates from the feces of children, with positive and negative predictive values of 80% and 100%, respectively.[107] Primary isolation of *H. pylori* from stool is difficult, although some research-based laboratories have been able to recover the organism from up to 50% of infected persons.[64,95] Oral-oral transmission also can occur in certain populations; the organism has been found in saliva, dental plaque, reflux of gastric contents, and vomitus, and transmission might be associated with premastication of food by mothers.[44,95,109–114]

Although transmission through contaminated, poorly sanitized water is debated, the evidence is compelling.[115–122] Studies have isolated *H. pylori* from well water and sewage-contaminated water, and one study showed that children whose water source was outside their homes had infection rates threefold higher than children whose homes had an internal water source.[6,123–126] Transmission in the healthcare setting also is important, even in the developed world.[88,127] A meta-analysis reviewed 11 cross-sectional and 3 prospective studies that evaluated the occupational risks of healthcare personnel for acquisition of *H. pylori*.[127] The risks are highest for gastroenterologists, some nurses, and employees caring for persons with mental disability; however, results for other groups are conflicting.[88,128] Moreover, the use of improperly disinfected endoscopes increases the risk for infection, whereas disinfection of endoscopes by soaking in glutaraldehyde cleaning agents and, more important, cleansing of the channels by vigorous brushing reduces the risk for *H. pylori* acquisition.[88,129]

Pathogenesis

H. pylori infection and its long-term effects, including peptic ulcer, MALT lymphoma, and gastric adenocarcinoma, result from a complex interaction between the organism's virulence factors, susceptibility and immunologic response of the host, and environmental factors that might modulate susceptibility to infection, disease, or both.[17,130–133] Pathogenesis and natural history are depicted in Fig. 174.2. Several mechanisms have been elucidated that allow the pathogen to persistently colonize the gastric epithelium, generate mucosal inflammation, and regulate gastric acid output, subsequently causing a wide spectrum of chronic ailments.

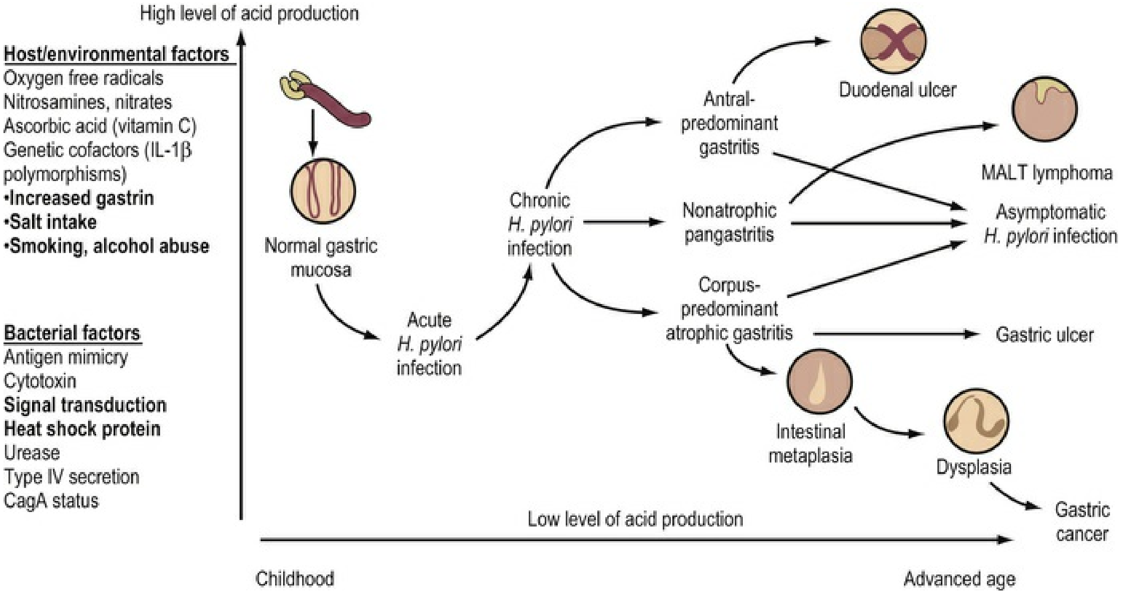

FIGURE 174.2 Pathogenesis and natural history of *Helicobacter pylori*. Bacterial, host, and environmental determinants affect disease outcome. MALT, mucosa-associated lymphoid tissue. (Modified from Suerbaum S, Michetti P. *Helicobacter pylori* infection. N Engl J Med 2002;347:1175–1186.)

H. pylori produces high quantities of urease enzyme, which converts urea into ammonium and bicarbonate, thereby creating an alkaline microenvironment that permits survival despite gastric acidity.[134,135] Colonization of gastric mucosa is initiated by a unique and specific tropism for gastric epithelial cells rich in Le^b blood group antigen with attachment mediated by the bacterial blood group antigen-binding adhesin BabA.[37,38,136–140] Although other bacterial adhesins may contribute to colonization, expression of BabA has been associated with duodenal ulcer and gastric adenocarcinoma.[38,139] The vacuolating cytotoxin VacA also is associated with an increased risk for gastroduodenal ulcers and, to a lesser extent, gastric cancer.[141–143] Polymorphisms, and the two main variable regions of the *vacA* gene, the signal sequence (*s*) and the mid region (*m*) properties, facilitate typing of isolated strains.[144] Expression of these regions reflects production of the vacuolating toxin; s1-m1, s1-m2, and s2-m1 genotypes correspond to high, medium, and low toxin-producing strains, respectively. However, the overall correlation between *vacA* and disease phenotype remains equivocal.

H. pylori is a potent inducer of gastric mucosal inflammation through various mechanisms, the most important of which is CagA.[145–147] TFSS are macromolecular assemblies, which are widespread in pathogenic bacteria, and often are used to deliver effectors into host cells. Encoded for in the *cag* PAI, *H. pylori* encodes Cag TFSS that mediates the injection of the toxin CagA into gastric epithelial cells, where it undergoes tyrosine phosphorylation by host cell kinases.[37,148] CagA then activates nuclear factor κB (NF-κB), the intracellular signaling pathway that regulates induction of the proinflammatory cytokines interleukin-8 (IL-8) and IL-1β.[149,150] The relative ability of *H. pylori* strains to induce epithelial cell inflammation is dependent on the presence of an intact *cag* PAI containing the *picB* gene.[151] Strains that possess the complete PAI induce pangastritis, which evolves to gastric ulceration, atrophy, intestinal metaplasia, and eventually, distal gastric cancer.[151] *CagA*$^+$ variant strains that have an incomplete *cag* PAI (because of deletions or mutations) induce antral-predominant gastritis, more likely leading to duodenal ulcer than to distal gastric cancer.[32,151]

H. pylori strains that possess toxigenic *vacA s1* allele, a complete *cag* PAI, *cagA* alleles containing multiple EPIYA phosphorylation sites, and expression of BabA adhesin, correlates with development of gastroduodenal disease in adults. In a study involving 47 North American children with a variety of gastroduodenal pathologies, a range of EPIYA motif configurations were observed for the *cagA* gene, which was present in strains from 47% of patients, but only 41% contained a complete *cag* PAI. Sixty-four percent of children were infected with a strain having the *vacA s1* allele, and 60% had the *babA* gene. The presence of a functional *cag* PAI had a significant correlation with ulcer disease.[152] Pediatric strains differ in their spectrum of strain-variable genes and percentage of absent genes compared with adult strains. Moreover, in this novel study, most children were infected with *H. pylori* strains lacking the *cag* PAI, but the presence of a complete *cag* PAI (in contrast to other virulence markers) was associated with more severe gastroduodenal disease.[152] Although *H. pylori* strains that possess the *cag* PAI and secrete a functional cytotoxin induce more severe gastric injury and further augment the risk for developing distal gastric cancer, carcinogenesis also is influenced by host genetic diversity, particularly involving immune response genes such as *IL-1β* and *TNF-α* as well as expression of tumor suppressor genes, including *p53* and *c-myc*.[153]

H. pylori urease binds to major histocompatibility complex class II molecules expressed on the surface of gastric epithelial cells, which in turn induces apoptosis and thus modulates cell growth.[154–156] A second mechanism is the induction of Fas-Fas ligand–regulated apoptosis through two different proinflammatory cytokines: (1) production of interferon γ (IFNγ) induced by a Th1 immune response triggered by *H. pylori* colonization and (2) induction of IL-1β by CagA.[157-159] CagA is one of the primary *H. pylori*–produced stimuli of production of the proinflammatory cytokine IL-1β, which also is a potent inhibitor of gastric acid secretion.[133,160,161] Gastric acidity may be further reduced in *H. pylori*–infected individuals with particular polymorphisms of the IL-1β gene promoter, thereby increasing the risk for atrophic gastritis and gastric adenocarcinoma.[161,162] Another virulence marker of *H. pylori* is the *iceA* gene, so called because its expression is induced after contact with epithelial cells.[143] The gene has two distinct genotypes, *iceA1* and *iceA2,* but the overall relevance of genotypes to disease phenotype remains unclear.[163–166]

Although more than 50% of the world's population is infected, most individuals remain clinically asymptomatic, suggesting that not all *H. pylori* strains are pathogenic. It is not clear why 15% to 20% of infected people develop gastroduodenal ulcer disease and <1% develop gastric adenocarcinoma.[17,167] Identifying markers that predict more severe disease outcomes is of great importance to implement cost-effective public health strategies to target eradication treatment efforts. In both children and adults, studies to determine associations between BabA, VacA, CagA, and PicB with peptic ulcer and gastric cancer continue to reveal conflicting results.[37,39,40,165,166] Although *cag* PAI appears to be the one marker of inflammation and clinical disease found in clinical isolates of *H. pylori,* other virulence factors appear to be markers of geographic distribution rather than predictors of disease outcome (see Fig. 174.2).[163,168,169]

Clinical Manifestations

Intestinal Disease

H. pylori infection in children generally is asymptomatic. However, when there is persistent colonization, gastritis develops almost universally. Although there are a number of reports of spontaneous elimination of *H. pylori* infection in children, many of these studies are limited by the methodology used to detect infection.[46,170–172] The association between *H. pylori* infection and gastritis and duodenal ulcer disease in children is very strong.[173–175] The rate and mechanism of spontaneous clearance of infection in children is not known. Nodular gastritis appears to be observed more commonly in children (Fig. 174.3); however, the time to development of endoscopically visible nodules and their natural history remains uncharacterized.[176–179] Additionally, it is not clear which children with lymphofollicular gastritis will progress to develop MALT lymphoma, and over what time period.[180,181] Studies have demonstrated that eradication of *H. pylori* in children with MALT lymphoma results in resolution of the mucosal disease, both gastric and extragastric.[181,182]

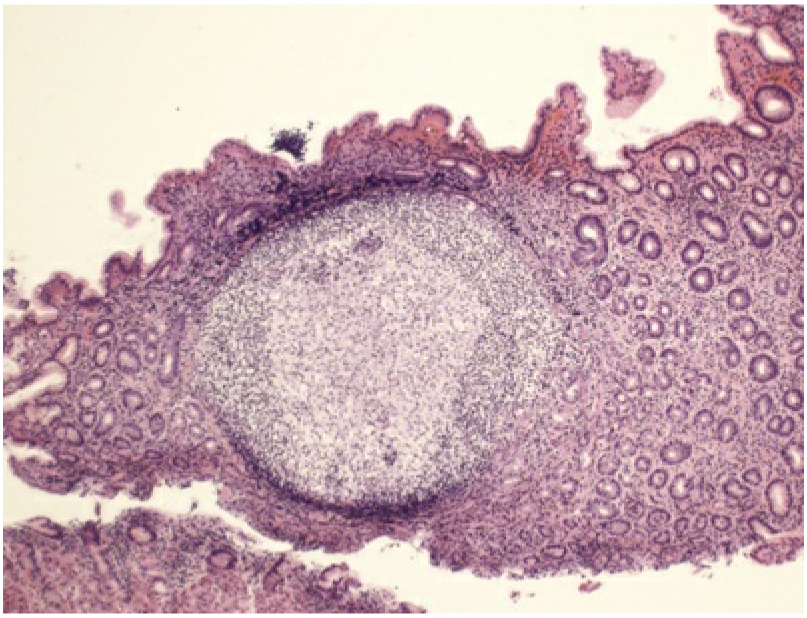

FIGURE 174.3 Large lymphoid nodule in inflamed antrum (hematoxylin-eosin stain; original magnification, ×50). (Courtesy of Dr. Milton Finegold, Department of Pathology, Baylor College of Medicine, Texas Children's Hospital.)

Although individual cases and case series of gastric adenocarcinoma and MALT lymphoma have been reported in the pediatric population, these conditions are rare in children.[181,183–185] However, early childhood acquisition and persistence of *H. pylori* significantly increase the risk for gastric malignancies in adults.[186,187] Atrophic gastritis and intestinal metaplasia, precursor lesions for gastric cancer, occur in *H. pylori*–infected children.[188,189] In a study of 173 children from countries with high incidence of gastric cancer, atrophic gastritis was noted in 16% of those with active *H. pylori* infection.[189] Atrophic mucosa was seen as pseudopyloric metaplasia (63%), intestinal metaplasia (31%), or both (6%). Investigators also suggested that identification of this specific disease phenotype requires targeted biopsies to include the lesser and greater curve of the gastric corpus, in addition to biopsies targeting the antrum and cardia.[189]

Landmark studies demonstrated that *IL-1* gene cluster polymorphisms leading to increased IL-1β production are associated with an increased risk for *H. pylori*–induced hypochlorhydria and gastric cancer.[8] Compared with healthy controls, relatives of patients with gastric cancer had a higher prevalence of hypochlorhydria (27% vs. 3%) despite having a similar prevalence of *H. pylori* infection (63% vs. 64%).[162,190]

Relatives of cancer patients matched for *H. pylori* prevalence also had a higher prevalence of atrophy (34%) than patients with nonulcer dyspepsia (5%). Increased prevalence of precancerous gastric abnormalities in relatives is limited to those with *H. pylori* infection. These findings prompted changes in current pediatric guidelines to target prophylactic eradication and prevention strategies to selected patients, especially those with a first-degree relative with gastric cancer.[10,191]

Although a relationship between ulcer disease and abdominal symptoms is apparent, it is unclear whether chronic gastritis causes symptoms in children. Results from studies around the world have been conflicting, precluding a definitive recommendation for treatment of *H. pylori* found in the child with gastrointestinal symptoms but no demonstrable disease. Some studies have reported an association of *H. pylori* infection with recurrent abdominal pain in children; however, it is difficult to reach definite conclusions from these studies given some methodologic flaws, including lack of randomization, lack of double blinding, absence of a validated symptom assessment instrument, and no assessment of the socioeconomic status as a confounding variable.[192–196] One population-based cross-sectional study that evaluated the relationship between *H. pylori* infection, recurrent abdominal pain, and social and familial factors in 1221 children aged 5–8 years showed an association between abdominal pain and social and familial factors but not between abdominal pain and *H. pylori* infection.[197] Other studies have confirmed these findings.[198,199] In a well-designed randomized placebo-controlled treatment trial of 20 children with *H. pylori* infection, gastritis, and recurrent abdominal pain, 8 of 10 in the treatment group had eradication of *H. pylori* compared with 0 of 10 in the placebo group. However, at 52 weeks, bacterial eradication and healing of gastric inflammation did not lead to relief of chronic abdominal pain.[200] Epigastric pain, abdominal pain causing nocturnal wakening, hematemesis, and recurrent vomiting are not associated with *H. pylori* infection, and no difference in frequency was found between colonized and noncolonized children.[192]

The true incidence of gastric and duodenal ulcer disease in children is unknown. However, children with duodenal or gastric ulcers have symptoms similar to those of adults, including sharp, burning pain in the epigastrium that generally occurs with an empty stomach, between meals, and during the early morning hours. In addition, signs of occult or frank bleeding can occur. Primary ulcers in the pediatric population (most of which are *H. pylori* associated) occur in the duodenum and are seen in older children. Gastric ulcers are less common and usually are secondary (i.e., due to another disease process such as Crohn disease or produced by chemical irritation of the gastric mucosa as caused by aspirin or nonsteroidal anti-inflammatory drugs).[201]

Whether *H. pylori* infection predisposes to or provides protection against diarrheal diseases in children remains a topic of debate. A number of studies provide compelling evidence that *H. pylori* −infected children are more at risk for diarrhea due to enteric infections.[202,203] For example, a study in Peru showed a high incidence of diarrhea in children with *H. pylori* infection, probably as a result of the transient achlorhydria that occurs during the acute phase of infection.[203] Increased rates of enteric infection in the face of early *H. pylori* infection likely are due to poor water sanitation or poor hygiene, resulting in increased exposure to enteric pathogens. Conversely, others studies have shown a protective effect of *H. pylori* infection against diarrheal diseases.[204–206] These conflicting observations may be explained by factors related to the age and socioeconomic status of the population studied, the geographic region in which the child resides, or the stage at which infection is detected because protection against diarrhea occurs when the pH returns to acid. Furthermore, the presence of *H. pylori* augments the local and systemic immune response to enteropathogens, as has been demonstrated in *Vibrio cholerae*.[207,208]

The controversy surrounding whether *H. pylori* infection is protective, causative, or unrelated to gastroesophageal reflux disease (GERD) in adults and children has for the most part been settled. *H. pylori* at most is an innocent bystander and is not protective against GERD or its sequelae in both children and adults.[48,209,210] Although there is reverse prevalence of GERD in countries with a high and low prevalence of *H. pylori,* conclusion of causality is overly simplistic.[211] In a study of 95 children and adolescents who were recruited and completed an eradication trial with a mean follow-up of 11.2 months, the distribution of outcomes for each GER symptom (better, worse, unchanged) was similar before and after eradication and did not depend on prior *H. pylori* status.[212] These data and other case series prompted guideline committees to recommend *H. pylori* eradication in children with GERD who are undergoing endoscopy.[10,191] However, when the diagnosis of GERD is made clinically or by pH monitoring, it is not necessary to screen for *H. pylori*.

Extraintestinal Disease

Multiple reports from around the world have demonstrated an association between *H. pylori* infection and iron deficiency anemia.[213–216] In the US NHANES survey for 1999–2000, *H. pylori* infection was associated with iron deficiency and iron deficiency anemia in 7462 survey participants 3 years or older. *H. pylori* infection also was associated with decreased serum ferritin levels, but not with levels of free erythrocyte protoporphyrin, transferrin saturation, or hemoglobin. Although multicenter, sufficiently powered, randomized controlled treatment trials have not been performed, evidence suggests that anemia and iron deficiency may benefit from *H. pylori* eradication.

The first reports of *H. pylori* infection effects on growth retardation were published from Gambia and demonstrated convincingly that *H. pylori* could be a cofactor for growth disturbance in children infected early in life.[217] Longitudinal studies in children have demonstrated a link between short stature and *H. pylori* infection, especially in girls, although the association of infection with failure to thrive needs further study.[218,219] In a large Colombian cohort study, among 105 children who were infected with *H. pylori*, a significant decrease in growth velocity was observed during the first 4 months after infection, without height catch-up in infected children. At 8 months after acquisition, an infected child had a cumulative difference of 0.24 cm (growth velocity) compared with uninfected children.[220] Likewise, in a Turkish study involving more than 3000 school-aged children, growth retardation was associated with *H. pylori* infection, independent of their poor living conditions.[221] Other studies have reached similar conclusions.[222–224] In at-risk populations, potential interventions that target infected preschool-aged children are likely to prevent growth retardation.

The role of *H. pylori* in idiopathic thrombocytopenic purpura (ITP) was first suggested in 1997.[225] Subsequent studies in adults have supported this initial observation.[226–229] In case series, eradication of *H. pylori* has been associated with platelet recovery in adults and children with ITP.[229,230] In a study of 17 children with ITP, *H. pylori* infection was not found.[231] In contrast, another investigation that used polyclonal *H. pylori* antigen stool testing found *H. pylori* infection in 9 of 22 children with ITP; after eradication therapy, 5 of these 9 children had increased platelet counts that persisted throughout the 24-month follow-up period.[227] Overall, eradication of *H. pylori* has been associated with remission of ITP in approximately half of patients. In a larger multicenter study in Italy, of 244 screened patients younger than 18 years with chronic ITP, 50 (20%) had *H. pylori* infection, 37 of whom received eradication therapy and completed follow-up. Eradication was successful in 89%; platelet recovery occurred in 39% of patients after eradication, whereas spontaneous remission occurred in 10% of *H. pylori*–negative patients ($P < 0.01$).[232] Screening and treatment for *H. pylori*-positive adults with ITP has been suggested.[233] Further controlled studies in children are needed.

Other clinical conditions that also have been associated with *H. pylori* infection include protein-losing gastropathy, periodontal disease, rosacea, food allergy, coronary artery disease, diabetes mellitus, neurologic disorders, and autoimmune diseases. However, these associations remain speculative.[234,235]

Diagnosis

There are no specific signs or symptoms that predict the presence of gastritis or peptic ulcer in children. Furthermore, most *H. pylori* infections and associated gastritis remain asymptomatic. However, children with warning symptoms or alarming signs, such as severe chronic abdominal pain, anorexia and failure to thrive, or persistent vomiting, require investigation. The presence of occult blood in feces, particularly in the face of iron deficiency anemia, should lead to investigation. The severity of symptoms determines the need for endoscopy; endoscopy and biopsy are performed to determine the cause of symptoms, not merely to investigate for *H. pylori* infection.[10,191] Management guidelines from the Canadian *H. pylori* study group and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) are summarized in Table 174.1.[10,191]

TABLE 174.1

Management Guidelines for *Helicobacter pylori* in Children

Canadian *H. pylori* Study[a]	**ESPGHAN-NASPGHAN**[b]
Population-based screening for *H. pylori* in asymptomatic children to prevent gastric cancer is not warranted. Testing for *H. pylori* in children should be considered if there is a family history of gastric cancer. The goal of diagnostic interventions should be to determine the cause of presenting gastrointestinal symptoms and not the presence of *H. pylori* infection. Recurrent abdominal pain of childhood is not an indication to test for *H. pylori* infection. *H. pylori* testing is not required in patients with newly diagnosed GERD. *H. pylori* testing may be considered before the use of long-term proton pump inhibitor therapy. Testing for *H. pylori* infection should be considered in children with refractory iron deficiency anemia when no other cause has been found. When investigation of pediatric patients with persistent or severe upper abdominal symptoms is indicated, upper endoscopy with biopsy is the investigation of choice. The UBT currently is the best noninvasive diagnostic test for *H. pylori* infection in children. There is insufficient evidence to recommend stool antigen tests as acceptable diagnostic tools for *H. pylori* infection. *H. pylori* serologic antibody tests are not recommended as diagnostic tools for infection in children	The primary goal of clinical investigation of gastrointestinal symptoms is to determine the underlying cause of symptoms and not solely the presence of *H. pylori* infection. Diagnostic testing for *H. pylori* infection is not recommended in children with functional abdominal pain. In children with first-degree relatives with gastric cancer, testing for *H. pylori* may be considered. In children with refractory iron deficiency anemia, in which other causes have been ruled out, testing for *H. pylori* infection may be considered. For the diagnosis of *H. pylori* infection during EGD, gastric biopsies (antrum and corpus) should be obtained for histopathology. Initial diagnosis of *H. pylori* infection can be based on either positive histopathology plus positive rapid urease test or a positive culture. The UBT is a reliable noninvasive test to determine eradication of *H. pylori*. A validated EIA test for *H. pylori* antigen in stool is a reliable noninvasive test to determine eradication of *H. pylori*. Tests to detect antibodies (IgG, IgA) against *H. pylori* in serum, whole blood, urine, and saliva are not reliable for clinical use. Clinicians should wait at least 2 weeks after stopping PPI therapy and 4 weeks after stopping antibiotics to perform biopsy-based and noninvasive tests (UBT, stool test) for *H. pylori*.

[a] Bourke B, Ceponis P, Chiba N, et al. Canadian *Helicobacter* Study Group Consensus Conference: update on the approach to *Helicobacter pylori* infection in children and adolescents—an evidence-based evaluation. Can J Gastroenterol 2005;19:399−408.

[b] Koletzko S, Jones NL, Goodman KJ, et al. Evidence-based guidelines from ESPGHAN and NASPGHAN for *Helicobacter pylori* infection in children. J Pediatr Gastroenterol Nutr 2011:53:230–243.

ESPGHAN, European Society for Pediatric Gastroenterology, Hepatology and Nutrition; EGD, esophagogastroduodenoscopy; EIA enzyme immunoassay; GERD, gastroesophageal reflux; Ig, immunoglobulin; NASPGHAN, North American Society for Pediatric Gastroenterology, Hepatology and Nutrition; PPI, proton pump inhibitor; UBT, ^{13}C-urea breath test.

The gold standard for the diagnosis of *H. pylori* infection is identification of the organism in culture and histologic examination of gastric biopsy samples. Compared with histologic changes in adults, children have (1) a higher density of *H. pylori* within the pits and on the surface of epithelial cells and a milder degree of infiltration with neutrophils, plasma cells, and eosinophils; (2) similar degree of infiltration with mononuclear cells and atrophy; and (3) less frequent ulcers or intestinal metaplasia.[236,237] In children, mucosal ulceration is located in the duodenum and is uncommon in the gastric corpus, but it can be seen in the gastric antrum.[238] Hematoxylin and eosin staining of gastric secretions is not as sensitive as other stains (i.e., Warthin-Starry silver stain, acridine orange, or Giemsa stain). The sensitivity of hematoxylin and eosin staining of gastric secretions is 77% versus 88% for biopsy specimens taken by endoscopy (Fig. 174.4).[191,238] *H. pylori* is a fastidious organism; therefore biopsy material can be transported in saline only if it is to be processed within 3 hours—otherwise transport medium must be used, and the specimen should be kept on ice before inoculation. Gastric biopsy material can be tested using a rapid urease test that exploits the urease enzyme of *H. pylori* and can be performed in the endoscopy suite.[239] The entero-test is a noninvasive method to obtain a sample for culture for *H. pylori,* in which a capsule attached to a highly absorbent nylon string is swallowed. Amplification of several genes (urease, 16S RNA, 29-kd antigen, *cag,* and *vacA*) by PCR was demonstrated to be a successful alternative to culture and histology for diagnosis.[240,241] Although 16S RNA may be more sensitive for the detection of *H. pylori,* amplification of the *cag* or *vacA* genes gives more information on the infecting strain.[143,242,243] Biopsy specimens from the gastric antrum and corpus are inoculated onto enriched horse or sheep blood agar supplemented with antibiotics (vancomycin, amphotericin B, and cefoperazone) and incubated at 37°C in a microaerophilic atmosphere with 7% nitrogen. Isolation of *H. pylori* in culture provides the additional benefit of susceptibility testing; however, few clinical microbiology laboratories have the capacity to perform culture for *H. pylori*.

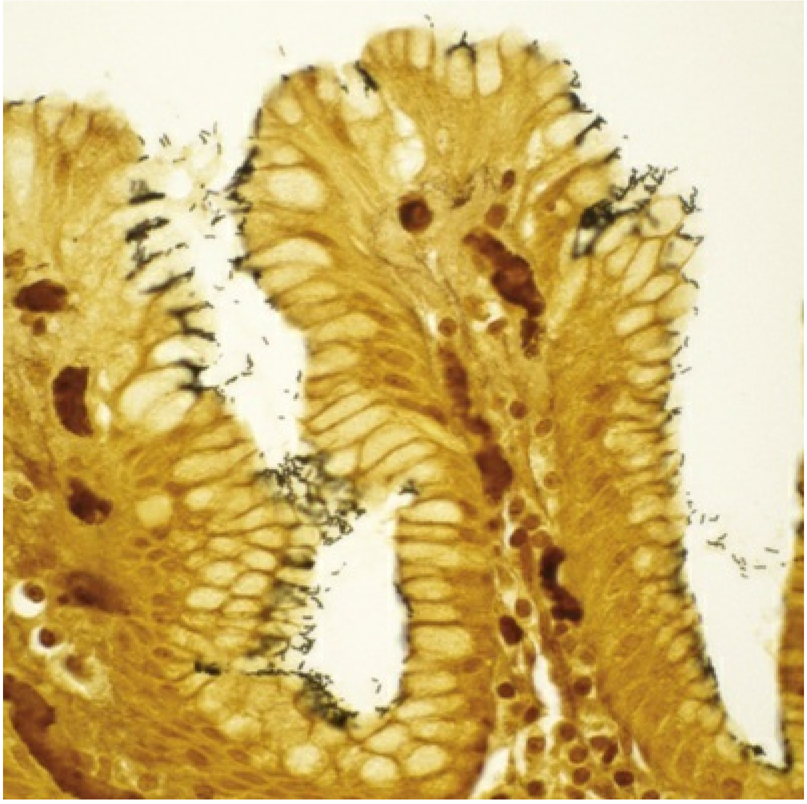

FIGURE 174.4 Gastric mucosa showing high density of *Helicobacter pylori* organisms on its surface (silver stain; original magnification, ×400). (Courtesy of Dr. Milton Finegold, Department of Pathology, Baylor College of Medicine, Texas Children's Hospital.)

The ^{13}C-urea breath test (UBT) using techniques such as a novel laser–associated ratio analysis (LARA)-^{13}C, and the stool antigen tests (particularly new-generation monoclonal tests) have been studied extensively in both adults and children.[10,106,188,191,244–248] Investigations clearly demonstrated utility of these assays in children both for diagnosis and as a test for cure.[244,249,250] Further validation of these assays is required for children younger than 6 years. The polyclonal stool antigen test demonstrated variable performance and had less favorable accuracy compared with the UBT and newer generation monoclonal stool antigen tests.[246,251]

Another method to diagnose *H. pylori* infection in children is detection of specific antibodies in serum, urine, or saliva.[252,253] Detection of serum immunoglobulin G antibodies by enzyme immunoassay (EIA) and Western blot is the most widely used.[254,255]

The sensitivity of most commercially available EIAs, however, is much lower in children than in adults.[256] More recently developed EIAs that use recombinant CagA and VacA antigens require further evaluation in children. As a result, three original pediatric *H. pylori* guidelines, as well as revised Canadian and ESPGHAN-NASGPHAN guidelines for children, recommend against clinical use of serology.[191,257–259]

The “string test” is a novel, relatively noninvasive method (requiring swallowing, 1-hour dwell time, and retrieval) that can provide both isolation of the organism for typing and antimicrobial susceptibility testing.[260–266] In a recent study, strains recovered from strings and biopsy specimens yielded identical or closely related profiles using molecular assays (i.e., randomly amplified polymorphic DNA and PCR for urease B gene) in each of 24 cases tested.[261] Genotypes of *H. pylori* from members of 62 households in Peru were compared using cultures and DNA assays by the string test. The randomly amplified polymorphic DNA fingerprints of 70% of child-mother pairs did not match, nor did the diagnostic gene sequences (>1% DNA sequence difference), independent of the child's age. Most strains from siblings or other paired family members also were unrelated.[264] These data suggest that *H. pylori* infections in the society studied often are community acquired. This small but novel study infers that effective prevention of *H. pylori* infection and associated gastroduodenal disease will require anti −*H. pylori* measures applied community-wide. Although both studies are small in size, they provide evidence that the string test is useful clinically, especially in settings such as in rural communities or areas where pediatric gastroenterologists are not available.

Treatment

Treatment Guidelines

ESPGHAN and NASPGHAN provide clinical practice guidelines recommendations for approach to treatment of *H. pylori* (Box 174.1) and an algorithm for evaluation of a child with suspected infection (Fig. 174.5).[10] The most effective *H. pylori* therapy currently accepted for children is a 2-week, triple therapy regimen that includes a proton pump inhibitor, such as omeprazole or lansoprazole, plus clarithromycin and amoxicillin. Box 174.2 lists accepted, evidence-based eradication therapies for children. *H. pylori* culture and antibiotic sensitivity testing should be made available to monitor population antibiotic resistance and to manage treatment failures. In a follow-up study of 209 children treated with sequential 5-day regimen (fourth in Box 174.2), eradication was achieved in 80% overall but was substantially lower in those with 1- or 2-drug resistance; the authors conclude that sequential therapy cannot be recommended for treatment-naïve children.[267] In studies in adults, quadruple therapy that also includes bismuth subsalicylate or citrate for 7 days has been demonstrated to be highly effective. Quadruple therapy in children, as well as levofloxacin-based therapy, requires additional studies for approval.[268,269] Ranitidine bismuth citrate plus two antibiotics also has been shown to have a high *H. pylori* eradication rate; however, further validation in children is required.[270] In adults, triple therapy including levofloxacin now is recommended as an important component of salvage therapeutic regimens for treatment failures and is being used more widely as part of first-line therapy.[271,272] A meta-analysis showed that rescue therapy with levofloxacin is better tolerated and more effective than quadruple therapy (i.e., proton pump inhibitor plus two antibiotics with a bismuth base).[273]

Box 174.1

Approach to Treatment of *Helicobacter pylori* in Children[a]

1. In the presence of *H. pylori*–positive peptic ulcer disease, eradication of *H. pylori* is recommended.

2. When *H. pylori* infection is detected by biopsy-based methods in the absence of peptic ulcer disease, treatment may be considered.

3. A “test and treat” strategy is not recommended in children.

4. In infected children whose first-degree relative has gastric cancer, treatment may be offered.

5. The duration of triple therapy should be 7 to 14 days. Cost, compliance, and adverse effects should be taken into account.

6. If treatment has failed, 3 options are recommended:

a. EGD with culture and susceptibility testing (including alternative antibiotics), if not performed before

b. FISH on previous paraffin-embedded biopsies if clarithromycin susceptibility testing was not performed previously

c. Modification of therapy by adding an antibiotic, using different antibiotics, adding bismuth, and/or increasing the dose and/or duration of therapy

EGD, esophagogastroduodenoscopy; FISH, fluorescent in situ hybridization; PPI, proton pump inhibitor.

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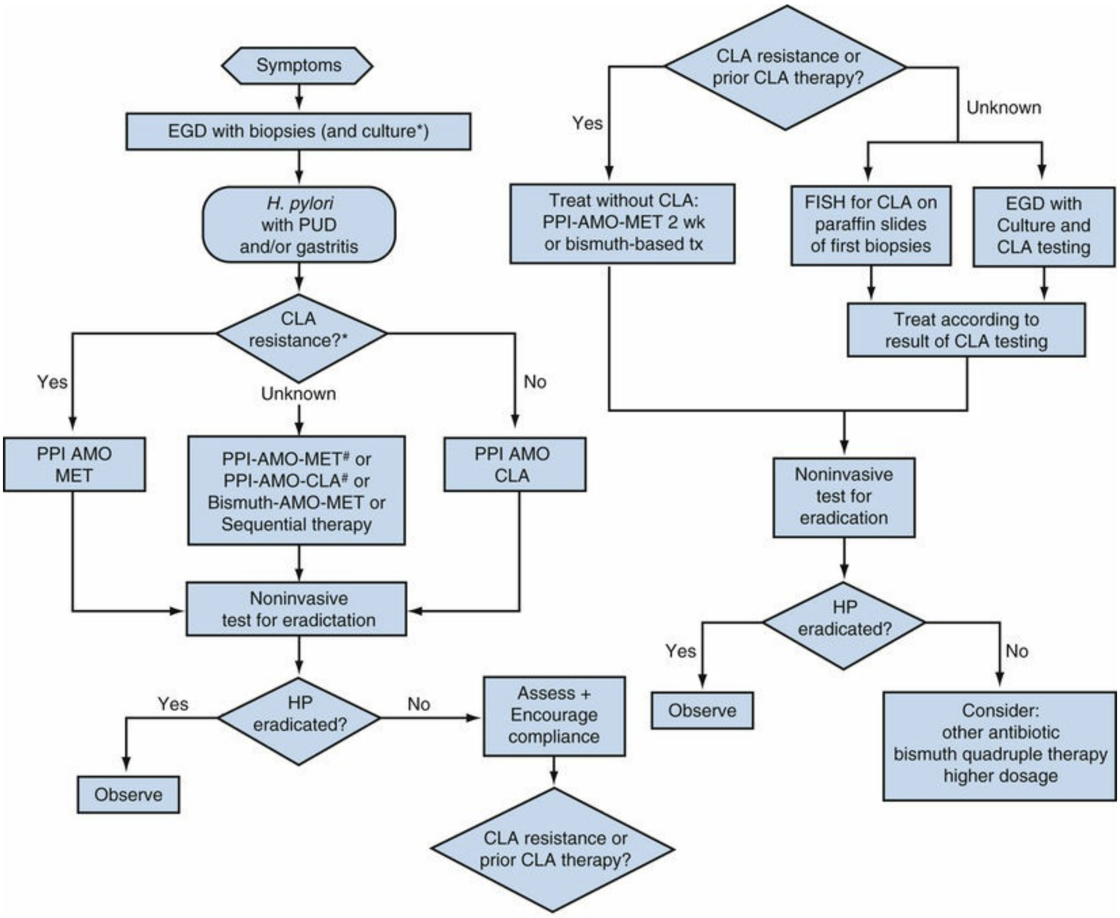
[a] Koletzko S, Jones NL, Goodman KJ, et al. Evidence-based guidelines from ESPGHAN and NASPGHAN for *Helicobacter pylori* infection in children. J Pediatr Gastroenterol Nutr 2011:53:230–243.


Symptoms
EGD with biopsies (and culture*)
H. pylori with PUD and/or gastritis
CLA resistance?*
Yes
Unknown
No
PPI AMO MET
PPI-AMO-MET# or PPI-AMO-CLA# or Bismuth-AMO-MET or Sequential therapy
PPI AMO CLA
Noninvasive test for eradictation
HP eradicated?
Yes
No
Observe
Assess + Encourage compliance
CLA resistance or prior CLA therapy?
CLA resistance or prior CLA therapy?
Yes
Unknown
Treat without CLA: PPI-AMO-MET 2 wk or bismuth-based tx
FISH for CLA on paraffin slides of first biopsies
EGD with Culture and CLA testing
Treat according to result of CLA testing
Noninvasive test for eradication
HP eradicated?
Yes
No
Observe
Consider: other antibiotic bismuth quadruple therapy higher dosage

*In areas or populations with a primary clarithromycin resistance rate of >20% or unknown background antibiotic resistance rates, culture and susceptibility testing should be performed, and the treatment should be chosen accordingly.

#If susceptibility testing has not been performed or has failed, antibiotics should be chosen according to the background of the child.

FIGURE 174.5 Algorithm for treatment of *Helicobacter pylori* infection in children. AMO, amoxicillin; CLA, clarithromycin; EGD, esophagogastroduodenoscopy; FISH, fluorescence in situ hybridization; HP, *Helicobacter pylori;* MET, metronidazole; PPI, proton pump inhibitor; PUD, peptic ulcer disease; tx, therapy. (From Koletzko S, Jones NL, Goodman KJ, et al. Evidence-based guidelines from ESPGHAN and NASPGHAN for Helicobacter pylori infection in children. *J Pediatr Gastroenterol Nutr* 2011;53:230–243.)

Box 174.2

First-Line Treatment Recommendations for *Helicobacter pylori* Eradication in Children

- PPI + amoxicillin + metronidazole
- PPI + amoxicillin + clarithromycin
- Bismuth salts (bismuth subsalicylate or subcitrate) + amoxicillin +

metronidazole

- PPI + amoxicillin for 5 days; then PPI + clarithromycin + metronidazole for 5 days

Doses are PPI, 1–2 mg/kg/day; amoxicillin, 50 mg/kg/day; metronidazole, 20 mg/kg/day; clarithromycin, 20 mg/kg/day; bismuth salts, 8 mg/kg/day. Therapy is given in 2 divided doses daily for 10–14 days. Maximal daily doses are amoxicillin, 2 g; metronidazole, 1 g; clarithromycin, 1 g.

See text for additional comment.

PPI, proton pump inhibitor.

From Koletzko S, Jones NL, Goodman KJ, et al. Evidence-based guidelines from ESPGHAN and NASPGHAN for Helicobacter pylori infection in children. *J Pediatr Gastroenterol Nutr* 2011;53:230–243.

Antibiotic Resistance and Follow-Up

Treatment should be guided by knowledge of specific geographic susceptibility patterns because efficacy of eradication is strongly influenced by antibiotic resistance and clinical relapses are invariably associated with failure to eradicate the organism. Emerging resistance makes options for therapy less definitive. In a multinational European study of 1233 patients from northern (3%), western (70%), eastern (9%), and southern Europe (18%), primary resistance rate of *H. pylori* strains obtained from unselected children was high; use of antibiotics for other indications was deemed a major risk factor for primary resistance.[274,275] In this study, overall resistance to clarithromycin was 24%, with higher rates in boys, in children older than 6 years compared with younger than 12 years, and in patients living in southern compared with northern Europe. Overall resistance to metronidazole was 25%, and was higher in children born outside of Europe.

Reports form the US and Europe show resistance rates of 21% to 41% for clarithromycin, 43% to 46% for metronidazole, and up to 5% for amoxicillin.[191,274,275] Metronidazole resistance in developing countries is even greater, up to 80%.[276,277] Follow-up to confirm cure and eradication should be performed using either UBT or *H. pylori* stool antigen test on weeks 4 to 6 after treatment. Reinfection rate appears to be <1% in developed countries but is much higher in developing populations and when more than 1 family member is infected. Monitoring is justified only when the risk for reinfection is increased.

Novel Therapies

Emerging data support the potential role for probiotics in treatment regimens for *H. pylori*. A systematic review with meta-analysis evaluating the addition of *Saccharomyces boulardii* to standard triple therapy significantly increased the rate of *H. pylori* eradication compared with triple therapy alone.[278] One randomized, blinded placebo-controlled trial found that *Lactobacillus casei* also provided higher eradication rates (85% vs. 58%, $P < 0.01$) when added to standard triple therapy.[279] A Cochrane Database review of the role of probiotics in *H. pylori* infection concluded that probiotics do not eradicate *H. pylori* but likely suppress levels in the stomach and, in combination with antibiotics, may increase eradication rates or decrease adverse effects of the multidrug treatment regimens.[280] The use of human lactoferrin as an adjuvant in the treatment of *H. pylori* is a promising novel treatment, but more data are needed to determine its efficacy in the pediatric population.[281,282]

Future Directions

H. pylori has a significant burden of disease in the world's population, especially in developing countries. New molecular assays provide a useful tool for accurate diagnosis; however, the emergence of antibiotic resistance makes treatment and eradication efforts challenging. Several *H. pylori* vaccines have been evaluated in clinical trials.[283–285] One randomized, double-blinded, placebo-controlled, phase 3 trial of an oral recombinant vaccine in >4000 children showed the vaccine was safe and immunogenic with an efficacy of 71%.[286] More studies with long-term follow-up are needed to determine duration of the observed protective effect. These data are promising for a vaccine that could potentially prevent gastric complications of *H. pylori* infection, including peptic ulcer disease and gastric cancer.

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Other Gastric and Enterohepatic *Helicobacter* Species

Jonathan D. Crews, Mark A. Gilger

Since the discovery of *Helicobacter pylori* and demonstration of its causal relationship with human gastroduodenal disease, investigators have identified numerous non–*Helicobacter pylori Helicobacter* (NHPH) species. These “other” *Helicobacter* spp., frequently found in domestic and wild animals, also have been recovered from the stomach, intestine, and hepatobiliary system of humans. Although the complete spectrum of human disease syndromes associated with NHPH remains to be fully defined, gastric and enterohepatic diseases have been described.

The Pathogens

There are now >30 formally named species in the genus *Helicobacter*.[1] In addition, there are a number of provisional species that have been named but not yet validated. NHPH are spiral-shaped bacilli that are gram-negative, motile, and microaerophilic. They are broadly grouped as gastric or enterohepatic, based on their biologic niche (Table 175.1).

TABLE 175.1

Gastric and Enterohepatic *Helicobacter* Species Identified in Humans

Species	Location
H. bizzozeronii	Gastric
H. felis	Gastric
H. heilmannii	Gastric
H. pylori	Gastric
H. salomonis	Gastric
H. suis	Gastric
H. bilis	Enterohepatic
H. canadensis	Enterohepatic
H. canis	Enterohepatic
H. cinaedi	Enterohepatic
H. fennelliae	Enterohepatic
H. ganmani	Enterohepatic
H. hepaticus	Enterohepatic
H. pullorum	Enterohepatic

The gastric NHPH spp. are urease- and catalase-positive. They can be distinguished from *H. pylori* by their longer, more tightly coiled morphology and their difficulty to culture in vitro (Fig. 175.1).[2–4] Microscopically, the gastric NHPH spp. are very similar to one another, although differences in size, the presence or absence of periplasmic fibers, and number and distribution of flagella have been described.[4,5] The first gastric NHPH to be discovered was an uncultivated organism, initially called *Gastrospirillum hominis*, and later *Helicobacter heilmannii*.[6,7] Subsequently several additional gastric *Helicobacter* spp. were identified, including *H. felis*, *H. suis*, *H. bizzozeronii*, and *H. salomonis*. The gastric NHPH spp. have been associated with gastritis, peptic ulcer disease, gastric carcinoma, and mucosa-associated lymphoid tissue (MALT) lymphoma in humans.

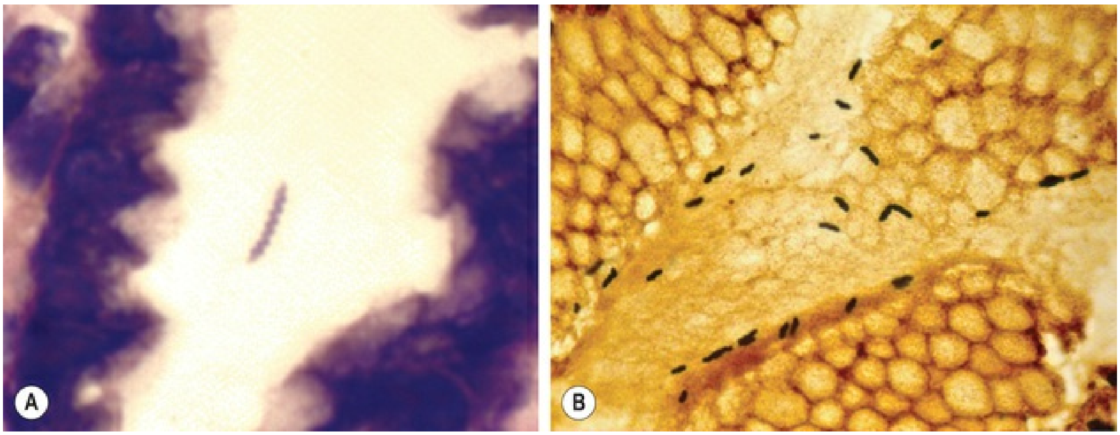

FIGURE 175.1 Morphologic differences between *H. pylori* and *H. heilmannii* s.l. The longer, more tightly-coiled *H. heilmannii* s.l. (A) can be distinguished from *H. pylori* (B) in gastric tissue. *Helicobacter* spp. can be viewed with hematoxylin and eosin stain, Giemsa stain (A), or silver stain (B). (Photo courtesy of Dr. Milton J. Finegold.)

The nomenclature of the gastric NHPH has produced confusion, largely owing to challenges in culturing the various organisms. Historically, long, spiral-shaped, uncultivable organisms in the human stomach were called *H. heilmannii*. However, the sequencing of specific target genes demonstrated that a group of *Helicobacter* spp. was actually present. Haesbrouck and colleagues proposed that *H. heilmannii* sensu lato (*H. heilmannii* s.l.) refer to the whole group of gastric NHPH spp. when only histopathologic or electron microscopic data are available and to reserve the use of species names when definitive identification at the species level is available. The term *H. heilmannii* sensu strictu (*H. heilmannii* s.s.) refers to the particular *H. heilmannii* species.[8] The complete genome for 4 of the 5 gastric NHPH spp. (i.e., *H. suis*, *H. felis*, *H. bizzozeronii*, and *H. heilmannii* s.s.) has been published.[9–12] The genomes reveal that these organisms, while possessing homologues to *H. pylori* genes associated with colonization, lack homologues to important *H. pylori* virulence genes, including the *cag* pathogenicity island and the genes encoding CagA and VacA. An exception is *H. suis*, which contains a VacA homologue.[12] These genetic differences may explain the pathologic differences that have been observed between the gastric NHPH and *H. pylori*.

The enterohepatic *Helicobacter* spp. are fastidious organisms found in the intestines, liver, and biliary tract of humans, other mammals, and birds. They have ultrastructural and physiologic features in common with gastric *Helicobacter* spp.; however, they generally do not colonize the gastric mucosa. Several enterohepatic NHPH spp. have been found in humans, including *H. bilis*, *H. canis*, *H. cinaedi*, *H. fennelliae*, *H. pullorum*, and *H. hepaticus* (see Table 175.1).[5] The enterohepatic NHPH spp. have been associated with gastroenteritis, hepatitis, benign biliary disease, and hepatobiliary malignancies. *H. cinaedi* has been reported to cause bacteremia, cellulitis, and arthritis.[13] Recent interest in the enterohepatic NHPH has resulted in sequencing of the entire genome for several species, including *H. cinaedi*, *H. bilis*, *H. canis*, *H. hepaticus*, and *H. pullorum*.[14–16]

Epidemiology

The other gastric and enterohepatic *Helicobacter* spp. are found in a wide variety of animals.[17] Early observations of NHPH infections were made in cats and dogs[18–20]; subsequently, organisms have been identified in other domestic animals, including cattle, pigs, chickens, sheep, ferrets, mice, rats, and hamsters.[5,21,22] Many wild animals are also colonized by NHPH, including monkeys, cheetahs, mountain lions, ocelots, and birds.[23–25] Marine animals, including dolphins and whales, have been reported to have gastric ulcerations associated with NHPH.[26–29] Although there appears to be a large degree of host specificity among the NHPH, interspecies transmission has been observed.[17,30] Notable *Helicobacter* spp. and their associated hosts include *H. felis*, *H. bizzozeronii,* and *H. heilmannii* in cats and dogs[18,19,31]; *H. suis* in pigs[4,32]; *H. bilis* and *H. hepaticus* in rodents[16,33]; *H. cinaedi* in gerbils and hamsters[34,35]; and *H. pullorum* in chickens and birds.[36] *H. cinaedi* seems to have the broadest host range of the *Helicobacter* spp.[17]

Because the NHPH spp. are common in animals, it has been postulated that infection in humans may represent zoonotic transmission. This position is supported by the finding of similar organisms in humans and their pet dogs or cats and by the frequency of animal contact among infected individuals.[37–43] The results of a questionnaire given to 662 patients with either *H. heilmannii* s.l. or *H. pylori* infection found that contact with dogs, cats, and pigs was strongly associated with *H. heilmannii* s.l. infection.[42] In a notable case, a 12-year-old girl developed gastritis and *H. heilmannii* s.l. infection after moving to a farm. After successful treatment of the infection, her symptoms returned. Endoscopy was performed on her pet dog, which had a long history of vomiting, revealing a morphologically identical *H. heilmannii* s.l. organism. The symptoms of both the child and the dog were eradicated after retreatment of the child with concurrent treatment of the dog.[39] Given the recent advances in genetic technologies, the dynamics of *Helicobacter* transmission is sure to become more evident in the near future.

The prevalence of *H. heilmannii* s.l. in adults and children undergoing upper gastrointestinal tract endoscopy is <0.5% to 2%.[44–48] Reports of children with gastritis or gastric ulcers associated with *H. heilmannii* s.l. infection have been published from most parts of the world, including Western and Eastern Europe, South America, North America, Japan, and other parts of Asia.[3,44–48] In one of the larger clinical-pathologic correlation studies, 6077 gastric mucosal biopsies (2 antrum and 1 corpus samples per patient) were systematically analyzed from patients with duodenal ulcers (n = 946) or nonsteroidal anti-inflammatory drug (NSAID)-associated gastric ulcers (n = 281 patients). *H. heilmannii* s.l. was detected in 6 (0.5%) of 1227 patients (0.2% of 7871 biopsies). Of these, 4 were patients with duodenal ulcers (4/946; 0.4%) and 2 were patients with NSAID-associated gastric ulcers (2/281; 0.7%).[45] Recently investigators have employed molecular methods, typically polymerase chain reaction (PCR) assays, to distinguish among the *H. heilmannii* s.l. species in human gastric mucosa. These studies have found that *H. suis* is the most common gastric NHPH and that 5% to 15% of individuals with gastric NHPH are infected with more than one species.[19,49–51]

The overall prevalence of the enterohepatic NHPH spp. in humans is unclear. Several enterohepatic NHPH spp., including *H. canadensis*, *H. canis*, *H. pullorum*, and *H. bilis*, have been isolated from the intestines of children and adults with gastroenteritis.[36,52–54] Additionally, enterohepatic NHPH spp. have been detected in liver, bile, and gallbladder tissue.[55,56] Although they have been associated with gastroenteritis, hepatitis, and hepatobiliary malignancies in humans, whether the enterohepatic NHPH spp. contribute to human intestinal and hepatobiliary disease has not been confirmed. An exception is found with *H. cinaedi* and *H. fennelliae,* which have been cultured from homosexual men with human immunodeficiency virus (HIV) infection and proctitis or proctocolitis.[57] Additionally, *H. cinaedi* is increasingly identified as a cause of bacteremia in immunocompromised hosts,[13] particularly in Japan, where it has been found in up to 0.2% of total positive blood culture samples.[58–60]

A role for *Helicobacter* spp. in inflammatory bowel disease (IBD) has been proposed; however, studies are conflicting.[61–65] For example, among 179 children undergoing colonoscopy, members of the Helicobacteraceae family were detected by PCR in 32 (42%) of 77 children with Crohn disease compared with 23 (23%) of 102 controls ($P < 0.01$). When stratified by *H. pylori* or non-*pylori Helicobacter*, infection with NHPH was significantly more prevalent in patients with Crohn disease than in controls ($P = 0.04$).[65] Alternatively, 44 children with treatment-naïve, de novo IBD had a similar prevalence of *Helicobacter* spp. as 42 children with normal colons (11% vs. 12%; $P = 1.00$).[63] Further research is needed to determine whether *Helicobacter* spp. contribute to the pathogenesis of IBD.

Clinical Manifestations

H. heilmannii s.l. has been reported in cases of gastritis, peptic ulcer disease, gastric carcinoma, and MALT lymphoma. Acute or chronic gastritis is the most frequent histopathologic finding among individuals with *H. heilmannii* s.l. infection.[44,66] Gastric and duodenal ulcers also have been described, although they appear to be less frequent.[44,66] In a prospective study among 580 children with dyspepsia who underwent upper gastrointestinal tract endoscopy, 5 (0.9%) children had *H. heilmannii*–like organisms. In addition, 4 of the 5 had mild to moderate gastritis noted in the antrum, and 1 child had a gastric ulcer.[44]

Investigators have noted differences in gastritis associated with *H. heilmannii* s.l. and that seen with *H. pylori*.[45,67,68] Stolte and colleagues compared 202 patients with gastritis associated with *H. heilmannii* s.l. and 202 matched control patients with *H. pylori* –associated gastritis. They found that most of the gastritis from *H. heilmannii* s.l. was focal and localized to the antrum. Additionally, *H. heilmannii*–associated gastritis had less severe neutrophilic and lymphocytic infiltration compared with those with *H. pylori*.[67]

H. heilmannii s.l. infection has been associated with MALT lymphomas and less commonly with gastric carcinoma.[46,67–71] In a retrospective study from Japan of 4074 patients undergoing esophagogastroduodenoscopy, 15 patients were found to have *H. heilmannii* s.l. infection: 11 had chronic gastritis, and 4 had MALT lymphoma.[46] Eradication of *H. heilmannii* s.l. infection resulted in remission of MALT lymphoma in this study and others.[46,68,69] MALT lymphomas have been observed in animals experimentally infected with *H. felis*, *H. heilmannii* s.s., and *H. suis*.[72,73] In a murine study (BALB/c mice), MALT lymphomas were detected in up to 25% of animals infected with *H. heilmannii* s.l., and the prevalence of lymphoma was dependent on the duration of infection.[72]

The causal relationship between infection with *H. heilmannii* s.l. and gastric disease in humans is supported by animal models, which demonstrate the capacity of the organisms to cause disease and the observation that eradication of the organism in humans is associated with a relief of symptoms and resolution of pathology.

Several enterohepatic NHPH spp. have been isolated from humans with acute and chronic diarrhea.[36,52–54] *H. canis* was isolated from the stool of a 5-year-old child with gastroenteritis.[54] Additionally, *H. bilis* and *H. pullorum* have been identified in humans with self-limited diarrheal illnesses.[36,53,74] Additional research, however, is needed to implicate these organisms in the pathogenesis of gastroenteritis.

H. cinaedi and *H. fennelliae* were originally described in 1984 in homosexual men with HIV infection who had proctitis or proctocolitis.[57] Since then, invasive disease from these organisms has been described predominantly in immunocompromised patients, with only rare reports of infection in immunocompetent hosts.[59,75,76] *H. cinaedi* is increasingly recognized to cause bacteremia. Fever is present in most patients with *H. cinaedi* bacteremia, with some patients experiencing a macular rash, abdominal pain, or diarrhea. An accompanying cellulitis, which can be multifocal, has been described.[13,77] *H. cinaedi* has also been reported to cause septic arthritis, endocarditis, and meningitis.[78,79] A case of neonatal sepsis and meningitis has been described.[80] Nosocomial acquisition of *H. cinaedi* bacteremia in immunocompromised patients can occur.[81]

H. hepaticus, *H. bilis*, and *H. pullorum* are capable of producing hepatobiliary disease in animals. They have been associated with hepatitis, cholecystitis, cholelithiasis, hepatocellular carcinoma, and cholangiocarcinoma in various animal models.[33,82–84] Their role, if any, in the pathogenesis of human hepatobiliary disease, however, has not been fully explained.

Enterohepatic NHPH can be detected in the hepatic tissue of adults and children with chronic liver disease. Casswall and colleagues analyzed pediatric liver samples with a *Helicobacter*-specific PCR assay and found that 3 (13%) of 23 liver samples from children with primary sclerosing cholangitis and ulcerative colitis had evidence of *Helicobacter* infection; additionally, 1 of 2 children with autoimmune hepatitis were infected.[55] Another pediatric study found *Helicobacter* spp. in 40 (66%) of 61 liver biopsies of patients with various liver disorders and in 4 (40%) of 10 liver biopsies from control subjects without liver disease. On molecular analysis of the 16S rDNA sequences, there was 99% to 100% similarity to *Helicobacter* spp. previously reported to colonize liver tissue, including *H. canis*, *H. bilis*, and *H. ganmani*, a recently described anaerobic *Helicobacter* species.[85,86] Additionally, a study found a greater prevalence of antibodies to enterohepatic NHPH in patients with autoimmune liver disease than in healthy blood donors.[87] Further studies are needed to determine whether there is a causal link between *Helicobacter* spp. and liver diseases in adults and children.

Helicobacter spp. have been identified in bile and gallbladder tissue in adults and children with hepatobiliary disease.[56,88] An early study among 46 Chileans with chronic cholecystitis undergoing cholecystectomy was unable to cultivate *Helicobacter* spp. from bile or gallbladder tissue; however, 13 (56%) of 23 bile samples and 9 (39%) of 23 gallbladder tissue were positive by PCR for *Helicobacter* spp. Subsequent 16S rRNA cloning and sequencing identified strains of *H. bilis* and *H. pullorum*.[56] The role of *Helicobacter* spp. in cholelithiasis has also been investigated. A meta-analysis of 18 case-control studies between 1998 and 2011 was performed to determine the association between *Helicobacter* spp. and biliary lithiasis. Although they found significant heterogeneity among the studies, a higher pooled infection rate was observed in the lithiasis group for *H. pylori* (36% vs. 27%, P = 0.01) and *H. hepaticus* (31% vs. 21%, P = 0.02).[88]

Research is ongoing to determine whether NHPH spp. contribute to the pathogenesis of hepatobiliary malignancies, similar to the carcinogenic role of *H. pylori* in stomach cancer.[84,89] Mice experimentally infected with *H. hepaticus* develop chronic hepatitis and liver tumors.[33,82] In one study of adult patients with hepatocellular carcinoma, liver samples from 3 (11%) of 28 patients were infected with NHPH.[90] Another study of liver samples from patients with primary liver carcinoma found *Helicobacter* spp. 16S rDNA in 8 (40%) of 20 samples, whereas none of the controls was positive.[91] More recently, Segura-López and colleagues found a higher *H. bilis* infection rate among individuals with extrahepatic cholangiocarcinoma (44 of 103 cases) than with benign biliary disease (19 of 91 controls). When analyzed by cancer site, *H. bilis* was strongly associated with cancer in the common bile duct.[92]

Whether enterohepatic NHPH contributes to the pathogenesis of human hepatobiliary disease is unclear. Nonetheless, as investigators continue to expand the use of advanced genetic technologies, the role of enterohepatic NHPH in human health is certain to become more apparent.

Diagnosis

Most gastric and enterohepatic NHPH spp. are identified by histopathologic detection or through molecular techniques because in vitro isolation is difficult.[93,94] Growth of NHPH is complex and requires special conditions, including a microaerobic environment; many strains grow better in an atmosphere of 5% to 10% hydrogen. The *Helicobacter* spp. grow slowly and can be overgrown easily by contaminating gastric or enteric flora. Enterohepatic *Helicobacter* are usually identified from stool through the use of methods for isolating *Campylobacter* spp. However, they can be susceptible to common antimicrobial agents added to commercial *Campylobacter* media.

The gastric NHPH spp. are typically diagnosed by histopathology based on the organism's morphology or by molecular testing. The longer, more tightly coiled *H. heilmannii* s.l. can be distinguished from *H. pylori* in gastric tissue on light microscopy with hematoxylin and eosin, Giemsa, or Warthin-Starry stain. Very few laboratories have been able to culture the gastric

NHPH; only *H. bizzozeronii* and *H. felis* have successfully been grown from human gastric mucosa.[95–97] For species identification, 16S and 23S rRNA sequencing permits distinction between *H. suis* and *H. heilmannii* s.l. species.[3,32] Multiplex PCR assays targeting urease A and B genes (*ureA*, *ureB*), are used by research laboratories for further species identification.[93,94] This level of identification is rarely clinically necessary.

The urea breath test and rapid urease test have limited use in the diagnosis of gastric NHPH in humans because of their low sensitivity, although they appear to perform well in domestic animals. Additionally, testing for *H. pylori* antibodies and *H. pylori* stool antigen has not been found to be useful in identifying NHPH spp.[98]

H. cinaedi can be recovered by automated blood culture systems, usually from the aerobic bottle. Most isolates are detected after ≥5 days of incubation.[13,58] The organism can be difficult to observe with Gram staining, and thus acridine orange staining, darkfield microscopy, or Giemsa staining may be required. Because of morphology and biochemical properties that are similar to enteric *Campylobacter* spp., definitive identification often requires PCR. Rapid identification of *H. cinaedi* from blood culture samples may be possible in the future with matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) mass spectrometry.[99]

Treatment

Treatment for *H. heilmannii* s.l. infection is indicated when gastric pathologic changes are severe and are associated with gastrointestinal symptoms. The same guidelines for when to initiate *H. pylori* eradication should be followed for *H. heilmannii* s.l. infection. Likewise, the treatment regimen for *H. heilmannii* s.l. infection is identical to the triple-therapy regimen for *H. pylori*—a proton pump inhibitor and clarithromycin with amoxicillin or metronidazole.[3] Antimicrobial susceptibility testing of gastric NHPH spp. has found them to be highly susceptible to ampicillin, clarithromycin, and tetracycline, although *H. felis* strains with an elevated minimal inhibitory concentration (MIC) for metronidazole have been reported.[100]

When an NHPH is identified from a nonsterile site, the significance of the patient's illness and the likelihood that it could be explained by the identified organism should be considered before embarking on treatment. Generally, treatment is warranted when NHPH is identified from a sterile site.

Bacteremia from *H. cinaedi* has been successfully treated with 14 days of third-generation cephalosporins or tetracyclines.[77] Alternatively, several authors prefer prolonged treatment for 2 to 6 weeks given the risk for recurrence.[13,59,101] Susceptibility breakpoints have not been defined for *H. cinaedi*. Nonetheless, the MICs of imipenem, minocycline, and gentamicin are generally low for *H. cinaedi*, whereas elevated MICs to ciprofloxacin and clarithromycin have been observed. Isolates with mutations conferring resistance to ciprofloxacin and clarithromycin have been described.[102]

Key Points

Gastric and Enterohepatic *Helicobacter*

- Gastric and enterohepatic *Helicobacter* are widespread among animals and have infrequently been associated with infections of the stomach, intestine, and hepatobiliary system of adults and children.
- *Helicobacter heilmannii* sensu lato organisms are distinguished from *Helicobacter pylori* on gastric tissue based on their longer, more tightly coiled morphology.
- *Helicobacter cinaedi* bacteremia occurs in immunocompromised patients and can be associated with multifocal cellulitis and arthritis.
- Detection of *H. cinaedi* in blood cultures requires prolonged incubation.
- Research is ongoing to determine the contribution, if any, of enterohepatic *Helicobacter* to adult and pediatric diseases of the intestines and hepatobiliary system.

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176

Kingella Species

Pablo Yagupsky

The genus *Kingella* comprises four species, of which *Kingella potus* has been isolated from a wound caused an animal bite in an adult patient,[1] and three other species that have been implicated in pediatric infections: *Kingella denitrificans,* which is an opportunistic and a rare cause of endocarditis[2] and child vaginitis[3]; *Kingella oralis,* which is associated with periodontitis[4]; and *Kingella kingae,* which is a common pathogen of young children and will be discussed in detail in this chapter.

Microbiology

Kingella kingae is a facultative anaerobic ß-hemolytic bacterium that appears as short chains of plump bacilli with tapered ends (Fig. 176.1).[5] *Kingella kingae* grows on blood agar and chocolate agar plates, producing marked impressions on the medium's surface. It fails to grow on MacConkey or Krigler agar, and its growth is enhanced in a CO_2-enriched atmosphere.[5] The organism is nonmotile, exhibits positive oxidase activity, produces acid from glucose and maltose but not from other sugars, and can be identified readily by commercial systems such as API NH and VITEK 2 (bioMérieux, Marcy-l'Etoile, France),[6] matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) mass spectrometry technology,[7] and 16S rDNA gene sequencing.[8]

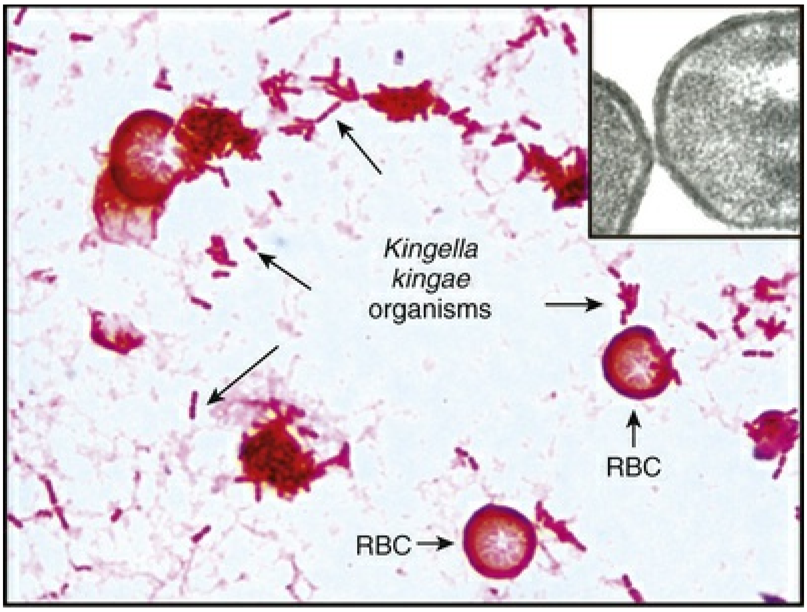

FIGURE 176.1 Gram-stain of a positive Bactec 9240 blood culture vial showing pairs and short chains of gram-negative coccobacilli typical of *Kingella kingae* organisms. *Right upper corner insert:* Electron microscopic picture showing the characteristic gram-negative cell wall structure (original magnification, ×75,000). RBC, red blood cell.

Virulence and Pathogenesis

The pathogenesis of invasive *K. kingae* disease is believed to begin with colonization of the tonsillar crypts,[9] and organisms recovered from the blood of children with invasive infections are genotypically identical to those isolated from the oropharynx.[10] Colonization involves adherence to epithelial cells, which is mediated by type IV pili that share homology with the major pilin of other gram-negative pathogens.[11–13] Children with *K. kingae* disease frequently have had symptoms consistent with a viral upper respiratory tract infection, herpetic gingivostomatitis, hand-foot-and-mouth disease, or herpangina, suggesting that breach of the mucosal lining facilitates bloodstream invasion.[5,14–18] In addition, the organism produces a potent extracellular toxin that belongs to the RTX family, capable of lysing epithelial and synovial cells, leukocytes, and macrophages.[19] This toxin may disrupt the respiratory epithelium and contribute to pathogenesis by damaging skeletal tissues.[19] *K. kingae* strains exhibit remarkable variation in their invasive capacities. Whereas some strains frequently are carried without symptoms and seldom if ever are isolated from patients with clinical disease, other strains cause a substantial proportion of the disease burden, including bacteremia, skeletal system infections, and endocarditis.[5] Preliminary studies suggest that *K. kingae* elaborates a polysaccharide capsule to promote survival in the bloodstream, explaining the tendency of the organism to infect young children who have not yet developed a mature T-lymphocyte–independent immune response.[5,20]

Immunity

In a longitudinal study, serum titers of immunoglobulin G (IgG) antibodies against *K. kingae* outer membrane proteins were high at 2 months of age, reached a nadir at the age of 6–7 months, remained low until the age of 18 months, and increased at 24 months, whereas serum IgA levels were lowest at 2 months and peaked in the second year.[21] These findings and the low attack rate of disease and absence of pharyngeal carriage in early infancy suggest that immunity to colonization and disease is conferred by maternal antibodies. The high pharyngeal prevalence of *K. kingae* and the increased incidence of invasive disease among children 6 to 24 months old coincide with the age at which antibody levels are lowest. Increasing antibody levels in older children presumably reflect immunologic maturation and cumulative experience with *K. kingae* or with cross-reacting antigens, resulting in an efficient reduction of carriage and burden of disease.[21] Asymptomatic pharyngeal colonization probably is the immunizing event. Exposed epitopes, however, are polymorphic, and the immune response appears to be incomplete and strain specific and does not prevent colonization by an antigenically dissimilar strain.[22]

Epidemiology

Carriage

K. kingae is carried asymptomatically on the tonsils and is almost never isolated from nasopharyngeal cultures.[23,24] Children usually acquire *K. kingae* after the age of 6 months, and colonization is characterized by frequent turnover of strains.[25,26] The colonization rate increases to 9% to 12% at the ages of 12 through 24 months and declines thereafter, paralleling the age-related incidence of invasive disease (Fig. 176.2).[26] *K. kingae* spreads from child to child by close contact between siblings and playmates, and childcare center attendance increases the risks for colonization and transmission.[23,25] A carriage rate of 28% has been found among children in childcare,[23] and clusters of invasive infections have been detected in childcare facilities in the United States,[27,28] France,[16,29] and Israel.[30,31] In a study of 3 clusters of invasive infection in closed communities, 54% of asymptomatic preschool-aged children carried the *K. kingae* outbreak strain, indicating high transmissibility and successful colonization.[31]

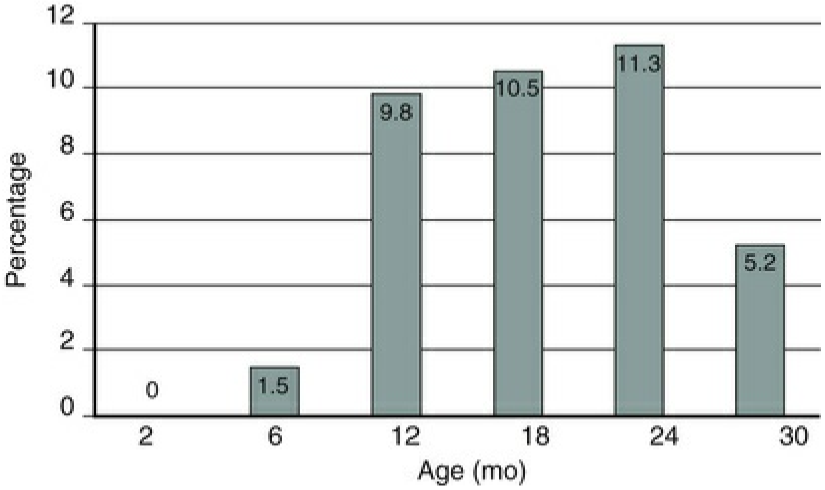

FIGURE 176.2 Point prevalence of pharyngeal carriage of *Kingella kingae* in a cohort of 716 children sampled sequentially between the ages of 2 and 30 months.

Invasive Infections

K. kingae infections are almost limited to young children. Of 147 infected patients over a 27-year period in southern Israel, only 1 was an adult; 145 of the 146 children were younger than 4 years, yielding an annual incidence of invasive disease of 9.4/100,000 in this age group.[32] Infection is rare in the first 6 months of age, paralleling lack of *K. kingae* colonization in early childhood (Fig. 176.3).[26,32]

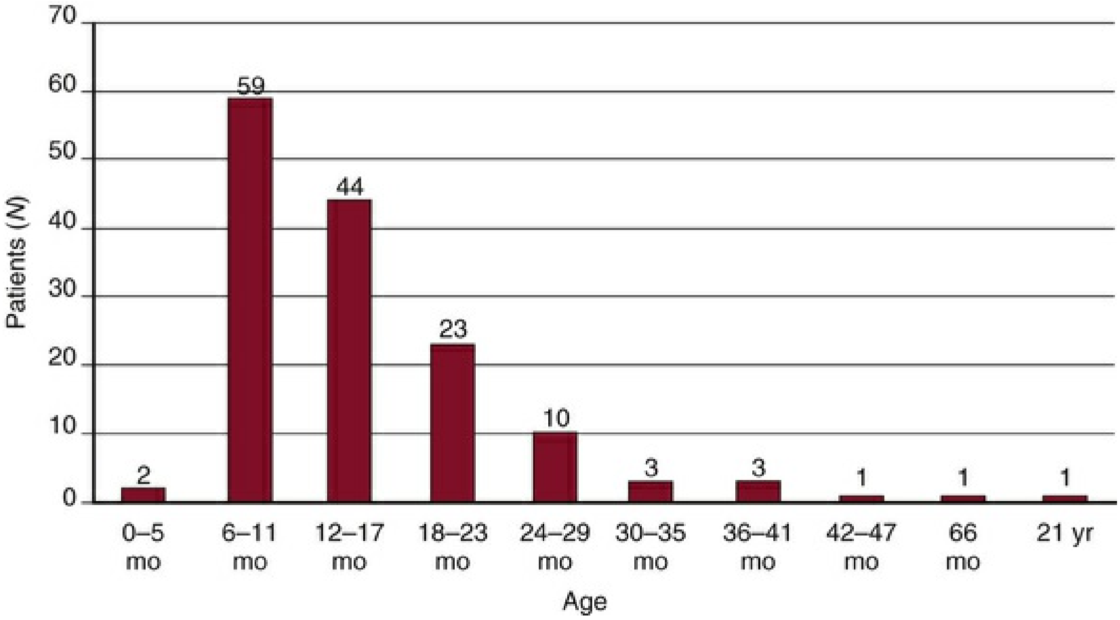

FIGURE 176.3 Age distribution of 147 Israeli patients with culture-proven *Kingella kingae* infections.

Most infected children younger 4 years are otherwise healthy, whereas older children and adults often have immunosuppressing conditions, malignancy, or cardiac valve pathology.[5,18,32,33] In a multicenter Israeli study, none of 291 previously healthy children with an invasive *K. kingae* infection were older than 48 months, whereas 9 of 22 (41%) children with underlying diseases were older than 48 months.[32] The disease is more common among males, with a male-to-female ratio of 1.3.[32]

Invasive *K. kingae* infections occur throughout the year and are most common during November and December and least common between February and April.[5,18,32–34]

Clinical Manifestations

Children with *K. kingae* infections other than endocarditis usually are only mildly or moderately ill,[5,18,32,35–40] and generally, a single focus of infection is detected.[41] Most children have moderate fever, but 23% are afebrile, and acute phase reactants frequently are normal or only slightly elevated.[5,32] In a series of children with culture-proven *K. kingae* disease, 172 of 301 (57%) had a white blood cell (WBC) count of <15,000/mm^3, and 18 of 82 (22%) had normal C-reactive protein values.[32] In the 321 children with invasive *K. kingae* infection enrolled in a nationwide collaborative study in Israel, involvement of the skeletal system was observed in 169 (53%), bacteremia with no focus in 140 (44%), endocarditis in 8 (2%), and pneumonia in 1 (1%) case.[32]

Osteoarticular Infections

Pyogenic Arthritis.

Pyogenic arthritis is the single most common presentation of *K. kingae* infection and usually affects the knee, ankle, or hip.[5,32] Less frequently, *K. kingae* invades the wrist, shoulder, elbow, and small articulations such as metacarpophalangeal, sternoclavicular, and tarsal joints, which are rarely infected by other bacteria.[5,32,42,43]

Lack of leukocytosis has been observed in 76 of 149 (51%) children with *K. kingae* arthritis, and 18 of 8 (23%) had <50,000 WBC/mm^3 in synovial fluid.[32] Gram stain of synovial fluid usually is negative, probably owing to low bacterial density.[5,32,38,44–46] Because of mild symptoms and benign laboratory findings, diagnosis of *K. kingae* arthritis requires a high index of suspicion, and the disease can be misdiagnosed as transient synovitis. Children younger than 3 years presenting with an “irritable hip” should be carefully evaluated to exclude *K. kingae* arthritis, including performance of blood culture and joint tap, and the aspirated synovial fluid should be inoculated in blood culture vials and submitted for nucleic acid amplification testing.[47]

Osteomyelitis.

K. kingae osteomyelitis especially affects the long bones, although involvement of the calcaneus, talus, sternum, clavicle, or patella also can occur.[5,38,42] Primary involvement of the epiphysis or apophysis of the long bones, which is only exceptionally observed in osteomyelitis caused by traditional pathogens, is frequently documented in *K. kingae* infections.[48,49] Patients with *K. kingae* osteomyelitis have a significantly more prolonged duration of symptoms before admission compared with children with other bacterial arthritides (9.2 ± 9.4 days vs. 3.2 ± 3 days, respectively) and have a lower body temperature (37.7° ± 1°C vs. 38.4° ± 0.9°C, respectively).[32] Despite the diagnostic delay of *K. kingae* osteomyelitis, chronicity and orthopedic sequelae are the exception.[5,50]

Spondylodiskitis.

K. kingae is the most common etiology of hematogenous spondylodiskitis in children 6–48 months of age.[32,51–53] Bloodstream organisms appear to reach the intervertebral disks through a network of vessels that enters the annulus from the cartilaginous vertebral end plates and is obliterated in older children.[52] *K. kingae* spondylodiskitis generally involves the lumbar discs, followed by the thoracolumbar, lumbosacral and cervical intervertebral spaces. Diskitis manifests with limping, lumbar pain, back stiffness and loss of the normal lordotic curvature on examination, refusal to sit or walk, neurologic symptoms, or abdominal complaints. Plain radiograph or magnetic resonance imaging demonstrates narrowing of the intervertebral space.[5] Because blood cultures are negative in most patients and obtaining a tissue specimen for culture is difficult, nucleic acid amplification tests on blood play an important role in establishing the etiology.[53,54] Children with *K. kingae* spondylodiskitis respond well to antibiotic therapy and recover without sequelae.[5]

Abortive Skeletal System Infections.

Although bone and joint infections are not considered self-limited diseases, transient involvement of the skeletal system during *K. kingae* bacteremia is reported.[55–57] Children may limp or refuse to walk or bear weight but have objective signs of osteoarthritis and may have a normal blood WBC and imaging study; fever and symptoms have resolved when blood cultures become positive. It seems prudent to administer antimicrobial therapy to all patients from whom *K. kingae* is isolated from a normally sterile site.

Other Infections

Soft Tissue Infections.

Soft tissue infections, including cellulitis,[58] tenosynovitis or dactilytis,[18,59] bursitis,[60] subcutaneous,[61] presternal,[42,62] and intramuscular[63] abscesses have been reported.

Bloodstream Infections.

Bloodstream infection (BSI) without focus is the second most frequent presentation of pediatric *K. kingae* infections.[14,18,32,33] In a large study, only one half of children with this condition had a body temperature of ≥39°C, and one third had a WBC count of <15,000 cells/mm^3. Algorithms that rely on body temperature and WBC count to pursue BSI are not sensitive to detect *K. kingae*.[32,64] A maculopapular rash, resembling disseminated neisserial infection, has been described in a few patients.[44,65–67]

Endocarditis.

K. kingae is included in the so-called HACEK group of organisms that is collectively responsible for up to 5% of cases of bacterial endocarditis. In contrast to other *K. kingae* infections, endocarditis also has occurred in older children and adults.[5] In approximately one half of patients, the infection affects a native valve. Predisposing cardiac malformation or rheumatic disease is observed commonly, but many pediatric patients have previously normal valves.[5,28,68–72] Typically the left side of the heart is involved, usually the mitral valve. Despite the remarkable susceptibility of the bacterium to antibiotics and the benign clinical picture observed in other invasive *K. kingae* infections, the course of endocarditis is severe and frequently is characterized by life-threatening complications such as cardiac failure, septic shock, mycotic aneurysms, pulmonary infarctions, meningitis, and cerebrovascular septic emboli. Case-fatality rate exceeds 10%.[28,68–72] Because of the potential severity of endocarditis, routine echocardiographic evaluation of all individuals from whom *K. kingae* is isolated from a normally sterile site has been recommended.[73]

Lower Respiratory Tract Infections.

K. kingae has been isolated from the blood or respiratory secretions of previously healthy and immunocompromised adult and pediatric patients with epiglottitis, laryngotracheobronchitis, pneumonia, or pyothorax, suggesting that the organism can cause middle and lower respiratory tract infections.[5,32]

Meningitis.

K. kingae meningitis can occur as a primary infection[74–78] or as a complication of endocarditis.[41,79,80] The age distribution is noticeable in that one-half of cases have occurred in adolescents and young adults.[5]

Ocular Infections.

K. kingae has been isolated from patients with a variety of ocular infections such as orbital and periorbital cellulitis,[5,81] eyelid abscess,[82] endophthalmitis,[44,83] and corneal ulcer.[84]

Diagnosis

Attempts to isolate *K. kingae* on routine solid media frequently are unsuccessful, and recovery can be improved substantially by inoculating synovial fluid aspirates and bone exudates into blood culture vials of the BACTEC (Becton Dickinson, Cockeysville, MD),[85] BacT/Alert (Organon Teknika Corporation, Durham, NC),[86,87] Hémoline DUO (bioMérieux, Paris, France),[88] and Isolator 1.5 Microbial Tube (Wampole Laboratories, Cranbury, NJ)[46] systems, suggesting that pus exerts an inhibitory effect and dilution enables bacterial growth.[85] In two studies in which joint fluid aspirates from young children with arthritis was inoculated into broth blood culture vials, *K. kingae* was isolated in one half of culture-proven bacterial arthritis.[37,89]

Detection of *K. kingae* by nucleic acid amplification techniques is a remarkable aid to diagnosis and is rapid.[90] Using homemade nucleic acid amplification assays targeting the RTX toxin or *cpn60* encoding genes, enhanced detection of *K. kingae* in bone and joint specimens by fourfold compared with routine and blood culture vial cultures, and demonstrated that the organism is responsible for a large fraction of culture-negative cases of pyogenic arthritis and osteomyelitis and is the leading etiology of skeletal system infections in children 6–48 months of age.[5,38–40,91,92]

Treatment

K. kingae is almost always susceptible to penicillins, cephalosporins, aminoglycosides, macrolides, trimethoprim-sulfamethoxazole, and fluoroquinolones.[5] β-Lactamase production is limited to a few clones, and its prevalence shows wide geographic variability, being rare among invasive isolates in continental Europe and Israel but common in Minnesota and Iceland.[93–98] The trait, encoded in the chromosome or in a plasmid, confers low-level resistance to penicillin and ampicillin, but the organism remains susceptible to cephalosporins.[99] As a measure of caution, all *K. kingae* isolates from normally sterile sites should be tested routinely for β-lactamase production.[96] The organism exhibits decreased susceptibility to oxacillin and is fully resistant to trimethoprim and glycopeptide antibiotics.[18,94,100] Nearly 40% of isolates are resistant to clindamycin.[100]

Because of the lack of specific guidelines for the treatment of *K. kingae* infections, patients have been administered a variety of antibiotics, drug combinations, and courses of therapy typical of infections caused by more traditional pathogens.

Bone and Joint Infections.

Empiric drug therapy for skeletal infections usually consists of intravenous administration of a second- or third-generation cephalosporin, pending culture results. When vancomycin and clindamycin are used instead for empiric treatment for skeletal system infections, a β-lactamase–inhibiting agent should be added in children younger than 4 years.[5,101]

When *K. kingae* is detected, therapy frequently is changed to parenteral ampicillin (after β-lactamase production is excluded), cefuroxime, or a third-generation cephalosporin. Parenteral administration of a first-generation cephalosporin such as cefazolin, followed by oral cephalexin, also is suitable. Normalization of body temperature, improvement of local signs, decreasing erythrocyte sedimentation rate, and C-reactive protein levels are used to guide a change to oral antibiotics and to determine the duration of therapy.[5,102–104] Treatment has varied from 2 weeks to 3 months for *K. kingae* arthritis,[18] from 3 weeks to 6 months for osteomyelitis,[18] and from 3 to 12 weeks for spondylodiskitis.[51,52]

Bloodstream Infection.

Children with *K. kingae* BSI and no focal infection generally are treated with an intravenous cephalosporin and subsequently are given an oral β-lactam agent. Patients respond favorably to a 1- to 2-week antibiotic course.[14,18]

Endocarditis.

Patients with *K. kingae* endocarditis usually are treated with an intravenous β-lactam drug alone or in combination with an aminoglycoside for 4 to 7 weeks. Careful assessment and early surgical intervention are necessary for life-threatening complications unresponsive to medical therapy.[5,72]

Key Points

Diagnosis and Management of *Kingella kingae* Infection

Microbiology

- Gram-negative encapsulated coccobacillus in pairs or short chains
- Strains differ in their invasive capabilities.
- β-Lactamase production (variable prevalence) causes penicillin and ampicillin resistance.

Epidemiology

- Normal oropharyngeal flora
- Highest prevalence (10%) at 1–2 years of age, especially among attendees of childcare centers
- Clustering of infection in childcare settings supports person-to-person transmission.
- Antecedent upper respiratory tract infection or stomatitis suggests that disruption of mucosal barrier facilitates invasion.
- Causes bacteremic infections with predilection for osteoarticular or cardiac focus
- Mildly abnormal (or normal) temperature and acute phase reactants are common.

- Endocarditis has severe complications and high mortality rate

Diagnosis

- Inoculation of skeletal system exudates onto solid media is suboptimal.

- Recovery from osteoarticular specimens is enhanced by inoculation of Bactec or BacT/Alert automated blood culture systems.

- Polymerase chain reaction assay improves detection of *K. kingae* from blood and osteoarticular specimens.

Treatment

- Isolates from normally sterile sites should be tested for β-lactamase production.

- Penicillin is drug of choice for β-lactamase–negative infections.

- Susceptible generally to cephalosporins, amoxicillin-clavulanate, and ciprofloxacin

- Resistant to vancomycin and clindamycin

- Addition of gentamicin may be beneficial for treating endocarditis.

Duration of Therapy

- Response to therapy usually is rapid, and early transition from parenteral to oral therapy is possible (see text).

- Recovery without sequelae is expected for osteoarticular infections.

- Patients with endocarditis require intravenous therapy, may require early surgery for life-threatening complications, and can have chronic sequelae.

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Legionella Species

Lorry G. Rubin

Investigation of an outbreak of pneumonia among attendees at an American Legion Convention in Philadelphia in 1976 revealed a previously unrecognized causative pathogen, *Legionella pneumophila.*[1,2] Infection with *Legionella* spp. occurs in sporadic and outbreak forms and is one etiology of both community-acquired and nososcomial pneumonia and is called *legionnaires' disease*, or *legionellosis*. *Legionella* spp. also is associated with Pontiac fever, a rare illness that occurs in outbreak form consisting of a short-incubation, self-limited influenza-like illness primarily affecting adults and causing symptoms of fever, malaise, myalgia, chills, and headache.[3,4]

The genus *Legionella* in the family Legionellaceae currently consists of at least 55 species and at least 70 serogroups.[5–7] *L. pneumophila* serogroup 1 is responsible for 50% to 90% of human infections.[6–8] Other *L. pneumophila* serogroups, especially serogroup 6 and *L. bozemanii, L. micdadei,* and *L. longbeachae,* cause most of the remainder of human infections.[7,8] Patients with infections caused by *Legionella* spp. other than *L. pneumophila* are more likely to be immunocompromised.[7] *Legionella* are nutritionally fastidious, motile, non–spore-forming aerobic bacilli. In tissue, *Legionella* organisms appear as short bacilli or coccobacilli with nonparallel sides tapering to rounded ends. In vitro growth of *Legionella* from clinical specimens requires a source of amino acids, iron, and L-cysteine, such as buffered charcoal yeast extract (BCYE) agar enriched with α-ketoglutarate.[5] After recovery on artificial media, *Legionella* stain as gram-negative bacilli.

Pathogenesis and Epidemiology

Legionella species are facultative intracellular pathogens capable of surviving and multiplying both in mammalian macrophages and monocytes (e.g., in the alveolar spaces) to cause human infection and in free-living amebas to survive in the environment. After internalization of bacteria in an antibody-independent process, the bacterial phagosome becomes covered by smooth vesicles that likely originate from the endoplasmic reticulum. This results in evasion of the endocytic pathways and avoidance of phagosomal acidification and fusion with lysosomes that otherwise would result in bacterial digestion. The Dot/Icm type IV secretion system encoded by genes in *L. pneumophila* is critical for evasion of killing, intracellular multiplication, and virulence.[9] The pathogenesis of Pontiac fever may involve a host response to endotoxin from lipopolysaccharide of *Legionella* or other gram-negative bacteria without multiplication of *Legionella* in the host.[10]

L. pneumophila is not transmitted from human to human. Infection most commonly results from the inhalation or aspiration of contaminated aerosol from environmental or aquatic sources.[11–15] *Legionella* spp. naturally occur in freshwater habitats such as lakes, rivers, and ground water. From these sources organisms gain entry into water systems of buildings, including hospitals. These bacteria grow optimally at 35°C–37°C but thrive in warm water (temperature range, 30°C–54°C) and generally are killed at temperatures above 60°C.[5,6] *Legionella* have been found in cooling towers and evaporative condensers, water heaters, plumbing systems, shower heads, respiratory therapy devices, air conditioners, whirlpool spas, and humidifiers.[6] Survival and persistence of these nutritionally fastidious organisms in the environment make it likely that protozoa, particularly amebas, act as reservoirs in water sources. Legionnaires' disease due to *L. longbeachae* has been associated with exposure to potting soil.[7]

Nosocomial infections and hospital outbreaks due to *L. pneumophila* or other *Legionella* spp. have occurred. The source generally is water, most commonly the hot water supply.[12–15] Strains associated with nosocomial infection can colonize water supplies over long periods.[13] Community-acquired outbreaks of legionnaires' disease almost always are due to *L. pneumophila*,[7] and such outbreaks frequently have been associated with a nearby cooling tower, as proved by isolation of the same strain as confirmed by DNA-based molecular typing from infected patients, the cooling tower, and aerosols from the cooling tower.[11] In addition, outbreaks have been associated with other sources of water, including whirlpool baths, decorative fountains, and ultrasonic mist machines used to humidify fresh produce in a grocery store.[6] Sporadic cases of legionellosis have been linked to home water heaters, particularly electric water heaters. In 40% of 20 sporadic cases studied, isolates identical to the infecting isolates were found in the potable water at the patient's home or workplace, or at an ambulatory medical facility visited by the patient.[14]

Most cases of legionnaires' disease occur in susceptible elderly or middle-aged adults. Based on the outbreak in Philadelphia, the incubation period is estimated to range from 2 to 10 days, with a mean of approximately 7 days.[1] Risk factors for infection in adults include cigarette smoking, alcoholism, chronic lung or heart disease, and treatment with high doses of corticosteroids or other immunosuppressive drugs, including those given to prevent rejection of transplanted organs, and tumor necrosis factor-α antagonists.[1,6,16] Legionellosis is an occasional cause of pneumonia in adults with acquired immunodeficiency syndrome, in whom it accounts for 1% to 3% of pneumonia episodes.[17] *L. pneumophila* has caused pneumonia in patients infected with 2009 pandemic influenza A:H1N1.[18] In the United States, higher numbers of cases are reported during the warmer months.[19]

Legionellosis remains a rarely reported infection in children. Despite a 53% increase in rate of legionellosis from 2003 to 2012, only 8 cases (0.22%) of legionellosis reported to the Centers for Disease Control and Prevention in 2012 were patients younger than 15 years.[19] *Legionella* bacteria probably are responsible for 1% to 5% of episodes of pneumonia in immunocompetent children.[20–23] Infection is being recognized increasingly in neonates related to healthcare-associated contaminated water sources that include potable water for preparing infant formula, water tubs for water births, and humidifiers in nurseries.[24–27] In pediatric legionellosis, risk factors for serious infection are neonatal age group, immune compromise as a result of cancer or organ transplantation and their treatments, corticosteroid or adrenocorticotropic hormone therapy, primary immunodeficiency, or underlying lung disease[12,28–31] (Table 177.1). Most published cases of legionellosis in children are hospital acquired, but this may represent a reporting bias.[29] In a review of legionellosis in children, the overall mortality rate was 33%, with the highest mortality rates in immunosuppressed children and children younger than 1 year.[29]

TABLE 177.1

Legionella Pneumonia in Children

Patient Population	Features
Neonates	Previously healthy or premature infants; can have bronchopulmonary dysplasia, corticosteroid therapy, or congenital heart disease; frequently nosocomial; typically healthcare associated, related to contaminated water source, including water birth; frequently unsuspected and diagnosed at autopsy
Immunocompetent children hospitalized with pneumonia	Mild to moderate severity; recovery can occur without the use of effective antibiotics
Children with underlying pulmonary disease or receiving mechanical ventilation	Nosocomial source is common
Immunocompromised children: corticosteroid or ACTH treatment, anticancer or antiorgan rejection therapies, congenital immune deficiency (severe combined immunodeficiency, chronic granulomatous disease)	Nosocomial or community-acquired; onset often within weeks of transplantation, beginning ACTH therapy, or induction chemotherapy for malignancy

ACTH, adrenocorticotropic hormone.

Clinical Manifestations

Legionella infection can be classified into the following four categories: (1) pneumonia; (2) subclinical infection; (3) nonpneumonic disease, referred to as *Pontiac fever;* and (4) extrapulmonary inflammatory disease. The most important clinical infection in children and adults is pneumonia, which manifests as an acute febrile illness with cough and often with respiratory distress.[29] Initially, nonpulmonary symptoms can predominate and include chills, abdominal pain, myalgia, confusion, malaise, anorexia, and diarrhea. Extrapulmonary manifestations, particularly confusion and diarrhea, are common, but the combination of pulmonary and extrapulmonary clinical findings is not sufficiently specific to differentiate *Legionella* pneumonia from community-acquired or nosocomial pneumonia of other etiologies.[32] The nonproductive cough suggests atypical pneumonia, which requires differentiation from *Mycoplasma pneumoniae,* viral, and *Chlamydophila pneumoniae* infections.

Chest radiograph shows patchy alveolar rather than interstitial infiltrates. In most cases, pulmonary disease is unilateral. Pulmonary nodules, with or without cavitation, or cavitating pneumonia can develop, particularly in immunocompromised hosts.[28,29,33,34] Pleural effusion occurs, with an incidence similar to that of other bacterial pneumonias.[34] Progressive respiratory distress and respiratory failure can develop over a period of several days. Copathogens are recovered from respiratory tract specimens in only a few cases.[18,31] *Legionella* infection causing fever and pulmonary nodules is relatively common in adult renal or cardiac transplant recipients and occurs within several weeks of transplantation. Alternatively, these patients may have prodromal symptoms of malaise, myalgia, and headache followed by an abrupt onset of symptoms indicative of pneumonia: dyspnea, cough, and pleuritic chest pain.[35,36]

Serious or fatal *Legionella* pneumonia is being reported increasingly in neonates.[24–27] Many infants were born at term and manifested septicemia, pneumonia, or both, but several were born prematurely or had congenital heart disease.[24] An outbreak of 11 cases of *Legionella* pneumonia in term neonates from a single nursery included 3 fatal cases; evaluation implicated a *Legionella*-contaminated humidifier in the nursery.[25] At least 4 cases of *L. pneumophila* pneumonia with 2 fatalities have been reported after water birth at home or in a hospital birthing pool.[27] The mortality rate of neonatal legionellosis is high, and survival correlates with macrolide/azalide treatment.

Infections in immunocompromised hosts and neonates represent the most severe form of pediatric disease. At the other end of the clinical spectrum, community-acquired pneumonia due to *Legionella* in healthy children usually resolves without effective antibiotic therapy.[20–22] Subclinical infection also occurs, as evidenced by increasing seroprevalence with age,[20,21,23] and by antibody rises in the absence of recognized episodes of pneumonia.

Epidemic, nonpneumonic disease, also known as *Pontiac fever*, is characterized by a high attack rate in exposed individuals. After a short incubation period of 12 to 48 hours, infection is characterized by the abrupt onset of an influenza-like illness without pneumonia. Prominent signs and symptoms include fever, malaise, myalgia, and cough. The illness is self-limited, although a cluster of cases with respiratory compromise is described.[37] The initial outbreak of Pontiac fever was associated with *L. pneumophila* serogroup 1, but other *Legionella* spp. have been associated with outbreaks.[10]

In adults, a spectrum of extrapulmonary *Legionella* infections have been documented, including sinusitis, perirectal abscess, pyelonephritis, peritonitis, pancreatitis, pericarditis, and endocarditis.[32] In children, extrapulmonary sites of infection in the liver, spleen, and brain have been documented at autopsy.[24,30] Localized extrapulmonary infection, such as infection of postoperative wounds after wound irrigation with *Legionella*-contaminated tap water, also can occur.

Laboratory Diagnosis

Nonspecific laboratory abnormalities in legionellosis can include leukocytosis with a left shift of neutrophils, hyponatremia, proteinuria, or elevated serum concentrations of hepatic enzymes. In adults, hyponatremia is significantly more frequent in the initial stage of legionellosis than in pneumonia of other etiologies.

A specific laboratory diagnosis can be established by (1) isolation of the organism in culture; (2) detection of organisms, bacterial antigens, or nucleic acids in clinical specimens; or (3) documentation of a serologic response to the organism.[5,6] Although culture is the gold standard for diagnosis, only ~5% of diagnoses are based on culture, and most diagnoses are based on urine antigen testing that primarily detects *L. pneumophila* serogroup 1.[6] Compared with culture, the common use of urine antigen assays for diagnosis may have biased the distribution of *Legionella* spp. and serogroups causing disease.[6] A clue to suspect legionellosis is the presence of characteristic neutrophilic inflammatory response without bacteria on a gram-stained preparation of lower respiratory tract secretions because *Legionella* stain poorly with Gram stain. However, the absence of the failure to produce sputum or absence of neutrophils in specimens does not exclude the diagnosis[38]

Microscopic screening protocols of sputa (to evaluate for the presence of leukocytes as a measure of adequacy of the specimen for bacterial culture) are not useful for selecting samples to be cultured for *Legionella. Legionella* spp., particularly *L. micdadei*, may stain with acid-fast stain[39]; modified acid-fast stain can be useful.

Culture

Legionella is best grown on BCYE agar containing 0.1% *α*-ketoglutarate and L-cysteine supplemented with dyes to aid identification of colonies and antimicrobial agents such as vancomycin, polymyxin B, and anisomycin to inhibit overgrowth by other bacteria and yeast; incubation is at 35°C in a humidified atmosphere containing 2.5% CO_2.[5,6] Heating or washing sputum specimens with acid before inoculation reduces contamination and enhances recovery.[5,6] Although BCYE agar is available commercially, some lots exhibit poor clinical performance. Colonies take ≥3 days to appear and exhibit ground-glass morphology. *L. pneumophila* has been isolated from both aerobic and anaerobic broth blood culture systems, but only after blind subculture. Laboratory personnel should be apprised when legionellosis is suspected.

Bacterial Detection

Tests for antigen detection in urine are used most frequently to diagnose legionellosis. Detection of *L. pneumophila* serogroup 1 lipopolysaccharide antigens in urine by commercially available immunochromatographic membrane assays or enzyme immunoassay is possible as early as a few days after the onset of infection. These assays have high sensitivity (90%) and specificity (80%).[5,6,40] Sensitivity is higher in patients with more severe pneumonia and when urine is concentrated before testing and when incubation time is prolonged.[41,42] In addition to detection of *L. pneumophila* serogroup 1, a positive result sometimes is noted in patients infected with *L. pneumophila* non–serogroup 1 or other *Legionella* spp.[43,44] Antigenuria typically is prolonged beyond resolution of clinical infection and should not be used to judge adequacy of therapy.[45] In one outbreak, urine antigen assay was useful in diagnosing Pontiac fever.[46]

Detection of organisms on smears of respiratory tract secretions by direct (or indirect) immunofluorescence assay) using polyclonal or monoclonal antibody is no longer performed in most laboratories because of required technical expertise and test performance similar to urine antigen tests.

Nucleic acid amplification–based assays to detect DNA from all *Legionella* spp. (e.g., assays targeting a conserved segment of the ribosomal RNA genes for the 5S and 16S subunits) or *L. pneumophila* (e.g., assays targeting the macrophage inhibitor protein *mip* gene in respiratory specimens) have been developed. These assays have a sensitivity comparable with or superior to that of culture or urinary antigen detection and have excellent specificity, but commercial assays are not available widely.[5,6,47,48]

Serology

Serology is rarely used to diagnose *Legionella* infection because of the requirement for a convalescent specimen and the limited validation of tests for infection other than due to *L. pneumophila* serogroup 1. Serologic confirmation requires a fourfold rise in antibody titer to ≥1 : 128 in paired specimens, typically taken 4 to 8 weeks or longer apart.[5,6,49] An indirect immunofluorescence assay (IFA) is the gold standard for serologic testing. In the setting of sporadic disease, neither a single elevated IFA titer nor measurement of immunoglobulin M antibody is useful for diagnosis.[5,6,49] “Seroconversion” occasionally is due to cross-reaction after infection with another organism such as *Citrobacter freundii, Bacteroides fragilis, Chlamydophila psittaci,* or *Coxiella burnetii.*[50,51] A false-positive serologic test is frequent in patients with cystic fibrosis and is related to cross-reaction with *Pseudomonas* spp.[52] Seroconversion has been documented in several young children with legionellosis.[21,53,54] Most cases of Pontiac fever have been diagnosed using serologic tests.

Treatment

Options for antibiotic treatment of legionellosis are summarized in Table 177.2. Based on clinical experience, intravenously administered azithromycin is the antibiotic of choice for the treatment of *Legionella* infection in healthy children, whereas levofloxacin is the antibiotic of choice for the treatment of *Legionella* infection in immunocompromised or severely ill children. Fluoroquinolone antibiotics, unlike erythromycin, are bactericidal for *Legionella* and therefore may be superior to macrolide/azalide therapy, at least in immunocompromised patients.[55,56] However, here have been no randomized clinical treatment trials comparing a fluoroquinolone with a macrolide or azalide. In a metaanalysis of 12 observational studies in adults with *Legionella* pneumonia, patients treated with a fluoroquinolone, primarily levofloxacin, had a shorter hospital stay and a trend toward a lower mortality rate, higher clinical cure rate, and lower rate of complications than patients treated with a macrolide or azalide.[57] In contrast, in a retrospective cohort analysis of 3152 adults hospitalized in 427 US hospitals with a diagnosis of *Legionella* pneumonia, among adults treated with either a macrolide or a fluoroquinolone there were no differences in crude or adjusted mortality, hospital length of stay, development of *Clostridium difficile* colitis, or total hospital cost.[58]

TABLE 177.2

Antimicrobial Therapy for Legionellosis[a]

	Intravenous Dose		Oral Dose	
Antimicrobial Agent(s)	**Pediatric**	**Adult**	**Pediatric**	**Adult**
FIRST CHOICE				
Normal host: azithromycin[b]	10 mg/kg every 24 hr (maximum, 500 mg/day)	500 mg every 24 hr	10 mg/kg every 24 hr (maximum, 500 mg/day)	500 mg every 24 hr
Immunocompromised host or severely ill: levofloxacin[c]	Not approved for patients younger than 18 yr for routine use. Age 6 mo–4 yr: 10 mg/kg every 12 hr; 5–17 yr: 10 mg/kg every 24 hr (maximum, 750 mg/day)	750 mg every 24 hr	Not approved for patients younger than 18 yr for routine use. Age 6 mo–4 yr: 10 mg/kg every 12 hr; 5–17 yr: 10 mg/kg every 24 hr (maximum, 750 mg/day)	750 mg every 24 hr
SECOND CHOICES				
Clarithromycin	Not available	Not available	7.5 mg/kg every 12 hr (maximum, 500 mg every 12 hr)	500 mg every 12 hr
Ciprofloxacin	Not approved for patients younger than 18 yr for routine use; 10 mg/kg	400 mg every 8 hr	Not approved for patients younger than 18 yr for routine use; 15	750 mg every

	every 8 hr (maximum, 400 mg every 8 hr)		mg/kg every 12 hr (maximum, 750 mg every 12 hr)	12 hr
Erythromycin[d]	40 mg/kg/day	1 g every 6 hr	40 mg/kg/day	500 mg every 6 hr
POTENTIAL ALTERNATIVES				
Moxifloxacin	Not approved for patients younger than 18 yr	400 mg every 24 hr	Not approved for patients younger than 18 yr	400 mg every 24 hr
TMP-SMX	5 mg TMP/kg every 8 hr	160 mg TMP every 8 hr	5 mg TMP/kg every 8 hr	160 mg TMP every 12 hr
Doxycycline	2 mg/kg every 12 hr (maximum, 100 mg/dose)[d]	200 mg once; 12 hr later start 100 mg every 12 hr	2 mg/kg every 12 hr (maximum, 100 mg/dose)[e]	100 mg every 12 hr

[a] The duration of therapy is 14−21 days, except for therapy with azithromycin, which is 5–10 days.

[b] Some patients have been treated with an initial loading dose of 20 mg/kg (maximum, 1000 mg) followed 24 hours later by the dose in the table.

[c] In severely ill patients, combination therapy with levofloxacin and azithromycin can be considered, but clinical experience is very limited.

[d] Erythromycin is likely to be less effective than azithromycin. Intravenous erythromycin doses up to 100 mg/kg/day have been administered to children without difficulty.

[e] Generally not prescribed in children younger than 9 years of age.

TMP-SMX, trimethoprim-sulfamethoxazole.

Azithromycin is preferred over erythromycin intravenously because of azithromycin's ease of administration (one daily dose, smaller fluid volume, and less vein injury), superior activity in vitro and in an animal model of infection, higher lung levels, and better intracellular penetration.[56,59] Oral azithromycin can be substituted after definite clinical response, to complete a 5- to 10-day course of therapy. The longer duration of therapy is used for immunocompromised patients. The addition of rifampin has not been demonstrated to enhance the efficacy of azithromycin or levofloxacin, and some treated patients have developed elevated serum bilirubin levels.[56] When treating recipients of transplanted solid organs, caution is required because azithromycin (and erythromycin) inhibit the metabolism of cyclosporine.[35]

Many antibiotics show activity against *Legionella* in vitro, but only antibiotics with intracellular penetration are effective. Testing of antibiotics in vitro against intracellular *Legionella* in a *Legionella*-infected cell line or in vivo (e.g., with a guinea pig model of infection) may more accurately predict the effectiveness of an antibiotic against human infection.[56,59] For example, β-lactam antibiotics are active in vitro but are ineffective in treating *Legionella* pneumonia. Clindamycin and aminoglycosides also are ineffective.[7] Doxycycline or trimethoprim-sulfamethoxazole has been used successfully in some patients. In a few cases of infection with *L. micdadei,* patients who failed erythromycin treatment responded to trimethoprim-sulfamethoxazole.

Prevention

Primary prevention of *Legionella* infection in healthcare facilities involves testing of water and eradication of contamination before cases occur. Efforts to prevent healthcare-associated *Legionella* infection where cases have occurred or where *Legionella* has been detected in the water systems are directed toward treating water distribution systems to inactivate or remove organisms.[60,61] Methods include (1) copper-silver ionization by electrolysis; (2) chlorine dioxide, monochloramine, or hyperchlorination followed by continuous chlorination (to achieve 1–2 mg of free residual chlorine per liter); (3) periodic superheating to temperatures greater than 60°C and flushing of distal sites (with or without maintenance of the water temperature above 50°C); (4) point-of-use filtration; (5) ultraviolet light; or a combination of methods.[62] Copper-silver ionization may be the method of choice as the best studied method,[63,64] although this requires relatively expensive equipment, does not reliably eradicate *Legionella* from the water system,[65] and may lose effectiveness after several years because of the emergence of *Legionella* strains tolerant of silver ions.[66] Over time, continuous chlorination can cause corrosion of pipes and leakage, and chlorination is associated with the production of carcinogenic trihalomethane byproducts.[7,62] Superheating is advantageous in that it can be instituted rapidly to interrupt an outbreak. In one hospital with a high incidence of nosocomial *Legionella* pneumonia in renal transplant recipients, prophylactic erythromycin therapy was successful.[67] A vaccine is not available.

Key Points

Epidemiology, Clinical Features, and Diagnosis of *Legionella* Infection

Epidemiology

- Risk groups
    - Elderly
    - Immunosuppressed adults and children, particularly organ transplant recipients
    - Adults and children treated with corticosteroids
    - Adults and children with chronic lung disease
    - Neonates
- Bacterial reservoir: freshwater habitats and potable water
- Mode of transmission: inhalation or aspiration of *Legionella*-contaminated water
- Pediatric infections frequently are nosocomial

Clinical Features

- Pneumonia is the most common manifestation.
- Clinical manifestations: fever, nonproductive cough, respiratory distress
- Chest radiograph: patchy alveolar infiltrates, usually unilateral, at times nodular

Diagnosis

- Urine antigen detection is the most practical diagnostic test.

▪ High specificity

▪ Sensitive for *Legionella pneumophila* serotype 1

▪ Occasionally detects other serotypes or species

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Rickettsia rickettsii (Rocky Mountain Spotted Fever)

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Description of the Pathogen

Rickettsia rickettsii, the etiologic agent of Rocky Mountain spotted fever (RMSF), is a small, obligately intracellular, gram-negative, rod-shaped organism that is among the most pathogenic of all known bacteria. Although *R. rickettsii* can infect several different cell types, its primary targets in mammalian hosts are the endothelial cells lining capillaries, arterioles, and venules of all major tissues and organ systems (Fig. 178.1).[1] Damage to endothelium of the dermis, skeletal muscle, and vital organs such as brain, heart, lungs, kidneys, and gastrointestinal tract results in the systemic manifestations characteristically observed in people with RMSF.

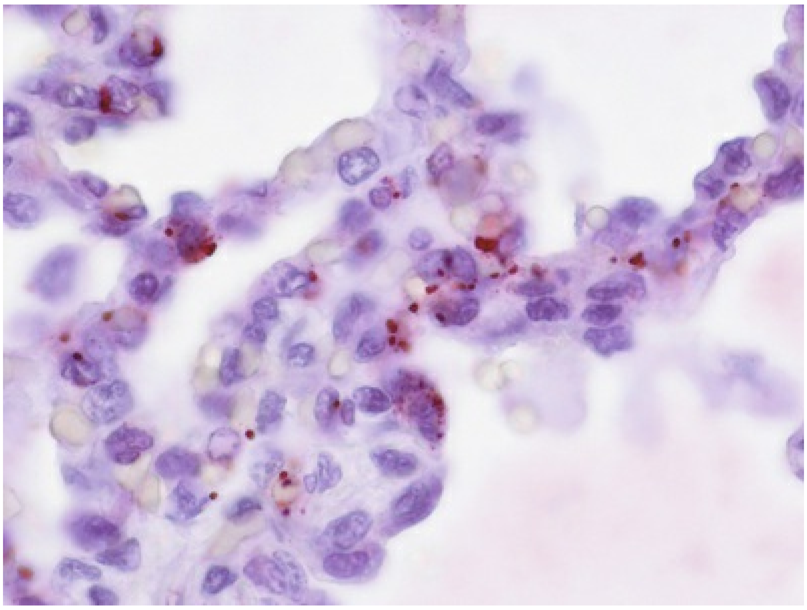

FIGURE 178.1 Immunohistochemical stain demonstrating *Rickettsia rickettsii* bacteria *(red)* infecting endothelial cells of alveolar capillaries in the lung of a 5-year-old child with fatal Rocky Mountain spotted fever. Immunoalkaline phosphatase with naphthol fast-red and hematoxylin counterstain; original magnification, ×158.

Ku70, a high molecular weight protein that is expressed at the plasma membrane of mammalian endothelial cells, monocytes, and macrophages, is believed to serve as a receptor for cell invasion by *R. rickettsii*.[2] Several rickettsial outer membrane proteins, including rOmpB (sca5), rOmpA (sca0), and sca1, are involved in the attachment to and subsequent endocytosis by the mammalian host cell. When inside the cell, *R. rickettsii* rapidly escapes a transient invasion vacuole to reside freely in the cytoplasm, where it replicates by binary fission. *R. rickettsii* is capable of intracellular movement that involves rickettsia-mediated polymerization of host-cell actin.[3,4] Rickettsiae that collide with the plasma membrane of the host cell create protrusions that extend into and become internalized by adjacent cells or may be released into the extracellular space and attach to neighboring cells.[5,6] *R. rickettsii* severely damages the plasma membrane of endothelial cells and disrupts the structural organization of intracellular organelles and cytoskeleton. Oxidative injury to host cells leads to diffuse microvascular injury and fluid leakage into extravascular spaces.[7–11] Different strains of *R. rickettsii* produce varying levels of injury to cultured human endothelial cells; however, these differences have not been characterized in vivo, and severe or fatal disease has resulted from infections with at least 4 genetically distinct strains of *R. rickettsii*.[12,13] The genetic basis for the virulence of *R. rickettsii* is not well understood.[14,15]

Epidemiology

RMSF occurs throughout much of the Western Hemisphere and is maintained in nature by several species of ticks and mammals. Humans are incidental hosts and become infected with *R. rickettsii* from the bite of an infected tick. Throughout much of the United States, *Dermacentor variabilis* (the American dog tick) and *Dermacentor andersoni* (the Rocky Mountain wood tick) are considered primary tick vectors. *Rhipicephalus sanguineus* sensu lato (the brown dog tick) is also a primary vector in some regions, particularly in northern and central Mexico and the southwestern United States.[16–18] In South America, other hard tick species, including *Amblyomma sculptum* and *Amblyomma aureolatum*, are important vectors.[19]

RMSF is a nationally notifiable disease in the US, and the reported incidence of RMSF and other tickborne spotted fever group rickettsioses, including *Rickettsia parkeri* rickettsiosis and *Rickettsia* sp. 364D rickettsiosis, increased markedly during the past 15 years. During 2000–2007, the reported incidence of these infections rose from 1.7 to more than 7 cases per million persons.[20] During 2008–2012, the estimated average annual incidence of all spotted fever group rickettsioses was 8.9 cases per million persons, with 63% of all reports originating from Arkansas, Missouri, North Carolina, Oklahoma, and Tennessee (Fig. 178.2). Most US cases are reported during April–September, corresponding with periods of increased host-seeking activity of adult-stage *Dermacentor* ticks.

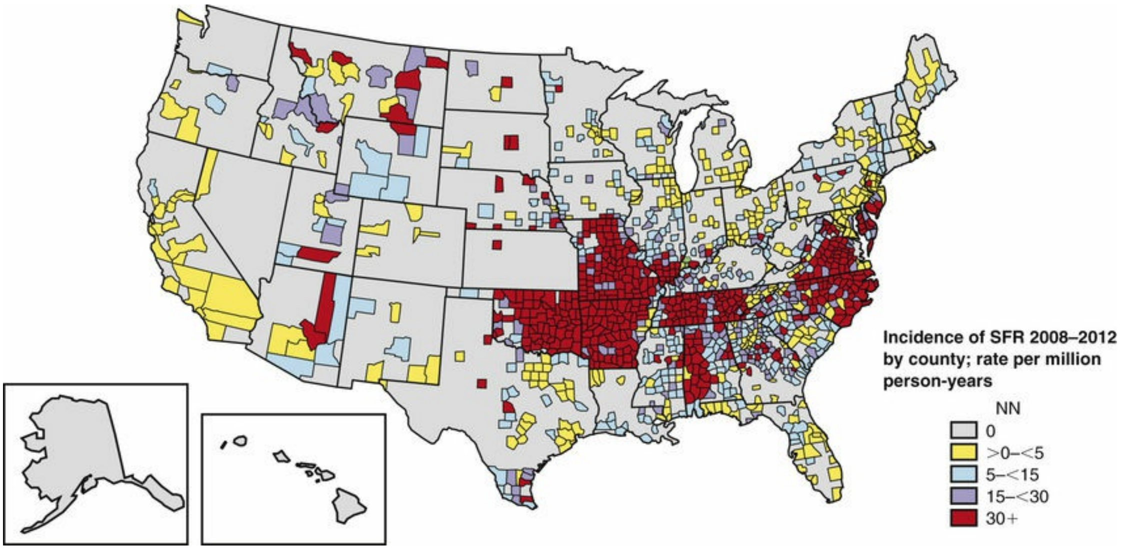

FIGURE 178.2 Reported incidence rate of spotted fever group rickettsiosis, by county—United States, 2000–2013, per 1,000,000 persons per year.[26] The reporting category “Rocky Mountain spotted fever” (RMSF) was changed in 2010 to “spotted fever rickettsiosis” (SFR), and current passive surveillance does separate RMSF from other spotted fever group rickettsiosis. (From Drexler NA, Dahlgren FS, Heitman KN, et al. National surveillance of spotted fever group rickettsioses in the United States, 2008−2012. Am J Trop Med Hyg 2016;94:26−34.)

Surveillance data indicate that RMSF occurs more frequently in older adults than in children.[20–22] On a national scale, age-specific incidence rates of RMSF are highest for persons aged 60 to 69 years; nonetheless, in one recently characterized outbreak, approximately 50% of 205 RMSF patients were younger than 10 years.[23] In general, case-fatality rates are disproportionately higher among young children compared with adults. During 1983–2007, approximately 15% of all reported fatal cases of RMSF were in children younger than 10 years,[24,25] and from 2008–2012, case-fatality rates in this cohort were approximately 5 times greater than all other age groups combined.[26] Prevalence of anti−*R. rickettsii* antibodies appears to increase with age as a function of increased risk for exposure to *R. rickettsii* or other spotted fever group *Rickettsia* spp. over a lifetime.[27,28] A survey of approximately 2000 children from the southeast and south central US reported a 12% prevalence of antibodies reactive with *R. rickettsii* using routinely available serologic assays but may include infections caused by *Rickettsia* spp. other than *R. rickettsii*.[29,30]

Most cases of RMSF occur sporadically, but family and community clusters can occur and are related to *R. rickettsii* infections in focal tick populations around a home, neighborhood, or park.[16,31–36] As a result, multiple infections can occur simultaneously or sequentially in the same household after identification of an index case.[31]

Clinical Manifestations

RMSF can be difficult to diagnose clinically in its early stages.[37] Although most patients seek care within the first 3 days after onset of fever, prodromal signs and symptoms are nonspecific, and even in areas where disease awareness is high, 60% to 86% of patients with RMSF are not diagnosed correctly on their first visit for medical care.[37–39] The early signs, symptoms, and laboratory features of RMSF often are insufficient to differentiate this disease from other viral or bacterial illnesses that present as an acute sepsis syndrome.[23] Epidemiologic clues such as history of outdoor activity, contact with animals (particularly dogs) or exposure to ticks may be helpful; however, a history of a tick bite or exposure is absent in 40% to 50% of patients included in several US pediatric case series (Table 178.1).[37,40,41]

TABLE 178.1

Characteristics of Rocky Mountain Spotted Fever in Children Determined From Patient Series in the United States and Mexico, 1935–2015

	Haynes et al., 1970[40]	**Bradford & Hawkins, 1977[41]**	**Buckingham et al., 2007[37]**	**De Lara Huerta & Barragán, 2008[42]**	**Alvarez-Hernandez et al., 2015[43]**
Location	Ohio, North Carolina	North Carolina, Virginia	Arkansas, Kentucky Missouri, North Carolina, Tennessee	Coahuila (Mexico)	Sonora (Mexico)
Years of evaluation	1947–1968	1935–1974	1990–2002	1975–2007	2004–2013
No. of patients	78	138	92	115	104
Male/female ratio	39/39	77/61	43/61	54/61	57/47
Known tick bite or exposure	58%	61%	49%	NR	89%

CLINICAL FEATURES					
Fever	100%	100%	98%	100%	100%
Any rash	100%	96%	97%	100%	89%
Headache	41%	NR	61%	70%	80%
Nausea or vomiting	28%	NR	73%	NR	NR
Myalgia	27%	NR	45%	70%	80%
Abdominal pain	23%	NR	36%	30%	NR
Periorbital edema	24%	NR	12%	35%	71%
Peripheral edema	22%	NR	25%	NR	61%
Seizure	4%	NR	17%	NR	6%
Coma	4%	NR	10%	NR	NR
Death	4%	13%	3%	55%	20%

NR, not reported.

Most patients develop symptoms within 2 to 10 days after the bite of an infected tick.[44,45] The disease begins with abrupt onset of fever often accompanied by severe frontal headache, nausea or vomiting, and generalized myalgia. The temperature generally is high and often >40°C. Headache, which may be less commonly noted in young children, is often intractable to therapy. Other findings recorded with varying frequency in pediatric case series include calf tenderness, abdominal pain, irritability, splenomegaly, conjunctivitis, periorbital edema, and peripheral edema, particularly involving the dorsum of the hands (Fig. 178.3A and B; see Table 178.1;).[37,40–46]

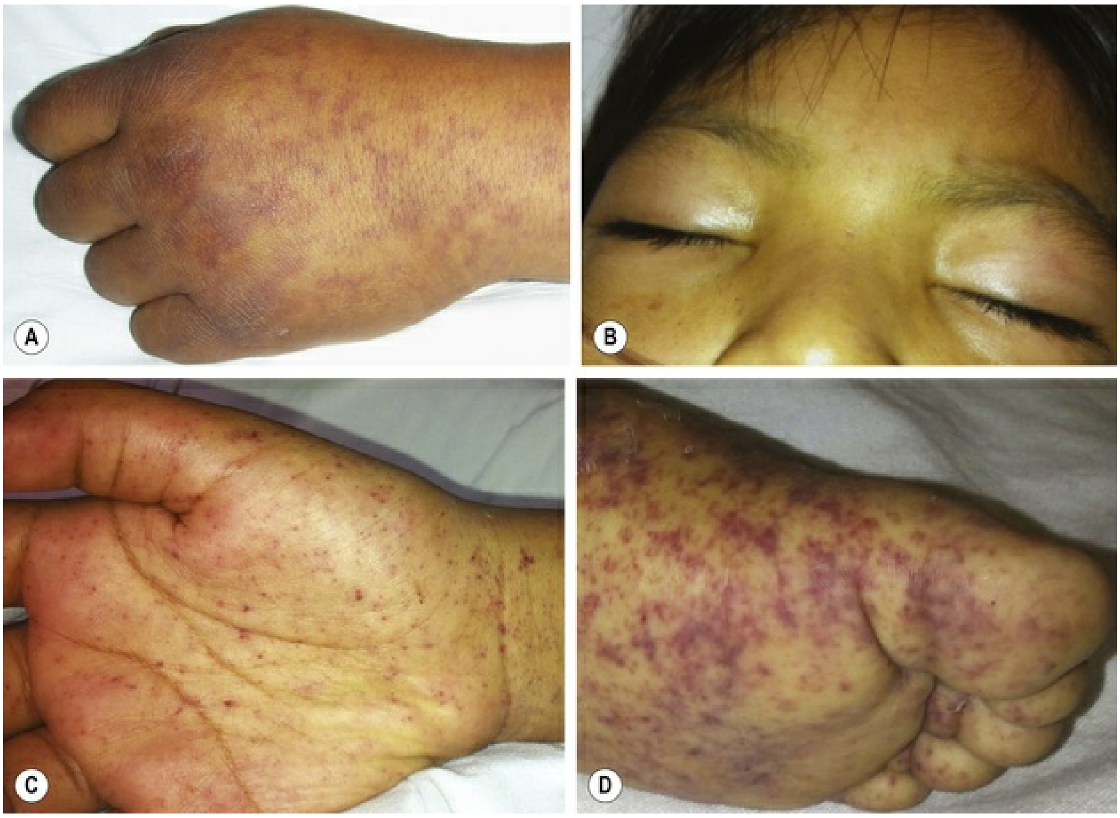

FIGURE 178.3 Clinical signs identified in children with Rocky Mountain spotted fever. (A) Edema of the dorsum of the hand. (B) Periorbital edema. (C and D) Petechial rashes involving the palm and sole.

A generalized maculopapular rash, consisting of discrete, 1- to 5-mm blanching macules, is considered a hallmark feature of RMSF. However, the rash may be absent until 2 to 5 days after fever onset, especially in older patients, and may be difficult to identify in patients with dark skin.[45–48] Therefore, clinicians must not await appearance of the distinctive rash to establish a diagnosis and initiate therapy. In most cases, the rash begins on the wrists, ankles, and forearms and then spreads centrally to involve the legs, buttocks, trunk, and face. In more advanced cases of disease, the rash frequently involves the palms and soles (Fig. 178.3C and D). In some patients, the mucous membranes of the palate and pharynx also can be affected.[37,39] With progression of disease, the rash becomes more petechial, and individual lesions often enlarge and coalesce to form ecchymoses. In approximately 10% of patients, the rash is evanescent, atypical in distribution, or entirely absent.[33,47–49]

RMSF can progress rapidly to catastrophic disease involving multiple organ systems. Severe infections often are characterized by concomitant life-threatening manifestations that may include acute respiratory distress syndrome, first-degree atrioventricular block, cardiac failure, disseminated intravascular coagulation, gangrene, acute renal failure, seizure, coma, or tonsillar herniation.[23,33,42,43,50–52] Central nervous system disease generally occurs later in the illness and manifests as parenchymal edema, perivascular infarcts, and leptomeningeal vasculitis. Computed tomography is generally unremarkable, although images may demonstrate sulcal effacement consistent with generalized edema, or low-density white-matter foci consistent with infarcts. Magnetic resonance imaging is generally more distinctive and may identify punctate perivascular infarcts in the deep white matter, referred to as a "starry sky" pattern (Fig. 178.4).[53]

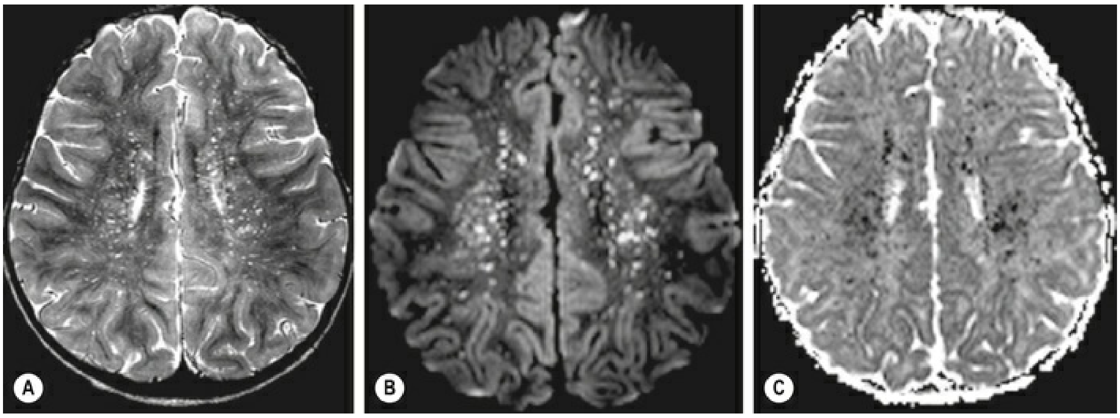

FIGURE 178.4 Axial magnetic resonance imaging (MRI) of the brain of a 2-year-old child with Rocky Mountain spotted fever and altered mental status. (A) T2-weighted MRI demonstrating numerous, punctate, hyperintense foci scattered bilaterally in the subcortical and deep white matter in a perivascular distribution. (B) Diffusion-weighted image at same level as A showing increased signal corresponding to T2 white-matter lesions. (C) Corresponding ADC map confirms restricted diffusion. (Courtesy of Sumit Pruthi, MD. From Crapp S, Harrar D, Strother M, et al. Rocky Mountain spotted fever: "starry sky" appearance with diffusion-weighted imaging in a child. Pediatr Radiol 2012;42:499−502.)

During the years immediately preceding the introduction of effective antirickettsial therapies, an estimated 19% of all US patients infected with *R. rickettsii* died from RMSF.[54] With advances in treatment and medical care, US deaths attributable to RMSF declined considerably; nonetheless, from one well-characterized US outbreak during 2002–2011 involving approximately 200 patients, the case-fatality rate was 7%.[52] In many countries in Latin America, case-fatality rates are much higher, including recent estimates from pediatric case series in Mexico that documented fatal outcomes in 20% to 55% of infected children.[42,43] Most RMSF deaths are attributable to delayed diagnosis and failure to initiate specific antimicrobial therapy within the first 5 to 6 days of illness.[43,52,55–58] Timely administration of appropriate therapy is critical because at least one half of all deaths occur within 8 days of disease onset.[15,59] Patients with glucose-6-phosphate dehydrogenase deficiency typically experience severe and accelerated illness that often culminates in death in ≤5 days.[60]

Laboratory Findings and Diagnosis

Decisions to treat are guided principally by an overall awareness of the disease and by epidemiologic clues garnered during a careful history.[58,61] Routine laboratory tests may reveal hyponatremia, hypoalbuminemia, anemia, or thrombocytopenia to reflect vascular injury and increasing vascular permeability.[9] Low serum sodium levels or platelet counts (often <100,000/mm^3) occur in 50% to 60% of all patients. The white blood cell count is usually normal during the first several days of the infection, but leukocytosis occurs in 40% to 80% of patients with severe disease.[43]

The diagnosis can be confirmed by serology, polymerase chain reaction assays, immunohistochemical staining of tissue specimens, or isolation of *R. rickettsii* in cell culture; nonetheless, the decision to initiate appropriate antibiotic therapy should never be delayed pending results of laboratory testing. The indirect immunofluorescence antibody (IFA) assay is the recommended method for detecting antibodies to *R. rickettsii*; nonetheless, in approximately 50% of patients, diagnostic levels of antibody are not detectable by this method until the second week of disease.[62,63] Most patients come to medical attention during the first 3 days after the onset of illness, and the initial serum sample in these patients frequently is negative. Evaluation of a second serum sample, obtained 2 to 4 weeks later, typically reveals a fourfold or greater change in antibody titer between the initial and second specimen and is necessary to serologically confirm a diagnosis. A single IFA serum titer of ≥1 : 64 suggests only a probable diagnosis.[61] Enzyme immunoassay (EIA) techniques generally are limited in their ability to confirm active infection. IFA and EIA assays that detect immunoglobulin G (IgG) antibodies specifically are preferred over assays that measure IgM antibodies because the latter often are associated with nonspecific reactivity and should not be interpreted in the absence of an IgG antibody titer to *R. rickettsii*.[64]

Immunohistochemical and immunofluorescence staining of antigens in formalin-fixed, paraffin-embedded biopsy specimens of rash lesions or autopsy tissues are diagnostic methods that provide direct observation of the pathogen in the appropriate histopathologic context. Immunostaining of tissue is most likely to reveal organisms within the first 48 hours after initiating appropriate antibiotic therapy. These techniques have been used to diagnose nonfatal and fatal cases of RMSF.[15,60,65–67]

Molecular detection of *R. rickettsii* in whole blood generally is insensitive during the early stages of illness because of low density of circulating organisms before advanced disease.[68,69] Polymerase chain reaction assay generally is more useful for detecting *R. rickettsii* in skin biopsy or autopsy tissue specimens. *R. rickettsii* requires cell culture for microbiologic isolation and should be attempted only in laboratories equipped with biosafety level 3 facilities.[70]

Treatment

RMSF is a life-threatening illness, and appropriate antimicrobial therapy must be initiated quickly and empirically on the basis of clinical and epidemiologic findings. Clinicians must treat presumptively and should never delay or stop therapy while waiting for the results of a confirmatory test, or on the basis of an initially negative test result. Tetracycline-class antibiotics, most often doxycycline, are the treatment of choice. Patients treated with tetracycylines within the first 5 days of symptoms are significantly less likely to be hospitalized, require admission to an intensive care unit, or die than people treated later in the course of disease with the same tetracycline antibiotic or treated with antibiotics with no efficacy against *R. rickettsii*.[43,52,56,59] For children of any age, doxycycline is the drug of choice.[61,71] For children weighing >45 kg

(100 lb), the recommended treatment is 100 mg every 12 hours. For children <45 kg, doxycycline is given at a dose 2.2 mg/kg every 12 hours. Both oral and intravenous formulations are available in the US. Doxycycline generally is preferred over other tetracyclines because of its reduced phototoxicity, safety in patients with renal insufficiency, lower binding to calcium, and longer plasma half-life. Most patients with uncomplicated RMSF defervesce within 24 to 48 hours after initiation of doxycycline therapy.[61] Resolution of symptoms typically occurs more slowly in patients with severe illness, particularly in people with damage to multiple organ systems; nonetheless, absence of clinical improvement within 72 hours should suggest the need to consider an alternate diagnosis. Therapy should be continued for at least 3 days after unequivocal evidence of clinical improvement is seen. The usual duration of treatment is 7 to 10 days.

Previous studies of children who received older tetracycline-class antibiotics (e.g., tetracycline, oxytetracycline, or chlortetracycline) during tooth crown calcification (which typically occurs before 8 years of age) linked these drugs with enamel hypoplasia and yellow, grey, and brown staining of permanent teeth. However, these observations have not been associated with the use of doxycycline, and several series examining the permanent teeth of children who received multiple courses of doxycycline while younger than 8 years, including those treated specifically for RMSF, have failed to demonstrate tooth staining, enamel hypoplasia, or tooth color differences attributable to this antibiotic.[72–74] Despite recommendations by the Centers for Disease Control and Prevention and the American Academy of Pediatrics Committee on Infectious Diseases that advocate the use of doxycycline as primary therapy for RMSF in children of all ages,[61,71] recent surveys indicate that many US healthcare providers remain reluctant to prescribe doxycycline to children younger than 8 years, even in areas where RMSF is endemic.[75–77] Clinicians should always prescribe doxycycline to children when a diagnosis of RMSF is suspected.

Chloramphenicol is the only other antibiotic with demonstrated clinical efficacy against *R. rickettsia*. However, this drug is no longer available in the oral form in the US. In addition, epidemiologic data suggest that patients treated with chloramphenicol have a higher risk for severe illness and death than children treated with a tetracycline.[57] In vitro evidence suggests that chloramphenicol may not be effective treatment of infections caused by *Ehrlichia* and *Anaplasma* spp., which often manifest similar clinical syndromes to RMSF. The pediatric parenteral dose of chloramphenicol is 50 to 100 mg/kg/day in four divided doses.[71] Reversible dose-related toxicities include bone marrow suppression and cardiomyopathy, and monitoring of serum levels is advisable when treating patients younger than 2 years, patients with hepatic disease, or people receiving therapy for more than 5 days. Peak serum levels of chloramphenicol should be maintained within the range of 10 to 30 μg/mL.

Prophylactic antibiotic therapy in asymptomatic people with a recent history of a tick bite is not warranted. Tetracyclines and chloramphenicol are bacteriostatic drugs; therefore, presumptive therapy before onset of symptoms is unlikely to prevent infection and may instead result in a delayed onset of disease.[78]

Special Considerations

Penicillins, cephalosporins, macrolides, aminoglycosides, and sulfa-containing antibiotics are ineffective in treating RMSF. Sulfonamides have no activity against *R. rickettsii* and may exacerbate the disease.[38,48,79,80] Some fluoroquinolones demonstrate strong bacteriostatic activity against *R. rickettsii* in vitro[81]; however, clinical efficacy data are not available on this class of drugs for the treatment of RMSF in humans. Tetracyclines generally are contraindicated in pregnant women because of the risks associated with malformation of teeth and bones in the developing fetus. Chloramphenicol has been used successfully to treat women with RMSF in the third trimester of pregnancy.[82,83] Because chloramphenicol crosses the placenta, low maternal dosages are given if the drug is administered during labor to avoid grey baby syndrome in the neonate, and use of doxycycline may be warranted in pregnant patients experiencing life-threatening complications due to RMSF.[61] Clinical findings of invasive meningococcal infection can overlap findings of RMSF, and empiric treatment for both diseases may be necessary. In these situations an appropriate parenteral penicillin or cephalosporin with activity against *Neisseria meningitidis* should be administered in addition to doxycycline.[61]

Advanced stages of RMSF are characterized by septic shock and systemic injury to the microvasculature, resulting in increased capillary permeability to multiple organ systems. Severely ill patients can have hemodynamic instability, disseminated intravascular coagulation, oliguria, azotemia, and severe pulmonary and cerebral edema. Close hemodynamic and electrolyte monitoring, coupled with inotropic support and administration of intravenous fluids, is warranted in these patients; however, because of increased capillary permeability, fluid replacement should be provided cautiously to avoid increasing pulmonary or cerebral edema. The ability to restore blood volume adequately in these patients is ultimately dependent on vascular integrity, which further emphasizes the need to rapidly initiate appropriate antibiotic therapy when RMSF is considered as a potential cause of illness.

Longterm neurologic sequelae, including hearing loss, speech dysfunction, hypertonia, paresis, parethesias, bladder and bowel dysfunction, and vestibular and swallowing disorders, can occur in people who survive severe disease.[84] In a recent series of 93 children diagnosed with RMSF, 13 had neurologic deficits at hospital discharge.[37] In children, behavioral disturbances and learning disabilities are among the most frequently described sequelae and generally occur in patients in whom severe alterations in consciousness occurred during the acute illness.[37,85] Gangrene and extensive skin necrosis are relatively uncommon manifestations that occur in patients recovering from severe disease and may involve digits, hands, feet, ears, nose, scrotum, or entire limbs (Fig. 178.5); more than 50% of surviving patients with these manifestations require amputation or extensive debridement.[86,87]

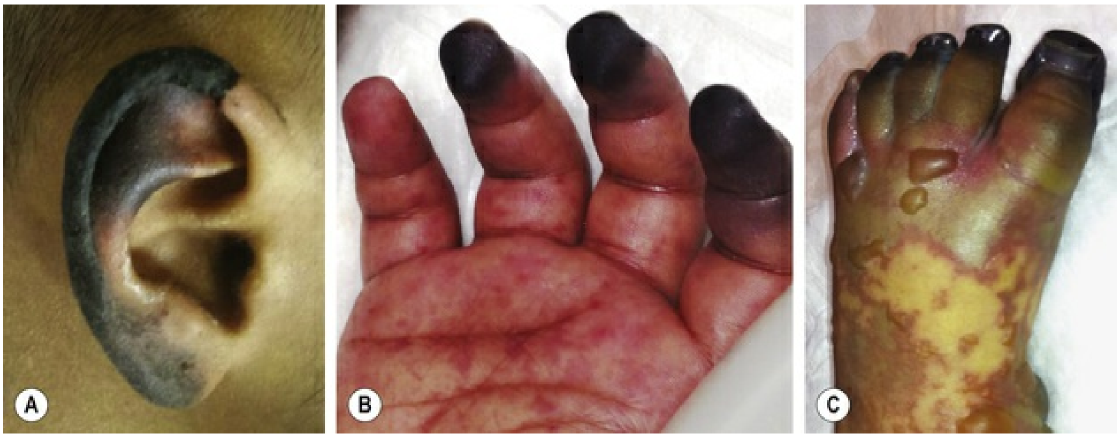

FIGURE 178.5 Gangrene involving the external ear (A), hand (B), and foot (C) of children with severe Rocky Mountain spotted fever.

Prevention and Control

Because RMSF can be difficult to diagnose clinically and requires specialized laboratory methods to confirm a suspected diagnosis, many cases likely are missed, misdiagnosed, or underreported. Confirmed cases should be reported promptly to state public health authorities. Accurate and timely reporting is essential for assessing the magnitude and distribution of cases of RMSF to develop effective public health education programs and prevention strategies.

There is no commercially available vaccine to prevent RMSF. Limiting exposure to ticks is the most effective way of reducing the likelihood of acquiring RMSF and depends primarily on avoidance of tick-infested sites. Because several important tick vectors of *R. rickettsii* are closely associated with dogs, treatment of family pets with appropriate tick preventives, including collars, sprays, or topical medications, is an important method to reduce ticks in the peridomestic settings.[88,89] Although dogs do not pose a direct communicable disease risk to humans, they can transport infected ticks into or around homes of the pet owner and represent important sentinels for human risk.[90,91] In recent outbreaks in the southwestern US and northwestern Mexico, many patients lived in poverty and in close association with large numbers of tick-infested, free-roaming dogs.[16,43] In these settings, socioeconomic and environmental conditions can contribute to epidemic levels of disease, particularly in vulnerable populations with limited resources to guarantee pet care.[92]

When engaging in outdoor activities, especially during spring and summer months, topical application of 30% *N*,*N*-diethyl-*m*-toluamide (DEET) is recommended as an acaricide repellent for use on children older than 2 months.[93,94] Additional personal protective measures include wearing light-colored clothing to help visualize crawling ticks and use of permethrin-impregnated clothing.[95] Parents whose children are frequently exposed to tick-infested habitats should employ daily tick checks, removing ticks as soon as possible to reduce the chance of disease transmission. Ticks can attach to concealed areas, including the scalp, axilla, and perineum, so careful searches are necessary. Expeditious removal of attached ticks reduces the chance of acquiring the disease after a tick bite because disease transmission may require several hours of attachment. To remove an attached tick, blunt curved forceps or tweezers should be used to grasp the tick as close to the skin surface as possible then pull upward with steady, even pressure. The person removing the tick should wear disposable gloves and avoid crushing the body of the tick. Irritating the attached tick with petroleum jelly, gasoline, finger nail polish, hot matches, or isopropyl alcohol is ineffective and should never be done.[96,97]

Key Points

Diagnosis and Management of Rocky Mountain Spotted Fever

Microbiology

- Caused by *Rickettsia rickettsii*
- Small, obligately intracellular, gram-negative rod
- Targets mammalian endothelial cells
- Requires cell culture for isolation

Epidemiology

- Tickborne pathogen that is endemic throughout much of the Western Hemisphere

- Majority of US cases reported from Arkansas, Missouri, North Carolina, Oklahoma, and Tennessee
- Most US cases documented during April through September
- Case-fatality rates highest in children younger than 10 years
- Most cases occur sporadically, although family and community clusters are reported occasionally.

Diagnosis

- Clinical diagnosis of early disease is difficult; epidemiologic clues and awareness of pathogen endemicity are crucial to establishing an early diagnosis.
- Diagnosis can be confirmed by serology, molecular methods, immunohistochemistry, or cell culture isolation.
- The indirect immunofluorescence antibody assay is the reference standard for serologic diagnosis; however, diagnostic levels of antibody are absent in approximately 50% of patients during the first week of disease.
- Molecular detection of the pathogen in whole blood generally is insensitive during the early stages of infection.

Treatment

- Tetracycline-class antibiotics are the most effective antibiotics; doxycycline is the preferred drug for children of any age.
- For children weighing less than 45 kg, administer doxycycline at a dose of 2.2 mg/kg every 12 hours for 7 to 10 days, to be continued for at least 3 days after unequivocal evidence of clinical improvement.
- For children weighing 45 kg or greater, administer doxycycline at a dose of 100 mg every 12 hours for 7 to 10 days, to be continued for at least 3 days after unequivocal evidence of clinical improvement.

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Other *Rickettsia* Species

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Rickettsia prowazekii (Classic Louse-Borne Epidemic Typhus; Brill-Zinsser Disease or Recrudescent Typhus; Sylvatic or Flying Squirrel–Associated Typhus)

Description of Pathogen

Rickettsia prowazekii is a small, gram-negative, obligately intracellular, rod-shaped bacterium.[1,2] *R. prowazekii* possesses a surface autotransporter protein (OmpB) layer external to the cell envelope that has a peptidoglycan sacculus located between the inner cytoplasmic and outer membranes. It does not possess flagella. Both humoral and cellular immune responses are directed against the surface layer protein and result in protective immunity that is dependent on methylation of lysine residues in this protein.[3,4] *R. prowazekii* grows freely in the cytoplasm of infected host cells and preferentially infects endothelial cells in humans.[5] *R. prowazekii* is the prototype species of the typhus group (TG), which is differentiated from the more diverse and numerous rickettsial agents in the spotted fever group (SFG) by its lipopolysaccharide

(LPS) group antigen and some biologic characteristics. Unlike SFG rickettsiae, which can survive and replicate for several days after death of their host cells, TG rickettsiae rapidly die after killing their host cells. However, *R. prowazekii* can retain high aerosol infectivity and viability in dried louse feces.[6] Similarly, it remains highly infectious after drying in media with high osmolarity and has been weaponized so that it could be used as an agent of bioterrorism. Consequently, *R. prowazekii* is a “select agent,” possession and distribution of which is tightly regulated in the United States and other countries.[7] Genetic variants of *R. prowazekii* with different geographic distributions are known.[8]

Epidemiology

Classic epidemic typhus is spread from infected to uninfected people by migration of the human body louse (*Pediculus humanus corporis*).[6,8,9] Infected lice defecate during feeding and excrete copious amounts of rickettsiae in their feces. Transmission occurs to nonimmune humans when louse fecal material or crushed lice are inoculated into the bite site or skin abrasions or conjunctiva (more rarely), or when they are inhaled. The lice die from the rickettsial infection within 2 weeks, but desiccated dead lice and fecal materials may remain infectious for much longer. Epidemic typhus is one of the classic plagues of humankind, having infected and killed millions of people in the preantibiotic era during epidemics until the middle of the 20th century.[10,11] However, major outbreaks still occur infrequently in sub-Saharan Africa, and sporadic cases continue to be reported from North Africa, Ethiopia, Peru, Russia, and the US.[12] Body lice live in clothing; classic epidemic typhus occurs typically in conditions where poverty, famine, and war, frequently accompanied by cold weather, lead to unhygienic conditions favoring louse infestation. Head and pubic lice have not been shown to be significant human vectors for epidemic typhus, although head lice can be infected with *R. prowazekii* and are closely related to body lice.[13,14]

Humans are the primary reservoir for *R. prowazekii*, in whom organisms persist despite strong humoral and cellular immune responses. Formerly infected people can suffer a relapse of typhus, known as *Brill-Zinsser disease* or *recrudescent typhus*.[15,16] The precise factors causing relapses are not well understood, but recrudescence of disease is thought to constitute the source of *R. prowazekii* that permits initiation of new outbreaks of louse-transmitted typhus. Because infestation with body lice is now uncommon in much of the world and fewer people who experienced primary epidemic typhus now exist in the population, both primary epidemic typhus and herd immunity have declined throughout the world since the 1970s. Indigenous louse-borne epidemic typhus has not occurred in the US since 1922, but Brill-Zinsser disease occasionally is seen among immigrants from historically endemic foci of epidemic typhus or people infected in concentration camps. Healthcare personnel and military personnel may be at particular risk for infection. The last major Burundi outbreak was first detected because of the fatal infection of an evacuated Swiss Red Cross worker.[17]

In 1975, Bozeman and colleagues first reported a sylvatic cycle of *R. prowazekii* in southern flying squirrels (*Glaucomys volans*) in Florida and Virginia, but it is likely that this reservoir extends through much of the range of this squirrel in the eastern US.[18] *R. prowazekii* can be transmitted experimentally between flying squirrels by squirrel lice *(Neohaematopinus sciuropteri)* and their fleas *(Orchopeas howardi)*. About 40 cases of human sylvatic typhus infections, including several in children, have been reported in the eastern US.[19,20] Cases usually occur during the winter months when squirrels may enter houses; many such patients report contact with flying squirrels or their nests and associated ectoparasites. The mechanism by which disease is transmitted to humans is unclear, and although squirrel fleas occasionally bite humans, it is more likely that aerosolized infected ectoparasite feces are the primary source of infection. The genetic types of *R. prowazekii* from flying squirrels differ from European and African types.[8,21]

R. prowazekii has been detected in *Hyalomma* ticks in Ethiopia and *Amblyomma* ticks from Mexico.[22,23] If confirmed, this unusual source may account for sporadic cases of primary epidemic typhus that are not associated with human body lice, infected flying squirrels, or recrudescent typhus.[12]

Clinical Manifestations

Epidemic typhus is fatal in 10% to 50% of untreated patients and is more likely to be clinically severe or fatal in people with concurrent malnourishment or other disease.[11,24,25] Onset of epidemic typhus is abrupt and occurs 7 to 14 days after exposure, whereas Brill-Zinsser disease can occur >40 years after primary infection. Patients manifest high prostrating fever with severe headache, limb pains, and vomiting. The patient often appears vacant and semi-mute and can have epistaxis and a dry cough. The classical macular or maculopapular, sometimes petechial, rash appears 5 to 7 days after onset of symptoms; later it becomes purpuric. The exanthem, which may be difficult to see on dark skin, begins on the trunk and spreads to the arms and legs but rarely involves the palms, soles, or face. Constipation is common, and paralytic ileus can occur. Typhus infrequently induces diarrhea or splenomegaly, which helps in its differentiation from typhoid and malaria, respectively. A cough and pneumonia is observed in two thirds of patients and nervous system involvement (drowsiness, disorientation, and delirium) is frequent. In severe cases, a meningoencephalitic syndrome occurs with meningismus, tinnitus, and hyperacusis, followed by deafness, dysphoria, agitation, and coma. Thrombocytopenia, jaundice, and abnormal liver function can occur in severe cases. Survivors can experience hemiparesis, acute transverse myelitis, or peripheral neuropathy. Complications include secondary bacterial infections, myocarditis, and peripheral gangrene or venous thromboembolism. Convalescence is rapid and uneventful if appropriate antibiotic therapy is initiated early after onset of disease. Classic epidemic typhus in pediatric patients often is a milder illness and has a lower fatality rate compared with adults and elderly people. Intoxication syndrome and cardiovascular and neurologic symptoms usually are less pronounced. Observations from the preantibiotic era indicate that epidemic typhus in pregnant women clinically resembles Brill-Zinsser disease with a good prognosis and low mortality; however, spontaneous abortion and premature birth can occur in 20% to 50% of pregnant patients.

In contrast to primary epidemic typhus, delirium is rarely noted in recrudescent typhus. Although Brill-Zinsser disease often is considered to be milder than primary disease, exceptions occur. Late in the second week of illness, fever and headache subside abruptly, and patients feel generally well. The clinical presentation of flying squirrel–associated typhus fever also appears to be milder than that observed in louse-borne epidemic typhus. Whether this difference in clinical presentation is related to the different strains associated with sylvatic *R. prowazekii* or to the relatively good nutrition, health, and supportive care in US cases is unknown.[18–20]

Clinical diagnosis of epidemic typhus can be difficult because of its resemblance to influenza, typhoid, meningococcal meningitis, hemorrhagic fevers, infectious mononucleosis, sepsis, measles, and malaria.

Laboratory Findings and Diagnosis

The white blood cell count frequently is reduced with a relative lymphocytosis during the first week of epidemic typhus, and can be elevated as disease progresses.[24] Eosinophils are decreased or absent during the entire febrile period. Anemia and increased erythrocyte sedimentation rate frequently are detected but return to normal after treatment. Nephritis occurs with azotemia and moderate amounts of albumin and granular casts in urine.

Diagnosis of epidemic typhus generally is suspected because of specific epidemiologic circumstances and clinical findings. Diagnosis of acute epidemic typhus can be made by polymerase chain reaction (PCR) assays for rickettsial DNA extracted from whole blood or the buffy coat fraction, or biopsies of the rash; PCR is sensitive and specific.[26,27] Detection of rickettsial DNA in squirrel tissues and ectoparasites provides alternative detection of the etiologic agent.[18,28] Immunohistochemical procedures also can be applied to biopsy and ectoparasite samples. However, these procedures are available only in specialty laboratories, and prompt submission and correct handling of samples is essential for agent detection. Isolation is possible from acute phase blood and biopsy samples collected before initiation of antimicrobial therapy, in laboratories with access to embryonated chicken eggs, susceptible animals, or antibiotic-free cell cultures.[29] Isolation can require up to several weeks. Isolates of *R. prowazekii* are differentiated readily from other species of *Rickettsia* by genetic, biologic, and antigenic criteria.

The indirect immunofluorescence assay (IFA) is the current gold standard for serologic diagnosis of epidemic typhus.[30–32] Diagnosis is based on a fourfold rise in immunoglobulin G (IgG) antibody titers between acute and convalescent paired sera to *R. prowazekii* antigen or a high single titer of antibody with compatible clinical symptoms. Other serologic procedures for the specific detection of TG antibodies include enzyme immunoassay (EIA), complement fixation, latex agglutination, dipsticks, and chromatographic flow assays. Commercial testing usually employs IFA or EIA methods. The nonspecific Weil-Felix febrile agglutination test, which detects IgM antibodies to a typhus cross-reactive LPS epitope found in *Proteus* OX19 antigen, is not used in the US but is sometimes employed in less developed countries. Serologic cross-reactions can occur between TG and SFG of *Rickettsia,* and IgM antibodies can react with some *Legionella* and *Proteus* spp.[31] Cross-absorption of sera for IFA testing or Western blotting analysis differentiates epidemic and murine typhus and excludes other cross-reactions.[32]

Treatment

Treatment must be instituted before the diagnosis of epidemic typhus is confirmed by laboratory testing. Tetracyclines and chloramphenicol are effective against all forms of typhus infections, whereas ciprofloxacin and azithromycin have failed in the treatment of primary disease and Brill-Zinsser disease, respectively.[15,33,34] Doxycycline is the preferred treatment for both adults and children of all ages.[35,36] Dosage is 4 mg/kg/day (maximal dose, 200 mg/day), given orally or intravenously divided into doses every 12 hours, for 7 to 10 days. A single dose of 200 mg of doxycycline orally for adults and 100 mg for children is efficient in the control of epidemics where continuous patient management can be difficult. Chloramphenicol (50 mg/kg/day divided into doses every 6 hours for children for 7 to 10 days) also is effective; however, the use of chloramphenicol has been associated with increased risk for fatal outcome and relapses in Rocky Mountain spotted fever and typhus.[37] Marked improvement with defervescence should be apparent within 48 hours after treatment, but other symptoms can persist for up to 1 week. Development of specific immune responses is important for full recovery because the antibiotics of choice are bacteriostatic, not bactericidal.

Prevention and Control

Sporadic cases of Brill-Zinsser disease can occur in the US, primarily among immigrants from areas endemic for epidemic typhus, but they pose little risk for spread except from individuals infested with body lice. Head lice have never been associated with outbreaks of epidemic typhus, but body lice continue to be present in many regions of the world and can serve as a source of epidemic typhus in areas that presently are free of lice. No licensed vaccine is available. Exclusion of flying squirrels and their nests from domiciles to prevent concomitant exposure to their ectoparasites, use of pyrethrin-containing insecticides, and decontamination of infested clothing by washing with detergent at high temperatures are recommended for prevention and control.

Rickettsia typhi (Murine Typhus; Endemic or Flea-Borne Typhus)

Description of Pathogen and Epidemiology

Rickettsia typhi is a member of the TG of rickettsiae and closely resembles the other member of that group, *R. prowazekii*, in its genetic, biologic, and immunologic properties.[1,2,38,39] *R. typhi* replicates to higher titers in the yolk sacs of embryonated chicken eggs and is more infectious for laboratory mice and guinea pigs than *R. prowazekii*, but it is not regulated as a “select agent” in the US.

Commensal rats of the genus *Rattus* are the primary zoonotic reservoirs for *R. typhi*.[39] The oriental rat flea (*Xenopsylla cheopis*) is the classic vector that transmits murine typhus to humans but six genera and seven species of flea, including the cat flea (*Ctenocephalides felis*), have been found to be naturally infected with *R. typhi*.[39] Cats and peridomestic opossums infested with cat fleas have been implicated in the maintenance of *R. typhi* in the US; however, murine typhus from this source likely is rare.[40–42] Fleas are infected for life after feeding on *R. typhi*–infected rodents. The fleas shed organisms in their feces, and humans become infected through contact between flea feces and abraded skin, or possibly through inhalation of fecal material. Besides rats, fleas may be an important reservoir of *R. typhi* because they can transmit the organism transovarially to their progeny.[43]

Murine typhus has been diagnosed throughout the world but is reported most frequently from warmer climates and coastal areas where *Rattus* and fleas flourish.[44–50] Typically, seaports, coastal areas, and the major commercial arteries are disease-endemic sites. Only 333 cases of murine typhus were described in the US in 1931 and 2000 cases in 1933; however, by World War II, more than 5000 cases were documented annually in the US.[49,50] After World War II, flea and rodent control programs caused a precipitous drop in the number of reported cases. The current prevalence and distribution of murine typhus in the US are unclear; infection has been reported most commonly from focal areas in California, Texas, and Hawaii.[40–42,51,52] Both sporadic cases and small outbreaks can occur. Disease can be imported by travelers returning to the US from southern Europe, Asia, and Africa.[53,54] The disease occurs both in urban and rural settings, and travelers may be exposed by entering commercial areas and marketing districts infested with rats. The homeless appear to be exposed to this urban disease as well.[55] Based on the World Health Organization Reference Center in Marseille, France, half of the travel-associated cases of murine typhus were diagnosed in August and September, and most tourists were returning from Africa and Southeast Asia.[54]

Clinical Manifestations

Murine typhus manifests with fever, chills, headache, and myalgia. Although the disease generally is mild clinically, up to 10% of adults require intensive care with mortality approaching 4% for untreated cases. Most cases of murine typhus in the US occur in adults, but children are infected frequently in many parts of the world. A series of 96 serologically confirmed cases of murine typhus in children younger than 16 years from Texas provides the most complete clinical pediatric data available.[56] Fever occurred in all patients 8 to 16 days after exposure; headaches occurred in 76% with frontal distribution and dengue-like intensity. Rash occurred in 63% with a median onset at 6 days of illness, whereas the triad of rash, fever, and headache was found in only 49% of patients. Rash generally was macular (50%) or maculopapular (25%), and less frequently was erythematous, petechial, or papular. Although flea bites were reported in only 34% of patients, potential patient contact with animal reservoirs that likely were flea infested was found in 85% of the cases.

Nausea and vomiting occur during the early stage of illness in almost all infected adults. In contrast, children tolerate early disease symptoms well, with gastrointestinal tract symptoms (anorexia, vomiting, nausea, diarrhea, and abdominal pain) occurring in 27% to 46%, and pharyngitis, lymphadenopathy, and cough in 15% to 20%.[56] Pneumonitis, stupor, conjunctivitis, or photophobia occurred in only 5% to 12% of children. Splenomegaly and hepatomegaly were not common in this series, but these symptoms have been described previously in populations in the tropics.[57,58] Differences may be ascribed to early treatment of children in Texas or to coinfection with other common diseases in the tropics. Neurologic findings appear to be more common in adults (15%–45% in different studies) than children.

Most patients with murine typhus are hospitalized, and many patients have signs of sepsis and shock. Complications of murine typhus can include meningitis, meningoencephalitis, facial paralysis, hearing loss, ocular abnormalities, myocarditis, and renal and respiratory failure.[44–48,56–62] Severe hemolysis has been associated with glucose-6-phosphate dehydrogenase deficiency. Pediatric case reports of *R. typhi* have included parinaud oculoglandular syndrome, splenic rupture, myositis and paraparesis, and meningoencephalitis resulting in chronic cognitive impairment despite treatment.[63–66]

Laboratory Findings and Diagnosis

Laboratory findings are nonspecifically abnormal in murine typhus in children.[56] In the Texas case series, 81% had high erythrocyte sedimentation rate, 77% had a left shift in differential leukocyte count, 68% had absolute neutropenia, and 51% had absolute lymphopenia. Serum hepatic enzyme levels were measured infrequently but generally were abnormal. Serum electrolyte changes included hyponatremia (58%), hypokalemia (21%), and elevated serum creatinine (21%).

Although all patients in the pediatric case series were confirmed serologically by IFA, diagnostic titers were present in only 15% of patients at 7 days and 62% by 14 days after onset of illness. More than 28 days were required for all patients to exhibit diagnostic titers. Serologic tests for murine typhus use *R. typhi* antigen and detect cross-reactive antibodies that usually are elicited during both epidemic and murine typhus infections but less frequently in SFG infections.[30,32] With murine typhus, antibody titers to *R. typhi* may be higher than to *R. prowazekii*; antibody cross-absorption studies often are necessary to clearly distinguish murine and epidemic typhus.[32] Because circulation of *R. felis* also has been demonstrated in states traditionally endemic for murine typhus and *R. typhi* and *R. felis* share a number of cross-reactive antigens, differential serology of these flea-borne agents also may be necessary.[40–42,52,67–70] PCR tests that readily discriminate *R. typhi*, *R. prowazekii,* and *R. felis* are available.[68–70] Because fleas have high-density infections with *R. typhi*, PCR and immunologic detection of the agent in fleas are effective assays.[67–69,71]

Treatment and Prevention

Treatment regimens for suspected *R. typhi* infections are the same as those for *R. prowazekii* and other rickettsial infections.[35,72–74] Relapses have been reported in patients treated with chloramphenicol, but not those treated with tetracyclines, indicating that tetracycline or tetracycline analogs are preferable.[73] Ciprofloxacin also has been used successfully for treating adults with murine typhus. In a cohort of 87 adult patients from Greece, doxycycline treatment led to defervescence in 2.9 days (median), chloramphenicol in 4 days, and ciprofloxacin in 4.2 days.[74] Treatment regimens combining doxycycline with chloramphenicol or ciprofloxacin did not improve the clinical effectiveness of doxycycline. In children, median time to defervescence was 2 days for tetracycline and 2.5 days for chloramphenicol.[56,58]

No vaccine is available. Avoidance or elimination of rodent-infested areas are the best methods for preventing infection.[39] Rodent and flea eradication programs are recommended for areas where harborages already exist. Essential measures include rat proofing of homes and buildings, elimination of crowded and unsanitary housing conditions, and elimination or reduction of agricultural food sources and rat harborages in the domestic environment. Workers trapping and removing rats or working in rat harborages can use aerosol sprays of pyrethroid insecticides and protective clothing and masks to reduce risk for infection from fleas seeking new hosts and from residual flea feces. Control of opossums and their fleas has not yet been shown to be a necessary or effective strategy for murine typhus.

Rickettsia felis (Cat Flea Rickettsiosis) and Related Agents

Description of Pathogen and Epidemiology

Rickettsia felis was first recognized as a new rickettsial agent in 1992, shortly after its discovery by electron microscopy in the midgut epithelium and ovaries of the cat flea (*Ctenocephalides felis*), where it is maintained by transovarial passage.[75] *R. felis* can be isolated and grown in a variety of cells but is generally grown in arthropod cell cultures at 28°C. By comparative genomic analysis, *R. felis* appeared to be related most closely to *R. akari* and *R. australis*.[76] However, a group of new "*R. felis*–like" agents (e.g., *R. asemboensis* and *R. senegalensis*) have been discovered in a wide variety of arthropods, including ticks, mosquitoes, and tsetse flies since the mid-2000s.[77–80] The pathogenicity and antigenic characteristics of many of these related agents remains to be determined.[81–86] As with *R. akari,* the LPS of *R. felis* differs from that of prototypical SFG rickettsiae (i.e., *R. rickettsii* and *R. conorii*). Like other rickettsiae, *R. felis* has large surface layer protein antigens (Sca proteins) that are important targets in immune responses, but little is known about their biologic properties.[87–89]

R. felis has a worldwide distribution in association with many flea species and animal hosts.[40,51,52,68,70,75,81–84,90,91] Cat fleas infected with *R. felis* have been collected in many US states. The fleas are not affected by the presence of *R. felis* despite their location in midgut epithelial linings, tracheal matrix, muscle, ovaries, and epithelial sheath of the testes. *R. felis*–infected cat fleas can acquire *R. typhi* during a blood meal and maintain *R. typhi* for up to 9 days; however, effects of coinfection on the subsequent transovarial transmission of each agent were not determined.[69] *R. felis* also can coinfect fleas harboring *Bartonella quintana, B. henselae,* and *Wolbachia pipientis*.[92]

The capacity of vertebrate hosts to be infected or act as reservoirs for *R. felis* is not fully understood. *R. felis* DNA has been detected by PCR in opossums.[91,93] Up to 11% of US cats are seropositive for *R. felis*.[94] However, cats, rarely have detectable *R. felis* DNA, so it is likely that infected cat fleas are the main source of infections.[95]

Given the commonplace presence of *R. felis* in fleas in the domestic and peridomestic environments, it is surprising that so few PCR confirmed cases of infection with *R. felis* have been identified worldwide and that only one molecularly confirmed case has been reported in the US.[74–77,82,96,97] Of 32 human serum samples from Texas that were positive for antirickettsial antibodies, only three were positive for *R. felis* while the others reacted to *R. typhi* antigen; however, *R. felis* was more common than *R. typhi* in fleas and opossums.[97] Low case numbers may be due to lack of laboratories that are able to identify *R. felis,* lack of diagnostic testing in patients with mild influenza-like symptoms, low human susceptibility, or low pathogenicity of this agent. Serologic and molecular evidence for human infection with *R. felis* has been reported for patients from at least 18 countries around the world, including a travel case.[82,98]

Clinical Manifestations

An increasing number of human cases of *R. felis* infection with reliable laboratory support have been described, but the diagnostic criteria vary widely, and the specific agents involved may not all be the same. Confirmation by serology is the least certain. Clinical presentations of *R. felis* illnesses diagnosed in different countries vary. The *R. felis* case from Texas initially was diagnosed as murine typhus because the patient presented with a fever and headache and no apparent rash.[96] Two French cases were first diagnosed clinically as murine typhus or Mediterranean spotted fever.[81] Five patients treated in Mexico and Brazil had rash and systemic symptoms, including fever, headache, and myalgia; four had visceral involvement with abdominal pain, nausea, vomiting, and diarrhea; and four had involvement of the central nervous system (photophobia in two patients, hearing loss and signs of meningismus in one patient, and coma in one patient).[99] Some Mexican cases in the Yucatan had dengue-like illness, and others presented with pulmonary symptoms, a skin lesion consistent with an ulcer, or peripheral erythema.[100] Complications of *R. felis* infection in humans include hepatitis, polynephropathy, subacute meningitis, and splenic infarction.[100–104] A syndrome of vesicular fever called "yaaf" has been described in cases from Senegal.[105] The presence of *R. felis* DNA in fecal samples has been reported in Africa, but this is atypical for rickettsioses.[106] Seroprevalence to *R. felis* appears to be the same in healthy and HIV-infected individuals surveyed in Spain.[101] Recent reports from Africa suggested a correlation between geographic distribution, seasonality, asymptomatic infections, mosquito vectors for malaria, and the occurrence of *R. felis* infection.[107] Although there is conceivable concern that doxycycline prophylaxis for malaria in travelers may cause treatment failures or delayed onset of *R. felis* infections, the overall prevalence of *R. felis* infection in cases of undifferentiated fevers appears to be quite low.[82,108–110]

Laboratory Findings and Diagnosis

Patients with *R. felis* infection can have thrombocytopenia and increased levels of serum aspartate transaminase; anemia, leukocytosis, thrombocytosis, and prolonged prothrombin time; or leukopenia.[81]

Most cases lack detectable antibodies to rickettsiae in acute serum samples. Convalescent sera contain high antibody titers to *R. felis* (IFA IgG ≥512 and IgM titers of ≥64). Because *R. felis* shares antigens with typhus and SFG rickettsiae, cross-absorption of sera is necessary for specific diagnosis.[111]

Definitive diagnosis requires detection of *R. felis* DNA by PCR amplification.[74,76,77,80,81,99–103,108] PCR amplification and sequencing of *R. felis* DNA from skin biopsy, whole blood, and serum samples is done with primers for the *Rickettsia* 17-kd protein gene, 120-kd protein gene *(sca4), ompA, ompB,* and *R. felis* plasmid genes. A quantitative PCR assay that can differentiate *R. felis* from *R. felis*-like agents also has been described.[112]

No isolates have been obtained directly from patients. Conditions for optimal detection of *R. felis* in shell vial cultures have been evaluated, and *R. asemboensis* has been isolated in cell culture.[113,114] Although such methods have improved the rate of isolation of *R. felis* and *R. felis*–like agents present in high density in invertebrates, tests have been difficult to apply to clinical samples with typical low rickettsial density.

Treatment and Prevention

R. felis infections are treated with doxycycline. Chloramphenicol is an alternative when doxycycline is not available.[100] In vitro quantitative PCR data indicate that *R. felis* is susceptible to doxycycline (minimal inhibitory concentration [MIC], 0.06–0.125 μg/mL), rifampin (MIC, 0.06–0.25 μg/mL), thiamphenicol (MIC, 1–2 μg/mL), and fluoroquinolones (MIC, 0.5–1 μg/mL). Gentamicin, erythromycin, amoxicillin, and trimethoprim-sulfamethoxazole are not suitable therapies.[115]

R. felis appears to be maintained primarily in cat fleas infesting opossums in Texas and southern California. Rodents and other fleas may be more important hosts in other parts of the world. Cat fleas are promiscuous feeders on free-ranging wild and domestic cats and dogs and their owners. Elimination of open food sources like garbage, trapping and removal of opossums, and flea control of domestic animals are recommended for prevention of cat flea rickettsiosis.[116]

Rickettsia akari (Rickettsialpox)

Description of Pathogen and Epidemiology

Until the discoveries of *R. felis* and many other *Rickettsia* spp. associated with other arthropods, *R. akari* was considered the most unusual species of *Rickettsia* because it is transmitted by mites rather than ticks.[117–119] The SFG LPS of *R. akari* is unusual because it does not elicit typical OX2 and OX19 Weil-Felix agglutinin responses in humans like other SFG rickettsiae. Its surface protein antigens are important in protective immune responses and permit serologic discrimination from other SFG rickettsiae by IFA and Western blotting assays.[120] Inbred strains of mice differ in resistance to intraperitoneal challenge with different isolates of *R. akari*. Molecular differences between US and Ukrainian isolates also have been detected.

R. akari appears to be distributed widely in the world, but its natural history is incompletely understood. In the US, *R. akari* is best known for causing focal urban outbreaks of rickettsialpox after the bite of the house mouse mite (*Liponyssoides sanguineus*). After rickettsialpox was first identified in New York City in 1946, cases were reported from many other US cities.[118] However, of the more than 800 cases reported in the US, 500 were reported within the first 3 years after discovery, most in New York City. By the 1960s, a sharp decline occurred in reported cases of rickettsialpox, but it was unclear whether this was due to a change in incidence or recognition; increased alertness for eschar lesions after the anthrax investigation in New York City in 2001 led to the identification of rickettsialpox cases.[121–123] Human cases of rickettsialpox also have been reported from the former Yugoslavia, Northern Europe, Turkey, and Mexico.[124–127] A major outbreak in Ukraine occurred during 1949–1952, but no subsequent cases were reported there after elimination of the endemic foci.[119]

L. sanguineus is the major reservoir of *R. akari* because it maintains the agent by both transstadial and transovarial passage. Isolates also have been obtained from infected house mice and other rodents, and they can transmit *R. akari* to uninfected mites. *R. akari* has been isolated from commensal rats in the Ukraine and from voles in Korea.[128,129] However, the importance of rodents as reservoirs of *R. akari* in nature is unclear. *L. sanguineus* is a parasite of house mice *(Mus musculus)* and rats *(Rattus norvegicus* and *R. rattus)*, but voles and gerbils can be infected in the laboratory. Rodents and humans from California and dogs in New York City have been shown to have antibodies to *R. akari,* and *R. akari* was detected in *Rhipicephalus sanguineus* collected from a sick dog in Mexico.[130–132]

The mite abandons the host after feeding and can be found in mouse bedding and walls of infested rooms. Rickettsialpox appears to occur primarily when mice and rats are not available as the primary vertebrate hosts when the mites feed on humans as an available alternative host.[133] The decline in rickettsialpox in the inner city may be due to replacement of *L. sanguineus* with the tropical rat mite *(Ornithonyssus bacoti),* which can maintain *R. akari* by transovarial passage but is an inefficient vector of rickettsialpox.[134]

Clinical Manifestations

Rickettsialpox is a relatively mild illness and is rarely fatal, although more severe cases have been reported from Mexico.[126,132] Rickettsialpox affects males and females equally and has no age dependence. Three features are characteristic of the disease. First, after an incubation period of 7 to 14 days after the bite of the mite, the skin inoculation site has a firm red papule 1 to 1.5 cm in diameter. Shortly thereafter, the painless lesion vesiculates and becomes filled with cloudy fluid. As the lesion dries, it leaves a brown to black crust surrounded by a 0.5- to 3-cm area of induration. The initial lesion can be located anywhere on covered areas of the body; having more than one lesion is rare. Regional draining lymph nodes often are swollen, but lymphangitis has not been reported. In the second stage, an influenza-like syndrome begins abruptly about 1 week after exposure (up to 17 days later) with chills, fever, sweats, and myalgia. The peak temperature usually is 39°C to 40°C; without treatment, fever persists for about 7 to 11 days. Other common symptoms include profuse diaphoresis, headache (usually frontal), and photophobia; occasionally vertigo, rhinorrhea, cough, sore throat, nausea, vomiting, and constipation are present. Finally, usually within 1 to 3 days after the onset of constitutional symptoms, an exanthem appears as a single crop, with 5 to 100 discrete, firm erythematous papules on the face, trunk, and extremities; lesions are 2 to 10 mm in diameter and can develop a small vesicle or pustule in the center. Lesions can involve the palate, tongue, and pharynx, and less frequently (<10%) the palms or soles. In about 1 week, vesicles dry and form scales that do not scar but can result in postinflammatory hyperpigmentation. Untreated rickettsialpox usually resolves uneventfully in 2 to 3 weeks. Rickettsialpox most often is confused with chickenpox, but chickenpox lacks a primary eschar, and the vesicles rest on an erythematous base. The appearance of the eschar in rickettsialpox resembles the skin lesion developed in patients with cutaneous anthrax.[122,123]

Laboratory Findings and Diagnosis

Leukopenia (2400–4000 cells/mm^3) with relative lymphocytosis usually is detected during the early febrile stage of rickettsialpox. Hematocrit, hemoglobin, erythrocyte sedimentation rate, and electrolyte and serum transaminase values are normal; urinalysis can show mild proteinuria.[119,121,122]

Specific diagnosis typically requires a combination of clinical and epidemiologic findings in conjunction with group-specific serologic tests. Patients with a compatible illness and known or possible mite exposure should be tested for antibodies to SFG rickettsiae. *R. rickettsii* typically is used as a surrogate antigen because it is antigenically related to *R. akari* and is more widely available. Seroconversion in a clinically compatible case provides good evidence of rickettsialpox, but definitive evidence requires cross-absorption with SFG rickettsial antigens.[135] IFA tests or immunohistochemical staining of punch biopsies taken from skin lesions also have been used to confirm the diagnosis of rickettsialpox, but use of a species-specific antibody is necessary to confirm *R. akari* infection.[120,122,123,136] PCR amplification of a rickettsial 17-kd protein gene fragment or OmpB gene fragment followed by DNA sequencing has good diagnostic efficiency.[120,126] *R. akari* can be isolated from skin biopsy samples, and a multiplex PCR assay has been developed to differentiate rickettsialpox in skin samples from other spotted fever rickettsioses that are common in the US.[120,137]

Treatment and Prevention

No fatalities have been reported for rickettsialpox. Uncontrolled studies show that treatment with tetracyclines hastens defervescence and abatement of systemic symptoms within 48 hours. Dosage is the same as for other rickettsial infections; duration generally is 3 days after defervescence. Chloramphenicol is an alternative treatment when doxycycline is not available.[126]

No vaccine has been developed. Disease can be prevented by enforcing sanitary measures that preclude development of urban rodent harborages and their ectoparasites. Rodent eradication programs can eliminate infestation problems, but insecticides and acaricides must be applied simultaneously so that the ectoparasites do not seek alternative human hosts and initiate an outbreak.[116–118,133]

Rickettsia parkeri Rickettsiosis and Atlantic Rain Forest Rickettsiosis

Description of Pathogen and Epidemiology

Rickettsia parkeri, also called "maculatum agent," is a SFG rickettsia that was first recovered from the tick *Amblyomma maculatum* in the US in 1939.[138,139] Phylogenetically and microbiologically, *R. parkeri* clusters most closely in a genetic lineage together with *R. africae, R. sibirica,* and the unnamed isolate "S" obtained from *Rh. sanguineus* ticks in Armenia.[102a] Another genetic type (Atlantic Rain Forest) closely related to *R. parkeri* has been detected in *Amblyomma ovale* ticks from Colombia, Brazil, and Argentina.[140–144] Several cases of Atlantic Rain Forest rickettsioses have been described in Brazil, but *R. parkeri* infections are much more common and probably occur from the southern US to Argentina.[145–152]

The ecology and distribution of *R. parkeri* is not completely understood. In North America the Gulf Coast tick (*A. maculatum*) is the primary vector, and *R. parkeri* is transmitted transovarially and transstadially in these ticks.[152] *A. maculatum* is found in the US in southeastern and Gulf Coast states; inland populations also exist in Kansas and Oklahoma.[151,152] *A. maculatum* also is found in some countries of Central and South America and some Caribbean islands. *R. parkeri* also has been found in several other *Amblyomma* spp. ticks.[23,144,147–150] Human cases due to *R. parkeri* infection have been diagnosed in at least nine US states, Brazil, Uruguay, and Argentina.[150,153–155] Dogs develop *R. parkeri* rickettsiemia and may serve as a source of infected ticks to transmit infection to humans.[156]

The prevalence of *R. parkeri*–like agents in *Amblyomma* ticks is quite high compared with *R. rickettsii*, but acquisition or transmission may be limited by prior infection of ticks with *Rickettsia andeanae*.[157,158]

The Atlantic Rain Forest strain appears to be restricted to areas of tropical rain forest along the Atlantic Ocean and is most often detected in *Amblyomma ovale* but also has been found in *A. dubitatum*.[140–144] Other *R. parkeri*–like strains have been identified, but their reservoirs, vectors, and pathogenicity are unknown.[159–161]

Clinical Manifestations, Laboratory Findings, and Diagnosis

Patients infected with classical *R. parkeri* isolates in North and South America present with fever, headache, diffuse myalgia, and arthralgia. Single or multiple eschars are present in >90% of cases. An erythematous maculopapular rash develops on the trunk and spreads to the extremities, including the palms and soles. Some patients have a diffuse nonpruritic maculopapular and vesicular rash.

A mild leukopenia, elevated levels of serum hepatic enzymes, lactate dehydrogenase, and total bilirubin were detected in the blood of acutely ill patients. Paired acute and convalescent serum specimens show increases of IgG antibodies reactive with SFG rickettsiae. Because significant cross-reactivity exists among SFG rickettsiae, cross-absorption and Western blotting analyses are necessary to obtain specific serologic diagnoses, but these are insufficient for distinguishing among the isolates considered here. Histopathologic evaluation of biopsy specimens obtained from the rash or eschar reveal the presence of rickettsiae and lymphohistiocytic perivascular infiltrates. PCR amplification and sequencing of DNA from skin biopsy samples allow precise identification of the rickettsial etiologic agent.[137,150,154,162] Isolation in cell culture provides the best confirmation of the specific rickettsial etiology and permits further characterization of the biologic and immunologic properties of the organism.

Only two confirmed cases of Atlantic Rain Forest rickettsiosis have been reported, and their clinical differentiation from *R. parkeri* infection is not yet possible.[145,146] Both infections could be distinguished from Brazilian spotted fever by the presence of eschars and milder presentation.

Treatment, Prevention, and Control

Patients are treated with doxycycline as for other rickettsial diseases. Fever resolves within 24 to 48 hours, whereas malaise and rash have more gradual resolution. Laboratory test values return to normal within 1 month.

Prevention measures rely on reduction of exposure to ticks by avoiding tick habitat, reducing tick abundance in infested areas, wearing protective clothing, and checking for and removing ticks after exposure. Wearing long pants, long sleeves, and long socks will reduce tick attachment, but tucking pant legs into socks or boots and tucking shirts into pants is more effective. Light-colored clothing also can aid in spotting ticks more easily. Using insect repellent with 20% to 30% *N*,*N*-diethyl-*m*-toluamide (DEET) on skin and clothing to prevent tick attachment is recommended. Permethrin, another repellent that also kills ticks on contact, can be applied to clothing and gear.

Prophylactic antibiotic therapy is not recommended for people with attached ticks because it may only delay onset of disease and many ticks are not infected. People should remove attached ticks properly without crushing to avoid aerosolization and contamination of skin wounds.

Rickettsia philipii (Pacific Coast Tick Fever)

Description of Pathogen and Epidemiology

Rickettsia philipii is an SFG rickettsia that was first isolated from the Pacific Coast tick (*Dermacentor occidentalis*) in 1966; it can be distinguished by microimmunofluorescence typing from other SFG agents.[163,164] Its microbiologic characteristics are typical of other SFG rickettsiae. *R. philipii* is closely related to *R. rickettsii*, but it has less in vitro cytopathic effect. The first laboratory confirmed cases of *R.*

philipii were identified in adults in California in 2008; the first pediatric cases were reported in 2013.[165,166,166a]

D. occidentalis, the *R. philipii* vector, has a limited distribution spanning from Baja, Mexico to southern Oregon.[167] Approximately 7% of *D. occidentalis* in southern and northern California are infected with *R. philipii*, compared with <1% with *R. rickettsii*.[168] In northern California, adult *D. occidentalis* are most active March through May, whereas nymphal *D. occidentalis* are encountered more commonly during June through August, the peak times for occurrence of disease.[166a]

Clinical Manifestations, Laboratory Findings, and Diagnosis

R. philipii infection causes nonspecific clinical symptoms, including fever, fatigue, headache, and lymphadenitis or lymphadenopathy.[165,166,166a] The presence of a single, sometimes painful ulcerated eschar (or scab) on the neck, forearm, shoulder, neck, back, or eyebrow and lymphadenopathy associated with a previous tick bite at that site are significant diagnostic clues for clinical diagnosis. Rash is observed infrequently but may manifest as erythematous macules on the cheek and chest.[166] Most cases are mild and managed on an outpatient basis; however, cases requiring hospitalization have been reported.[166,166a]

Routine laboratory findings are not remarkable, although patients may exhibit elevated liver enzymes and C-reactive protein and low white blood cell counts.[166] Elevated antirickettsial IgG antibody titers can be detected after the second week after illness onset.[165] Etiologic diagnosis is made by PCR detection and sequencing *R. philipii* DNA present in skin punch biopsy samples collected from the eschar site.[165] If a skin biopsy is not indicated because of mild disease, collection of the eschar scab or a swab of the lesion might be sufficient for DNA detection.[166,166a,170]

Treatment, Control, and Prevention

Treatment is the same as for other rickettsial diseases and requires a full course of doxycycline. Pediatric patients of all ages are treated with 2 mg/kg/dose twice daily for 14 days and recover uneventfully; nearly complete resolution of the symptoms may be seen within 3 days.[36,166,171] Treatment with sulfa drugs may worsen the course of infection and prolong clinical symptoms and healing of skin lesions.[165]

Control and prevention of *R. philipii* infection is the same as for *R. parkeri*, discussed previously.

Orientia and Other *Rickettsia* Agents (African Tick Bite Fever and Other Travel-Associated Rickettsioses, Including Scrub Typhus)

Description of Pathogens and Epidemiology

The SFG rickettsiae comprise a large number of pathogenic agents with varied geographic distributions that are dependent on the presence of their different tick vectors (Table 179.1).[144,153,169,172–179] Recent studies suggest that 7% of bacterial illness in travelers returning from developing countries is due to rickettsioses.[176] *Rickettsia africae,* the agent of African tick bite fever, is the most common cause of rickettsial infection in travelers and is diagnosed in approximately 5% of European visitors to South Africa.[173] Based on serosurveys, the prevalence of infection in some populations in Africa may approach 55%, but the incidence of disease is less clear.[109,180]

TABLE 179.1

Differential Characteristics of Spotted Fever Rickettsioses Acquired Outside the United States

		Epidemiologic Features			
***Rickettsia* sp.**	**Disease**	**Arthropod Vector**	**Location**	**Season**	**Outbreaks**
R. aeschlimannii	Unnamed spotted fever rickettsiosis[a]	*Hyalomma marginatum marginatum, Hyalomma marginatum*	Southern Europe, northern Africa, South Africa	Year-round	Not reported

		rufipes, Rhipicephalus appendiculatus			
R. africae	African tick bite fever[a]	*Amblyomma hebraeum, Amblyomma variegatum*	Sub-Saharan Africa, West Indies	Year-round	Common
R. akari	Rickettsialpox	*Liponyssoides sanguineus*	Europe, Africa, Asia, Mexico	Year-round	Originally discovered as outbreaks, sporadic cases now
R. australis	Queensland tick typhus	*Ixodes holocyclus, Ixodes tasmanii*	Eastern Australia	June to November	None reported
R. conorii* subsp. *conorii	Mediterranean spotted fever	*Rhipicephalus sanguineus*	Southern Europe, Africa	Summer months	Sporadic cases
R. conorii* subsp. *caspia	Astrakhan spotted fever	*Rhipicephalus sanguineus, Rhipicephalus pumilio*	Volga delta of Russia, Kosovo, Chad	May through September	Sporadic cases
R. conorii* subsp. *israelensis	Israeli spotted fever[a]	*Rhipicephalus sanguineus*	Southern Europe from Portugal to Italy and Israel	Summer months	Sporadic cases
R. felis	Cat flea rickettsiosis	*Ctenocephalides felis*	Worldwide	Year-round	Sporadic cases
R. heilongjiangensis	Far Eastern spotted fever	*Dermacentor silvarum*	Far east of Russia, Northern China	Summer months	Sporadic cases
R. honei	Flinders Island spotted fever	*Aponomma hydrosauri, Ixodes granulatus*	Southeastern Australia, Thailand	December to January	Sporadic cases
R. honei* strain *marmionii	Flinders Island spotted fever	*Haemaphysalis novaeguineae*	Eastern seaboard of Australia	February to June	Sporadic cases
R. japonica	Oriental (Japanese) spotted fever	*Ixodes ovatus, Dermacentor taiwanensis, Haemaphysalis longicornis, Haemaphysalis flava*	Japan, Korea, Taiwan	April to October	Sporadic cases
R. kellyi	Unnamed rickettsiosis	Unknown	India subcontinent, Sri Lanka	Unknown	Sporadic cases
R. massiliae	Unnamed rickettsiosis	*Rhipicephalus sanguineus Rhipicephalus turanicus*	Mediterranean countries, Africa, South America	Spring and summer months	Sporadic cases
R. parkeri	Maculatum infection	*Amblyomma maculatum,*	Argentina, Bolivia, Brazil,	Spring to summer	Sporadic cases

		Amblyomma cajennense, *Amblyomma triste* *Amblyomma tigrinum* *Amblyomma nodosum*	Uruguay	months	
R. raoultii	Tickborne lymphadenopathy, *Dermacentor*-borne necrosis and lymphadenopathy	*Dermacentor marginatus* *Dermacentor reticulatus*	Europe to Asia	March–May to September–November	Sporadic cases
R. rickettsii	Rocky Mountain spotted fever, São Paulo exanthematic typhus, Minas Gerais exanthematic typhus, Brazilian spotted fever[a]	*Amblyomma cajennense* *Rhipicephalus sanguineus* *Amblyomma imitator*	Mexico, Costa Rica, Panama, Brazil, Argentina	Spring to fall months	Sporadic cases, also outbreaks and family cluster cases can occur
R. sibirica	Siberian tick typhus[a]	*Dermacentor nuttalli*, *Dermacentor marginatus*, *Dermacentor silvarum*, *Haemaphysalis concinna*	Europe, Asia	Spring to summer months	Sporadic cases
R. sibirica* subsp. *mongolotimonae	Lymphangitis-associated rickettsiosis	*Hyalomma asiaticum*, *Hyalomma reticulatus*	Southern France, Asia, Africa[b]	Late spring to early summer	Sporadic cases
R. slovaca	Tickborne lymphadenopathy, *Dermacentor*-borne necrosis and lymphadenopathy	*Dermacentor marginatus*, *Dermacentor reticulatus*	Europe, Asia	October through May	Sporadic cases
R. tarasevichiae	Unnamed spotted fever rickettsiosis[a]	*Ixodes persulcatus*	Arkhangelsk region of Russia to the Far East and to Northern China	Spring to fall months	Sporadic cases

[a] Indicates diseases reported for international travelers from endemic areas.

[b] Original isolation of a reference strain of *R. sibirica* subsp. *mongolotimonae* was made from *Hyalomma asiaticum* ticks from Northern China.[209–211]

[c] Prevalence has not been reported if numbers in parentheses are not shown.

[d] The case-fatality rate due to *R. rickettsii* infection depends on patient's age and time of initiation of antibiotic therapy.

R. africae is transmitted by *Amblyomma* ticks (e.g., *A. herbraeum* and *A. variegatum*) that are found on cattle and game in rural areas of tropical and subtropical sub-Saharan Africa.[173,177] *R. africae* also has been detected in *Rhipicephalus* spp. ticks, but their role in transmission is unknown. Although most cases of African tick bite fever occur in sub-Saharan Africa, *R. africae* also is found in ticks on Indian Ocean islands and in north Africa, the Middle East, parts of Europe, and the Caribbean.[181–191]

Other spotted fever group rickettsioses and their epidemiologic features are summarized in Table 179.1.[177,178] Boutonneuse fever (Mediterranean spotted fever) is caused by *R. conorii* subsp. *conorii,* which is distributed throughout Africa, southern Europe, and the Indian subcontinent.[192,193] *R. conorii* subsp. *caspia* and *R. conorii* subsp. *israelensis* have been described primarily in the Mediterranean-Caspian region, but distribution likely extends to the Indian subcontinent.[193,194] *Rickettsia massiliae* has been identified as a cause of rifampin-resistant rickettsiosis in Spain, Italy, France, and Argentina.[195–197] It has been detected in ticks in Arizona, California, and Maryland.[198–200] *Rickettsia honei* has been found in Southeast Asia, Nepal, and Australia.[172,177,201,202] *Rickettsia japonica* (Japanese spotted fever) and *Rickettsia tamurae* cause infections in Japan and Korea.[177,203,204] *Rickettsia heilongjiangensis* has been identified in patients in China, Russia, and Japan.[177,205,206] Siberian tick typhus, which is caused by *Rickettsia sibirica* sensu stricto, is transmitted by *Dermacentor* spp. ticks in a large area from Russia to India and China.[207,208] *Rickettsia sibirica* subsp. *mongolotimonae* causes infections in southern Europe, Africa, and Asia and can be diagnosed by eschar swab.[209–211] *Rickettsia aeschlimannii* and similar rickettsiae are implicated in human disease cases reported from Africa, southern Europe, and Central Asia.[177,212–214] *Rickettsia slovaca* and *Rickettsia raoultii* cause sporadic and atypical rickettsioses in Eurasia, and *Rickettsia helvetica* is found throughout the wide distribution of *Ixodes ricinus* ticks.[215–218]

Orientia tsutsugamushi, the etiologic agent of scrub typhus, is related to *Rickettsia* but differs in its cell wall structure, staining properties, and morphology; it lacks peptidoglycan and LPS and has a unique set of major surface antigens.[1] This antigenically diverse agent is transmitted by numerous species of trombiculid mites (chiggers) in the Asia-Pacific region from Australia to Russia and from New Guinea to Afghanistan and causes an estimated 1 million disease cases per year.[219,220] Other similar agents recently have been identified in the Middle East, Africa, Europe, and South America, but the clinical and public health implications of these findings are unknown.[221–223]

Clinical Manifestations

Differential clinical features of these rickettsioses are described in Table 179.1. A characteristic of many of these infections is the development of an eschar at the site of a tick or mite bite, either immediately before or coincident with the onset of constitutional symptoms.[120,146,161,165,166,170,197,211,215] Multiple eschars are common in African tick bite fever and *R. parkeri* rickettsiosis. Illness typically occurs 1 week after a tick bite and is characterized by the abrupt onset of fever, headache, lymphadenopathy, and malaise. With *R. conorii* and *R. australis* infection, a maculopapular rash usually appears between days 3 and 5 and typically affects the extremities first before spreading to include the trunk. *R. africae* infections may be less likely to cause a rash; they also are characterized by a delayed antibody response compared with Mediterranean spotted fever. Other symptoms include hepatomegaly, splenomegaly, conjunctivitis, and gastrointestinal tract manifestations. These agents usually cause mild to moderate disease, with occasional severe complications reported, including neuropathy and skin necrosis. However, case-fatality rates of up to 3% have been reported for *R. conorii* subsp. *conorii,* with similar rates for *R. australis, R. japonica,* and *R. honei*. Different inflammatory and immunologic responses underlying the pathogenesis of rickettsial infections are in part due to expression of homeostatic chemokines (CCL19, CCL27, and CCR7), proinflammatory cytokines (interleukin-8), and cell adhesion molecules.[224,225]

R. slovaca and *R. raoultii* cause tickborne lymphadenopathy or *Dermacentor*-borne necrosis and lymphadenopathy.[215,216] Patients have a large eschar on the scalp and enlargement of the cervical lymph nodes; only one third of patients develop fever. Peak incidence months are March through May and September through November, when *Dermacentor* ticks are most active. Patients infected with *R. helvetica* develop acute illness with rash, meningitis, or persistent myasthenia.[217,218] Most cases of scrub typhus have a heralding eschar. Scrub typhus can cause multiorgan involvement, pulmonary complications, meningoencephalitis, renal failure, jaundice, hepatitis, gastrointestinal tract dysfunction, and sepsis complicated by secondary bacterial, viral, fungal, or parasitic infections.[226–228]

Diagnosis

Diagnosis of these rickettsioses is most commonly made retrospectively by serologic testing.[229] Because specific tests are available only in specialty laboratories in the US, assays employing *R. rickettsii* are used as a surrogate cross-reactive antigen by commercial and state laboratories. Antigen-specific serologic tests for most of the SFG rickettsioses and scrub typhus are available on request from the Centers for Disease Control and Prevention. Confirmed infections exhibit a fourfold change in antibody titer between acute and convalescent serum specimens. A single high titer with a clinically compatible illness is considered a probable case. Acute phase samples, particularly whole blood and skin biopsy samples collected before antibiotic treatment, can be used for the direct identification of rickettsial DNA by PCR amplicon sequencing. Invasive punch biopsy procedures can be replaced by sampling the scab or a cutaneous swab collected before or within 24 hours after antibiotic therapy is initiated.[170,177,211] Rickettsial etiology also can be confirmed by immunohistochemistry tests performed on formalin-fixed paraffin-embedded tissues or direct cell culture isolation of rickettsiae from appropriately collected specimens and identification of the specific agent by PCR.[122,136,137,203]

Treatment and Prevention

Therapy is given empirically using drugs and dosage as for other rickettsioses. Doxycycline is the drug of choice for children of all ages and adults.[36,171] For patients in whom life-threatening reactions to doxycycline have been documented, intravenous chloramphenicol is an alternate antibiotic. Rifampin should be excluded as an antibiotic of choice if infection with *R. massiliae* or *R. aeschlimannii* is suspected because these rickettsiae are resistant to rifampin.[230] Cases of scrub typhus from northern Thailand responding poorly to doxycycline and chloramphenicol have been described in which 900 mg of daily rifampin was effective.[231,232] Azithromycin can be used for treatment of scrub typhus in patients for whom tetracyclines and chloramphenicol are not recommended.[233] Intravenous azithromycin has been shown to be as effective as intravenous doxycycline in the treatment of complicated scrub typhus.[234] Fluoroquinolones are ineffective in the treatment of scrub typhus because of intrinsic resistance of *Orientia*.[235,236]

Vaccines are not available. Prevention depends on avoiding arthropod bites and rodent- and ectoparasite-infested habitats. When traveling in these environments, people should wear long sleeves and pants, with the ends tucked into socks or sealed with tape. Use of permethrin-treated clothing may help repel ticks and mites. Repellents containing DEET can be applied to the skin. Adults should perform a body check on themselves and children daily after exposure to wild habitats and carefully and immediately remove any ticks and mites that are found to reduce the likelihood of transmission of rickettsiae.

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Streptobacillus moniliformis (Rat-Bite Fever)

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Streptobacillus moniliformis and the recently described *S. hongkongensis*[1] are the only species in the genus *Streptobacillus.* They are fastidious, nonmotile, gram-negative, pleomorphic and often filamentous, beaded, facultative anaerobic bacilli. *S. moniliformis* can exist in two phases: the bacillary phase and the cell wall-deficient L-phase.[2,3] In addition to being the main etiologic agent of a systemic illness called *rat-bite fever, S. moniliformis* causes Haverhill fever. Sodoku (spirillary rat-bite fever), an extremely rare disease in the United States, is the name given to rat-bite fever caused by *Spirillum minus,* which manifests 1 to 4 weeks after a bite with relapsing fever, ulceration at the site of the bite, and associated regional lymphadenopathy. *S. minus* is a spiral gram-negative coiled bacillus with two or more helical turns and is motile. *S. minus* has not been isolated on solid media, and its diagnosis relies on visualization by darkfield microscopic examination of an ulcer or blood smear or on a Giemsa- or Wright-stained smear. This infection responds rapidly to therapy with penicillin.[3]

Epidemiology

The natural habitat of *S. moniliformis* is the upper respiratory tract of rodents, including wild or laboratory rats as well as mice, gerbils, and squirrels, where carriage is common and asymptomatic.[4] The organism can be excreted in rat urine. Humans are infected by the bite of a rat (or rarely mouse or squirrel) or, less commonly, from a scratch by a rat, from rat contact in the presence or absence of a break in the skin, from handling a dead animal, from skin injury from the cage of a rat,[5] or from contact with a rat-eating carnivore such as a dog, cat, or weasel.[2,3] In some cases a pet rat had died recently of an unknown illness.[6] Contact with pet rats account for most cases in some areas.[7] In some persons with no history of rodent contact, infection may have been acquired through ingestion of milk or water contaminated with rat excreta, as occurred in epidemic form in 1916 in Haverhill, Massachusetts, and in the 1980s in England.[8] Approximately 50% of cases of rat-bite fever are reported in children.

Clinical Findings

Two to 10 days (or up to 3 weeks) after a rat bite, there is an abrupt onset of fever accompanied by chills, headache, vomiting, myalgia, sore throat, and a rash that is maculopapular in appearance and frequently includes petechiae and at times pustules.[6] The rash is most prominent on the extremities and frequently involves the palms and soles. The bite wound usually has healed and exhibits no or minimal inflammation. Regional lymphadenopathy can occur in up to 25% of cases. Fifty percent of patients experience a migratory polyarthritis or polyarthralgia (erythema arthriticum epidemicum) typically involving the knees and ankles. Young children can have diarrhea and weight loss. Clinical features can be similar to Rocky Mountain spotted fever, septicemia due to *Neisseria meningitidis*, disseminated gonococcal infection, or secondary syphilis.

Untreated *S. moniliformis* infection usually follows a relapsing course for a mean of 3 weeks before spontaneous resolution. However, in untreated patients the mortality rate is approximately 10% and appears to be highest in young infants and those with endocarditis; cases of rapidly fatal infection have been reported.[2,3,7,9,10] Arthritis persisting for several months can occur.[3,10] Other reported manifestations are fever without a focus, endocarditis, myocarditis, meningitis, spinal epidural abscess, focal abscesses including brain and skin,[11] pyogenic arthritis typically with polyarticular involvement but without rash, or bacteremia,[12] pneumonia, hepatitis, nephritis, and amnionitis.[3,9,10]

When the infection is acquired through ingestion of the organism from water, milk, or food contaminated with rat excrements, it is known as *Haverhill fever*. Fever, chills, headache, pharyngitis, and vomiting are prominent and often are followed by rash and polyarthralgia or polyarthritis.

Diagnosis

The diagnosis is established by recovery of the organism from culture of blood, joint fluid, or abscess specimens in broth or on solid media. Identification often is established using polymerase chain reaction amplification of a segment of the 16S rRNA gene using specific primers. Media enriched with horse serum, sheep or rabbit blood, or ascites fluid and yeast extract and incubation in a 5% to 10% CO_2 atmosphere are required to recover *S. moniliformis*.[3,4] On solid media, small round grey colonies are noted within 3 days; in addition, mycoplasma-like colonies with a fried-egg appearance can develop. Isolation of the more fastidious L-phase variants requires an enrichment medium such as brain-heart infusion broth supplemented with horse serum and yeast extract. Sodium polyanethol sulfonate can inhibit *S. moniliformis*.[4,13] Although Bactec blood culture medium contains sodium polyanethol sulfonate, *S. moniliformis* has been recovered using Bactec Peds-Plus and Bactec Plus media,[11] perhaps because they contain resin. Growth in broth appears as "puffball" colonies at the bottom of the vial after 2 to 6 days. Occasionally, gram-negative pleomorphic bacilli are visualized on a smear of a clinical specimen such as a skin lesion, or bacilli are visualized on a blood smear.[9]

Alternatively, diagnosis can be established by polymerase chain reaction amplification of a segment of the 16S rRNA gene using broad-range primers followed by sequencing or electrospray ionization followed by mass spectrometry. Using this method, *S. bacilliformis* has been detected in clinical specimens such as joint fluid or post-mortem tissues as well as in incubated culture media.[4,5,14] At least 25% of patients infected with *S. moniliformis* have a false-positive reaction to the Venereal Disease Research Laboratories (VDRL) test for syphilis.[3]

Treatment

Penicillin is the drug of choice for treatment of persons with rat-bite fever, although penicillin-resistant strains have been reported rarely.[3] Isolates are susceptible in vitro to penicillin, ampicillin, cefuroxime, cefotaxime, clindamycin, tetracycline (doxycycline), streptomycin, and vancomycin. Doxycycline is an acceptable alternative agent to penicillin.[15] Failure of erythromycin treatment and successful treatment with clarithromycin have been described.[11,16] The L-phase of *S. moniliformis* is resistant to penicillin but responds to tetracycline.[2] For therapy of endocarditis caused by *S. moniliformis*, the addition of streptomycin to high dosages of penicillin should be considered.[3] Susceptibility to aminoglycosides and fluoroquinolones is variable. *S. moniliformis* is resistant to trimethoprim-sulfamethoxazole, nalidixic acid, and colistin[4] and sulfonamides are ineffective.[3]

Prevention

Avoiding contact with rodents and their excreta or wearing gloves for such contact is the best means of prevention. The rate of rat-bite fever after a rat bite is approximately 10%.[3] Individuals who sustain rat-bite wounds should be observed closely; penicillin prophylaxis can be considered.

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Other Gram-Negative Coccobacilli

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A large number of gram-negative coccobacilli have been reported to cause infections in humans. This chapter describes four coccobacilli not discussed in other chapters. These organisms are important in specific epidemiologic and clinical settings and present special problems of diagnosis and therapy.

Aggregatibacter Species

Aggregatibacter (formerly *Actinobacillus*) *actinomycetemcomitans,*[1] a small, fastidious gram-negative coccobacillus, is a cause of endocarditis, of periodontal infection, and, in conjunction with *Actinomyces israelii,* of pneumonia and soft tissue abscesses (see Chapters 187 and 195). The other species of this newly formed genus are *Aggregatibacter* (formerly *Haemophilus*) *aphrophilus*, which can cause bone and joint infections, spondylodiscitis, brain abscess, and endocarditis; and *Aggregatibacter* (formerly *Haemophilus) paraphrophilus* and *Aggregatibacter* (formerly *Haemophilus*) *segnis,* both of which can cause endocarditis. The other *Actinobacillus* species—*A. equuli* subsp. *equuli, A. equuli* subsp. *haemolyticus, A. lignieresii, A. ureae,* and *A. hominis*—occasionally are associated with human disease; the first three primarily infect animals.

A. actinomycetemcomitans commonly is part of the normal flora of the mouth of humans, especially in gingival and supragingival crevices and also of various animal species.[2] The incidence of carriage is markedly higher in individuals with refractory periodontitis and in people with juvenile periodontal disease.[2] The organism can be transmitted among household members.[2]

A. actinomycetemcomitans contributes to the HACEK organisms, an acronym for a group of fastidious gram-negative coccobacilli that also include *Haemophilus parainfluenzae, Aggregatibacter* (formerly *Haemophilus*) *aphrophilus, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella kingae* that cause endocarditis. Poor dentition or recent dental manipulation is a risk factor for *A. actinomycetemcomitans* endocarditis, and most patients are adults with underlying valvular heart disease. Infection manifests subacutely with a mean interval from onset of symptoms to diagnosis of 3 months. Symptoms include fever, chills, malaise, anorexia, and weight loss.[3] Hepatosplenomegaly and peripheral stigmata, including petechiae, are common clinical findings. The incidence of embolic phenomena is similar to that in persons with endocarditis from other causes. Anemia and an elevated erythrocyte sedimentation rate are common laboratory findings.

The most common illness associated with *A. actinomycetemcomitans* is juvenile and adult periodontal disease. *A. actinomycetemcomitans* also causes soft tissue abscesses, particularly of the chest wall or mandibular area, often as a coinfection with *A. israelii.* Chest wall lesions often are associated with pulmonary or pleural lesions, and lesions of the mandibular area typically are associated with dental caries or periodontal disease. Cases of pneumonia, empyema, osteomyelitis, septic arthritis, brain abscess, cervical lymphadenitis, intra-abdominal abscess, and urinary tract infection have been reported with *A. actinomycetemcomitans* as a sole pathogen or copathogen.

Isolation of the organism is hampered by slow and fastidious growth; a carbon dioxide–enriched environment improves growth. Growth in nutrient broth, such as trypticase soy or Schaedler, can occur without turbidity in blood culture bottles, including radiometric blood culture bottles, or can appear as tiny puffballs growing in the blood cell layer or as granules that adhere to the sides or bottom of the bottle. *A. actinomycetemcomitans* grows on blood or chocolate agar, forming small colonies after up to 7 days of incubation, but grows poorly on MacConkey agar.[4]

Although penicillin or ampicillin has been used commonly to treat infections caused by *A. actinomycetemcomitans*, resistance can occur, and response to ampicillin may be unsatisfactory. Strains are uniformly susceptible to the third-generation cephalosporin antibiotics cefotaxime and ceftriaxone, and either of these agents can be considered the drug of choice. Isolates usually are susceptible to aminoglycosides, rifampin, metronidazole, tetracycline, trimethoprim-sulfamethoxazole, fluoroquinolones, azithromycin, imipenem, and chloramphenicol and generally are resistant to antistaphylococcal penicillins, clindamycin, vancomycin, and erythromycin.[2,3,5,6]

Clinical experience suggests that treatment of endocarditis with penicillin and gentamicin usually is successful. Cefotaxime or ceftriaxone with or without an aminoglycoside or rifampin may be optimal therapy for endocarditis.[3] Oral ciprofloxacin also has been used successfully. Severe periodontal disease usually is treated with mechanical debridement in combination with tetracycline, a fluoroquinolone, or with the combination of metronidazole and amoxicillin.[6]

Bartonella Species

Bartonella bacilliformis is a member of the family Bartonellaceae and the genus *Bartonella*.[7] In addition to *B. bacilliformis*, human pathogens and their main clinical syndromes in this genus include *B. clarridgeiae* (cat-scratch disease), *B. elizabethae* (neurologic, bacteremia, neuroretinitis, endocarditis), *B. henselae* (cat-scratch disease, bacillary angiomatosis, endocarditis), *B. koehlerae* (endocarditis), *B. quintana* (trench fever, bacillary angiomatosis, endocarditis), and *B. vinsonii* subsp. *berkhoffi* and subsp. *arupensis* (endocarditis).[7] *B. bacilliformis* is the etiologic agent of bartonellosis or Carrión disease. *B. bacilliformis* is motile by means of flagella and is transmitted to humans through the bite of the nocturnal sandfly (*Lutzomyia verrucarum*), which is endemic solely in the Andes regions of Peru, Ecuador, and Colombia at elevations between 600 and 2400 meters (2000 and 8000 feet). The incubation period is approximately 2 to 3 weeks (range, 1–12 weeks), and one half of cases occur in children and adolescents.[8–10] A case of possible vertical transmission has been described.[11] The organism adheres to and invades erythrocytes and endothelial cells.

Carrión disease manifests in two distinct stages.[9,12,13] Bacteremic illness (Oroya fever) is the first stage of infection, in which erythrocytes are parasitized, generally resulting in an acute onset of febrile illness associated with severe hemolytic anemia. The most common findings are sustained fever, pallor, malaise, hepatomegaly, and lymphadenopathy.[10] There also is transient immune suppression that can result in disseminated opportunistic infections such as septicemia due to *Salmonella* or other gram-negative bacteria or reactivation and dissemination of latent toxoplasmosis, tuberculosis, or histoplasmosis.[9] Without antibiotic therapy, this stage of infection is fatal in up to 40% of cases, with death due to complications of profound anemia or opportunistic coinfection during the immune deficiency state, or both. Some infected individuals experience fever, headache, and musculoskeletal pain but do not have anemia. Subclinical infection, documented by asymptomatic bacteremia or seroconversion, occurs commonly.[14]

There is a 1- to 2-month or longer interval before the onset of the secondary or eruptive stage of infection.[9] Cutaneous lesions occur after bacterial invasion of capillary endothelial cells with stimulation of cellular proliferation; lesions may contain bacteria.[9] In this stage, one of three types of lesions known as *verruca peruana* are observed: miliary lesions that are the most common and consist of multiple 1- to 4-mm papular, erythematous, round lesions that frequently are on the lower extremities and are pruritic; nodular raised lesions with normal overlying skin; and mular (eruptive-phase) lesions that are >5 mm in diameter, erythematous, and bleed easily.[10] Patients can manifest verruca peruana without a preceding fever.[14]

Diagnosis of Oroya fever can be made through examination of a blood smear, which reveals bacteria adherent to most erythrocytes. The organism can be isolated by inoculation of blood or material from cutaneous lesions onto supplemented brain-heart infusion agar and incubation for 1 to 2 weeks at 25°C to 30°C in 5% carbon dioxide. During an outbreak of acute bartonellosis, detection of the organism on a blood smear had a sensitivity of only 36% compared with bacterial isolation.[15] A serum titer of ≥1 : 256 in an indirect fluorescence antibody assay has been shown to have a sensitivity of 86% for diagnosis of infection in a highly endemic area.[12] Immunoblot and enzyme immunoassay detection of antibodies can be used, although the latter may be most useful for seroprevalence testing.[12] Polymerase chain reaction–based DNA detection in blood is more sensitive than blood culture or examination of a blood smear.[16,17] Diagnosis of verruca peruana is confirmed by biopsy of a lesion that characteristically demonstrates hyperplasia of endothelial cells with swollen nuclei, abundant mitosis, and proliferation of capillaries.

Chloramphenicol, penicillin, tetracycline, or erythromycin is effective treatment for Oroya fever, although spontaneous resolution of erythrocyte parasitism occurs in milder cases after a few days.[8,9] Verruca peruana lesions can be self-limited[11] or may respond to treatment with rifampin or streptomycin or azithromycin[12]; ciprofloxacin can be used, but some isolates exhibit in vitro resistance to fluoroquinolones.[18] Large lesions may require surgical excision.

Cardiobacterium hominis

Cardiobacterium hominis, a microaerophilic, pleomorphic gram-negative bacillus, is one of the HACEK organisms. *C. hominis* is a component of the normal flora colonizing the nose and oral cavity. The principal clinical disease caused by *C. hominis* is endocarditis,[19] but focal soft tissue infection and peritoneal dialysis–related infection have occurred.[20] A case of *C. hominis* bacteremia without endocarditis has been reported in a 28-day-old infant 10 days after a pyloromyotomy with a complicated postoperative course.[21] Endocarditis occurs almost exclusively in adults with preexisting valvular disease. Onset is insidious, often occurring after an oral infection, a dental procedure, or upper gastrointestinal endoscopy. Prosthetic valve endocarditis also occurs.[22] Endocarditis has been reported in a few children, all with underlying congenital heart disease.[23] Common findings of endocarditis are moderate fever, splenomegaly, cutaneous lesions such as petechiae, an elevated erythrocyte sedimentation rate, and mild anemia. Large vegetations and large vessel emboli are characteristic. At least 6 cases of aortic valve endocarditis in adults have been reported due to

Cardiobacterium valvarum, a *Cardiobacterium* species also found in the oral cavity.[24]

Diagnosis is made through recovery of *C. hominis* in blood culture, which takes an average of 5 days of incubation. In broth culture, growth can occur adjacent to the red cell layer in the absence of turbidity and can remain undetected if blind subculture is not performed. The organism grows on sheep blood, chocolate, Mueller-Hinton, and trypticase soy agars, provided that incubation conditions include high humidity and ≥3% CO_2 concentration. In cases of culture-negative endocarditis, the diagnosis has been made using broad-range polymerase chain reaction assay performed on heart valve tissue.[4]

Isolates generally are susceptible to penicillin, ampicillin, cephalosporins, fluoroquinolones (including ciprofloxacin and levofloxacin), chloramphenicol, and tetracycline.[5] However, penicillin-resistant, β-lactamase−producing strains have been described.[25] Susceptibility to vancomycin, aminoglycosides, erythromycin, and clindamycin is variable. Penicillin with or without an aminoglycoside is the therapy of choice for susceptible isolates and achieves a high cure rate; a third-generation cephalosporin with an aminoglycoside is recommended until the results of antibiotic susceptibility testing are available.

Psychrobacter immobilis

Psychrobacter immobilis is a psychrotropic (cold-loving), gram-negative coccobacillus and a member of the family Moraxellaceae that grows best at 20°C. Previously called *Moraxella*-like, *P. immobilis* is related to *Moraxella* and *Acinetobacter. P. immobilis* is associated with fish, processed meat, and poultry and has been isolated from various clinical sites.[26] Clinically significant isolates have been recovered from the blood of a hospitalized adult with AIDS,[27] the blood of a 16-year old boy with chronic granulomatous disease with fatal sepsis,[28] the cerebrospinal fluid of a 2-day-old infant in Micronesia with insidious meningitis, and a conjunctival swab of a 12-day-old infant in Guatemala who developed bilateral purulent conjunctivitis while receiving penicillin.[29,30] The isolate recovered from the 2-day-old infant initially was thought to be *Neisseria gonorrhoeae.* Clinical isolates were recovered on sheep blood agar incubated at 35°C, although growth is best at 20°C. In a recent study of 16 *Psychrobacter* isolates from humans, 10 were identified as *Psychrobacter faecalis,* four were identified as *Psychrobacter pulmonis,* and two could not be identified, findings that led the study authors to question species identification of the reports of clinically significant isolates as *P. immobilis* rather than *P. faecalis* or *P. pulmonis.*[4] Isolates were resistant to penicillin or ampicillin, 2 of 3 were susceptible to gentamicin, and the isolate causing septicemia in the man with AIDS was susceptible to cefotaxime, ceftazidime, piperacillin, amikacin, and ciprofloxacin.

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Gram-Negative Coccobacilli

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Treponema pallidum (Syphilis)

Sarah A. Rawstron, Sarah J. Hawkes

Four diseases are associated with pathogenic treponemes: (1) venereal syphilis, caused by *Treponema pallidum* subsp. *pallidum;* (2) yaws, caused by *T. pallidum* subsp. *pertenue;* (3) endemic syphilis, or bejel, caused by *T. pallidum* subsp. *endemicum;* and (4) pinta, caused by *T. carateum.* These diseases are thought to have diverged from a single disease 10,000 to 100,000 years ago under the influence of population migration and environmental factors.[1] The pathogenic treponemes cannot be distinguished by serologic tests (nontreponemal and treponemal) or morphologic features,[2] but newer molecular techniques can distinguish *T. pallidum* from the other treponemes.[3] The treponemal diseases evolve over many years in 3 symptomatic stages: a primary stage, marked by a single highly contagious cutaneous or mucous membrane lesion; a secondary stage, the consequence of disseminated organisms, which results in highly infectious cutaneous and mucous membrane lesions, with other organs also affected; an asymptomatic latent stage; and a tertiary symptomatic stage, marked by destructive lesions. These diseases also share an early immune response that modifies the course but does not prevent the disease from progressing. In all cases, a cure is achievable by relatively small doses of penicillin, and humans are the only host.

Treponemal diseases can be differentiated by epidemiology and mode of transmission. Syphilis is caused by *T. pallidum* subsp.

pallidum, occurs globally, and is acquired by sexual contact or congenital infection.

Microbiology and Pathogenesis

Between 1905 and 1910, Schaudinn and Hoffmann identified *T. pallidum* as the cause of syphilis, Wasserman described a diagnostic serologic test, and Ehrlich discovered that salvarsan (an arsenic-based compound) could be used for treatment. *T. pallidum* cultivation in the laboratory still requires propagation in rabbit testes, but application of modern molecular techniques is providing an increased understanding of the interaction between treponemes and the host.[4–7] The *T. pallidum* Nichols strain DNA sequence was published in 1998,[8] and this led to other advances in understanding the structure and function of the organism.[9–11] Molecular techniques led to subtyping of *T. pallidum*,[12] and with increasing discrimination these techniques have improved knowledge of geographic subtype differences and have been used to investigate the epidemiology and spread of syphilis.[13–17] Molecular techniques also have identified significant sequence changes in genes (*tpr*) that cluster in *T. pallidum* subspecies, thus supporting a genetic basis for species classification.[18]

Treponemes are tapered, thin, spiral bacilli (5–15 µm in length, 0.15 µm in width) that exhibit corkscrew locomotion. Infection starts with penetration through minor abrasions in the skin or intact mucous membrane. Only spirochetes that adhere to cells replicate, and cell division occurs every 30 to 33 hours. At least 50 *T. pallidum* organisms are necessary to initiate infection; larger inocula shorten the incubation period. *T. pallidum* structure consists of outer and cytoplasmic membranes, a thin peptidoglycan layer, and 3 endoflagella that lie in the periplasmic space at each end and are responsible for motility.[19] The outer membrane contains a small number of poorly immunogenic transmembrane proteins (*T. pallidum* rare outer membrane proteins, or TROMP), but it does not contain lipopolysaccharide.[20] Highly antigenic lipoproteins (47, 34, 17, and 15 kd) are localized to the subsurface cytoplasmic membrane and are not exposed on the cell surface.[20,21] Host reaction to infection includes cellular and humoral immune responses with more than 60 specific antibodies identified by sodium dodecyl sulfate–polyacrylamide gel electrophoresis. Antibodies directed to the prominent, 47-kd treponemal antigen are the earliest detected by Western blot. Macrophages activated in the presence of specific antibody ingest and destroy large numbers of organisms.[22] However, it is unclear why this process and other immune reactivity hasten healing of the primary lesion but do not halt infection. Various hypotheses suggest that (1) a lack of antigenic reactivity in the outer membrane acts as an immunologic barrier, (2) a change in membrane-bound immunoproteins after dissemination allows organisms to evade antibody-mediated immunity, or (3) treponemes surround themselves with host material and thus delay the host cell response.

Spirochetes preferentially adhere to endothelial cells. Vasculitis with a predominance of mononuclear and plasma cells surrounding the involved vessels is typical of syphilitic lesions. In primary and secondary disease, infectious treponemes are demonstrated easily in lesions. These lesions heal completely, whereas tertiary lesions result in irreversible tissue destruction and fibrosis. Tertiary lesions consist of gummas and cardiovascular and central nervous system (CNS) disease. Gummas are large, granulatomous lesions with a central necrotic mass surrounded by plasma cells, lymphocytes, and monocytes; multinucleated giant cells are not present. Organisms usually are not found in these lesions, which are thought to represent a hypersensitivity phenomenon. Gummas occur in both acquired and congenital disease. Cardiovascular syphilis, another tertiary manifestation, is associated with pathologic changes in the proximal aorta that consist of inflammation-induced obliterative endarteritis of the vasa vasorum leading to medial necrosis. Although inflammatory changes begin in the early stages of infection, clinical manifestations appear 10 to 40 years later. Tertiary neurosyphilis is the result of chronic meningeal inflammation, which affects primarily the meninges but also can involve the brain and spinal cord.[23] Meningeal, meningovascular, parenchymatous, and gummatous neurosyphilis also occurs after untreated congenital infection.

Epidemiology

Syphilis is acquired by sexual contact (including oral sex)[24] and, extremely rarely, by other forms of close contact. Congenital syphilis is a consequence of undiagnosed, untreated, or inadequately treated maternal syphilis. The World Health Organization (WHO) estimates that more than 10 million new syphilis infections occur annually in adults, and more than 1.3 million pregnant women are infected with "active syphilis" each year.[25] Regional rates of seropositivity in pregnant women range from 0.06% in the Middle East to 2.13% in sub-Saharan Africa.

An understanding of transmission, the development of serologic tests to detect asymptomatic infections, and effective penicillin treatment led to a steady decline in the numbers of cases in Western Europe and the United States after a peak during World War II. Reported cases of syphilis in the US remained at low levels until 1986, when the number of cases increased sharply, with the epidemic peaking in 1990.[26] This epidemic was associated mostly with heterosexual transmission, poverty, use of crack cocaine, human immunodeficiency virus (HIV) infection, and minority (predominantly black) ethnic background. Primary and secondary syphilis rates declined from 1990 to 2000, but they have since doubled following the lowest ever rate in 2000.[27] Men accounted for most (91.1%) primary and secondary cases of syphilis in 2013, predominantly men who have sex with men (MSM).[28] However, heterosexual outbreaks continue to occur.[29,30] Geographic variations are seen, with the southern and the western US tending to have higher rates than the rest of the country. Syphilis rates differ among racial and ethnic groups; in 2013, compared with the white population, the rate of primary and secondary syphilis was sixfold higher in the black population and twofold higher in the Hispanic population.[31]

The prevalence of seroreactivity in pregnant women in the US generally is less than 1%. The syphilis epidemic of the early 1990s was associated with an increase in congenital syphilis in the US.[32] In 1988, the US Centers for Disease Control and Prevention (CDC) modified the criteria for case surveillance, which also contributed to increases in reports.[33] The number of cases of congenital syphilis declined after 1991[34]; it increased 23% from 2005 to 2008, primarily in the South,[35] and it fell again from 2009 to 2012. The 2012 nationally reported rate of 7.8 cases of congenital syphilis per 100,000 live births is the lowest recorded rate since 1988. Risk factors for maternal-to-child transmission include lack of prenatal care, first prenatal visit late in pregnancy, and lack of maternal screening and treatment. Because the most important risk is birth to a mother who received no prenatal care, tests for syphilis always should be offered when pregnant women with no record of prenatal screening seek any type of healthcare.[36]

Clinical Manifestations

Acquired Syphilis

Primary Syphilis

Untreated syphilis is a chronic disease evolving in 3 symptomatic stages. Primary syphilis follows approximately 30% of sexual exposures. The incubation period of 1 to 4 weeks is influenced by the number of organisms in the inoculum. The typical primary chancre is a single, painless papule that erodes to form an ulcer with a reddened base and rolled edges. A small inoculum may produce only a papule. Primary lesions can occur in both the genital and oral areas.[24] Women may not notice primary disease because a chancre in the vagina or on the cervix is not visible. Both men and women may ignore a visible lesion because it is painless (unless secondarily infected) and heals completely in 3 to 6 weeks. Painless nonsuppurative enlargement of local lymph nodes accompanies the chancre and can persist for months. Primary lesions contain infectious treponemes, and hematogenous dissemination begins within hours after superficial invasion of organisms and continues throughout primary and secondary disease.

Secondary and Latent Syphilis

Secondary syphilis is a systemic, multiorgan disease that begins 6 to 12 weeks after infection. In 15% of patients, the primary chancre is still present when symptoms of secondary disease begin. Mucocutaneous lesions are common, usually beginning on the trunk and eventually involving most of the body, including palms and soles. Salmon-pink macules, 5 to 10 mm in size, evolve to copper-colored papules that occasionally develop a follicular or pustular appearance. Untreated, skin lesions regress to hypopigmented or hyperpigmented papules that persist for months. Painless generalized lymphadenopathy is found in 85% of patients. In 10% of patients, raised, enlarged, broad, flat papules (condylomata lata) develop in warm, moist areas (vulva, anus, scrotum, and axilla). White-to-grey patches on mucous membranes also are detected in 10% of patients. Fewer than 10% of patients develop transient patchy alopecia and loss of other body hair, including eyebrows and beard, as a result of spirochetal invasion of hair follicles. Arthritis, osteitis, gastritis, hepatitis, splenomegaly, and nephrotic syndrome occur in some patients. CNS involvement is common in secondary syphilis, and, although it is usually asymptomatic, 1% to 2% of patients have acute meningitis. Lukehart and associates,[37] using the rabbit infectivity test (RIT), demonstrated that 40% of patients with early syphilis had either treponemes in the cerebrospinal fluid (CSF) or a reactive CSF Venereal Disease Research Laboratory (VDRL) test result. Common constitutional symptoms of fever, malaise, aches, pains, and sore throat are nonspecific; the diagnosis relies on serologic testing.

Even without treatment, complete resolution of secondary syphilis occurs after 3 to 12 weeks, and disease enters the latent phase. Early latent syphilis is defined as the first year after infection, and late latent syphilis is defined as more than a year after infection. Relapses of secondary syphilis occur in approximately 25% of untreated patients during early latent syphilis, but patients with late latent syphilis are asymptomatic. Although patients are asymptomatic, CSF examination is included in evaluation of latent syphilis because CSF abnormalities correlate with subsequent symptomatic tertiary neurosyphilis.[38] A study evaluating CSF findings in adults with syphilis (most with late latent syphilis and also HIV infection) showed that a serum rapid plasma regain (RPR) titer ≥1 : 32 was predictive of neurosyphilis in all patients, and a $CD4^+$ T-lymphocyte count of ≤350 cells/mm^3 was a second risk factor in adults with HIV infection.[39] Patients' immunity during late latency seems to protect against relapse, but it does not prevent progression of syphilis to the tertiary stage.

Tertiary Syphilis

Tertiary disease occurs in approximately 30% of untreated patients.

Manifestations are divided into 3 main subgroups: neurosyphilis, cardiovascular syphilis, and late benign syphilis (gummas).

Tertiary neurosyphilis includes several clinical syndromes: meningeal, meningovascular, and parenchymatous syphilis (including general paresis and tabes dorsalis). Manifestations appear within a few months of primary infection (meningeal syphilis) or 20 to 30 years later. Meningeal syphilis manifests as cranial nerve palsies, sensorineural deafness, and hydrocephalus. Meningovascular syphilis causes a stroke syndrome resulting from infarction secondary to syphilitic endarteritis, with the middle cerebral artery the most common site. The findings of general paresis can be summarized by the mnemonic PARESIS: personality; affect; reflexes (hyperactive); eye (Argyll Robertson pupils, which react to accommodation but not to light); and abnormalities of sensorium (illusions, delusions, hallucinations), intellect (decreased recent memory, orientation, judgment, insight), and speech.[40] Tabes dorsalis describes the symptoms and signs of demyelination of the posterior column and roots of the spinal cord. Patients can have more than one form of neurologic disease. Treatment can arrest the disease; however, the extent of underlying disease determines whether signs and symptoms resolve.

Cardiovascular syphilis, which occurs from 10 to 40 years after infection, is seen in 10% of patients with tertiary disease. An aneurysm in the ascending portion of the aorta, aortic insufficiency from aortic root dilation, and coronary artery disease are commonly recognized signs.

Benign tertiary syphilis refers to the presence of gummatous lesions in skin, bones, and, rarely, in other organs. Lesions vary in size from microscopic to clearly visible. Gummas are considered benign because they rarely involve vital body structures, but gummas can be destructive. Cutaneous gummas can ulcerate, and bone lesions are painful. Failure to treat or a delay in treatment is associated with disfiguring scars.

Syphilis Associated With Human Immunodeficiency Virus Infection

Syphilis and HIV infection exhibit “epidemiologic synergy,”[41] and coinfection is common.[42–44] The presence of HIV infection is thought to alter the clinical expression of syphilis, response to therapy, and the results of serologic tests.[41] Antibody titers can be higher than expected, but occasionally false-negative results or delayed seroreactivity can occur.[44] In addition, people with HIV infection and early syphilis can be at higher risk for both neurologic complications and treatment failure with currently recommended regimens.[45] Adults with neurosyphilis and HIV infection are less likely to revert from a reactive CSF VDRL test result than are adults without HIV infection.[46] Patients with syphilis should be tested for HIV infection and vice versa. Patients with coinfection require careful and more frequent follow-up.

Mother-to-Child Transmission

Transplacental transmission of syphilis can give rise to a range of adverse outcomes. A meta-analysis of 6 studies found that 52% of pregnancies in women with untreated syphilis led to adverse fetal-neonatal outcomes.[47] This percentage included 21% of pregnancies ending in fetal loss or stillbirth, 9% in neonatal death, and 6% in prematurity or low birth weight. Signs or symptoms of infection (i.e., congenital syphilis) occurred in 15% of maternal infections. These data confirm the findings in historical studies.[48–51] Preventing adverse outcomes of pregnancy (through screening and treatment) is most effective when interventions are delivered in the first 2 trimesters. Women who first attend antenatal care in the third trimester are more than twice as likely to have an adverse outcome compared with women screened and treated in the first 2 trimesters, and in the case of congenital syphilis the risk is almost threefold higher.[52]

Congenital Syphilis

Congenital syphilis is divided into early disease (detected at <2 years of age) and late disease (detected at ≥2 years of age). Most children with early disease are <3 months of age.

Transmission rates are higher (60%–90%) in untreated maternal primary or secondary syphilis, decreasing to 40% in early latent syphilis and to <10% in late latent syphilis. Placental and umbilical cord abnormalities are common; the placenta can appear pale and large, and immature villi and focal villitis with endovascular and perivascular proliferation are seen microscopically. Changes are not pathognomonic, although necrotizing funisitis within the matrix of the umbilical cord is considered highly indicative of syphilis. *T. pallidum* usually can be identified in tissue specimens by silver or immunofluorescent stains.

Early Disease

Congenital syphilis lacks a primary stage because it is a consequence of hematogenously disseminated *T. pallidum* and is similar to secondary syphilis. The typical stillborn or highly symptomatic newborn is born prematurely, has an enlarged liver and spleen, has skeletal involvement, and often has pneumonia (pneumonia alba) and skin lesions. Less severely affected infants have a variety of signs. Hepatomegaly is reported in almost 100%, and biochemical evidence of liver dysfunction usually is observed; serum alkaline phosphatase levels are elevated, but elevation of hepatic transaminase levels may occur only after treatment is initiated and an immune response occurs.[53] Approximately 40% to 60% of infected infants have 1 or more of the following: hepatosplenomegaly, rash, generalized lymphadenopathy, skeletal abnormality, or nasal discharge. The rash usually is maculopapular and initially erythematous, changing to a papular desquamating rash of coppery color and often involving the palms and soles. Petechial lesions, secondary to thrombocytopenia, also can be seen. Pemphigus syphiliticus is a rash unique to infected newborns and consists of vesiculobullous lesions, containing many organisms, that rupture easily and leave a macerated appearance.

Radiographic abnormalities are common in early syphilis; 95% of symptomatic infants and up to 20% with asymptomatic disease have bony abnormalities.[54] Lesions include metaphysitis, periostitis, and osteitis. Findings are symmetric and involve multiple long bones; the lower extremities are almost always affected. Metaphyseal lesions (osteochondritis) (Fig. 182.1A), which vary from punctate lucencies to more destructive changes, are seen earlier than periostitis. Wimberger sign ("cat bite") describes osteitis and destruction of the proximal medial tibial metaphysis (see Fig. 182.1B), and although it is occasionally seen in other conditions, this sign is highly suggestive of congenital syphilis. Occasionally, the lesions are painful, resulting in pseudoparalysis of the affected limb (pseudoparalysis of Parrot). Periostitis appears radiographically as multiple layers of periosteal new bone formation.

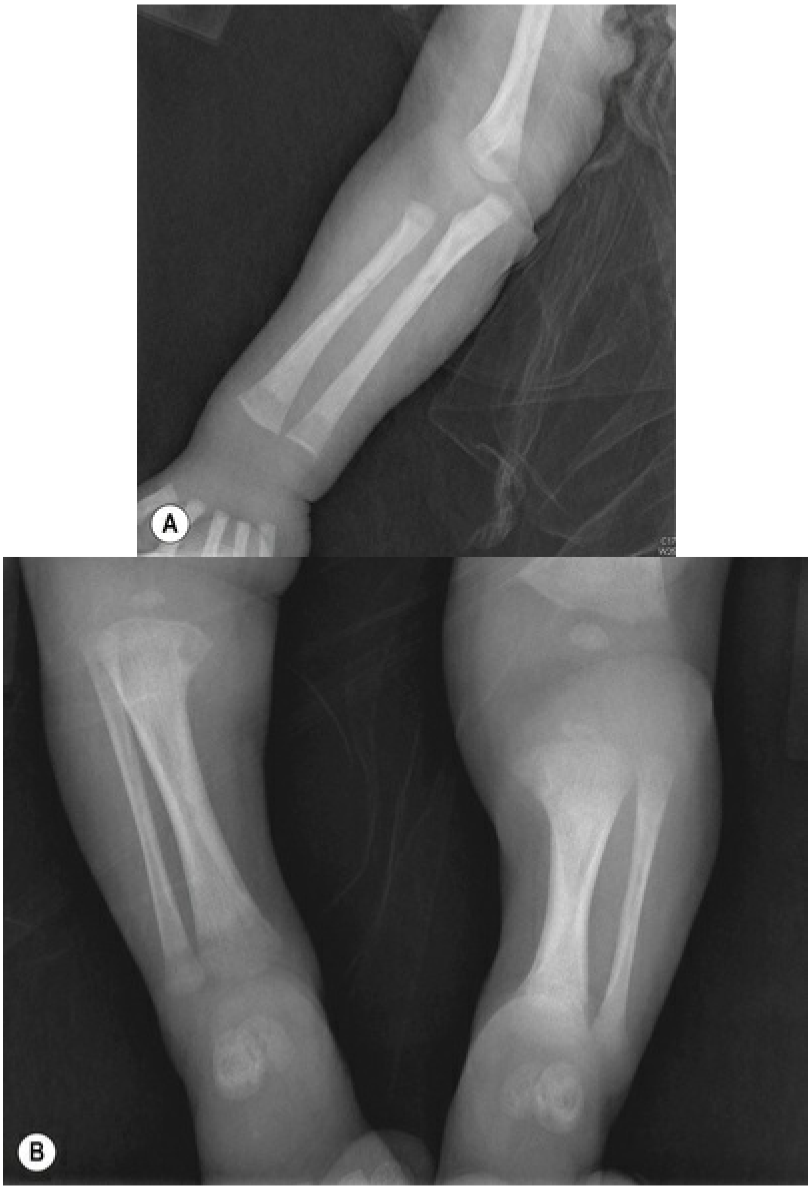


FIGURE 182.1 **Plain radiographs of an infant with congenital syphilis. Note decreased mineralization of the metaphyses of long bones of the (A) upper and (B) lower extremities, as well as bilateral lytic lesions of the talus, calcaneus, and (B) proximal tibia (Wimberger sign) medially.** **(Copyright by J. H. Brien ©.)**

The CSF is abnormal in 50% of symptomatically infected infants and in up to 10% of asymptomatic infants. The diagnosis of neurosyphilis is made with a reactive CSF VDRL test result or with abnormal elevation of CSF white blood cell (WBC) count or protein levels (although the definition of “abnormal” varies).[41] However, this standard for diagnosing congenital neurosyphilis is insensitive in comparison with RIT.[55] Although no single laboratory test identifies all patients with neurosyphilis as confirmed by RIT, most infants with neurosyphilis are identified by conventional testing (physical examination, complete blood count, bone radiography, and lumbar puncture); the addition of immunoglobulin M (IgM) immunoblotting and polymerase chain reaction (PCR) tests identifies almost all others. Even when CSF is abnormal, neurologic symptoms or signs usually are absent. Rhinitis, or “snuffles,” occurs rarely now and consists of a clear nasal discharge (containing many spirochetes) that becomes chronic and turns bloody as a result of mucosal erosion. Nephrotic syndrome, which occurs less commonly than other manifestations, is caused by immune complex disease rather than by direct invasion by treponemes.[56] Hematologic disturbances are seen in symptomatic infection; more than 75% of infants have anemia, and 50% have an elevated WBC count with significant monocytosis.

The appearance of symptomatic congenital syphilis after discharge from the nursery most often is caused by a failure to perform maternal serologic testing at delivery or to obtain results of serologic tests before discharge. Infants born to recently infected mothers whose serologic test results are negative at delivery escape detection until these children become symptomatic. In such cases, onset of symptoms before 3 months of age is expected, with a spectrum of disease similar to that seen in symptomatic newborn infants, except that fever can be a prominent initial complaint.[57]

Late Disease

Late congenital disease is seen in patients ≥2 years of age and is not considered contagious. Malformations in bones (frontal bossing, saddle nose [a result of osteochondritis], and saber shins), teeth (Hutchinson peg-shaped, notched central incisors, mulberry multicusped first molars), and skin (rhagades, or linear scars, fanning out from the corner of the mouth) result from growth disturbances in these organs. Other manifestations (e.g., interstitial keratitis and eighth nerve deafness) result from longstanding chronic inflammation. Symmetric, chronic painless swelling of the knees (Clutton joints) has been described in a few affected patients. Asymptomatic neurosyphilis is more common in these children than is symptomatic disease. Pathologic changes in the nervous system and mental, motor, and sensory deficits are similar to those seen in acquired tertiary disease. During the 19th century, Hutchinson noted that the triad of defects in the incisors, interstitial keratitis, and eighth nerve deafness was unique to congenital syphilis. A more recent review, encompassing 271 cases of congenital syphilis, reconfirmed the pathognomonic constellation.[58]

Diagnosis

Antibody Tests

Serologic testing is the standard method to identify asymptomatic infection and confirm clinical diagnosis. Seroreactivity is present in all stages of disease but cannot be used to distinguish among stages. Serologic tests include nontreponemal and treponemal tests. The traditional algorithm for testing is a nontreponemal test followed by treponemal test.

Nontreponemal Tests

Nontreponemal tests are performed easily and detect IgM and IgG antibodies to cellular lipids and lecithin. The 2 commonly used nontreponemal tests are the RPR test and the VDRL test. Reactive sera produce flocculation of the antigenic material. Nontreponemal antibodies appear from 4 to 8 weeks after infection; seroreactivity is present in 70% of patients within 2 weeks of the eruption of a chancre and in 100% of patients who have secondary and latent disease. No nontreponemal serologic test is reactive in the first weeks of infection. Nontreponemal tests can be quantified by serial serum dilution; a 2-tube (fourfold) change or more in reactivity is significant. A fourfold to eightfold decrease in titer 6 to 12 months after successful treatment is expected for all patients with early disease (primary and secondary), with a slower decline in treated patients with later stages of disease.[59] A titer that does not fall or that rises after an initial significant decline indicates inadequate therapy or new infection. Seroreversion to negative occurs after treatment in some patients and depends on the original titer and the stage of disease during therapy.[59] For other patients, titers fall significantly but persist at low levels; such patients are considered to be serofast. Untreated people remain seroreactive for life, although titers fall with time even without treatment. The VDRL test is primarily used for testing CSF (and is the only test approved for testing CSF). A false-positive nontreponemal serum test result usually has a titer ≤1 : 4 and can occur in patients with connective tissue disorders, in patients with viral diseases (e.g., hepatitis, chickenpox, and infectious mononucleosis), in approximately 10% of injecting drug users, and, occasionally, in pregnancy. The prozone effect describes a false-negative reaction that results from excess antibody concentration that inhibits formation of the antigen-antibody lattice needed for flocculation. This effect is overcome by serial serum dilutions. The prozone effect must be considered when a neonate shows signs of congenital syphilis and the mother is seronegative. Nontreponemal tests are useful for screening and monitoring therapy. Treponemal tests are required for confirmation that the nontreponemal reactivity is caused by syphilis or another treponemal infection.

Treponemal Tests

Older treponemal tests include the fluorescent treponemal antibody-absorbed test (FTA-ABS), the microhemagglutination test for *T. pallidum* (MHA-TP), and the *T. pallidum* particle agglutination test (TP-PA). Characteristics of treponemal tests are positivity slightly earlier than nontreponemal tests, positivity for life, and an inability to reflect activity of infection. False-positive treponemal test results can occur in various conditions, especially spirochetal infections, including Lyme disease (in which the nontreponemal test shows negative results).[60] Newer treponemal assays, including enzyme immunoassays (EIAs),[61,62] chemiluminescence immunoassays (CIAs), and recombinant *T. pallidum* antigen tests[63] are automated and easily adapted for population-level screening. In so-called reverse sequence testing, an automated treponemal test is used for screening (EIA/CIA), followed by confirmation testing in reactive specimens by using a second different treponemal test and a quantitative RPR or VDRL test.[64,65] The details of reverse sequence testing vary between Europe and North America.[65–67] Reverse sequence testing is not recommended by the CDC.[41,67] An analysis by the CDC of data from 5 laboratories from 2006 to 2010 showed significant discordant results, with 57% of patients with positive treponemal EIA/CIA results having a nonreactive RPR test; among these patients, 32% did not have a confirmatory TP-PA test result.[67] Reverse sequence testing increases false-positive results (particularly in low-prevalence populations), and it can be more expensive because of the increased number of confirmatory tests, follow-up, and overtreatment.[67–71] In many resource-poor settings a new generation of point-of-care treponemal tests, which use whole blood, have been evaluated and are being promoted as a component of syphilis control programs among higher-risk populations, as well as in prenatal care services (e.g., as initial screening tests with a nontreponemal test as confirmatory).[72–74]

Tests for Organisms

The most sensitive diagnostic method for identifying viable treponemes in CSF and exudate is the RIT,[75] which involves serial passage of infected material in the testes of rabbits. Although not clinically useful, this test is the gold standard for measuring infectivity and for determining the sensitivity of other *T. pallidum* detection methods, including newer tests such as PCR.[55] Darkfield microscopy can be used to examine exudates; motile organisms too thin to be seen by light microscopy can be visible. Drawbacks include the need for specialized equipment, personnel skilled in its use, and urgency of examination before drying immobilizes treponemes.

Treponemes in tissue specimens can be visualized with silver stain, but fluorescent antibody or immunohistochemistry tests are more specific. The direct fluorescent antibody *T. pallidum* (DFA-TP) test uses a fluorescein-labeled rabbit or monoclonal *T. pallidum* antibody for identifying organisms in body fluids and exudate, and it has been modified for use on biopsy and autopsy material.[76] Newer PCR tests have high sensitivity and specificity but may not be readily available commercially.[77–79]

Diagnosis of Congenital Syphilis

Definition

To optimize testing and to maximize treatment of potentially infected infants, the CDC developed a broad definition of congenital syphilis. A *confirmed* case is one with laboratory confirmation.[80] A *presumed* case (symptomatic or asymptomatic) is as follows: (1) an infant born to a mother with reactive serologic test results whose mother was not treated, was inadequately treated, or was treated <1 month before delivery; or (2) an infant who has physical signs, CSF abnormalities, or evidence of congenital disease on skeletal radiographs.[33,80] The definition of a presumed case of congenital syphilis ensures that all patients with possible cases are treated, although all may not be infected.

The WHO defines congenital syphilis as follows: (1) a stillbirth, live birth, or fetal loss at >20 weeks of gestation or >500 g to a syphilis-seropositive mother without adequate syphilis treatment; or (2) a stillbirth, live birth, or child <2 years of age with microbiologic evidence of syphilis infection, which includes any 1 of the following: demonstration by darkfield microscopy or fluorescent antibody detection of *T. pallidum* in the umbilical cord, the placenta, nasal discharge, or skin lesion material; detection of *T. pallidum*–specific IgM in serum; or a positive serologic nontreponemal titer at least fourfold that of the mother.[81]

Both the CDC and WHO definitions include a range of outcomes of pregnancy in women with positive syphilis serologic results; in other words, syphilis should be considered not only in live-born infants, but also in stillbirths and any fetal loss after 20 weeks of gestation (with a fetal weight >500 g). Treatment should include the mother, her sexual partner or partners, and infants as appropriate.[82]

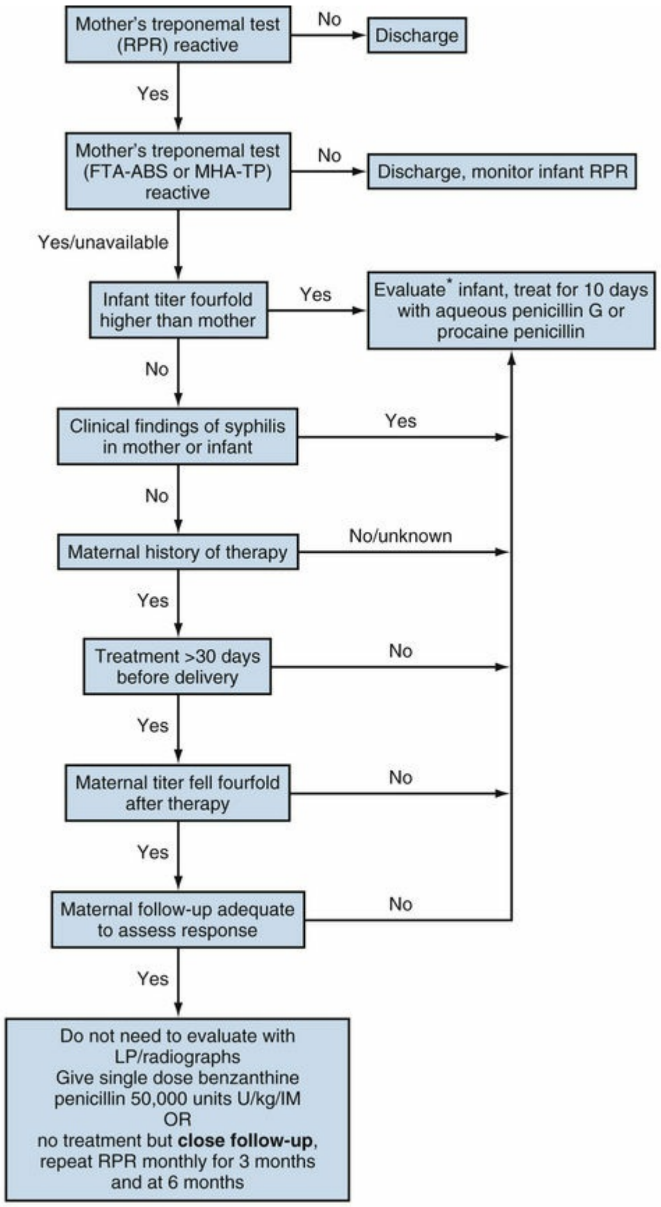
Testing Considerations

A screening test for syphilis should be performed at the first antenatal visit and repeated at delivery. In high-risk patients, an additional serologic test at the beginning of the third trimester also is suggested.[83] In 1 report, 13% of women found to be seroreactive at delivery were seronegative earlier in the pregnancy.[57] Sexual partners of syphilis-seropositive women also should be offered treatment.

Several problems confound the diagnosis of congenital syphilis, particularly in an asymptomatic infant. Results of any nontreponemal or treponemal test performed on the infant may reflect maternal antibody titers and do not prove congenital infection.[84,85] Passively acquired nontreponemal antibody usually reverts to negative by 6 months, whereas treponemal antibody can persist for 1 year or longer. An infant treated for congenital syphilis could have similar test results. Children who retain reactive nontreponemal and treponemal antibody at 18 months of age or older should be re-evaluated (see the later section on acquired syphilis).[86] Treponemal IgM tests can identify the infant's production of antibodies (i.e., congenital infection), but not every infant with congenital syphilis produces IgM antibodies.[87] Identification of treponemes in lesions, or in the placenta or umbilical cord, can identify infected infants, but these findings are not seen in every infected infant, and the tests are not available readily. Additional tests, such as CSF VDRL and skeletal radiographs, can identify infected asymptomatic babies, but the sensitivity of these tests is not known.

Evaluation

The evaluation of each newborn infant whose mother has a positive serologic test result for syphilis requires careful and individualized attention (Fig. 182.2). The CDC recommends that all infants born to seroreactive mothers should have a quantitative nontreponemal serum test performed (because umbilical cord blood can be falsely positive or negative).[41,85] In addition to obtaining the maternal history, all infants born to seroreactive mothers should be examined for physical evidence of congenital syphilis (e.g., hepatosplenomegaly, rash). Examination of the placenta and umbilical cord by a pathologist using direct fluorescent antibody is suggested. Additional tests to evaluate congenital syphilis (CSF analysis by VDRL, WBC count, protein level, long bone radiographs, complete blood cell count, and serum hepatic enzyme levels) should be performed if the infant is suspected of having congenital syphilis or has any abnormal physical findings.


Mother's treponemal test (RPR) reactive
No
Discharge
Yes
Mother's treponemal test (FTA-ABS or MHA-TP) reactive
No
Discharge, monitor infant RPR
Yes/unavailable
Infant titer fourfold higher than mother
Yes
Evaluate* infant, treat for 10 days with aqueous penicillin G or procaine penicillin
No
Clinical findings of syphilis in mother or infant
Yes
No
Maternal history of therapy
No/unknown
Yes
Treatment >30 days before delivery
No
Yes
Maternal titer fell fourfold after therapy
No
Yes
Maternal follow-up adequate to assess response
No
Yes
Do not need to evaluate with LP/radiographs
Give single dose benzanthine penicillin 50,000 units U/kg/IM
OR
no treatment but **close follow-up**, repeat RPR monthly for 3 months and at 6 months

*Evaluation includes physical examination, pathologic study of placenta (with direct fluorescent antibody [DFA] test, if possible) and cerebrospinal fluid (including Venereal Disease Research Laboratory [VDRL] test, white blood cell count, protein levels), complete blood cell count, and other tests as clinically indicated (e.g., long bone and chest radiographs, liver function tests, cranial ultrasonography, ophthalmologic examination, and auditory brainstem response).

FIGURE 182.2 Assessment and management of congenital syphilis. FTA-ABS, fluorescent treponemal antibody-absorbed test; IM, intramuscularly; LP, lumbar puncture; MHA-TP, microhemagglutination test for *Treponema pallidum*; RPR, rapid plasma reagin. (Data from Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep 2010;59[RR-12]:26–39; and American Academy of Pediatrics. Syphilis. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS [eds]. Red Book: 2009 Report of the Committee on Infectious Diseases, 28th ed. Elk Grove Village, IL, American Academy of Pediatrics, 2009, pp. 638–651.)

Unfortunately, confirming a diagnosis of congenital syphilis has not improved in the US because validated serologic tests for *T. pallidum* IgM antibodies, and tests for treponemal antigens or DNA, have not become available widely. Despite carefully designed screening programs, some neonatal infections are missed because recently acquired maternal infection can be associated with seronegativity at birth in both mother and neonate.[57]

Diagnosis of Acquired Syphilis in Children

Children can acquire syphilis after the neonatal period, predominantly from sexual abuse, but this is rare.[88] Adolescents can acquire syphilis through sexual activity, and they should be evaluated and managed as appropriate for the stage of syphilis. In younger children, determining whether syphilis is congenital or acquired can be difficult in the absence of physical findings or a clear history.[89,90] Similarly, children immigrating from areas of the world endemic for other treponematoses who have reactive serologic tests pose a diagnostic problem.[91] Differentiating yaws from syphilis (both congenital and acquired) may not be possible, even if additional information is available. Important information that can help in decision making include the maternal history of syphilis, titer results and treatment during pregnancy, maternal and infant titers, and evaluation and treatment for congenital syphilis at birth. If the child has no physical findings, a reactive nontreponemal test result (confirmed by treponemal test) can indicate either congenital or acquired disease. In such a case, the child should be evaluated fully for congenital syphilis, including lumbar puncture to evaluate for possible neurosyphilis, skeletal radiographs, an eye examination, and complete blood cell count. Positive results on an FTA-ABS test can persist in infants appropriately treated for congenital syphilis at birth.[86] If the nontreponemal test result is negative, further workup is not recommended; however, if the nontreponemal test result is positive at ≥18 months, the infant should be re-evaluated fully and treated for congenital syphilis.

Treatment and Follow-Up

Syphilis has been treated successfully since the late 1940s using penicillin. Treatment regimens are updated regularly by the CDC (http://www.cdc.gov/std/treatment), and the American Academy of

Pediatrics[83] (Table 182.1).[41,92] Treatment failures are uncommon; more than 95% of otherwise healthy patients with primary disease and approximately 90% of patients with secondary and early latent disease are cured with a single injection of benzathine penicillin G. Failure to cure acquired disease may be more common in patients with symptomatic secondary disease and in patients infected with HIV infection. However, the data suggesting a different response to syphilis treatment in HIV-infected patients is largely from the pre-antiretroviral treatment era.[37,45,93] Data that include HIV-infected patients receiving antiretroviral treatment show a good response and reduced failure of recommended therapy,[94,95] although patients with syphilis and HIV infection should still be closely monitored for appropriate treatment response.[96,97]

TABLE 182.1
Syphilis Therapy

Condition	Treatment[a]	Comments
ACQUIRED DISEASE		
Primary, secondary, early latent disease (normal host)	Adults: 2.4 million U BPG × 1 Children: 50,000 U/kg BPG × 1	Penicillin-allergic adult can be treated with doxycycline 100 mg bid for 2 wk or tetracycline 500 mg orally q6h; penicillin-allergic child (<age 8 yr) should be desensitized and treated with penicillin
Late latent disease, disease of unknown duration, gumma, aortitis	Adults: 2.4 million U BPG weekly × 3 Children: 50,000 U/kg BPG weekly × 3	Penicillin-allergic adult can be treated with doxycycline 100 mg bid or tetracycline 500 mg q6h orally for 28 days Perform lumbar puncture if neurologic or ophthalmologic signs or symptoms, active tertiary syphilis or treatment failure; if CSF is abnormal, treat for neurosyphilis
Neurosyphilis	Adults: 18–24 million U/day APG, divided into q4h doses (3–4 million U/dose) or continuous IV infusion for 10–14 days; or APPG 2.4 million U once daily IM and probenecid 500 mg 4 times daily for 10–14 days	Penicillin-allergic patients should be desensitized and treated with penicillin
	Children: 200,000–300,000 U/kg/day APG divided into q4–6h doses for 10 days	
Pregnancy	Treat as for acquired disease; see text	Penicillin is the only drug used in pregnancy; penicillin-allergic patients should be desensitized and treated with a 10-day course of APG
HIV infection	Treat as for acquired disease; see text	Perform lumbar puncture for same indications as for late latent disease; strongly consider lumbar puncture if serum

		nontreponemal antibody titer does not fall fourfold 6–12 months after therapy; if CSF is abnormal, treat for neurosyphilis; if penicillin-allergic, desensitize and treat with APG penicillin
CONGENITAL DISEASE	≤4 wk of age: 100,000 U/kg/day APG IV divided into q12h doses during first 7 days of life and 150,000 U/kg/day APG divided into q8h doses thereafter for total of 10 days *or* 50,000 U/kg once/day APPG IM × 10 days >4 wk of age: 200,000–300,000 U/kg/day APG divided into q4–6h doses × 10 days	See text

[a] Children who weigh >50 kg are treated with adult dosing schedule.

APG, aqueous penicillin G; APPG, aqueous procaine penicillin G; BPG, benzathine penicillin G; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; IV, intravenous(ly); IM, intramuscularly.

From Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep 2010;59(RR-12):26–39.

Prenatal treatment that has effectively cured maternal disease sometimes fails to prevent adverse pregnancy outcomes.[98,99] In 1 report, 60 (14%) of 437 infants with congenital disease were born to mothers who were treated during pregnancy.[99] Failures were highest with treatment in the third trimester, especially in the month before delivery. Failure of maternal treatment also is associated with preterm delivery.[100] Pregnant patients should be treated only with penicillin regimens, appropriate for the stage of syphilis.

Patients with congenital infection, either proved or presumed, are treated with a 10-day course of aqueous penicillin G or procaine penicillin G. Azimi and colleagues[101] noted that, in some neonates, the level of penicillin in CSF 18 to 24 hours after a dose of procaine penicillin G was lower than that considered to be treponemicidal; these investigators suggested that, for infants with severe or proven CNS disease, aqueous penicillin G could be superior therapy. CDC guidelines suggest that benzathine penicillin G could be used when the risk of congenital syphilis is low (i.e., a well infant with a normal examination born to a mother treated in the month before delivery). However, the development of congenital syphilis in some infants whose mothers were treated toward the end of pregnancy and the failure of benzathine penicillin G to cure early congenital syphilis suggest that such infants could optimally be treated with a 10-day regimen of aqueous or procaine penicillin G.[98,99,102] In the future, tests currently under investigation to detect the presence of spirochetes or spirochetal DNA in CSF should better determine CNS infection and provide a more precise basis for therapy.[103]

Patients who are allergic to penicillin but not pregnant can be given tetracycline or doxycycline for early, latent, and tertiary disease that has not affected the CNS. Because oral tetracycline or doxycycline must be given daily for 2 weeks, it should be used only when adherence and follow-up are ensured. Children with acquired syphilis who are <8 years of age, pregnant women, HIV-infected patients, and adults with later stages of syphilis or tertiary disease who are allergic to penicillin should be desensitized and treated with penicillin.[41] Although single-dose azithromycin in the treatment of early syphilis showed equivalent treatment efficacy compared with the recommended penicillin regimen,[104] macrolide resistance has been identified in *T. pallidum* in several geographic areas (associated with mutations in the 23S rDNA [A2058G and A2059G]).[105–108] In addition, treatment failures resulting in congenital syphilis have been reported with the use of azithromycin in pregnant women.[109] Macrolides are not an acceptable alternative therapy for penicillin-allergic pregnant women.

The Jarisch-Herxheimer reaction, the major complication of therapy, occurs most commonly among patients with early syphilis, both children and adults. Fever is the major symptom and can be accompanied by headache and myalgia. Hypotension, tachycardia, and an increase in respiratory rate occur in some patients. During pregnancy, the Jarisch-Herxheimer reaction can cause uterine contractions and decreased fetal activity, and occasionally it can result in premature delivery or fetal death.[110]

Patients with primary, secondary, or early latent syphilis should be re-examined clinically and serologically at 6 and 12 months after therapy. Late latent syphilis requires a further re-examination at 24 months after therapy. Patients with HIV infection and syphilis require careful clinical and serologic follow-up at 3, 6, 9, 12, and 24 months after therapy for early syphilis and at 6, 12, 18, and 24 months for patients with latent syphilis. Infants with congenital syphilis and all seroreactive infants, regardless of infection status, should be examined and have repeated quantitative nontreponemal tests every 2 to 3 months until nonreactivity is documented.

Prevention

Prevention of congenital syphilis requires a multifaceted approach,[111,112] including the following: (1) information, education, and counseling regarding syphilis transmission and prevention (including promotion of safer sexual activity); (2) adequate and equitable health systems, including access to comprehensive reproductive and sexual healthcare for those at highest risk of infection; (3) partner management (notification and treatment) for all sexual partners of primary patients; (4) early access to prenatal care for all pregnant women, including syphilis testing at the first visit and at the time of delivery, and adequate treatment; (5) detection and treatment of congenital infection before appearance of symptoms; and (6) recognition and treatment of symptomatic infection when it occurs after the neonatal period. A systematic review and meta-analysis of implementing these types of interventions showed that the syphilis-attributable incidence of stillbirth and perinatal death could be reduced by 50%.[74]

Key Points

Epidemiology, Clinical Features, Diagnosis, and Treatment of Syphilis

Epidemiology

- Worldwide
- Epidemiology variable by geographic region, by sexuality (more common in US in men who have sex with men), and among some minority populations
- Acquired transplacentally (mother to child transmission) or by sexual contact

Clinical Features

- Primary stage: painless genital chancre with regional lymphadenopathy

- Secondary stage: disseminated disease with rash (especially palms and soles), constitutional symptoms, condylomatous lesions

- Tertiary stage: cardiovascular, neurologic, gummas

- Mother-to-child transmission results in stillbirth, late fetal loss, low birth weight baby, neonatal death, and infant with congenital syphilis.

- Early congenital syphilis (<2 years): symptomatic (hepatosplenomegaly, small for gestational age, rash, bone, cerebrospinal fluid findings), or asymptomatic

- Late congenital syphilis (≥2 years): bone or dental findings, hearing loss

Diagnosis

- Serology: nontreponemal test (RPR, VDRL) for screening and to follow adequacy of treatment; treponemal test (FTA-ABS, TP-PA) for confirmation of positive nontreponemal test result as caused by syphilis

Treatment

- Penicillin

- Alternative: doxycycline (≥8 years old and not pregnant)

- Follow nontreponemal titers to monitor for success (i.e., fourfold decrease in titer)

Prevention

- Promote comprehensive sexuality education and safer sexual practice (e.g., use of barrier methods)

- Treat infected people and sexual partners

- Screen all pregnant women at first antenatal visit; treat and follow infected women

FTA-ABS, fluorescent treponemal antibody-absorbed test; RPR, rapid plasma reagin; TP-PA, *Treponema pallidum* particle agglutination; VDRL, Venereal Disease Research Laboratory.

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Other *Treponema* Species

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Yaws

Yaws (*Treponema pallidum* subsp. *Pertenue* infection) is an infectious disease of childhood. It is seen in warm, humid tropical regions in rural, often inaccessible areas, associated with poverty, overcrowding, poor hygiene, and lack of access to health services. "Yaws begins where the road ends."[1] Endemic areas include Africa, Southeast Asia, the Western Pacific, and South and Central America.[2] Yaws is also known as framboesia, pian, parangi, paru, bouba, and buba.

Mass treatment campaigns of approximately 50 million people in the 1950s and 1960s eradicated yaws from many areas. However, a resurgence of the disease occurred in the 1980s, particularly in parts of West and Central Africa and Southeast Asia.[3,4] The successful yaws eradication campaign in India[5] renewed energy and efforts to eliminate yaws worldwide. In 2012 the World Health Organization (WHO) devised the Morges Strategy to eradicate yaws by 2020.[6] This plan includes treating entire communities with 1 dose of azithromycin with close follow-up for 3 years with serosurveys and retreatment if necessary. A successful mass treatment campaign in Papua New Guinea using this strategy strongly supports this approach.[7]

Clinical Manifestations

Yaws is passed from child to child through nonsexual contact with primary or secondary skin lesions. The primary lesion, the mother yaw, generally occurs on the lower half of the body at sites of minor trauma. The lesion begins as a painless, erythematous papule that enlarges, ulcerates, and becomes covered by a honey-colored crust 9 to 90 days after inoculation. Painless, regional lymphadenopathy occurs. The primary lesion heals after several weeks to months.

Organisms disseminated during the primary stage form the basis of secondary disease. This stage manifests as multiple cutaneous lesions (daughter yaws), which resemble the mother yaw both clinically and histologically but are smaller, as well as painful periostitis involving bones of the extremities, especially the hands and feet. Secondary lesions heal spontaneously and without scarring.

The pathologic features of primary and secondary lesions resemble those seen in sexually acquired syphilis. Latent yaws is characterized by intermittent relapses of skin lesions at intervals for up to 5 years, but congenital infection is not seen. Experimental infections of guinea pigs have confirmed the lack of congenital infection in yaws.[8]

Tertiary yaws, which develops in approximately 10% of untreated patients after several years, consists of destructive lesions of bone, cartilage, soft tissue, and skin. Characteristic findings are as follows: palmar-plantar hyperkeratosis; goundou, a rare lesion in which symmetric involvement of the nasal processes of the maxilla leads to excessive bone formation and obstruction of the airway; gangosa (destructive ulcerative rhinopharyngitis); and chronic osteitis leading to saber tibia.

Diagnosis

In endemic areas, the diagnosis is made clinically. In addition, treponemes are identified easily with darkfield microscopy of exudate from primary and secondary lesions, and serologic tests for syphilis are reactive. Point-of-care tests that detect both treponemal and nontreponemal antibodies appear promising.[9] Polymerase chain reaction testing also can be used to identify *T. pallidum pertenue,* as well as macrolide resistance,[10] but this test is not readily available clinically. The Centers for Disease Control and Prevention has recommended screening children who come from areas of the world with endemic treponematoses by using nontreponemal serologic tests.[11]

Endemic Syphilis (Bejel)

Endemic syphilis (bejel), caused by *Treponema pallidum* subsp. *endemicum,* is found in areas with a hot, dry climate in North Africa, Southwest Asia, and the eastern Mediterranean. Until 1960, this disease also was present in Bulgaria and the former country of Yugoslavia; a treatment and prevention program eliminated these foci.

Infection occurs in childhood and is acquired from contaminated fomites (e.g., communal drinking vessels) or through oral-oral contact. The primary lesion, a small, painless papule or ulcer in the mouth, usually is not detected. The secondary stage, resulting from treponemal dissemination, is characterized by numerous, highly infectious mucous membrane patches, often accompanied by hoarseness from syphilitic laryngitis, and regional lymphadenopathy. Axillary and anogenital condylomata can be seen, and osteoperiostitis of the long bones can cause nocturnal leg pain.

After a latent period, untreated bejel progresses to tertiary symptoms in most patients; sometimes it is characterized by destructive lesions (gummas) involving the nasopharynx, skin, and bones, but involvement of other organs, including the eye, can occur. As living conditions improve in endemic areas, a form of the disease has been observed in which the number of lesions and the signs and symptoms are less severe.

The disease has some similarities to sexually acquired syphilis. However, the method of acquisition, the site of the primary lesion, the lack of congenital disease, and the absence of cardiovascular and neurologic symptoms in endemic syphilis differentiate the 2 diseases. When symptoms consistent with either endemic syphilis or venereal syphilis occur in an area where both diseases exist, epidemiologic features of an outbreak can be useful for differentiation.

Pinta

Pinta (*Treponema carateum* infection), which occurs only in the Western Hemisphere, has been described in Central and South America, Cuba, and the Caribbean islands. Control with penicillin has made pinta a rare disease. Pinta begins during childhood and adolescence, and the clinical stages are confined to the skin, with lymphadenopathy the only systemic manifestation. The word *pinta* is taken from the Spanish verb to paint and is indicative of the various colors seen as the skin lesions mature: red, white, violet, blue, brown, or black.

Pinta is transmitted through contact with broken skin, and the primary lesion occurs mainly on the lower leg, dorsum of the foot, forearm, or back of the hands. One to 8 weeks after inoculation, a tiny erythematous papule or cluster of papules appears and then enlarges and coalesces. An irregular and heaped border surrounds the erythematous, scaly central lesion. Dissemination from the primary site results in secondary skin lesions known as *pintids,* which develop 3 to 9 months after the initial inoculation and before the primary lesion has healed completely. Secondary lesions are indistinguishable clinically and histologically from the primary lesion.

Primary and secondary lesions are highly contagious and heal slowly. Three months to many years later, tertiary disease manifests as achromic, atrophic lesions. These lesions are not considered infectious.

Treatment

Treatment of all nonvenereal treponematoses once was the same, namely a single dose of benzathine penicillin (1.2 million units for adults and 0.6 million units for children younger than 10 years of age). Family members, contacts, and patients with latent infection also receive the same dose as those with active disease. Later treatment results in slower healing, and serologic reactivity can persist.

Newer, alternative therapies for yaws have been studied. In Guyana, oral penicillin V therapy for 7 to 10 days appeared promising.[12] The most promising newer oral therapy is a single dose of azithromycin (30 mg/kg; maximum dose 2 g), which was shown to be noninferior to benzathine penicillin.[13] A mass treatment campaign using this regimen has been successful,[7] and it demonstrated that the Morges Strategy[6] (which includes azithromycin therapy) is an effective approach to reach the WHO yaws eradication goal by 2020.[14] Because of the concern that macrolide resistance may develop (as has occurred in *T. pallidum* subsp. *pallidum* infection in some areas), surveillance for macrolide resistance during mass treatment campaigns will be needed as part of the eradication plan.[15]

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Leptospira Species (Leptospirosis)

Eugene D. Shapiro

Pathogenesis

The *Leptospira* genus consists of a group of motile, finely coiled, catalase-producing spirochetal bacteria that are obligate aerobes. The *Leptospira* genus is classified into at least 20 species and genomospecies. *L. biflexa* is a free-living saprophytic organism that is found in water and soil and does not cause human disease. At least 8 other species, *including L. interrogans,* are highly pathogenic for humans, and several others are intermediately pathogenic. Serologic classification is important because specific serogroups (>25) and serovars (>250) are associated with specific animal species and vary in their pathogenicity and virulence for humans. The application of molecular genetic techniques to understanding the biology of the organism and the mechanisms by which *Leptospira* organisms are pathogenic for humans is beginning to provide new insights into this ancient disease.[1] Stimson, who first saw the organism under the microscope in 1907, named it *interrogans* because it was shaped like a question mark.

Pathogenic *Leptospira* organisms infect humans through intact mucous membranes or disrupted skin, invade the bloodstream, and disseminate rapidly to multiple organs. Although the precise mechanism by which *Leptospira* causes disease has not been defined, tissue injury is apparently mediated by direct effects of the bacterium.[1]

Leptospira organisms have a predilection for infecting the liver and kidney, although any tissue can be infected. The organism causes hepatocellular dysfunction, which can lead to jaundice, in most instances without producing necrosis. The bacteria also can cause renal tubular dysfunction resulting in renal failure and hemorrhagic vasculitis. The signs and symptoms of leptospirosis during the initial "septicemic" phase of illness are caused by a direct effect of the organism; inflammation during the second or "immune" phase of the illness is related to antigen-antibody complexes.

Epidemiology

Leptospirosis is a zoonosis,[2] and infection with *Leptospira* is widespread in both wild and domestic animals throughout the world.[3] Humans, who are incidental hosts, rarely transmit the organism to other humans or to animals and are unimportant in the maintenance of *Leptospira* in nature; concentrations of bacteria in the urine of infected humans are not sufficient to lead to transmission of the organism. By contrast, *Leptospira* can be shed in the urine of wild animals such as rodents (particularly mice and rats) and by domestic animals such as dogs, cows, and pigs for long periods. Such animals serve as reservoirs for the organism and, because of their close association with people, are the sources of most human infections.

The epidemiology of human leptospirosis largely is determined by the nature of the contact between humans and infected animals and the level of sanitation in the community. In the United States, most cases are reported from the southern states, which may reflect high year-round potential for exposure.[4] In developing countries, rats are the primary reservoir for leptospirosis. In the US, dogs and farm animals are important reservoirs in addition to rats.[4] However, *Leptospira* organisms also have been identified in many wild mammals such as raccoons, foxes, skunks, opossums, and wolves.[4] Although any animal can be infected with any serovar of *Leptospira,* certain serovars seem to infect certain species preferentially. For example, *L. interrogans* serovar *pomona* is isolated most frequently from cows and pigs, serovar *canicola* from dogs, and serovar *icterohaemorrhagiae* from rats and mice. The prevalence of infection in certain animal species is high. Up to 90% of Norway rats have been found to be infected with *L. interrogans;* once infection is established in rats, *L. interrogans* is shed for life. Many other animals, such as dogs (even those immunized), cattle, and pigs, can shed high concentrations of *Leptospira* in urine for months after the initial infection, but shedding diminishes substantially or halts within 6 to 12 months. Organisms survive for 3 months or more in neutral or slightly alkaline water but not in acidic environments.

Infection in humans often occurs through contact with the urine of infected animals, either directly or by contaminated water or soil; human infection also can occur through contact with organs of infected animals. People with occupational, recreational, or accidental contact have an increased risk of leptospirosis. In a case-control study conducted in France, skin lesions, canoeing, contact with wild rodents, and residing in the country were independently associated with leptospirosis, findings showing that leisure activity is an important risk factor for this illness.[5] Dogs have been implicated as a major source of cases in the US.[4] People who live or work on dairy, cattle, or pig farms, as well as abattoir (slaughterhouse) workers and veterinarians, are at increased risk. Field workers, even in developed countries, also may have increased risk of leptospirosis.[6]

The incidence of leptospirosis is unknown because most cases either are asymptomatic or are diagnosed incorrectly. The diagnosis is made most often in teenage boys and young men, presumably because their activities expose them more frequently to the urine of infected animals. However, infection can occur regardless of age or sex.[4–7] Children usually become infected by exposure to stagnant, contaminated water. Common-source outbreaks have occurred after swimming in contaminated ponds.[8] Outbreaks also have occurred in athletes who participated in triathlons.[9]

Clinical Manifestations

The incubation period is approximately 10 days (usual range, 7–14 days), although incubation can be as short as 2 days and as long as 25 days. Clinical manifestations are divided into the initial "septicemic" phase and the subsequent "immune" phase.[10–13] The severity of illness ranges from the classic, icteric Weil syndrome (which affects ~10% of patients) to the more common, less severe anicteric form of leptospirosis.[10–13] The correlations among fever, other clinical findings, and the presence of organisms in body fluids in the different stages of disease are shown in Fig. 184.1.

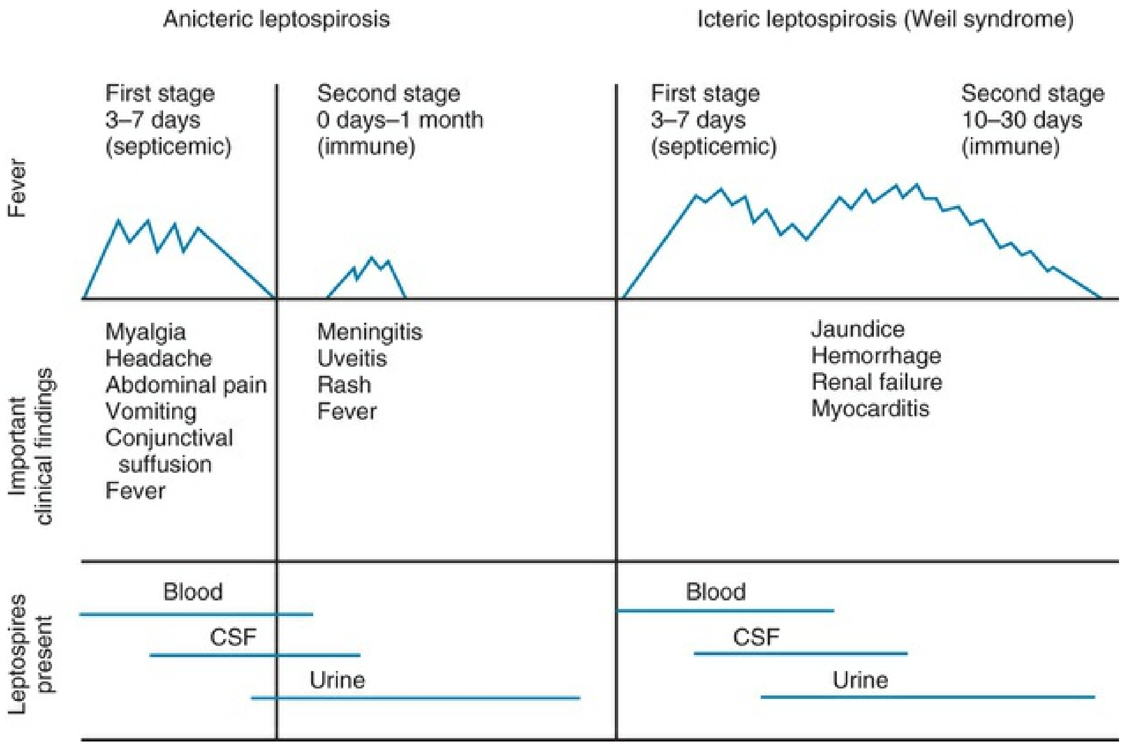

FIGURE 184.1 **Stages of anicteric and icteric leptospirosis. Correlation between clinical findings and the presence of leptospires in body fluids. CSF, cerebrospinal fluid.** (Redrawn from Feigin RD, Anderson DC. Human leptospirosis. CRC Crit Rev Clin Lab Sci 1975;5:413–467.)

Anicteric Leptospirosis

Symptoms of leptospirosis begin abruptly, with virus-like illness marked by fever, headache, and myalgia. Abdominal pain, vomiting, diarrhea, anorexia, and conjunctival suffusion can be present. Rarely, circulatory collapse ensues. During this phase of illness, organisms are present in the bloodstream and cerebrospinal fluid. The severity of illness varies substantially during this phase; symptoms usually last 4 to 7 days and resolve spontaneously.

Some patients have a second, immunologic phase of the illness that begins 1 to 3 days later with low-grade or no fever. During this phase, headache, myalgia, rash, conjunctival suffusion, and hepatomegaly are typical. Nausea, vomiting, and abdominal pain also are common. Typically, headache is severe and can be associated with nuchal rigidity. These manifestations of aseptic meningitis usually last for several days, but they can persist occasionally for 2 to 3 weeks. Other much less frequent manifestations of immune-mediated nervous system disease include encephalitis, Guillain-Barré syndrome, radiculomyelitis, and mononeuropathy or polyneuropathy of the cranial or peripheral nerves.

Interstitial nephritis also is common; manifestations range from incidental pyuria, hematuria, and proteinuria to renal failure. Patients can have right upper quadrant abdominal pain and a mass from acalculous cholecystitis with hydrops of the gallbladder. Pulmonary involvement also can occur. The rash of leptospirosis is immune mediated and nonspecific and can be macular, maculopapular, urticarial, petechial, or purpuric. The infectious and immune phases of anicteric leptospirosis usually resolve within 2 weeks of the onset of symptoms.

Icteric Leptospirosis (Weil Syndrome)

The severe, icteric form of leptospirosis, also called Weil syndrome, can be caused by multiple serovars of *Leptospira.* In the early phase it can be indistinguishable from the benign, anicteric form of leptospirosis, but ultimately it has a mortality rate of 5% to 10%. The hallmarks of Weil syndrome (jaundice, azotemia, and hemorrhage) become apparent 4 to 6 days after the onset of symptoms and can progress through the second week of the illness. Persistent fever (lasting up to 2–3 weeks) and the severity of the illness obscure the biphasic characteristics of the symptoms. Acute (often fatal) pulmonary hemorrhage is one of the most catastrophic manifestations of severe leptospirosis.

Although hepatomegaly, hepatocellular injury, and jaundice are prominent features of Weil syndrome, necrosis and frank hepatic failure do not occur, and survivors have no residual hepatic damage. By contrast, renal impairment, which occurs to a varying degree in both forms of leptospirosis, can be profound in patients with Weil syndrome.[11–14] Bacterially mediated toxicity to the renal tubules can be aggravated by shock and, rarely, by hemoglobinemia from hemolysis and leads to acute tubular necrosis and renal failure. Because of advances in supportive care, the survival rate has improved substantially in recent years. Renal dysfunction is reversible in most but not all cases.

Significant cardiac dysfunction is rare, although many patients have nonspecific electrocardiographic abnormalities (e.g., first-degree heart block) during the first week of the illness. Rarely, congestive heart failure and cardiovascular collapse develop in patients with Weil syndrome.

Laboratory Findings and Diagnosis

Many different laboratory abnormalities are present in patients with leptospirosis, depending on the severity and phase of the illness and the organ systems involved. None is specific. Weil syndrome is associated with leukocytosis and neutrophilia, especially during the early phase of the illness. Anemia is unusual in anicteric leptospirosis but can be severe in Weil syndrome. Serum concentrations of hepatic enzymes, creatinine, and blood urea nitrogen usually are elevated modestly (if at all) in patients with anicteric leptospirosis, but they can be extremely elevated in Weil syndrome. Approximately one half of patients with leptospirosis have clinical signs of meningitis during the immune phase of the illness, and three fourths have cerebrospinal fluid pleocytosis; neutrophils predominate very early in the illness, but a change to mononuclear cells occurs rapidly; protein concentration is normal or elevated; the glucose concentration usually is normal. In the early phase of the illness, the urine usually contains protein, red and white blood cells, and cellular casts.

The number of conditions that could be included in the differential diagnosis of leptospirosis is myriad. Most often, leptospirosis must be differentiated from viral illness and other causes of aseptic meningitis or meningoencephalitis. Leptospirosis can mimic Kawasaki disease, other causes of hepatitis, acute tubular necrosis, interstitial nephritis, and hepatorenal syndrome.

The diagnosis is confirmed by recovery of *Leptospira* from fluid or tissue or by a fourfold or greater rise in antileptospiral antibodies by the microscopic agglutination test in acute and convalescent sera in a patient with a compatible clinical illness. A presumptive diagnosis of leptospirosis can be made in a patient who has a clinically compatible illness and either a titer of antileptospiral antibodies of ≥1 : 100 by the microscopic agglutination test or a positive macroscopic agglutination test result. *Leptospira* organisms cannot be visualized with routine light microscopy; they can be seen by the use of modified silver stains on tissue or fluorescent antibody techniques on urine or tissue specimens. Rarely, *Leptospira* can be visualized by darkfield microscopy when the density of organisms is high.

Culture

Leptospira can be isolated from blood or cerebrospinal fluid during the septicemic phase, and from urine during the immune phase, of leptospirosis. Special media are required and include Tween 80-albumin ([polysorbate 80 with albumin] Sigma-Aldrich, St. Louis, Mo.), Fletcher, and Ellinghausen-McCullough-Johnson-Harris semisolid media; Tween 80-albumin is available commercially and may be superior. Solid media are less reliable for primary isolation of organisms but are useful for secondary isolation of *Leptospira* from semisolid media contaminated with other organisms. Because of difficulty of isolating *Leptospira* and inexperience in clinical microbiology laboratories, specimens for culture from suspected cases should be sent to the National Leptospirosis Laboratory at the Centers for Disease Control and Prevention. Newer molecular diagnostic techniques, such as loop-mediated isothermal amplification and real-time polymerase chain reaction, are promising modalities likely to be substantially more sensitive than currently available serologic and culture methods, but they are not widely available.[15,16] Next-generation sequencing was used to diagnose a case of neuroleptospirosis in an immunocompromised child.[17]

Serology

The macroscopic slide agglutination test is the most useful test for rapid screening.[18,19] Twelve serotypes of killed *Leptospira* (including strains responsible for most infections in the US) are included in this test. The microscopic agglutination test uses live organisms and is the gold standard for detecting antibodies to *Leptospira.*

Generally, agglutination test results are not positive until after the first week of infection; antibody levels peak 3 to 4 weeks after the onset of symptoms and can persist for years, although concentrations may decline over time. Demonstration of at least a fourfold rise in antibodies between acute and convalescent serum samples tested together is most definitive. Newer serologic tests may become useful and include indirect hemagglutination tests, passive microcapsule agglutination test, and enzyme immunoassays.[20–24]

Treatment

Leptospirosis generally is self-limited. Treatment, even if begun late in the course of a relatively severe infection, however, potentially is beneficial. This positive effect of treatment is based on limited data from clinical trials,[25,26] in vitro susceptibility of *Leptospira,* the efficacy of antimicrobial treatment of experimental leptospirosis in animal models (when treatment is begun early), and numerous case reports.[27] An open-label randomized clinical trial conducted in Thailand found that for treatment of patients with severe leptospirosis, penicillin G, cefotaxime, and doxycycline all were highly efficacious.[28] Frequent occurrence of a Jarisch-Herxheimer reaction also supports an effect of treatment.[29]

Treatment should begin as early in the course of the illness as possible. Aqueous penicillin G (200,000–250,000 U/kg/day in divided doses administered every 4 to 6 hours; maximal dose, 12 million U/day) is recommended for serious infection. Ceftriaxone (50 mg/kg up to 1 g/day) is a satisfactory alternative. Less seriously ill patients can be treated with doxycycline orally (2 mg/kg/day divided into 2 doses with maximum of 100 mg twice a day) or amoxicillin (50 mg/kg/day in divided doses 3 times a day; maximum of 500 mg per dose). Therapy is continued for 7 to 14 days. Azithromycin (20 mg/kg, up to 1 g in a single dose the first day followed by 10 mg/kg, up to 500 mg/dose once a day for 2 days) is a satisfactory alternative regimen.

Special Considerations

Congenital Leptospirosis

Although leptospirosis commonly causes abortion in pregnant animals, little information is available on the effect of leptospirosis on the human fetus. The limited information is primarily derived from pregnant women with relatively severe disease. A review of 16 reported cases of leptospirosis during pregnancy revealed that 5 of 8 women (63%) who aborted had leptospirosis during the first or second trimester.[30] Four of the 16 infants were born with evidence of congenital infection (hepatosplenomegaly), 3 were treated successfully, and 1 who died on the second day of life had leptospires seen on stained tissue specimens from the liver and kidneys. Three women with untreated anicteric leptospirosis late in the third trimester gave birth to children who were not infected. No congenital malformations were observed.

Pregnant women in whom leptospirosis develops should be treated promptly with penicillin or ampicillin administered intravenously. At the time of delivery, infants should be examined carefully, and if signs of congenital leptospirosis (jaundice, hepatomegaly) are present, these neonates should be treated promptly with parenterally administered penicillin. Rare cases of leptospirosis from breastfeeding have been described.

Prevention

Widespread infection with *Leptospira* in animals precludes elimination of leptospirosis. Good sanitation reduces the population of the rodent reservoir. Immunization of domestic animals reduces the risk of disease and decreases but does not eliminate leptospiruria.[31] People with occupational exposure to *Leptospira* should take precautions (e.g., wearing gloves), especially when in direct contact with potentially infected fluid, water, soil, or organs of animals. Children should not swim in potentially contaminated ponds; pools should be chlorinated adequately. Doxycycline (200 mg, once weekly) administered to soldiers in Panama reduced the risk of leptospirosis; prophylaxis could be considered in extraordinary circumstances for travelers who are expected to be at risk for a limited time.[32]

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185

Borrelia burgdorferi (Lyme Disease)

Eugene D. Shapiro

Pathogenesis and Immunity

Lyme disease is caused by the spirochete *Borrelia burgdorferi,*[1–3] a cylindrical, fastidious, microaerophilic bacterium that replicates very slowly and requires special medium for in vitro growth. Its cell membrane is covered by flagella and a loosely associated outer membrane. The 3 major outer surface proteins, OspA, OspB, and OspC (which are highly charged basic proteins with molecular weights of ~31, 34, and 23 kd, respectively), as well as the 41-kd flagellar protein, are important targets for the immune response of humans. Biologic differences in strains of *B. burgdorferi* sensu lato presumably are responsible for differences in the clinical manifestations of Lyme borreliosis in Europe and in the United States. *B. burgdorferi* sensu stricto is the only genomospecies that causes disease in the US (with the exception of a recently discovered species, *B. mayonii,* which appears to be a rare cause of Lyme disease in the upper Midwest[3a]), whereas considerable variation exists in the genomospecies, which also include *B. garinii, B. afzelli,* and several others, that cause disease in Europe.[4] The greater frequency of radiculoneuritis in Europe and of arthritis in the US likely is related to these differences.

Lyme disease is a zoonosis with complex pathogenesis.[3] *B. burgdorferi* is inoculated by the tick into the skin and begins to spread locally. Local inflammation results in erythema migrans in most patients with symptomatic infection (~90%). Days to weeks later, the spirochete can disseminate, through the bloodstream, to many other sites, including eye, muscle, bone, synovial tissue, central nervous system, and heart. Despite the low density of organisms and the fastidious nature of growth in vitro, *B. burgdorferi* has been isolated from blood or from affected tissues at all stages of illness. Relatively few organisms invade. Host mediators amplify the inflammatory response and cause much of the tissue damage. Preferring cell surfaces, the spirochete can adhere to many different cell types, a feature that may explain clinical manifestations of involvement in a broad array of organ systems. Because the organism can persist in tissues for prolonged periods when untreated, symptoms can appear months after infection. The host's immune response is an important element in the pathogenesis of Lyme disease.[4] Symptoms of early localized disease, early disseminated disease, and late disease usually are caused by inflammation as a direct result of the spirochete's presence (it does not produce toxins). Some people with Lyme disease who are treated early in the course of infection do not develop antibodies and remain susceptible to subsequent infections. However, evidence indicates that serotype-specific (as opposed to species-specific) immunity can develop after a single episode of erythema migrans[5]; a second case of erythema migrans virtually always results from a strain different from the one that caused the initial case of erythema migrans.[6] People with late Lyme disease rarely develop erythema migrans again, even with repeated exposure to ixodid ticks in endemic areas, a finding suggesting that these people have developed immunity.

Epidemiology

Disease in Humans

Although Lyme disease occurs throughout the world, endemicity varies widely. In the US, from 1992 to 2013 >90% of reported cases came from 10 states.[7] Most cases occur in southern New England and in the eastern Mid-Atlantic states; fewer cases occur in Minnesota and Wisconsin. Rarely, cases occur along the northern

Pacific coast (Fig. 185.1).[7] In Europe, most cases occur in the Scandinavian countries and in central Europe, although the disease occurs throughout the region.

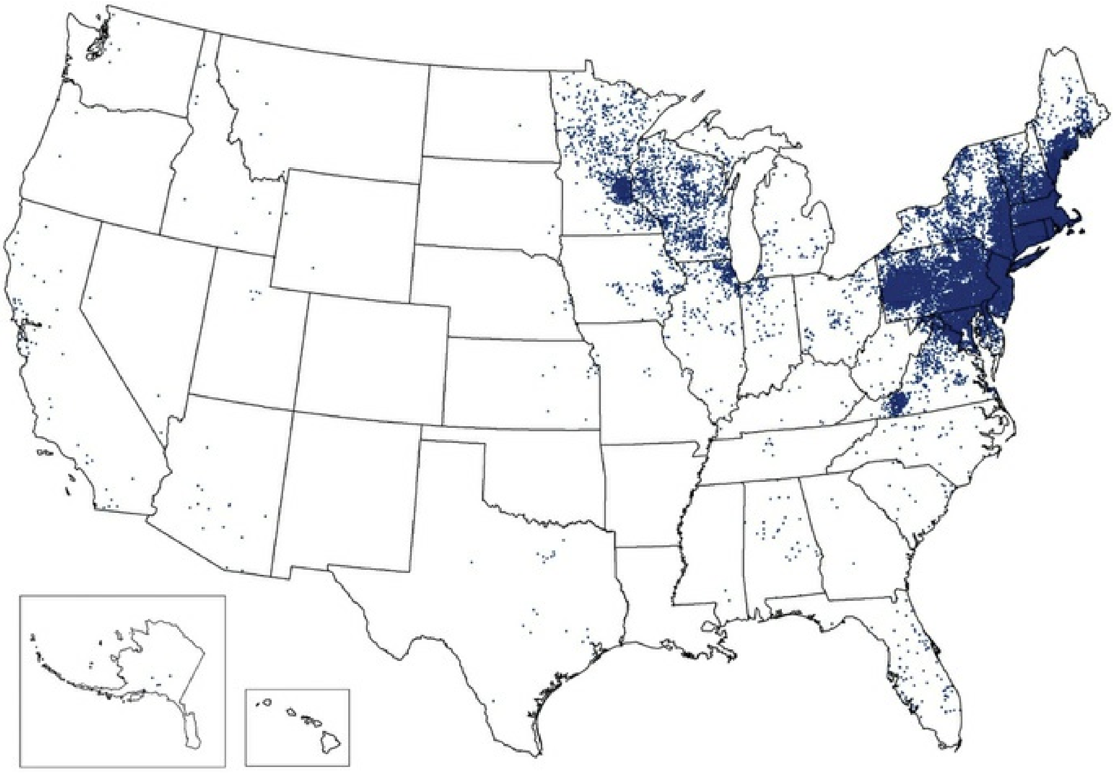

1 dot placed randomly within county of residence for each confirmed case

FIGURE 185.1 **Reported cases of Lyme disease: 2013.** (From Centers for Disease Control and Prevention. Lyme Disease: Data and Statistics. http://www.cdc.gov/lyme/stats/.)

Although frequency has increased and the geographic distribution of Lyme disease in the US has expanded, the incidence of Lyme disease varies substantially from region to region and within local areas.[1–3,7] The annual number of reported cases in the US increased from 9908 cases in 1992 to 27,203 cases in 2013.[7] This change likely reflects both the increased incidence and the improved recognition and reporting of disease. Estimates of the incidence of disease are complicated by reliance on passive reporting of cases as well as by the high frequency of misdiagnosis of disease. Furthermore, seroepidemiologic studies indicate that some patients who have evidence of recent infection with *B. burgdorferi* are asymptomatic.[8,9] The reported annual incidence in the most highly endemic areas, such as Connecticut, is approximately 75 cases per 100,000 persons, although in certain localized areas in which the disease is hyperendemic (e.g., Lyme, Conn.), the annual incidence can be as high as 1000 or more per 100,000 persons. The reported incidence is highest among children 5 to 14 years old. Most cases occur during the summer months.

Ecology

Lyme disease is a zoonosis.[3,10] *B. burgdorferi* is transmitted by ticks of the *Ixodes* genus. In the US, vectors are *I. scapularis* (the black-legged tick, also called the deer tick) in both the Northeast and Midwest and *I. pacificus* (the Western black-legged tick) in the Pacific states. The life cycle of these ticks consists of 3 stages (larva, nymph, and adult) that develop during a 2-year period. Larvae are not infected with *B. burgdorferi*. Ticks become infected as they feed on infected small mammals, such as *Peromyscus leucopus* (the white-footed mouse), which are natural reservoirs for the bacteria. Deer are important hosts for adult ticks but are not a competent reservoir for *B. burgdorferi*.

Multiple factors affect the risk of transmission of *B. burgdorferi* from ticks to humans. The first is the likelihood that a tick is infected. The proportion of infected ticks varies tremendously by geography as well as by species and stage of life cycle. Most cases of Lyme disease are transmitted by nymphal deer ticks because they outnumber adult ticks, are active during times of the year when many more people are outdoors, and are very small and therefore less likely to be detected and removed before transmitting infection. *I. pacificus* often feeds on lizards, which are not a competent reservoir for *B. burgdorferi;* lizard blood contains factors that kill the bacteria. Consequently, fewer than 10% of these ticks are infected with *B. burgdorferi.* By contrast, *I. scapularis* feeds on small mammals that constitute the natural reservoir for *B. burgdorferi.* In southeastern Connecticut and in Westchester County, New York, which have very high incidences of Lyme disease, rates of infection for *I. scapularis* are 0% for larvae, 15% to 25% for nymphs, and 30% to 50% for adults.

Clinical Manifestations

Lyme disease generally is divided into 3 clinical stages: early localized disease, early disseminated disease, and late disease.[1–4] Box 185.1 shows the major clinical features of these stages.

Box 185.1

Clinical Manifestations of Lyme Disease in Children According to Stage of the Disease

Early Localized Disease (3–32 Days After Tick Bite)

- Erythema migrans (single), sometimes accompanied by any of the following nonspecific symptoms or signs:
    - Myalgia
    - Headache
    - Fatigue
    - Fever
    - Lymphadenopathy (regional or generalized)

Early Disseminated Disease (3–10 Weeks After Tick Bite)

- Erythema migrans (multiple)
- Cranial neuritis (especially facial palsy)
- Meningitis
- Carditis (especially heart block)
- Radiculoneuritis

All of the above can be accompanied by any of the following nonspecific symptoms or signs:

- Myalgia
- Headache

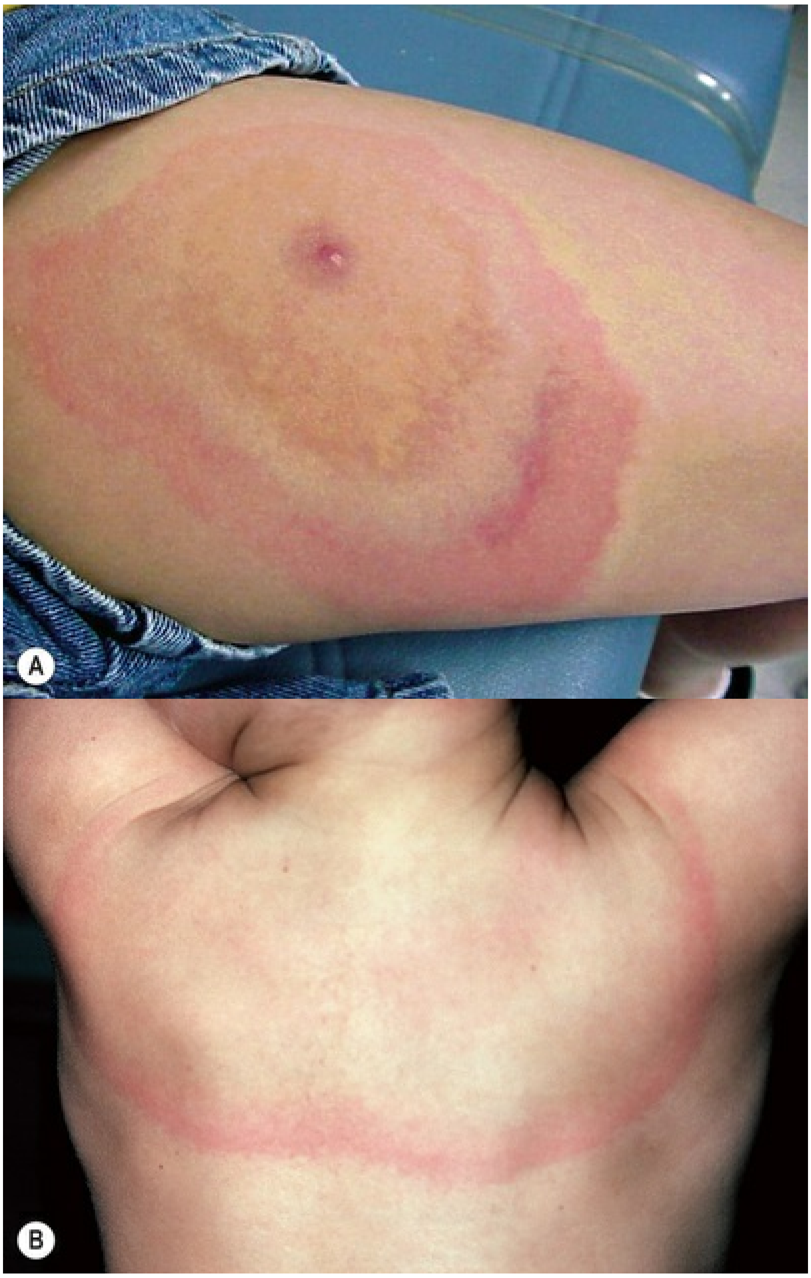
- Fatigue
- Fever
- Lymphadenopathy (regional or generalized)
- Conjunctivitis
- Neck pain and stiffness

Late Disseminated Disease (2–12 Months After Tick Bite)

- Arthritis (usually monoarticular or pauciarticular with involvement of the knee)

Early Localized Disease

The first clinical manifestation of Lyme disease is a typical annular rash, erythema migrans (Fig. 185.2).[2] Approximately two thirds of children with symptomatic infection have a single erythema migrans lesion, which occurs at the site of the tick bite (although typically the bite was not recognized).[11] Onset of rash is usually 7 to 14 days after the bite (range, 3–32 days). The rash most often is uniformly erythematous, but it can appear as a target lesion with central clearing. Occasionally it can have a vesicular or necrotic center. The rash can be pruritic, painful, or asymptomatic. Associated systemic symptoms (e.g., fever, myalgia, headache, and malaise) are variably present.[2] Untreated, the rash gradually expands (hence the name *migrans*) to an average diameter of 15 cm (although lesions >30 cm can occur) and persists for 1 to 4 weeks. Lesions can occur anywhere on the body, although they are more common in the head and neck area in children than in adults.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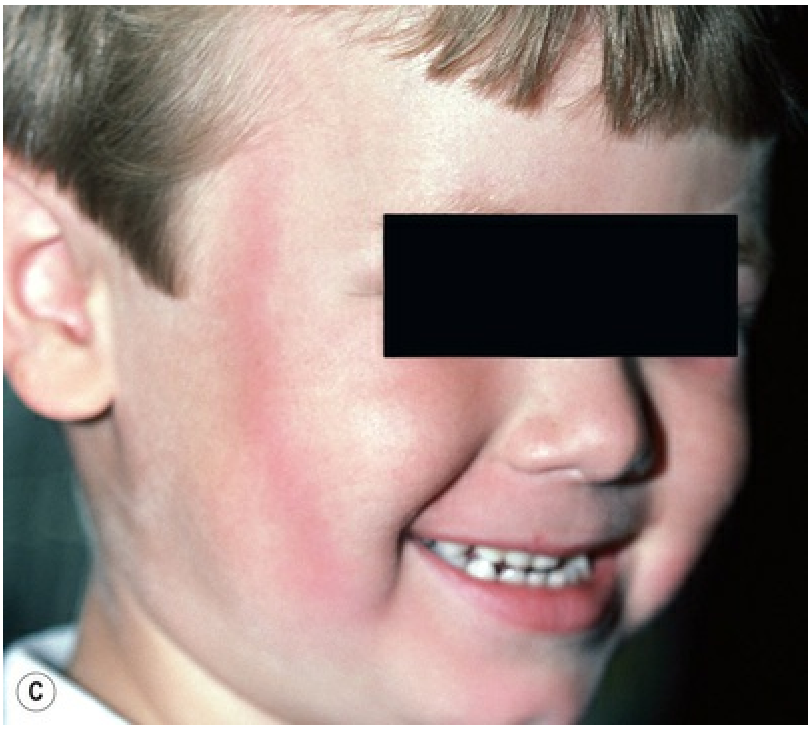

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FIGURE 185.2 (A) Typical expanding annular lesion of erythema migrans at the site of a tick bite. The central area underwent minor necrosis. (B, C) A 5-year-old boy had a giant expanding lesion of erythema migrans with central clearing on (B) his back and another on (C) his face, probably from bacteremic dissemination. (A, Courtesy of J. Capra, Abilene, Tex.; B and C, Courtesy of M. Weir, Temple, Tex.)

Early Disseminated Disease

The likelihood of dissemination is related to strain-specific characteristics of the bacteria.[12] Approximately one fourth of children with Lyme disease initially receive a diagnosis of early disseminated infection when, as a consequence of bacteremic dissemination to multiple sites, secondary erythema migrans lesions develop days or weeks after initial infection[11] (Fig. 185.3). Secondary lesions usually are smaller than the primary lesion and often are accompanied by fever, myalgia, headache, and fatigue; conjunctivitis and lymphadenopathy also can develop. Meningitis with clinical evidence of meningeal irritation (e.g., nuchal rigidity accompanied by a headache) is the presentation in approximately 2% of patients. Carditis, usually marked by varying degrees of heart block, can occur at this stage, but complete heart block is rare

(<1% of patients). Rare instances of sudden death secondary to Lyme carditis have been reported.[13]

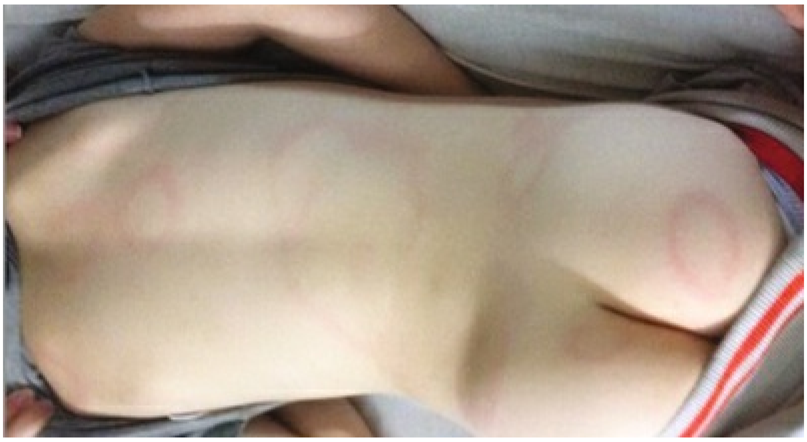

FIGURE 185.3 **Multiple erythema migrans lesions.**

Focal neurologic involvement, in particular cranioneuropathy, is a manifestation of early disseminated infection. The most common sign, paralysis of the facial (seventh cranial) nerve, is relatively common in children (3%–5% of cases) and can be the only manifestation of Lyme disease. Palsy usually lasts from 2 to 8 weeks and resolves completely. Rarely, palsy resolves partially or not at all. No evidence indicates that the clinical course of facial palsy is affected by antimicrobial therapy. Radiculoneuritis, manifested as radicular pain with motor and sensory abnormalities of peripheral nerves, has been reported in children in the US, although it is more common among adults and in Europe.

Late Disease

Arthritis, the usual manifestation of late Lyme disease, is the presenting complaint in approximately 7% of children with Lyme disease. Large joints are affected primarily, and the knee is involved in more than 90% of cases. Characteristically, the affected joint is swollen and tender, and it has an effusion, although pain and limitation of motion usually are modest and are less marked than in other bacterial arthritides. With treatment, the primary episode of arthritis usually abates over 4 to 7 days, with complete resolution over 2 to 6 weeks. Arthritis recurs or persists in 10% to 20% of treated patients and usually resolves with retreatment. In virtually all untreated patients, arthritis recurs, often in other joints, but signs and symptoms eventually resolve even without treatment.[14] Baker cyst is a well-described complication of Lyme arthritis and can occur unilaterally or bilaterally, with or without frank arthritis, and before, during, or after therapy (Fig. 185.4).[15,16] Immune-mediated chronic arthritis associated with Lyme disease (sometimes called antibiotic-refractory Lyme arthritis) is rare in adults and is extremely rare in children. Some controversy exists about whether this is caused by an autoimmune process or by delayed clearance of borrelial antigens from killed bacteria.[17–19] Late manifestations of Lyme disease of the central nervous system have been reported only rarely in children.

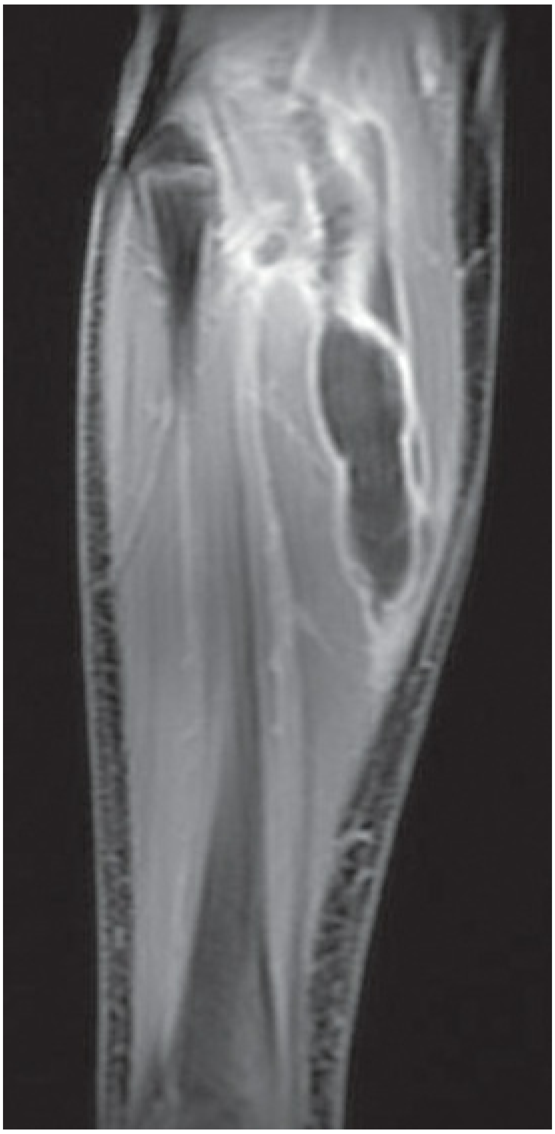

FIGURE 185.4 A 12-year-old boy came to attention after 2 weeks of pain and swelling in his knee and then

in his calf, which was warm, swollen, and tender. Fat-suppressed T1-weighted coronal magnetic resonance imaging with contrast shows an enhancing, multilobulated, fluid-filled mass (Baker cyst) with atypical inferior extension. Fluid had 140,000 white blood cells/mm^3 and was sterile. Serum Lyme antibody was 13 EU/mL. (Case courtesy of S. S. Long.)

Laboratory Findings and Diagnosis

Except for erythema migrans, the clinical manifestations of Lyme disease are nonspecific. Erythema migrans can be confused with several other skin lesions (ringworm, nummular eczema, cellulitis, granuloma annulare, and insect bites), but its rapid and continuing expansion is distinctive. Lyme meningitis (with lymphocytic pleocytosis) tends to have a slower onset and to be more prolonged than typical aseptic meningitis caused by enteroviruses, and papilledema and increased intracranial pressure often occur.[20] Lyme arthritis usually is subacute in onset, with effusion out of proportion to pain or disability, but sometimes it can mimic acute pyogenic arthritis.

Routine laboratory tests rarely aid the diagnosis of Lyme disease because most laboratory abnormalities also are nonspecific. Not uncommonly, mild cerebrospinal fluid pleocytosis can be found in patients with facial nerve palsy despite the absence of clinical manifestations of meningitis.[21]

Isolation of *B. burgdorferi* in a specimen from a symptomatic patient is diagnostic of Lyme disease; however, the appropriate medium is expensive, time to isolation can be 4 weeks, and sensitivity of culture is poor because of the low concentration of organisms. In addition, an invasive procedure is required to obtain appropriate material for culture. Diagnostic tests based on the identification of DNA of *B. burgdorferi,* including the polymerase chain reaction, also generally have poor sensitivity in addition to the substantial risk of a false-positive result because of contamination. Consequently, laboratory diagnosis of Lyme disease usually rests on detection of antibodies to *B. burgdorferi.*[22]

Typical antibody responses to acute infection with *B. burgdorferi* are well described. Specific immunoglobulin (Ig) M antibody appears 3 to 4 weeks after infection begins, peaks by 6 to 8 weeks, and subsequently declines. However, prolonged (years) elevation of IgM antibodies despite clinical cure is not unusual.[23] Specific IgG antibody usually appears 4 to 8 weeks after onset of infection, peaks 3 to 6 months later, and can remain elevated indefinitely after cure of infection.[22–24] Effective antimicrobial therapy may or may not be associated with a decline in specific IgG or IgM antibody level.[23,24]

Enzyme immunoassay (EIA) is the most widely used procedure for the detection of antibodies against *B. burgdorferi.* The procedure is associated with false-positive results because of cross-reactive antibodies in patients with other spirochetal infections (e.g., syphilis, leptospirosis, or relapsing fever), certain viral infections (e.g., varicella), or certain autoimmune diseases (e.g., systemic lupus erythematosus), or from antibodies that cross-react with spirochetes of normal oral flora. The immunoblot test (Western blot) is used to detect serum antibodies against specific proteins of *B. burgdorferi.* Because many uninfected patients have antibodies against certain proteins of *B. burgdorferi* (especially against the 41-kd flagellar protein), guidelines have been established for diagnosing Lyme disease with the immunoblot test.[22,25] Currently, a 2-tier approach to diagnose Lyme disease is recommended, beginning with a sensitive EIA; if that result is either positive or equivocal, then a Western blot is used to validate the result.[25] Western blot tests should be performed only in conjunction with a positive or equivocal EIA or other quantitative test result. A 1-step EIA assay (VIsE C6) for IgG antibody to the variable major protein-like sequence-expressed lipoprotein (VlsE) sixth invariant region (C6) has good sensitivity but is somewhat less specific than the 2-step approach for determining the presence of specific antibody.[26]

Antibody test results often are negative in patients with early infection, such as patients with a single erythema migrans lesion.[2] People with disseminated or late Lyme disease virtually always have a strong IgG response to *B. burgdorferi.* Antibody response can be abrogated if invading organisms are killed when patients are treated early in the course of erythema migrans.

The interpretation of serologic test results for Lyme disease has multiple pitfalls. Some commercial laboratories are performing tests for Lyme disease by using assays for which accuracy and clinical usefulness have not been established.[27] Serologic tests performed in several reference laboratories throughout the US are relatively accurate, with good sensitivity and specificity. However, the predictive value of a positive result, even of a Western blot, depends primarily on the pretest likelihood (on the basis of the clinical and epidemiologic history and the results of the physical examination) that the patient's problem is caused by Lyme disease. Although nonspecific, subjective symptoms such as fatigue, arthralgia, or headache can accompany Lyme disease, such widely prevalent symptoms alone, in the absence of a specific objective sign of infection such as erythema migrans, facial nerve palsy, or arthritis, hardly ever signify Lyme disease. Positive antibody test results in such patients almost always are false-positive results.[28,29] Such nonspecific symptoms can have a variety of causes, including fibromyalgia or medically unexplained symptoms.[30,31]

Serologic tests for Lyme disease, even those performed by reference laboratories, should be performed selectively to confirm specific clinical findings suggestive of Lyme disease. A positive serologic test result does not necessarily denote active infection. It can reflect previous asymptomatic infection or previously cured clinical infection.[22–24] Test results generally cannot be used to assess either activity or relapse of past infection.

Treatment and Outcomes

Antimicrobial treatment of Lyme disease is highly effective; expert guidelines for management are published.[32] Box 185.2 lists the recommended therapy for children with Lyme disease. Although children younger than 8 years of age are not treated with doxycycline because of concern that it may permanently discolor teeth, growing evidence indicates that such concern may not be justified.[33] Patients who are treated with doxycycline should be alerted to the risk of drug-related, sun-induced dermatitis.

Box 185.2

Antimicrobial Treatment of Lyme Borreliosis

Early Disease

- **Erythema migrans and early disseminated disease**

Doxycycline, 4 mg/kg/day divided bid (maximum, 100 mg/dose) for 14 days (range, 10–21 days; see text for children <8 years of age) *or* amoxicillin, 50 mg/kg/day divided tid (maximum, 500 mg/dose) for 14 days (range, 10–21 days)

Alternative agent for patients who cannot take either amoxicillin or doxycycline: cefuroxime axetil (preferred), 30–50 mg/kg/day divided bid (maximum, 500 mg/dose) *or* erythromycin, 50 mg/kg/day divided qid (maximum, 250 mg/dose) *or* clarithromycin, 15 mg/kg/day divided bid (maximum, 500 mg/dose), all for same duration as above, *or* azithromycin, 10 mg/kg/day (maximum, 500 mg/dose) in a single daily dose for 7–10 days

- **Seventh nerve palsy or palsy of other cranial nerves**

Treat as for erythema migrans for 14–21 days (doxycycline preferred if possible); do not use corticosteroids

- **Carditis**

First- or second-degree heart block: same treatment as for erythema migrans

Third-degree heart block: treat as for meningitis

- **Meningitis**[a]

Ceftriaxone, 75–100 mg/kg/day in a single daily dose (maximum, 2 g) for 14 days (range, 14–28 days administered IV or IM) *or* cefotaxime, 150–200 mg/kg/day (maximum, 6 g/day) divided q8h administered IV for 14 days (range, 14–28 days) *or* penicillin G, 200,000–400,000 U/kg/day (maximum, 20 million U/day) divided q4h administered IV for 14–28 days

Late Disease

- **Central or peripheral nervous system**[b]

Same as for meningitis

- **Arthritis**

Initial treatment is the same as for erythema migrans, except treatment should be given for 28 days; if swelling fails to resolve after 2 months or if the patient has a recurrence, consider a second course of oral therapy, or use parenteral therapy and treat as for meningitis

bid, twice daily; IM, intramuscularly; IV, intravenously; qid, 4 times daily; tid, 3 times daily.

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[a] Evidence indicates that oral doxycycline is as effective as intravenous ceftriaxone to treat Lyme meningitis.[57]

[b] For isolated palsy of the facial nerve or other cranial nerves, see under Early Disease.

From Wormser GP, Nadelman RB, Dattwyler RJ, et al. Infectious Diseases Society of America practice guidelines for the treatment of Lyme Disease, human granulocytic anaplasmosis, and babesiosis. Clin Infect Dis 2006;43:1089–1134. (http://www.idsociety.org/uploadedfiles/idsa/guidelines-patient_care/pdf_library/lyme%20disease.pdf)

Some patients experience a Jarisch-Herxheimer reaction within 48 hours after treatment; this reaction results from bacteriolysis and release of cellular products. Symptoms of fever, sweating, and myalgia resolve spontaneously within 1 to 3 days. Treatment with nonsteroidal anti-inflammatory agents can be useful in treating a Jarisch-Herxheimer reaction as well as myalgia, arthralgia, headache, and other symptoms of Lyme disease; the duration of anti-inflammatory therapy is determined empirically.

Cefuroxime is preferable to a macrolide antibiotic as an alternative for patients for whom both doxycycline and amoxicillin are contraindicated. Little need exists for new agents because the results of treatment with standard therapy (e.g., amoxicillin or doxycycline) have been excellent.[11,32] Reinfection after treatment can occur after localized erythema migrans, but it is rare after either early disseminated or late Lyme disease. Clinicians also should keep in mind the possibility of coinfection with other pathogens (*Babesia microti* or *Anaplasma phagocytophilum*) that are also transmitted by *Ixodes* ticks.

A substantial body of literature indicates that the outcomes for people with Lyme disease who receive conventional antimicrobial treatment are excellent.[2,32,34–39] The most common reason for “failure” of treatment of Lyme disease is that the diagnosis was erroneous.[28,29,40–43] Although patients with Lyme disease who are successfully treated may have fatigue, arthralgia, or myalgia that resolves over weeks to months after completion of therapy, no evidence indicates that such symptoms are related to persistence of the organism. Repeated courses of antimicrobial agents do not speed the resolution of persistent musculoskeletal pain, neurocognitive symptoms, dysesthesia, or fatigue.[32,43–46] Misinterpretation of the cause of persistent symptoms or of antibody test results, augmented by inaccurate information on the Internet and in the lay press,[47] has led to unfounded anxiety about the longterm consequences of Lyme disease among both the public and physicians.

Special Consideration: Congenital Lyme Disease

Because another spirochete, *Treponema pallidum,* is transmissible transplacentally, concern exists that *B. burgdorferi* could be transmitted from an infected pregnant woman to her fetus. Case reports have documented isolation of *B. burgdorferi* from abortuses and infection in a few live-born infants with congenital anomalies, but placentas, abortuses, and tissue in which the spirochete was identified did not show histologic evidence of inflammation. In addition, no consistent pattern of congenital malformation has been observed, unlike with other diseases caused by intrauterine infections.

Two serosurveys conducted in endemic areas found no difference in the prevalence of congenital malformations among women who were seropositive versus seronegative for *B. burgdorferi.* In the largest study of Lyme disease in pregnancy, investigators prospectively observed 2000 pregnant women in Westchester County, New York, 79 of whom had Lyme disease according to history or serologic test results. Although the number of infected women was relatively small (15 had Lyme disease during the pregnancy), no association was found between maternal exposure to *B. burgdorferi* before conception or during pregnancy and fetal death, prematurity, or congenital malformations.[48] An extensive survey of 162 pediatric neurologists in endemic areas revealed that none had observed a clinically significant neurologic disorder either attributable to congenital Lyme disease or after Lyme disease during pregnancy.[49]

No definite evidence indicates that *B. burgdorferi* causes congenital disease. If congenital Lyme disease exists, it is extremely rare. Pregnant women with Lyme disease should be treated as stage and severity of illness dictate (although doxycycline is contraindicated). Transmission of *B. burgdorferi* through breastfeeding has not been documented.

Prevention

In areas where deer ticks are prevalent, children are commonly bitten. The overall risk of acquiring Lyme disease after a recognized tick bite is approximately 1% to 3% in areas where the disease is highly endemic.[50–52] The risk of becoming infected is greater if the tick is in the nymphal stage and is engorged when discovered (indicating substantial feeding time, which is necessary for transmission of the organism to occur). Treatment of infection, if it develops, is highly effective. Consequently, routine administration of antimicrobial prophylaxis after a deer tick bite is not recommended.[32,52,53] In contrast, in endemic areas of the Northeast or the Upper Midwest in the US, if the tick is reliably identified as either a nymphal or an adult deer tick that is engorged and the child is ≥8 years of age, treatment with a single dose (4 mg/kg up to 200 mg maximum) of doxycycline (administered with food to minimize nausea) may be indicated.[51–53] The routine testing of ticks that have been removed from humans for infection with *B. burgdorferi* also is not recommended because the sensitivity, specificity, and predictive values of the results of such tests on ticks for predicting infection of the human who was bitten are unknown. Hypersensitivity reactions to tick products frequently result in erythematous or nodular lesions <2 cm in diameter that do not expand and should not be misinterpreted as erythema migrans. Topical antimicrobial treatment of a tick bite has successfully prevented dissemination of infection in an animal model but has not been tested in humans.[54]

A reasonable approach to avoiding Lyme disease consists of (1) wearing appropriate protective clothing (e.g., lightweight long pants tucked into socks) when entering tick-infested areas; (2) checking for ticks after spending time in such areas; and (3) removing ticks promptly.[55,56] Insect repellents also may provide temporary protection.

Antibodies against the OspA protein protect against Lyme disease in animal models. A recombinant OspA vaccine was licensed for people 15 to 70 years of age,[9] but it was removed from the market in 2002 by the manufacturer because of poor sales.

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Other *Borrelia* Species and *Spirillum minus*

Eugene D. Shapiro

Borrelia Species (Relapsing Fever)

Microbiology

Members of the genus *Borrelia* are microaerophilic spirochetal bacteria characterized morphologically by coarse and irregularly shaped coils, with a cell wall and an inner cytoplasmic membrane, between which are multiple flagella that provide corkscrew-like motility. Substantially thicker than the *Treponema* spp., *Borrelia* spp. stain easily with aniline or acid dyes and can be visualized on light microscopy in Wright- or Giemsa-stained blood smears. Isolation of the organism is difficult, requiring special media, and growth is slow.[1]

Borrelia spp. can change the antigenic structure of their surface proteins by transposition of structural genes on a linear plasmid.[2] This ability allows them temporarily to elude host defenses, thus resulting in "relapsing fever" in infected humans.[3,4] The resolution of symptomatic stages of the illness correlates with peak concentrations of antibodies against specific antigens.[5] Borreliae cause vasculitis, with a predilection for capillaries and small arterioles of any organ, especially the reticuloendothelial system, bone marrow, and central nervous system.

Epidemiology

Ticks and lice are vectors that transmit the bacteria to humans. The epidemiology of the disease is determined by environmental conditions conducive to vectors and, in the case of the ticks, the likelihood of contact with humans.[6] Risk factors, organisms, and vectors associated with each form of disease are shown in Table 186.1.

TABLE 186.1

Causes of *Borrelia* Relapsing Fever

Vector	Bacteria	Risk Factors
LOUSE		
Pediculus humanus	*B. recurrentis*	Crowding, poverty, war, famine
TICK		
Ornithodoros ticks[a] *O. hermsi* *O. parkeri* *O. tholozani* *O. talaje* *Ixodes* ticks *I. scapularis* *I. pacificus* *I. ricinus* *I. persulcatus*	*B. duttoni*[b] *B. hermsii* *B. parkeri* *B. persica* *B. mazzottii* *B. miyamotoi*	Exposure to environments where rodents thrive: old cabins, caves, primitive huts Exposure to areas (e.g., fields, woods, residential yards adjacent to woods) where these ticks are prevalent

[a] These are only some of the many species that are vectors for relapsing fever.

[b] These are only some of the many species that cause relapsing fever.

Louse-borne relapsing fever, caused by *Borrelia recurrentis,* is transmitted by the body louse, *Pediculus humanus.* Crab lice *(Phthirus pubis)* cannot transmit this organism. No animal reservoir for *B. recurrentis* has been found; the existence of this organism depends on human-to-human transmission by lice. Bacteria multiply in the hemolymph of the louse, but infected fluid is not inoculated into humans. Human infection occurs when the louse is crushed (usually inadvertently) and the organisms come in contact with skin or mucous membranes. Infection with *B. recurrentis* is associated with crowding and poor hygiene; epidemics are associated with war, famine, and natural disasters such as earthquakes. A major epidemic of louseborne relapsing fever occurred in Europe during World War II. The disease is endemic in Ethiopia and Sudan. Infection with *B. recurrentis* is virtually unknown in the United States.

Tickborne relapsing fever, caused by several species of *Borrelia,* is transmitted primarily by soft ticks of the genus *Ornithodoros.* Many small animals (chipmunks, rats, mice, squirrels, and others) serve as reservoirs for *Borrelia* spp. and as hosts for *Ornithodoros* ticks. Variable transovarial transmission of bacteria to larval ticks occurs, and an enzootic cycle is well established in certain areas of the US. Ticks thrive in warm, humid environments and at altitudes from 1500 to 6500 feet (450–2000 m).

Unlike hard ixodid ticks that transmit *B. burgdorferi* only after feeding for days, soft ticks feed for less than an hour yet are able to transmit *Borrelia* during this relatively brief period. Transmission occurs by inoculation of saliva from an infected tick. Ticks often feed at night, and the human host rarely is aware of the bite, which can be associated with up to a 50% risk of disease if the tick is infected. Unlike with louseborne recurrent fever, humans are incidental hosts for bacteria that cause tickborne relapsing fever. Humans become infected when they enter environments where the ticks thrive, such as old cabins and caves. Tickborne recurrent fever has a worldwide distribution. The disease is endemic in parts of East Africa, Asia, and South America. Most cases in the US occur in rural areas in the Western states. Outbreaks have occurred among tourists staying in log cabins at Western parks and among spelunkers.[7–9]

A more recently discovered bacterium, *B. miyamotoi*, is the first *Borrelia* species in the relapsing fever group that is transmitted by hard ticks (*Ixodes* species).[10,11] *B. miyamotoi* has been found in all species of *Ixodes* ticks in North America, Europe, and Asia, and apparently it also shares animal reservoirs with *B. burgdorferi.* The full ecology and epidemiology of disease caused by *B. miyamotoi* have not yet been determined. However, *Ixodes* ticks clearly can transmit *B. miyamotoi* without, or with, *B. burgdorferi.*

Clinical Manifestations

Tickborne and louseborne relapsing fevers are indistinguishable from each other clinically (manifestations of infection with *B. miyamotoi* are discussed separately), although louseborne disease tends to have fewer (though more severe) recurrences.[12–17] The exact time of exposure usually is unknown because lice typically cause chronic infestations and the bites of ticks often are unrecognized. Symptoms begin 5 to 10 days after exposure, with sudden onset of fever and chills usually accompanied by headache, myalgia, arthralgia, photophobia, and cough. Common physical findings include petechiae or frank purpura, conjunctivitis, and abdominal tenderness (often with an enlarged and tender liver or spleen). Nuchal rigidity often occurs,[18] and some patients have jaundice, epistaxis, or gastrointestinal hemorrhage. This phase of the illness is associated with bacteremia, usually lasts for 3 to 7 days, and resolves spontaneously.

During the next (crisis) phase, patients are afebrile or have low-grade fever and may have a diffuse maculopapular rash. Diaphoresis, extreme fatigue, and, occasionally, hypotension characterize this phase. Borreliae are not found in the blood but presumably are present in organs such as the spleen and liver, where antigenically variant strains propagate.

The relapse phase of illness, which typically occurs 5 to 7 days after primary spirochetemia resolves, is marked by rapid onset of high fever and chills as well as the other signs and symptoms of the initial spirochetemic phase. In untreated patients, 3 to 5 relapses are typical (although many more are possible) in tickborne infections, and up to 2 or 3 relapses occur in louseborne infections. Relapsing fever usually resolves even if untreated, although deaths have occurred. During some epidemics, mortality rates as high as 20% to 30% have been reported; poor general health and poor nutrition can be responsible. Severe hepatitis, lobar pneumonia, myocarditis, ruptured spleen, and cerebral hemorrhage are rare causes of death. Pregnant women who become infected often have spontaneous abortion, in most instances because of thrombocytopenia and retroplacental hemorrhage. Longterm sequelae are uncommon among survivors, although iridocyclitis can result in scars and impairment of vision.

Although *B. miyamotoi* is classified in the relapsing fever group of *Borrelia*, manifestations of infection may not be the same as those of other tickborne *Borrelia* infections. Although relapsing fever–like illness can occur, prolonged fever, presentations similar to anaplasmosis, and meningoencephalitis in immunocompromised patients have been reported.[11,19–21] Generally, reports are anecdotal and are likely to remain so until better and more widely available diagnostic tests are developed.

Laboratory Findings and Diagnosis

Laboratory abnormalities are nonspecific. Leukocytosis (with a left shift) and a markedly elevated erythrocyte sedimentation rate are typical. Cerebrospinal fluid often is abnormal, usually with 10 to 2000 predominantly mononuclear white blood cells/mm,[3] elevated protein levels, and normal glucose concentrations.

Awareness of epidemiology is crucial to making the diagnosis. Louseborne relapsing fever usually occurs in epidemics at times of unstable social conditions; in these circumstances, the symptoms are rarely confused with those of any other condition except epidemic typhus, which also is transmitted by the body louse. By contrast, except in certain developing countries, tickborne relapsing fever is uncommon and occurs sporadically. For patients with compatible symptoms, a history of recent exposure to old cabins, caves, or other environments where rodents reside should lead to consideration of relapsing fever.

Culture is an insensitive method for confirming the diagnosis, which is best made by examination of peripheral blood during febrile episodes using darkfield microscopy or Wright or Giemsa staining.[22] Diagnostic yield can be enhanced by staining of a smear with acridine orange and use of fluorescence microscopy. Polymerase chain reaction assay is a promising diagnostic test but is not available generally.[23]

Treatment

Tetracycline (500 mg/dose administered 4 times a day) or doxycycline (2 mg/kg/day divided into 2 doses with maximum dose of 100 mg twice a day) are the drugs of choice for relapsing fever.[12,17] Treatment is administered for 7 to 10 days; however, for louseborne relapsing fever, 100 mg of doxycycline or 500 mg of either tetracycline or erythromycin given once orally has been effective.[24–26] In children <8 years of age, erythromycin (30–50 mg/kg/day divided into 4 doses) is preferred, although penicillin also is effective. *B. miyamotoi* appears to be susceptible to doxycycline and to amoxicillin.[11]

If vomiting is severe, the initial dose of the antimicrobial agent can be administered intravenously, although a severe Jarisch-Herxheimer reaction can occur. This reaction, marked by rigors, increased fever, and, in severe cases, hypotension, typically occurs within a few hours after initiation of antimicrobial therapy and cannot be prevented by previous administration of corticosteroid. Nonsteroidal anti-inflammatory medications and, in severe instances, intravenously administered fluids have been used for treatment.

Prevention

The primary means of preventing relapsing fever consists of control and avoidance of vectors that transmit the disease. Ticks that transmit relapsing fever are dispersed widely throughout the world. The use of insecticides around the inner walls of primitive buildings and huts (where ticks often are found) in developing countries has reduced the frequency of disease.[27] Postexposure chemoprophylaxis with 5 days of doxycycline was highly effective in persons thought to be at high risk after a tick bite.[28] The risk of louseborne disease can be controlled through good personal hygiene and prompt treatment if an infestation occurs.

Spirillum Minus (Rat-Bite Fever)

Spirillum minus, a short, spiral bacterium, is a cause of rat-bite fever.[29–33] *S. minus* is more common in Asia than in the US and elsewhere in North America, where most cases of rat-bite fever are caused by *Streptobacillus moniliformis.* In Japan, the disease is known as *sodoku* (*so*, “rat”; *doku*, “poison”).

S. minus is a tightly coiled, gram-negative spiral bacillus. Infection results from inoculation during the bite of a rat. Up to one fourth of rats are colonized with *S. minus* in sputum, conjunctiva, blood, or nasopharynx. Unlike streptobacillary rat-bite fever, *S.*

minus infection has not followed ingestion of the organism. Transmission of infection between humans does not occur.

One to 4 weeks after the bite, patients have abrupt onset of fever, chills, and headache, usually in association with an inflamed, tender, ulcerated wound at the site of the rat bite. Typically, the wound, which had healed previously, ulcerates concurrently with onset of systemic symptoms. Musculoskeletal symptoms (arthralgia or myalgia) are less common in infections with *S. minus* than in streptobacillary rat-bite fever. Most patients have a generalized red or purple macular rash that can be urticarial. The rash, usually prominent during the first week of illness and during febrile periods, may fade with resolution of symptoms. In untreated patients, high fever and systemic symptoms last for 3 to 7 days, remit, and recur 3 to 10 days later, followed by recurring cycles for 3 to 8 weeks. In severe cases, pneumonia, meningitis, myocarditis, or (especially in patients with preexisting valvular disease) endocarditis can develop.

S. minus has not been cultivated on artificial media but can be identified on darkfield microscopy and, occasionally, in Wright- or Giemsa-stained smears of peripheral blood. No serologic test is available. Organisms can be identified in guinea pig blood 2 to 3 weeks after intraperitoneal inoculation of infected blood.

S. minus is exquisitely susceptible to penicillin. Excellent response is expected with the use of procaine penicillin given intramuscularly (20,000–50,000 U/kg once daily), penicillin G given intravenously, or penicillin V given orally (1–2 g/day divided into 3 doses).[29–31] Streptomycin and tetracycline are effective alternative agents. Therapy is given for 10 to 14 days.

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Anaerobic Bacteria

OUTLINE

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Anaerobic Bacteria

Classification, Normal Flora, and Clinical Concepts

Itzhak Brook, Sarah S. Long

Classification

Anaerobic bacteria predominate on normal skin and among the bacterial flora of mucous membranes.[1,2] Infections caused by anaerobic bacteria are common, arise from the sites where they are normal flora (endogenous), and can be serious or life-threatening. Anaerobic bacteria are fastidious, difficult to isolate, and often overlooked. Their recovery requires proper methods of collection, transportation, and cultivation.[3–7] Their ubiquity on mucocutaneous surfaces often interferes with obtaining meaningful cultures. Although no universally accepted or simple and accurate way has been established to classify microorganisms according to conditions required for their replication, Table 187.1 presents a useful framework for the clinician. Nevertheless, differences among strains exist within the same species.

TABLE 187.1

Classification of Microorganisms by Conditions of Replication

Class	Requirement for Replication	Examples
Strict anaerobe	Requires reduced oxygen tension; does not	*Bacteroides, Prevotella,*

	replicate on agar surface in air or 10% carbon dioxide	*Peptostreptococcus*, and *Fusobacterium* spp.
Microaerophilic organism	Replicates poorly on agar surface in the presence of oxygen but distinctly grows better under 10% carbon dioxide in air or anaerobically	Most streptococci of normal oropharyngeal flora
Facultative anaerobe	Replicates in the presence or absence of oxygen	Groups A, B, and C streptococci, *Streptococcus pneumoniae, Staphylococcus* spp., *Escherichia coli*
Strict aerobe	Replicates only in the presence of oxygen	Most *Pseudomonas* and *Mycobacterium* spp.

Anaerobic bacteria do not replicate in the presence of oxygen; however, they exhibit substantial differences in lethal effect of oxygen. In general, anaerobic organisms found exclusively as normal flora are strict anaerobes (i.e., die within minutes in <0.5% oxygen), whereas those of clinical significance are somewhat aerotolerant (i.e., tolerate 2% to 8% oxygen). Strict anaerobes do not grow in 10% carbon dioxide in air; microaerophilic bacteria can grow in 10% carbon dioxide in air or under aerobic or anaerobic conditions, and facultative organisms can grow in the presence or absence of air. The physiologic basis for oxygen sensitivity is not well understood. Common teaching is that negative oxidation-reduction potential (Eh) of the environment is the critical factor. However, studies with *Bacteroides fragilis* reveal that oxygen has a direct toxic effect; chemical manipulation of oxidation-reduction potential has no effect if oxygen is not introduced. Furthermore, aerotolerance and possibly virulence of anaerobic bacteria correlate with the ability to induce the protective enzyme superoxide dismutase on exposure to oxygen.[4]

The clinically important anaerobic genera are shown in Table 187.2. The taxonomy of anaerobic bacteria has changed because of improved characterization through the use of genetic studies.[3,5] Discriminating among strains enables better characterization of the source of infection and prediction of antimicrobial susceptibility. The genera and groups most frequently isolated from clinical infections, in descending frequency are: *Bacteroides/Prevotella* spp., *Peptostreptococcus* spp., *Clostridium* spp., *Fusobacterium* spp., gram-positive bacilli, and gram-negative cocci.[2,3]

TABLE 187.2

Genera of Clinically Significant Anaerobic Bacteria

GRAM-NEGATIVE BACILLI

Bacteroides (*B. fragilis* group and others)
Fusobacterium
Porphyromonas
Prevotella
Other Bacteroidaceae *(Bilophila, Centipeda, Leptotrichia, Mobiluncus, Seleonomonas, Sutterella)*
Campylobacter
GRAM-NEGATIVE COCCI
Veillonella
NON–SPORE-FORMING GRAM-POSITIVE BACILLI
Actinomyces
Arcanobacterium
Bifidobacterium
Eubacterium
Lactobacillus
Propionibacterium
ENDOSPORE-FORMING GRAM-POSITIVE BACILLI
Clostridium
GRAM-POSITIVE COCCI
Gemella
Parvimonas
Peptococcus
Peptostreptococcus
Ruminococcus
Staphylococcus (S. saccharolyticus)
Streptococcus[a] *(S. anginosus, S. constellatus, S. intermedius)*

[a] Microaerophilic streptococci.

The use of DNA technology (e.g., determination of DNA mole percent guanine plus cytosine content, ribosomal RNA homology, gel electrophoresis sequencing) and chemotaxonomic analyses (e.g., analysis of peptidoglycans, gas-liquid chromatography of whole cell fatty acids) has enlightened taxonomic relationships among anaerobic bacteria. Wide-ranging taxonomic changes have affected the family Bacteroidaceae and anaerobic gram-positive cocci. *Bacteroides melaninogenicus,* a single species until 1977, now encompasses 2 genera (*Prevotella* and *Porphyromonas*) and >15 species.[8] Minor changes have been made in the classification of gram-positive bacilli, and the genus *Eubacterium* remains heterogeneous and inadequately examined.

Indigenous Flora

Establishment and Composition of Normal Flora

The frequency of recovery of anaerobic bacteria as normal flora varies by body site and age. Table 187.3 shows sites of colonization of clinically important anaerobic bacteria. Mucocutaneous surfaces in humans have complex indigenous flora composed of anaerobic, microaerophilic, facultative, and aerobic bacteria. Flora is remarkably predictable within days after birth, depending on the type of delivery, feeding, and receipt of antibiotics.[9] Successive colonization of the gut simulates that in germ-free laboratory animals after exposure to peers.[10] Facultative organisms, such as oral streptococci, intestinal *Escherichia coli,* and skin staphylococci, precede anaerobic species, but by the end of the first few weeks of life, flora is complex and predictable. Infants fed human milk exclusively have a fermentative gut flora with predominance of *Bifidobacterium*, fewer *Bacteroides* and facultative gram-negative bacilli, and *Enterococcus* spp., whereas infants fed cow's milk have putrefactive flora similar to that of adults, with gram-negative anaerobic and facultative bacilli predominating.[11,12] Early colonization at <3 weeks with *B. fragilis* has been associated with the risk of asthma at a later age.[13] Remarkable perturbation of gut flora is noted at weaning from human milk,[14] and disruption of flora occurs with the use of antibiotics, especially in infancy.

TABLE 187.3

Selected Anaerobic Bacteria of Normal Flora

	Body Site (Ratio of Total Anaerobic to Aerobic Flora)[a]					
Bacteria	**Mouth (1,000 : 1)**	**Upper Respiratory Tract (4 : 1)**	**Upper Intestine (1 : 1)**	**Lower Intestine (1,000 : 1)**	**Lower Genitourinary Tract (5 : 1)**	**Skin (2 : 1)**
GRAM-POSITIVE BACILLI						
Actinomyces spp.	+	+	+/−	+	+/−	

Bifidobacterium spp.	+	+	+/−	++	+	
Eubacterium spp.	+	+/−		+	+	+/−
Lactobacillus spp.	+			++	++	
Propionibacterium spp.	+	+	+/−	+	+	++
Clostridium perfringens, Clostridium ramosum			+/−	++	+	
GRAM-POSITIVE COCCI						
Gemella spp.	++	+		+	+	
Peptostreptococcus spp.	++	++	+	++	++	+
Streptococcus anginosus, Streptococcus constellatus, Streptococcus intermedius	++	+				
GRAM-NEGATIVE BACILLI						
Bacteroides fragilis	+/−	+/−	+/−	++	+/−	
Bacteroides spp. (other)	+	+	+/−	++	++	
Fusobacterium spp.	++	+	+/−	+	+	
Porphyromonas spp.	++	+		+	++	
Prevotella melaninogenica	++	++		+	++	
Prevotella spp. (other)	++	+		+	++	
Wolinella spp.	+	+		+		+/−
GRAM-NEGATIVE COCCI						
Veillonella spp.	++	+	+/−	+	++	

[a]Mouth includes gingiva, teeth, saliva, anterior mucosa; upper respiratory tract includes nasal passages, nasopharynx, oropharyx, and tonsils; upper intestine includes duodenum, jejunum, midileum; lower intestine includes lower ileum, colon, rectum; lower genitourinary tract includes vagina, urethra, genital skin in adults.

+/−, irregularly present; +, usually present; ++, usually present in large numbers.

Data from Shah HN, Gharbia SE. Progress in the identification of nonmotile Bacteroidaceae from dental plaque. Clin Infect Dis 1994;18(Suppl 4):S287–S292; Hentges DJ. The anaerobic microflora of the human body. Clin Infect Dis 1993;16(Suppl 4):S175–S180; and Finegold SM. Anaerobic bacteria: their role in infection and their management. Postgrad Med 1987;81:141–148.

Colonization of the mouth similarly is rapid and predictable. Viridans streptococci and *Streptococcus salivarius* are present and predominate, usually within 12 hours after birth, with successive representation by facultatively anaerobic *Neisseria* and *Staphylococcus* spp. and then anaerobic streptococci, *Veillonella,* and *Bifidobacterium* spp. on the second day.[15–17] Nasopharyngeal and oropharyngeal *Streptococcus pneumoniae,* nontypable *Haemophilus influenzae,* and *Moraxella catarrhalis* follow and remain as facultative flora throughout childhood. *Prevotella melaninogenica* becomes predominant at gingival crevices, seemingly under hormonal influences, at puberty.[15,16] Predominant oral flora organisms are *Prevotella, Porphyromonas, Fusobacterium,* and non-*fragilis Bacteroides* species.

Colonization of skin varies by site and age.[17,18] Coagulase-negative staphylococci (or *Staphylococcus aureus* in nurseries where it is prevalent) appear, followed by Enterobacteriaceae at diapered sites. *Propionibacterium acnes* becomes the dominant anaerobe, quantitatively accounting for almost one half of culturable flora at most anatomic sites; anaerobic cocci also are important. Anaerobic bacteria predominate in vaginal flora, even prepubertally, with gram-positive bacilli and cocci and *Prevotella* highly represented.[19]

Clostridium ramosum and *Clostridium perfringens* are dominant clostridial species in intestinal flora. *Clostridium difficile* is found in only 1% to 4% of healthy adults and children >6 months of age. Findings of asymptomatic colonization in up to 60% of infants in neonatal intensive care units in occasional studies probably reflect unusual nosocomial phenomena.[20]

The qualitative and quantitative complexity of flora and the difficulty of its study cannot be overestimated. Within the mouth, for example, the gingival crevice has an oxidation-reduction potential of −300 mV (similar to that in the colon); the ratio of anaerobes to aerobes is 1000 : 1, yet saliva and teeth have ratios closer to 1 : 1. The normal flora of the colon contains more than 500 obligate anaerobic species in a total concentration of 10^{11} to 10^{12} colony-forming units (CFU) per gram of feces, and most organisms are unculturable.[21] The predominant gram-negative anaerobes are *Bacteroides* and *Fusobacterium* spp. Although <0.1% of normal flora consists of facultative or aerobic organisms (e.g., 10^8 CFU/g of feces), ease of recovery from endogenous infections has led to overestimation of their importance of these organisms in the microbial ecology of the gut. Similarly, the erroneous tendency is to focus on the clinically most significant anaerobic bacteria as critical in ecology. *B. fragilis,* for example, is quantitatively among the least important species of the *Bacteroides* group in normal flora. Animal models and continuous-flow in vitro culture models have been established to study microbial ecology, mechanisms of microbial interaction, and the importance of microbes in health; studies are painstaking, and conclusions are difficult to establish.[22]

Anaerobes reach a concentration of 10^6 organism/mL in vaginal secretions, with predominance of *Prevotella, Bacteroides, Fusobacterium,* and *Clostridium* spp. Anaerobes isolated most commonly from clinical specimens are *Prevotella bivia* and *Prevotella disiens.*[17]

Role of Indigenous Flora

Multiple observations lead to the conclusion that indigenous, especially anaerobic, flora organisms provide resistance to colonization and invasion by nonindigenous microorganisms. A few such observations follow:

1. Infants in an intensive care nursery are at higher risk of pharyngeal colonization with potentially pathogenic organisms if they are not colonized initially with viridans streptococci.[16]

2. Children who are colonized with group A *Streptococcus* (GAS), have recurrent GAS tonsillitis, or have recurrent otitis media or sinusitis are less likely to have inhibitory facultative (α-hemolytic streptococci) and anaerobic (*Prevotella* and *Peptostreptococcus* spp.) oropharyngeal flora.[23]

3. *Propionibacterium* spp. hydrolyze triglycerides, thus producing free fatty acids that are inhibitory to GAS and *S. aureus.*[17]

4. Primary metabolic byproducts of anaerobes, volatile fatty acids, inhibit the multiplication of nonindigenous organisms in the intestine.[17]

5. *Lactobacillus* spp. produce hydrogen peroxide, which is bactericidal for *P. bivia*, and *Gardnerella vaginalis* presence in vaginal flora is inversely related to bacterial vaginosis.[24]

6. Susceptibility of germ-free mice to colonization and outgrowth of *Clostridium botulinum* can be manipulated dramatically by selective colonization, especially with anaerobic flora.[25]

7. Infant botulism occurs exclusively in the first year of life, especially at the time of perturbation of anaerobic gut flora at weaning.[14]

8. *C. difficile* pseudomembranous colitis is highly associated with the use of antibiotics. Protection from colonization or cure of disease can be afforded to animals and humans by intestinal administration of probiotics or fecal transplant.[26–28]

9. Experimental infectivity of *Salmonella* or *Shigella* spp. is enhanced by pretreatment of animals with antibiotics; infectivity is reduced when germ-free animals are fed mixed cultures of pathogens with anaerobic bacteria.[29]

10. Susceptibility of children <2 years of age to all enteric pathogens correlates with the relative ease of disruption of indigenous flora.

11. In a double-blind, placebo-controlled trial, infants 5 to 24 months old who were admitted to a longterm care facility and whose formula was supplemented with *Bifidobacterium bifidum* and *Streptococcus thermophilus* had significantly less diarrhea and shedding of rotavirus.[30]

12. Prophylactic administration of a probiotic mixture of *Lactobacillus acidophilus* and *Bifidobacterium infantis* given to very low birth weight infants reduced the incidence of all cases of necrotizing enterocolitis as well as severe stage III necrotizing enterocolitis.[31]

13. The ability to interfere with potential pathogens has been observed for *B. fragilis, Prevotella oralis, Peptostreptococcus anaerobius, Veillonella* spp., and *Bifidobacterium* spp.[32]

Mechanisms by which normal flora provide resistance to colonization have been reviewed.[23,33,34] They include (1) production of bacteriocins and other metabolic products (e.g., volatile fatty acids) that inhibit multiplication of nonindigenous flora at local conditions of pH and oxidation-reduction potential, (2) competition for limited nutrients, and (3) competition for available attachment sites. Host factors undoubtedly provide exquisitely specific microbial niches by means of the unique properties of epithelial surfaces, enzymes, secretory immunoglobulins, pH, nutrients, exfoliation of skin and mucous membranes, motility of the gastrointestinal tract, and mucociliary movement in the respiratory tract. Coliform organisms are present in the oropharyngeal or nasopharyngeal flora of only approximately 3% of healthy adults[35] and children.[36–38] Severe noninfectious illness, viral infection, malignant disease, diabetes, chemotherapy, antibiotic therapy, and antacid therapy affect changes in colonizing bacteria.[37] Changes in attachment properties of epithelial cells in vitro correlate with changes in flora.[39] A relative or absolute increase in nasopharyngeal *S. pneumoniae, H. influenzae,* or *M. catarrhalis* occurs in association with viral illness and acute otitis media, and it predicts the presence of concordant middle ear pathogens in the acute otitis media.[36,38]

Organisms of the normal anaerobic intestinal flora also have broadly ranging metabolic effects, mainly through provision of catabolic enzymes for organic compounds that cannot be digested by enzymes of eukaryotic origin. The enzymes are necessary to: (1) process diverse dietary and host polysaccharides, thus aiding human digestion[40]; (2) catabolize cholesterol, bile acids, and steroid hormones; (3) hydrolyze certain flavonoid glycosides of plant origin to anticarcinogens; and (4) detoxify certain carcinogens and drugs.[41] Erythromycin or tetracycline treatment raises the serum digoxin level 50%, almost certainly by reducing gut *Eubacterium lentum,* which inactivates digoxin through hydrogenation of the double bond of its lactone ring.[42]

Normal flora provides “education” of the host's immune system from birth onward, and possibly earlier. Germ-free animals (and probably heavily antibiotic-exposed infants) have immune defects, such as diminished production of complement and immunoglobulins as well as reticuloendothelial and lymphoid tissues.[37] *B. fragilis* zwitterionic polysaccharide A regulates an immunologic equilibrium in the intestine by balancing colonic helper T lymphocytes, subtypes 1 and 2, and promotes anti-inflammatory interleukin-10 production.

Role of the Human Microbiome in Health and Disease

The pool of microbes inhabiting the body, the microbiota, and their collective genomes, the metagenome, comprise the microbiome. The metabolome acknowledges presence and function of microbial metabolites. The healthy human microbiome is the consequence of highly regulated host-microbial interactions. These interactions have been unraveled.[37,43] The colon is the most densely populated organ in the human body, although other surfaces (e.g., the skin, vaginal or respiratory mucosa) also harbor specific microbiota. The very existence of “commensal” aerobic and anaerobic bacteria in the gut, oropharynx, and nasal cavity infers their useful purpose.

This now has been confirmed for processes such as digestion of food and development of immune tolerance to avoid certain autoimmune and allergic diseases.

Alterations in composition and function of the microbiota have been associated with several gastrointestinal diseases (inflammatory bowel disease, colorectal cancer or irritable bowel syndrome), as well as extraintestinal diseases, such as those affecting the liver or the respiratory tract (e.g., allergy, bronchial asthma, and cystic fibrosis), among others.[44]

Effect of Antimicrobial Agents

The effect of antibiotics on normal flora is extremely complex and varies with dose and route of administration, spectrum of antimicrobial activity (breadth, potency, and specificity for anaerobes), and chemical and pharmacokinetic properties. The clinical impact depends on the duration of antibiotic use, the presence and severity of underlying conditions, exposure to nonindigenous pathogens (*Pseudomonas, C. difficile*), and host susceptibility to indigenous and nonindigenous microbes (underlying valvular heart disease, malignant disease, surgical procedures, inserted devices, and age). In general, agents that have a major impact on anaerobic flora cause the greatest disruption of homeostasis.

The main determinant of effect on oropharyngeal flora is secretion of the agent in saliva or from mucous membranes, thus correlating with lipophilicity. Clindamycin, erythromycin, and rifampin are present in high concentrations; penicillins and ampicillin, despite relatively low concentrations, have potent activity against oral facultative and anaerobic bacteria. The use of β-lactam antibiotics (even penicillin) may not supplant a species from its microbial niche but can select for organisms in the oropharynx and nasopharynx with reduced antimicrobial susceptibility (*S. pneumoniae,*[45] viridans streptococci)[46] or β-lactamase production (*Moraxella, Prevotella* spp.).[47] The nasopharyngeal flora are depleted of organisms with protective potential more with amoxicillin-clavulanate therapy than with a narrower-spectrum agent.[48]

The most profound effects on gut flora occur with administration of agents that have exquisite activity against anaerobic bacteria, which are present in high concentration at the ileal-colonic mucosa. The pharmacodynamics of specific agents is important. Exquisite activity against anaerobes (clindamycin, amoxicillin-clavulanate), high biliary excretion (ceftriaxone, cefoperazone), or the use of oral nonabsorbable agents (neomycin, gentamicin) ensures an effect on flora, but high absorption of oral agents does not necessarily predict low colonic concentrations because antibiotic is delivered to the mucosal site by blood (amoxicillin).[49] Outgrowth of *Enterococcus* and *Candida* spp. occurs rapidly when potent agents have selective nonactivity (aztreonam, ceftriaxone, cefoxitin)[50–53] or poor activity (imipenem) for enterococci.[54] The β-lactamases of certain facultative organisms (the SPACEY group [*Serratia, Pseudomonas, Acinetobacter, Citrobacter, Enterobacter,* and *Yersinia* spp.]) can be induced by cefoxitin and several third-generation cephalosporins[4,55]; β-lactamase production by anaerobes can increase[56]; or resistant nosocomial pathogens can be acquired. The use of broad-spectrum, exquisitely active cephalosporins, carbapenems, and fluoroquinolones with profound effects on normal flora undeniably have changed the incidence, microbiology, and susceptibility of superinfecting microbes in children.[55,57,58] Attempts to reconstitute flora, as with lactobacilli, have an overall positive but uncertain impact.[23,59]

Pathogenesis

Anaerobic infections are predictable because these organisms are not intrinsically highly pathogenic. Most anaerobic infections are caused by the host endogenous flora and occur at sites contiguous or related to sites of their normal residence, under permissive or instigating circumstances. Such circumstances include the following: (1) access to deep tissue through surgical intervention, trauma, tuberculous lesions, endoscopic procedures, right-to-left cardiac shunt, perforation of viscus, or massive aspiration of oropharyngeal flora; (2) impairment of normal clearance of a hollow viscus (obstruction by a foreign body, fecalith, stricture, tumor, lymph node), decreased patency of a respiratory passage (chronic otitis media and sinusitis), or dysfunctional mucociliary movement, cough, or alveolar macrophage function; and (3) lowering of oxygen reduction potential through tissue necrosis (surgical intervention, trauma), impairment of blood supply, or the presence of infection with aerobic bacteria or foreign material (aspirated foreign body, sutures, catheter, intrauterine device).

Traditionally defined host susceptibility factors (e.g., disorders of complement, hypofunction of spleen, human immunodeficiency virus infection, and cellular immune deficiencies) increase risk of infection with facultative and aerobic pathogens but generally not with anaerobic infections. Severe debilitation, malnutrition, diabetes, corticosteroid use, collagen vascular disease, cytotoxic drugs, neutropenia or neutrophil dysfunction, malignant diseases, and lymphopenia are associated with anaerobic necrotizing soft tissue infections and other invasive disease. Certain specific associations have been observed between some underlying diseases and infections involving anaerobic bacteria. They include acatalasemia with oral gangrene, trisomy 21 or human immunodeficiency virus infection with severe periodontal disease, colon cancer and neutropenia with clostridial infection and colitis, and diabetes mellitus with cholecystitis and osteomyelitis.[2,3] In an animal model, T-lymphocyte–mediated responses governed protection from *B. fragilis.*[60] *B. fragilis* bacteremia was reported in several children who underwent elective appendectomy at the time of renal transplantation and corticosteroid therapy; infection was correlated with severity of lymphopenia.[61,62]

A few anaerobic infections are of exogenous origin. These include gas gangrene after trauma, *C. difficile*–associated disease, *C. perfringens* food poisoning or diarrhea, infant botulism, and *Clostridium botulinum* and *Clostridium tetani* wound infections.

Anaerobes responsible for infection do not always correlate with their quantitative presence in normal flora. *B. fragilis, Fusobacterium necrophorum, Fusobacterium nucleatum, P. melaninogenica,* and *Actinomyces israelii* are highly overrepresented, implying specific virulence. *Bilophila wadsworthia* is associated specifically with acute appendicitis,[63] *Clostridium septicum* with typhlitis and septicemia in hematologic malignant disease,[64] *Eubacterium* and *Actinomyces* spp. with intrauterine devices,[65] and *Peptostreptococcus* and *Propionibacterium* spp. with prosthetic devices,[66] thus implying specific microbial niches. Additionally, spore-forming anaerobes, *C. botulinum, C. difficile,* and *C. tetani,* produce potent exotoxins that are responsible primarily for disease manifestations.

Virulence factors of anaerobic bacteria have been reviewed,[67] and they include the following:

- Promotion of adhesion by capsular polysaccharide and fimbriae (*B. fragilis*) and lectin (*F. nucleatum*)
- Invasion by phospholipase C (*C. perfringens*), lipopolysaccharides (*Porphyromonas gingivalis, F. nucleatum, F. necrophorum, Prevotella* spp.), and protease (*B. fragilis, F. nucleatum, F. necrophorum, Prevotella* spp.)
- Tissue infection and damage by multiple exoenzymes, such as fibrinolysin, neuraminidase, heparinase, *N*-acetylglucosaminidase (*B. fragilis, Porphyromonas,* and others), and collagenase (*C. perfringens*)
- Capsular resistance to phagocytosis, macrophage migration, and lysis by immunoglobulin A protease (*B. fragilis, Porphyromonas, Prevotella* spp.).[68] The capsule of *B. fragilis* activates host $CD4^+$ T lymphocytes, the release of interleukin-17 and chemokines,[69] and tumor necrotic factor-α and interleukin-1β from peritoneal macrophages. These cytokines lead to an increase in neutrophil adherence to mesothelial cells and abscess formation.[70]
- Production of other toxins and enzymes (elastase, hydrolytic enzymes, fibrinolysin, chondroitin sulfatase, lipase, lecithinase, gelatinase, immunoglobulin protease, botulinum toxin, tetanolysin, neuraminidase, leukocidin), various other leukotoxins (volatile fatty acids, hemolysins, hemagglutinins, lysophospholipase, proteases), endotoxins, deoxyribonuclease, ribonuclease, phosphatase, heparinase, other proteases, and other sulfatases
- Production of metabolites that are harmful to other bacteria, such as volatile fatty acids, sulfur compounds, and amines (most anaerobes)
- Production of lipopolysaccharide (*F. necrophorum*) that stimulates host-mediated damage
- Production of superoxide dismutase and catalase that permits aerotolerance

Certain clinical findings that typify anaerobic infection, such as abscess production (*B. fragilis*), burrowing through tissue planes (*A. israelii*), phlebitis, thrombosis, persistent bacteremia (*Bacteroides,* *Fusobacterium* spp.), and putrid purulence, are caused by specific components of organisms or their metabolic byproducts.[71] Although *Fusobacterium* spp. produce biologically active endotoxin, the endotoxins of *B. fragilis* and *P. melaninogenica* are chemically different and biologically inactive compared with those of coliform organisms.

An experimental animal model of intra-abdominal infection and septicemia has been studied extensively, and corollaries in the pathophysiology of human infection have been observed.[72] In summary, intraperitoneal inoculation of cecal contents, with an adjuvant such as barium sulfate or hog mucin, led to death in almost one half of animals in the first 4 days after challenge, always from *E. coli* septicemia (although the inoculum was polymicrobic). All surviving animals later demonstrated abscesses, with predominant isolation of *B. fragilis.* “Antibiotic probes” confirmed relative bacterial roles; after microbial challenge, administration of clindamycin (which activity excludes *E. coli*) did not reduce the mortality rate compared with untreated animals, but only 5% of the surviving animals had abscesses, whereas administration of gentamicin (which activity excludes *B. fragilis*) reduced the mortality rate to 4%, and 98% of surviving animals had abscesses. Administration of both antibiotics showed salutary advantages of each drug. Although these experiments suggest separate roles of microorganisms, synergistic roles of anaerobe with anaerobe, and with facultative anaerobe and aerobe, are more likely. Synergistic pathogenesis is supported by the observation of complexity of anaerobic infections (average of 3–6 microbial species), as well as by unsuccessful attempts to induce singular anaerobic infections in experimental models. The “synergy” provided could be the creation of a favorable milieu or pH, the provision of an obligatory vitamin, or an enzyme to enhance tissue spread.

Anaerobic bacteria can produce certain growth factors that confer their own selective advantage or can facilitate synergistic capabilities with other bacteria. These factors include hemin, succinate, menadione, peptides, amino acids, and steroids. Critical study remains elusive; simple therapeutic elimination of the facultative partner or partners does not reliably eradicate existing infection.[67]

Clinical Clues and Approach

Although anaerobic infections overall are not common in children and account for <2% of bloodstream infections (BSIs) in childhood, certain clinical settings or characteristics of infection are so typical as to make diagnosis of anaerobic infection almost certain (Table 187.4). Equally important, confirmation of an anaerobic infection mandates explanation of or investigation for a predisposing event or circumstance. For example, bronchoscopy is indicated for unexplained anaerobic lung abscess or empyema in children (if congenital pulmonary sequestration or cyst is not likely) or to remove a foreign body (despite a forgotten or negative history) or obstructing granulation tissue. Repeated pneumonia, bronchiectasis, or hemorrhage otherwise will result.

TABLE 187.4

Clinical Clues to Infection With Anaerobic Bacteria

Predisposition and Characteristics	Examples and Comments
PREDISPOSITION	
Infection contiguous to site of mucosal colonization	Sinuses, periodontal, oropharyngeal-orofacial (noma) pulmonary, periappendiceal, intra-abdominal, perirectal sites
Obstruction or perforation of hollow viscus	Nasal or pulmonary foreign body or anatomic abnormality, bronchiectasis, perforated appendix, chronic cervicitis or salpingitis, surgical breach of mucosa
Disruption of normal clearance mechanism	Impaired cough, gag, laryngopharyngeal function, mucociliary movement, alveolar macrophage function; unconsciousness
Excessive bacterial inoculation	Periodontal disease, massive aspiration, bite wound, right-to-left cardiac-pulmonary shunt, surgical peritoneal soilage
CHARACTERISTICS	
Marked tendency to tissue necrosis and abscess formation	Necrotizing pneumonia or lung abscess, tubo-ovarian or intra-abdominal abscess
Necrotizing cellulitis or myositis, sometimes with gas or gangrene and abscess formation	Meleney synergistic gangrene, noma,[98] and omphalitis (severe underlying malnutrition, crush injury, or ischemic tissue expected); *Clostridium*, *Peptostreptococcus*, *Bacteroides* spp. produce gas, but so do coliforms and *Pseudomonas*
Putrid exudate, putrid breath	Pathognomonic but present in less than half of anaerobic abscesses, related to volatile fatty acid byproducts; severe halitosis can be the initial or predominant complaint in nasal foreign body or lung abscess
Marked tendency to septic thrombophlebitis	Pelvic thrombophlebitis with appendiceal or genital tract infection; jugular vein thrombosis with oropharyngeal infection; clues are persistently positive blood culture or pulmonary septic emboli
Polymicrobial Gram stain of exudate	Pathognomonic; irregular uptake of Gram stain and pleomorphic, gracile, beaded, or branched morphologic features also a clue
Failure to isolate	"Sterile pus," despite positive Gram stain, especially if processing

pathogens in aerobic cultures or isolation of facultative normal flora	inadequate; isolation of microaerophilic streptococci or *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans*
Failure to respond to antibiotics without activity against anaerobes	Failure of monotherapy aminoglycoside for *Escherichia coli* intra-abdominal abscess, penicillin for lung abscess, cephalosporin for brain abscess

Intra-abdominal polymicrobial abscess in children is almost always the result of subacute ruptured appendix.[73] Table 187.5 lists infections that commonly (chronic sinusitis, aspiration pneumonia, brain abscess) or virtually always (bite or periappendicular abscess) involve anaerobic bacteria. Characteristic syndromes occur, such as that of Lemierre[74] (see Chapter 193). The triad of parenchymal lung infection, osteomyelitis of a contiguous rib, and soft tissue abscess is typical of actinomycosis[75] (see Chapter 195). Putrid odor of breath can be the clue to the presence of a nasal foreign body or anaerobic lung abscess.[76]

TABLE 187.5

Infections Commonly Involving Anaerobic Bacteria in Children and Adolescents

Oropharyngeal Flora	Intestinal or Genital Flora
Chronic sinusitis Chronic otitis media Subacute or chronic, tonsillar, parapharyngeal, peritonsillar, or parotid abscess Gingivitis, odontofacial cellulitis or abscess, noma Ludwig angina (sublingual and submandibular infection) Lemierre infection (posterior and lateral pharyngeal infection) Bite or clenched fist, fight injury abscess Paronychia Septicemia or metastatic infection related to lymphoreticular malignancy Infection of congenital cyst (pulmonary, cervical, thryroglossal) Aspiration pneumonia Necrotizing pneumonia Pneumonia with empyema Lung abscess Pneumonia–rib osteomyelitis–soft tissue abscess triad Superinfected bronchiectasis Subdural or epidural empyema Brain abscess (after sinopulmonary	Wound abscess after intestinal, genitourinary surgical procedures Perirectal, pilonidal abscess Infection related to enterocutaneous or genitourinary fistula (acquired or congenital) Peritonitis and abdominal abscess secondary to intestinal perforation (spontaneous or surgical) Periappendiceal, subphrenic, guttural abscess Hepatic, pancreatic, splenic, nephric abscess Obstructive cholangitis Septicemia or metastatic abscess related to intestinal tumor or abdominal infection Meningitis, brain abscess associated with anterior meningomyelocele; after instrumentation, dilation, surgical procedures, or trauma to colon or rectum; metastatic from *Bacteroides fragilis* bacteremia in neonate Bartholin abscess Infection related to vaginal or endometrial foreign body, surgical procedures, or instrumentation Pelvic inflammatory disease Tubo-ovarian abscess Suppurative pelvic thrombophlebitis Puerperal septicemia

infection or operation, tracheal or esophageal instrumentation for dilation, congenital heart disease)	

Microbiologic Methods

Specimen Collection

The diagnosis of anaerobic infection requires collection of appropriate specimens followed by their expeditious transportation and careful laboratory processing. The use of inadequate techniques or media can lead to an erroneous assumption that only aerobic organisms are present in a mixed infection (Table 187.6).[3] Specimens must be obtained with techniques that bypass the normal flora. Direct needle aspiration or surgical exposure is the best method of obtaining a specimen for culture (see Table 187.6).

TABLE 187.6

Methods for Collection of Specimen for Anaerobic Bacteria

Infection Site	Methods
Abscess or body cavity	Incised abscesses—syringe or swab (less desirable); specimen obtained during surgical procedure after skin is cleansed
Tissue or bone	Surgical specimen using tissue biopsy or curette
Sinuses or mucous surface abscesses	Aspiration after decontamination or surgical specimen
Ear	Aspiration after decontamination of ear canal and membrane; in perforation, cleanse ear canal and aspirate through perforation
Pulmonary	Transtracheal aspirate, lung puncture, bronchoscopic aspirate[a]
Pleural	Thoracentesis
Urinary tract	Suprapubic bladder aspirate
Female genital tract	Intrauterine brush specimen[a]

[a] Using double-lumen catheter and quantitative culture.

Transport

Liquid or tissue specimens always are preferred to swabs. Specimens should be placed into an anaerobic transporter immediately. These devices generally contain an oxygen-free environment, provided by a mixture of carbon dioxide, hydrogen, and nitrogen, in addition to an aerobic condition indicator. A liquid specimen is inoculated into an anaerobic transport vial. A syringe also can be used after all air bubbles are expelled. Because air gradually diffuses through the plastic syringe wall, however, specimens should be processed in <30 minutes. Swabs are placed in sterilized tubes containing carbon dioxide or prereduced, anaerobically sterile Cary and Blair semisolid media. A tissue specimen can be transported in an anaerobic jar or in a sealed plastic bag that has been rendered anaerobic.

Several transport systems have been developed and are useful in certain settings, such as for smaller specimens, with delayed processing, or unavoidable use of a swab specimen (Table 187.7). Compared with the Vacutainer (Becton, Dickinson, Franklin Lakes, NJ)anaerobic specimen collector, the Port-A-Cul (Becton, Dickinson) was found to be superior for isolation of anaerobic bacteria from abscesses in one study, especially when transit time was >24 hours.[77]

TABLE 187.7

Specimen Transport System for Anaerobic Bacteria

Type of System	Examples
HOLDING SYSTEM	
Enclosed tube or vial, anaerobic atmosphere, isotonic agar, moist environment	Port-A-Cul system (Becton, Dickinson, Franklin Lakes, NJ) Anaerobic transport medium (Anaerobe Systems, Morgan Hill, Calif) Agar gel transport swab[a] (Copan Diagnostics, Murietta, Calif)
PREREDUCED MEDIA SYSTEM	
Tube with anaerobic atmosphere and prereduced, anaerobically sterilized (PRAS) medium	Anaerobic transport system (Starplex Scientific, Cleveland, Tenn) Anaerobic Transport Medium (Anaerobe Systems, Morgan Hill, Calif)

[a] Care should be taken to flick off excess gel when preparing Gram stain because the gel itself can contain nonviable but Gram-stainable organisms.

Direct Examination

The general appearance (necrosis, purulence) and putrid odor of the specimen can suggest the presence of anaerobes. Inspection of clinical specimens can reveal sulfur granules, which are pathognomonic for *Actinomyces* infection. Gram stain can provide important clues, as follows[4]: (1) the presence of multiple species typifies anaerobic infection; (2) certain morphologic features are discernible (pale-staining pleomorphic *Bacteroides,* gracile fusiform *Fusobacterium,* tiny gram-negative coccal *Veillonella,* branching *Actinomyces,* boxcar *Clostridium*); and (3) findings aid interpretation of the relative importance of subsequent isolates or a sterile culture result. Immunofluorescence staining of specimens can be helpful in detection of special organisms, such as *Propionibacterium propionicum* and *Actinomyces* spp. However, this method is not yet sufficiently refined to be used for the detection of gram-negative anaerobic bacilli. Direct analysis for characteristic short-chain fatty acids by gas-liquid chromatography has been applied to blood cultures and exudate specimens, as have detection methods for *C. difficile* to stool specimens (see Chapter 190). Each examination method has limitations of practicality, sensitivity, or cost. Nucleic acid probes can detect and identify anaerobic organisms (especially for *Bacteroides* spp. and potential periodontal pathogens), and polymerase chain reaction can detect oral anaerobes, *C. difficile,* and toxins.[3] In addition, 16S (small subunit) ribosomal RNA gene sequencing can be used for strains that cannot be identified phenotypically.

Primary Isolation

Table 187.8 lists media used for primary isolation of anaerobic bacteria. Because most infections are polymicrobial, optimal recovery requires the use of nonselective and selective aerobic and anaerobic media. A minimum for isolation of anaerobic bacteria is inoculation onto supplemented blood agar and a medium selective for growth of *B. fragilis* and *Prevotella* groups (see Chapter 286).

TABLE 187.8

Media Used for Recovery of Anaerobic Bacteria

Media	Purpose
NONSELECTIVE MEDIA	
Anaerobic blood agar: *Brucella*, brain-heart infusion with yeast extract, Columbia, CDC (Centers for Disease Control and Prevention), Schaedler	Supports growth of anaerobic and facultatively anaerobic bacteria; requires vitamin K supplementation; CDC agar best for cocci, *Brucella;* Schaedler best for gram-negative bacilli
SELECTIVE MEDIA	
Bacteroides bile esculin (BBE) agar	Selects growth of *Bacteroides fragilis* group, and most hydrolyze esculin to brown-black colonies; contains bile and gentamicin, which inhibit most other

	organisms
Kanamycin-vancomycin laked blood (KVLB) agar	Selects growth of *Bacteroides* and *Prevotella* spp.; enhances pigment production of *Prevotella melaninogenica*
Phenylethyl alcohol (PEA) sheep blood agar	Supports growth of anaerobic bacteria; inhibits coliforms
Colistin-nalidixic acid blood agar	Selects growth of gram-positive bacteria; inhibits gram-negative bacteria
Cycloserine-cefoxitin-fructosec agar (CCFA)	Selects growth of *Clostridium difficile*
ENRICHMENT BROTHS	
Enriched thioglycolate (BBL-135C), chopped meat broth	Used in addition to agar, as holding, enrichment media for slow-growing organisms and for heat shock treatment for selection of spore-forming bacteria; requires vitamin K and hemin

Susceptibility Testing

Antimicrobial susceptibility patterns of anaerobes have become less predictable. Resistance to several agents, especially by gram-negative bacilli, has increased.[78,79] Screening of anaerobic gram-negative bacilli isolates for β-lactamase activity can be helpful. However, occasional strains can be resistant through other mechanisms. Susceptibility testing of anaerobes should be performed primarily to determine the activity of new agents and to monitor local, national, or international susceptibility patterns periodically. Susceptibility testing should be performed on organisms that are recovered from sterile body sites, on organisms isolated in pure culture, or on organisms that are clinically important and have unpredictable or unique susceptibility patterns. Highly virulent pathogens for which susceptibility cannot be predicted include *Bacteroides, Prevotella, Fusobacterium,* and *Clostridium* spp., *Bilophila wadsworthia,* and *Sutterella wadsworthensis*. Testing of an individual patient's isolates also can be required for serious or chronic infection, such as endocarditis, bacteremia, osteomyelitis, brain abscess, or device-related infection.[80]

Problems in antimicrobial susceptibility testing of anaerobic bacteria include lack of standardization of techniques, idiosyncrasies and fastidiousness of bacterial growth, appropriate choice of antimicrobial susceptibility breakpoints, clustering of isolates at breakpoints, lengthy testing period, and limited clinical correlation of in vitro observations. Treatment usually is based on statistical knowledge of suspected or proven pathogens and antimicrobial susceptibility patterns as tested in batches in reference laboratories. Problems with the antimicrobial susceptibility testing in reference laboratories include sources of test strains (clinical isolates versus laboratory strains versus normal flora), currency, number and relevance of representative species, and accuracy of identification.

The standardization of testing methods by the Clinical and Laboratory Standards Institute (CLSI) allows comparison of resistance trends across various laboratories.[81] This organization describes 2 reference methods (agar dilution and broth microdilution) and emphasizes that other techniques, such as gradient techniques (generally referring to E-test) or commercial broth microdilution plates, can be used as long as equivalence to the reference methods is established.[82] Nitrocefin (chromogenic cephalosporin) testing is useful for the detection of β-lactamase production and attendant resistance of *Bacteroides* spp. and *P. melaninogenica* to β-lactam agents; however, resistance of some *Bacteroides* spp. (especially *B. gracilis* and *B. distasonis*) can occur by other mechanisms, and hydrolysis of imipenem and cefoxitin may not be predicted accurately.[83,84]

Mechanisms of Resistance

Mechanisms of antibiotic resistance of anaerobic bacteria are at least as broad as those for facultative and aerobic organisms; they include β-lactamase inactivation, hydrolysis, blocking of drug target site, alteration in affinity of penicillin-binding proteins, ribosomal protection or alteration, active efflux, RNA methyltransferase, and production of adenyltransferase and acetyltransferase.[84] Determinants of resistance are transferable by multiple mechanisms, such as a conjugation-like process, transposons, plasmid self-transfer, and mobilization. At the genetic level, some resistance determinants are highly specific for one or several anaerobes or can exhibit homology with genes from facultative bacteria.[83,85]

Treatment

Principles of Management

Managing principles for anaerobic infections are (1) neutralization of toxins; (2) prevention of local proliferation of bacteria by changing the environment and (3) deterrence of bacterial spread.[86] Toxin neutralization by specific antitoxins is essential in infections caused by certain clostridia (tetanus and botulism). Control of the environment is achieved by débriding necrotic tissue, draining pus, improving circulation, alleviating obstruction, and increasing tissue oxygenation. Debridement and removal of foreign bodies are essential for successful therapy. Drainage of abscesses also is important, although certain small or multifocal tubo-ovarian, brain, and intra-abdominal abscesses can respond to antimicrobial therapy alone or in combination with percutaneous aspiration or catheter drainage.[87–90] Lung abscesses commonly drain spontaneously, or bronchoscopy is performed for diagnostic and therapeutic reasons; empyema must be drained. Lobectomy or decortication should not be performed because resolution, even of necrotizing infection, is surprisingly complete.

The use of clostridial antitoxin for gas gangrene is still controversial because (1) the necessity is less clear with aggressive surgical debridement, and (2) immediate anaphylaxis and delayed serum sickness are attendant risks.[91] The use of specific antitoxins for management of botulism, tetanus, and diphtheria is addressed in the individual chapters on these diseases.

Certain types of adjunctive therapies (e.g., such as hyperbaric oxygen therapy for infection with spore-forming gram-positive anaerobic bacilli) are controversial but can be useful. Uncontrolled reports demonstrate efficacy in individual cases.[92] The use of hyperbaric oxygen therapy is contraindicated when it could delay other essential procedures. The topical application of oxygen-releasing compounds can be useful.

Surgical therapy is the most important, and sometimes the only, form of treatment required. This includes drainage, debridement, resection, restoration of airspaces, or maintenance of blood supply. Some of these procedures can be performed percutaneously when assisted by computed tomography, magnetic resonance imaging, or ultrasonography.

Few controlled, comparative efficacy studies of treatments of anaerobic infections have been conducted, and no clinical data are available for many microbes and antimicrobial agents. Additionally, most studies involve adults or are case reports involving children. Investigations in the 1970s showed lower mortality rates in patients with anaerobic BSIs who were treated with appropriate antimicrobial agents. Later case reports and series of BSIs related to devices or malignant disease collectively suggested clinical failure of therapy using agents without activity in vitro.[93,94] The notion that treatment of infection with facultative or aerobic copathogens is sufficient for cure can be correct early in the course of certain infections, such as aspiration pneumonia and paranasal sinusitis, especially when drainage can be promoted. Established, necrotizing infections, abscesses, or BSIs, however, require specific use of effective agents. Randomized clinical studies have shown superiority of clindamycin over penicillin,[95,96] and of clindamycin over metronidazole,[97] for treatment of anaerobic lung abscess or necrotizing anaerobic pneumonia.

Antimicrobial Agents

Susceptibility of anaerobic bacteria to antimicrobial agents is shown in Table 187.9, and drugs of choice are listed in Table 187.10. Certain agents have activity against virtually all anaerobes: carbapenems (imipenem, meropenem, doripenem), chloramphenicol, and β-lactam agents combined with a β-lactamase inhibitor.[98,99] Metronidazole is the most bactericidal agent against *Bacteroides* spp. and other gram-negative anaerobes, but it has variable or minimal activity against important gram-positive cocci and bacilli, including *Actinomyces* and *Lactobacillus* spp., and some *Propionibacterium* spp. *B. fragilis* resistance to clindamycin is increasing worldwide, and clindamycin no longer is recommended as empiric therapy for intra-abdominal infections.[100–104] A study of pediatric intra-abdominal isolates revealed clindamycin resistance in only 6% of *B. fragilis* isolates, compared with 80% for *B. thetaiotaomicron* and 45% for other *B. fragilis* group isolates.[105] Resistance also has increased for many non-*Bacteroides* anaerobes including up to 10% for *Prevotella, Fusobacterium, Porphyromonas,* and *Peptostreptococcus* spp. and *Propionibacterium acnes*, with higher rates for some *Clostridium* spp. (especially *C. difficile*).[104]

TABLE 187.9

Susceptibility of Anaerobic Bacteria to Antimicrobial Agents[a]

Bacteria	Penicillin	A Penicillin and a β-Lactamase Inhibitor	Ureidopenicillin or Carboxypenicillin	Cefoxitin	Chloram-phenicol	Clindamy
Peptostreptococcus spp.	4	4	3	3	3	3
Fusobacterium spp.	3–4	3–4	3	3	3	2–3
Bacteroides fragilis group	1	4	2–3	3	3	2-3
Prevotella and *Porphyromonas* spp.	1–3	4	2–3	3	3	3–4
Clostridium perfringens	4	4	3	3	3	3
Clostridium spp.	3	3	3	2–3	3	2
Actinomyces spp.	4	4	3	3	3	3

[a] Degrees of activity: 1, minimal; 2, moderate; 3, good; 4, excellent.

TABLE 187.10

Drugs of Choice for Infections Caused by Anaerobic Bacteria

Bacteria	First Choice	Alternative
Peptostreptococcus spp.	Penicillin	Clindamycin, chloramphenicol, cephalosporins
Clostridium spp.	Penicillin	Metronidazole, chloramphenicol, cefoxitin, clindamycin
Clostridium difficile	Metronidazole, vancomycin	Bacitracin
Gram-negative bacilli (BL negative)[a]	Penicillin	Metronidazole, clindamycin, chloramphenicol
Gram-negative bacilli (BL positive)[a]	Metronidazole, imipenem, a penicillin and β-lactamase inhibitor, clindamycin	Cefoxitin, chloramphenicol, piperacillin

[a] *Bacteroides fragilis* group; *Prevotella* spp., *Porphyromonas* spp., *Fusobacterium* spp.

BL, β-lactamase.

Penicillin and ampicillin, first-, second- and third-generation cephalosporins, and vancomycin are active against most gram-positive anaerobes but have unpredictable or little activity against most anaerobic gram-negative bacilli.[98,99] Penicillin derivatives, isoxazoyl penicillins, and nafcillin are considerably less active than penicillin G against most anaerobes. Many anaerobes possess cephalosporinases, and therefore, as a class, cephalosporins have limited utility. Approximately 85% of *B. fragilis* isolates are susceptible to cefoxitin, but the other *B. fragilis* group species are more resistant.[81] Cefotetan is less effective than cefoxitin against *B. fragilis* and other members of the *B. fragilis* group. Ceftriaxone, cefoperazone, and cefotaxime are not reliable enough against gram-negative anaerobes to be useful, and ceftazidime and cefepime have poor activity against both gram-positive and gram-negative anaerobes.[105] Vancomycin and daptomycin have good activity against many gram-positive anaerobes, but they have not been studied clinically.[106]

The macrolides have moderate to good in vitro activity against anaerobes other than the *B. fragilis* group and fusobacteria.[86] Macrolides are active against pigmented *Prevotella* and *Porphyromonas* spp. and microaerophilic streptococci, gram-positive non–spore-forming anaerobic bacilli, and certain clostridia. They are less active against *Fusobacterium* and *Peptostreptococcus* spp.[107,108] For penicillins, extended-spectrum penicillins, cephalosporins (excluding carbapenems), and chloramphenicol (for *B. fragilis*), minimal inhibitory concentrations effective against susceptible anaerobic bacteria are high (requiring use of maximal doses of agents), vary by inoculum size and other in vitro conditions, and cluster around breakpoints; these features all lead to interassay, interlaboratory, and interstudy variability in reports of percentage of resistant organisms. Tetracyclines and older fluoroquinolones have unreliable activity against anaerobes. Doxycycline and minocycline are more active than the parent compound.[82] Some broad-spectrum fluoroquinolones (gatifloxacin and moxifloxacin)[109] and tigecycline[110] have significant antianaerobic activity. The carbapenems (imipenem, meropenem, doripenem, and ertapenem) have excellent activity against most clinically relevant gram-positive and gram-negative anaerobes (including *Bacteroides* and *Prevotella* spp.) except *C. difficile.*[111]

Antimicrobial resistance of anaerobes has increased for clindamycin, cefoxitin, cefotetan, cefotaxime, and piperacillin. Anaerobic bacteria always have been resistant to aminoglycosides and trimethoprim-sulfamethoxazole. Resistant isolates have been recovered infrequently for the carbapenems, metronidazole, and the combinations of β-lactam and β-lactamase inhibitors.[75,82,112,113] The production of β-lactamase is the resistance mechanism of the *B. fragilis* group, as well as increasing numbers of other *Bacteroides, Prevotella, Porphyromonas,* and *Fusobacterium* spp.

Although susceptibility testing of isolates recovered from selected cases can provide information that affects management, therapy often is empiric and is based on knowledge of likely anaerobic and aerobic organisms, expected in vitro susceptibility, and pharmacodynamics of agents. Treatment of mixed infection should cover most aerobic and anaerobic pathogens.[73] Combination therapy is always required for intracranial abscesses (e.g., with penicillin or vancomycin plus metronidazole plus a third-generation cephalosporin) and for intra-abdominal infection (e.g., with metronidazole plus ampicillin plus cefepime or gentamicin).[102] Cefoxitin or ceftizoxime (neither of which is active against *Enterococcus* spp.), piperacillin-tazobactam, or a carbapenem if needed for expected gram-negative aerobes, could be used as monotherapy.[73] In a retrospective cohort study, monotherapy (piperacillin-tazobactam, meropenem, cefoxitin, or ceftriaxone) versus aminoglycoside-based triple-antibiotic therapy for children with ruptured appendicitis showed at least equal efficacy.[114] Nosocomial acquisition of infection affects antibiotic choice, especially to include agents with activity against expected or proven facultative or aerobic organisms.

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188

Clostridium tetani (Tetanus)

Itzhak Brook

Tetanus is caused by a neurotoxin produced by *Clostridium tetani*. It is common in warmer climates. The worldwide incidence of tetanus is approximately 1 million cases annually. Although a major cause of morbidity and mortality in developing countries, tetanus is rare in the United States, with approximately 35 to 70 cases reported annually to the Centers for Disease Control and Prevention (CDC).[1] Reported cases are estimated to represent 60% of actual cases. Tetanus remains a likely diagnosis in certain clinical situations even in developed countries, and individual patients suffer severe morbidity. The decline in tetanus in developed countries is the result of an effective immunization program.

Most cases of tetanus occur in unvaccinated people and in adults; people older than 60 years of age account for 60% of the cases and for 75% of deaths from tetanus in the US. In the US, the current average annual incidence of tetanus is 0.1 cases/million and 0.023 cases/million among people ≥65 years of age.[1] The case-fatality rate is 13.2% overall but 31.3% in people ≥65 years of age. Approximately 15% of cases occur in diabetic patients or intravenous drug users. Approximately 75% of cases of tetanus in the US follow acute injuries, with less than one half of these injuries occurring outdoors. Chronic wounds and abscesses, wounds associated with a foreign body (e.g., splinters, thorns), surgical wounds, major trauma, parenteral drug abuse, and animal-related injuries are responsible for 25% of tetanus-associated injuries; approximately 20% of wounds are from unknown circumstances, and in 5% of cases of tetanus, no wound source can be identified. Rare causes of tetanus are burns and otitis media.[2]

Microbiology and Pathogenesis

C. tetani is a slender, gram-positive, nonencapsulated, motile, obligatively anaerobic bacillus that exists in vegetative and sporulated forms. The genome of the organism has been sequenced.[3] The sporulated form has a characteristic drumstick microscopic appearance because of the terminal position of spores. Spores are highly resistant to disinfection by chemicals or heat, but vegetative forms are susceptible to the bactericidal effect of heat (autoclaving at 121°C and 103 kPa [15 psi] for 15 minutes), to chemical disinfectants (iodine, glutaraldehyde, hydrogen peroxide), and to certain antibiotics.[4]

Spores are ubiquitous in soil and the gut of mammals; they are dormant and nonpathogenic in soil or contaminated tissue until conditions are favorable for transformation to the vegetative, pathogenic form. Such conditions are those of locally decreased oxygen reduction potential as created in devitalized tissue by a foreign body, trauma (especially crush injury), or suppurative infection.

C. tetani is noninvasive and does not cause an inflammatory response or tissue destruction. Disease is initiated by exotoxins. Two toxins are produced, tetanolysin (of uncertain importance) and tetanospasmin (a potent neurotoxin responsible for clinical tetanus). Tetanospasmin, often referred to as “tetanus toxin,” is encoded on a plasmid present in all toxigenic strains,[5] and it is released with growth of *C. tetani* at the site of infection. Tetanospasmin affects the neuromuscular end plates and the motor nuclei of the central nervous system, thereby causing skeletal muscle spasm and convulsions. Mechanisms of absorption and transport of tetanospasmin are not understood completely, but 2 mechanisms are speculated.[6] If a large amount of tetanospasmin is produced, spread to neurons through the bloodstream and lymphatic system occurs, causing spasm at sites distant from the site of infection that first affect muscles with the shortest neural pathway. Lockjaw and risus sardonicus, often seen in generalized tetanus, reflect this pathophysiologic process and are associated with rapidly progressive, severe disease. From the site of production, small amounts of neurotoxin also can ascend the neural axis (and sometimes the spinal axis cranially) to cause localized tetanus. The timing of onset of muscle involvement is proportional to the neural distance from the site of injury.

Tetanospasmin primarily gains access to the nervous system through the neuromuscular junction, where it migrates in retrograde fashion transsynaptically, protected from neutralizing antitoxin, to affect inhibitory synapses, where it prevents release of acetylcholine.[5] Uninhibited lower motor neurons increase tone of agonist and antagonist muscles, thereby causing characteristic localized spasms and rigidity.

Tetanospasmin also can prevent transmission at neuromuscular junctions and thus cause paralysis. The effect of the toxin on the brain is controversial; direct inoculation can cause seizures, but spasms of tetanus probably result from the spinal rather than the supraspinal action of tetanospasmin. Affected patients are fully conscious. Some clinical manifestations of tetanus suggest involvement of the sympathetic nervous system. The effect of tetanospasmin is permanent; recovery depends on ultrasprouting of neurons.

Clinical Manifestations

Tetanus is divided into clinical patterns that reflect host factors and the site of inoculation: generalized, localized, cephalic, and neonatal. In most cases, the site of injury, which often is minor, can be determined. Inability to identify a portal of entry does not exclude the diagnosis, especially in unimmunized people. The appearance of a wound is not helpful in diagnosis, but circumstances of occurrence are (e.g., severity of crush injury and soil contamination). In the US, most cases of tetanus occur after puncture wounds, farming or gardening activities,[2] or the use of illicit drugs.

The interval between the time of injury and the appearance of symptoms has important prognostic significance; the shorter the interval (<7 days), the worse the prognosis. The frequency and severity of clinical manifestations depend on the amount of toxin that reaches the nervous system. The portal of entry also is an important prognostic factor. Certain injuries (e.g., compound fracture, puncture wound in a drug user) or infections (e.g., that following abortion, infection of a neonate's umbilical stump, burn wound) have poor prognoses. Involvement of the autonomic nervous system portends a poor prognosis. Such data have been used to develop scoring systems to predict severity and prognosis.[5]

Generalized Tetanus

Generalized tetanus, which is a neurologic disease manifesting as trismus, dysphagia, and severe muscular spasms, is the most common manifestation of tetanus, usually occurring as a complication of localized tetanus that is recognized only in retrospect. The onset can be insidious over a period of 1 to 7 days. Trismus (lockjaw), the most common presenting symptom, commonly is mistaken as a manifestation of parapharyngeal infection or temporomandibular joint problems. A history of stiffness of the back or rigidity of the neck or abdomen frequently is recognized in retrospect. A subtle “sarcastic smile” (risus sardonicus) may be noticed, and rigidity of the abdominal muscles is detectable on examination.

As the disease progresses, additional muscle groups become involved, the most striking involvement being of the paraspinal musculature. The most dramatic feature of generalized tetanus is the very painful, generalized tetanic, opisthotonic spasm manifest as arching of the back (sometimes with just head and feet touching the bed) to resemble decorticate posturing (Fig. 188.1). The force can produce fractures of the vertebrae or other bones and hemorrhage into muscles. The periodicity of tetanic spells can cause confusion with seizures; however, patients with tetanus, unlike patients with seizures, do not lose consciousness. Spasms often are triggered by sensory stimuli. Respiratory compromise during tetanic spells can be life-threatening; upper airway obstruction is common, and with additional involvement of abdominal and diaphragmatic muscle, apnea can occur.

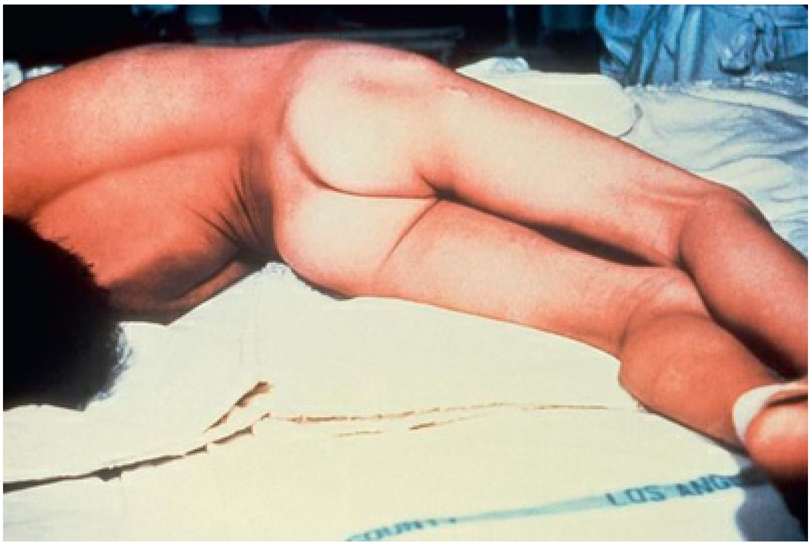

FIGURE 188.1 The patient is displaying opisthotonic posturing caused by *Clostridium tetani* exotoxin. (Courtesy of US Centers for Disease Control and Prevention.)

Symptoms of autonomic overactivity generally are manifest in early phases as irritability, restlessness, sweating, and tachycardia. In later phases, profuse sweating, cardiac arrhythmias, labile hypertension or hypotension, and fever commonly are present.[7] Episodes of bradycardia and hypotension can lead to cardiac arrest. Cardiac arrest also has been attributed to myocardial damage caused by the high catecholamine level,[8] as well as by toxic damage to the brainstem.[9] Fever can result from sympathetic overactivity or from superinfections, such as pneumonia.[10] Spasms and cardiovascular complications occur most commonly during the first week and resolve slowly during the ensuing 2 to 4 weeks.

Even with available treatment, generalized tetanus usually worsens in the first 2 weeks after diagnosis, with recovery occurring over the subsequent 3 to 5 weeks. If antitoxin is not given, disease persists for weeks to months until cessation of production and binding of tetanospasmin and the formation of new neuromuscular junctions.

Localized Tetanus

Localized tetanus is an unusual presentation. Muscles near the entry wound become painful and weak within 2 to 3 days after the injury and then become rigid; deep tendon reflexes are hyperactive. Rigidity usually persists for weeks to months and resolves spontaneously without progressing, although disease can progress to generalized tetanus.[11] Localized tetanus has a mortality rate <1%. In partially immune patients, neutralization of local toxin and heightened production of antitoxin can prevent generalized tetanus.

Cephalic Tetanus

Cephalic tetanus is a rare presentation, the result of decreased neuromuscular transmission of the lower cranial nerves affected because of wounds on the head and neck. Clinical manifestations usually occur 1 to 2 days after injury and can include facial palsy, dysphagia, paresis of extraocular muscles (ophthalmoplegic tetanus),[12] and supranuclear oculomotor palsies.[1,13] The mechanism of the last clinical manifestation is not clear. Usually, cephalic tetanus has a poor prognosis, although some patients have good outcome. Cephalic tetanus has been reported in patients after complete immunization. Cephalic tetanus can precede generalized tetanus.

Neonatal Tetanus

Neonatal tetanus is a generalized form of the disease that occurs only in infants born to inadequately immunized mothers. Tetanus usually follows infection of the umbilical stump, which can result from poor obstetric procedures, delivery outside a healthcare environment, inadequate postnatal care, or cultural practices such as application of cow dung or soil to the umbilical stump. Immunization of adolescent girls and women of childbearing age, appropriate training of midwives, and topical application of antibiotics can reduce the risk of neonatal tetanus. Neonatal tetanus is rare in developed countries but remains a significant problem in developing countries.[1,14]

Weakness and inability to suck are the most common manifestations, often appearing between 5 and 7 days of age (range, 3–24 days). Later, generalized tetanic spasms, rigidity, and opisthotonus occur (Fig. 188.2). The mortality rate is >90%, and death can be secondary to a hypersympathetic state. The major causes of death are apnea in the first week and septicemia in the second week, generally as a result of infection that originated at the umbilical stump. Other complications are pneumonia, pulmonary or central nervous system hemorrhage, and laryngeal spasm. Poor prognosis is associated with risus sardonicus, fever, age <10 days, and delayed presentation for medical care.[15]

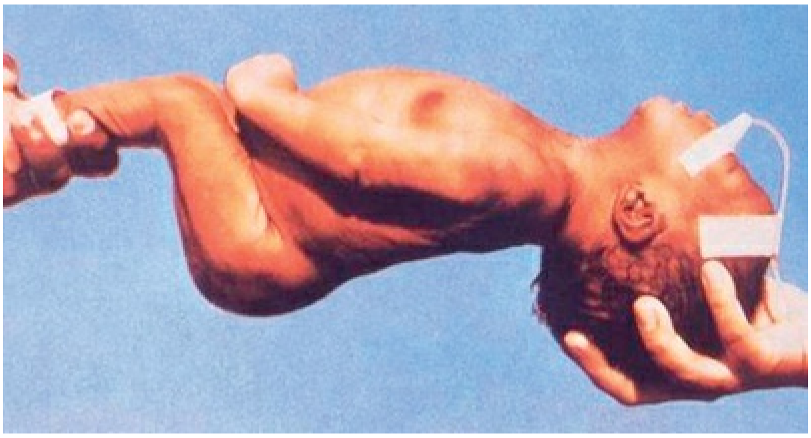

FIGURE 188.2 This infant with neonatal tetanus is displaying body rigidity produced by *Clostridium tetani* exotoxin. (Courtesy of US Centers for Disease Control and Prevention.)

Improvement is heralded by defervescence (usually within 3–7 days), decrease in the number of episodes of spasm, and slow resolution of rigidity. Complete resolution can take up to 6 weeks. Developmental disability often occurs in survivors.

Diagnosis and Differential Diagnosis

The diagnosis of tetanus is made from clinical findings in a setting of risk and by excluding other causes of tetanic spasms. Recovery of *C. tetani* from wounds is not helpful because the presence of this organism does not necessarily indicate toxin production. Laboratory tests are useful only to exclude other diseases; management cannot be delayed until test results are available. Although generalized tetanus and cephalic tetanus are recognized easily, the diagnosis can be unsuspected if no portal of entry is identified. Given the clinical suspicion, a history should be elicited regarding chronic otitis media, otitis externa, recent intramuscular injection, a minor surgical procedure, intravenous drug abuse, and rectal or vaginal instrumentation. Neonatal tetanus becomes apparent shortly after initial manifestations. Localized tetanus can be unrecognized until generalized manifestations occur. Trismus must be differentiated from manifestations of parapharyngeal and retropharyngeal infections.

The differential diagnosis of generalized tetanus includes stiff man syndrome,[16] pseudotetanus,[17] meningitis, encephalitis, hypocalcemic tetany, seizures, rabies, dystonic reactions to neuroleptic drugs or other central dopamine antagonists (for which treatment with an anticholinergic agent is rapidly effective), hysterical conversion reaction, and strychnine poisoning. Although strychnine poisoning is the most commonly confused intoxication, patients with such poisoning lack trismus and abdominal rigidity between spasms. Biochemical analysis of blood and urine for strychnine is performed in patients with suspected generalized tetanus. Conversely, tetanus always should be considered when strychnine poisoning is suspected.

Treatment and Outcome

The goals of management of tetanus are eradication of *C. tetani*, neutralization of toxin, and provision of specific supportive care.[18]

Providing aggressive, yet restrained, supportive care with a minimum of stimulation is challenging. Transfer to an optimal setting should be accomplished early in the disease, before the severity of spasms precludes moving the patient. Survival depends on minimizing morbid or fatal spasms over a prolonged period. The patient is protected from stimuli by isolation in a noise-free, darkened room, with a nurse in the room at all times, monitors silenced, and a sentry nurse positioned outside the door to limit entry and to reinforce minimal examination and manipulation of the patient.

The child with tetanus should be sedated, and human tetanus immune globulin (TIG) should be administered immediately. TIG neutralizes circulating tetanospasmin. Recommended dosage and administration of TIG are shown in Table 188.1.[19,20] Local infiltration of part of the dose around the wound is recommended. However, the efficacy of this technique has not been proven. In countries where TIG is not available, equine tetanus antitoxin (TAT) is an alternative. It is administered after adequate testing for sensitivity and desensitization if needed. Immune globulin intravenous (IGIV) can be given if TIG is not available.

TABLE 188.1

Treatment of Tetanus

Agent	Dosage and Administration
Tetanus immune globulin, human (TIG)	Single dose, 3,000–6,000 U IM[a]
Tetanus antitoxin (TAT)[b]	Single dose, 50,000–100,000 U after appropriate testing is performed for sensitivity and desensitization if necessary; part of dose (20,000 U) is given IV, and the remainder IM
Immune globulin intravenous (IGIV)	Single dose of 200–400 mg/kg IV can be considered if TIG is not available; not approved for this indication
Metronidazole	30 mg/kg/day (maximum, 4 g/day) divided into q6h doses PO or IV for 10–14 days
Penicillin G	100,000 units/kg/day (maximum, 12 million U/day) divided into q6h doses IV for 10–14 days
Tetracycline	25–50 mg/kg/day; an alternative; not approved for children <8 years old

[a] Some experts recommend a single dose of 500 units IM, which appears to be as effective and causes less discomfort.[14,15]

[b] TAT is not available in the United States; it should be used elsewhere only if TIG is not available.

IM, intramuscularly; IV, intravenously; PO, orally.

Local wound care is essential. Foreign bodies, if present, are removed; the wound is irrigated vigorously and debrided to remove devitalized tissue. Extensive debridement of puncture wounds is not needed. Excision of necrotic tissue may be required, but excision of the umbilical stump is no longer recommended in cases of neonatal tetanus.

C. tetani is susceptible to penicillins, cephalosporins, metronidazole, macrolides, tetracyclines, and imipenem.[21] Although the utility of antimicrobial therapy in tetanus is controversial, specific therapy should be given (see Table 188.1). Oral or intravenous metronidazole or parenteral penicillin G is appropriate. Oral tetracycline and intravenous vancomycin are effective against *C. tetani*, but the cephalosporins are not reliably active. When a polymicrobial infection is present, broad antimicrobial coverage may be necessary.

A single, nonblinded clinical study performed in Indonesia compared oral metronidazole with intramuscular penicillin for treatment of tetanus.[22] Patients treated with metronidazole had less progression of disease (i.e., severity and frequency of spasms), shorter hospital stays, and better overall survival rates. The validity of these findings may have been compromised by an inadequate dose of penicillin given intramuscularly, the administration of which can increase the severity and frequency of tetanic spasms. Although theoretically penicillin could act synergistically with tetanospasmin to worsen neuromuscular effects,[23] extensive experience has been accrued for penicillin treatment of tetanus.[24]

Sedation and muscle relaxation in patients with mild cases should be accomplished, generally with diazepam, 0.1 to 0.2 mg/kg given intravenously every 4 to 6 hours. Ventilatory assistance is imperative at higher doses. Other benzodiazepines (lorazepam or midazolam) are equally effective. Additional sedation with a phenothiazine drug is appropriate; use of phenothiazine alone is less effective than sedation with diazepam. If spasms are not controlled effectively, therapeutic paralysis is necessary. Neuromuscular blockade can be achieved with curariform drugs. The agents used most often are pancuronium and vecuronium.

Suppression of excessive catecholamine release (which induces the autonomic dysfunction) can control the dysautonomia. Labetalol (0.25–1.0 mg/min) frequently has been administered because of its dual α- and β-blocking potential. β-Blockade alone (i.e., with propranolol) should be avoided because of the danger of sudden death.[25] Morphine sulfate (0.5–1.0 mg/kg/hr by continuous intravenous infusion) is used commonly to induce sedation and to control autonomic dysfunction by reducing sympathetic tone in the heart and the vascular system, thus controlling cardiac instability without causing cardiac compromise.[26] Other agents available for the treatment of various autonomic events are atropine, clonidine, and epidural bupivacaine.[27]

Of the foregoing drugs only magnesium sulfate was evaluated in a randomized clinical trial,[28] as well as in clinical series for controlling spasms.[29–32] The results of these studies brought about the use of magnesium titrated to clinical end points as a first-line agent in the management of tetanus. Magnesium is a vasodilator, and it reduces catecholamine release from the adrenal medulla[33] and adrenergic nerve endings.[34]

In a randomized, double-blind study of 256 patients, magnesium sulfate infusion (loading dose 40 mg/kg over 30 minutes, followed by continuous infusion of 2 g/hr for patients >45 kg or 1.5 g/hr for patients ≤45 kg) was compared with placebo.[28] Magnesium sulfate significantly reduced the need for other drugs to control muscle spasms, and patients were 4.7 times (95% confidence interval, 1.4–15.9) less likely to require verapamil to treat cardiovascular instability than were subjects in the placebo group.

Hypotension, if present, is treated initially with saline solution; if hypotension remains unresolved, a pulmonary catheter is placed for monitoring, and fluid, dopamine, or norepinephrine is administered as indicated.

Nutritional support should be initiated as soon as possible to sustain the patient's high caloric and protein needs. Enteral feeding is preferred; a percutaneous endoscopic gastrostomy tube is used commonly to limit gastroesophageal reflux compared with a nasogastric tube. Prevention of thromboembolism can be attained with heparin, low-molecular-weight heparin, or other anticoagulants, and it should be begun early. Because patients often become disabled because of the drug-induced paralysis and immobilization, physical therapy should be initiated as soon as spasms have abated.

Complications of tetanus are shown in Table 188.2.

TABLE 188.2
Complications of Tetanus

Complications	Comments
Cardiomyopathy	Direct toxic effect
Phrenic nerve palsy	Direct toxic effect
Laryngeal nerve palsy	Direct toxic effect
Respiratory compromise	Secondary to spasms
Rhabdomyolysis	Secondary to spasms
Myositis ossificans circumscripta	Secondary to spasms
Vertebral compression fracture	Secondary to spasms
Hypoxic cerebral injury	Secondary to respiratory compromise
Acute renal failure	Secondary to rhabdomyolysis
Psychological effects	Most prominent after recovery

Prevention

No reliable natural immunity to tetanus exists. Prevention consists of providing neutralizing antibody to tetanospasmin in case *C. tetani* contaminates and multiplies in a wound.

Primary Prevention

Primary prevention is pre-exposure immunization, consisting of primary immunization followed by booster doses of tetanus toxoid–containing vaccines (TT) throughout life.[35] Schedules are shown in Table 188.3.[36] The goal of immunization is to provide a continuous serum concentration of 0.01 IU/mL of neutralizing antitoxin.[37,38] Protection between levels of 0.01 and 1.0 IU/mL is not absolute; some authorities consider an antibody level of 0.15 IU/mL or greater as protective.[39]

TABLE 188.3

Prevention of Tetanus

PRIMARY IMMUNIZATION[a]				
Age	**Vaccine**			
2 mo	DTaP			
4 mo	DTaP			
6 mo	DTaP			
12–18 mo	DTaP			
4–6 yr	DTaP			
≥11–12 yr	Tdap once			
Every 10 yr (booster)	Td			
SECONDARY IMMUNIZATION[b]				
History or Dose of Tetanus Toxoid Administration	**Clean Minor Wound**		**All Other Wounds**[c]	
	TIG	**Td**[d]	**TIG**	**Td**[d]
<3 doses or unknown	No	Yes	Yes	Yes
≥3 doses[e]	No	No[f]	No	No[g]

[a] If an infant has contraindications to pertussis vaccine, diphtheria and tetanus toxoids (DT) are given on the same schedule; if primary immunization is begun at 7 years, Td/Tdap is used (see Chapter 162).

[b] See text for important details.

[c] Such as, but not limited to, the following: wounds contaminated with dirt, feces, soil, or saliva; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns, and frostbite.

[d] For children <7 years old, DTaP (DT if pertussis vaccine is contraindicated) is preferred to tetanus toxoid alone; for persons >7 years old, Td is preferred to tetanus toxoid alone. For children and adolescents, Tdap should be used when Td is indicated if the patient has not already received Tdap.

[e] If the patient has received only 3 doses of fluid toxoid, a fourth dose of toxoid, preferably an adsorbed toxoid, should be given.

[f] Yes, if >10 years since last dose.

[g] Yes, if >5 years since last dose (more frequent boosters are not needed and can accentuate side effects).

DTaP, diphtheria and tetanus toxoids and acellular pertussis; Td, tetanus and diphtheria toxoids; Tdap, tetanus and diphtheria toxoids and reduced acellular pertussis; TIG, tetanus immune globulin.

Several longterm follow-up studies indicated that protective antitoxin levels persist in 91% to 96% of people 10 years after receipt of the initial 3-dose series of TT as infants.[40–42] In 1 study, 70% of the subjects >6 years of age and living in the US had antibody levels ≥0.15 IU/mL.[43] The presence of protective antibody dropped with age from >90% in children 6 to 9 years of age to 80% in children 10 to 16 years of age, to <28% in adults ≥70 years of age. Rates of seronegativity reflect the time since immunization or the lack of immunization.

Immunodeficient people may not acquire adequate response to TT and require passive immunization. Stem cell or bone marrow transplant recipients must be revaccinated with at least 2 doses.[44] In 1 study, although only 38% of human immunodeficiency virus–infected children and adolescents had protective tetanus antibody levels, most developed and maintained protective levels after booster administration.[45] Severe anaphylactic reactions, brachial neuritis, and Guillain-Barré syndrome following TT administration have been reported rarely.

Secondary Prevention

Secondary prevention consists of administration of vaccine and antitoxin (TIG) after a tetanus-prone injury (see Table 188.3), with the need determined by the type of injury and the patient's immunization history. Although wounds with major tissue injury are most tetanus prone, any type of wound, if contaminated, can lead to tetanus.[14] Immunization is given immediately if the patient's tetanus immunization history is not available or is uncertain or if 60 months or more have elapsed since the last TT booster dose. When indicated by immunization history, TIG is given intramuscularly in a dose of 250 units (regardless of age or weight). Immune globulin intravenous or equine tetanus antitoxin is recommended if TIG is unavailable. Decisions on the need for TIG for infants <6 months of age who have not received a full 3-dose primary vaccine series should be based on the mother's TT immunization status at the time of delivery. Additional circumstances warrant the use of TIG in immunized people, including anticipated impairment of response to vaccine, and in certain wounds, such as major burns, frostbite, crush injury, or injury by avulsion, puncture, or missile.

Hyperimmunization (multiple booster doses of toxoid over a short time) can cause severe local reactions at the injection site, such as swelling of the entire arm. Patients with such reactions have high antitoxin levels.[46] Preformed antitoxin forms complexes with administered toxoid and induces an Arthus type II hypersensitivity response. The use of tetanus toxoid in situations where it is not indicated is inappropriate.

Tertiary Prevention

Tertiary prevention consists of antitoxin and immunization given after clinical tetanus is manifest. Tetanus does not provide protective immunity, probably because the minute amount of toxin produced is insufficient to elicit an immune response.[47] All patients should complete a series of immunizations with tetanus toxoid, beginning at presentation.

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189

Clostridium botulinum (Botulism)

Sarah S. Long

Botulism is a neuroparalytic disease caused by the action of a heat-labile neurotoxin produced almost exclusively by *Clostridium botulinum.* Botulism is categorized by modes of acquisition: (1) *foodborne botulism,* which results from the ingestion of preformed toxin elaborated in food that was naturally contaminated with spores and improperly preserved; (2) *infant botulism,* which results from intestinal colonization, outgrowth, replication, and toxin elaboration after the ingestion of spores; and (3) *other,* which includes wound botulism resulting from contamination of wounds with spores, outgrowth, and toxin elaboration; adult intestinal toxemia botulism resulting from intestinal colonization and in vivo toxin production, usually in the context of abdominal surgical procedures, gastrointestinal tract abnormalities, and recent antibiotic treatment; and accidental botulism resulting from high-dose injection of toxin for treatment of muscular movement disorders or injection of an unlicensed product for cosmetic purposes.[1–5]

Since recognition of infant botulism in 1976, approximately 3300 cases were reported in the United States through 2014. Although the US reports 90% of botulism cases worldwide, cases have been reported from every continent except Africa.[6] Infant botulism is the most common form of botulism, accounting for approximately 75% of all US cases, with a mean of 112 cases annually from 2001 through 2014.[7] Increase in cases over time may be real or related to increased awareness (Fig. 189.1). Infant botulism is the primary focus of this chapter.

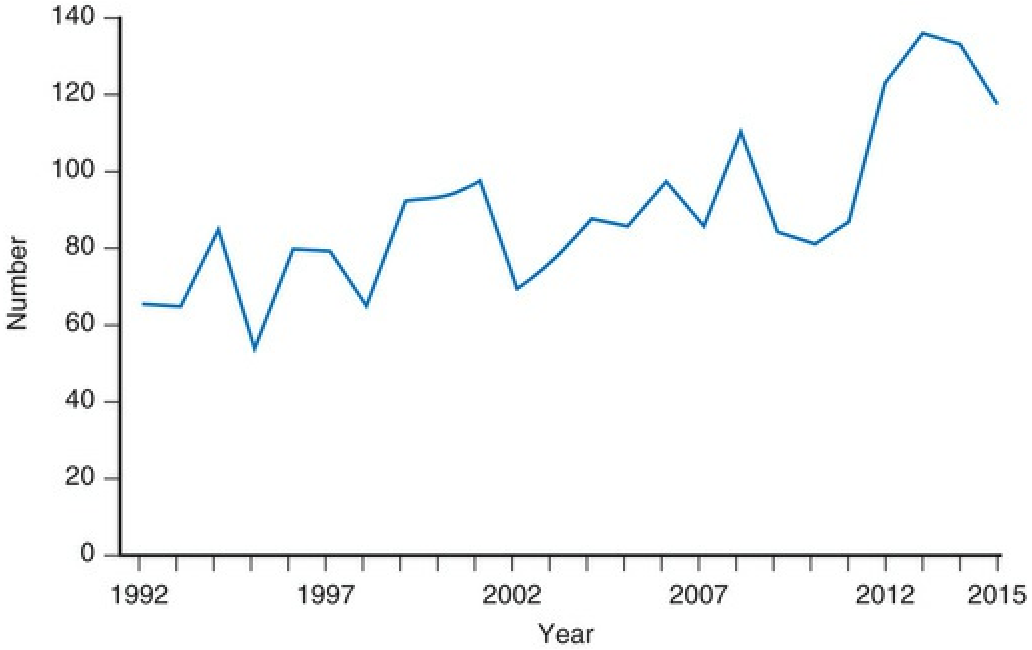

FIGURE 189.1 Number of reported cases of infant botulism by year in the United States from 1992 to 2015. Cases numbers for 2015 are provisional. (Redrawn from data from the National Notifiable Diseases Surveillance System in Centers for Disease Control and Prevention. Summary of notifiable diseases—United States, 2012. MMWR Morb Mortal Wkly Rep 2014;61:1–55.)

Etiology and Pathogenesis

Organisms and Toxins

C. botulinum represents a heterogeneous group of gram-positive, anaerobic, spore-forming bacilli, individual strains of which can produce 1 of 7 serologically distinctive neurotoxins (BoNT) types A through G. More than 98% of cases of infant botulism in the US are caused by BoNT/A or BoNT/B; rare cases cause by BoNT/C,[8] BoNT/E,[9–11] BoNT/F,[11,12] and BoNT/G[13] are reported in the US or elsewhere. *Clostridium butyricum*[10,11] is responsible for rare cases caused by BoNT/E, and *Clostridium baratii* is responsible for BoNT/F cases of infant botulism in neonates.[12,14,15] Clinical cases occasionally demonstrate mixed toxin types and are designated by primary toxin and secondary toxin, (e.g., BoNT/Ba or BoNT/Af).

Unexpressed botulinum toxin genes can be found in a variety of clostridial species, and more than 1 toxin type can be found in a single *C. botulinum* strain.[16,17] Amplified fragment length polymorphism (AFLP) analysis of a national collection from cases and related environmental samples showed 154 clades and co-location of clades between individual cases and their environment (with 52% of isolates clustered in 2 clades). A single clade could be associated with a spectrum of case severity.[6]

After systemic absorption, BoNT is concentrated at the plasma membrane of the neuron, and it is taken into the synaptic vesicle where it binds irreversibly to receptors on presynaptic cholinergic and adrenergic nerve endings; a portion is internalized, cleaving synaptosomal-associated protein of 25 kd (SNAP-25) and shutting down the neuroexocytosis apparatus within the cell and acetylcholine release.[13,18] With intoxication at 70% or more junctions, clinical voluntary muscular and autonomic function is impaired; with intoxication at 90%, diaphragmatic muscular function is impaired. Recovery depends on the 30-day regeneration of SNAP-25. Neutralizing antitoxin effectively binds toxin only before internalization of the toxin molecule. *C. baratii* BoNT/F cleaves synaptobrevin, which in a rat model has a 7-day regeneration time.[12]

Botulinum toxins are similarly structured, large, single polypeptides and are the most potent toxins known; 10^{11} molecules (0.3 ng) reaching neuromuscular junctions are enough to cause clinical botulism. BoNT/A is the most avidly binding and potent toxin and is associated with the most severe disease. BoNT is acid and enzyme resistant but can be destroyed by heating of food to the boiling point (100°C) for 10 minutes. Certain environmental conditions, such as anaerobic conditions, pH >4.6, warm temperature (>39°C), and high moisture content, promote outgrowth of spores to vegetative forms and production of toxin in food. Spores of *C. botulinum* are heat resistant, withstanding 100°C for hours; food must be heated under pressure to temperatures of 116°C to destroy spores.

Pathophysiology

In more than 90% of cases in the US, infant botulism results from unrecognizable ingestion of botulinal spores from dust. Since the recommendation to avoid feeding honey to infants,[2,4,5] infant botulism has been infrequently associated with honey, but honey still is a significant source of spores for cases in other countries.[9,19,20] The gastrointestinal tract of children and adults is resistant to outgrowth of *C. botulinum* spores, but in infants younger than 12 months of age occasionally it is permissive of such outgrowth. Age-related vulnerability is related at least partially to lack of competitive flora and possibly to pH and motility. Experimentation and observation in a mouse model provided compelling evidence of the importance of competitive flora in protection, such as the following: (1) age-limited (7–13 days) natural susceptibility to intestinal colonization by *C. botulinum* spores; (2) ongoing susceptibility in germ-free adults; (3) acquisition of resistance in germ-free adults after replacement in a normal cohort colony for 3 days; (4) resistance after establishment of selective, limited intestinal flora; and (5) loss of resistance after antibiotic suppression of intestinal flora.[21,22]

The necessary components of resistance are undoubtedly complex, but *Bacteroides, Lactobacillus,* and other *Clostridium* spp. are inhibitory to *C. botulinum.* Stool flora of 7 infants delineated at first manifestations of botulism showed a relative paucity of *Bacteroides* and *Lactobacillus* spp.[23] The putrefactive intestinal flora of the infant who is fed formula and the fermentative flora of the infant who is fed human milk would be expected to be inhibitory. Epidemiologic data support the theory that the period of permissiveness of the gut of the infant fed formula is brief (i.e., competing flora is established rapidly[24]), and that of the infant fed human milk is more extended and is especially heightened during perturbation of flora during weaning.[25] Infant botulism is more often associated with feeding of formula in infants <1 month of age, but by 4 months of age almost 100% of infants with cases are fed human milk.[26] The natural occurrence of infant botulism in horses (shaker foal syndrome) and ducks (limberneck) suggests a similar age-related vulnerability to colonization in animals. The rare cases of intestinal toxemia botulism in older persons almost always have been associated with an underlying gut anomaly[3] or a presumed alteration of gut flora, pH, or motility by surgical procedures and drugs.[27]

Epidemiology

Environmental Exposure

Potential sources of *C. botulinum* spores are the environment and naturally contaminated foodstuffs. *C. botulinum* spores are ubiquitous worldwide, found in cultivated and virgin soil, in aquatic sediment and marine life, and in the intestinal content of birds. *C. botulinum* strains producing BoNT/A, BoNT/B, and BoNT/F generally are found in areas of low rainfall and moderate temperature, whereas those producing BoNT/D and BoNT/E are associated with water.[9,28] In the most recent soil survey in the US performed in 1975, 23% of soil samples contained botulinal spores, and *C. botulinum* spores producing BoNT/A, BoNT/B, BoNT/C, BoNT/D and BoNT/E were found.[29] In the US almost all *C. botulinum*-producing BoNT/A spores are found west of the Mississippi River, where the Rocky Mountain cordillera rise out of the Middle and Great Plains (Fig. 189.2). BoNT/B spores have a more general east-west distribution but are confined almost totally to areas between 35 and 55 degrees of north latitude and occur in soil with high organic content. BoNT/E spores are found in marine life and sediment around fresh water from the Pacific northwest and the Great Lakes region of the US,[9,28] and *C. botulinum* BoNT/F spores have been isolated from marine sediment from the Pacific coast and from crabs in the Chesapeake Bay. The reasons for the geographic distribution of *C. botulinum* that produce different neurotoxins largely are unknown. Soil sampling in Argentina showed that 23% of samples were positive for a variety of *C. botulinum* types; the distribution was uneven, with a higher prevalence in cultivated soil.[30]

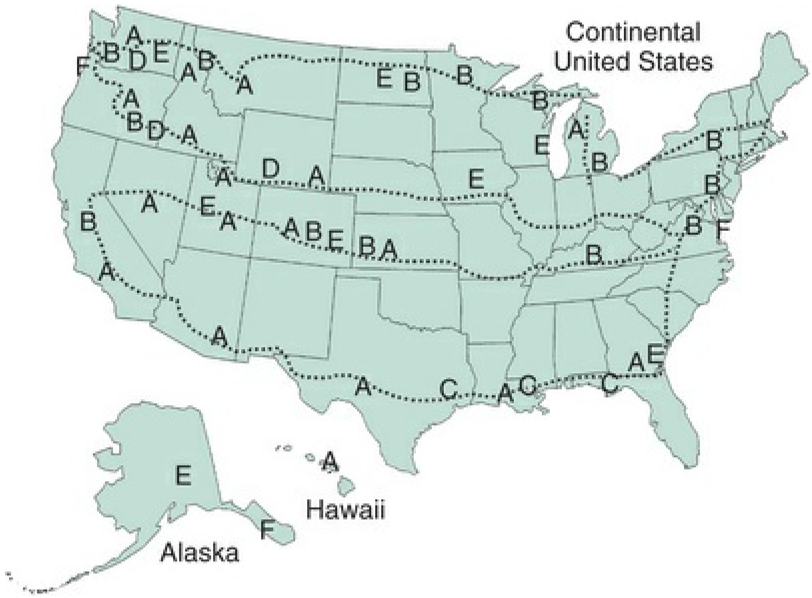

FIGURE 189.2 **Natural occurrence of *Clostridium botulinum* spores by toxin type. Data primarily represent 4 east-west crossings of the United States (dotted lines) during which soil samples were collected every 50 miles. Multiple samplings were positive in some states (not shown).**

(Data from Smith LD. The occurrence of *Clostridium botulinum* and *Clostridium tetani* in the soil of the United States. Health Lab Sci 1978;15:74–80.)

The geographic distribution of *C. baratii*–producing BoNT/F is less certain because the organism would not be detected by microbiologic screening for *C. botulinum;* the source was thought to be the environment in cases of infant botulism from California and Iowa, and the environment or contaminated food in adults, but the source of *C. baratii* botulism has not been proved.[13,15,31–34]

Botulism case density and toxin types in humans (and animals) mirror the geography and density of *C. botulinum* spores in the environment. Infant botulism undoubtedly is underrecognized, but cases have been reported from all continents except Africa and from all states in the US.[35] The highest reported incidence of disease in the US is the Delaware–Pennsylvania–New Jersey region arching Philadelphia, followed by California and Utah.[7] Argentina, Australia, Canada, Italy, and Japan, respectively, have reported the next largest numbers of cases.[35]

Among US cases of infant botulism overall, approximately one half are caused by BoNT/A and one half by BoNT/B, with rare cases usually caused by to BoNT/F or BoNT/E. Cases in California are divided between BoNT/A and BoNT/B,[36] but BoNT/B accounts for >90% of cases in Pennsylvania.[23] One or more samples from an affected infant's environment, such as yard soil, vacuum cleaner dust, crib, father's shoes, or consumed honey, usually will yield *C.*

botulinum spores, always of matching toxin type.[23,36] Samples do not contain preformed toxin.

Unusual epidemiologic findings also suggest uneven distribution of spores within limited geographic areas. In 1 Pennsylvania study, residences of 83% of the 53 patients with botulism formed an arc around Philadelphia, with remarkable sparing of the city itself, counties surrounding the arc, and the western parts of the state.[25] In Colorado, 3 of only 6 cases reported between 1977 and 1985 were from the same town of 800 people; 2 of 3 infants shared a crib (years apart), and all samples from their environments (including the crib) yielded *C. botulinum*–producing BoNT/A.[37] Nearly all of 39 infants with botulism in Utah over a 20-year period resided within a 70-mile metropolitan corridor including Salt Lake City, Ogden, and Provo.[38] A cluster of 12 cases occurring over 2 years in Utah suggested an association with wind and rain[39]; such a correlation was not found in Pennsylvania.[23]

Many parents of infants with botulism report nearby soil disruption (e.g., home or commercial construction or road work) or a dusty “event” before the onset of the infant's illness.[23,39] Nearby construction was common but was not significantly associated with botulism in a prospective case-control study performed by the US Centers for Disease Control and Prevention (CDC).[26] In Pennsylvania, 50% of the infants' fathers had occupations that required daily contact with soil; on testing, spores were found on work shoes or at a work site in most cases.[23] Organisms of matching toxin type were found in yard soil and drinking water in cases in Australia,[40] as well as in vacuum cleaner dust in a case in Finland.[41]

In the 1970s and 1980s, honey and light and dark corn syrups were found to harbor *C. botulinum* spores and tested positive in 0.5% to 20% of samples.[42,43] Following changes in corn syrup production, the Food and Drug Administration (FDA) laboratory found that samples tested negative for *C. botulinum*.[44] Corn syrup has not been a proven vehicle for spores in any case of infant botulism and can be given to young infants safely. Consumption of honey is a clear risk factor for infant botulism (odds ratio [OR] = 9.8 in 1 study),[30,34] but because of avoidance, honey accounts for <5% of cases currently in the US. A case of infant botulism BoNT/B in the United Kingdom was linked to isolation of *C. botulinum* spores from powdered infant formula[45,46]; nonbotulinal clostridial spores have been found in commercial powdered formula in the US, a finding suggesting potential vulnerability of this foodsource.[47] A few cases of infant botulism have been linked to unusual environmental sources, for example, 2 BoNT/E cases in Ireland related to pet terrapins or terrapin feed,[48] BoNT/B related to chamomile and fennel infusion in Spain,[49] and BoNT/Ab related to well water in Japan.[50]

Host Susceptibility

Infant botulism has both a striking age group for susceptibility and an association with feeding. The youngest reported patient had an onset of disease at 38 hours of age,[30] and the oldest had an onset at 11.7 months.[26] More than 90% of cases occur between 6 weeks and 6 months of age. The median age at onset of infant botulism is significantly earlier in infants fed formula (7.6 weeks) than in infants fed human milk (13.7 weeks).[23,39] The age at onset of BoNT/F (caused by *C. baratii*) and BoNT/E (caused by *C. butyricum*) is <14 days of age, which is significantly younger than the median age of 84 days for BoNT/A or BoNT/B.[12,14,15,31–33] Breastfeeding is a clear risk factor for infant botulism, present in 66% to 100% of cases in published series.[23,26,27,39] Breastfeeding was not a risk factor for infants with disease before 2 months of age in 1 study, and it appeared to be protective against a rapidly fatal course.[26] Long and colleagues[23] found that 66% of breastfed infants with botulism who had received human milk exclusively had introduction of the first nonhuman food substances (cereal, formula, fruit) within 2 to 4 weeks before the onset of symptoms.

Many sociodemographic and racial factors associated with infant botulism probably are markers for breastfeeding. Additional age-specific risk factors were living in a rural or farming area for infants younger than 2 months (OR = 6.4) and having less than 1 bowel movement per day for at least 2 months (OR = 2.9) for older infants.[26] Fig. 189.3 is a schematic summary of environmental factors, host factors, and pathophysiologic events in infant botulism.

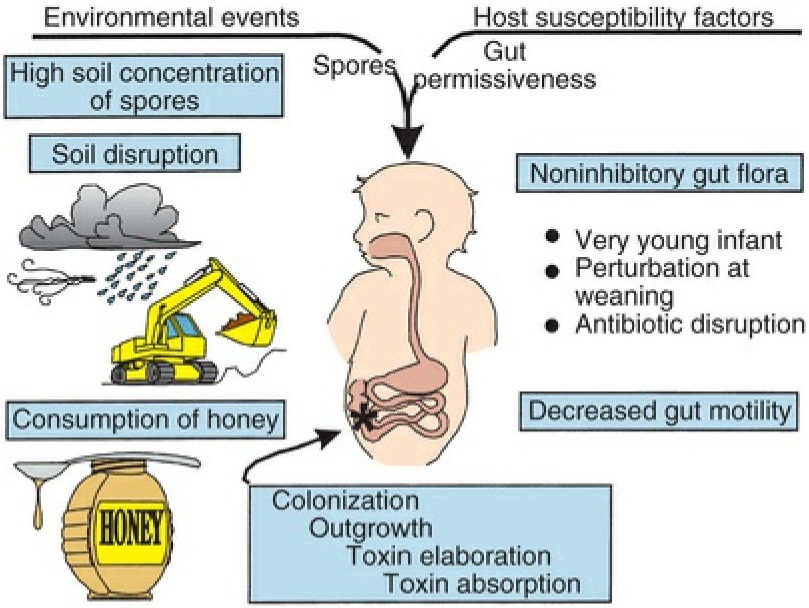

FIGURE 189.3 **Environmental, host, and pathophysiologic events in infant botulism.**

Immunity

C. botulinum is not part of the normal intestinal flora. No apparent natural acquisition of immunity to the organism or its toxin occurs. Infants recovering from botulism have a continued presence of organisms and toxin in stool for weeks to months.[51] These infants develop demonstrable specific serum antibody to toxin, the extent and duration of protective effect of which is not known.[52] Cases of relapsing hypotonia within weeks of hospital discharge in untreated infants have been reported, but no distant recurrences; occurrence after 12 months of age is rare in all people.

Clinical Manifestations

The clinical manifestations of botulism are similar regardless of the mode of acquisition. The spectrum of infant botulism is broad, with sudden infant death syndrome (SIDS) an occasional presentation at one extreme and transient mild weakness and hypotonia, slow feeding, or constipation alone at the other. Clinical manifestations have not changed over 4 decades of discovery.[5,39]

Classic Manifestations

After an unknown incubation period, symptoms of descending symmetric paralysis progress over 6 hours to 20 days (median, 4.2 days) before medical recognition or hospitalization.[23] Cranial nerves are affected first, with a subtly flat facial expression, quiet voice, and less avid suck—usually noted only by parents. The relative frequency of symptoms and signs is shown in Table 189.1.[23,38,39,53,54] Decreased frequency of bowel movements, floppiness, poor feeding, gurgling, and drooling are noted almost universally by the time of hospitalization.

TABLE 189.1

Symptoms and Signs at the Time of Hospitalization in 251 Infants With Botulism

Finding	Percent Occurrence Across Studies	
	Average (%)	Range (%)
HISTORY		
Decreased bowel movements	83	65–100
Poor feeding, weak suck	92	79–100
Floppiness, weakness	93	88–100
Weak cry	65	18–100
PHYSICAL EXAMINATION		
Temperature ≥38.3°C	14	—
Decreased spontaneous movement	82	—
Decreased phonation	80	—
Poor head control	97	96–98
Ptosis	84	75–97
Sluggish pupils	55	50–79
Ophthalmoplegia	55	18–61
Facial weakness	75	69–84
Decreased gag reflex	89	75–100
Difficulty swallowing	90	75–92
Hyporeflexia	54	52–57
Absence of reflexes	6	0–7
Flushed robust appearance	18	—
Decreased tears or saliva	18	18–79

Data from references 23, 38, 39, 53, and 54 (not all findings were reported in all studies).

The physical examination is most notable for the infant's quiet, still demeanor. Poor head control and hypotonia (inability of sustained postural control and movement against gravity) are universal. Although frequently misinterpreted as “lethargic” and “septic,” the infant is alert but rendered (by motor weakness) unable to smile, regard, vocalize, or move; skin color is normal or robust (Fig. 189.4). The diagnosis should not be made in the absence of head lag and cranial nerve palsies as first neurologic manifestations; swallowing function is most affected, and corneal reflexes are most preserved. Disconjugate gaze precedes ophthalmoplegia. Pupils become dilated or sluggishly reactive. Hyporeflexia is unimpressive early in the course relative to profound hypotonia, but it progresses over time. Respiratory difficulty is present in <20% of patients at hospitalization, but it is variable by case, age, and promptness of diagnosis.

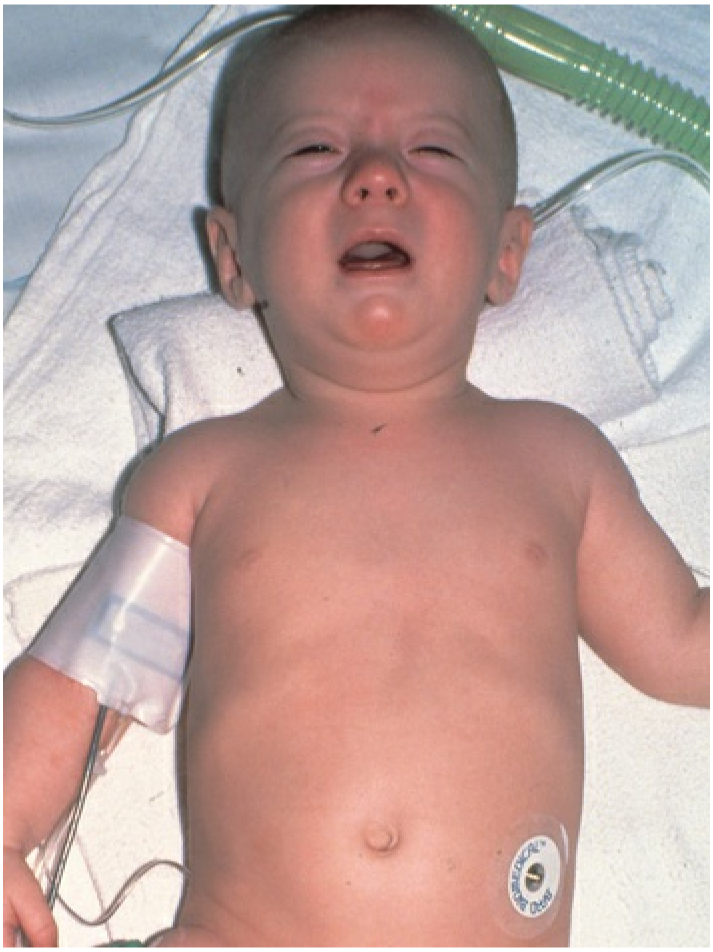

FIGURE 189.4 A 3-month-old infant with botulism just before intubation. Note bilateral ptosis and facial palsy and the absence of tears.

Autonomic dysfunction is underrecognized. Decreased tearing and salivation can be misinterpreted as dehydration. Erythema of oral mucosa can be misinterpreted as pharyngitis. Blood pressure, heart rate, and skin tone fluctuate frequently. Harlequin flushing can occur. Decreased intestinal motility, poor anal sphincter tone, and bladder atony are present commonly. No abnormality of sensation occurs.

Infants Younger Than 2 Months of Age

Progression is most rapid and severe in infants younger than 2 months of age.[26,55] Hypotonia leads rapidly to an inability to protect the airway and collapse of hypopharyngeal support, which can manifest within hours of the appearance of subtle clues of poor feeding or muscle weakness, or it can be the sentinel event. Very young infants with *C. baratii* BoNT/F have rapid progression to respiratory failure and have not had heralding constipation.[12,31]

Sudden apnea, fulminant paralysis, a brief resolved unexpected event (BRUE), or sudden infant or unexpected death syndrome (SIDS/SUDS)[55] can occur in young infants with botulism. Arnon and colleagues[56] proposed a significant association by the age of epidemic curves of botulism and SIDS, and they further associated the SIDS presentation of botulism with formula feeding (and possibly iron fortification). Spika[26] found that the severity of botulism in infants younger than 2 months of age was unrelated to feeding. In 2 studies, *C. botulinum* was isolated from intestinal contents in 4%[56] and 15%[13] of SIDS cases; in the latter study performed in Switzerland, unusual toxin types, such as BoNT/C, BoNT/F, and BoNT/G, were identified.[13] A prospective study in Australia failed to confirm the presence of *C. botulinum* in 248 victims of SIDS.[57]

Differential Diagnosis

Several disorders associated with weakness or hypotonia can mimic infant botulism superficially,[58,59] but the constellation of findings in the setting of age, feeding history, and exposures usually is classic, and the possibility of another diagnosis is remote. In the approximately 5% of infants treated empirically for botulism that was not confirmed in 1 report, multiple conditions were responsible, especially metabolic disorders, neurologic conditions, and spinal muscular atrophy.[58] Table 189.2 shows differentiating features of conditions frequently considered.[59] Tick paralysis (rare in infants) causes symmetric ascending flaccidity, with gait abnormality the usual first manifestation. In the Miller Fisher variant of Guillain-Barré syndrome (rare in infants), ataxia and areflexia occur early in the course of ophthalmoplegia. In a case of a 9-week-old infant with botulism, biopsy for possible Hirschsprung disease was performed because of constipation before neurologic abnormalities were noted.[60]

TABLE 189.2

Differentiating Features of Conditions Considered or Misdiagnosed in Infants With Botulism

Conditions	Expected Findings
Septicemia	Fever, lethargy, mottling
Meningitis or encephalitis	Fever, irritability, nuchal rigidity; specific or predominant CNS abnormalities; abnormal CSF
Cerebrovascular event	Focal neurologic deficits; abnormal CT or MRI
Genetic metabolic disorder	Onset with vomiting, irritability, or intellectual or neurologic abnormality; no weakness
Hypothyroidism	Hypotonia, lethargy, poor development; onset over weeks to months
Myasthenia gravis	Neonatal, or older age at onset; ptosis usually sole finding early
Spinal muscular atrophy	Inherited, progressive hypotonia and weakness; involvement of tongue, face, jaw, with sparing extraocular muscles and sphincters; areflexia
Anticholinergic poisoning	Agitation, coma, extrapyramidal movements
Polio-like condition or AFP	Asymmetric, spotty paralysis; aseptic meningitis; spasms
Guillain-Barré syndrome	Rare before 2 years of age; progressive symmetric ascending paralysis; areflexia; CSF proteinosis

AFP, acute flaccid paralysis; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging.

Diagnosis

Results of routine laboratory tests are normal (i.e., complete blood count, erythrocyte sedimentation rate, and cerebrospinal fluid values). Definitive diagnosis requires detection of the toxin in stool by mouse bioassay; the test result is positive in all likely cases of infant botulism when an adequate specimen is obtained. Assays are available through state health department laboratories or the CDC. Polymerase chain reaction testing usually is used to screen foodstuffs or to focus the neutralization part of the mouse bioassay.[16,61] *C. botulinum* organisms and toxin routinely are recoverable from stool of affected infants for weeks, and recovery is reported for as long as 7 months.[51]

Isolation of Organisms

Culture is performed only in special circumstances. *C. botulinum* can be isolated from stool, intestinal contents from autopsy specimens, wound, food specimens, or dust or dirt with the use of enrichment in chopped meat broth and then anaerobic incubation on selective egg yolk agar. Specimens for culture should be refrigerated if inoculation is not prompt. Density of organism in stool can be as high as 10^8 colony-forming units/g. *C. botulinum*–producing BoNT/A through BoNT/F produce lipase, which is detected as an iridescent film surrounding colonies. Vegetative cells are straight or slightly curved, motile, gram-positive bacilli with oval subterminal spores. Identity is confirmed by carbohydrate fermentation, biochemical reactions, and gas chromatography; typing is assigned according to toxin production by using mouse toxin neutralization assay or PCR assay.

C. botulinum–producing BoNT/G, *C. butyricum* BoNT/E,[11] and *C. baratii* BoNT/F[4,59] are lipase negative and may not be detected by usual screening and isolation techniques. *C. botulinum*–producing BoNT/G also is asaccharolytic. Isolation of *C. botulinum*–producing BoNT/E from the stool of an affected infant was successful only after enrichment following identification of the toxin gene by PCR testing of culture supernatant.[9]

Identification of Toxin

Bioassay performed on sterile stool filtrate is the only reliable confirmatory test for infant botulism. Passed stool is the preferred specimen for bioassay, but effluent obtained after a small-volume enema using sterile, nonbacteriostatic water is acceptable. In the latter instance, subsequent specimens are collected if the initial test result is negative and the diagnosis is likely. Specimens for assay should be refrigerated but not frozen pending shipping directions from public health officials. Serum assay results are positive in <10% of infants with botulism, and implicated honey does not have preformed toxin.

Neurologic Tests

Electromyographic findings characteristic of botulism are (1) motor unit action potentials of brief duration and small amplitude that are overly abundant for the amount of stimulus (so-called BSAP pattern), (2) enhancement of compound action potential in response to rapidly repetitive nerve stimulation at 30 Hz, (3) normal velocity of nerve conduction, and (4) no significant clinical response to injection of edrophonium chloride or neostigmine. Findings of electromyography depend on the stage of disease and the timing and amount of nerve stimulation. Because the age and clinical findings are unique and the diagnosis can be proved by toxin assay, painful electromyography usually is not justified; this study provides no prognostic information. An edrophonium (Tensilon) test to exclude myasthenia gravis rarely is performed in infants because safe doses for infants are not established, and borderline-positive test results have been reported in adults with botulism. Barring a hypoxic event, electroencephalographic and neuroimaging study results are normal. Abnormal auditory and visual evoked potentials reflect cranial nerve involvement. Seizures, which occur in 2% to 5% of cases, are rarely unexplained. A patient with raised intraocular pressure has been reported.[62]

Hospital Course

Disease Progression

The natural course of a typical case in a patient with infant botulism is progressive weakness over 2 to 10 days in hospital, remaining at a nadir for 1 to 2 weeks, followed by regaining of abilities slowly.[3,23,39,63,64] Mean duration of hospitalization in California was 3.8 weeks for BoNT/B cases and 5.4 weeks for BoNT/A cases.[63] Manifestations of disease progression are shown in Table 189.3.[23,53,63] Most infants have a progressive inability to swallow or protect the airway that leads to discontinuation of oral feeding, and 75% of these infants require intubation. Some patients require intubation for protection of the airway without the need for mechanical ventilation. Acute respiratory distress syndrome, reported in 5% of patients with botulism in 1 study,[23] was associated with artificial ventilation but otherwise was unexplained.

TABLE 189.3

Associated Events and Complicating Conditions in 111 Hospitalized Infants With Botulism

Percent Occurrence Across Studies		
Associated Events	**Average (%)**	**Range (%)**
Intubation required	77	20–89
Seizures	4	2–5
Acute respiratory distress syndrome	5	—
Failure of oral feeding	89	77–93
Excessive production of antidiuretic hormone	17	16–18
Autonomic instability	11	11
COMPLICATIONS		
Acute otitis media	30	—
Pneumonia	15	7–25
Urinary tract infection	6	0–11
Septicemia	3	0–5

Data from references 23, 53, and 63 (not all findings were reported in all studies).

Seizures are uncommon but are difficult to note clinically in the paralyzed infant; sudden tachycardia is a clue. Seizures are related almost invariably to hypoxia or hyponatremia. The syndrome of excessive secretion of antidiuretic hormone (ADH), reported anecdotally[39] and in 17% in 2 series,[23,53] is almost certainly the result of venous pooling in the paralyzed infant, decreased left atrial filling, and subsequent stimulus to ADH production. Hyponatremia and hypo-osmolality can be profound. Hyponatremic seizure occurred in 1 patient in Philadelphia without the syndrome of inappropriate secretion of ADH as a result of extreme hyponatremia of the mother's milk (a recognized consequence of stress).

Complications

Except for complications directly related to muscular dysfunction, secondary infections are most common in botulism (see Table 189.3), predominantly acute otitis media, aspiration pneumonia, and urinary tract infection. Schechter and associates[65] reported 5 cases of *Clostridium difficile* colitis in infants during or after hospitalization for botulism; toxic megacolon and necrotizing enterocolitis distinguished 2 cases.

Management

The challenges of management are to recognize the diagnosis promptly and before catastrophic events, administer antitoxin urgently, and prevent complications until neuromuscular function recovers. Successful treatment depends on meticulous attention to protect the airway and prevent sudden catastrophic hypoxia, provide adequate ventilation and nutrition, and prevent nosocomial complications. The sensory system is unaffected, and intellectual function is preserved throughout (as documented in adults paralyzed from foodborne botulism).

Antitoxin Therapy

All infants with the suspected clinical diagnosis should be treated urgently with human botulism immune globulin intravenous (BIG-IV/BabyBIG), which neutralizes botulinum toxins. Treatment halts the progression of neuromuscular blockade and should not be delayed for confirmatory testing. This pentavalent antitoxin product is derived from plasmapheresis of donors who received multiple doses of BoNT/A, BoNT/B, BoNT/C, BoNT/D, BoNT/E toxoid vaccine.[66] BabyBIG does not cover the rare occurrence of BoNT/F disease. A 5-year, randomized placebo-controlled (with immune globulin intravenous), blinded clinical trial of the efficacy of BIG-IV was performed in 129 California infants under the sponsorship of the Orphan Drug Program of the FDA and the California Department of Health Services (CDHS).[5] Infants treated with BIG-IV had reductions in duration of hospitalization by 3.1 weeks (from 7.7 weeks to 2.6 weeks), mechanical ventilation by 2.6 weeks, tube or intravenous feedings by 6.4 weeks, and mean hospital charges by $88,600 (in 2004 US dollars).[5] No serious adverse event was attributed to BIG-IV. In the subsequent open-label study of the use of BIG-IV in 366 infants with ultimate laboratory-confirmed botulism who were treated within 7 days of hospitalization, the duration of hospitalization was significantly shorter for those infants treated before 4 days (2.0 weeks) compared with those treated on days 4 to 7 (2.9 weeks).[64] In 2003, BIG-IV was licensed by the FDA to the CDHS as BabyBIG for treatment of infant BoNT/A and BoNT/B cases (and is used with expected effectiveness against BoNT/E). The drug is obtained after consultation with the CDHS Botulism Treatment and Prevention Program (510-231-7600; http://www.infantbotulism.org) and approval of the treating institution's financial officer. The 2015 price was $45,300. BabyBIG, 50 mg/kg body weight, is administered as a single dose intravenously. The mean serum half-life of BabyBIG is 28 days, which is reassuring in light of prolonged intraluminal toxin production in infants. Although the earliest possible treatment is optimal, and only treatment given within 7 days has proven efficacy, BabyBIG usually is given even later to protect against subsequent toxin absorption. Equine heptavalent botulinum antitoxin (BAT) (dosed at approximately 10% of the dose for foodborne botulism) usually is given following confirmation of infant BoNT/F cases,[15] and it has been used occasionally in other BoNT/non-F infant cases outside the US because of cost or expediency.[67] BAT is not without risk and should not be given to infants with botulism if BabyBIG is available. BabyBIG is not licensed, appropriate, or available for use for other forms of botulism. Newer purified recombinant bivalent (rBV A/B) receptor protein antigen vaccine has replaced pentavalent toxoid vaccine in the US,[68] is the current boosting vaccine for BabyBIG donors, and eventually will be the priming vaccine for refresher lots of BabyBIG; BabyBIG then will be effective only for BoNT/A or BoNT/B cases.

Antimicrobial Therapy

Antibiotic therapy is indicated only for the treatment of secondary bacterial infection. Antibiotics with bactericidal activity against *C. botulinum* (e.g., β-lactam agents) do not have an apparent beneficial or detrimental effect on the course of paralysis. Aminoglycoside agents are avoided because they contribute to neuromuscular blockade and have been associated temporally with rapid deterioration in infant botulism. Fever and an abnormal white blood cell count suggest a complicating infection. Ampicillin or amoxicillin is appropriate for treatment of pneumonia, acute otitis media, or sinusitis.

Respiratory Management

Respiratory arrest is the primary cause of death and sequelae, and it can follow days of progressive paresis or occur suddenly, sometimes before the diagnosis or as the diagnosis is suspected. In infants older than 2 months of age, the tempo of progression is apparent over 24 hours, and respiratory failure usually is predictable. In younger infants, obstruction, aspiration, and weakness are concurrent problems requiring preemptive intubation.

The patient is observed under intensive care with continuous monitoring to determine the progression of disease. In general, a history of rapid onset of impairment (over 24 hours rather than days) portends total paralysis and a requirement for ventilation. Nasotracheal or endotracheal intubation is performed when the patient's ability to cough, gag, swallow, or move against gravity (e.g., raising arms or legs while supine) is substantially impaired. Waiting for the appearance of fatigue, apnea, tachypnea, hypercarbia, or hypoxemia is inappropriate.

Positioning with elevation of the planar mattress to 30 degrees at the head allows the flow of saliva by gravity to the posterior hypopharynx, where it is swallowed most easily. Placement of a small blanket roll behind the neck minimizes neck flexion, which can compromise the airway. Optimal positioning with frequent suctioning and the use of nasogastric feeding can avert endotracheal intubation in mildly affected patients. A cloth “bumper” placed below the buttocks prevents sliding and elevates the legs slightly to minimize venous pooling.

Tracheostomy was performed because of prolonged intubation or for fear of postextubation subglottic stenosis in approximately 50% of infants with botulism in 1 institution in Philadelphia before 1981,[53] but not in another institution in the same city,[23] and in <1% of infants reported from California. Immediate or late sequelae of airway trauma are unusual, even when intubation was required for >1 month in the pre-antitoxin era. Tracheostomy should not be performed prophylactically.

Atelectasis and pneumonia can be minimized by careful physiotherapy, suctioning, and positioning and by provision of periodic sighing respirations (even for intubated patients who do not require continuous ventilation). Plugging of the tube and accidental extubation largely are avoidable; experienced personnel must be vigilant and capable of immediate intervention when necessary.

Criteria for extubation are return of gag, cough, and sustained movement against gravity. The mean duration of intubation calculated for all studies before the use of antitoxin was approximately 21 days, with a relatively longer duration for BoNT/A disease. With timely antitoxin treatment, intubation usually occurs for less than 7 days.[5,64]

Nutrition

Enteral feeding is well absorbed and well tolerated because of an apparent relative sparing of paralytic effect on the small bowel. Additionally, enteral feeding stimulates gut motility (which may help purge organisms and toxin), protects the integrity of the enteric mucosa, and obviates the need for an indwelling intravenous catheter. Continuous small-volume nasoenteric (usually nasojejunal) feeding is begun within 48 hours of hospitalization. Caloric needs of the immobile, ventilated infant are approximately two thirds of predicted. A small enema is used judiciously to obtain a stool sample for diagnosis; a therapeutic benefit is not apparent, and vigorous enema or use of a cathartic agent is contraindicated. Human milk or formula is appropriate for feeding.

Oral feedings are resumed when strong swallow, gag, and suck reflexes return, the infant has sustained strength against gravity, and bolus nasogastric feedings have been tolerated.

Weight and fluids and electrolytes are monitored carefully through the nadir of muscular function, to correct initial dehydration and observe for hyponatremia. Intravenous catheters and an indwelling urinary bladder catheter are unnecessary, and their use carries risks of mechanical and infectious complications.

Infection Control

No case of person-to-person transmission of botulism in the home or hospital has been reported. No special isolation of hospitalized infants is recommended. Infants' stools are likely to contain *C. botulinum* organisms and toxin for the duration of hospitalization and beyond. Careful handwashing practices and disposal of diapers as contaminated waste are important. After discharge, circumstances for potential fecal-oral transmission to other young infants (e.g., sharing of cribs) should be avoided for 3 to 4 months.

Outcome and Prevention

Patients who have supportive care before a hypoxic episode have an excellent prognosis, with a <1% mortality rate even before the availability of human BabyBIG. Full recovery without neurologic or neuromuscular sequelae depends on maintaining vigilance and meticulous supportive care while minimizing interventions that increase complications. Peripheral muscular strength and muscles of cranial nerve innervation recover quickly, whereas strength to control the head and trunk recovers slowly (Fig. 189.5), even after BabyBIG.

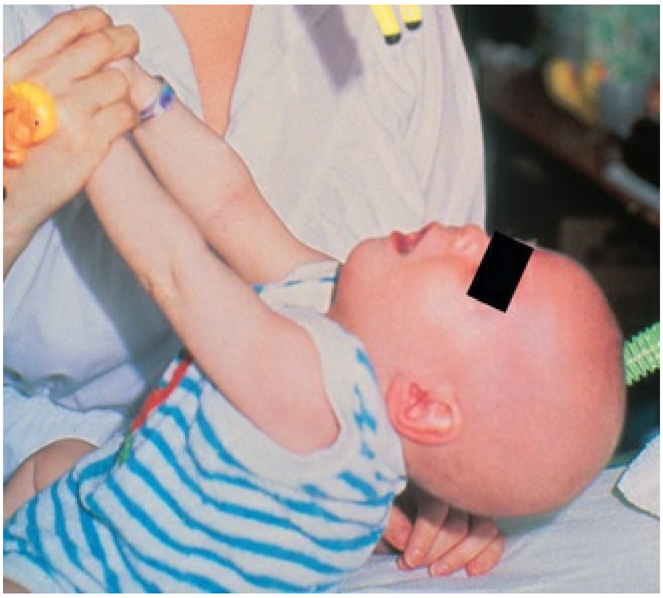

FIGURE 189.5 **Severe head lag in a 4-month-old infant 2 months after infant botulism (1 month after extubation; before the availability of BabyBIG).**

Botulism is uncommon despite unavoidable, frequent environmental exposure to spores. Honey is an avoidable source of spores. The American Academy of Pediatrics and the CDC recommend avoidance of honey for children younger than 12 months of age.[69]

Foodborne Botulism

Foodborne botulism in the US rarely occurs in children. The <10 to 30 cases occurring annually in adults over the past several decades have resulted from improper preparation, preservation, or storage of food (e.g., foiled wrapped or stored in oil) in the home, in restaurants, and in traditional ethnic foods. Most cases are sporadic, and most outbreaks are small, involving 2 or 3 persons. Larger outbreaks, however, occur from commercial and restaurant sources,[70] and in Utah, Arizona and most recently Mississippi in prisons because of consumption of an illicit alcoholic brew (pruno, hooch) (BoNT/A).[71] Toxin types other than BoNT/A and BoNT/B have emerged, especially *C. botulinum* BoNT/E in Arctic regions globally[28,72] and cases caused by *C. baratii* BoNT/F (presumed but not proved to be foodborne).[14,33,34]

Symptoms of descending symmetric paralysis begin 12 to 36 hours (range, 6 hours to 8 days) after consumption of the contaminated food, which usually does not taste tainted. Classic symptoms, including dysphagia, diplopia, dilated and fixed pupils, and dry mouth and throat, occur in an alert patient and are followed by musculoskeletal weakness, postural hypotension, and respiratory paralysis. Ocular symptoms can be heralding manifestations, including blurred near or distant vision (i.e., impairment of accommodation) and diplopia.[73,74] Intoxication caused by BoNT/E has the shortest (1 day) but variable (≤8 days) incubation period and commonly is heralded by nausea and vomiting. Disease caused by BoNT/A is most severe; the rates of required intubation for BoNT/A, BoNT/B, and BoNT/E intoxications are 67%, 52%, and 39%, respectively.[75] Atypical features, such as asymmetric weakness, paresthesia, and sensory abnormalities, have been documented.

Diagnostic methods for foodborne botulism are similar to those for infants, except that toxin assays on serum and potential food source are always performed and results are expected to be positive; results of culture and toxin assay on stool also are positive frequently. Equine antitoxin and supportive care are mainstays of therapy. Antitoxin reduces the mortality rate from BoNT/A intoxication from 46% to 26% and shortens hospital stays.[2,76,77] Since March 2010, BAT—(containing antitoxin to types A, B, C, D, E, F, and G) manufactured with additional steps of purification, immunoglobulin fragmentation, and viral inactivation—has been made under contract by the US Department of Health and Human Services with Cangene Corporation in Canada and is the only product available in the US for noninfant botulism.[77] BAT is available only through the CDC (770-488-7100). Immediate hypersensitivity reaction or serum sickness illness following administration of BAT appears to occur less frequently compared with previous products.[77]

Wound Botulism

Wound botulism was rare in the US in the last half century until the early 1990s in the western US and 2000s in the UK, when a dramatic increase in cases occurred, associated with injection drug users of "black tar heroin" and "skin popping."[4,78] The 12 to 32 cases of wound botulism in the US annually result from *C. botulinum* infection and toxin production in a wound that typically is traumatic and contaminated with soil. Toxin types mirror the soil distribution of spores. When neuroparalytic symptoms and signs begin, the wound itself is clinically unimpressive, with minimal erythema, induration, or serosanguineous discharge and no crepitus or warmth. Gastrointestinal symptoms are less common than in foodborne botulism. Children are affected infrequently, usually after an accidental crush injury and with direct major soil contamination.[79] Facial abscess after laceration from a thrown wood chip was the source of BoNT/A botulism in a 5-year-old child in Washington State.[80]

Diagnostic methods include serum toxin assay and unroofing of lesions to obtain specimens for culture and toxin assay. BAT is given, and the wound is debrided and irrigated vigorously. An anticlostridial agent, such as penicillin or vancomycin, usually is given parenterally, although the benefit is unclear. Wound botulism has occurred despite the use of antibiotic prophylaxis at the time of accidental injury. Debridement of devitalized tissue and vigorous irrigation of wounds are the most effective means of prevention.

Vaccines

The only vaccine existing in the US currently is an rBV A/B vaccine developed at the US Army Medical Research Institute of Infectious Diseases.[68]

Key Points

Infant Botulism

- Age of onset is 2 days through 11 months (median age onset formula fed, 7.6 weeks; human milk fed, 13.7 weeks).
- Beginning of weaning is a period of heightened risk for infants fed human milk exclusively.
- Exposures to *C. botulinum* spores usually are incidental and unavoidable.
- Nearby soil disruption (e.g., construction, dust) or bringing soil into the home (e.g., shoes of construction worker) is common in the history.
- Constipation is a heralding feature.
- Descending symmetric paralysis over hours to days with primary cranial nerve and bulbar involvement and involving the muscles of head control is universal.
- All infants in whom the diagnosis is considered should be monitored under intensive care.
- All infants with suspected cases should be treated urgently with BabyBIG under consultation with the California Department of Health.
- Administration of BabyBIG is associated with an average reduction of hospital stay by 3.1 weeks, mechanical ventilation by 2.6 weeks, and tube feedings by 6.4 weeks.

- Full recovery is expected but slow.

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Clostridium difficile

Nalini Singh, Karl Klontz

Description of Pathogen

Clostridium difficile is an anaerobic spore-forming, toxin producing, noninvasive gram-positive bacillus that was first described as part of a study of the intestinal flora of newborn infants.[1,2] *C. difficile* can exist in vegetative or spore forms. Once spores reach the colon, they convert to the functional vegetative form in which the organism becomes susceptible to antimicrobial agents and begins producing exotoxins A (TcdA) and B (TcdB) that cause colitis in susceptible hosts.

Not all colonized patients become symptomatic. For example, colonized young infants can produce antibodies to *C. difficile* without clinical infection, and these antibodies are protective against symptomatic infections later in life.[1] Disturbances in the microbiota of the gut, often as a result of antibiotic use, are believed to permit infection with *C. difficile*[2] (Fig. 190.1). Alteration of the intestinal ecosystem decreases resistance to *C. difficile* colonization.[3] Subsequent ingestion and colonization of *C. difficile* lead to production of exotoxins TcdA and TcbB, which cause intestinal mucosal injury, inflammation, and diarrhea. Animal model studies demonstrated that these toxins disrupt the cytoskeleton and tight junctions of epithelial cells and cause apoptosis.[4,5] TcdB is 10-fold more potent than TcdA in causing human colonic mucosal damage, and certain *C. difficile* strains that produce only TcdB can cause severe disease.[6,7] Various molecular diagnostic tools have been valuable for epidemiologic investigations. For example, a virulent strain of *C. difficile* that emerged in outbreaks in healthcare facilities in the United States and Canada associated with high rates of treatment failure was identified as North American pulsed-field gel electrophoresis type 1 (NAP1), group B1 by restriction endonuclease analysis and as ribotype 027 by polymerase chain reaction testing.[7,8] The epidemic NAP1 strain has upregulated production of TcdA and TcdB compared with other strains, likely secondary to genetic differences in regulatory genes.[8,9] This *C. difficile* strain has a high level of resistance to fluoroquinolones. The hypervirulent NAP1 strain of *C. difficile* has been reported in a small proportion (20%) of affected children.[10]

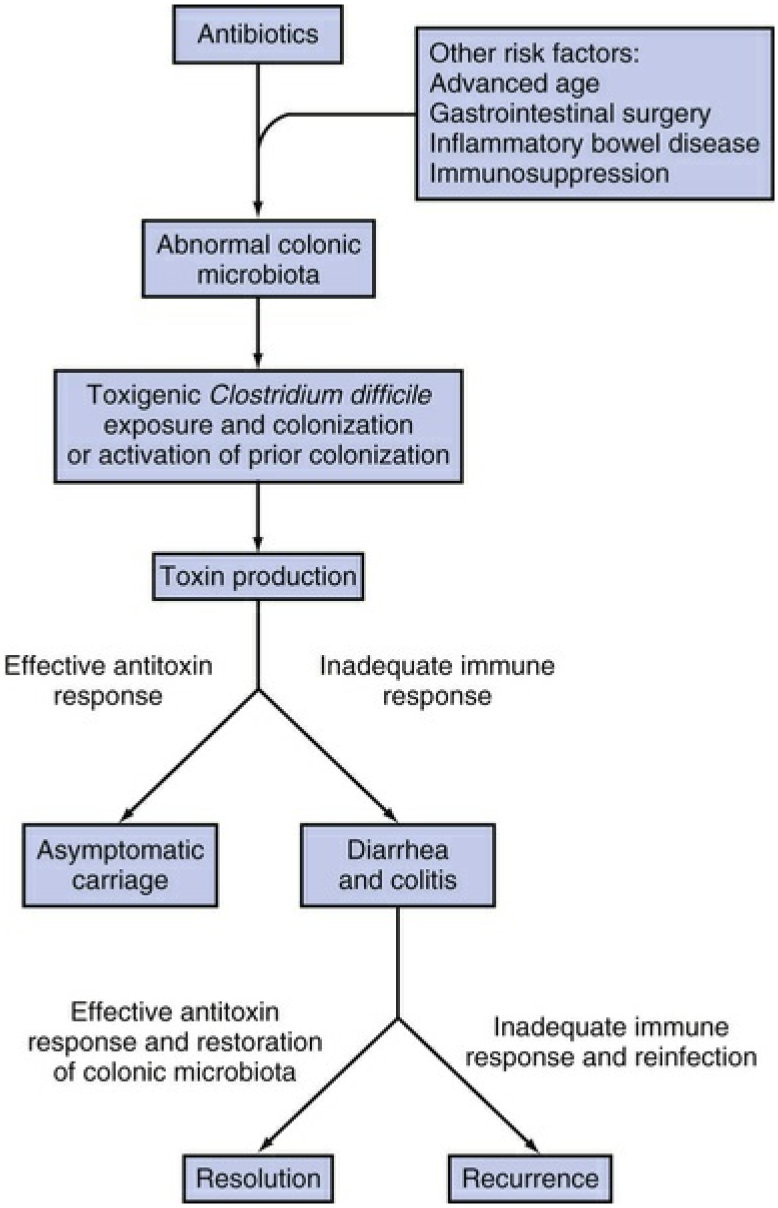
Antibiotics
Other risk factors:
Advanced age
Gastrointestinal surgery
Inflammatory bowel disease
Immunosuppression
Abnormal colonic microbiota
Toxigenic *Clostridium difficile* exposure and colonization or activation of prior colonization
Toxin production
Effective antitoxin response
Inadequate immune response
Asymptomatic carriage
Diarrhea and colitis
Effective antitoxin response and restoration of colonic microbiota
Inadequate immune response and reinfection
Resolution
Recurrence

FIGURE 190.1 **Pathogenesis of *Clostridium difficile* infection.** (From Leffler

DA, Lamont JT. *Clostridium difficile* Infection. N Engl J Med 2015;372:1539–1548.)

Epidemiology

In the past decade, *C. difficile* infection in children has extended from healthcare to community settings.[11,12] *C. difficile* spores are present in asymptomatic neonates, healthy young infants, soil, and healthcare and childcare environments. *C. difficile* spores are resistant to heat, acidic environments, antibiotics, and most antiseptics, and this resistance allows the organisms to survive in the environment for prolonged periods.[13] *C. difficile* can be acquired from infected or colonized people and from contaminated environments or equipment. Neonates can become colonized without developing symptomatic illness. In a study involving active population- and laboratory-based surveillance across 10 geographic areas in the US, the Centers for Disease Control and Prevention (CDC) reported that, in 2011, the estimated number of incident *C. difficile*–associated diarrhea (CDAD) infections in the US was 453,000, and the estimated number of deaths caused by *C. difficile* infection was 29,300; overall, 35% of cases were community associated.[14] In the same study, the lowest incidence of infection was seen in children 1 to 17 years of age (24.2 cases per 100,000 population); in this age group, the incidence of community-associated and healthcare-associated CDAD was 17.9 and 6.3 per 100,000 persons, respectively.[14]

Molecular diagnostic tools such as nucleic acid amplification tests have helped define the incidence of CDAD further.[15,16] CDAD in adults has become the most common cause of healthcare-associated infection in the US, with excess healthcare costs estimated to be $4.8 billion annually.[17,18] Among children evaluated for diarrhea in a children's hospital emergency department in Seattle, Washington, *C. difficile* was the third most common cause, trailing viral and other bacterial causes.[19] Similarly, in the Washington, DC area in 2004 to 2005, increased numbers of community-acquired CDAD infections were documented in children with few previous antibiotic exposures.[11]

Some US states and Canadian provinces require hospitals to report incidence rates of CDAD.[20,21] Risk factors associated with

CDAD include exposure to antimicrobial therapy, use of antineoplastic agents, repeated enemas or use of gastrointestinal stimulants, underlying bowel disease (e.g., inflammatory bowel disease or Hirschsprung disease), gastrointestinal surgical procedures, and renal insufficiency.[22–27] CDAD has been associated with almost every antibiotic, but it is associated more frequently with penicillins, macrolides, clindamycin, cephalosporins, and fluoroquinolones.[28]

Clinical Manifestations

The spectrum of clinical manifestations associated with *C. difficile* infection ranges from asymptomatic colonization with toxigenic strains to pseudomembranous colitis and toxic megacolon. Asymptomatic colonization and toxin production are common in infants, with up to 50% of children <1 year of age being carriers. The most common clinical presentation of CDAD is mild to moderate diarrhea; some patients have mucus or blood in stool. Children with pseudomembranous colitis can have diarrhea, fever, abdominal distention, cramps, pain, and systemic toxicity such as malaise, anorexia, and dehydration. Occasionally, some children develop severe disease associated with complications such as toxic megacolon. Other complications such as sepsis, ascites, intestinal perforation, intussusception, pneumatosis, and rectal prolapse are reported rarely.[29,30] Severe cases of CDAD occur most frequently in neutropenic children with leukemia and in patients with inflammatory bowel disease. Extraintestinal manifestations of *C. difficile* are extremely rare, but cases of bacteremia, osteomyelitis, reactive arthritis, and splenic abscesses are reported.[31–34] Disease characteristically begins while the child is hospitalized and receiving antimicrobial therapy, but it can occur weeks after hospital discharge. Coinfection with enteric viruses (e.g., rotavirus or calicivirus, or both) has been reported in patients with severe cases of CDAD requiring intensive care.[35]

Laboratory Findings and Diagnosis

Detection of *C. difficile* toxins in stool specimens provides the most practical and clinically relevant method for diagnosis of *C. difficile*–associated diseases. *C. difficile* testing should be performed only on diarrheal stool samples, usually from children who have received antibiotics within the previous 2 months or in whom diarrhea began 72 hours after hospitalization and especially in patients with other risk factors. Testing also is appropriate for children with community-associated colitis whose cultures do not reveal other bacterial pathogens. Enzyme immunoassay kits can detect TcdA and TcdB, but have relatively low sensitivity (63%–94%), with higher specificity (75%–100%).[28,38] In the preferred 2-step method, enzyme immunoassay first is used to detect *C. difficile* glutamate dehydrogenase, an enzyme constitutively produced by toxigenic and nontoxigenic *C. difficile*.[39–41] Stools with a positive rapid screen result then are tested for toxin.[41,42] Nucleic acid amplification tests combine good sensitivity and specificity and are rapid stand-alone tests. Positive predictive value, especially in children <5 years of age, remains to be determined.[42]

Direct visualization of mucosal plaques or pseudomembranes on colonic mucosa by endoscopy is required to establish the diagnosis of pseudomembranous colitis. Because of the cost and risk associated with the procedure, endoscopy should be reserved for patients in whom other disease processes are being considered or for severely ill patients in whom a strong clinical suspicion for *C. difficile* infection exists despite negative results of noninvasive tests such as a toxin assay.[43]

Differential Diagnosis

Viral gastroenteritis caused by agents such as rotavirus, adenovirus, and enterovirus can have manifestations similar to those of mild *C. difficile* infections. For moderate to severe CDAD, bacterial causes such as *Salmonella, Shigella, Yersinia, Campylobacter,* or toxigenic *E. coli* should be considered because these infections can cause local and systemic inflammation. Parasitic infections such as with *Giardia* or *Cryptosporidium* also should be considered, especially if the course of diarrhea is protracted and stools are not bloody. Noninfectious causes such as inflammatory bowel disease also can mimic *C. difficile* infections. Appendicitis, typhlitis, intussusception, necrotizing enterocolitis, neutropenia-associated colitis, or other acute intra-abdominal diseases should be considered in extremely ill patients.

Treatment

Treatment for initial episodes of *C. difficile* infection consists of discontinuation of the precipitating antimicrobial agent or agents and initiation of metronidazole (oral or intravenous) or vancomycin (oral only) therapy.[28] The efficacy of these antimicrobial regimens for *C. difficile* infection has been demonstrated in randomized studies, mostly involving adult patients.[44,45] Oral metronidazole (30 mg/kg/day in 4 divided doses, maximum 2 g/day) is the drug of choice for initial treatment of mild to moderate *C. difficile* infections. Oral vancomycin (40 mg/kg/day in 4 divided doses, maximum of 2 g/day) is indicated in patients with severe disease (e.g., hospitalized in an intensive care unit), patients with underlying intestinal disease, or patients who are unresponsive to metronidazole therapy; efficacy is modestly superior to that of metronidazole.[46,47] Vancomycin is not effective if given intravenously. For patients with severe disease and complications such as shock, ileus, or toxic megacolon, addition of intravenous metronidazole to vancomycin orally or by enema is recommended. The duration of therapy for any regimen should be a minimum of 10 days; most patients demonstrate clinical improvement within 24 to 48 hours of initiation of therapy and resolution of diarrhea within 4 to 5 days. Toxin testing as a routine follow-up study is not recommended.

In addition to antimicrobial therapy, supportive care with fluid, electrolyte, and nutrition replacement should be provided. Antimotility drugs should not be administered to patients with *C. difficile* infections because of the associated risk of developing ileus or toxic megacolon.[48] Surgical intervention, such as colectomy, can be lifesaving in selected patients with complications such as intestinal perforation or toxic megacolon.[49]

Relapses of *C. difficile* infection are observed in up to 25% of patients after initial therapy is discontinued. The first relapse episode is treated with the same regimen as the initial episode. For second or later relapses, an oral vancomycin regimen tapered over weeks, or pulse therapy of repeated interspersed 1 week of therapy followed by 1 week without therapy, is preferred based on studies involving adults.[50] Use of metronidazole beyond the first relapse episode should be avoided because of the potential for cumulative neurotoxicity.[47] Use of fidaxomicin, a poorly absorbed, bactericidal antibiotic, has been approved for use in adults with CDAD, is noninferior to oral vancomycin for treatment, and appeared to reduce the risk of recurrence to 15% versus 25% for patients receiving oral vancomycin.[51,52] Nitazoxanide also is an effective therapy in adults. Adults with multiple relapses have been treated with fecal transplantation to restore gut microbiota.[53–55] Studies evaluating the efficacy of the probiotic *Saccharomyces boulardii* in preventing relapses have been inconclusive[56]; caution must be taken because *S. boulardii* has been associated with bloodstream invasion in immunocompromised patients and in patients with a central venous catheter.[57] In 1958 Eiseman et al. reported the use of fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis.[58] Since that report, multiple studies have demonstrated fecal microbiata transplantation (FMT) to be more effective for the treatment of recurrent *C. dificile* infections in adults than antibiotics, with resolution of symptoms without recurrence varying from 77% to 100%, depending on route of administration.[59] Based on small case series in the absence of randomized clinical trials, similar rates of success have been reported for FMT in the setting of pediatric recurrent *C. dificile* infections.[60]

Prevention

Meticulous hand hygiene with soap and water should be performed before and after donning gloves when any contact is expected with patients infected with *C. difficile*. All healthcare personnel should use glove and gown precautions when in contact with the patient *and* the surrounding environment.[61,62] Waterless gel is ineffective in killing spores of *C. difficile*. Cases of healthcare-associated CDAD in healthcare personnel have occurred. Children with CDAD should not attend out-of-home childcare facilities while symptomatic with diarrhea.

Environmental contamination plays an important role in the transmission of *C. difficile*.[28] *C. difficile* has been transmitted through electronic thermometers.[63] Endoscopes have not been implicated in *C. difficile* transmission. The degree to which the environment becomes contaminated is proportionate to the patient's severity of disease. Diluted sodium hypochlorite successfully eradicates spores, whereas routine hospital cleaning agents such as quaternary ammonium compounds are ineffective. Vaporized hydrogen peroxide delivered through a special apparatus is successful in reducing environmental contamination of *C. difficile*.[64] This procedure can be carried out in vacant hospital rooms and requires that the room be sealed off to ensure efficacy and avoid inadvertent exposure to patients. The effectiveness of this technology needs further evaluation. Comprehensive strategies to prevent *C. difficile* that include antimicrobial stewardship have been published.[65] A promising first-in-human phase 1 vaccine trial in adults using toxoid antigens was published in 2016.[66]

Key Points

Diagnosis and Management of *Clostridium difficile* Infection

Epidemiology

- Acquired from infected people or contaminated environments, especially healthcare environments
- Evolving from healthcare-associated to community-acquired infection
- Exposure to antibiotic therapy a risk factor for developing disease
- Neonates can be colonized without symptomatic illness.

Clinical Features

- Most commonly manifesting as mild to moderate diarrhea with or without mucus or blood in stool
- Pseudomembranous colitis
- Complications including toxic megacolon, intestinal perforation, sepsis, ascites, intussusception, and pneumatosis intestinalis

Diagnosis

- Detection of C. *difficile* toxins
  - Two-step enzyme immunoassay first to detect glutamate dehydrogenase (sensitive but nonspecific) and then to detect toxin if step 1 is positive
  - Stand-alone nucleic acid amplification test

Treatment

- Discontinuation of precipitating antibiotic
- Initial infection:
  - Mild to moderate disease: oral metronidazole 30 mg/kg/day in 4 divided doses, maximum 2 g/day
  - Severe disease, as in patients who are in an intensive care unit, have proven pseudomembranous colitis, have underlying intestinal disease, or are unresponsive to metronidazole therapy: oral vancomycin 40 mg/kg/day in 4 divided doses, maximum 2 g/day
  - Severe disease with shock, ileus, or megacolon: vancomycin enema and intravenous metronidazole
  - Duration of therapy a minimum of 10 days
- Relapse infection:
  - First relapse: same regimen as the initial episode

- Second or later relapse: oral vancomycin in therapeutic and then tapered or pulsed therapy are recommended. Metronidazole should not be used for treatment of a second recurrence because neurotoxicity is possible.
- Fidaxomicin approved for treatment in adults

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Other *Clostridium* Species

Itzhak Brook

Clostridia are gram-positive, spore-forming bacilli that cause up to 10% of anaerobic infections[1–5] and occur at diverse clinical sites. Of the more than 200 recognized species of *Clostridium*, <20 are associated with invasive and toxigenic human diseases. Clostridial species vary in oxygen tolerance, nutritional needs, motility, and optimal temperature for growth. They can cause distinct clostridial histotoxic syndromes by means of specific clostridial toxins (e.g., gas gangrene, food poisoning) and other, nonsyndromic clostridial infections (e.g., bloodstream infection [BSI]). Clostridia also are recovered from various sites as part of polymicrobial infections,[4,5] including intra-abdominal, biliary tract, female genital tract, pleuropulmonary, central nervous system, and skin and soft tissue infections.[3]

Clostridia are members of the normal human flora, present primarily in the intestinal tract and vagina.[4] They colonize the gut of other vertebrates and insects and are ubiquitous in soil. Clostridia are part of the phylum Firmicutes and based on 16S (small subunit) ribosomal DNA sequence analysis can be divided into 11 homology groups. Most of the clinically significant species are part of group 1.[6] Most clostridial infections in children are polymicrobial and arise from the site of endogenous colonization; the organisms gain access when normal mucocutaneous barriers are disrupted as from surgical procedures, trauma, a perforated viscus, necrotizing enterocolitis, or chemotherapy-related mucositis.[3] Devitalized tissue and low oxidation reduction potential enhance the growth of clostridia. Contamination of existing wounds or surgical sites with organisms from soil, unsanitary water, contaminated objects, and human and animal feces can lead to infection.

Clostridial species that cause gas gangrene produce extracellular toxins or possess virulence factors such as enzymes or lysis factors. Clostridia that cause gastrointestinal disease produce enterotoxins.[7]

Clostridium perfringens is the most common clinical isolate of the genus. It is a ubiquitous bacterium associated with several exotoxin-mediated clinical diseases. *C. perfringens* has 12 recognized toxins, and the species is divided into types A through E on the basis of toxins produced.[7] *C. perfringens* causes food poisoning,[8] necrotizing enteritis,[9] and gas gangrene.

Clinical Manifestations

Histotoxic Infections

Table 191.1 shows characteristics of histotoxic infections and the likely responsible *Clostridium* spp. *C. perfringens* is the most common pathogen associated with gas gangrene.[10] Other responsible organisms that can also produce exotoxins are *C. bifermentans, C. sordellii, C. septicum, C. novyi,* and *C. histolyticum.* The spectrum of infection includes cellulitis, necrotizing fasciitis, and severe myonecrosis (gas gangrene).[11] Severe myonecrosis often is a polymicrobial infection that occurs after bacteremic spread from an intestinal site of colonization to traumatized soft tissue.

TABLE 191.1

Clinical Manifestations of Histotoxic Clostridial Infection

Disease	Comment
Localized skin or soft tissue infection	Polymicrobial; related to trauma or ischemia; frequently remains localized but with extensive necrosis; perirectal abscess, decubitus ulcers
Spreading cellulitis or fasciitis	*Clostridium ramosum, Clostridium perfringens, Clostridium septicum* usual pathogens; compartment syndromes; 50% mortality rate
Myonecrosis	*C. perfringens, C. sordellii* responsible for >75%; related to trauma or ischemia;

(gas gangrene)	extremities or abdominal wall; aggressive surgical debridement required; usually fatal
Disseminated myonecrosis	*C. septicum, C. sordellii,* or *C. perfringens* usually responsible; no predisposing trauma; highly associated with profound neutropenia, colorectal or hematologic malignant disease, intestinal insult; spreading cellulitis and crepitation; survival rare
Suppurative visceral infection	Polymicrobic, with *C. perfringens, C. ramosum* especially; associated with cholangitis, pancreatic disease, pelvic infections, intra-abdominal abscess, pulmonary aspiration
Bacteremia or septicemia	*C. perfringens* associated sometimes with relatively benign course; *C. septicum* and *C. sordellii* rapidly progressive, causing disseminated gas gangrene

In adults, the predisposing factor for BSI often is colorectal or hematologic malignant disease, inflammatory bowel disease, or hemodialysis.[12,13] Trauma to the colon or female genital tract or injection drug abuse is present in most patients with BSIs. *C. sordellii* and *C. septicum* deserve special note because of the generally rapidly fatal course of infection. *C. septicum* septicemia in children usually is associated with profound neutropenia (as a primary genetic disorder or related to malignant disease or chemotherapy).[14] Typhlitis, mucositis, or necrotizing enterocolitis frequently is present, but some cases occur spontaneously.[15] In such cases, BSI and generalized soft tissue infection progress rapidly, and gas production is evident clinically at widely distributed body sites (Fig. 191.1).[16] Survival is unusual. *C. septicum* septicemia and secondary brain abscess can complicate hemolytic uremic syndrome caused by *Escherichia coli* O157:H7,[17,18] bowel ischemia, or trauma, and the combination often is fatal.[19] *C. sordellii* infections occur in previously healthy people following induced or spontaneous abortion, childbirth, genital tract operations, skin or soft tissue trauma, or injection drug abuse.[20] Lethal and hemorrhage toxins are thought to be responsible for typical leukemoid reactions and high fatality rates.[21] Clostridial endocarditis is rare. Clostridial bacteremia can be transient, without clinical consequence, or it can represent a contamination. In infants, BSI can be associated with necrotizing enterocolitis.[22]

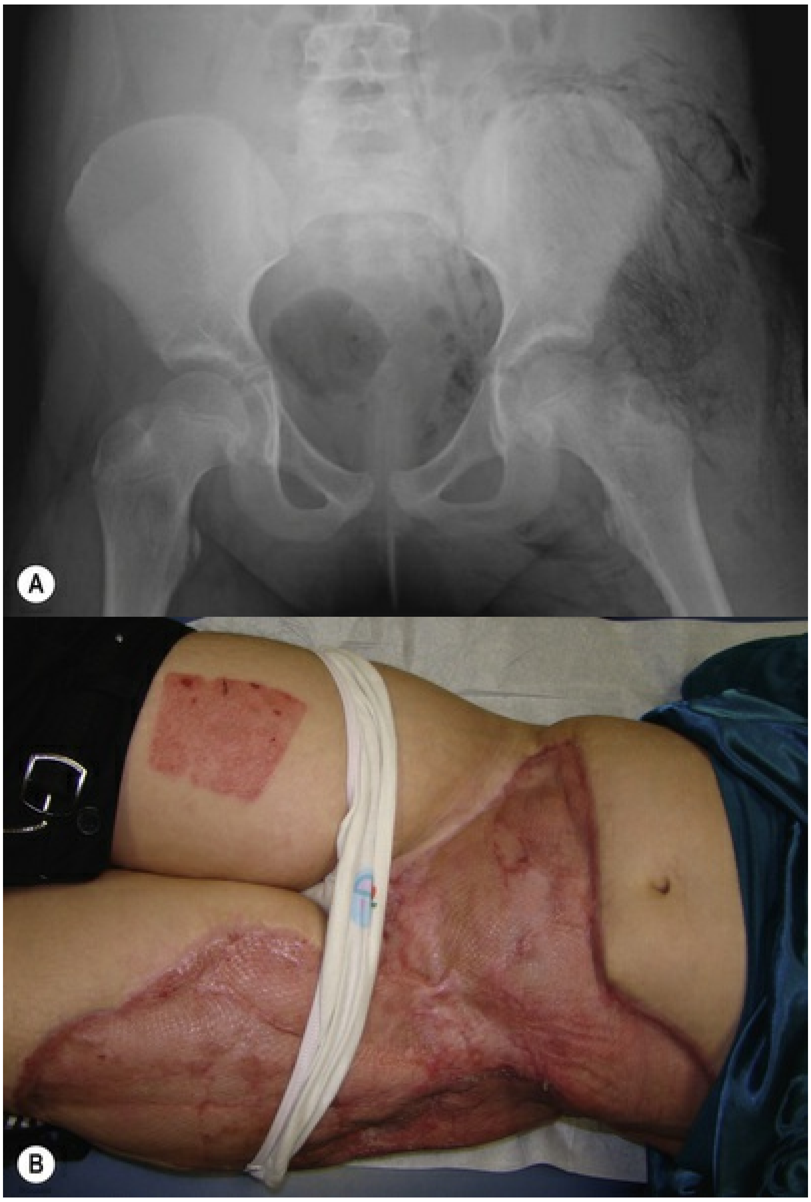

FIGURE 191.1 A 9-year-old girl with MyD88 deficiency (caused by myeloid differentiation primary response gene) had a 5-day history of abdominal pain and acute onset of left thigh and buttock pain. (A) Frontal radiograph shows diffuse, left-sided linear radiolucencies indicative of gas in muscle planes and soft tissues. (B) Urgent, widely extensive, and frequent operative debridement procedures were performed, followed by muscle flap and grafting. *Clostridium septicum* was isolated from tissue. (Courtesy of D. Conway, W. Davis, and S. S. Long, St. Christopher's Hospital for Children, Philadelphia, Pa.)

Gas gangrene affects muscle tissue that has been compromised by surgical procedures, trauma, or vascular insufficiency and that is contaminated with *C. perfringens* spores, usually from foreign material, such as clothing, dirt, or a medical device.[23] The ubiquitous nature of *C. perfringens* spores in dirt, soil, and clothing and on skin, especially of the lower trunk, provides multiple opportunities for inoculation of wounds.[24] The metabolic requirements of *C. perfringens* for growth are the major factors in the establishment of clostridial myonecrosis.

After inoculation and outgrowth of C*. perfringens* in the muscle, severe, rapidly progressive myonecrosis results from toxins elaborated, principally the α-toxin.[7] The α-toxin is a lecithinase that rapidly lyses cell membranes and causes hemolysis, myofibrillar injury, and vascular permeability. Severe systemic manifestations accompany local infection and may be toxin related. The patient has fever, tachycardia, and diaphoresis and is alert, anxious, and apprehensive or apathetic. Shock and attendant multiorgan failure ensue in most cases.

Gas gangrene characteristically begins 1 to 4 days (range, 6 hours to 21 days) after an injury.[24] The onset is heralded by sudden and persistent pain at the site of injury and an accompanying limb "heaviness." Overlying skin appears normal at the onset but quickly becomes cool, pale, and waxy as a result of ischemia. Local tense swelling, tenderness, pallor, and a thin hemorrhagic exudate are noted first; pallor gives way to a bronze or magenta discoloration, and hemorrhagic (purplish) bullae appear. Pain remains the most prominent symptom. Soft tissue crepitation can be present, but if the amount of gas is small, this finding may be noted first on a plain radiograph or other imaging study. As the condition worsens, a peculiar offensive odor (sometimes described as sweet) is noted, and a brown serosanguineous discharge is present. Gram stain of discharge shows large numbers of gram-positive bacilli with few or no white blood cells. Involved muscle can be edematous and pale initially, advancing to a mottled appearance and greenish black gangrene. Consistency of the muscle changes from pasty and mucoid to friable and liquefied.

Tachycardia, widespread myalgia, anxiety, and diaphoresis despite low-grade fever appear early and progress rapidly to hypotension, poor perfusion, disseminated intravascular coagulation, and mental status changes.[23,24] Without definitive therapy, the disease progresses inexorably, with high fever (often with rigors), shock, renal failure, metabolic acidosis, and coma, to death. Clostridial septicemia can occur terminally.

Food Poisoning

Acute self-limiting gastroenteritis caused by contaminated food products (mostly meat products) often is associated with *C. perfringens* and its toxins.[8] *C. perfringens* has been documented as the third most common cause of outbreaks of foodborne disease (after *Salmonella* and *Staphylococcus aureus*). Food poisoning occurs as a result of ingestion of vegetative forms of *C. perfringens* that develop in foods standing at a temperature between 30°C and 50°C.[25] Primary contamination of meat with *C. perfringens* spores is common. The temperature of cooking meat must exceed 120°C to ensure that spores are killed. With cooking at lower temperatures, spores can be converted to vegetative forms during cooling of food, thus risking the growth of *C. perfringens* in the gastrointestinal tract.

Although the symptoms of *C. perfringens* food poisoning are attributable largely to the action of enterotoxins, these enterotoxins usually are formed in the gut after ingestion of the organisms. Ingestion of preformed toxin results only in diarrhea if gastric acidity has been neutralized. The enterotoxin formed in vivo is a 35-kd polypeptide that is heat and acid labile and is inactivated by some proteolytic enzymes.[7] The enterotoxin gene *cpe* can be used to detect illness-causing strains. The toxin inhibits absorption of glucose and secretion of water, sodium, and chloride, and it strips the epithelium of villous tips. The in vitro cytotoxic effect is similar to that of *Shigella* toxin but differs from that of cholera or *E. coli* enterotoxins. Adenyl cyclase appears not to be involved in the mediation of *C. perfringens* toxin activity. The resultant gastroenteritis has components of secretory and inflammatory diarrhea.

C. perfringens food poisoning is an acute, self-limiting diarrheal illness with an onset 6 to 24 hours after consumption of contaminated food.[25] Crampy abdominal pain commonly accompanies watery diarrhea, which does not contain blood or mucus. Fever, nausea, and vomiting occur rarely. The duration of disease is commonly <24 hours, and medical intervention usually is not warranted or sought, except in the case of outbreaks. Making the distinction between food poisoning caused by *C. perfringens* and that caused by *Bacillus cereus* is difficult.

Differentiating this acute diarrheal disease from the numerous other viral, bacterial, and toxic causes of diarrhea on clinical grounds can be difficult unless an outbreak has occurred.[26] The absence of fever, nausea, vomiting, and blood or mucus in stools in a patient with *C. perfringens* diarrhea makes *Salmonella, Shigella, Campylobacter, Yersinia,* and rotavirus infection unlikely. The duration of infection caused by these pathogens usually is more prolonged than *C. perfringens* food poisoning. The diagnosis can be confirmed only by isolation of large quantities of *C. perfringens* from the suspect food ($>10^6$ colony-forming units/g) and the patient's fecal samples. The enterotoxin can be detected using a cytopathic toxin neutralization assay, latex agglutination, or enzyme immunoassays.[27] However, this approach is not useful in clinical diagnosis.

Miscellaneous Infections

Clostridia can contribute to various polymicrobial infections in children, including arthritis, osteomyelitis, skin and soft tissue (often after trauma or foreign body penetration), intra-abdominal, pulmonary, intracranial, and pelvic infections and abscesses.[5] Clostridial septicemia is rare in children without malignant disease, aplastic anemia, or immunodeficiency and usually follows an ischemic gastrointestinal insult, such as with neonatal necrotizing enterocolitis or toxic megacolon.[5] Pneumatosis cystoides intestinalis is present and extensive. Highly lethal enteritis necroticans, uncommon in the United States, is associated with consumption of undercooked pork (pigbel); *C. perfringens* with type C enterotoxin is usually the cause.[28] Neutropenic enterocolitis (typhlitis) is seen in patients with congenital neutropenia, leukemia, or neutropenia resulting from cytotoxic chemotherapy and usually is associated with *C. septicum*, but other clostridia have been implicated.[29] *Clostridium* spp. of normal flora (especially *C. perfringens* and *C. ramosum*) also are associated with septic abortion and puerperal septicemia, and mortality rates are high.[30] *C. perfringens* has been reported to cause panophthalmitis in children.[31]

Diagnosis

Gas gangrene is a clinical diagnosis. Myonecrosis and crepitation are classic findings but are not pathognomonic because several facultative and anaerobic bacteria produce gas. Synergistic nonclostridial anaerobic myonecrosis can have local clinical manifestations similar to those of gas gangrene but usually with less severe systemic symptoms. Localized anaerobic cellulitis is more likely to have gradual onset and less pain or systemic toxicity and is difficult to distinguish locally from group A streptococcal infection associated with exotoxin A–producing strains. A preexisting wound in streptococcal disease, however, usually is minor, whereas in anaerobic cellulitis and myonecrosis, severe crush injury is the expected predisposing injury[3,23]

Gram stain of local lesions reveals gram-positive bacilli, usually in the absence of neutrophils. Isolation of *C. perfringens* from a wound is not diagnostic of gas gangrene, and an inability to isolate *C. perfringens* does not exclude the diagnosis.[32,33] Isolation from a deep tissue site should be attempted (see Chapter 187).

Treatment

Histotoxic Infections

Early and aggressive surgical debridement of affected tissues is critical to successful outcome. Urgent intervention may require radical debridement to decompress fascial compartments and prevent further tissue anoxia and to provide drainage. Amputation of extremities may be required. Commonly, several surgical procedures must be performed to remove all necrotic tissue and any compromised tissue as it becomes necrotic.

Specific antimicrobial therapy directed at *Clostridium* spp. should be administered while recognizing that the anoxic and acidic environment of dead muscle is not conducive to antimicrobial efficacy. Penicillin G has excellent activity against most *Clostridium* spp. and always should be included in regimens for treatment of rapidly spreading clostridial cellulitis, myonecrosis, or septicemia. However, increasing resistance of *Clostridium* spp. to penicillin has been noted.[34] Clindamycin, cefoxitin, and metronidazole are clinically inferior, and some *Clostridium* spp. (especially *C. ramosum, C. tertium, C. sporogenes*) are resistant. The drug of choice is penicillin G, in a dose of 200,000 to 400,000 U/kg/day given intravenously in divided doses every 4 hours. Clindamycin has an advantage over penicillin because it suppresses bacterial toxin synthesis. The combination of penicillin and clindamycin was found to be more effective than penicillin alone in a mouse model.[35] Other effective antimicrobial agents are chloramphenicol, later-generation cephalosporins, the carbapenems, and vancomycin. Treatment should be continued until BSI has cleared and symptoms have resolved.

Aggressive supportive care is essential and predictably is complex. Although no controlled data are available and pediatric studies are lacking, hyperbaric oxygen appears to be useful in treating gas gangrene.[36] However, if fasciotomy is indicated, the procedure should not be delayed for hyperbaric oxygen therapy, nor should aggressive support be forfeited. The major advantages of hyperbaric oxygen may be in minimizing tissue loss and diminishing the extent of debridement required. Complications, including oxygen toxicity, mental status changes, and tympanic membrane perforation, are significant; survival may not exceed that obtained by an aggressive surgical approach. The use of polyvalent antitoxin (of equine origin) has been advocated, but substantive supportive data are not available. Other adjuvant therapies include granulocyte colony-stimulating factor, granulocyte transfusions, and immunoglobulin intravenous.[19]

The prognosis for survival depends on the location and extent of disease and the promptness of appropriate debridement. Death is virtually certain if surgical treatment is delayed (e.g., in a wartime situation). The overall survival rate, however, approaches 75% to 90% with early, modern, aggressive treatment.

Food Poisoning

Because of the self-limiting nature of *C. perfringens* food poisoning, medical intervention rarely is warranted. Oral rehydration with hypotonic fluids generally suffices, although in unusual circumstances, particularly in infants, intravenous hydration may be required. Antibiotics serve no useful purpose in this disease and should not be used; no antitoxin is available.

Prevention

Histotoxic Infections

The keys to prevention of histotoxic infections are adequate cleaning and debridement of contaminated wounds. Antimicrobial treatment, best considered therapeutic rather than prophylactic in this setting, should be administered to patients with heavily contaminated wounds, and care should be taken to avoid the anaerobic environments created by closing the wounds. Meticulous attention to the principles of surgical wound management prevents most cases of surgical wound gas gangrene.

Food Poisoning

The best means of preventing food poisoning from *C. perfringens* is appropriate handling of cooked foods (especially meats). Meats should reach at least 120°C during cooking and, if not consumed while hot, should be stored at <5°C.[37] Meat allowed to stand at room temperature is permissive to growth of *C. perfringens.* Preformed toxin is destroyed with reheating to serving temperature, although this temperature does not affect spores. Inhomogeneous heating, as can occur in microwave ovens, can leave some toxin undestroyed and should be avoided.

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Bacteroides and *Prevotella* Species and Other Anaerobic Gram-Negative Bacilli

Itzhak Brook

Clinically important anaerobic gram-negative bacilli (AGNB) include *Bacteroides, Prevotella, Porphyromonas,* and *Fusobacterium. Fusobacterium* is discussed in Chapter 193. Infection with *Porphyromonas* and *Prevotella* (previously mainly *Bacteroides* species) is not common in children, except for *Prevotella melaninogenica* and *Prevotella intermedia.*[1,2] Changing taxonomy has caused considerable clinical confusion in recategorization of *Bacteroides* species. Additionally, many new genera and several new species have been created to accommodate pathogens such as *Bilophila wadsworthia, Sutterella wadsworthensis, Centipeda periodontii,* and *Anaerobiospirillum thomasii* (see Chapter 187).

Bacteroides and *Prevotella* are gram-negative, obligate anaerobic bacteria that constitute a major part of the normal flora of the mouth, gastrointestinal tract, and female genital tract.[3] The

Bacteroides fragilis group comprises the species of Bacteroidaceae that occur with greatest frequency in clinical infections. These organisms are resistant to penicillins mostly through the production of β-lactamase.[4] The group includes *B. fragilis* (the most commonly recovered member), *B. ovatus, B. thetaiotaomicron,* and *B. vulgatus.*[5] *B. distasonis* is classified now as *Parabacteroides distasonis.*[6] *Bacteroides* spp. reside primarily in the large intestine and predominate in infections that originate from gut flora (e.g., perirectal abscesses following perforation or surgical procedures, intra-abdominal abscesses, decubitus ulcers). A heterogeneous group of *Bacteroides* spp. *(B. ureolyticus, B. gracilis, B. forsythus)* have a less clear taxonomic relationship and may be more closely related genetically to *Campylobacter.* Pigmented *Prevotella,* previously called the *Bacteroides melaninogenicus* group *(P. melaninogenica* and *P. intermedia),* and *Porphyromonas (Porphyromonas asaccharolytica)* and nonpigmented *Prevotella (P. oralis, P. oris)* are part of the normal oral and vaginal flora and are the predominant gram-negative anaerobic species isolated from contiguous oral respiratory tract infections, such as aspiration pneumonia, lung abscess, chronic otitis media, chronic sinusitis, abscesses around the oral cavity, human bites, paronychia, brain abscesses, and osteomyelitis. *Prevotella bivia* and *P. disiens* (previously also called *Bacteroides*) are important in obstetric and gynecologic infections.

Bacteroides spp. possess virulence factors or special characteristics to compete successfully for microbial niches, including pili and fimbriae (which enhance adherence),[1,7] hemagglutination, enzymes (collagenase, phospholipase A, hemolysin, peroxidase, protease, fibrolysin, heparinase, neuraminase, superoxide dismutase),[8,9] and lipopolysaccharide and capsular polysaccharide (which enhance invasion and evasion from host phagocytosis). *B. fragilis* and *P. melaninogenica* are associated more frequently with infection than their relative density in normal flora would predict, and they are especially associated with abscess formation (see Chapter 187).

Pathophysiology

Most infections with AGNB originate from the endogenous mucosal flora. This feature allows for logical selection of antimicrobial agents for the treatment of infections predictably caused by anaerobic bacteria. AGNB infections generally are polymicrobial, and the number of unique isolates can reach 5 to 10. The types of other copathogens depend on the site and circumstances of the infection. AGNB promote infection through synergy with their aerobic and anaerobic counterparts. An indirect pathogenic role of AGNB is conferred by the ability of these organisms to produce a β-lactamase enzyme. Such organisms may protect not only themselves but also other penicillin-susceptible organisms from the activity of penicillins.[10]

Clinical Manifestation and Prediction of Pathogens

Central Nervous System Infections

Anaerobic bacteria, including AGNB, can cause a variety of intracranial infections: brain abscess, subdural empyema, epidural abscess, and meningitis.[11,12] Infection generally is polymicrobial, mixed with microaerophilic streptococci. The main source of brain abscess is an adjacent, generally chronic infection in the middle ear, mastoid, sinus, oropharynx, teeth, or lungs. Middle ear or mastoid infections tend to spread to the temporal lobe or cerebellum, whereas sinusitis often causes abscess of the frontal lobe. Hematogenous spread often occurs after dental, oropharyngeal, or pulmonary infection.[13,14] Rarely, bloodstream infection (BSI) has another origin, or endocarditis can lead to central nervous system infection. Meningitis is rare and can follow respiratory tract infection, or it can occur as a complication of a cerebrospinal fluid shunt. Ventriculoperitoneal shunt infection with the *B. fragilis* group can have an enteric origin after perforation of the gut.[15]

At the stage of encephalitis, antimicrobial therapy can prevent the formation of abscesses. Once an abscess has formed, excision or drainage generally are needed, combined with 4 to 8 weeks of antibiotics. Administration of antibiotics for an extended period is an alternative approach that can replace surgical drainage in selected patients. Depending on the organism or organisms isolated and β-lactamase production, metronidazole, penicillins, and chloramphenicol frequently are chosen because of their spectrum and favorable pharmacodynamic profile.

Head and Neck Infections

Anaerobic bacteria are recovered from a variety of head and neck infections, especially chronic infections.[16]

Odontogenic Infections.

Most dental infections involve anaerobic bacteria, including *Prevotella* and *Porphyromonas* of oral flora origin.[17] These infections include pulpitis and periodontal and endodontal (gingivitis and periodontitis) infections, periapical and dental abscesses, and perimandibular space infections. Vincent angina (trench mouth or acute necrotizing ulcerative gingivitis) is an acute, destructive ulcerative gingivitis that causes severe pain and putrid breath odor. Oral fusospirochetes and other oral flora are causative.[18]

Peritonsillar, Lateral Pharyngeal, and Retropharyngeal Abscesses.

The predominant anaerobes isolated are *Prevotella, Porphyromonas, Fusobacterium,* and *Peptostreptococcus* spp. *Streptococcus pyogenes* is isolated in approximately one third of cases.[19] More than two thirds of abscesses contain β-lactamase–producing organisms.[19] Systemic antimicrobial therapy should be given in large doses; when pus is formed, adequate surgical drainage is needed. Untreated abscesses can rupture spontaneously into the pharynx and cause aspiration. Other complications are lateral extension or dissection into the posterior mediastinum and the prevertebral space.

Deep Neck Infections.

These infections generally follow oral, dental, and pharyngeal infections, usually are polymicrobial, and involve the organisms that caused the primary infection. Mediastinitis after esophageal perforation or extension of a retropharyngeal abscess or cellulitis often involves anaerobic bacteria, including AGNB.[20]

Chronic Otitis Media and Chronic Mastoiditis.

AGNB can be recovered from patients with chronic suppurative otitis media,[21] chronic mastoiditis,[22] or an infected cholesteatoma and can lead to complicating intracranial abscesses.

Sinusitis.

AGNB become involved when the sinusitis is chronic and oxygen levels decline.[23] Anaerobic bacteria are isolated from 10% of patients with acute maxillary sinusitis (most often in disease secondary to periodontal infection)[24] and in up to 67% of chronic infections (average of 3 species per aspirate).[25] Infection can spread through the anastomosing veins or contiguously, thereby causing orbital cellulitis, meningitis, cavernous sinus thrombosis, and epidural, subdural, and brain abscesses.[14]

Cervical Lymphadenitis and Cysts.

AGNB can be isolated in cervical lymphadenitis,[26] especially in association with dental, periodontal, or tonsillar infection. Thyroglossal duct cysts, cystic hygromas, branchial cleft cysts, laryngoceles, and dermoid cysts can become infected.[27]

Infection After Head and Neck Operations.

These infections follow exposure of the surgical site to the oropharyngeal flora. Infections generally are polymicrobial and therefore warrant the use of proper prophylaxis.[28]

Chronic Tonsillitis.

AGNB can be involved in acute tonsillitis, chronic tonsillitis, and their complications, including internal jugular vein thrombophlebitis. Evidence of pathophysiologic features of anaerobes in nonstreptococcal tonsillitis includes the following: reduction of fever and clinical symptoms in patients treated with metronidazole compared with untreated children[29]; a detectable immune response against AGNB in patients with tonsillitis, peritonsillar cellulitis or abscess, and infectious mononucleosis[30]; isolation of AGNB from the cores of tonsils of children with recurrent tonsillitis[23] and peritonsillar and retropharyngeal abscesses[31]; and isolation of aerobic and anaerobic β-lactamase–producing organisms from the tonsils of more than 75% of children with recurrent streptococcal tonsillitis.[32] The ability to measure β-lactamase activity in the core of tonsils and patients' responses to agents effective against β-lactamase–producing bacteria (i.e., clindamycin or amoxicillin plus clavulanic acid) support the role of AGNB in children in whom penicillin has failed to eradicate streptococcal tonsillitis.[32]

Pleuropulmonary Infections

Aspiration of oropharyngeal or gastric secretions and periodontal or gingival disease are risk factors for the development of anaerobic (including AGNB) pleuropulmonary infection. Infection can progress from pneumonitis to necrotizing pneumonia and abscess, with or without empyema. AGNB can be recovered from patients with community-acquired and nosocomially acquired aspiration pneumonia,[33] and as well as with pneumonia associated with tracheostomy[34] with and without mechanical ventilation, in which case AGNB generally are recovered along with Enterobacteriaceae, *Pseudomonas,* and *Staphylococcus aureus.* Anaerobes can be recovered in empyema associated with aspiration pneumonia, lung abscess, subdiaphragmatic abscess, and abscesses of dental or oropharyngeal origin.[35]

Management of these infections includes drainage of the pleural space when indicated and antimicrobial therapy.

Intra-Abdominal Infections

Intra-abdominal infections characteristically are biphasic; initial peritonitis is associated with *Escherichia coli* sepsis, and later intra-abdominal abscesses are caused by *B. fragilis*.[36]

Perforated appendicitis, inflammatory bowel disease with perforation, gastrointestinal operations, obstruction, infarction, and trauma often are predisposing factors to secondary peritonitis and intra-abdominal abscesses, which invariably are polymicrobial (average of 12 isolates).[37] The predominant isolates are AGNB (including *Biophila wadsworthia*).[38] Similar aerobic and anaerobic bacteria are found in pyogenic liver,[39] splenic,[40] pancreatic,[41] and retroperitoneal abscesses.[42] In neonates, peritonitis and abscesses often occur as a result of necrotizing enterocolitis.[43] Management of intra-abdominal infections requires the use of agents effective against aerobic and anaerobic pathogens, as well as surgical correction and drainage.[44] Single and easily accessible abscesses can be drained percutaneously.

Therapy directed at Enterobacteriaceae and AGNB can be achieved with combinations or single agents in certain circumstances.[44] Potential single agents could be a carbapenem (imipenem, meropenem) or a penicillin plus a β-lactamase inhibitor (e.g., piperacillin-tazobactam, ticarcillin-clavulanate). Combination therapy includes an anti-Enterobacteriaceae agent (e.g., aminoglycoside, fluoroquinolone, third-generation cephalosporin) plus an antianaerobic agent (e.g., metronidazole). The need to add amoxicillin or vancomycin routinely for *Enterococcus* therapy is controversial.

Antimicrobial prophylaxis before colonic surgical procedures could consist of an oral preparation such as erythromycin plus neomycin or a parenteral agent such as cefoxitin. The use of prophylaxis has reduced the rate of postsurgical wound infection.

Enterotoxigenic *B. fragilis* has been associated with acute diarrhea, colitis, and colonic inflammatory bowel disease.[45] Abdominal pain and nonfebrile inflammatory diarrhea are usual manifestations.[46]

Genital Tract Infections

Infections of the female genital tract are polymicrobial and include the following: bacterial vaginosis; soft tissue perineal, vulvar, and Bartholin gland abscesses; endometritis; pyometra; salpingitis; tubo-ovarian abscesses; adnexal abscesses; and pelvic inflammatory disease. The pelvic inflammatory disease category includes pelvic cellulitis and abscess, amnionitis, septic pelvic thrombophlebitis, intrauterine device–associated infection, septic abortion, and postsurgical obstetric and gynecologic infections.[1,2]

AGNB play a role in prostatic and scrotal infections including Fournier gangrene.[47] Therapy should include agents effective against all potential aerobic and anaerobic pathogens. Additionally, coverage against sexually transmissible pathogens should be provided.

Skin and Soft Tissue Infections

AGNB can cause superficial infections such as infected cutaneous ulcers, cellulitis, secondary diaper rash, gastrostomy or tracheostomy site wounds, infected subcutaneous sebaceous or inclusion cysts, eczema, scabies or kerion infections, paronychia, hidradenitis suppurativa, and pyoderma.[48] Subcutaneous tissue infections and postsurgical wound infection also can include skin flora and AGNB.[28,37] Such infections include cutaneous and subcutaneous abscesses, decubitus ulcers,[49] infected diabetic (vascular or trophic) ulcers, breast abscesses, bite wounds,[50] anaerobic cellulitis and gas gangrene, bacterial synergistic gangrene, infected pilonidal cyst or sinus, Meleney ulcers, and burn wound infection. Deeper anaerobic soft tissue infections include necrotizing fasciitis, necrotizing synergistic cellulitis, gas gangrene, and crepitus cellulitis.[51] These infections can involve only the fascia, the muscle surrounded by the fascia (inducing myositis and myonecrosis), or both the fascia and the muscle.

The organisms recovered from soft tissue infections vary according to the type and location of the infection and the circumstances leading to the infection. Wound and subcutaneous tissue infections and abscesses of the rectal area (decubitus ulcer, perirectal abscess) or infections originating from gut flora (e.g., diabetic foot infection) tend to yield colonic flora. Sites in and around the oropharynx (e.g., paronychia, bites) generally contain oral flora. Skin flora organisms such as *S. aureus* and *Streptococcus* or nosocomially acquired organisms (gram-negative aerobic bacilli) can be isolated at all body sites. In addition to oral flora, human bite infections often contain *Eikenella* species, and animal bite infections can include *Pasteurella multocida*.[50] Anaerobic infections (e.g., decubitus ulcers, diabetic foot ulcer) generally are polymicrobial and often are complicated by osteomyelitis or BSI. Deep tissue infections such as necrotizing cellulitis, fasciitis, and myositis often involve clostridia or *Streptococcus pyogenes* or are polymicrobial; they contain gas and grey, thin, putrid-like pus and are associated with BSI and substantial mortality rates.

Management of deep-seated soft tissue infection includes surgical debridement and drainage, improvement in the blood supply when indicated, and administration of hyperbaric oxygen, especially in patients with clostridial infection.

Osteomyelitis and Pyogenic Arthritis

Osteomyelitis is associated with AGNB in patients with peripheral vascular disease and decubitus ulcers and when infection occurs in long bones and in cranial and facial bones.[52] Osteomyelitis of cranial and facial bones generally is caused by spread from a contiguous soft tissue source or from sinus, ear, or dental infections. Osteomyelitis of long bones generally is caused by hematogenous spread, trauma, or the presence of a prosthetic device.

Recovery of AGNB is associated with certain settings: *Prevotella, Porphyromonas,* and *Fusobacterium* with skull osteomyelitis and bites; *B. fragilis* with vascular disease or neuropathy; and clostridia with long bone osteomyelitis, especially in wounds contaminated after trauma.[53]

Most cases of pyogenic arthritis resulting from anaerobic bacteria are monomicrobial and occur after hematogenous and contiguous spread, trauma, and arthritis associated with prosthetic joints. The predominant isolates are peptostreptococci and *Propionibacterium acnes* (often in prosthetic joint infection), *B. fragilis* and fusobacteria (often in infections of hematogenic origin), and clostridia (associated with trauma).

Bloodstream Infection

AGNB are responsible for up to 5% to 15% of BSIs. Common isolates are the *B. fragilis* group (60%–75% of isolates). The *B. fragilis* group and clostridia are associated with a gastrointestinal source, pigmented *Prevotella* and *Porphyromonas* and *Fusobacterium* are assocoiated with oropharyngeal and pulmonary sites, *P. bivia* and *P. disiens* are associated with the female genital tract, *P. acnes* is associated with foreign bodies, and peptostreptococci are associated with all sources, but especially with oropharyngeal, pulmonary, and female genital tract sources.[54]

Predisposing factors include the following: neoplasms; hematologic disorders; organ transplantation; recent gastrointestinal, obstetric, or gynecologic surgical procedures; intestinal obstruction; decubitus ulcers; dental extraction; diabetes mellitus; the postsplenectomy state; and the use of cytotoxic agents or corticosteroid therapy. Features typical of BSI with AGNB include metastatic lesions, hyperbilirubinemia, and suppurative thrombophlebitis. Shock and disseminated intravascular coagulation are less common compared with aerobic gram-negative BSI. The mortality rate is 15% to 30%, but it improves with early appropriate antimicrobial therapy and aggressive management of the root cause.

Anaerobic bacteremia in newborns is caused by AGNB, *Clostridium,* and *Peptostreptococcus* spp., and it is associated with perinatal maternal complications (primarily premature rupture of membranes and chorioamnionitis), prematurity, and necrotizing enterocolitis.[55]

Treatment

In most cases, surgical therapy is of critical importance. Surgical treatment includes draining abscesses, débriding necrotic tissues, identifying the primary source of infection, removing devitalized tissue, decompressing closed-space infections, and relieving obstructions. In selected cases, an abscess can be drained with the use of imaging modalities to guide catheter placement without surgical or laparoscopic intervention.[56] When surgical drainage is not performed, the infection can persist, and serious complications can develop. The duration of antimicrobial therapy for anaerobic infections generally is longer than that for infections with aerobic and facultative organisms.

Resistance to antimicrobial agents has a broad basis, but β-lactamase production has the most clinical significance. All *B. fragilis* group strains produce β-lactamase, as do many clinical isolates of *Prevotella, Porphyromonas, Fusobacterium, S. wadsworthensis,* and *Bacteroides splanchnicus,* and this feature renders these organisms resistant to penicillins. Agents active in vitro against β-lactamase–producing AGNB include metronidazole, chloramphenicol, clindamycin, cefoxitin, carbapenems, and combinations of a penicillin and a β-lactamase inhibitor (e.g., ampicillin-sulbactam, ampicillin-clavulanate, ticarcillin-clavulanate, and piperacillin-tazobactam) (see Chapter 187). Large databases show the following resistance rates of the *B. fragilis* group in the United States and Europe, respectively: clindamycin, >35% and 32%; moxifloxacin, 32% and 14%, cefoxitin, 10% and 9%; tigecycline, 4%, and 5%; ampicillin-sulbactam/amoxicillin-clavulanate, 3% and 10%; piperacillin-tazobactam, <1% and 3%; meropenem/imipenem, <1% and 1%; and metronidazole, <1%.,[4,57] *Prevotella, Fusobacterium,* and *Porphyromonas* species isolates are more likely than *B. fragilis* group to be susceptible to clindamycin. Although antibiotic susceptibility of *P. melaninogenica* and *P. intermedia* can vary geographically, most of these organisms are β-lactamase producing (penicillin resistant), 10% are resistant to clindamycin, and none is metronidazole resistant.[58] The *B. gracilis* group, found primarily in gingival crevices, is more likely than *B. ureolyticus* (now *Campylobacter ureolyticus*) to be recovered from serious, deep infections and is more resistant to antibiotics (e.g., clindamycin and metronidazole), but it is sensitive to gentamicin[59]; *Sutterella wadsworthensis* is predominantly responsible for resistant organisms in the former *B. gracilis* group, with clindamycin resistance rates of 15% to 30%[60] in some areas. Despite difficulties in breakpoint determinations and exact clinical correlation with in vitro results, agents active in vitro are more likely to be associated with a good clinical outcome and vice versa.[59,61] The choice of agents depends on the site and stage of infection and the probable coinfecting pathogens. Although early infection such as aspiration pneumonia can be treated effectively with agents active primarily against facultative and some anaerobic organisms (not necessarily *Bacteroides* or *Prevotella*), necrotizing infection or abscess is best treated with specifically directed therapy.

The role of hyperbaric oxygen in the treatment of anaerobic infections remains unclear, with some suggestion of benefit as adjunctive therapy to surgical debridement and antibiotics.[62,63]

Prevention

Elimination of acute infection can prevent chronic infections in which AGNB and other anaerobes predominate. When anaerobic infections are anticipated complications of surgical procedures at heavily colonized mucosal sites, proper antimicrobial prophylaxis reduces the infection rate. Early treatment of conditions that may lead to anaerobic infection also can reduce this rate. Preventing aspiration of oral flora by improving the patient's neurologic status, suctioning, improving oral hygiene, and maintaining lower stomach pH can reduce the risk of aspiration pneumonia and its complications.

Skin and soft tissue infections can be prevented by irrigation and debridement of wounds and necrotic tissue, drainage of pus, and improvement of perfusion. Prophylaxis generally is instituted preoperatively when contamination by normal flora is expected at the operative site.[64] Cefazolin is effective prophylaxis at sites distant from the oral or rectal areas. Cefoxitin is the drug of choice in procedures that involve the oral, rectal, or vulvovaginal surfaces.

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Fusobacterium Species

Neil Rellosa, Jennifer Vodzak

Fusobacteria are non–spore-forming, nonmotile, pleomorphic, gram-negative (Fig. 193.1), obligate anaerobic bacilli that can cause a wide spectrum of human disease ranging from mild pharyngitis to sepsis, and these organisms are most notorious for causing septic thrombophlebitis of the internal jugular vein, commonly referred to as Lemierre syndrome.[1–15] *Fusobacterium* infections in children and adolescents often are associated with abscess formation and intracranial complications.[16] *F. nucleatum* and *F. necrophorum* subspecies *funduliforme* are the most common fusobacteria identified in human disease.[1,6,17,18]

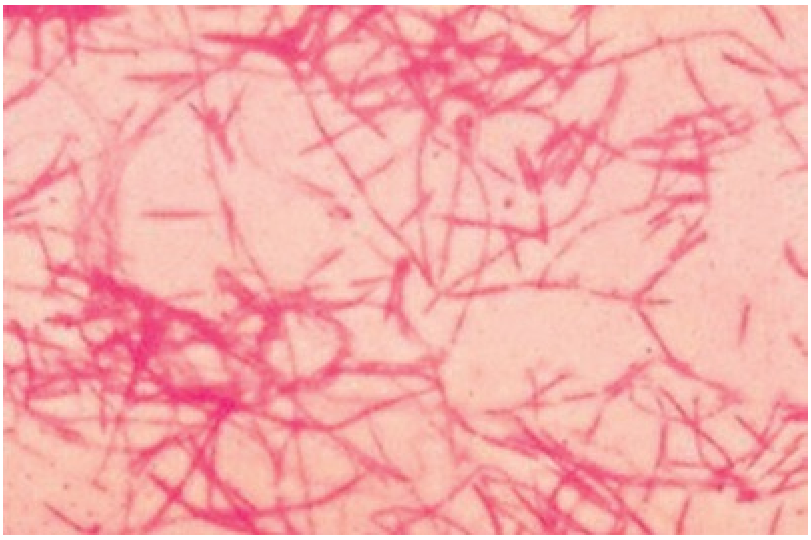

FIGURE 193.1 **Gram stain of *Fusobacterium nucleatum*, magnification 1000×.** (From Baron EJ, Peterson LR, Finegold SM [eds]. Bailey and Scott's Diagnostic Microbiology, 8th ed. St. Louis, Mosby, 1990.)

Description of the Pathogen

The genus *Fusobacterium* includes 9 disease-causing species that are part of the normal flora of the human oropharynx and the upper respiratory, gastrointestinal, and female genitourinary tracts: *F. nucleatum* (subspecies *nucleatum, polymorphum, vincentii, animalis, fusiforme,* and *canifelium*[6]), *F. necrophorum* (subspecies *necrophorum* and *funduliforme*), *F. ulcerans, F. gonidiaformans, F. mortiferum, F. naviforme, F. necrogenes, F. russii,* and *F. varium*.[6,7,18–26] Because molecular techniques are redefining the taxonomy and role of fusobacteria as commensals and pathogens, this compilation is evolving.[6,25]

Unlike other anaerobes, *F. necrophorum* produces lipopolysaccharide, which contributes to its intrinsic virulence.[4,5] Overall, one third of fusobacterial infections are polymicrobial,[27] and animal studies demonstrated increased virulence of *F. necrophorum* in the presence of fecal organisms.[28] Additional, less well-characterized virulence factors include production of leukocidins, hemolysins, lipases, DNases, hemagglutinins, β-lactamases (by *F. nucleatum*), and the ability to aggregate platelets (*F. necrophorum*).[4,5,14,18] Molecular thrombophilic predisposition has been identified in children with invasive fusobacteriosis.[29–32] Whole-genome sequencing of a diverse set of *Fusobacterium* spp. revealed that actively invading species have larger genomes than passively invading species and possess a complement of genes that have evolved to enable host cell adherence and invasion.[33] A single nucleotide polymorphism in the toll-like receptor 5 gene was found in 1 affected child,[29] a finding suggesting that underlying host factors also may predispose to infection.

Epidemiology

Well recognized in the preantibiotic era, invasive fusobacteriosis was rarely reported after the advent of antibiotic therapy for pharyngitis,[34] and it became a forgotten disease.[5] Since the 1990s, both incidence and disease reporting have been increasing.[4,35–37] The increase in incidence may be the result of decreased empiric use of antibiotics for sore throat, increased use of corticosteroid therapy for mononucleosis or sore throat, superior blood culture methods, improved techniques for diagnosis of anaerobic infections, and use of non–culture-based molecular diagnostic tools.[1,4,5,14] Fewer tonsillectomies also could contribute to the increased incidence.[4,5] However, a Swedish study in adolescents and adults found persistent pharyngeal colonization with *F. necrophorum* despite tonsillectomy (30% versus 16% in pre tonsillectomy versus posttonsillectomy throat cultures).[38] Estimates of disease incidence range from 0.8 to 3.6 cases per million people.[27,35,39] A prospective study in Denmark demonstrated an incidence of Lemierre disease of 14.4 cases per million people 15 to 24 years of age.[39] The infection may have a peak in late winter.[34] Boys and men are more commonly afflicted.[1–4,34]

Three age-related disease patterns are observed for fusobacteriosis (Table 193.1).[1,4,39,40] Localized head and neck disease tends to arise from the middle ear (and occasionally, cervical lymph nodes) in young children, the throat and tonsil in adolescents, and the sinuses and carious teeth and gums in adults.[40] Similarly, invasive or disseminated fusobacterial infection tends to vary with age. Children tend to develop infection, often associated with otitis media,[40] that can disseminate systemically but more often results in intracranial complications.[1,16,41] Otogenic Lemierre disease was reported in patients 2 months to 51 years of age (median, 5 years), whereas pharyngitis-associated Lemierre disease occurred in patients 8 months to 63 years of age (median, 19 years).[1] Other investigators have noted peak ages for Lemierre disease of 16 to 23 years[36] (median age range, 17–21.5 years).[27,42,43] In another series of cases in patients ranging in age from 2 months to 78 years, distribution of cases was 51%, 20%, and 8% in the second, third, and first decades of life, respectively.[2] In a prospectively collected series of 391 isolates of *F. necrophorum* from localized and disseminated infections, 343 isolates had subspeciation performed; >99% were *F. necrophorum* subspecies *funduliforme,* and a single isolate was *F. necrophorum* subspecies *necrophorum*.[39,40]

TABLE 193.1

Prospectively Collected Series of 388 Cases of *Fusobacterium necrophorum* Infection

Classification	Source of Infection	Number of Cases	Age Range (Yr)	Median Age (Yr)
Localized disease (n = 288)	Otogenic source	7	0–26	4
	Cervical lymphadenitis	9	0–46	3
	Tonsillitis	26	13–57	20
	Peritonsillar abscess	215	4–72	19
	Sinus- or teeth-associated source	10	29–73	44
	Localized disease caudal to the head and neck	21	9–83	38
Disseminated disease (n = 100)	Otogenic Lemierre disease	5	0–16	2
	Oropharyngeal-associated Lemierre disease	37	6–66	20
	Disseminated disease originating from sinus or teeth	16	7–89	24–55[a]
	Disseminated disease originating from the gastrointestinal tract	30	5–89	61
	Disseminated disease originating from the genitourinary tract	6	25–96	78
	Disseminated disease originating from an unknown focus	6	66–87	76

[a] Group subdivided with 2 medians reported in Hagelskjær Kristensen L, Prag J. Lemierre's syndrome and other disseminated *Fusobacterium necrophorum* infections in Denmark: a prospective epidemiological and clinical survey. Eur J Clin Microbiol Infect Dis 2008;27:779–789.

Data from Hagelskjær Kristensen L, Prag J. Lemierre's syndrome and other disseminated *Fusobacterium necrophorum* infections in Denmark: a prospective epidemiological and clinical survey. Eur J Clin Microbiol Infect Dis 2008;27:779–789; and Hagelskjær Kristensen L, Prag J. Localised *Fusobacterium necrophorum* infections: a prospective laboratory-based Danish study. Eur J Clin Microbiol Infect Dis 2008;27:733–739.

Clinical Manifestations

Fusobacterial infection can be divided into invasive disease and localized disease (exemplified by peritonsillar abscess); localized disease occurs more frequently although it is reported less often. Lemierre disease can be diagnosed by clinical manifestations.[44] The most common symptoms and findings include sore throat, fever, rigors, neck mass, neck pain, trismus, tenderness along the neck vasculature, anorexia, malaise, cough, chest pain, shortness of breath, and prostration.[1–5] Typically, sore throat is followed by fevers and rigors (a distinctive feature) on the fourth or fifth day and by painful swelling in the neck (often mistakenly attributed to lymphadenopathy, which is tender but rarely is painful).[1–5] Phlebothrombosis leads to septic embolization to the lungs, but metastatic foci of infection also can occur in joints, muscles, bones, liver, skin, spleen, and endocardium.[1]

Otogenic disseminated fusobacteriosis more often results in intracranial complications, including meningitis[16,41,45–51] and vascular thrombosis,[16,50,51] but it rarely results in internal jugular involvement.[51] Meningitis also can complicate fusobacterial sinusitis in older children and adults,[52–54] as can brain abscesses, but brain abscesses are more often secondary to periodontal disease with bloodstream infection (BSI).[55–57]

Bloodstream infection in adults usually is associated with predisposing conditions.[39,58] Bloodstream infection has been reported in healthy[59] and neutropenic[3] children.

The most common clinical manifestations of fusobacterial infection are pharyngitis (especially recurring, persisting, and poorly responsive to typically prescribed antibiotic therapy),[21,60–62] tonsillitis,[24] and peritonsillar abscess.[40,63–65] Using appropriate culture and polymerase chain reaction (PCR)–based techniques, *F. necrophorum* has been identified in 10% to 21% of cases of persistent sore throat or tonsillitis.[21,24,60,61] In a prospective Danish study, *F. necrophorum* was identified in 21% of 1001 peritonsillar abscesses.[40] In a Finnish study, *F. nucleatum* and *F. necrophorum* were isolated from 26% and 38% of peritonsillar abscesses, respectively (compared with *Streptococcus pyogenes* from 46%).[63] In another Danish series of 847 patients with peritonsillar abscess, *F. necrophorum* was the most frequent cause (23%) compared with 17%

for *S. pyogenes*.[65]

Lung and liver abscesses are recognized complications of Lemierre syndrome,[66] although isolated localized infection can occur even in immunocompetent patients.[67–69] Less common manifestations of fusobacteriosis include pyogenic arthritis (most frequently involving the knee, hip, ankle, shoulder, elbow, sacroiliac, or sternoclavicular joint),[41,70–72] osteomyelitis (affecting facial bones more often than the vertebrae, pubic bone, or extremities),[72–75] and spondylodiscitis.[76,77] Wound and zoonotic infections occur rarely.[4,6,18] Single cases of multiple cranial nerve impairments[71] and sensorineural hearing loss[41] have been reported. Finally, *F. necrophorum* has been implicated in orofacial gangrene (cancrum oris or noma)[78–80] and tropical ulcer.[20] Bacterial 16S ribosomal RNA gene sequencing of appendiceal samples from children with acute appendicitis and controls has suggested a possible pathologic role of *Fusobacterium* species.[81]

Laboratory Findings and Diagnosis

Laboratory findings are nonspecific[1–3]; leukocytosis with increased band forms is common, as is elevated C-reactive protein.[2,3,39,40,65] Abnormal results of hepatic biochemical tests, particularly hyperbilirubinemia, are found in 11% to 49% of patients with Lemierre disease.[27,39,43] Less commonly, thrombocytopenia and evidence of disseminated intravascular coagulopathy are present in Lemierre disease.[39,71] Culture confirmation of *Fusobacterium* infection requires adequate or protected specimen collection and optimized transport, culture medium, and identification. Increasingly, PCR-based molecular methods including broad-range 16S (small subunit) ribosomal DNA PCR are used to confirm fusobacterial infections.[17,21,24,82,83]

Imaging studies generally are helpful to confirm clinical suspicion and evaluate for intravascular, local, and metastatic complications (Fig. 193.2).[84] Multiple imaging modalities may be employed because patients often are quite ill, and the extent of the disease may not be established on clinical grounds alone.

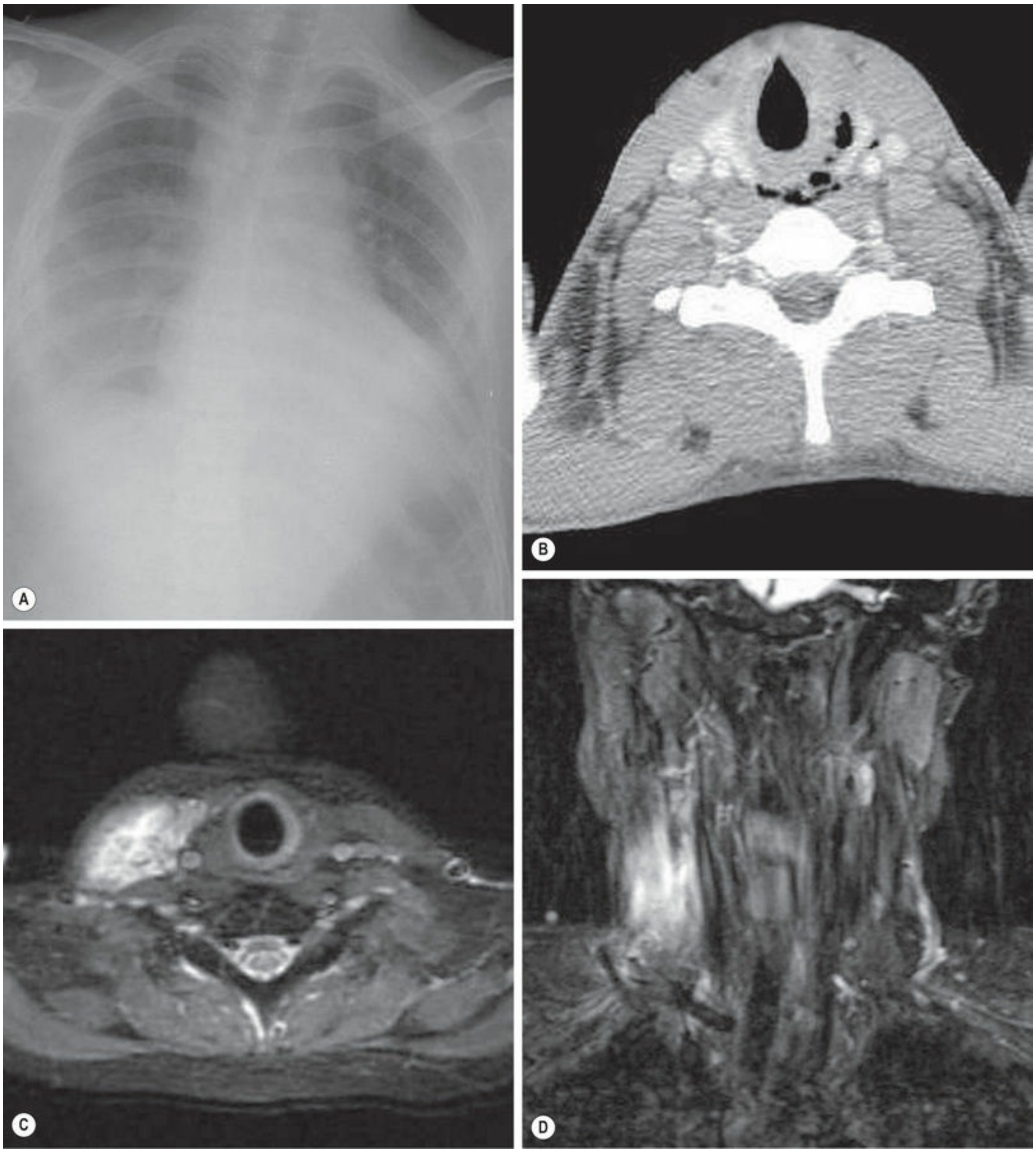

FIGURE 193.2 **Images of 2 adolescents with Lemierre disease. (A) Chest radiograph shows left lower lobe consolidation, bilateral pleural effusions, and widened mediastinum. (B) Axial computed tomography of the neck shows left-sided soft tissue swelling and perivascular gas, which extended into the mediastinum. (C) Axial and (D) coronal magnetic resonance imaging of the neck in another patient shows right-sided soft tissue swelling, perivascular edema, and filling defects in the internal jugular vein.** (Courtesy of S. Underberg-Davis and S. Schonfeld, the Children's Hospital at St. Peter's University Hospital, New Brunswick, NJ.)

Treatment

In a series from Wales conducted before 2000, 15% of *F. necrophorum* isolates were resistant to erythromycin, 2% were resistant to penicillin, and 1% to tetracycline.[36] Increasingly, β-lactamase–

producing strains of *F. necrophorum* and *F. nucleatum* are reported.[85,86] A *Fusobacterium* isolate with carbapenem resistance has been reported, with clinical failure during meropenem monotherapy.[87] Metronidazole resistance has not been reported among isolates of *Fusobacterium*.[84,86] Most experts recommend antibacterial therapy with metronidazole (in combination with a penicillin for severe or invasive disease); additionally, clinical outcomes (particularly of central nervous system disease) seem to be improved when metronidazole is included.[1,4,86] Combination therapy is preferable to monotherapy for serious infection because cultures may not be properly obtained, infections occasionally are polymicrobial, and infection with other organisms can mimic fusobacteriosis.[1,4,86] The median duration of fever after initiation of appropriate antibiotic therapy for Lemierre disease is 8 to 12 days.[4] The duration of reported therapy ranges from 9 to 84 days, with a median of 42 days,[13] but some experts recommend a 2- to 3-week course of antibiotics parenterally if the clinical course is reassuring, followed by oral therapy to complete 6 weeks.[1] Important adjunctive therapy includes operative intervention as necessary to drain abscesses.[4] Ligation of the thrombosed internal jugular vein rarely is necessary in the antibiotic era, unless the thrombus progresses or repeated embolization occurs despite medical therapy.[88] The role of anticoagulation remains controversial, with inadequate data to make recommendations.[30–32,88]

Special Considerations

F. nucleatum infections have been implicated in preterm delivery and chorioamnionitis.[3,89-91] In 1 series, 36% of women with preterm delivery (compared with none who delivered at term) had *F. nucleatum* isolated from vagina specimens.[89] *F. nucleatum* is the organism most frequently isolated from the amniotic fluid of women with preterm labor and intact membranes.[90,91] *F. nucleatum* subspecies *nucleatum* and *vincentii* colonize the oral cavity rather than the lower genital tract, a finding suggesting that hematogenous infection of the amniotic fluid and resultant preterm labor were the result of periodontal disease.[90,91]

Prevention

Most fusobacterial infections cannot be prevented. However, optimized oral hygiene can be recommended. Furthermore, a thoughtful approach to the patient with throat infection seems prudent. Withholding empiric antibiotic therapy for simple pharyngitis in the absence of evidence of streptococcal disease is appropriate. However, patients (particularly adolescents and young adults) without coryza who have a high fever lasting >3 days (especially with rigors) with neck pain, swelling, or tenderness, or who have a severe sore throat lasting >3 days, require special consideration.[5,62]

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Anaerobic Cocci

Debrah Meislich, Anat R. Feingold

The anaerobic cocci are major components of the normal microbiota of the mouth, upper respiratory tract, gastrointestinal tract, vagina, and skin.[1] Gram-positive cocci and gram-negative cocci (*Veillonella* spp.) are the anaerobic bacteria most commonly isolated from clinical specimens.[1–3] Traditional methods of isolating anaerobes is time consuming and can require multiple subcultures and biochemical analyses; the use of inappropriate culture and transport methods further reduces the ability to isolate anaerobic cocci.[4] Newer techniques such as polymerase chain reaction 16S (small subunit) ribosomal RNA sequencing and matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) mass spectrometric analysis more rapidly and sensitively identify anaerobes from clinical specimens,[1,5,6] and these techniques have added to our understanding of the role of these anaerobes in human infections.[7]

Compared with all gram-positive anaerobes, the gram-positive cocci are most prominent, accounting for approximately ≥25% of all anaerobes grown from clinical specimens.[1] Gram-positive anaerobic cocci are most often a part of the following infections: deep soft tissue, central nervous system, intra-abdominal, bone and joint, and gynecologic. Although anaerobic bloodstream infection (BSI) is rare in children, anaerobic cocci have been isolated, especially in cases of polymicrobial BSI.[8] The classification of anaerobic gram-positive cocci is changing continually as new species are added or reclassified.[7] At present, 6 clinically significant genera of anaerobic gram-positive cocci are recognized: *Peptostreptococcus*, *Finegoldia*, *Parvimonas*, *Anaerococcus*, *Petoniphilus*, and *Peptococcus*.[7] The first 5 genera are most often associated with infection.[1] *Finegoldia magna* is more often isolated in pure culture from clinical infection sites.[6,8] Of the 3 genera of anaerobic gram-negative cocci, only 1, *Veillonella,* is found in clinical isolates. *Veillonella parvula* is a commensal in the oral, gastrointestinal, respiratory, and female genital tract biota, and it is the species most commonly isolated from human specimens.[7,9] In a 20-year review documenting anaerobes isolated from children with clinical infections, *Veillonella* spp. were recovered most often from abscesses, aspiration pneumonias, burns, bites, and sinuses.[10] Most often a part of a polymicrobial infection, *Veillonella* was isolated alone in 5% of these children.[10] *Veillonella parvula* causes serious infection occasionally in association with malignant disease, corticosteroid use, previous surgical procedures, indwelling devices, or intravenous drug use and rarely in otherwise healthy people.[10,11]

Pathophysiology and Predisposing Conditions

Infection by anaerobic cocci occurs at sites contiguous to their commensal habitats. Anaerobic coccal infections can occur in all body sites, including the central nervous system, head, neck, chest, abdomen, pelvis, skin, and soft tissues.[3,12] These organisms can be sole pathogens in osteoarticular infections, occasionally in soft tissue infections, and in BSI.

Synergy has been found between anaerobic gram-positive cocci and their aerobic and anaerobic counterparts.[13–15] Synergy is indicated by mutual enhancement of the induction of sepsis, higher mortality rates, greater ability to induce abscesses, and enhancement of growth of the bacteria in mixed infection. The ability of anaerobic gram-positive cocci to produce capsular material is an important virulence mechanism.[13,16] *Finegoldia magna* and *Veillonella* spp. produce biofilms and form tighter aggregates when these organisms are grown synergistically with other anaerobes.[17] *Parvimonas* and *Finegoldia* also produce surface proteins that function as virulence factors.[1]

Clinical Manifestations

Central Nervous System Infections.

Anaerobic gram-positive cocci can be isolated from subdural empyema and brain abscesses that develop as sequelae of chronic infections of the ear, mastoid, sinuses, teeth, and pleuropulmonary sites.[18,19] An anatomic abnormality leading to communication with a mucosal site should be sought if a predisposing infection is not found. Anaerobic gram-positive cocci have been isolated from 46% of brain abscesses. *Peptostreptococcus* and *Veillonella* are rare causes of meningitis in children.[19] An infant with *Veillonella* and *Bifidobacterium* meningitis was found to have a sacral dimple and tethered spinal cord as a predisposing condition.[20]

Upper Respiratory Tract and Dental Infections.

Anaerobic gram-positive cocci frequently are recovered from patients with acute and chronic upper respiratory tract infections. The role of anaerobic bacteria in children with tonsillitis is unclear because these organisms are part of the normal flora of the pharynx, tonsils, and adenoids.[21] However, gram-positive anaerobic cocci play a prominent role in peritonsillar abscesses. In 1 study, *Peptostreptococcus* was isolated in 27% of aspirated specimens from patients with peritonsillar abscess.[21] Peptostreptococci are the predominant anaerobes recovered from aspirates in children with the following: chronic otitis media with effusion; retropharyngeal, parapharyngeal, and deep neck abscesses; and chronic sinusitis and chronic mastoiditis.[22,23] Peptostreptococci are isolated commonly with *Staphylococcus aureus* from children with parotitis.[24] *Parvimonas micros*, a part of the commensal flora of the gingival crevice, also is the most common isolate in polymicrobial periodontitis. *P. micros* is prominent in polymicrobial apical abscesses.[1] When polymerase chain reaction techniques were used, *P. micros* was the most prominent anaerobic gram-positive coccus detected in young adults with odontogenic infections.[4]

Anaerobic Pleuropulmonary Infections.

Anaerobic gram-positive cocci often are involved in pulmonary infections, especially pulmonary infections associated with odontogenic infections or as a consequence of aspiration of oropharyngeal secretions or gastric contents.[19] Sampling by transtracheal aspiration, aspiration through a double-lumen catheter, or direct lung puncture is required to obtain meaningful specimens. In a clinical study of patients with pleural empyema, 4 of whom were children <18 years of age, gram-positive anaerobic cocci were isolated in approximately 35% of patients (*F. magna* and *P. micros* each in 8%).[25]

Intra-Abdominal Infections.

Anaerobic gram-positive cocci can be recovered from 3% to 20% of specimens from patients with intra-abdominal infections, such as peritonitis and liver, spleen, and abdominal abscesses,[26,27] concurrently with other organisms of intestinal origin, including *Escherichia coli, Pseudomonas aeruginosa*, streptococci, enterococci, and the *Bacteroides fragilis* group.[27,28]

Female Pelvic Infections.

Anaerobic gram-positive cocci can be isolated from 25% to 50% of patients with endometritis, pyoderma, pelvic abscess, Bartholin gland abscess, postsurgical infections of the pelvis, and pelvic inflammatory disease. Anaerobic gram-positive cocci also can cause BSI in septic abortion. *Peptostreptococcus anaerobius* is isolated most commonly in these infections. Anaerobic gram-positive cocci generally are found with *Prevotella* species.[19] The presence of *Prevotella bivia* creates an environment that facilitates growth of *P. anaerobius* and is found in bacterial vaginosis.[1]

Osteomyelitis and Arthritis.

When anaerobes cause osteomyelitis or arthritis, gram-positive cocci account for 40% and 20% of isolates, respectively.[29] In longitudinal studies that included children and adults, anaerobic gram-positive cocci, especially *F. magna*, were predominant especially in patients with postsurgical or posttraumatic pyogenic arthritis.[30] Anaerobic osteomyelitis usually follows spread from a contiguous infection rather than spread through the hematogenous route.[31] Anaerobic gram-positive coccal osteomyelitis has been associated with bites, decubitus ulcers, and paronychiae.[30] Most osteoarticular infections follow orthopedic surgical procedures and placement of prosthetic material. In a 20-year review in children with osteomyelitis whose specimens were sent for anaerobic culture, *Veillonella* was isolated in 3.8%.[10]

Skin and Soft Tissue Infections.

Anaerobic gram-positive cocci often are recovered in polymicrobial skin and soft tissue infections in combination with other organisms specific to the site or setting. Such infections include necrotizing synergistic gangrene, necrotizing fasciitis,[32] decubitus ulcers,[33] paronychia,[34] burns,[35] human or animal bite infections,[36] infected cysts,[37] and abscesses of the breast,[38] rectum, and anus.[39] Anaerobic gram-positive cocci are more often isolated from soft tissue infections in and around the oropharynx.[19] *F. magna* is highly prevalent in patients with chronic wounds.[1]

Bloodstream Infections.

Anaerobic bacteremia is uncommon in pediatric patients, and anaerobic gram-positive cocci account for approximately 10% of isolates from patients with clinically significant anaerobic BSI.[40,41] *Veillonella* endocarditis is reported in adolescents and young adult intravenous drug users.[9] The most common sources of BSI are oropharyngeal, pulmonary, female genital tract, abdominal, and skin and soft tissue infections. The most frequent predisposing conditions are malignant disease, recent surgical intervention (gastrointestinal, obstetric, or gynecologic), immunosuppression, intravenous drug use, and dental procedures. Neonatal anaerobic BSI caused by *Peptostreptococcus* and *Veillonella* is reproted.[40]

Treatment

Infection usually is polymicrobial, and treatment is empiric, without laboratory confirmation of anaerobes or susceptibility testing.[11,42] Knowledge of trends of antimicrobial resistance comes from multicenter and longitudinal surveys.[8,43–47] Most anaerobic gram-positive coccal infections can be treated with penicillin G. A 2008, large multicenter European report noted that 7% of the gram-positive anaerobic cocci isolated from clinical specimens were resistant to penicillin.[48] Most resistant strains were *F. magna*. All clinical isolates were susceptible to metronidazole, vancomycin, imipenem, and linezolid.[48] A 2010 to 2011 multicenter study in Canada found ≤2% of the anaerobic cocci resistant to penicillin. Of 9 *Veillonella* isolates tested, one half were penicillin resistant.[44] European surveys document metronidazole resistance of anaerobic gram-positive cocci ranging from 6% to 30%.[46,47] Clindamycin-resistant gram-positive anaerobic cocci are isolated from 3% to 23% of clinical specimens.[44–47,49] These surveys also reveal trends in fluoroquinolone resistance of anaerobic gram-positive cocci. Although 1 study found moxifloxacin more potent than ofloxacin and ciprofloxacin with no moxifloxacin-resistant organisms,[49] a Belgian multicenter survey found only 68% moxifloxacin susceptibility among anaerobic cocci isolates.[50] A US study of 31 isolates of anaerobic gram-positive cocci found no resistance to meropenem, ampicillin-sulbactam, piperacillin-tazobactam, or ceftolozane-tazobactam, but approximately 10% resistance to moxifloxacin.[51] Linezolid has excellent activity against these organisms in vitro.[38,51]

In mixed infection with β-lactamase–producing bacteria, "susceptible" anaerobic gram-positive cocci can survive penicillin or cephalosporin therapy because of inactivation by the free enzyme. In such instances, agents with a wider spectrum of activity may be more effective.

In most cases, surgical drainage of abscesses, debridement of necrotic tissues, and removal of foreign material are critical. Without surgical drainage, infection can persist, and serious complications can develop.

Duration of therapy for anaerobic infections generally is prolonged and must be individualized. In some cases, the treatment course is 6 to 8 weeks, but it can be shortened following early, complete surgical management.

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Anaerobic Gram-Positive Nonsporulating Bacilli (Including *Actinomyces*)

Anat R. Feingold, Debrah Meislich

Anaerobic gram-positive, nonsporulating bacilli of clinical significance include *Actinomyces, Bifidobacterium, Eubacterium, Lactobacillus, Mobiluncus,* and *Propionibacterium. Actinomyces* and *Propionibacterium* are the most common clinical pathogens and can be differentiated by biochemical reactions and metabolic products. Both pathogens show indole-positive reactions. Typically, *Propionibacterium* produces copious amounts of propionic acid and acetic acid, whereas *Actinomyces* produces acetic acid in addition to succinic and lactic acid. *Actinomyces* and *Propionibacterium* do not have mitochondria or a nuclear membrane. *Actinomyces* has diaminopimelic and muramic acid in the cell wall, whereas *Propionibacterium* has lysine. The genus *Mobiluncus* consists of gram-variable or gram-negative, curved rods with tapered ends, sometimes occurring in pairs with a gull wing appearance.

Previously aligned with Bacteroidaceae, *Mobiluncus* is more closely related to *Actinomyces.*

Propionibacterium Species

Propionibacterium spp. are pleomorphic, occasionally branching, anaerobic aerotolerant, diphtheroid, gram-positive bacteria. *P. acnes* is an important part of the normal flora of human skin, and it lives in and around sweat glands and sebaceous glands. Newer genomic, transcriptomic, and phylogenetic studies have allowed better understanding of this pathogen's importance as the causes of chronic and recurrent infection.[1] *P. acnes* is present in a biofilm with reduced metabolic activity in medical device–related infections and is most common in children with altered host defenses.[1] Predisposing conditions include a history of surgical manipulation, the presence of a foreign body or medical device, trauma, malignant disease, and primary or acquired immunodeficiency.[2] *Propionibacterium* spp.[3] (especially *P. acnes*) can cause bloodstream infection in immunocompromised people. *P. acnes* is catalase positive and causes pneumonia in children with chronic granulomatous disease,[4] as well as the following infections: endocarditis in patients with prosthetic or damaged heart valves[5]; conjunctivitis in contact lens wearers; and infections related to ventriculoperitoneal (VP) shunts, prosthetic joints, peritoneal dialysis, or intravascular catheters. *P. acnes* osteomyelitis most often follows orthopedic surgical procedures or instrumentation and placement of hardware (e.g., following spinal fusion).[6] Infections can be divided into early (first postoperative month) or late infections. Although *P. acnes* and *Staphylococcus epidermidis* are the most common bacterial causes of late postoperative infections,[7] *P. acnes* also is found in 10% to 40% of early postoperative infections.[6]

P. acnes causes inflammation of acne lesions.[7] It causes host proinflammatory activity, thus targeting molecules involved in innate cutaneous immunity, keratinocytes, and sebaceous glands of the pilosebaceous follicle and leading to the development of comedones.[8] In otherwise healthy adolescents with moderate to severe acne, *P. acnes* can be a rare cause of osteomyelitis, even in the absence of orthopedic surgical procedures or instrumentation.[9] *P. acnes* also can cause delayed VP shunt infection identified only when cerebrospinal fluid (CSF) and shunt catheters routinely are cultured anaerobically. *P. acnes* VP shunt infections more often follow valve puncture or distal catheter revision for distal obstruction. Compared with other causes of infection, children with *P. acnes* VP shunt infections tend to be less systemically ill, and they have only mild CSF pleocytosis and minor changes in CSF glucose and protein concentrations. Because of the slower rate of growth of *P. acnes*, CSF and catheter tips must be incubated for 5 to 7 days anaerobically when this organism is suspected.[10–12] P. *acnes* can be isolated alone, but more commonly it is mixed with other aerobic or anaerobic bacteria in the following infections: brain abscesses; subdural empyema; parotid, pulmonary, or dental infections, peritonitis; and osteomyelitis.[2] Isolation, however, most frequently represents skin contamination of cultures. Repeated isolation or visualization of *Propionibacterium* on Gram stain is required to identify true infection.

Surgical debridement, incision and drainage, and removal of foreign material are important in the management of *Propionibacterium* infections. Topical and oral antibiotics play a role in the treatment of moderate to severe acne. One study of children and adults with moderate to severe acne found that antibiotic-experienced (in the preceding 2–6 months) patients were more likely to be colonized with *P. acnes* resistant to clindamycin, erythromycin, and tetracycline.[13] The rate of antibiotic resistance, especially to macrolides and tetracyclines, has increased since 2000.[1] When nonskin clinical isolates of *P. acnes* were examined for antimicrobial susceptibility, approximately 3% were resistant to tetracycline, 15% to clindamycin, and 18% to erythromycin. No isolate was resistant to linezolid, penicillin, or vancomycin.[14] Metronidazole does not have predictable activity against *Propionibacterium* and cannot be used for therapy.[15]

Actinomyces Species

Actinomyces spp. are filamentous, branching, gram-positive, pleomorphic, non–spore-forming, catalase-negative, anaerobic or microaerophilic/capnophilic bacilli. Although many species have been associated with disease in humans, actinomycetes usually are soil dwelling organisms.[16] *Actinomyces* cannot be distinguished from *Nocardia* on Gram stain.[17] However, *Nocardia* spp. grow aerobically and stain with acid-fast technique, and *Actinomyces* spp. do neither. With the use of 16S (small subunit) ribosomal RNA (16S rRNA) sequencing, at least 21 species of *Actinomyces* have been identified in humans. *A. israelii* is the predominant disease-causing species (median, 73% of cases), although other *Actinomyces* spp., including *A. naeslundii* (the second most frequent *Actinomyces* sp.)[16] *A. meyeri, A. odontolyticus, A. gerencseriae,* and *A. viscosus,* as well as *Propionibacterium propionicum,* also have been implicated.[18,19] Many different *Actinomyces* spp. are associated increasingly with infections at many body sites, and currently, 25 *Actinomyces* spp. have been described from human material.[20] Most actinomycotic infections are polymicrobial, involving other aerobic and anaerobic bacteria. Coisolates depend on the source or site of infection and include *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans, Eikenella corrodens, Bacteroides, Fusobacterium, Capnocytophaga,* aerobic and anaerobic streptococci, *Staphylococcus,* and Enterobacteriaceae.

Pathogenesis

Actinomyces spp. generally have low virulence and are part of the normal flora of the mouth, other sites in the gastrointestinal tract, and the female genital tract. *Actinomyces* spp. are prevalent in the mouth from infancy and are recoverable from periodontal pockets, carious teeth, dental plaque, and tonsillar crypts.[20,21] *Actinomyces* infections have an endogenous source and are infrequent in children <10 years of age, but these infections are underrecognized probably because of fastidious growth requirements.[22–28] *Actinomyces* spp. take advantage of breaches in mucosal barriers or obstruction or aspiration to become pathogenic.[20,29] Cervicofacial and oral disease is associated with trauma, dental procedures, eruption of a molar tooth, oral surgical procedures, or dental infection. Pulmonary infections usually follow aspiration of oropharyngeal or gastrointestinal secretions. Other less common routes of infection are extension from cervicofacial disease or spread from the abdomen and, rarely, dissemination through blood from other sites of infection (e.g., pelvic or orofacial). Gastrointestinal infection frequently follows loss of mucosal integrity, as can occur with appendicitis, trauma, or foreign bodies. The use of an intrauterine contraceptive device is linked to the development of actinomycosis of the female genital tract.

Actinomyces infections are uncommon and indolent, but invasive. Infection generally is polymicrobial and can involve any body organ,[30] including the heart. Other copathogens with *Actinomyces* act synergistically by enhancing the spread of infection through inhibition of host defenses and reduction of local oxygen tension. The diagnosis often is delayed because of nonspecific and prolonged symptoms.[31] Patients with chronic granulomatous disease have an unusual susceptibility to *Actinomyces*.[32] Two cases of cutaneous actinomycosis have been associated with anti–tumor necrosis factor-α therapy.[33]

Clinical Manifestations

Unique characteristics of actinomycosis are indolent inflammation with spreading (“burrowing”) through soft and bony tissue planes to contiguous sites or along fascial planes to remarkably distant sites. The hallmark of actinomycosis is spread that fails to respect tissue planes. Classically, small abscesses form at the site of origin, with extension to form multiple sinus tracts that can drain yellow, gritty, purulent material (sulfur granules) composed of spheroid colonies of radiating club-shaped filaments, neutrophils, debris, and granulomatous reaction. *Actinomyces* grows in tissues in microscopic or macroscopic clusters of tangled filaments surrounded by neutrophils. The differential diagnosis includes other chronic infections at these sites, including tuberculosis, nocardiosis, and complications of foreign bodies. The most common sites of infection are cervicofacial, abdominopelvic, thoracic, and central nervous system.

Cervicofacial Actinomycosis

Most infections in immunocompetent people are cervicofacial. Depending on the composition of the concomitant synergistic flora, the onset can be acute, subacute, or chronic. The most commonly recognized manifestations are “lumpy jaw,” which is either a slowly enlarging, fluctuant, painless swelling over the lower border of the mandible or a widely spread infection that involves the submandibular area; or osteomyelitis of the mandible or maxilla. Infection spreads slowly, and draining fistulas can occur (usually to the mucosal side) and can be accompanied by trismus.[23,24] Fever or systemic illness usually is absent. Chronic tonsillitis, dental decay, mastoiditis, and otitis media are risk factors, but some patients have no recognizable disorder or preceding event. Periostitis or osteomyelitis can develop if the infection extends to the facial and maxillary bones (or rarely can complicate a primary disorder of bone such as fibrous dysplasia) (see Fig. 78.6). Primary infection can develop in the palate, scalp, salivary glands, maxilla, paranasal sinuses, tongue, larynx, hypopharynx, trachea, and neck.[34,35] Meningitis also can occur if the process extends through sinus tracts into the cranial bones.[36] The prognosis for soft tissue infections is excellent with extremely prolonged antimicrobial therapy (sometimes >1 year), frequently without surgical intervention. In a review of 19 cases of actinomycosis presenting as osteomyelitis in children, however, the mandible was most commonly affected, age was predominantly young school age, only one half had a predisposing factor, and patients with mandibular cases required >1 debridement procedure for cure.[37]

Abdominal and Pelvic Actinomycosis

The appendix is the most frequent gastrointestinal site. Appendicitis with perforation is the most common predisposing event; unrecognized foreign body perforation (e.g., needle, pin) also has occurred. The inciting event can precede the diagnosis by months to years. Chronic nonspecific symptoms consisting of fever, chills, weight loss, diarrhea or constipation, abdominal pain, and night sweats, with few abdominal symptoms, are typical and can mimic tuberculosis or lymphoreticular malignant disease. Infection can spread to other intra-abdominal (e.g., hepatic) and pelvic viscera. Primary pelvic infection can complicate abortion, retained surgical suture, intrauterine device endometritis, tubo-ovarian abscess, or pelvic inflammatory disease.[38] Patients can have an indolent vaginal discharge, abdominal or pelvic pain, menorrhagia, fever, and weight loss.

Thoracic Actinomycosis

Thoracic actinomycosis usually starts as undetected aspiration pneumonia in a predisposed host (Fig. 195.1). Neurologically impaired children, who frequently aspirate and also have poor dentition, account for some of these cases. In a review of thoracic actinomycosis in 55 children, however, only 5 (9%) children had this risk factor.[31] Chronic indolent and slowly progressing pneumonia with or without pleural involvement is the most common manifestation. Tachypnea, chest pain, and productive cough are not prominent. Fever and weight loss can be the only manifestations. A high index of suspicion is required. Infection typically burrows through ribs (to cause an osteolytic lesion) and can manifest as a subcutaneous mass on the thorax with or without a draining sinus,[19,26] so called *empyema necessitans*.[39] Infection can mimic malignant disease, tuberculosis, and lung abscess. Thoracic infection can traverse tissue planes or can follow fascial planes to the soft tissues of distal extremities or through the diaphragm into the abdomen.[40]

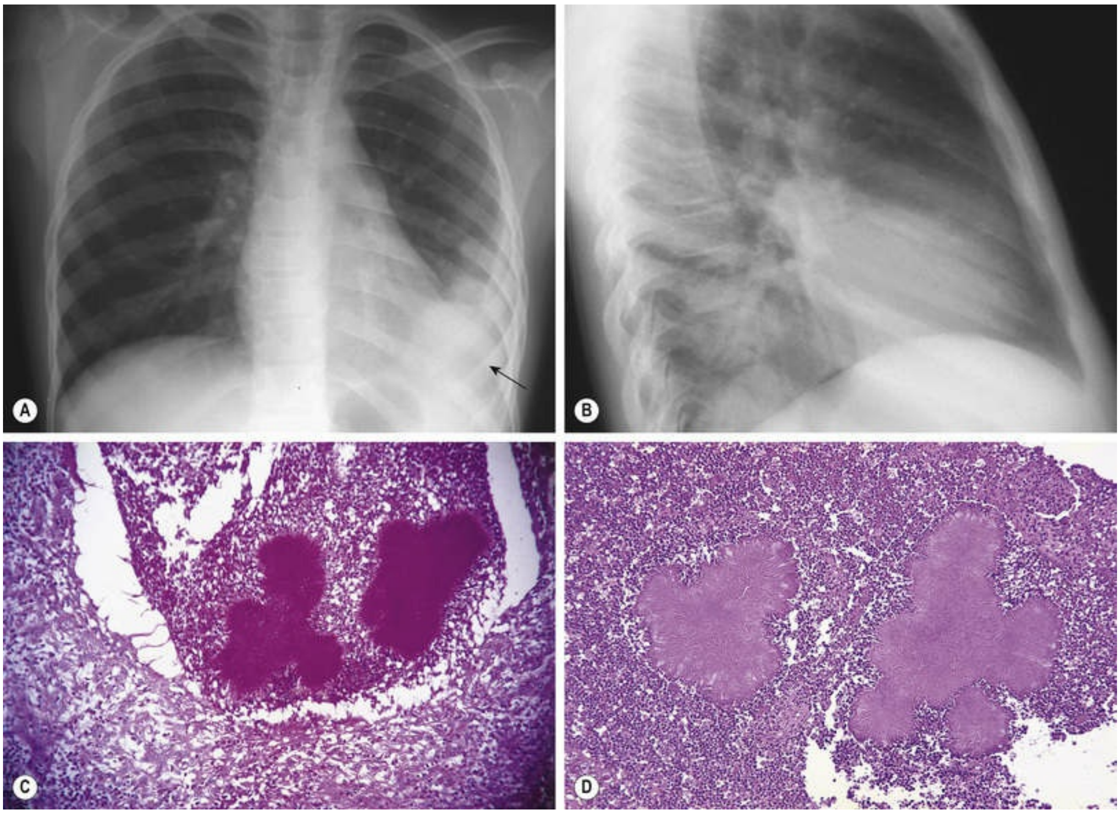

FIGURE 195.1 **Thoracic actinomycosis. A 9-year-old girl had a lump noted on her lateral chest wall. She was afebrile, had no respiratory**

tract complaints or abnormal findings except a nodular mass on the 10th rib anteriorly. She had a history of left lower lobe pneumonia and atelectasis 8 months earlier. (A and B) Chest radiographs show left lower lobe pneumonia, loculated pleural collection, and a lytic lesion of the rib (*arrow* in A). Biopsy of the rib lesion stained by (C) periodic acid–Schiff and (D) hematoxylin and eosin show histologic findings of chronic osteomyelitis and sulfur granules. Culture of specimens from lung, pleura, and rib yielded growth of *Aggregatibacter actinomycetemcomitans* and *Actinomyces israelii.* (Case courtesy of D. V. Schidlow and E. N. Faerber, St. Christopher's Hospital for Children, Philadelphia, Pa.)

Diagnosis and Treatment

The diagnosis of actinomycosis often is delayed because of its subacute clinical course and the frequent lack of inflammatory symptoms. Actinomycosis can mimic tumors, tuberculosis, nocardiosis, or fungal infections. Histologic identification of sulfur granules is pathognomonic but is not a universal finding. Gram and acid-fast stains are helpful in differentiating probable *Actinomyces*. Isolation of organisms is extremely important to confirm the diagnosis. Immediate transport of clinical specimens in anaerobic media is required.[39] Matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) spectrometry is useful for rapid identification.[16] Molecular methods, including 16S rRNA gene sequencing, aid accurate identification.[20] Frequently, a less fastidious copathogen, *Aggregatibacter actinomycetemcomitans*, is the sole isolate and predicts the presence of *Actinomyces*.[23,24,40] A singular role of *Aggregatibacter* is possible, and some patients have responded poorly to therapy when clindamycin, erythromycin, or vancomycin was used (to which *Aggregatibacter* but not *Actinomyces* is resistant).[30,40] Prolonged antimicrobial therapy is the cornerstone of treatment. Usually, cervicofacial infection responds to antibiotics alone. Drainage of large thoracic, abdominal, or soft tissue abscesses, extensive resection of affected tissues, and excision of sinus tracts generally are required. *Actinomyces* and *Aggregatibacter* are exquisitely susceptible to penicillin and extended-spectrum penicillins. *Actinomyces* is susceptible in vitro to a wide range of β-lactam agents, and these drugs, combined with a β-lactamase inhibiting agent, are regarded as agents of first choice when polymicrobial infection is likely.[16] The duration of therapy is more important than the route of administration. Initially, aqueous penicillin G can be used intravenously (depending on the patient's clinical status), followed by 6 to 12 months of oral penicillin or amoxicillin, with or without probenecid. Success is reported with shorter and oral-only antibiotic regimens.[16]

Other Gram-Positive Bacilli

Other gram-positive anaerobic bacilli include *Lactobacillus*, *Bifidobacterium*, and *Eubacterium* species. These genera are part of the normal flora of the female genital tract, oral cavity, and gastrointestinal tract.[40] Polymicrobial infection usually occurs at contiguous body sites (e.g., periodontal disease and infections of the female genital tract and abdominal viscera). Rarely, bloodstream infection also can occur. Most *Bifidobacterium* isolates are recovered from specimens from patients with chronic otitis media, abscesses, peritonitis, aspiration pneumonia, and paronychia. Most *Eubacterium* isolates are associated with abscesses, peritonitis, decubitus ulcers, and bite wound infections. *Lactobacillus* is recovered mainly from abscesses, aspiration pneumonia, bloodstream infection, and conjunctivitis.[40] Predisposing conditions are previous surgical procedures, malignant disease, corticosteroid therapy, and immunodeficiency. These genera usually are susceptible to penicillins, carbapenems, and clindamycin. However, *Lactobacillus*, some *Eubacterium*, and other facultative anaerobes are resistant to nitroimidazoles. Cephalosporins, erythromycin, and tetracycline have variable activity.

Key Points

Actinomyces Species

Description

- Filamentous branching gram-positive catalase-negative bacillus
- Anaerobic or microaerophilic growth in vitro
- *Actinomyces israelii* the predominant species causing disease

Epidemiology

- Colonizes human oral cavity early in childhood
- Normal flora of mouth, gastrointestinal, and female genital tracts
- Attains access to tissue through a breach in mucous membranes (i.e., following trauma) or by aspiration
- Infections usually polymicrobial
- Special hosts at risk: patients with chronic granulomatous disease

Clinical Features

- Infections are indolent.
- Diagnosis often is delayed.
- Hallmark is spread that fails to respect tissue planes.
- Development of sinus tracts also is characteristic.
- Most common sites of infection:

▪ Cervicofacial (normal hosts)

▪ Abdominopelvic

▪ Thoracic

▪ Central nervous system

Diagnosis and Treatment

- “Sulfur granules” (clumps of microorganisms in vivo) can be seen.
- Bacteriologic identification confirms diagnosis
- Prolonged antimicrobial therapy is key to successful treatment.

- Penicillins, clindamycin, cephalosporins all are active.

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Mycoplasma

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Mycoplasma pneumoniae

Samir S. Shah

Description of the Pathogen

Mycoplasma pneumoniae is a member of the class Mollicutes, which includes bacterial pathogens and commensals found in many animals and plants. These pathogens comprise the smallest self-replicating prokaryotes known to cause infection in humans.[1] *M. pneumoniae* is approximately 120 to 150 nm, about the size of myxoviruses, and it passes easily through membrane filters intended to prevent bacterial contamination. Humans are the only known natural hosts for *M. pneumoniae*.

The absence of a cell wall distinguishes *Mycoplasma* from other pathogenic bacteria and results in the following additional characteristics: (1) growth on cell-free media only if sterols and other nutrients are provided by yeast extract and animal serum; (2) pleomorphism, preventing classification as either cocci or bacilli in the manner of conventional eubacteria, and variable ability to take up bacteriologic dyes such as Gram stain; (3) resistance to penicillins and cephalosporins, which act by inhibiting cell wall synthesis; and (4) susceptibility to desiccation, a factor that mandates proper handling of clinical specimens for culture and explains close contact as a means of person-to-person transmission.

Pathogenesis

M. pneumoniae gains access to the respiratory tract through aerosolized droplets spread among close contacts. Specific attachment to the respiratory epithelial tissue occurs primarily through interaction between a host epithelial cell receptor and the organism's P1 attachment protein, a 169-kd surface antigen.[2–4] Other structures that participate in cytadherence have been identified.[5] Following attachment, hydrogen peroxide and superoxide radicals synthesized by *M. pneumoniae* act in concert with endogenous toxic oxygen molecules generated by host cells to induce oxidative stress in the respiratory epithelium.[6] Once *M. pneumoniae* reaches the lower respiratory tract, the organism may be opsonized by complement or antibodies. Activated macrophages begin phagocytosis and undergo chemotactic migration to the site of infection. $CD4^+$ T lymphocytes, B lymphocytes, and plasma cells infiltrate the lung. Further amplification of the immune response occurs in association with lymphocyte proliferation, production of immunoglobulins, and release of tumor necrosis factor-α, interferon-γ, and various interleukins.[7] Lymphocyte activation and cytokine production either can minimize disease by controlling infection or exacerbate disease by stimulating immune-mediated lung injury.

Extrapulmonary complications of *M. pneumoniae* infection can occur as a consequence of immune-mediated injury or direct invasion. *M. pneumoniae* has been identified by polymerase chain reaction (PCR) in cerebrospinal fluid (CSF)[8] and serum,[9] thus indicating that dissemination occurs in some cases. Effects of cross-reactive antibody with host tissues remain the proposed mechanisms for hemolysis and cutaneous manifestations.[10]

Epidemiology

The age at which *M. pneumoniae* should be considered among causes of lower respiratory tract infection is uncertain. Although primarily a disease of adolescents and young adults,[11–13] *M. pneumoniae* infection has been recognized as a cause of lower respiratory tract disease in young children.[14–22] In Finland, *M. pneumoniae* was the attributed cause of community-acquired pneumonia (CAP) in 9% of children 0 to 4 years of age and in 40% of children 5 to 9 years of age.[18] *M. pneumoniae* accounts for approximately 20% to 40% of cases of CAP in junior high school and high school students and for up to 50% of cases among college students and military recruits.[23–27] The incidence of endemic *M. pneumoniae* CAP ranges from 1 to 2 per 1000 children <5 years of age, 3 to 4 per 1000 children 5 to 15 years of age, and <1 per 1000 adults <70 years of age.[13,26,28]

Epidemic *M. pneumoniae* infection occurs at 3- to 7-year intervals in the United States, superimposed on low-level endemic disease.[26,29] Community epidemics can be unrecognized until clusters of extrapulmonary complications occur because testing is not performed routinely in the office setting and *M. pneumoniae* is not a publicly reportable disease.[30] Factors that facilitate the occurrence and persistence of outbreaks of *M. pneumoniae* infection in institutional and military settings include the difficulty of making a rapid diagnosis, the long incubation period (2–3 weeks), and prolonged respiratory tract shedding (weeks to months following infection).[31,32] Persistence of the organism in many cases despite antibiotic therapy contributes to protracted outbreaks.[33]

Epidemics of *M. pneumoniae* infection commonly begin in the fall and can persist for months. Young children often serve as the index case within a family; they commonly have symptoms of upper respiratory tract infection or few overt symptoms.[12] Sequential transmission to family members frequently occurs with 2- to 4-week lapses between cases; approximately 40% of family members develop infection.[11,31,33] The attack rate is approximately 25% in other closed populations, including nursing homes.[27,34] Smoking appears to modify the risk of infection. During an epidemic among military trainees, preexisting immunoglobulin G (IgG) anti–*M. pneumoniae* was protective in nonsmokers, with an attack rate of 30%, whereas the attack rates in antibody-positive smokers and antibody-negative nonsmokers ranged from 77% to 86%.[35] Longitudinal community surveillance and studies of military recruits demonstrate that *M. pneumoniae* infection provides at least shortterm protection from subsequent infection and that immunity after pneumonia lasts longer than that after asymptomatic infection or upper respiratory tract disease alone.[36–38] The relatively mild course of infection in very young children has led to speculation that infection in early childhood results in a sensitizing immunologic response necessary for the development of lower respiratory tract disease later in life.

Clinical Manifestations

Respiratory Tract Disease

M. pneumoniae was first isolated during efforts to determine the cause of the clinical syndrome referred to as "primary atypical pneumonia."[39] Failure of patients with this infection to respond to penicillin or sulfonamide therapy (the standard therapy for pneumococcal pneumonia) was considered "atypical."

In young children, *M. pneumoniae* can be indistinguishable from viral causes of respiratory tract infection; concomitant *Mycoplasma* and viral infection also occurs.[40–42] *M. pneumoniae* infection in young children can be asymptomatic or associated with rhinorrhea, pharyngitis, otitis media, croup, bronchiolitis, or pneumonia.[11,19,29,43,44] *M. pneumoniae* infection in older children and adolescents causes both upper or lower respiratory tract illness. Initial symptoms typically consist of general malaise, myalgia, sore throat, retrobulbar headache, and fever.[29,45] Sinus pain or fullness and ear pain often are described. These symptoms are indistinguishable from those caused by influenza and other respiratory viruses. Physical findings include sinus tenderness, nonexudative posterior pharyngeal erythema, and otitis media reflecting sites of infection. Although experimental *M. pneumoniae* infection in adults was associated with bullous myringitis,[46] numerous other causes of bullous myringitis have been identified.[47,48] *M. pneumoniae* was not detected by PCR in any of 37 children with either bullous or hemorrhagic myringitis.[49] Additionally, *M. pneumoniae* was isolated from culture of middle ear fluid in only 1 of 771 children with otitis media.[50]

The characteristic course of *M. pneumoniae* pneumonia is depicted in Fig. 196.1. Patients with pneumonia usually have had fever, myalgia, and other constitutional symptoms in the first week of illness that resolves when a dry, nonproductive cough develops; this cough can become productive of mucopurulent or blood-streaked sputum. The cough usually brings the patient to medical attention 5 to 7 days after onset, and it can be paroxysmal and worse at night. Coughing from either *M. pneumoniae* tracheobronchitis or pneumonia can persist for ≥2 weeks after resolution of fever and other constitutional signs and symptoms, thus resulting in a 4-week illness that can resemble pertussis.[50] Palpation of the neck can produce paroxysms of coughing. Auscultation of the chest frequently reveals crackles or wheezes or both, hence the appellation "walking pneumonia." *M. pneumoniae* has been documented to cause parapneumonic effusions and necrotizing pneumonitis in children.[51,53,54] Severe and sometimes fatal *M. pneumoniae* pneumonia is reported in both adults and children.[55–61]

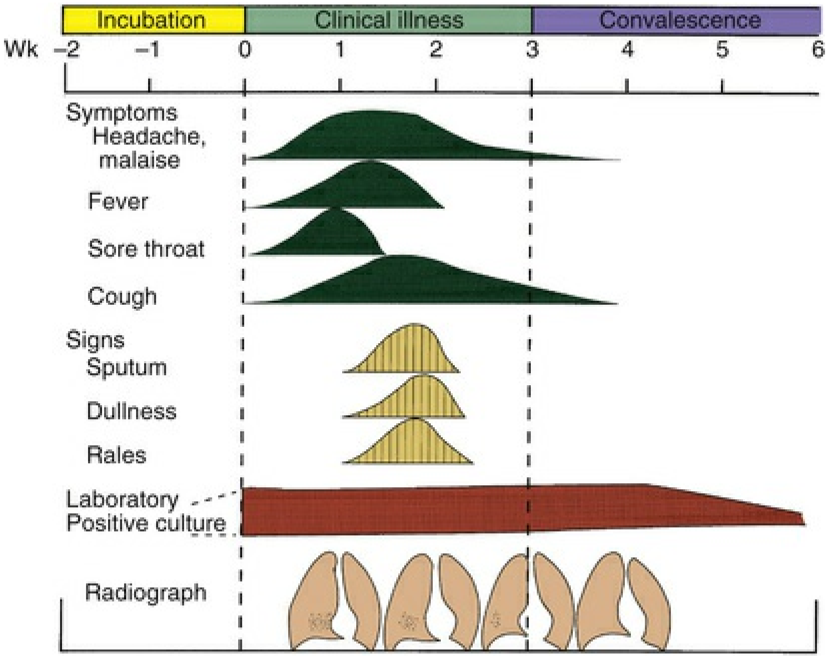


FIGURE 196.1 **Characteristic clinical course of pneumonia caused by *Mycoplasma pneumoniae*.** (Redrawn from Denny FW, Clyde WA Jr, Glezen WP. *Mycoplasma pneumoniae* disease: clinical spectrum, pathophysiology, epidemiology, and control. J Infect Dis 1971;123:74.)

M. pneumoniae infections frequently are associated with exacerbations of asthma. In a prospective study, *M. pneumoniae* was detected by either PCR or serologic study in 20% of children hospitalized for exacerbation of asthma and in 50% of children hospitalized for first-episode wheezing; in contrast, *M. pneumoniae* infection was diagnosed in only 5% of control children with either stable asthma or allergic rhinitis.[62] *M. pneumoniae* also can have a role in chronic lung disease. Mice experimentally inoculated with *M. pneumoniae* into the respiratory tract were more likely than control mice to have chronic pulmonary disease characterized by airway hyperreactivity, airway obstruction, and histologic inflammation.[63] In children, pulmonary abnormalities, including reduced pulmonary clearance and airway hyperresponsiveness, can persist for months to years following *M. pneumoniae* infection.[64,65]

Numerous case reports describe severe respiratory illness caused by *M. pneumoniae* in immunodeficient children. *M. pneumoniae* was detected in 2% of bronchoalveolar lavage specimens from human immunodeficiency virus–infected patients with pneumonia.[66] Serologic evidence of *M. pneumoniae* infection was demonstrated in 9% of 538 children with sickle cell disease and acute chest syndrome.[67] Patients with sickle cell disease or sickle cell–related hemoglobinopathies and Down syndrome often develop severe respiratory illness as a consequence of *M. pneumoniae* infection.[68–71]

Extrapulmonary Disease

Extrapulmonary complications of *M. pneumoniae* infection occur (Table 196.1).[72–98] A causative role is confirmed by PCR detection at extrapulmonary sites, but many reports remain anecdotal, with diagnosis resting on elevation of cold agglutinin or complement fixation (CF) antibody values. Because CF antibodies can cross-react with human tissue, particularly brain and pancreas, antibody elevation can occur during inflammation or destruction of tissue from multiple causes. In the context of family and community outbreaks of *M. pneumoniae* infection, however, and in patients with concomitant pulmonary involvement, reports of extrapulmonary involvement are more credible.[99–102] Additionally, occasional isolation of *M. pneumoniae* from blood, CSF, synovial fluid, and skin lesions (primarily in immunocompromised patients) indicates that dissemination occurs in some cases. PCR testing has confirmed the role of *M. pneumoniae* in isolated cases of encephalitis and transverse myelitis,[8,103–105] pleural effusion,[54] and bacteremia.[9] It remains unclear, however, whether most "*Mycoplasma*-associated" extrapulmonary cases reported are caused by *Mycoplasma* infection or *Mycoplasma*-related immune-mediated mechanisms or are unrelated to *Mycoplasma*.

TABLE 196.1

Extrapulmonary Disease Associated With *Mycoplasma pneumoniae*[a]

Disease by Organ System	Manifestation
Dermatologic disease	Discrete maculopapules
	Erythema multiforme
	Stevens-Johnson syndrome
	Gianotti-Crosti syndrome
	Urticaria
	Morbilliform exanthem
	Vesicles or bullae
	Ulcerative stomatitis
	Erythema marginatum
Hematologic disease or condition	Complement-dependent, Coombs-positive, anti-I antigen, immunoglobulin M antibody
	Thrombosis (transient antiphospholipid antibody response)
	Thrombotic thrombocytopenic purpura
Central nervous system disease	Encephalitis/meningoencephalitis
	Transverse myelitis
	Guillain-Barré syndrome
	Focal encephalitis
	Polyradiculitis
	Bell palsy
	Asymmetric paralysis
	Cerebellar ataxia
	Psychosis
	Cerebral infarction
Arthritis	Acute or chronic course
	Monoarticular, migratory, or polyarticular arthritis
Cardiac disease	Pericarditis
	Myocarditis
	Heart block
	Myocardial infarction
	Congestive heart failure
Hepatic dysfunction	Mild hepatic enzyme elevation[b]
Pancreatitis	Acute inflammation
Ocular disease	Conjunctivitis
	Glomerulonephritis
	Iritis
	Optic disc edema
Other	Rhabdomyolysis

[a] Organ system or finding occurs in <10% of cases except where noted.

[b] Occurs in approximately 30% of cases with pneumonia.

The central nervous system appears to be the most common extrapulmonary site of *M. pneumoniae* disease. Of 1988 patients enrolled in the California Encephalitis Project, 111 (5.6%) had evidence of recent or current *M. pneumoniae* infection.[106] In some series, central nervous system involvement is reported in 1% to 7% of patients requiring hospitalization for *M. pneumoniae* infection.[79,107,108] Neurologic symptoms of children with *M. pneumoniae* in the California Encephalitis Project included altered consciousness (58%), seizures (40%), focal neurologic signs (37%), and hallucinations (18%).[106] Respiratory tract symptoms, reported in >80% of children with central nervous system involvement, precede neurologic symptoms by 7 to 10 days.[79,108] In patients with *M. pneumoniae* encephalitis or meningitis, CSF findings often are normal, but a mild, predominantly mononuclear pleocytosis (≤200 cells/mm^3) and protein elevation up to 70 to 80 mg/dL can occur; higher CSF white blood cell counts (>900 cells/mm^3) and protein concentrations (>170 mg/dL), although uncommon, have been described.[80–82,106]

Joint involvement in children appears to be less common than in adults. Monarthritis, polyarthritis, and migratory arthritis mimicking acute rheumatic fever have been described.[86,87,109–114] Limited information is available regarding synovial fluid analysis in patients with *M. pneumoniae*–associated arthritis; synovial pleocytosis has ranged from 1000 white bold cells/mm^3 in a child with hypogammaglobulinemia to approximately 50,000/mm^3 in an otherwise healthy child.[87,112] *M. pneumoniae*–associated glomerulonephritis has been described.[115–120] Glomerulonephritis appeared either concomitantly with other symptoms or 5 to 10 days later. Serum C3 complement level is decreased initially in some cases. Hematologic complications include the development of hemolytic anemia attributable to cross-reacting cold agglutinins,[76,105,121] thrombotic thrombocytopenic purpura,[122] and transient antiphospholipid antibody syndromes.[123,124]

Laboratory Findings and Diagnosis

Pathogen-Specific Identification

Culture

Many *Mycoplasma* species grow best in 5% to 10% carbon dioxide, but *M. pneumoniae* also grows well under aerobic conditions. The fermentation of simple carbohydrates, such as glucose, xylose, mannose, and maltose, provides a method for recognizing the growth of *Mycoplasma* in the laboratory. The complex nutritional requirements and slow growth on artificial media make identification by culture impractical for most laboratories and of limited value clinically. Because *M. pneumoniae* can persist in the respiratory tract for weeks to months after symptomatic or asymptomatic infection, recovery of the organism from the throat or sputum does not necessarily confirm causation of current disease.[25,44]

Cold Agglutinins

Cold-reacting antibodies against red blood cells can be detected in the serum of patients with primary atypical pneumonia.[39] Cold-agglutinating antibodies are immunoglobulin M (IgM) autoantibodies directed against the I antigen on human erythrocytes, which appear within 7 to 10 days of initial symptoms and drop sharply after 2 to 3 weeks.[29,45,125,126] In the laboratory, the highest dilution of serum causing hemagglutination or "clumping" of type O erythrocytes at 4°C is reported as the cold agglutinin titer. Titers >1 : 64 are present at the time of acute illness in approximately 75% of adults with *M. pneumoniae* pneumonia. The test is less well studied in children. Specificity of a titer <1 : 64 is low because various other respiratory tract pathogens provoke modest increases in cold agglutinins. For example, 18% of military recruits with adenoviral pneumonia had a cold agglutinin titer of ≥1 : 32.[127] Cold agglutinins should not be used for the diagnosis of *M. pneumoniae* infections if other methods are available. Bedside cold agglutinin testing lacks rigorous standards for performance and interpretation and is not recommended.

Serologic Examination

Methods to measure serum antibody include CF, indirect fluorescence, enzyme-immunoassays (EIA), and rapid EIA cards. Although CF testing has been the most widely available assay for detection of antibody to *M. pneumoniae,*[128] CF measures mainly IgM antibody, thus limiting its diagnostic value to initial rather than repeated infections.[96] An elevated CF antibody titer also should be interpreted with caution in patients with nonrespiratory disease because the antigens used in the CF test can cross-react with human tissue.[94–96]

CF tests have largely been replaced by less time-consuming and labor-intensive immunoglobulin assays, including EIA and immunofluorescence assay, and an indirect hemagglutination assay. These assays can be performed on a single serum specimen obtained during the acute infection, and they appear to be as sensitive as the CF test in children with pneumonia.[96,129–131] In adults, *M. pneumoniae* frequently represents a second infection, and IgM response does not occur reliably.[132,133]

EIA IgM assays are reported to be sensitive in children with pneumonia.[130] The ImmunoCard rapid IgM test (Meridian Bioscience, Cincinnati, Ohio) compared with other serologic tests (but not with PCR), using indirect fluorescence as the gold standard, had sensitivities ranging from 74% compared with EIA to 96% compared with CF; specificities ranged from 85% compared with the IgM-specific EIA to 98% compared with the IgM-specific indirect fluorescence.[134] Results were similar in a subsequent study of 145 children tested for *M. pneumoniae*.[135] False-positive IgM test results can occur, however, and predictive values of test results depend on pretest probability of *M. pneumoniae* infection. The specificity of IgM detection during a university and community outbreak of *M. pneumoniae* pneumonia was only 43% for children 10 to 18 years of age and 82% for those ≥19 years of age compared with a case-definition gold standard for diagnosis.[136] A combined IgG-IgM assay (Remel, Thermo Fisher Scientific, Lenexa, Kan) assessed during this outbreak had a higher specificity in children 10 to 18 years of age (74%) but a lower sensitivity (52%) compared with IgM detection (89%).[136] Other IgM assays appear to be as sensitive as PCR for detection of *M. pneumoniae* in CAP in children.[130]

IgG anti–*M. pneumoniae* can persist for months to years following infection. Testing for both IgM and IgG in paired specimens collected 2 to 3 weeks apart may provide the most accurate serologic diagnosis.[137] A fourfold or greater rise in antibody indicates a recent or current *M. pneumoniae* infection. Therefore accurate diagnosis often is made only retrospectively.

Molecular Methods

Molecular assays to detect *M. pneumoniae* are available.[130,131,138–143] PCR testing has detected *M. pneumoniae* in a variety of syndromes.

Use of primers against 2 different targets maximizes the ability to detect the organism; potential targets include the adenosine triphosphatase operon gene, P1 gene, conserved regions of 16S (small subunit) RNA, and the *tuf* gene.[144–148] Direct comparison of studies using PCR is difficult because specimens were obtained from different sites (e.g., nasal wash, nasopharyngeal swab, throat, sputum), and different primer sets and amplification techniques were used. Compared with seroconversion, sensitivity of some PCR-based tests has ranged from 79% for pharyngeal specimens to 90% for nasopharyngeal specimens; specificity was 98% when using these specimens.[148] Compared with culture, PCR has the advantage of an ability to detect *M. pneumoniae* genome in clinical settings when the organism may no longer be viable (e.g., in contaminated specimens or from tissue that has already been processed for histologic examination). Additionally, PCR test results can be positive earlier in the course of infection than serologic test results.

Testing of Extrapulmonary Specimens

Verification of extrapulmonary complications attributable to *M. pneumoniae* is challenging. Among children with encephalitis attributable to *M. pneumoniae* (defined by the presence of IgM anti–*M. pneumoniae* in acute or convalescent serum), intrathecal *M. pneumoniae* antibodies were detected rarely; IgM was found in 1 (3%) of 32 and IgG in 2 (12%) of 17 CSF samples.[106] The CSF PCR result was positive in 1 of 62 children with *M. pneumoniae* encephalitis; the patients with a positive CSF PCR result also had positive CSF IgM anti–*M. pneumoniae* result.[106] Smaller case series yielded similar findings.[149,150]

Additional Tests

Routine laboratory studies cannot distinguish among respiratory tract infections caused by *M. pneumoniae*, viruses, or other bacteria. The peripheral blood white blood cell count is normal or slightly elevated, with neutrophilia. Reported erythrocyte sedimentation rates range from 20 to >100 mm/hr, with higher rates reflecting more severe pulmonary disease.[40,151–153]

Chest radiography documents lower respiratory involvement, but few features differentiate *M. pneumoniae* infection from other conditions. Chest radiographs can show significant abnormality despite insignificant clinical symptoms. Bilateral interstitial infiltrates, as well as patchy, unilateral, segmental, or subsegmental consolidation, are described (Figs. 196.2 and 196.3).[154–156] Pleural effusions, reported in 20% of patients in 1 study when lateral decubitus views were obtained, usually are small and bilateral,[153–157] although large pleural effusions occur occasionally (Fig. 196.4).[51,53,54] Hilar lymphadenopathy, observed in 34% of children in 1 study, is seen more frequently in *M. pneumoniae* pneumonia than in pneumonia from most other common causes.[154]

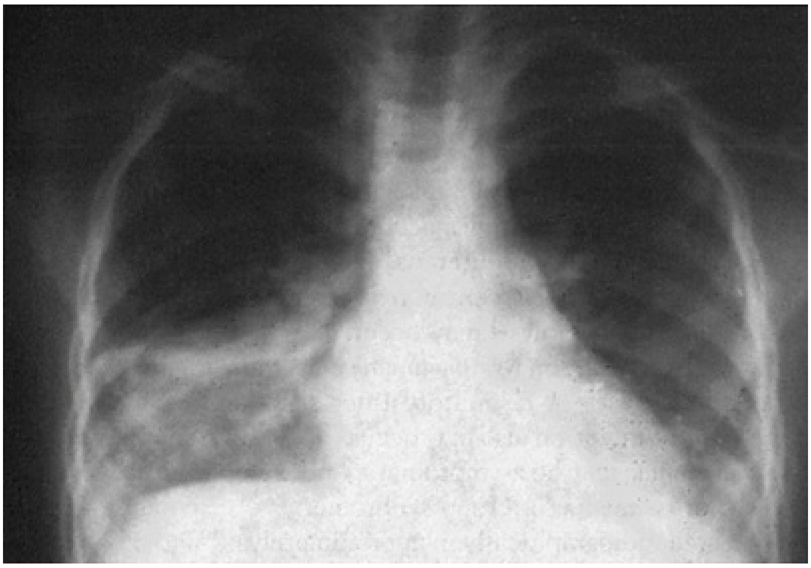


FIGURE 196.2 Chest radiograph of a 10-year-old girl with *Mycoplasma pneumoniae* pneumonia.

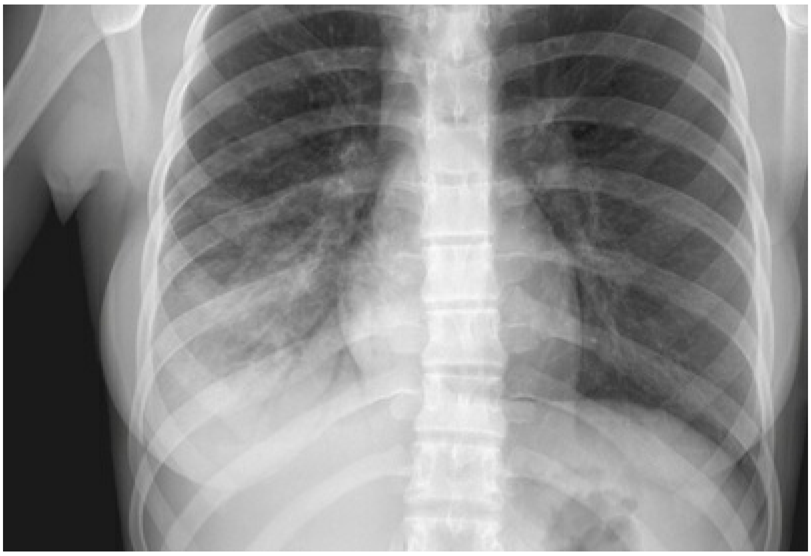
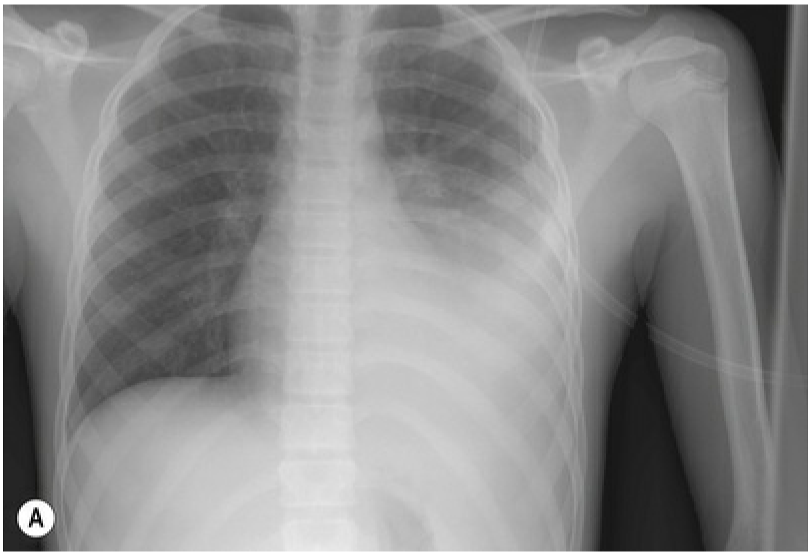


FIGURE 196.3 Chest radiograph in a 14-year-old boy with lobar pneumonia. Air bronchograms can be seen in the right lower lobe. *Mycoplasma pneumoniae* genome was detected in his nasopharynx and throat by polymerase chain reaction testing.



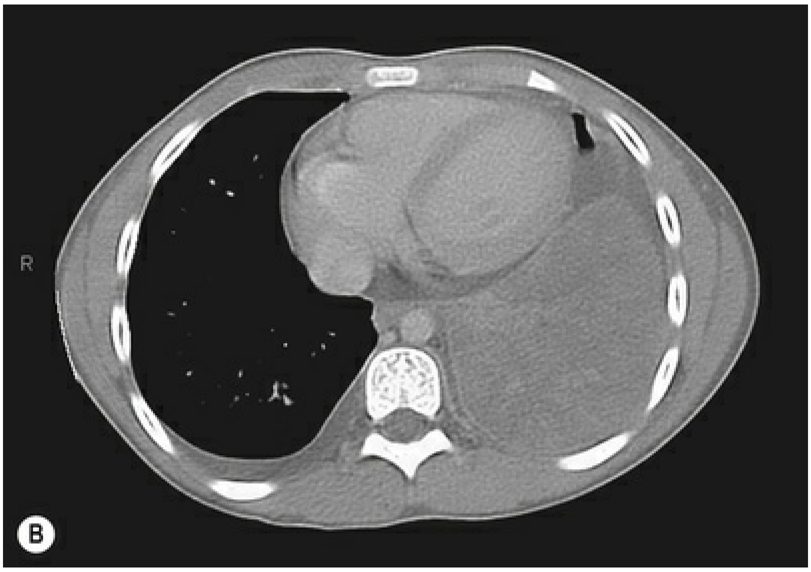


FIGURE 196.4 Radiography and computed tomography of the chest of a 13-year-old girl with *Mycoplasma pneumoniae* pneumonia complicated by parapneumonic effusion. (A) The radiograph demonstrates opacification of the left lung base with a moderate pleural effusion. (B) The computed tomography scan of the same patient also demonstrates a small right-sided pleural effusion and a trivial pericardial effusion.

Therapy

Antimicrobial Therapy

M. pneumoniae is inhibited in vitro by tetracyclines, macrolides, ketolides, and fluoroquinolones.[158–160] Fluoroquinolones appear bactericidal for *M. pneumoniae,* whereas macrolides, ketolides, and tetracyclines primarily are bacteriostatic[158]; the significance in patient outcomes is not known. The minimum inhibitory concentration (MIC) required to inhibit the growth of 90% of organisms (MIC_{90}) for levofloxacin ranges from 0.25 to 2 μg/mL[158,161–164]; the minimum bactericidal concentration is twofold higher. Moxifloxacin and gatifloxacin have somewhat greater activity in vitro compared with levofloxacin and ofloxacin. MIC_{90} values for all fluoroquinolones generally are severalfold higher than those of macrolides.[159,160] For azithromycin, clarithromycin, and telithromycin, the MIC_{90} values range from 0.001 to 0.015 μg/mL; minimum bactericidal concentration values often are eightfold to 16-fold higher.[158,159,161] Linezolid has minimal activity against *M. pneumoniae* (MIC_{90} >64 μg/mL).[163] Several other agents, including streptogramins, clindamycin, chloramphenicol, and aminoglycosides, demonstrate activity in vitro but are not effective clinically. β-Lactam and glycopeptide antibiotics have no activity against mycoplasmas.

The prevalence of clinically significant antibiotic resistance among *M. pneumoniae* isolates is not known; organisms from acute infection rarely are isolated in culture or tested in vitro for susceptibility to antibiotics. Macrolide resistance was reported in 12 (6.2%) of 195 clinical isolates in Japan.[165] The median MIC values were >32 μg/mL for azithromycin, clarithromycin, and telithromycin and 8 μg/mL for josamycin; however, the MIC values for minocycline and levofloxacin were similar between macrolide-susceptible and macrolide-resistant *M. pneumoniae* isolates.[165] Mutations in the peptidyl transferase loop of domain V of the 23S ribosomal RNA gene reduces the affinity of macrolides for ribosomes in both experimental models and clinical isolates.[166,167]

The benefit of antibiotic treatment of *M. pneumoniae* respiratory tract infections is uncertain. Azithromycin improves microbiologic, histologic, and immunologic markers of disease in experimental *M. pneumoniae* pneumonia in mice.[168] Studies comparing β-lactam and macrolide agents in the treatment of CAP in children included too few patients with *M. pneumoniae* to draw meaningful conclusions.[169] However, several lines of evidence suggest a possible therapeutic benefit. First, prophylactic oxytetracycline administered to family members of patients with *M. pneumoniae* infection prevented symptomatic infection (but not seroconversion).[170] Second, during epidemic *M. pneumoniae* infections in institutional settings, patients receiving azithromycin prophylaxis had significantly lower secondary attack rates than did patients not receiving prophylaxis.[34,171] Third, small retrospective studies showed that among children with atypical CAP (including *M. pneumoniae*), those treated with macrolides had a shorter duration of fever[172] and were less likely to have persistence or progression of signs and symptoms after 3 days of therapy.[173,174] In adults, Shames and colleagues[175] found a shorter duration of fever and hospitalization among erythromycin recipients compared with controls. No data suggest benefit of therapy for respiratory tract infections other than pneumonia.

Macrolide-class antibiotics also have been explored as potential treatments for *M. pneumoniae* because of their anti-inflammatory properties.[176–180] The importance of anti-inflammatory properties is supported by studies showing clinical cure in patients treated with macrolides despite persistence of *M. pneumoniae* organisms,[11,29,181,182] clinical improvement despite the administration of doses that provide tissue levels lower than the MIC of the organism,[183–185] and clinical cure in patients with macrolide-resistant *M. pneumoniae* infection.[166,186] The relative importance of the antimicrobial and anti-inflammatory effects of macrolide antibiotics in the treatment of *M. pneumoniae* is not known.

Therapy, if prescribed, may be more effective when started within 3 to 4 days of illness onset.[28,181,187] Therapeutic options for children include erythromycin (30–40 mg/kg/day divided into 4 doses for 7–14 days), clarithromycin (15 mg/kg/day divided into 2 doses for 7 to 14 days), or azithromycin (10 mg/kg once on the first day, followed by 5 mg/kg/day once daily for the next 4 days). Studies comparing erythromycin with clarithromycin[14,188] or azithromycin[189,190] for treatment of pneumonia did not identify a difference in frequency of therapeutic failure between the 2 groups; however, patients receiving erythromycin were twice as likely to have a drug-related adverse event, usually related to the gastrointestinal system. For adolescents, doxycycline (100 mg twice daily for 7–14 days), clarithromycin (500 mg twice daily for 7–14 days), azithromycin (500 mg on day 1, and 250 mg on days 2 to 5), or levofloxacin (500 mg once daily for 7–14 days) can be used. As few as 2% of patients with *M. pneumoniae* pneumonia require hospitalization, even in the presence of radiographic pneumonia.[28] Antibiotic therapy of *M. pneumoniae* infections has important limitations. The organism persists in many patients despite the antibiotic therapy; contagiousness thus extends through and after treatment. Because of the pathogen's persistence, relapsing infection should be considered in patients whose symptoms recur. Increasing resistance of *Streptococcus pneumoniae* to macrolides should prompt caution against using these agents alone for treatment of CAP.

No controlled studies of antibiotic or immunologic therapies for the nonrespiratory manifestations of *M. pneumoniae* infection have been conducted; no consistent benefit has been noted with antibiotic or corticosteroid therapy in individual patients. Because of the possibility of severe disseminated infection in immunocompromised patients, it is reasonable to administer an antibiotic with antimycoplasmal activity to patients with arthritis, central nervous system disease, hemolysis, or cardiac disease when *M. pneumoniae* infection is suspected.

Adjunctive Therapy

The effect of systemic or inhaled corticosteroids on infection-induced airway inflammation is poorly understood. Inhaled corticosteroids do not increase the infectious load of *M. pneumoniae*.[191] However, evidence supports efficacy. In experimentally infected mice, dexamethasone alone did not reduce *M. pneumoniae*–induced lung inflammation substantively compared with either placebo or clarithromycin monotherapy; however, combination therapy with clarithromycin and dexamethasone showed a significant reduction in lung inflammation compared with the other treatment regimens.[192] Anecdotal reports in children with *M. pneumoniae* pneumonia reveal temporal improvement of fever and radiologic abnormalities in association with corticosteroid therapy.[193]

Key Points

Diagnosis and Management of *Mycoplasma pneumoniae* Infection

Microbiology

- Pleomorphic bacteria without a cell wall, thus making it resistant to β-lactam antibiotics

Epidemiology

- Primarily a cause of upper and lower respiratory tract infection, although extrapulmonary complications occur

- Highest prevalence in school-aged children and adolescents, although younger children have less overt symptoms

- Attack rate among close contacts of 25% to 40%

- Clusters of infection in closed populations such as in institutionalized children and the military

Diagnosis

- Clinical findings suggestive
- Serologic testing (IgM anti–*Mycoplasma pneumoniae* detection in children or at least a fourfold rise in IgM or IgG) or PCR testing of nasopharyngeal washing or throat swab specimen

Treatment

- Role of antibiotic treatment for pneumonia uncertain
- Generally susceptible in vitro to macrolides, fluoroquinolones, and tetracyclines

IgG, immunoglobulin G; IgM, immunoglobulin M; PCR, polymerase chain reaction.

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197

Other *Mycoplasma* Species

Samir S. Shah

Many Mollicutes colonize the mucosal surfaces of humans (Table 197.1). Of these organisms, only *Mycoplasma genitalium, Mycoplasma hominis, Mycoplasma pneumoniae* (see Chapter 196), and *Ureaplasma urealyticum* (see Chapter 198) are known to be pathogenic for healthy humans. Other *Mycoplasma* spp. have been isolated in pure culture from nonmucosal sites in immunocompromised people, a finding indicating that commensal species can cause disease in some circumstances. In addition, animal *Mycoplasma* spp. occasionally cause local wound infection in humans.[1]

TABLE 197.1

Sites of Colonization or Infection of Mollicutes in Humans

Species	Primary Colonization Site
Acholeplasma laidlawii	Oropharynx
Acholeplasma oculi	?
Mycoplasma amphoriforme	Oropharynx
Mycoplasma buccale	Oropharynx
Mycoplasma faucium	Oropharynx
Mycoplasma fermentans	Lower genital tract, respiratory tract
Mycoplasma genitalium	Oropharynx, genital tract
Mycoplasma hominis	Lower genital tract, oropharynx
Mycoplasma lipophilum	Oropharynx
Mycoplasma orale	Oropharynx
Mycoplasma penetrans	Genital tract
Mycoplasma pirum	?
Mycoplasma pneumoniae	Oropharynx, trachea, bronchial tree, lung, pleural fluid

Mycoplasma primatum	Genital tract
Mycoplasma salivarium	Oropharynx
Mycoplasma spermatophilum	Cervix, sperm
Ureaplasma parvum	Genital tract
Ureaplasma urealyticum	Genital tract

Adapted from Tully G. Current status of the mollicute flora of humans. Clin Infect Dis 1993;17(Suppl 1):S2.

Mycoplasma hominis

M. hominis commonly colonizes the lower genitourinary tract of healthy men and women. In general, women are more likely to be colonized than men, and the likelihood of colonization increases with the number of sexual partners.[2–4] *M. hominis* is found in <5% of asymptomatic men and in as many as 20% of men attending sexually transmitted disease clinics.[5] The rate of colonization in asymptomatic women ranges from 10% to 30%[6,7]; the rate of isolation may be higher in women with bacterial vaginosis,[8,9] urethritis, or cervicitis.[10] Adolescent girls and boys are colonized infrequently, with reported rates of approximately 5% and 2%, respectively.[11] *M. hominis* seldom colonizes the upper respiratory tract; it has been recovered from the oral or respiratory tracts of 1% to 3% of healthy adults and in a greater proportion of those adults who engage in oral-genital sexual practices.[12] *M. hominis* also was identified in 4.7% of 319 children undergoing bronchoscopy, with the prevalence decreasing with increasing age; the clinical relevance of this finding is uncertain.[13]

The respiratory and genitourinary tracts of neonates also can be colonized (incidence, 2%–7%), particularly after birth complicated by prolonged rupture of amniotic membranes or amnionitis.[7]

Isolation of the organism from normally sterile sites and documentation of immunologic response to infection have implicated *M. hominis* as a cause of the conditions listed in Table 197.2. Numerous case reports implicate *M. hominis* as a cause of amnionitis, postpartum fever,[14–21] and other postpartum infections.[22] However, the clinical importance of neonatal *M. hominis* infection is less clear.[23] Neonatal central nervous system infections attributed to *M. hominis* include ventriculitis, meningitis, meningoencephalitis, and subdural empyema.[24–35] *M. hominis* was isolated from the cerebrospinal fluid (CSF) of 5 (5%) of 100 preterm infants 1 to 6 days of age; the 1 infant with CSF pleocytosis had 71 white blood cells/mm^3 and a mononuclear cell predominance.[28] Valencia and colleagues[26] isolated *M. hominis* from 9 (13%) of 69 neonates undergoing lumbar puncture; the CSF white blood cell count ranged from 0 to 28 white blood cells/mm^3. *M. hominis* also was isolated from the CSF in 9 (2.8%) of 318 infants evaluated by lumbar puncture in the peripartum period at 4 community hospitals; the 1 infant who died had concomitant *Haemophilus influenzae* sepsis.[27] Neonates who did not receive specific therapy for *M. hominis* in these studies did not appear to have any apparent clinical consequence of infection.[26–28] In contrast, Wolthers and associates[33] reported a term infant with early onset meningoencephalitis attributed to *M. hominis* that was identified by both culture and polymerase chain reaction (PCR) testing of the CSF; this infant had improvement in CSF abnormalities that coincided with the administration of ciprofloxacin.

TABLE 197.2

Infection Associated With *Mycoplasma hominis*[a]

Age Group	Type of Infection
Neonate	Septicemia
	Meningitis
	Ventriculitis
	Brain abscess or subdural empyema
	Pneumonia
	Pericarditis
	Wound infection
	Submandibular adenitis
	Subcutaneous abscess
Infants and children	Septicemia
	Ventriculitis
	Pleural effusion
Adolescents and adults	Amnionitis
	Postpartum fever
	Pyelonephritis or perinephric abscess
	Septicemia
	Wound infection
	Intravascular infection
	Arthritis
	Ventriculitis
	Upper respiratory tract infection (parapharyngeal abscess)
	Pneumonia or pleural infection

[a] Nongenitourinary infections almost always occur in patients with immune compromise because of severe burns, collagen-vascular disease, severe trauma, malignant disease, organ transplantation, or congenital immunodeficiency,

particularly hypogammaglobulinemia.

Recovery of *M. hominis* from the respiratory or urinary tract of neonates generally has not been associated with clinical infection.[36,37] However, neonates with *M. hominis* isolated from sterile sites appear to have worse clinical outcomes. In a study of 351 preterm infants (23–32 weeks of gestational age), *M. hominis* was isolated from umbilical cord blood cultures alone (n = 21; 6.0%) or in combination with *Ureaplasma urealyticum* (n = 18; 5.1%); earlier gestational age correlated with a higher rate of positive umbilical cord blood culture results. Furthermore, infants with positive umbilical cord blood culture results were more likely to have systemic inflammatory response syndrome compared with infants with negative cord blood culture results.[38]

Numerous anecdotal reports have recorded *M. hominis* infection occurring outside the genitourinary system in other populations, including immunocompromised patients[39–49] and patients undergoing intracranial oeprations.[50,51] In a series of 36 adults with extragenital *M. hominis* infection, patients most commonly had abdominal wound infections following genitourinary tract operations.[52]

M. hominis infection should be suspected when specimens from localized purulent infection, especially following genitourinary tract exposure (e.g., neonate) or manipulation, fails to yield a pathogen by conventional laboratory methods. Isolation and identification of *M. hominis* require inoculation and initial incubation in beef heart infusion broth containing horse serum and yeast extract, available commercially as pleuropneumonia-like organism (PPLO) broth. Arginine, which is metabolized by *M. hominis,* is added to the broth, along with phenol red. Metabolism of arginine increases the pH so that growth can be detected by a change in the color of the broth, usually within 24 to 48 hours. Subculture onto solid agar and incubation in 95% nitrogen and 5% carbon dioxide yield, within 7 days, colonies of 200 to 300 μm that develop the characteristic “fried egg” appearance. *M. hominis* (but not *M. pneumoniae* or *U. urealyticum*) also grows on conventional blood agar and in most broth media used for blood culture. Laboratory personnel should be alerted to look for pinpoint, translucent colonies that develop within 2 to 3 days on blood agar that should be subcultured as described. Recognition of *M. hominis* growth in blood culture broth depends on blind subculture, even if results of Gram stain of broth are negative. Growth causes little turbidity in broth, but radiometric assays show a positive growth index within 5 to 7 days.[21] Automated, continuous-monitoring blood culture systems do not permit reliable recovery of *M. hominis*.[53] Multiplex PCR[54] and PCR-based microtiter plate hybridization assays[55] also have been described; their accuracy and usefulness in the clinical setting remain to be determined.

Generally, *M. hominis* is susceptible to tetracyclines, fluoroquinolones, and clindamycin.[56–59] The minimum inhibitory concentration required to inhibit the growth of 90% of organisms (MIC_{90}) values are lower for levofloxacin (0.19–0.5 μg/mL), gatifloxacin (0.063 μg/mL), and moxifloxacin (0.063 μg/mL) than for ciprofloxacin (0.5–1 μg/mL).[56,58,60] Chloramphenicol, rifampin, and linezolid (MIC_{90}, 8.0 μg/mL) demonstrate modest in vitro activity.[61] Up to 20% of *M. hominis* clinical isolates can be resistant to tetracycline and doxycycline, but antibiotic susceptibility patterns vary by country.[56,62–64] Fluoroquinolone resistance occurs occasionally.[39,65] Unlike the other pathogenic mycoplasmas, *M. hominis* is almost always resistant to macrolides, azalides, and ketolides, including erythromycin, azithromycin, clarithromycin, and telithromycin.[61,64,66,67] The benefit of immune globulin intravenous therapy in patients with hypogammaglobulinemia and *M. hominis* infection is not known.

Mycoplasma Genitalium

M. genitalium was first isolated in 1980 from urethral specimens of 2 men with symptoms of nongonococcal urethritis.[68] Clarifying the subsequent role of *M. genitalium* in human disease has been hampered by the organism's slow growth, fastidious cultivation requirements, and serologic cross-reactivity of surface antigens with *M. pneumoniae*.[69] The 38% to 63% rate of detection of *M. genitalium* in sexual partners of index cases compared with 6% in a control population suggests that the infection is sexually transmitted.[70,71] Numerous studies using PCR confirm the association of *M. genitalium* with nongonococcal urethritis in men.[71–75] Fewer studies of *M. genitalium* have been carried out in women. The prevalence of *M. genitalium* of 6% among asymptomatic women attending a sexual health clinic was comparable with that of *Neisseria gonorrhoeae* and *Chlamydia trachomatis*.[76] *M. genitalium* has been detected using PCR techniques in women with acute and chronic urethritis and pelvic inflammatory disease.[77–79] Women with pelvic inflammatory disease attributed to *M. genitalium* have a milder spectrum of symptoms compared with women with gonococcal pelvic inflammatory disease.[80]

Repeat examination of presumed *M. pneumoniae* isolates from respiratory specimens obtained in the 1970s and from synovial fluid of a patient with hypogammaglobulinemia and polyarthritis showed that some isolates actually were mixed *M. pneumoniae* and *M. genitalium* infections.[81,82] Although *M. genitalium* is associated with nongonococcal urethritis in men, its association with other human diseases of the genitourinary or respiratory tract remains uncertain. The twofold higher prevalence of *M. genitalium* among HIV-infected patients also warrants investigation of potential causal associations.[83]

The organism is typically detected by PCR of urethral or cervical swabs or urine specimens.[84–86] *M. genitalium* is susceptible to tetracyclines, fluoroquinolones, and macrolides.[87,88] MICs vary widely; MICs <0.01 µg/mL for macrolides, azalides, fluoroquinolones, and tetracyclines generally are considered susceptible, and MICs ≥2 µg/mL generally are considered resistant.[89] Mutations that occur in region V of the 23S ribosomal RNA gene prevent macrolide binding.[90] Such mutations are present in more than one third of isolates in studies including at least 100 specimens[91–93]; the prevalence of resistance is higher in posttreatment specimens obtained from patients whose therapy failed.[89]

Azithromycin may be preferable to doxycycline for treatment of *M. genitalium* infection because doxycycline does not consistently eradicate *M. genitalium* from the genitourinary tract.[94–96] Among 398 men with urethritis who were enrolled in a randomized clinical trial, 13% of azithromycin-treated men remained culture positive compared with 55% of doxycycline-treated men.[96] In 1 study, colonization persisted in 20 (67%) of 30 patients treated with doxycycline but in 0 of 36 patients treated with azithromycin.[95]

Observational studies suggest that a single 1-g dose of azithromycin, versus doses given over 5 to 7 days,[70,97–100] results in a similar rate of eradication. Clinical and microbiologic treatment failure following moxifloxacin, previously rare, is reported in up to 30% of patients in contemporary studies; however, most of these patients received moxifloxacin after having treatment failure with another antimicrobial agent.[89,91,101]

Other *Mycoplasma* Infections

M. fermentans, M. penetrans, and other "nonpathogenic" species have been isolated from patients, including children with human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome.[102–104] In most instances, infection appeared to be asymptomatic, but serious and fatal disease has been reported.[105,106] Investigators have speculated that *Mycoplasma* spp. can enhance the pathogenicity of HIV by a variety of mechanisms, but evidence is insufficient to prove that *Mycoplasma* spp. are more than opportunistic pathogens.

Human infections with zoonotic *Mycoplasma* spp. have been reported predominantly in immunocompromised patients[107] and in patients with trauma and wound contamination.[1] Because these infections appear to be uncommon, routine attempts to recover *Mycoplasma* spp. are not warranted. However, in unusual circumstances, such as an immunocompromised patient with negative results of routine bacterial cultures or a patient with an infected wound after a seal bite, culture for *Mycoplasma* spp. should be considered. "Seal finger," an infection known to occur in seal hunters and wildlife workers, can result from a seal bite or from skinning or handling seals.[1,108,109] Several different species of marine *Mycoplasma* found in the mouths and respiratory tracts of seals are the presumed cause. Tetracyclines are considered first-line therapy for seal finger.

Certain illnesses including chronic fatigue syndrome, Gulf War syndrome, and fibromyalgia have been associated with positive results of PCR testing of blood for 1 or more *Mycoplasma* spp.[110,111] These associations should be considered speculative at best. Additional studies in subjects with Gulf War syndrome have shown no such association.[112] Further, a placebo-controlled trial of doxycycline in 491 subjects with Gulf War veterans' illnesses that were characterized by pain, fatigue, and cognitive symptoms, and detectable *Mycoplasma* DNA in blood did not demonstrate benefit in functional status 1 year after randomization.[113] Although such reports may warrant further well-designed studies, PCR testing for *Mycoplasma* spp. should not be considered part of the clinical investigation for such patients.

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Ureaplasma urealyticum

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Microbiology

Members of the family Mycoplasmataceae are small pleomorphic bacteria that characteristically lack a cell wall. Shapes range from filamentous to spherical, with diameters up to 0.8 µm. The genus *Ureaplasma* is biochemically unique in that all members possess urease and therefore hydrolyze urea to produce adenosine triphosphate. Ammonia also is produced, and it increases the pH and limits growth in culture. *Ureaplasma urealyticum* was first described in 1950 by Shepard, who noted minute colonies growing amid larger *Mycoplasma* colonies in specimens taken from the urethra and urine of men with nongonococcal urethritis.[1] These bacteria were initially called “T-strain” *Mycoplasma* because of their tiny colony size. Urease production led to the name *Ureaplasma urealyticum.*

U. urealyticum, a human pathogen, has historically been divided into 14 serotypes, which are divided into 2 distinct biovars on the basis of biochemical and genetic features. Genetic study suggests that the 2 biovars represent 2 separate species; *U. urealyticum* biovar 1 (*Ureaplasma parvum*) includes serovars 1, 3, 6, and 14, and *U. urealyticum* biovar 2 is further divided into 3 subtypes. Subtype 1 includes serovars 2, 5, 8, and 9. Subtype 2 includes serovars 4, 10, 12, and 13, and subtype 3 includes serovars 7 and 11.[2] The entire genome of *U. urealyticum* has been sequenced.[3] It is the smallest sequenced prokaryotic genome, except for *Mycoplasma genitalium,* and it consists of only 75 DNA kilobase pairs. The function of at least 50% of the 652 identified genes remains unknown. The description of the genome facilitates improved understanding of the mechanism of disease caused by these elusive organisms.

Epidemiology

Ureaplasma spp. colonize the urogenital tract of healthy adults and adolescents. *Ureaplasma* spp. can be found on the mucosal surfaces of the cervix or vagina of 40% to 80% of healthy women. Reported rates of asymptomatic urethral carriage of *U. urealyticum* among men typically range from 20% to 50%; however, most studies have assessed only sexually active men in the context of medical visits for urologic evaluation or sexually transmitted infection.[4–7] One report found that urethral carriage was detected in only 8 (7%) of 114 asymptomatic male volunteers recruited from hospital staff and from primary care practices.[8] Although colonization occurs less frequently among adolescents and young children, its presence is related to both sex and sexual activity. Foy and colleagues[9] isolated *Ureaplasma* spp. from the urine of 1% of adolescent boys and 15% of adolescent girls; girls who reported dating members of the opposite sex were more likely to be colonized. The organism was not recovered from any of 101 children <13 years of age.[9] Approximately 50% of colonized mothers transmit the organisms to their infants.[10–12] Peripartum colonization occurs most often in infants born >1 hour following rupture of membranes[10] and in infants weighing <1000 g.[11] Sites of colonization in infants, in order of decreasing frequency, include the vagina, nasopharynx and throat, rectum, and conjunctiva.[10–12] Colonization persisted at 3 months of age in 37%, 68%, and 33% of infants with initial vaginal, throat, or conjunctival colonization, respectively, in 1 study.[12] Other studies have noted disappearance of peripartum colonization by 2 years of age.[13]

Clinical Manifestations

A causal relationship between *U. urealyticum* and various clinical syndromes has been difficult to confirm, given the relatively high frequency of asymptomatic carriage and the difficulty in collecting samples from normally sterile sites. Many published studies failed to adjust for potentially important confounding variables or were underpowered to detect significant associations. Nevertheless, *U. urealyticum* has been shown to cause urethritis. In pregnant women, *Ureaplasma* is an implicated cause of chorioamnionitis, spontaneous abortion, stillbirth, preterm delivery, and postpartum endometritis. *U. urealyticum* has been associated with longterm sequelae such as chronic lung disease in preterm infants. Invasive infections have been reported, predominantly in neonates and immunocompromised people. The reported association with infertility in adults is controversial.

Urethritis

Nongonococcal urethritis in men appears to be associated with *U. urealyticum* biovar 2 but not biovar 1 (*U. parvum*).[14,15] Clinical symptoms do not distinguish *Ureaplasma* spp. infection from other causes of nongonococcal urethritis. Among men, biovar 2 has been isolated 2 to 3 times more frequently from men with nongonococcal urethritis than from asymptomatic men.[5,6,16] Among men with *U. urealyticum* detected in urine by 16S ribosomal RNA (rRNA) polymerase chain reaction (PCR), quantity of detection was significantly higher in men with urethritis compared with men without symptoms.[14,17] A bacterial load of $\geq 10^4$ *U. urealyticum* 16S rRNA gene copies/mL in a first-void urine specimen (initial 20–30 mL of urine after not having urinated for at least 2 hours) has been proposed to distinguish urethritis from asymptomatic colonization, although validation in larger populations is required.[17] Coinfection with *U. urealyticum* also conferred 3.6-fold greater odds of postgonococcal urethritis (urethritis that persists after successful eradication of laboratory-confirmed gonococcal infection).[18] Although young boys usually are not colonized, recurrent urethritis was attributed to *U. urealyticum* in a 7-year-old boy.[19]

Although the role of *U. parvum* in urethritis is unclear, current data suggest that this organism rarely causes urethritis. In a meta-analysis, *U. parvum* was detected more often from urethral specimens of 1223 control subjects (17.7%) than from 1507 subjects with nongonococcal urethritis (10.2%; $P < 0.001$).[15] Additionally, the quantity of *U. parvum* detected usually is low and does not differ significantly between men with and men without urethritis.[14] However, higher loads of *U. parvum* were associated with higher first-void urine white blood cell counts in a male study.[20] Although *U. parvum* could contribute to urethritis, routine testing or treatment is not warranted.

Intrauterine and Neonatal Infection

Ureaplasma spp. have been isolated from the placenta and fetus after spontaneous abortion in individual case reports.[21,22] *U. urealyticum* was isolated from the placenta more often in cases of spontaneous abortion, stillbirth, or neonatal death (31%) than in control liveborn infants (9%) in 1 study.[23] Several studies supported the association between *U. urealyticum* and chorioamnionitis. In a case-control study, Abele-Horn and associates[24] demonstrated a dose-response relationship between the density of vaginal colonization with *U. urealyticum* and clinical chorioamnionitis risk; chorioamnionitis was more likely in women with moderate (odds ratio [OR], 2.5; 95% confidence interval [CI], 1.0–5.9) or heavy (OR, 7.2; 95% CI, 3.3–15.5) vaginal colonization than in uncolonized women. Histologic evidence of chorioamnionitis is present more frequently when *U. urealyticum* is isolated from either amniotic fluid[25] or newborn infants.[26] Colonization was detected in 18 (38%) of 48 infants whose placentas exhibited histologic evidence of chorioamnionitis and in 22 (19%) of 116 infants with normal maternal placentas ($P = 0.02$).[26] Although smaller studies have not shown differences in frequency of *U. urealyticum* isolation from amniotic fluid of women with or without chorioamnionitis,[27] a nonrandomized study of women colonized with *U. urealyticum* revealed significantly fewer midtrimester losses in the 35 women who received oral erythromycin (11%) compared with the 9 women who were not treated (44%; $P = 0.04$).[28]

Isolation of *U. urealyticum* from the amniotic fluid (but not from the lower vaginal tract) appears to be associated with preterm delivery. *U. urealyticum* has been detected in the amniotic fluid of approximately 9% of women in preterm labor and is associated with a higher risk of preterm delivery and adverse neonatal outcomes in this setting.[29–31] Cytokines elaborated in the amniotic fluid in response to the presence of microorganisms, including *U. urealyticum*, trigger prostaglandin synthesis, which can lead to uterine contractions and cervical dilation.[32] However, in a prospective study of 4934 women from 5 medical centers who were evaluated for vaginal colonization with *U. urealyticum* between 23 and 26 weeks of gestation and who were followed to delivery, preterm delivery was not associated with *U. urealyticum* vaginal colonization after adjustment for medical and sociodemographic factors (OR, 1.0; 95% CI, 0.8–1.2).[33]

U. urealyticum appears to have a causal role in chronic lung disease of prematurity, perhaps by stimulating the production of proinflammatory mediators, including neutrophils, tumor necrosis factor-α, and interleukin-8.[34,35] Animal models supported this assertion. Rodent macrophage cell lines released nitric oxide in the presence of *U. urealyticum.*[36] Premature baboons artificially colonized with *U. urealyticum* developed classic hyaline membrane disease and necrotizing bronchiolitis.[37,38] In a meta-analysis, pulmonary colonization with *Ureaplasma* spp. was associated with chronic lung disease when measured at 28 days of life (31 studies; OR, 3.0; 95% CI, 2.4–3.8) and at 36 weeks of postmenstrual age (17 studies; OR, 2.2; 95% CI, 1.4–3.5).[39] Gestational age did not influence this relationship, a finding suggesting a causal role rather than a confounding factor of gestational age. Limitations of the meta-analysis,[39] and of other studies,[40–48] include differences in methods to detect *Ureaplasma* spp. and inconsistent reporting of the use of surfactant and corticosteroids. *U. parvum* was detected in tracheal secretions more than twice as often as *U. urealyticum*; no difference was observed between infants harboring *U. parvum* versus *U. urealyticum* in development of chronic lung disease.[44] However, detection of both species simultaneously occurred more often in infants with than without chronic lung disease (17 vs. 7 infants, respectively) (OR, 3.0; 95% CI, 1.2–7.7; P = 0.01).

U. urealyticum can cause invasive disease in neonates. Individual cases of congenital pneumonia have been associated with *Ureaplasma* spp.[49] One study demonstrated concomitant *U. urealyticum* bacteremia in 26% of preterm neonates with *U. urealyticum* isolated from endotracheal aspirates.[50] The clinical manifestations in infants with *U. urealyticum* isolated from cerebrospinal fluid (CSF) specimens range from subclinical infections with complete recovery to suppurative infections associated with longterm sequelae. In 1 study, *U. urealyticum* was isolated from the CSF of 8 of 100 infants undergoing lumbar puncture either for suspected meningitis or for treatment of hydrocephalus[51]; some infants had *U. urealyticum* isolated from multiple CSF specimens. The CSF white blood cell counts ranged from 0 to 5240 cells/mm^3.[51] Case reports include a 3-week-old infant with brain abscess attributed to mixed infection with *U. urealyticum* and *Mycoplasma hominis*,[52] a 7-day old infant with meningitis complicated by subdural collections with *U. urealyticum* isolated from CSF and improvement following azithromycin and ciprofloxacin therapy,[53] an untreated neonate with *Ureaplasma* isolated from CSF who remained well,[54] and a premature infant with intraventricular hemorrhage and isolation of *U. urealyticum* from CSF without pleocytosis.[55] The prognosis and neurodevelopmental outcomes of infants with *Ureaplasma* spp. infections of the CSF have not been studied.

Other Infections

Some reports suggested an etiologic role for *U. urealyticum* in several focal infections, including pneumonia,[56–61] arthritis,[62–64] meningitis,[65] renal abscesses,[66,67] and postoperative mediastinitis.[68] Focal infections usually have been reported in immunocompromised patients. *U. urealyticum* has been recovered in cultures of respiratory tract secretions (usually in combination with other respiratory pathogens) obtained from both immunocompetent and immunocompromised infants with lower respiratory tract infections,[56,58–61] as well as from bronchoalveolar lavage fluid in 3 children with cancer during a period of acute respiratory deterioration.[57] *U. urealyticum* has been recovered from blood or joint fluid in patients with agammaglobulinemia and pyogenic arthritis,[62,63] and it has been detected by PCR in joint fluid in a patient with reactive polyarthritis[64] and in a patient with recurrent arthritis following treatment with rituximab and adalimumab for juvenile idiopathic arthritis.[69] Meningitis[65] and renal abscesses[66,67] have been described in adults following renal transplantation.

Laboratory Findings and Diagnosis

Ureaplasma spp. are fastidious. Body fluid specimens or material collected on calcium alginate or Dacron-tipped swabs should be inoculated at the bedside into a special transport or growth medium, such as Shepard 10B broth, and then inoculated onto solid media as soon as possible. Freezing decreases viability, but if the sample must be held, freezing at −70°C is recommended. Inoculation onto A8 or a commercial solid medium that contains urea allows rapid growth, generally within 2 to 5 days. An indicator dye added to the medium to detect hydrolysis of urea permits early identification of *Ureaplasma* spp.

In culture, the organisms are ovoid. On solid media, the organism shares the upside-down "fried egg" appearance typical of Mycoplasmataceae. Organisms vary in size but are approximately 350 nm in diameter, too small to be seen with a light microscope. Growth can be detected in broth or on agar when a specialized culture medium is used. Distinct small colony morphologic features (on appropriate media) and passage in selective broth permit culture identification but not serovar classification.

PCR is a faster and more practical approach to detection. Gene targets include the urease,[70] 16S rRNA,[71] and multiple-banded antigen[72,73] genes. Amplification of the multiple-banded antigen gene allows biovar and, possibly, serovar identification.[2,72–74] Multiplex PCR for simultaneous detection of *U. urealyticum*, *Trichomonas vaginalis*, and *Mycoplasma hominis* has been developed.[75] The sensitivity of multiplex PCR for detection of *U. urealyticum* was 96% compared with culture or one of several PCR assays.[75] PCR for *Ureaplasma* spp. performed on gastric fluid on the day of birth has high specificity but poor sensitivity (27%) compared with PCR of amniotic fluid within the 7 days before delivery.[76]

Treatment

No well-established breakpoints exist for determining antimicrobial susceptibility of *U. urealyticum*. However, most *Ureaplasma* spp.

have minimal inhibitory concentrations (MICs) for erythromycin in the range of 0.125 to 4 μg/mL, a finding that suggests susceptibility. Resistant strains (MIC, e.g., ≥8 μg/mL) are reported.[77] The MICs of azithromycin (range, 0.125–2 μg/mL) and clarithromycin (range, 0.06–2 μg/mL) are slightly lower compared with the MIC of erythromycin.[78–81] MICs of doxycycline range from 0.016 to 1 μg/mL.[77,78] Acquisition of the *tet*M determinant mediates tetracycline resistance.[82,83] Generally, >90% of clinical isolates are susceptible in vitro to levofloxacin, moxifloxacin, ofloxacin, and chloramphenicol in most studies, whereas <50% are susceptible to ciprofloxacin or clindamycin.[78,79,81,84–86] Quinupristin-dalfopristin and telithromycin also appear to have adequate activity against *U. urealyticum* (MIC_{90} [MIC required to inhibit the growth of 90% of organisms] <0.25 μg/mL).[81] Although some *Ureaplasma* spp. isolates appear susceptible to aminoglycosides in vitro, these agents do not have clinical efficacy. *Ureaplasma* spp. lack peptidoglycan and are not susceptible to β-lactam agents or vancomycin.

Urethritis can be treated with azithromycin, doxycycline, or newer-generation fluoroquinolones. In a randomized, double-blind multicenter trial, microbiologic cure rates of *U. urealyticum* urethritis among men were 45% for those receiving azithromycin (1 g, single dose) and 47% for those receiving doxycycline (100 mg, twice daily for 7 days).[87] A subsequent double-blind clinical trial of men with *U. urealyticum* nongonococcal urethritis found higher microbiologic cure rates: 75% for azithromycin recipients (n = 65; 1 g) and 70% for doxycycline recipients (n = 77; 100 mg, twice daily for 7 days).[88] In a treatment follow-up study, persistent detection of *U. urealyticum* was not associated with persistent urethritis.[89] Women with >3 weeks of symptoms had higher rates of clinical cure and eradication after the administration of azithromycin at a dose of 500 mg daily for 6 days than after a single 1-g dose.[90] Macrolides may be less effective than doxycycline in the acidic environment of the female genital tract.[81,91]

Making specific recommendations for treating invasive *Ureaplasma* spp. infections in neonates is difficult because the spectrum of disease in this population has not been elucidated fully. Furthermore, drug options are limited, clinical studies of antibiotic efficacy are not available, conditions under which treatment should be offered are controversial, and the optimal duration of therapy, when prescribed, is not known. Because of the proven ability of *U. urealyticum* to induce inflammation in the lung and CSF, detection from a normally sterile body site in the absence of another organism would seem to justify specific therapy. Erythromycin (25–40 mg/kg/day in 4 divided doses) is the drug of choice for treating infections outside the central nervous system. In older children, azithromycin is associated with less gastrointestinal discomfort and better adherence. Therapy generally is continued for 5 (azithromycin) or 10 days (erythromycin or clarithromycin). If therapy of central nervous system infection is considered, an agent with better penetration of the blood-brain barrier than erythromycin should be selected. In such cases, it may be prudent to document recovery of the organism from multiple CSF samples before initiating therapy. In a report of a neonate with a brain abscess attributed to *U. urealyticum* and *M. hominis* treated with a combination of doxycycline 4 mg/kg/day and erythromycin for 6 weeks, a doxycycline concentration of 1.0 µg/mL in ventricular fluid was documented.[52]

Although *U. urealyticum* colonization is associated with development of chronic lung disease, treatment of colonized neonates does not improve their outcomes. In a meta-analysis of 6 studies involving 469 preterm infants, no significant reduction was noted in chronic lung disease (relative risk, 0.64; 95% CI, 0.31–1.31) or in the composite outcome of chronic lung disease or death (relative risk, 0.41; 95% CI, 0.05–3.13) when macrolides (azithromycin in 3 studies, erythromycin in 2, and clarithromycin in 1) were used in *Ureaplasma*-positive infants.[92] In the largest study, which contributed one third of the patients to the meta-analysis and did not observe a reduction in chronic lung disease, azithromycin was given at a dose of 10 mg/kg/day for 7 days followed by 5 mg/kg/day for up to 6 weeks.[93] Higher doses of azithromycin (i.e., 20 mg/kg/day) have better *Ureaplasma* clearance and greater anti-inflammatory action.[84,94] Whether these higher doses lead to better outcomes in preterm infants with *Ureaplasma* pulmonary colonization is unknown. Evidence is also insufficient to determine benefit of treatment of women with *Ureaplasma* vaginal colonization to prevent preterm birth[95,96]; such treatment is therefore not recommended.

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Diseases of Possible Infectious or Unknown Etiology

OUTLINE

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199

Kawasaki Disease

Anne H. Rowley

Kawasaki disease (KD) is the most common cause of acquired heart disease in children in the developed world.[1] The epidemiology and clinical features of the illness point to an infectious etiology, but the cause remains unknown. KD is a unique vasculitis that occurs in previously healthy young children and can result in serious long-term coronary artery disease or death.[2] Approximately 20% of children with KD who are not treated with intravenously administered immune globulin (IGIV) develop coronary artery abnormalities.[3]

KD is named after Tomisaku Kawasaki, who first recognized the clinical features of the illness in Japanese children in the 1960s.[4] By 1970, the coronary artery sequelae became apparent when some children who were recovering from KD suddenly died from coronary artery aneurysms with thrombosis and myocardial infarction. Before Kawasaki's description of the clinical features, the disease was recognized only at autopsy and was called *infantile periarteritis nodosa* by pathologists.[5]

The illness is recognized worldwide and affects children of all ethnic groups. More than 290,000 cases were diagnosed in Japan by 2012.[6] The total number of cases diagnosed to date in the United States and other countries is uncertain. Symptomatic or fatal ischemic coronary artery disease in adolescents and young adults with angiographic or pathologic characteristics highly suggestive of KD sequelae has been recognized increasingly.[7,8]

Etiology and Epidemiology

KD is an illness of infants and young children. Approximately 80% of patients are younger than 5 years of age.[6,9] Because children older than 8 years of age account for a small percentage of KD patients, the diagnosis may be delayed for this age group.[10] Males are more commonly affected than females (3 : 2). Epidemics of KD have been observed in Japan and other countries, with a geographic wave-like spread of cases as the epidemic progresses.[11,12] The illness recurs in about 3% of Japanese children; the recurrence rate in the United States likely is lower.[6]

The annual incidence of KD among Japanese children is about 260 cases per 100,000 children younger than 5 years of age.[6] Approximately 1% of Japanese children develop KD by age 5 years. Asian children who live in non-Asian countries continue to experience high rates of KD. The attack rate of KD among white children is 10-fold lower than among Asians, and African Americans appear to have an intermediate incidence. Attack rates can increase substantially during epidemics in all ethnic groups; a calculated annual attack rate during an outbreak of KD in the Rochester, NY, area increased from about 10 to 180 cases per 100,000 children younger than 5 years of age.[13]

Epidemiologic features strongly suggest a ubiquitous microbe as the causative agent. The rarity of KD in infants younger than 3 months is compatible with protection from passive maternal antibodies, and the virtual lack of KD in adults suggests widespread immunity. The winter-to-spring predominance of cases in temperate climates, epidemics of illness, and the wave-like spread of illness during outbreaks are all consistent with an infectious cause. Little evidence of person-to-person spread of KD exists. However, because most ubiquitous microbes result in asymptomatic infection in most of the population, person-to-person spread may be difficult to document without knowledge of the causative agent.

In a study of Japanese children with KD, the risk of developing a second case in a family within 1 year after onset of the first case was significantly higher than the risk of KD for the general population of age-matched children. Moreover, more than one half of second cases in families developed within 10 days of the first case.[14] These findings suggest common exposure to an infectious agent in genetically predisposed individuals. Children with KD usually are healthy before the onset of illness and are not more likely than unaffected children to develop subsequent autoimmune disease or recurrent infections.

A variety of known infectious agents have been proposed to be causative, but none has been associated consistently, leading some investigators to propose multiple causes for KD. However, research studies support the hypothesis that KD results from infection with a single, currently unidentified respiratory viral agent.[15–17]

Pathology

In acute KD, inflammatory cells, including T lymphocytes, particularly CD8$^+$ cells; plasma cells, many of the IgA isotype; eosinophils; and macrophages infiltrate medium-sized muscular arteries, particularly the coronary arteries,[18–20] and selected nonvascular tissues.[21] This remarkable IgA immune response suggests a mucosal portal of entry of the etiologic agent.

The stimulus for inflammatory cell infiltration in tissues in acute KD is unclear. Possibilities include direct infection of tissues by the etiologic agent or an immune response to self, perhaps triggered by a mechanism of molecular mimicry. The former seems more likely because the systemic inflammatory process resolves spontaneously within a few months of onset. The result is necrotizing arteritis of the coronary artery walls, which can be catastrophic. The walls can balloon and form aneurysms. Sluggish blood flow in these abnormal vessels encourages coronary thrombosis and resultant myocardial infarction. If the wall is severely weakened, it can rupture, causing sudden death. Marked myocarditis can result in arrhythmia. Pericarditis commonly leads to pericardial effusion, and as inflammation of the sac progresses, more fluid is produced.

Marked innate immune activation in acute KD manifests by upregulation of cytokines in the peripheral blood.[22,23] The robust oligoclonal, antigen-driven immune responses by T lymphocytes[24] and immunoglobulin M (IgM) and IgA B lymphocytes[25,26] attest to strong adaptive immune responses. Other immunologic findings include decreased CD8$^+$ T lymphocytes in the peripheral blood[27] and elevation of all serum immunoglobulins in the subacute phase of illness.[28] Polymorphisms in several immune system genes are associated with KD susceptibility and the risk of coronary artery abnormalities, but even in combination, these genes do not explain the increased incidence among Asian children.[29]

Although the systemic inflammatory process gradually subsides within 2 to 3 months after onset in most cases, subacute or chronic arteritis can persist for months to years in the most severely affected patients, and pathologic changes of severely affected arteries can persist over time.[30] Luminal myofibroblastic proliferation can occur in arteries damaged by KD and lead to progressive stenosis of the vessel, with the potential for myocardial ischemia and infarction.[30]

Clinical Manifestations

The clinical course of KD can be divided into three phases. The acute phase usually lasts 7 to 14 days and manifests as fever, conjunctival injection without exudate; oral and pharyngeal redness, strawberry tongue and red, cracked, bleeding lips without oral ulcerations; swelling and erythema of the hands and feet; polymorphous rash; and cervical lymphadenopathy. These findings form the basis for the classic diagnostic criteria (Box 199.1), which requires fever plus four of five of the clinical features of illness.

Box 199.1

Diagnostic Criteria for Kawasaki Disease

Fever persisting for at least 5 days[a]

Four of the following clinical findings:

- Bilateral conjunctival injection
- Erythema of the oropharynx, with fissuring of the lips and strawberry tongue
- Erythema and swelling of the hands and feet, with subsequent periungual desquamation
- Erythematous rash

- Cervical lymph node enlargement to >1.5 cm in diameter

Illness not explained by other known disease process

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[a]The diagnosis of Kawasaki disease may be made by experienced physicians before the fifth day of fever.

Young children are very irritable and often refuse to walk or bear weight during the acute phase. Marked tachycardia resulting from myocarditis is common. Although cervical lymphadenopathy usually is the least common of the five clinical features of KD, it can be the predominant symptom. Enlarged cervical lymph nodes in KD usually are tender to palpation, occasionally erythematous, and typically unilateral, with a diameter of greater than 2 cm. These patients often are treated for bacterial adenitis without success and referred with that diagnosis; they can also have retropharyngeal nonsuppurative phlegmon.[31,32]

The rash in KD can be maculopapular, scarlatiniform, or erythema multiforme–like (Fig. 199.1). Vesicles and bullae do not occur. Perineal accentuation of the rash occurs in two thirds of patients.[33] Perineal involvement commonly is misdiagnosed as candidal diaper dermatitis; it also occurs in toilet-trained children. Associated features of the illness are described in Table 199.1.[3,34–49]

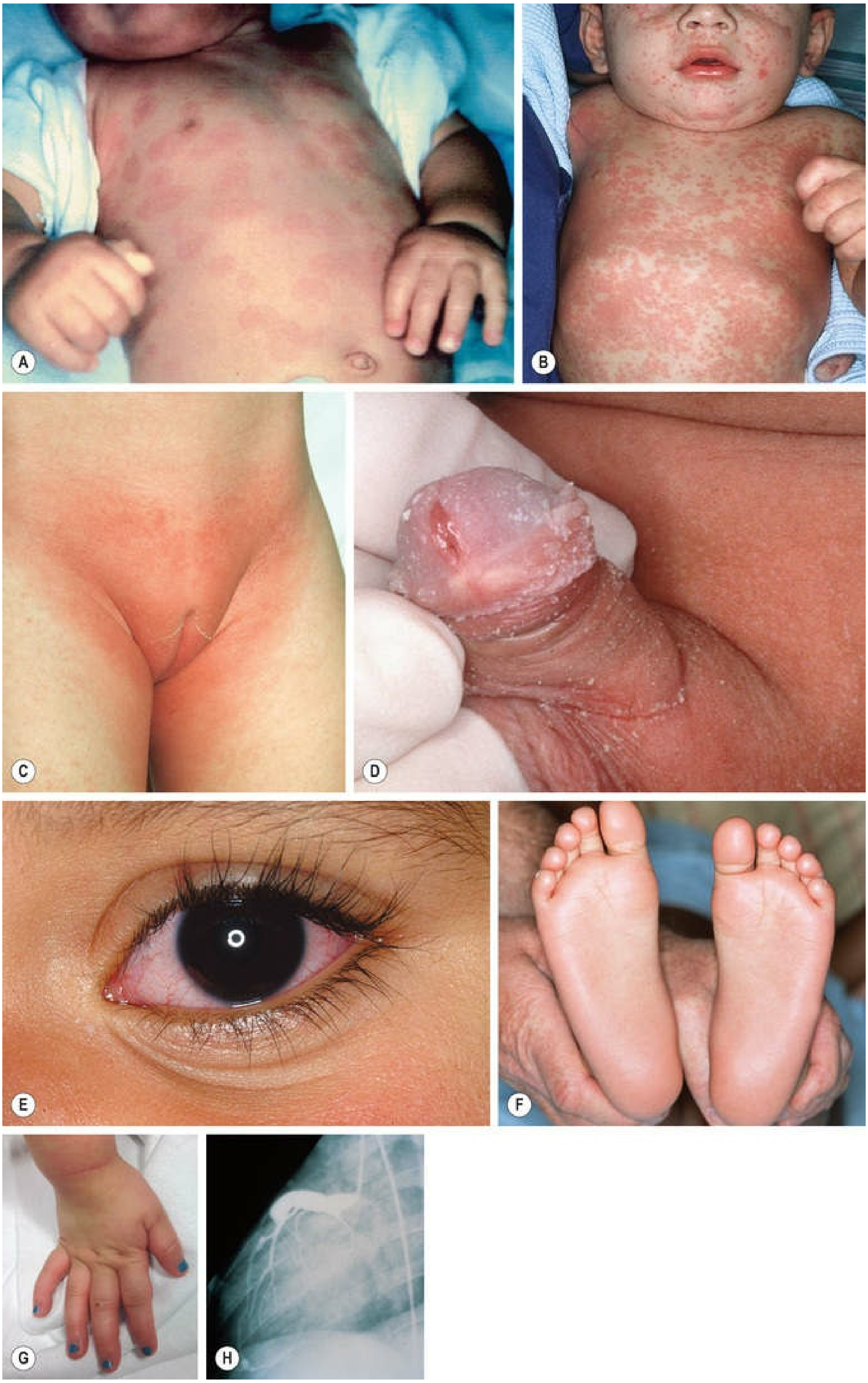

FIGURE 199.1 Clinical manifestations of Kawasaki

disease. (A) Erythema multiforme-like rash and swollen hands. (B) Morbilliform rash. (C) Erythematous, desquamating perineal rash. (D) Desquamating periurethral rash. (E) Bulbar conjunctival erythema. (F) Erythema and edema of feet (i.e., loss of plantar creases). (G) Glove-like distribution of erythema of the hand. (H) Saccular aneurysm of the right coronary artery on day 8 of fever in 6-month-old boy. (A, Courtesy of A.H. Rowley; B–F, courtesy of J.H. Brien ©; G and H, courtesy of S.S. Long.)

TABLE 199.1

Features of Kawasaki Disease

Feature	Incidence	References
CARDIOVASCULAR		
Coronary artery aneurysms	25% untreated; 4% IGIV treated	3, 34
Other systemic artery aneurysms	2%	35
Myocarditis	>50%	36
Pericarditis	25%	36
Valvular disease	1%	36
NEUROLOGIC		
Extreme irritability	>90% in infants; less common in older children	37
Aseptic meningitis	40%	38
Facial palsy	<1%	39
GASTROINTESTINAL		
Hepatitis	50%	40
Jaundice	<10%	40
Pancreatitis	Unknown; probably common but usually mild	41, 42
Gallbladder hydrops	10%	37
Diarrhea	25–50%	37
GENITOURINARY		
Urethritis	50–90%	43
Hydrocele	25–50%	44
MUSCULOSKELETAL		
Arthralgia and arthritis	33% untreated; 8% IGIV treated	45
RESPIRATORY		
Preceding respiratory illness	50–90%	13
Pneumonitis, radiologic but not clinical evidence	15%	46
OTHER FINDINGS		
Anterior uveitis	25–50%	47
Erythema and induration at BCG inoculation site	50%	48
Peripheral gangrene	<1%	49

BCG, bacille Calmette-Guérin; IGIV, immune globulin intravenous.

Rarely, patients with KD can be in shock at presentation, often resulting in a delayed diagnosis. They can have thrombocytopenia, are more likely to have refractory KD, and have an increased risk of coronary artery abnormalities.[50–52]

In the subacute phase, fever, rash, and lymphadenopathy resolve, but conjunctival injection and irritability often persist. Periungual desquamation of the fingers and toes, arthritis, and thrombocytosis are characteristic of the subacute phase, which occurs from about day 10 to day 25 after the onset of fever. Beau lines (i.e., transverse grooves in the nails) can be observed in the late subacute stage. Temporary hair loss can occur.

The convalescent phase begins when all clinical signs of illness have resolved and continues until the erythrocyte sedimentation rate (ESR) becomes normal, usually 6 to 8 weeks after the onset of illness. Prolonged fever and recurrence of fever after apparent resolution are associated with an increased risk of coronary artery sequelae.[53] Other risk factors include age younger than 1 year, duration of fever for more than 16 days, recurrence of fever after an afebrile period of at least 48 hours, anemia, thrombocytopenia, and hypoalbuminemia.[53–55]

Incomplete KD is a challenge. Incomplete KD (preferred to the term *atypical KD*) refers to the lack of full diagnostic criteria for KD, not atypical or extra clinical findings. Worldwide, young children (often infants) with KD can have fever and fewer than four clinical features of the illness. Unfortunately, infants are at higher risk than older children for coronary artery abnormalities.[56]

Patients with incomplete KD appear to have laboratory features similar to those of patients with classic presentations. If coronary artery dilation is detected on echocardiography (i.e., Z score for left anterior descending or right coronary artery ≥2.5), the patient should be treated for KD. An algorithm published by the American Heart Association incorporates clinical features, laboratory data, and echocardiographic findings to assist the clinician in decision making regarding diagnosis and treatment for suspected incomplete KD.[54]

Laboratory Findings and Diagnosis

Certain laboratory findings are characteristic, although none is diagnostic (Table 199.2).[34,37,38,40,43,45,54–56] Thrombocytosis occurs at a mean time of 2 weeks after onset and is therefore not useful in making a diagnosis in the acute stage, during which therapy should be instituted. IGIV therapy does not appear to prevent thrombocytosis.[54] The ESR usually is elevated markedly, but the ESR can be artifactually low in the acute phase in a subset of KD patients with consumption coagulopathy; the C-reactive protein level in these children is very high.[57] A persistently elevated ESR for 4 to 6 weeks after fever onset is characteristic of KD in IGIV-treated and untreated patients. A transient increase in the ESR can occur in IGIV-treated patients due to the effect of immune globulins on red blood cell sedimentation. After administering IGIV, the C-reactive protein level is a more useful assay for monitoring inflammation in a persistently febrile child.

TABLE 199.2

Characteristic Laboratory Findings in Kawasaki Disease

Finding	Incidence	Comment	References
Leukocytosis	All	≥15,000/mm^3 or left shift	3, 34
Anemia[a]	50–90%	Normochromic, normocytic	53, 54, 55
Hypoalbuminemia[a]	10–50%		54
Elevated acute phase reactants	>90%	ESR usually >40 mm/hr C-reactive protein[a] ≥3 mg/dL	3, 34
Sterile pyuria	50–90%	Can be intermittent	43
Proteinuria	<10%		37
Serum transaminase elevation[a]	37%	Mean serum ALT of 100 U/L	40
Serum bilirubin elevation	13%		40
Arthritis	33% untreated	Cell count >25,000/mm^3, predominantly neutrophils, in 80% of patients	45
	8% IGIV treated		
CSF pleocytosis	40%	Median cell count 20 cells/mm^3 with 90% neutrophils, 10% mononuclear cells; glucose and protein levels usually normal	38
Thrombocytosis	>90%	In subacute phase, 500,000 to 2,000,000/mm^3	34, 54

[a] Severity correlates with risk of coronary artery disease.

ALT, alanine aminotransferase; CSF, cerebrospinal fluid; ESR, erythrocyte sedimentation rate; IGIV, immune globulin intravenous.

Echocardiographic studies should be obtained at diagnosis, 1 to 2 weeks later, and 6 to 8 weeks after fever onset. Additional studies may be unnecessary if all three studies are normal. If a patient demonstrates abnormalities on any of the three echocardiograms, additional studies are necessary.

KD can be difficult to differentiate from other febrile illnesses of childhood (Box 199.2). Measles and group A streptococcal or staphylococcal infections most closely resemble KD. In uncomplicated measles, the white blood cell count and ESR usually are low; a measles IgM antibody test can confirm the diagnosis. It is sometimes difficult to differentiate acute infection due to group A *Streptococcus* from KD in a group A streptococcal carrier. Treatment with penicillin for 24 to 48 hours followed by clinical reassessment usually clarifies the diagnosis because patients with KD do not respond to antibiotic therapy. The finding of a concurrent respiratory viral infection should not exclude a diagnosis of KD because the incidence peaks during the winter months, when many respiratory viruses are circulating. Unilateral cervical lymphadenitis in KD is not suppurative.[32]

Box 199.2

Conditions That Share Clinical Features With Kawasaki Disease

Measles

Group A streptococcal infection (including scarlet fever)

Toxic shock syndrome

Stevens-Johnson syndrome

Drug reactions

Juvenile idiopathic arthritis

Adenovirus infection

Leptospirosis

Rocky Mountain spotted fever

Although some of the clinical features in KD are found in a variety of infectious and inflammatory diseases of childhood, certain clinical features strongly suggest KD as the diagnosis.[58]

Conjunctival injection in KD is primarily bulbar and usually without exudate. Lip redness and swelling can be severe enough to cause cracking and bleeding, and strawberry tongue is characteristic. Oral ulcerations and exudative pharyngitis are not features. Firm induration of the hands and feet with or without palmar and plantar erythema is distinctive, often is associated with refusal to walk or hold objects, and is rarely seen in other childhood febrile illnesses. Perineal accentuation of the rash without accentuation at other skin folds is common in KD but not in other disorders. Vesicles, bullae, petechiae, or purpura make KD unlikely.

Treatment

Current therapy for KD during the acute phase of illness is aimed at reducing clinical symptoms, reducing inflammation in the myocardium and in the coronary artery wall to prevent coronary aneurysm formation, and preventing thrombosis by inhibiting platelet aggregation. Discovery of the cause of KD will allow more specific treatment.

IGIV was first used in Japan to successfully treat KD.[59] The mechanism of action of IGIV in KD is unknown. Subsequent multicenter studies in the United States confirmed the efficacy of IGIV with aspirin for KD. IGIV given within the first 10 days of illness hastens resolution of fever and a decrease in levels of acute phase reactants. The prevalence of coronary artery abnormalities is about 20% among aspirin-treated patients but about 5% among those treated with IGIV and aspirin.[3,35] All KD patients should be treated as early as possible after diagnosis; it is not necessary to wait until the fifth day of fever in patients who clearly have the disease. Data regarding treatment after the 10th day of illness are lacking; however, patients who remain febrile or continue to have markedly elevated inflammatory markers are likely to benefit from IGIV even after the 10th day. For patients who receive IGIV but nonetheless develop coronary aneurysms, there is a higher rate of normalization of coronary artery diameter than for untreated patients.

The recommended dosage of IGIV is 2 g/kg, given as a single infusion over 10 to 12 hours.[35] Patients also should receive anti-inflammatory doses of aspirin (80 to 100 mg/kg/day), given orally in divided doses every 6 hours; high doses are given because of poor aspirin absorption and increased clearance in acute KD. The aspirin dose is reduced to 3 to 5 mg/kg/day for antithrombotic effects on the 14th day of illness or when the patient has been afebrile for 3 days. Low-dose aspirin therapy is discontinued 6 to 8 weeks after onset of disease if coronary arteries are normal by echocardiography and if the ESR is normal. Aspirin therapy can be interrupted if the patient develops an illness suspected to be varicella or influenza to reduce the risk of Reye syndrome. For patients at particularly high risk for myocardial infarction, the use of an alternative antiplatelet agent should be considered.

Most patients have a dramatic response to IGIV, but about 10% to 15% continue to be febrile 36 hours or longer after completing the IGIV infusion. A second 2-g/kg dose of IGIV appears to be effective in most of these patients,[60–62] although a controlled study of retreatment has not been performed. In patients who do not respond to two doses of IGIV, pulsed methylprednisolone therapy at 30 mg/kg/day for 3 days or a single dose of infliximab (i.e., monoclonal antibody to tumor necrosis factor-α) at 5 mg/kg has been associated with apparent clinical response.[63–66]

Patients who fail to respond to multiple therapies have been treated with calcineurin inhibitors such as cyclosporine to reduce T-lymphocyte activation.[67] The efficacy of various treatments for patients unresponsive to IGIV is uncertain because controlled trials have not been performed and the clinical features of acute KD are self-limited. Rarely, IGIV therapy can result in complications such as aseptic meningitis or hemolytic anemia.

Although corticosteroid therapy did not appear useful in the primary treatment of KD before the advent of IGIV therapy,[64,68,69] it was studied in combination with IGIV for primary therapy of selected high-risk patients. A trial of single-dose intravenous methylprednisolone with IGIV and aspirin for primary therapy of nonselected US children with acute KD showed no benefit in coronary outcomes or fever days.[70]

In contrast, a study of Japanese children considered to be at high risk because of a Kobayashi score of 5 or more showed a significant benefit for the addition of prednisolone to IGIV for primary therapy.[71] Prednisolone was given intravenously as 2 mg/kg/day for 5 days and then orally until the C-reactive protein level normalized, followed by tapering over the next 15 days.[71] Unfortunately, KD risk scoring systems have not proved sufficiently sensitive to allow identification of high-risk, multiethnic North American children, limiting the applicability of this regimen to non-Japanese populations.[72] A trial of IGIV plus adjunctive infliximab for primary therapy in nonselected US children did not show a clear benefit.[73]

For patients who develop persistent coronary artery abnormalities, long-term, low-dose aspirin therapy at 3 to 5 mg/kg/day is indicated. This therapy often is recommended for patients with coronary artery aneurysmal dilation that has resolved as determined by echocardiography. Studies show that regression of aneurysms occurs by thrombosis or luminal myofibroblastic proliferation; these arteries are not normal.[30,74–77] KD patients with large aneurysms may benefit from warfarin or low-dose heparin therapy. Occasionally, acute thrombolytic therapy is needed in patients with thrombosis of large aneurysms; the decisions should be made in consultation with a pediatric cardiologist.

Long-term management of coronary artery sequelae of KD has been summarized by the American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease.[54] Rarely, patients with KD require intervention such as transluminal coronary angioplasty, transluminal coronary rotational ablation, coronary atherectomy or stent implantation,[78] coronary artery bypass surgery,[79] or heart transplantation.[80] Long-term prognosis depends on the severity of coronary artery disease. Patients with giant or many large aneurysms are most likely to require multiple catheter interventions or bypass procedures, and long-term survival is likely to be shortened. Data on increased risk of atherosclerosis among KD patients during adulthood are lacking.

The routine administration of live, attenuated viral vaccines, such as measles, mumps, rubella, and varicella vaccines, should be delayed for 11 months after IGIV treatment for KD. Schedules for administration of other routine childhood vaccinations should not be interrupted. Inactivated injectable influenza vaccine is recommended annually for all children and is crucial for those receiving long-term aspirin therapy.

Special Considerations

After establishment of normative data for coronary artery diameter based on body surface area, it was reported that 30% of KD children have coronary artery dilation as established by echocardiogram at diagnosis in the first 10 days of illness.[81,82] The peak time to observe coronary artery aneurysms is in the second to third week after the onset of illness. The development of aneurysms after the sixth week of illness is rare. At 1 year after onset of KD, echocardiographic resolution of coronary artery luminal dilation is seen for 50% of patients. However, intracoronary ultrasonography demonstrates that these vessels have persistent abnormalities, such as luminal narrowing.[76,77]

Patients with giant coronary artery aneurysms, which historically were defined by an internal diameter of at least 8 mm but are more accurately defined by a coronary artery diameter Z score of ≥10, are at greatest risk for coronary thrombosis, stenosis, and myocardial infarction.[2,83] Patients with giant coronary artery aneurysms can sometimes develop aneurysms of the iliac, axillary, femoral, and renal arteries.

Prevention of KD is not possible until the cause of the disorder is identified.

Key Points

Diagnosis and Management of Kawasaki Disease

Epidemiology

- Most patients are 6 months to 5 years of age, but KD can occur in younger and older children.

- Highest attack rate is among Asian children; 1% of Japanese children develop KD by age 5.

- Epidemics have a geographic wave-like spread.

- KD probably is caused by a ubiquitous infectious agent that results in disease in a small subset of genetically predisposed children.

Clinical Features

- Multisystem inflammatory disorder

- Classic KD: fever for ≥5 days with four of the five other findings (see Box 199.1)

- Incomplete KD: prolonged fever with fewer than four of the five clinical findings, with compatible laboratory and echocardiographic findings and no other explanation for illness

- Most serious complication is coronary artery dilation with aneurysm formation.

Diagnosis

- Diagnosis of classic KD is based on clinical criteria.

- Diagnosis of incomplete KD is based on clinical, laboratory, and echocardiographic findings.

Treatment

- IGIV (2 g/kg) is given over 10–12 hr with aspirin (80–100 mg/kg/day divided every 6 hr).

- Aspirin is reduced to 3–5 mg/kg/day as a single daily dose when the patient has been afebrile for at least 3 days and is continued until acute phase reactants and echocardiogram are normal at 6–8 weeks after onset of fever or indefinitely if coronary artery abnormalities develop or persist.

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200

Chronic Fatigue Syndrome

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Chronic fatigue syndrome (CFS) manifests as profound, debilitating fatigue associated with subjective complaints and resulting in functional impairment. Symptoms begin abruptly and persist for years. In the 1980s, case clusters and associations with Epstein-Barr virus (EBV) infection heightened awareness of the condition and led to the use of terms such as *chronic mononucleosis* and *chronic EBV*.[1–5] These terms imply a causal relationship with EBV infection that has not been established. The term *myalgic encephalomyelitis* implies an unproven pathogenesis, and the term *chronic fatigue syndrome* may be stigmatizing. In 2015, the Institute of Medicine (IOM) recommended abandoning previous terminology in favor of *systemic exertion intolerance disease*.[6]

Skepticism about CFS as a distinct diagnosis has yielded to acceptance.[7] Clinicians usually have little difficulty suspecting the syndrome but may have great difficulty diagnosing by exclusion, sorting comorbidities, and guiding patients to recovery.

Case Definition

A case definition that was formulated by the Centers for Disease Control and Prevention (CDC) in 1994,[8] modified in 2003,[9] and validated in 2005[10] has been widely used in research. Alternative definitions—notably the 2003 Canadian Clinical Case Definition[11] and the 2011 International Consensus Criteria[12]—have been offered. In 2015, the IOM proposed new diagnostic criteria (Box 200.1) focused on core symptoms of the disease: impaired functioning, postexertional malaise, and unrefreshing sleep.[6]

Box 200.1

Proposed Diagnostic Criteria for Chronic Fatigue Syndrome, 2015[a]

Each of the following symptoms

- Substantial reduction or impairment in ability to engage in preillness levels of occupational, educational, social, or personal activities that persists for >6 months and is accompanied by fatigue[b]
- Postexertional malaise[c,d]
- Unrefreshing sleep[d,e]

And at least one of the following manifestations

- Cognitive impairment[d]
- Orthostatic intolerance[f]

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[a] The 2015 Institute of Medicine report[6] used the term *myalgic encephalomyelitis/chronic fatigue syndrome* but recommended renaming the syndrome *systemic exertion intolerance disease*.

[b] Fatigue is often profound and of new or definite onset (not lifelong); it is not the result of ongoing excessive exertion and not substantially alleviated by rest.

[c] Prolonged exacerbation of baseline symptoms occurs after physical, cognitive, or orthostatic stress (may be delayed relative to the trigger).

[d] The diagnosis should be questioned if these symptoms are not present at least one half of the time with moderate, substantial, or severe intensity.

[e] Polysomnography is not required for the diagnosis but may be indicated to screen for treatable sleep disorders; diagnosis of a primary sleep disorder does not rule out a diagnosis of chronic fatigue syndrome.

[f] Prolonged orthostatic testing (i.e., standing test or upright tilt test) is not required for diagnosis but may be indicated to diagnose conditions such as postural tachycardia syndrome, neurally mediated hypotension, or orthostatic hypotension

that would be amenable to therapy.

Modified from Institute of Medicine. Beyond myalgic encephalomyelitis/chronic fatigue syndrome: redefining an illness. Washington, DC, National Academies Press, 2015. http://www.nap.edu/openbook.php?record_id=19012.

Few adults with fatigue met the 1994 CDC case definition,[13–18] and diagnosing CFS was complicated by overlap with other unexplained syndromes and comorbid conditions.[8,9,11,19–23] Moreover, CFS in adults is a heterogeneous disorder, and distinct subgroups may exist.[10,24–27] Historical definitions of CFS were difficult to apply to children[28–32]; guidelines for pediatric diagnosis include those from the Royal College of Paediatrics and Child Health (2004),[33] the International Association for CFS/ME (2006),[34] the National Institute for Health and Care Excellence (2007),[35] and the International Consensus Panel (2011).[12] The 2015 IOM definition, which requires symptoms to be present for more than 6 months, is meant to apply to children; however, many pediatric experts do not wait that long to begin investigation.[11,28–30,35] Phenotypes in children are heterogeneous, and only a subset of children have adult-like CFS.[36]

Epidemiology

Separate studies in Wichita, Kansas, and Chicago, Illinois, estimated the prevalence of CFS to be about 200 to 400 cases per 100,000 adults.[37,38] In another study, Georgia residents were screened for *unwellness,* and standardized instruments were used to identify CFS cases[39]; the prevalence of CFS was 2.5% and did not vary by geographic region. CFS was less prevalent among men in metropolitan areas (0.4%) than in rural areas (2.9%), and the prevalence among women in metropolitan areas was 11 times higher than among men. There was no relationship with race, level of education, or income. Similar prevalence rates have been found in England[40] and Australia.[41]

Whereas upper middle class individuals appear to be overrepresented in clinics,[2–5,16,42–44] population-based studies show high rates in minority and lower socioeconomic groups.[37,38,45] To some extent, this can be explained by social strain, lack of social support, physical inactivity, anxiety, and depression.[46] Clusters of

CFS have been reported,[5,47,48] but there is no evidence of person-to-person transmission.

Fatigue is extremely common among adolescents[49–51] and is a common reason for referral to pediatric infectious diseases specialists.[52,53] Few children, however, meet historical case definitions of CFS,[49] and CFS-like illness appears to be rare in children younger than 12 years of age.[54,55] The Wichita study failed to identify any adolescents who met the 1994 CDC case definition, but CFS-like illness was seen at a rate of 338 cases per 100,000 adolescents.[56] The prevalence of CFS was estimated at 111 cases per 100,000 Dutch adolescents[57]; 45% of CFS patients reported a rate of school absence of more than 50% for the previous 6 months, highlighting CFS as a cause of extreme dysfunction and disability among teenagers. Some population-based studies show that girls are more commonly affected than boys,[31,54,55] and girls are overrepresented in clinic populations.[52,53,58,59–62]

Pathophysiology

Infection

Although CFS often follows a distinct infectious mononucleosis– or flu-like illness, there is no evidence that any single infectious agent causes CFS. Many agents have been investigated (Box 200.2)[1–5,16,47,63–140]; invariably, initial excitement that the cause of CFS was found has yielded to skepticism and ultimately to disappointment.

Box 200.2

Infectious Agents That Have Been Studied as a Cause of Chronic Fatigue Syndrome[a]

Herpesviruses

Epstein-Barr virus[1–5,16,47,63–71]

Cytomegalovirus[5,16,66,67,69,71,76,77]

Herpes simplex virus[66,69]

Human herpesvirus 6[16,44,47,52,66,67,69,71–75,78,79–81]

Human herpesvirus 7[67,69,72–75]

Human herpesvirus 8[69,78]

Varicella-zoster virus[8,69]

Other Viruses

Adenovirus[71]

Arboviruses[8]

BK virus[69]

Borna disease virus[86,87,88]

Enteroviruses[66,71,89–102]

GB virus-C[109]

Hepatitis B virus (or vaccine)[66,110]

Hepatitis C virus[66,112]

Inoue–Melnick virus[124]

JC virus[69]

Measles virus[66]

Parvovirus[66,69,71,82–85]

Respiratory viruses[66]

Retroviruses (including human endogenous retroviruses)[47,66,75,103–108]

Rubella[66]

Stealth virus[111]

Xenotropic murine leukemia virus-related virus[113–123]

Bacteria, Fungi, and Parasites

Bartonella henselae[66]

Borrelia burgdorferi[71,126,127]

Candida[66,133–136]

Chlamydia[66,137]

Ehrlichia[66]

Gram-negative enteric bacteria[139,140]

Gram-positive enteric bacteria[125]

Mycoplasma[128–132]

Rickettsia[66]

Toxoplasma[16]

16S rDNA sequences[138]

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[a] None of these agents is demonstrably causal in the pathogenesis of chronic fatigue syndrome, although infection with some (e.g., Epstein-Barr virus) can trigger the disease.

A good example was the purported association between CFS and infection with xenotropic murine leukemia virus–related virus (XMRV) suggested in papers (subsequently retracted) from different laboratories in 2009[113] and 2010.[114] XMRV is a retrovirus originally thought to be associated with human prostate cancer, but it was later determined to have arisen from the recombination of two murine proviruses during passage of prostate cancer cells through mice.[115] Many laboratories were unable to replicate the initial findings.[116–121] A multicenter, blinded study of 147 geographically diverse CFS patients and 146 healthy controls found no evidence of XMRV DNA or DNA of the related polytropic murine leukemia virus in any subject.[122]

In another study, blinded specimens from patients previously reported to have XMRV were sent along with controls to nine different laboratories; only two laboratories reported positive results, replicate samples were discordant, and no differences were found between patients and controls.[123] Findings in the earlier studies likely resulted from contamination.

The complex relationship between infectious agents and CFS is illustrated by EBV. EBV-induced infectious mononucleosis often results in fatigue for more than 6 months.[141,142] All EBV infections are chronic in that the virus establishes lifelong latency. Initial serologic findings suggested that CFS patients had continued active EBV infection,[1–4] but subsequent studies showed inconsistencies in serologic results, nonspecifically elevated antibodies to several viruses, and failure of virus detection to identify cases.[5,16,47,64–70] Patients with true chronic active EBV infection have end-organ involvement and low levels of antibody to EBV nuclear antigen,[143] findings that are not seen in CFS.

A distinct, disabling, persistent fatigue syndrome can follow a variety of acute infections.[144] In the case of EBV, postinfectious fatigue syndrome (PIFS) is not associated with increased viral load or lytic replication.[70] Whether associated with EBV or other infectious agents, PIFS is not associated with increased cytokine production, a surprising finding given the overlap between the physiologic effects of cytokines and symptoms of CFS.[145,146] Some CFS patients may have PIFS triggered by EBV, but the condition is not specifically driven by the virus. Poor physical functioning early in the course of infectious mononucleosis predicts prolonged fatigue afterward, suggesting that the acute illness leads to deconditioning, which leads to perpetuation of symptoms.[147] Likewise, the severity of illness is linked to the risk of developing CFS.[148]

Immunology

Patients with CFS do not manifest immunodeficiency in the classic sense, with recurrent or opportunistic infections. However, symptoms of the illness suggest viral infection, and reactivation of latent viruses suggests relaxation of immunologic surveillance. Allergy symptoms are common and autoantibodies have been reported.[149,150]

There are many controlled studies of the immunology of CFS.[a] The most consistent finding is decreased NK cell function despite normal numbers of NK cells.[b] B-lymphocyte number, B-lymphocyte function, and immunoglobulin levels usually are normal.[151–153,155–161,163] Inconsistent results have been seen in T-lymphocyte number and function,[16,151–165] mononuclear cell activation,[c] and circulating cytokines, cytokine production, soluble receptors, and other inflammatory or antiviral markers.[d] Any proposed connection between laboratory abnormalities and clinical manifestations is confounded by interactions among psychological well-being, the neuroendocrine system, and immune function.

Cardiovascular Physiology

Some studies suggest an etiologic role for orthostatic intolerance in CFS,[193–196] whereas others provide less convincing evidence for altered autonomic function.[197,198] Many children and adolescents with CFS have orthostatic tachycardia associated with hypotension, acrocyanosis, and peripheral edema.[199,200] Adolescents who develop CFS after infectious mononucleosis have abnormal exercise tolerance and more autonomic symptoms than recovered controls, suggesting they were predisposed to autonomic dysfunction before the illness or that the illness was particularly severe and led to autonomic dysfunction.[201,202] Moreover, improvement in symptoms over time correlates with improved measures of autonomic cardiovascular control.[203] In a matched case-control study, 50% of 26 children and adolescents with CFS and 20% of controls had orthostatic intolerance demonstrated on tilt-table test.[204] Additional evidence of autonomic dysfunction comes from the demonstration of abnormal catecholaminergic-dependent thermoregulatory responses.[205]

In the Wichita surveillance study, tilt-table testing caused orthostatic instability in 30% of adult CFS subjects and 48% of nonfatigued controls.[206] These results were particularly powerful because subjects were drawn from the general population rather than tertiary center clinics. It seems unlikely that preexisting orthostatic intolerance causes CFS; rather, the inciting event and ensuing decrease in activity may lead to deconditioning and orthostatic intolerance that is detectable in the laboratory.[204]

Early studies pointed to connective tissue disorders, which can be associated with orthostatic intolerance, in children with CFS.[207,208] A later study, however, failed to demonstrate constitutional laxity or differences in collagen metabolism in patients.[209]

Neuroendocrine and Metabolic Function

Some studies of adults with CFS suggest mild central adrenal insufficiency.[210–212] Although modest improvements have been seen with the use of low-dose hydrocortisone,[213,214] adrenal suppression outweighs the potential benefits.[213]

There may be connections among hypothalamic-pituitary axis (HPA) abnormalities, orthostatic intolerance, and immune dysfunction. It is possible that an HPA disturbance evolves over time and is related to factors such as inactivity, sleep disturbance, psychiatric comorbidity, and stress.[215] One study showed decreased salivary cortisol awakening responses in a population-based sample of CFS subjects who had experienced childhood trauma, suggesting that an HPA disturbance in CFS may have its origins before symptoms manifest.[216]

Metabolic defects in skeletal muscle also have been proposed.[217,218] At least one paper demonstrated increased oxidative stress in pediatric CFS patients.[180]

Sleep and Neurocognitive Function

Unrefreshing sleep is common among CFS patients.[219] Patients also have neurocognitive impairment, including problems with memory, difficulty expressing thoughts, paying attention and understanding, slowness of thought, and absent-mindedness.[219]

Parallels have been drawn between CFS and postpolio syndrome.[220,221] Of particular interest are reports of patients with CFS in whom punctate subcortical white matter hyperintensities were visualized on magnetic resonance imaging (MRI).[44,222,223] Some functional studies demonstrate alterations in regional cerebral blood flow and metabolic activity,[224–228] but others do not.[228] Although the significance of these findings is unclear, there is evidence of neuropsychological impairment in patients with

CFS.[229,231] Other evidence for neurobiologic alterations includes sleep disturbance[231–234] and the possibility of a central mechanism for muscle fatiguability.[235,236]

Genomics

Early studies of CFS patients suggested differential expression of genes involved in immunologic, neuronal, and mitochondrial function[237,238] and dramatic differences in exercise-responsive genes.[239] The most extensive study published examined the expression of 39,174 genes in 55 CFS patients and 75 controls[240]; 85 genes were upregulated, and 3 genes were downregulated. Seven subtypes were seen based on the pattern of gene expression, and they were associated with different clinical phenotypes.[241] In a follow-up study that included 62 additional CFS patients, there was evidence of subtype-specific relationships for EBV and enterovirus infection, consistent with the idea that these viruses can trigger CFS.[242]

Heterogeneity in CFS cohorts has made interpretation of genomic studies difficult. In an attempt to study gene expression in a more homogenous group, investigators analyzed the peripheral blood transcriptome in patients with postinfectious fatigue, comparing results within subjects (i.e., early illness vs. late recovery), between cohorts (i.e., various infectious triggers), and with controls who did not develop prolonged fatigue.[243] No genes were consistently associated with illness.

Psychology

In a population-based study, 89% of adults with CFS had at least one lifetime psychiatric diagnosis.[244] Some studies suggest that psychiatric illness is more likely to precede the onset of CFS than to follow it,[245] and a prospective birth cohort study in the United Kingdom highlighted the importance of adulthood psychopathology—and childhood adversity in a few people—in the cause of CFS.[246] Other studies show that the premorbid incidence of psychological disturbance in adults with CFS is similar to that in general medical populations[247] and that the development of prolonged fatigue is not related to initial levels of psychological stress.[248] Premorbid psychiatric disorders and psychological distress do not seem to predict prolonged fatigue after infectious mononucleosis.[249–251]

Pediatric patients with CFS have a high prevalence of anxiety and mood symptoms. As many as three fourths meet diagnostic criteria for affective disorder.[53] Longitudinal studies suggest that depression and anxiety may serve as risk factors for the development of chronic fatigue[49–51] and may predict fatigue severity.[252] Youths with CFS have higher levels of reported depression than healthy peers and those with other medical conditions.[53,58,253] Although adolescents with CFS do not report major problems with their social skills and self-esteem, they do experience diminished competence in domains such as athletics, recreational activities, and romantic involvement.[254] Adolescent patients also have difficulty identifying, labeling, and expressing affective states (i.e., alexithymia), which can lead to mood difficulties.[255]

Mood symptoms of children and adolescents with CFS are qualitatively different from those of children with clinical depression,[256] with less suicidal ideation and severe dysphoria.[257] This suggests that depressive symptoms may be a response to prolonged fatigue, associated physical symptoms, and declines in academic performance and social participation.[253] The mood problems reported by adolescents with CFS may be more accurately described as anhedonia (i.e., experiencing decreased enjoyment from previously enjoyable experiences) rather than a more globally negative mood or self-image.[53] Gene expression profiles of CFS patients are markedly different from those with endogenous depression, supporting the idea that CFS does not equal depression.[242]

Some studies show that adolescent CFS patients endorse palliative coping strategies (i.e., avoidance, distraction, escape, activity reduction, and resting) as the primary approach to symptom management.[258] School absenteeism is disproportionately higher among adolescent CFS patients than among peers with other chronic illnesses.[259,260] Patients who see a relationship between psychological factors and illness manifestation and recovery and whose parents encourage participation in activities and have higher expectations about performance have more favorable outcomes.[261]

However, parents of children with CFS tend to overestimate their child's cognitive skills, suggesting that parental expectations also may create a stressful dynamic that affects symptom maintenance and functional disability.[262]

A subset of pediatric patients with CFS exhibits qualities suggesting an eating disorder.[263] Being underweight at the time of diagnosis may be a predictor of poor outcome.[264]

Box 200.3 summarizes the most consistent findings of psychological studies of pediatric CFS.[53,58,252–267] Physicians should resist the temptation to align themselves with the organic or the psychological camp and should understand that transcendence of such mind-body dualism is crucial to effective treatment.

Box 200.3

Major Psychological Findings in Children and Adolescents With Chronic Fatigue Syndrome

Depression[a]

Somatization

Impairment in social activities

Reduced self-esteem and social competence

Anxiety

Alexithymia[b]

Anhedonia[c]

Disordered eating

Palliative coping strategies

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[a] Depressive symptoms are less severe than in patients with endogenous depressive illness.

[b] Difficulty identifying, labeling, and expressing affective states.

[c] Decreased enjoyment from previously enjoyable experiences.

Data from references 53, 58, 252–267.

Pathogenesis

CFS is probably not caused by a unique infectious agent but instead is the final common pathway of a variety of insults, which cause a cascade of pathologic events in genetically and psychologically susceptible hosts. Associated immune dysregulation may result in inflammation and epiphenomena such as reactivation of latent viruses, all of which may contribute to fatigue and associated symptoms[268]; deconditioning sustains and magnifies the problem.

The PIFS model suggests that symptoms can be triggered by an acute infection and perpetuated in the absence of a sustained systemic inflammatory response.[144,145] Support for this model comes from the finding of gene expression pattern subtypes that are associated with infection.[241,242] The severity of the acute illness predicts PIFS, which follows relatively severe infectious syndromes such as infectious mononucleosis,[144] Lyme disease,[269] dengue,[270] viral meningitis,[271] Ross River virus infection,[144] and Q fever[144] but not minor upper respiratory infections.[272]

CFS is not strictly a psychological disorder; rather, patients may enter a cycle of attribution and avoidant behaviors after an acute illness associated with fatigue.[273] They attribute their symptoms to an external agent ("my virus") and retreat from an active lifestyle. Self-esteem is preserved because the cause is perceived to be external and beyond control. Vulnerability genes, early life experiences, and comorbid conditions may play a role in magnifying stress responses and symptoms.[192] Early childhood trauma is associated with a sixfold increased risk of CFS with neuroendocrine dysfunction, suggesting that in some patients, CFS is a disorder of adaptation promoted by early environmental insults.[216]

Avoidant behavior further reduces tolerance for physical activity, and re-exposure to activity elicits further symptoms. Intercurrent illnesses perpetuate the cycle of symptoms, attribution, avoidance, fatigue, and withdrawal. Children and adults with CFS maintain strong convictions that the fatigue is physiologic, rejecting psychological explanations.[153,273] Beliefs about medical illness correlate with functional impairment.[274–277]

Clinical Manifestations and Evaluation

The sentinel complaint is profound, debilitating, pervasive fatigue that dramatically interferes with normal activity. It begins suddenly and stands in marked contrast to the patient's previous well-being. Patients may complain that they “never recovered from that virus.” Children experience disruption in school attendance and extracurricular activities.[57,230,278]

Aside from the core symptoms of fatigue, postexertional malaise, unrefreshing sleep, cognitive impairment, and orthostatic intolerance, patients may complain of myalgia, arthralgia, feverishness (but seldom documented fever), headache, muscle weakness, sore throat, abdominal pain, lymph node enlargement or pain, dizziness, and nausea. Symptoms manifest to a pathologic degree and are continuous, but objective confirmation is often difficult.

The typical teenage patient is previously energetic, athletic, high achieving, and female. She is from an upper middle class suburban family, has been affected for many months, and has had exacerbations and remissions. Significant social, family, or interpersonal changes often predate the onset of illness. There may be a close relative with CFS. Some patients participate in usual activities but complain of exhaustion afterward, whereas others essentially are bedridden. Some patients are overcome by worry, distress, and frustration, but others are seemingly indifferent.

Outcome

The overall prognosis for adult patients is guarded.[274,279] Among adolescents, fatigue is a relatively stable complaint.[49,50] Most case series document a favorable prognosis (Table 200.1),[52,53,58–62,203,280,281] with rates of improvement ranging from 53% to 100% over a period of several years.

TABLE 200.1

Selected Case Series of Pediatric Patients With Chronic Fatigue[a]

Feature	Study							
	Marshall[52]	Smith[58]	Feder[59]	Carter[53]	Krilov[60]	Bell[61]	Gill[62]	va

	Marshall[52]	**Smith**[58]	**Feder**[59]	**Carter**[53]	**Krilov**[60]	**Bell**[61]	**Gill**[62]	**G**
Location of cohort	Philadelphia, PA	Seattle, WA	Farmington, CT	Louisville, KY	Long Island, NY	Lyndonville, NY	Sydney, Australia	U N
Years of study	1986–1988	1991	1986–1990	1990–1992	1989–1994	1984–2000	1993–2001	2
Number of patients	23 (14 girls)	15 (9 girls)	48 (35 girls)	20 (13 girls)	58 (41 girls)	35 (24 girls)	49 (33 girls)	5
Age (yr)	4–17	13–17	7–21	8–19	7–21	5–18	14[b]	1
Follow-up (years)[c]	1.4–3.3	1.1–2.7	2–6	1.5[d]	1–4	13[e]	4.1[b,e]	2.
Improved (%)[c]	76	53	94	100	95	80[e]	56[e]	5

[a] Not all patients in each study met the 1994 US Centers for Disease Control and Prevention (CDC) case definition of chronic fatigue syndrome.

[b] Mean.

[c] Follow-up data were not available for every subject in each study.

[d] Median.

[e] Patients meeting the Centers for Disease Control and Prevention (CDC) case definition.

Management

The patient's conviction that “something is wrong” should not be dismissed, even in the face of normal physical findings and laboratory test results. However, the physician should not endorse unfounded pathogenic theories because further psychological investment in such theories can increase the patient's helplessness, frustration, and isolation.

Medical Evaluation

The initial history, physical examination, and laboratory evaluation focus on eliciting core features and discovering other possible causes for the patient's symptoms. A useful guideline for eliciting the core features of CFS is given in Table 200.2,[6] and clues to alternative diagnoses that can manifest with fatigue are listed in Box 200.4.[35,282] Suggested laboratory testing and potential alternative diagnoses are given in Box 200.5.[8,33,35] Although EBV serology has no diagnostic value in CFS, some children referred for fatigue are commercial testing packages that include, for example, immunophenotyping is unwarranted.[8]

TABLE 200.2

Eliciting Symptoms of Chronic Fatigue Syndrome in Children

Clinical Manifestation[a]	Questions to Ask	What Patients May Report
Fatigue	How fatigued are you? Does it help to rest, lie down, find a quiet place, or avoid exercise?	Flu-like fatigue and exhaustion I'm "wired but tired" (exhausted but unable to relax). I feel like a battery that is never able to recharge. Thinking takes a lot more work than it used to. My arms, legs, and body feel heavy and harder to move.
Substantial decrease or impairment in function	How much has the illness affected your ability to work, attend school, and take care of chores? What are you able to do now and how does that compare with before you became ill? Are you able to participate in extracurricular activities or sports?	Severe limitation in personal management Decline in grades or loss of job Predominantly homebound Decreased social interaction and increased isolation
Postexertional malaise	What happens after you engage in normal physical or mental exertion? How long before you feel bad? How long before you recover? What happens if you go beyond your limits? Are there activities you avoid because of your illness?	After exertion I "crash," "relapse," or "collapse." I'm mentally tired after the slightest effort. I'm physically drained or sick after mild activity. The more demanding or prolonged the activity, the more severe and prolonged the payback.
Unrefreshing sleep	Do you have any problems getting to sleep or staying asleep? How do you feel after you've slept? Do you need too much sleep? Do you nap more than other people?	I feel like I never sleep. I cannot fall asleep or stay asleep. I don't feel good after a night's sleep.
Cognitive impairment	Do you have problems driving, watching a movie, reading, completing tasks under time constraints, or following a conversation? How is your performance at school or work compared with before you became ill? Are you having problems thinking?	I feel like I have "brain fog." I'm often confused or disoriented. It's hard to concentrate and focus. I cannot process information or find the right words. I have trouble with multitasking and decision making. I've become absent-minded and forgetful.
Orthostatic intolerance	How do you feel when you've been standing still for more than 1 or 2 minutes? How do you feel when you stand	LightheadednessDizzinessSpatial disorientationFaintingFeeling dizzy, lightheaded, or unwell when sitting up or standing still for a long period of time

	up rapidly after sitting for a long time? How long can you stand still (e.g., waiting for the school bus or taking a hot shower) before feeling ill? Are your symptoms worse in hot weather? Do you study in a reclining or lying-down position? Do you prefer to sit with knees to your chest or with your legs under you?	

[a] It may be helpful for patients to keep a diary to document symptoms and activities. In addition to the listed symptoms, patients may complain of pain, describing their muscles as "constantly burning" or the head as "ready to explode." Many report a triggering infection from which they never fully recovered, and some may report more or less susceptibility to infection.

Modified from Institute of Medicine. Beyond myalgic encephalomyelitis/chronic fatigue syndrome: redefining an illness. Washington, DC, National Academies Press, 2015. http://www.nap.edu/openbook.php?record_id=19012.

Box 200.4

Clues to Alternative Causes of Fatigue

Focal neurologic abnormalities

Signs and symptoms of inflammatory arthritis or connective tissue disease

Signs and symptoms of cardiorespiratory disease

Significant weight loss

Sleep apnea

Clinically significant lymphadenopathy

Growth failure

Abnormal pubertal development

Signs of an eating disorder or major psychiatric morbidity

Modified from National Institute for Health and Care Excellence. Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy): diagnosis and management. Clinical guideline CG53. 2007. http://www.nice.org.uk/guidance/CG53 and Werker CL, Nijhof SL, van de Putte EM. Clinical practice: chronic fatigue syndrome. Eur J Pediatr

Nijhof SL, van de Putte EM. Clinical practice: chronic fatigue syndrome. Eur J Pediatr 2013;172:1293–1298.

Box 200.5

Medical Laboratory Evaluation for Children With Persistent Fatigue

Tests	Primary and Alternative Diagnoses Screened For
ROUTINELY PERFORMED TESTS	
Complete blood count	Anemia, hematologic malignancy
Comprehensive metabolic panel	Electrolyte disturbance, diabetes, occult hepatopathy, renal insufficiency, eating disorder, adrenal insufficiency
Urinalysis	Chronic urinary tract infection, nephritis, nephrosis, diabetes
Thyroid-stimulating hormone and free thyroxine	Hypothyroidism
Erythrocyte sedimentation rate and C-reactive protein	Chronic infection, malignancy, autoinflammatory or rheumatologic disorders
IgA anti-endomysial antibody or IgA anti–tissue transglutaminase antibody	Gluten-sensitive enteropathy
Creatine kinase	Myopathy, myositis
Serum ferritin	Iron deficiency anemia
Epstein-Barr virus serology panel	Infectious mononucleosis[a]
OTHER TESTS (INDICATIONS)	
Serum cobalamin and folate concentration (macrocytosis)	Vitamin B_{12} or folic acid deficiency
Brucella and *Borrelia* serology (exposure history)	Chronic bacterial infection
HIV antigen/antibody test (risk factors, lymphadenopathy)	HIV infection
Hepatitis B virus and hepatitis C virus serology or nucleic acid test (risk factors, transaminase elevation)	Chronic viral hepatitis
Epstein-Barr virus, cytomegalovirus, and *Toxoplasma gondii* serology (unexplained fever, lymphadenopathy)	Reactivation of latent infection
Antinuclear antibody, rheumatoid factor, autoantibody panel (prominent joint complaints, acute phase reaction)	Rheumatologic disease
Serum immunoglobulins, total hemolytic complement, specific antibody (recurrent infections)	Primary immune deficiency
Toxicology (clinical suspicion)	Substance abuse
Cortisol levels (weakness, salt craving, hyperpigmentation)	Addison disease
TESTS NOT ROUTINELY PERFORMED	
Auditory brainstem responses	—
Electrodermal conductivity	—
Immunophenotyping	—

[a] Prolonged symptoms after acute Epstein-Barr virus–induced infectious

to the viral capsid antigen and IgG antibodies to the nuclear antigen can help to determine the time of onset and immunologic resolution of infection.

HIV, human immunodeficiency virus infection; Ig, immunoglobulin.

Modified from Fukuda K, Straus SE, Hickie I, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. Ann Intern Med 1994;121:953–959; Royal College of Paediatrics and Child Health. Evidence based guideline for the management of CFS/ME (chronic fatigue syndrome/myalgic encephalopathy) in children and young people. 2004. http://www.rcpch.ac.uk/system/files/protected/page/RCPCH%20CFS.pdf; and National Institute for Health and Care Excellence. Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy): diagnosis and management. Clinical guideline CG53. 2007. http://www.nice.org.uk/guidance/CG53.

Quantification of symptoms (e.g., duration of illness, hours spent sleeping per day, changes in grades, weeks of school missed, time spent in social, sporting, or recreational activities) provides useful measurements for baseline assessment and follow-up. Documentation of illnesses or exposures preceding the onset of fatigue, provocative and palliative factors, occurrence of CFS in family members, and recent major psychosocial changes is sought. The patient's experience with healthcare providers and beliefs about diagnosis are elicited. The evaluation process helps solidify the doctor-patient relationship, assures the patient that the illness is being taken seriously, and protects the patient from unnecessary procedures.

For some patients, labeling the illness as CFS provides a sense of relief from diagnostic confusion. For others, adopting the CFS label leads to further withdrawal by focusing on illness rather than on rehabilitation.

Psychological Evaluation

Evaluation for mood and anxiety symptoms and screening for disordered eating is important, and data should be obtained from the child, parents, siblings, and teachers. A comprehensive psychological evaluation is warranted, including measures of cognitive, executive, and neuropsychological function; depression and anxiety; somatoform disorder; and family dynamics. Physicians should emphasize that any chronic condition can have psychological concomitants, and psychological services should be an integral part of assessment and treatment programs.

Therapy

Medical treatments that have been subjected to randomized or controlled clinical trials, or both, are listed in Box 200.6.[283–328] These studies have shown inconsistent results, and no medical treatment is specifically indicated for CFS. Drugs targeted at comorbidities, however, may be useful, including antidepressants for patients with depressive illness and sleep aids for patients with profound sleep disturbance. A host of unconventional therapies have been advocated for CFS, most of which have no theoretical basis for utility.

Box 200.6

Trials of Medical Therapies for Chronic Fatigue Syndrome

IMMUNOLOGIC AGENTS	
α-Interferon[283,284]	Rintatolimod (poly[I]-poly[C12U])[285,286]
BioBran MGN-3[287]	Rituximab[288]
Immunoglobulin[289–292]	Staphylococcus toxoid[293,294]
Inosine pranobex[295]	Terfenadine[296]
ANTIVIRALS	
Acyclovir[297]	Valganciclovir[298]
Gancyclovir[299]	
ANTI-INFLAMMATORIES	
Fludrocortisone[300,301]	Hydrocortisone and fludrocortisone[302]
Hydrocortisone[213,214,303]	Intranasal flunisolide[304]
PSYCHOTROPIC AND CENTRAL NERVOUS SYSTEM AGENTS	
Dexamphetamine[305]	Moclobemide[306]
Fluoxetine[307]	Phenelzine[308]
Galantamine[309,310]	Selegiline[311]
Methylphenidate[312]	
HORMONES	
Growth hormone[313]	Melatonin[314]
METABOLIC[a] AND AUTONOMIC AGENTS	
Acclydine and amino acids[315]	Liver extract[316]
Carnitine[317]	Magnesium[318]
Clonidine[71,319]	Nicotinamide adenine dinucleotide[320,321]
Essential fatty acids[322,323]	Sulbutiamine[324]
General nutritional supplements[325–327]	

[a] Includes over-the-counter nutritional supplements.

Modified from Chambers D, Bagnall A-M, Hempel, et al. Interventions for the treatment, management and rehabilitation of patients with chronic fatigue syndrome/myalgic encephalomyelitis: an updated systematic review. J R Soc Med 2006;99:506–520.

The emerging standard of care for CFS includes graded exercise programs and cognitive-behavioral therapy (CBT).[329,330] CBT is

The emerging standard of care for CFS includes graded exercise programs and cognitive-behavioral therapy (CBT).[329,330] CBT is directed at modifying maladaptive thinking and attributional patterns to enhance feelings of self-efficacy and decrease activity avoidance. Benefit has been demonstrated in adult and pediatric patients.[273,331–334] In a novel approach, Dutch investigators randomized adolescent CFS patients to an internet-based CBT program or standard care; after 6 months, improvement was seen in full school attendance (75% vs. 16%), absence of severe fatigue (85% vs. 27%), and normal physical functioning (78% vs. 20%).[335] The dramatic success of this intervention was in part attributed to the fact that patients and parents were involved, the large therapeutic dose (i.e., 255 logons per participant), the ready availability of the intervention, and the intrinsic appeal of the internet to adolescents.[336]

The importance of cognition in recovery from CFS was illustrated in a landmark study of adult patients, who were randomized to standard medical care alone or to standard care plus adaptive pacing therapy, CBT, or graded exercise therapy.[330] The latter two treatments, which were more effective, involve positive cognitive constructs (“I am able to do more than I thought I could.”) than the former (“I need to focus on how fatigued I am to stop in time.”).[337]

Supportive counseling combined with behavioral techniques and increased physical activity can be beneficial.[338] Success has been reported using a program focused on breaking the association between experiencing symptoms and stopping activity.[339] In a randomized trial, CBT was effective in reducing the severity of fatigue, improving physical functioning, and increasing school attendance.[340] Decreases in fatigue associated with CBT are associated with decreases in reported pain.[341] CBT reduced self-reported cognitive impairment but did not improve performance on specific neuropsychological tests,[342] which suggests that distorted perception of cognitive processes may be more central to CFS than actual cognitive performance.

Studies of related and overlapping conditions point to useful interventions.[343,344] The mainstay of these programs is an emphasis on improved functioning, whereas symptomatic improvement is viewed as secondary. Supported CBT strategies include training in relaxation strategies and cognitive interventions to modify and decreased activity avoidance,[340,344] increased physical activity,[338] and decreased intensity of symptoms such as headache and body aches and pains.[341]

Improvement has been seen using multidimensional cognitive-behavioral interventions in which adolescents and parents are educated in a holistic model of CFS that discourages adoption of exclusively physical or psychological models of the illness.[345] Vicious cycles that exacerbate illness are explained. Families are taught to reduce attention to and secondary gain from CFS symptoms and to promote independent use of positive coping skills. Behavioral management strategies, such as praise, rewards, and consequences, are employed to motivate the child to use coping and stress management strategies as they progress toward improved functioning.[346]

Some centers have adopted inpatient rehabilitation models, which include parent education and highly structured programs conducted over several weeks that rely on individual and group interventions. These strategies have improved overall functioning, school attendance, sleep, medication use, and emotional well-being, although improvement in fatigue symptoms has been more modest.[347–349]

Activity

Return to physical activity and schoolwork is an essential part of treatment. Excused absences from school must be time-limited and linked to gradual increases in activity and integration. Committing to gradual increases in activity and keeping formal records may engender feelings of self-efficacy and hopefulness. Clinical trials of graded exercise programs for adults have shown benefits.[350–353]

Follow-Up

Regular medical and psychological follow-up visits are an important part of treatment. Serial evaluations enable the physician to monitor for alternative, potentially treatable diagnoses and to repeat some laboratory tests as indicated. Follow-up visits allay the patient's fear of abandonment and provide reassurance through exacerbations until improvement occurs.

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[b] References 151, 152, 155, 157, 160, 176.

[c] References 16, 151, 153, 157, 159, 160 ,164, 166–174.

[d] References 43, 127, 146, 156, 161, 163, 168, 182–192.

B

Viruses

OUTLINE

201 Classification of Human Viruses
DNA Viruses: Poxviridae
DNA Viruses: Herpesviridae
DNA Viruses: Adenoviridae
DNA Viruses: Adenoviridae
DNA Viruses: Hepadnaviridae
DNA Viruses: Parvoviridae
RNA Viruses: Reoviridae
RNA Viruses: Togaviridae, Flaviviridae, and Bunyaviridae
RNA Viruses: Coronaviridae
RNA Viruses: Paramyxoviridae
RNA Viruses: Rhabdoviridae
RNA Viruses: Orthomyxoviridae
RNA Viruses: Arenaviridae and Filoviridae
RNA Viruses: Retroviridae
RNA Viruses: Picornaviridae
RNA Viruses: Caliciviridae

201

Classification of Human Viruses

Robert David Siegel

The virus family concept is fundamentally important in understanding the biologic classification of viruses.[1] By specifying the family to which a virus belongs, much can be inferred about its physical, chemical, and biologic properties and its evolutionary relationships and modes of gene expression.[2] Virus families are designated with the suffix *-viridae.*[3] Families are distinguished largely on the basis of physiochemical properties, genome structure, size, morphology, and molecular processes.[4] Table 201.1 lists some criteria that are used to differentiate human virus families.

TABLE 201.1

Major Criteria for Classifying Human Virus Families

Criterion	Basis of Classification
Type of genomic nucleic acid	DNA or RNA
Nucleic acid strandedness	ds, ss, partially ds
Sense of ss nucleic acid	+, −, − with ambisense
Capsid morphology	Icosahedral, helical, or complex
Envelope	Present or absent
Genome segmentation	Number of segments
Genomic structure	For example, type of RNA cap, location of structural genes or repeat

	sequences
Electron micrographic (EM) appearance	For example, bullet-shaped rhabdoviruses or star-shaped astroviruses
Size of virion and/or genome	For example, large-genome DNA viruses (e.g., poxviruses, herpesviruses) versus small-genome viruses (e.g., picornaviruses, parvoviruses, hepadnaviruses)
Nature of gene expression, including nature and number of mRNA transcripts	For example, use of genomic polyproteins (e.g., picornaviruses, flaviviruses); use of reverse transcriptase (e.g., retroviruses, hepadnaviruses); use of multiple 3′ nested genes (e.g., coronaviruses); use of RNA ambisense coding (e.g., arenaviruses, bunyaviruses)

ds, double stranded; ss, single stranded.

The 26 virus families implicated in human disease[5] are listed in Table 201.2. In some cases, humans serve as a reservoir for the viruses and the link to human disease is clear. In other cases, humans may be incidental hosts or the link to disease may be more tenuous. Table 201.3 lists specific viruses within each family that are linked to human disease.

TABLE 201.2

Families of Viruses That Infect Humans

Family Name	Derivation of Family Name	Genome	Segmentation	Capsid Morphology	Envelope
Adenoviridae	Gland	dsDNA	1	Icosahedral	Naked
Anelloviridae	Ring-shaped	ssDNA(−)[f]	1	Icosahedral	Naked
Arenaviridae	Sand	ssRNA(−)[g,h]	2	Helical	Enveloped
Astroviridae	Star	ssRNA(+)[i]	1	Icosahedral	Naked
Bornaviridae[a]	Location in Germany	ssRNA(−)[g]	1	Helical	Enveloped
Bunyaviridae	Location in Uganda	ssRNA(−)[g,h]	3	Helical	Enveloped
Caliciviridae	Cup or chalice	ssRNA(+)[i]	1	Icosahedral	Naked
Coronaviridae[b]	Crown	ssRNA(+)[i]	1	Helical	Enveloped
Filoviridae[a]	Thread	ssRNA(−)[g]	1	Helical	Enveloped
Flaviviridae	Yellow	ssRNA(+)[i]	1	Icosahedral	Enveloped
Hepadnaviridae	Liver, DNA	Partially ssDNA	1	Icosahedral	Enveloped
Hepeviridae	*Hep*atitis E	ssRNA(+)[i]	1	Icosahedral	Naked
Herpesviridae[c]	Creeping	dsDNA	1	Icosahedral	Enveloped
Orthomyxoviridae	True, slime or mucus	ssRNA(−)[g]	6–8	Helical	Enveloped
Papillomaviridae	Bumpy, tumor	dsDNA	1	Icosahedral	Naked
Paramyxoviridae[a]	Alongside, slime or mucus	ssRNA(−)[g]	1	Helical	Enveloped
Parvoviridae	Little	ssDNA	1	Icosahedral	Naked
Picobirnaviridae	“Little”; “two”, RNA	dsRNA	2	Icosahedral	Naked
Picobirna	Little, two, RNA	dsRNA	2	Icosahedral	Naked
Picornaviridae[d]	Little, RNA	ssRNA(+)[i]	1	Icosahedral	Naked

Pneumoviridae	“Lung”	ssRNA(−)[g]	1	Helical	Enveloped
Polyomaviridae	Many, tumor	dsDNA	1	Icosahedral	Naked
Poxviridae	Pustule	dsDNA	1	Complex	Varies
Reoviridae	*R*espiratory, *e*nteric, *o*rphan	dsRNA	10–12	Icosahedral	Naked
Retroviridae	Backward	ssRNA(+)[i]	1 but diploid	Complex	Enveloped
Rhabdoviridae[a]	Rod	ssRNA(−)[g]	1	Helical	Enveloped
Togaviridae	Cloak	ssRNA(+)[i]	1	Icosahedral	Enveloped
Delta[e]	Fourth hepatitis group	ssRNA(−)[g]	1	Icosahedral	Enveloped

[a] Mononegavirales.

[b] Nidovirales.

[c] Herpesvirales.

[d] Picornavirales.

[e] Floating genus, which is not currently assigned to a viral family. It bears some similarities to viroid pathogens of plants.

[f] ssDNA(+) indicates the mRNA-coding strand.

[g] ssRNA(−) indicates the complement of the message-sense strand.

[h] Some segments are ambisense.

[i] ssRNA(+) indicates a message-sense strand.

ds, double stranded; ss, single stranded.

TABLE 201.3

Human Viral Infections Listed by Family[a]

Family Name	**Representative Viruses**[b]
Adenoviridae	Human adenovirus types 1 to 57 in seven species (human adenovirus species A to G)[28,29]
Anelloviridae[8]	Torque teno virus 1 (TTV1),[c] Torque teno mini virus 1, Torque teno midi virus 1[29] (type species for numerous viruses in 3 genera)
Arenaviridae	Lassa virus, lymphocytic choriomeningitis virus, Junin virus, Machupo virus, Guanarito virus, Sabiá virus, Whitewater Arroyo virus,[30] Chapare virus,[31] Lujo virus
Astroviridae	Human astroviruses (eight serotypes)
Bornaviridae	Mammalian 1 bornavirus (formerly Borna disease virus [BDV])[29]
Bunyaviridae	California encephalitis virus, Sin Nombre virus, La Crosse virus, Hantaan virus, Muerto Canyon virus, Crimean-Congo hemorrhagic fever virus, Sandfly fever viruses, Rift Valley fever virus, Heartland virus, and many others
Caliciviridae	Noroviruses, sapoviruses
Coronaviridae	SARS coronavirus; MERS coronavirus[29]; human coronaviruses OC43,[32] 229E, NL63,[33] and HKU1[34]; human torovirus and other human enteric coronaviruses
Filoviridae	Ebola viruses (e.g., Zaire ebolavirus, Bundibugyo ebolavirus, Reston ebolavirus, Sudan ebolavirus, Taï Forest ebolavirus),[29] Marburg virus
Flaviviridae	Genus *Alphavirus*: dengue virus, yellow fever virus, Japanese encephalitis virus, West Nile virus, Murray Valley encephalitis virus, Kyasanur

	encephalitis virus, tick-borne encephalitis virus, Zika virus, and others Genus *Hepacivirus*: hepatitis C virus (HCV) Genus *Pegivirus*[d]: GB virus-C[c] (GBV-C) (formerly hepatitis G virus [HGV])[35]
Hepadnaviridae	Hepatitis B virus (HBV)
Hepeviridae[9]	Hepatitis E virus (HEV)
Herpesviridae	Herpes simplex virus type 1, herpes simplex virus type 2, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, human herpesvirus 6, human herpesvirus 7, human herpesvirus 8 (i.e., Kaposi sarcoma-associated herpesvirus), herpes simian B virus
Orthomyxoviridae	Influenza A virus (e.g. subtype H1N1), influenza B virus, influenza C virus, Thogoto virus, Dhori virus,[36] Bourbon virus
Papillomaviridae	Human papilloma virus (>150 types with various degrees of oncogenicity)[37]
Paramyxoviridae	Measles (rubeola) virus, mumps virus, parainfluenza viruses, Hendra virus, Nipah virus, Menangle virus[38]
Parvoviridae	Human parvovirus B19, human bocavirus,[39] adeno-associated viruses[c,e]
Picobirnaviridae	Human picobirnavirus
Picornaviridae[40]	Genus *Enterovirus*: human rhinoviruses (>100 serotypes), enteroviruses (>100 serotypes, including poliovirus 1–3, coxsackievirus A and B, echoviruses, and other human enteroviruses) Genus *Hepatovirus*: hepatitis A virus (HAV) Genus *Parechovirus*: human parechoviruses Genus *Kobuvirus*: Aichi virus Genus *Cosavirus*: human cosaviruses[41] Genus *Cardiovirus*: Vilyuisk human encephalomyelitis virus, Saffold viruses[42] Genus *Salivirus*: human klassevirus,[43] salivirus A Genus *Senecavirus*: Seneca Valley virus[f] Unassigned: Syr-Darya Valley fever virus
Pneumoviridae	Respiratory syncytial virus, human metapneumoviruses
Polyomaviridae	JC virus, BK virus, KI virus, WU virus, Merkel cell polyomavirus, lymphotropic polyomavirus, human polyomavirus 6, human polyomavirus 7, trichodysplasia spinulosa-associated polyomavirus, human polyomavirus 9[44,45]
Poxviridae	Molluscum contagiosum virus, variola (smallpox) virus, monkeypox virus, vaccinia virus, orf virus, pseudocowpox virus, Tanapox virus, Yaba monkey tumor virus[46]
Reoviridae	Human rotavirus, Colorado tick fever virus, human reovirus,[c] Kemerovo virus
Retroviridae	Human immunodeficiency viruses types 1 and 2, human T-lymphocyte lymphotropic viruses,[47] xenotropic murine leukemia virus-related virus,[g] human endogenous retroviruses (HERVs), simian foamy virus
Rhabdoviridae	Rabies virus, vesicular stomatitis virus, Australian bat lyssavirus, Duvenhage virus, Mokola virus
Togaviridae	Rubella virus; Chikungunya virus; eastern equine, western equine, and Venezuelan equine encephalitis viruses; Ross River, Sindbis, and Semliki Forest viruses
Delta[h]	Hepatitis delta virus[e] (HDV)

[a] Examples listed correspond to common usage and do not necessarily comply with the official International Committee on Taxonomy of Viruses (ICTV) designations of virus species.

[b] Some zoonoses are included.

[c] Orphan virus for which a link to human disease has not been determined.

[d] Proposed genus name.

[e] Satellite virus requiring coinfection with heterologous virus for replication.

[f] Porcine virus being used clinically in humans as an oncolytic agent.[48]

[g] Possible laboratory contaminant.

[h] Floating genus, which is not currently assigned to a viral family. It bears some similarities to viroid pathogens of plants.

Facilitated by advances in molecular methods, the discovery of new viruses and more careful characterization of known viruses[6,7] have resulted in frequent changes in family taxonomy. Examples of such changes include de novo creation of a virus family (e.g., Anelloviridae),[8] splitting a new family off of an existing one (e.g., Hepeviridae from Caliciviridae),[9] dividing a family into two new families (e.g., Papovaviridae into Papillomaviridae and Polyomaviridae),[10] and uniting formerly separate families (e.g., incorporation of Toroviridae into Coronaviridae).[11,12] Working groups[13] within the International Committee on Taxonomy of Viruses (ICTV)[14] have the responsibility of approving new names and making changes in classification. Figs. 201.1, 201.2, and 201.3 illustrate the relationships among human virus families in terms of key biologic criteria listed in Table 201.1.

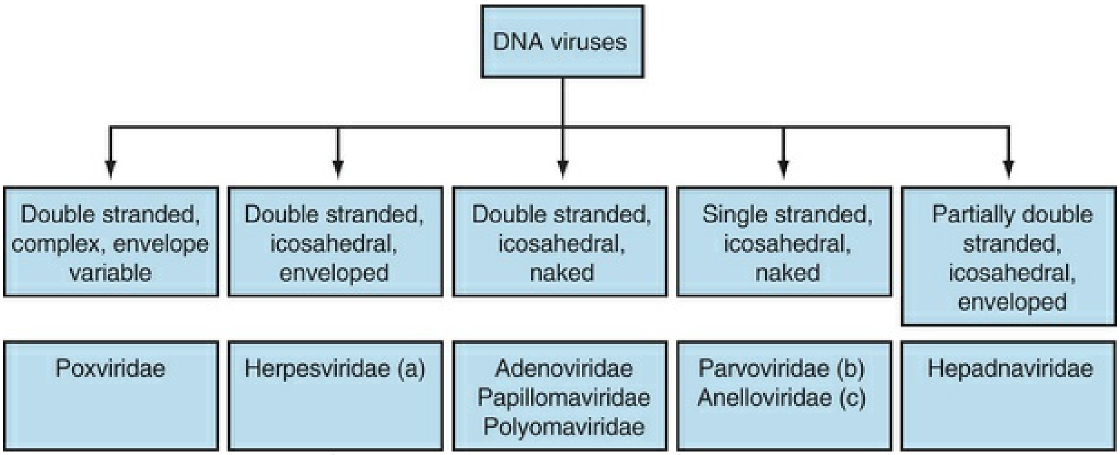
DNA viruses
Double stranded, complex, envelope variable
Double stranded, icosahedral, enveloped
Double stranded, icosahedral, naked
Single stranded, icosahedral, naked
Partially double stranded, icosahedral, enveloped
Poxviridae
Herpesviridae (a)
Adenoviridae
Papillomaviridae
Polyomaviridae
Parvoviridae (b)
Anelloviridae (c)
Hepadnaviridae

FIGURE 201.1 Organizational chart of the eight human virus families with DNA genomes. The chart groups virus families using the strandedness of the viral genome, the structure of the capsid, and the presence or absence of an envelope. All of these viruses are nonsegmented. Like retroviruses, hepadnaviruses contain reverse transcriptase. One family of viruses has been assigned to the Herpesvirales (a) order of viruses. Parvoviruses (b) vary in the percentage of

positive- and negative-sense single-stranded DNA (ssDNA) genomes that are packaged, depending on the genus. Anelloviruses (c) package negative-sense ssDNA genomes; this strand is transcribed into mRNA.

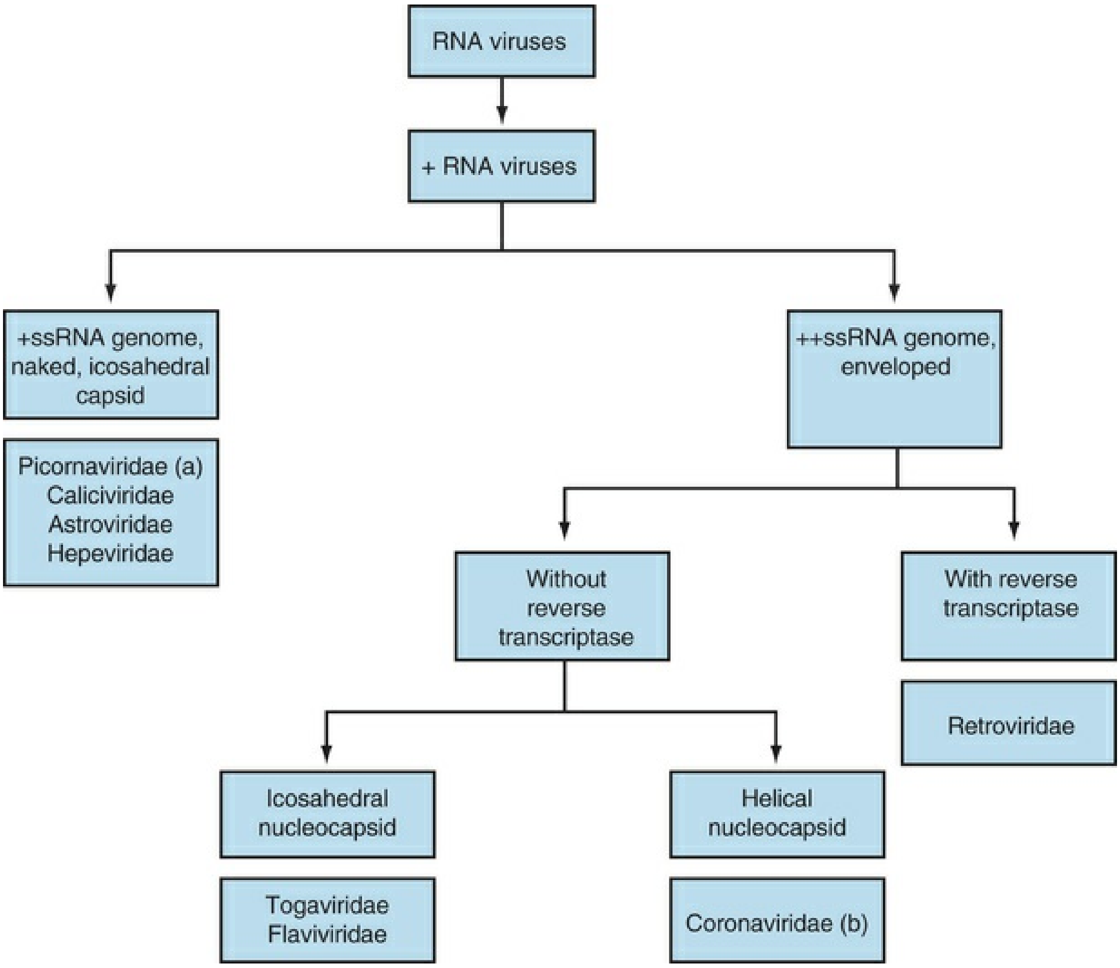

FIGURE 201.2 Organizational chart of the eight human virus families with positive-sense (+) RNA (i.e., mRNA-like) genomes. The chart groups virus families using the presence or absence of an envelope, the presence of reverse transcriptase, and the structure of the capsid. All of these viruses have a single-stranded (ss), nonsegmented viral genome. One family of viruses (a) has been assigned to the Picornavirales order of viruses. Another family of viruses (b) has been assigned to the Nidovirales order of viruses.

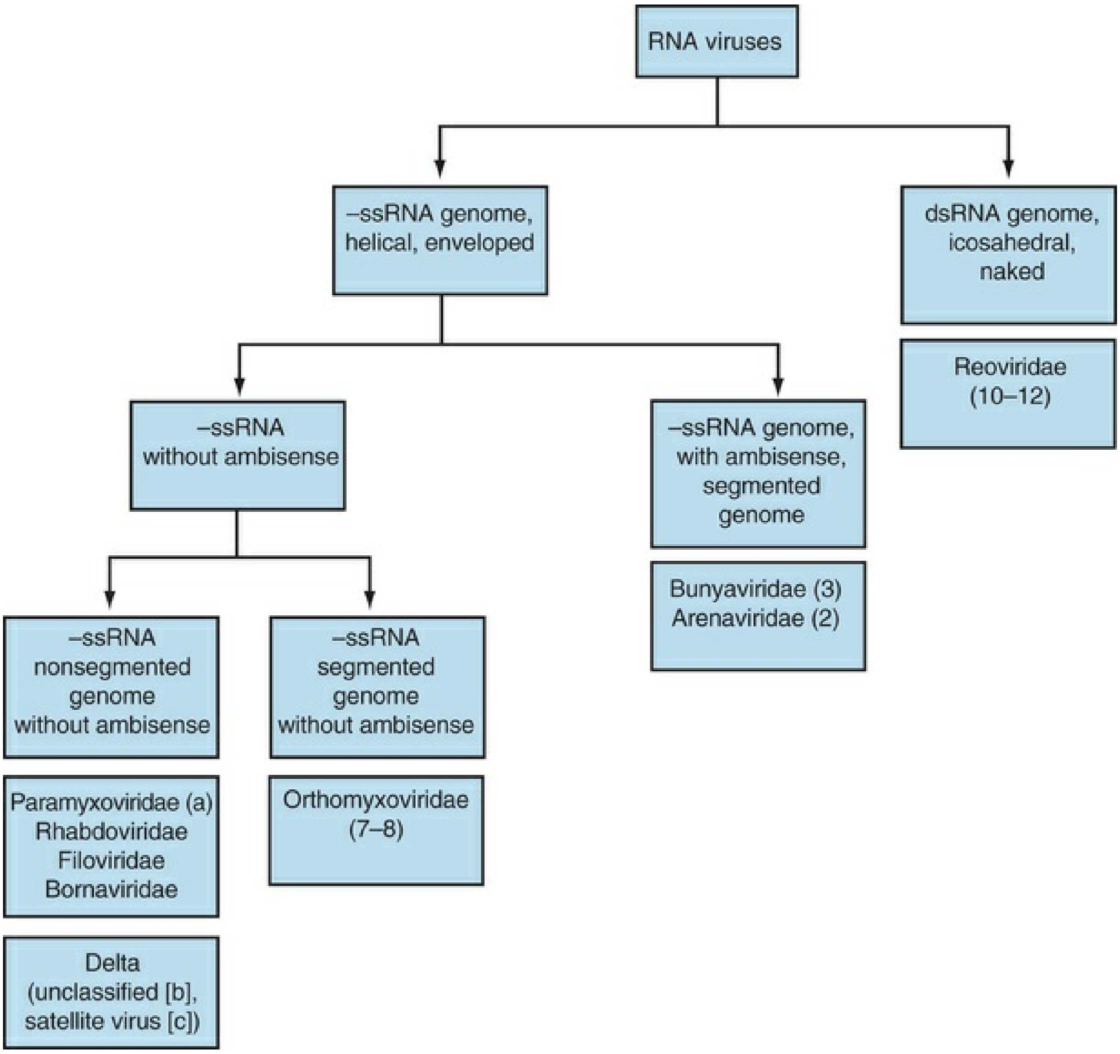
RNA viruses
–ssRNA genome, helical, enveloped
dsRNA genome, icosahedral, naked
Reoviridae (10–12)
–ssRNA without ambisense
–ssRNA genome, with ambisense, segmented genome
Bunyaviridae (3)
Arenaviridae (2)
–ssRNA nonsegmented genome without ambisense
–ssRNA segmented genome without ambisense
Paramyxoviridae (a)
Rhabdoviridae
Filoviridae
Bornaviridae
Orthomyxoviridae (7–8)
Delta (unclassified [b], satellite virus [c])

FIGURE 201.3 Organizational chart of the remaining eight human RNA virus families, including the negative (−) singled-stranded (ss) (i.e., complementary to message sense) and double-stranded (ds) RNA viruses. The chart groups the families using the structure of the genome, presence or absence of an envelope, and the presence or absence of ambisense gene expression. For segmented viruses, the number of genome segments is listed in parentheses. One group of virus families (a) is assigned to the Mononegavirales (i.e., monosegmented and negative-stranded) order of viruses. The unclassified or floating genus (b) is not currently assigned to a viral family. It bears some similarities to viroid pathogens of plants. Satellite virus (c) refers to the fact that hepatitis D virus (HDV) depends on HBV, a genomically unrelated virus, for its successful replication.

Next-generation nucleic acid sequencing has facilitated rapid and massive screening of samples obtained from healthy individuals, patients, nonhuman organisms, and environmental sources, resulting in the ongoing discovery of numerous viruses.[15,16] The clinical significance of most of these viruses has yet to be established. Advances in understanding the human microbiome are providing insights into the impact of microbial viruses in causing or modulating human disease. A well-characterized example is the role of *Vibrio cholerae* phage CTXψ in producing the clinical symptoms of cholera.[17]

Families hierarchically are subdivided in a variety of ways, including into subfamilies (suffix *-virinae*), genera (suffix *-virus*), and species (suffix *-virus*).[18] In the past, the conventions for naming species were somewhat arbitrary and varied from family to family. The ICTV has instituted a more uniform system. A virus species, as defined by van Regenmortel, is "a polythetic class of viruses that constitutes a replicating lineage and occupies a particular ecologic niche."[19] *Polythetic* refers to the fact that viruses grouped within a species share many properties. Species criteria may include genetic structure, sequence homology, host range, tissue tropism, biologic reservoir, route of transmission, immunologic cross-reactivity, epidemiology, and pathogenicity.[20] With the advent of rapid nucleic acid sequencing, sequence homology has taken precedence over other species classification criteria.[21]

The current system of species classification does not always correspond to common usage or historical concepts of species. For example, the three immunologically distinct viruses targeted by the trivalent poliovirus vaccine are considered to be the same species: human enterovirus C.[22,23] This species includes at least 23 additional serotypes with diverse clinical presentations, as well as circulating recombinant forms.[24] The practicality of distinguishing serotypes is emphasized by the eradication of wild poliovirus type 2 in 2000[25] and wild poliovirus type 3 in 2012.[26] Species can be subdivided further into groups, clades, types, subtypes, serotypes, variants, and isolates, depending on the family involved and the degree of similarity. Selected representatives called *type viruses* may be used to illustrate the properties of a particular taxon.

A number of virus families are assigned to higher-level orders, which are designated with the suffix *-virales*. Examples are Herpesvirales, Mononegavirales, Picornavirales, and Nidovirales.[27]

They are indicated by footnotes in Table 201.2. Most families are unassigned to orders.

In addition to biologic classification, viruses often are categorized according to their clinical presentation (i.e., syndromic classification), epidemiology, or mode of transmission. Box 201.1 lists the major routes of transmission for human diseases, with representative examples of viruses transmitted by each route.

Box 201.1

Common Routes of Virus Transmission to Humans

Respiratory route (i.e., droplet, aerosol, and respiratory secretions on the hands and elsewhere; oral exchange): influenza virus, varicella-zoster virus, human rhinovirus, human adenovirus, respiratory syncytial virus, parainfluenza virus, metapneumovirus

Fecal-oral route: polioviruses, coxsackieviruses, hepatitis A virus, rotavirus, astrovirus, norovirus

Direct contact: human papillomavirus (HPV), molluscum contagiosum, herpes simplex virus type 1 (HSV-1)

Sexual: human immunodeficiency virus type 1 (HIV-1), human T-lymphotropic virus type 1 (HTLV-1), hepatitis B virus (HBV), human papillomavirus types 16 and 18 (HPV-16, HPV18), HSV-2

Urine-associated: cytomegalovirus (CMV)

Parenteral route (i.e., blood and blood products, transplantation, tattooing, and scarification): HIV-1, HBV, hepatitis C virus (HCV)

Animal bite: rabies virus, Duvenhage virus

Vertical route (e.g., germline, intrauterine, perinatal, human milk): HIV-1, HTLV-1, germline transmission of endogenous retroviruses

Arthropod-borne route (e.g., mosquitos, ticks, sandflies): Japanese encephalitis virus, West Nile virus, dengue virus, yellow fever virus, Zika virus, chikungunya virus, and many others

Rodent-associated transmission: Lassa fever virus, sin nombre, and other hanta viruses (e.g., Hantaan virus, Seoul virus, and Puumala virus)

Bat-associated transmission: rabies virus, Nipah virus, Ebola virus, severe acute respiratory syndrome coronavirus (SARS CoV)

Monkey-associated transmission: herpes B virus, monkeypox virus, orf virus

Other zoonotic associations (e.g., cows, sheep): orf virus, cowpox virus

Understanding virus classification can lead to important generalizations regarding the prevention and treatment of viral infection and insights into the distribution and evolution of viruses. In addition, insights from viral taxonomy play key roles in preventing and staunching the spread of viral disease at the population level.

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DNA Viruses: Poxviridae

OUTLINE

202 Poxviridae

202

Poxviridae

Brett W. Petersen

Despite the eradication of smallpox, several poxviruses remain clinically significant, including vaccinia (i.e., virus used for smallpox vaccination), molluscum contagiosum, and several relatively uncommon zoonotic viruses. Concern about smallpox as a bioterrorist weapon also has led to continued interest in poxvirus research. Concurrently, interest in poxviruses (vaccinia virus in particular) as vaccine vectors and potential immunotherapeutic agents has contributed to a rapid expansion of knowledge regarding poxvirus genetics and pathogenesis.[1,2]

Poxviruses are the largest and most complex viruses infecting humans. Virions are 220 to 450 nm long and have a characteristic brick-shaped appearance on electron microscopy (except the ovoid parapoxviruses).[3] The genome consists of linear, double-stranded DNA ranging from 130 to 375 kbp. Four genera within subfamily Chordopoxvirinae contain recognized human pathogens (Table 202.1).

TABLE 202.1

Poxvirus Diseases of Humans

Genus and Species	Clinical Syndrome	Lesion Type	Frequency	Geography	Animal Vectors
ORTHOPOXVIRUS					
Variola virus	Febrile rash illness (smallpox)	Vesicopustular	Eradicated	Laboratory only	None
Monkeypox virus	Febrile rash illness (monkeypox)	Vesicopustular	Rare	West-central Africa,	Rodent, monkey

				United States[a]	
Vaccinia virus	Localized skin lesions	Vesicopustular	Rare	Worldwide	Cattle, milking buffalo
Cowpox virus	Localized skin lesions (cowpox)	Vesicopustular	Rare	Eurasia	Rodent, cat, cow, others
MOLLUSCIPOXVIRUS					
Molluscum contagiosum	Multiple skin lesions	Epidermal hyperplasia	Common	Worldwide	None
PARAPOXVIRUS					
Orf virus	Localized skin lesions (orf, ecthyma contagiosum)	Proliferative	Rare	Worldwide	Sheep, goat
Pseudocowpox virus	Localized skin lesions (milker's nodules, pseudocowpox, paravaccinia)	Proliferative	Rare	Worldwide	Dairy cow
Bovine papular stomatitis virus	Localized skin lesions	Proliferative	Rare	Worldwide	Calves, beef cattle
Deerpox virus, sealpox virus	Localized skin lesions	Proliferative	Rare	Variable	Various
YATAPOXVIRUS					
Tanapox virus	Localized skin lesions	Nodular	Rare	East-central Africa	Monkey
Yaba-like disease virus **(of monkeys),** *Yaba monkey tumor virus*	Localized skin lesions	Nodular	Rare	West Africa	Monkey

[a] Single outbreak in Midwestern United States, 2003.

Poxviruses share several features. All poxviruses replicate in the cytoplasm, and their genes therefore encode the proteins necessary for replication.[4] Poxviruses are notable for their ability to evade or subvert the host immune system. Several poxviruses encode proteins that mimic or inhibit mediators of the host inflammatory response.[5–7] Poxviruses exhibit various degrees of tropism for host species and cell types through mechanisms that are not completely understood.[8,9]

Variola and Vaccinia

Epidemiology

Variola, the virus causing smallpox, is among the most feared viruses in human history. Smallpox has had a tremendous impact on human civilizations throughout history. Significant milestones are summarized in Box 202.1. Currently, smallpox is primarily a concern because of its use as a potential weapon of bioterrorism.

Box 202.1

History of Smallpox (Variola Virus)

10,000 BC	Smallpox postulated to emerge in early northeast African settlements from unknown source
1580–1100 BC	Three Egyptian mummies (including Ramses V) interred with possible smallpox lesions
340 AD	First reliable descriptions of smallpox appear in Chinese writings
1500s	Smallpox spread to New World by Europeans
1600–1800s	Severe smallpox epidemics occur globally
1763	Smallpox intentionally used against Native Americans during French and Indian Wars
1949	Last United States smallpox outbreak occurs in Texas
1959	World Health Assembly (WHA) resolves to undertake global eradication of smallpox
1967	World Health Organization (WHO) Intensified Smallpox Eradication Programme commences using surveillance and containment strategy
1977	Last naturally occurring case of smallpox occurs in Somalia
1978	Laboratory accident in United Kingdom results in last smallpox case (and fatality)
1979	WHO Global Commission for the Certification of Smallpox Eradication declares global eradication of smallpox; report accepted by WHA in 1980
1987	WHO sets first target date for destruction of remaining variola virus stocks in United States and Russia
1999	Former deputy director of Soviet bioweapons program alleges that USSR engaged in large-scale weaponization of smallpox virus
2002, 2014	WHO indefinitely extends target for variola destruction

Modified from Long SS. Smallpox bioterrorism. In: Long SS, Pickering LK, Prober CG (eds). Principles and Practice of Pediatric Infectious Diseases, 2nd ed. Philadelphia, Churchill-Livingstone, 2003, p. 1559.

Smallpox is a human disease. The lack of an animal reservoir and the availability of an effective intervention to prevent transmission of the virus (i.e., smallpox vaccine) were critical factors allowing eradication. Smallpox spreads by respiratory droplets, with transmission typically resulting from close or prolonged contact. In pre-eradication studies, 37% to 88% of unvaccinated household members developed smallpox after contact with a known case, compared with 90% for measles and pertussis.[3,10–12]

Acquisition of variola infection usually occurs through the respiratory tract. Skin and eye inoculation and transplacental spread also have been documented.[3] The incubation period averages 10 to 14 days, with a range of 7 to 19 days.[3,13,14] During incubation, the virus replicates in the upper respiratory tract and reaches the reticuloendothelial system through a transient primary viremia. Most virus transmission occurred during the first 7 to 10 days after lesion onset because the highest amount of viral shedding occurred during this period.

Vaccinia is the virus used for smallpox vaccination. Its origins are unclear; phylogenetic analysis indicates that it was not recently derived from variola or cowpox.[2–4] Eradication of smallpox using the smallpox vaccine is among the greatest achievements in public health.

Vaccinia has a broader host range than most poxviruses, which has allowed it to be used as a model for smallpox infection in laboratory animals. Certain strains have become enzootic in sylvatic animal reservoirs, resulting in occasional zoonotic transmission.[15–19] These infections usually are localized and self-limited.

Clinical Manifestations

Smallpox begins abruptly with a prostrating febrile prodrome characterized by high fever, chills, headache, backache, vomiting, and severe abdominal pain. In ordinary-type smallpox infections, the first lesions appear in the oropharynx 1 to 4 days after the onset of fever. Skin lesions develop first on the face or forearms and then spread to the rest of the body. The highest concentration of lesions is on the face and distal extremities. The palms and soles commonly are involved. Lesions develop slowly from macules to papules to vesicles to pustules, with each stage lasting approximately 2 days. Lesions on any one part of the body are characteristically in the same stage of development at any given time. Crusting of lesions is usually complete within 2 to 3 weeks after the onset of rash.[3]

Variola major produced several distinct clinical syndromes and had an overall mortality rate of about 30%.[13,20] The mortality rate was higher for very young children.[3] Approximately 90% of cases in the largest series were ordinary smallpox, characterized by round, firm, well-circumscribed pustules 7 to 10 mm in diameter.[20] The mortality rate was approximately 10% for patients with discrete lesions and 60% for patients with confluent lesions.[20] Less common clinical presentations were characterized by flat or hemorrhagic lesions and were associated with case-fatality rates greater than 90%. Modified smallpox (i.e., 2% of unvaccinated and 25% of vaccinated cases) was similar to ordinary smallpox but had a milder and more accelerated course. Fever and other constitutional symptoms without rash (i.e., variola sine eruptione) occurred in rare instances.[3,20]

Variola minor (alastrim) usually produced milder disease. It rarely was fatal.

Laboratory Findings and Diagnosis

To aid those evaluating patients with rash illnesses that are suspected to be smallpox, the Centers for Disease Control and Prevention (CDC) and collaborating organizations created an algorithm based on the clinical features of ordinary smallpox. Three major criteria and five minor criteria are combined to assess the risk of smallpox (i.e., low, medium, or high risk) (Box 202.2). Specific diagnostic measures are recommended based on the risk level (Fig. 202.1).

Box 202.2

Major and Minor Smallpox Criteria and Risk of Smallpox

Major Smallpox Criteria

Febrile prodrome: occurring 1–4 days before rash onset; fever ≥101°F (38°C) and at least one of the following: prostration, headache, backache, chills, vomiting, or severe abdominal pain

Classic smallpox lesions: deep-seated, firm or hard, round, well-circumscribed vesicles or pustules; as they evolve, lesions may become umbilicated or confluent

Lesions in same stage of development: on any part of the body (e.g., face, arm), all the lesions are in the same stage of development (i.e., all are vesicles or all are pustules)

Minor Smallpox Criteria

Centrifugal distribution: greatest concentration of lesions on face and distal extremities

First lesions on the oral mucosa or palate, face, or forearms

Patient appears toxic or moribund

Slow evolution: lesions evolve from macules to papules to pustules over days (each stage lasts 1–2 days)

Lesions on the palms and soles

Risk of Smallpox

High Risk of Smallpox (Report Immediately)

Febrile prodrome *and*

Classic smallpox lesion *and*

Lesions in same stage of development

Moderate Risk of Smallpox (Urgent Evaluation)

Febrile prodrome *and*

One other MAJOR smallpox criterion

or

Febrile prodrome *and*

≥4 MINOR smallpox criteria

Low Risk of Smallpox (Manage as Clinically Indicated)

No febrile prodrome

or

Febrile prodrome *and*

<4 MINOR smallpox criteria

From Centers for Disease Control and Prevention. https://emergency.cdc.gov/agent/smallpox/diagnosis/evalposter.asp.

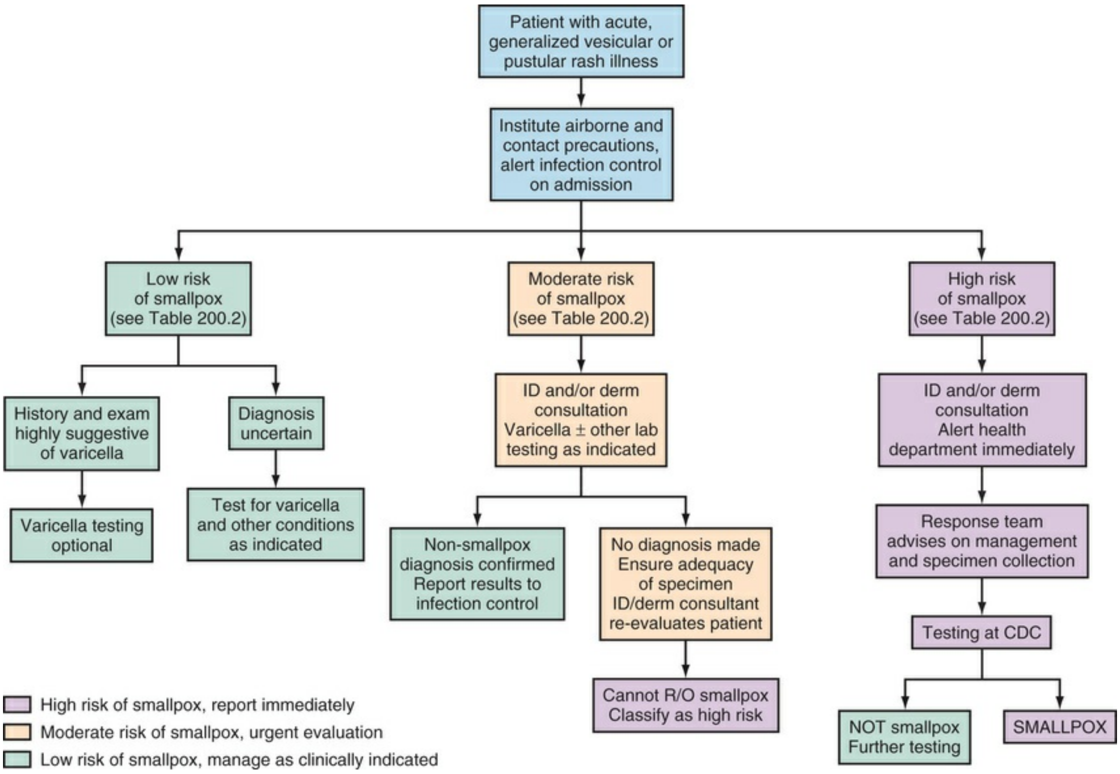

Patient with acute, generalized vesicular or pustular rash illness
Institute airborne and contact precautions, alert infection control on admission
Low risk of smallpox (see Table 200.2)
Moderate risk of smallpox (see Table 200.2)
High risk of smallpox (see Table 200.2)
History and exam highly suggestive of varicella
Diagnosis uncertain
Varicella testing optional
Test for varicella and other conditions as indicated
ID and/or derm consultation Varicella ± other lab testing as indicated
Non-smallpox diagnosis confirmed Report results to infection control
No diagnosis made Ensure adequacy of specimen ID/derm consultant re-evaluates patient
Cannot R/O smallpox Classify as high risk
ID and/or derm consultation Alert health department immediately
Response team advises on management and specimen collection
Testing at CDC
NOT smallpox Further testing
SMALLPOX
High risk of smallpox, report immediately
Moderate risk of smallpox, urgent evaluation
Low risk of smallpox, manage as clinically indicated

FIGURE 202.1 Algorithm for evaluating patients for smallpox. ID, infectious diseases; CDC, Centers for Disease Control and Prevention; derm, dermatologic; exam, examination; lab, laboratory; R/O, rule out.

(Modified from Centers for Disease Control and Prevention. https://www.cdc.gov/smallpox/clinicians/algorithm-protocol.html.)

Laboratory testing for variola is not recommended for low- or moderate-risk cases in the absence of known circulating smallpox.[21] The positive predictive value of these tests is extremely low, and the public health implications of false-positive results could be considerable.[22,23] If undertaken, laboratory diagnostic testing for variola virus is available through the Laboratory Response Network (LRN) with confirmatory testing by the CDC.[24] Polymerase chain reaction (PCR) testing is the preferred method for laboratory confirmation, although electron microscopy, serology, and other methods may be useful for diagnosis.[25] CDC guidelines for laboratory testing of suspected smallpox cases are available at https://www.cdc.gov/smallpox/lab-personnel/index.html.

Illnesses that can be confused with smallpox are listed in Box 202.3. Chickenpox is the illness most commonly confused with smallpox. Important features useful in distinguishing these two diseases are listed in Table 202.2. Monkeypox also can be difficult to distinguish from smallpox in the absence of epidemiologic clues, although lymphadenopathy is more prominent with monkeypox.[3]

Box 202.3

Exanthems That Can Be Confused With Smallpox by Stage

Macular or Papular

Measles

Rubella

Drug eruptions

Secondary syphilis

Erythema multiforme

Scabies or insect bites

Acne

Scarlet fever

Vesicular or Pustular

Chickenpox

Disseminated herpes zoster

Disseminated herpes simplex virus

Drug eruptions

Contact dermatitis

Erythema multiforme (including Stevens-Johnson syndrome)

Enteroviral infections

Secondary syphilis

Acne

Generalized vaccinia

Monkeypox

Impetigo

Scabies or insect bites

Disseminated molluscum contagiosum

TABLE 202.2

Features Distinguishing Smallpox From Chickenpox

Feature	Smallpox	Chickenpox
Prodromal symptoms	Frequent, severe	Infrequent, usually mild
Mature lesion morphology	Firm, well-circumscribed pustules	Superficial vesicles
Lesion development	Same stage on any one part of body	Different stages on any one part of body
Lesion distribution	Centrifugal	Centripetal
Location of first lesions	Mouth, face, forearms	Face, trunk
Patient appearance	Often toxic or moribund	Rarely toxic or moribund
Lesion evolution	Slow; 1–2 days per stage	Rapid; <24 hours per stage
Palmar/plantar lesions	Frequent	Rare

Treatment

Before eradication, treatment of smallpox largely was supportive. Vaccination of contacts within the immediate postexposure period can prevent or modify disease.[10–12,26] Cidofovir inhibits the poxvirus DNA polymerase and has proved effective against other poxvirus infections in humans[27] and against lethal orthopox virus infections in animal models.[28,29] A newer lipid ester derivative of cidofovir (i.e., CMX-001) with improved oral bioavailability and decreased renal toxicity has proved effective against orthopoxvirus infections in animal models.[30–33]

Another orally bioavailable compound (i.e., ST-246) that prevents release of virus from infected cells has proved effective against orthopoxvirus infections (including variola) in vitro and in animal models.[34–37] Evidence from animal studies suggests that these compounds can function synergistically for treatment or prevention of orthopoxvirus infections.[38,39] Development of anti-orthopoxvirus therapeutics remains an active area of research.[40,41]

Prevention

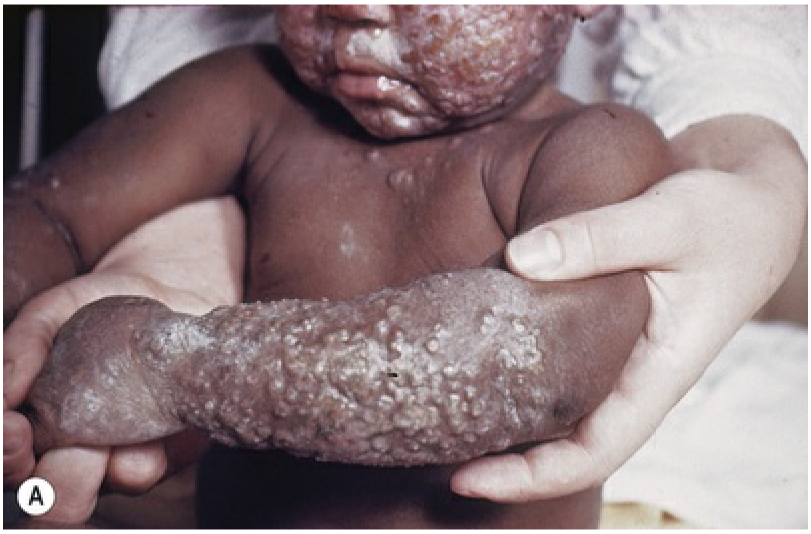
Several types of smallpox vaccine have been developed. First-generation vaccines contain live vaccinia grown in animals and then purified and treated to ensure stability.[3] Second-generation vaccines are single clones that have been isolated and grown in cell culture. They are usually similar to first-generation vaccines with regard to safety and immunogenicity.[42]

Third-generation vaccines are single clones further attenuated by serial passage or genetic manipulation. These vaccines appear to be safer than earlier vaccines, particularly among persons at high risk for severe adverse events such as those with human immunodeficiency virus (HIV) infection.[43–47] Third-generation vaccines protect against orthopoxvirus infection in animal models[44,48–50] and attenuate response to first-generation vaccines in humans,[51,52] but their ability to protect against smallpox has not been documented. Moreover, evidence suggests that third-generation vaccines may be less immunogenic than first-generation vaccines.[44,53] Subunit and DNA-based vaccines have shown promise in animal models.[54–59]

The first-generation vaccine that was used in the United States until recently (Dryvax, Wyeth) was derived from the New York City Board of Health (NYCBOH) strain, one of the strains recommended by the World Health Organization (WHO) during the eradication campaign.[3] A second-generation vaccine derived from the NYCBOH virus (ACAM2000, Sanofi Pasteur) was licensed in 2007[42,60] and has replaced Dryvax in the United States for ongoing vaccination and emergency use.[61] A third-generation smallpox vaccine (Imvamune, Bavarian Nordic) has been purchased for emergency use in persons with certain medical conditions placing them at high risk for adverse events after vaccination.[62]

First- and second-generation smallpox vaccines are delivered by multiple punctures with a bifurcated needle. Normally, a papule appears 3 to 4 days after inoculation and progresses to a vesicle and then a pustule, which crusts and separates by approximately 12 days after vaccination. Virus can be recovered from vaccination sites for 3 weeks or more if a lesion is still present. Covering the site with a porous bandage (e.g., gauze) is recommended.[63] Fever, local swelling, headache, and nonspecific rashes are common after vaccination. Images of a normal vaccination response and selected adverse reactions are available at https://emergency.cdc.gov/agent/smallpox/smallpox-images.

Severe adverse events include postvaccinial encephalitis, progressive vaccinia, eczema vaccinatum, and fetal vaccinia.[64] Generalized vaccinia occurs more commonly and is usually self-limited. Accidental inoculation of self or others (Fig. 202.2) (including ocular inoculation) can occur.[64,65] Myocarditis and pericarditis of unclear pathogenesis occurred more frequently than expected among those vaccinated in the United States since 2002.[66–68]



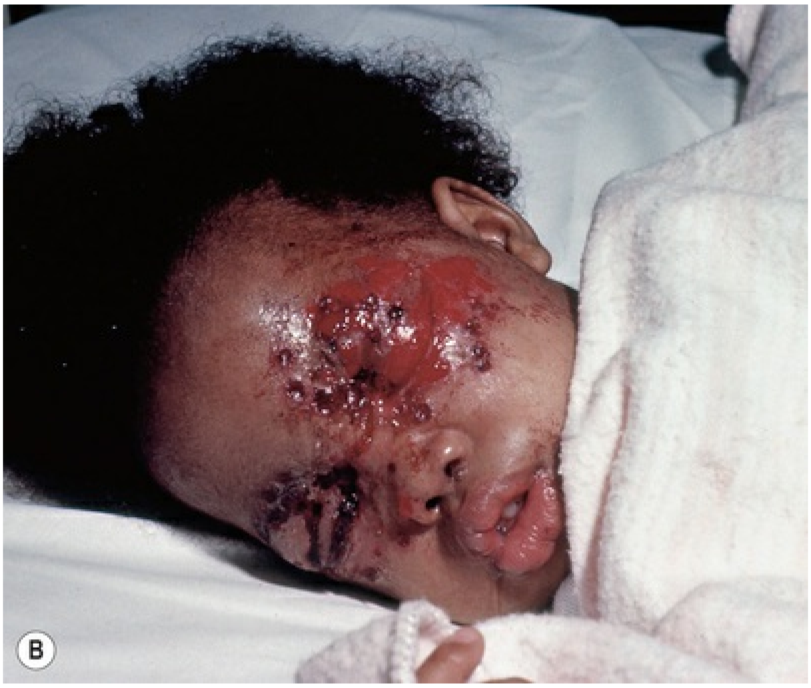


FIGURE 202.2 (A) A 6-month-old infant developed eczema vaccinatum after exposure to his vaccinated sibling. (B) An 18-month-old toddler had accidental self-inoculation of his eye and face. (Cases from Philadelphia in the 1960s. Courtesy of S.S. Long, MD.)

Vaccinia immune globulin (VIG) is indicated for certain adverse reactions, and it is available from the CDC.[69] Orally bioavailable antiviral agents hold promise for the treatment of certain vaccine complications.[70] CMX-001 and ST-246 have been used to treat severe human cases of eczema vaccinatum and progressive vaccinia, although the contributions of the individual agents is difficult to assess given the multitude of therapeutic interventions employed.[71,72]

In the absence of known circulating smallpox, vaccination is contraindicated for those with atopic dermatitis or other exfoliative skin conditions, those with diseases or treatments causing immunosuppression, pregnant women, and those with household members in any of these groups. Vaccination also is contraindicated for breastfeeding women, children younger than 12 months of age, persons with previous allergy to the vaccine, and those with moderate or severe illness or cardiac disease. Nonemergent vaccination of children younger than 18 years is not recommended by the Advisory Committee on Immunization Practices (ACIP).[73]

Zoonotic Poxviruses

Epidemiology

Four orthopoxviruses cause zoonotic infections: vaccinia, monkeypox, cowpox, and Akhmeta virus. Vaccinia and Akhmeta viruses cause sporadic human disease after exposure to infected bovine species.[74,75] Monkeypox and cowpox have been reported increasingly during recent years, possibly reflecting a decline in population-level immunity to orthopoxviruses after the end of the smallpox eradication campaign.[76,77]

Because of its similarity to smallpox, monkeypox was not recognized as a cause of human illness until 1970, 3 years after the start of the WHO's intensified smallpox eradication program.[78] Before 2003, monkeypox was limited to parts of central and western Africa, where it is endemic in several species of small mammals.[79] In 2003, an outbreak of human monkeypox in the United States resulted in 47 confirmed or probable cases.[80] The outbreak was linked to prairie dogs that had been housed with exotic animals shipped from Ghana.[81]

Genomic analysis has confirmed the existence of two monkeypox clades: Congo Basin and West African. Morbidity, mortality, and transmissibility rates are higher among persons infected with the Congo Basin clade.[82] Studies of African outbreaks indicate that 8% to 15% of unvaccinated household contacts develop infection.[78,83]

Cowpox is an emerging infection currently limited to Europe and Central Asia, where it is endemic in several species of rodents.[84–86] Despite the name, infection is most commonly contracted from domestic cats. Transmission from rats and other animals also has been reported.[86–88]

Several parapoxviruses also cause zoonotic infections. The most frequently reported is orf, also known as ecthyma contagiosum or contagious pustular dermatitis. Orf is contracted by exposure to saliva of infected sheep or goats.[89,90] Bovine papular stomatitis (caused by the bovine papular stomatitis virus) and milker's nodules or pseudocowpox (caused by the paravaccinia virus) are clinically identical to orf but occur after exposure to cattle.[3,91] Several other parapoxviruses cause human disease, including several newly discovered parapoxviruss.[18,92–94]

Tanapox is a mild zoonotic illness endemic to equatorial Africa. Only five cases have been reported in the United States, and all infected patients had recently traveled to endemic areas or were exposed to laboratory animals.[95] Epidemiologic evidence suggests transmission from nonhuman primate hosts by an arthropod vector or, rarely, by direct contact.[96,97] Two other yatapoxviruses have caused localized skin lesions in animal handlers.[25]

Clinical Manifestations

Clinically, monkeypox begins with a smallpox-like prodrome after a 10- to 14-day incubation period. The rash is similar to smallpox, but it usually is less extensive. Lymphadenopathy is prominent and may be useful in distinguishing monkeypox from smallpox.[3] Monkeypox is more common and more severe among children. Of 247 cases in Zaire between 1970 and 1984, 98% of severe cases and 100% of fatalities occurred in children.[3] Overall case-fatality rates range from 0% to 11%.[3,78,81,83,98]

Cowpox infection manifests with lesions similar to those occurring after smallpox vaccination. Lesions develop at sites of inoculation approximately 7 days after exposure, usually in association with localized lymphadenopathy, fever, and malaise. Eschars form after the lesions crust, and residual scarring is common. Cowpox has been mistaken for cutaneous anthrax, although anthrax lesions evolve more rapidly and usually are not painful.[84] Cowpox is usually mild and self-limited, although disseminated disease and fatalities have been reported among patients with atopic dermatitis.[99,100]

The lesions of orf, bovine papular stomatitis, and milker's nodules or pseudocowpox develop at the site of exposure (usually hands or arms) after a 3- to 7-day incubation period and classically progress over 14 to 72 days.[91,101] Fever, regional lymphadenopathy, and erythema multiforme can occur. Severe or widespread lesions have been reported in immunocompromised patients.[102,103]

Yatapox infections manifest with fever and other systemic symptoms that usually precede skin lesions by 1 to 4 days. Lesions are solitary in more than 75% of cases. They are characterized by slow evolution from macule to papule to nodule (with frequent ulceration), and they often are accompanied by regional lymphadenopathy.[95,96]

Laboratory Findings and Diagnosis

Monkeypox can be difficult to distinguish from chickenpox.[104] Lesion characteristics and animal exposure history are critical factors in diagnosing and differentiating localized zoonotic poxvirus infections. Laboratory diagnostic options include PCR, serology, electron microscopy, and histopathology.[89,90,95,105]

Treatment

Treatment for monkeypox primarily is supportive, although antiviral drugs can be considered.[106] Cidofovir, CMX-001, and ST-246 have proved effective against monkeypox, vaccinia, and cowpox in animal models, but human data are lacking.[27,28,29,,31,35,36,107] Parapoxvirus and yatapoxvirus infections are self-limited in most cases. Treatment of orf with topical cidofovir or topical imiquimod has been reported to be effective, although no data from controlled trials are available.[102,103,108] Excision and even amputation have been required in severe cases among immunocompromised patients.[103]

Prevention

The likelihood of acquiring a zoonotic poxvirus infection can be decreased by observing appropriate hygiene measures around animals and by limiting exposure to ill or exotic animals. Smallpox vaccination is effective in preventing monkeypox transmission, and vaccination after exposure may prevent or ameliorate disease.[78,106] Antiviral prophylaxis also has proved effective in animal models.[31,38]

Molluscum Contagiosum

Epidemiology

Molluscum contagiosum is a common infection worldwide. Incidence is highest among children younger than 5 years and those with atopic dermatitis.[109] Transmission results from direct contact or through fomites such as towels. Molluscum contagiosum can be spread by sexual contact, with resulting lesions on the genitalia, inner thighs, and abdomen. Autoinoculation is common, particularly in individuals with conditions that compromise the epidermal barrier. Autoinoculation is thought to be the most common cause of lesions on the genitalia of infants and young children. However, the possibility of sexual abuse should be considered.[110] Vertical transmission also has been reported.[111]

The incubation period varies from 2 weeks to 6 months. Molluscum contagiosum has been associated with outbreaks,[112] but it usually occurs sporadically.

Clinical Manifestations

Infection results in multiple, small (1 to 5 mm), umbilicated papules that are pearly white or flesh colored. In approximately 10% of cases, localized eczematous dermatitis (i.e., molluscum dermatitis) develops around a molluscum papule.[113] Four clinically indistinguishable subtypes have been identified, with molluscum contagiosum virus type 1 (MCV1) predominating.[109]

Molluscum contagiosum is a common opportunistic infection in patients with acquired immunodeficiency syndrome (AIDS), cancer, or neutropenia, and it can be problematic in primary immunodeficiency syndromes, especially hyperimmunoglobulinemia E syndromes.[114–117] The extensive and unusual molluscum lesions observed in these patients include multiple papules and giant hyperkeratotic lesions. Keratoconjunctivitis can develop due to eyelid lesions.[116]

Laboratory Findings and Diagnosis

The diagnosis of molluscum usually is made clinically, but it can be confirmed by examination of smears of lesions for the presence of intracytoplasmic inclusion bodies.[109] Biopsy usually is not required. Molecular diagnostic assays have been developed,[118] but they are not used widely. Molluscum contagiosum is difficult to propagate in tissue culture. The presence of genital lesions in sexually active adolescents should prompt evaluation for other sexually transmitted infections.[110]

Treatment

Molluscum lesions usually resolve spontaneously within 6 to 18 months, and recurrences are rare. Intervention often is warranted for patients with underlying skin conditions or immunodeficiency.

Several topical treatments are available, including imiquimod, tretinoin, and cantharidin.[109,119,120] Therapeutic options are listed in Box 202.4. Molluscum lesions in patients with AIDS often spread despite aggressive therapy.[114] Topical cidofovir and other investigational treatments have been used in refractory cases.[109,121] Surgery may be required for removal of large, solitary lesions.

Box 202.4

Treatment Options for Molluscum Contagiosum

Physical Disruption

Curettage

Cryotherapy

Laser

Electrosurgery

Chemical Disruption

Cantharidin (topical)

Podophyllin (topical)

Trichloroacetic acid (topical)

Silver nitrate (topical)

Potassium hydroxide (topical)

Immune Modulation

Imiquimod (topical)

Tretinoin cream (topical)

Cimetidine (systemic)

Interferon α (intralesional)[a]

OK-432 (intralesional)[a]

Antiviral Therapy

Cidofovir (topical or systemic)[a]

Unknown

Taping or occlusion

---

[a] Investigational therapies reserved for severe cases.

Prevention

Isolation or exclusion of infected children from school or childcare settings is not warranted. The likelihood of transmission can be decreased by restricting sharing of towels and other potential fomites with infected persons. Genital lesions in adolescents should be treated to prevent sexual transmission.[122]

Acknowledgment

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Key Points

Epidemiology, Clinical Features, Diagnosis, and Treatment of Poxvirus Infections

Epidemiology

- Smallpox has been eradicated as a human disease but concerns remain about its use as a potential weapon of bioterrorism.
- Vaccinia virus continues to be used as a vaccine and can cause disease in vaccinees and contacts of vaccinees.

- Infections due to zoonotic poxviruses (e.g., monkeypox, vaccinia, cowpox, parapoxviruses) usually occur sporadically in persons with animal exposure in enzootic areas.

- Molluscum contagiosum is a common infection worldwide, with the highest incidence among children younger than 5 years of age, those with atopic dermatitis, and those with certain immunodeficiencies.

Clinical Features

- Ordinary smallpox manifests as a febrile illness with characteristic development of a rash from macules to papules to vesicles to pustules in a centrifugal progression.

- Monkeypox is similar to smallpox clinically, but lymphadenopathy is more prominent in monkeypox and may help distinguish monkeypox from smallpox.

- Vaccinia, cowpox, and parapoxviruses usually cause self-limited, localized skin lesions, although more severe disease can occur in persons with immunocompromising or other medical conditions.

- Molluscum contagiosum manifests with multiple, small (1 to 5 mm), umbilicated papules that are pearly white or flesh colored.

Diagnosis

- Testing for poxviruses can include PCR, serology, electron microscopy, or other methods.

- Molluscum contagiosum usually is diagnosed clinically.

Treatment

- Vaccinia immune globulin (VIG) is licensed for the treatment of certain adverse events associated with vaccinia virus immunization.

- No antiviral drugs are licensed. Several investigational antiviral drugs show promise in treating orthopoxvirus infections in animal models.

- Development of orthopoxvirus antiviral therapeutics is an active area of research.

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DNA Viruses: Herpesviridae

OUTLINE

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Introduction to Herpesviridae

David W. Kimberlin, Charles G. Prober

The family Herpesviridae contains three subfamilies: Alphaherpesvirinae, Betaherpesvirinae, and Gammaherpesvirinae.[1,2] The eight known human herpesviruses are represented in six genera, which are shown with the typical characteristics of the subfamilies in Table 203.1.

TABLE 203.1

Members of Herpesviridae Family

Subfamily	Characteristics	Genus	Member
Alphaherpesvirinae	Short reproductive cycle Efficient destruction of infected cells with release of viral progeny Rapid spread in culture Latency in sensory ganglia	*Simplexvirus*	Herpes simplex virus type 1 (human herpesvirus 1) Herpes simplex virus type 2 (human herpesvirus 2)
		Varicellovirus	Varicella-zoster virus (human herpesvirus 3)
Betaherpesvirinae	Long reproductive cycle Slow cell-to-cell spread in culture Enlargement of infected cells Multiple nonganglionic sites of latency	*Cytomegalovirus*	Cytomegalovirus (human herpesvirus 5)
		Roseolovirus	Human herpesvirus 6 Human herpesvirus 7
Gammaherpesvirinae	Replication in lymphoblastoid	*Lymphocryptovirus*	Epstein-Barr

	cells Latency in lymphoid tissue Monocytes and B lymphocytes		virus (human herpesvirus 4)
		Rhadinovirus	Human herpesvirus 8

All members of the Herpesviridae family share several features (Box 203.1), but the architecture of the virion best defines family membership. The typical herpes virion is roughly spherical and 150 to 200 nm in diameter. The virion consists of a core of linear, double-stranded DNA wrapped around a fibrillar core spool, an icosadeltahedral capsid containing 162 capsomeres; a layer of amorphous, asymmetrically distributed material surrounding the capsid called the tegument; and a lipid-containing outer envelope containing multiple embedded glycoprotein protrusions.

Box 203.1

Common Features of Members of Herpesviridae Family

General Features

- Viral particle size: 150–200 nm
- More than 30 structural proteins
- Icosahedral nucleocapsid with 162 capsomers, 100 nm in diameter
- Surrounded by an envelope, acquired by budding through the inner lamella of the nuclear envelope
- Multiple surface projections embedded in the envelope

DNA

- Linear double-stranded genome wrapped around a fibrillar spool core
- Contains terminal and internal reiterated sequences; variation in the number of reiterations among members
- Genomic size: 120–230 kb; size variation related to the number of sequence reiterations
- Specifies a large number of enzymes involved in nucleic acid

metabolism

Features of Replication and Persistence

- Complex replication occurs in the nucleus
- Destruction of an infected cell accompanies production of progeny
- Latency follows primary infection, with lifetime persistence of viral DNA in infected hosts
- Potential for clinically apparent (symptomatic) or clinically inapparent (asymptomatic) reactivation throughout the life of the host

The most important biologic property of members of the Herpesviridae family is their ability to establish a latent state marked by persistence in an infected host after primary infection for the remainder of the host's lifetime. The different sites of latency are a distinguishing feature of the three Herpesviridae subfamilies (see Table 203.1). The viral genome takes the form of closed circular molecules within latently infected cells, but with reactivation, the genome again becomes linear. Clinical correlation of this biologic cycle is virus specific and is observed through a lifelong risk of viral reactivation, with or without recrudescence of symptoms.

Primary infection generally results in more severe symptoms than reactivated infection. However, mild or subclinical primary infection can be followed by more severe reactivated infection. The initial viral exposure results in primary infection, which can lead disease (i.e., clinically apparent symptoms and signs of the infection) or can be an asymptomatic infection. Reactivation of herpesviruses from a latent form also can be an asymptomatic infection, during which viral replication is occurring and transmission is possible, or can be symptomatic disease, with clinically apparent symptoms and signs due to viral replication and with the possibility of viral transmission. This concept of *active infection*, *latent infection*, and *clinically apparent disease* is critical to the appropriate interpretation of diagnostic tests and to the rationale of different treatment strategies in immunocompetent and immunocompromised hosts.

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Herpes Simplex Virus

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Herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) belong to the Alphaherpesvirinae subfamily of herpesviruses.[1] The large DNA viruses have a short reproductive cycle, rapidly produce lytic infection in tissue culture, and remain latent in sensory neural ganglia. After infection of the oral mucosa, usually by HSV-1, the virus becomes latent in the trigeminal ganglia. After genital infection by HSV-2 or HSV-1, the latent virus remains in the sacral ganglia.

In common with other herpesviruses, the HSV core of linear, double-stranded DNA is contained within an icosahedral capsid that consists of 162 capsomeres. The capsid is surrounded by a tightly adherent membrane of tegument protein and a phospholipid-rich envelope. The complete virion has an approximate diameter of 110 to 120 nm. Complete DNA sequencing demonstrates a greater than 90% homology between HSV-1 and HSV-2.

The HSV genome encodes at least 84 different polypeptides. They include glycoproteins embedded in the viral envelope; capsid proteins; DNA polymerase, protein kinase, and other viral enzymes; DNA-binding proteins involved in viral replication; and many other proteins with poorly understood biologic functions.[2] Attachment of HSV to cell surface receptors initiates infection. After attachment, the HSV envelope fuses to the plasma membrane, allowing the viral capsid to be transported to the nucleus, where the viral DNA is released. Transcription, DNA synthesis, capsid assembly, DNA packaging, envelopment, and release of new viral progeny ensue in infected cells.[2]

Several viral surface glycoproteins are important determinants of virulence. For example, glycoprotein B (gB) and gC mediate cellular attachment, gD is required for viral entry into cells, and gE is required for efficient expression of late genes, and with gI, it forms a potent Fc receptor.[2]

The first set of viral gene products to be synthesized includes the six immediate early (IE) proteins; five of the IE proteins regulate the reproductive cycle of the virus, and one blocks the presentation of antigenic peptides on the cell surface. The second set of proteins produced comprises the early proteins. These proteins, which include thymidine kinase and DNA polymerase, primarily are responsible for viral nucleic acid synthesis and are the main targets of the antiviral therapeutic drugs. The third set of proteins, known as late proteins, assembles to form the capsid and tegument. These proteins ultimately facilitate viral envelopment.

Pathophysiology

Infection of the susceptible host occurs when virus penetrates through abraded skin or mucosal surfaces. It is hypothesized that HSV enters cutaneous neurons after minimal replication at the site of inoculation and then migrates along innervating axons to the sensory ganglia, where infectious virus is produced.[3] Visible lesions result when virus subsequently travels back to the inoculation site through peripheral sensory nerves, replicates, and destroys epithelial cells.[4] Histology of skin lesions shows sequential changes of balloon degeneration of infected cells, with condensation of nuclear chromatin, degeneration of cell nuclei and plasma membranes, and formation of multinucleated giant cells. Initially, vesicular lesions appear between epidermal and dermal layers and contain large amounts of virus, cell debris, and inflammatory cells. As additional inflammatory cells are recruited, pustular lesions replace vesicles, and healing ensues. Mucosal membrane lesions are more ulcerative than skin lesions, because the thin layer of epithelium in mucosal lesions ruptures readily. Histologic changes observed in primary infection usually are more severe than those of recurrent episodes.

Occasionally, spread occurs beyond the dorsal root ganglia or the localized mucocutaneous eruption, leading to generalized infection. When the host is unable to contain viral replication, viremia can result in multiorgan involvement. Disseminated clinical infection occurs most often in neonates and patients with compromised immune systems, including pregnant women, but it also occurs rarely in immunocompetent hosts.

Establishment of lifelong latency, interrupted by periods of recrudescence, is an important feature of HSV infections. Maintenance of the latent state probably depends on several factors, including the number of neurons infected during the primary episode, the number involved with each reactivation, and the possible incremental involvement of additional neurons with each recurrent episode.[5] During latency, the HSV genome is maintained in a repressed, noninfectious, static state. Transcriptional latency patterns of HSV-1 and HSV-2 are similar.[6] The molecular basis of latency and reactivation involves the active expression of only a single diploid gene encoding latency-associated transcripts.[7] Maintenance of the virus in this nonreplicating state does not compromise the survival and normal function of host ganglion cells.

Periodic reactivation of HSV and centrifugal spread down the neural axon are associated with the development of recurrent lesions (i.e., clinically apparent disease) or asymptomatic viral excretion (i.e., asymptomatic infection). Several stimuli can precipitate reactivation from a latent state, including manipulation of nerve roots, direct trauma to ganglia or the skin or mucosa innervated by peripheral nerves, exposure to ultraviolet light, stress, hormonal changes such as those accompanying menses, administration of immunosuppressive agents, and illness from another cause.

The likelihood of viral reactivation is related to virus type and the interaction between the virus and the host's immunologic systems. Viral reactivation from latency is common after primary orolabial infection with HSV-1 and after genital infection with HSV-2. In contrast, when primary orolabial infection is caused by HSV-2 or primary genital infection is caused by HSV-1, recurrences are less common, reflecting the adaptation achieved by these two viruses for their usually preferred areas of the body. For example, less than 25% of people have recurrences after first-episode infections of the genital tract caused by HSV-1, whereas more than 60% have recurrences after genital HSV-2 infections.[7,8] The likelihood that recurrences are associated with symptoms depends on the quantity of reactivated virus, virus-cell interactions, and host immune factors.

Immunity

The immune response to HSV is initiated as a containment strategy and continues as a curative strategy.[9] The usual result in normal hosts is the localization of virus to a limited anatomic area with neutralization of infectivity, followed by establishment of latency. Despite extensive investigation, specific immunologic factors that modulate the clinical course and outcome of HSV infections remain incompletely understood. Although HSV infections tend to be more severe in patients with cellular rather than humoral immunodeficiencies, both antibody- and cell-mediated responses are important in influencing the acquisition of disease, the severity of infection, and the frequency of recurrences.[10]

The important role of antibody in HSV infections is evident from investigations of neonates exposed to HSV at the time of delivery. Those exposed to HSV-2 in the presence of transplacentally acquired neutralizing antibody are significantly less likely to contract infection[11] and, if infected, usually have localized disease manifesting later in the neonatal period.[12] Titers of antibodies that mediate antibody-dependent cellular cytotoxicity (ADCC) correlate inversely with severity of neonatal infection.[13]

Humoral immunity also seems to be relevant to the pathogenesis of HSV infections beyond the neonatal period. For example, HSV-1 seropositive stem cell transplant recipients who have HSV-1 seropositive donors have shorter and less frequent episodes of HSV-1 infection than do those who have HSV-1 seronegative donors.[14] Low levels of mononuclear cell ADCC activity in patients with leukemia correlate with greater susceptibility to HSV infections.[15] Antibodies against HSV-1 provide partial protection against HSV-2 infection. Prior HSV-1 infection reduces the risk of contracting HSV-2 infection by about 50%,[16] and a first episode of genital infection caused by HSV-2 is less severe if people have preexisting HSV-1 antibodies.[17] Investigations focused on local defense mechanisms have identified the protein targets of antibodies to HSV and their appearance in mucosal secretions.[18] These studies underscore the role of humoral immune response in HSV infections.

It is well established that the cellular immune response is critical for the control of HSV infections, but which HSV antigens are the most important inducers of protective responses remains unknown. Substantially diminished HSV antigen-stimulated lymphocyte proliferation and reduced interferon production are observed in infected neonates and postpartum women compared with responses in nonparturient adults.[19]

Epidemiology

Most infections caused by HSV are asymptomatic or nonspecific. Defining the epidemiology of HSV has depended on seroepidemiologic studies, which initially were confounded by extensive antigenic similarities between HSV-1 and HSV-2. The development over the past 2 decades of commercially available, type-specific assays for antibodies unique to HSV-1 and HSV-2 has provided a means of reliably determining prior infection with each virus.[20]

Beyond the neonatal period, primary infection with HSV-1 usually occurs in infancy or childhood, whereas primary infection with HSV-2 occurs after the onset of sexual activity. HSV infections occur throughout the world, with humans serving as the only reservoir. Acquisition of virus follows intimate mucocutaneous contact between a susceptible host and a person who is shedding virus during primary infection or reactivation. Because HSV infection results in lifelong latency, the prevalence in any population is cumulative. Because transmission and acquisition of virus usually occur in the absence of symptoms, the spread of infection throughout a population can be silent. These factors account for worldwide endemic HSV infection.

Infections caused by HSV have no seasonal predilection, but geographic location, socioeconomic status, age, and race influence the prevalence of infection in most studies.[3] Data from the United States and other industrialized countries document a decline in HSV-1 seroprevalence among adolescents over the past 1 to 2 decades due to improvements in living conditions, better hygiene, and less crowding.[21–25] Despite these declines, HSV-1 infection remains more common among non-Hispanic US blacks and Mexican Americans than among non-Hispanic US whites and among respondents with lower than higher incomes.[26,27] Approximately one third of children from lower socioeconomic populations and 20% from middle-income populations have serologic evidence of HSV infection by 5 years of age. Prevalence rises in lower socioeconomic populations to more than three fourths by adolescence, although not in middle-income populations until the second or third decade of life.

Beginning in the mid-1960s, population-based studies of genital herpes revealed a rising incidence of clinically evident genital disease, with most first infections occurring in those 18 to 36 years of age.[28] Estimating the prevalence of HSV-2 infection on the basis of clinically apparent genital disease has major limitations of misclassifying HSV-1 genital infections[29–32] and missing most HSV-2 infections, which are inapparent.[33]

Population-based serosurvey studies, which have used type-specific assays that reliably detect antibodies to HSV-2, demonstrated an increase of more than 30% in the prevalence of HSV-2 infections between the late 1970s and the early 1990s.[34] Subsequently, HSV-2 seroprevalence in the United States has decreased, and the current seroprevalence of HSV-2 among young adults is 10% to 20%.[22] Age, race, sex, and history of other sexually transmitted infections (STIs) affect seroprevalence rates. HSV-2 infection rates are comparatively higher among blacks, women, and persons attending STI clinics.[34] Seroprevalence of HSV-2 among pregnant women has ranged consistently from 15% to 30%.[35]

Transmission of HSV-2 typically results from contact with an asymptomatic sexual partner. In one study evaluating contacts of 66 people who had genital herpes, only one third of source partners reported recent genital herpetic lesions, one third described genital symptoms that were atypical of genital herpes, and one third had no prior symptoms.[36] In another prospective study evaluating 144 heterosexual partners in whom one partner was seronegative and the other had symptomatic, recurrent genital HSV, 70% of all transmissions resulted from contact during periods of asymptomatic viral shedding.[37] The reported risk of acquisition of infection in these cohorts is approximately 10% per year.[37,38]

Clinical Syndromes

Orolabial Infection

Primary Infection

Most HSV infections occurring above the waist are caused by HSV-1 and are localized to the mouth and oropharynx (Fig. 204.1). Limited data suggest that only about 10% to 30% of cases of perioral HSV infections in children are associated with signs and symptoms of illness.[39,40] The classic clinical presentation of primary herpetic gingivostomatitis as extensive orolabial HSV lesions with primary HSV infection in the young child is an unusual manifestation.

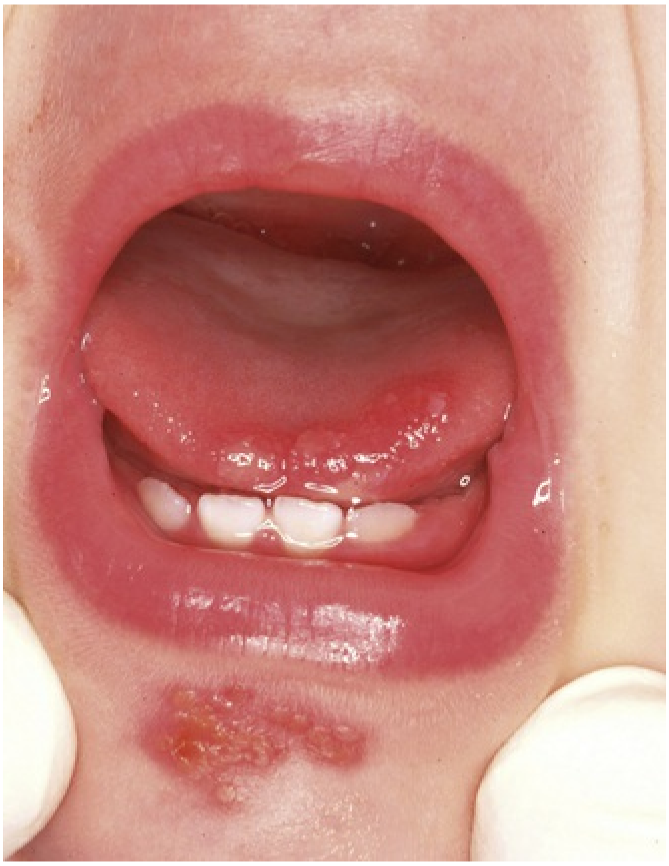

FIGURE 204.1 Toddler with 3 days of high fever and poor intake has typical herpes simplex virus

vesicoulcerative lesions on the tongue and cluster of vesiculobullous lesions below the lip. (Courtesy of J.H. Brien ©.)

When symptomatic disease occurs, high fever, irritability, tender submandibular lymphadenopathy, and mucocutaneous eruption evolve after a mean incubation period of 3 to 4 days. Detection of HSV DNA in the blood by polymerase chain reaction (PCR) occurs in about one third of symptomatic children.[41] Vesiculoulcerative lesions can involve the palate, gingiva, tongue, lip, and facial area.[42,43] Intraoral edema and pain are associated with lesions that evolve from vesicles to shallow ulcers on an erythematous base. The most common reason for hospital admission with primary gingivostomatitis is dehydration resulting from impaired eating and drinking. The duration of symptoms in primary gingivostomatitis ranges from 2 to 3 weeks.

Pharyngitis is a common manifestation of primary HSV infection in older children and adults. HSV has been isolated from the posterior pharynx of 5% to 24% of college students with pharyngeal symptoms.[44,45] HSV pharyngitis cannot be distinguished clinically from other viral and bacterial infections. Common manifestations of illness are pharyngeal erythema, exudative or ulcerative lesions on the posterior pharynx and tonsils, enlarged cervical lymph nodes, and fever.[44,45]

Reactivation of Infection

Reactivation of HSV from the trigeminal ganglia usually is not associated with clinical findings. It is estimated that silent excretion of virus in healthy, previously infected people occurs on about 1% of days for children and 5% to 10% of days for adults.[46] Reactivation of infection commonly follows manipulation of the trigeminal nerve route,[47] dental procedures,[48] or stimuli such as fever, ultraviolet radiation, or exposure to the sun.[49,50] The frequency of recurrences varies, but on average, approximately one third of people with prior infection have clinically evident recurrences.[51]

Signs and symptoms associated with clinical recurrences usually are mild.[52] Many patients have prodromal symptoms of pain, burning, or tingling that precede the eruption by 1 to 2 days. The most common site of recurrent orolabial lesions is the outer edge of the vermilion border. On average, three to five lesions are seen.

Lesions begin as vesicles, evolve into pustules or ulcers in 1 to 2 days, and heal completely within 8 to 10 days. Pain is greatest at the onset of eruption and resolves within 4 to 5 days. Unilateral clusters of lesions can occur on skin along trigeminal nerve distribution, with or without conjunctivitis (see Fig. 82.1 in Chapter 82). Viral excretion and infectivity last only 2 to 3 days; the titer of virus varies from less than 10 plaque-forming units (PFUs)/mL in the prodromal phase to almost 10^5 PFUs/mL in the vesicular phase.

Genital Infection

Familiarity with the serologic classification of genital herpes infection is important for understanding of the biologic and clinical features of the disease.[53] When a person with no prior HSV-1 or HSV-2 antibody acquires either virus in the genital tract, a *first-episode primary infection* results. If a person with preexisting HSV-1 antibody acquires HSV-2 genital infection, a *first-episode nonprimary infection* ensues. Viral reactivation from latency and subsequent antegrade translocation of virus to skin and mucosal surfaces produces a *recurrent infection*, which presupposes preexisting homologous antibody to the reactivating HSV.

Historically, most first-episode genital herpes infections were caused by HSV-2. However, an increasing proportion, especially among young adults, is caused by HSV-1.[29–32] Whereas only 5% to 10% of adults in the United States have a history suggesting prior genital herpes infection, seroepidemiologic studies show that approximately one in five people 30 to 39 years of age and one in four persons 40 to 49 years of age have been infected with HSV-2.[22] Seroprevalence rates exceed 40% among attendees of US STI clinics, with comparatively higher rates for women and blacks.[54]

First-Episode Primary Infection

About 40% of men and 70% of women seeking medical care for primary genital herpes have constitutional symptoms. Headache, fever, myalgia, and backache develop after a mean incubation period of 7 days. Symptoms peak within 4 days of onset of lesions and gradually abate over 7 to 10 days. Local symptoms such as itching and pain usually precede visible lesions by 1 to 2 days. New lesions appear over 7 to 8 days. Lesions evolve from vesicles and pustules to wet ulcers over approximately 10 days and then crust and heal during the ensuing 10 days.

Lesions are distributed over the labia majora, labia minora, mons pubis, vaginal mucosa, and cervix in women. In men, lesions typically occur over the shaft of the penis. About 85% of women have vaginal discharge, and 25% of men have urethral discharge. More than 80% of women and more than 40% of men have dysuria for 7 to 10 days. Tender inguinal lymphadenopathy typically appears during the second or third week of illness in about 80% of both sexes and usually is the last sign to resolve. Mean duration of viral shedding is 11 days.

Extragenital complications of primary HSV infections include aseptic meningitis, mucocutaneous lesions beyond the genital area, pharyngitis, and visceral dissemination. These complications are more common in women than in men.[17]

First-Episode Nonprimary Infection

Almost one half of people with their first clinical outbreak of genital herpes have preexisting antibodies to the heterologous herpes virus. Presumably as a result of the preexisting immunity to shared HSV antigens, these people have lower frequencies of systemic symptoms and extragenital complications, fewer lesions, shorter duration of pain, and more rapid healing than patients with primary infections.[17]

Recurrent Infection

Most recurrences of genital herpes are asymptomatic. About 1% of people previously infected with HSV-2 have active viral shedding without symptoms on any given day.[55] Shedding of HSV from the genital tract occurs in people seropositive for HSV-2, even if they have no prior history of genital herpes.[56] Average duration of episodes of asymptomatic viral shedding is 1.5 days, but it can be as short as a few hours.[57] Recurrent clinical genital herpes usually is mild, with constitutional symptoms in only 5% of men and 10% of women. Of those who have symptoms, more than 40% of women and more than 50% of men have local prodromal symptoms for several hours to 3 days.[17] Genital lesions, which usually are few and confined, typically increase in size over the first 3 days, reach a plateau at 6 days, and resolve rapidly. Mean time to complete healing is 9 to 10 days, and duration of viral shedding is 4 days. Tender lymphadenopathy, dysuria, vaginal discharge, and systemic complications occur less commonly.

Factors implicated in precipitating recurrences include emotional stress, menses, and sexual intercourse. Genital shedding of HSV-2 in women as determined by PCR is increased in the setting of hormonal use, bacterial vaginosis, and high-density vaginal colonization with group B *Streptococcus*.[58]

Keratoconjunctivitis

Ocular herpes infection beyond the neonatal period usually is caused by HSV-1. Approximately 300,000 cases of HSV infection of the eyes are diagnosed each year in the United States.[3] Infection involves one or both eyes, with a typical course of follicular conjunctivitis associated with pain, photophobia, and tearing and followed by chemosis, periorbital edema, and preauricular lymphadenopathy.[59] Periocular skin involvement can occur.

As infection progresses, diffuse punctate lesions occur on the cornea, followed within days by the appearance of serpiginous ulcers. Pathognomonic branching dendritic lesions (see Figs. 82.1, 82.2, and 82.3 in Chapter 82) of the cornea appear and are associated with blurred vision. Deeper stromal structures can be injured, especially after injudicious use of topical corticosteroids. Healing can require more than 1 month.

After primary ocular HSV infection, recurrences are observed in about one third of people during the ensuing 5 years. Recurrences can include reappearance of dendritic ulcerations or deep stromal injury that can threaten sight.

Cutaneous Infections

HSV can infect skin outside the perioral and genital areas. Infection of the pulp or nail bed of the finger is a typical site and is referred to as *herpetic whitlow*. Whitlow is most common in medical and dental professionals, in whom it results from digital contamination with genital and oral secretions, respectively.[60,61] Young children have herpetic whitlow as a result of autoinoculation of HSV-1 during primary oral herpes infection or when an infected adult inoculates the virus while trimming the child's nails by biting them[62] (Fig. 204.2). In adolescents and adults, herpetic whitlow usually follows autoinoculation from genital secretions during first-episode HSV-2 infection.[63]

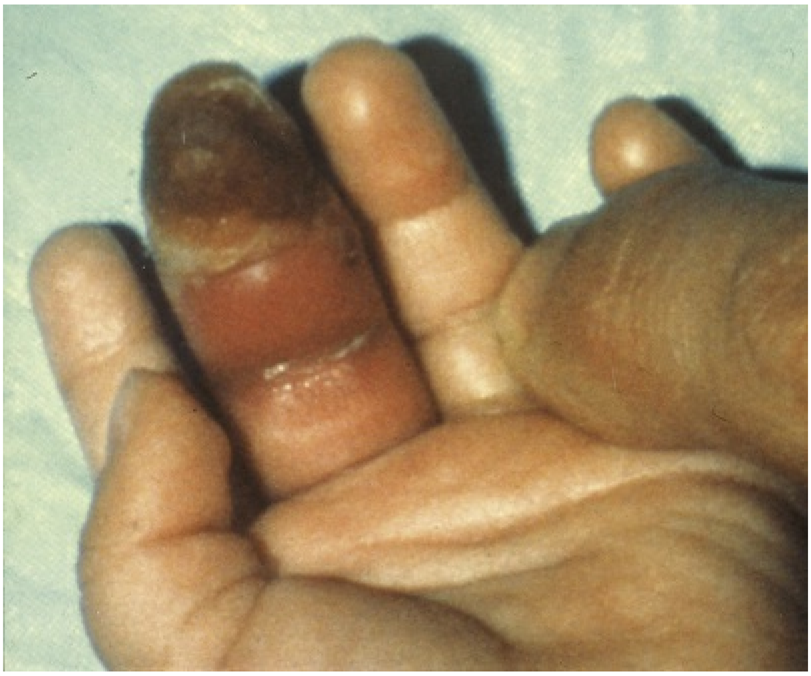

FIGURE 204.2 Herpetic whitlow due to herpes simplex virus type 1 (HSV-1) in an infant whose mother trimmed his nails with her teeth. (Courtesy of S.S. Long.)

Discrete vesicular or pustular lesions arise over the distal phalanx and coalesce over several days, frequently appearing purplish and dusky. Infection is associated with local tingling, burning pain, erythema, and edema, and it can be accompanied by fever, lymphangitis, and tender swelling of related lymph nodes. Lesions often are confused with bacterial cellulitis. Surgical intervention is contraindicated. Crusting of the lesions occurs after about 10 days and is followed by healing and reappearance of normal skin. Lesions recur but at rates lower than those observed with oral or genital disease.

HSV-1 causes cutaneous infection among athletes participating in contact sports, such as wrestling and rugby, referred to as *herpes gladiatorum* and *scrum-pox,* respectively.[64,65] Viral inoculation results from close contact between oral secretions and abraded skin.[66]

Surveys of athletic trainers suggest that this infection is endemic among young competitive wrestlers.[67] In the largest outbreak of herpes gladiatorum reported, infection was diagnosed in 60 high school wrestlers[68]; 73% of infected wrestlers had lesions on the head, 42% on the extremities, and 28% on the trunk. About 25% of the infected boys had fever, chills, and headache, and 40% had sore throat.

Herpes infections of skin damaged by diaper dermatitis, thermal burns, or atopic dermatitis/eczema (i.e., eczema herpeticum) can be particularly severe.[69–71] Rapidly spreading eruptions and visceral dissemination can occur.

HSV is the most commonly recognized precipitating factor for recurrent erythema multiforme and is identified as the precipitant in about one fourth of cases.[72] In one study, HSV type-common glycoprotein antigen (i.e., crude antigen) was found in 12 of 16 skin biopsy specimens of erythema multiforme lesions.[73]

Central Nervous System Infections

HSV causes a variety of central nervous system (CNS) illnesses during and after infection. Self-limited aseptic meningitis occurs after first-episode genital infection. HSV is the most common cause of sporadic fatal encephalitis, accounting for approximately 10% to 20% of viral encephalitis cases in developed countries.[74,75] Beyond the neonatal period, HSV encephalitis typically is caused by HSV-1.

Encephalitis has a biphasic age predilection, with about one third of cases occurring in people younger than 20 years of age and approximately one half of cases occurring in people older than 50 years of age. Encephalitis can occur as a result of primary (~25%–33% of cases) or recurrent infection (~67%–75% of cases).[76–78] Typically, patients have fever, altered consciousness, unusual behavior, and focal neurologic abnormalities, with signs and symptoms consistent with temporal lobe involvement. Although antiviral therapy has resulted in a dramatic decrease in mortality rates, a substantial number of survivors are left with various degrees of neurologic impairment, including cognitive deficits, behavioral disorders, and recurrent seizures.

Patients with HSV encephalitis may have an increased number of red blood cells in cerebrospinal fluid (CSF); counts greater than1000/mm^3 are common, and counts greater than 25,000/mm^3 have been observed.[70] This “hemorrhagic encephalitis” historically suggested HSV encephalitis and was related to HSV's propensity to cause damage across tissue planes, including across blood vessel walls. With earlier diagnosis of HSV encephalitis due to heightened awareness and improved diagnostic testing, CSF red blood cells are seen less often than in the 1970s and 1980s.

The CSF usually has a few hundred white blood cells (WBCs)/mm^3, with a predominance of lymphoid cells (75% to 100%). However, pleocytosis varies from a few to more than 1000 WBCs/mm^3, and occasionally neutrophils predominate; 10% to 20% of CSF specimens can be acellular, especially if obtained early in the disease.[79] Protein concentration is normal in about one half of CSF specimens obtained during the first week of illness, but thereafter, concentrations as high as 500 to 1200 mg/dL are observed.[79]

Production of HSV-specific antibody in the CNS occurs by the second week of illness, resulting in an increased ratio of CSF-to-serum concentration of HSV antibody.[79] Virus can be isolated from culture of CSF in approximately 4% of cases.[77] The finding of HSV DNA in CSF, identified by PCR testing, is sensitive and specific for the diagnosis of HSV encephalitis[80] and has revolutionized confirmation of infection by eliminating the need for brain biopsy. However, CSF obtained before the third day of illness can be falsely negative by PCR.[81,82] If the index of suspicion remains high for HSV encephalitis, a repeat lumbar puncture for CSF analysis by PCR should be performed.

Electroencephalography typically reveals focal spike and slow-wave abnormalities early in the course of HSV encephalitis. A characteristic finding is paroxysmal lateralizing epileptiform discharges (PLEDs). Neurodiagnostic images can be normal at the onset of infection, followed within days by development of edema associated with focal infection or hemorrhagic necrosis. Magnetic resonance imaging is a more sensitive early test than computed tomography (Fig. 204.3).[83]

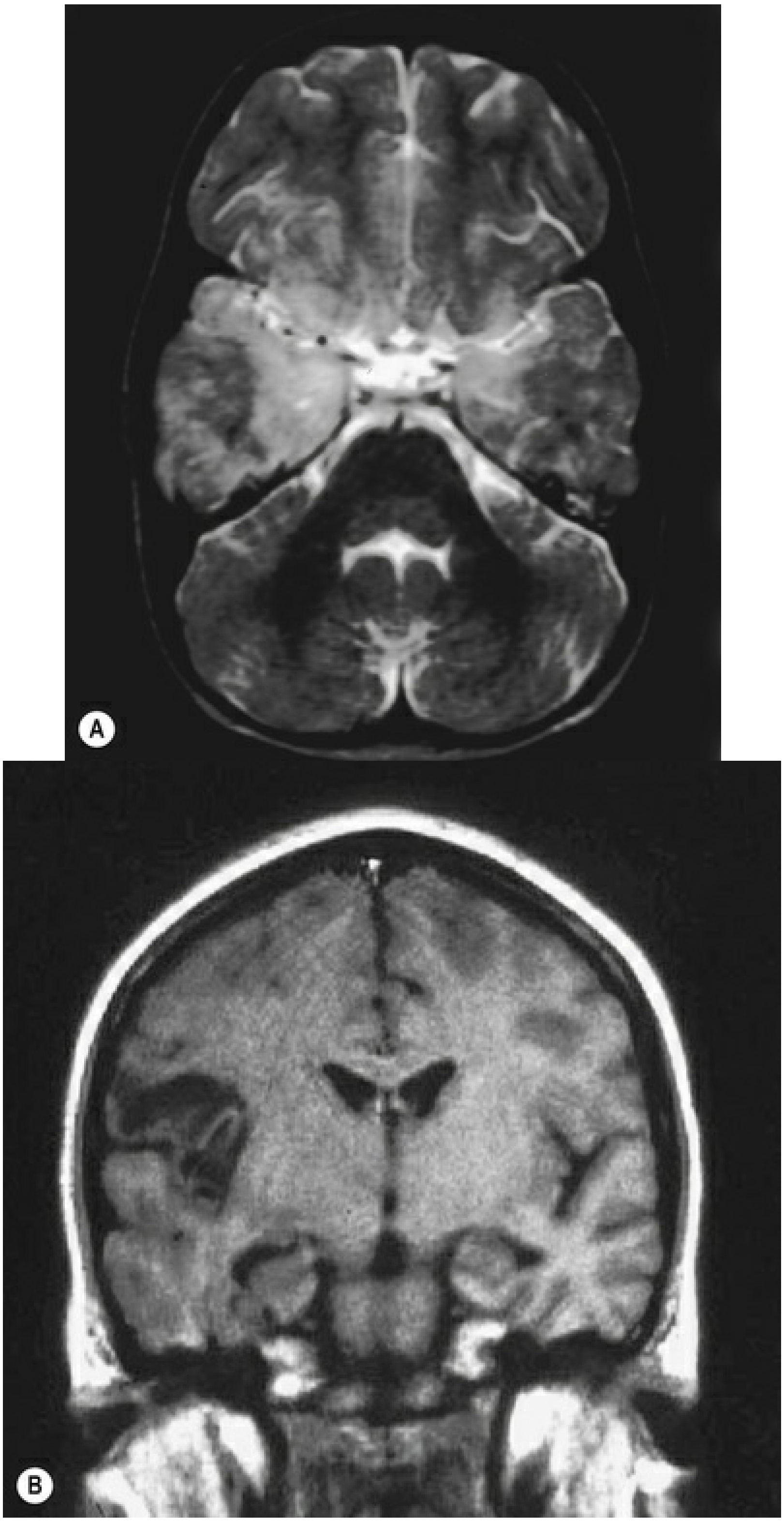

FIGURE 204.3 (A) Axial T2-weighted magnetic resonance imaging (MRI) of a 27-day-old infant with herpes simplex virus type 2 (HSV-2) encephalitis. The image shows edema with necrosis of the temporal lobes bilaterally, with less involvement of parietal lobes. The mother had only a distant history of genital HSV more than 15 years before this pregnancy and no

clinical recurrence within recent years. (B) Coronal T1-weighted MRI of a 13-year-old adolescent with acute onset of left-sided seizures due to HSV-1 encephalitis. Notice the right-sided temporal lobe necrosis and edema. (A, Courtesy of S.S. Long. B, Courtesy of J.H. Brien ©.)

Several unusual CNS manifestations attributed to HSV have been described. They include recurrent aseptic meningitis (i.e., Mollaret meningitis), brainstem encephalitis, ascending myelitis, parainfectious encephalomyelitis (i.e., acute disseminated encephalomyelitis), and encephalomyeloradiculitis.[84] HSV has been implicated in the pathogenesis of several other neurologic syndromes, including Bell palsy, atypical pain syndromes, trigeminal neuralgia, vestibular neuritis, and temporal lobe epilepsy.

Other Infections

Unusual clinical manifestations of HSV have been described in immunocompetent hosts. They include visceral dissemination, esophagitis, tracheobronchitis, pneumonitis, and hepatitis. Viremia with visceral dissemination can result in infection of any organ. Beyond the neonatal period, disseminated infection is more common in adults, especially pregnant women, than in children.

Isolated esophageal involvement has been described in some patients, with a mean age of 35 years.[85] Most infections were caused by HSV-1, and most were primary. Symptoms suggesting esophageal HSV include retrosternal chest pain and odynophagia.

Necrotizing and exudative tracheobronchitis due to HSV can precipitate bronchospasm, often necessitating mechanical ventilation. Most reported cases have involved elderly adults or immunocompromised hosts.[86] HSV pneumonitis can result from spread down the tracheobronchial tree, extension from esophageal involvement, or hematogenous dissemination.

Hepatic infection caused by HSV rarely occurs in normal hosts but rather affects neonates, pregnant women, and persons with underlying conditions.[87] Infection usually is fulminant in nature, with death commonly ensuing as a result of severe hepatic necrosis and consequent uncontrolled liver failure and coagulopathy.

Acute retinal necrosis can occur as a reactivation-immunologic event. It has been reported as long as 9 years after a perinatally acquired infection.[88]

Intrauterine and Perinatal Infections

Congenital (in utero) infection due to intrauterine exposure to HSV is rare.[89–91] Manifestations of congenital infection usually include the triad of cutaneous manifestations (e.g., active skin lesions, scarring from old lesions), ocular involvement (e.g., chorioretinitis, microphthalmia), and CNS abnormalities (e.g., microcephaly, hydranencephaly). Hydrops fetalis has been reported as a rare manifestation.[92] Neonates with in utero HSV infection have disease manifestations apparent within the first 24 to 48 hours of life (Fig. 204.4).

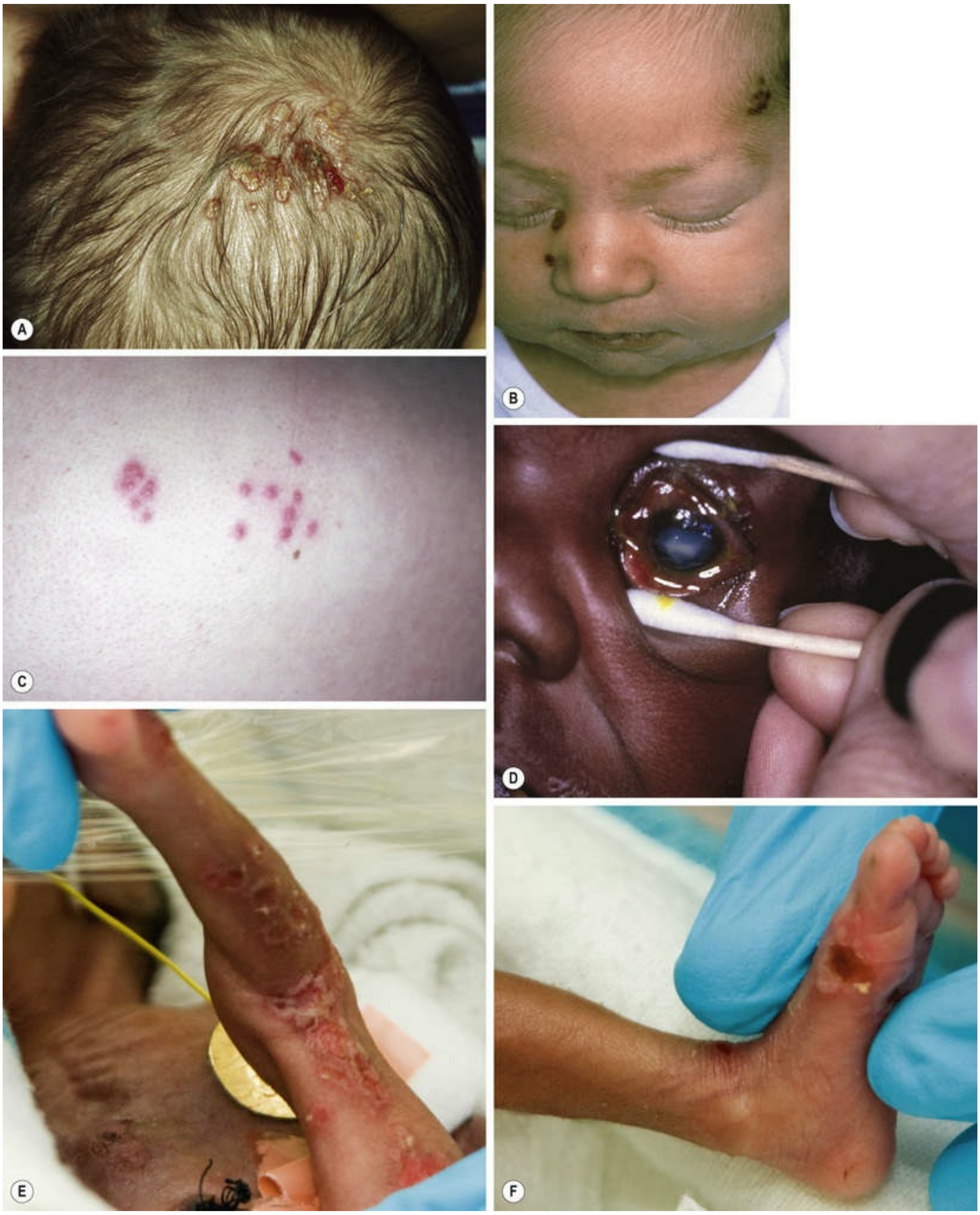

FIGURE 204.4 Mucocutaneous manifestations of herpes simplex virus (HSV) in the neonate. (A and B) Clusters of vesicular lesions are seen at the scalp electrode site and on the face of an infant. (C) Early skin vesicles are seen in another infant. (D) An infant was discharged from the nursery at 2 days of age with the diagnosis of chemical conjunctivitis. He returned at 8 days of age with keratoconjunctivitis. HSV-2 was isolated from the conjunctiva. (E and F) Infant who was born at 25 weeks' gestation and 72 hours after rupture of the membranes (i.e., footling presentation) had

onset of raised vesiculobullous lesions on day 4 of life, with rapid spread down the leg and ulceration. HSV-2 was recovered from mucocutaneous sites, and polymerase chain reaction (PCR) testing was positive for blood and cerebrospinal fluid samples. (A, B, and C, Courtesy of J.H. Brien ©. D, Courtesy of S.S. Long. E and F, Courtesy of S.G. Pinniti, K.N. Feja, M. Hiatt, and R.W. Tolan, Jr., The Children's Hospital at Saint Peter's University Hospital, New Brunswick, NJ.)

Most neonatal HSV infections are perinatally acquired; they result from exposure to virus in the maternal genital tract at delivery.[93] The risk of neonatal infection is largely influenced by the HSV antibody status of the mother. About 50% to 60% of neonates exposed to maternal primary infection acquire HSV infection, whereas infection occurs in approximately 2% of those exposed to recurrent infection at delivery.[11,94]

In neonates, HSV infection manifests in three ways (Table 204.1). Signs of neonatal infection are invariably evident by 4 to 6 weeks of age, and illness with onset after this time is unlikely to be caused by perinatally acquired HSV. Approximately 25% of neonatal HSV infections involve visceral organs (e.g., liver, lungs, bone marrow) with or without brain involvement (i.e., disseminated disease), whereas the other two manifestations by definition do not have dissemination. They are brain involvement with or without skin lesions (i.e., CNS disease), occurring in approximately 30% of neonatal HSV cases, and infection limited to the skin, eyes, and mouth (i.e., SEM disease), occurring in approximately 45% of cases.[95]

TABLE 204.1

Characteristics of Neonatal Herpes Simplex Virus Infections

Feature	Skin, Eye, and Mucous Membrane Infection	Central Nervous System Infection	Disseminated Infection
Usual age at onset	7–14 days	14–21 days	5–12 days
Clinical findings	Vesicles on an erythematous base; conjunctivitis	Lethargy, irritability, fever, seizures	Shock, hepatomegaly, jaundice, bleeding, respiratory distress
Diagnostic testing	Culture of skin lesions, with or	Culture of skin lesions, if present, with or without PCR; DFA of	Cultures of skin lesions, if present, with or without PCR;

	without PCR; DFA of skin lesions	skin lesions; indices and PCR on CSF; EEG; neuroimaging studies	DFA of skin lesions; culture of nasopharynx, axillae, rectum
Mortality rate if treated	0%	5%	30%
Sequelae rate if treated	0%	30%	15%

CSF, cerebrospinal fluid; DFA, direct fluorescent antibody test; EEG, electroencephalogram; PCR, polymerase chain reaction.

SEM disease (see Fig. 204.4) typically manifests during the first 2 weeks of life. Skin lesions tend to appear at sites of trauma, such as the site of attachment of fetal scalp electrodes, the bulb syringe trauma site on palatal mucosa, the margin of the eyes, or at a circumcision site or over the presenting body part. Lesions evolve rapidly from macules to vesicles on an erythematous base. HSV infection should be considered whenever any vesicle appears on a neonate. The outcome of SEM disease is excellent if the diagnosis is made promptly and antiviral therapy is initiated. When the disease is not treated, about 80% of cases progress to disseminated or CNS disease.[95,96]

HSV infection of the CNS tends to manifest slightly later in the neonatal period than other categories of neonatal HSV infection. Typically, fever and lethargy appear between 2 and 3 weeks of age, followed by the onset of seizures, which can be focal and difficult to control; skin lesions exist in about 35% to 40% of cases at the time of presentation. Some infants who come to medical attention quickly have only nonspecific signs and symptoms. In 8 of 8 cases, patients were younger than 14 days of age in one retrospective study,[97] and 15 of 16 were younger than 21 days of age in another.[98]

CSF examination usually reveals a mild pleocytosis (50–400 WBCs/mm^3, predominantly mononuclear), a slightly reduced glucose level, and a modestly to markedly elevated protein concentration (500–1000 mg/dL). The electroencephalogram typically is abnormal diffusely. Computed tomography can be normal early in the course of CNS disease; magnetic resonance imaging is a more sensitive study. Temporal lobe involvement is typical, but diffuse infection can occur. Without therapy, one half of neonates with CNS HSV infection die, and most survivors sustain severe neurologic impairment.[99]

Disseminated neonatal HSV infection often mimics severe bacterial infection, with onset typically occurring during the first 2 weeks of life. Common clinical findings include cardiovascular instability, hepatomegaly, jaundice, bleeding, and respiratory dysfunction. Almost 60% of patients have skin lesions at some time during their illness, but lesions often are absent at the onset of symptoms. Progression of infection is rapid, with death caused by unremitting shock, progressive liver failure, bleeding, respiratory failure, or neurologic deterioration.[96]

Infection in Compromised Hosts

HSV infection in immunocompromised hosts is a frequent source of morbidity but is uncommonly fatal. Risk of severe HSV parallels the extent of compromise of cellular immune responses. The most frequent complication of HSV infections among these patients is severe ulcerations that develop on keratinized and nonkeratinized mucosal surfaces.[100] Oral and genital lesions progress slowly, with accompanying tissue damage and necrosis. Healing takes an average of 6 weeks. Local cutaneous dissemination can occur. Contiguous mucosal spread of infection can result in esophageal, tracheal, or pulmonary involvement or in visceral dissemination.[101]

Laboratory Findings and Diagnostic Techniques

Identification of Virus

Culture.

Culture is the most specific method for diagnosing an active HSV infection. Samples from skin lesions should be obtained by aspiration of the contents of intact skin lesions, swabbing of the bases of denuded skin lesions, or swabbing of the mucosal sites of prior outbreaks. Premoistened cotton swabs are preferred for collection of specimens for culture because calcium alginate–impregnated swabs inhibit virus isolation.[102] If direct inoculation onto culture media at the time of collection is not feasible, specimens should be placed into 1 to 2 mL of medium for viral transport. Specimens transported to reference laboratories at room temperature within 3 days yield adequate recovery of HSV.[103] For prolonged storage, specimens should be maintained at −70°C. Freezing at −20°C before processing and multiple cycles of freezing and thawing reduce the viability of HSV.

The typical cytopathic effect of HSV in vitro is foci of enlarged, refractile cells in the monolayer of a variety of cell culture lines. The time required to observe a cytopathic effect after incubation depends on the concentration of virus in the sample; a cytopathic effect is evident within 24 hours if the sample contains high concentrations of virus and within 4 to 5 days if there is a low concentration. Timing of specimen collection is critical; HSV can be recovered from more than 90% of genital herpes lesions sampled during the vesicular stage but from only about 25% sampled during the crusted stage.[104]

The availability of HSV-specific monoclonal antibody has facilitated the confirmation of virus isolated and the specification of viral type.[105] Specificity of these reagents corresponds well with typing of isolates by restriction enzyme analysis.[106]

Immunofluorescence.

Rapid, reliable direct methods have been developed to detect HSV in specimens obtained from mucocutaneous lesions. The most commonly used method is direct immunofluorescent staining.[106] The best method for specimen collection consists of unroofing a lesion to expose its base, removing cells with the blunt end of a cotton applicator stick, and streaking the sample onto a glass slide. With the use of fluorescein-conjugated monoclonal HSV antibody, direct staining of samples from lesion scrapings is 80% to 90% as sensitive as tissue culture isolation, with few false-positive reactions.[105,107] The Papanicolaou stain or Tzanck test no longer should be used to demonstrate cytologic changes in specimens obtained from suspected HSV lesions because these methods are less sensitive and nonspecific.[96]

Polymerase Chain Reaction.

PCR amplification of HSV DNA is a sensitive and specific diagnostic technique. The most important application of HSV PCR testing is in the diagnosis of HSV encephalitis. First reported in 1990,[108] subsequent studies from several laboratories confirmed the utility of PCR for the diagnosis of HSV encephalitis, with sensitivity and specificity consistently exceeding 90%.[80,109,110,111,112,113] PCR testing is considered the gold standard for the laboratory diagnosis of HSV CNS disease.[80]

PCR testing also is applied increasingly to blood or swab specimens collected from skin or mucosal sites. In one study of 63 infants, 83% had HSV DNA detected in blood, including 64% with CNS disease and 78% with SEM disease.[114] Performance characteristics for specimens collected from genital swabs are well defined,[115,116] but utility for skin and mucous membrane specimens from neonates suspected of having HSV has not been delineated.[117]

Serology

Before 2000, commercially available serologic assays were unable to distinguish between HSV-1 and HSV-2 antibodies, severely limiting their utility. Several type-specific serologic assays that reliably distinguish between immunoglobulin G (IgG) directed against HSV-1 and HSV-2 have since been approved by the US Food and Drug Administration. Many of these products are sold as kits that are used by clinical laboratories throughout the United States.

Monoclonal antibodies to the unique glycoprotein G (gG) of HSV-2 are used to capture protein from an HSV-infected cell sonicated in a solid-phase enzyme immunoassay or to prepare immunoaffinity-purified antigen for use in a dot blot assay.[118] Several additional tests that claim to distinguish between HSV-1 and HSV-2 antibody are available commercially, but high cross-reactivity due to the use of crude antigen preparations limit their utility,[119] and their use is not recommended.

Serologic tests that detect immunoglobulin G (IgG) antibodies cannot be used to diagnose recurrent HSV infection because a rise in antibody titer does not always occur. Primary infections can be confirmed by documenting seroconversion between acute and convalescent sera. A finding of IgM anti-HSV does not distinguish primary infection because reactivation can cause production of IgM antibody. HSV IgM assays also can have unacceptably high false-positive rates.

Treatment

Acyclovir or a derivative is the drug of choice for most HSV infections (Table 204.2).[120] Available formulations include topical ointment, oral tablets and liquid, and a preparation for intravenous delivery. The mechanisms of action, pharmacokinetics, dosages, and toxicities are detailed in Chapter 295.

TABLE 204.2

Systemic Acyclovir Therapy for Herpes Simplex Virus Infections

Type of Infection	Usefulness of Acyclovir Therapy
Orolabial	Possibly effective in severe, primary gingivostomatitis
	Marginally effective in recurrent infections
	Useful prophylactically in limited circumstances
Genital	Effective in treatment of first episode and, to a limited extent, of recurrent infections
	Effective in suppressing frequently recurrent attacks
Keratoconjunctivitis	Topical therapy beneficial (i.e., vidarabine, trifluridine, or acyclovir)
Cutaneous	Possibly effective in severe eruptions in those with compromised integument (e.g., burns, eczema)
	Possibly effective in whitlow infections
	Possibly effective prophylactically in limited circumstances
Central nervous system	Effective in reducing mortality and morbidity of encephalitis
Neonates	Effective in reducing mortality and morbidity rates
Compromised hosts	Effective for therapy of localized and disseminated infections
	Effective prophylactically against recurrent infection
	Resistance can emerge during long-term therapy

Orolabial Infection

In a study of 72 children with documented HSV primary herpetic gingivostomatitis, those who received oral acyclovir compared with placebo had a shorter duration of oral lesions (4 vs. 10 days) and earlier disappearance of fever, extraoral lesions, and drinking and eating difficulties. Duration of viral shedding also was significantly shorter in the group treated with acyclovir (1 vs. 5 days).[121]

Topical and oral acyclovir regimens have been evaluated in the treatment of recurrent herpes labialis. Topical acyclovir is not effective, and oral acyclovir, even when administered immediately at the onset of symptoms, affords marginal benefit in immunocompetent hosts.[122,123] Prophylactic administration of oral acyclovir may be useful in persons with frequently recurrent herpes labialis. In one randomized, double-blind, placebo-controlled study, 56 adults who previously experienced more than six recurrent episodes of herpes labialis in a year had a 53% reduction in clinical recurrences while receiving suppressive therapy with oral acyclovir.[124] Oral acyclovir also has had some benefit in reducing the extent of herpes labialis outbreaks in people who are prone to recurrences as a result of precipitants such as ultraviolet light exposure[49] and alpine skiing.[50]

Genital Infection

Acyclovir is useful in the management of patients with genital herpes, affording greatest benefit in first-episode primary infections and least benefit in recurrent genital herpes.[125,126] Valacyclovir and famciclovir, two antiviral agents with superior bioavailability for oral dosing compared with acyclovir, are safe and equally effective as acyclovir in the therapy of genital herpes.

Intravenous and oral administrations of acyclovir are more effective than topical therapy for primary and nonprimary first clinical episodes of genital HSV infections.[127] Oral administration is preferred for ambulatory patients because it is almost equal in efficacy to intravenous therapy. For primary infection, treatment reduces the duration of viral shedding and the time to complete healing by more than 1 week. In some studies, acyclovir therapy also shortens the duration of new lesion formation, pain, dysuria, and other symptoms.

Treatment does not prevent the establishment of latency or reduce the frequency of subsequent recurrences. Acyclovir has a beneficial although less pronounced effect on the course of recurrent genital herpes, resulting in a reduction of viral shedding and time to healing by 1 to 2 days; the effect on pain and itching is less.[127,128] Patients who tend to have more severe recurrent attacks, with multiple lesions persisting for more than 1 week, may benefit most from treatment. To ensure maximal benefit of therapy, patients may be provided a prescription for acyclovir tablets with instructions to begin the drug at the first indication of recurrence.

Long-term suppressive therapy with acyclovir has substantial value for frequently recurrent genital herpes. Recurrences are reduced by more than 75%, and when lesions occur, they are more likely to be mild. Although the frequency of asymptomatic shedding of HSV is substantially reduced during long-term suppressive therapy, shedding is not eliminated, and sexual transmission of the virus still can occur.[129]

Keratoconjunctivitis

Ocular infections caused by HSV usually are treated topically in conjunction with parenteral therapy in the neonate. Trifluridine or ganciclovir ophthalmic drops or ointment are used commonly (see Chapter 82). Oral acyclovir as prophylaxis against recurrent stromal keratitis appears to be effective at reducing long-term scarring from herpes infection.[130]

Cutaneous Infections

Sparse data exist regarding the treatment of cutaneous HSV infections in the normal host beyond the neonatal period. One study of nine evaluable subjects with recurrent lesions on the hand caused by HSV-2 concluded that oral acyclovir therapy had a beneficial effect on the duration of symptoms, signs, and culture positivity.[131] Treatment of cutaneous infections should be considered for burned patients or patients with eczema because infections in these hosts are potentially serious.

Central Nervous System Infection

In the first study that documented the efficacy of antiviral therapy of a CNS viral disease, vidarabine was shown to significantly improve the outcome of patients with HSV encephalitis.[132] The mortality rate was reduced from 70% among placebo recipients to 44% among drug recipients. A subsequent controlled intervention trial determined acyclovir to be superior to vidarabine.[76] The mortality rate was reduced from 54% among vidarabine recipients to 28% among acyclovir recipients. Survival was significantly affected by the age of the patient, the Glasgow Coma Scale score, and the duration of disease at onset of therapy. Age and the Glasgow score also significantly influenced morbidity observed 6 months after diagnosis. Outcome was best for those younger than 30 years of age with a Glasgow score greater than10 at the onset of therapy.[76]

A subsequent uncontrolled study of acyclovir therapy for HSV encephalitis in adults observed a worse long-term prognosis for subjects with a poor physiology score on hospitalization and for those for whom therapy was delayed more than 2 days after admission.[133] A low Glasgow score (but not necessarily presence of seizures) and age younger than 3 years appear to predict a poor outcome of HSV encephalitis in children treated with acyclovir.[112] Beyond the perinatal period, which is discussed later, acyclovir is given at a dose of 30 to 45 mg/kg/day in divided doses every 8 hours. Administration calculation as 500 mg/m^2/dose every 8 hours may be superior, particularly to avoid excessive dosing and renal injury associated with weights less than 50 kg.[134]

Other Infections

There are no controlled data regarding the effectiveness of antiviral therapy in patients with unusual manifestations of HSV infection. It is prudent to administer parenteral acyclovir to those with severe, life-threatening infections.

Intrauterine and Perinatal Infections

Antiviral therapy is beneficial for neonates with HSV infections. Vidarabine was the first agent with demonstrable benefit, reducing the mortality rate of disseminated or CNS infection from 70% among placebo recipients to 40% among vidarabine recipients. Acyclovir is now the drug of choice.[135]

An open-label evaluation of increasing dosages of intravenous acyclovir support the use of a 21-day course of 60 mg/kg/day to treat neonatal CNS and disseminated infection.[117,136] A 14-day course of 60 mg/kg/day is recommended for infants with SEM infection, even if HSV is detected in blood by PCR.

The best therapeutic results are obtained for localized SEM infection, with no deaths and with universally good neurodevelopmental outcomes.[95] In contrast, approximately 30% of infants with disseminated infection die.[136] There have been anecdotal reports of recovery from or survival of fulminant hepatic failure after liver transplantation and while receiving plasmapheresis of hemofiltration awaiting transplantation. About 5% of infants with CNS disease die despite therapy, and only 30% of survivors are normal at 1 year of age without additional suppressive therapy.[135,136] Recurrence of CNS symptoms with abnormal CSF findings occurs in about 8% of survivors of disseminated or CNS disease.[135] Six months of suppressive oral acyclovir (300 mg/m^2 per dose, 3 times daily) begun immediately after initial therapy of CNS infection improves neurodevelopment outcome assessed at 12 months of age and decreases the number of skin recurrences in all disease classifications of neonatal HSV.[137]

Although neonates with proven HSV infections should receive acyclovir promptly, the role of empiric acyclovir therapy is not clear. The relative risks of drug exposure and potential prolongation of hospitalization are weighed against the risk of delayed therapy.[138] Clinical settings in which empiric acyclovir therapy should be considered include the appearance of skin lesions typical of HSV while awaiting results of diagnostic tests, fever or other unexplained signs of infection in a neonate known to have been exposed to HSV at delivery, progressive clinical deterioration in an infant initially suspected to have bacterial sepsis for whom bacterial culture results are negative, and unexplained encephalitis in a neonate with unremitting seizures.[95,139]

When considering antiviral therapy in a neonate suspected of having HSV infection, the following specimens should be obtained: swab specimens from the mouth, nasopharynx, conjunctivae, and anus (i.e., surface cultures) for HSV culture and, if desired, for PCR testing; specimens of skin vesicles and CSF for HSV culture and PCR testing, respectively; whole blood for PCR testing; and serum samples for measuring alanine aminotransferase (ALT).[117] Guidance is available from the American Academy of Pediatrics (AAP) for the evaluation and treatment of infants born to women with active genital lesions.[140]

Compromised Hosts

Acyclovir is the drug of choice for the management of progressive mucocutaneous HSV in patients with compromised immune function. Therapy speeds healing of localized lesions and reduces the morbidity and mortality rates due to visceral dissemination.[141]

Emergence of HSV strains resistant to acyclovir is more common in the management of HSV infections in immunocompromised hosts than in normal hosts.[142] The prevalence of acyclovir-resistant strains among immunocompromised hosts varies according to the type and degree of immunosuppression, but it usually ranges between 5% and 10%.[143] HSV strains resistant to both acyclovir and foscarnet have been isolated from patients in whom sequential therapy with the two drugs failed.[144]

Prevention

Several candidate HSV vaccines have been developed from extracts of infected cells or recombinant virus glycoproteins, and newer vaccine approaches include DNA-based vaccines and replication-impaired viruses.[145–147] No tested vaccine has effectively prevented infection or establishment of latency,[31,145] and prevention of HSV infection depends on reducing transmission, acquisition, and reactivation of the virus. Complete prevention of transmission of genital HSV infection requires sexual abstinence because most infections are subclinical; consistent condom use provides some protection.

Reduction in the vertical transmission of HSV could be accomplished by reducing maternal infections or the likelihood of transmission to the neonate. Although suppressive acyclovir reduces clinical genital HSV reactivation, it does not eliminate asymptomatic viral shedding.[129] Because most women infected with HSV-2 have no history of genital herpes, it is unlikely that this method will be a practical approach to reducing the risk of infection of neonates born to previously infected mothers. Development of neonatal HSV disease in infants born to women on suppressive antiviral therapy has been reported.[148] Preventing the acquisition of new infections during pregnancy is complicated by the high proportion of genital infections transmitted from partners not known to be infected with HSV-2 and by the increasing incidence of genital HSV-1 infection.

Strategies to identify women who are shedding virus at parturition and thereby prevent transmission by cesarean delivery have been confounded by the need to recognize clinical lesions before progression of labor. These strategies are further frustrated by the occurrence of asymptomatic viral shedding, even in primary episodes. Use of prenatal cultures fails to predict shedding of virus at delivery and is not recommended.[149] Recognizing these limitations, the AAP has provided guidance for management of infants born to women with active genital lesions.[140]

Long-term suppressive therapy with acyclovir reduces reactivation of latent genital and orolabial HSV infections.[124,129] Once-daily suppressive valacyclovir therapy, administered to the infected partner of immunocompetent, heterosexual, monogamous couples who are discordant for HSV-2 infection reduces transmission of HSV to the uninfected partner.[150] Prophylactic acyclovir also has been used successfully in immunocompromised hosts, including those with bone marrow and renal transplants, cancer, and other immunodeficiencies. In these immunocompromised hosts, the frequency of HSV reactivation typically is reduced from 60% to 80% among placebo recipients to 0% to 10% among acyclovir recipients.[151] Availability of rapid virus identification and specific serologic tests could inform a graded approach in the future.

Key Points

Diagnosis and Management of Neonatal Herpes Simplex Virus Infections

Epidemiology

- The rate of neonatal infection is 1 case per 1700 to 1 case per 12,500 live births in the United States; the most reliable incidence rate is 1 case per 3200 live births.
- Infections acquired in utero (congenital) are rare, representing less that 5% of all cases.
- Most infections result from exposure at delivery to mothers shedding virus in the absence of symptoms.
- Maternal primary infection is associated with a much higher neonatal attack rate than maternal recurrent infection (50–60% vs. 2%).

Clinical Features

- There are three classic presentations
  - Skin, eye, and mucous membrane (SEM) infection characterized by skin vesicles at sites of trauma, mucosal lesions, and conjunctivitis (45% of cases of neonatal herpes simplex virus [HSV] disease)
  - Disseminated infection resembling bacterial sepsis with shock, liver failure, bleeding diatheses, and respiratory failure (25% of cases of neonatal HSV disease)
  - Central nervous system infection with irritability, lethargy, and typified by seizures (30% of cases of neonatal HSV disease)
- Usual age of onset is 5 to 21 days; SEM and disseminated infection typically is earlier (average, 10–12 days of life); central nervous system (CNS) infection typically is later (average, 17–19 days of life).
- High (>70%) mortality rate for untreated disseminated disease
- Reduced mortality rate with antiviral therapy but persistent morbidity, except for SEM infection

Diagnosis

- Culture and direct fluorescent antibody test of skin lesions, with or without polymerase chain reaction (PCR)
- Viral cultures of specimens obtained from skin and mucous membranes (i.e., surface sites), with or without PCR
- Cerebrospinal fluid analysis, including PCR
- Whole blood PCR

- Serum alanine aminotransferase (ALT) level
- Electroencephalography and brain imaging (i.e., computed tomography, magnetic resonance imaging, or cranial ultrasonography)

Treatment

- Intravenously administered acyclovir, 60 mg/kg/day in 3 divided doses for 14 days (SEM infection) to 21 days (disseminated and CNS infection) days; followed by orally administered acyclovir, 300 mg/m^2/dose × 3 doses/day (900 mg/m^2/day) for 6 months

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205

Varicella-Zoster Virus

Ann M. Arvin

Varicella-zoster virus (VZV) is an alphaherpesvirus that is related most closely to herpes simplex virus (HSV). Primary infection with VZV causes varicella, commonly called *chickenpox.* VZV establishes latent infection in dorsal root ganglia and can reactivate to cause herpes zoster, often referred to as *shingles.* The double-stranded DNA genome of the virus encodes more than 70 proteins, including regulatory and virion structural proteins and envelope glycoproteins.[1,2] VZV replication usually involves synthesis of a viral thymidine kinase, making the virus susceptible to inhibition by acyclovir and related antiviral agents.

Pathogenesis

The pathogenesis of primary VZV infection (Fig. 205.1) begins with mucosal inoculation by virus transferred by the respiratory route or by direct contact with skin lesions of patients with varicella or herpes zoster. T lymphocytes from tonsils are highly susceptible to VZV infection. Because tonsillar crypts are lined with epithelial cells, VZV is presumed to gain access to lymphocytes in lymphoid tissues of the oropharynx, initiating a cell-associated viremia.

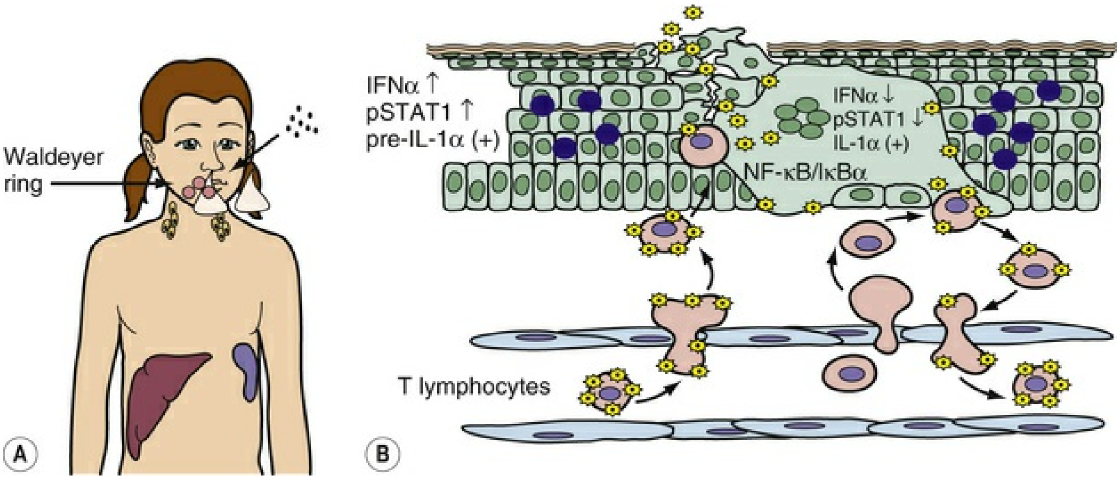

FIGURE 205.1 Modeling the pathogenesis of varicella-zoster virus (VZV) infection. (A) Primary infection with VZV is initiated by inoculation of respiratory epithelial cells, from which the virus gains access to highly permissive T lymphocytes in the tonsillar lymphoid tissues that comprise Waldeyer ring. During the 10- to 21-day incubation period, the virus is transferred to skin sites of replication and can replicate in reticuloendothelial organs (e.g., liver, spleen). Replication in epidermal cells causes the characteristic rash of varicella, which often is referred to as *chickenpox.* The virus reaches neurons in sensory ganglia during primary infection by the hematogenous route or by anterograde transport along neurons from skin lesions, where it establishes latency. (B) The formation of skin lesions that penetrate the skin surfaces requires 10 to 21 days because cell-to-cell spread of the virus after T lymphocyte transfer is countered by the potent innate antiviral responses of epidermal cells. Uninfected T lymphocytes that traffic through sites of VZV lesion formation may amplify VZV viremia. This well-regulated virus-host interaction in skin enhances opportunities for VZV transmission. IFNα, interferon α; pSTAT1, phosphorylated signal transducer and activator of transcription 1; pre-IL-1α, pre-interleukin-1α; NF-κB, nuclear factor-κB; ↓,decreased; ↑,increased; +, positive. (Modified from Cohen J, Straus S, Arvin A. Varicella-zoster virus. In: Fields BN, Knipe DH, Chanock R, et al. [eds]. Virology, 5th ed. Philadelphia, Lippincott-Raven, 2007, pp. 2774–2808.)

Studies in the SCID-hu mouse model of VZV pathogenesis show that the virus is transported by infected human T lymphocytes to skin xenografts within 24 hours. These experiments indicate that

VZV reaches skin early, but viral replication is countered by an innate antiviral response, characterized by interferon α/β (IFNα/β) production.[3] The 10- to 21-day incubation period appears to be the interval required for VZV to overcome this vigorous innate epidermal cell response (see Fig. 205.1). VZV viremia then is enhanced as uninfected T lymphocytes traffic through infected skin; replication in reticuloendothelial tissues also may contribute to amplification.[4]

VZV is carried back to respiratory mucosal sites during the late incubation period, as is evident from transmission to susceptible contacts exposed 24 to 48 hours before the appearance of cutaneous lesions in the index case.[5] The release of infectious virus into respiratory droplets is a pathogenic characteristic that differentiates VZV from other human herpesviruses. Latent infection of cells in dorsal root ganglia appears to be an invariable consequence of primary VZV infection. VZV persists predominantly or exclusively in neurons.[1]

VZV reactivation causes a localized vesicular rash that usually involves the dermatomal distribution of a single sensory nerve. Infectious VZV is present in herpes zoster lesions, but the virus does not appear to be released into respiratory secretions during reactivation. Although subclinical reactivation has been difficult to document, it is likely to occur unless maintenance of VZV latency is unusually effective compared with that of other herpesviruses.[1]

Reinfection with VZV is rare. Apparent second episodes of varicella are encountered in clinical practice, but laboratory diagnosis of the first episode usually is lacking, and vesicular rashes in childhood have many possible causes. Immunocompromised patients who have had varicella can have scattered cutaneous lesions suggesting reinfection, but most cases probably represent generalized atypical reactivation of latent virus without limitation to a dermatomal distribution.

Primary VZV infection elicits immunoglobulin G (IgG), IgM, and IgA antibodies directed against viral proteins.[6,7] Antibodies to VZV proteins have neutralizing activity and mediate destruction of infected cells by antibody-mediated cellular cytotoxicity. However, intact cellular immunity appears to be critical for the host to terminate viremia and virus replication at localized cutaneous sites.[8] Children with untreated agammaglobulinemia usually have uncomplicated varicella, whereas those with primary cell-mediated immunodeficiency diseases often die. Among children with malignancy, failure to acquire T lymphocytes that recognize VZV antigens correlates with persistent viremia and a high risk of visceral dissemination.[1] Early nonspecific immunity, such as natural killer cell cytotoxicity and the induction of IFNα production, also may be beneficial. Administration of exogenous IFNα has modified the severity of varicella in immunocompromised children.[9]

Primary VZV infection elicits memory T lymphocytes that exhibit helper and cytotoxic activity and continued production of specific antibodies. Persistent VZV immunity may be maintained by periodic re-exposure to the virus during annual epidemics or by repeated antigenic stimulation from subclinical reactivation. Diminished T-lymphocyte recognition of VZV antigens probably accounts for the increased risk of herpes zoster in immunocompromised children.[6] The short interval between primary and recurrent VZV infections in children with human immunodeficiency virus (HIV) infection and herpes zoster in young children after intrauterine or early postnatal varicella probably reflects poor induction of cell-mediated immunity.[10–13]

Epidemiology

VZV is restricted to the human host and is found worldwide. Before the licensure of varicella vaccine, an estimated 4 million cases of varicella occurred annually in the United States, which is equivalent to the annual birth cohort. In temperate climates, 90% to 95% of people acquire VZV in childhood as a result of annual varicella epidemics that occur during the late winter and spring. Adults with herpes zoster provide a continuing source for potential exposures to VZV, causing varicella in susceptible contacts who perpetuate transmission by the respiratory route and because of high titers of cell-free infectious virus in skin lesions.[1,2]

The attack rate for previously uninfected household contacts exposed to varicella is approximately 90%, whereas the transmission rate from less sustained exposures, such as in school classrooms or hospitals, is much less predictable and may be as low as 12% to 33%. For unexplained reasons, because the attack rates for varicella are much lower in tropical areas, more adults remain susceptible. Molecular analyses of virus isolates from various geographic areas do not suggest major alterations in the pathogen that could account for variations in geographic prevalence.[14]

Herpes zoster shows no seasonal variation. Herpes zoster is uncommon among children younger than 10 years of age (0.74 cases per 1000) compared with 3.4 cases per 1000 persons annually among people in the general population.[15] The incidence of herpes zoster is higher among children with prior VZV infection who are immunocompromised.[10] Primary VZV infection acquired in utero or during the first year of life also is associated with an increased risk of herpes zoster in early childhood.[11–13]

Wild-type strains of VZV that cause annual epidemics of varicella do not exhibit changes in virulence, as judged from the clinical severity of primary VZV infections from year to year. The risk of severe or life-threatening primary or recurrent VZV infections appears to depend on host factors rather than alterations of the virus.

Varicella

Clinical Manifestations

The incubation period of primary VZV infection is 10 to 21 days; symptoms most commonly begin between 14 and 16 days after exposure.[1,2] Varicella often is mild enough to escape diagnosis, but subclinical varicella is rare when exposed, susceptible children are examined prospectively during the period of risk.[16] About one half of children have prodromal symptoms, including fever, malaise, anorexia, headache, and occasionally, mild abdominal pain for 24 to 48 hours before the appearance of rash. Constitutional symptoms are prominent during the 24 to 72 hours after the first cutaneous lesions develop, but significant respiratory or gastrointestinal symptoms are unusual. Temperature elevation usually is moderate, ranging from 37.8°C to 38.8°C, but it can be as high as 41.1°C.

Varicella lesions appear first on the scalp, face, or trunk. The initial exanthem consists of erythematous macules that evolve to form clear, fluid-filled vesicles. Vesicles with a surrounding irregular margin of erythema often are described as resembling a dewdrop on a rose petal (Fig. 205.2). Varicella lesions in early stages usually are pruritic. After 24 to 48 hours, fluid becomes cloudy, and some lesions exhibit characteristic umbilication as crusting begins. As initial lesions begin to resolve, new crops form on the trunk and then the extremities. Late lesions may disappear without progressing to vesicle formation. Crusts are sloughed during the final phase as new epithelium is generated beneath the lesion site. Vesicles or small ulcers are common on mucous membranes of the oropharynx, conjunctivae, and vagina.

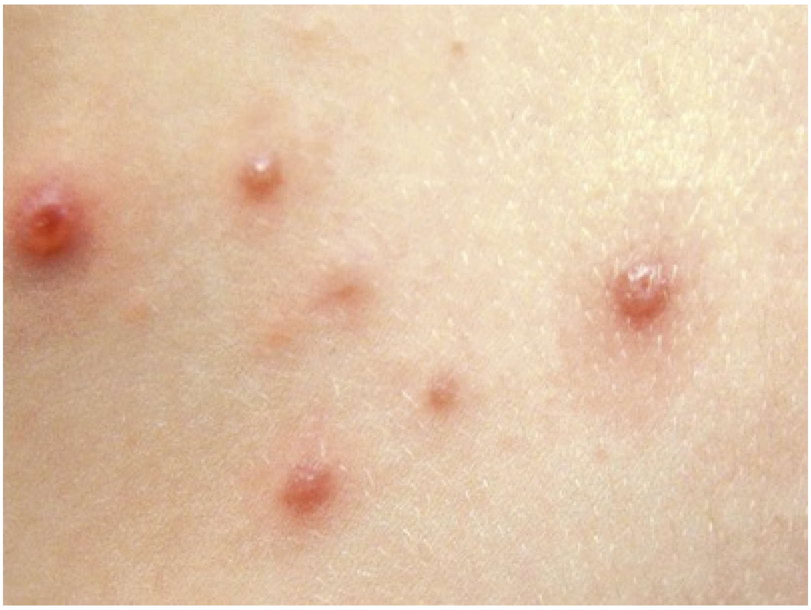

FIGURE 205.2 Early varicella lesions in various stages, including one called *dewdrop on a rose petal*.

In otherwise healthy children, new lesions appear for 1 to 7 days. In a prospective study of 521 children, more than one half demonstrated new lesions for 3 to 6 days, whereas only 1 child had new lesions for 7 days.[16] The total number of varicella lesions ranged from 12 to 1968 per child, with most children having more than 300 lesions. The duration of fever and new lesion formation is likely to be longer among children who have varicella after household exposure.[16,17] The severity of the illness also increases with increasing age. Preexisting skin trauma, such as eczema or scarring acquired during the incubation period (e.g., sunburn, surgery), exacerbates the exanthem at those sites. Extensive scarring is unusual, but hypopigmentation often persists for several weeks, especially in older children and children with darker skin. A single, shallow scar on the forehead is a common consequence of varicella because the initial lesions, which often occur along the hairline or eyebrow, involve deeper layers of the skin.

Varicella eruption must be differentiated from vesicular rashes associated with infections caused by other common pathogens, such as enterovirus or *Staphylococcus aureus*, or from rashes due to drug reactions, contact dermatitis, or insect bites. Early skin lesions may be particularly difficult to recognize clinically.

Complications in Healthy Children

Bacterial Infections

Secondary bacterial infections constitute the most common cause of morbidity in otherwise healthy children.[18–26] *S. aureus* and *Streptococcus pyogenes* are usual pathogens (see Fig. 118.3 in Chapter 118). Impetigo often is diagnosed, but it is difficult to differentiate from larger lesions caused by the virus alone. Bullous varicella can represent an unusual presentation of cutaneous VZV lesions or can be caused by bacterial superinfection.

Cellulitis is the most common complicating infection, but lymphadenitis and subcutaneous abscesses also occur. Cellulitis of the soft tissues of the neck can result in severe edema that compromises the airway. Life-threatening varicella gangrenosa associated with exotoxin A–producing *S. pyogenes* typically manifests as erythema, warmth, and pain of the skin around a single varicella lesion that enlarges rapidly over a few hours, often turning a dusky, dark red color. Extensive edema develops in the soft tissue around the lesion, producing necrotizing fasciitis (Fig. 205.3).

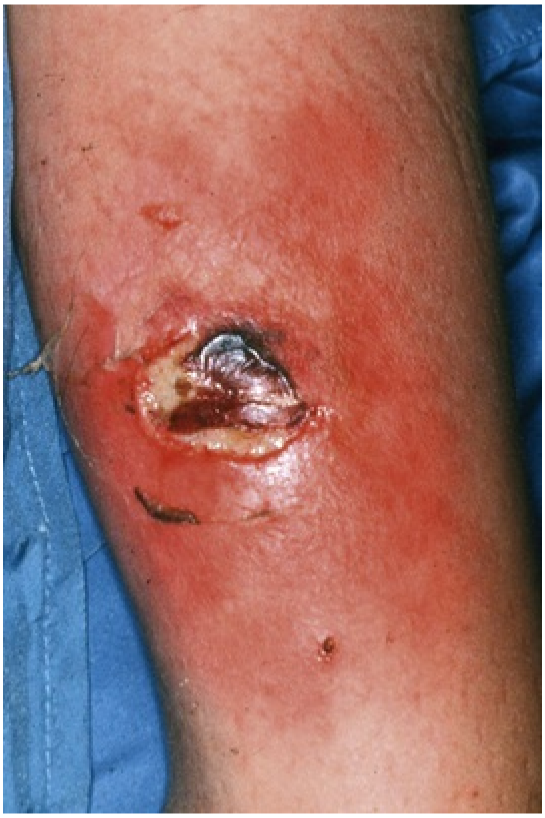

FIGURE 205.3 Group A streptococcal necrotizing fasciitis complicating otherwise mild varicella. (Courtesy of J.H. Brien ©.)

Varicella lesions provide a portal of entry, occasionally resulting in transient bacteremia or septicemia associated with high fever, cardiovascular collapse, and disseminated intravascular coagulopathy. Varicella can be complicated by community-associated methicillin-resistant *S. aureus* (CA-MRSA).[27] Hematogenous spread of *S. aureus* or *S. pyogenes* can result in focal infection, including pneumonia, arthritis, and osteomyelitis.

Neurologic Complications

Varicella is associated with a spectrum of central nervous system (CNS) complications in children. Neurologic complications are the second most common indication for hospitalization of immunocompetent children with varicella.[19–29] Varicella accounted for 13% of reported encephalitis cases of known cause in the United States between 1972 and 1977.[24] The incidence of CNS morbidity is highest among patients younger than 5 and older than 20 years of age.[20,26]

Neurologic manifestations include acute cerebellar ataxia, encephalitis, meningitis, isolated seizures, Guillain-Barré syndrome, transverse myelitis, acute disseminated encephalomyelitis, and ischemic stroke.[28,29] Signs of varicella encephalitis and of cerebellar ataxia have been described during the incubation period and after resolution of cutaneous disease, but in most cases, the neurologic symptoms occur between 2 and 6 days after onset of the rash.[7,28,29]

In two self-controlled case series of adults (with some children included), the stroke rate was increased for 6 months after chickenpox (fourfold increase among children)[30] and herpes zoster.[31] In a report of neurologic complications after chickenpox in 84 children hospitalized in Toronto from 1999 to 2012, 10 had arterial ischemic stroke. The median age was 4.25 years (range, 2–11.5 years), and the time from VZV exanthem to stroke was 16 weeks (range, 2–16 weeks). The median cerebrospinal fluid (CSF) cell count was 2 cells/mm^3 (range, 0–84), and the median protein level was 19 mg/dL (range, <10–133).[28]

The prognosis varies. Rapid improvement in acute encephalitis and cerebellar ataxia is usual. Reye syndrome can accompany varicella, but it has become rare because salicylates are contraindicated in children with varicella.[32]

Other Complications

In a prospective study of healthy children with varicella, 49% had mild elevations of aspartate aminotransferase (AST) (32–50 IU/L), and 28% had AST concentrations greater than 50 IU/L. Varicella hepatitis usually is subclinical, although some children with the highest elevations of AST (200–800 IU/L) have severe vomiting.[33] These cases can be differentiated from stage 1 Reye syndrome only by liver biopsy.

Acute thrombocytopenia, which is associated with petechiae and purpuric skin lesions, hemorrhage into the varicella vesicles, epistaxis, hematuria, and gastrointestinal bleeding, is a reported complication of varicella,[1] with cell counts remaining low for days to weeks. Postinfectious thrombocytopenia occurs 1 to 2 weeks after varicella, and bleeding complications can persist for an average of 5 weeks. Purpura fulminans due to arterial thrombosis is a rare but life-threatening complication of varicella.

Renal complications of primary VZV infection are rare.[1] Nephritis with hematuria, diffuse edema, and hypertension is described within 3 weeks after varicella exanthem; many cases represent poststreptococcal glomerulonephritis. Nephrotic syndrome and hemolytic uremic syndrome have been reported in a few children. Viral arthritis is an infrequent complication, with isolation of VZV from joint fluid. Arthritis resolves spontaneously within 3 to 5 days and is not associated with residual joint disease.

Other rare complications of varicella are myocarditis, pericarditis, pancreatitis, and orchitis. Many children have vesicular lesions on the eyelids and conjunctivae, but serious ocular complications of varicella are unusual.

Complications in High-Risk Populations

Progressive disease caused by primary VZV infection occurs in older adolescents and adults, immunocompromised children, pregnant women, and neonates.

Adolescents and Adults.

Clinically significant varicella pneumonia is rare in children, but otherwise healthy adults are more susceptible to pneumonia, which accounts for most of the increased morbidity and mortality rates attributed to primary VZV infection in this age group.[26,34,35] VZV pneumonia is associated with cough and dyspnea, usually beginning within 1 to 6 days (average, 3 days) after onset of the rash. Patients have cough, with or without cyanosis, pleuritic chest pain, and hemoptysis. Hypoxemia often is more severe than is suggested by the physical findings. The chest radiograph can be normal or can show diffuse bilateral infiltrates with small nodular densities, especially in the perihilar area.

Varicella pneumonia often is transient, resolving completely within 24 to 72 hours. In severe cases, interstitial pneumonia can progress rapidly to respiratory failure.

Pregnancy.

Varicella acquired during pregnancy can have severe consequences for the mother and fetus. Because most adults born in the United States are immune, the incidence of maternal varicella is low, affecting 0.7 in 1000 women in a study of 30,000 pregnancies in the 1960s.[36] Varicella pneumonia is the major cause of maternal morbidity and mortality.[37–39] Spontaneous abortion, fetal demise, and premature delivery can occur, although the frequency of these complications is low.[37–40]

In rare instances, maternal varicella results in congenital varicella syndrome (Box 205.1).[2] The highest risk of severe embryopathy accompanies varicella acquired during the first 20 weeks of gestation and is estimated to occur in less than 2% of cases of maternal varicella.[2,36–41] Infants affected after maternal varicella contracted later in pregnancy are described, but defects are limited to cutaneous scarring, diminished limb growth, or unilateral ocular defects.[41]

Box 205.1

Clinical Manifestations of the Congenital Varicella Syndrome

Skin

Cutaneous defects

Cicatricial scars

Hypopigmentation

Bullous lesions

Extremities

Hypoplastic limb

Muscular atrophy and denervation

Joint abnormalities

Absent or malformed digits

Eye

Chorioretinitis

Microphthalmia

Anisocoria

Central Nervous System

Intrauterine encephalitis with cortical atrophy

Seizures

Mental retardation

Urinary Tract

Hydronephrosis or hydroureter

Gastrointestinal Tract

Esophageal dilation or reflux

The most striking anomalies of the congenital varicella syndrome are unusual cutaneous defects with cicatricial skin scars, atrophy of an extremity, and evidence of damage to the autonomic nervous system. Many affected infants have microcephaly and cortical atrophy due to probable intrauterine VZV encephalitis. Seizures and global developmental delay are common sequelae. Chorioretinitis, microphthalmia, and cataracts also occur. Dysfunction of the autonomic nervous system produces neurogenic bladder, hydroureter, hydronephrosis, and severe gastroesophageal reflux with recurrent aspiration pneumonia.[42] Limb anomalies and other sequelae of intrauterine varicella infection can be detected with fetal ultrasonography.[43] Some intrauterine infections are asymptomatic, as shown by VZV-specific immunity or the occurrence of herpes zoster in infancy without an intervening episode of varicella.

When maternal varicella occurs during the last few days of gestation, the infant is at risk for neonatal varicella infection, with an attack rate of approximately 20%.[43,44] Infants who are born at least 5 days after the onset of varicella infection in the mother are not at high risk. Although these infants have lesions at birth or within the first 5 days of life, they are protected from severe disease transplacental transfer of maternal IgG anti-VZV. Those who are born within 4 days after or 2 days before the onset of maternal varicella can exhibit progressive varicella infection, with an untreated mortality rate of 30%. Exposure of an infant to nonmaternal contacts with varicella rarely causes varicella in the infant because most infants are born to seropositive mothers.

Rare cases of postnatally acquired varicella that have occurred in infants younger than 2 months of age who were born to seronegative mothers do not suggest a severe course. Occasionally, infants born to immune mothers who have close household exposure to varicella have mild varicella or subclinical infection that manifests as herpes zoster later in childhood.[11–13]

Malignancy.

Without effective antiviral drugs, 32% to 50% of children with lymphoproliferative malignancies or solid tumors experience visceral dissemination. Varicella pneumonia occurs in 20% of cases, and mortality rates range from 7% to 17%.[45–48]

Progressive disease is characterized by a prolonged period of new lesion formation, pneumonia, hepatitis, encephalitis, and disseminated intravascular coagulopathy.[1,2] The risk of progressive varicella is highest if chemotherapy is given during the incubation period, especially within 5 days before the appearance of the rash, and when the absolute lymphocyte count is less than 500 cells/mm^3 at the onset of the rash.

Pneumonia is the most common life-threatening complication. In one large series, all varicella-related deaths occurred within 3 days after the diagnosis of varicella pneumonia.[48] Hemorrhage into cutaneous lesions or severe abdominal or back pain is associated with potentially life-threatening varicella. Some patients experience progressive encephalitis with coma, but varicella encephalitis is rarely the immediate cause of death among immunocompromised patients. The syndrome of inappropriate secretion of antidiuretic hormone can accompany disseminated varicella with or without clinical encephalitis. Disseminated VZV infection in children with cancer also can be associated with pancreatitis, necrotizing splenitis, esophagitis, and enterocolitis.

Other Immunodeficiency States.

Children who acquire varicella after organ transplantation are at risk for progressive VZV infection unless they receive antiviral therapy.[48–52] Thrombocytopenia and hepatitis are the major clinical complications in renal transplant recipients. Children receiving long-term, low-dose corticosteroid therapy for asthma usually are not at risk for serious varicella. However, fatal varicella is described in patients who receive higher doses of prednisone, especially during the incubation period.[53]

Untreated varicella is severe or fatal in children with defects of T-lymphocyte function, including severe combined immunodeficiency, cartilage-hair hypoplasia (i.e., short-limbed dwarfism), Wiskott-Aldrich syndrome, and ataxia telangiectasia.[6] Unusual clinical findings in varicella, including lesions that develop a unique hyperkeratotic appearance and formation of new lesions for weeks or months, have been described in children with HIV infection.[54–57]

Herpes Zoster

Clinical Manifestations

Herpes zoster is unusual in children. When it occurs, the cutaneous eruption is mild, and symptoms of acute neuritis are minimal or absent. Herpes zoster is characterized by vesicular lesions clustered unilaterally in the dermatomal distribution of one or more adjacent sensory nerves (Fig. 205.4). Discrete vesicles resembling varicella lesions appear first and then enlarge and coalesce as the exanthem evolves. The rash is preceded or accompanied by localized pain, hyperesthesias, and pruritus. In healthy people, formation of new lesions in the primary dermatome stops within 3 to 7 days, and crusting occurs within 2 weeks.

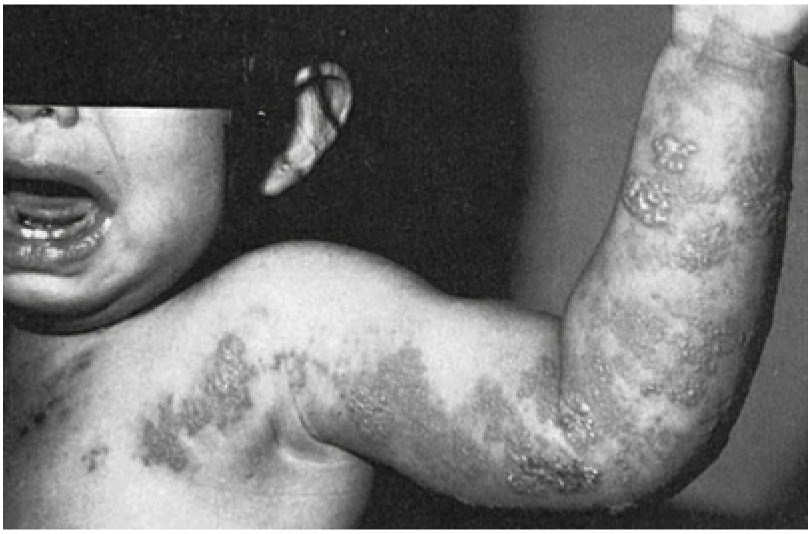

FIGURE 205.4 Characteristic unilateral dermatomal distribution of discrete and coalescent vesicles in a 10-month-old child with herpes zoster.

VZV reactivation without skin lesions (i.e., zoster sine herpete) has been diagnosed in adults with idiopathic facial palsy or other pain syndromes. It occurs rarely in children.

Complications

Healthy children are not at risk for the complication of postherpetic neuralgia, which causes debilitating chronic pain in adults.[1] Complications of herpes zoster involving cranial nerves include conjunctivitis, dendritic keratitis (Fig. 205.5), anterior uveitis, iridocyclitis, retinitis, and facial palsies.[58] Neurogenic bladder dysfunction or ileus with intestinal obstruction can accompany lumbosacral herpes zoster. Transverse myelitis is a rare, severe complication that produces transient or persistent paralysis and sensory deficits.

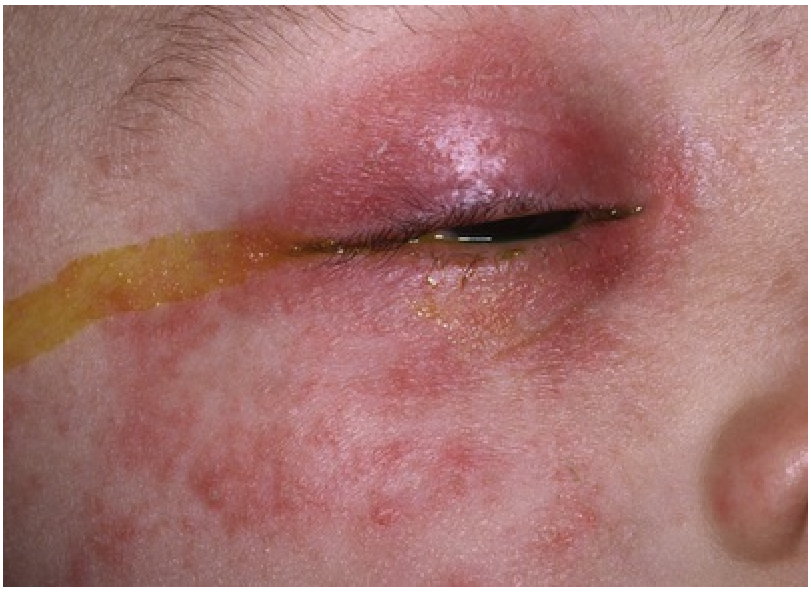

FIGURE 205.5 Zoster with keratitis in an otherwise healthy child. (Courtesy of J.H. Brien ©.)

Herpes zoster in immunocompromised children can result in severe local dermatomal infection and visceral dissemination.[48] Cutaneous lesions outside the primary dermatome or an adjacent dermatome indicate VZV viremia, which is a risk factor for visceral dissemination. Hematogenous spread can cause pneumonia, hepatitis, encephalitis, and disseminated intravascular coagulopathy. Atypical nonlocalized herpes zoster occurs in severely immunocompromised patients, especially bone marrow transplant recipients, and the widely scattered vesicular lesions cannot be distinguished from varicella.

Severely immunocompromised children, particularly those with HIV infection, can have unusual chronic or relapsing cutaneous disease, retinitis, and CNS infections that occur without associated cutaneous disease or that progress after resolution of signs of herpes zoster.[54–57] Unusual neurologic complications (e.g., multifocal leukoencephalopathy) are described in patients with prolonged, severe immunosuppression.

Laboratory Findings and Diagnosis

Laboratory tests are not necessary for management of previously healthy children with varicella. Abnormal laboratory values are common. The total white blood cell count often is decreased during the first 72 hours of rash, followed by lymphocytosis; lymphoblasts and prolymphocytes can be seen in peripheral blood.[6] Slight to moderate abnormalities of serum hepatic enzyme values are common.

The CSF in patients with neurologic complications of varicella usually shows a mild lymphocytic pleocytosis with fewer than 100 cells/mm^3 and a slight to moderate elevation of the protein level (<200 mg/dL). The glucose concentration usually is normal. CSF pleocytosis and protein concentrations are higher in patients with encephalitis than in those with cerebellar disease.[28] Patients with uncomplicated herpes zoster can have CSF pleocytosis consisting predominantly of mononuclear cells and an elevated protein concentration.

A definitive diagnosis is desirable when varicella or herpes zoster is suspected in immunocompromised children. Isolation of VZV in culture has been a gold standard but is difficult, and the time to viral identification is 3 to 7 days. Rapid diagnosis of cutaneous VZV infection is accomplished by obtaining epithelial cells from the base of a newly formed vesicle and staining the specimen with immunohistochemical reagents that detect viral proteins in infected cells or by enzyme immunoassay methods to detect VZV antigens in solubilized preparations of cells and vesicle fluid from cutaneous VZV lesions. VZV can be detected in clinical specimens through in situ hybridization or polymerase chain reaction (PCR) testing.[59,60] Interpretation of positive results as causal can be difficult to distinguish from subclinical reactivation. In the case of fetal exposures, interpretation of PCR results is difficult because infection can occur without damaging the fetus.[37,38,40]

IgG anti-VZV levels are detectable in most patients within 3 days of onset of symptoms, and they exhibit a marked increase during convalescence. IgG anti-VZV persists for life after primary infection and is not useful in most diagnostic settings. Testing for IgM anti-VZV should not be used for clinical diagnosis because false-positive and false-negative results occur with all commercially available methods.

Assays for IgG anti-VZV are valuable to determine the immune status of people whose clinical history of varicella and immunization is unknown or equivocal; to evaluate the risk of primary VZV infection in exposed people or the risk of reactivation in patients who are receiving immunosuppressive therapy; and to guide decisions about the need for varicella immunization.[61,62] Immunofluorescence testing performed with unfixed, VZV-infected cells is a highly sensitive method for detecting IgG anti-VZV, but it involves complex methodology, and immunofluorescence testing using fixed cells is subject to false-positive interpretation.

Commercial enzyme immunoassay methods to assess VZV antibodies usually have a high degree of specificity, generating few false-positive results, but they are not as sensitive as research methods. Between 10% and 15% of people who are immune to VZV may be identified as susceptible. Latex agglutination methods are somewhat more sensitive and specific than enzyme immunoassay, providing a simple and rapid alternative for detecting IgG anti-VZV.[63,64]

A positive history of varicella predicts immunity in more than 95% of people. The likelihood of immunity in an adult born before 1980 with a negative history also is high, unless the patient's childhood was spent in an area such as the tropics, where varicella is less common. Serologic testing after varicella vaccination is not advisable because false-negative results using commercially available serologic methods may be more common than is observed in naturally immune people.

Treatment

Acyclovir is used most commonly to treat varicella and herpes zoster (Box 205.2).[17,45,46,65] Famciclovir and valacyclovir, nucleoside analogues that are structurally similar to acyclovir, are absorbed more efficiently after oral administration. These drugs have been licensed for treatment of herpes zoster in adults, with some extrapolation of dosing for children.[66]

Box 205.2

Use of Acyclovir for the Treatment of Varicella

Acyclovir Indicated

Patients

Malignancy, bone marrow or organ transplantation, high-dose steroid therapy

Congenital T-lymphocyte immunodeficiencies

Human immunodeficiency virus infection

Neonatal varicella after maternal varicella beginning within 5 days before or 2 days after delivery

Associated pneumonia or encephalitis

Administration

Initiate as soon as possible after initial lesions appear

Intravenous route[a]

Dosage

<1 year old: 30 mg/kg/day divided into 8 hourly doses given as a 1-hour infusion

>1 year old: 1.5 g/m^2/day divided into 8 hourly doses given as a 1-hour infusion

Duration: 7 days or until no new lesions have appeared for 48 hours

Acyclovir Optional

Patients

Chronic cutaneous disorders

Chronic diseases that may be exacerbated by acute VZV infection, such as cystic fibrosis or other pulmonary disorders, diabetes mellitus, or disorders requiring chronic salicylate therapy or intermittent corticosteroid therapy

Otherwise healthy children, especially those >12 years old or secondary household contacts

Administration

Initiate within 24 hours after the initial lesions appear

Oral route

Dosage

80 mg/kg/day divided into 4 doses (maximum of 800 mg/dose)

Duration: 5 days

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[a] Selected patients who are considered at relatively low risk for varicella-zoster virus (VZV) dissemination can be treated with oral acyclovir and carefully monitored for progression.

Acyclovir is metabolized to the triphosphate form within VZV-infected cells. The phosphorylated compound functions as a competitive inhibitor and chain terminator of viral DNA polymerase. The antiviral activity of acyclovir is lower against VZV than against HSV. Ensuring that plasma concentrations are several-fold higher than in vitro inhibitory concentrations for most VZV isolates requires the use of high-dose acyclovir. Prolonged exposure of VZV isolates to acyclovir in vitro selects for thymidine kinase–negative mutants. Resistant strains of VZV have been recovered from severely immunocompromised patients who have been treated with acyclovir for repeated or chronic episodes of VZV infection.[66]

Varicella

Healthy Children and Adolescents.

Placebo-controlled clinical studies show that orally administered acyclovir diminishes the clinical symptoms of varicella in otherwise healthy children, adolescents, and adults when administered within 24 hours after the appearance of the initial cutaneous lesions.[17,67–69] In a study in which healthy children 2 to 12 years old were treated with 80 mg/kg/day (20 mg/kg per dose 4 times daily; maximum of 800 mg/dose) of acyclovir administered orally for 5 days, reductions in fever, pruritus, number of days of new lesion formation, and total number of cutaneous lesions were observed.[17] Acyclovir recipients also had fewer lesions that progressed from the maculopapular to the vesicular stage. Among younger children, immediate acyclovir therapy converted all cases of varicella to the mildest form of illness that might be observed without treatment (i.e., new lesions ≤3 days and total lesions <300).[17]

The impact of orally administered acyclovir on varicella in adolescents (i.e., 13–18 years of age) and in young adults was similar to that observed in young children. However, the effects have more clinical relevance because varicella is more severe among untreated patients in these older age groups.[67] Adolescents in the treated group were significantly less likely to have residual hypopigmented skin lesions at 4 weeks, suggesting that drug therapy minimized the spread of virus to cells deeper in the dermis. Although study groups were not large enough to document it, the evidence of diminished viremia and cutaneous viral replication supports the assumption that oral acyclovir can reduce the risk of varicella pneumonia in otherwise healthy adults. In adults and young children, acyclovir must be given within 24 hours after initial lesions to have demonstrable clinical efficacy.[32] All patients with varicella pneumonia should receive acyclovir intravenously.

Oral acyclovir is licensed for the treatment of varicella in healthy children and adults. Acyclovir therapy does not have a detrimental effect on the host response to VZV.[17,68] The American Academy of Pediatrics recommends that acyclovir be considered for unvaccinated patients with varicella who are 12 years of age or older, have chronic cutaneous or pulmonary diseases requiring long-term salicylate therapy, or are being treated with short or intermittent courses of corticosteroids or aerosolized corticosteroids.[65]

Immunocompromised Patients.

Acyclovir therapy diminishes the clinical severity of varicella in immunocompromised children by terminating cell-associated viremia despite impaired host responses.[70,71] Early antiviral therapy prevents progressive varicella and visceral dissemination. The mortality rate is decreased because the risk of varicella pneumonia is reduced. When acyclovir was given intravenously to children with malignancy in a placebo-controlled trial, the incidence of varicella pneumonia was decreased from 45% to 0%.[72] The dosage of acyclovir for varicella in high-risk patients is 1.5 $g/m^2/day$, administered intravenously in 3 divided doses for 7 days.

The optimal use of acyclovir in immunocompromised children with varicella requires initiation of treatment within the first 24 to 72 hours after the onset of rash. Intravenous administration should be started immediately if the patient has signs of pneumonia, hepatitis, thrombocytopenia, or encephalitis. Waiting to initiate treatment until prolonged new lesion formation has been documented is inappropriate because visceral dissemination occurs during the same period. In addition to preventing life-threatening dissemination, early acyclovir therapy can be expected to minimize cutaneous disease, possibly reducing the risk of secondary bacterial infections.

Oral administration of acyclovir, famciclovir, or valacyclovir has not been evaluated in clinical trials for high-risk children. The use of these agents should be considered only in selected patients with minimal immunosuppression, and it requires careful follow-up during the illness.

Herpes Zoster

Acyclovir has been effective for the treatment of herpes zoster in healthy and immunocompromised patients participating in placebo-controlled trials.[65,70] For patients who are at high risk for disseminated disease, the dose of acyclovir is 1.5 g/m^2/day or 30 mg/kg/ day divided into doses every 8 hours and given intravenously. Acyclovir is given for a total of 7 days or for 2 days after the cessation of new lesion formation, whichever is longer.

Acyclovir therapy initiated within 72 hours after the onset of herpes zoster reduces the duration of new lesion formation from 1 or more weeks to approximately 3 days. Antiviral treatment is associated with earlier cessation of acute pain and crusting and with complete healing by 2 to 3 weeks. Although early acyclovir treatment is likely to produce the best results, clinical benefit is observed even when therapy is delayed for more than 3 days in immunocompromised patients. Relapse of herpes zoster is a clinical problem in some immunocompromised patients, but most patients show a response to treatment with a second course of acyclovir. Oral acyclovir administration for herpes zoster in high-risk patients is reserved for patients who are considered unlikely to develop visceral dissemination.

Famciclovir and valacyclovir are effective oral agents for herpes zoster.[71,73] Ganciclovir has in vitro activity against VZV that is equivalent to acyclovir but is more toxic. Foscarnet is the drug of choice for the treatment of infections due to acyclovir-resistant VZV.[74]

Prevention

Preventing the transmission of VZV to susceptible people is difficult because infected people are contagious for 24 to 48 hours before the onset of clinical signs of varicella. For example, restrictions on attendance do not alter the course of varicella epidemics in schools.[75] Infection control practices, including caring for infected patients in isolation rooms with filtered air systems, are essential in hospitals that care for immunocompromised children. Filtration is necessary because VZV has been transmitted to hospitalized patients by airflow systems, and VZV can be detected in air samples by PCR testing.[76–78]

Susceptible healthcare personnel who have had a close exposure to varicella should not care for high-risk patients during the incubation period because secondary cases have occurred in this clinical setting. Similar precautions should be taken in vaccinated healthcare personnel who have had close exposures; breakthrough varicella can occur in adults, although the infection is much less severe. Serologic testing is not helpful in these people because breakthrough infection can occur in those with or without detectable levels of IgG anti-VZV.

Passive Antibody Prophylaxis

Varicella-zoster immune globulin (VZIG), which was prepared from high-titer immune human serum, reduced the attack rate for varicella when given just after exposure.[79–82] Breakthrough infections occurred, but the extent of exanthem and risk of varicella pneumonia were diminished. VZIG given after the appearance of varicella rash did not alter the disease process.

VZIG is no longer available in the United States. The alternative preparation, VariZIG, which is a high-titer VZV immune globulin, is available through an investigational new drug expanded access program (FFF Enterprises, Temecula, CA; 24-hour phone: 800-843-7477).[83] VariZIG also may be obtained from ASD HealthCare (Frisco, TX; phone: 800-746-6273. Immune globulin intravenous (IGIV, 400 mg/kg) may be given to high-risk patients exposed to varicella as an alternative to VariZIG.[69,83,84]

The decision to administer VariZIG or IGIV depends on three factors: the likelihood that the exposed person is susceptible to VZV, the probability that the exposure will result in infection, and the likelihood that VZV infection will be severe or complicated[69] (Box 205.3). VariZIG or IGIV should be given to susceptible high-risk patients within 96 hours and, if possible, within 48 hours after a close exposure to a person with varicella or herpes zoster.

Box 205.3

Use of Varicella-Zoster Antibody After Exposure

Patients at Risk

Immunocompromised child with no history of varicella or varicella immunization

Pregnant woman with no history of varicella and no antibody to varicella-zoster virus (VZV)[a]

Newborn infant whose mother had onset of chickenpox within 5 days before or 48 hours after delivery

Hospitalized preterm infant <28 weeks' gestation or birth weight <1000 g, regardless of maternal history of chickenpox or VZV serostatus

Hospitalized preterm infant ≥28 weeks' gestation whose mother lacks a reliable history of chickenpox or lacks antibody to VZV

Criteria for Close Exposure

Household: residing in the same household

Playmate, schoolmate, or other: face-to-face indoor contact[b]

Hospital: varicella

- In the same 2- to 4-bed room or in an adjacent bed in an open ward
- Face-to-face contact with a contagious staff member, visitor, or other person[b]

Hospital: herpes zoster

- Intimate contact (e.g., touching, hugging) with a person deemed contagious
- Newborn infant
- Onset of chickenpox in the mother within 5 days before or 48 hours after delivery (varicella-zoster immune globulin [VariZIG] is not indicated if mother has herpes zoster)

Administration of Varizig

VariZIG should be administered as soon as possible and at least within 96 hours after exposure.

Dose: 1 vial (125 U)/10 kg of body weight (maximum of 5 vials) by intramuscular injection; VariZIG cannot be given intravenously. Minimum dose is 125 U

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[a] Serologic testing is recommended if results can be obtained immediately because most adult women with no history of varicella are immune.

[b] Experts differ about estimates of minimum duration of contact to be considered significant (5 minutes to >1 hour).

Data from American Academy of Pediatrics. Varicella-zoster infections. In: Pickering LK (ed). 2009 Red Book: Report of the Committee on Infectious Diseases, 28th ed. Elk Grove

Village, IL, American Academy of Pediatrics, 2006, p. 717; Centers for Disease Control and Prevention (CDC). A new product (VariZIG) for postexposure prophylaxis of varicella available under an investigational new drug application expanded access protocol. MMWR Morb Mortal Wkly Rep 2006;55:209–210.

Passive antibody prophylaxis is recommended for immunocompromised children, pregnant women, and neonates exposed to mothers with onset of varicella 5 or fewer days before delivery or within 48 hours after delivery.[42,82] VariZIG or IGIV is not indicated for healthy, term infants exposed postnatally, including those whose mothers' rash developed more than 48 hours after delivery. If possible, pregnant women should be tested for IgG anti-VZV before passive antibody administration because many adults with no clinical history of varicella are immune.

The administration of passive antibody prophylaxis does not eliminate the possibility of disease in high-risk patients.[44,82] The incidence of varicella despite VZIG prophylaxis was significantly higher after household exposures. In one study, passive administration of antibody preparations to immunocompromised children lowered the risk of severe varicella significantly, but 11% of the children still experienced pneumonitis.[45] Immunocompromised patients who have received high-dose IGIV (100 to 400 mg/kg) for other indications within 2 to 3 weeks before the exposure can be expected to have serum antibodies to VZV.[84] Because passive antibody titers decline by 2 weeks in some patients and by 4 weeks in most, a second dose should be given if a new exposure occurs more than 2 weeks later. Although the risk of VZV transmission from a person with herpes zoster is low, close contact between a susceptible high-risk patient and a person with herpes zoster justifies administration of VariZIG or IGIV.

Administration of VZIG can prolong the incubation period to 28 days; whether other passive antibody preparations will have this effect is not known. Passive antibody prophylaxis does not reduce the risk of VZV reactivation in high-risk populations or alter the clinical course of herpes zoster when given after the onset of symptoms.

Antiviral Prophylaxis

Although the use of acyclovir as prophylaxis against varicella has been described, it is not recommended because data are limited. In one study, the attack rate after household exposure was reduced to 16% when oral acyclovir (40 or 80 mg/kg/day in 4 divided doses for 7 days) was given to 25 healthy children beginning 7 to 9 days after the onset of varicella in the index case; seroconversion was observed in 84% of the patients.[85]

Additional data about acyclovir prophylaxis is needed because of the potential for interference with the host response, which may predispose to early recurrent infection or incomplete protection from subsequent exposures, and enhanced selection of resistant VZV. In most circumstances, the objective of modifying the severity of varicella can be achieved by following the patient closely and giving the drug immediately after the onset of symptoms. However, if follow-up cannot be ensured, chemoprophylaxis with acyclovir (80 mg/kg/day divided into 4 doses of 20 mg/kg, for 7 days) may be considered.

Acyclovir prophylaxis reduces the risk of recurrent VZV infection in bone marrow transplant recipients, but VZV reactivation occurs when acyclovir is discontinued. Acyclovir prophylaxis for herpes zoster is not essential because the prompt initiation of acyclovir for the treatment of recurrent VZV infections is effective in reducing morbidity and mortality rates for immunocompromised patients.[65] In some centers, acyclovir prophylaxis is used in the early months after transplantation, and it sometimes is continued for 12 months. However, prolonged low-dose administration of acyclovir has the potential to result in the emergence of drug-resistant VZV.

Varicella Vaccine

The development and initial clinical evaluation of a live, attenuated varicella vaccine were first reported by Takahashi in 1974. Live, attenuated varicella vaccine, made from the Oka strain, was the first human herpesvirus vaccine licensed for clinical use in several countries. The varicella vaccine was licensed in the United States in 1995, and 2 doses are recommended for universal administration in early childhood.[86,87] The recommendations and contraindications for these are outlined in Box 205.4.

Box 205.4

Indications and Contraindications for

Administration of Live, Attenuated Varicella Vaccine

Indications

- Age 12 months to 13 years: 2 doses at minimum 3-month interval in patients susceptible according to history[a]
- Age 13 years to young adult:; 2 doses at 4–8-week interval; consider serologic testing to evaluate susceptibility
- Postexposure prophylaxis for unvaccinated people without other evidence of immunity

Contraindications

- Congenital or acquired immunodeficiency or systemic immunosuppression therapy, blood dyscrasia
- Leukemia, lymphoma, other malignancy until chemotherapy has been terminated for at least 3 months[b]
- Symptomatic human immunodeficiency virus infection
- High-dose systemic corticosteroids (≥2 mg/kg/day of prednisone for ≥1 month or 20 mg daily)
- Pregnancy
- Anaphylaxis to neomycin or other vaccine component

Precautions

- Intercurrent illness (if more than minor)
- Immunoglobulin or other blood products within 3 to 11 months, depending on the product (similar to measles vaccine)
- Salicylates should be avoided for 6 weeks after vaccination[c]
- Thrombocytopenia

Based on Committee on Infectious Diseases, American Academy of Pediatrics. Prevention of varicella: recommendations for use of varicella vaccine in children, including a recommendation for a routine 2-dose varicella immunization schedule. Pediatrics 2007;120:221–231.

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[a] One dose is 0.5 mL SC. Simultaneous administration with measles-mumps-rubella (MMR) vaccine is acceptable but requires the use of separate syringes and injection sites. Quadrivalent measles-mumps-rubella-varicella (MMRV) is associated with a higher risk of febrile seizures after the first dose.

[b] Vaccination of children with acute lymphocytic leukemia who are in remission and who do not have evidence of immunity to varicella should be undertaken only with expert guidance and with availability of antiviral therapy in case complications ensue.

[c] Unless the risk of natural varicella is considered to outweigh the theoretical risk of Reye syndrome.

From Marin M, Güris D, Chaves SS, et al. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2007;56(RR-04):1–40.

Since the introduction of varicella vaccine, there has been a 90% to 95% reduction in the US rates of incidence, morbidity, and hospitalizations due to varicella. Fifteen years after introduction of vaccination, there is no evidence of a shift in the burden of disease to older age groups.[88]

Before its licensure, the investigational live, attenuated varicella vaccine (i.e., Oka-Merck strain) was administered to more than 7000 children and more than 1600 healthy susceptible adults in the United States.[89] The vaccine, given as a high-titer preparation, induced protection against household exposure, with an efficacy rate of more than 95% in an initial placebo-controlled study.[90–93] Subsequent evaluations of children immunized in the clinical trials demonstrated high seroconversion rates by the glycoprotein enzyme immunoassay (gpEIA) method. Mild breakthrough infections were observed in some children, but disease was modified to fewer than 50 cutaneous lesions without associated fever in most cases.[94,95]

In 2163 vaccinees evaluated at one center, varicella developed in 114 children at a median of 44 months after immunization. The median number of skin lesions was 18, and the incidence of transmission to other vaccinated children in the household from these cases was 12%.[94] Persistence of VZV immunity over an interval of 1 to 6 years was documented in 94% to 100% of children by means of assays for IgG antibodies and T-lymphocyte proliferation to VZV.[95–97] Sustained protective efficacy of 95% was shown among vaccine recipients from the original placebo-controlled trial, who were monitored for 7 years.[90]

The varicella vaccine was introduced for routine use as a single-dose regimen in children 12 months to 12 years of age and showed substantial impact on varicella morbidity and mortality rates in the United States.[98–101] However, active and passive surveillance studies demonstrated that many vaccinated children developed breakthrough varicella after close exposure and could transmit the virus.[102–105] US postlicensure experience led to the recommendation of a two-dose varicella vaccine schedule in 2006, with the first dose given at 12 to 15 months of age and the second dose given at 4 to 6 years of age. The second dose is given to ensure that people who have primary vaccine failure or a limited initial immune response have more complete and persistent protection.[106]

A population-based study of varicella vaccine in Germany in 1- to 4-year-old children found an overall vaccine effectiveness of 87% after one dose and 97% after two doses (the second dose was recommended at least 4 weeks after the first and before 2 years of age), an incremental vaccine effectiveness of two doses of 85%.[107] Catch-up immunization is recommended for children, adolescents, and young adults who previously received only one dose. Children and adults who do not have evidence of VZV immunity should be vaccinated. The criteria for VZV immunity is documentation of two doses of vaccine or birth in the United States before 1980, verification of a history of varicella diagnosed by healthcare personnel, or laboratory evidence of immunity or disease.[69]

Varicella vaccine elicits VZV immunity when administered concurrently with the measles-mumps-rubella (MMR) vaccine and as a quadrivalent measles-mumps-rubella-varicella (MMRV) formulation.[108–110] A single dose of the MMRV vaccine elicited VZV antibody responses in young children that were comparable to those in children who were given a single dose of varicella vaccine; seroconversion rates were approximately 90%.[109,110] A two-dose regimen of the MMRV vaccine was substantially more immunogenic.[109,110]

Postlicensure surveillance showed that young children given the MMRV vaccine were more likely to have fever than those who received MMR and varicella vaccines as separate inoculations (21.5% vs. 14.9%) at the time of their first immunization.[111,112] MMRV vaccine recipients 12 to 23 months of age had a 2.3 times higher relative risk for febrile seizures than those given separate inoculations. These risks of fever and febrile seizures were not observed with the second MMRV vaccine dose. The MMRV vaccine can be given for initial vaccination if after informing parent, the combination is preferred; otherwise MMR and varicella vaccines are given at separate sites. MMRV vaccine is preferred for the second dose.[113]

Two doses of varicella vaccine must be given to susceptible adolescents and adults.[60] Adults are more likely than children to have transient local reactions and rash and to have less persistent VZV antibodies. However, immunization of susceptible adults has important clinical benefit because of their tendency to develop serious varicella and because protection or modified severity of illness is documented despite lower antibody titers.

When it causes skin lesions in healthy recipients, the vaccine virus can be transmitted to susceptible close contacts. In one case, a pregnant woman had generalized cutaneous lesions due to vaccine virus after exposure to a vaccine-related rash in her child. No spread to the fetus was detected.[103]

The Oka-Merck varicella vaccine has been given to children with acute leukemia in remission, reducing the attack rate after household exposure to 13%.[61] Seroconversion in these patients is associated with a high level of protection, but most children required two doses of the vaccine to elicit immunity. A recently published small study of 24 children with a hematologic malignancy and 7 with a solid tumor who received VZV vaccination early during their course of uninterrupted chemotherapy indicated that adaptive immunity, even without seroconversion, could be safely induced.

Varicella vaccination is recommended for children infected with human immunodeficiency virus 1 (HIV-1) with 15% or more $CD4^+$ cells. Sustained protection has been demonstrated in most of these children after two doses of vaccine. The varicella vaccine virus has caused disseminated and chronic infection in children with immunodeficiencies that were not recognized before vaccination.[114–116] Susceptible healthy household contacts should be immunized with varicella vaccine to reduce the risk of household exposure of the high-risk child.[117]

VZV reactivation has been described in a few healthy vaccine recipients,[118] but changes in herpes zoster epidemiology have not been detected as varicella incidence has declined.[119] When the incidence of herpes zoster was assessed among children with leukemia who had vaccine-induced immunity or past natural infection, reactivation was less common after exposure to vaccine virus than wild-type VZV.[120] Because vaccine virus is inhibited by acyclovir, episodes of vaccine-related herpes zoster can be treated with antiviral therapy if necessary. Generalized rashes that occur late after immunization have been caused by breakthrough infections with wild-type VZV.[121] Herpes zoster due to natural VZV can occur after subclinical infection in vaccinated people.[122]

An analysis of medical and other costs related to the annual epidemics of varicella indicates that universal immunization programs directed at healthy children and susceptible adults are cost-effective and safe.[123] Use of varicella vaccine has reduced the incidence of varicella in the United States and other countries.[124] Vaccination also has been associated with reduction of invasive group A streptococcal infections.[125,126] There is limited evidence that suggests that postexposure varicella vaccination of children within 3 days after household contact with a varicella case may reduce the rate and severity of infection.[127]

Herpes zoster vaccine (Zostavax) was licensed in 2006. It is recommended by Advisory Committee on Immunization Practices (ACIP) for prevention of herpes zoster (i.e., shingles) and its complications among adults 60 years or older.[128]

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Cytomegalovirus

Robert F. Pass

Cytomegalovirus (CMV) is the most common cause of congenital infection in the United States. Approximately 10% to 20% of affected infants suffer sensorineural hearing loss, ocular damage, or impairment of cognitive or motor function. In addition, CMV is an important opportunistic pathogen in patients with impaired immune function, especially organ transplant recipients, patients with congenital immunodeficiency, and patients with acquired immunodeficiency syndrome (AIDS).

The Virus

Human CMV is a member of the β-herpesvirus group that also includes human herpesvirus (HHV)-6A, HHV-6B, HHV-7, and a large number of related viruses that infect other mammals. Human CMV is a large, complex virus with characteristic morphology and a distinctive focal cytopathic effect in tissue culture. The virus is approximately 200 to 300 nm in diameter; the complete virion is composed of a linear, double-stranded DNA genome within an icosahedral capsid of 162 capsomeres. The capsid is contained within the amorphous tegument comprised mostly of numerous, virus-encoded proteins; the tegument is surrounded by a lipid bilayer envelope derived from the host cell's endoplasmic reticulum–Golgi complex intermediate compartment and containing more than 20 virus-encoded glycoproteins. The genome of human CMV is composed of approximately 235,000 base pairs with 166 protein coding genes.[1] Reiterated terminal and internal base pair sequences divide the genome into unique long (U_L) and unique short (U_S) regions.

Many different cell types are infected by CMV. The virus is able to enter the cell by fusion of specific envelope glycoproteins (gB, gH, gM/gN) with cell surface proteins, including heparan sulfate, cellular integrins, and platelet-derived growth factor-α receptor.[1] CMV also is capable of using an endocytic pathway dependent on proteins from the *UL128, UL130, UL131* gene complex. Viral proteins involved in attachment and entry are important targets for a neutralizing antibody. As with other herpesviruses, synthesis of CMV proteins is directed by sequential transcription of genes. Viral DNA replication, protein synthesis, and assembly of nonenveloped particles take place within the nucleus, where the accumulation of nucleocapsids accounts for the typical “owl's eye” appearance of the intranuclear inclusion. Envelopment of the virus appears to be a multistep process initiated by budding through the nuclear membrane and continued with acquisition of endosomal membranes in the cytoplasm. Virus is transported via the Golgi apparatus to the cell surface for release through exocytosis. The typical cytoplasmic inclusion seen in CMV-infected cells represents the accumulation of nucleocapsids and dense bodies (enveloped tegument without nucleocapsid or DNA) in the Golgi complex.

Pathogenesis

CMV infection in humans involves a complex balance between virus and host, the usual outcome of which is clinically inapparent, persistent infection with establishment of latency. Human CMV encodes numerous genes for proteins that could influence host cell activation, leukocyte movement, inflammatory response, and both innate and adaptive immunity in ways that favor persistence of CMV in the human host.[1,2]

Dissemination, Tissue Tropism, and Persistence

The usual site of inoculation of CMV in a healthy person is a mucosal surface in the upper respiratory or genital tract. Viremia is the likely mechanism for dissemination of CMV to tissues in many different organs, and infection of leukocytes and vascular endothelial cells plays a role. CMV-encoded chemokines, chemokine receptors, and cytokines have the potential to influence the level of viremia by modulating cell trafficking, intracellular signaling, and host cell activation.[1]

Cytopathology caused by CMV often is found in many organs (salivary glands, lung, kidney, liver, pancreas, adrenals, intestinal mucosa), even in people (both healthy individuals and immunocompromised patients) with no premortem evidence of CMV disease. After initial infection the virus is readily isolated from urine, saliva, tears, semen, cervical secretions, and breast milk. On the basis of experience with perinatal, transfusion, and organ transplant transmission of CMV, viral shedding begins around 4 to 6 weeks after acquisition of CMV. Viremia often is detectable at this time and can persist for months, even in a healthy person with asymptomatic infection.[3] Shedding of virus in saliva, urine, and genital secretions typically continues for months to years. Active CMV replication persists in the face of antibody response and the more slowly developing cell-mediated immune response. Viral mechanisms for evading the host's immune response may account for this remarkable persistence. Human CMVs carry multiple genes with the ability to interfere with the host's immune response at different times in the virus replication cycle and by multiple mechanisms.[4–8] Specific functions have been identified that interfere with antigen processing and presentation (trapping or destroying major histocompatibility complex [MHC] class I molecules, degrading MHC class II proteins), impair immune recognition of infected cells, downregulate type I interferon activity, and inhibit natural killer (NK) cell killing. Persistence of CMV in humans is thought to be due to maintenance of the viral genome in stem cells in bone marrow, although persistent replication in epithelial cells of kidney and salivary glands could play a role.[1]

Immune Response

The frequency and severity of disease caused by CMV parallels the extent of impairment of the person's immunity. Patients who are immunocompromised because of chemotherapy, organ transplantation, or AIDS shed CMV from multiple sites, often have persistent viremia, and frequently develop CMV-related disease. Antibody plays an important role in modifying or preventing infection. Infections in transplant recipients who are CMV antibody negative are more likely to be associated with morbidity than infections in patients who are CMV antibody positive before transplantation. Disease from transfusion-acquired CMV infection in small premature neonates almost always occurs in those who lack maternal antibody. Passive and active immunization of seronegative recipients of kidney transplants from seropositive donors reduces the severity of primary CMV infection.[9,10] In addition, immunization with a CMV glycoprotein B (gB) vaccine that stimulated robust antibody responses reduced infection rates in seronegative young women and diminished the impact of infection in patients who had received solid-organ transplants.[11,12] The critical role of cell-mediated immunity in controlling CMV infections is supported by the observation that most severe infections occur in patients with profound impairment of cell-mediated immunity: recipients of solid-organ transplants treated with antithymocyte globulins; recipients of bone marrow transplants; patients with AIDS who have very low numbers of CD4 T lymphocytes; and infants with severe combined immunodeficiency.[13]

Pathogenesis of Congenital Infection

Autopsy studies of fetuses or newborns with congenital infection show that CMV infects numerous cell types and damages multiple organs. A study of 34 fetuses with congenital CMV infection diagnosed in utero reported immunohistochemical detection of CMV in placenta and pancreas specimens from all subjects; lung and kidney each were positive in 87%, liver in 71%, brain in 55%, and heart in 44%.[14] Inflammatory infiltrates were present in CMV-positive organs and correlated with organ damage. Human CMV has been shown to infect neural progenitor cells and impair their growth and differentiation.[15] Brain cells of many different types (nervosa, glia, ependyma, choroid plexus, meninges, vascular endothelium) show cytopathologic lesions and inclusions, but involvement typically is patchy, with focal areas of necrosis. Inclusion-bearing epithelial cells are found in the semicircular canals, vestibular membrane, cochleae, and other structures of the ear.[16,17] Temporal bone anomalies with cochlear, vestibular, and auditory canal defects (Mondini dysplasia) have been associated with deafness in infants with congenital CMV infection. Cytomegalic cells and focal necrosis can be seen in the retina.

Examination of liver specimens reveals periportal lymphoid infiltration, bile stasis, inclusion-bearing cells in bile ducts, giant cell transformation, and necrosis of parenchymal cells.[18] Inclusion-bearing cells without necrosis or inflammatory cell infiltrate usually are found in abundance in glandular epithelial cells (salivary, pancreas, endocrine) and in the lung and kidney. Results with an animal model suggest that CMV damages the developing brain through a number of mechanisms, including lytic infection of cells, interference with neuronal migration, loss of neuronal stem cells, and vascular compromise.[19] In addition to its direct effects on the fetus, CMV impairs fetal development through placental infection, as evidenced by villitis, villous necrosis, and vascular lesions.[20] The predominant placental cell type infected is a fixed connective tissue or stromal cell; CMV also is found in placental macrophages, endothelial cells, and syncytiotrophoblast cells.[21,22] In an in vitro model, CMV infection impaired the ability of cytotrophoblasts to differentiate and invade, suggesting that CMV infection could impair placental function.[23]

Newborns with congenital CMV infection and infants who acquire CMV perinatally do not control the infection as well as adults, shedding virus for much longer periods, sometimes up to years. Developmental immaturity of the immune response to CMV probably contributes to the severity of fetal infection and the inability of infants to control ongoing virus replication. Newborns have reduced antigen-presenting cell (monocytes and dendritic cells) function and reduced NK cell function compared with adults. Fetuses have cellular immune responses to CMV as early as 22 weeks of gestation.[24] A study of mothers with primary CMV infection and their fetuses with congenital infection showed that they had similar levels of activated and memory CD8$^+$ T lymphocytes, but fetuses had lower numbers of PP65-specific (CMV tegument protein) cytotoxic T cells.[25] Newborns with congenital

CMV infection have virus-specific, functional $CD8^+$ T cells that are present in numbers similar to those measured in healthy adults with CMV infection.[26] After in vitro CMV infection myeloid dendritic cells from cord blood produced lower levels of immunomodulatory cytokines than did dendritic cells from adult peripheral blood, deficiencies that could affect T-lymphocyte responses to infection.[27] Impaired lymphocyte proliferative responses to CMV and lower numbers of interferon-γ–producing $CD4^+$ T lymphocytes are found in infants with both congenital and acquired CMV infection.[28,29]

Cytomegalovirus can be transmitted from mother to fetus even if the mother was infected years before conception. In a mother with established immunity, transmission of CMV to the fetus could be the result of reactivation of latent virus or, more commonly, reinfection with new strains. Strong evidence indicates that preconception maternal immunity reduces the risk of congenital CMV infection by threefold to fourfold.[30] Long-term follow-up of children in Europe and North America with congenital CMV infection suggests that sequelae, such as deafness and impaired cognitive function, are more common and more severe when congenital CMV infection is the result of primary gestational infection (Table 206.1).

TABLE 206.1

Sequelae in Children With Congenital Cytomegalovirus Infection by Type of Maternal Infection

Sequela	Primary (% With Sequela)[a]	Recurrence/Reinfection (% With Sequela)[b]
Sensorineural hearing loss	15	5[c]
Bilateral hearing loss	8	0[c]
Speech threshold ≥60 dB[d]	8	0[c]
IQ ≤70	13[e]	0[c,f]
Chorioretinitis	6	2
Other neurological sequelae[g]	6	2
Microcephaly	5	2
Seizures	5	0
Paresis or paralysis	1	0
Any sequel	25	8[c]

[a] Number evaluated equals 112–125 except where noted otherwise.

[b] Number evaluated equals 54–65 except where noted otherwise.

[c] $P \leq 0.05$ for difference between maternal primary and recurrent infection.

[d] For the ear with better hearing.

[e] Number evaluated equals 68.

[f] Number evaluated equals 32.

[g] Four of eight affected children (50%) had more than one abnormality.

Adapted from Fowler KB, Stagno S, Pass RF, et al. The outcome of congenital cytomegalovirus infection in relation to maternal antibody status. N Engl J Med 1992;326:663.

Overall about 35% to 40% of maternal primary infections are transmitted to the fetus. The transmission rate is higher in late gestation infection compared with the early gestation type.[31] However, first trimester maternal infections are more likely to cause congenital infections that are manifest at birth and to be associated with sequelae (retinitis, deafness, mental retardation) than are late gestational infections. Abnormalities (evidenced by prenatal ultrasonography, fetal autopsy, or neonatal examination) were found in 26% of cases when primary maternal infection occurred before 20 weeks of gestation, compared with 6.2% of cases when maternal infection occurred later in gestation.[32] A study of newborns with congenital CMV infection reported that central nervous system (CNS) sequelae occurred in 32% when primary maternal infection occurred in the first trimester, compared with 15% with later gestational infection.[33] A similar study reported hearing loss in 4 of 5 affected infants with first trimester CMV infections; 1 of 12 with second trimester infections; and 0 of 11 with third trimester infections.[34]

Epidemiology

Age-Related Prevalence and Modes of Transmission

Age-related prevalence of CMV infection varies widely, depending on living circumstances and social customs. In areas where the rate of maternal seropositivity is high and breastfeeding is common, more than 50% of all infants acquire CMV during the first year of life. Group care of children facilitates the spread of CMV, especially in toddlers; this leads to a higher prevalence of infection in children attending childcare centers and their caregivers.[35] A seroepidemiologic survey of CMV prevalence based on sera collected from 1988 to 1994 from a random sample of the U.S. population found that the overall prevalence for the United States was 59%.[36] The prevalence was higher in females than males (64% versus 54%), and notably higher in non-Hispanic blacks (76%) and Mexican-Americans (82%) than among non-Hispanic whites (51%). A follow-up report based on sera collected a decade later observed similar rates and reported that CMV seropositivity was independently associated with older age, female sex, foreign birthplace, low household income, household crowding, and low household education.[37] In Africa, Asia, and Latin America, the majority of children are infected by CMV prior to adolescence. Breastfeeding, child-rearing practices, crowding, sanitation, and sexual behavior probably all influence age-related variations in CMV prevalence.

Exposures to young children and sexual contacts are important sources of CMV infection for young women.[38] Young children readily transmit CMV to peers and caregivers, including parents and childcare workers.[35] Oral shedding is common and persists for months or longer; the high frequency of mouthing behaviors in toddlers facilitates transmission of CMV through salivary transfer directly on toys or surfaces or the hands of children and workers. Sexual transmission of CMV is important among adolescents and adults. An early sexual debut, a greater number of partners, nonwhite race, and the presence of other sexually transmitted infections were associated with a higher prevalence of CMV infection among attendees of clinics for treating sexually transmitted infections and among adolescents.[39–41] Restriction enzyme studies of viral DNA provide evidence for transmission of CMV among toddlers and their caregivers in childcare centers, between sex partners, and from child to mother to fetus.[42–44] A population-based study of CMV seropositivity and sexual activity in the U.S. concluded that sexual activity significantly influences rates of CMV infection and that prevention efforts should address this risk.[45]

CMV can be transmitted from mother to offspring transplacentally, at delivery by exposure to virus in the maternal genital tract, and by human milk. Approximately 10% of seropositive mothers shed CMV in the genital tract at delivery, and about 50% of neonates exposed to CMV during birth or from breast milk are infected. CMV can be detected by polymerase chain reaction (PCR) testing in the breast milk of almost all seropositive mothers. Infants who are infected early in life shed virus for years; they are an important source of CMV for other children and caregivers.

Epidemiology of Congenital Infection

Congenital CMV infection is worldwide in distribution; rates range from about 0.3% to 4% of live births.[46] Rates are higher in developing countries and in low-income groups in developed countries. Rates of congenital CMV infection tend to parallel those of maternal seropositivity; populations with a high prevalence of maternal CMV infection also have higher rates of congenital CMV infection. Young maternal age, single marital status, and nonwhite race are associated with higher rates of congenital CMV infection in the United Kingdom and the U.S. Maternal infection with the human immunodeficiency virus (HIV) is a risk factor for congenital CMV infection in some populations in developing countries; lower maternal CD4 counts are associated with greater risk of congenital CMV infection, and antiretroviral prophylaxis reduces the risk.[47–49]

Nosocomial Infection

Most hospital-acquired CMV infections result from transfusions or transplantation. Banked human milk could be a source of infection for newborns. Transfusion-acquired CMV infections in healthy people usually are asymptomatic. Among recipients of bone marrow transplants, blood products, especially leukocytes, can be an important source of CMV infection and disease. The risk of acquiring CMV from blood products is greatest if CMV-seronegative recipients are given multiple transfusions from CMV-seropositive donors. In one study 9.7% of 93 CMV-seronegative children undergoing open heart surgery demonstrated seroconversion; the risk of posttransfusion CMV infection was estimated to be 2.7% per unit.[50] Infection rates of 13.5% and 9.2% were reported in transfused offspring of seronegative mothers in two other studies.[51,52] The risks of infection and disease acquired through transfusion or human milk are increased in neonates with a birth weight less than 1250 g compared with larger infants.[53] Urine, saliva, and other body fluids of CMV-infected patients, especially newborns, often contain high concentrations of virus. Adherence to standard precautions should prevent nosocomial infections from this source.

Occupational Risk of Infection

Nurses, other patient care personnel in hospitals and clinics, childcare workers, schoolteachers, and mothers have frequent close contact with young children; women of childbearing age constitute the majority of individuals in each of these areas. Among hospital workers the risk of CMV infection does not appear to be increased, which suggests that handwashing and other routine precautions in hospitals reduce CMV transmission. In contrast, studies of childcare workers in the U.S. and Canada have shown a consistently higher incidence of CMV infection, with rates from 8% to 20% per year, compared with an expected rate of approximately 2% per year.[35] The risk of acquiring CMV is higher for childcare workers who have contact with younger children.

Clinical Manifestations

Acquired Infections in Healthy People

CMV infection in immunologically normal children and adults usually is asymptomatic, although heterophile antibody-negative mononucleosis is a common manifestation. Clinically, mononucleosis syndrome caused by CMV is indistinguishable from that caused by the Epstein-Barr virus (EBV). Malaise, headache, fever, and fatigue are common among patients with mononucleosis caused by either virus. More than 90% of adults who develop CMV mononucleosis have a fever.[54] High temperatures are common (39°C to 40°C), and the mean duration of fever is longer than 2 weeks. Other clinical findings include pharyngitis, tonsillitis, lymphadenopathy, hepatomegaly, and splenomegaly. A review of clinical findings in 116 immunocompetent adults hospitalized with symptomatic CMV infection reported chills in 39% of patients, sweats in 35%, abdominal pain in 17%, and weight loss in 10%.[55] Rash associated with ampicillin therapy is common with both CMV and EBV mononucleosis.

Elevated serum hepatic transaminase levels occur in more than 90% of patients with CMV mononucleosis; peak alanine transferase levels rarely are higher than 300 mIU/mL. Elevation of the bilirubin level above 2 mg/dL occurs in less than 5% of patients. Lymphocytosis with atypical lymphocytes (usually 10% to 35%) occurs consistently. Children with CMV mononucleosis are less likely than adults to have fever (43% versus 94%) but are more likely to have hepatomegaly (100% versus 53%) and splenomegaly (86% versus 53%).[56] The expected outcome of CMV mononucleosis in healthy people, including those with transfusion-acquired infection, is recovery without sequelae. However, symptoms can persist for 4 weeks or longer. A laboratory-based study that identified 124 immunocompetent, symptomatic adults with serologic evidence of recent CMV infection reported that symptoms persisted for an average of 7.8 weeks.[57]

Severe illness caused by CMV infection in healthy people has been described in a small number of patients. Complications infrequently associated with CMV infection in a healthy person include venous thromboembolism, uveitis with iris atrophy, persistent thrombocytopenia, hemolytic anemia, myocarditis, gastrointestinal ulceration, transverse myelitis, Guillain-Barré syndrome, and encephalitis.[1] A review of 21 healthy people with encephalitis attributed to CMV infection found that the patients presented with confusion, coma, seizures, aphasia, dysphasia, and cranial nerve abnormalities; recovery was slow, and some patients had persistent abnormalities.[58] Severe CMV infection in a health person is sufficiently uncommon that when it is suspected, a careful evaluation of the patient's immunocompetence is warranted.

Congenital Infection

The clinical manifestations of congenital CMV infection can be divided into findings in the neonate and signs of CNS damage that usually are not fully apparent until later in childhood. More than 90% of neonates with congenital CMV infection appear healthy at birth. A study of 267 cases of congenital CMV infection, identified by virologic screening of more than 27,000 neonates, found that 7% of infected subjects had petechiae, hepatosplenomegaly, microcephaly, thrombocytopenia, or jaundice with conjugated hyperbilirubinemia, and the remainder had no signs of congenital infection at birth.[59]

Clinical and laboratory findings for 106 neonates with symptomatic congenital CMV infection are summarized in Tables 206.2 and 206.3. Symptomatic congenital CMV infection portends significant morbidity; 13 of 106 (12%) of the affected infants died by 6 weeks of age, and the mean duration of hospitalization was 16 days.[60] Evidence of CNS involvement (microcephaly, lethargy-hypotonia, poor suck, seizures, optic atrophy, decreased hearing sensitivity, or intracranial calcifications) is present in approximately two thirds of symptomatic neonates.[60,61] Infants with symptomatic congenital CMV infection at birth are likely to have CNS and sensory impairments, including mental retardation, cerebral palsy, sensorineural hearing loss, and vision loss.

TABLE 206.2

Newborn Clinical Findings in 106 Infants With Congenital Cytomegalovirus Infection Who Were Symptomatic at Birth

Abnormality	%[a]
Prematurity[b]	34
Small for gestational age[c]	50
Reticuloendothelial abnormality (one or more of the following):	
Petechiae	76
Jaundice	67
Hepatosplenomegaly	60
Purpura	13
Neurological abnormality (one or more of the following):	68
Microcephaly[d]	53
Lethargy/hypotonia	27
Poor suck	19
Seizures	7

[a] Number evaluated equals 102–106.

[b] Gestational age <38 weeks.

[c] Weight <10th percentile for gestational age.

[d] Head circumference <10th percentile based on Colorado Intrauterine Growth Charts for premature newborns.

From Boppana SB, Pass RF, Britt WJ, et al. Symptomatic congenital cytomegalovirus infection: neonatal morbidity and mortality. Pediatr Infect Dis J 1992;11:93.

TABLE 206.3

Laboratory Abnormalities in 106 Infants With Congenital Cytomegalovirus Infection Who Were Symptomatic at Birth

Test	Abnormal/Total Examined (%)
Elevated ALT (>80 units/L)	46/58 (83)
Thrombocytopenia	
<100,000/mm^3	62/81 (77)
<50,000/mm^3	43/81 (53)
Conjugated hyperbilirubinemia	
Direct serum bilirubin >2 mg/dL	55/68 (81)
Direct serum bilirubin >4 mg/dL	47/68 (69)
Hemolysis	37/72 (51)
Increased cerebrospinal fluid protein (>120 mg/dL)[a]	24/52 (46)

[a] Determinations made in the first week of life.

From Boppana SB, Pass RF, Britt WJ, et al. Symptomatic congenital cytomegalovirus infection: neonatal morbidity and mortality. Pediatr Infect Dis J 1992;11:93.

A review of 15 studies that screened infants for congenital CMV infection reported that 40% to 58% of symptomatic newborns and 13.5% of those without symptoms at birth had permanent sequelae, with the caveat that these likely are underestimates.[62] Neonates with symptomatic congenital CMV infection should be considered at high risk for sequelae, even if clinical findings are mild. Chorioretinitis, microcephaly, and neurological abnormalities are associated with an increased risk of mental retardation. Computed tomography, ultrasound, and magnetic resonance imaging techniques can provide evidence of CNS involvement in newborns with congenital CMV infection, and abnormal imaging results are predictive of CNS sequelae.[63,64] Abnormalities noted in patients with symptomatic congenital CMV infection include periventricular calcifications, lenticulostriate vasculopathy, periventricular cysts, ventricular dilatation, cortical atrophy, cerebellar hypoplasia, polymicrogyria, and lissencephaly. CNS imaging usually is performed only in newborns with signs of congenital infection; however, CNS abnormalities have been found in a small number of newborns in whom the virus was detected by virologic screening, but who had no signs of congenital infection. Ultrasonography has been recommended as the initial neuroimaging study.[63] It does not require sedation or involve exposure to radiation, and ultrasound findings have correlated with outcome.

In contrast to the high rate of CNS impairments among infants with symptomatic congenital CMV infection, most infected newborns with no clinical abnormalities at birth remain free of sequelae. However, infants with asymptomatic congenital CMV infection have higher than expected rates of sensorineural hearing loss, which is similar in severity and clinical course to hearing loss in symptomatic patients. Congenital CMV infection is a leading cause of sensorineural deafness and of mental retardation in children.

Hearing loss caused by congenital CMV infection often is progressive during childhood. Children with normal hearing at birth can develop hearing loss later, and a high proportion of infants with hearing loss experience further decline in hearing sensitivity. Late onset or progressive hearing loss usually occurs during the first 2 years of life, but decline in hearing sensitivity has been observed in school-aged children with congenital CMV infection. Retinitis also can reactivate, leading to further impairment of vision. Little evidence exists for postnatal progression of brain lesions, but this possibility has received insufficient study.

Acquired Infection in Premature Newborns

Transfusion-acquired CMV infection in premature newborns can produce a clinical syndrome of hepatosplenomegaly, atypical lymphocytosis, thrombocytopenia, worsening of respiratory status, and a septic appearance. The risk of CMV infection and disease is related to a very low birth weight (<1250 g), exposure to multiple units of blood, and birth to a seronegative mother. Fortunately, transfusion-acquired CMV infection in newborns is now prevented by limiting transfusion to seronegative donors or blood that has been filtered through cotton wool to remove leukocytes. However, some small premature newborns acquire CMV from a maternal source (e.g., maternal milk) and develop clinical syndromes similar to those observed with transfusion-acquired infection. Postnatal CMV infection was found in 59% of newborns of less than 32 weeks' gestation and less than 1500 g birth weight who were fed mother's milk that tested CMV positive.[65] The onset of CMV infection was accompanied by symptoms in approximately half of patients. A sepsislike syndrome (apnea, bradycardia, gray pallor, bowel distention), with onset of infection during the first 2 months after birth, occurred in some of the more premature newborns. Laboratory abnormalities, including leukopenia, thrombocytopenia, abnormal serum hepatic enzymes, and elevated C-reactive protein, have been observed.[65,66] Compared with term infants small premature newborns have lower levels of transplacentally acquired maternal CMV immunoglobulin G (IgG), and their levels of antibody can decline rapidly after birth as a result of repeated blood sampling. Although early postnatal acquisition of CMV infection in small premature newborns has been associated with CNS sequelae, the impact is controversial.[67] Because of the established benefits of mother's milk in preterm infants, there is no consensus on steps that should be taken to prevent or treat CMV infection transmitted from mother to very low birth weight premature newborns.[68]

Cytomegalovirus in Solid-Organ Transplantation

When either the donor or the recipient of an organ is seropositive, CMV infection occurs in 50% to 100% of patients after immunosuppression and transplantation. The principal sources of infection are reactivation of endogenous latent virus, the transplanted organ or tissue, and transfusion of untreated blood from seropositive donors. Disease attributed to CMV is most common among seronegative recipients of solid organs or tissue from seropositive donors, although immunosuppression can lead to severe disease in transplant recipients who are CMV seropositive before transplantation. Before the use of antiviral agents to prevent CMV disease became widespread, CMV disease occurred in most CMV-seronegative solid-organ transplant (SOT) recipients who received organs from CMV-seropositive donors (D^+/R^-) and in approximately 5% to 25% of CMV-seropositive recipients. CMV disease substantially increases the duration and costs of hospitalization for SOT recipients.

The onset of viremia, virus shedding, and CMV disease usually occurs 4 to 12 weeks after transplantation. The hallmarks of CMV disease in SOT recipients are fever, malaise, arthralgia, leukopenia or pancytopenia, and laboratory evidence of hepatitis. More serious consequences of CMV infection include pneumonitis, retinitis, and gastrointestinal ulceration. Indirect effects attributed to CMV infection include coinfection with opportunistic pathogens (e.g., *Pneumocystis jirovecii, Aspergillus* spp.), and deterioration of graft function. Primary CMV infection in renal transplant recipients is associated with graft rejection or acute glomerular injury. Persistent hepatitis and hepatic failure are associated with CMV infection in liver transplant recipients. Pneumonitis is more common in patients infected with CMV who have received lung or heart-lung transplants. Accelerated development of coronary artery atherosclerosis has been associated with CMV infection in cardiac transplant recipients. Rates of CMV disease vary widely among transplant centers. Risk factors for greater severity of CMV infection in SOT recipients include primary infection, intensive T-lymphocyte suppressive regimens, and high levels of viremia. Recent reviews provide detailed discussions of the clinical manifestations, diagnosis, prevention, preemptive therapy, and management of CMV infection in SOTs.[69–71]

Cytomegalovirus in Hematopoietic Stem Cell Transplantation

The sources of CMV among recipients of a hematopoietic stem cell transplant (HSCT) are similar to those among SOT recipients. The CMV syndrome (fever, malaise, leukopenia, hepatitis) that sometimes accompanies the onset of CMV infection in SOT patients also can occur in HSCT patients. The two most troublesome manifestations of CMV disease in HSCT patients are pneumonitis and gastrointestinal disease. Before antiviral agents were used routinely to prevent CMV disease in HSCT patients, interstitial pneumonia caused by CMV was common and the mortality was high in affected patients. A 1996 review of CMV disease among patients receiving allogeneic HSCT over a 20-year period found that in 8.6% of transplantations in which either the donor or the recipient was CMV positive before the procedure, the recipient developed CMV disease.[72] Among patients with CMV disease, 64% had pneumonitis alone, 18% had gastrointestinal disease alone, and

9% had pneumonitis plus gastrointestinal disease; there was one case each of retinitis, hepatitis, and encephalitis. Analysis of factors related to outcome of CMV pneumonia among HSCT patients reported survival at 6 months of 30%; lymphopenia and a need for mechanical ventilation were associated with increased mortality, and treatment with ganciclovir or foscarnet was associated with improved outcome.[73] Indirect effects of CMV disease in HSCT patients include greater frequency of opportunistic bacterial and fungal infections and possibly greater all-cause mortality. Factors associated with an increased risk of CMV disease among HSCT patients include D^+/R^- transplants, donor-recipient histoincompatibility, myeloablative conditioning regimens, graft-versus-host disease, and immunosuppressive regimens that induce lymphopenia or profound impairment of T lymphocytes (high-dose corticosteroids, mycophenolate mofetil, T-lymphocyte depletion, anti-CD52 or antithymocyte globulin).[74]

Prevention of CMV disease in D^+ or R^+ HSCT patients during the first 90 to 120 days after transplantation, largely by the use of antiviral agents, has reduced the rate of CMV disease during this period. However, late onset CMV disease remains a problem. Among HSCT patients who received either prophylactic or preemptive antiviral therapy to prevent CMV disease in the first 100 days after transplantation, 18% experienced late onset CMV disease, at an average of 5.5 months after the procedure.[75]

Cytomegalovirus in HIV Infection

Treatment with combination antiretroviral therapy (ART) has significantly reduced the occurrence of CMV disease among adults and children with HIV or AIDS. Most CMV disease in adults with AIDS occurs in those with extremely low CD4 lymphocyte counts (usually $<50/\text{mm}^3$). The most common manifestations of CMV disease in adults with AIDS are retinitis, esophagitis, colitis, or some combination of these. Encephalitis, peripheral neuropathy, polyradiculoneuritis, pneumonitis, gastritis, hepatitis, adrenalitis, skin lesions, oral mucosal ulceration, and sialoadenitis are less common. CMV disease has similar manifestations in children with HIV. In HIV-infected infants, CMV disease is not as strongly associated with profoundly low CD4 counts as it is in adults. Before control of HIV infection was achieved with antiretroviral drugs, coinfection with CMV was associated with more rapid progression to AIDS.[76] Data from the Perinatal AIDS Collaborative Transmission Study showed a more than 10-fold reduction in nonocular CMV disease and a similar dramatic reduction in retinitis in the era of ART compared with pre-ART days.[77] Now CMV disease rarely is encountered in children with HIV infection living in the U.S. The rate of congenital CMV infection in HIV-uninfected infants born to HIV-infected mothers also has decreased from 3.5% to 1.2% in the era of ART, according to data from the French Perinatal Cohort.[78]

Laboratory Diagnosis

Serologic Tests.

Although serologic methods are of limited value for diagnosis of CMV infection in immunocompromised patients, they are used widely for screening and to provide the basis for distinguishing primary infection from past infection in a healthy person (Box 206.1). Enzyme immunoassays are commonly used to detect both IgG and IgM antibodies to CMV.

Box 206.1

Clinical Uses of Cytomegalovirus Serology

CMV IgG

Screening to determine whether subject ever has been infected

- Blood and organ donors
- Organ transplant candidates
- Immunocompromised patients
- Pregnant women

Detection of seroconversion from Cytomegalovirus (CMV) IgG negative to CMV IgG positive, proving primary infection

CMV IgM

Testing for recent CMV infection in an immunocompetent patient with a compatible illness

Testing of pregnant women for primary CMV infection, using CMV IgG avidity testing for confirmation

Not useful in immunocompromised patients

Not recommended for diagnosis of congenital infection

Serum IgG antibody to CMV is used to screen for past CMV infection, so as to determine several risks: the risk of virus transmission (blood and organ donors); the risk of reactivation disease in immunocompromised patients; and the risk of acquiring the virus for those likely to be exposed. Although CMV IgM antibody assays are widely used to detect primary infection, they vary in accuracy for this purpose. Demonstration of low-avidity CMV IgG antibody testing improves the specificity of a positive CMV IgM test result.

Diagnosis of Congenital Infection.

The diagnosis of congenital CMV infection is confirmed by detection of the virus in body fluids within the first 3 weeks of life. Urine and saliva are the preferred specimens for testing. CMV can be detected easily in the urine of newborns with congenital infection by its characteristic cytopathic effect in tissue culture, or by rapid, centrifugation-enhanced (shell vial) culture using monoclonal antibody to early antigens. However, currently PCR and real-time PCR have advantages in sensitivity, rapid turnaround time and potential for automation and are used widely. A prenatal diagnosis of fetal infection is made by detection of CMV in amniotic fluid.

After 3 weeks of age excretion of CMV could be the result of acquisition of the virus during birth or through breast milk. Serologic methods should not be used for diagnosis of congenital CMV infection. Higher levels of CMV in the blood, as measured by quantitative competitive or real-time PCR, have been associated with an increased risk of hearing loss and other sequelae. However, a threshold quantity of CMV in the blood or urine that can be used as a basis for management of newborns with congenital infection has not been established.

Diagnosis in Immunocompromised Patients.

The detection of CMV in body fluids or tissues of immunocompromised people does not prove that clinical findings are related to CMV. However, because primary CMV infection commonly causes disease, the development of antibodies to CMV or documentation of viremia or viral excretion in a previously seronegative patient provides strong support for a causal role. In transplant recipients with primary CMV infection, viremia, virus excretion, seroconversion, and clinical abnormalities usually occur 4 to 12 weeks after transplantation. In immunocompromised patients with reactivated CMV infection, neither antibody response nor excretion of virus in urine, saliva, or respiratory tract secretions is a reliable indicator of CMV disease.

In both SOT and HSCT management, all donors and recipients should be tested for CMV IgG antibody before transplantation to identify patients who are at risk for primary infection and those likely to experience reactivation after immunosuppression. After transplantation the most widely used laboratory tests to identify patients with or at risk for CMV disease are assays that estimate the quantity of virus in the blood. A number of assays have been used for this purpose: antigenemia (quantitation of white blood cells [WBCs] positive for CMV PP65), assays that amplify virus-specific messenger ribonucleic acid (mRNA), antigen capture with monoclonal antibody, quantitative competitive PCR, and real-time PCR. The quantity of CMV DNA in blood predictive of disease varies with the method of measurement, the type of sample (whole blood, plasma, leukocytes), and the clinical setting. Real-time PCR of plasma or whole blood now is used widely because of its sensitivity, ability to quantify viral DNA in clinical specimens over a wide range of concentrations, and adaptability to automation. A World Health Organization (WHO) International Standard for human cytomegalovirus (HCMV) DNA is available; calibrating secondary standards for commercial and laboratory-based assays on clinical samples should make it possible to achieve interlaboratory consistency in quantitative results. However, significant differences in quantitative results can occur between laboratories using the WHO standard and with secondary standards, probably as a result of laboratory-specific variability in DNA extraction and other testing procedures.[79] The lack of standardization in laboratory assays and the fact that the level of CMV in blood that predicts disease varies with the clinical setting make it difficult to establish recommendations on cutpoint levels for clinical significance.

Treatment

Treatment of CMV mononucleosis is not indicated for an immunocompetent person because the illness is expected to resolve without sequelae. In rare cases of severe or life-threatening disease in an immunocompetent person, a thorough evaluation of immune function should be performed, and the infection reasonably can be managed the same way as infection in an immunodeficient person.

Congenital Infection.

Antiviral treatment of newborns with symptomatic congenital CMV infection is recommended to improve hearing and developmental outcome.[80] Valganciclovir (mono-valyl ester of ganciclovir) given orally is recommended (16 mg/kg/dose twice daily for 6 months).[81] Ganciclovir given intravenously (6 mg/kg/dose every 12 hours) can be substituted if the patient is unable to take oral medications. Treatment is associated with neutropenia, which is reversible with dosage adjustment or discontinuation of the medication. Animal studies indicate the potential for reproductive toxicity and carcinogenicity at levels similar to those achieved in treating humans, but similar toxicity has not been reported in humans. Most newborns with congenital CMV infection have no clinical evidence of CMV disease in the first month of life and will not develop hearing loss or other sequelae. Neither screening for the virus at birth nor antiviral treatment of asymptomatic neonates is recommended at this time because the evidence is insufficient to allow a risk-versus-benefit assessment.

Infection in Immunocompromised Patients.

Detailed guidelines for preventing and treating opportunistic infections, including CMV, in HIV-infected adults and adolescents can be found at the AIDSinfo website (http://aidsinfo.nih.gov).[82] A separate guideline for children is available on the website.[83] Key points from these evidence-based guidelines are summarized here. Preventing CMV disease is best achieved by maintaining patients on effective ART and achieving a CD4 count higher than 100 cells/mm^3 for adults, adolescents, and children 6 years of age or older; and, for children younger than 6 years, a CD4 percent greater than 10%. Annual CMV antibody testing is recommended beginning at 1 year for HIV-infected children who are initially CMV seronegative and have not exceeded these CD4 cell thresholds.

Antiviral treatment to prevent CMV disease is recommended for HIV-infected adults, adolescents, and children 6 years or older who are CMV seropositive and whose CD4$^+$ cell counts are lower than 50 cells/mm^3; for children younger than age 6 years, a CD4 percentage below 5% is the threshold for prophylaxis. Oral valganciclovir is recommended for preventive treatment under these circumstances. Patients should be taught the importance of recognizing visual symptoms and performing regular eye examinations so that CMV retinitis can be detected and treated promptly. In HIV-infected patients, CMV retinitis and other end-organ disease are treated with ganciclovir intravenously or valganciclovir orally. Foscarnet is the preferred alternative if viral resistance to ganciclovir is detected. After active disease has been controlled, patients are continued on maintenance antiviral therapy until immune reconstitution is achieved. Maintenance therapy is not recommended for patients with disease limited to the lungs or gastrointestinal system. Combination antiviral therapy with ganciclovir and foscarnet should be considered for patients with CMV CNS disease, resistance to ganciclovir, or failure to respond to monotherapy. Although guidelines are detailed and updated regularly, consultation with a specialist experienced in the prevention and treatment of CMV infections is recommended.

Prevention and Treatment of CMV Infection in Patients Who Have Received Transplants.

Consensus guidelines and literature reviews of published studies on approaches to the prevention and treatment of CMV disease in

SOT and HSCT patients are helpful, but consultation with an expert in the management of CMV infections in these patients is recommended.[84–86] Most guidelines endorse the use of antiviral agents to prevent or treat CMV disease in SOT recipients, with the possible exception of those who are CMV seropositive before transplantation and are perceived to be at low risk of CMV disease based on donor match, immunosuppressive regimen, and type of transplant.[84–86] All D^+/R^- SOT patients require an approach to prevent CMV disease, as do R^+ patients, especially those at greater risk of severe disease because of an immunosuppressive regimen or the type of transplant (e.g., heart-lung). Antiviral prophylaxis (usually with oral valganciclovir) is used for high-risk patients (i.e., D^+/R^- recipients) and when the donor or recipient is CMV positive and T-cell depletion is used. The duration of prophylaxis can vary from 100 days to a full year. In a preemptive approach recommended for lower risk patients (i.e., those not treated with T-cell depleting antibodies), the CMV viral load in the blood is monitored regularly, and antiviral therapy is initiated when a threshold viral load is reached.[84]

Antiviral prophylaxis has the disadvantage of exposing many patients to antiviral agents who would not develop CMV disease, and it could increase the prevalence of drug-resistant virus. In addition, late onset disease (after the antiviral agent has been discontinued) seems to occur more frequently in patients given prophylaxis than in those managed with a preemptive approach. The preemptive strategy has the advantage of reducing antiviral use substantially, but it requires a laboratory capable of providing frequent viral load results (weekly or more often) for months. CMV immune globulin (CMV-IG) is used commonly in SOTs as part of a prophylactic regimen for preventing CMV disease. A multicenter, randomized, placebo-controlled clinical trial of CMV-IG in D^+/R^- renal transplant patients in the 1980s showed a statistically significant reduction in CMV disease and opportunistic fungal and parasitic infections among treated patients compared with placebo controls, although the rate of CMV infection was not reduced.[10] A 2007 Cochrane review examined published randomized trials in SOT patients comparing CMV-IG or standard immune globulin intravenous (IGIV) with placebo and with no treatment.[87] No difference in outcome was found between patients receiving CMV-

IG or IGIV compared with those receiving a placebo or no treatment. Transplantations in which the donor and recipient are CMV seronegative pose little or no risk of CMV disease. Assuming that steps are taken to prevent infection through blood products, D^-/R^- transplants do not need a preventive antiviral regimen.

Intravenous ganciclovir is the preferred antiviral agent for treatment of CMV disease in transplant recipients, although oral valganciclovir can be used if the patient is not seriously ill and can take medication. Antiviral treatment is continued until clinical and laboratory abnormalities related to CMV infection show substantial improvement and the viral load declines (usually in 14 to 21 days). If the viral load is used to assess the effectiveness of treatment, antiviral therapy usually is continued until the quantity of virus in the blood drops below the threshold that would trigger initiation of treatment. Failure to clear viremia has been associated with recurrence of CMV disease. After initial control of the CMV infection has been achieved, maintenance therapy with oral valganciclovir is used to prevent recurrence. Foscarnet alone or with ganciclovir can be used as an alternate agent if CMV is resistant to ganciclovir, ganciclovir is not tolerated, or the patient fails to respond to treatment.

Guidelines for prevention of opportunistic infections in HSCT patients and protocols from leading HSCT centers are good sources of information on preventing and treating CMV infection.[88–90] A CMV disease prevention program should be used for all R^+ and all D^+/R^- HSCT patients from the time of engraftment until 100 days after transplantation. Either prophylactic or preemptive treatment with intravenous ganciclovir is recommended for recipients of allogeneic hematopoietic cells; foscarnet is an alternative agent for prophylaxis. Oral valganciclovir now is widely used in place of intravenous ganciclovir. Blood products from seronegative donors or leukocyte-reduced, filtered blood should be used for CMV-seronegative HSCT patients to prevent infection from transfused blood products. Randomized, placebo-controlled clinical trials in seronegative recipients of allogeneic stem cells have failed to show efficacy of CMV-IG for preventing CMV disease, and CMV-IG currently is not recommended for prophylaxis.[91,92]

Although autologous HSCT recipients are considered low risk for CMV disease, weekly viral load monitoring for 60 days after transplantation is recommended for CMV-seropositive HSCT recipients who have underlying hematologic malignancies or receive intense immunosuppressive regimens. CMV viremia is associated with an increased risk of overall mortality in the first year after transplantation.[93] About 8% to 10% of CMV-seropositive HSCT patients develop CMV disease in the first year after transplantation. Treatment of CMV disease in HSCT patients is similar to the approach used in SOT patients. Induction treatment is given for 2 to 3 weeks, followed by maintenance therapy for weeks to months. Treatment is initiated with intravenous ganciclovir (or foscarnet); transition to valganciclovir can be considered after substantial improvement has been achieved, assuming the patient can take medications. The duration of maintenance therapy is longer for patients recovering from CMV pneumonia and in those in whom immunosuppression could not be reduced. Although the protocol is controversial, some centers use CMV-IG or IGIV in addition to antiviral therapy in HSCT patients to treat CMV pneumonia.

Cytomegalovirus Antiviral Drug Resistance.

CMV resistance to antiviral agents is encountered when prolonged treatment is required and ongoing viral replication cannot be suppressed effectively. Relatively high rates of CMV resistance to ganciclovir were common in adult patients with AIDS in the pre-ART era. Transplant patients often require prolonged courses of antivirals to treat CMV infection, and rates of antiviral drug resistance of 5% to 10% have been reported (higher rates are associated with more severe CMV disease).[94] Antiviral drug resistance should be suspected in patients with CMV disease who are not improving clinically on treatment and who do not show a decrease in the viral load of blood or plasma. Three currently licensed CMV antiviral agents (ganciclovir/valganciclovir, foscarnet, and cidofovir) all act on the viral DNA polymerase. Ganciclovir requires phosphorylation by a viral kinase before it can complete phosphorylation by cellular kinases. Mutations in the CMV gene, *UL97*, that encodes the viral kinase, and mutations in the viral DNA polymerase gene, *UL54*, can lead to ganciclovir resistance. Resistance to foscarnet and cidofovir is mediated by mutations in the DNA polymerase gene. Genotypic testing for resistance mutations is available from specialty laboratories.

Management of patients in whom antiviral resistance is suspected or proven is challenging because these usually are patients who are severely immunocompromised, have high levels of CMV in the blood despite treatment, and have uncontrolled CMV disease. Their management should include consideration of modification of immunosuppressive regimens, in addition to an alternative antiviral regimen. Depending on the results of genotypic resistance testing, an advantageous approach might be to increase the dose of ganciclovir to overcome *UL97* mutations that confer low-level resistance; to change to foscarnet; or to use combination therapy. If ganciclovir resistance is due to *UL54* mutations, resistance to cidofovir also is likely. For a more detailed discussion of this topic, the reader should study a review of the biology and clinical significance of CMV antiviral resistance.[94]

Prevention

Transmission of CMV appears to require direct contact with infected body fluids. The two leading sources of community-acquired CMV infection are contact with young children and intimate contact. Prevention of these exposures is challenging because they are a normal part of family and social life and child rearing. Because CMV infection in a healthy person almost always is silent clinically, it is prudent to assume that contact with saliva, urine, or other body fluids from anyone is a potential source of CMV.

Prevention of Maternal and Congenital Infection.

Handwashing and following Standard Precautions are recommended to prevent CMV infection in pregnant women and in those who care for infants and children.[95,96] Specific steps that can be taken by pregnant women (and others) to avoid exposure to body fluids that might contain CMV are presented in (Box 206.2).

Box 206.2

Centers for Disease Control Recommendations for Pregnant Women to Reduce Exposure to Cytomegalovirus and

the Risk of Fetal Infection

Wash your hands often with soap and water for 15 to 20 seconds, especially after:

- Changing diapers
- Feeding a young child
- Wiping a young child's nose or drool
- Handling children's toys

Do not share food, drinks, or eating utensils used by young children

Do not put a child's pacifier in your mouth

Do not share a toothbrush with a young child

Avoid contact with saliva when kissing a child

Clean toys, countertops, and other surfaces that come into contact with children's urine or saliva

Studies in pregnant women suggest that providing them with information on the risks of CMV, in addition to clear steps for prevention, results in reduced rates of infection during pregnancy.[97,98] Most primary CMV infections in pregnant women go unrecognized because they are asymptomatic. Prenatal screening for CMV infection currently is not recommended. CMV immune globulin treatment of pregnant women with primary CMV infection has been studied as a means of preventing transmission to the fetus and improving the outcome for infected fetuses.[99–101] The only randomized, observer-blind clinical trial performed thus far reported no statistically significant reduction in the rate of fetal infection or the outcome of fetal infection among babies born to women who received CMV-IG; however, because of the study's limited sample size and power, a modest treatment effect could not be excluded.[101] A larger phase 3 clinical trial in mothers with primary gestational CMV infection currently is testing the efficacy of CMV-IG treatment for preventing congenital infection.[102]

Prevention of Healthcare-Acquired Infection.

Nosocomial CMV infections that occur by transmission between patients and healthcare workers are rare, probably because of the handwashing and body fluid precautions that are part of routine hospital care. Transfusion-acquired CMV infections can be prevented either by filtering blood to remove WBCs or by screening donors so that only seronegative blood products are provided to seronegative high-risk patients. However, these two strategies are not equally effective for high-risk HSCT patients; some unexpected CMV infections still occur in patients receiving filtered blood products.[103]

CMV potentially can be transmitted through assisted reproductive technology. The American Society for Reproductive Medicine has published guidelines for screening sperm and oocyte donors, and for preventing CMV infection in recipients.[104,105]

Cytomegalovirus Vaccine.

Currently no vaccine for preventing CMV infection and disease has won the approval of the U.S. Food and Drug Administration. The Towne strain live-attenuated CMV vaccine showed limited efficacy for preventing severe disease in renal transplant recipients, but vaccination did not prevent infection either in transplant recipients or in healthy adults exposed to young children shedding CMV.[9,106] The results of phase 2 randomized, placebo-controlled clinical trials of a recombinant, subunit CMV vaccine based on the envelope glycoprotein gB are encouraging. This vaccine achieved 50% efficacy for prevention of maternal infection in high-risk young women.[12] In addition, pretransplant immunization with the CMV gB vaccine improved control of CMV infection in SOT patients.[11] Another phase 2 randomized, placebo-controlled clinical trial, involving a therapeutic DNA vaccine with plasmids encoding CMV glycoprotein B and PP65, was conducted in CMV-seropositive HSCT patients; vaccination decreased the occurrence of clinically significant viremia.[107] A number of other CMV vaccines are in development, but it is unlikely that any will be licensed in the next few years.

Key Points

Cytomegalovirus Infections

Virology

- Large, complex virus, member of herpesvirus family
- Double-stranded DNA with about 160 open reading frames
- Much of genome devoted to immune evasion or interaction with host's immune functions
- Persists in latent form indefinitely

Epidemiology

- Endemic in all human populations
- Prevalence increases with age but varies depending on child-rearing and other practices.
- Perinatal transmission is an important epidemiologic feature.
- Transmission of CMV primarily is by direct contact with body fluids.
- CMV is shed in body fluids for months to years after primary infection.
- Transplacental transmission infects about 0.7% of fetuses worldwide.

Clinical Features

- Almost all postnatal infections in normal infants are clinically silent.
- CMV rarely causes a mononucleosis syndrome.

- Approximately 10% of newborns with fetal infections show typical signs of congenital infection at birth.

- Congenital infection is a leading cause of hearing loss and CNS impairments.

- CMV is a major cause of morbidity in immunocompromised patients.

Diagnosis

- Serum IgG antibody identifies patients who have ever been infected.

- Congenital infection is diagnosed by detection of the virus in body fluids before 3 weeks of age.

- Quantity of virus in body fluids is used to identify immunocompromised patients at risk for disease.

Prevention

- Specific measures are used to prevent disease in immunocompromised patients.

- Specific measures are recommended for avoiding exposure during pregnancy.

Treatment and Chemoprophylaxis

- Newborns with symptomatic congenital CMV infection likely will benefit from antiviral treatment.

- Antiviral chemoprophylaxis is used to prevent CMV disease in certain immunocompromised patients.

- CMV disease in immunocompromised patients is treated with antiviral agents.

- Immunocompromised patients who develop CMV disease may require maintenance antiviral treatment to prevent recurrent disease.

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Human Herpesviruses 6 and 7 (Roseola, Exanthem Subitum)

Mary T. Caserta

Human Herpesvirus 6

Human herpesvirus 6 (HHV-6) was first isolated from the peripheral blood lymphocytes of adults with lymphoproliferative diseases and human immunodeficiency virus (HIV) infection and was named human B-lymphotropic virus.[1] When additional isolates were identified in CD4$^+$ lymphocytes, further characterization indicated that the virus was a herpesvirus. Because it was the sixth member of the herpesvirus family, it was renamed *Human herpesvirus 6*. Two years after its initial isolation, HHV-6 was discovered in the lymphocytes of four infants with roseola.[2] Subsequently, HHV-6 was established as the prime cause of this common illness of the young, which for many decades was prophetically known as “the sixth exanthematous disease of childhood.” HHV-6 is an important pathogen in young children globally, and as is characteristic of herpesviruses, it subsequently establishes persistent, latent, and lifelong infection.

Description of the Pathogen

HHV-6A, HHV-6B, and HHV-7 comprise the *Roseolovirus* genus of the subfamily β-Herpesvirinae. They have the characteristic human herpesvirus family's morphology and structure: an electron-dense nucleic acid core encased in an icosahedral capsid surrounded by proteins collectively known as the tegument, and an outer envelope containing proteins and glycoproteins in a lipid bilayer. The linear, double-stranded deoxyribonucleic acid (DNA) genome of HHV-6 is 160 to 170 kilobases (kb) and has a unique central region (U), which contains open reading frames (ORFs) U1–U100 bounded on each end by terminal direct repeats (tDR). HHV-6A, HHV-6B and HHV-7 all share limited homology with human cytomegalovirus (CMV), the only other human β-herpesvirus.[3,4] The overall nucleotide sequence identity between HHV-6A and HHV-6B is approximately 90%, but less in the direct repeats (85%) and U86–U100 (72%).[5,6] HHV-6A and HHV-6B are colinear with minimal (<1%) intragroup variation.[3] Although HHV-6A and HHV-6B initially were classified as separate subgroups of HHV-6, in 2012 the two were recognized officially as distinct species based on differences in biology, immunology, epidemiology, and disease associations.[7]

HHV-6B causes almost all primary infections in infants and is the predominant virus associated with reactivated infection in immunocompetent and immunocompromised individuals.[3,7] However, in a previous report from an African population, most of the infant infections were associated with HHV-6A.[8] More recent data have not confirmed this finding.[9] HHV-6 infects mature T lymphocytes in vitro, especially activated CD4$^+$ cells. However, in contrast to the findings of the in vitro studies, HHV-6B replicates more efficiently in monocytes and macrophages during acute infection than in CD4$^+$ cells.[10] HHV-6 also can infect multiple other cell types, including B lymphocytes, fibroblasts, natural killer cells, and neuronal, epithelial, and endothelial cells.[3,11,12] Growth is characterized by cellular ballooning, lysis, and cell death.

HHV-6A uses CD46 as a cellular receptor. This receptor is expressed on the surface of all human nucleated cells, which may partly explain the wide in vitro cellular tropism and tissue distribution of HHV-6A.[6] Viral binding occurs through the interaction of CD46 with the glycoprotein complex HHV-6A gHgLgQ1gQ2. The same complex is responsible for binding of HHV-6B to the newly identified receptor CD134 (OX40), a member of the tumor necrosis factor (TNF) superfamily present on the surface of activated T lymphocytes.[13] Differences in the nucleotide sequences gQ1 and gQ2 between HHV-6A and HHV-6B are thought to play a role in defining receptor specificity and tissue tropism.[9]

After primary infection HHV-6A and HHV-6B establish latency in monocytes and macrophages and possibly in other sites, such as hematopoietic stem cells ($CD34^+$) and the central nervous system (CNS).[14,15] Persistent infection can occur in the salivary glands.[15,16] The structure of the HHV-6 genome during latency appears to be maintained by chromosomal integration and/or by closed circular molecules, similar to episomes of other herpesviruses, and only a few viral genes are expressed.[3,17]

Reactivation occurs with multiple but poorly defined stimuli and can be asymptomatic or can result in organ-specific diseases.[18–20] Usually reactivation in a healthy person is clinically occult. Occasionally primary infection with a closely related virus (e.g., HHV-7) can result in HHV-6 reactivation associated with viremia and a febrile illness.[21]

Neutralizing antibodies to multiple HHV-6 proteins, especially to linear and conformational epitopes of the glycoproteins, develop after primary HHV-6B infection. Immunoglobulin M (IgM) antibody usually appears in the first week of illness and disappears within 1 to 2 months. IgG antibody appears during the second week after the onset of illness, and concentrations and avidity peak within 1 to 2 months.[3,15,22] The antibody response to primary infection occurs despite the presence of maternal antibody but can be dampened by high levels of passive antibody. Humoral antibody appears to be protective because illness is uncommon during the first few months of life when maternal antibody is present in high concentration (Fig. 207.1).[19] As transplacental antibody concentrations decline, infants rapidly acquire HHV-6B infection.[19] HHV-6 IgG antibody titers subsequently fluctuate and can be boosted by infection with other closely related herpesviruses. However, the immunologic response after primary infection usually protects against subsequent episodes of viremia and clinical illness. HHV-6 antibody is detectable throughout life, as evidenced by its almost universal presence in the cord blood of neonates.[23]

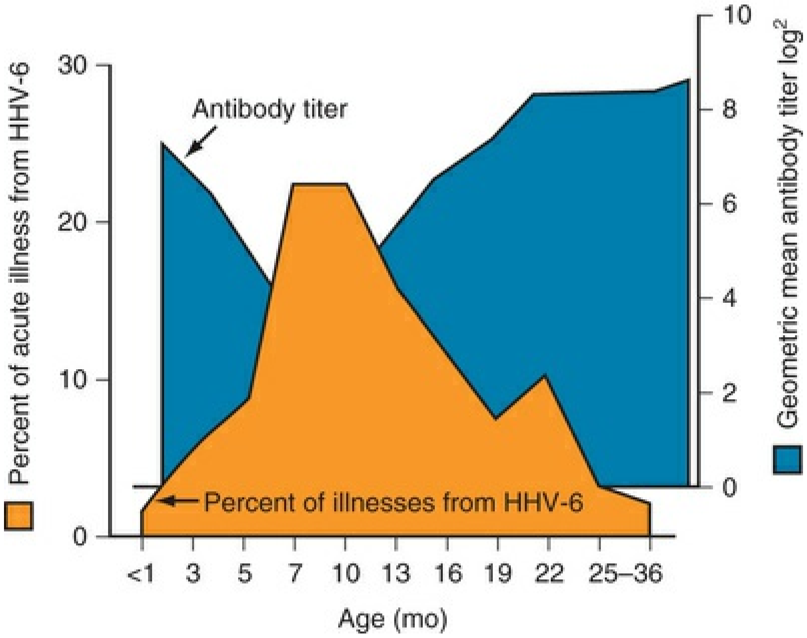

FIGURE 207.1 Percentage of visits to an emergency department in Rochester, NY, by children from birth to 36 months of age, attributable to acute febrile illness caused by primary infection with human herpesvirus 6 (HHV-6). The data are shown in relation to the average titer ($\log^2$) of antibody to HHV-6 present. (Data from Hall C, Long C, Schnabel K, et al. Human herpesvirus-6 infection in children: a prospective study of complications and reactivation. N Engl J Med 1994;331:432–438.)

Clinical observations suggest that cellular immunity is critical in the control, persistence, and reactivation of HHV-6B infection. Patients with compromised cellular immunity, especially hematopoietic stem cell (HCT) and solid-organ transplant (SOT) recipients, are most prone to developing disease with HHV-6B reactivation.[24–26] The effects of HHV-6 on the innate and adaptive cellular responses are incompletely defined but appear to be complex. Multiple observations indicate that HHV-6 can modulate and circumvent the body's immune response, enhancing the pathogenesis of primary infection and favoring lifetime survival of the virus.[3,27]

Epidemiology

HHV-6B infection has a worldwide distribution and no seasonal or gender predilection.[15,19,28] Primary infection usually occurs between 6 months and 3 years of age,[16,19] which matches the typical age distribution of roseola.[29,30] Studies of HHV-6B primary illness in Japan and the United States show similar age distributions, with relatively few cases before 6 months or after 2 to 3 years of age.[3,16,19] The peak period of acquisition is between 6 and 12 months; the median is about 8 months of age.[15,16,19,31]

HHV-6B is a major cause of acute febrile illness in infants 6 to 18 months of age, and it is responsible for about 20% of visits to emergency departments for acute illness in infants 6 to 12 months of age (see Fig. 207.1).[19,32] Infection is ubiquitous, and in most areas studied essentially all adults are seropositive.[15,19] Some geographic differences may exist, and in some countries the age of acquisition of initial infection is later than in the U.S.[33–35] HHV-6A has not been associated clearly with a distinct disease, and significant cross-reactivity between HHV-6A and HHV-6B in standard serologic assays has limited epidemiologic investigations.[36]

Mode of Transmission

Postnatal Infection

The major mode of transmission of HHV-6B to young children appears to be through respiratory secretions containing the virus that are asymptomatically shed by close contacts. This possibility is supported by data demonstrating that children who acquired HHV-6B infection before their first birthday were more likely to practice saliva sharing behaviors.[37] Additionally, HHV-6B DNA has been identified in 60% of nasal mucus specimens from healthy volunteers, which suggests that respiratory droplet transmission is probable.[38] In a prospective study of the epidemiology of roseola in 1941 Breese[29] observed that infants with roseola lacked a history of contact with children with similar disease and likely acquired the virus from asymptomatically shedding family members. Kempe and colleagues[30] in 1950 demonstrated that both the serum and respiratory secretions of an infant with clinical roseola could transmit the disease after an incubation period of 10 days in humans (after about 5 days in monkeys). Subsequent molecular and epidemiologic studies have confirmed that HHV-6B DNA is detectable after primary infection in peripheral blood mononuclear cells, saliva, and salivary glands.[15,16,39–41] Although HHV-6 persists in salivary glands, isolation of HHV-6B from oropharyngeal secretions is rare.[3,42,43]

Although the incubation period for HHV-6B infection has not been established, the Kempe study[30] suggests it is about 10 days, and primary infection has been documented in the first several weeks of life.[16,19,44,45] The detection of HHV-6B DNA in the genital secretions of pregnant women and in peripheral blood mononuclear cells of some infants in the first few weeks of life further supports the possibility of perinatal HHV-6B transmission.[19,44,46–49] Human milk is not a likely source of perinatal infection because the prevalence among breastfed and bottle-fed infants does not differ, and HHV-6 DNA has not been identified in human milk.[50,51]

HHV-6B is latent in bone marrow progenitor cells and therefore can be transmitted to recipients of bone marrow transplants or to those receiving solid-organ transplants.[52–55] HHV-6 infection with chromosomally integrated virus (ciHHV-6), characterized by high viral loads, also can be established in bone marrow recipients after transplantation from a donor with ciHHV-6.[56–59]

Congenital Infection

Congenitally acquired infections determined by detection of HHV-6 DNA in cord blood occur in about 1% of newborns.[23,60,61] Intrauterine HHV-6 infections can result from transplacentally passed maternal infection or from ciHHV-6 passed through the germline.[46,62] The latter appears to account for most (86%) congenital infections. HHV-6 has the unique ability among human herpesviruses to integrate as a whole, partial, or rearranged genome into chromosomes of some normal and immunocompromised individuals.[59,63–71] ciHHV-6 is estimated to occur in 0.2% to 1% of Japanese, United Kingdom, and U.S. populations.[62,69,71,72] Among the small number of people reported to have ciHHV-6 infection, integration has occurred invariably in the telomeric region of one chromosome's short or long arm.[17,62,71,73,74] Thus far at least eight different chromosomes have been identified.[63,69]

When ciHHV-6 is passed through the germline, the HHV-6 genome is present in every nucleated cell[57–59,62]; as a result, high viral loads are seen in all blood and other specimens.[57–59,62] These two distinctive biologic characteristics allow the diagnosis of ciHHV-6 infection by the detection of HHV-6 DNA in all cells of two different lineages (e.g., cord or peripheral blood mononuclear cells and hair follicles) or by demonstration of constantly and persistently high viral loads in peripheral blood mononuclear cells.[57–59,62] A sizeable proportion of these congenital infections are caused by HHV-6A, whereas HHV-6B accounts for essentially all postnatally acquired infections.[75] Children with ciHHV-6 infection have no distinctive clinical findings at birth.[62] However, one study found that children with ciHHV-6 had significantly lower global developmental test scores at 1 year of age compared with children without congenital HHV-6 infection, which supports a possible pathologic effect.[76] Evidence suggesting that ciHHV-6 can reactivate, replicate, and cause disease in immunocompromised people supports this as a possibility.[77–80]

Children with a transplacentally acquired congenital infection usually appear normal at birth. The initial diagnosis requires detection of HHV-6 DNA in cord blood mononuclear cells.[62,76] HHV-6 DNA subsequently can be detected in peripheral blood mononuclear cells and saliva, but not consistently or in the high viral loads observed with ciHHV-6 congenital infections. Most transplacentally acquired congenital infections appear to result from maternal reactivated ciHHV-6.[78,79]

Clinical Manifestations

Acute Febrile Illness

Yamanishi and associates[2] first isolated HHV-6B from four Japanese infants with roseola (exanthem subitum), the major clinical expression of primary HHV-6B infection in Japan.[81–83] In the U.S. a wide spectrum of febrile illnesses occur in infants with a primary infection (Fig. 207.2). Roseola is the clinical diagnosis in 10% to 30% of infected infants (Fig. 207.3).[16,19,31,84] Initial HHV-6B infection mimics a myriad of common, often nonspecific, illnesses of young children, making clinical differentiation difficult. However, some features provide clues to the diagnosis of HHV-6B infection, especially if the child is 6 to 24 months old. The abrupt onset of high fever (average, 40°C) is characteristic (see Fig. 207.2 and also Fig.

207.4). Children with an HHV-6B infection who were evaluated in emergency departments have shown substantially higher average temperatures and appear more acutely ill and irritable than age-matched children with acute febrile illnesses attributable to other etiologies.[19,31]

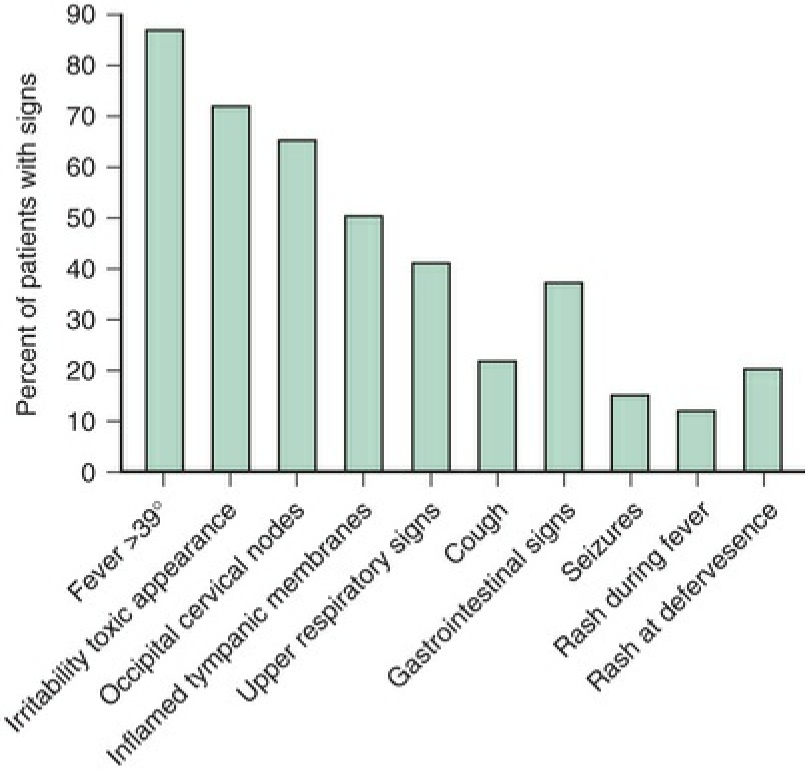

FIGURE 207.2 Clinical signs associated with a primary infection with human herpesvirus 6 (HHV-6) and the proportion of infected children who manifested each sign, as documented both by viremia and by seroconversion, in 335 children studied in Rochester, NY. (Data from Hall C, Long C, Schnabel K, et al. Human herpesvirus-6 infection in children: a prospective study of complications and reactivation. N Engl J Med 1994;331:432–438; and Hall CB. Human herpesvirus 6, 7, and 8. In: Gershon A, Katz S, Hotez P (eds). Krugman's Infectious Diseases in Children, 11th ed. Philadelphia, Mosby, 2003, pp. 277–291.)

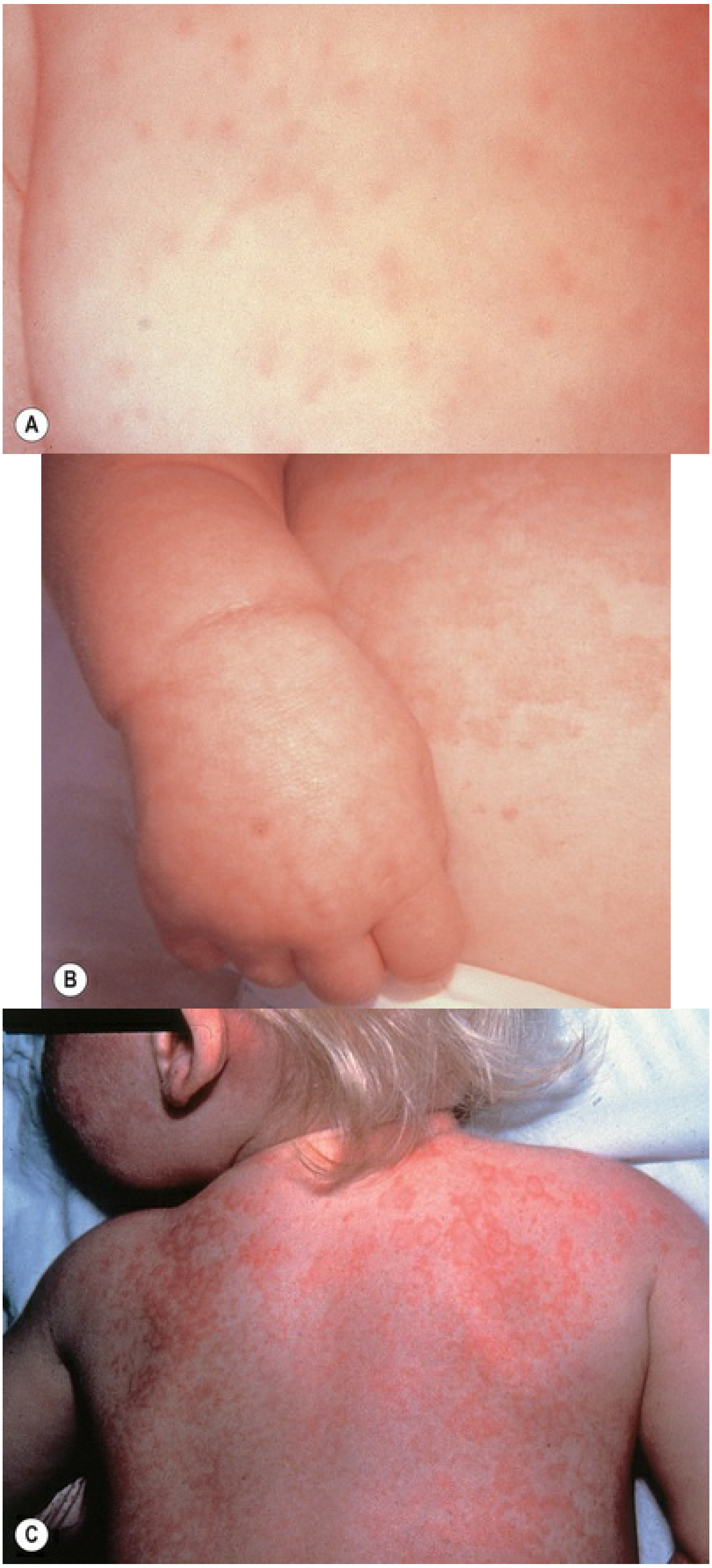

FIGURE 207.3 Exanthems associated with roseola. The rash observed with roseola historically was

described as the “rash of roses,” which denoted the sudden blooming of a pink to red exanthem. The lesions tend to appear first on the trunk, and then spread to the face and extremities. They can be morbilliform or can resemble rubella, with 1- to 3-mm macular, blanching lesions that sometimes coalesce into patches. As shown in A to C, the rash can vary in appearance and extent.

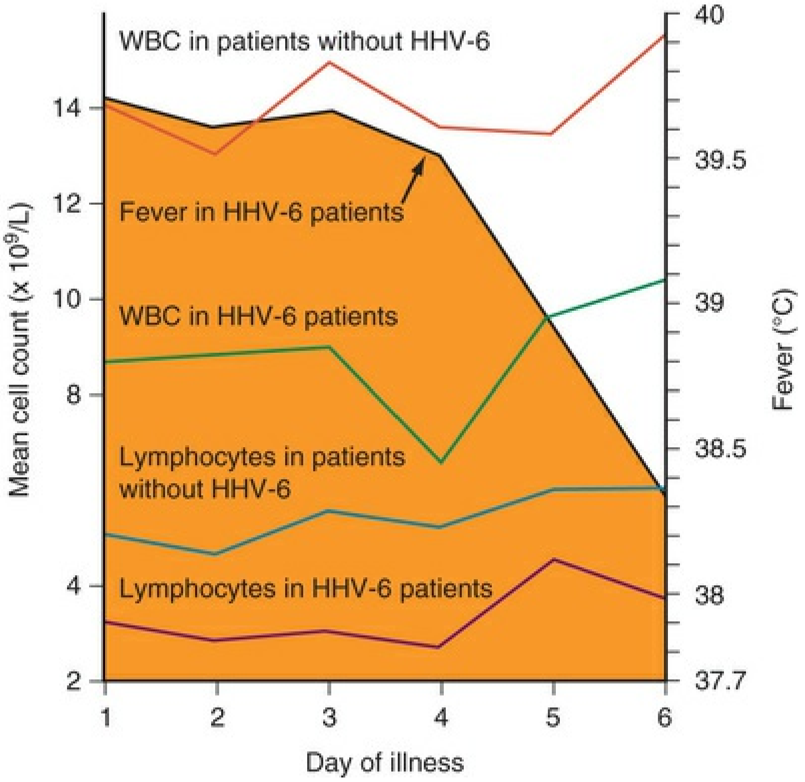

FIGURE 207.4 Mean total white blood cell (WBC) and lymphocyte counts in patients with a primary infection caused by human herpesvirus 6 (HHV-6). The counts are shown by day of illness in relation to the average course of the fever. For comparison, the figure shows the mean WBC and lymphocyte counts for children matched for age and season with similar acute febrile illnesses that were not caused by HHV-6. (From Pruksananonda P, Hall C, Insel R, et al. Primary human herpesvirus 6 infection in young children. N Engl J Med 1992;326:1445–1450.)

Among children ill with primary HHV-6B infection, about one third have fever with no localizing signs, one half manifest nasal congestion and other upper respiratory tract signs, and in about one third diarrhea and vomiting are prominent. Diffuse pharyngeal erythema, a mild maculopapular enanthem on the soft palate and uvula (Nagayama spots), and inflamed tympanic membranes are common. The eyelids can appear puffy and the palpebral conjunctivae erythematous. A maculopapular rash occasionally may be present during the early febrile phase rather than appearing later at defervescence, as is classic for roseola. Although mild cervical and postoccipital lymphadenopathy can be present at the initial evaluation, the distinctive prominent nodes in the posterior occipital region usually appear around days 3 to 4.[29,31]

The course of acute illness in most infants is 3 to 7 days. Fever usually remains high for 3 to 5 days (see Fig. 207.4). Recovery generally is rapid and complete after defervescence. Ten percent to 15% of infants with HHV-6B infection are hospitalized. The usual indications for admission include a toxic appearance and CNS manifestations, including seizures, a bulging fontanel, and encephalopathy.

Central Nervous System Manifestations

CNS manifestations are common among infants with a primary HHV-6B infection.[19,85] Case reports have noted the association between roseola and CNS signs, particularly a bulging anterior fontanel, which occurs in up to one fourth of patients with roseola.

Seizures are the most common manifestation of CNS involvement among infants with a primary infection.[19,31,86,87] HHV-6B infection has been identified as the cause of 10% to 20% of febrile seizures.[31,88] Among approximately 200 children younger than 24 months of age with a primary HHV-6B infection who were evaluated for acute illness in an emergency department, 13% had febrile seizures, which sometimes were recurrent or prolonged.[31] Only about one half of the seizures developed on the initial day of fever. In a prospective study of children with febrile status epilepticus, one quarter had a primary HHV-6B infection.[89] An association also appears to exist between the development of mesial temporal lobe epilepsy (MTLE) and HHV-6B infection of the hippocampus and amygdala that is persistent or reactivated years after the primary infection.[90,91] Although the detection rate for HHV-6B DNA does not appear to be uniformly higher in tissue samples from patients with MTLE, significantly elevated viral loads have been reported consistently.[90,91] These observations are in keeping with the recognized link between complicated febrile seizures and damage to the hippocampus, with subsequent mesial temporal sclerosis. HHV-6B infection of astrocytes that causes aberrant glutamate transport is one proposed mechanism linking viral infection with epilepsy.[92] Up-regulation of monocyte chemotactic protein-1 and glial fibrillary acidic protein RNA transcripts in amygdala specimens has been associated with HHV-6B viral loads in samples from patients with MTLE, suggesting that HHV-6B–induced neuroinflammation may play a role in pathogenesis.[91]

Reported cases of encephalitis and encephalopathy associated with HHV-6B primary infection have been variable in spectrum, severity, and outcome.[93–95] However, the incidence of HHV-6B encephalitis/encephalopathy and the full scope of clinical findings are unclear because mild cases in children likely are underreported. Although severe disease appears unusual in the U.S. and Europe, a national survey in Japan estimated that exanthem subitum–associated encephalitis/encephalopathy was responsible for 62 hospitalizations yearly, a rate of 5.5 per 100,000 cases of exanthem subitum.[96] Neurologic sequelae were reported in 47% of cases, and 2.5% of these patients died. Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD), a newly defined subtype of encephalopathy in Japan, is reported most commonly in association with primary HHV-6B infection.[85,97,98] The fatality rate for AESD is low, but full recovery is noted in less than one third of patients.[97,98] Severe CNS syndromes in patients with primary HHV-6B infection and thermolabile variants of carnitine palmitoyltransferase 2, an enzyme involved in energy metabolism, have been reported in Japan.[85,99,100] Two infants with *POLG* mitochondrial mutations and severe encephalitis with progressive encephalopathy associated with primary HHV-6B infection have been reported in the U.S.[101] Taken together these observations suggest that primary HHV-6B infection may act as a trigger for severe neurologic disease in genetically susceptible individuals. Confirmation of this possibility in a larger number of cases might help explain population differences in the incidence of severe encephalitis/encephalopathy associated with primary infection.

Clinical and laboratory findings associated with CNS disease complicating primary HHV-6B infection generally are not distinct from those seen in other infectious causes of encephalitis/encephalopathy. Cerebrospinal fluid (CSF) abnormalities are infrequent.[85,96] Magnetic resonance imaging can produce normal findings, or it can show transient involvement of cerebral white matter or involvement of multiple areas of the brain, including the temporal lobe, hippocampus, and amygdala.[102–104]

Encephalitis caused by reactivation of HHV-6B in immunocompetent adults and children is rare, and case reports likely are confounded by ciHHV-6.[105] However, the syndrome of posttransplant acute limbic encephalitis (PALE) caused by HHV-6B reactivation has been described, especially in those undergoing HCT.[106] Clinical risk factors associated with the development of PALE include receipt of an umbilical cord blood transplant (UCBT) or a mismatched adult donor transplant, and the development of acute graft-versus-host disease (GvHD). The incidence ranges from 0.5% to 8.3% and is significantly higher among patients receiving a UCBT.[106–108] Reactivation of HHV-6B, with high levels of viral DNA identified in plasma, has been associated with the onset of PALE, suggesting that a substantial viremia immediately precedes or is coincident with the development of disease.[106,109] Commonly reported symptoms include altered mental status with confusion, insomnia, hallucinations, anterograde amnesia, seizures, and the syndrome of inappropriate secretion of antidiuretic hormone. Symptoms typically occur 2 to 6 weeks after transplantation.[107,109–111] Imaging abnormalities are identified frequently in the medial temporal lobes, specifically in the hippocampus, amygdaloid complex, and entorhinoral cortex, which consist of T2 hyperintense lesions on fluid attenuation inversion recover (FLAIR) images.[107,109–111] Long-term neurologic sequelae, including generalized epilepsy and cognitive decline, frequently have been reported in children.[85,112,113] In addition to PALE, an association between HHV-6B reactivation and the development of delirium and neurocognitive decline was identified in a prospective study of patients after HCT, suggesting that HHV-6B reactivation causes more varied and widespread CNS dysfunction in this patient population than previously recognized.[114]

The diagnosis of HHV-6 as a cause of CNS disease in both normal and immunocompromised patients often is made by detection of

HHV-6B DNA in the CSF and sometimes in CNS tissue. However, the diagnosis may be confounded by the presence of ciHHV-6 or the ability of HHV-6 to become latent in the CNS of healthy and diseased individuals.[105,115–117] HHV-6B DNA is commonly detected in the CSF of children during primary HHV-6 infection and also can be identified after acute infection.[117–120] Additionally HHV-6B viral DNA can be detected in the CSF without neurologic signs or symptoms in patients after HCT, which suggests that asymptomatic reactivation in the CNS can occur.[121] The currently accepted criteria for the diagnosis of PALE are detection of HHV-6B DNA in the CSF of a transplant recipient with persistent neurologic symptoms and no alternative explanation.[106,122]

Other Associated Illnesses

Many uncommon findings have been associated with primary HHV-6 infection, but a causal role of HHV-6 remains unclear. Among these uncommon findings are a severe febrile course with recurrent rash and arthritis, hepatitis, hemophagocytic syndrome, thrombocytopenia, granulocytopenia, cardiomyopathy, drug-induced hypersensitivity syndrome, an infectious mononucleosis-like syndrome, and Gianotti-Crosti syndrome.[22,123–126]

Diagnosis

No clinical or laboratory finding at the time of initial assessment is sufficiently specific or distinctive to assure accurate diagnosis of an HHV-6B primary infection (see Fig. 207.4). Multiple assays are available to detect the infectious virus, HHV-6B antigens, nucleic acids, and antibodies (Table 207.1). Nevertheless, the diagnosis is confounded by the ubiquity of infection, subsequent latency, and ciHHV-6, making differentiation of acute HHV-6B infection from past latent infection or ciHHV-6 difficult.[127] Primary infection is best ascertained by the isolation of HHV-6B from peripheral blood mononuclear cells (testing limited to research laboratories) and seroconversion, or by serologic confirmation of new infection. Diagnosis based solely on a rise in antibody titers, seroconversion, or even virus isolation can be misleading (Table 207.1). Viremia is rare in healthy children except during a primary infection. However, viremia can occur during reactivation in immunocompromised patients and occasionally in immunocompetent children experiencing primary infection with other β-herpesviruses.[128] Marked fluctuations in antibody titer may result from changes in the replicative state of latent virus and from cross-reactive antibodies. Absence of detectable seroconversion in infants can result from the presence of passive maternal antibody. However, some currently available assays for virus antigen and HHV-6B DNA and RNA allow differentiation of active, productive infection from latent infection, and ciHHV-6 (Table 207.1).[127,129]

TABLE 207.1

Diagnosis of Infections Caused by Human Herpesvirus 6 (HHV-6) and Human Herpesvirus 7 (HHV-7)

		Type of Infection Diagnosed				
Assay[a]	**Specimen**	**Acute Primary**	**Recent Active**	**Past/Latent**	**Reactivated**	**Comments**
SEROLOGY[b]						
Antibody Titers	Serum/plasma					
IgG titers		+	+	+	±	Sensitive. Seroconversion indicates primary infection HHV-6 species are not differentiated HHV-6 and HHV-7 cross-reactivity is limited, depending on assay used Results are not available during acute illness because testing of two or more serial specimens is required Single specimen that is antibody negative and DNA positive suggests early, primary infection Maternal antibody can be present in infants <6 mo of age; confounds results
IgM titers		+	+			Not detected in all primary infections

						May be detected in a small percentage of healthy people and in some reactivated infections
Avidity titers		+	+	+		Testing of single specimen indicates acute infection within 6 wk (low avidity) or after 6 wk (high avidity)
DNA/RNA DETECTION						
DNA PCR	Mononuclear cells in blood and other specimens	+	+	+	+	DNA detection can indicate acute and/or past infection; requires serology and/or RT-PCR for clarification Differentiates HHV-6 species
	Serum/plasma or whole blood	+			+	Lysis of peripheral blood mononuclear cells can produce appreciable proportion of false-positive results[127,218]
Real-time DNA PCR	Serum/plasma or whole blood	+			+	Quantitative, very sensitive, costly Lysis of peripheral blood mononuclear cells can produce an appreciable proportion of false-positive results[127,218]
RNA PCR						
RT-PCR	Mononuclear cells	+			+	Very sensitive, semiquantitative Differentiates HHV-6 species, costly
Real-time RT-PCR	Mononuclear cells	+			+	Very sensitive, quantitative, costly
VIRAL GROWTH AND DETECTION						
Viral growth	Mononuclear cells of blood and other specimens	+			+	Available only in research laboratories HHV-6 species can be differentiated Results usually are not available during acute illness
Viral antigen detection	Blood, secretions	+			+	Suggests active replication, semiquantitative Differentiates HHV-

						6 species Sensitivity and specificity variable

[a] Congenital infection with HHV-6 can confound interpretation of diagnostic tests; see text on Congenital Infections.

[b] Multiple serologic tests are available including immunofluorescent assays (IFA), neutralizing antibody assays, enzyme immunoassays (EIA), immunoblots, anticomplement assays.[2,3,15,214,215]

Ig, immunoglobulin; DNA, deoxyribonucleic acid; RNA, ribonucleic acid; PCR, polymerase chain reaction; RT-PCR, reverse transcriptase PCR; HHV-6, human herpesvirus 6.

Management and Therapy

Because primary HHV-6 infection generally is benign and self-limited, management consists mainly of supportive treatment, control of fever, and adequate fluid intake.

Antiviral therapy has been used primarily in immunocompromised patients and those who have severe disease (e.g., PALE). However, no antiviral agent has been approved for the treatment or prevention of HHV-6 infections. Currently available antiviral agents that have been used for HHV-6B infections are ganciclovir, foscarnet, valganciclovir, and cidofovir.[3,122,130] These agents inhibit replication in vitro. Ganciclovir or foscarnet (or a combination of the two drugs) is used most commonly. The results for benefit of treatment have been mixed, but no controlled trials exist. Resistant HHV-6B strains have been reported.[3,131,132] Many new antiviral compounds are in development. Some that appear promising include both nucleoside/nucleotide analogues and nonnucleoside analogues, including brincidofovir (CMX001), and the antimalarial drug artesunate.[3,130] Additionally, generation of HHV-6B–specific T-cell clones for use in immunotherapy has been described.[133]

Complications in Special Patient Populations

The role of HHV-6 in the genesis of cancer is unclear, and the question is complicated by viral latency in diverse body sites.[20] Reactivation of HHV-6B occurs in approximately 20% to 50% of immunocompromised patients. The highest rates are observed in bone marrow and solid-organ transplant recipients.[3,26,108,109,134] HHV-

6B reactivation usually occurs in the first 2 to 4 weeks after transplantation and can be accompanied by viremia. Whether disease is associated with the reactivation of endogenous HHV-6B infection or reactivation associated with transplantation is not clear and is confounded by the presence of other opportunistic infections.[135,136] Most HHV-6B reactivations are asymptomatic, but a variety of associated findings and symptoms have been reported. Most frequent are fever and rash, sometimes with leukopenia. Acute GvHD, myelosuppression, interstitial pneumonitis, hepatitis, graft failure, and delayed engraftment (especially of platelets), in addition to CNS disease and death, have been associated with HHV-6B reactivation.[26,52,122] The risk of HHV-6B reactivation has been correlated with the degree of immunosuppression, unrelated solid-organ and cord blood donor, low anti-HHV-6 antibody titers before transplantation, young age, and the concurrence of other herpesvirus infections.[20]

HHV-6 has been shown in vitro to act as a cofactor in augmenting HIV infection and simian immunodeficiency disease (SIV) in a macaque animal model.[137-139] However, the adverse consequences of HHV-6B infection in patients with HIV or AIDS are less clear, and progression of HIV disease caused by HHV-6 reactivation has not been proven.[20,140]

Interest in the contribution of HHV to the development of demyelinating disease, primarily multiple sclerosis (MS), has been sparked by the identification of HHV-6 DNA in the oligodendrocytes of MS plaques and the greater frequency of detection of HHV-6 DNA and proteins in specimens from patients with MS compared with unaffected controls.[141,142] Additional studies have found active HHV-6 replication in blood, CSF, and CNS specimens in patients with relapsing and remitting MS.[143-145] Recent evidence includes the identification of oligoclonal bands specific for HHV-6A and HHV-6B from the CSF of patients with demyelinating disorders.[146] However, findings associating HHV-6 with MS are inconsistent and require further clarification.[147]

Human Herpesvirus 7

The discovery of *Human herpesvirus 7* in the peripheral blood lymphocytes of a healthy adult was reported 4 years after the initial isolation of HHV-6.[148] As mentioned earlier, HHV-7, HHV-6A, and HHV-6B are closely related biologically.[22,149] Similar to HHV-6B, primary infection with HHV-7 occurs in most individuals during childhood, and persistent infection is established in the salivary glands. In contrast to HHV-6B, HHV-7 can be isolated easily from the saliva of previously infected individuals.[42,149] Furthermore, clinical expression of HHV-7 infection appears to be substantially less common, and its virologic characteristics and cellular tropism differ from those of HHV-6A and HHV-6B.

Description of the Pathogen

HHV-7 belongs to the *Roseolovirus* genus of the β-Herpesvirinae subfamily. Among the human herpesviruses, HHV-7 is most closely related to HHV-6A, HHV-6B, and CMV.[149] The genomic structure and properties of HHV-7, HHV-6A, and HHV-6B are similar. They have genetically colinear genomes with analogous gene arrangements. However, the HHV-7 genome is more compact, and it is about 10% shorter in length. The amino acid sequence identity between HHV-6 and HHV-7 ranges from 24% to 83%. The antigenic relatedness between the viruses is sufficient to result in serologic cross-reactivity. Little variation among strains exists (about 0.1%), and no HHV-7 variant groups have been identified. The HHV-7 genome encodes approximately 86 different proteins, some of which appear to be unique to the β-herpesviruses.[149]

The growth properties of HHV-7 and its cytopathic effects in cell culture resemble those of HHV-6.[42] HHV-7 is tropic for $CD4^+$ T lymphocytes and, in contrast to HHV-6A and HHV-6B, it uses the $CD4^+$ molecule for at least part of its essential receptor for cell entry.[150] Isolation of HHV-7 requires growth in primary phytohemagglutinin-stimulated $CD4^+$ T lymphocytes from peripheral blood mononuclear cells or cord blood, or in a continuous $CD4^+$ lymphoblastic cell line, SupTl. The cytopathic effect, characteristic of both HHV-6 and HHV-7, is ballooning, refractile, multinucleated giant cell formation.[42,149] HHV-7 usually grows more slowly and is less cytopathic than HHV-6.

HHV-7 establishes both active and latent infection in $CD4^+$ T lymphocytes and readily produces ongoing persistent infection in the salivary glands.[42,149] HHV-7 latent or persistent infection has been detected in a wide range of tissues, including skin, lungs, mammary glands, tonsils, liver, and kidneys. In vitro, HHV-7 infects but does not replicate in monocytes and macrophages. HHV-7 also infects CD34$^+$ hematopoietic progenitor cells and CD68$^+$ monocytes and macrophages in lesions of Kaposi sarcoma.[151–153]

Epidemiology

The epidemiology of HHV-7 has been determined mostly from seroepidemiologic studies.[15,42,154,155] Infection is ubiquitous in childhood, acquired more slowly and later than HHV-6B infection.[128,156] The median age of acquisition is about 2 years. In Rochester, New York, about 20% of healthy children acquired HHV-7 by 1 year, 50% by 2 years, and 75% by 5 years of age.[128,156] The prevalence of HHV-7 antibody gradually rises thereafter, reaching 80% to 98% in adults, and passive antibody is present in almost all newborns.[128,157] HHV-7 and HHV-6B infections appear to be acquired independently, but cross-reacting antibodies from the initial infection of one may exert some protective effect against the acquisition or clinical expression of the other.[15,42,128,158]

Transmission of HHV-7 likely occurs most frequently from contact with the saliva of previously infected people. Infectious virus is shed in the saliva of more than 90% of adults.[15,42] The detection of HHV-7 DNA in 3 of 29 human milk samples suggests another possible means of transmission to infants.[159] However, antibody to HHV-7 also has been detected in human milk, and breastfeeding has been associated with a lower risk of early acquisition of HHV-7 infection.[156,159] Although HHV-7 infection during the first months of life is uncommon, perinatal transmission can result from contact with infected maternal cervical secretions at birth.[46,128,160,161] HHV-7 DNA has been detected in the cervical swabs of 2.7% to 9.6% of pregnant women, and in 0% to 3% of nonpregnant control women.[46,49,161] Despite this, and in contrast to HHV-6A and HHV-6B, intrauterine transmission of HHV-7 does not appear to occur.[23,46]

Clinical Manifestations

The clinical presentation of primary HHV-7 infection resembles that of HHV-6B.[128,158,162–166] Acute HHV-7 infection has been identified in a few children with febrile illnesses, which may explain the occasional observation of second or recurrent cases of roseola. However, clinical disease with a confirmed primary infection has been reported infrequently, which suggests that most primary HHV-7 infections are asymptomatic or mild.

Among the few reported cases of primary HHV-7 infection, the most common presentation is a nonspecific, highly febrile illness.[128,158,162–166] However, CNS manifestations, especially febrile seizures and status epilepticus, occur in a high proportion of infections.[87,89] Of 8 children with primary HHV-7 infection demonstrated by isolation of the virus from the blood and seroconversion, 6 had seizures accompanying the febrile illness (Table 207.2).[158] HHV-7 also has been associated with more serious neurologic manifestations, including encephalitis, Guillain-Barré syndrome, and hemiplegia, especially with delayed primary infection.[22,117,167–169] HHV-7 DNA has been detected in the CSF of a few patients with and without neurologic disease and in about 5% of brain tissue samples from healthy adults.[a]

TABLE 207.2

Clinical and Laboratory Findings in Patients With Primary Infections Caused by Human Herpesvirus 7 (HHV-6) and Human Herpesvirus (HHV-6)

	HHV-7	HHV-6	P
Median age (months)	26	9	0.001
Range	3–34	1–28	
Mean temperature (°C)	39.8	39.8	NS
Range (°C)	38.9–40.4	37.8–40.6	
Seizures (%)	6 (75)	5 (17)	0.004
Irritability (%)	7 (88)	20 (69)	NS
Vomiting or diarrhea (%)	3 (38)	10 (34)	NS
Rash (%)	1 (13)	14 (48)	0.11
Hospitalized (%)	1 (13)	5 (17)	NS
Mean days of fever	3	4	NS
Mean WBC count (× 10^3/mm^3)	7.44	6.31	NS
Range (× 10^3/mm^3)	4.2–13.3	3.6–13.9	
Mean absolute lymphocyte count (× 10^3/mm^3)	1.85	2.63	NS
Mean absolute neutrophil count (× 10^3/mm^3)	4.93	2.86	0.018

From Caserta T, Hall CB, Schnabel KC, et al. Primary human herpesvirus 7 infection: a comparison of human herpesvirus 7 and human herpesvirus 6 infections in children. J Pediatr 1998;133:386–389.

Much interest has arisen in the potential immunomodulatory effects of HHV-7 infection. As with HHV-6, HHV-7 encodes genes that can alter, inhibit, and evade the immune response elicited by HHV-7 infection. An important mechanism of host evasion is the downregulation of both class I major histocompatibility (MHC) molecules and natural killer (NK) cell–activating ligands by the HHV-7 U21 gene product.[174,175] In addition HHV-7 can downregulate the expression of $CD4^+$ on T lymphocytes, and it encodes two functional β-chemokine receptors by means of the open reading frames U12 and U51, similar to the previously identified CMV and HHV-6 homologues.[150,174,176–180]

The downregulation of $CD4^+$ expression potentially can exert a beneficial effect. Both HHV-7 and HIV-1 use the $CD4^+$ molecule as a receptor for T-lymphocyte infection, and HHV-7 infection has been shown to produce an antagonistic effect on HIV infection of $CD4^+$ T lymphocytes. This appears not to be dependent on viral replication, but more likely represents competition for the $CD4^+$ receptor.[181–184] HHV-7 DNA has been found more frequently among HIV-seropositive patients than those who are HIV-seronegative, and among HIV patients who have long-term, nonprogression compared with those with progressive disease.[181] However, no relationship between viral loads of HHV-7 and HIV or $CD4^+$ T lymphocytes has been observed. Clinical correlates require further study.[181]

The role of HHV-7 in causing disease among immunosuppressed patients is less clear than that of HHV-6B, although often the two are reactivated simultaneously.[122,185,186] In these patients, HHV-7 infection is most likely reactivation of a latent endogenous infection, considering the high prevalence of HHV-7 infection at an early age. However, primary infection can occur (especially among seronegative young children), acquired from the secretions of close contacts or from donor-positive transplants. Information is limited on the frequency of occurrence of active HHV-7 infection in immunodeficient groups of people. Active HHV-7 infection affects up to 88% of solid-organ transplant recipients; in addition, like HHV-6B, it occurs about 2 to 4 weeks after transplantation.[185–187]

HHV-7 appears to be less pathogenic than HHV-6B, causing disease in less than 1% of solid-organ transplant recipients.[186] However, pathogenicity is difficult to assess because infection is ubiquitous and multiple other infections occur simultaneously in immunocompromised patients.[187,188]

Although symptomatic disease caused by HHV-7 has not been demonstrated clearly in transplant recipients, fever and CNS disease have been reported with reactivated HHV-7 infection.[186,189] Diminished survival time and acute GvHD also have been associated with HHV-7 infection. Unlike with HHV-6B infection, however, the circulating load of HHV-7 does not correlate with disease.[185,187,190] Reactivated HHV-7 infection also has been suggested as a cofactor in CMV reactivation and progression to disease in solid-organ transplant recipients, but the evidence is conflicting.[186,187,191–194]

Multiple studies have explored the association between HHV-7 infection and various skin diseases; however, whether the virus plays a role is unclear, and the question is confounded by the detection of HHV-7 in normal skin.[195–199] HHV-7 has been detected more frequently in biopsy specimens from patients with pityriasis rosea than from controls, and it has been isolated from the peripheral blood mononuclear cells of patients with pityriasis rosea during acute illness. Other studies, however, have not verified a role for HHV-7 in pityriasis rosea.[200–202]

HHV-7 has been associated anecdotally with a variety of other syndromes, including connective tissue and autoimmune diseases, chronic fatigue syndrome, hepatitis, a mononucleosis-like syndrome, and Kawasaki disease, but these associations remain unproven.[42,203–212]

Diagnosis

Many diagnostic tests can detect the presence of HHV-7 infection, but they do not determine the correlation with acute clinical manifestations because tests do not differentiate primary, past, latent, and reactivated HHV-7 infection (see Table 207.1). Active infection can be identified by the detection of HHV-7 RNA or suggested by the detection of HHV-7 at multiple times in some specimens (e.g., plasma), or these tests can be combined with the determination of viral loads or serologic studies (see Table 207.1).[15,127,129,213–215]

Management and Therapy

Specific antiviral therapy for HHV-7 generally is not needed because most primary and reactivated HHV-7 infections are asymptomatic or mild, both in normal and immunocompromised children.[122,186] Compounds similar to those that inhibit HHV-6 have variably suppressed the growth of HHV-7 in vitro. However, the clinical benefit of antiviral agents for HHV-7 infection has not been determined adequately, and no controlled trials exist.[216] Limited evidence suggests that ganciclovir has no impact on the reactivation of HHV-7 in solid-organ recipients.[186,217] Antiviral drugs, therefore, usually are not recommended for use therapeutically or prophylactically. More effective measures may be to reduce the immunosuppression that augments both the reactivation of HHV-7 and, more important, the manifestations associated with other commonly concurrent opportunistic viruses, such as CMV.

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Key Points

Epidemiology, Clinical Features, Diagnosis and Management of Roseolovirus Infections

Epidemiology

- Human herpesviruses 6 (HHV-6A, HHV-6B) and HHV-7 comprise the *Roseolovirus* genus of the β-herpesviruses subfamily (β-Herpesvirinae).
- Primary infection with HHV-6B occurs almost universally by 3 years of age, with peak acquisition at 6 to 12 months of age.
- After primary infection HHV-6B remains latent or persistent at several body sites, including the central nervous system and salivary glands.

- HHV-6 integrates into the host genome in about 1% of the U.S. population and is passed by means of germline transmission.
- The major mode of transmission of HHV-6B is through respiratory secretions from asymptomatic close contacts, which occurs year round.
- Ten percent to 15% of children with primary HHV-6B infection are hospitalized.
- Primary HHV-6B infection accounts for approximately 20% of emergency department visits for acute illness in infants 6 to 12 months of age.
- HHV-7 causes ubiquitous infection in childhood; 75% of children are infected by 5 years of age.

Clinical Features

- HHV-6B infections

- High fever, fussiness, and nasal congestion are the most common symptoms in infants with a primary infection.
- Fever usually begins abruptly and typically lasts 3 to 7 days.
- Only 25% of primary infections in the United States manifest as roseola infantum.
- Seizures, including febrile status epilepticus, are the most common complications.
- Posttransplant acute limbic encephalitis (PALE), caused by reactivation of HHV-6B, is a serious complication in immunocompromised patients,

especially after transplantation of umbilical cord blood.

- HHV-7 infections
  - Most infections are mild and transient, although complications (e.g., seizures) can occur with primary infection.
- HHV-6A infections
  - Primary infection has been described rarely and is not associated with any known illness or disease.

Diagnosis

- Primary HHV-6B infection can be confirmed using the combination of seroconversion and detection of viral DNA in plasma.
- Diagnosis of PALE requires detection of HHV-6B DNA in the cerebrospinal fluid of a transplant patient with persistent neurologic symptoms that have no alternative explanation.

Management

- Most primary infections with roseoloviruses are self-limited and do not require specific treatment.
- No antiviral medications are currently licensed for the treatment of roseolovirus infections.

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[a] References 15, 22, 117, 167, 168, and 170–173.

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Epstein-Barr Virus (Mononucleosis and Lymphoproliferative Disorders)

Ben Z. Katz

Epstein-Barr virus (EBV), a ubiquitous herpesvirus of humans, was discovered in 1964. The causal relationship between EBV and infectious mononucleosis (IM) was observed in 1968.[1] The spectrum of associated infections ranges from asymptomatic, to self-limited mononucleosis in healthy hosts, to progressive infections in patients with acquired or inherited disorders of immunity.[2]

Description of Pathogen

EBV is a γ-herpesvirus. Mature, infectious particles are 150 to 200 nm in diameter and are composed of a 172-kb, double-stranded DNA genome, capsid, protein tegument, and lipid-containing outer envelope. The viral capsid has icosahedral symmetry and is composed of 162 capsomeres.[3] The entire nucleotide sequence of several strains is known.[4] EBV, like other herpesviruses, is easily degraded and has a latent and a lytic life cycle.

Latent and Lytic Life Cycles.

Cells that are latently infected with EBV grow continuously, the viral genome is maintained as a circle (plasmid), a limited number of regions of the EBV genome are transcribed, and a relatively small number of viral proteins are synthesized. One latent protein, Epstein-Barr nuclear antigen-1 (EBNA-1), is necessary for plasmid maintenance. Cells that are permissive to the lytic life cycle (differentiated plasma cells and differentiated epithelial cells) linearize the EBV genome, transcribe a larger portion of the genome than latently infected cells, synthesize more proteins, release infectious EBV, and perish. The switch between latency and replication is tightly regulated and is initiated by two EBV early proteins termed BZLF1 or ZEBRA and BRLF1.[3] Another EBV protein, BCRF1, is homologous to IL-10 and stimulates B-cell proliferation while suppressing T-cell proliferation.[2]

In vitro, the virus has a narrow host range and infects B lymphocytes of humans and other primates. In vivo, the virus also can be found in epithelial cells, T lymphocytes, or natural killer (NK) cells.[5–7]

B-Lymphocyte Immortalization and Activation.

Generally, EBV infects B lymphocytes and confers on them the ability to grow continuously in cell culture, a process termed *immortalization*. B-lymphocyte immortalization is the hallmark of EBV infection. EBV latent membrane protein (LMP)-1 mimics B-lymphocyte activation antigen CD40,[8] promoting B-lymphocyte activation and immortalization by preventing programmed cell death (apoptosis). LMP-2 prevents EBV from reactivating in latently infected B cells. The role played by EBV latent proteins in the immortalization process has been reviewed.[9]

EBV Antigens.

Up to 11 messenger RNAs (mRNAs) and 9 EBV antigens are expressed during latency. EBNA, the classic EBV-induced latent neoantigen defined by immunofluorescence microscopy, is composed of 6 proteins (including EBNA-1). About 60 mRNAs are produced when the virus replicates lytically. Early antigens (EAs) are lytic proteins produced by the virus before viral DNA replication; these antigens consist mainly of viral enzymes necessary for genome replication. The classic EA complex, also defined by immunofluorescence microscopy, consists of diffuse (EA-D) and restricted (EA-R) components. The viral capsid antigen (VCA) is the classic EBV late antigen and is synthesized after EBV DNA replication. Genes encoding some of these classic EBV lytic antigens have been identified.[3]

Epidemiology

In developing countries and in lower socioeconomic populations in industrialized nations, up to 90% of children contract EBV infection by 8 years of age. In contrast, in higher socioeconomic groups, from 30% to 75% of adolescents are EBV seronegative[10] (Fig. 208.1).

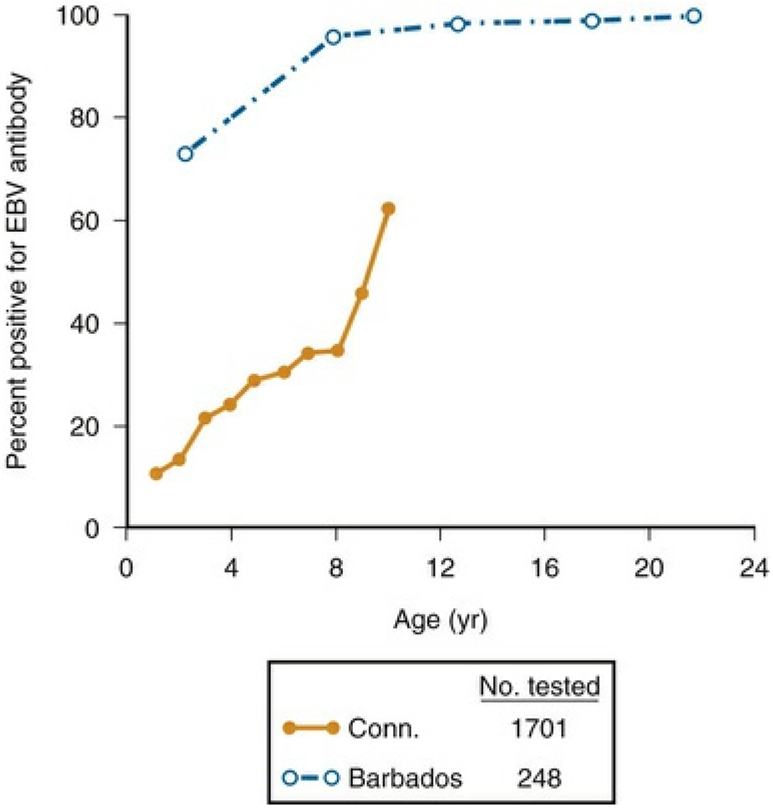

FIGURE 208.1 Differences in rates of acquisition of Epstein-Barr virus (EBV) by socioeconomic status. In Connecticut, by 8 years of age, only 30% of children are EBV seropositive, whereas in Barbados, by the age of 8 years, 90% have been infected with the virus. (Modified from Evans AS, Niederman JC. Epstein-Barr virus. In: Evans AS (ed). Viral Infections of Humans: Epidemiology and Control, 3rd ed. New York, Plenum, 1991, p. 265.)

Young children who acquire primary EBV infection usually do so asymptomatically or with only mild, nonspecific symptoms. IM occurs mainly in adolescents and young adults of higher socioeconomic groups who escaped primary EBV infection when younger. Approximately 1% to 5% of susceptible adolescents and adults contract EBV infection annually, about one half of whom develop symptomatic IM.[11] Many of the symptoms of IM are secondary to the immune response directed at EBV. The annual incidence of IM in the United States is about 500 per 100,000; peak ages affected are 15 to 24 years.[10]

EBV is shed in oropharyngeal secretions during acute infection and intermittently thereafter; these secretions are the major source of infectious virus. It is not clear how EBV transitions between B lymphocytes and oral epithelium; however, because patients with X-linked agammaglobulinemia do not contract EBV infection, B lymphocytes must play a critical role in this process.[8,12]

Infection usually is transmitted through close personal contact. EBV also can be transmitted sexually.[11,13,14] Infection is only modestly communicable, and secondary attack rates are low. Rarely, transmission of IM has been documented after blood transfusion.

Pathogenesis of Infectious Mononucleosis in Previously Healthy Children

Infection in a susceptible person probably begins in the epithelial cells of the buccal mucosa or salivary glands. Subsequently, virus gains access to B lymphocytes (probably memory B lymphocytes,[15] the primary site of EBV persistence) in the lymphoid tissue of the pharynx, and disseminates to the entire lymphoid system (Fig. 208.2). CD21, the major B-lymphocyte receptor for EBV, binds to the viral glycoprotein gp350. Various HLA molecules can act as coreceptors, and other viral glycoproteins allow the virus to penetrate the cell.[16,17]

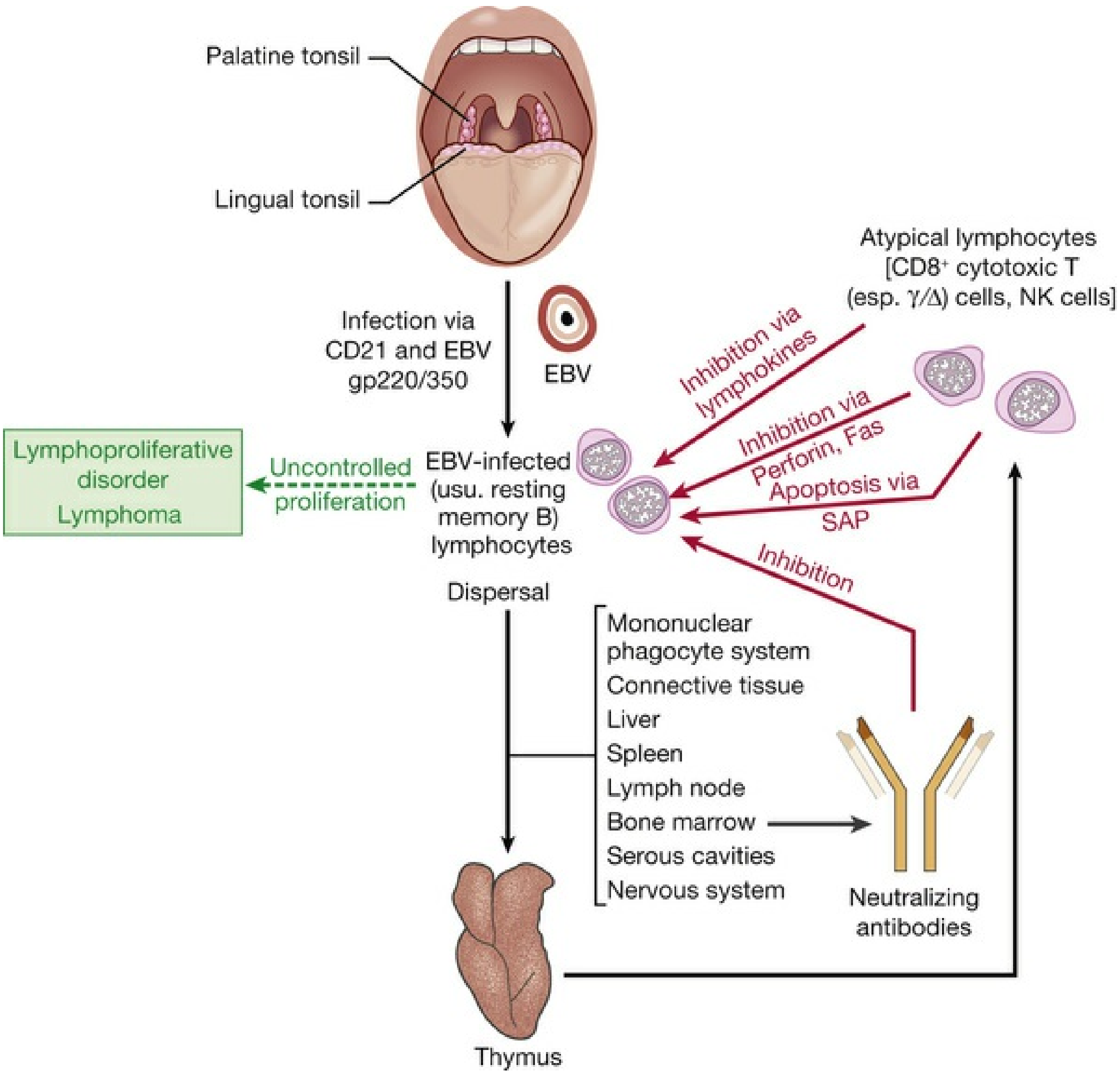
Palatine tonsil
Lingual tonsil
Infection via CD21 and EBV gp220/350
EBV
Atypical lymphocytes [CD8⁺ cytotoxic T (esp. γ/Δ) cells, NK cells]
Inhibition via lymphokines
Inhibition via Perforin, Fas
Apoptosis via SAP
Inhibition
Lymphoproliferative disorder
Lymphoma
Uncontrolled proliferation
EBV-infected (usu. resting memory B) lymphocytes
Dispersal
Mononuclear phagocyte system
Connective tissue
Liver
Spleen
Lymph node
Bone marrow
Serous cavities
Nervous system
Neutralizing antibodies
Thymus

FIGURE 208.2 Pathogenesis and control (or lack therefore) of primary Epstein-Barr virus (EBV) infection. (Figure not drawn to scale.) SAP, signal lymphocyte activation molecule (SLAM)-associated protein.

Early in the course of primary EBV infection, up to 20% of circulating B lymphocytes are infected and immortalized, with EBV DNA present within their nuclei. Most of the characteristic atypical lymphocytes of IM are activated, EBV-specific cytotoxic/suppressor T lymphocytes, which account for up to 30% of the $CD8^+$ T cells in the blood of patients with IM. These cells can kill EBV-infected B lymphocytes and are themselves subject to enhanced apoptosis.[18,19] NK lymphocytes that lyse EBV-infected B lymphocytes also are produced.[20] Probably because of this $CD8^+$ T-lymphocyte and NK-cell activity, a transient general depression in cellular immunity can occur during acute IM, with anergy to skin test antigens and decreased lymphocyte responses to plant mitogens, soluble antigens, and mixed leukocyte culture.[1,18–20] Infection ultimately is brought under control by a combination of neutralizing antibodies, cytotoxic T lymphocytes, NK cells, and their secreted products (e.g., lymphokines).

Clinical Aspects of Infectious Mononucleosis

Clinical Manifestations

EBV causes almost all cases of heterophil-positive and most cases of heterophil-negative IM. Other causes of heterophil-negative mononucleosis include cytomegalovirus, toxoplasmosis, human immunodeficiency virus (HIV); rubella; hepatitis A and B viruses; human herpesviruses 6, 7, and 8; and adenovirus. Pharyngitis, lymphadenopathy, hepatitis, and splenomegaly tend to be more common and more severe in EBV-induced IM.[21–26]

The incubation period for IM is approximately 4 to 6 weeks.[27–29] Infection often is heralded by 3 to 5 days of mild headache, malaise, and fatigue. Major clinical manifestations include fever, sore throat or pharyngitis, and lymphadenopathy. Hepatosplenomegaly, jaundice, and rash also can be present.[30] Recurrence is rare.[31]

Body temperature usually rises to 39.4°C and gradually falls over about 6 days. In severe cases, temperature can remain >40°C for 2 weeks or longer.[32,33]

Generalized lymphadenopathy is a hallmark of IM. Involvement of anterior and posterior cervical nodes is most common. Enlarged nodes usually are single, firm, tender, 2 to 4 cm in diameter, and not matted. Massive mediastinal and hilar lymph node enlargement leading to airway obstruction can occur. Mesenteric lymphadenopathy can mimic acute appendicitis symptoms. Lymphadenopathy gradually subsides over days to weeks.[32,33]

Pharyngitis can be indistinguishable from that caused by group A streptococci. The tonsils are enlarged, erythematous, and covered with exudate in more than 50% of cases. Petechiae appear on the palate, characteristically at the junction of the hard and soft palate, between days 5 and 17 of illness in up to 25% of patients.[32–34]

Moderate enlargement of the spleen occurs in about 20% of cases between the second and third weeks of illness and usually is asymptomatic.[35] After splenomegaly is detected, repeated splenic examination should be avoided because of the rare possibility of precipitating splenic rupture.[36] Splenic rupture, leading to hemorrhage, shock, and even death, can follow trauma or can occur spontaneously (1 per 500 to 1 per 1600 cases of IM).[37,38] Splenic rupture should be suspected in any patient with IM and abdominal pain, especially if there are signs of peritoneal irritation, shock, tachycardia, or shoulder pain.[39] Most cases of splenic rupture occur within 3 weeks of the diagnosis of IM,[40] although rupture can occur as late as 7 weeks into the illness.[10,41] Splenic infarction also has been reported.[42]

Hepatomegaly is present in 10% to 35%,[35] hyperbilirubinemia (typically direct) in up to 25%, and moderately elevated serum concentrations of hepatic transaminases in more than 65% of patients with IM.[35,43] Hepatitis can be associated with anorexia, nausea, and vomiting.

An exanthem occurs in about 5% to 20% of cases.[32–34,44–46] The rash usually is located on the trunk and arms; rarely, palmar dermatitis occurs.[47] Rash appears during the first few days of illness, lasts 1 to 6 days, and can be erythematous, macular, papular, or morbilliform. Sometimes an urticarial or scarlatiniform eruption or acrocyanosis is observed.[48–51] Rarely, the rash is petechial, vesicular, umbilicated, or hemorrhagic.[52] Rashes can resemble those of Gianotti-Crosti syndrome and secondary syphilis.[53,54] Eyelid edema occurs in up to 50% of patients, and presternal edema is not infrequent.[34]

In 1967, Pullen and colleagues[55] and Patel[56] observed an increased incidence of rash in hospitalized patients with IM who received ampicillin. The copper-colored exanthem is mainly over the trunk but can progress into an extensive, confluent, maculopapular pruritic eruption that includes the palms and soles. It usually occurs within 3 days of administration and can persist for up to 1 week, with subsequent desquamation. The rash also has been reported with other antibiotics, occurring in ≥30% of patients with IM treated with antibiotics; however, the magnitude of the association has recently been questioned.[10,57–59] Exanthems do not represent hypersensitivity to the antibiotic, which can be used safely when the infection subsides.[60–63]

Paroxysmal cough and radiographic findings of patchy alveolar and interstitial pneumonia develop in a small percentage of patients. Pleural effusion and empyema have also been reported.[64,64a]

Neurologic complications occur in 1% to 5% of cases of IM.[10] Meningoencephalitis is most common.[65] Other reported neurologic complications include aseptic meningitis, Guillain-Barré syndrome, optic neuritis, cranial nerve palsy, transverse myelitis, acute cerebellitis (ataxia or cognitive syndromes), dysautonomia, subacute sclerosing panencephalitis, peripheral neuritis, optic neuritis, psychosis, Parkinson-like syndrome, acute disseminated encephalomyelitis, and central nervous system (CNS) lymphoma.[66–70] These can occur as the singular manifestation of EBV or in association with typical IM.[71]

Hematologic complications generally are mild and occur in about 25% of cases.[10] Transient thrombocytopenic purpura and hemolytic anemia are most common.[72] Rare hematologic complications include aplastic anemia, agranulocytosis, agammaglobulinemia, hemolytic uremic syndrome, and disseminated intravascular coagulation.[10]

Unilateral or bilateral orchitis lasting 2 to 4 weeks and scrotal edema can occur. Renal insufficiency can be present in up to 15% of cases, but renal complications occur <2% of the time and include interstitial nephritis, acute renal failure, and glomerulonephritis.[73–74a] Electrocardiographic abnormalities, as well as pericarditis and myocarditis, have been reported.[75] Endocrinopathies include thyroiditis and polyglandular syndrome.[76,77] Arthritis, pancreatitis, proctitis, ocular involvement, lacrimal gland inflammation, genital ulcerations, necrotizing epiglottitis, hyperuricemia, cholecystitis, extrahepatic biliary obstruction, and hydrops of the gallbladder also have been observed.[78–87]

Death from IM in previously healthy individuals is rare. In a review of the literature from 1932 to 1970, only 20 deaths were attributable to IM. Causes of death, in decreasing frequency, included neurologic complications, secondary infections, splenic rupture, hepatic failure, and myocarditis. Mortality rate was estimated to be less than 1 per 3000 cases.[88]

Laboratory Findings and Diagnosis

IM usually is diagnosed on the basis of typical clinical features, hematologic abnormalities, and a positive heterophil antibody agglutination test. Antibodies to specific EBV antigens can be used to confirm the diagnosis. Younger children often experience primary EBV infection in the absence of characteristic symptoms, hematologic abnormalities, and heterophil antibody response; a specific antibody response to EBV antigens is present, however.[89,90] Histology of lymph nodes can resemble that of a lymphoma.[91]

During the first week of illness, leukopenia or leukocytosis can be so prominent that leukemia is suspected. Absolute increase in the number of atypical lymphocytes is characteristic during the second week of illness. Atypical lymphocytes (Downey cells) are a hallmark of IM. Cells vary markedly in size and shape, and after Wright staining, the cytoplasm is dark blue and vacuolated, with a foamy appearance. Nuclei are round, bean-shaped, or lobulated and contain no nucleoli. Presence of >10% atypical lymphocytes is characteristic, although not specific, for IM.

Serologic Response

The heterophil antibody is a lymphocytotoxic, principally immunoglobulin M (IgM), which appears during the first or second week of illness and gradually disappears over 6 to 8 months. Differential absorption increases specificity for the diagnosis of EBV infection. Typically, serum from patients with IM causes agglutination of sheep red blood cells after absorption with guinea pig kidney antigens, but not after absorption with beef red blood cells. Rapid heterophil slide tests show a high correlation with standard Paul-Bunnell heterophil test results,[91a,92] and the specificity of the test for EBV infection is high (>95% in some studies). False-positive heterophil test results can occur with rubella, cytomegalovirus, adenovirus, hepatitis C, HIV, malaria, systemic lupus erythematosus, leukemia, and lymphoma.[92–96] Sensitivity ranges between 70% and 90% and is lower in younger patients and in Asians.[97]

The first antibodies produced during the course of primary EBV infection are IgM antibodies directed against VCA (Fig. 208.3), which are transient, usually disappearing in 4 to 8 weeks,[10] whereas

IgG antibodies to VCA persist for life. Antibodies against the EA complex appear later in the course of acute infection and usually disappear after 6 months; however, low levels of antibody (mainly to the R component) of the EA complex can be detected in up to 20% of healthy individuals for years after IM.[98]

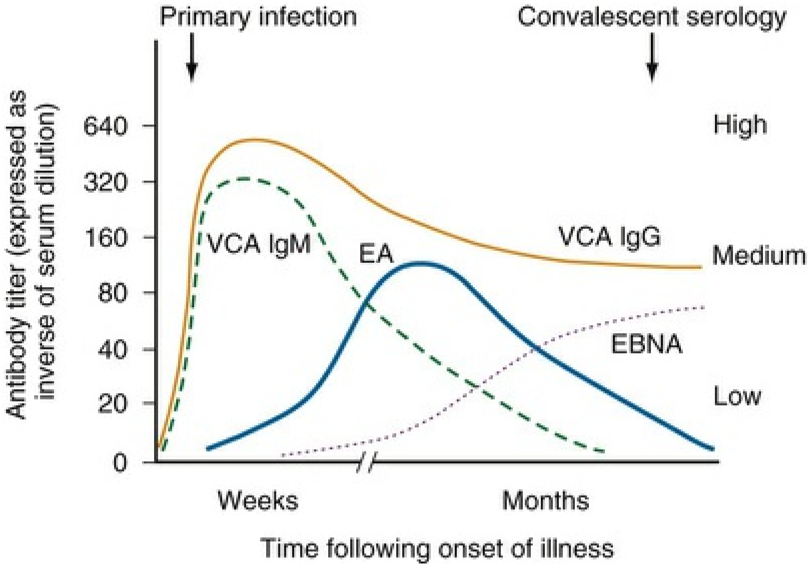

FIGURE 208.3 Idealized time course for the development of antibody to different Epstein-Barr virus antigens after primary infection with the virus. EA, early antigen; EBNA, Epstein-Barr nuclear antigen-1; IgG, immunoglobulin G; IgM, immunoglobulin M; VCA, viral capsid antigen.

Antibodies against the EBNA complex usually are detectable only after 1 to 6 months, rising during convalescence, unlike antibodies to VCA and EA. All late convalescent sera from healthy, previously infected individuals contain high titers of antibodies against EBNA. Thus the presence of IgG antibody against VCA and the absence of antibody to EBNA are diagnostic of primary EBV infection. IgM antibody to VCA also denotes acute infection; however, this assay is technically difficult and can yield false-positive reactions in the presence of rheumatoid factor. Extremely elevated antibody to VCA or EA in the presence of antibody to EBNA is compatible with reactivated EBV infection (Table 208.1).[99–100]

TABLE 208.1

Typical Serologic Findings Related to the Stage of Epstein-Barr Virus Infection

Stage of Infection	Presence of Antibody
Primary	VCA IgM or IgG (usually high) ± EA (usually high), no (or low) EBNA
Convalescent/past	VCA IgG ± EA (low), EBNA (high)
Reactivation	VCA IgG (high) ± EA (high), EBNA

EA, early antigen; EBNA, Epstein-Barr nuclear antigen; IgG, immunoglobulin G; IgM, immunoglobulin M; VCA, viral capsid antigen.

Autoantibodies, including antinuclear antibody, rheumatoid factor, a false-positive reagin test for syphilis, and false-positive mumps and rubella IgM tests, occur occasionally during IM.[101,102] Some EBV-induced antibodies can have clinical importance. For example, IgM and IgG antiplatelet antibodies can be associated with thrombocytopenia,[103] and anti-I,[104] anti-i, and anti-HLA class I antibodies can cause severe hemolytic disease.[104,105] Hypogammaglobulinemia or isolated IgA deficiency also can occur.[106,107]

Detection of Epstein-Barr Virus

Detection of EBV usually is not required for making a diagnosis of acute IM in immune competent individuals; in most cases, serology remains the standard for diagnosis. Nevertheless, several techniques are available for direct detection of EBV.

The immortalization assay assesses the ability of patient's specimen (saliva, peripheral blood, lymph node tissue) to cause lymphoblastic transformation of laboratory-cultured lymphocytes (usually umbilical cord cells). This test is time-consuming (6 to 8 weeks) and requires specialized tissue culture facilities.

Immunofluorescence or immunoperoxidase staining or Western blot or immunoblot of proteins can be used to demonstrate latent viral antigens (e.g., EBNA) in tissue. The most specific method for demonstrating EBV in pathologic material is nucleic acid hybridization. Two techniques are currently used: (1) in situ hybridization, which identifies cells that contain EBV nucleic acid; and (2) polymerase chain reaction (PCR), which amplifies a segment of DNA. PCR generally is more sensitive than immortalization assays.[108]

In many cases of acute infection and in some asymptomatic, healthy individuals with primary infection, EBV DNA can be detected in blood for up to 50 days by PCR. EBV DNA load in the blood and $CD8^+$ lymphocytosis correlate with severity of disease; median amounts of EBV DNA in the blood during acute IM are 10^3 to 10^4 genome copies/mL.[109–114]

In situ hybridization for the abundant EBV-encoded small RNAs (EBERs, which are expressed in latency[115] and play multiple roles in the growth transformation of B lymphocytes[116]) is a specific and sensitive technique for detecting EBV-infected cells in pathologic specimens. Often the number and type of infected cells can be determined.[117]

Treatment

IM is a self-limited illness; treatment is supportive. Bed rest is indicated in the acute stage of disease. Most patients resume normal activities in 2 to 3 months, although about 10% of individuals are still symptomatic at 6 months.[10] Acetaminophen and saline gargles can be used to control the discomfort caused by enlarged lymph nodes and pharyngitis; in severe cases, codeine or meperidine may be required.

A Cochrane review concluded that there was insufficient evidence to recommend corticosteroid therapy for symptomatic relief of uncomplicated IM.[118] Although often prescribed,[119] caution is warranted because of reports of neurologic complications and secondary bacterial infections after corticosteroid use.[120,121] Corticosteroid therapy should only be considered for the treatment of severe complications such as obstruction of the airway or thrombocytopenic purpura.

Contact sports should be avoided until patients are fully recovered and the spleen is not palpable at an examination at least 3 to 4 weeks after onset of illness.[41] Splenic enlargement can occur after the first or diagnostic visit.

Acyclovir and ganciclovir act only on the lytic phase of EBV replication. Ganciclovir also can inhibit EBV-induced B-lymphocyte immortalization,[122] and its antiviral effect is more potent than that of acyclovir or valacyclovir.[123,124]

Parenteral administration of acyclovir to patients with acute IM reduces the replication of oropharyngeal EBV; however, there is little effect on clinical course.[125,126] A randomized, double-blind, placebo-controlled treatment trial of oral acyclovir plus prednisolone in 94 adolescents and young adults showed no significant effect of treatment.[127] One small, unblinded, non–placebo-controlled trial using a nonvalidated symptom questionnaire showed a trend toward clinical improvement with valacyclovir use.[124] In cases of severe EBV-related complications (e.g., encephalitis) or in the immunocompromised host, treatment often is used based on anecdotal data and expert opinion.[128]

Pathogenesis and Disease in Immunosuppressed Children

After primary infection, EBV persists in about 1 in 10^5 to 1 in 10^6 B lymphocytes in a latently infected, immortalized form. These infected B cells periodically undergo lytic replication to produce cell-free virus. Neutralizing antibodies (to viral envelope glycoprotein, gp350[129]) and cytotoxic lymphocytes (which include NK lymphocytes and $CD8^+$ cytotoxic T lymphocytes directed mainly against EBNA-3[129,130]) limit primary infection and keep the immortalized, EBV-infected B-lymphocyte pool in check. Cytotoxic T lymphocytes and NK lymphocytes exert effect at least partly through the secretion of a protein termed *perforin,* which causes target cells (i.e., EBV-infected B lymphocytes) to undergo apoptosis.[131] $CD4^+$ T lymphocytes also may play a role in inhibiting B lymphocytes recently infected by EBV.[132] If the immune response is dysfunctional, the normally small pool of EBV-infected cells can expand, perhaps allowing an EBV-activated B lymphocyte to transform into a lymphoma cell (see Fig. 208.2).

Posttransplantation Lymphoproliferative Disorder

Patients undergoing solid organ transplantation (SOT) or bone marrow or hematopoietic stem cell transplantation (HSCT) can develop posttransplantation lymphoproliferative disorder (PTLD) as a result of immunosuppression. In SOT patients, immunosuppression is due to medications required to prevent rejection. In HSCT patients, immunosuppression begins with the conditioning regimen. The greater the immunosuppression, the greater is the risk for developing PTLD. In SOT patients, therapies associated with greater risk include calcineurin inhibitors (cyclosporine and tacrolimus [FK-506]). For HSCT patients, risk factors include the use of antibodies against T lymphocytes (especially antithymocyte globulin or anti-CD3 antibody) or use of an HLA-mismatched donor.

In SOT patients, EBV-naiveté before transplantation (especially when receiving an organ from an EBV seropositive donor) presents a 5- to 10-fold higher risk for PTLD. Unfortunately, children and adolescents are more likely to be EBV naïve before transplantation, and, because of their scarcity, it is not feasible to use only EBV-naïve donors for EBV-naïve recipients.

The risk for developing PTLD is greatest (50%–90%) in the first year after transplantation.[133] Because HSCT recipients usually have immune reconstitution within 1 year of transplantation, PTLD rarely occurs >1 year after HSCT. In SOT patients, PTLD can occur many years after transplantation.

Most PTLD lesions occurring early after transplantation originate from B lymphocytes, and most cells are EBV positive. In contrast, only 15% to 40% of lesions occurring >1 year after SOT are EBV positive, and some originate from T lymphocytes or NK cells.[134] PTLD can range from a self-limited IM-like illness to a fatal illness characterized by solid tumors that usually resemble large cell non-Hodgkin lymphoma (NHL). A substantial number of PTLD tumors developing in solid organ recipients involve the CNS, gastrointestinal tract, or grafted organ.[129]

The histology of PTLD ranges from plasmacytic, hyperplastic, or polymorphic lesions to lesions that can be monomorphic or lymphomatous. Plasma cell hyperplasias usually are polyclonal and often regress with decreased immunosuppression. However, polymorphic PTLD lesions can contain subpopulations of genetically monoclonal cells, which are less likely to regress with tapering immunosuppression, and even frank lymphomas occasionally regress when immunosuppression is reduced.[135] Recurrences, which develop in about 5% cases, are more likely to be clonal and aggressive than the original lesion.[136]

The diagnosis of PTLD can be difficult. Serologic evidence of disease includes a primary or reactivated EBV response with or without decreasing EBNA titers.[137,138] Virologic evidence of disease includes demonstrating the presence of EBV within the lesion by PCR or in situ hybridization. A definitive diagnosis of PTLD only can be made histologically.[139]

Increasing levels of EBV DNA in the peripheral blood, as measured by PCR, correlate with the development of PTLD in both SOT and HSCT patients.[140] Wide variability in reported EBV load, depending on the units and the laboratory used, precludes the establishment of cutoff limits that are generalizable.[141] Knowledge of the ranges of EBV load that correlate with disease for each laboratory is crucial.

There is no proven method to prevent PTLD. Although not everyone with high EBV loads in the blood develops PTLD,[142,143] most transplantation physicians trend EBV loads to determine which patients are at highest risk for PTLD, so that diagnostic testing can be performed as early as possible.[144] Some retrospective data suggest that ganciclovir or acyclovir therapy can reduce the risk for PTLD. This effect could be due to direct activity against lytic EBV or to prevention of cytomegalovirus infection, which may be a risk factor for PTLD.[145] Retrospective data also suggest that CMV hyperimmune globulin can prevent PTLD in the first year following kidney transplantation.[145a] Pre-emptive management, which includes decreasing immune suppression plus use of rituximab or cytotoxic T-lymphocytic infusions, or both, has been evaluated in transplant recipients with increased EBV loads.[146–152] Prophylactic rituximab has been used as well.[152a,152b]

Treatment of PTLD is not optimal. Recent estimates of mortality range from 10% to 35% and may be higher in adolescents and in those with multiple sites of disease or CNS involvement, in patients with T- or NK-cell disease, or in EBV-negative or CD20-negative disease.[133,153,154] Although no controlled trial is available to guide therapy, attempts to standardize management are based on large case series.

Reduction of immunosuppression[135] is the first step in treatment for PTLD in SOT patients, despite the risk for rejection.[129] Usually azathioprine and mycophenolate mofetil are discontinued, and doses of cyclosporine, tacrolimus, and prednisone are halved.

Use of 4 weekly infusions of the anti-CD20 monoclonal antibody, rituximab, has been examined systemically in patients failing reduction of immunosuppression.[144,155] Normal B lymphocytes and most B-lymphocyte malignancies express CD20. By eliminating all $CD20^+$ lymphocytes within days, rituximab eliminates most PTLD lesions. The complication rate after rituximab therapy is low (although rare, fatal complications such as hepatitis B reactivation have been reported[155a]), whereas the PTLD remission rate is about 70%.[156,157] Rituximab does not penetrate the CNS well; thus CNS lesions are unlikely to respond without intrathecal administration.[158,159] The recurrence rate following rituximab therapy is about 20%, usually occurring after the biologic effect of rituximab wanes (i.e., after about 6 months) or due to the development of PTLD lesions that are CD20 negative.[160,161]

In patients who fail rituximab therapy, chemotherapy has about a 75% response rate, but with a rate of toxicity of about 25%.[162–164] Low-dose chemotherapy (with or without rituximab) also has been used.[165] Antiviral agents generally are not recommended for treatment of PTLD.[144] For treating focal PTLD tumors, local radiation or surgery, or both, may be useful.[166]

Disease Associated With Acquired Immunodeficiency Syndrome

Four major EBV-associated conditions can develop in patients with HIV infection: lymphocytic interstitial pneumonitis (LIP), NHL,; (3) oral “hairy” leukoplakia, and leiomyosarcoma. These conditions have become uncommon since the advent of combination antiretroviral therapy (cART).[167]

Lymphocytic Interstitial Pneumonitis.

Before the AIDS epidemic, LIP usually was observed only in adults with immunologic abnormalities.[168] LIP in children with AIDS is associated with generalized lymphadenopathy and parotitis and may be part of a more diffuse, predominantly $CD8^+$ lymphoproliferative process, in which dominant manifestations are bilateral and diffuse reticulonodular densities are seen on chest radiography.[169–171] LIP occurs in about 30% of untreated HIV-infected children.[172,173] Diagnosis is confirmed by lung biopsy.

EBV DNA is detected in the lungs of approximately 80% of children with LIP.[174–176] In a case-control study, all children with LIP had evidence of primary or reactivated EBV infection compared with significantly fewer matched, HIV-infected control subjects.[177] In a prospective study, LIP developed in 1 of 18 HIV-infected children 7 months after primary EBV infection.[178] LIP is uncommon in adults with AIDS likely because LIP is a manifestation of primary EBV infection. LIP has been reported to regress with acyclovir therapy, although corticosteroids may be more effective.[179] Resolution after cART also is reported.[171,180] LIP is not a lymphoma and has a better outcome than other opportunistic infections in untreated HIV-infected children.

Non-Hodgkin Lymphoma.

In the general population, Hodgkin disease is more prevalent than NHL. In immunocompromised individuals, however, NHL is more common. NHL in patients with AIDS is more aggressive, more likely to be manifest at extranodal sites, and more likely to be composed mainly of oligoclonal B lymphocytes.[181–188]

EBV is detected in at least one half of NHL lesions in patients with AIDS. EBV load correlates with cancer risk in pediatric HIV-infected patients with CD4 counts >200/mm^3. More than 90% of CNS lymphomas are EBV associated.[189,190] PCR of cerebrospinal fluid has been used to distinguish AIDS-associated CNS NHL from other CNS mass lesions; this test is sensitive but not specific.[191]

Oral Hairy Leukoplakia.

A form of oral leukoplakia was recognized in HIV-seropositive men who had sex with men, beginning in 1984. Oral leukoplakia occurs rarely in children[192] and manifests on the lateral surface of the tongue with lesions resembling flat warts.[193] The presence of EBV DNA and antigens in biopsy material, documentation of lytic EBV DNA replication in epithelial cells of lesions,[194] and regression of lesions after treatment with acyclovir support an EBV etiologic role.[194,195] EBV DNA also has been identified in esophageal ulcers in HIV-infected patients, the pathology of which resembles oral hairy leukoplakia.[196]

Leiomyosarcoma.

Leiomyosarcomas are malignant cancers of smooth muscle and are rare in childhood. However, cases associated with EBV have been seen mainly in children and young adults with AIDS and in transplant recipients. There is one case report in a child with NK cell deficiency as well. The tumors are monoclonal, biclonal, or oligoclonal and often are multifocal. Serologic data revealed a reactivated EBV infection in 1 of 3 patients with AIDS and in 9 of 9 transplant recipients who were EBV naïve before transplantation. Most reported patients also had a high EBV load, and leiomyosarcoma can be associated with PTLD.[197–199] Surgery is the mainstay of therapy, especially with focal disease, although reduction of immunosuppression, antiviral medication, rituximab, and radiation therapy also have been used, sometimes in combination.[199] Prognosis is poor, with mortality in >50% of transplant recipients.[199]

X-Linked Lymphoproliferative Syndrome, Infection-Associated Hemophagocytic Syndrome, and Chronic Active Epstein-Barr Virus Infection

X-linked lymphoproliferative syndrome (XLPS), infection-associated hemophagocytic syndrome (IAHS), and chronic active EBV infection (CAEBVI) are clinically overlapping syndromes associated with EBV infection. All are related to the inability of NK or cytotoxic T lymphocytes, or both, to regulate EBV proliferation. All three can be classified under the rubric of hemophagocytic lymphohistiocytosis (HLH), which is a disorder of NK cells, cytotoxic T lymphocytes, and macrophages and characterized by hypercytokinemia ("cytokine storm").[200]

HLH was first described in 1939, recognized as possibly being familial in 1952, and first associated with viral infections in 1979[201] (see Chapter 12). Some forms of HLH are genetic in origin. Others are triggered by infection, malignancy, or rheumatologic conditions. It is suspected that there are as yet largely unknown, perhaps more subtle predisposing genetic factors to these acquired forms as well. Both forms can be associated with EBV.[200] In some of these conditions, EBV infects T or NK lymphocytes, rather than B lymphocytes.

X-Linked Lymphoproliferative Syndrome

Rare individuals with an X-linked genetic predisposition are incapable of mounting a normal immune response to primary infection with EBV. Thus this disorder has *both* a known genetic mutation and a known extrinsic trigger (EBV infection). Up to 90% of patients with XLPS have evidence of hemophagocytosis.[200,202,203]

A progressive *proliferative* response develops in about 60% of individuals affected by XLPS (Box 208.1). The cause of death in these individuals is usually liver necrosis secondary to infiltration of lymphoid cells. Pathologic examination reveals widespread mononucleosis-like changes in two thirds of patients and malignant B-cell lymphoma, usually of the Burkitt type, in one third of patients. Approximately one third of patients with XLPS survive the initial EBV infection, and an aproliferative disease develops. Findings in these patients include hypogammaglobulinemia, aplastic anemia, agranulocytosis, increased susceptibility to bacterial infection, and the development of malignancies.[202,203]

Box 208.1

Major Manifestations of X-Linked Lymphoproliferative Syndrome

Proliferative

Fatal infectious mononucleosis

Malignant lymphoma

Associated with hemophagocytic syndrome

Aproliferative

Hypogammaglobulinemia

Aplastic anemia

Agranulocytosis

Associated with bacterial infections, late malignancies

Most patients with XLPS have normal responses to bacterial and other viral infections of childhood and have normal cell-mediated immune responses and T- and B-lymphocyte numbers.[204] Immunologic evaluation of patients with XLPS during the course of their acute EBV infection reveals exaggerated $CD8^+$ T-lymphocyte activity against EBV-infected B lymphocytes. In survivors, a global deficiency in immunoglobulin production, T-lymphocyte and NK-cell function is observed, and almost all survivors fail to produce or lose antibody to EBNA and have abnormalities in VCA antibody production, suggesting an inability to regulate primary EBV infection.[202] Perhaps because EBV is the first lymphoproliferative challenge that many individuals face, and the only human pathogen that is exclusively B-cell tropic, the subtle immune dysregulation in patients with XLPS is not manifest until they experience primary EBV infection.

There are two known gene defects that cause XLPS. The SAP (signal lymphocyte activation molecule [SLAM]-associated protein) genetic defect, found in about 80% of patients with XLPS, is a defect in an inhibitory T-lymphocyte signaling pathway important for T-lymphocyte development and function.[202,203] SAP normally is important for the control of T-lymphocyte activation, NK-cell activation and cytotoxicity, and memory B-lymphocyte development[203,205] (see also Fig. 208.2). Untreated, about 75% of boys with the SAP defect die within a month of primary EBV infection.[206] It has been postulated that an apoptotic defect of cytotoxic T lymphocytes might lead to the fatal IM phenotype because of an inability to downregulate the cytotoxic T-lymphocyte response against EBV, whereas an apoptotic defect of B-lymphocyte subpopulations might lead to B-cell lymphomas.[203] A second genetic defect (X-linked inhibitor of apoptosis [XIAP]) has been observed in most of the remaining patients with XLPS.[207] Lymphomas have not been reported in these patients, perhaps explaining some of the phenotypic heterogeneity of XLPS, although an exact genotype-phenotype correlation and an understanding of the pathophysiology of both forms of XLPS remain incomplete. Seventeen percent of patients with XIAP deficiency have been reported to suffer from hemorrhagic colitis, which is not reported in SAP-deficient patients.[190] Flow cytometry is often used for diagnosis.[208] Other, rare related syndromes have been reported recently in which patients have a heightened susceptibility to EBV-associated lymphomas.[208a]

Therapeutic options for XLPS are limited. Patients with proliferative responses often are treated with regimens similar to those used for IAHS.[209] Definitive therapy is stem cell transplantation; outcome is improved after transplantation for all categories of illness, especially in patients with SAP deficiency and a history of HLH.[200,202] Boys who are discovered before acquiring infection with EBV have been treated with monthly immune globulin intravenous (IGIV) therapy to prevent acquisition of EBV and occasionally have undergone pre-emptive transplantation or have been treated with rituximab, corticosteroids, immunoglobulin, and ganciclovir after acquiring primary EBV infection.[210,211] If HSCT is not undertaken immediately, a donor should at least be identified and the patient followed carefully for signs of disease progression. The prospect of an EBV vaccine to prevent primary infection is still years away.[212,213]

Infection-Associated Hemophagocytic Syndrome

Familial HLH is a rare genetic syndrome associated with defects in the pro-apoptotic perforin (or related granulocyte-mediated cytotoxic) gene pathways and with excessive and persistent activation of macrophages and hypercytokinemia. Left untreated, the 3-year survival rate is about 10%[131,214,215] (see Chapter 12).

IAHS is thought to be a secondary, acquired form of HLH, although it is likely that it, too, has a genetic basis. The most common infectious trigger of IAHS is primary EBV infection. A similar syndrome can be triggered by malignancies or rheumatologic disorders. When triggered by a rheumatologic disorder, HLH is referred to as *macrophage activation syndrome*.[200] Patients diagnosed with IAHS can have compound heterozygous genetic mutations, promoter variants, or missense mutations of apoptotic pathways.[216,217] Children diagnosed with familial HLH often are younger (<1 year of age) than those diagnosed with IAHS (or other acquired forms of HLH) (see Box 208.2).[200] In children <3 years of age, a serum ferritin level >10,000 ng/mL is about 95% sensitive and specific for diagnosing IAHS, and a normal level has a high negative predictive value for ruling out IAHS.[217a]

Box 208.2

Hemophagocytic Lymphohistiocytosis

Familial/Homozygous Genetic Causes

- Perforin or other gene mutations; onset <1 year of age in 70%–80%
- Decreased SAP or XIAP (X-linked lymphoproliferative syndrome; usually triggered by EBV); mean age at diagnosis 5 years

Acquired/Secondary/Heterozygous or Missense Genetic Causes

- Triggered by infection (infection-associated hemophagocytic syndrome), EBV responsible 75% of the time; mean age at diagnosis 4 years
- Triggered by rheumatologic (macrophage activation syndrome) and malignant conditions

EBV, Epstein-Barr virus; SAP, signal lymphocyte activation molecule (SLAM)-associated protein; XIAP, X-linked inhibitor of apoptosis.

When triggered by EBV, IAHS appears to be due to macrophages reacting against EBV-infected CD8$^+$ T lymphocytes.[218] Etoposide, which reduces macrophage activation, and dexamethasone, with or without cyclosporine, are used to treat HLH. The 5-year survival rate for presumed nonfamilial cases is 55% ± 5%. Definitive therapy and potential cure of familial HLH require stem cell transplantation[219]; presumably, as more genetic causes are discovered, the pathophysiology becomes better understood, and the techniques for HSCT are improved, the indications for HSCT will expand.

Chronic Active Epstein-Barr Virus Infection

CAEBVI has been reported mainly in Asians and appears to have two subtypes: a T-lymphocyte form and an NK-cell form, depending on which cells are infected with EBV.[220] Clinically, patients with CAEBVI have chronic or recurrent mononucleosis-like symptoms, including fever, lymphadenopathy, and hepatosplenomegaly, for at least 3 months. Hepatitis, pancytopenia, uveitis, interstitial pneumonitis, skin manifestations (e.g., photosensitivity, hypersensitivity to mosquito bites), sicca syndrome, neuropathy, cardiomyopathy and carditis, neutropenia, eosinophilia, thrombocytopenia, and hypergammaglobulinemia or hypogammaglobulinemia also can occur; a similar cytokine storm as previously described can be present.[221] The disease is clonal and occasionally can mimic leukemia.[222] Rarely, coronary artery ectasia or aneurysms are observed.[223] Patients have prolonged, severe, relapsing, and often fatal courses. Death can be associated with respiratory failure secondary to interstitial pneumonia or with diffuse T-lymphocyte infiltrate, lymphoma, or hemophagocytic syndrome.[224,225] Distinguishing clinically between CAEBVI and IAHS is difficult. A rare, chronic blistering photodermatosis, hydroa vacciniforme, also can be a part of this syndrome.[223a]

Patients with CAEBVI have markedly abnormal EBV serologic responses, such as extremely high levels of antibody to the EA and VCA complexes and low or absent antibody to EBNA. Some patients have selective absence of antibody to EBNA-1.[226] Impaired cytotoxic T-lymphocyte responses against EBV-infected NK cells are reported.[227] EBV loads typically also are extremely high, especially in patients with complications. Elevated EBV load in cerebrospinal fluid in patients with CNS involvement is reported.[228–231] Before EBV infection, there is no clinical evidence of an immunologic abnormality. These patients do not have the gene defect associated with XLPS,[232] although there is a case report of a patient with CAEBVI and a perforin gene defect.[233] In general, a different apoptotic pathway (Fas[CD95]/Fas ligand) seems to be involved in this disease.[234]

The NK-cell form of CAEBVI is characterized by high EBV DNA loads, high serum IgE level, NK-cell lymphocytosis, and hypersensitivity to mosquito bites. The T-lymphocyte form of the disease is associated with anemia and a poor prognosis. In contrast to IAHS, mainly non-$CD8^+$ T lymphocytes are involved in CAEBVI.[235] Other poor prognostic signs are age >8 years and platelet count <12,000/mm^3 on presentation.[236]

Several families have been described in which this syndrome has occurred in multiple members.[237] Stem cell transplantation[238] or autologous cytotoxic T-lymphocyte infusions are the most effective therapies, although mortality remains high (20%–50%)[239];

chemotherapy also has been used.[240]

Chronic active EBV infection must not be confused with chronic fatigue syndrome (CFS).[241] In CFS, few, if any, objective signs of illness exist. EBV serologies are not helpful for diagnosis,[242] despite the finding that a few patients have elevated antibody titers to EA[243] and may lack antibody to EBNA-1.[226] Six months after IM, about 10% of adolescents will meet the criteria for CFS; whether severity of illness, autonomic dysfunction, or other factors play a role in prolonged recovery from IM is unclear.[244–249]

Congenital Infection

Rare infants with birth defects attributed to congenital infection following maternal primary EBV infection have been reported. One infant had bilateral congenital cataracts, cryptorchidism, hypotonia, and mild micrognathia. A "celery stalk" appearance of long bones was noted radiographically, similar to that seen with congenital rubella.[250] Nevertheless, a prospective study of more than 4000 pregnant women failed to document intrauterine EBV infection.[251] Another report described nearly 700 pregnant women with serologic evidence of EBV infection during pregnancy. Pregnancies were several times more likely to result in early fetal death, premature labor, or delivery of an infant who became ill soon or after birth[252]; however, the association of these conditions with EBV infection is unknown. A comprehensive review of this topic has been published.[253]

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Human Herpesvirus 8 (Kaposi Sarcoma–Associated Herpesvirus)

Mary T. Caserta

In 1872, Moritz Kaposi, a Hungarian dermatologist, first described in five men an aggressive, pigmented, multicentric sarcoma of the skin that disseminated to multiple sites.[1] It was rare and received little attention until similar lesions were observed in African children and adults, and subsequently when found in association with human immunodeficiency virus (HIV) infection in the 1980s. Although the cause of Kaposi sarcoma (KS) was suspected to be infectious, it was not confirmed until 1994 when Chang and colleagues[2] isolated two novel DNA fragments with homologies to two oncogenic γ-herpesviruses from a sarcoma in an HIV-infected patient. This led to classification of human herpesvirus-8 (HHV-8), also referred to as Kaposi sarcoma–associated herpesvirus (KSHV), as a lymphotropic γ-herpesvirus. Except for the endemic and epidemic forms observed primarily in Africa, HHV-8 disease rarely occurs in children.

Description of the Pathogen

HHV-8 is the only human γ2-herpesvirus. Epstein-Barr virus (EBV), a γ1-herpesvirus, is the most closely related human virus. HHV-8 is a large, double-stranded, enveloped DNA virus. Its genome has a central unique region of about 140 kb, encoding the known open reading frames and flanked by terminal repeat sequences that contain signals for packaging and cleavage.[3,4] The genome contains micro RNAs and several cellular homologs related to human oncogenes, cytokines, and chemokines. These molecules inhibit tumor suppressor pathways by affecting control of cellular growth and inhibition of apoptosis as well as promoting inflammation and angiogenesis.[5,6]

HHV-8 infects multiple cell types, with evidence suggesting that glycoprotein B (gB) is the virus attachment protein.[7] Additionally, DC-SIGN (dendritic cell–specific intercellular adhesion molecule-3–grabbing nonintegrin, also known as CD209) and its isomer DC-SIGNR have been identified as cell receptor molecules on dendritic cells, activated macrophages, and B lymphocytes and on endothelial cells, respectively.[7] After initial infection, the HHV-8 genome persists as covalently closed episomal circles, establishing lifelong latent infection. Monocytes and B lymphocytes are the major reservoirs.[7,8] HHV-8 can be propagated in cell cultures, but most patients are latently infected and lytic infection must be induced.[8]

Epidemiology

In contrast to other herpesviruses, HHV-8 does not cause ubiquitous worldwide infection. Its prevalence mirrors the incidence of KS.[9] Seroprevalence studies show substantial geographic variation, with the highest rates in sub-Saharan Africa, ranging from 20% to >60%.[10–14] In Cameroon, Ghana, Uganda, Zambia, Tanzania, and among indigenous groups in the Amazon of Brazil, 30% to 60% of children <10 years of age are seropositive.[11–13,15,16] Seroprevalence is 6% to 20% in most Mediterranean countries and are lowest, 0% to 5%, in northern Europe, the United States, Latin America, and Asia.[9] Seropositivity and disease can vary widely among countries within the same region. Furthermore, high-risk groups exist in countries with low

HHV-8 seroprevalence. For example, in the US, 15% to 40% of men who have sex with men (MSM) are seropositive, with the highest rates occurring among HIV-infected MSM.[10,17] Seroprevalence is not as high among other HIV-infected populations, especially children.[18]

The putative modes of acquisition of HHV-8 include nonsexual and sexual horizontal transmission, vertical transmission, blood transfusions, and organ transplantation.[9,11,13,18,19] In areas with low HHV-8 prevalence, transmission is mainly sexual and predominantly among MSM. In areas with high HHV-8 seroprevalence, transmission appears to be nonsexual, occurring among families and close contacts, with high seropositivity present among children before adolescence and continuing to increase thereafter.[12,13] Secretions, primarily saliva, are likely the major source of infection.[9,13]

Viral DNA is detected most frequently and in highest levels in saliva, but also is in semen and peripheral blood mononuclear cells.[9,20,21] Blood transfusions have been correlated with HHV-8 seropositivity among children from endemic countries, but appear to have no appreciable role in transmission in the US.[19,22,23] No evidence exists for transmission through breast milk.[24] Vertical transmission has been suggested by detection of HHV-8 DNA in the blood of a few neonates.[25]

Clinical Manifestations

HHV-8 has a clear causal role only in KS, primary effusion lymphoma, multicentric Castleman disease, and a KSHV cytokine inflammatory syndrome associated with HIV infection.[26,27] Many diseases have been associated with HHV-8 infection, but not confirmed causally, including multiple myeloma, sarcoidosis, and basal and squamous cell carcinomas in transplant recipients.

Clinical manifestations of HHV-8 infection primarily are associated with KS, a multifocal neoplasm of vascular endothelium.[18,28] KS lesions are vascular, purplish nodules that range from isolated cutaneous lesions to widespread disease involving the lung, biliary tract, and other viscera (Fig. 209.1).

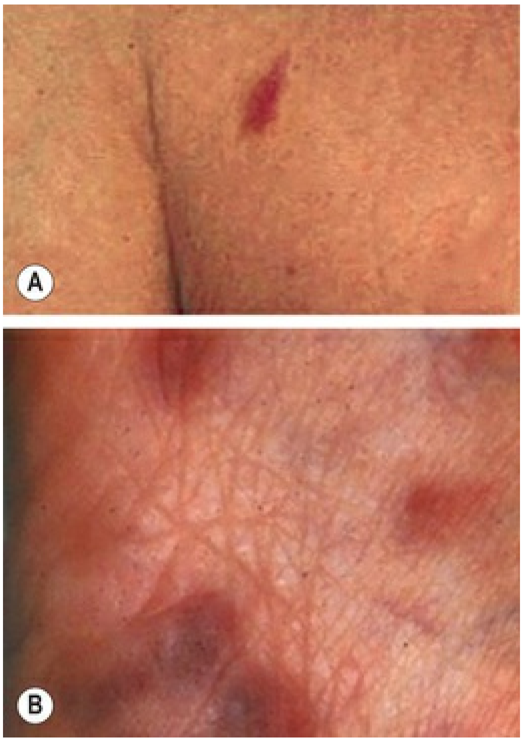

FIGURE 209.1 Kaposi sarcoma lesions of the chest (A) and foot (B). (Courtesy of Susan Cohn, MD, Northwestern University, Evanston, IL.)

HHV-8 infection is a necessary, but not sufficient, factor contributing to the development of KS.[28,29] Four KS variants have been described: classical, endemic/sub-Saharan African, epidemic (AIDS-associated), and immunosuppression-associated forms. The classical type, primarily affecting older men from Mediterranean and eastern European countries, is indolent, involves mainly the skin, and is associated with long survival. The endemic form occurs predominantly in parts of sub-Saharan Africa and affects both adults and children.[18] In some areas of Central Africa, KS is among the most common tumors, causing up to 25% of all childhood malignancies.[18,30] Endemic HIV-negative KS in African children is distinct from the adult form and characteristically is a more aggressive, often fatal, lymphadenopathic disease, usually with no cutaneous manifestations.[31,32] Endemic KS has been reported in children born to consanguineous parents, suggesting inherited immunodeficiency as a possible mechanism of KS disease development in areas of high HHV-8 prevalence.[33]

Epidemic KS associated with HIV usually is aggressive, with widespread cutaneous and visceral involvement, and is associated with a poor prognosis without treatment. Since the advent of combination antiretroviral treatment (cART) for HIV infection, the incidence of KS has declined and the outcome improved substantially.[9,28,34,35] Epidemic KS in children more closely resembles the endemic form, with lymphadenopathy as a prominent feature.[36] Other common sites of involvement include the oral mucosa and the gastrointestinal and respiratory tracts.[18] Immune reconstitution inflammatory syndrome KS may cause worsening signs and symptoms of KS in children newly started on cART and necessitate more aggressive treatment.[18,28] KS associated with immunosuppression not related to HIV most frequently occurs in endemic areas in solid-organ transplant recipients with previous HHV-8 infection.[37]

Descriptions of primary infection are limited but indicate that most are likely asymptomatic. Clinical expression varies geographically and according to comorbidities.[38,39] Among young immunocompetent children residing in endemic areas, primary infection was identified in 7% of those presenting with acute febrile illnesses.[38] Clinical manifestations included fever, upper respiratory tract signs, and a nonspecific maculopapular rash. A mononucleosis-like illness also has been described.[40] Acquisition of primary HHV-8 infection in children following transfusion is associated with increased mortality for 2 to 10 weeks after the event.[22]

Among immunocompromised patients, primary infection often is asymptomatic but sometimes manifests as a febrile illness of varying severity, with lymphadenopathy, splenomegaly, arthralgia, pancytopenia, and occasionally acute onset of KS.[39,41,42]

Diagnosis

Laboratory methods for diagnosing HHV-8 infection are not standardized. Many polymerase chain reaction (PCR) and serologic assays are available, but their sensitivity, specificity, and clinical usefulness vary widely.[39,43,44] However, when combined with histopathology and immunocytochemistry, these tests permit accurate diagnosis of KS and other HHV-8–associated lymphoproliferative disorders.

Serologic tests include indirect immunofluorescence assays to detect latency-associated nuclear antigen and lytic antigens, enzyme immunoassays, and immunoblot assays.[13,44] Their usefulness is dependent on which antigens are detected because gene expression varies among different HHV-8–related entities.[43] Combining several serologic assays generally increases the sensitivity and specificity of detecting infection.[44]

PCR assays can detect HHV-8 in blood and tissue specimens, but results can be confounded by the variable and often low number of HHV-8 genomic copies present in infected tissue and peripheral blood and by the occurrence of asymptomatic viremia.[45] PCR assays have been used to support the diagnosis of HHV-8–associated disorders, detect exacerbations, and help determine prognosis.[45–47]

Management and Therapy

No antiviral therapy is approved in the US for the treatment of HHV-8 infection. The use of cART for HIV infection decreases the incidence of KS and provides treatment benefit in early-stage disease.[28,35,45,46] In addition, ganciclovir and valganciclovir have been shown to decrease the incidence of KS in HIV-infected patients, decrease the frequency and quantity of HHV-8 oral shedding, and be useful as consolidation treatment in patients with HIV-associated multicentric Castleman disease.[20,45,48,49]

Current treatment efforts directed at controlling the lymphoproliferative complications of HHV-8 infections in HIV-infected individuals typically include therapy with cART and traditional chemotherapeutic regimens based on the resources of the region.[49–53]

Acknowledgment

The author acknowledges the substantial contribution of Caroline Breese Hall to previous editions of this chapter. The infectious diseases community recognizes her major contributions to our field and our great sadness in her loss. – Sarah S. Long

Key Points

Epidemiology, Clinical Features, Diagnosis, and Management of Human Herpesvirus 8 Infections

Epidemiology

- Human herpesvirus 8 (HHV-8) is also known as Kaposi sarcoma herpesvirus (KSHV), a lymphotropic γ2-herpesvirus most closely related to Epstein-Barr virus.
- After primary infection, HHV-8 persists as a lifelong latent infection.
- Prevalence of infection mirrors the incidence of Kaposi sarcoma (KS), with notable geographic variability.
- The highest seroprevalence is in sub-Sahara Africa, followed by the Mediterranean and Middle East; the lowest rates are in Europe and North America.
- In areas of low prevalence, high-risk groups, such as men who have sex with men, have increased rates of infection.
- Transmission is thought to be through saliva; young children in endemic areas acquire infection nonsexually from household contacts.

Clinical Features

- HHV-8 causes lymphoproliferative disorders, the most common of which is KS.
- Four KS variants exist: classical, endemic/sub-Saharan African, epidemic (AIDS associated), and immunosuppression associated.
- In Central Africa, HHV-8–associated KS accounts for up to 25% of childhood malignancies.
- Endemic and epidemic KS in children characteristically is an aggressive lymphadenopathic disease with no cutaneous manifestations.
- Initiation of combination antiretroviral treatment (cART) in children with KS can be associated with immune reconstitution inflammatory syndrome and worsening signs and symptoms.
- Primary infection often is asymptomatic but can cause fever,

upper respiratory tract signs, and a nonspecific maculopapular rash.

- HHV-8 can cause primary effusion lymphoma, multicentric Castleman disease, and KSHV cytokine inflammatory syndrome associated with HIV infection.

Diagnosis

- Most diagnoses are based on combination of serologic tests for both latent and lytic antigens, combined with histologic examination of tissue specimens.

Management

- Most primary infections are self-limited and do not require specific treatment.

- No antiviral medications are currently licensed for the treatment of HHV-8 infections.

- cART of HIV infection decreases the risk for KS and is used as treatment for early-stage disease, with traditional chemotherapy added for more advanced KS.

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DNA Viruses: Adenoviridae

OUTLINE

210 Adenoviruses

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Adenoviruses

Upton D. Allen, Gail J. Demmler-Harrison

Adenoviruses are relatively small, nonenveloped double-stranded DNA viruses. They belong to the family Adenoviridae (from *adenos*, the Greek word meaning "gland") because they were first isolated from adenoid tissue. There are 51 human serotypes defined by biologic characteristics, including immunochemical methods, such as serum neutralization and hemagglutination.[1–5] However, the use of the term *type* has replaced *serotype*, given that the more recently identified types were determined using genomics and bioinformatics and not serotyping.[1,6] To date, there are 67 types that have been identified using different technologies. Types 1 to 51 were characterized by serotyping, whereas types 52 to 67 were determined by genomic and bioinformatics analyses. Typing and reclassification of adenoviruses remains in a state of flux. The types are classified according to their biochemical, structural, biologic, and immunologic characteristics into seven subgroups, A to G.[1–5] The current spectrum of adenovirus species and types in humans is shown in Table 210.1. Adenoviruses in subgroups B and C (notably C) have the ability to cause latent infections in lymphoid cells.

TABLE 210.1
Human Adenoviruses

Species	Types (Serotypes/Genotypes)
A	12, 18, 31, 61
B	3, 7, 11, 14, 16, 21, 34, 35, 50, 55, 66
C	1, 2, 5, 6, 57
D	8–10, 13, 15, 17, 19, 20, 22–30, 32, 33, 36–39, 42–49, 51, 53, 54, 56, 58–60, 63–67

E	4
F	40, 41
G	52

Epidemiology

Transmission is mainly by direct spread from person to person through contact with infected respiratory tract secretions, fomites, and aerosols; enteric strains are transmitted by the fecal-oral route. Transmission also can occur through organ transplantation. Among transplant patients, reactivation of latent or persistent virus from the host can occur after the start of immunosuppressive therapy.[7,8] Reinfections with the same serotype can occur; these infections often are asymptomatic.[9]

Coinfections with more than one adenoviral type and with other respiratory viruses occur. Although not having the definite seasonality that is seen with other respiratory viruses, adenoviruses can produce sporadic outbreaks, most commonly during winter, spring, and early summer. No differences in incidence are apparent between males and females or among racial or ethnic groups. The incidence of infection appears greatest in lower socioeconomic groups and in situations of crowding. Epidemic disease commonly occurs in military recruits. Outbreaks, especially of pharyngoconjunctival fever, have followed exposure at swimming pools, summer camps, and childcare centers and in healthcare settings.

Adenoviruses can infect all age groups; however, the incidence peaks between the ages of 6 months and 5 years, and they are a leading cause of febrile illnesses in children. The use of molecular detection techniques has demonstrated a greater burden of adenoviral infections among childcare attendees than previously appreciated.[10] Tables 210.2 and 210.3 show the association between serotypes/types and clinical syndromes. The most common serotypes associated with respiratory tract disease are serotypes 1 through 7 and 21. Types 8, 19, and 37 are most commonly associated with epidemic keratoconjunctivitis, and serotypes 3, 7, 32, 40, and 41 have been associated with diarrhea. Disseminated adenovirus disease in immunocompromised children can be associated with several serotypes including 1 to 3, 5, 7, 11, 31, 34, 35, and 40 (see Table 210.2).[1,7,11,12]

TABLE 210.2

Clinical Illnesses and Associated Adenovirus Serotypes (Serotypes 1−51)

		Serotypes Involved[a]	
Syndrome	Signs and Symptoms	Frequently	Infrequently
Upper respiratory illness	Coryza, pharyngitis, fever, tonsillitis, with diarrhea	1–3, 5, 7	4, 6, 11, 14, 15, 18, 21, 29, 31
Lower respiratory illness	Bronchitis, laryngotracheobronchitis, bronchiolitis, pneumonia, fever, coryza, cough	3, 4, 7, 21	1, 2, 5, 8, 11, 14, 35
Pertussis-like cough illness	Paroxysmal cough, vomiting, fever, with upper respiratory tract symptoms	5	1–3, 12, 19
Infectious mononucleosis-like or Kawasaki-like illness	Fever, malaise, irritability, cervical lymphadenopathy, pharyngitis, rash, conjunctivitis	ND	ND
Acute conjunctivitis	Clear, watery discharge, chemosis, conjunctival injection, pruritus	1–4, 7	6, 9−11, 15−17, 19, 20, 22, 37
Acute hemorrhagic (follicular) conjunctivitis	Chemosis, subconjunctival hemorrhage, preauricular adenopathy, fever, sticky discharge	11	2–8, 14, 15, 19, 37
Pharyngoconjunctival fever	Pharyngitis, conjunctivitis, fever, coryza, headache, rash, adenopathy, with diarrhea	2, 3, 4, 7, 14	1, 5, 6, 8, 11−17, 19−21, 29, 37
Epidemic keratoconjunctivitis	Keratitis, headache, preauricular adenopathy, pharyngitis, diarrhea	3, 8, 19, 37	2, 4, 5, 7, 10, 11, 13−17, 21, 23, 29
Genitourinary tract disease	Cystitis (usually hemorrhagic), nephritis, orchitis, urethritis, cervicitis, ulcerative genital lesions, pharyngitis, fever	2, 37	1, 4, 5, 7, 9, 11, 18, 19, 31, 49
Gastrointestinal disease	Gastroenteritis with diarrhea and vomiting; abdominal pain with intussusception, pseudoappendicitis syndrome, or mesenteric lymphadenitis	3, 5, 7, 31, 40, 41	1, 2, 12–18, 21, 25, 26, 29, 31
Liver disease	Hepatitis	1–3, 5, 7	4, 31
Central nervous system disease	Meningitis, encephalitis, Reye syndrome	7	1−3, 5, 6, 11, 12, 26, 32
Cardiac disease	Myocarditis, pericarditis	7, 21	ND
Infection in immunocompromised hosts	Diarrhea, rash, upper respiratory tract illness, pneumonia, hepatitis, hemorrhagic enterocolitis, cystitis, disseminated disease	1, 2, 3, 5, 7,11, 34, 35	21, 29–31, 37–39, 43, 45
Fetus and newborn	Hydrops fetalis, myocarditis, pneumonia, hepatitis, disseminated disease	3	35

[a] Novel candidate types are being identified that are associated with disease (see Table 210.3).

ND, not determined.

Modified from Robinson C, Echarvarria M. Adenoviruses. In: Balows A (ed). Manual of Clinical Microbiology, 6th ed. Washington, DC, American Society for Microbiology, 1994, pp. 947–955.

TABLE 210.3

Clinical Illnesses and Associated Adenovirus Types (Types 52−67)

Types[a]	Disease States	References
52	Gastroenteritis	25
53	Keratoconjunctivitis	26–29
54	Keratoconjunctivitis	30–33
55	Acute respiratory distress syndrome	34, 35
56	Keratoconjunctivitis, neonatal pneumonia, urethritis	36–38
57	Conjunctivitis	39, 40
58	Gastroenteritis	41–43
59	Conjunctivitis	44
60	Conjunctivitis/keratitis (experimental)	45, 46
61	Gastroenteritis, hepatitis (proposed to be previously serotype 31)	47, 48
62	Gastroenteritis	49
63	TBD	50–52
64	Keratoconjunctivitis	53
65	Gastroenteritis	54, 55
66	Acute lower respiratory tract infections	56, 57
67	Gastroenteritis	58

[a] Data are emerging on the association between types 52−67 and disease states. In this regard, the documented associations with diseases are less than for the first 51 serotypes that were described. Some of the above types were previously designated as serotypes numbered less than 51.

TBD, to be determined.

Nosocomial adenovirus infections can spread rapidly to cause serious morbidity and substantial mortality, especially in neonatal intensive care or hematopoietic stem cell transplantation (HSCT) units.[13–20] Nosocomial adenovirus infections can be spread by contaminated hands of healthcare workers,[15] infected ophthalmologic specula, retractors and solutions,[13] and equipment such as pneumotonometers,[18,21] endotracheal tubes, and suction catheters.[15] Alcohol, detergents, and chlorhexidine do not eradicate adenovirus from hands or equipment because adenoviruses are nonenveloped viruses and therefore are resistant to these agents. Instruments contaminated with adenoviruses can be disinfected by immersion in a 1% solution of sodium hypochlorite for 10 minutes[22] or by steam autoclaving.[23] Adenoviruses can persist on hands despite handwashing for 10 seconds; therefore, disposable gloves that are changed between contacts with patients should be used to help control institutional outbreaks.[18,21] The use of gowns and masks is recommended for tracheostomy care.[16] Other measures to control adenovirus nosocomial infections are isolation and cohorting of ill patients.[13,14,18] Healthcare workers with epidemic keratoconjunctivitis should not have direct contact with patients until 14 days after the onset of disease in the second eye.[18] The incubation period usually is 2 to 14 days for adenovirus respiratory tract infection and 3 to 10 days for gastrointestinal infection.[23]

Clinical Disease

Adenoviruses cause a variety of syndromes (see Table 210.2),[24] which can be influenced by age, immune status, and site of infection. Syndromes associated with the newer types (52–67)[25–58] are less well defined than those associated with serotypes 1 to 51. Many endemic adenoviruses, such as subgenus C, types 1, 2, 5, and 6, can cause infection throughout the year and are associated commonly with prolonged but asymptomatic fecal excretion of virus. Other adenoviruses are associated with epidemic disease, common environmental exposure, or novel virus types to which most hosts are susceptible. Among asymptomatic individuals, virus can be present in peripheral blood lymphocytes, lung tissue, and normal duodenal epithelium.[59–62]

Respiratory Tract Infections

Adenoviruses cause 2% to 5% of respiratory tract infections, including rhinitis, otitis media, pharyngitis, exudative tonsillitis, cervical adenopathy, bronchitis, laryngotracheobronchitis, pertussis-like syndrome, bronchiolitis, pneumonia, pleural effusions, and hyperlucent lung syndrome.[63]

Tonsillitis is a common manifestation of adenoviral infections. This tends to occur in younger children (<3 years of age) compared with group A streptococcal tonsillitis, which occurs in an older age group (5–17 years of age).[64,65]

Adenoviruses account for approximately 10% to 20% of childhood pneumonias.[66,67] The most severe respiratory tract infections are due to adenovirus types 3 and 7, serotypes that also can cause necrotizing diseases.[15,68–70] Adenovirus genome type 7h has been associated with fatalities among children with lower respiratory tract infection (LRI).[69,70] Fatality was originally reported among adults infected with serotype 14 in the United States[71,72] Fatal serotype 14 cases also have been reported from Europe, and the occurrence of this serotype (variant 14p1) has been documented in other regions.[73–75] Obliterative bronchiolitis can develop in children with severe respiratory compromise associated with adenovirus LRI.[76,77] This complication is most common in those who require intensive care, mechanical ventilation, oxygen supplementation, corticosteroid therapy, or β-agonist agents.[76] Hyperlucent lung syndrome, bronchiectasis, and bronchopulmonary dysplasia in premature infants also have been linked to prior adenovirus infections.[13,17] Pertussis and pertussis-like cough illness can be caused by adenovirus alone or associated with a mixed infection with *Bordetella pertussis*.[78]

Pharyngoconjunctival Fever and Keratoconjunctivitis

Adenoviral pharyngoconjunctival fever is the constellation of conjunctivitis, fever, pharyngitis, and cervical or preauricular lymphadenopathy. Eye involvement consists of acute follicular conjunctivitis; sequelae are rare.

Epidemic keratoconjunctivitis, caused mainly by types 3, 8, 19, and 37, is a severe eye disease that usually occurs in adults. Novel serotypes also have been causative.[5,6] Pharyngitis can be associated. The clinical course is characterized by slow progression from foreign body sensation and photophobia to impaired vision, edema of conjunctiva and eyelids, and subconjunctival hemorrhage.[18] Acute symptoms can last 4 to 6 weeks. Diffuse epithelial engorgement can progress to punctate epithelial lesions followed by subepithelial keratitis, which may persist. Preauricular lymphadenopathy often is present. Epidemic keratoconjunctivitis can progress to pseudomembranous conjunctivitis and eyelid erythema and edema mimicking periorbital bacterial cellulitis.[17,79]

Gastrointestinal Infections

Adenovirus types 40 and 41 of subgroup F[80–82] and serotypes 3, 5, 7, and 31[81] are associated most commonly with a gastroenteritis syndrome, especially in children younger than 2 years of age. Other serotypes, including serotypes 2 and 8, also have been implicated.[81] Enteric adenoviruses are second only to rotavirus as a cause of infantile diarrhea.[82–85] Illness with fever and dehydration associated with enteric adenovirus infection is comparable with group A rotavirus illness.[85–88] However, enteric adenovirus diarrhea usually has no seasonality, lasts longer than most other infectious diarrhea syndromes, and is associated with more vomiting than that caused by rotavirus infection.[86,89]

Adenoviruses also have been associated with mesenteric lymphadenitis, appendicitis, and intussusception. Fulminant hepatic necrosis can occur in patients with disseminated adenoviral disease and in immunosuppressed patients.

Genitourinary Infections

Genitourinary adenoviral infection can result in acute hemorrhagic cystitis in both healthy and immunocompromised patients. Infection has been associated with nephritis, orchitis, and hemolytic uremic syndrome. In bone marrow transplant recipients, adenovirus-associated hemorrhagic cystitis can be prolonged and is associated with substantial morbidity, including severe pain and the need for blood transfusions. If infection occurs during the first 100 days after transplantation, disseminated disease can develop and mortality may be high.[12,90,91] Coinfection with other DNA viruses such as the polyomavirus BK virus has been reported.[90]

Cardiac Infections

Adenoviruses have been detected in specimens of pericardial fluid and myocardial tissue from patients with subclinical or mild acute myocarditis and pericarditis associated with disseminated disease.[92–94] Intrauterine adenoviral myocarditis with cardiac failure rarely is a cause of nonimmune fetal hydrops.[95,96]

Neurologic Infections

Adenoviral neurologic disease, including aseptic meningitis, encephalitis, and transverse myelitis occurs rarely. Adenoviruses have been detected in cerebrospinal fluid by cell culture and by polymerase chain reaction (PCR) and in brain tissue by histopathology using immunohistochemical staining.[97,98] Central nervous system involvement can occur as part of severe, disseminated disease, especially in immunocompromised patients. Adenoviruses have been associated with febrile seizures.[99]

Other Illnesses

Uncomplicated adenovirus-associated upper respiratory tract illness can cause fever beyond a week and also can cause persistent fever without a focus.[100,101] Adenovirus also can cause an infectious mononucleosis (IM)-like syndrome as well as a Kawasaki disease (KD)-like syndrome.[102,103] Distinctive features in children with adenovirus infection in one study were <4 KD-like features, predominance of species B or E, and higher viral burden compared with children with KD and incidental adenovirus detection.[104]

Immunocompromised and Special Hosts

Adenoviruses are important pathogens in immunocompromised hosts, especially HSCT and solid-organ transplantation patients.[1,2,105–109] In HSCT patients, the rates of adenovirus infections are 4% to 18%, with reported fatality rates up to 75%.[110] Most infections occur before engraftment during the first months after transplantation. Fever, pneumonia, hepatitis, hemorrhagic cystitis, gastroenteritis, and colitis are the most common clinical presentations, and widespread virus dissemination can be fatal.[110–115] Risk factors for adenoviral infection and death in HSCT patients include graft-versus-host disease, total-body irradiation, type of marrow graft, pulmonary disease, isolation of the virus from more than one site, and type of immunosuppressive regimen.[109,112]

Adenovirus infections occur in 10% of liver transplant recipients, often causing hepatitis in the transplanted organ or disseminated disease, with an overall fatality rate of 53%.[1,115,116] Infection in lung transplant recipients can be severe, causing pneumonia, obliterative bronchiolitis, and disseminated disease.[117,118]

Adenovirus infections occur in approximately 10% of renal transplant recipients. Acute hemorrhagic cystitis, with hematuria, frequency, dysuria, and fever, and rarely with renal injury, can result.[119]

Children with malignancies and AIDS can be infected with a variety of adenovirus serotypes, and serious, even fatal disease, involving liver and lungs, has been reported.[120,121]

Adenovirus infections in the fetus and newborn are rare but often severe.[122–129] Fetal death can result from nonimmune hydrops.[58,59,86,87] In addition, infections contracted during the first month of life can be fatal. These infections can be acquired nosocomially during outbreaks in neonatal special care units, perinatally from the mother, or postnatally from family members or other close contacts.[13–15,126,127,129] Risk factors for perinatal adenovirus infection include premature labor, prolonged rupture of membranes, and maternal fever with upper respiratory tract illness at the time of delivery.[126] Neonatal illness usually manifests with lethargy, fever, and hepatosplenomegaly, with onset within 10 days of birth. After a brief period of apparent stabilization, virus disseminates and hepatitis, pneumonitis, disseminated intravascular coagulation, and death ensue.

Diagnosis

Optimal methods to detect adenovirus infection vary according to the disease being investigated. Conventional methods include electron microscopy to detect adenovirus particles in feces or respiratory tract secretions, histopathology with immunohistochemical staining of tissue, virus isolation by culture, direct antigen, and molecular methods of detection.[103,130,131]

Adenoviruses can be isolated in a variety of cell culture systems.[131] Isolation of adenovirus from the nasopharynx, throat, urine, and stool supports the diagnosis of acute infection, although isolation of virus from these sites can occur in the absence of disease. Isolation of virus from blood, pleural, pericardial, or cerebrospinal fluid or from tissue provides strong evidence of invasive or disseminated adenovirus disease. Adenovirus produces a characteristic rounded “cluster of grapes” cytopathic effect in cell culture, usually within 3 to 5 days of incubation; virus-specific immunofluorescence assays can be used for definitive identification. Identification of adenovirus serotype requires neutralization or hemagglutination-inhibition tests. Some serotypes of adenovirus, such as types 40 and 41, are fastidious, and culture is not a sensitive method for detection. Some serotypes can be excreted for prolonged periods, thereby making the association between diseases and virus detection challenging.

Adenovirus antigens can be detected in respiratory tract secretions by direct fluorescence assay using commercially available reagents, with results available within 24 hours.[103] Other rapid antigen detection methods include immunochromatography and latex agglutination, which are particularly useful for stool samples for which immunofluorescence cannot be performed. A commercially available rapid immunochromatographic test can detect most adenovirus serotypes, in a wide variety of specimens, including feces, nasopharyngeal and respiratory tract secretions, eye and conjunctival swabs, and urine. The test is simple to perform, and results are available in <30 minutes.[132] The test is sensitive and specific compared with reference standards such as virus culture and DNA detection by PCR. False-positive reactions can be caused by the local eye anesthetic oxybuprocaine.[133]

Molecular methods of detection are favored by many laboratories. These methods can detect or quantify adenovirus DNA in respiratory tract secretions, feces, blood, and urine. Gene amplification techniques, such as PCR, are sensitive and can detect any adenovirus or specific adenovirus serotypes using unique genomic regions of primers, probes, or both.[134–136] In addition, serial quantitative PCR assays can be used to monitor transplant recipients prospectively.[137] If high or rising viral DNA levels are detected by serial quantitative PCR assays, intervention with antiviral and immunomodulating therapies and adjustment of immunosuppression regimens may be indicated to prevent serious or fatal disease.[138] Assays that amplify and detect partial or unique regions of the hexon genomic region have also been used to study the molecular epidemiology of adenoviruses.[44,139] Other test modalities (e.g., DNA microarray technology) are the subject of current research.[140–142]

Serologic methods can detect significant rises in antibody levels between serum collected during acute illness and convalescence 2 to 4 weeks later. Serologic methods include testing for group-reactive antibody (complement fixation test, enzyme immunoassay) or type-specific antibody (neutralization or hemagglutination-inhibition assay). Serologic diagnosis is not recommended because sensitivity may be ≤50% in acute infections in normal hosts and possibly lower in immunocompromised hosts.

Treatment and Prevention

Treatment of adenoviral diseases is primarily supportive. Most adenovirus infections in otherwise healthy people are self-limited and do not require treatment. Symptomatic infection of immunocompromised hosts should be treated with antiviral agents and reduction of immunosuppressants, if feasible. No consensus exists regarding the optimal management of symptom-free patients with detectable adenovirus viremia.

Trifluridine, ribavirin, and cidofovir are active against adenoviruses in vitro.[143–145] There are only anecdotal case reports and uncontrolled case series of treatment of serious adenovirus disease. Ribavirin has been administered with variable success, depending on the location and extent of the infection and immune function of the host.[11,144–146] Cidofovir has emerged as the preferred antiviral agent for treatment of adenoviral disease. Cidofovir at a dosage of 5 mg/kg administered intravenously once weekly, or at a reduced dosage of 1 to 1.5 mg/kg administered intravenously 3 times weekly has demonstrated clinical and virologic benefit in some patients.[147–151] Brincidofovir (1-*O*-hexadecyloxypropyl-cidofovir [CMX001]) is a lipid conjugate of cidofovir that is orally bioavailable and has substantially less nephrotoxicity than the parent drug.[152–155] Ganciclovir has activity against adenoviruses; however, studies are needed to clarify its effectiveness and role in the management of adenoviral disease.[156–158] Foscarnet has no demonstrable activity against adenoviruses.[156]

Treatment of hypoxemia or respiratory failure may require oxygen supplementation, mechanical ventilation, inhaled nitric oxide, or extracorporeal membrane oxygenation.[159]

Intravenous immunoglobulin has been used to treat patients with acute myocarditis and immunodeficient patients with pneumonia and disseminated disease due to adenovirus.[160,161] Novel immunoadoptive therapies that transfer virus-specific T-lymphocyte immunity to hosts who lack specific adenovirus T-lymphocyte immunity are being explored as therapeutic options in HSCT patients.[107,162,163]

Active immunization against adenovirus is not available outside of the military setting, and passive immunization with immunoglobulin has not been shown to be effective for immunoprophylaxis or outbreak control. Careful hand hygiene by caregivers and optimal disinfection of instruments and objects in the environment remain primary tools for preventing the spread of adenovirus in home, group childcare, and healthcare settings.

Key Points

Adenoviruses

Virology

- Double-stranded, nonenveloped DNA viruses in the Adenoviridae family
- Recently described type, resulting in at least 67 serotypes belonging to 7 subgroups
- Ability to cause latent or persistent infections

Epidemiology

- Affects all age groups, but peaks between ages 6 months and 5 years
- Transmission mainly by direct person-to-person spread
- Transmitted by contact with infected respiratory secretions
- Enteric strains transmitted by fecal-oral route
- Transmission possible by transplanted organs
- No classic seasonality as seen with other respiratory viruses; sporadic outbreaks can occur in winter, spring, and early summer

Clinical Features

- Symptoms depend on age, immune status, and sites of infection.
- Relationship exists between serotypes and sites of infection.
- Severe disease can occur in the immunocompromised host.

Diagnosis

- Conventional methods of detection include electron microscopy, histopathology, immunohistochemistry, culture, and direct antigen detection.
- Molecular methods have improved detection rates.
- Serology lacks utility in clinical setting and is notably unreliable in immunocompromised hosts.

Treatment

- Infections in normal hosts often are self-limited.
- There is no consensus on treatment of asymptomatic patients with detectable viremia.
- Early treatment of disease in the immunocompromised host is desirable.
- Effectiveness of antiviral agents is limited; intravenous cidofovir has emerged as the preferred agent for the treatment of systemic disease; brincidofovir is the orally bioavailable lipid conjugate of cidofovir and is associated with less toxicity.

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DNA Viruses: Adenoviridae

OUTLINE

211 Human Papillomaviruses
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211

Human Papillomaviruses

Loris Y. Hwang, Anna-Barbara Moscicki

Papillomaviruses are species specific and widely distributed among mammals and nonmammalian animal species. Human papillomaviruses (HPVs) are strictly epitheliotropic and cause infections and cancer of the skin and mucous membranes. Clinical conditions include anogenital infections and cancers, oral infections and cancers, and recurrent respiratory papillomatosis.

The Virus and Pathogenesis

HPVs are nonenveloped, double-stranded DNA viruses with a small circular genome of approximately 8000 base pairs. HPV genes are classified by their expression, occurring either early or late in the virus replication cycle. The early gene *E6* disrupts the antioncogene *p53*. *E7* disrupts the E2F/pRb complex, leading to activation of E2F, an important cellular transcription factor.[1] Both events lead to abnormal cellular proliferation. *E6* and *E7* also activate telomerase to lengthen telomeres, leading to the prolonged life of epithelial cells and blockade of apoptosis. *E6* and *E7* transcription is regulated by *E2*. Interestingly, viral integration, which occurs in more than 80% of HPV-related cancers, results in *E2* loss and the enhanced transcription of *E6* and *E7*.

HPV infection begins with viral invasion of the epithelial basal cells, particularly in the setting of epithelial disruption due to minor abrasions or inflammation. In the basal and parabasal layers, only the early viral genes are expressed, and viral DNA is replicated in low copy numbers, which likely contributes to evasion of the host immune system. In the more differentiated upper layers of the epithelium, expression of the late genes, *L1* and *L2,* produces capsid antigens that allow the release of fully infectious viral particles with physiologic epithelial desquamation. Inflammatory signals are absent because initial HPV infection does not induce cell death.

Extensive study of HPV as a cause of invasive cervical cancer has formed the basis of our understanding of HPV pathogenesis. Cervical cancer originates in the cervical transformation zone, where the proximal single-layered columnar epithelium transitions to the distal stratified squamous epithelium. At this juncture, the physiologic process of squamous metaplasia transforms the columnar cells into squamous cells. Squamous metaplastic activity is thought to be triggered by pubertal hormonal changes and thus is most common during adolescence and young adulthood, when initial HPV infection also commonly occurs.[2–4] However, the time between initial HPV infection and the development of invasive cancer is several decades in most healthy women. Active viral replication results in the benign changes of mild basal cell proliferation and perinuclear halos. In the past, these changes were described using different nomenclature when evaluated by cytology and by histology. In 2012, terminology was revised so that both cytologic and histologic results are reported according to the Bethesda system.[5,6] Benign changes are referred to as atypical squamous cells of undetermined significance (ASC-US) and low-grade squamous intraepithelial lesion (LSIL) (equivalent to cervical intraepithelial neoplasia, grade 1 (CIN 1) (Table 211.1).[7] High-grade squamous intraepithelial lesion (HSIL) (equivalent to CIN 2, 3) is considered a potential precancerous lesion. The changes of aneuploidy, altered chromatin texture, and increased nuclear volume are thought to be related to *E6* and *E7* expression in the epithelial stem cells. These cells have lost the ability to differentiate and demonstrate mutagenic consequences, including damage of chromosomal integrity, recombination of diverse DNA, and viral integration. The final mechanisms leading to invasive cancer are unexplained.

TABLE 211.1

Bethesda Terminology for Cytology and Histology

SQUAMOUS CELL ABNORMALITIES
Atypical squamous cells of undetermined significance (ASC-US)[a]
Atypical squamous cells, cannot exclude HSIL (ASC-H)[b]
Low-grade squamous intraepithelial lesion (LSIL)[a]
High-grade squamous intraepithelial lesion (HSIL)[b]
GLANDULAR CELL ABNORMALITIES
Atypical glandular cells (AGC)[c]
Endocervical adenocarcinoma in situ (AIS)[c]
Adenocarcinoma[d]

[a] Repeat cytology in 12 months.

[b] Refer to a gynecology specialist for colposcopy.

[c] Refer to a gynecology specialist for colposcopy including endocervical sampling; consider endometrial sampling depending on clinical history.

[d] Refer to gynecology specialist.

Immunity

Cell-mediated immunity is critical for HPV control, as evidenced by the increased risk for HPV-related anogenital cancer in individuals with depressed cell-mediated immunity.[8] Likely both genetic and epigenetic factors influence the host immune response. The primary mechanism for HPV persistence is thought to be evasion of both innate and adaptive immune responses. The antibody response to natural HPV infections is relatively low in titer compared with other systemic viral infections and is not universally detected.[9] Antibodies associated with natural infection may not be protective because women with HPV-associated invasive cervical cancer are more likely to have antibodies than women without cancer. In contrast, antibody levels induced by HPV vaccines are 60 to 100 times higher than those elicited by natural infections.[10]

Epidemiology and Clinical Features

The more than 200 HPV types are catalogued into the genera alpha, beta, gamma, mu, and nu.[11] Alpha types are further divided according to their natural tropism for cutaneous or mucosal sites. The types associated with cutaneous warts include HPV types 1, 2, 3, and 10. Of the 40 mucosal alpha types found in the anogenital or oral tracts, several are termed *high risk* (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 73, 82) based on their association with cancers of these regions.[12] Notably, HPV-16 and HPV-18 are responsible for about 70% of cervical cancers. HPV-16 plays a greater role in other HPV-associated cancers, being associated with more than 90% of HPV-associated anal and head and neck cancers. HPV-18 is more commonly associated with adenocarcinoma of the cervix. High-risk types also are associated with 50% of vulvar, vaginal, and penile cancers, although this association is dependent on histologic type.

The more common low-risk anogenital types (types 6, 11, 40, 42, 43, 44, 54, 61, 72, 73, 83) cause benign or low-grade cervical cellular changes and anogenital warts. Anogenital warts are caused most commonly by HPV-6 and HPV-11. HPVs associated with cutaneous warts are likely transmitted through nonsexual skin-to-skin contact. Fomite reservoirs appear to be important, as evidenced by a higher risk for plantar warts in those who expose their bare feet in communal bathrooms and showers. Anogenital HPV transmission occurs predominantly through sexual contact. Perinatal transmission can occur at birth from an infected mother to her newborn. Although consequent clinical disease in infants is rare, HPV-6 and HPV-11 can cause juvenile-onset recurrent respiratory papillomatosis or anogenital warts.

Anogenital Tract Infections

Initial HPV infection in the female anogenital tract typically occurs within 3 years of sexual debut. Lifetime risk reaches 80% in sexually active individuals. In developed countries, women aged 15 to 25 years exhibit the highest prevalence rates of 25% to 40%. Prevalence rates decline to approximately 15% in women 30 years and older and plateau at 10% at about age 40 years. The strongest risk factors for infection are new sexual partners and lack of condom use in women of any age. Ninety percent of infections detected by DNA testing resolve spontaneously within 36 months.[13] Thus infection by high-risk HPVs is common in the female anogenital tract and by itself is not concerning. Most young women with HPV demonstrate either no detectable lesion by cytology or only LSIL. LSIL is a benign manifestation of HPV, and studies show that most CIN 1 lesions regress spontaneously.[13]

Recurrent infections with new HPV types as well as the same types are common in young women.[14] Whether recurrence of the same type represents repeated new infections or reactivation of latent infection remains controversial. However, the rare persistent infection with a high-risk type is the necessary step for progression to cervical cancer. HPV infection detected in an older woman likely represents a persistent infection acquired years earlier. Hence HPV DNA cotesting, along with cytology, is recommended for primary screening in women older than 30 years.[15]

HPV prevalence in the male anogenital tract is estimated at 50% but varies widely from 1% to 73% according to sampling techniques and the number of HPV types and genital areas tested.[16] In contrast to women, prevalence does not vary with age,[17] leading to the hypotheses that male infections are primarily superficial and transient without inducing a protective immune response. The finding that within 6 months most men clear the initial HPV type detected supports this hypothesis.[18] Antibody titers are lower in men than women at all ages despite the higher prevalence of DNA detection in men than women at all ages.[19] It is hypothesized that HPV persistence also is essential to the development of penile cancer; however, there are no natural history data because penile cancer is very rare. Information about anal infection has been derived predominantly from studies of men who have sex with men (MSM). Prevalence of anal infection is approximately 60% in HIV-negative persons and approaches 100% in HIV-positive persons.[20–22] Anal HPV also is common in women, including adolescents.[23] The cumulative 1-year incidence of anal HPV in women was 70% in one study.[24] Clearance of anal HPV is slightly faster than cervical HPV infection.[25] It is thought that anal HPV has a similar natural history to cervical infection because similar precancerous lesions (i.e., anal intraepithelial neoplasia [AIN], grades 2 and 3) can be detected. The few studies in healthy women find that about 4% of women have AIN.[26] The natural history of these lesions remains unknown, but it is assumed they have similar potential to progress as do cervical precancers.

Anogenital Cancers

Cervical cancer is the second most common female malignancy worldwide, following breast cancer. About 500,000 new cases of cervical cancer are diagnosed annually worldwide, with 12,900 new cases projected for the United States during 2015.[27] The age-adjusted incidence is 7.7 per 100,000 women. US rates have decreased significantly since the 1970s because of the availability of routine cervical screening and management of precancerous lesions, but little to no change has occurred since the early 2000s. Barriers to healthcare remain a contributing factor in these new cases.

The rates for cancers of the vulva, vagina, anus, and penis are considerably lower than the rates for cervical cancer. In the US, the projected number of newly diagnosed cases during 2015 is 5150 for vulvar cancer; 4070 for vaginal cancer; 7270 for anal cancer; and 1820 for penile cancer.[27] Age-adjusted incidence rates for anal cancer are 2 per 100,000 women and 1.5 per 100,000 men. Rates are increased in MSM (non−HIV infected) to 37 per 100,000.[28,29] HIV increases the risk for anal cancer in men and women. Risk factors for anal cancer in women also include a history of cancers of the cervix, vulva, or vagina, and CIN 3.[30–32]

Oral Infections and Cancers

The prevalence of oral HPV infection has been reported to be 4% to 10%[33]; however, sampling techniques likely are inadequate to detect HPV from the areas around the tonsils and base of the tongue. Most cases of oral cancers are associated with alcohol and tobacco use. However, about 25% of head and neck cancers are HPV associated.[34] HPV association is increased in cancers at the tonsils and base of the tongue, with estimates as high as 75%. It is estimated that 2370 HPV-associated oropharyngeal cancers will occur in 2015 in women and 9356 in men.[35]

HPV Infection in Immunocompromised

Individuals

Individuals who are HIV infected or otherwise immunocompromised experience increased HPV prevalence, persistence, and progression to cancer. In HIV-infected MSM, the incidence of anal cancer is approximately 78 per 100,000 person-years.[20–22,29] Prevalence of cervical HPV infection reaches 80% in HIV-infected women, who also experience increased rates of cervical, vulvar, and anal cancers.[36] Invasive cervical cancer is an AIDS-defining condition.

Anogenital Warts

Warts (condylomas) are the most common clinical manifestations of anogenital HPV. US physicians see more than 1 million individuals yearly for anogenital warts, and 6% of sexually active 18- to 59-year-olds report a history of diagnosis of anogenital warts.[37] Approximately 90% of warts are caused by infections with HPV-6 and HPV-11, which almost never are associated with invasive cancers.

Anogenital warts are found in the external genitalia, upper thighs, inguinal folds, vagina, uterine cervix, and periurethral, intraurethral, perianal, and intra-anal areas. Anogenital warts can be papular, cauliflower-shaped, keratotic, flat, or pedunculated. They can be single or multiple. Individuals with a history of receptive anal sex are at higher risk for intra-anal warts. Infants can acquire anogenital or respiratory warts through perinatal acquisition from an infected mother. Congenital infection is rare. Anogenital warts in children of any age can indicate sexual abuse, with a particularly higher association with abuse in those older than 3 years.

Cutaneous Warts

Cutaneous warts commonly are papular, cauliflower-shaped, and keratotic. Plantar and palmar warts typically are flat. Cutaneous warts can occur in the perineal skin, but these HPVs rarely infect mucosal surfaces. Skin warts are most prevalent in school-aged children and young adults. Malignant transformation of skin warts rarely occurs in immunocompetent individuals. In contrast, immunocompromised patients can experience extensive skin warts with the potential for malignant transformation.

Recurrent Respiratory Papillomatosis

Juvenile-onset recurrent respiratory papillomatosis (JORRP) is a rare but serious disease usually caused by HPV-6 or HPV-11 acquired at birth. Incidence is estimated at 1 to 4 cases per 100,000 births annually.[38] Risk factors for JORRP are first-order birth, young maternal age, and maternal condylomas at delivery. Most cases are diagnosed by 5 years of age. Although most cases are isolated to the larynx, mucosal papillomas can affect the nasopharynx, oropharynx, trachea, and esophagus. Infants can exhibit a hoarse or weak cry, stridor, feeding difficulties, and failure to thrive. Older children can manifest hoarseness, stridor, and dysphonia. Rare cases of bronchopulmonary involvement with malignant degeneration have been reported. Papillomas are not precancerous, but airway obstruction is a serious consequence. Diagnosis is by direct laryngoscopic visualization and histologic analysis. Management can require extensive surgical excisions and chemotherapy. Many patients experience frequent recurrences necessitating multiple surgeries.

Epidermodysplasia Verruciformis

Epidermodysplasia verruciformis is a rare genetic disorder characterized by susceptibility to persistent and extensive cutaneous HPV warts, with malignant transformation in up to one half of cases.

Laboratory Screening and Diagnosis

Cutaneous and anogenital warts are diagnosed reliably by history and examination. However, if therapy is ineffective, biopsy may be warranted to verify the diagnosis.

The primary mode of screening for cervical precancers and cancers is by cytology (Papanicolaou smear or liquid-based cytology) and HPV testing. Sampling should include both ectocervical scrapings and brush sampling within the cervical os to ensure sampling of the squamocolumnar junction. Screening guidelines for the general population were updated in 2012 by an expert panel convened by the American Cancer Society (ACS), American Society for Colposcopy and Cervical Pathology (ASCCP), and American Society for Clinical Pathology, and attended by 25 organizations.[39,40] Routine cervical cytology is recommended to begin at 21 years of age, with immunocompromise as the only exception. Screening frequency for immunocompetent women aged 21 to 65 years is cytology every 3 years. HIV-infected or immunocompromised women of any age should have cytology screening twice during the first year after diagnosis of HIV and then at 12 months. If all 3 tests are normal, screening can occur every 3 years. Starting at age 30 years, cotesting (cytology, as well as HPV testing with negative results for antibody to high-risk types) at 5-year intervals can be used as another mode of screening. The US Food and Drug Administration (FDA) recently approved a single HPV test for primary screening, which can start at 25 years of age and be done at 3-year intervals.

Direct cervical visualization is warranted in patients with bleeding, dyspareunia, or other symptoms. Overt cancer can be visualized without the assistance of magnification.

Abnormal cytology can warrant further diagnostic verification by colposcopy and histology sampling. Colposcopy at 10× to 16× magnifications with application of 3% to 5% acetic acid enhances vascular and tissue abnormalities and guides the clinician to optimal biopsy sites.

Screening for anal precancers and cancers remains controversial. However, because HIV-infected persons have the highest incidence, many clinicians perform anal cytologic screening in this group.[41] Anal screening practices must be conducted by skilled clinicians and supported by appropriate referrals. Some advocate for screening in women with a history of cervical or vulvar cancer or CIN 3. At minimum, these women should have routine digital rectal examinations and screening for anal cancer symptoms. There are no screening recommendations for vulvar, vaginal, penile, or oropharyngeal cancers.

Management

Current treatment for cutaneous and anogenital warts is directed toward destruction or excision of visible lesions. Treatment of cutaneous warts usually is for cosmetic reasons because the risk for malignant transformation is low and immune-mediated regression of lesions over a period of months to a few years is expected. Noteworthy exceptions are warts that cause bleeding, pruritus, or pain, especially plantar and subungual warts. Warts typically require costly repeated treatments associated with significant discomfort and high failure rates.

Cutaneous warts are treated with provider-applied cryotherapy, electrocautery, laser therapy, surgical excision, or patient-applied combinations of acetic acid–salicylic acid. External anogenital warts are treated with cryotherapy, surgical excision, or application of caustic agents. The 2010 Centers for Disease Control and Prevention (CDC) guidelines for patient-applied and provider-administered treatment of external anogenital warts are summarized in Box 211.1[42]

Box 211.1

Recommended Therapy for Genital Warts

Patient Applied

Podofilox 0.5% solution or gel: apply with swab or finger to visible warts twice daily for 3 days, followed by 4 days without treatment. Repeat this cycle for up to 4 cycles, using a maximum of 0.5 mL per day.

Or

Imiquimod 5% cream: apply once daily 3 times per week (or 3.75% cream, apply once daily) for up to 16 weeks. Wash the treatment area with soap and water 6–10 hours after the application.

Or

Sinecatechins (Veregen ointment 15%): apply 3 times daily for up to 16 weeks.

Provider Administered

Cryotherapy with liquid nitrogen or cryoprobe: repeat every 1–2 weeks.

Or

Trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80%–90%: apply small amounts to each wart weekly, followed by air-drying. Take care to avoid applying to normal skin.

Or

Surgical removal by scissor excision, shave excision, curettage, laser, or electrosurgery

Alternative

Intralesional interferon

Or

Photodynamic therapy

Adapted from Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Morb Mortal Wkly Rep 2015;64(RR-3):84–93.

The 2012 ASCCP guidelines for the management of abnormal cervical cytology in females of all ages are found at www.asccp.org/asccp-guidelines.[43] Women 21 to 24 years of age with ASC-US or LSIL should be observed with repeat cytology every 12 months for 24 months because many cases self-resolve.[39,44] Women with persistent ASC-US or LSIL at 24 months of follow-up or HSIL at any visit should be referred for further evaluation by colposcopy. Immediate treatment using excisional therapy without histologic confirmation of HSIL is unwarranted in young women. In HIV-infected or immunocompromised women, referral to a gynecologist for colposcopy should be made if ASC-US is found at two consecutive visits, or if LSIL or HSIL is found at any time.

Currently, HPV DNA testing serves as a triage test for risk stratification of women 25 years and older who have a cytologic diagnosis of ASC-US. HPV testing in women younger than 25 years is not recommended. Adults with ASC-US and a positive high-risk HPV DNA test result require colposcopy. Those with ASC-US but a negative HPV result can resume routine screening. The current FDA-approved assays detect the presence of 1 or more of 13 to 14 of the high-risk HPVs.

Prevention

Genital HPV infection is decreased by sexual abstinence, monogamy, limiting the number of sexual partners, and choosing a partner who has had fewer sexual partners. Condom use reduces the risk for infection and hastens LSIL resolution.[45,46] Cesarean delivery to prevent perinatal transmission is not recommended.

Three HPV vaccines are licensed by the FDA. The recombinant 9-valent vaccine (9vHPV, Gardasil-9), containing the L1 virus−like particles (VLPs) of HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58, is licensed for females aged 9 to 26 years and males aged 9 to 15 years (2014).[47] The quadrivalent vaccine (4vHPV, Gardasil), containing the L1 VLPs of HPV types 6, 11, 16, and 18, is licensed for females (2006) and males (2009) aged 9 to 26 years.[48] The bivalent vaccine (2vHPV, Cervarix), containing the L1 VLPs of HPV-16 and HPV-18, is licensed for females (2009) aged 9 to 26 years. All vaccines demonstrate >90% efficacy in preventing cervical cancer precursor lesions caused by their respective HPV vaccine types, among females who have not already been infected with those types.[49–53,54,55] Additionally, the 9vHPV and 4vHPV are efficacious in preventing vaginal and vulvar precancer lesions and anogenital warts in males and females caused by the respective HPV vaccine types.[10,56] Studies of MSM suggest high vaccine efficacy in reducing anal precancer lesions. There is no evidence of protection against any HPV disease in patients already infected with the vaccine types before vaccination.

The target group for HPV vaccination is young adolescents who have not initiated sexual activity. The CDC Advisory Committee on Immunization Practices recommends either the 9vHPV, 4vHPV, or 2vHPV vaccines for routine universal vaccination of females aged 11 to 12 years, and either the 9vHPV or 4vHPV for males aged 11 to 12 years. Routine "catch-up" vaccination is advised for females aged 13 to 26 years, males ages 13 to 21 years, and MSM and immunocompromised patients through age 26 years (Box 211.2). Additionally, any male 21 to 26 years old may be vaccinated.

Immunization can begin as young as 9 years of age. Any of the 3 approved vaccine products is acceptable and considered adequate. As of 2017, only the 9-valent vaccine is being distributed in the U.S. Patients who initiate vaccine at ages 9 through 14 years (nonimmunocompromised) should receive 2 doses at 0 and 6–12 months. Patients who initiate vaccine at ages 15–26, as well as immunocompromised patients, should receive 3 doses at 0, 1–2, and 6 months. If the schedule has been interrupted, vaccination can be resumed without repeating any doses. The vaccine series can be started and completed with different products: 9vHPV, 4vHPV, or 2vHPV for females, and 9vHPV or 4vHPV for males. Several studies have demonstrated the public health impact of marked drops in genital wart diagnoses after vaccine introduction, with evidence of herd immunity.[57] Other potential benefits may include prevention of penile, anal, and oropharyngeal cancers. Clinicians should remain alert for future vaccine updates and evolving information on the long-term duration of immunity and any new dosing schedules.

Box 211.2

Recommendations for 9-Valent, 4-Valent, and 2-Valent Human Papillomavirus Vaccines[a]; Advisory Committee on Immunization Practices, Centers for Disease Control[47]

Nine-valent, 4-valent, or 2-valent vaccine for females; 9-valent or 4-valent vaccine for males

Routine vaccination of females and males 11–12 years of age

Vaccination series can be started as young as 9 years of age at discretion of provider and parent

Catch-up vaccination for females 13–26 years of age and males 13-21 years of age who have not been vaccinated previously

Catch-up vaccination for males who have sex with males and immunocompromised males 22–26 years of age

[a] All 3 vaccines are approved and acceptable. As of early 2017, only the 9-valent vaccine is being distributed in the US. Patients who initiate the vaccine at ages 9–14 years (not immunocompromised) should receive a series of 2 doses of any of the products. Patients who initiate the vaccine at ages 15–26 and immunocompromised patients should receive a series of 3 doses.

Data from Meites E, Kempe A, Markowitz LE. Use of a 2-dose schedule for human papillomavirus vaccination—updated recommendations of the advisory committee on immunization practices. MMWR Morb Mortal Wkly Rep 2016;65(49):1405–1408.

Key Points

Human Papillomaviruses

Microbiology

- Double-stranded DNA virus contains 8000 base pairs.
- HPV infects basal cells of the mucosal or cutaneous epithelium.
- Early genes *E6* and *E7* are considered oncogenes.
- Late genes *L1* and *L2* are responsible for capsid antigens, necessary for release of fully infectious viral particles through physiologic epithelial desquamation.
- Vaccines are based on L1 antigens.

Epidemiology

- Transmission is person to person, including perinatal.
- Anogenital infection is common within 3 to 5 years after onset of sexual activity.
- Clearance of infections is common, with 90% of patients demonstrating clearance within 3 years.
- Persistence is essential for cancer development.
- Mucosal α types are classified as high-risk based on association with cancers of the cervix, anogenital area, and head and neck area.

- Herpesvirus-16 and herpesvirus-18 are responsible for approximately 70% of cervical cancer cases.

Screening and Diagnosis

- Cutaneous and anogenital warts are diagnosed visually by experienced clinicians.

- Clinically significant cervical infections are diagnosed by cytology screening; 2012 American Cancer Society, American Society for Colposcopy and Cervical Pathology (ASCCP), and American Society for Clinical Pathology guidelines advise routine screening to begin at age 21 years for the general population.

- Sexually active women who are HIV infected or immunocompromised should begin screening regardless of age.

- Women with high-grade squamous intraepithelial lesion (HSIL) on cytology should be referred to a gynecology specialist for colposcopy and histology to confirm results.

- Women aged 21–24 years with atypical squamous cells of undetermined significance and low-grade squamous intraepithelial lesion on cytology should be observed for 2 years for possible self-resolution.

- There are no clinical guidelines for screening for anal human papillomavirus infection.

Treatment

- Cutaneous and anogenital warts are treated by several patient-applied or provider-applied treatment options, as stated in the 2015 Centers for Disease Control and Prevention guidelines.

- Women with HSIL on histology should be treated by a gynecology specialist according to 2012 ASCCP guidelines.

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BK, JC, and Other Human Polyomaviruses

Suchitra Rao

Viruses

Polyomaviruses are a family of small, ubiquitous DNA viruses. The two most commonly known human polyomaviruses are BK virus and JC virus, which were first described in 1971.[1,2] Subsequently, 10 other human polyomaviruses have been identified: WU and KI polyomaviruses in 2007; Merkel cell polyomavirus in 2008; human polyomavirus 6, human polyomavirus 7, and trichodysplasia spinulosa virus in 2010; human polyomavirus 9 in 2011; MW and MX polyomaviruses in 2012; and St. Louis polyomavirus in 2013.[3–12]

Polyomaviruses are small (40 nm in diameter), nonenveloped viruses with a double-stranded DNA genome and an icosahedral capsid comprising three structural proteins: VP1, VP2, and VP3. The viral DNA is a supercoiled, circular, double-stranded DNA of approximately 5000 base pairs. The genome is organized into three regions (early, late, and regulatory); each of which has specific functions.[13,14]

The outcome of polyomavirus infection is species specific. The polyomaviruses are important in human disease for two main reasons. Although polyomavirus infection usually is asymptomatic, in some cases it can be associated with a specific pathology. Infection of human cells by the human-specific viruses generally is limited to epithelial cells, fibroblasts, lymphocytes, or cells derived from the central nervous system (CNS). For example, JC virus infection can lead to progressive multifocal leukoencephalopathy (PML), whereas BK virus infection can lead to polyomavirus-associated nephropathy. Furthermore, several polyomaviruses encode oncogenic proteins that can undergo transformation in cell cultures, have tumorigenic activity in animals, and might be associated with cancer in humans.[15]

Epidemiology

Seroprevalence rates for the human polyomaviruses in adults are 82% for BK virus, 39% for JC virus, 55% for KI polyomavirus, 69% for WU polyomavirus, 25% for Merkel cell polyomavirus strain 350, 42% for Merkel cell polyomavirus strain 339, and 70% for trichodysplasia spinulosa virus.[16,17] Age-specific prevalence studies indicate that BK virus seroconversion peaks during childhood and that JC virus seroprevalence increases steadily from childhood into late adulthood.[18,19]

Fecal-oral, oral, and respiratory routes of transmission have been suggested for different human polyomaviruses.[20] Studies of urban sewage samples suggest that JC and BK viruses might be acquired through fecally contaminated water, food, and fomites.[21,22] Salivary shedding suggests that BK virus might be transmitted orally, KI and WU polyomaviruses have been isolated from respiratory tract specimens of children and immunosuppressed adults, and Merkel cell polyomavirus DNA can be detected in respiratory tract specimens of symptomatic individuals.[3,4,23–27] Other routes implicated for transmission of some polyomaviruses include blood transfusion, placenta, semen, and organ transplantation.[28,29] Transmission occurs predominantly through close contact.[30]

BK Virus

BK virus was isolated from urine of a renal transplant recipient whose initials were BK.[4] BK virus is an important cause of significant morbidity in kidney transplant recipients, with a predilection to cause severe nephritis in the allograft, leading to loss of the graft in up to 80% of cases.[31,32] It is also associated with hemorrhagic cystitis in 25% to 50% of patients with hematopoietic stem cell transplants.[33–36]

Primary infection typically occurs in childhood and is usually asymptomatic or associated with mild upper respiratory symptoms.[37] Primary infection is followed by dissemination of the virus to sites where infection persists, predominantly the urinary tract.[38] BK viruria usually correlates with the degree of immunosuppression, but asymptomatic viruria has been described in healthy as well as immunocompromised patients.[39] After renal or bone marrow transplantation, immunosuppression can lead to reactivation of BK virus in host renal cells. Risk factors for reactivation include older age, BK virus seropositivity, and high pretransplantation anti-BK virus immunoglobulin G.[40]

Hematopoietic Stem Cell Transplant Recipients

Hemorrhagic cystitis usually is seen 2 weeks after transplantation, which is later than the hemorrhagic cystitis associated with cyclophosphamide.[36] Symptoms include dysuria, urinary frequency and urgency, suprapubic pain, and hematuria. There is little difference between allogenic and autologous transplant recipients with respect to viruria.[41] There is a higher incidence of hemorrhagic cystitis in allogenic transplant recipients with graft-versus-host disease, which is likely associated with immune reconstitution.[42] Diagnosis is made by detection of BK virus DNA in the urine but ideally should be confirmed with renal biopsy.[43]

BK virus nephritis has been reported infrequently in hematopoietic stem cell transplant recipients and patients with leukemia.[44–48] However, this complication is severe and can lead to permanent renal failure. Therefore, patients with unexplained deteriorating kidney function should be evaluated for BK virus infection by polymerase chain reaction analysis of urine and blood followed by renal biopsy for immunostaining. BK virus also can cause pneumonitis, hepatitis, retinitis, and meningoencephalitis in patients with cancer.[49]

Kidney Allograft Recipients

BK virus–associated nephropathy is seen most commonly in renal transplant recipients and includes hemorrhagic and nonhemorrhagic cystitis, asymptomatic hematuria, ureteral stenosis, and interstitial nephritis.[43] Reactivation of latent virus has been observed in 30% to 50% of renal transplant recipients within 3 months after transplantation.[50,51] Clinical presentation varies from asymptomatic to elevated serum creatinine, fever, or hematuria.[52,53] About 80% of renal transplant recipients have BK viruria, 5% to 10% of those develop BK virus–associated nephropathy, and 50% to 80% of patients who develop nephropathy go on to graft failure.[50,54–56]

The diagnosis of BK virus–associated nephropathy usually is made in patients with viruria and renal insufficiency.[43] The presence of decoy cells (virally infected epithelial cells with irregular shape and enlarged, abnormal nuclei) is suggestive of BK virus infection, but decoy cells also are present in JC virus and adenovirus infections.[57,58]

Quantitative measurement of BK viral load in the plasma has a negative predictive value of 100% but a positive predictive value of only 50%.[31] A plasma viral load of $>10^4$/copies per milliliter has both 93% sensitivity and specificity for positive tissue histology of BK virus nephropathy.[59] Renal biopsy is the most definitive test for diagnosis through visualization of intranuclear inclusions and cell detachment; however, false-negative results can occur in up to one third of biopsies owing to the focality of virus in renal tissue.[59,60]

Treatment

Treatment usually is supportive, with hyperhydration, forced diuresis, bladder irrigation, and transfusion as indicated.[61–63] If hematuria is severe with clots, cystoscopy with clot removal and cauterization of the source may be necessary. Cystectomy may be required if intractable bleeding occurs.[64,65]

First-line therapy for BK virus–associated disease is reduction of immunosuppression.[66,67] Recommendations for adjunctive antiviral therapy are not established because of the paucity of data and lack of randomized clinical trials. Treatment with low-dose cidofovir (0.25 to 1 mg/kg up to twice a week) without probenecid, and leflunomide or quinolones, in combination with immunosuppression reduction, has been used with some reported success.[68,69] However, there is some concern that these agents are ineffective in vivo and have the potential for adverse side effects.[70]

JC Virus

JC virus is the etiologic agent of PML. The infectious nature of the disease was described in 1964 with the finding of virions within intranuclear inclusion bodies of oligodendrocytes.[71] In 1971, JC virus was isolated from the brain tissue of and named after a patient with Hodgkin disease.[2] The disease rarely has been reported in transplant recipients or patients with hematologic malignancies.[72–76]

Progressive Multifocal Leukoencephalopathy

PML is a demyelinating disease preferentially affecting the white matter of the brain and is caused by the replication of JC virus in myelin sheath–producing oligodendrocytes. The clinical presentation of PML can include visual disturbances, alterations in behavior, cognitive decline, difficulty with coordination, and limb paresis. Lesions are adjacent to hemispheric cortical structures. PML is usually fatal.[77]

PML occurs more often in immunocompromised patients with HIV infection, after solid organ transplantation, or after allogenic hematopoietic stem cell transplantation. An increased incidence also has been reported in patients treated with natalizumab for multiple sclerosis and efalizumab for psoriasis.[78,79] Rituximab also has also been implicated in development of PML; however, most of these patients had other immunocompromising conditions.[80] Other neurologic disorders associated with JC virus infection include granule cell neuropathy, encephalopathy, and meningitis.[81]

Brain biopsy is considered the gold standard for diagnosis of PML, with a sensitivity of 64% to 96% and specificity of 100%.[43] Viral DNA also can be detected in cerebrospinal fluid, with a sensitivity of 72% to 92% and specificity of 92% to 100%.[76,82] Cerebrospinal fluid usually shows mild pleocytosis and slight elevation in protein.

Magnetic resonance imaging in patients with PML typically shows supratentorial white matter disease with confluent, bilateral, but asymmetric lesions.[83] However, findings can be unilateral, and there may only be a single lesion. The parietal lobe is most commonly involved, followed by the frontal lobe. Occasionally, there is grey matter involvement, with the thalamus and basal ganglia most commonly affected.

Treatment

There is no specific antiviral therapy for JC virus infection. In HIV-infected patients, the primary goal is to optimize antiretroviral therapy. If this can be achieved, 1-year survival rates increase from 10% to 50%.[84] For patients not infected with HIV, immunosuppressive therapy should be reduced.[43,85] Cidofovir has activity in vitro, but in vivo efficacy remains unknown.[86] Other agents such as mefloquine, interleukin-2, cytarabine, chlorpromazine, and serotonin 5-HT2A receptor blockers (e.g., ziprasidone, risperidone, olanzapine, and mirtazapine) have been used for individual patients, and trials for some of these agents are underway.[87,88]

WU and KI Polyomaviruses

WU and KI polyomaviruses were discovered in 2007 in respiratory tract specimens and were named after the institutions in which they were discovered: Washington University and Karolinska Institutet. The clinical presentation appears to be similar to other respiratory viruses, including fever, cough, and other upper and lower respiratory symptoms.[89–91] Studies in healthy blood donors detected serologic evidence of WU polyomavirus infection in 69% and KI polyomavirus in 55%.[16] However, their causative role in respiratory tract illness remains controversial, even in immunocompromised patients, owing to the high rate of codetection with other respiratory pathogens and the presence of WU in symptom-free individuals.[3,4,90,92–94]

Merkel Cell Virus

The oncogenic potential for polyomaviruses has been reported in natural and experimental infections but remains controversial, except for Merkel cell carcinoma.[95] Merkel cell polyomavirus was detected in 2008 in patients with Merkel cell carcinoma, a rare but aggressive form of skin cancer. The overall age-adjusted incidence is 0.2 to 0.4 per 100,000 person-years, but the incidence is increased in immunocompromised patients.[5,96–99] Merkel cell polyomavirus DNA has been detected in 59% to 100% of Merkel cell carcinomas, and patients with this tumor have very high antibody titers compared with the general population.[100–104] The mode of transmission and pathogenesis of the virus remains unknown. There are no data regarding specific antiviral therapy.

Trichodysplasia Spinulosa −Associated Polyomavirus

Trichodysplasia spinulosa is a rare skin disease characterized by development of papules and alopecia on the face and is observed exclusively in immunocompromised patients.[105–107] In 2010, the trichodysplasia spinulosa−associated polyomavirus was discovered and identified in a skin lesion from a child who developed trichodysplasia spinulosa after cardiac transplantation.[7,108] A second confirmed case was reported in a 7-year-old girl with leukemia.[108] The overall seroprevalence has been reported to be 70%, and the presence of the virus in clinically unaffected individuals suggests that the virus can cause subclinical or latent infection.[7,17]

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DNA Viruses: Hepadnaviridae

OUTLINE

213 Hepatitis B and Hepatitis D Viruses

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Hepatitis B and Hepatitis D Viruses

Melissa G. Collier, Sarah Schillie

Hepatitis B Virus

Description of the Pathogen

Hepatitis B virus (HBV), a member of the Hepadnaviridae family, is an enveloped virus that contains a circular partially double-stranded DNA genome that is 3.2 kb in length. The small genome consists of four overlapping reading frames.[1,2] Because the presence of HBV is necessary for infection with the hepatitis delta virus (HDV), both pathogens are discussed in this chapter.

HBV has been subclassified by serologic subtype and genotype. Nine serologic subtypes of HBV (*adrq*$^{+}$, *adrq*$^{-}$, *ayr*, *ayw1*, *ayw2*, *ayw3*, *ayw4*, *adw2*, *adw4*) initially were described on the basis of the serologic heterogeneity of HBsAg.[2] At least 9 HBV genotypes have been described, designated A through I, with a 10th genotype J isolated from a single individual. HBV serotypes and genotypes vary geographically. Infection or immunization to one genotype confers immunity to all genotypes.[3,4]

Pathogenesis

HBV-associated liver damage is not a direct cytopathic effect of the virus but rather the consequence of the host immune response to infection (e.g., cytotoxic T-lymphocyte–mediated lysis of infected hepatocytes).[5,6] Viral clearance and resolution of infection or development of chronic infection depends on the effectiveness and specificity of the initial cytotoxic T-lymphocyte response. For patients in whom acute HBV infection resolves, the response is vigorous, with cytokine-mediated control of virus replication and relative sparing of infected cells.[7] For patients in whom chronic infection develops, the initial T-lymphocyte response might be suboptimal and more narrowly focused, with enough cytokines produced to suppress some viral gene expression but insufficient to clear the virus. Persistent infection develops because of "immune tolerance."[8,9] HBV integrates into human DNA, potentially resulting in oncogene activation and carcinogenesis by insertional mutagenesis. Some studies suggest that regenerative hyperplasia resulting from chronic inflammation eventually might lead to carcinogenesis.[10]

Hepatitis B surface antigen (HBsAg) indicates either acute or chronic HBV infection. People with positive HBsAg are infectious and can transmit the virus to others. The immunoglobulin M (IgM) subclass of antibody to the hepatitis B core antigen (IgM anti-HBc) indicates acute infection, whereas total IgG anti-HBc is a nonspecific marker of infection that can indicate acute, chronic, or resolved acute infection. Antibody to HBsAg (anti-HBs) is a marker of immunity and is present after resolution of acute infection, after vaccination, or through passively acquired antibody (i.e., hepatitis B immune globulin [HBIG]). Hepatitis B e antigen (HBeAg) indicates ongoing virus replication and increased infectivity. Antibody to HBeAg (anti-HBe) can be found in both acute and chronic infection; its presence usually is accompanied by decreased viral load and decreased infectivity (Table 213.1). Hepatitis B DNA (HBV DNA) is a marker of virus replication. Higher viral loads correlate with greater infectivity.[3]

TABLE 213.1

Interpretation of Serologic Markers for Hepatitis B Virus Infection

Serologic Marker				Interpretation
HBsAg	Anti-HBs	IgM Anti-HBc	Total Anti-HBc	

–	–	–	–	Susceptible; never infected
+	–	–	–	Acute infection, early incubation; transient, up to 3 weeks after vaccination
+	–	+	+	Acute infection
–	–	+	+	Acute infection, resolving
–	+	–	+	Past infection, recovered and immune
+	–	–	+	Chronic infection
–	–	–	+	False-positive (i.e., susceptible) past infection, or "low-level" chronic infection
–	+	–	–	Immune from vaccination

HBsAg, hepatitis B surface antigen; anti-HBs, antibody to hepatitis B surface antigen; IgM anti-HBc, IgM antibody to hepatitis B core antigen; total anti-HBc, total antibody to hepatitis B core antigen.

Epidemiology

Worldwide, HBV infection is one of the leading causes of infectious disease–related morbidity and mortality. An estimated 2 billion people—one third of the world's population—have serologic evidence of past or present HBV infection, and more than 240 million people are infected chronically. Each year, an estimated 780,000 people die from HBV-related liver disease, including cirrhosis and hepatocellular carcinoma (HCC).[11] In the United States, HBV infects an estimated 700,000 to 1.4 million persons and results in approximately 1800 deaths annually.[12]

Transmission

The principal modes of HBV transmission are (1) percutaneous, (2) sexual, and (3) perinatal.[13] HBV is present in high titers in blood and exudates (e.g., skin lesions) of acutely and chronically infected people. Moderate viral titers are found in semen, vaginal secretions, and saliva. Other body fluids that do not contain blood or serous fluid, such as feces or urine, are not generally a source of HBV transmission. Although HBV is found in human milk, breastfeeding has not been shown to increase HBV transmission.[14,15] Transmission between household contacts, especially in developing countries, can occur through contact with skin lesions such as eczema or impetigo; sharing of potentially blood-contaminated objects such as toothbrushes and razor blades; and in rare instances, in association with human bites.[16–18] All people who are HBsAg positive are potentially infectious and can transmit the virus to others.

HBV is stable in the environment for at least 7 days and can be found in high titers on environmental surfaces, even in the absence of visible blood.[19] Inoculation can occur from contact with environmental surfaces or equipment contaminated with HBV. The virus is inactivated by household bleach solution.[20]

Percutaneous and permucosal transmission of HBV results from transfusion of unscreened blood, injection-drug use, occupational exposure (e.g., needlestick injuries), and other nosocomial exposures (e.g., unsafe injections, breach in aseptic technique). In the US, blood transfusion is no longer a significant mode of transmission because all donor blood is screened for HBV markers. However, blood transfusion remains an important source of infection in many developing countries. Globally, unsafe injection practices are thought to account for 32% of new HBV infections annually[21]; the burden of disease from other unsafe medical practices is unknown. Nosocomial transmission is not limited to developing countries; in the US and other developed countries, nosocomial transmission is associated with improper infection control and continues to occur despite longstanding infection control recommendations and guidelines.[22–25] Since the mid-2000s, nosocomial HBV outbreaks have involved reuse of fingerstick devices (meant for individual use) for multiple persons, during assisted blood glucose monitoring, and reuse of single-use vials or devices for multiple patients.[26]

Horizontal transmission (or intrafamilial or household transmission) refers to percutaneous transmission from infected family members within the household (most often mothers and older siblings to young children).[27–37] Although this mode of transmission is most important in countries of high HBV endemicity, its occurrence in the US has been well documented.[38–41]

Sexual transmission of HBV results from sexual contact (heterosexual or homosexual) with an infected person. Increased risk has been associated with ≥1 sexual partners in a 6-month period; history of another sexually transmitted infection; and sexual practices that facilitate HBV transmission, such as anal intercourse.[42] Among young men who have sex with men (MSM), the prevalence of past or chronic HBV infection was reported to be 21%.[42,43]

Perinatal HBV transmission occurs during delivery and is highly efficient. In utero transmission is relatively rare, accounting for <3%

of vertical infections.[44–48] Risk for perinatal transmission is related to the HBeAg status of the mother; presence of HBeAg indicates increased viral load and infectivity. The risk for perinatal transmission is 70% to 90% for infants born to mothers who are both HBsAg positive and HBeAg positive, and 5% to 20%, for infants born to mothers who are HBsAg positive but HBeAg negative.[3,49–57]

Risk Factors, Prevalence, and Incidence of Infection in the United States

Risk factors for acute HBV infection in the US, including children ≥12 years of age, include injection-drug use, high-risk sexual behaviors (e.g., multiple sex partners and MSM).[12] Acquisition of HBV infection from transfused blood is rare in the US.[58,59] Other characteristics found in HBV-infected adolescents are homelessness and having run away from home.[60,61]

Data from the National Health and Nutrition Examination Survey (1999–2008) indicate that the lifetime risk for HBV infection in the US population is approximately 5%; chronic HBV infection is present among 0.3% of the population, corresponding to about 700,000 chronically infected persons. The prevalence of past or current HBV infection was higher among non-Hispanic blacks and persons of “other” race than among non-Hispanic whites and Mexican Americans, and prevalence was significantly higher among foreign-born persons. The US prevalence of past or current HBV infection was 0.5% among those 13 to 17 years of age and 4% among persons 30 to 39 years of age.[62]

Since the mid-1990s, the incidence of acute HBV infection in the U.S. has declined significantly. National surveillance data indicate that the incidence decreased from 11.5 per 100,000 population in 1985 to 0.9 per 100,000 in 2012 (Fig. 213.1). Incidence is estimated to be about 6 times the reported number of cases after adjustment for underreporting of cases and asymptomatic infections. In 2008, an estimated 19,000 people were newly infected.[12]

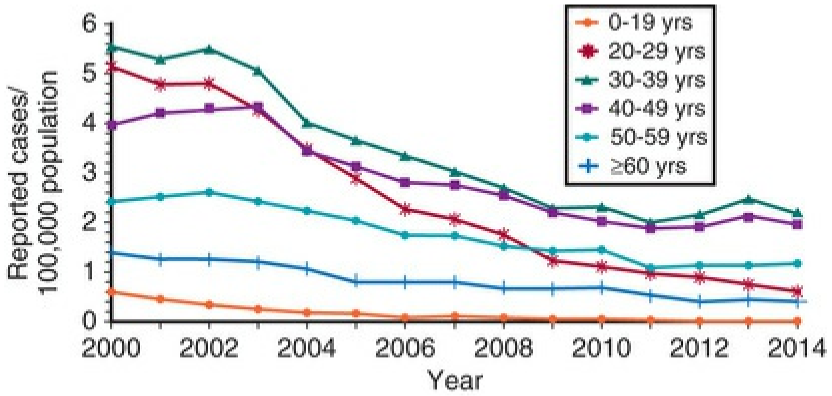

FIGURE 213.1 Reported incidence of acute hepatitis B in the United States, 2000–2014. (From the National Notifiable Diseases Surveillance System [NNDSS], Centers for Disease Control and Prevention. https://www.cdc.gov/hepatitis/statistics/2014surveillance/index.htm.)

The effect of hepatitis B vaccination is reflected in the dramatic decline in incident cases among the cohort of children for whom recommendations for routine infant and adolescent catch-up vaccination applied.[3] From 2000 through 2012, the incidence of acute HBV infection declined 95% (from 0.6 per 100,000 to 0.03 per 100,000) among children younger than 20 years.[12]

Global Prevalence of Infection and Patterns of Transmission

Countries and regions can be divided into areas of low (HBsAg prevalence <2%), intermediate (HBsAg prevalence of 2%–7%), and high (HBsAg prevalence of ≥8%) HBV endemicity based on the prevalence of chronic HBV infection in the general population.[3] Most high-endemic countries are in Africa and Asia. Western sub-Saharan African countries have some of the highest global age-specific HBsAg prevalence rates. East Asia has the highest prevalence of HBV infection among Asian regions. Global differences of HBsAg prevalence between males (3.9%) and females (3.5%) are small.[63]

Clinical Manifestations

Acute Infection

The usual incubation period for HBV infection is about 3 months but can vary from 6 weeks to 6 months. Clinical manifestations range from asymptomatic infection to fulminant hepatitis. The likelihood that symptoms will develop is age dependent. Perinatal HBV infections usually are subclinical, whereas symptomatic illness is noted in 5% to 15% of children 1 to 5 years of age and in 33% to 50% of older children, adolescents, and adults.[3,64]

Clinical signs and symptoms of acute HBV infection can include nausea, abdominal pain, vomiting, fever, jaundice, dark urine, changes in stool color, hepatomegaly, or splenomegaly. Malaise and anorexia might precede jaundice by 1 to 2 weeks. Fulminant hepatitis B is uncommon (<1%) but frequently leads to death or liver failure necessitating liver transplantation.[3]

Chronic Infection

Chronic infection is associated with progressive liver disease, including cirrhosis, liver failure, and HCC. Chronic infection is defined as persistence of HBsAg in serum for ≥6 months after acute infection.[3]

Most chronically infected people remain asymptomatic until development of cirrhosis or end-stage liver disease.[65] Cirrhosis can lead to the development of liver failure manifest by coagulopathy, ascites, encephalopathy, and increased risk for HCC. Among people with chronic infection, the overall annual incidence of cirrhosis is 2% to 3%.[66,67] At 5 years, the survival rate of people with compensated and uncompensated cirrhosis is 84% and 14%, respectively.[68] Risk factors for HBV-related cirrhosis and HCC include earlier age at infection, prolonged immune active phase of chronic infection, HBeAg positivity, and prolonged elevation of HBV DNA.[65,69] Although severe HBV-related liver disease is uncommon in childhood, chronic infection during infancy and childhood can lead to development of cirrhosis and HCC as early as the first decade of life.[70] Up to 25% of infants and older children with chronic infection eventually develop HBV-related cirrhosis or HCC.[3,71,72]

Extrahepatic Manifestations

Both acute and chronic HBV infection can be associated with extrahepatic clinical entities, including polyarteritis nodosa, membranous and membranoproliferative glomerulonephritis, polyradiculoneuritis, essential mixed cryoglobulinemia, porphyria cutanea tarda, polyneuritis, papular acrodermatitis, and thyroid dysfunction.[73–78] Urticarial rashes, arthralgia, and arthritis commonly are associated with acute HBV infection; thrombocytopenia preceding jaundice also has been reported.[79]

Natural History of Chronic Infection

There are four phases of chronic HBV infection: (1) immune tolerant, (2) immune active, (3) immune inactive, (4) and reactivation (or HBeAg-negative immune active).[68,80,81]

People in the *immune tolerant phase* are HBsAg positive and HBeAg positive and have high HBV DNA levels (>20,000 IU/mL), normal serum alanine aminotransferase (ALT) levels, and no to minimal hepatic inflammation or fibrosis.[68] Most chronically infected children will remain in the immune tolerant phase until late childhood or adolescence.[82]

The *immune active phase* is characterized by an active immune response resulting in inflammation (with or without fibrosis), hepatocyte damage and a resultant rise in serum ALT levels. Persons in the immune active phase are HBsAg positive, have HBV DNA levels >2000 IU/mL, and can be either HBeAg positive or HBeAg negative/anti-HBe positive.[68] People who remain in the immune active phase for prolonged periods are at high risk for developing cirrhosis and HCC.[69]

Persons in the *immune inactive phase* are HBsAg positive, have HBV DNA <2000 IU/mL, are HBeAg negative and anti-HBe positive, and have improvement of hepatic inflammation and fibrosis.[68] Risk for progression to HCC is lower among persons in the inactive phase than among persons in the active phase.[83]

Persons in the *reactivation phase* (or HBeAg-negative immune active phase) are HBsAg positive, HBeAg negative, and anti-HBe positive with HBV DNA levels >2000 IU/mL. There is active liver inflammation (with or without fibrosis), and serum ALT levels can be elevated or normal.[68] HBeAg-negative immune active disease often is caused by a mutant HBV, which can be more virulent than nonmutant forms.[84]

Chronically infected persons do not necessarily pass through the phases of chronic infection in a linear fashion. Chronically infected persons may spend little to no time in the immune tolerant phase. Twenty percent of HBeAg-negative persons will revert back to

HBeAg positivity[85]; 10% to 30% of HBeAg-negative/anti-HBe –positive persons will remain in the immune active phase with elevated serum ALT and HBV DNA levels; and 10% to 30% of HBeAg-negative/anti-HBe–positive persons will revert from the inactive phase to an anti-HBe–positive hepatitis with elevated serum ALT and HBV DNA levels.[86,87] As such, the current practice guidelines of the American Association for the Study of Liver Diseases recommend lifelong follow-up with repeated testing to monitor changes in the phase of chronic infection.[83]

Influence of Age and Hepatitis B e Antigen

Age at time of acute infection is the primary determinant of progression to chronic infection. More than 90% of perinatally infected infants develop chronic infection. Between 25% and 50% of children infected between 1 and 5 years of age become chronically infected, whereas only 6% to 10% of acutely infected older children and adults develop chronic infection.[3,64,88] Elderly adults have higher rates of developing chronic infection,[89,90]as do patients who have acute HBV infection while immunosuppressed or concurrently with an underlying chronic illness.[71]

Perinatally infected children usually remain in the immune tolerant phase for extended periods, whereas chronic infection acquired during later childhood or adolescence usually is accompanied by more active liver disease and elevated serum ALT values.[91] Children infected perinatally have lower annual rates of HBeAg loss than children infected later in childhood or in adolescence. Of Taiwanese children infected perinatally, HBeAg seroconversion occurred in <2% annually during the first 3 years of life and only in one third by 10 years of age.[92,93] Children infected horizontally clear HBeAg more rapidly; in one study, 35% of older Asian children cleared HBeAg >5 years after infection,[93] and 83% of European children cleared HBeAg during an average of 13 years of follow-up.[94]

Presence of HBeAg indicates ongoing virus replication. HBeAg-positive patients usually have high serum levels of HBV DNA. Clearance of HBeAg and development of anti-HBe (HBeAg seroconversion) are accompanied by reductions in serum HBV DNA and ALT levels and might be preceded by a temporary exacerbation of liver disease. HBeAg seroconversion occurs at a rate of 5% to 10% per year.[84] Most patients who seroconvert have little to no progression of liver disease (immune inactive phase). In these patients, the risk for HCC is reduced but remains higher than in patients without chronic infection.[95] Serologic reversion (reappearance of HBeAg) is common in the absence of anti-HBe. However, reversion to HBeAg positivity also can occur with loss of anti-HBe.[85]

HBeAg positivity during pregnancy greatly increases the risk for perinatal transmission. In the absence of appropriate postexposure prophylaxis, nearly all neonates born to mothers who are both HBsAg and HBeAg positive become infected, and 90% develop chronic infection. Clearance of HBeAg and development of anti-HBe is associated with decreased risk for perinatal transmission; approximately 25% of infants born to HBsAg-positive and anti-HBe−positive mothers become infected, and 10% to 15% develop chronic infection.[46,54] In a setting where infants generally receive postexposure prophylaxis, the relative risk for transmission for maternal HBeAg-positive status was an incidence rate ratio of nearly 80.[50]

Influence of Genotype

The clinical significance of HBV genotypes remains unclear. Existing studies suggest that genotype influences the time to HBeAg seroconversion and response to treatment. Among Alaska Natives, the median time to seroconversion is approximately 18 years among people with genotype C, 8 years among people with genotype F, and <6 years among people with genotypes A, B, and D. Reversion to HBeAg positivity is more common among Alaska Natives infected with genotypes C and F. Because genotype influences the rate of HBeAg seroconversion during childbearing years, genotype might play a role in the risk for perinatal transmission.[96,97]

An improved response to treatment with interferon α-2b (IFNα-2b) has been observed in adults with genotype A compared with adults with genotype D, and among adults with genotype B compared with genotype C.[98,99] Studies in children have shown mixed results. In one study, Chinese children with genotype B had an improved response to IFNα compared with children with genotype C.[100] In another study, Taiwanese children showed no difference in treatment response by genotype.[101]

Resolved Acute Infection and the “Recovery Phase” of Chronic Infection

Resolved acute infection is defined as the clearance of HBsAg, loss of detectable HBV DNA, and normalization of serum ALT levels; development of anti-HBs might occur. Resolved acute infection is not a risk factor for subsequent chronic liver disease or HCC.[102] However, viral clearance still might be incomplete; patients with a history of acute hepatitis B and apparent resolution (anti-HBs positivity and HBsAg negativity) can experience reactivation of hepatitis B if they become immunosuppressed,[103] and HBV DNA has been detected in blood of patients 20 years after resolution of acute infection.[104]

People with chronic infection who clear HBsAg enter what is often called the *recovery phase*. During childhood, the annual clearance rate of HBsAg is <1%.[83,105] People who clear HBsAg generally have a better prognosis, with improvements in hepatic inflammation and fibrosis over time.[106,107] However, HCC still can develop in HBsAg-negative people, and HBV DNA can be found in serum of a significant minority of HBsAg-negative people.[106,107] Practice guidelines recommend continued follow-up for previously chronically infected, HBsAg-negative people, to monitor for HCC.[108]

Laboratory Findings and Diagnostic Tests

Serum HBsAg and anti-HBs are the most useful screening tests for chronic HBV infection or immunity to HBV. HBsAg is present in most chronically infected persons. Lack of anti-HBs in an unvaccinated HBsAg-negative person indicates susceptibility to HBV infection.[3]

Routine screening for HBV infection is recommended for the following people: (1) all pregnant women; (2) all infants born to HBsAg-positive women after completing the vaccination series; (3) immigrants from regions of high or intermediate HBV endemicity (e.g., most areas of Asia, Africa, the Middle East, and Pacific Islands); (4) US-born people, who were not vaccinated as infants, whose parents were born in regions with HBsAg prevalence ≥8%;

(5) people with elevated serum ALT or aspartate transaminase levels of unknown etiology; (6) people with behavioral risks, including MSM and injection-drug users; (7) hemodialysis patients, (8) HIV-positive persons; (9) persons needing immunosuppressive therapy; (10) donors of blood, plasma, organs, tissues, or semen; (11) household, needle-sharing, or sexual contacts of persons known to be HBsAg positive; and (12) persons who are the source of blood or body fluids for exposures that might require postexposure prophylaxis.[65]

Screening for HBsAg is recommended at the first prenatal visit for all pregnant women.[3,109] Women in labor without HBsAg test information should have HBsAg serology on arrival. In addition, pretested women who have a history of certain risk factors (i.e., HBsAg-positive sexual partner or more than one sexual partner in the previous 6 months, evaluation or treatment for a sexually transmitted disease, injection-drug use, and clinical hepatitis) should be retested at the time of admission to the hospital for delivery.[3,110]

Serologic Diagnosis

Acute Infection.

After infection, the first serologic markers to become detectable are HBsAg and IgM anti-HBc, which appear within 1 to 2 months and are present when initial symptoms appear (Fig. 213.2). IgM anti-HBc is diagnostic of recent HBV infection. The presence of HBeAg, also detectable in acute infection, reflects viral replication and increased infectivity.[3,109]

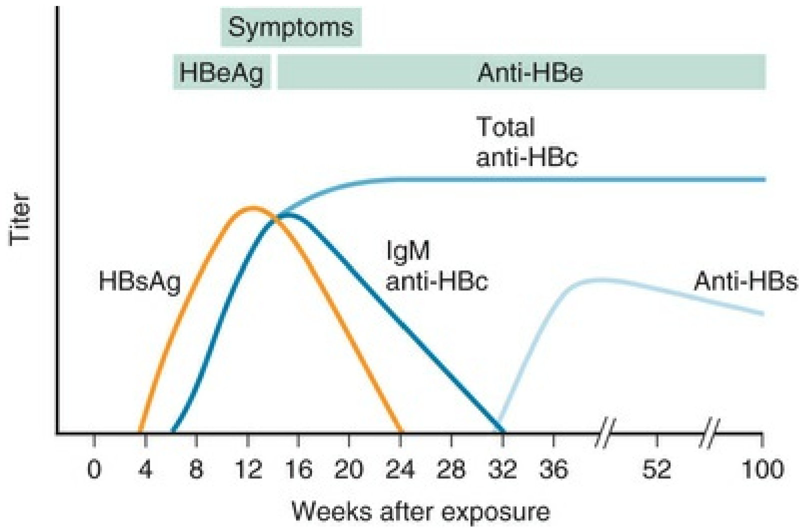

FIGURE 213.2 Serologic response to hepatitis B virus infection with recovery. Anti-HBc, antibody to hepatitis B core antigen; anti-HBe, antibody to hepatitis B e antigen; anti-HBs, antibody to hepatitis B surface antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; IgM anti-HBc, antibody of the immunoglobulin M subclass to hepatitis B core antigen.

Resolution of Acute Infection.

During resolution of acute infection, IgM anti-HBc is replaced by antibody of the IgG subclass (IgG anti-HBc), and anti-HBs develops (see Fig. 213.2). Anti-HBs is a protective, neutralizing antibody, and its presence indicates recovery from acute infection and immunity to reinfection. The period when all HBsAg has been neutralized by anti-HBs, and neither HBsAg nor anti-HBs is detectable, is referred to as the *window period*. During the window period, the only serologic marker of infection is IgM anti-HBc. During resolution, anti-HBe replaces HBeAg. In people with past HBV infection, IgG anti-HBc usually remains detectable for life, but anti-HBs might become undetectable in remote infection.[3,109]

Chronic Infection.

In chronic infection, HBsAg persists for >6 months, and anti-HBs does not develop (Fig. 213.3). People initially identified as HBsAg positive should be retested 6 months later to document clearance or chronic infection. Similar to acute infection with resolution, in chronic infection, IgM anti-HBc disappears and is replaced by IgG anti-HBc. HBeAg is variably present in chronic infection. When HBeAg is not present, anti-HBe usually is detectable.[3,109]

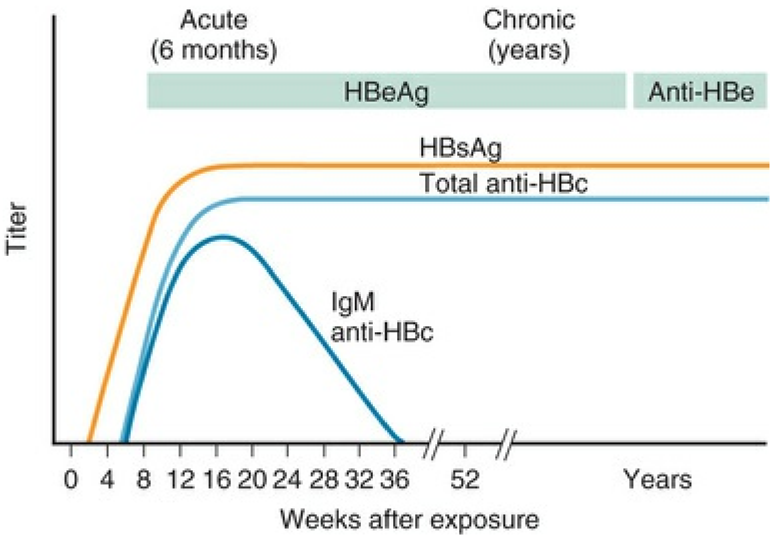

FIGURE 213.3 Serologic response to hepatitis B virus (HBV) infection with progression to chronic HBV. Anti-HBc, antibody to hepatitis B core antigen; anti-HBe, antibody to hepatitis B e antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; IgM anti-HBc, antibody of the immunoglobulin M subclass to hepatitis B core antigen.

Perinatal Infection.

Maternal HBsAg generally does not cross the placenta; therefore, HBsAg found in serum of an infant shortly after birth usually indicates infection but can result from specimen contamination or can occur transiently after vaccination.[111] IgG anti-HBc and anti-HBs are transferred from mother to fetus through the placenta, and neither is a useful diagnostic marker of infection in infants. Passively acquired maternal anti-HBs and anti-HBc antibodies usually disappear within the first 1 to 2 years of life.[112,113]

Special Serologic Considerations.

Anti-HBs, with no other serologic marker of infection, is present after hepatitis B vaccination. HBsAg alone, with no other markers of infection, might be present very early in infection, before development of IgM anti-HBc, or immediately after hepatitis B vaccination (see Fig. 213.2). Transient HBsAg positivity from vaccine antigen, within the first 3 weeks after vaccination, has been documented in infants, adolescents, and adults.[114–116]

Anti-HBc without other markers of infection might be detected in three situations: (1) false-positive result; (2) remote, past infection with the loss of detectable anti-HBs levels; or (3) chronic infection in which the HBsAg level is below the level of detection for commercial assays. In the latter situation, person-to-person transmission is unlikely to occur.[3,117]

Assessment, Monitoring, and Referral

Although chronic HBV infection in childhood usually is asymptomatic, sequelae can become manifest in adolescence or adulthood. Chronically infected children are at increased risk for developing cirrhosis and HCC; as such, they require lifelong monitoring for disease progression.[3,84]

HBsAg-positive people should be retested 6 months later to determine whether they have developed chronic infection. Initial evaluation of chronically infected children includes laboratory testing for serum ALT, white blood cell (WBC) count, platelet count, HBeAg, anti-HBe, HBV DNA, and α-fetoprotein (AFP) level. Hepatitis B serology and serum ALT level are used to determine the phase of chronic infection. Decreased WBC and platelet counts can indicate liver fibrosis; AFP is a nonspecific marker for HCC. Family history of liver cancer and liver disease should be elicited and a baseline hepatic ultrasound performed.[84]

An expert panel commissioned by the Hepatitis B Foundation recommends that children in the immune tolerant and immune inactive phases of chronic infection have serum ALT and AFP levels tested every 6 to 12 months and HBeAg and anti-HBe tested annually. To determine whether children in the immune inactive phase have entered the reactivation phase, annual HBV DNA testing also may be useful. Children with elevated ALT, elevated AFP (≥10 ng/mL), or a family history of liver cancer or liver disease and children in the reactivation phase should be referred to a pediatric liver specialist for further evaluation.[84]

Treatment

No specific treatment is available for people with acute HBV infection. Neither HBIG nor corticosteroids are effective.[118,119]

An expert panel commissioned by the Hepatitis B Foundation recommends treatment for children with chronic infection based on serum ALT levels, age, liver biopsy findings, comorbidities, and family history of liver disease or liver cancer. Children with normal serum ALT levels should be monitored regularly. Persistently elevated serum ALT levels are defined as >1.5 times the laboratory upper limit of normal or >60 IU/mL, whichever is lower, on at least 2 occasions over 6 months in HBeAg-positive children or on at least 3 occasions over 12 months in HBeAg-negative children. Children with persistently elevated ALT levels are divided into 2 categories: children in the immune active phase and those in the reactivation phase. Treatment is indicated for children in the reactivation phase with persistently elevated serum ALT levels and moderate to severe hepatic inflammation or fibrosis. Benefit from treatment is unclear among children in the immune active phase with elevated serum ALT levels and minimal or mild hepatitis inflammation or fibrosis.[120]

Treatment response is not assessed until at least 6 months after completion of therapy. A response usually is defined as clearance of HBeAg. Other measurable markers of response are (1) development of anti-HBe, (2) clearance of HBsAg, (3) normalization of serum ALT levels, (4) reductions in serum levels of HBV DNA, and (5) improvement in histologic features of the liver.[105] The natural history of chronic HBV infection is an important consideration in the evaluation of results from clinical trials because spontaneous improvement occurs in many untreated patients.[121]

US Food and Drug Administration (FDA)-approved therapies for chronic hepatitis B are IFNα-2b, pegylated IFNα-2a (PEG-IFNα-2a), lamivudine, adefovir, entecavir, tenofovir, and telbivudine. The youngest age of approved use is 1 year for IFNα, 2 years for lamivudine, 12 years for adefovir, 2 years for entecavir, 12 years for tenofovir, and 16 years for telbivudine. PEG-IFN is not licensed for use in children with chronic HBV infection.[122]

Interferon-Based Therapies

Although few data are available for children treated with IFNα, some experts regard it as the drug of choice for patients aged 1 to 12 years with compensated liver disease. Available studies in Western countries report success (defined as HBeAg seroconversion) in 20% to 58% of treated children and 8% to 17% of untreated, control subjects.[123–126] In a large randomized controlled trial, chronically infected children with consistently elevated serum ALT levels treated with IFNα for 6 months were more likely than untreated controls to lose HBeAg (35% vs. 11%) and HBsAg (10% vs. 1%). No difference in treatment success was reported between children born in Asian or Western countries. For children who responded to treatment, serum ALT levels normalized and liver histologic features improved. Five of 70 treated children had virologic response (loss of HBV DNA and HBeAg) after completion of therapy; therefore it is not appropriate to declare treatment failure or to initiate another therapy until at least 6 to 12 months after treatment unless signs of decompensation are present.[126] A meta-analysis of 6 other studies concluded that children treated with IFNα had significantly increased clearance of HBV DNA and HBeAg compared with untreated controls.[127] In addition, other studies have shown that children younger than 5 years have improved response to treatment.[124,128]

Generally, IFNα is administered thrice weekly for 6 months for pediatric patients. Adverse effects of IFNα can be moderate to severe, including fever, headache, myalgia, neutropenia, worsening hepatitis, and depression or irritability, limiting a patient's ability to tolerate full doses or to complete a course of treatment. IFN therapy is contraindicated in patients with cirrhosis; therapy has been associated with exacerbation of hepatitis and hepatic decompensation.[120] Development of resistance has not been observed.

Antiviral Agents

Nucleoside and nucleotide analogues have emerged as alternative treatments for chronic hepatitis B. These agents have fewer adverse events than IFN-based therapies, although they induce resistant mutations.[84,120–141]

A randomized clinical trial indicated that chronically infected children with elevated serum ALT levels who received oral lamivudine once daily for 52 weeks were significantly more likely to have a virologic response compared with children receiving placebo (23% vs. 13%).[142] This response was maintained in 89% of participants at 24 months after discontinuing therapy. Patients from this study who did not respond to 1 year of treatment were continued for 24 additional months. Further clinical response was observed at 3 years, with an additional 21% achieving a virologic response. However, lamivudine resistance developed in 19%, 49%, and 64% of participants at 1, 2, and 3 years, respectively.[142,143] Children were followed for an additional 2 years (5 years total); 75% of controls maintained HBeAg seroconversion compared with 82% who received 1 year of treatment and 90% who received at least 2 years of treatment. Elevated serum ALT levels before treatment were associated with treatment success.[144] Lamivudine treatment was well tolerated.[142,143] Because lamivudine selects for mutations in the HBV polymerase (*YMDD* mutants), its usefulness as monotherapy may be limited. The optimal duration of therapy with lamivudine is unknown; children with HBeAg-positive chronic HBV infection should continue treatment for at least 6 months after seroconversion. The risk for virus-resistant mutants increases substantially over time; therefore discontinuation of lamivudine should be considered if there is incomplete viral suppression after 24 weeks of therapy, especially in the absence of advanced liver disease.[84,120,129,132,135]

In a randomized controlled study of adefovir, 173 HBeAg-positive children with elevated serum ALT levels were treated for 48 weeks. Children aged 12 to 17 years in the treatment group reached the treatment end point (HBV DNA <1000 copies/mL and normal serum ALT levels) more often than the untreated controls (23% versus 0%). Treated children aged 2 to 11 years did not have a significantly different outcome from untreated counterparts. No viral mutations were noted among any of the treated children, and treatment generally was well tolerated.[145]

Management of Patients With Chronic Hepatitis B Virus Infection and Their Contacts

Chronically infected patients should be counseled to limit alcohol consumption to avoid acceleration and progression of disease and should be immunized against hepatitis A.[146] Household, sexual, and needle-sharing contacts of chronically infected people should be identified. Unvaccinated contacts should be screened and receive the first dose of hepatitis B vaccine; contacts who are susceptible should complete the vaccination series. Sex partners of HBsAg-positive people should be counseled to use methods to protect themselves from sexual exposure until they are proved nonsusceptible.[3,109]

Special Considerations

There are special circumstances for which data from randomized controlled trials are unlikely to be available (e.g., pregnant adolescents, organ transplant recipients, and persons undergoing chemotherapy). These are cases for which individualized clinical judgment based on the best available information must be applied.[120,129]

Prevention

Hepatitis B vaccination has resulted in a significant decrease in incident hepatitis B cases in the US (see Fig. 213.1). Incidence has decreased most notably among children and adolescents since the 1991 Advisory Committee on Immunization Practices recommendation for universal infant hepatitis B vaccination, and later recommendations for vaccinating older unvaccinated children and adolescents.[12,147]

Vaccines and Schedules

Hepatitis B (HepB) vaccines are composed of HBsAg adsorbed to an adjuvant of aluminum hydroxide or aluminum hydroxyphosphate sulfate.[148,149] HBsAg elicits development of the neutralizing antibody, anti-HBs, which confers protection from infection. Plasma-derived vaccines were manufactured from HBsAg purified from the plasma of persons with chronic HBV infection. Recombinant vaccines have replaced plasma-derived vaccines and are produced through the insertion of the gene for HBsAg into yeast cells (*Saccharomyces cerevisiae*, or baker's yeast) and, less commonly, mammalian cells (Chinese hamster ovary cells). Recombinant vaccines are considered equivalent to plasma-derived vaccines in their immunogenicity and effectiveness. HepB vaccines are formulated to contain 5 to 40 μg of HBsAg protein per dose of vaccine and in the US do not contain the preservative thimerosal.[3,109,148,149]

In the US, DTaP-HepB-IPV is the only combination vaccine currently licensed for use in pediatric populations (infants and children through 10 years of age).[150–152] Combination vaccines should not be administered to infants younger than 6 weeks; monovalent HepB should be used for the birth dose.[3,109]

HepB typically is administered as a 3-dose series on a variety of vaccination schedules. In the US, the recommended schedule is administration of a first dose, followed by a second dose in 1 to 2 months, and a third dose 6 to 18 months after the first dose (i.e., 0, 1–2, and 6–18 months). For routine infant immunization, the first dose of vaccine should be administered at birth before hospital discharge, and the third dose should not be given before 6 months (24 weeks) of age. When DTaP-HepB-IPV is used to complete the series, a total of 4 doses of HepB are administered.[3,109] A 2-dose series for adolescents aged 11 to 15 years and a 4-dose series also are approved for use in the US.[3,109,153]

Prevention of Perinatal Hepatitis B Infection.

Infants born to HBsAg-positive women have a 90% risk for developing chronic infection if infected at birth. Infants not infected at birth remain at risk from transmission within the household. HepB combined with HBIG is highly effective in preventing perinatal and household HBV transmission when administered within 12 hours of birth and followed by completion of the vaccination series. Although HBIG should be administered if maternal HBsAg-positive status is learned through the infant's first week, every attempt should be made to administer HBIG within 12 hours of birth. HBIG should be administered in a separate site from the vaccine. HepB administered at birth, with or without HBIG, eliminates any theoretical risk for virus transmission through breastfeeding (Box 213.1).[3]

Box 213.1

Immunization Strategy to Eliminate Perinatal Hepatitis B Virus Transmission in the United States

Routine screening of all pregnant women for hepatitis B surface antigen (HBsAg), *plus*

Immunoprophylaxis of infants born to HBsAg-positive women and infants born to women with unknown HBsAg status

Universal routine vaccination of infants, beginning at birth

Infants born to HBsAg-positive pregnant women should receive postvaccination serologic testing (anti-HBs and HBsAg) at 1 to 2 months after completion of the vaccination series to determine their response to vaccination and their chronic HBV infection status. Infants who fail to respond to an initial HepB series, and are not infected, should be revaccinated with 3 additional doses and retested. Infants who develop chronic HBV infection should be referred for appropriate follow-up and care.[3]

A high HBV viral load (HBV DNA $\geq 10^8$ copies/mL) during pregnancy is associated with an increased risk for perinatal transmission despite appropriate infant postexposure prophylaxis. Some evidence suggests that antiviral treatment of these HBsAg-positive women during the third trimester of pregnancy might lower perinatal transmission risk.[50,154] However, no current recommendation exists for routine determination of viral load among HBsAg-positive pregnant women.[3,50]

Immunization of Infants With Birth Weight <2000 Grams.

Routine HepB immunization of preterm infants born to HBsAg-negative women weighing <2000 grams at birth should be delayed until the infant is 1 month of age or is discharged from the hospital, whichever is first; the 3-dose series should then be completed. If the infant's mother is HBsAg positive or her HBsAg status is unknown, the infant should receive HepB and HBIG within 12 hours of birth and complete 3 additional doses.[109] The birth dose does not count as part of the vaccine series for infants weighing <2000 grams.[3]

Vaccine Dosage and Administration.

The vaccine dosage varies by manufacturer and age of recipient. The typical dosage for infants, children, and adolescents ranges from 5 to 10 µg, and for adults from 10 to 20 µg.[3,109] A dosage of 40 µg is recommended for people with certain immunocompromising conditions such as those on hemodialysis.[109,155]

Vaccine Immunogenicity and Efficacy.

A seroprotective immune response to HepB is defined as development of anti-HBs ≥10 mIU/mL at 1 to 2 months after completion of the vaccine series. HepB is highly immunogenic, with seroconversion rates of ≥95% in healthy infants, children, and adolescents after completion of the 3-dose series.[156,157] Seroconversion rates vary, however, depending on the number of doses in the vaccine series, with much lower seroconversion after 1 dose compared with after series completion. Concurrent administration of HBIG does not reduce seroconversion rates. Lower rates of seroconversion are associated with prematurity, older ages (>40 years), and diabetes or other immunocompromising conditions.[158,159] In studies among infants and children infected with HIV, 20% to 78% attained seroprotective levels of anti-HBs after series completion.[160–165]

HepB starting at birth is 70% to 90% effective in preventing perinatal HBV infection, and HBIG administered within 12 hours of birth with completion of the vaccine series is 85% to 95% effective.[166,167]

Prevaccination and Postvaccination Testing.

Prevaccination testing for immunity is not indicated before routine vaccination of infants, children, and adolescents. However, children born in high- or intermediate-endemic countries should be tested before the first dose of vaccine is given.[65]

Because HepB is highly immunogenic, postvaccination serologic testing is not indicated after routine vaccination, except for the following groups: (1) infants born to HBsAg-positive mothers; (2) healthcare personnel; (3) persons with HIV and other immunosuppressive conditions, including those undergoing long-term hemodialysis; and (4) sex partners of HBsAg-positive people.[109,155,168] Postvaccination serology should be performed 1 to 2 months after administration of the last dose of vaccine. In people who do not respond to the primary series (i.e., anti-HBs concentration <10 mIU/mL), revaccination is recommended. Revaccination (usually 3 doses) is not associated with an increase in adverse events and substantially increases the rates of seroprotection in low responders or nonresponders. People who do not respond to a second series should be tested for HBsAg to determine whether they are chronically infected. Persons who are not chronically infected and do not respond to two vaccine series are unlikely to respond to further vaccination.[109,168]

Vaccine Safety.

The safety of HepB has been demonstrated in a large, prospective clinical trial[169] and in postlicensure safety analyses.[170] Pain at the injection site and increased temperature of >37.7°C are the most frequently reported adverse events.[169] The incidence of anaphylaxis to HepB is estimated to be 1 case per 1.1 million doses of vaccine distributed.[171] Several case reports of demyelinating or other neurologic diseases temporally associated with HepB have been reported, but no association has been observed in large, controlled studies.[172–175] Expert reviewers have found no supportive evidence for an association between HepB and neurologic disease.[176–178]

HepB is contraindicated for people with a history of hypersensitivity to yeast or to any vaccine component.[109] Pregnancy is not a contraindication to vaccination. Persons with a history of a serious adverse event (e.g., anaphylaxis) after receipt of HepB should not receive additional doses.[3,109]

Hepatitis B Immune Globulin and Postexposure Prophylaxis

HBIG is prepared from plasma containing high concentrations of anti-HBs. HBIG provides short-term protection (i.e., 3 to 6 months) from infection.[3,109,168] Currently, HBIG administered in conjunction with HepB is recommended for (1) infants born to HBsAg-positive mothers (or infants with birth weight of <2000 grams born to mothers with unknown HBsAg status)[3]; (2) unvaccinated sexual or needle-sharing contacts of an HBsAg-positive source person[109]; (3) unvaccinated persons with a percutaneous or mucosal exposure to HBsAg-positive blood or body fluids[109]; and (4) certain healthcare personnel after exposure to an HBsAg-positive (or unknown) source patient.[168] Administration of HBIG alone is the primary means of protection after exposure to HBV in known nonresponders to vaccination.[109,168] HBIG also is used in patients with HBV-related chronic liver disease who have undergone liver transplantation to reduce the incidence of recurrent HBV infection.[179]

Long-Term Protection

HepB provides long-term protection against HBV infection. Despite the loss of detectable levels of anti-HBs, immunocompetent persons who responded to vaccination remain protected, and a booster dose of vaccine is not recommended currently.[109,155,180–186] In most studies among infants and children who responded to the primary vaccine series, 40% to 85% had detectable levels of anti-HBs 10 to 22 years after vaccination.[187–199] Although breakthrough infections have been observed in a small proportion of children and adolescents as evidenced by development of anti-HBc, chronic infection (i.e., development of HBsAg) occurred rarely, and there were no reports of clinically apparent acute hepatitis B. Long-term studies among vaccinated adults have shown similar findings.[198,200,201]

Long-term protection from HepB is thought to be related to sensitization of B lymphocytes to HBsAg in the vaccine and development of an anamnestic antibody response on HBV challenge.[184,186] Booster dose studies have been used to simulate natural infection with HBV. In studies of children and adolescents who were vaccinated in infancy and childhood and who had a documented response to the primary vaccine series and lost detectable levels of anti-HBs, most (>90% in most studies) responded to a booster dose of vaccine 10 to 15 years after the initial vaccine series.[187–189,195,196] In people with immunosuppressive conditions, vaccine-induced protection might persist only as long as antibody levels remain ≥10 mIU/mL. In hemodialysis patients, anti-HBs levels should be tested annually and booster doses given when antibody levels are <10 mIU/mL; for other immunocompromised people (e.g., HIV-infected persons and hematopoietic stem cell transplant recipients), repeat testing may be considered.[109]

Hepatitis Delta Virus

Pathogenesis

HDV is an RNA virus that was first detected in hepatocytes of patients infected with HBV. HDV is a unique pathogen that can only infect cells and cause disease in the presence of HBV. As such, HDV is classified as a satellite virus or subviral agent because of its inability to encode its own envelope protein. HDV encodes a single protein, the hepatitis delta antigen (HDAg), which is encapsulated with HBsAg encoded by HBV (Fig. 213.4). Because of the unique requirement for HBV, infections with HDV occur in two forms: HBV-HDV coinfection and HDV superinfection. In HBV-HDV coinfection, HBV and HDV are transmitted simultaneously to a person who is susceptible to HBV infection. People who are immune to HBV infection, through either prior infection or vaccination, cannot be infected with HDV. In HDV superinfection, HDV is transmitted to a person with preexisting chronic HBV infection, which provides the HBsAg needed to establish the HDV infection.

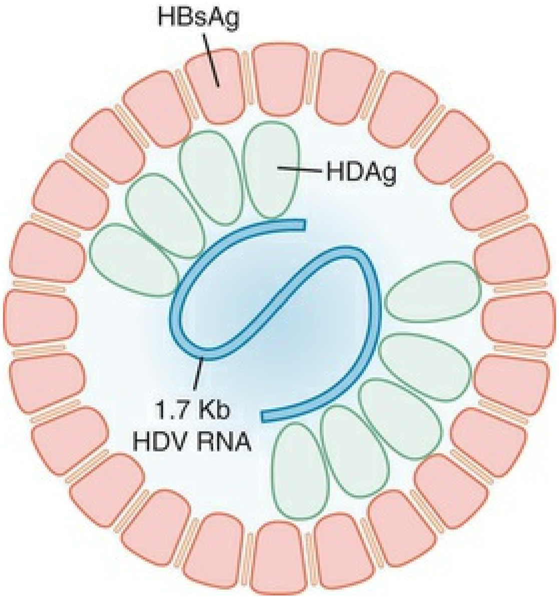

FIGURE 213.4 Schematic diagram of hepatitis D (delta) virus (HDV). HDAg, hepatitis D antigen; HBsAg, hepatitis B surface antigen.

Epidemiology

The epidemiology of HDV infection is similar to that of HBV infection. Percutaneous transmission of HDV is very efficient, as evidenced by the high prevalence of HDV among people who have frequent percutaneous exposures such as injection-drug users. An estimated 15 to 20 million people are infected with HDV worldwide, with areas of high endemicity in parts of the Mediterranean basin, the Middle East, Central Africa, and northern parts of South America.[202–204] In Western countries, prevalence of HDV infection can vary significantly among different populations of persons who inject drugs infected with HBV.[205,206] Hepatitis B vaccination can have a large effect on decreasing prevalence of HDV.[206] Although most HDV infections in low-endemic areas occur sporadically, outbreaks of HBV-HDV coinfection and HDV superinfection among injection-drug users and their sexual contacts have been described.[207] In high-endemic areas, transmission of HDV occurs primarily through person-to-person contact, especially in households, and usually results from HDV superinfection.

Clinical Manifestations

The incubation period for HBV-HDV coinfection ranges from 6 to 24 weeks. One feature that might distinguish HBV-HDV coinfection from other viral hepatitides is a biphasic course of illness, with two peaks of liver cell damage: the first is related to the appearance of HBV antigens in the liver, and the second to the appearance of HDV antigens. Approximately 2% of coinfected people become chronically infected.[208] In people HBV-HDV coinfection, fulminant hepatitis develops more often than in people with HBV monoinfection.[209]

The incubation period for HDV superinfection ranges from 2 to 8 weeks. Fulminant hepatitis occurs more often with HDV superinfection than with acute HBV infection alone.[210] In contrast to HBV-HDV coinfection, HDV superinfection results in chronic HDV infection in up to 90% of patients, and most patients progress to cirrhosis.[211,212]

Laboratory Findings and Diagnosis

HDV-infected people produce both IgM and IgG antibodies to the hepatitis delta antigen (anti-HDV). During acute HBV-HDV coinfection, antibodies are produced to both HBV and HDV antigens, but the anti-HDV response often is weak and might be delayed by several months. Because anti-HDV might not be present until several weeks after onset of illness, diagnosis of HDV infection might require testing of acute and convalescent sera; HDV infection also can be diagnosed using polymerase chain reaction assays.[213] Anti-HDV often does not persist, making diagnosis of past coinfection difficult. In contrast, HDV superinfection produces a brisk anti-HDV response that persists throughout chronic infection.[214] Acute HBV-HDV coinfection usually can be distinguished from HDV superinfection by the presence of IgM anti-HBc. The IgM anti-HDV response is not useful for distinguishing acute from chronic HDV infection because IgM anti-HDV production persists throughout chronic infection.[215]

Treatment

IFNα-2a is the only therapy approved by the FDA for chronic HDV infection. Data are limited on the effectiveness of IFNα in children. In a study using 3 to 5 MU/m^2 of IFNα, clearance of HDV viremia occurred in 2 (15%) of 13 children treated for 24 months; however, no significant improvement in liver histology was noted.[216]

Liver transplantation for end-stage chronic HDV infection has a 5-year survival rate as high as 88%. The success of liver transplantation for chronic HDV infection is attributed to the suppressive effect of HDV on HBV replication, which greatly reduces the posttransplantation HBV reinfection rate in the grafted liver. When HBIG is used for prophylaxis before liver transplantation for chronic HDV infection, the HBV-HDV reinfection rate is about 10%, compared with close to 100% HBV reinfection rate due to HBV alone.[217]

Prevention

Hepatitis B vaccine is the single most important tool to prevent HBV-HDV coinfection. Administration of HepB, and HBIG if indicated, at birth provides protection against HBV infection and HBV-HDV coinfection.[109] No vaccine exists to prevent HDV superinfection in HBV-infected persons; prevention depends on modification of behaviors, such as safer sexual and drug-injection practices.

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DNA Viruses: Parvoviridae

OUTLINE

214 Human Parvoviruses

214

Human Parvoviruses

Kevin E. Brown

Parvoviruses, small (20 to 25 nm), nonenveloped, icosahedral, single-stranded DNA viruses with a linear genome of between 4500 and 5600 nucleotides, are common infectious agents of animals, including birds and insects, as well as humans.[1] At least five different genera of parvovirus have been detected in humans: bocaparvoviruses; dependoparvoviruses; erythroparvoviruses; protoparvoviruses; and tetraparvoviruses. Human bocavirus (HBoV)[2] has been identified in respiratory secretions of young children with acute wheezing and lower respiratory tract infections.[3] However, the contribution of HBoV as an etiologic pathogen for respiratory disease currently is unclear because HBoV often is found in the presence of other pathogens.[4,5] Dependoparvoviruses are nonpathogenic, and the role of the human partetraviruses (Parv4/5[6]) found in blood and the protoparvoviruses (Bufavirus,[7] Tusavirus[8]) is unclear. Parvovirus B19 (B19V), a member of the *Erythroparvovirus* genus, is the best characterized human parvovirus and is the cause of erythema infectiosum, transient aplastic crisis, pure red cell aplasia, and hydrops fetalis and is the focus of this chapter.

Microbiology and Pathogenesis

The single-stranded DNA genome encodes one major nonstructural protein,[9] which mediates cytotoxicity,[10] and two capsid proteins, VP1 and VP2, which self-assemble to form virus-like particles in vitro.[11] Based on the viral sequence, B19V can be divided into three distinct genotypes (genotypes 1, 2, and 3),[12] but all cause similar disease patterns, and there is serologic cross-reactivity—and thus a single serotype has been described.[13]

B19V is highly erythrotropic with efficient viral replication only occurring in late erythroid precursor cells. Virus-induced cytotoxicity therefore results in arrest of red cell production and reticulocytopenia. In patients who have increased erythropoiesis, such as those with sickle cell or hemolytic anemia, B19V infection may induce a transient aplastic crisis. In patients who are immunosuppressed and unable to mount an appropriate neutralizing antibody response, B19V infection can cause pure red cell aplasia and chronic anemia.

The erythroid specificity is in part due to the tissue distribution of the receptor for B19V, the blood group P antigen, also known as *globoside*.[14] This antigen is found in the erythrocyte precursors in bone marrow as well as in a variety of other tissues, including megakaryocytes, endothelial cells, placenta, fetal myocardium, and fetal liver. Rare individuals who lack blood group P antigen are naturally resistant to parvovirus B19 infection.[15] Some of the clinical consequences of B19V infection, including the rash, are immune mediated.

After infection there is a brisk viremia, which peaks at $>10^{12}$ virus particles (international units)/mL of blood (Fig. 214.1). Viremia often is accompanied by a nonspecific febrile illness. In immunocompetent individuals, an immunoglobulin M (IgM) and IgG antibody response is mounted, and the concentration of virus in blood drops. The second, immune-mediated phase of illness coincides with the antibody response (see Fig. 214.1). Typical manifestations of this phase of the illness are the rash of fifth disease, arthralgia, and arthritis. In normal immunocompetent hosts, infection resolves, although low levels of B19V DNA can be detected by polymerase chain reaction (PCR) in blood and tissues for months to years after acute infection.[16–18] Chronic, high-level viremia can occur in immunocompromised individuals, who do not make neutralizing antibody (see Fig. 214.1).[19]

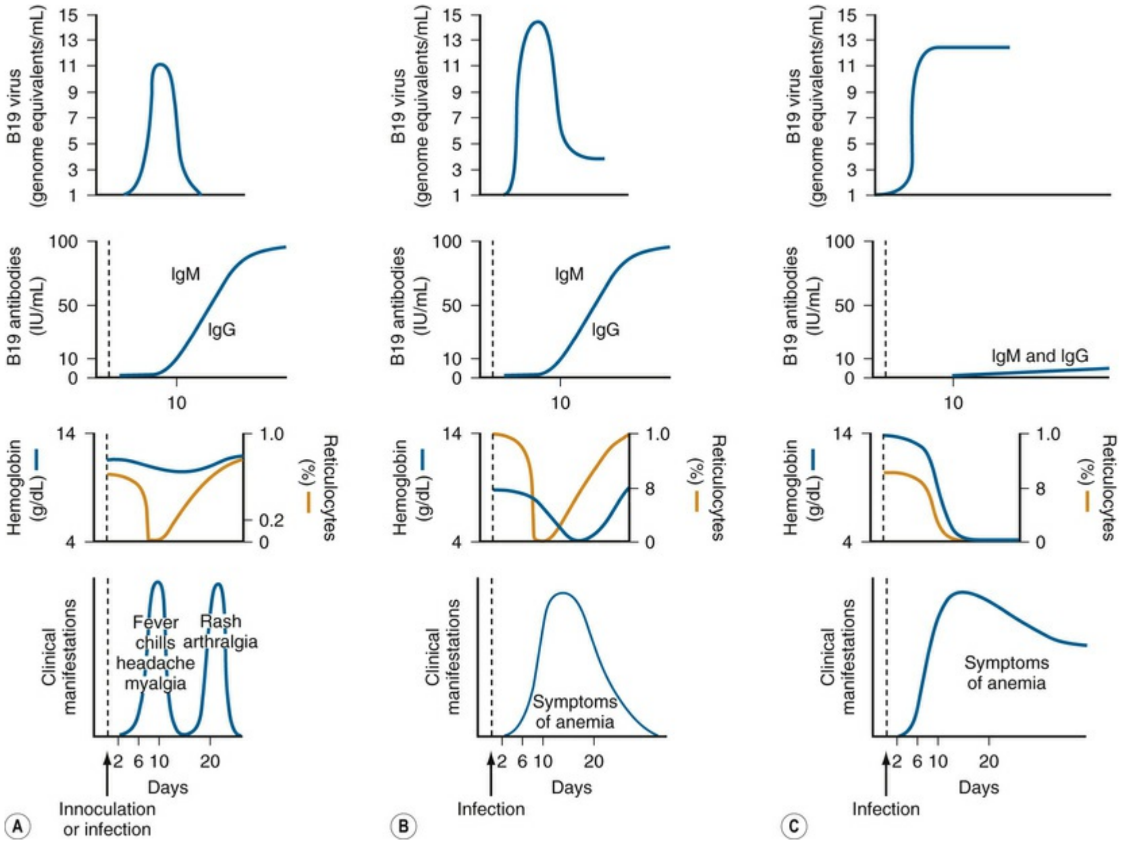

FIGURE 214.1 Schematic of the time course of parvovirus B19 infection, showing the associations of viremia, antibody production, and clinical symptoms in three groups of individuals: (A) fifth disease; (B) transient aplastic crisis; and (C) chronic bone marrow failure. IgG, immunoglobulin G; IgM, immunoglobulin M. (Redrawn from Young NS, Brown KE. Parvovirus B19. N Engl J Med 2004;350:586–597.)

Epidemiology

Key Points

Parvovirus B19

Epidemiology

- Parvovirus B19 (B19V) infection is common worldwide
- In temperate climates, most infections occur in the spring, with epidemics occurring every several years
- Approximately 50% of persons aged ≥15 years have evidence of

past infection

- Transmission is predominantly through the respiratory route, although transmission through blood and blood products can occur

Pathogenesis

- B19V replication occurs in late erythroid progenitor cells in bone marrow, leading to cessation of red cell production

Clinical Features

- Depend on host immune and hematopoietic status

Treatment and Prevention

- No specific antiviral treatment

- B19V vaccine in development

Parvovirus B19 infection is a common illness of childhood; by 15 years of age, approximately 50% of children have detectable IgG antibody.[20,21]

In temperate climates, most infections occur in the spring, with mini-epidemics occurring at regular intervals several years apart.[22,23] The highest risks for transmission are between close contact within households and schools,[24] and secondary infection rates approach 50% in households.[25] Transmission is predominantly through the respiratory route, probably by droplet spread, and is highest at the time of viremia, before the onset of rash or arthralgia.

Persons who have hemolytic anemias or decreased red cell production are at increased risk for severe anemia or transient aplastic crisis when infected with B19V. Globally, many children have severe anemia due to malaria, chronic parasitic infections (e.g., hookworm), and nutritional deficiencies (e.g., iron, vitamin A, vitamin B_{12}). Studies investigating the relationship between parvovirus B19 and these conditions indicate that B19V infection may be an important contributor to severe anemia, especially in malaria endemic regions.[26–31]

B19V infections also can occur as a result of transfusion of blood or blood products.[32] Most reported cases of transfusion-related infection are due to pooled components, especially factor VIII and IX concentrate, rather than individual units. B19V is resistant to both heat and solvent-detergent inactivation.[33] In July 2009, the US Food and Drug Administration issued a guidance for nucleic acid testing of blood to reduce the risk for transmission of B19V by plasma-derived products. Other countries have similar policies.[34]

Clinical Manifestations

Most infections caused by B19V are asymptomatic or mild. When infection is associated with symptoms, a variety of disease manifestations, depending on the immune status of the host, can be observed (Table 214.1).

TABLE 214.1

Diseases Associated With Human Parvovirus B19 Infection

Disease	Acute or Chronic	Host(s)
Fifth disease (erythema infectiosum)	Acute	Normal children
Polyarthropathy syndrome	Acute	Normal adults
Transient aplastic crisis	Acute	Patients with increased erythropoiesis
Persistent anemia	Chronic	Immunodeficient or immunocompromised patients
Hydrops fetalis or congenital anemia	Chronic	Fetus (<20 weeks)

Erythema Infectiosum

Key Points

Erythema Infectiosum (Fifth Disease)

Epidemiology

- Common presentation in childhood

Clinical Features

- Initially, a nonspecific febrile illness

- Classical slapped cheek appearance only seen in children
- Followed by lacy rash over rest of body
- Joint pain or arthritis can accompany rash

Diagnosis

- Difficult to distinguish from other childhood exanthems
- Laboratory diagnosis by detection of parvovirus B19–specific immunoglobulin M antibody

Treatment

- Symptomatic treatment only

The most common manifestation of B19V infection is erythema infectiosum (also known as *fifth disease,* or *slapped cheek disease*), a mild febrile illness with rash.[35] Studies in adult volunteers demonstrated a minor febrile illness that began about 8 days after nasal inoculation of virus and was associated with mild hematologic abnormalities during the second week and facial rash at 17 to 18 days (see Fig. 214.1A).[36]

After the appearance of the classical "slapped cheek" rash (Fig. 214.2), the rash can spread to the trunk and limbs, often in a lacy reticular pattern (see Fig. 214.2B). The rash can be exacerbated by exercise, emotion, hot baths, or sunlight. The intensity and distribution of the rash varies. Among adults, the slapped cheek rash may not be apparent. The rash can be difficult to appreciate in dark-skinned individuals, or to distinguish from other viral exanthems, such as rubella (see Fig. 214.2D).

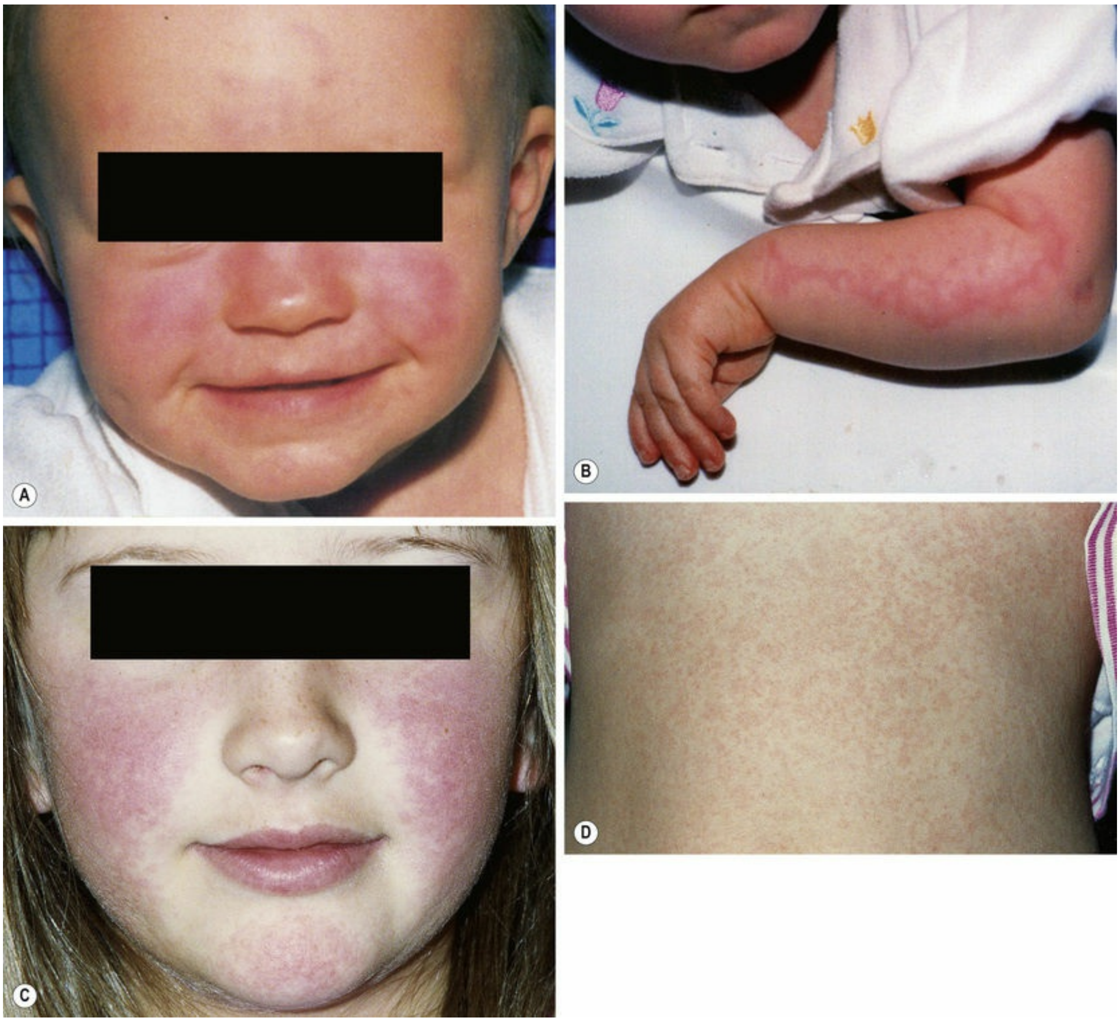

FIGURE 214.2 Toddler (A, B) and child (C, D) with typical exanthems of fifth disease. (Courtesy of J. H. Brien© and M. Prober.)

Polyarthropathy Syndrome

Although uncommon in children, arthropathy occurs in about 50% of adults and is more common in women than men.[37] The joint distribution often is symmetric, with arthralgia and even frank arthritis affecting the small joints of the hands and occasionally the ankles, knees, and wrists. Resolution usually occurs within a few weeks, but persistent or recurring symptoms can continue for years. Rarely B19V infection can be associated with chronic arthritides, including juvenile idiopathic arthritis.[38,39]

Transient Aplastic Crisis

Transient reticulocytopenia followed by rebound reticulocytosis occurs in most subjects infected with parvovirus B19.[40] This transient marrow suppression is not associated with symptoms in most individuals. However, among those who depend on continual rapid production of red blood cells, parvovirus B19 infection often causes transient aplastic crisis (see Fig. 214.1B).[25] Affected individuals include those with hemolytic disorders (e.g., hereditary spherocytosis), hemoglobinopathies (e.g., sickle-cell disease, thalassemia), red cell enzymopathies (e.g., glucose-6′-phosphate dehydrogenase deficiency, pyruvate kinase deficiency, pyrimidine-5′ nucleotidase deficiency) and autoimmune hemolytic anemias.[41] Aplastic crises precipitated by parvovirus B19 infection often necessitate treatment with blood transfusions and can be associated with a high rate of severe complications.[42] Patients with aplastic crisis have high levels of viremia, have no rash, and are infectious at the time of clinical presentation.[43]

Chronic Bone Marrow Failure and Pure Red Cell Aplasia

Key Points

Immunocompromised or Immunosuppressed Children

Epidemiology

- Can be acquired from respiratory secretions, blood, and blood products

Clinical Features

- Infection manifests as severe anemia.

- Other bone marrow lineages also can be affected.

Diagnosis

- Absence of reticulocytes in peripheral blood and red cell precursors in bone marrow

- Quantitative polymerase chain reaction for high-level ($>10^6$ IU/mL) parvovirus B19 (B19V) DNA in peripheral blood

- B19V-specific immunoglobulin M (IgM) and IgG antibody can be low level or absent.

Treatment

- Immune globulin intravenous

Persistent B19V infection resulting in pure red cell aplasia has been reported in a wide range of immunosuppressed patients, including those with congenital immunodeficiency (e.g., Nezelof syndrome), acquired immunodeficiency syndrome, and lymphoproliferative disorders (especially acute lymphoblastic leukemia), as well as transplant recipients.[41,44] Patients manifest persistent anemia associated with reticulocytopenia, absent or low levels of parvovirus B19–specific antibody, and high concentrations of parvovirus B19 DNA in serum (see Fig. 214.1C). Bone marrow examination often reveals the presence of scattered giant pronormoblasts. Temporary reduction of chemotherapy may result in an immune response to parvovirus B19 and resolution of infection. Alternatively, administration of immunoglobulin can lead to a prompt drop in viral DNA titers in the blood and resolution of infection.[45,46]

Other Hematologic Complications

Although parvovirus B19 primarily targets the red cell precursor, other hematologic lineages can be affected. Transient neutropenia, lymphopenia, and thrombocytopenia have been observed during acute parvovirus B19 infection.[36,41] Parvovirus infection can be associated with a hemophagocytic syndrome,[47] idiopathic thrombocytopenia, Henoch-Schönlein purpura, and papular purpuric gloves and socks syndrome.[48,49]

Transient erythroblastopenia of childhood and aplastic anemia do not appear to be caused by the virus.

Unusual Manifestations

A large number of unusual clinical presentations associated with detection of parvovirus DNA in serum and tissue have been reported, including neurologic disease, myocarditis, kidney disease, hepatitis, and a wide range of vasculitides.[49] However, the observation that parvovirus B19 DNA can be detected by PCR for years in normal tissue in healthy individuals confounds conclusion of a causal role.[16,50] B19V infection appears to be causally associated with some cases of childhood myocarditis.[51]

Infection and the Fetus

Maternal infection with B19V during pregnancy can lead to miscarriage or the development of hydrops fetalis.[52,53] The risk for adverse outcome primarily is associated with maternal infection occurring during the first half of gestation. In a British study of 427 pregnant women who contracted B19V infection during gestation, excess fetal loss was observed only among those infected during the first 20 weeks of pregnancy. The observed risk for fetal hydrops was 2.9% (95% confidence interval, 1.2–5.9),[54] with no abnormalities found at birth in surviving infants. Similar findings have been found in studies in other countries.[55–58]

Parvovirus B19 probably causes approximately 10% of all cases of nonimmune hydrops.[59–61] The pathogenesis is a combination of cardiac decompensation due to severe anemia and B19V-induced fetal myocarditis. Many cases of B19V-induced hydrops fetalis are treated with intrauterine blood transfusion, with high rates of success.[62–65]

B19V does not appear to be teratogenic, although anecdotal reports of possible eye damage and central nervous system abnormalities in infants whose mothers were infected with parvovirus B19 during pregnancy have been reported,[66] and cases of congenital anemia following maternal gestational infection have been described.[67,68]

Diagnosis

Key Points

Children With Increased Red Cell Turnover

Epidemiology

- Can be acquired from respiratory secretions, blood, and blood products

Clinical Features

- Infection manifests as transient aplastic crisis.
- Infection usually is self-limited, with production of neutralizing antibody.
- Aplastic crisis can lead to severe complications and can be life-threatening.

Diagnosis

- Absence of reticulocytes in peripheral blood and red cell precursors in bone marrow
- Quantitative polymerase chain reaction for high-level ($>10^6$ IU/mL) parvovirus B19 (B19V) DNA in peripheral blood
- B19V-specific immunoglobulin M (IgM) and IgG antibody can be absent at diagnosis.

Treatment

- Symptomatic treatment with blood transfusion as necessary

Parvovirus B19 is difficult to isolate in culture. Detection of virus in serum, tissues, or cells depends on detection of viral DNA, generally quantitative PCR.

Diagnosis of erythema infectiosum generally is based on the detection of IgM antibodies, which are detectable at the time of onset of the rash (see Fig. 214.1) Commercial assays, based on recombinant virus-like particles are sensitive and specific. IgM antibodies remain detectable for 2 to 3 months after primary infection.

IgG antibodies are detectable at the same time as IgM antibodies and remain detectable for life. Because >50% of the population has parvovirus B19 IgG antibodies, the test is not as useful for diagnosis of acute infection but can be helpful in determining prior infection or excluding the diagnosis.

Quantitative PCR assays are highly sensitive and specific tests that can be used to identify acute and chronic B19V infection. Because B19V DNA can be detected by PCR for many months after acute infection, quantitative PCR is critical, and the viral load can be useful in estimating the time of infection.[69] In acute infection, viremia peaks at $>10^{12}$ parvovirus B19 DNA genome copies/mL of serum and falls rapidly within days. Patients with aplastic crisis or pure red cell aplasia due to parvovirus B19 generally have $>10^{6}$ parvovirus B19 DNA international units (genome copies)/mL of serum at the time of the crisis.

Treatment and Prevention

No antiviral drug is licensed for treatment of B19V infection, although cidofovir has antiviral properties in vitro.[70] Because the humoral immune response plays a prominent role in controlling parvovirus B19 infection, commercial immune globulin preparations from healthy blood donors can clear or ameliorate persistent parvovirus B19 infection in immunosuppressed patients.[46,71] Treatment of patients with polyarthropathy is symptomatic only; administration of immunoglobulin is not beneficial. Patients with chronic anemia due to B19V infection, including fetuses with hydrops fetalis, are treated with blood transfusions.

Patient with the rash of erythema infectiosum are no longer infectious and do not need to be isolated. In contrast, persons with transient aplastic crisis or chronic parvovirus B19 infection have high levels of viremia and are contagious. For hospitalized persons, Droplet Precautions, in addition to Standard Precautions, are recommended. The duration of these precautions depends on clinical presentation and immunologic competency.[72]

No vaccine is approved for parvovirus B19, although research for a candidate vaccines is ongoing.[73,74] A vaccine would be advantageous in specific populations where parvovirus B19 potentially can cause substantial morbidity, such as those who are pregnant, immunocompromised, or have underlying hemolytic disorders or increased red cell production.

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RNA Viruses: Reoviridae

OUTLINE

215 Coltivirus (Colorado Tick Fever)
216 Rotaviruses

215

Coltivirus (Colorado Tick Fever)

J. Erin Staples, Marc Fischer

Colorado tick fever (CTF) is an acute febrile illness caused by the Colorado tick fever virus (CTFV). CTFV is a double-stranded RNA virus assigned to the *Coltivirus* genus of the family Reoviridae (Box 215.1).[1,2] The virus is transmitted to humans through the bite of an infected Rocky Mountain wood tick, *Dermacentor andersoni* (Fig. 215.1)

Box 215.1

Colorado Tick Fever: Agent and Epidemiology

Agent

Colorado tick fever virus, *Coltivirus* genus, Reoviridae family

Vector

Dermacentor andersoni, Rocky Mountain wood tick

Natural Reservoir

Rodent, small mammal–tick cycle

Distribution

Western United States and southwestern Canada at elevations from 4000 to 10,000 feet

Seasonality

March–September with an April–July peak

Risk Factors

Outdoor exposure in an endemic area

One transfusion-acquired case and 16 laboratory-associated cases reported

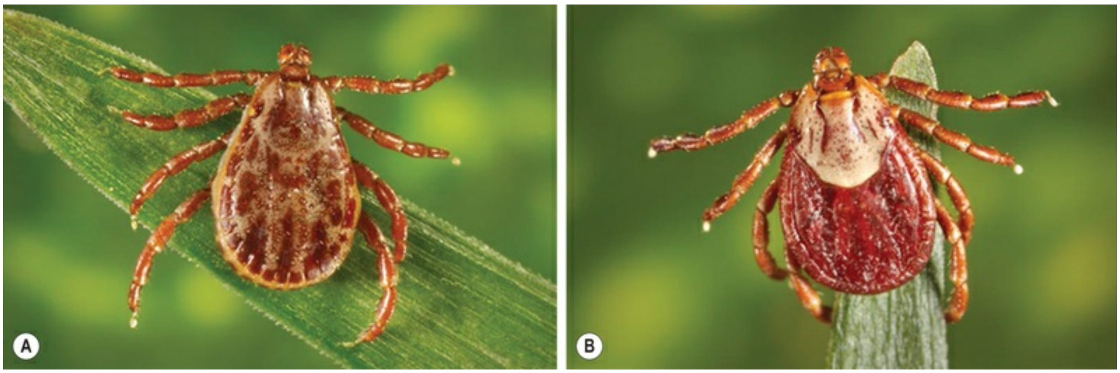

FIGURE 215.1 Both adult male (A) and female (B) *Dermacentor andersoni* ticks can transmit Colorado tick fever virus.

Tick Vector and Vertebrate Hosts

CTFV is maintained in an epizootic cycle between *D. andersoni* and small mammals, principally rodents.[3–13] The virus-amplifying mammal hosts develop apparently silent infections but remain viremic for weeks to months. Larval ticks become infected as a result of feeding on viremic mammals. Infection then passes from larval ticks to the nymphal and adult stages. Humans usually are infected by bites of adult ticks.[5,7,12]

Epidemiology

D. andersoni is found in the western United States and southwestern Canada at elevations from 4000 to 10,000 feet, typically in grassy areas near sage or other brush (Fig. 215.2).[3,8–12] Up to 90% of CTFV-infected persons report a recent history of tick bite or outdoor exposure in *D. andersoni*–endemic areas.[14–16] Most human cases occur between April and July.[14–17] Though CTF cases were originally reported more frequently among people aged 10 to 49 years, two recent studies found a higher proportion of CTF cases reported among adults aged ≥40 years.[14,16,17]

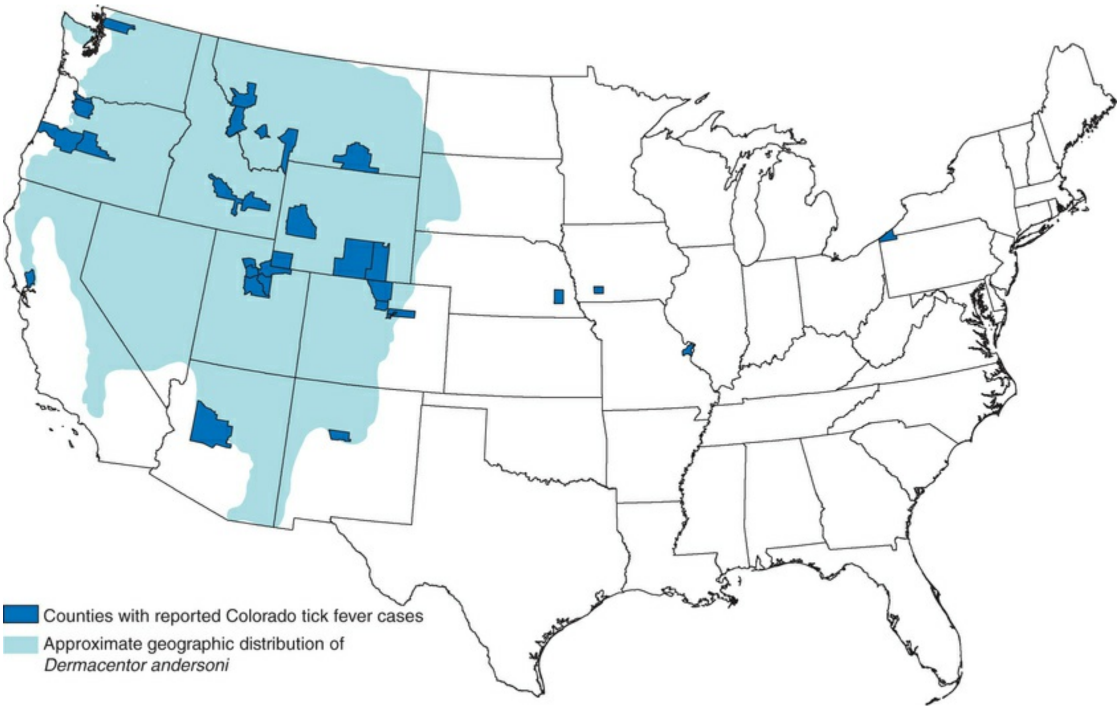
Counties with reported Colorado tick fever cases
Approximate geographic distribution of *Dermacentor andersoni*

FIGURE 215.2 Approximate geographic distribution of *Dermacentor andersoni* ticks and counties of residence for confirmed and probable Colorado tick fever virus disease cases, United States, 2002−2012. (*Light blue,* data from James AM, Freier JE, Keirans JE, Durden LA, et al. Distribution, seasonality, and hosts of the Rocky Mountain wood tick in the United States. J Med Entomol 2006; 43:17–24.)

CTF is not a nationally notifiable disease, but it is reportable in some states where the disease is endemic. From 2002 through 2012, 75 CTF cases were reported from 14 US state health departments, with Wyoming, Montana, and Utah reporting more than two thirds of cases (see Fig. 215.2).[17] These three states also had the highest annual incidence of reported CTF among residents, with 3.4 cases per million residents in Wyoming, 1.5 per million in Montana, and 0.5 per million in Utah.

From 1987 through 2001, a median of 55 CTF cases were reported in the United States.[8] However, that number declined consistently over the 15-year period, with a median of 80 cases annually from 1987 to 1994 and 18 cases per year from 1995 to 2001. From 2002 to 2012, the number of CTF cases has further declined, with a median of 5 cases per year.[17] This decrease in case counts over time likely reflects changes in testing and reporting practices. For example, Colorado historically reported the largest number of CTF cases.[8] However, CTF was not a notifiable condition in Colorado from 1997 to 2013, and during 2002 through 2012, Wyoming, Montana, Utah, and Oregon each reported more CTF cases than Colorado.[17] A survey in one endemic area suggested that only 10% of CTF cases were reported.[3] However, changes in the environment or human exposure also may have played a role.[9] One transfusion-acquired and 16 laboratory-associated cases of CTF have been reported.[18–23]

Clinical and Laboratory Findings

The incubation period for CTF is usually 3 to 4 days (range, 1−14 days).[3,14,15] Symptoms include fever, chills, headache, myalgias, and lethargy (Box 215.2).[14,15,24] Sore throat, vomiting, abdominal pain, and stiff neck are less common manifestations. Physical examination may reveal conjunctival injection, pharyngeal erythema, lymphadenopathy, or hepatosplenomegaly. A maculopapular or petechial rash has been reported in 5% to 16% of patients.[14,16,24]

Box 215.2

Colorado Tick Fever: Clinical Features

History

Recent tick bite or outdoor exposure in endemic areas within 2 weeks of illness onset

Incubation Period

Usually 3–4 days; range 1–14 days

Symptoms

Fever, chills, headache, myalgias, lethargy

Sore throat, vomiting, abdominal pain, and stiff neck are less common

Signs

Elevated temperature, conjunctival injection, pharyngeal erythema, lymphadenopathy, or mild hepatosplenomegaly

Maculopapular or petechial rash (5%–12% of cases)

Clinical Course

Fever and symptoms remit in 2–4 days

Recurrence of symptoms after 1–3 days (50% of cases)

Approximately 15%–30% of reported cases are hospitalized

Prolonged convalescence especially among persons >30 years old

Leukopenia is the most characteristic laboratory finding in CTF (Box 215.3).[14,24–26] There is often a relative lymphocytosis with atypical lymphocytes. Thrombocytopenia can occur.[15,27] CTFV infects erythrocytic precursors in the bone marrow. Although red blood cells remain infected for their lifespan, anemia is rare.[14,21,26,28] Patients with central nervous system involvement typically have lymphocytic pleocytosis and elevated protein in their cerebrospinal fluid.[15]

Box 215.3

Colorado Tick Fever: Complications, Laboratory Findings, and Diagnosis

Complications

Life-threatening complications and deaths rare and often associated with meningoencephalitis or disseminated intravascular coagulation

Hepatitis, pericarditis, myocarditis, pneumonitis, epididymo-orchitis also have been reported

Laboratory Findings

Leukopenia (2000–4000/mm^3) is the most characteristic laboratory finding

Relative lymphocytosis with atypical lymphocytes

Moderate thrombocytopenia (20,000–60,000/mm^3) common

Diagnosis

Viral isolation from whole blood or red blood cells

Immunofluorescent staining of peripheral blood smear

Reverse transcriptase-polymerase chain reaction (RT-PCR) assay on serum or whole blood

Serologic assays (e.g., indirect fluorescent antibody and plaque reduction neutralization)

About one half of all patients experience a biphasic illness. In these cases, symptoms remit after 2 to 4 days, but then recur 1 to 3 days later.[14,15,24] Patients often are bedridden, with 15% to 30% requiring hospitalization.[15–17] A prolonged convalescence characterized by weakness and fatigue is common but age dependent, with symptoms often continuing for >3 weeks in persons older than 30 years.[14]

Life-threatening complications and deaths due to CTF are rare; most fatalities have been associated with disseminated intravascular coagulation or meningoencephalitis.[3,13,15,17,24,29] Other reported complications include hepatitis, pericarditis, myocarditis, pneumonia, and epididymo-orchitis.[14,20,29–32] Teratogenic effects and fetal loss have been found in mice experimentally infected with CTFV, but this association has not been clearly established in humans.[3,33,34]

Diagnosis

A history of exposure to an enzootic location is the most helpful clue to the diagnosis. The differential diagnosis includes other vector-borne infectious diseases (e.g., tularemia, Rocky Mountain spotted fever, tickborne relapsing fever, and mosquito-borne arboviral fevers), and non–arthropod-borne infections such as enteroviruses and leptospirosis.[1,8] Distinguishing CTF from Rocky Mountain spotted fever can be difficult. However, a biphasic fever pattern, prominent leukopenia, and absence of a hemorrhagic rash all favor a diagnosis of CTF. The geographic distributions of other tickborne diseases such as human anaplasmosis (i.e., human granulocytic ehrlichiosis), human monocytic ehrlichiosis, and babesiosis have minimal overlap with that of CTF; therefore residence and travel history may help in the differentiation of these diseases.

CTFV can be isolated from whole blood or red blood cells in suckling mice or cell culture.[3,8,21,35] CTFV antigens also can be detected in peripheral blood smears by immunofluorescent staining.[36] Although culture and immunofluorescent staining are most sensitive during the acute illness, CTFV has been isolated from nearly 50% of patients 4 weeks after onset, and viral antigen can be detected in red blood cells in peripheral blood smears for up to 20 weeks.[14,21,35] Reverse transcriptase polymerase chain reaction (RT-PCR) assays can detect CTFV RNA in serum or whole blood reliably during the first 2 weeks of illness and for up to 6 weeks after onset.[17,37–39]

The most commonly used serologic assays for CTF are indirect fluorescent antibody and plaque-reduction neutralization testing.[1,37,40–42] Antibodies to CTFV are slow to develop, with <50% of patients having detectable antibodies by 2 weeks after illness onset.[17,40,41] However, by 30 days, >90% of patients have neutralizing antibodies, with titers peaking around 20 weeks after onset.[14,17] Other tests that have been used to detect CTFV antibodies include enzyme immunoassay (EIA), complement fixation, and Western blot. IgM antibodies measured by EIA usually do not appear until 14 to 21 days after illness onset and decline abruptly after 6 weeks.[1,40] Complement-fixing antibodies develop late after CTFV infection and are not detected in 25% of patients.[1,41]

Testing for CTFV and CTFV-specific antibodies are available only at a few laboratories. Many laboratory tests for CTF have not been adequately standardized or evaluated.

Treatment and Prevention

Patients with CTF should be given supportive care under standard infection control precautions. No specific therapy is available. Ribavirin variably inhibits CTFV growth in vitro,[43] but safety and efficacy data in humans are lacking. Patients with CTF should defer blood and bone marrow donation for at least 6 months after recovery.[8,21,44]

Residents or travelers with outdoor exposures in endemic areas should wear protective clothing, spray clothing with permethrin, apply repellent to exposed skin, and periodically check for and remove ticks.[3,8,10] CTFV should be handled under Biosafety Level 2 conditions to minimize risk for laboratory-acquired infection.[23]

Other Related Tickborne Coltiviruses

Historically, coltiviruses have been divided into subgroup A (North American and European species) and subgroup B (Asian species). However, the subgroup B mosquito-borne viruses were recently reassigned to a new genus designated *Seadornavirus* (Southeast Asian dodeca RNA virus).[1,45] One other tickborne coltivirus, Eyach virus, has been associated with human neurologic disease in Europe.[8,46–48]

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Rotaviruses

Catherine Yen, Margaret M. Cortese

Before the availability of rotavirus vaccines, rotaviruses were the most common cause of severe infant and childhood gastroenteritis worldwide, responsible for 40% of all diarrheal hospitalizations and more than half a million deaths among children under 5 years of age annually.[1] To mitigate this substantial burden of disease, rotavirus vaccines have been developed and now are licensed in many countries. By 2016, 81 countries had introduced rotavirus vaccines in their national immunization programs, including 33 countries in Africa.[2]

Description of the Pathogen

Rotaviruses were first discovered in humans in 1973 when researchers identified wheel-shaped particles on electron microscopy of duodenal mucosa biopsies from infants with severe gastroenteritis (Fig. 216.1).[3,4] Rotaviruses are 100-nm, nonenveloped RNA viruses belonging to the family Reoviridae.[5,6] Viral particles contain a triple-layered capsid surrounding a viral genome of 11 segments of double-stranded RNA.[5] These RNA segments code for six structural proteins (VP1–VP4, VP6, and VP7) and six nonstructural proteins (NSP1–NSP6). The VP7 protein (a glycoprotein, or G-type protein) and VP4 protein (a protease-activated protein, or P-type protein) constitutes the outer layer of the capsid. These proteins are the principal targets of neutralizing antibodies and are critical to vaccine development. The VP6 protein makes up the middle layer of the capsid and is the protein to which common immune diagnostics are directed. The other three structural proteins make up the inner core of the capsid (VP2) or are associated with viral RNA (VP1 and VP3). The NSP4 protein is an enterotoxin that mediates some of the early symptoms and signs of disease and may be a protein to which antibodies are developed in the immune response to infection.[6]

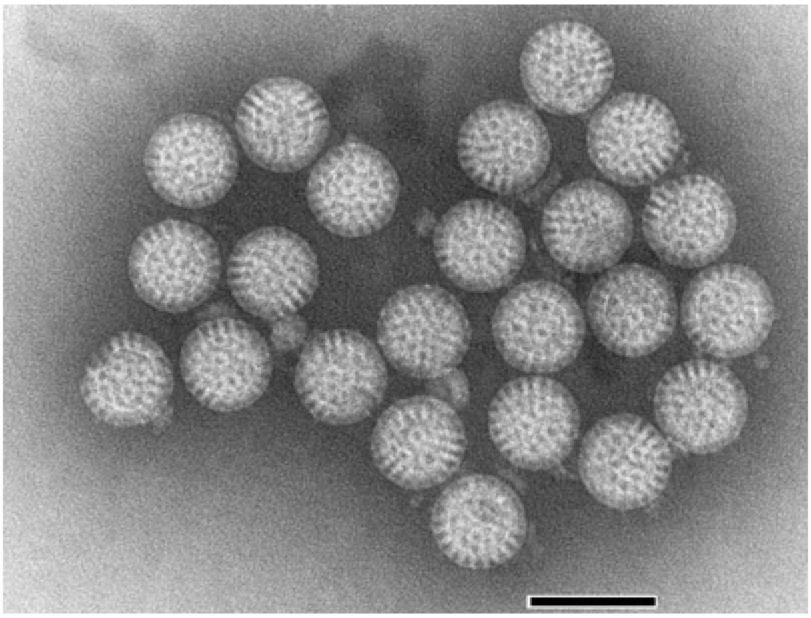

FIGURE 216.1 Electron micrograph of rotavirus particles in stool specimens, visualized by negative staining. Note typical double-shelled appearance of intact virions. Spikes formed by VP4 and protruding from the outer shell are not apparent in this image. (Courtesy of Charles D. Humphrey, PhD, Centers for Disease Control and Prevention, Atlanta, GA.)

Rotaviruses most commonly are classified according to group and serotype. Eight groups of rotavirus have been described (A–H) and are based on genetic and antigenic differences in the VP6 protein.[5] Only those viruses in groups A, B, and C are known to cause disease in humans. Group A rotaviruses are the principal cause of human disease and the main subject of this chapter. Group B rotaviruses have been associated with epidemic gastroenteritis in Asia,[7–9] and group C rotaviruses have been associated with sporadic mild gastroenteritis.[10–12] Of note, several animal species are susceptible to rotavirus infection (e.g., primates and cows).

However, the rotavirus strains that infect these animals differ from those that infect humans, and animal-to-human transmission appears to be uncommon.[13,14]

Group A rotaviruses are further classified by serotype based on their VP7 (G-type) and VP4 (P-type) proteins. G types commonly are determined by either enzyme immunoassay (EIA) using type-specific monoclonal antibodies for predominant serotypes or by reverse transcriptase polymerase chain reaction (RT-PCR).[13,15] P types usually are determined using molecular methods, such as RT-PCR or sequencing, because characterization by more traditional methods is difficult. To date, at least 27 G serotypes and 37 P genotypes have been described.[16] Globally, five G types (G1–G4 and G9) and three P types (P[4], P[6], and P[8]) predominate.[13,15–17] Although the genes that code for VP7 and VP4 segregate independently, five combinations of these common types generally account for 80% to 90% of circulating viruses: P[8]G1, P[4]G2, P[8]G3, P[8]G4, and P[8]G9.[17] Of note, certain histo-blood group antigens on enterocytes have been proposed as receptors or ligands for the P protein of rotaviruses and associations between a population's frequency of particular histo-blood group antigens and disease (or lack of disease) from particular rotavirus P genotypes have been made.[18–21]

Epidemiology

Rotaviruses are the most common cause of severe, dehydrating gastroenteritis among children worldwide.[22,23] However, the epidemiology of infection in different settings can be distinct. Before the availability of rotavirus vaccines, an estimated 527,000 children younger than 5 years died each year from rotavirus disease worldwide, accounting for about 40% of all diarrheal deaths and 5% of all deaths in this age group. More than 85% of these deaths occurred in low-income countries (Fig. 216.2).[1] Although rotavirus-associated deaths were rare in high-income countries, hospitalizations were common in both developed and economically developing countries.[24–27] In the United States, before implementation of the rotavirus vaccination program in 2006, rotavirus gastroenteritis accounted for 55,000 to 70,000 hospitalizations, 205,000 to 272,000 emergency department visits, and 410,000 physician visits annually, with total annual direct and indirect costs of about $1 billion.[28–32] Studies in countries in Asia estimate that about 24% to 50% of gastroenteritis hospitalizations are attributable to rotavirus.[33–37] These estimates are similar to those from Africa and during the prevaccine era in Latin America.[38,39]

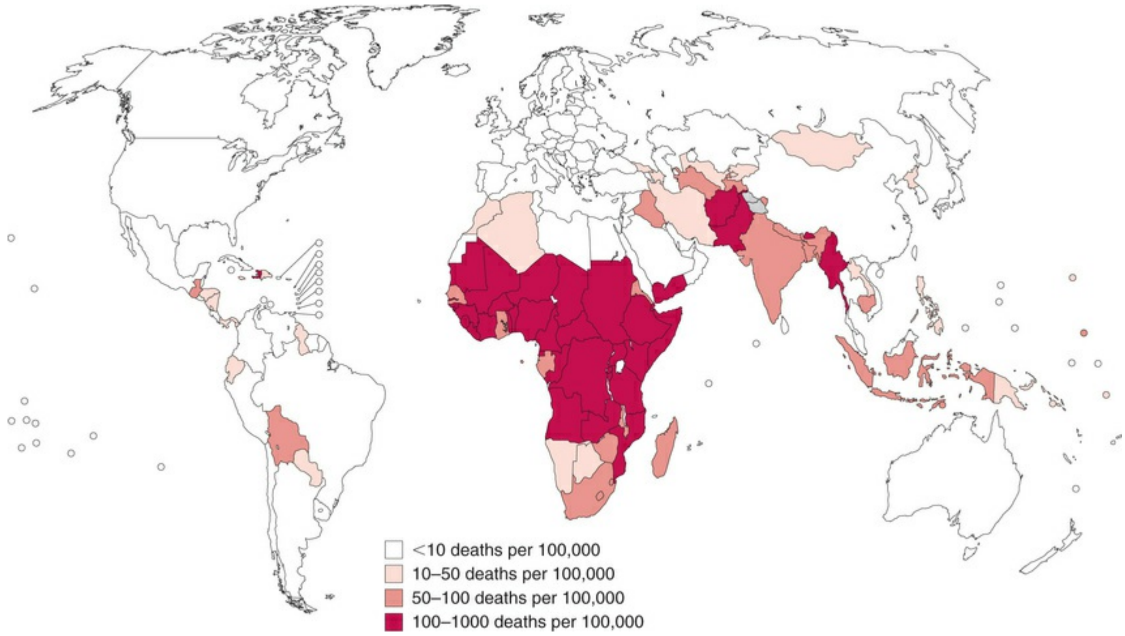

FIGURE 216.2 Estimated distribution of rotavirus deaths among children younger than 5 years, by country. (Adapted from Tate JE, Burton AH, Boschi-Pinto C, et al. 2008 Estimate of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus vaccination programmes: a systematic review and meta-analysis. Lancet Infect Dis 2012;12:136−141.)

In temperate climates, rotavirus disease occurs in distinct winter seasonal peaks.[27,40–44] Before introduction of vaccine in the United States, rotavirus activity usually began in early winter in the Southwest and moved across the country, ending in northeastern states in the spring.[42] In tropical settings, rotavirus can circulate year-round, but often has seasonal peaks during the cool or dry months.[26,39,45,46] Rotaviruses are spread through fecal-oral contamination, predominantly by close person-to-person contact.[5] Spread also likely occurs through contaminated fomites, especially in out-of-homecare settings and hospitals.[47–49] Very few infectious virions are needed to cause disease in susceptible hosts.[50] Although probable waterborne transmission has been described, spread through food and water is likely to be rare.[51] Transmission through airborne droplets has been hypothesized because of rapid seasonal transmission through populations, but is not proved.[5,52]

In areas without rotavirus vaccine, almost all children are infected at least once with rotavirus by the age of 5 years.[53,54] The highest rates of rotavirus gastroenteritis occur among children 4 to 23 months of age, who also are more likely to experience severe, dehydrating rotavirus gastroenteritis.[53,55–57] Infants younger than 3 months have lower rates of infection, and full-term neonates are more likely to be asymptomatic when infected, possibly owing to protection from passively transferred maternal antibody.[58,59] After a single natural infection, 38% of children are protected against subsequent rotavirus infection, 77% are protected against subsequent rotavirus gastroenteritis, and 87% are protected against severe rotavirus gastroenteritis; second and third infections confer progressively greater protection against rotavirus gastroenteritis.[54] Because natural infection confers protection against subsequent infection and disease, symptomatic illness is less common among those older than 5 years.[54,58] Even so, rotavirus can cause gastroenteritis among older children and adults, often in households with young children, or among adults who care for young children with rotavirus.[60,61] Rotavirus outbreaks have been reported among elderly adults in residential facilities.[62]

Clinical Manifestations

Rotavirus infects the villus enterocytes of the proximal small intestine, leading to destruction of the absorptive enterocytes, downregulation of the expression of absorptive enzymes, functional changes in tight junctions between enterocytes, and production of an enterotoxin.[6] This leads to symptoms of gastroenteritis after a mean incubation period of 1 to 3 days.[5] The initial manifestations of illness are often fever and abrupt onset of vomiting.[63–68] Most children have profuse, frequent diarrhea that can occur 8 to 20 times per day. Vomiting often resolves in 1 to 3 days, whereas diarrhea can persist for 5 to 8 days.[22,69] Some children initially have fever without gastrointestinal tract symptoms.[69] Complications and fatalities are related almost exclusively to the adverse effects of dehydration, electrolyte imbalance, and acidosis. Symptoms and asymptomatic viral shedding can be prolonged in immunocompromised patients, such as those with primary immunodeficiencies and those who have undergone bone marrow or solid-organ transplantation.[70–73] Rotavirus infection does not appear to cause more severe disease in children infected with HIV.[74] An important feature of rotavirus is that it is associated with more severe gastroenteritis than other enteric pathogens and is more likely to result in dehydration.[66]

Rare cases of meningoencephalitis possibly due to rotavirus have been reported.[75] Other extraintestinal rotavirus manifestations have been described, including acute myositis, hepatitis, hemophagocytic lymphohistiocytosis, and polio-like paralysis, but their relationship to rotavirus infection remains unclear.[76] Rotavirus antigenemia and viremia have been identified in children with rotavirus disease, but the clinical significance of these findings is unclear.[77–79] Rotavirus has been detected in some surveys of children with intussusception, although the studies usually are uncontrolled and the results variable.[80] A large case-control study did not find an association between rotavirus infection and intussusception.[81] Rotavirus is not thought to be a principal cause of intussusception.[81,82]

Laboratory Findings and Diagnostic Tests

Stool examination from patients infected with rotavirus reveals watery or soft stools, which rarely have gross blood and usually are guaiac-test negative. Fecal leukocytes generally are not observed. Patients can demonstrate electrolyte abnormalities associated with accompanying dehydration.[64] Additionally, rotavirus causes a transient rise in serum hepatic enzyme levels in about two thirds of children hospitalized for rotavirus gastroenteritis.[83]

The diagnosis of rotavirus is primarily made by testing of fresh, whole stool samples using one of many available commercial kits that detect group A rotavirus antigen by EIA, immunochromatography, or latex agglutination.[84] EIA assays are the most widely used because of their high sensitivity and specificity.[84,85] Rotavirus can be detected in stool using EIA tests during the symptomatic period and immediately before onset and for days after resolution of symptoms.[86,87] Virus also can be identified in stool by electron microscopy, electrophoresis and silver staining, and RT-PCR assay for detection of viral RNA. RT-PCR is more sensitive than antigen detection for rotavirus infection but remains primarily a research tool.

Treatment

No specific therapies exist for rotavirus infection. Care requires assessment of hydration status, appropriate correction of fluid loss and electrolyte disturbances, and maintenance of adequate hydration and nutrition. Oral rehydration using appropriate solutions is sufficient for most patients. Intravenous rehydration is required for some patients. Continuation or early reintroduction of oral feeding according to management guidelines should be a priority.[88] Breastfed infants should continue to nurse on demand. Infants fed with formula should continue their usual formula immediately upon rehydration. Children receiving semisolid or solid foods should continue to receive their usual diet during episodes of diarrhea, although it may be useful to avoid substantial amounts of foods high in simple sugars (e.g., carbonated soft drinks, juice, gelatin desserts) because the osmotic content might worsen diarrhea. Human or bovine colostrum and human serum immunoglobulin contain antibodies to rotavirus and may be beneficial in decreasing or preventing rotavirus diarrhea, but these are not used in routine practice.[72,89–91]

Prevention

Rotavirus Vaccines

Live, orally administered rotavirus vaccines currently are the best strategy for prevention of rotavirus morbidity and mortality. The available rotavirus vaccines are attenuated strains given in multiple doses and are designed to replace a child's first exposure to wild-type rotavirus with exposure to strains that will not cause disease but will generate a protective immune response.[92] Distinct approaches to rotavirus immunization have been taken with respect to strain type (i.e., use of attenuated, human strains, nonhuman strains, and human-animal reassortants), the number of strains in a vaccine (monovalent vs. polyvalent), and the number of doses.[92,93] Two rotavirus vaccines are used in immunization programs globally: RotaTeq (RV5) (Merck) and Rotarix (RV1) (GlaxoSmithKline). Both are licensed for use in the US. In the US recommendations, for both vaccines, maximal age to give the first dose is 14 weeks, 6 days, and maximal age for last dose is 8 months, 0 days.

RV5 is a live, pentavalent human-bovine reassortant vaccine that contains five separate reassortant viruses, four expressing a unique human G-type protein (G1–G4) and one expressing a human P-type protein (P[8]).[94] The vaccine is given to infants in the US in three orally administered doses at ages 2, 4, and 6 months.[95] Before licensure, a large efficacy trial performed predominantly in the US and Finland demonstrated a vaccine efficacy of 74% against G1–G4 rotavirus gastroenteritis of any severity through the first full rotavirus season after vaccination. Efficacy was 98% against severe G1–G4 rotavirus gastroenteritis.[94] Vaccine trials performed in Africa and Asia where disease burden is higher demonstrated lower efficacy; vaccine efficacy against severe rotavirus gastroenteritis was 64% in a trial conducted in Ghana, Kenya, and Mali and 51% in a trial conducted in Bangladesh and Vietnam.[96,97] This lower efficacy is consistent with the performance of oral vaccines in developing country settings.[98] In these settings, the immune response to oral vaccines may be reduced because of higher levels of transplacental maternal antibody, micronutrient malnutrition (e.g., vitamin A and zinc), interfering gut flora, and the disease state of the infant (e.g., HIV infection or concomitant diarrhea).[98,99] Although in vitro data suggest that human milk fed at the time of oral rotavirus vaccine administration may interfere with vaccine taken by immune and nonimmune components of breast milk, withholding breastfeeding for 30 to 60 minutes before and after vaccination did not statistically significantly improve the immune response to oral rotavirus vaccines in three studies.[100–102]

RV1 is a live, monovalent vaccine that contains an attenuated, human P[8]G1 strain. The vaccine is given to infants in the US in two orally administered doses at 2 and 4 months of age.[95] Vaccine efficacy of the 2-dose series against severe rotavirus gastroenteritis through the first year of life was 85% in Latin America and 96% in Europe.[103,104] Efficacy against rotavirus disease of any severity was 87% in Europe. In both Latin America and Europe, efficacy against non-G1 strains was observed. Clinical trials conducted in Africa demonstrated lower vaccine efficacy against severe rotavirus gastroenteritis, ranging from 49% in Malawi to 77% in South Africa for the 2- and 3-dose arms combined.[105] Despite lower vaccine efficacy, the number of rotavirus cases prevented per 100 infants vaccinated was substantial: 7 cases per 100 vaccinated in Malawi and 4 cases per 100 vaccinated in South Africa.[105]

In 2010, porcine circovirus or porcine circovirus DNA was detected in both rotavirus vaccines. The US Food and Drug Administration and other agencies concluded that this was not a safety risk; both manufacturers are working to remove it.[106,107]

Vaccine Impact

Many countries have documented substantial declines in the burden of rotavirus disease shortly after rotavirus vaccine introduction. In the US, RV5 was licensed in 2006 and RV1 was licensed in 2008. Data from a national laboratory surveillance network have demonstrated delayed, shorter rotavirus seasons and a sustained reduction in the number of rotavirus antigen-positive tests through the 2013–2014 rotavirus season compared with prevaccine years (Fig. 216.3).[108] Additionally, many studies have observed substantial declines in diarrhea-related and rotavirus-specific healthcare visits (i.e., outpatient, emergency department, and hospitalizations) among children younger than 5 years after rotavirus vaccine introduction.[109–114] An estimated 177,000 fewer gastroenteritis-related hospitalizations occurred during the 4-year period of 2007–2011 compared with prevaccine seasons among children younger than 5 years.[113] Declines in disease have also been noted among older age groups who are age-ineligible to receive vaccine, suggesting possible indirect benefits of vaccination.[115–117]

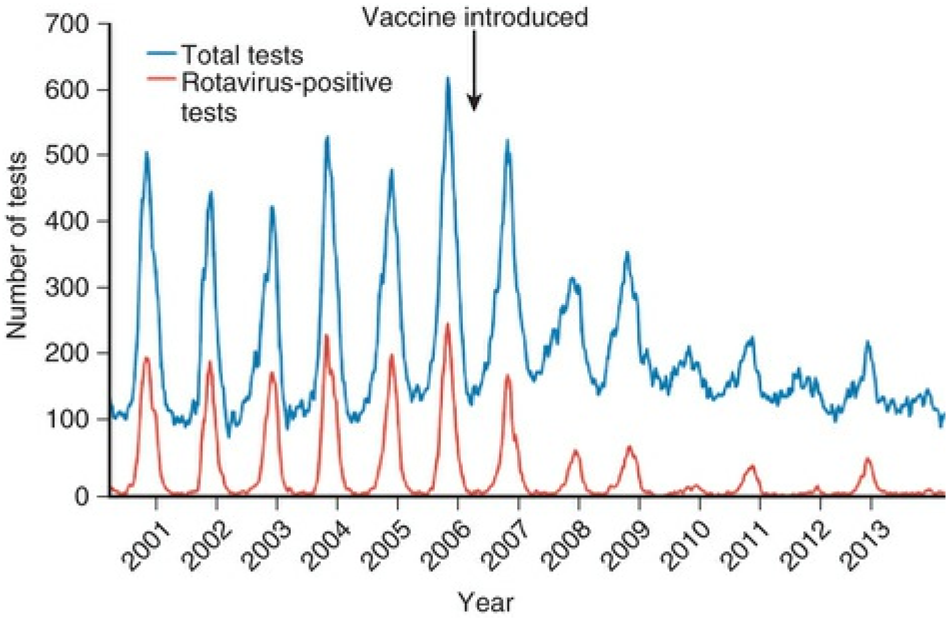

FIGURE 216.3 Number of total rotavirus enzyme immunoassay (EIA) tests performed and number of positive rotavirus EIA tests from 23 continuously reporting laboratories in the US National Respiratory and Enteric Viruses Surveillance System, by week of year, July 2000–August 2014, 3-week moving average. (Adapted from Aliabadi N, Tate JE, Haynes AK, et al. Sustained decrease in laboratory detection of rotavirus after implementation of routine vaccination: United States, 2000–2014. MMWR Morb Mortal Wkly Rep 2015;64:337−142.)

In Latin America, where rotavirus vaccines have been integrated into the national immunization programs of many countries since 2006–2007, reductions in both mortality and morbidity have been observed. In Mexico, sustained declines of 41% to 52% in diarrhea-related mortality rates among infants younger than 1 year were observed during the 3 years after rotavirus vaccine introduction in 2007 compared with prevaccine years.[118,119] Additionally, the number of diarrhea-related hospitalizations among infants in this age group decreased by 48% during 2008–2011.[120] In Brazil, a 25% to 39% reduction in diarrhea-related deaths, a 25% to 50% reduction in diarrhea-related hospitalizations, and an 82% decrease in rotavirus hospitalizations occurred among infants younger than 1 year after introduction of RV1.[121,122] In El Salvador in 2008 and 2009, a sustained decrease of >65% in the rate of rotavirus hospitalizations among children younger than 5 years was observed after introduction of RV1.[123]

In Australia, where both RV5 and RV1 were introduced in 2006, decreases of 50% to 93% in rotavirus hospitalizations among children younger than 1 year were observed during the 2 to 3 years after vaccine introduction.[124–127] Similar declines in rotavirus hospitalizations have been observed in several other high-income countries. For example, Austria, Finland, and Israel have documented reductions in rotavirus hospitalization rates of 72% to 88% among children younger than 1 year after vaccine introduction.[128–132]

Encouragingly, RV1 introduction in South Africa in 2009 resulted in at estimated 45% to 50% reduction in rotavirus hospitalizations among infants in first 2 years after introduction.[133] In Malawi, an estimated 43% reduction in the incidence of rotavirus hospitalizations among infants occurred in the second season after RV1 introduction in 2012.[134]

Vaccine Safety

Neither RV1 nor RV5 was found to be associated with intussusception in prelicensure trials.[94,103] Concerns that these vaccines might be associated with an increased risk for intussusception after vaccination are based on the demonstrated association between a previous quadrivalent, human-rhesus reassortant rotavirus vaccine (Rotashield, Wyeth Laboratories) and intussusception.[135,136] This vaccine was estimated to cause 1 excess case of intussusception per 10,000 vaccinated infants and was withdrawn from use in 1999, less than a year after being licensed and introduced in the US.[82,137] Postmarketing studies designed specifically to assess the association between receipt of RV5 or RV1 and intussusception have been conducted in Australia, Brazil, Mexico, and the US. Overall, data indicate that the available rotavirus vaccines are associated with a lower risk for intussusception than that seen with Rotashield—approximately 1 to 6 excess intussusception cases per 100,000 vaccinated infants.[138–142]

Considering currently available data that suggest a small risk of intussusception caused by rotavirus vaccine and considering that the benefits of rotavirus vaccination are great (>53,000 rotavirus hospitalizations and 14 deaths prevented by vaccination in one vaccinated birth cohort to age 5 years, versus 45–213 intussusception cases and <1 death potentially caused by vaccination), the Centers for Disease Control and Prevention continues to recommend both RV1 and RV5 to prevent severe rotavirus disease in US infants and children.[139]

Future Vaccines

Additional rotavirus vaccines are in various stages of development or licensure.[93,143] Although most are live, orally administered vaccines, parenterally administered vaccines also are being investigated.[92,143]

Other Preventive Measures

Nonvaccine approaches to prevention include breastfeeding and hand hygiene. Breastfeeding may protect young infants against rotavirus infection through antirotavirus antibodies and other nonimmunologic factors in human milk.[144] Appropriate hand hygiene practices should be encouraged, particularly in institutional settings such as childcare centers and hospitals.

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Key Points

Epidemiology, Clinical Features, Diagnosis, Treatment, and Prevention of Rotavirus-Associated Gastroenteritis

Epidemiology

- Most common cause of severe, dehydrating gastroenteritis among children worldwide

- Can affect all age groups and areas in the United States

- Most children are infected at least once by the age of 5 years unless vaccinated.

▪ Highest rates of infection are among children 4 to 23 months of age.

- Main modes of transmission: fecal-oral contamination through person-to-person contact, contact with contaminated fomites; rarely foodborne or waterborne
- Infectious dose is as little as a few virions.

Clinical Features

- Mean incubation period: 1 to 3 days
- Main symptoms: watery diarrhea, fever, vomiting
- Potential complications: dehydration, electrolyte imbalance, acidosis, hepatitis; possibly meningoencephalitis (rare)
- Duration of illness: 3 to 8 days

Diagnosis

- Detection of rotavirus antigen in stool by enzyme immunoassay
- Sequencing by reverse transcriptase polymerase chain reaction testing to characterize strain type if needed

Treatment

- Replacement of fluid and electrolytes
- No antiviral drug available

Prevention

- Universal rotavirus vaccination during infancy

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RNA Viruses: Togaviridae, Flaviviridae, and Bunyaviridae

OUTLINE

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Togaviridae

Alphaviruses

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Alphaviruses are arthropod-borne members of the family Togaviridae. They are small, enveloped RNA viruses.[1,2] Members of the western equine encephalitis virus, eastern equine encephalitis virus, and Venezuelan equine encephalitis virus serocomplexes cause encephalitis in horses and humans, whereas members of the Semliki Forest virus serocomplex, such as chikungunya, o'nyong-nyong, Mayaro, and Ross River viruses, cause epidemic fever and arthralgia.[3–5]

Viruses

Chikungunya Virus

Chikungunya virus is transmitted from one human to another primarily by infected *Aedes aegypti* and *Aedes albopictus* mosquitoes. Enzootic transmission cycles between forest-dwelling mosquitoes and wild mammals are documented in Africa.[6,7] Before 2013, chikungunya outbreaks were documented in countries in Africa, Asia, Europe, and the Indian and Pacific Oceans.[8] In 2013, the first locally acquired cases in the Americas were identified on islands in the Caribbean.[9] By the end of 2014, local transmission of chikungunya virus had been reported from 44 countries and territories in the Americas, with more than 1 million suspected cases reported.[10]

After an incubation period of 3 to 7 days (range, 2–12 days), chikungunya virus infection causes acute fever and polyarthralgia in most (72%–98%) infected persons.[11–17] Joint pains are usually bilateral and symmetric, and they can be severe and debilitating.[6,18] Other symptoms may include headache, myalgia, arthritis, conjunctivitis, vomiting, and maculopapular rash.[19–21] During large outbreaks of disease that occurred in and around the Indian Ocean from 2004 to 2007, a number of atypical disease manifestations were noted, including neurologic disease (e.g., meningoencephalitis, Guillain-Barré syndrome), eye and other organ involvement (e.g., uveitis, retinitis, hepatitis, nephritis, or myocarditis), and unusual dermatologic manifestations (e.g., bullous lesions).[18,22–30]

The acute symptoms of chikungunya typically resolve in 7 to 10 days. Mortality is rare and mostly occurs in older adults and those with underlying comorbidities.[23,31] Some patients have a relapse of rheumatologic symptoms, such as polyarthralgia, polyarthritis, tenosynovitis, or Raynaud syndrome, in the months following acute illness.[32] Studies have reported variable proportions (5%–60%) of patients with persistent joint pains lasting from months to years after their illness.[17,20,33–51]

There is no specific antiviral therapy to treat chikungunya virus infection. Treatment is palliative and includes rest, fluids, analgesics, and antipyretics.[11] In dengue-endemic areas, acetaminophen or paracetamol is the preferred first-line treatment for fever and joint pain to reduce the risk for hemorrhage until dengue can be ruled out. Persistent joint pain from chikungunya may be reduced by nonsteroidal antiinflammatory drugs, corticosteroids, or physiotherapy.[30,33,52]

Modes of transmission other than mosquitoes have been reported. Intrapartum transmission occurs in almost 50% of neonates when the mother was viremic around the time of delivery.[26,53,54] Infected neonates most commonly have had fever, pain, rash, and edema, but intracerebral and gastrointestinal hemorrhage and severe encephalopathy with seizures also have been reported.[25,26] In utero transmission has been reported in the second trimester associated with three miscarriages, in which chikungunya viral RNA was detected in fetal tissue.[26,55] Two small studies did not identify chikungunya virus or viral RNA in breast milk from viremic women, making transmission through breast milk less likely.[26,56] The virus has been transmitted through percutaneous needlestick and laboratory exposure to infected blood or virus culture.[57,58] Given that humans develop a high level of viremia, it is expected but not yet documented that transmission can occur through blood transfusions and organ or tissue transplantation.[59–64]

O'nyong-Nyong Virus

O'nyong-nyong virus and its variant virus, Igbo-Ora virus, are unusual among arboviruses in that they are transmitted between humans in Africa by infected anopheline mosquitoes, primarily *Anopheles funestus* and *Anopheles gambiae*, which also are vectors of malaria.[65,66] After an incubation period of about 8 days, the virus causes epidemic febrile polyarthralgia often accompanied by headache, pruritic rash, lymphadenopathy, and conjunctivitis.[67] There is no specific treatment; virtually all patients recover completely, but many are incapacitated for up to 2 weeks during the illness.[67] Mild or asymptomatic cases also may occur as indicated by the presence of o'nyong-nyong virus–specific antibodies in areas without epidemic disease transmission.[68]

Ross River Virus

Ross River virus is transmitted to humans in Australia and the Western Pacific by a broad range of mosquito vectors but primarily *Aedes vigilax, Aedes camptorhyncus, Aedes polynesiensis,* and *Culex annulirostris.*[69–72] The virus is transmitted enzootically between mosquitoes and kangaroos, horses, and other vertebrates; human-to-mosquito-to-human transmission also occurs.[70,73,74] One case of transfusion-associated transmission has been documented.[75] After an average incubation period of 7 to 9 days (range, 3–21 days), Ross River virus causes sudden onset of arthralgia, arthritis, rash, myalgias, fatigue, and fever to a variable degree.[69,72,73] Glomerulonephritis and suspected encephalitis have been reported rarely.[69,72] Disease affects primarily those between 20 and 60 years of age, whereas symptomatic illness is rare in children.[72,76,77]

Infection generally is not life-threatening, and symptoms usually resolve within 6 months.[69] Joint pain and inflammation can be treated with nonsteroidal anti-inflammatory drugs.[69,72]

Venezuelan Equine Encephalitis Virus

Venezuelan equine encephalitis virus is transmitted in tropical areas of the western hemisphere by a variety of mosquitoes, including *Psorophora confinnis, Psorophora columbiae, Aedes sollicitans, Aedes taeniorhynchus,* and *Culex (Melanoconion)* species.[78,79] Enzootic Venezuelan equine encephalitis virus strains are transmitted in sylvatic cycles between mosquitoes, primarily *Culex (Melanoconion)* species, and rodents; equines are the primary amplifying hosts for epizootic strains. Direct human-to-human transmission appears to be rare, but the virus has been isolated from the oropharynx of ill humans, aerosol transmission has occurred in laboratories, and the virus has been considered a possible bioterrorism threat.[78,80–82] After an incubation period of 2 to 5 days, Venezuelan equine encephalitis virus causes the abrupt onset of fever, headache, malaise, tremor, myalgia, nausea, and vomiting.[78,83,84] A high proportion of fatal cases in one epidemic had pneumonia.[85] During an outbreak in Colombia, <5% of all symptomatic infections were estimated to result in neurologic disease.[81] Two more recent studies of hospitalized patients infected with enzootic strains in Panama found that neurologic disease was seen most frequently in children.[83,84] Overall, the case-fatality rate for symptomatic disease is <1% but can be as high as 5% among patients who are hospitalized.[81,86,87]

Eastern Equine Encephalitis Virus

Eastern equine encephalitis virus is transmitted in enzootic cycles between mosquitoes and birds in wetland habitats of tropical and temperate areas of the western hemisphere. In eastern regions of North America, eastern equine encephalitis virus is maintained by the ornithophillic *Culiseta melanura* mosquitoes in an avian cycle. The virus is sporadically transmitted to horses and humans, which are dead-end hosts, by bridging mosquito vectors such as *Coquillettidia perturbans* and *Aedes vexans*.[88,89] In the southern United

States, reptiles may play a role in zoonotic maintenance of the virus.[90] The closely related Madariaga virus (previously known as South American strains of eastern equine encephalitis virus) has been found in *Culex* spp. (*Cx. pedroi* and *Cx. taeniopus*) and have been typically associated with equine disease.[91,92] However, several human disease cases associated with the Lineage III Madariaga viruses were identified in Panama during 2010.[84] The virus also has been experimentally transmitted to animals through aerosols.[93] After a typical incubation period of 5 to 8 days, eastern equine encephalitis virus causes the abrupt onset of fever, headache, vomiting, and diarrhea, followed by lethargy, weakness, paralysis, seizures, and coma.[84,88,89,94–96] The overall case-fatality rate is estimated to be 30% but has been reported to be as high as 75% in some case series, and survivors often have permanent neurologic damage.[84,89,94,97]

Other Alphaviruses of Medical Importance

A variety of other alphaviruses have been reported to cause either epidemic or sporadic illness in humans. Western equine encephalitis virus is transmitted between mosquitoes and birds in rural areas in the western hemisphere.[89] In recent years, western equine encephalitis virus disease in humans has not been documented despite continued enzootic transmission.[98–100] Aerosol transmission of western equine encephalitis virus in laboratories has been reported.[101] The risk for symptomatic infection, with manifestations ranging from mild febrile illness to meningitis or encephalitis, is highest in infants and young children.[88] Overall mortality is <5%; most adults recover completely, but children may have lasting neurologic sequelae.[3,88,89]

Sindbis virus has been reported from Europe, Africa, Asia, and Australia and has caused fever, rash, and arthritis.[1,102] Variants of Sindbis virus, including Ockelbo, Pogosta, and Karelian fever viruses, cause fever and arthralgia in Scandinavia and Russia.[1,102,103] Mayaro virus causes a febrile illness with rash and arthralgia in South America.[102,104] Barmah Forest virus disease appears to be similar to Ross River virus in its epidemiology and clinical manifestations and has resulted in small outbreaks of fever, arthralgia, arthritis, and rash in Australia.[102,105]

Laboratory Diagnosis

Routine clinical laboratory tests do not distinguish alphavirus infections from many other viral infections. Initial peripheral leukopenia with thrombocytopenia and eventual lymphocytosis occur.[106] Peripheral leukocytosis with a neutrophilic predominance is common with eastern equine encephalitis virus infection.[89] In patients with alphaviral encephalitis, cerebrospinal fluid (CSF) examination can show an initial neutrophilic and then lymphocytic pleocytosis; CSF protein is normal or elevated, and CSF glucose usually is normal.[88,89,107] Hyponatremia can develop in some cases due to inappropriate secretion of antidiuretic hormone.[89] A variety of abnormalities on brain imaging have been reported, but these are not pathognomonic.[26,27,94,108,109]

A specific diagnosis can be determined by finding virus, viral antigen, or viral RNA in serum, CSF, or tissues. However, most cases are diagnosed by detecting virus-specific immunoglobulin M (IgM) antibody in CSF or serum using an enzyme immunoassay or indirect immunofluorescent assay.[88,89] The IgM antibody assays usually distinguish between alphaviruses of different serogroups but can show occasional cross-reactivity for viruses of the same serogroup.[110] A fourfold or greater rise in specific neutralizing antibody titers between two serum samples obtained several weeks apart can confirm the infecting virus. Some alphaviruses, such as chikungunya and o’nyong-nyong viruses, can be identified in acute serum by real-time reverse transcriptase polymerase chain reaction or virus isolation.[6,111] Isolation of the neurotropic viruses from CSF is variably successful; tests for viral RNA in CSF are more sensitive.[112] Finally, immunohistochemical staining of fixed tissues can be performed to detect viral antigens. Diagnostic assays are available through many state health departments, a few commercial laboratories, and the Centers for Disease Control and Prevention.

Prevention

Alphavirus infection can be prevented by avoiding exposure to mosquitoes that transmit these viruses. Personal protective strategies include wearing repellent, staying in screened or air-conditioned dwellings, and avoiding outdoor activities during times when the vectors are most avidly seeking blood meals. Vaccines against Venezuelan equine encephalitis virus, eastern equine encephalitis virus, western equine encephalitis virus, and chikungunya virus have been used to protect laboratory workers and others with occupational exposure to these viruses.[113,114] In addition, one inactivated Ross River virus vaccine and several chikungunya virus vaccines are in various stages of clinical development.[114,115] However, no alphavirus vaccines are currently available for public use.

Key Points

Agents, Epidemiology, Clinical Features, Diagnosis, and Treatment of Alphavirus Infections

Agents

- Family Togaviridae; genus *Alphavirus*
- Arthritogenic viruses: Barmah Forest, chikungunya, Mayaro, o'nyong-nyong, Ross River, and Sindbis viruses
- Neurotropic viruses: Eastern equine encephalitis, Venezuelan equine encephalitis, and western equine encephalitis viruses

Epidemiology

- Transmitted to humans through the bite of various mosquito species
- Cause human disease throughout the world though specific viruses have regional distributions

Clinical Features

- Incubation period is typically a few days to a week.
- Two main clinical presentations:
  - Fever and polyarthralgia: acute onset of fever and joint pain, typically involving multiple joints

symmetrically

- Neuroinvasive disease: acute onset of fever and headache, often with abdominal symptoms; and progression to altered mental states, lethargy, and weakness, often with paralysis, seizures, and coma

- All ages can be infected, although more severe disease occurs in older adults and, for some viruses, in younger children and infants.

- Persons with less severe disease typically recover in 1 to 2 weeks.

- Morbidity can include permanent neurologic damage with neurotropic viruses and longer-term joint symptoms with arthritogenic viruses.

- Case-fatality rate varies by virus from rare (e.g., chikungunya virus) up to 30% (i.e., eastern equine encephalitis virus).

Diagnosis

- Most infections are diagnosed by serologic assays to detect virus-specific immunoglobulin M antibodies in serum or cerebrospinal fluid.

- Reverse transcriptase polymerase chain reaction testing of acute serum typically is positive with chikungunya and o’nyong-nyong viral infections.

- Immunohistochemistry can be used to test fixed tissues.

Treatment

- No specific antiviral drugs

- Supportive therapy including antipyrectic drugs, analgesics, and treatment of complications

Prevention

- No commercially available vaccines
- Personal protective measures to avoid mosquito bites:

Wear insect repellent

Stay in screened or air-conditioned dwelling

Wear long sleeves and pants

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Flaviviruses

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The flaviviruses are single-stranded, enveloped RNA viruses that are transmitted to humans primarily through the bites of arthropods.[1] Although more than 40 arthropod-borne flaviviruses have been described, this chapter discusses those that are most important in causing human illness: yellow fever virus (YFV), dengue viruses, Japanese encephalitis virus (JEV), West Nile virus (WNV), tickborne encephalitis virus (TBEV), and Zika virus (ZIKV). Other flaviviruses not discussed in this chapter can cause sporadic or epidemic human illness and elicit cross-reactive antibody.

Specific Agents

Yellow Fever Virus

YFV, the prototype flavivirus, is transmitted to humans primarily by infected *Aedes* spp. and *Haemogogus* spp. mosquitoes in tropical areas of Africa and South America. Sporadic human infections occur after exposure to the enzootic mosquito vectors (*Haemogogus* spp. in South America and *Aedes africanus, Aedes furcifer, Aedes vittatus, Aedes luteocephalus,* and *Aedes simpsoni* in Africa).[2] These mosquitoes acquire YFV from infected monkeys and transmit the virus to humans who enter or live in the forest or savannah. Large urban outbreaks occur when viremic humans infect peridomestic *Aedes aegypti* mosquitoes, which can then transmit the virus to other humans. Direct person-to-person transmission of YFV has not been reported. However, the live, attenuated vaccine strain of the virus has been transmitted transplacentally, through breastfeeding, and through blood transfusion.[3–5]

Most YFV infections are asymptomatic. In symptomatic infection, after an incubation period of 3 to 6 days, yellow fever begins with the acute onset of fever, chills, headache, and myalgia, often accompanied by photophobia, back pain, anorexia, vomiting, and restlessness.[2,6] During this phase, patients are viremic. Viremia usually clears about 4 days after illness onset, as fever and other symptoms subside. Most patients remain anicteric and then fully recover. However, about 15% of all infected people develop severe yellow fever with jaundice.[7] After a brief remission lasting from a few hours up to 2 days, these patients have a recurrence of initial symptoms with progression to jaundice and sometimes hemorrhagic symptoms, including epistaxis, gingival bleeding, hematemesis, hematuria, or melena.[2] Patients can develop dysfunction of multiple organs, including the hepatic, renal, and cardiovascular systems. Viral invasion of the central nervous system is rare, but neurologic manifestations can include delirium, convulsions, and coma. Laboratory abnormalities include elevated aspartate and alanine aminotransferases, proteinuria, thrombocytopenia, leukopenia, and prolonged blood coagulation.[8] Complications include bacterial pneumonia and parotitis.[2] Most persons with mild yellow fever recover without long-term sequelae. For those with severe disease involving hepatorenal dysfunction, the case-fatality rate ranges from 20% to 50%.

The treatment of yellow fever is supportive and based on symptoms and organ systems involved. Supportive care should include maintenance of nutrition, optimization of fluid and metabolic balance, nasogastric suction to prevent gastric distention and aspiration, treatment of bleeding with fresh frozen plasma, and treatment of secondary infections as necessary.[2] Although multiple drugs have been evaluated or used empirically to treat yellow fever, to date, none has demonstrated specific benefit.[9]

An effective live, attenuated yellow fever vaccine has been available since 1937 and is recommended for persons 9 months and older who reside in or travel to endemic areas.[10] The vaccine is contraindicated in infants younger than 6 months and should only be given to infants aged 6 to 8 months when the risk for yellow fever outweighs the risk for adverse events in this age group.[10] In children aged 9 months and older, serious adverse events are rare but have been described, including cases of neurotropic and viscerotropic disease. The vaccine virus can be transmitted transplacentally and through breastfeeding.[3,4,10] Limited data suggest that vaccination during pregnancy does not increase the risk for congenital malformations or other adverse pregnancy outcomes. However, three infants developed encephalitis after being exposed to yellow fever vaccine virus through breastfeeding.[4,10,11] Thus, yellow fever vaccine should not be given to pregnant or breastfeeding women unless they have a clear risk for acquiring yellow fever.[10]

Dengue Viruses

There are four dengue virus (DENV) types, designated as DENV-1, DENV-2, DENV-3, and DENV-4; all are transmitted to humans through the bite of *Aedes* spp. mosquitoes, most frequently *A. aegypti* and *Aedes albopictus.*[12] Infection with any of the DENVs produces long-term immunity specific to the infecting DENV. Cross-protective heterotypic immunity usually is short-term. Dengue occurs throughout the tropics worldwide.[13] In the United States, DENV transmission has occurred in Texas, Hawaii, and Florida.[14–16]

The incubation period of dengue usually is from 3 to 10 days.[17] About 75% of infections with dengue viruses are asymptomatic or cause a relatively mild febrile illness. Previously, three overlapping syndromes of dengue were described: dengue fever, dengue hemorrhagic fever, and dengue shock syndrome. However, recent World Health Organization (WHO) guidelines have modified the clinical classification of dengue into three revised categories: dengue, dengue with warning signs, and severe dengue.[18] Dengue can be acutely incapacitating but is self-limited and usually resolves within 7 days without sequelae. Severe dengue, which occurs in about 5% of clinically apparent cases in endemic areas, is manifest by one or more of the following: severe plasma leakage, leading to shock or fluid accumulation with respiratory distress; severe hemorrhage; or severe organ dysfunction. If not appropriately treated, severe dengue has a case-fatality rate of up to 5%.[18,19] Secondary infection with a different DENV has been associated with increased risk for developing severe dengue.[18] Rarer manifestations of dengue include hepatitis, myocarditis, and encephalitis.[18]

Current WHO guidelines divide the clinical course of dengue into three phases: febrile, critical, and convalescent.[18] The acute febrile phase typically begins abruptly with high-grade fever. Other symptoms include headache, retro-orbital pain, myalgia, anorexia, nausea, vomiting, arthralgia, facial flushing, maculopapular rash, and conjunctival injection. Many patients with dengue have a positive tourniquet test (appearance of ≥10 petechiae in a 2.5-cm square patch of skin after inflation of a blood pressure cuff), and about 25% have mild hemorrhagic manifestations such as epistaxis or gum bleeding. Common laboratory abnormalities include thrombocytopenia, leukopenia, hyponatremia, and elevated aspartate and alanine aminotransferases. Differentiating acute phase dengue from other acute febrile illnesses is difficult, and the discriminating manifestations may vary with age. In a report from one endemic area, the presence of retro-orbital pain was predictive of laboratory-confirmed dengue in patients of all ages, whereas rash was predictive of dengue only in patients older than 9 years.[20] Leukopenia was predictive of dengue in patients older than 20 years, whereas thrombocytopenia was predictive for those older than 10 years.

The critical phase of dengue commences in the 24 to 48 hours after defervescence, which typically occurs 2 to 7 days after illness onset. At this point, most patients improve, and their illness resolves. Warning signs for development of severe dengue include abdominal pain, persistent vomiting, extravascular fluid accumulation, severe mucosal bleeding, lethargy, restlessness, hepatomegaly, and increasing hematocrit with decreasing platelet count.[18] A chest radiograph or abdominal ultrasound may reveal pleural effusion or ascites. Plasma leakage can progress to shock, often associated with narrowed pulse pressure and disseminated intravascular coagulation.[18] In rare cases, severe hemorrhage or critical organ dysfunction occurs without evidence of plasma leakage or shock.[18] Detailed WHO guidelines for treatment and management of severe dengue with carefully monitored intravenous fluid administration are available.[20a] The case-fatality rate of severe dengue can be reduced to <0.5% with early detection and appropriate fluid management.[18,21]

The critical phase of dengue usually resolves within 48 hours, and patients enter the convalescent phase. This phase is characterized by reabsorption of extravascular fluid over 2 to 3 days, typically with diuresis.[18] Some patients develop a confluent erythematous rash with "isles of white," pruritus, bradycardia, or electrocardiographic abnormalities during this phase.[18] Pulmonary edema or congestive heart failure can occur, particularly with excessive fluid administration.[18]

Patients with dengue who do not have warning signs or other indications for hospitalization can be managed as outpatients with rest, vigilant monitoring of clinical parameters, attention to hydration, and pain management with acetaminophen.[18] Aspirin and other nonsteroidal anti-inflammatory drugs should be avoided because of increased risk for bleeding.[18] WHO provides more detailed guidelines for management of nonsevere dengue as well as criteria for hospitalization,[20a] and the Centers for Disease Control and Prevention (CDC) has an online clinical case management course (http://www.cdc.gov/dengue/).

Congenital DENV infection has been described, but accurate estimates of the risk for maternal-fetal transmission are not available.[22] Some studies have suggested that maternal dengue infection during pregnancy might increase the risk for preterm birth and low birth weight.[22] Neonates with congenital dengue have had clinical manifestations ranging from fever with thrombocytopenia to pleural effusions, severe hemorrhage, and shock.[22]

Several dengue vaccines are in clinical trials, but none is available commercially at this writing.[23]

Japanese Encephalitis Virus

JEV is the leading vaccine-preventable cause of encephalitis in Asia. Japanese encephalitis (JE) occurs throughout most of Asia and parts of the Western Pacific.[24,25] JEV is maintained in an enzootic cycle between mosquitoes and amplifying vertebrate hosts, primarily pigs and wading birds.[26,27] The virus is transmitted to humans through the bites of infected mosquitoes. Humans usually do not develop a level or duration of viremia sufficient to infect mosquitoes and, therefore, are dead-end hosts.[28,29] Direct person-to-person spread of JEV does not occur except rarely through intrauterine transmission.[30,31] *Culex* spp. mosquitoes, especially *Culex tritaeniorhynchus,* are the principal JEV vectors.[26,32] The risk for JE is increased in rural areas with irrigated fields and where pigs are raised close to human dwellings.[33] In temperate areas of Asia, transmission is seasonal, and human disease usually peaks in summer and fall.[26,27,34] In the subtropics and tropics, seasonal transmission varies with monsoon rains and irrigation practices and may be extended or even occur year-round. Most JE cases occur among children, but in areas of recent viral introduction or where population immunity has waned, adults also develop the disease.[26,27] For most travelers to Asia, the risk for JE is very low but varies on the basis of destination, duration, season, and activities.[24] From 1973 through 2013, 68 JE cases among travelers or expatriates from nonendemic countries were published in the literature or reported to the CDC.[25,35]

Most human JEV infections are asymptomatic; <1% of infected people develop clinical disease.[27,34] Acute encephalitis is the most commonly identified clinical syndrome; aseptic meningitis and undifferentiated febrile illness also can occur but have been reported more commonly among adults.[27,36,37] Among patients who develop clinical symptoms, illness usually begins with acute onset of fever, headache, and vomiting, after an incubation period of 5 to 15 days. Mental status changes, seizures, focal neurologic deficits, generalized weakness, parkinsonism, and other movement disorders often develop over the next few days.[38] Acute flaccid paralysis, with clinical and pathologic features similar to poliomyelitis, also has been associated with JEV infection.[39] Laboratory findings can include a moderate leukocytosis, mild anemia, and hyponatremia.[36,37] Cerebrospinal fluid (CSF) typically shows a mild to moderate pleocytosis with a lymphocytic predominance, slightly elevated protein, and normal glucose concentration. The case-fatality rate is approximately 20% to 30%.[36] Among survivors, 30% to 50% have significant neurologic, cognitive, or psychiatric sequelae.[24] There is no specific treatment.[40] Supportive care includes maintenance of adequate cerebral perfusion and management of increased intracerebral pressure, aspiration, seizures, hypoglycemia, hyponatremia, and secondary infections.[38]

One JE vaccine, the inactivated Vero cell culture−derived vaccine Ixiaro (Valneva Scotland Ltd, Livingston, UK), is available in the US.[24] Ixiaro was licensed in March 2009 for use in persons 17 years and older and in 2013 for use in children 2 months through 16 years of age.[41] The primary series for Ixiaro is 2 intramuscular doses administered 28 days apart. For children aged 2 months through 2 years, each dose is 0.25 mL, and for adults and children 3 years and older, each dose is 0.5 mL. JE vaccine is recommended for travelers who plan to spend a month or longer in endemic areas during the JE virus transmission season. JE vaccine should be considered for short-term (<1 month) travelers whose itinerary or activities might increase their risk for exposure to JEV. Other inactivated and live, attenuated JE vaccines are available in Asia and Australia but are not licensed for use in the US.

West Nile Virus

WNV is transmitted primarily through the bite of several *Culex* spp. mosquitoes.[42] WNV is found in many parts of Africa, Asia, Australia, Europe, and North America and in some areas of Latin America. After the first detection of WNV in the Western Hemisphere in New York City in 1999, the virus spread over the entire continental US, with most intense transmission occurring in the central and western Great Plains states.[43]

Mosquitoes that acquire WNV from birds incidentally infect humans.[42] In immunocompetent people, viremia usually lasts <7 days, and viral concentrations in blood are too low to effectively infect mosquitoes. However, WNV can be transmitted through transfusion of infected blood and organ transplantation.[44–49] Screening of blood donations for WNV began in 2003 and has substantially reduced the risk for transmission through transfusion, but rare instances of breakthrough transmission can occur.[50,51] Occupationally acquired WNV infection has raised the possibility of aerosol transmission.[52,53]

Transplacental transmission of WNV and possible transmission through breastfeeding have been described but appear to occur infrequently.[54–56] Most women known to have been infected with WNV during pregnancy have delivered infants without evidence of infection or clinical abnormalities.[56] In the best-documented case of congenital WNV infection, the mother developed neuroinvasive WNV disease during the 27th week of gestation, and the infant was born with cystic destruction of cerebral tissue and chorioretinitis.[57] One infant who apparently acquired WNV infection through breastfeeding remained healthy.[58]

Most WNV infections are asymptomatic.[59–61] After an incubation period of 2 to 14 days, about 20% to 30% of infected people develop a systemic febrile illness (i.e., West Nile fever). Less than 1% of infected people develop neuroinvasive disease (e.g., meningitis, encephalitis, or acute flaccid paralysis).[59–61] The risk for neuroinvasive disease is highest in elderly people and in solid-organ transplant recipients.[62–66] From 2003 to 2012, a total of 13,108 WNV neuroinvasive disease cases were reported in the US.[67] Of these, 505 (4%) occurred in children, for an average annual incidence of 0.68 cases per 1 million children. Half of the pediatric cases (295) were classified as meningitis, 236 (47%) as encephalitis, and 14 (3%) as acute flaccid paralysis. For up-to-date WNV surveillance data, see http://www.cdc.gov/ncidod/dvbid/westnile/index.htm.

Patients with WNV nonneuroinvasive disease typically have an abrupt onset of fever, headache, myalgia, and weakness, variably accompanied by abdominal pain, nausea, vomiting, diarrhea, and a maculopapular rash.[68,69] The acute phase of illness usually resolves within several days, but fatigue, malaise, and weakness can linger for weeks. Patients with neuroinvasive disease can present with neck stiffness and headache, mental status changes, movement disorders such as tremor or parkinsonism, seizures, or acute flaccid paralysis with or without meningitis or encephalitis.[68–71] CSF reveals neutrophilic pleocytosis early in the infection evolving over several days to lymphocytosis.[72,73] Isolated limb paralysis can occur without fever or apparent viral prodrome.[71,74] Flaccid paralysis caused by WNV infection is similar clinically and pathologically to poliomyelitis caused by poliovirus, with damage of anterior horn cells.[71,75] Progression can occur to respiratory muscle paralysis requiring mechanical ventilation. Guillain-Barré syndrome can follow WNV infection and can be distinguished from anterior horn cell damage by CSF findings of elevated protein with few white cells and electrophysiologic findings indicating damage to peripheral myelin. Chorioretinitis, cardiac dysrhythmias, myocarditis, rhabdomyolysis, optic neuritis, uveitis, orchitis, pancreatitis, and hepatitis have been reported.[43,71,76] The mortality rate after WNV neuroinvasive disease in adults is about 10%; the case-fatality rate for neuroinvasive disease in children in the US is <1%.[43,77]

Clinical management of WNV disease is supportive. No antiviral or adjunctive therapies are approved or recommended for treatment.[78–80] There are numerous case reports and case series regarding the use of various products; however, the studies often had small sample sizes, and the results from some of the clinical trials have not been published. Because polyclonal immune globulin and interferon α-n3 are available, some physicians have chosen to use them to treat transplant recipients and other severely immunocompromised patients, but there is no proven benefit.[43,78,79,81] No vaccine is licensed for humans. Despite development of several vaccine candidates, phase 3 clinical trials have not been initiated because of the uncertain market potential and logistical difficulties in conducting these trials.[43,79]

Tickborne Encephalitis Virus

Tickborne encephalitis (TBE) is endemic in focal areas of Europe and northern Asia, with approximately 5000 to 13,000 cases reported annually.[82,83] TBEV infections are usually acquired in forested areas during outdoor occupational or recreational activities. Most cases occur from April through November, with peaks in early and late summer. The incidence and severity of disease are highest in persons older than 50 years.[84,85]

There are three subtypes of TBEV: European, Siberian, and Far Eastern.[84] Each is transmitted to humans through the bite of an infected *Ixodes* spp. tick, primarily *Ixodes ricinus* (European subtype) or *Ixodes persulcatus* (Siberian and Far Eastern subtypes). TBEV transmission can also occur through ingestion of unpasteurized dairy products, slaughtering viremic animals, and laboratory exposure.[84,86–88] Direct person-to-person spread of TBEV does not occur except rarely through blood transfusion or breastfeeding.[84]

About two thirds of TBEV infections are asymptomatic.[89,90] In people who develop clinical illness, the median incubation time is about 8 days (range, 2–28 days).[84,87,88,91] Typically, patients infected with the European subtype have a biphasic illness.[85,92] The first (viremic) phase consists of a nonspecific febrile illness, often followed by a remission of symptoms. About one third of these patients then develop the second, more severe (neuroinvasive) phase of illness, resulting in meningitis (about 50%), encephalitis (about 40%), or myelitis (about 10%).[85,92] Laboratory abnormalities include leukopenia and thrombocytopenia in the first stage, followed by leukocytosis in the second stage, and pleocytosis that can be polymorphonuclear progressing to monocytic, with elevated CSF protein.[84,85] The case-fatality rate associated with the European and Siberian subtypes is 1% to 3%. The Far Eastern subtype typically causes a more severe monophasic illness with a case-fatality rate of about 20% and neurologic sequelae in up to 80% of survivors. Most children with TBE recover without severe sequelae; however, residual problems, including cognitive deficits, headache, fatigue, and irritability, have been reported 2 to 7 years after acute illness.[93]

There is no specific antiviral treatment; therapy consists of supportive care and management of complications.[84] No TBE vaccines are licensed in the US.[82] Two safe, effective inactivated TBE vaccines are available in Europe, in adult and pediatric formulations: FSME-IMMUN (Baxter, Austria) and Encepur (Novartis, Germany).[82,91,94] Two other inactivated TBE vaccines are available in Russia: TBE-Moscow (Chumakov Institute, Russia) and EnceVir (Microgen, Russia).[82,91,94] Immunogenicity studies suggest that the vaccines should provide cross-protection against all three TBE virus subtypes.[82,91,94] Although no formal efficacy trials of these vaccines have been conducted, indirect evidence suggests that their efficacy is higher than 95%.[82,91]

Zika Virus

For several decades after ZIKV was first isolated from a monkey in Uganda in 1947, only sporadic human cases were reported from Africa and Asia.[96,97] In 2007, the first documented ZIKV outbreak was reported in Yap State, Federated States of Micronesia, and subsequently outbreaks were identified in Southeast Asia and the Pacific Islands.[98] In May 2015, the WHO reported the first local transmission of ZIKV in the Region of the Americas, with autochthonous cases identified in Brazil.[99] By December 2015, the Brazilian Ministry of Health estimated that 440,000 to 1,300,000 suspected cases of ZIKV disease had occurred in Brazil, and there had been further spread to many other countries.[100] Evidence suggesting an association of ZIKV infection with an increased risk for neonatal malformations and neurologic disorders prompted the WHO to declare the ZIKV outbreak a Public Health Emergency of International Concern on February 1, 2016.[101] By the end of 2016, local transmission had been reported in 48 countries or territories in the Americas. In the US between January 1, 2015 and June 8, 2016, 691 travel-associated cases had been reported from the 50 US states. In July 2016, local mosquito-borne transmission was reported for the first time in the US, in the state of Florida.

The primary mode of transmission of ZIKV is through the bite of an infected *Aedes* spp. mosquito. Other documented modes of transmission include intrauterine, intrapartum, and sexual transmission, and through laboratory exposure and blood transfusion.[102,103] Other theoretical modes include through breast milk and organ or tissue transplantation.

Most people infected with ZIKV do not develop symptoms. Characteristic clinical findings in patients who have symptoms are acute onset of fever with maculopapular rash, arthralgia, or conjunctivitis. Other commonly reported symptoms include myalgia, headache, retro-orbital pain, edema, and vomiting. ZIKV is transmitted in similar areas as dengue and chikungunya viruses, and it is difficult to distinguish diseases caused by these viruses on clinical features alone. ZIKV disease usually is mild, with symptoms lasting several days to weeks; hospitalization is uncommon; and the case-fatality rate is low. However, more severe presentations have been recognized, including severe thrombocytopenia, Guillain-Barré syndrome, meningoencephalitis, and acute myelitis.[102,104,105] Congenital ZIKV infection is of particular concern. The full spectrum of fetal and infant outcomes as a result of symptomatic or asymptomatic ZIKV infection in pregnant women is yet to be determined. An association between ZIKV infection and microcephaly has been confirmed, and additional severe brain, ocular, and other abnormalities have been reported.[106–109]

Prevention measures focus on avoidance of mosquito bites. Vaccine candidates are under development. Because of the potential severity of congenital ZIKV infection, the CDC recommends that all pregnant women consider postponing travel to areas where ZIKV transmission is ongoing. In addition, couples in which a woman is pregnant and the man has traveled to an area with active ZIKV transmission should use condoms or abstain from sex for the duration of the pregnancy. Prevention guidelines for other couples concerned about sexual transmission are also available[109] (http://www.cdc.gov/zika/transmission/sexual-transmission.html).

Persons with an illness consistent with ZIKV infection and possible exposure to ZIKV, including travel to an area with ZIKV transmission or sex without a condom with a man who traveled to an area of transmission, can be tested for ZIKV infection. Testing also can be considered for symptom-free pregnant women with possible exposure to ZIKV. Molecular and serologic testing methodologies are available for diagnosis; the appropriate test depends on the timing of possible exposure and symptom onset (http://www.cdc.gov/zika/hc-providers/diagnostic.html). No specific antiviral treatment is available. Treatment of symptoms may include rest, fluids, antipyretics, and analgesics. Aspirin and other nonsteroidal anti-inflammatory drugs should be avoided until dengue can be ruled out to reduce the risk for hemorrhage. In pregnant women with laboratory evidence of ZIKV virus infection, serial ultrasound examination should be considered to monitor fetal growth and anatomy, and referral to a maternal-fetal medicine or infectious diseases specialist is recommended. The CDC has developed guidelines for testing and management of pregnant women carrying a possibly infected fetus. Because maternal-infant transmission of ZIKV during delivery is possible, acute ZIKV disease should be suspected in an infant during the first 2 weeks of life who has a consistent illness and whose mother potentially was exposed within 2 weeks of delivery.[110] The most current information, including areas with ongoing ZIKV transmission, prevention measures, diagnostic testing recommendations, and guidelines on clinical management are available on the CDC website (http://www.cdc.gov/zika/index.html).

Other Flaviviruses of Medical Importance

Many other flaviviruses can cause sporadic or epidemic illness in humans and may cross-react in serologic tests for the viruses discussed above.[1] St. Louis encephalitis virus (SLEV) and Murray Valley encephalitis virus are mosquito-borne viruses in the same antigenic complex as JEV and WNV. Kyasanur Forest disease virus, louping ill virus, Omsk hemorrhagic fever virus, and Powassan virus are tickborne and genetically related to TBEV. Other flaviviruses reported to cause human illness are Apoi, Bagaza, Banzi, Bussuquara, Dakar bat, Ilheus, Koutango, Langat, Modoc, Ntaya, Rocio, Sepik, Spondweni, Usutu, and Wesselsbron viruses.[1]

Among these other medically important flaviviruses, SLEV and Powassan virus are found in the US. SLEV has been identified throughout much of the US and in parts of Central and South America. SLEV causes sporadic human cases and rare outbreaks, and disease is clinically indistinguishable from WNV disease. SLEV disease incidence has been substantially lower than WNV disease incidence since WNV was first identified in the US in 1999.[111] Powassan virus is endemic in parts of the northeastern and upper midwestern US and in parts of Canada and Russia. From 2003 to 2012, 45 cases of Powassan virus neuroinvasive disease were reported to in the US, but cases in children are rare.[67]

Diagnosis

Flavivirus infections are confirmed most frequently by measurement of virus-specific antibody in serum or CSF. Acute-phase serum specimens should be tested for virus-specific immunoglobulin M (IgM) antibody using an enzyme immunoassay or microsphere immunoassay. With clinical and epidemiologic correlation, a positive IgM test has good diagnostic predictive value, but cross-reaction with related arboviruses from the same family can occur. For most flavivirus infections, IgM is detectable 3 to 8 days after onset of illness and persists for 30 to 90 days, but longer persistence has been documented. Therefore, a positive IgM test result occasionally can reflect a past infection. Serum collected within 10 days of illness onset may not have detectable IgM, and the test should be repeated on a convalescent sample. IgG antibody generally is detectable shortly after IgM and persists for years. Plaque-reduction neutralization tests can be performed to measure virus-specific neutralizing antibodies. A fourfold or greater rise in virus-specific neutralizing antibodies between acute and convalescent phase serum specimens collected 2 to 3 weeks apart may be used to confirm recent infection or discriminate between cross-reacting antibodies in primary flavivirus infections. In patients who have been immunized or infected with another arbovirus from the same virus family in the past (i.e., who have secondary flavivirus infections), cross-reactive antibodies in both the IgM and neutralization assays may make it difficult to identify which flavivirus is causing the patient's illness.

Laboratory confirmation for patients with suspected DENV infection and disease onset ≤5 days prior can be made by detecting DENV nonstructural protein 1 antigen by immunoassay or DENV RNA by reverse transcriptase polymerase chain reaction; later in the illness, an IgM enzyme immunoassay can be used.[112] Diagnosis of all flavivirus infections can be made by nucleic acid amplification tests for RNA and viral culture on acute phase serum, CSF, or tissue specimens; however, YFV, DENV, and ZIKV are more likely to be detected using culture or nucleic acid amplification tests than are the neurotropic flaviviruses. Immunohistochemical staining can detect specific viral antigen in fixed tissue.

Antibody testing for common flavivirus diseases is performed in most state public health and many commercial laboratories. Confirmatory neutralizing antibodies, viral culture, nucleic acid amplification testing, immunohistochemical staining, and testing for less common flaviviruses are performed only at the CDC and selected other reference laboratories.

Prevention

Flaviviral infection can be prevented by avoiding exposure to the arthropods that transmit these viruses. Personal protective strategies include wearing repellent, staying in screened or air-conditioned dwellings, and avoiding outdoor activities during times when the vectors are most avidly seeking blood meals. The times of peak feeding vary between vectors; for example, *Aedes aegypti*, the principal vector of YFV in urban areas, DENV, and ZIKV, feeds primarily during the day. The *Culex* spp. vectors of WNV and JEV typically feed from dusk to dawn. Thus sleeping under insecticide-impregnated bed nets may help reduce the risk for JE but not the risk for dengue.[24,113] Wearing light-colored clothing and checking one's body for ticks and removing them promptly may decrease the risk for TBEV and other tickborne infections. Programs to decrease abundance of vector mosquitoes are important to reduce risk but may be difficult to implement and maintain. Effective vaccines are available for prevention of yellow fever, JE, and TBE; vaccines against dengue and WNV disease are under development.

Key Points

Epidemiology, Clinical Features, Diagnosis, Management, and Prevention of Flavirus Infections

Epidemiology

- More than 40 arthropod-borne flaviviruses described, but those most important in causing human illness are yellow fever, dengue, Japanese encephalitis, West Nile, tickborne encephalitis, and Zika viruses

- Transmitted to humans primarily through the bites of arthropods

- Worldwide distribution, but different flaviviruses found in specific geographical regions

Clinical Features

- Most infections asymptomatic

- Symptomatic illness usually manifests as one of three primary clinical syndromes: generalized febrile illness, neurologic disease, or hemorrhagic fever

Diagnosis

- Confirmed most frequently by measurement of virus-specific antibody in serum or cerebrospinal fluid, but cross-reaction with related flaviviruses can occur

Management

- No specific antiviral therapy available
- Treatment is supportive

Prevention

- Personal protective measures to avoid exposure to the arthropods that transmit these viruses
- Vaccines available for yellow fever, Japanese encephalitis, and tickborne encephalitis viruses

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Bunyaviruses

Barbara Knust, Marc Fischer

Description of Pathogen

The family Bunyaviridae contains five genera of viruses, including four that have important human pathogens: *Hantavirus, Nairovirus, Phlebovirus,* and *Orthobunyavirus.*[1] A wide range of clinical syndromes in humans exist among the pathogenic bunyaviruses, with severity of human infections ranging from mild febrile illnesses to illnesses with a high case-fatality rate. Important diseases include hantavirus pulmonary syndrome (HPS; *Hantavirus* genus), hemorrhagic fever with renal syndrome (HFRS; *Hantavirus* genus), Crimean-Congo hemorrhagic fever (CCHF; *Nairovirus* genus), Heartland virus disease (*Phlebovirus* genus), severe fever and thrombocytopenia syndrome (SFTS; *Phlebovirus* genus), Rift Valley fever (RVF; *Phlebovirus* genus), and encephalitis caused by California serogroup viruses (*Orthobunyavirus* genus). Owing to pathogenic potential and human-to-human transmission, CCHF virus is considered a biosafety level 4 agent and hantaviruses and RVF virus are biosafety level 3 agents.[2]

The biology of bunyaviruses, including reservoirs, disease syndromes, and transmission modalities, is diverse. All known pathogenic bunyaviruses have either mammal or arthropod reservoirs. Viruses of the *Nairovirus, Phlebovirus,* and *Orthobunyavirus* genera involve an arthropod vector as part of the long-term ecologic maintenance of the virus, with vector-borne transmission commonly involved in human infection. In contrast, hantaviruses are directly maintained in rodent and insectivore/arvicoline reservoirs without a vector-borne component to the transmission cycle.

Epidemiology

Hantaviruses

A wide diversity of hantavirus species have been discovered around the world (Table 219.1). All have been associated with rodent reservoirs and are distributed according to their reservoir. Viruses that are pathogenic to humans are divided among Old World and New World hantaviruses.

TABLE 219.1

Taxonomy and Epidemiologic Characteristics of Select Bunyaviruses

Genus	Species	Geographic Location	Reservoirs	Infection Route
Hantavirus	Important HPS-associated viruses include Sin Nombre virus and Andes virus; many other species exist	Large portions of North and South America	Rodents	Inhalation of rodent excreta, rodent bite
	Important HFRS-associated viruses include Hantaan virus, Dobrava virus, Saaremaa virus, Seoul virus, Puumala virus; other species exist	Large portions of Europe and Asia	Rodents	Inhalation of rodent excreta, rodent bite
Phlebovirus	Rift Valley fever virus	Central and South Africa, Egypt, Saudi Arabia, Yemen	Mosquitoes, ruminants serve as amplifying hosts	Blood or tissue of infected animals, mosquito bite
	Heartland virus	Midwest and southern United States	Unknown	Likely tick bite
	Severe fever with thrombocytopenia syndrome virus	China, Japan, Korea	Unknown	Likely tick bite, possible nosocomial bloodborne transmission
Nairovirus	Crimean-Congo hemorrhagic fever virus	Africa, eastern Europe,	Maintained between ticks and small	Tick bite, blood or tissue of infected animals;

		Middle East, central Asia	mammals, farm animals can be infected	nosocomial and person-to-person transmission
Orthobunyavirus	La Crosse virus	Eastern United States	Rodents	Mosquito bite
	Jamestown Canyon virus	Widely distributed throughout United States	Deer	Mosquito bite

HFRS, hemorrhagic fever with renal syndrome; HPS, hantavirus pulmonary syndrome.

A wide variety of New World hantaviruses can cause disease in humans. All have rodent reservoirs, and pathogenic viruses are known to exist in the United States, Canada, Panama, and across a large portion of South America.[3] Within the US, most cases are due to Sin Nombre virus infection and occur in the western portion of the country.[4,5] A number of species of hantavirus are associated with HPS across South America.[6,7] The route of infection is typically through inhalation of rodent urine or feces or by bite from an infected rodent. Infections are often associated with cleaning or other activities that result in the aerosolization of infectious material from buildings or structures with rodent contamination.[8–10]

Pathogenic Old World hantaviruses are found across Europe and Asia, with Hantaan and Seoul viruses associated primarily with China, Korea, and far east Russia; Dobrava and Puumala viruses are found in western Russia and Europe.[11–15] The globally distributed Norway Rat (*Rattus norvegicus*) is the reservoir for Seoul virus, and cases of Seoul virus can therefore be found across the world. Domestically acquired cases of HFRS due to Seoul virus have been documented in North America, and serologic evidence suggests the presence of the virus in rodent populations in a number of cities in North and South America.[16–18] As with HPS, hantavirus infections resulting in HFRS occur through inhalation of rodent excreta or by rodent bite.

Rift Valley Fever

RVF is known for explosive outbreaks in animals and people. The causative virus is maintained though transovarian transmission in mosquitoes (most commonly *Aedes* spp.), and infected eggs can remain dormant for many years in dried waterbeds and flood plains, with no evidence of activity. Small numbers of wild ungulates may become infected in this enzootic cycle. Outbreaks typically occur after heavy rains and flooding, where expanded wetland areas lead to increased mosquito breeding, resulting in large numbers of infected mosquitoes from reservoir pools. Domestic ruminants (e.g., cattle, sheep, and goats) become clinically affected, with high fatality and abortions observed due to infections. Evidence of RVF activity in animals often precedes evidence of human infections during outbreaks.[19,20]

Farmers, abattoir workers, and other persons with occupational exposures to animals are at greater risk for developing RVF because infections occur through direct contact with blood or bodily fluids of infected animals, often through slaughtering or handling meat.[21,22] Although less common, humans also can be infected through a mosquito bite. There is no evidence of person-to-person or nosocomial transmission. RVF is endemic across a large portion of Africa, and in recent decades, outbreaks also have occurred in the Middle East (Saudi Arabia and Yemen).[20,23–25] Major outbreaks have recently occurred in Kenya, Tanzania, Sudan (2006–2007), Madagascar (2008–2009), South Africa (2010), and Mauritania (2012).[26–31]

Crimean-Congo Hemorrhagic Fever

CCHF virus is transmitted primarily by *Hyalomma* spp. ticks, which are distributed across much of Europe, Africa, and Asia. Cases or seroprevalence has been documented in central Africa, South Africa, the Middle East, central Asia, and southeastern Europe.[32–34] Although not apparent before 2002, thousands of cases occur each year in Turkey.[35] CCHF virus is maintained through a 2-year transmission cycle in which the tick nymphs feed on small mammals in their first year of life and then molt to adults and feed on livestock (e.g., cattle, sheep, and goats) and humans. Overt symptomatic disease is known to occur only in humans. Human infection results from the bite of an infected tick or by contact with tissues, blood, or milk from infected animals.[36–38] Persons who work closely with livestock are at greater risk for developing CCHF, either through direct contact with the animals or tissues, or from bites of ticks or handling ticks associated with the livestock.

California Serogroup Viruses

Several California serogroup viruses are endemic in the US (i.e., La Crosse, Jamestown Canyon, snowshoe hare, Trivittatus, Keystone, and California encephalitis viruses); however, most human disease is associated with La Crosse virus.[39–42] La Crosse virus is the most common cause of arthropod-borne viral (arboviral) infections of the central nervous system among children in the US.[43–47] On average, 80 to 100 cases of La Crosse virus meningitis or encephalitis are reported annually in the US, with almost 90% of them occurring in children.[43–45] La Crosse virus is transmitted by *Aedes triseriatus*, a tree-hole breeding mosquito; small rodents (e.g., grey squirrels and chipmunks) serve as the primary amplifying hosts.[47–49] The virus is endemic in the eastern half of the US, with the highest numbers of cases in Ohio, West Virginia, North Carolina, and Tennessee.[43–45] Infections peak in the summer months of July to September.[43–45]

Jamestown Canyon virus is another mosquito-borne California serogroup orthobunyavirus that is closely related to La Crosse virus.[39–42,49] *Aedes* and *Ochlerotatus* spp. mosquitoes likely are the primary vectors, and deer appear to be important amplifying hosts.[41,50] Although Jamestown canyon virus is widely distributed throughout temperate North America, reports of human Jamestown canyon virus infection have been rare, in part owing to a lack of available diagnostic testing. From 2000 to 2013, 31 cases of Jamestown Canyon virus disease were identified among residents of 13 US states.[51] Most cases occurred during late spring to early fall, but, in contrast to La Crosse virus, only 15% occurred in children. Sixteen (52%) of the cases were identified in 2013, the first year the Centers for Disease Control and Prevention (CDC) implemented routine Jamestown Canyon virus antibody testing, suggesting the disease has been historically under recognized.

Heartland Virus

Heartland virus is a newly identified phlebovirus that was first isolated from two northwestern Missouri farmers hospitalized with fever, leukopenia, and thrombocytopenia in 2009.[52] Based on the patients' clinical findings and their reported exposures, the virus was suspected to be transmitted by ticks. Heartland virus is found in the Lone Star tick (*Amblyomma americanum*).[53] Six additional cases of Heartland virus disease were identified during 2012–2013; four of those patients were hospitalized, including one with comorbidities who died.[54,55] All patients were men 50 years and older (median, 58 years; range, 50–80 years). Patients had symptom onset during May to September (three cases in May, one in July, and two in September). All of the patients had fever, leukopenia, and thrombocytopenia when first evaluated.

Severe Fever With Thrombocytopenia Syndrome Virus

Severe fever with thrombocytopenia syndrome virus (SFTSV) was identified in China in 2011 from patients presenting with fever, leukopenia, thrombocytopenia, and multiorgan dysfunction.[56] One case series of four pediatric SFTSV cases suggests that the clinical findings in children are less specific (e.g., fever, malaise, and gastrointestinal symptoms) and less severe.[57] Only one patient had thrombocytopenia; there were no hemorrhagic or neurologic manifestations and no deaths.

A reported tick bite in the 2 weeks before illness onset was an independent risk factor for SFTSV disease, and SFTSV or viral RNA has been identified in *Haemaphysalis longicornis* and *Rhipicephalus microplus* ticks.[58–60] Subsequent studies have identified SFTSV-positive ticks and human cases in South Korea and Japan, and the widespread geographical distribution of *H. longicornis* ticks (e.g., China, Korea, Japan, Australia, New Zealand, and Pacific Islands) suggests that SFTSV may have a broader distribution.[61–63] Several cluster investigations have suggested person-to-person transmission of SFTSV through direct contact with blood or bloody secretions.[64–66]

Clinical Manifestations

Hantavirus Pulmonary Syndrome

The incubation of HPS is from 1 to 8 weeks.[67] Cases begin with a prodromal syndrome, with symptoms including fever, myalgia, nausea, vomiting, and diarrhea (Table 219.2). For patients who develop pulmonary symptoms, bilateral noncardiogenic pulmonary edema can develop within a matter of hours, which may radiographically resemble acute respiratory distress syndrome.[4,68–70] Myocardial depression occurs in severe cases of HPS, with death often due to hypoxia and hypovolemia; the case-fatality rate is approximately 35%.[71] Clinically, HPS is similar in children and adults.[72,73] Mild cases of laboratory-confirmed hantavirus infection without pulmonary symptoms have been reported, although it appears to be less frequently observed than HPS.[16]

TABLE 219.2

Clinical Characteristics of Bunyavirus Diseases

Disease	Viruses	Common Symptoms	Treatment
Hantavirus pulmonary syndrome	Important viruses include Sin Nombre virus and Andes virus; many other species exist	Febrile prodrome followed by acute respiratory distress	Supportive; extracorporeal membrane oxygenation as possible salvage therapy
Hemorrhagic fever with renal syndrome	Hantaan virus, Dobrava virus, Saaremaa virus, Seoul virus, Puumala virus; other species exist	Febrile prodrome, possible renal failure, hemorrhage, and shock	Supportive; ribavirin if administered early in disease (patients usually seen late)
Rift Valley fever	Rift Valley fever virus	Febrile illness, possible hemorrhage, hepatitis, meningitis, retinitis	Supportive
Crimean-Congo hemorrhagic fever	Crimean-Congo hemorrhagic fever virus	Febrile prodrome, myalgia, nausea/vomiting, diarrhea, hemorrhage; high case-fatality rate	Supportive: ribavirin if administered early in disease
La Crosse virus disease	La Crosse virus	Commonly asymptomatic or nonspecific febrile illness; possible encephalitis or meningitis	Supportive
Heartland virus disease	Heartland virus	Fever, leukopenia, and thrombocytopenia	Supportive
Severe fever with thrombocytopenia syndrome	Severe fever with thrombocytopenia syndrome virus	Fever, leukopenia, thrombocytopenia, and multiorgan dysfunction	Supportive

Hemorrhagic Fever With Renal Syndrome

The incubation period for HFRS ranges from 7 to 42 days. After clinical disease occurs, it typically progresses through five stages: febrile, hypotensive, oliguric, polyuric, and convalescent (see Table 219.2).[74] Severe manifestations of HFRS include renal insufficiency, shock, and hemorrhage.[11,75,76] Prognosis of HFRS varies, depending on the viral species. The most severe disease is associated with Hantaan and Dobrova/Saaremaa viruses, with case-fatality rates as high as 15%. For Seoul virus disease, the case-fatality rate is about 1%.[11,74,75] Puumala virus, which is endemic to central and northern Europe, causes a similar but less severe form of disease called *neuropathica epidemica,* with an overall case-fatality rate of <0.1%.[77]

Rift Valley Fever

Most human cases of RVF result in mild febrile illness, with myalgias, nausea, and vomiting. A small proportion of cases result in severe disease which can include hemorrhagic symptoms, hepatitis, or encephalitis (see Table 219.2).[21] Hepatitis or retinitis also may develop 1 to 4 weeks after onset of illness.[21,78,79] The overall case-fatality rate for RVF is 1% to 2%.

Crimean-Congo Hemorrhagic Fever

CCHF has an estimated incubation period of 3 to 7 days.[80] The prehemorrhagic stage of the disease is characterized by fever, headaches, dizziness, myalgias, nausea, vomiting, abdominal pain, and diarrhea (see Table 219.2).[36,37] Of the bunyaviruses, CCHF virus has the highest propensity for hemorrhagic manifestations that can include petechiae, epistaxis, hematemesis, melena, gingival bleeding, hematuria, and vaginal bleeding.[32,36,81] Case-fatality rates range from 1% to >50%.

California Serogroup Viruses

Most La Crosse virus infections are asymptomatic or clinically inapparent (see Table 219.2).[41,82–84] The incubation period for symptomatic infections ranges from 5 to 15 days. Clinical findings include fever, headache, vomiting, and fatigue.[41,82–84] Neuroinvasive disease is most common in children and manifests as meningitis or encephalitis.[43–47,83–88] In these cases, cerebrospinal fluid shows a moderately elevated white blood cell count, normal to mildly elevated protein, and normal glucose.[84–88] Computed tomography of the brain is usually normal, whereas electroencephalographic abnormalities are more common and often resemble those seen in cases of herpes simplex virus encephalitis.[41,84,85] Although seizures are common during the acute illness, fatal cases are rare (<1%), and most patients recover completely. However, neurologic sequelae have been reported, including recurrent seizures, hemiparesis, and cognitive and neurobehavioral abnormalities.[84–89]

Of the 31 Jamestown Canyon virus disease cases identified in the US from 2000 to 2013, 17 (54%) presented with meningitis or encephalitis.[51] Fifteen (48%) patients were hospitalized, but there were no deaths. In addition to undifferentiated febrile illness and neuroinvasive disease due to Jamestown Canyon virus infection, previous reports have described a respiratory syndrome with cough, rhinitis, and sore throat.[41]

Laboratory Findings and Diagnosis

Bunyaviruses result in acute infections in humans, with a short period of viremia and no long-term or latent maintenance of the virus. For some diseases (e.g., CCHF, RVF, Heartland virus, SFTSV), direct detection of the virus can be performed by polymerase chain reaction assay, antigen detection, or viral culture during acute stages of disease. However, most bunyavirus infections are confirmed by serology.

Laboratory diagnosis of California serogroup arboviral infections is generally accomplished by testing of serum or cerebrospinal fluid to detect virus-specific immunoglobulin M antibodies.[47] Plaque reduction neutralization tests can be performed to measure virus-specific neutralizing antibodies and to potentially discriminate among cross-reacting antibodies from closely related California serogroup viruses. In fatal cases, nucleic acid amplification, histopathology with immunohistochemistry, and virus culture of autopsy tissues can also be useful. Only a few state laboratories or other specialized laboratories, including those at CDC, are capable of performing this specialized testing.

Treatment

Ribavirin is not efficacious in the treatment of HPS, and no other specific antiviral therapies are available.[90,91] Some studies suggest the utility of extracardiopulmonary oxygenation as a salvage therapy in the management of HPS.[92,93] Data suggest efficacy of ribavirin in improving the course of HFRS (due to Hantaan virus), when administered early in clinical disease.[94] The efficacy of ribavirin in the treatment of CCHF remains controversial. Some data suggest efficacy if administered as postexposure prophylaxis, as well as possible improved disease prognosis if administered early in the disease.[95] Treatment for RVF, La Crosse virus and other California serogroup viruses, Heartland virus, and SFTSV is supportive.

Prevention

Although veterinary vaccines are available for RVF, no human vaccines are licensed and widely available for any of the bunyaviruses, with the exception of hantavirus vaccines available in Korea and China.[96,97] In North America, there is no evidence of person-to-person or nosocomial transmission of hantaviruses, whereas person-to-person transmission of Andes virus in Argentina and Chile has been documented,[98–100] and thus contact precautions are advised when caring for suspected cases in endemic areas. Person-to-person, particularly nosocomial, transmission of CCHF and SFTSV has been documented.[64–66,101,102] Transmission is most probable after contact with blood or body fluids of infected individuals; standard contact precautions are recommended for handling CCHF and STSFV disease cases. Prevention of La Crosse virus and other California serogroup viruses relies on personal protection and vector control measures to reduce the risk for mosquito bites. Because Heartland virus and SFTSV likely are transmitted through infected ticks, prevention depends on using insect repellents, wearing long sleeves and pants, avoiding bushy and wooded areas, and performing tick checks after spending time outdoors.

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Hepatitis C Virus

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In the 1970s, after development of routine diagnostic testing for hepatitis A and hepatitis B viruses, a small proportion of acute viral hepatitis could not be attributed to these or other known pathogens. The search for the major etiologic agent of "non-A, non-B hepatitis" culminated in 1989 with discovery of hepatitis C virus (HCV).[1] Although substantially more prevalent among the adult population, HCV infection does occur in children and should be considered a potential diagnosis when relevant clinical or epidemiologic factors are present.

Pathogen

HCV is an enveloped single-stranded RNA virus, of approximately 9500 nucleotides, belonging to the *Hepacivirus* genus in the Flaviviridae family. There are at least six genotypes of HCV, numbered 1 through 7, the nucleic acid sequences of which differ by >30%.[2] More than 50 subtypes that differ by 20% to 25% also have been described. The most common subtypes are 1a, 1b, 2a, and 2b.[3] The prevalence of the genotypes varies by continent and region of the world. Genotype 1 is most prevalent worldwide, comprising 46% of all HCV cases globally and accounting for >75% of cases in the United States; genotype 3 is the next most prevalent worldwide with 30% of cases; genotype 4 is prevalent in Africa and the Middle East, especially Egypt; genotype 5 is prevalent in southern Africa; and genotype 6 is the least prevalent genotype worldwide and is found in a few Southeast Asian countries.[3] Genotype 7 recently was discovered as a new lineage distinct from genotypes 1 to 6 and originated in the Democratic Republic of Congo.[2]

Data on environmental survival, disinfection, sterilization, and decontamination procedures for HCV are limited. Techniques to culture HCV have been developed[4] but are difficult to perform and not always reliable. The inability to culture HCV easily has limited many research efforts, including development of vaccines. One study suggests that HCV in dried plasma can cause infection in experimental animals when left at room temperature for at least 16 hours but not after 4 days.[5] A more recent study suggests that an HCV reporter virus still can infect human tissue cultures after remaining at room temperature for up to 6 weeks.[6] Use of chemical germicides that are capable of producing at least an intermediate level of disinfection activity (e.g., 0.1% glutaraldehyde or 500 ppm free chlorine from sodium hypochlorite – 2 tablespoons of household bleach in 1 gallon of water) or conventional sterilization processing such as steam autoclaving is thought to be suitable for inactivating HCV.[7]

Pathogenesis and Immunity

The primary site of hepatitis C viral replication is the hepatocyte. In the acute phase, histopathologic findings in the liver are typical of acute viral hepatitis and include ballooning degeneration, focal necrosis, and hepatocellular apoptosis.[8,9] These findings are believed to be due to the immune response to virus-infected cells rather than to a direct cytopathic effect of the virus.

The high rate of chronicity with HCV infection in adults is partly attributable to failure of the virus to elicit effective neutralizing antibody. High rates of mutation in the single-stranded RNA genome of HCV are believed to play a role in the pathogen's ability to evade the immune system. In an infected person, several closely related but genetically distinct strains of HCV, termed *quasispecies,* generally occur.[10] Typically, one dominant variant accounts for the majority of circulating virus at any given time. Over time, this variant often loses dominance and is replaced by a new dominant variant.[11,12] Presumably, evolution of quasispecies is a result of the immune response to the dominant variant, resulting in sequential selection of resistant mutants. In addition, sequential infection with different genotypes has been observed in humans.[13,14] Mechanisms associated with persistence and clearance of HCV are not well understood and likely involve both host and viral factors. The heterogeneity of HCV prevents development of conventional vaccines, allows the virus to escape eradication by the host's immune system, and affects the completeness of the response to antiviral therapies with interferon (IFN).[15]

Epidemiology

Prevalence and Incidence

In the United States, the National Health and Nutrition Examination Survey (NHANES) conducted during 2003–2010 found that 1.3% of the noninstitutionalized population older than 6 years were anti-HCV positive, and 1% were HCV RNA positive.[16] Prevalence estimates among children 6 to 19 years of age from NHANES 2003–2010 could not be calculated because so few HCV infections were identified in this age group; therefore it is presumed to be very rare.[16] The prevalence of HCV infection among adolescents with risk factors for HCV infection, such as injection drug use, has been shown to be higher than in the general pediatric population.[17] In a survey of newly incarcerated adolescent detainees, 2% had evidence of HCV infection, 95% of whom reported injection drug use.[18] In a survey of homeless adolescents, of whom one third were injection drug users, the prevalence of HCV infection was 4.4%.[19]

The incidence of HCV infection in the US reached a peak in the 1980s, with approximately 250,000 infections per year, but fell rapidly during the early 1990s. In 2012, an estimated 21,870 new infections occurred.[20] If the incidence remains relatively low, the prevalence of HCV infection among women of childbearing age without behavioral risk factors such as intravenous drug use will continue to decline, and the prevalence among children and adolescents should decline as well.

Transmission

HCV is transmitted most efficiently through direct percutaneous exposure to blood. Mucous membrane exposures to blood also can result in HCV transmission, but this route is less efficient. Although HCV can be detected in saliva, semen, human milk, and other body fluids of some infected persons, these body fluids are not believed to be efficient vehicles of transmission.[21] HCV does not penetrate intact skin spontaneously, and airborne transmission does not occur.[22]

In pediatric practice, perinatal infection currently accounts for most cases of HCV infection, although older children and adolescents can be at risk for HCV infection from injection drug use, sexual transmission, or acquisition from blood, blood products, or solid organ transplants.

Perinatal Transmission and Risk Factors

Among HCV-infected infants and young children in developed countries, perinatal exposure is the most common source of infection. The rate of vertical transmission of HCV is estimated to be 5%, with rates varying between 0% and 25%.[23–26] Most infected infants do not have a positive RNA test during the first month after birth, suggesting that infection occurs at the time of delivery rather than in utero. By 3 months of age, 90% of infected infants test positive for HCV RNA, and by 6 months of age, almost all test positive.[24,27–30] Because maternal antibody can remain detectable in uninfected infants for more than a year, anti-HCV testing is not recommended before 18 months of age.[31]

HCV Viremia.

Perinatal transmission is almost always limited to women with detectable HCV RNA.[25,29,30,32–34] The level of viremia has been shown to be a determinant of perinatal transmission in some studies. For example, women with viral loads $<10^5$ copies/mL were less likely to transmit HCV, even if they were coinfected with HIV.[33–38] However, other studies have failed to demonstrate this association.[24,29,39]

Maternal HIV Coinfection.

The risk for transmission of HCV is 2- to 7-fold higher in infants born to mothers coinfected with HCV and HIV compared with children born to mothers infected with HCV alone.[24,40–42] Higher HCV RNA levels among HIV-coinfected women may explain in part the increased risk for vertical transmission. HIV infection also was shown to facilitate entry and replication of HCV in blood cells which might increase the risk for perinatal transmission.[43,44] In addition, compared with infants who do not become infected with HIV, infants of coinfected mothers who develop HIV infection have a higher risk for developing HCV infection.[38]

Prolonged Rupture of Membranes.

Rupture of membranes ≥6 hours before delivery has been associated with higher rates of transmission in several studies.[24,27,33,45]

Obstetric Procedures.

Data remain limited on the role of obstetric procedures in promoting HCV transmission. Internal fetal monitoring was shown to be associated with transmission of infection.[24,46] One study linked amniocentesis to HCV transmission in infants[47]; however, another study showed that only 6% of women who underwent amniocentesis during the fourth month of pregnancy had HCV in their amniotic fluid.[48]

Sex of the Infant.

A few studies have indicated that the rate of perinatal transmission of HCV infection is twofold higher in females compared with males, suggesting that hormonal or genetic factors may influence susceptibility or response to infection.[33,49]

Factors Not Associated With Perinatal Transmission

Mode of Delivery.

Based on well-controlled cohort studies, the mode of delivery (vaginal versus cesarean) does not appear to affect risk for transmission.[25,29,39,45,50,51]

Breastfeeding.

More than 20 prospective cohort studies have not shown any increased risk for HCV infection among breastfed infants compared with formula-fed infants despite 2 years of follow-up after delivery.[23,25,28,29,33,39,45,46,50,51–62] Only one prospective study showed potential perinatal transmission of HCV through breastfeeding. In this study, all three women who transmitted the infection to their babies developed symptomatic liver disease during the transmission period and had high HCV RNA titers in serum.[63]

Other Modes of Transmission and Risk Factors

Injection Drug Use.

HCV is spread efficiently through sharing of materials used to inject drugs. Several studies have demonstrated that, in addition to sharing of needles and syringes, sharing of paraphernalia used to inject drugs (e.g., water for rinsing needles and syringes or dissolving drugs, "spoons" or "cookers" used for preparing drugs, and "cottons" used to filter the drug solution as it is drawn into the syringe) also plays an important role in transmitting HCV.[64–66] In the US, injection drug use accounts for about 75% of acute HCV infections among persons 30 years or younger.[17] Historically, approximately 80% of injection drug users became infected within the first 2 years of beginning to inject, with >90% infected within 5 years.[66] The incidence of HCV infection among injection drug users in the past decade may be lower, but is still in the range of 15% to 20% per year.[67] As a consequence, people who have ever injected drugs, even if only briefly, may have been infected with HCV and should be screened for evidence of infection (Box 220.1).

Box 220.1

Recommendations for Hepatitis C Virus Testing

Test Routinely on the Basis of Risk

Persons who ever injected illegal drugs, including those who injected once or only a few times many years ago

Persons with selected medical conditions, including:

- Persons who received clotting factor concentrates produced before 1987

- Persons who ever received long-term hemodialysis
- Persons with persistently abnormal serum alanine aminotransferase levels

Prior recipients of transfusions or organ transplants, including:

- Persons who were notified that they received blood from a donor who later tested positive for hepatitis C virus (HCV) infection
- Persons who received a transfusion of blood or blood components before July 1992
- Persons who received an organ transplant before July 1992

All persons born between 1945 and 1965

Test Routinely on the Basis of a Recognized Exposure

Healthcare, emergency medical, and public safety personnel after needlesticks, sharps, or mucosal exposures to HCV-positive blood

Children born to HCV-positive women:

- Testing of infants for anti-HCV should be performed no sooner than 18 months of age.
- If earlier diagnosis of HCV infection is desired, reverse transcriptase polymerase chain reaction testing for HCV RNA can be performed at 1–2

months of age and repeated at 6 months of age.

Routine Testing Is Not Recommended (Unless Risk Factors or Exposures as Above)

Healthcare, emergency medical, and public safety workers

Pregnant women

Household (nonsexual) contacts of HCV-positive persons

The general population

Routine Testing Is of Uncertain Need

Settings not confirmed as risk factor or in which prevalence of infection unknown:

- Recipients of transplanted tissue (e.g., corneal, musculoskeletal, skin, ova, sperm)
- Users of intranasal cocaine and other noninjecting illegal drugs
- Persons with a history of tattooing or body piercing

Settings confirmed as risk factor but in which prevalence of infection low:

- Persons with a history of multiple sex partners or sexually transmitted infections
- Long-term steady sex partners of HCV-positive persons

Testing Request by Any Person

Anyone who wishes to know or is concerned regarding their HCV infection status should be provided the opportunity for counseling, testing, and appropriate follow-up.

Sexual Contact.

Sexual contact is not an efficient mode for transmission of HCV infection.[68] Based on available data, there is no increased risk for transmission of HCV among heterosexual couples in monogamous relationships. However, the risk is almost double among people having multiple sexual partners (although this association may be confounded by increased likelihood of injection drug use with increased number of partners) or among those already having a sexually transmitted infection. In addition, the risk for HCV infection through sexual contact increases fourfold among HIV-infected men and women.[68]

Household Contact.

Although rare, transmission among nonsexual household contacts also can occur. The presumed mechanism of transmission is direct or inapparent percutaneous or permucosal exposure to infectious blood or body fluids containing blood.[69] In one documented episode, an HCV-infected mother transmitted HCV to her hemophiliac child during performance of home infusion therapy, presumably when she sustained an unintentional needlestick injury and subsequently used the contaminated needle in the child.[70]

Healthcare Settings.

HCV can be spread through exposures in the healthcare setting. Some body fluids, including cerebrospinal fluid, synovial fluid, pleural fluid, peritoneal fluid, and amniotic fluid, are considered potentially infectious. Feces, nasal secretions, saliva, sputum, sweat, tears, urine, and vomitus are not considered potentially infectious unless they contain blood. Transmission between patients in the healthcare setting generally is associated with inadequate infection prevention practices, such as reuse of needles and syringes and other failures of aseptic technique, contamination of multidose vials, or inadequate cleaning of equipment.[71–75]

There are no formal screening recommendations for people who may have undergone injections or medical procedures in settings with inadequate infection prevention practices. Nonetheless, clinicians should be aware that infection control procedures in many parts of the world are poor and that patients may have been exposed to HCV through unsafe injection practices and failure to follow appropriate aseptic techniques during provision of medical care.

Transfusion of Blood and Blood Products.

Transfusion-acquired HCV infection probably accounted for most HCV infections in children in the 1970s and 1980s, particularly among children undergoing cancer chemotherapy or open-heart surgery.[76–78] A preliminary survey of cancer survivors who received blood transfusions at St. Jude Children's Research Hospital from 1961 to 1992 found 7% to be infected with HCV.[79] Prevalence was highest (11%) in children who received transfusions before 1986. Since 1992, when second-generation HCV enzyme immunoassay (EIA) screening was implemented, the risk for HCV infection from a single transfusion was considered to be <1 per 100,000 units.[79] Nucleic acid testing (NAT) of all donors for HCV RNA, implemented in 1999, has reduced this risk even further to 1 per ≥2 million blood units.[80]

Plasma-derived products such as clotting factor concentrates frequently were contaminated with HCV until 1987, when manufacturers incorporated effective viral inactivation steps into their purification processes.[81] Consequently, people with hemophilia who were treated with factors XIII and IX manufactured before 1987 have a high prevalence of HCV infection.[82] Since December 1994, all immunoglobulin products (intravenous and intramuscular) commercially available in the US must undergo an inactivation procedure or be confirmed as not containing HCV RNA before release.

Organs and Tissues.

Organ and tissue donors are routinely tested for HCV NAT, and transmission through this route is rare. In the past when anti-HCV testing was used instead of NAT, it was possible for a donor to have been infected recently enough to have not seroconverted by the time the organs were procured.[83] Transmission of HCV from an infected deceased tissue donor to a pediatric recipient through use of a cardiopulmonary patch has occurred.[84]

Clinical Manifestations and Natural History

Infants with vertically acquired HCV infection do not usually become icteric or symptomatic, and a substantial proportion have normal or only mildly elevated serum alanine aminotransferase (ALT) levels.[34,49,85] In the 20% to 30% of acutely infected older children and adults who are symptomatic, symptoms usually are mild and indistinguishable from symptoms of other acute viral hepatitides, including jaundice, nausea, anorexia, and right upper-quadrant abdominal pain.[86] Fulminant hepatitis C has been reported, including cases in an infant and a child, but is rare.[87]

The natural history of HCV infection in children differs slightly between perinatally acquired and transfusion-acquired infections (Fig. 220.1). Although the long-term progression of liver disease in HCV infection acquired in infancy and childhood is not well understood, longitudinal studies conducted to date indicate a milder progression of HCV infection in children compared with adults. Infections acquired in infancy are more likely to resolve spontaneously than infections acquired during adulthood. About 20% of perinatally infected children clear the virus during the first 2 years of life, and up to 55% of children with posttransfusion-acquired HCV clear the virus.[49,78,88,89] Most children with chronic infection are symptom free, and hepatomegaly is observed in only 10%. However, fatigue, particularly in teens and young adults, is associated commonly with persistent HCV infection.

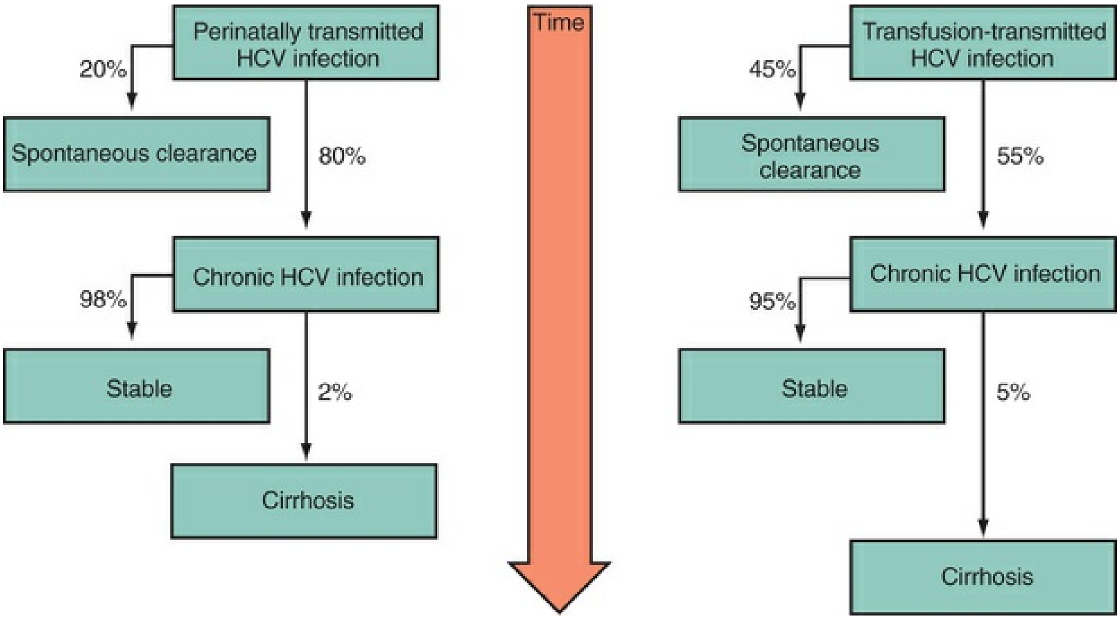


FIGURE 220.1 Natural history of hepatitis C virus (HCV) infection in children.

During chronic infection, about 23% of children have normal serum ALT levels, whereas 25% have consistently high serum ALT levels.[88,90,91] Progression to fibrosis increases with age, and development of advanced liver disease in children is uncommon until >20 years have elapsed since infection. Patients with anorexia, weight loss, abdominal pain, hepatomegaly, and splenomegaly are likely to have advanced liver disease. A study in a quaternary referral center showed that 7 (8%) of 91 children with other comorbid medical conditions developed cirrhosis at a mean age of 12 years. Four of the 7 required transplantation, all of whom had recurrent HCV infection after transplantation and 2 of whom died.[92] The authors recommended treatment to clear the infection before transplantation in order to achieve better prognosis. In another study, 5 (4%) of 121 infected children had bridging fibrosis, and 2 had cirrhosis. Children with fibrosis were older and more likely to have higher serum ALT levels and inflammation on biopsy, suggesting that likelihood of fibrosis increases with time.[93] In another series of 332 HCV-infected children with persistent viremia, 6 (2%) children progressed to decompensated cirrhosis with a mean duration of 10 years (±6 years) between HCV exposure and diagnosis of cirrhosis.[49] Children with genotype 1 are more likely to progress to advanced disease compared with those with genotype 3. Vertically infected children develop cirrhosis earlier than transfused children with no underlying systemic disease. In a study of 67 adolescents and young adults (mean age, 20 years) who tested positive for anti-HCV and had received blood transfusions as infants or young children, 45% of participants cleared the infection, and only three had histologic evidence of progressive liver damage, two of whom also had congestive heart failure.[78] The median time to develop end-stage liver disease among 392 patients with posttransfusion HCV infection was 33 years for those infected between the ages of 21 and 30 years, and only 4% of patients infected before 20 years of age had cirrhosis.[94]

Progression of HCV infection and development of severe liver disease is accelerated in the presence of comorbid conditions such as thalassemia, iron overload, childhood cancer, and HIV coinfection. Children who received blood transfusions for thalassemia are at risk for liver injury from hemochromatosis and after HCV infection have higher risk for progression to cirrhosis.[95–97] A nationwide survey of complications of thalassemia major in North America revealed cirrhosis rates to be 4%, 10%, and 15% for people 0–15, 16–24, and 25 years or older, respectively.[98] Iron overload also may diminish the response to treatment for HCV infection.[99] Children with hemophilia have higher risk for morbidity and mortality due to HCV infection, although end-stage liver disease is uncommon before adulthood.[100] Among children with leukemia, advanced liver disease did not develop during 13 to 27 years of follow-up.[101] In a study of the natural history of HCV among children with inherited bleeding disorders, cirrhosis developed in 75% of children with HIV coinfection, and death was reported in one child also coinfected with HIV.[89]

Hepatocellular carcinoma has been reported rarely among HCV-infected children. A retrospective survey of survivors of childhood cancer from a single medical center who had received blood transfusions before donor screening identified two HCV-infected patients who developed cirrhosis and died of hepatocellular carcinoma approximately 25 years after they were likely to have been infected.[102]

A number of extrahepatic conditions associated with HCV infection in adults, including cryoglobulinemia, glomerulonephritis, and porphyria cutanea tarda, are not common in children.

Data from people infected with HCV at a young age indicate that one third or more apparently resolve their infections. Among the other two thirds, chronic liver disease appears to progress slowly, and serious sequelae are rare during the first 2 decades after infection. The slower progression of HCV in childhood probably is related to the reduced frequency of comorbid factors such as alcohol consumption, hemochromatosis, and nonalcoholic fatty liver disease compared with adults.

Screening and Diagnostic Testing

Screening

Healthcare professionals should ascertain the risk for HCV infection in all patients, including pregnant women and adolescents. In addition, any person with persistent, unexplained elevations in serum ALT level, regardless of risk factors, should be tested for HCV. Furthermore, because people with HCV infection might be reluctant to disclose certain risk factors, any person concerned about his or her infection status should be given appropriate counseling and testing.[31]

Infants of women known to be HCV infected should be screened for HCV RNA on two occasions between the ages of 2 and 6 months or be tested for anti-HCV after 18 months of age. HCV testing should be offered routinely to people most likely to be infected with the virus (see Box 220.1). Routine HCV testing is not recommended for household contacts of HCV-positive persons unless a history exists of a direct percutaneous or mucosal exposure to blood. Identification of people at risk for HCV infection provides an opportunity for testing to determine their infection status, medical evaluation to determine their disease status if infected, and antiviral therapy if appropriate. It also provides the infected person an opportunity to obtain information about how to prevent further liver damage and prevent transmitting infection to others (Box 220.2).

Box 220.2

Key Counseling Messages for Persons Who Test Positive for Hepatitis C Virus Infection

To Protect the Liver From Further Harm, Hepatitis C

Virus (HCV)-Positive Persons Should:

Not start any new medicines, including over-the-counter and herbal medicines, without checking with their physician

Be vaccinated against hepatitis A and B

Avoid drinking alcohol

HCV-Positive Persons Should Be Advised:

HCV is *not* spread by sneezing, hugging, coughing, food or water, sharing eating utensils or drinking glasses, or casual contact.

HCV-positive persons should *not* be excluded from work, school, play, childcare, or other settings on the basis of their HCV infection status.

To cover cuts and sores on the skin to keep from spreading infectious blood or secretions

Not to share toothbrushes, dental appliances, razors, or other personal-care articles that might have blood on them with other people

To discuss the risk for transmitting HCV with their sexual partners. Although risk for transmission is low, they may decide to use barrier precautions (e.g., latex condoms).

For HCV-Positive Women Considering Pregnancy or Who Have Had Children:

No evidence exists that mode of delivery (vaginal versus cesarean) is related to transmission; therefore, determining the need for cesarean delivery versus vaginal delivery should not be made on the basis of maternal HCV infection status.

Data indicate that breastfeeding does not transmit HCV, although HCV-positive mothers should not breastfeed if their nipples are cracked or bleeding.

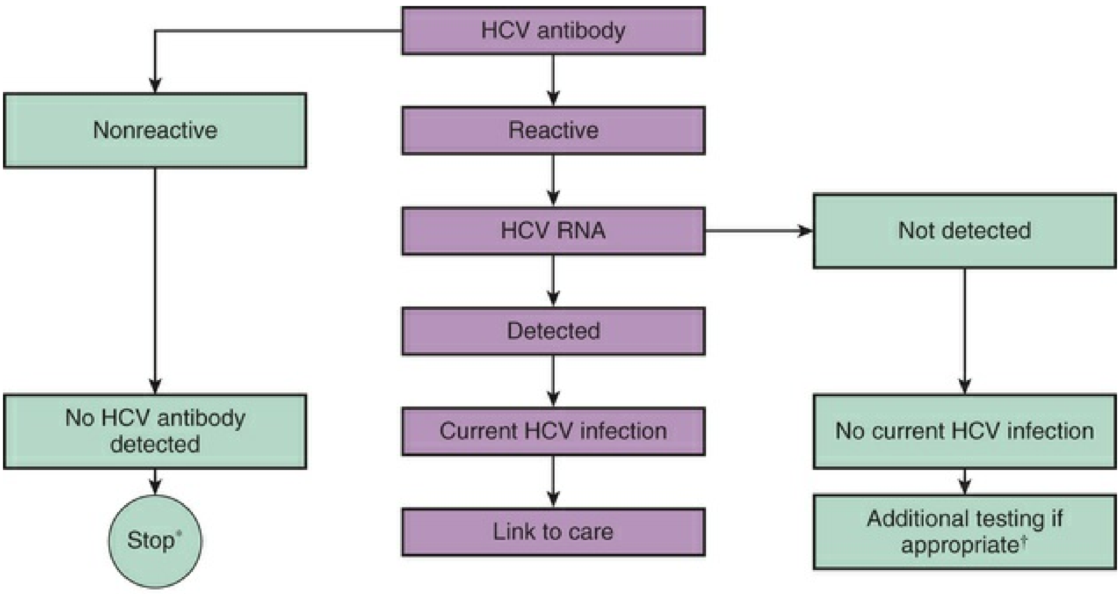
HCV-Positive Persons Should Be Evaluated for Presence or Development of Chronic Liver Disease, Including:

Assessment for biochemical evidence of chronic liver disease

Assessment for severity of disease and possible treatment according to current practice guidelines in consultation with, or by referral to, a specialist knowledgeable in this area

The incubation period for HCV infection averages 6 to 7 weeks, with a range of 2 weeks to 6 months. The time from exposure to development of viremia is usually 1 to 2 weeks. Because HCV infection is asymptomatic in most cases, diagnostic testing in the pediatric age group is recommended in the following circumstances: (1) infants born to HCV-infected women and infants born to mothers with risk factors for HCV infection, such as history of injection drug use; and (2) adolescents with risk factors for HCV infection, including history of drug use and multiple sexual partners.[31] Although HCV is not efficiently transmitted through sexual contact, adolescents with multiple sexual partners are more likely to engage in other high-risk behaviors, notably drug use.[103]

Box 220.1 summarizes the recommendations for HCV testing. A suggested testing algorithm for people with suspected HCV infection is provided in Fig. 220.2.



* Testing for HCV RNA or follow-up testing for HCV antibody is recommended for person exposed to HCV within the past 6 months.

† Past, resolved infections can be distinguished from false-positive anti-HCV testing results by testing with another anti-HCV assay. Repeat HCV RNA testing if HCV exposure occurred within the past 6 months or if clinical disease is present and specimen storage or handling was suspect.

FIGURE 220.2 Testing algorithm for identifying active hepatitis C virus (HCV) infection. (Adapted from Centers for Disease Control and Prevention. Testing for HCV infection: an update of guidance for clinicians and laboratorians. MMWR Morb Mortal Wkly Rep 2013,62:362−365.)

Diagnostic Testing

The goal of HCV testing is to identify persons currently infected with the virus. All persons requiring HCV screening should first be tested for anti-HCV antibodies using a US Food and Drug Administration (FDA)-approved assay and, if positive, tested for HCV RNA. Anti-HCV testing includes both laboratory-based assays and a point-of-care assay.[104] The current EIAs for anti-HCV antibodies are 97% sensitive and >99% specific, but antibody testing cannot distinguish between acute, chronic, and resolved infections. The recombinant immunoblot assay (RIBA) was used in the past to confirm HCV infection; however, this assay is no longer available.[105] In the absence of RIBA, positive anti-HCV antibody tests should be followed by HCV reverse transcriptase polymerase chain reaction to detect HCV RNA in blood. Quantitative or qualitative NAT tests approved by the FDA with detection levels of ≤25 IU/mL should be used. True-positive anti-HCV test results can be distinguished from false-positive anti-HCV test results in the case of resolved infections by including a second HCV antibody FDA-approved assay that is different from the initial assay (see Fig. 220.2).[105]

Infants who are infected perinatally should not be tested for anti-HCV antibodies before 18 months of age because passively acquired maternal antibodies might be detected up until 18 months. The presence of HCV RNA in the mother and infant is the most reliable means of detecting perinatal transmission of HCV. Infants born to HCV-positive mothers can be tested for HCV RNA on two occasions between the ages of 2 and 6 months to detect perinatal transmission because seroconversion occurs on average 8 to 9 weeks after infection and can be delayed up to 6 months after exposure.[106] A small percentage of people with symptomatic acute HCV infection have negative antibody test results at the onset of symptoms; thus serologic testing too early in the course of the infection may not detect and cannot rule out HCV as the cause of acute hepatitis. Also, by the same logic, persons who are immunocompromised should be tested using HCV RNA.

Among people infected with HCV, genotyping is recommended for guiding the duration of therapy and predicting the response to treatment regimens. Currently, treatment of HCV genotypes 1 and 4 using IFN and ribavirin requires twice as long (48 weeks) as treatment of genotypes 2 and 3 (24 weeks). Infection due to the latter genotypes also are much more likely to be treated successfully with IFN and ribavirin. This may change with licensure in children of new all-oral direct-acting antiviral therapy.

Management of Hepatitis C Virus Infection

There are no specific recommendations for management of HCV infection in children and adolescents, and most management strategies are derived from adult studies. However, in view of the long duration of infection among children and adolescents compared with adults, regular follow-up for chronic HCV infection is necessary.

Monitoring Serum Aminotransferase Levels

Normal serum ALT levels are not reliable indicators for lack of hepatic inflammation; however, elevated serum ALT levels are suggestive of hepatic inflammation. Therefore serial measurement of serum ALT can be used to monitor disease activity. HCV-infected children can be followed regularly by physical examination and measurement of serum ALT level every 6 to 12 months.[107] More frequent follow-up is needed in children suffering from comorbidities such as HIV coinfection, thalassemia, or malignancy.

Evaluation of Liver Damage

Liver biopsy can provide important information about the amount and pattern of scar tissue in the liver to guide monitoring and treatment. Liver specimens are evaluated for the grade and stage of disease using the Metavir fibrosis score (F0–F4) and Ishak fibrosis score (0–6).[108] Although liver biopsy often is viewed as a gold standard, the accuracy of liver biopsy is affected by sampling and interpretation errors. Also, there is a small risk for complications associated with the procedure. Obtaining an adequate number of biopsy samples of appropriate size and using standard grading and staging criteria improve diagnostic accuracy. Noninvasive methods to monitor stage of liver disease have become popular in recent years, using combinations of routine blood tests (aspartate aminotransferase, ALT, albumin, bilirubin, international normalized ratio, and complete blood count), serum fibrosis marker panels, liver imaging (ultrasound or computed tomography), and transient elastography.[109,110] These methods are reliable in identifying cirrhosis and in excluding fibrosis, but they are less accurate in identifying patients with moderate levels of fibrosis.

For clinicians, the liver biopsy is most frequently used to determine whether to proceed with therapy, but this invasive procedure currently is being supplanted at many medical centers by elastography (Fibrotest) or noninvasive serum biomarkers (FIB-4 or APRI scores). However, because new all-oral therapies for adults have become highly efficacious for all genotypes and stages of liver fibrosis or cirrhosis—with >90% cure rates after 12 weeks or less—some adult clinicians no longer perform liver biopsy.

Children and young adults with genotype 2 or 3 HCV infection are more responsive to IFN-based treatment.[111,112] However, progression to cirrhosis and hepatocellular carcinoma is highly unlikely in children. Because of this, deferring treatment until the child reaches adulthood or until direct-acting antiviral therapies are available in children is a valid approach and should be considered. Patients to consider treating with IFN and ribavirin before direct-acting antiviral regimens are available include patients with comorbid medical conditions (i.e., requiring immunosuppressive therapy) that would necessitate prompt treatment or signs of severe or rapidly progressive liver dysfunction, confirmed by liver biopsy. Patients with cirrhosis or a coexisting malignancy can be followed by annual measurement of serum α-fetoprotein level and a liver ultrasonography.[112]

For children and young adults with HCV infection, decisions regarding treatment can be based on genotype and patient age.[111,112]

Treatment

Treatment aims to prevent complications and death from HCV infection. Several virologic measures are used to document response to treatment. The most important is sustained virologic response (SVR), which is defined as the absence of HCV RNA for ≥12 weeks after discontinuation of therapy. Most patients who achieve an SVR show definitive absence of viremia and normal liver function.[111]

Acute Infection

Several studies of adult patients have examined the effectiveness of antiviral agents during the early phase of infection and suggest higher SVR rates among people acutely infected compared with response rates observed among people with chronic HCV infection.[113–115] Currently, there is no consensus on the type or duration of therapy required or the timing of initiation of therapy. Only one study reported treatment of acute HCV infection (genotype 4) in a pediatric patient with pegylated IFNα-2b (PEG-IFNα-2b), and the child achieved SVR.[116] Treatment of acute HCV infection is a rapidly evolving area of research, and more specific guidelines for treatment of acute HCV infection in children are likely to be forthcoming. The American Association for the Study of

Liver Diseases, the Infectious Diseases Society of America, and the International Antiviral Society—USA jointly prepared a document providing guidelines for testing, management, and treatment of hepatitis C in adults on their website.[117]

Chronic Infection

HCV is the only chronic viral infection that can be cured (i.e., achievement of SVR). This is a rapidly evolving field because new oral direct-acting antiviral agents (e.g., sofosbuvir, simeprevir, and ledipasvir) are making therapy all-oral, of shorter duration (8–12 weeks), without side effects, and highly curative. The decision to treat chronic HCV infection traditionally has depended on assessing the patient's age and severity of disease and the efficacy of the chosen therapy and its adverse events as well as the patient's adherence to treatment and willingness to complete the regimen. The very high cost of the new direct-acting antiviral agents must be considered because many public and private insurance programs are limiting access to these drugs to patients with advanced fibrosis or cirrhosis. Because of rapid evolution of options and practices, treating clinicians should consult the latest American Association for the Study of Liver Disease/Infectious Diseases Society of America guidelines.[117] IFN-based regimens are the only chronic HCV treatments approved by the FDA for children.

Because of the possibility of spontaneous clearance of the virus among children <3 years of age, as well as the adverse effects of current medications, which include spastic diplegia, treatment of children in this age group has not been approved.[111,118] In 2008, the FDA approved the use of PEG-IFNα-2b in combination with ribavirin for treatment of children 3 years and older. In 2011, the FDA approved the use of PEG-IFNα-2a with ribavirin in children 5 years and older. The Key Points box summarizes the currently approved FDA treatment regimens for chronic hepatitis C in children and adolescents. Before treatment initiation, it is necessary to know the viral genotype because this will affect the response to therapy. Higher SVR rates are achieved for infections due to genotypes 2 and 3 compared with genotypes 1 (the most common genotype in the US and Europe) and 4.[107,111,112,119] The durations of therapy are 24 weeks for genotypes 2 and 3 and 48 weeks for genotypes 1 and 4.

Combination treatment with PEG-IFNα-2b and ribavirin achieved the best SVR rates in all genotypes in the pediatric age group.[119] Large trials that included more than 100 children 3 years and older showed SVR rates ranging from 44% to 53% for genotype 1 and 80% to 100% for genotypes 2 and 3.[120–122] PEG-IFNα-2b should be discontinued temporarily if the neutrophil count falls below 750 to 1000 cells/mm^3 and should be resumed when the count increases.[119] Compared with regular IFNα-2b, PEG-IFNα-2b is more convenient because of the once-weekly administration and limited duration of influenza-like symptoms.[120–124] Ribavirin in combination with PEG-IFNα-2b enhances the second and third phases of viral decay, which reduces the probability of relapse.[125]

The most common adverse events associated with IFN are influenza-like symptoms, particularly fever, headache, fatigue, and irritability, which are almost universal after the first few doses but usually resolve in children by the second or third week of therapy.[121,123,126] Weight loss also is common, but a compensatory catch-up weight gain occurs after completion of treatment.[121–123] In addition, a temporary decrease in height growth occurs during therapy, which resolves after discontinuation.[121–123] Bone marrow suppression is the most severe adverse event and can lead to neutropenia or thrombocytopenia, but it can be managed by reduction of the IFN dosage.[121–123,126,127] With therapy, mood disturbances and suicidal ideation are common, and more so among adolescents and those with preexisting mood disorders.[119] Depression occurred in 13% of participants in one study.[126] Abnormalities of thyroid function also can occur, but these normalize after completion of treatment.[120,121,126] Hemolysis is a common adverse effect of ribavirin and can require discontinuation of the drug. Teratogenicity is a major concern for men as well as women, who should avoid conception during therapy and for 6 months thereafter. Treatment with IFN is contraindicated in patients with certain comorbid conditions such as depression, psychiatric conditions, seizures, renal insufficiency, and autoimmune hepatitis.[119]

Special attention is needed for children with anemia and thalassemia. Erythropoietin and darbepoetin might be used to decrease the hemolytic effect of ribavirin therapy in patients with preexisting anemia. However, the effect of erythropoietin on SVR is unknown.[128] Children with thalassemia may require more transfusions and chelation therapy as a result of hemolysis due to ribavirin therapy and iron overload.[128,129]

In summary, the efficacy of combined therapy in children reflected by SVR rates of 50% and 90% in genotype 1 and genotypes 2 and 3, respectively, warrants its use. However, longitudinal studies are needed to investigate adverse events after completion of therapy, such as thyroid function abnormalities and growth alterations.

Future Treatments

Therapy for hepatitis C is a rapidly evolving field with numerous drugs under development. Highly effective direct-acting antiviral agents have been approved by the FDA for the treatment of chronic HCV, are currently on the market, and promise to change the landscape of HCV therapy. This includes three different drug combinations: sofosbuvir (polymerase inhibitor) with ledipasvir (NS5A inhibitor); simeprevir (NS3/4A inhibitor) with sofosbuvir; and the four drugs ombitasvir (NS5A inhibitor), paritaprevir (NS3/4A serine protease inhibitor), dasabuvir (nonnucleoside NS5B polymerase inhibitor), and ritonavir (CYP3A4 inhibitor).[130–132] All of these drug combinations were well tolerated and achieved high SVR (>95%) after 12 weeks of therapy. Unfortunately, no safety and efficacy trials for these drugs have been completed yet in pediatric patients.

Prevention

Comprehensive recommendations for prevention and control of HCV infection have been published.[31] For example, immunoglobulin has not been shown to be effective for postexposure prophylaxis of hepatitis C, and its use is not recommended.[31] There is no recommendation to screen women for HCV infection either before or during pregnancy, unless they have risk factors for HCV infection. Currently, both the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists support breastfeeding in HCV-infected women.

However, HCV-infected women should abstain from breastfeeding if their nipples are cracked or bleeding. Box 220.2 provides key counseling messages for persons with HCV infection. Regardless of risk factors, all children should be immunized against hepatitis A and B.[133,134] Development of a vaccine for hepatitis C has been challenging given the genetic heterogeneity of HCV, the high mutation rate, and the lack of a cell culture system. However, novel vaccine candidates based on molecular technology are being explored.[135,136]

Key Points

Epidemiology, Clinical Features, Diagnosis, and Treatment of Hepatitis C Virus Infection

Epidemiology

- Incubation period: 2 weeks to 6 months
- At least 6 genotypes: genotype 1 most common in the US and Europe
- Prevalence in the US:
  - 0.2% among people aged 6 through 11 years
  - 0.4% among people aged 12 through 19 years
- Perinatal transmission accounts for most cases of HCV infection in children.
  - Estimated rate of vertical transmission of 5%

Clinical Features

- Usually asymptomatic in children
  - Only 20% to 30% with mild symptoms indistinguishable from other acute viral hepatitides

- Estimated rates of virus clearance:

- 20% for perinatally infected children

- Up to 55% for children with transfusion-acquired HCV

- Children with genotype 1 compared with other genotypes are more likely to progress to advanced disease.

Diagnosis

- Anti-HCV testing by EIA is the initial serologic assay to detect infection; confirmed by NAT or retest using a second FDA-approved EIA platform (see Fig. 220.2).

- Infants of women known to be infected with HCV should be screened for HCV RNA on two occasions between 2 and 6 months of age and/or be tested for anti-HCV after 18 months of age.

Treatment

- PEG-IFNα-2b SC: 60 μg/m^2/week

- PEG-IFNα-2a SC: 180 μg/1.73 m^2/week

- IFNα-2b SC: 3 million U/m^2 SC 3 times per week for children <61 kg, and 3 million U 3 times per week SC for children ≥61 kg

- Ribavirin: dose is dependent on the type of interferon being used in combination with ribavirin and the weight of the child

EIA, enzyme immunoassay; FDA, US Food and Drug Administration; HCV, hepatitis C virus; IFN, interferon; NAT, nucleic acid testing; PEG, pegylated; SC, subcutaneous; PO, oral.

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Rubella Virus

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Rubella (i.e., German measles) is a benign, self-limited, vaccine-preventable viral illness. Acquired rubella is characterized by an exanthem and lymphadenopathy, although infants and children with rubella frequently are asymptomatic. Much of the morbidity attributed to rubella virus (RuV) occurs from in utero transmission, especially during the first trimester, resulting in miscarriage, stillbirth, or congenital rubella syndrome (CRS). Sequelae of CRS include growth retardation, deafness, congenital heart disease, and mental retardation.

Routine childhood vaccination with rubella-containing vaccine (RCV) has resulted in elimination of rubella and CRS in the World Health Organization (WHO) Region of the Americas in 2009.[1] However, rubella and CRS remains a major public health problem in many countries worldwide.[2]

Pathogen, Pathogenesis, and Immune Response

RuV is the only member of the *Rubivirus* genus within the Togavirus family. It is a spherical virus that is 50 to 70 nm in diameter and contains a single-stranded, positive-sense RNA genome.[3] The nucleoprotein core is surrounded by a glycolipid envelope; the lipid component is host cell derived. There is only one antigenic type of RuV.[4] Humans are the only natural hosts of RuV.

RuV contains three major structural proteins: E1, E2, and C. E1 and E2 are glycosylated envelope proteins that make up the spiked 5- to 6-nm surface projections of the viral surface. C is the capsid nucleoprotein. Monoclonal antibodies directed against epitopes of E1 and E2 have neutralizing activity. However, E1 is the primary immunodominant epitope that binds hemagglutination and neutralizing antibodies. E1 plays a major role during virus entry into target cells due to its receptor-binding and membrane-fusion functions.[5] Although no definite cellular receptor has been identified for RuV, the E1 protein can bind to myelin oligodendrocyte glycoprotein (MOG), allowing virus entry into certain target cells.[6] MOG is expressed primarily on human central nervous system (CNS) cells and placenta and may be important in the neuropathogenesis of CRS.[7]

RuV is readily inactivated by chemical agents, lipid solvents, heat (>56°C), cold (−10°C to −20°C), ultraviolet light, and extremes in pH (<6.8 and >8.1). RuV grows well in a variety of primary and continuous cell lines.

Pathogenesis of Acquired Rubella Infection

Rubella is most likely transmitted by direct or aerosol contact with upper respiratory tract secretions of infected people. Infectivity, which correlates with virus shedding from the nasopharynx, can occur 1 week before to 2 weeks after rash onset.[8,9] People are most infectious from 5 days before until 6 days after the onset of rash.[10]

After exposure, the virus attaches to and invades respiratory epithelium and then spreads hematogenously to regional lymphatics. Primary viremia occurs 5 to 7 days after infection. Virus replicates in local and distant reticuloendothelial sites and is followed by secondary viremia at high levels, especially during the second week of infection. Cell-associated virus can be recovered from peripheral blood lymphocytes and monocytes for up to 4 weeks after infection.[11]

Within 8 to 14 days after exposure, active viral replication occurs throughout the body and can be recovered from numerous sites, including the respiratory tract, skin, lymph nodes, urine, cerebrospinal fluid, and breast milk.[12–14] Maximal nasopharyngeal shedding, the development of humoral immunity, and clinical manifestations of infection occur during this period.

Immune Response in Acquired Rubella Infection

Humoral immunity to natural and vaccine RuV is characterized by development of a variety of antibody types reactive to distinct viral antigens, including viral hemagglutinins, complement-fixing (CF) antigens, and precipitating antigens.[15] Development of hemagglutination inhibition and neutralizing antibodies occurs with the onset of the rash illness, and CF antibodies are detected 1 week later. Peak titers of hemagglutination inhibition and neutralizing antibodies occur about 2 weeks after rash onset; CF antibodies peak about 2 weeks later. The hemagglutination inhibition and neutralizing antibodies persist for life.

Although the antibody titers induced by the RA 27/3 vaccine virus currently used in the United States are lower than those induced by natural infection, the nature of the antibody response is similar to the response to natural infection.[16] High-avidity IgG antibodies against the neutralizing epitope of E1 glycoprotein is an important correlate of RuV protection.[17] Vaccine-induced immunity is long lasting, with detectable antibodies for 20 years found in 95% of patients.[18] Rarely, serologically confirmed reinfections can occur after earlier infection or vaccination.[19]

The role of cell-mediated immunity (CMI) in rubella is poorly understood. CMI to RuV develops at least 1 week before the development of humoral immunity and likely persists for life. Transient suppression of CMI and a decrease in numbers of leukocytes (i.e., neutrophils and lymphocytes) can occur after natural infection or vaccination.[3] Clinically significant immunosuppression has not been described in immunocompetent people after acquired rubella infection.

Pathogenesis of Congenital Rubella

In contrast to acquired rubella infection, congenital infection results in a persistent, progressive infection.[8,19] Infants with CRS can shed RuV in nasopharyngeal secretions and urine for up to 1 year and can transmit rubella to susceptible contacts. Placental and fetal infection with RuV occurs most consistently after maternal infection during the first trimester of pregnancy, and early fetal infection, especially during organogenesis, is associated with increased risk of fetal death or teratogenicity.[20,21] Maternal rubella infection in the first trimester of pregnancy results in fetal defects in 85% to 90% of cases; risk drops to 50% with maternal infection at 13 to 16 weeks' gestation and 25% at 15 to 16 weeks.[22,23] Fetal defects are rare if maternal infection occurs after 16 weeks' gestation.[23] However, sensorineural deafness can occur with maternal infection as late as 20 weeks' gestation.[24]

Factors associated with the greater susceptibility of the placenta and fetus to RuV during the first trimester are unknown. Pathologic effects of congenital infection primarily are the result of a generalized virus-induced, progressive, necrotizing vasculitis.[25] Human fetal endothelial cells are highly permissive to RuV.[26] Fetal histopathology is characterized by noninflammatory damage to endothelial cells of small blood vessels resulting in thrombosis and surrounding tissue necrosis.[27] The resulting parenchymal hypoplasia produces characteristic clinical findings associated with CRS.[8]

Other pathologic effects are focal inflammation, edema, and granulomatous changes. Evidence of mitotic arrest through cytoskeletal derangements, apoptosis, and chromosomal defects has been identified in congenitally infected fetuses and in chronically infected human embryonic cells and may represent other pathologic mechanisms leading to reduced cell numbers and hypoplasia.[28,29] The spectrum of fetal infection varies from extensive involvement of multiple organs when infection occurs early in the first trimester to focal involvement of a few organs, especially of the eye and auditory system, which occurs in fetal infections after 11 to 12 weeks' gestation.

Immune Response in Congenital Rubella Infection

Humoral and CMI responses in congenital rubella infection are distinct from those observed after acquired infection (Fig. 221.1). With congenital infection, fetal immunoglobulin (Ig) M antibodies to RuV can be detected as early as 20 weeks' gestation, and fetal IgG can be detected by the middle of the second trimester. Concentrations of IgM and IgG continue to rise throughout the first few months of life. IgM levels decline by about 6 months of age, and IgG levels persist for life.[30]

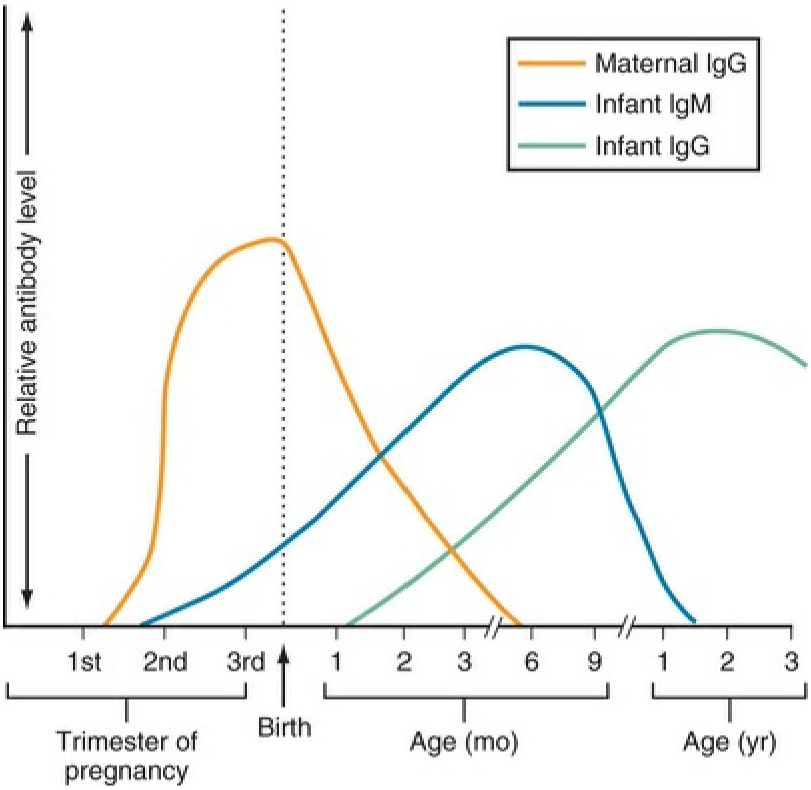
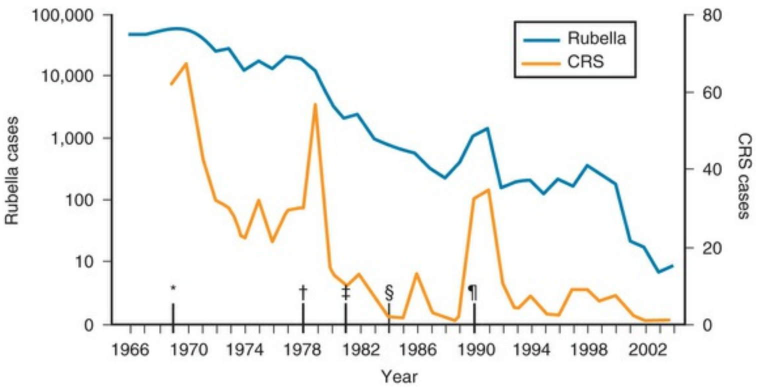


FIGURE 221.1 Immune responses in congenitally acquired rubella after maternal infection in the first trimester of pregnancy. IgG, immunoglobulin G; IgM, immunoglobulin M. (Modified from Best JM, O'Shea S. Rubella virus. In: Lennette EH, Schmidt NJ [eds]. Diagnostic Procedures for Viral, Rickettsial, and Chlamydial Infections, 6th ed. Washington, DC, American Public Health Association, 1989, pp. 731–795.)

Children with CRS have low-avidity IgG antibodies in contrast with the high-avidity IgG antibodies of their mothers or cases of postnatal infection.[31,32] CMI responses to congenital rubella, including delayed-type hypersensitivity reactions, lymphocyte-mediated cytotoxicity, phytohemagglutinin-induced lymphocyte transformation, and interferon production, are decreased compared with responses after acquired infection. The most depressed CMI responses are observed in infants infected earliest in gestation.[33]

Epidemiology

Rubella infection occurs most often in late winter and early spring. Before the introduction of rubella vaccine in 1969, rubella epidemics occurred in 2- to 4-year cycles; larger epidemics occurred at 6- to 9-year intervals. Young children were most susceptible to rubella infection (highest attack rate, 5–9 years of age).[34] Most adults were not susceptible during cyclic epidemics. Before licensure of rubella vaccine in 1969, 57,600 rubella cases and 62 CRS cases were reported annually in the United States.[35] After vaccine licensure, the incidence of rubella declined dramatically. Since 2001, fewer than 25 rubella cases/year and fewer than 4 CRS cases/year were reported. In 2004, rubella was no longer endemic in the United States (Fig. 221.2).[36]



* 1969 – First official recommendations are published for the use of rubella vaccine. Vaccination is recommended for children 1 year of age to puberty.
† 1978 – Recommendations for vaccination are expanded to include adolescents and certain adults, particularly females. Vaccination is recommended for adolescent or adult females and males in populations in colleges, certain places of employment (e.g., hospitals), and military bases.
‡ 1981 – Recommendations place increased emphasis on vaccination of susceptible people in training and educational settings (e.g., universities, colleges) and military settings, and vaccination of workers in health-care-settings.
§ 1984 – Recommendations are published for vaccination of workers in daycare centers, schools, colleges, companies, government offices, and industrial sites. Providers are encouraged to conduct prenatal testing and postpartum vaccination of susceptible women. Recommendations for vaccination are expanded to include susceptible people who travel abroad.
¶ 1990 – Recommendations include implementation of a new 2-dose schedule for measles-mumps-rubella vaccine.

FIGURE 221.2 Number of reported cases of rubella and congenital rubella syndrome (CRS) by year and chronology of rubella vaccination recommendations by the Advisory Committee on Immunization Practices in the United States, 1966–2004. (Modified from Centers for Disease Control and Prevention. Achievements in public health. Elimination of rubella and congenital rubella syndrome—United States, 1969–2004. MMWR Morb Mortal Wkly Rep 2005;54:279–282.)

In the postvaccination era, young unvaccinated adults were most susceptible to rubella infection. Rubella outbreaks in the mid-1970s and 1980s occurred mostly among unvaccinated adolescents and young adults in college campus and work settings.[37] Between 1989 and1991, rubella outbreaks occurred among unvaccinated people who belonged to religious groups that traditionally refuse vaccination.[38] Rubella attack rates among susceptible people in closed communities (e.g., college dormitories, military facilities) range from 75% to 90%; however, attack rates can approach 100%

among household contacts. In the mid-1990s, reported rubella cases occurred primarily among foreign-born, young Hispanic adults.[39] In recent outbreaks, cases have occurred among people born outside the United States or among underimmunized people.[40]

In 2004, a CDC panel verified rubella elimination in the United States.[41] In the postelimination period from 2004 through 2012, 79 rubella cases and 6 CRS cases (including 3 cases in 2012) were reported in the United States; all cases were known importations or from unknown sources (Fig. 221.3).[40] US rubella immunization programs include two strategies: universal immunization of all infants and targeted vaccination of susceptible prepubertal girls and women of child-bearing age. Success has been achieved primarily with universal childhood immunization. By 1998, more than 90% of 2-year-old US children had received at least one dose of a measles-containing vaccine, usually measles-mumps-rubella (MMR) vaccine.[42]

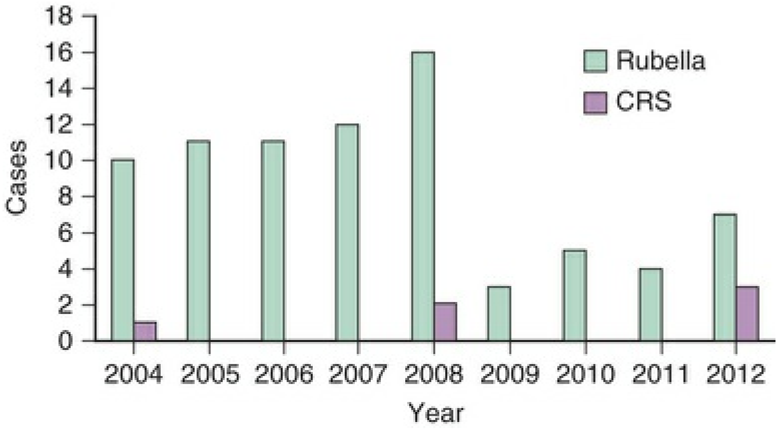


FIGURE 221.3 Number of reported cases of rubella and congenital rubella syndrome (CRS) according to the National Notifiable Diseases Surveillance System, United States, 2004–2012. (From Centers for Disease Control and Prevention. Three cases of congenital rubella syndrome in the postelimination era —Maryland, Alabama, and Illinois, 2012. MMWR Morb Mortal Weekly Rep 2013;62:226–229.)

Based on national serosurveys (1999–2004), rubella seropositivity rates were about 95% among children and adolescents between the ages of 6 and 19 years.[43] However, about 10% of women of childbearing age were rubella seronegative. Women born outside of the United States or from countries lacking rubella vaccination are more likely to be rubella nonimmune, predisposing their infants to CRS.[44]

In 2010, the Pan American Health Organization announced the elimination of rubella and CRS in the WHO Region of the Americas.[45] Although progress has been made in global rubella control, the burden of rubella and CRS remains substantial in low- and middle-income countries.[1,2] Approximately 100,000 infants are born annually with CRS.[2] Partial vaccination strategies have resulted in large rubella outbreaks in Japan, Poland, and Romania.[46–48]

WHO has targeted regional elimination of rubella by 2015 and measles and rubella elimination in five WHO regions by 2020 as part of the Global Vaccine Action Plan.[49] In 2011, the WHO recommended that all countries introduce RCV in their routine immunization programs as part of accelerated measles control and elimination.[50] By 2012, 132 (68%) of 194 WHO member states had included at least one dose of RCV, compared with 99 (51%) in 2000 (Fig. 221.4).[1] During 2000 through 2012, reported rubella cases globally declined by 86% from 670,894 to 94,030.[1] Rubella control and elimination worldwide largely depends on sustained, high-quality immunization programs and robust surveillance systems.[1,2]

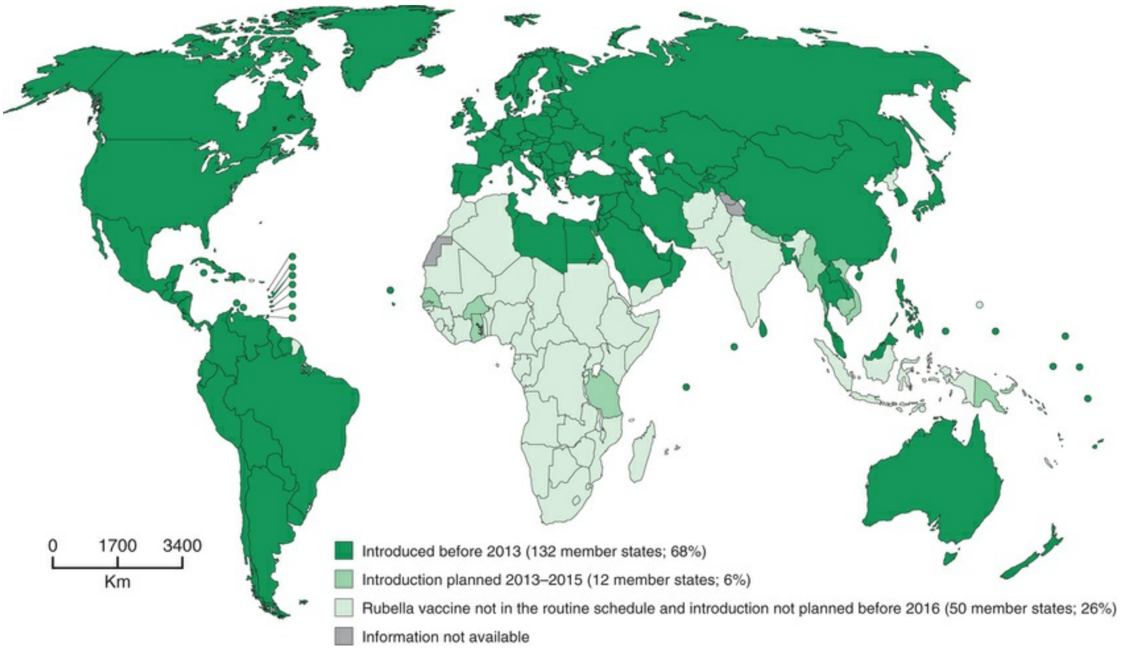

0
1700
3400
Km
Introduced before 2013 (132 member states; 68%)
Introduction planned 2013–2015 (12 member states; 6%)
Rubella vaccine not in the routine schedule and introduction not planned before 2016 (50 member states; 26%)
Information not available

FIGURE 221.4 Distribution of countries using rubella-containing vaccine in their routine immunization schedule in 2012 and countries planning introduction

during 2013 through 2015. (From Lambert N, Strebel P, Orenstein W, et al. Rubella. Lancet 2015;385[9984]:2297–2307.)

Clinical Manifestations

Acquired Rubella

The incubation period from exposure to onset of exanthem is 14 to 21 days (mean, 18 days). The illness is mild and often subclinical in up to 50% of cases.[44] Nonspecific prodromal symptoms, which occur 1 to 5 days before onset of exanthem, include fever, eye pain, sore throat, arthralgia, and gastrointestinal complaints. Prodrome is rare in infants and young children.

The characteristic clinical findings are rash and suboccipital adenopathy. Rash usually begins on the face, spreads in a cephalocaudal direction to involve the entire body over the next 24 hours, and fades during the ensuing 2 or 3 days, also in a cephalocaudal direction. The median duration of rash is 3 days. Usually erythematous and maculopapular, the exanthem also can be scarlatiniform, morbilliform, or macular. In adolescents, the rash can be confused with acne, whereas in adults, the rash may be pruritic. Other symptoms include low-grade fever and lymphadenopathy. Lymphadenopathy usually occurs with rubella infection and can be detected for up to 1 week before rash onset. The posterior auricular and suboccipital lymph nodes usually are involved, but generalized involvement can occur. Transient polyarthralgia and polyarthritis occur frequently in adults, especially in women.

Reinfection is uncommon. Reinfection that occurs during pregnancy and produces fetal infection is documented but is rare.[51,52] Reinfection usually is subclinical and nonspecific clinically, and the diagnosis is made only by serologic methods.

Congenital Rubella Syndrome

Clinical manifestations of CRS reflect the chronic, progressive nature of the infection.[8,19] Fetal infection can lead to early miscarriage, spontaneous abortion, or stillbirth. Up to 20% of maternal infections occurring up to 8 weeks' gestation result in miscarriage. The association between intrauterine rubella and congenital cataracts was first described in 1941.[53] Congenital defects occur in 85% to 90% of infants infected in the first trimester, and virtually no defects are identified in infants infected after the first 16 weeks' gestation (Fig. 221.5).[22,23] Infants infected in the first trimester are more likely to have multiple congenital defects, whereas those infants infected after 11 to 12 weeks of gestation more likely have only deafness or retinopathy as a clinical manifestation. Clinical manifestations of CRS can be evident at birth or, more commonly, can result in normal-appearing infants who have late-onset sequelae. Early clinical manifestations can be transient or progressive (Table 221.1).[8]

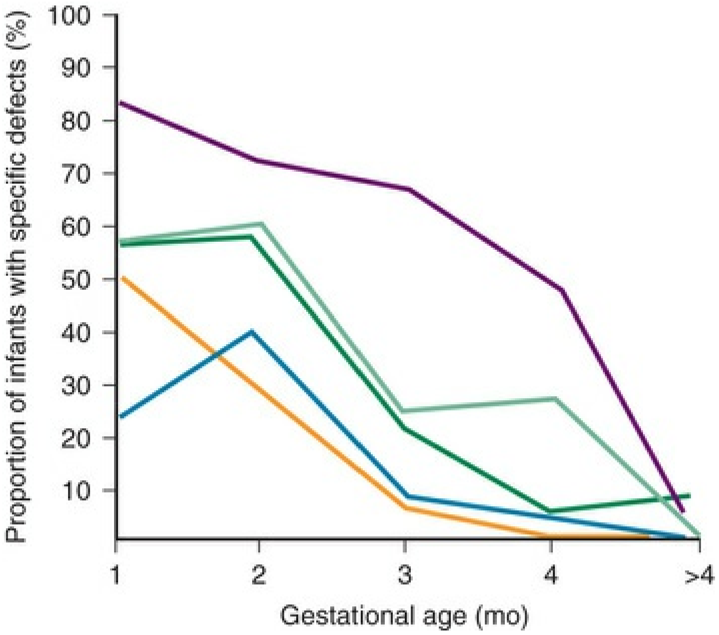


FIGURE 221.5 Time of maternal infection and clinical manifestations of congenital rubella: deafness *(purple)*; central nervous system deficit *(light green)*; heart disease *(dark green)*; cataract or glaucoma *(orange)*; neonatal purpura *(blue)*. (Redrawn from Best JM, O'Shea S. Rubella virus. In: Lennette EH, Schmidt NJ [eds]. Diagnostic procedures for viral, rickettsial, and chlamydial infections, 6th ed. Washington, DC, American Public Health Association, 1989, pp. 731–795.)

TABLE 221.1

Clinical Features Associated With Congenital Rubella Syndrome

Category	**Common**	**Uncommon**
PRESENT AT BIRTH		
Transient	Low birth weight Thrombocytopenic purpura Hepatomegaly Splenomegaly Bone lesions	Cloudy corneas Hepatitis Generalized lymphadenopathy Hemolytic anemia Pneumonitis
Permanent	Sensorineural deafness Peripheral pulmonary stenosis Pulmonary valvular stenosis Patent ductus arteriosus Ventricular septal defect Retinopathy Cataract Microphthalmia Psychomotor retardation Cryptorchidism Inguinal hernia Diabetes mellitus	Severe myopia Thyroid disorders Dermatoglyphic abnormalities Glaucoma Myocardial abnormalities Sensorineural deafness
DELAYED	Peripheral pulmonary artery stenosis Mental retardation Central language defects Diabetes mellitus Immune complex disease Hypogammaglobulinemia	Severe myopia Thyroiditis Hypothyroidism Growth hormone deficiency Chronic rash Pneumonitis Progressive panencephalitis

Modified from Banatvala JE, Best JM. Rubella. In: Brown F, Wilson R (eds). Topley and Wilson's Principles of Bacteriology, Virology, and Immunity, 7th ed, vol 4. London, Edward Arnold, 1984, pp. 271–302.

Transient, early clinical manifestations of CRS reflect acute nonspecific immunologic responses to congenital viral infection. In neonates, manifestations include generalized lymphadenopathy, hepatosplenomegaly, intrauterine growth retardation, hepatitis, jaundice, hemolytic anemia, pneumonitis, meningoencephalitis, cloudy corneas, bony radiolucencies, and diarrhea.[54–57] Thrombocytopenic purpura with petechiae and blueberry muffin lesions, which usually represent focal areas of dermal erythropoiesis, are associated more often with rubella than with other congenital viral infections. Transient manifestations typically resolve within days to weeks, usually without long-term sequelae. More than 50% of newborns with clinically apparent CRS have low birth weight, and persistent postnatal growth retardation.

Permanent or progressive manifestations of CRS can occur in any organ. Organ systems most commonly involved are the heart, eye, brain, and auditory system. Sensorineural deafness is the most common manifestation of CRS. Cardiac anomalies occur in more than 50% of infants born with symptomatic CRS. The most common lesions are patent ductus arteriosus, peripheral pulmonary arterial stenosis, and ventricular septal defects. The most common ocular manifestations are salt-and-pepper retinopathy and cataracts.[58] Retinopathy occurs in 20% to 50% of infants with symptomatic infection and usually is unilateral. Cataracts occur in up to one third of infants with retinopathy, are bilateral in about 50% of affected infants, and are associated with microphthalmia in about 60%.

Late-onset manifestations of CRS may not be identified before 2 years of age or later.[59,60] Findings include endocrinopathies, chronic immunologic defects, auditory and ocular dysfunction, and vascular and CNS disease. The most common endocrinopathy is insulin-dependent diabetes mellitus,[61] occurring at a more than fourfold the rate among otherwise unaffected children with CRS. The highest rate was reported in a series from Australia, in which 20% of young adults with symptomatic CRS had diabetes mellitus.[62] Thyroid disorders (e.g., hyperthyroidism, hypothyroidism, thyroiditis) have been diagnosed in CRS patients.[63,64]

Glaucoma and abnormalities of the cornea and lens also can have a late onset. Retinal neovascularization due to congenital retinal vascular atrophy can result in visual disturbances. Renal vascular stenosis can lead to hypertension.[8]

CNS defects associated with CRS can be present at birth. In some cases, they are transient manifestations with no permanent sequelae; in others, the symptoms are progressive. Some patients first demonstrate CNS manifestations later in life.[65] Permanent neurologic defects include developmental delay, microcephaly, behavioral disorders, and chronic encephalitis. Developmental delay can be the result of intrauterine damage of the CNS, acute and chronic encephalitis in the immediate postnatal period, or progressive effects of generalized failure to thrive. Microcephaly may not be associated with developmental delay if the decrease in head circumference is a result of generalized growth retardation.[66] Psychiatric and behavioral manifestations, such as reactive or neurotic disorders and autism, occur in up to one third of preschool- and school-age children after congenital rubella.[55,65] Late-onset progressive panencephalitis is a rare complication that usually manifests in the second decade of life.[67]

Permanent manifestations of CRS are common and result in long-term sequelae in 80% or more of infected infants. The most common complications are hearing deficits that can progress or can develop after years of normal hearing. The overall incidence of hearing deficits in children with CRS is about 50%, but they may be identified only after 4 to 6 years of age in up to 20% of children. Ophthalmologic defects, which occur in up to 50% of infants with clinically apparent infection at birth, can result in progressive visual disturbances, especially in children with retinopathy in whom progressive macular scarring develops. Cardiac defects may require surgical intervention. Developmental delay and behavioral disorders usually are progressive; the overall prevalence of permanent CNS involvement is about 10% among infants with symptomatic infection at birth. It is important to evaluate auditory and visual acuity in these children because of the possibility that hearing or vision disturbances are the primary cause of learning disorders.[68]

Laboratory Findings and Diagnosis

Acquired Rubella

Laboratory abnormalities during postnatally acquired rubella infection include leukopenia and relative neutropenia. Because the rubella exanthem is nonspecific, infection cannot be diagnosed on the basis of clinical presentation alone. Serologic tests usually are necessary to confirm the diagnosis. A single elevated rubella-specific immunoglobulin (Ig) M antibody level or a fourfold or greater rise in antibody titer between paired sera collected 2 weeks apart or IgG seroconversion indicates recent infection. Interpretation of serologic results must be based on the timing of the serum samples relative to the rash onset because IgM antibodies may be detectable only from 1 or 2 weeks until 3 weeks after onset of rash.[69]

Enzyme immunoassay (EIA) is widely available and often used for detection of rubella-specific IgG and IgM antibodies.[70,71] Latex agglutination, neutralization, and hemagglutination inhibition assays also can be used.[71] False-positive IgM serology results can occur for people with parvovirus B19 infections, heterophile antibodies, or rheumatoid factor.[44] Assays for IgG avidity are helpful to resolve false-positive IgM test results. The avidity assay should be performed at a CDC reference laboratory and can differentiate recent primary rubella infection (i.e., low-avidity IgG) from past infection or reinfection (i.e., high-avidity IgG).[71,72] An EIA antibody level of 10 IU/mL or higher is considered evidence of immunity.[73] Detection of functional neutralizing antibodies by high-throughput immunocolorimetric system may be useful to determine immunity to rubella in vaccinated people.[74]

RuV can be isolated from nasopharyngeal secretions, throat, and urine, but culture is impractical compared with serology. Detection of RuV genome by real-time reverse-transcriptase polymerase chain testing on nasal, throat or urine samples also has been described.[75] Molecular epidemiology and phylogenetic analysis is beneficial to monitor the source of RuV and transmission patterns, document maintenance of rubella elimination, and differentiate wild-type RuV from vaccine strains.[71,76]

The differential diagnosis of rubella infection includes other benign rash illnesses of childhood, such as enteroviral infections, exanthem subitum, adenovirus and Epstein-Barr virus infections, and streptococcal infections. Infection due to *Mycoplasma pneumoniae* and drug rashes also can mimic rubella infection.

Congenital Rubella

A maternal history of rubella during pregnancy or neonatal manifestations suggesting congenital infection, such as microcephaly, hepatosplenomegaly, generalized lymphadenopathy, thrombocytopenia, or ocular abnormalities, should prompt evaluation for CRS. The diagnosis of congenital rubella requires virologic or serologic confirmation. RuV can be isolated for 1 or more years from nasopharynx, the buffy coat of the blood, cerebrospinal fluid, and urine of infants with congenital infection (Table 221.2).[77]

TABLE 221.2

Frequency of Virus Excretion by Age of Infants With Congenitally Acquired Rubella

Age	Number With Positive Culture (%)
0–1 mo	71/85 (84)

1–4 mo	50/81 (62)
5–8 mo	26/80 (33)
9–12 mo	11/98 (11)
13–20 mo	4/115 (3)
3 mo–15 yr	0/20 (0)

Data from Cooper LZ, Krugman S. Clinical manifestations of postnatal and congenital rubella. Arch Ophthalmol 1967;77:434–439.

The serologic confirmation of congenital rubella is difficult. Rubella-specific IgM can be measured in cord blood or neonatal serum but is associated with false-positive reactions in the presence of rheumatoid factor or maternal IgG.[78–80] Serial measurement of IgG may therefore be necessary. Specimens drawn at 3 and 6 months of age should be tested in parallel. Persistence or increasing concentrations of rubella-specific IgG antibodies over several months is diagnostic of congenital infection.[81]

Treatment

No specific therapy is available for congenital or acquired rubella infection. The infant with presumed or proven congenital rubella infection should undergo complete evaluation for associated congenital defects, including ophthalmologic, auditory, cardiac, and neurodevelopmental assessments.

Complications of Acquired Rubella

Arthropathy is the most common complication of acquired rubella, occurring in up to 70% of adults. It is unusual in children.[44] Women are affected more often than men. Clinical manifestations include arthritis and arthralgia of multiple joints; fingers, knees, and wrists are involved most often.

Onset is usually 1 to 6 days after rash onset, and symptoms persist for a mean of 9 days. Arthritis can persist for up to 1 month and rarely relapses occur, but chronic arthritis is rare.[8,44] RuV has been detected in the synovial fluid and synovium in patients with arthritis after postnatal infection or vaccination. The pathogenesis of rubella arthritis likely is immune complex-mediated given the appearance of arthritis with the antibody response.[8]

An association between acquired rubella infection and rheumatoid arthritis has been reported.[82] Higher prevalence of rubella hemagglutination inhibition antibodies has been demonstrated among people with rheumatoid arthritis than matched controls, and RuV and antigens have been detected in the synovial fluid of a few patients with juvenile idiopathic arthritis. A cohort study of more than 3000 women failed to demonstrate an association between rubella vaccination and new-onset chronic arthropathy.[83]

Acute encephalitis occurs in 1 in 6000 cases and usually manifests within 4 days of the onset of rash.[44,84] CSF analysis demonstrates a mild pleocytosis, usually greater than 300/mm^3 (>50% lymphocytes), a normal or slightly elevated protein level, and a normal glucose concentration. The course of rubella encephalitis varies. In most people, illness is mild and self-limited, but deaths have occurred occasionally. Symptoms of peripheral neuritis are commonly reported. Rarely, progressive panencephalitis occurs in patients after acquired rubella.[85] The clinical course is similar to that of subacute sclerosing panencephalitis caused by rubeola virus.

Thrombocytopenia with purpura occurs in 1 of 3000 cases.[86] The prevalence is higher among children than adults, and the condition occurs more often in girls than in boys. Thrombocytopenia usually is self-limited but can last days to months. Rare complications of rubella are myocarditis, pericarditis, follicular conjunctivitis, hemolytic anemia, and hepatitis.

Prevention

Immunization

Rubella vaccination programs in the United States targeted universal immunization of infants to eliminate the CRS in subsequent generations.[87] Selective vaccination of prepubertal women or women of reproductive age also is recommended. The RA 27/3 strain of live, attenuated rubella virus constitutes the rubella vaccine currently licensed in the United States The vaccine strain is grown in WI-38 or MRC-5 human diploid cell cultures, and immunization produces a mild, noncommunicable infection.

In the United States, rubella vaccine is available in combination with mumps and measles (MMR) vaccine or as a quadrivalent vaccine in combination with measles, mumps, and varicella (MMRV). One dose of the vaccine administered at 12 or more months of age is immunogenic in more than 95% of recipients and confers lifelong immunity in more than 90% of vaccinees; the seroconversion rate is 99% after two doses of the MMR vaccine.[44,88–91] Reinfection after vaccination is rare. Polymorphisms in HLA genes (e.g., HLA-DPB1) are associated with interindividual differences in rubella virus–specific humoral immunity after vaccination.[92,93]

The CDC and the American Academy of Pediatrics (AAP) recommend universal rubella-containing vaccination (as part of MMR or MMRV) at 12 to 15 months of age, with a second dose before school entry (4–6 years) or sooner.[94–96] The second dose of vaccine is intended to provide immunity to children who do not seroconvert after the first dose (i.e., primary vaccine failure).

All people who have not received the vaccine at school entry must receive the second dose of MMR or MMRV as soon as possible, optimally before starting junior high or middle school (11–12 years). In two postlicensure studies, one additional febrile seizure per about 2300 to 2600 children between the ages of 12 and 23 months was observed in those who had received MMRV compared with those who received MMR vaccine and varicella vaccine administered as separate injections at the same visit.[97,98] There was no increased risk of febrile seizures when MMRV was administered as the second dose at 4 to 6 years of age.

The CDC and AAP recommend the administration of the MMR and varicella vaccines as two injections at a single visit at 12 through 47 months of age, unless the parent or caregiver expresses a preference for the MMRV vaccine. Use of the MMRV vaccine generally is preferred over separate injections for the second dose of the MMR and varicella vaccines at any age (15 months to 12 years) and for the first dose at 48 months of age or later.[96]

Rubella-containing vaccine is recommended for susceptible nonpregnant women of childbearing age, at-risk postpuberal males and females in colleges, military recruits, recent immigrants, teachers, childcare providers, and healthcare personnel.[94,95,99] People are considered to be susceptible to rubella if they were born in 1957 or later, did not receive at least 1 dose of vaccine, and have no serologic evidence of immunity.[44,95]

Rubella-containing vaccine is safe and well tolerated.[100] Adverse reactions include rash, fever, and lymphadenopathy in up to 15% of vaccine recipients. Joint pains occur in less than 1% of children, but arthritis and arthralgia occur in up to 25% of postpubertal women after vaccination.[44] Arthropathy begins 1 to 3 weeks after vaccination and is transient. Persistent arthropathy is reported but is uncommon. Transient peripheral neuropathy, thrombocytopenia, and CNS manifestations rarely have been described.

Rubella-containing vaccine should not be administered to pregnant women.[95] The risk of congenital rubella infection after vaccination is estimated at 1.3% based on accumulated data from 226 seronegative women who received rubella vaccine inadvertently during the first trimester of pregnancy and demonstrated seroconversion. Two percent of infants of these women had serologically confirmed rubella infection with no clinical manifestations; no infant had congenital defects.[95,100]

Although administration of live-virus vaccine is contraindicated in immunosuppressed children, those with human immunodeficiency virus (HIV) infection should be given MMR vaccine because of the excess risk of morbidity and mortality associated with measles in this population. HIV-infected children without severe immunosuppression should receive MMR vaccine at the standard recommended ages, although primary vaccine failure may be substantial. Persons who have received immune globulin, blood or blood products, or immunosuppressive therapy should not be vaccinated for at least 3 months and longer if a high dose of immune globulin was given intravenously (see Chapter 6).

Passive Immunity

Immune globulin can modify or suppress clinical manifestations of acquired rubella infection in exposed susceptible people, but it does not prevent rubella infection. Absence of clinical infection may not indicate the absence of viremia, and infants with congenital rubella have been born to women who received immune globulin soon after exposure to rubella during pregnancy. Immune globulin therefore is not recommended routinely for postexposure prophylaxis of susceptible pregnant women and should be considered only if termination of the pregnancy will not be considered.

Public Health Measures

Children with acquired rubella should be excluded from school or group childcare until 7 days after the onset of rash. In outbreak situations, children without evidence of immunity must be vaccinated or excluded for 21 days after rash onset in the last case in the outbreak.[95] Infants with congenital rubella should be considered contagious until 1 year of age unless results of two urine and nasopharyngeal cultures obtained 1 month apart in infants older than 3 months of age are negative for RuV.[95] Healthcare, childcare, military personnel, and college students should be screened for rubella immunity. Susceptible people should be immunized to prevent infection with and transmission of the virus.[94,95,99] Routine serologic screening of postpubertal women is not recommended.

Isolation Procedures

In addition to standard precautions, droplet precautions are recommended for hospitalized persons with postnatal rubella for 7 days after the onset of rash. Contact isolation is required for neonates with suspected congenital rubella.

Key Points

Epidemiology, Clinical Features, Diagnosis, and Prevention of Rubella

Epidemiology

- Vaccine-preventable viral disease of childhood
- Affects only humans and has no animal reservoirs
- Postnatal rubella is transmitted by direct or aerosol contact with respiratory secretions of infected people.
- Rubella has been eliminated from the Americas since 2009 after widespread vaccination.

- Rubella and congenital rubella syndrome (CRS) remain an important public health problem worldwide.

Clinical Features

- Postnatal rubella illness usually is mild and often is subclinical.

- Manifestations of CRS include growth retardation, deafness, cataract, congenital heart disease, and mental retardation.

Diagnosis

- Serology (i.e., positive rubella-specific IgM or significant rise in rubella IgG level) or virus RNA detection by real-time polymerase chain reaction (rt-PCR) testing of clinical samples

- Diagnosis of congenital rubella requires virologic or serologic confirmation.

Treatment

- No antiviral therapy is available.

Prevention

- Live, attenuated rubella-containing vaccines (i.e., MMR or MMRV)

- Rubella-containing vaccines are safe and well tolerated.

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RNA Viruses: Coronaviridae

OUTLINE

222 Human Coronaviruses

222

Human Coronaviruses

Susan M. Poutanen

Coronaviruses are included in the Coronaviridae family under the order Nidovirales. They are enveloped, nonsegmented, single-stranded, positive-sense RNA viruses named after their corona-like or crown-like surface projections seen on electron microscopy that correspond to large surface spike proteins (Figs. 222.1 and 222.2). They are host specific and can infect humans and a variety of animals.[1]

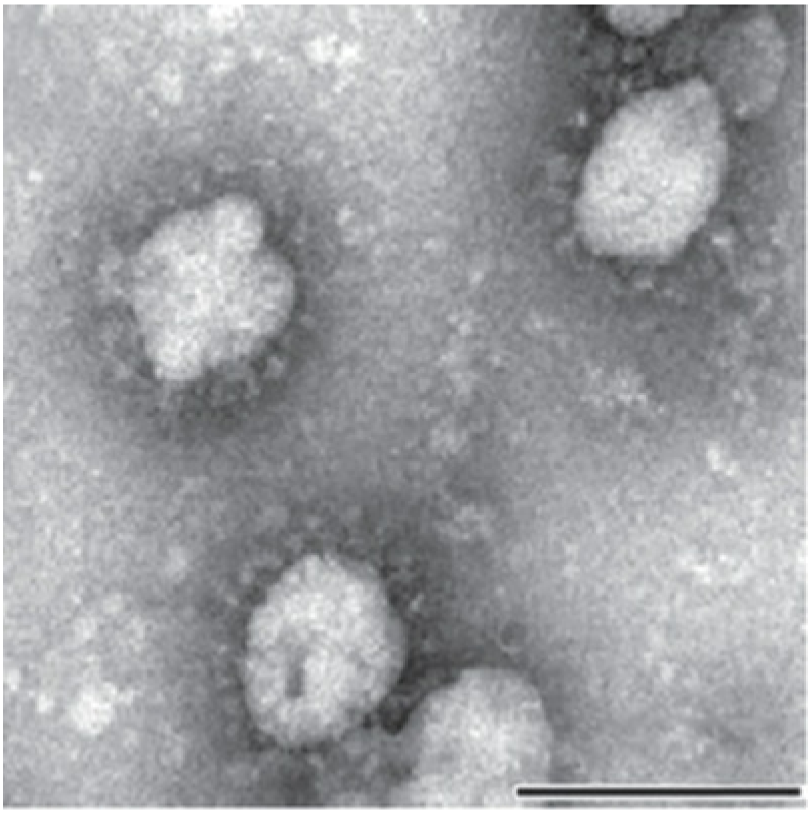

FIGURE 222.1 Negative-contrast electron micrograph of severe acute respiratory syndrome coronaviruses shows the typical crown-like spike proteins on the surface of the coronavirus particles (bar = 100 nm). (From Kuiken T, Fouchier RA, Schutten M, et al. Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. Lancet 2003;362:263–270.)

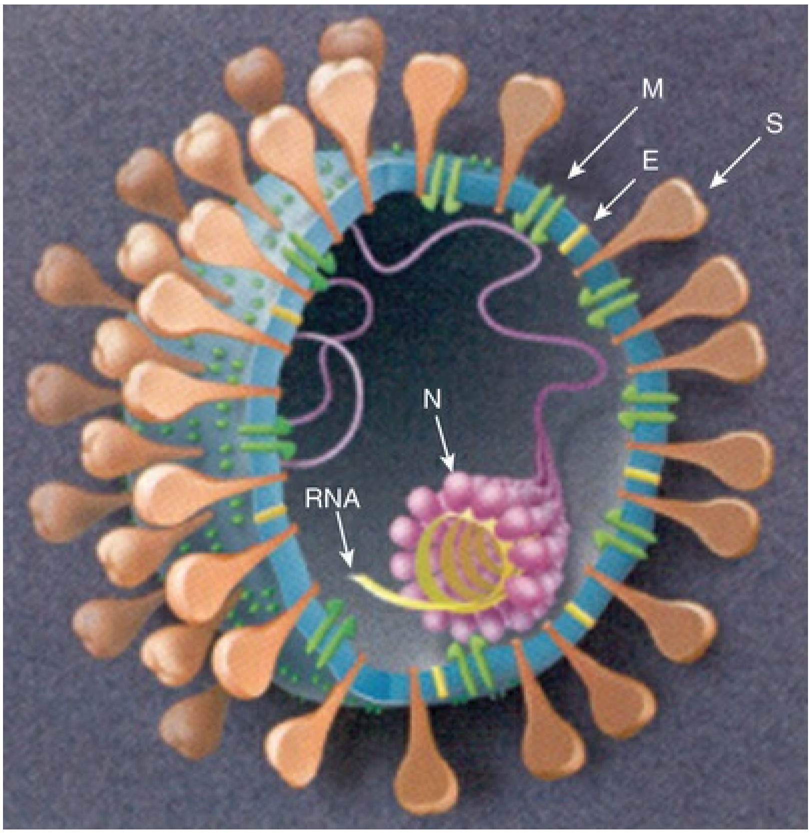

FIGURE 222.2 Organization of the spike (S), membrane (M), and envelope (E) glycoproteins in a typical coronavirus is shown for a typical coronavirus. The RNA is protected by the nucleocapsid proteins (N). (From Holmes KV, Enjuanes L. The SARS coronavirus: a postgenomic era. Science 2003;300:1377–1378.)

Four genera of coronaviruses have been described. Human coronaviruses (HCoVs) are part of the *Alphacoronavirus* and *Betacoronavirus* genera[1,2] (Table 222.1).

TABLE 222.1

Human Coronaviruses

Genus	Species	Acronym	Host	Associated Diseases
Alphacoronavirus	Human CoV-229E	HCoV-229E	Human	Respiratory tract infection
	Human CoV-NL63	HCoV-NL63	Human	Respiratory tract infection
Betacoronavirus				
Subgroup A	Human CoV-OC43[a]	HCoV-OC43	Human	Respiratory tract infection
	Human CoV-HKU1	HCoV-HKU1	Human	Respiratory tract infection and possibly gastroenteritis
Subgroup B	SARS CoV	SARS CoV	Human	Respiratory tract infection

Subgroup C	MERS CoV	MERS CoV	Human	Respiratory tract infection
Subgroup D	No human CoV identified	—	—	—
Deltacoronavirus	No human CoV identified	—	—	—
Gammacoronavirus	No human CoV identified	—	—	—

[a] This species has been abolished according to the International Committee on Taxonomy of Viruses. It is now considered part of the species *betacoronavirus 1*.[1] However, because the name HCoV-OC43 is still commonly used, the species is referred to as HCoV-OC43 in this chapter.

CoV, coronavirus; HCoV, human coronavirus; MERS, Middle East respiratory syndrome; SARS, Severe acute respiratory syndrome.

Epidemiology

In the 1930s, coronaviruses were recognized as animal pathogens.[3] Thirty years later, coronaviruses were identified as human respiratory pathogens. The first recognized HCoV strains included 229E and OC43. Strains such as B814, OC16, OC37, and OC48 also were described but were not characterized further.[4–6] Coronavirus-like particles have been detected in stool, primarily in infants with gastroenteritis and necrotizing enterocolitis, but further characterization has not been completed.[7–9]

In 2003, severe acute respiratory syndrome (SARS) CoV was identified as a novel respiratory pathogen responsible for a global outbreak of SARS. First emerging in 2002 in China, the outbreak lasted 9 months and resulted in 8098 people infected and 774 deaths.[10–14] Data suggest that SARS CoV evolved from SARS CoV–like viruses in horseshoe bats, with civet cats and other wild market animals serving as intermediate hosts.[15–20]

Renewed interest in CoV research let to the discovery of two novel HCoVs 2 years later: NL63 (also known as NL or NH) and HKU1.[21–23] HCoV-NL63 has been detected in human respiratory samples from as early as 1981.[24] It is unclear how HCoV-NL63 and HCoV-HKU1 relate to the HCoV strains originally described in the 1960s (i.e., B814, OC16, OC37, and OC48) or to the enteric coronavirus-like particles detected in stool.[25]

In 2012, the Middle East respiratory syndrome (MERS) CoV (also called hCoV-EMC) was identified as a novel CoV responsible for an epidemic of respiratory illness in the Kingdom of Saudi Arabia.[26,27] Data suggest that MERS CoV likely evolved from bat CoV, with camels acting as intermediate hosts.[28] A total of 1733 cases and 678 deaths were associated with MERS CoV as of May 2016.[29]

HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1 are found worldwide and cause disease predominantly in winter and spring months in temperate climates.[24,30] Seroprevalence data suggest that exposure is common in early childhood.[31,32] SARS CoV has not been identified since 2004, when 4 sporadic community-acquired cases of SARS were identified in China[33] and 13 cases linked to laboratory biosafety practice breaches were identified in Southeast Asia.[34–36] During the 2002–2003 outbreak, most SARS CoV transmission occurred within hospitals from patients with unrecognized illness.[37] MERS CoV cases continue in the Middle East, primarily linked to exposure to camel or camel products or close contact with unrecognized cases in hospitalized patients.[38–40] Household transmission also has occurred.[41] In 2015, a large outbreak of MERS CoV in South Korea, affecting 186 cases and associated with 36 deaths, was traced to an individual who returned from travel in the Middle East.[28,29,42]

Modes of transmission for HCoV other than SARS CoV and MERS CoV have not been well studied. Based on studies of other respiratory viruses, transmission likely occurs primarily by a combination of spread by droplet and direct and indirect contact.[43–45] The possible role of aerosol spread needs further study. Droplet spread and direct contact likely are the most common modes of transmission for SARS CoV, although evidence for spread by indirect contact and aerosol also exists.[46–53] There is no evidence of vertical transmission of SARS CoV.[54,55] Transmission of MERS CoV is thought to occur through droplet, contact, and possibly aerosol routes.[40,41,56]

HCoV-229E and HCoV-OC43 are most likely transmitted during the first few days of illness, when symptoms and respiratory tract viral load are maximal.[57,58] Further study is needed to confirm if this also is the case for HCoV-NL63 and HCoV-HKU1. SARS CoV and MERS CoV are most likely transmitted during the second week of illness, when symptoms and viral load in the respiratory tract peak.[59–62] Supershedding events have been associated with SARS CoV and MERS CoV.[39]

The incubation period for HCoV-229E is 2 to 5 days (median, 3 days).[58,63] Further study is needed to confirm the incubation periods for HCoV-OC43, HCoV-NL63, and HCoV-HKU1. The incubation period for SARS CoV is 2 to 10 days (median, 4 days).[59] The incubation for MERS CoV is 2 to 15 days (median, 5 days).[40]

Pathogenesis and Immunity

The pathogenesis of HCoVs has been best described for HCoV-229E, SARS CoV, and MERS CoV. For SARS CoV, most evidence is from infections in adults because few children were affected by the 2002–2003 outbreak.[64]

Human Coronavirus 229E.

HCoV-229E infections are initiated through inoculation of respiratory tract mucosal surfaces. Nasal mucosal plasma exudation and increased interferon γ (IFNγ) levels in nasal lavage specimens correlate with symptom severity.[65,66] Respiratory tract viral loads peak within the first 3 days after infection and drop off dramatically at 1 week, correlating with development and improvement in symptoms.[57,67] Antibodies can be detected at 1 week, correlating with the drop in viral load, and they reach maximal levels approximately 1 week later and decline thereafter.[68]

Immunity is not complete, and reinfection is common.[68,69] Higher circulating antibody levels, especially levels of specific IgA anti-HCoV, correlate with reduced symptoms and reduced virus shedding on re-exposure.[68,70]

Severe Acute Respiratory Syndrome Coronavirus.

SARS CoV infection is initiated through inoculation of the respiratory tract mucosa using angiotensin-converting enzyme 2 acting as the functional receptor for cell entry.[71] Viremia and replication in the lung and gastrointestinal tract follows.[72,73] Replication at other sites likely occurs given the wide distribution of SARS CoV in tissues examined at autopsy.[74,75]

Peak viral loads in nasopharyngeal specimens are detected during the second week of symptoms.[60,73] A rise in SARS CoV–specific antibodies typically is seen at the same time. Increasing antibody titers and symptomatic improvement during the second and third week are associated with a decrease in SARS CoV viral loads.[60,76] Paradoxically, despite a fall in viral load and a rise in SARS-specific antibodies, clinical deterioration is observed in some patients.[60] The host immune responses likely contribute to clinical deterioration in these patients. Elevated levels of IFNγ, inflammatory cytokines interleukin-1 (IL-1), IL-6, and IL-12; neutrophil chemokine IL-8; monocyte chemoattractant protein 1; and IFNγ-inducible protein-10 have been detected, with levels of IL-6 correlating with severity of disease.[77,78]

Middle East Respiratory Syndrome Coronavirus.

MERS CoV infection most likely is initiated through inoculation of the respiratory tract mucosa mediated by dipeptidyl peptidase 4 (DDP4) (i.e., CD26) acting as the functional receptor.[79,80] Viral loads are highest in lower respiratory tract specimens, but real-time polymerase chain reaction (rt-PCR) evidence of MERS CoV also can be found in the upper respiratory tract, serum, stool, and urine.[62] Autopsy data from a single patient did not show extrapulmonary MERS CoV dissemination, but because DPP4 is widely distributed in different tissues, extrapulmonary dissemination is thought to be possible.[79]

Clinical Manifestations

Human Coronaviruses 229E, OC43, NL63, and HKU1.

HCoVs 229E, OC43, NL63, and HKU1 are commonly associated with the common cold, which is typically characterized by rhinorrhea, nasal congestion, sore throat, sneezing, and cough that may be associated with fever.[22,24,67,81–84] Together, the HCoVs are the second most common cause of the common cold after rhinoviruses.[85,86]

Based on data for HCoV-229E, symptoms typically peak on day 3 or 4 of illness and are self-limited.[67,87] HCoVs also may be associated with acute otitis media or exacerbations of asthma.[24,82,84,88,89] Less frequently, these viruses are associated with lower respiratory tract infections, including bronchiolitis and pneumonia, primarily in infants and immunocompromised children and adults.[23,82,84,90–98]

Compared with other HCoVs, HCoV-NL63 more frequently is associated with croup and is the second most common cause after parainfluenza virus type 1.[99,100] A possible association of HCoV-NL63 with Kawasaki disease was not substantiated.[101,102]

HCoV-HKU1 has been associated with symptoms of gastroenteritis, including vomiting and diarrhea, which typically occur along with respiratory symptoms.[84,89,103] HCoV-HKU1 also appears to be more frequently associated with febrile seizures compared with other HCoVs.[84,89]

Severe Acute Respiratory Syndrome Coronavirus.

SARS CoV is associated with severe symptoms.[104–106] SARS CoV disproportionately affects adults, who typically manifest fever, myalgia, headache, malaise, and chills, followed by a nonproductive cough and dyspnea 3 to 5 days later. Approximately 25% develop watery diarrhea. Respiratory distress progresses and requires intubation and ventilation in 25% of cases. The overall associated mortality rate is approximately 10%, with most deaths occurring in the third week of illness.[105] The case-fatality rate for persons older than 60 years of age approaches 50%.[107]

Typical laboratory abnormalities include lymphopenia and increased serum lactate dehydrogenase (LDH) and creatine kinase levels.[108,109] Most patients have progressive unilateral or bilateral, ill-defined airspace infiltrates on chest imaging.[108,110–112] Pneumothoraces and other signs of barotrauma are common in patients receiving mechanical ventilation.[105]

Infants and children younger than 12 years of age who develop SARS typically have fever, cough, rhinorrhea, and milder symptoms compared with adolescents and adults. Associated lymphopenia is less severe, and radiographic changes are milder and usually resolve more quickly than in adolescents and adults. No infants or children died of SARS CoV infection in the 2002–2003 outbreak.[64,113–116] Adolescents who developed SARS had clinical courses more closely resembling that of adults, including fever, myalgia, headache, and chills, and they were more likely to have dyspnea, hypoxemia, and worsening chest radiographic findings.

Women infected with SARS CoV during pregnancy who survive have an increased risk of spontaneous miscarriage, preterm delivery, and intrauterine growth restriction.[54,55,117] Two neonates born to mothers with SARS in the 2002–2003 outbreak developed gastrointestinal complications (e.g., jejunal perforation, necrotizing enterocolitis with ileal perforation) soon after birth, but neither had clinical evidence of SARS CoV infection.[55] It is unclear whether these findings related to complications of maternal SARS or treatments for SARS, such as ribavirin and corticosteroids, used during pregnancy.

Middle East Respiratory Syndrome Coronavirus.

MERS CoV infection is associated with severe symptoms similar to those seen with SARS CoV, although a spectrum of disease, including asymptomatic infections and mild disease, can occur.[27] Most cases have been identified in male adults with comorbidities. Infected children typically have milder symptoms.[27] Fever, myalgia, and chills are followed a few days later by a nonproductive cough and dyspnea. Approximately 25% of patients also have vomiting, diarrhea, or abdominal pain.[27] Rapid deterioration of oxygenation with progressive unilateral or bilateral airspace infiltrates on chest imaging may follow, requiring mechanical ventilation and often associated with acute renal failure.[118]

Laboratory abnormalities include thrombocytopenia, lymphopenia, and an elevated LDH level.[27] The case-fatality rate is high, estimated at 36%.[28]

Diagnosis

Some laboratories offer comprehensive rt-PCR for respiratory tract specimens, which may include detection of HCoVs 229E, OC43, NL54, and HKU1.[84,119] Public health laboratories offer rt-PCR and antibody testing for SARS CoV and MERS CoV testing.[120,121]

Upper and lower respiratory tract specimens are the most appropriate samples for viral detection when testing is available.[62,73,82,84,122] Stool samples frequently are positive for patients with SARS and have been positive for some with MERS CoV[62] and HCoV-HKU1 infection.[73,89,103,122] Serum samples also may be positive by rt-PCR for patients with SARS CoV and MERS CoV infection.[62] For cases of HCoV-299E and HCoV-OC43 infection, specimens are most likely to be positive during the first few days of illness[57]; whether this also is true for HCoV-NL63 and HCoV-HKU1 needs further study. For SARS CoV infection, serum samples for RT-PCR testing are most likely to be positive in the first week of illness,[72,123] but respiratory and stool specimens may not be positive until the second week of illness, when symptoms and viral loads peak.[60,73] Infants and children with SARS CoV infections are less likely to have positive specimens, consistent with the milder symptoms and presumed correspondingly lower viral loads in children.[113,114] For cases of MERS CoV infection, specimens for rt-PCR should be collected from the lower respiratory and upper respiratory tract along with serum and stool samples.[62,124]

Laboratory guidance for SARS CoV and MERS CoV diagnostic testing is available on the Centers for Disease Control and Prevention (CDC) website.[124,125] Because of the potential for false-positive results and the associated public health implications, testing for SARS CoV in the absence of known person-to-person transmission should be done only in consultation with public health departments and when there is a high degree of clinical suspicion. Similarly, testing for MERS CoV should be done only in consultation with public health officials and in the context of known risk factors for MERS CoV infection.

Treatment

Because of the self-limited nature of infection with HCoV strains 229E, OC43, NL63, and HKU1, few treatment studies have been performed. Care typically is supportive.

SARS CoV infections are more serious. Corticosteroids, type 1 IFN agents, convalescent plasma, ribavirin, and lopinavir or ritonavir have been used to treat SARS.[108,126–129] For many of these agents, anecdotal reports suggest benefit, and in vitro assays and animal models offer supportive data,[108,126–138] with the exception of ribavirin, for which in vitro studies do not support efficacy.[135,139,140]

Since the SARS outbreak, viral entry– and protease-inhibiting agents, RNA-interfering agents, and glycyrrhizin have been tested in vitro and appear promising.[140,141] However, no definitive conclusions can be drawn. If SARS CoV re-emerges, clarification of the effectiveness of these treatments through controlled clinical trials will be needed. For MERS CoV, preliminary data suggest several treatments may be useful, but no definitive recommendations can be made at this time.[142]

Prevention

Practicing good hand and respiratory hygiene is the most useful control measure to curb the spread of all respiratory viruses, including HCoVs.[143,144] Prophylactic intranasal IFNα has reduced the duration and severity of HCoV-229E infection in research settings, but it has not been used clinically.[145,146] A proprietary extract of the roots of North American ginseng (*Panax quinquefolium*) can reduce the number of colds and the severity and duration of cold symptoms in adults when taken daily, presumably due to immune stimulation.[147–150] Efficacy for a decrease in the number of colds specifically due to HCoVs has not been studied.

Healthcare personnel should use a gown, gloves, mask, and eye protection for the duration of illness when caring for children hospitalized with signs and symptoms of a respiratory tract infection.[151] The same precautions, with the replacement of the mask by a respirator if available, and negative-pressure isolation are recommended for patients with SARS CoV infection for the duration of illness or 10 days after resolution of fever, provided respiratory symptoms are absent or improving.[151] The same precautions recommended for SARS CoV are recommended for MERS CoV except the duration of precautions should be decided in conjunction with public health authorities.[152]

Standard disinfectants should be used to clean and disinfect environmental surfaces that are frequently touched by infected persons. This can decrease the potential for indirect transmission of HCoVs by fomites.[153]

The control of the 2002–2003 SARS outbreak is credited to the rapid identification of cases and early implementation of infection control and public health measures, including contact tracing and quarantine. If SARS CoV re-emerges, all measures should be implemented urgently in an attempt to prevent a recurrent worldwide outbreak.[28,154,155]

Transmission of MERS CoV within hospitals and households can be averted with the use of infection control precautions,[55] but preventing the transmission from camels to humans is more challenging given the prevalent use of camels for transport, meat, and milk. Recommendations to reduce the likelihood of transmission include regulation of camel movement, enforcing the use of personal protective precautions while handling camels, and educating the public about the risks of consuming unpasteurized camel milk and urine.[156] Given the challenges of following these recommendations, it is likely that sporadic transmission will continue until an effective MERS CoV vaccine is found.[28,157]

Key Points

Epidemiology, Clinical Manifestations, Diagnosis, and Treatment of Human Coronavirus (HCoV) Infections

Epidemiology

- Human coronaviruses (HCoVs) 229E and OC43 (identified in the 1960s) and NL63 and HKU1 (identified in 2004) are found worldwide. Exposure is common in early childhood; in temperate climates, it primarily causes infections in the winter and spring months.

- Severe acute respiratory syndrome coronavirus (SARS CoV) was identified in 2003 as responsible for the 2002–2003 global outbreak of SARS.

- SARS CoV has not been associated with disease since 2004, and the possibility or probability of a large-scale re-emergence of SARS is unknown.

- Middle East respiratory syndrome coronavirus (MERS CoV) was identified in 2012 as responsible for an epidemic of respiratory illness in the Kingdom of Saudi Arabia. Transmission is ongoing and is primarily limited to countries in the Middle East.

- Risk factors include exposure to camels or camel products or close contact with persons infected with MERS CoV.

- The most common modes of transmission are through droplet and direct and indirect contact.

Clinical Manifestations

- HCoV strains 229E, OC43, NL63, and HKU1 are associated with the common cold, acute otitis media, asthma exacerbations, and less frequently, bronchiolitis and pneumonia.

- HCoV-NL63 is also associated with croup. HCoV-HKU1 is associated with vomiting and diarrhea and frequently with respiratory tract symptoms; it appears to be associated more frequently with febrile seizures compared with other HCoVs.

- SARS CoV causes SARS, with an attendant mortality rate of 10%, which primarily affects adults and adolescents. Children younger than 12 years of age who develop SARS typically have less severe manifestations (i.e., fever, cough, and rhinorrhea).

- MERS CoV is associated with a spectrum of disease, ranging from asymptomatic and mild disease to severe respiratory disease with an associated mortality rate of 36%.

- MERS CoV primarily affects male adults with comorbidities; children with MERS typically have milder symptoms.

Diagnosis

- Upper and lower respiratory tract specimens can be tested by HCoV real-time polymerase chain reaction.

- Stool samples frequently are positive for patients with SARS CoV and have been positive for some patients with MERS CoV and HCoV-HKU1 infection; antibody tests also are available for SARS CoV and MERS CoV infection.

- Serum samples may be positive for patients infected with SARS CoV and MERS CoV.

Treatment

- Infections with HCoV strains 229E, OC43, NL63, and HKU1 require supportive care.

- SARS CoV and MERS CoV infections have no definitive treatment recommendations because of a lack of controlled trials.

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Parainfluenza Viruses

Asunción Mejías, Octavio Ramilo

Human parainfluenza viruses (HPIVs) were first identified in humans in the late 1950s.[1] HPIVs were initially described in children with croup, but the use of molecular diagnostic tools has elucidated their causative role in acute respiratory tract infections in patients who are immunocompromised, have chronic conditions, or are elderly.[2–6] In otherwise healthy children, HPIVs commonly cause upper respiratory tract infections (URIs) and also lower respiratory tract infections (LRIs) such as pneumonia, bronchiolitis, and exacerbations of reactive airway disease.[3,7] HPIVs are responsible for 6% to 11% of total hospitalizations of children younger than 5 years of age, highlighting the need for effective vaccines and antiviral therapies.[3,8]

Description of the Pathogen

Microbiology

HPIVs are pleomorphic, enveloped RNA viruses that belong to the Paramyxoviridae family. There are four antigenically distinct types, 1, 2, 3, and 4, with two antigenic subtypes, 4A and 4B.[9,10] Parainfluenza viruses are divided into two genera based on complement fixation and hemagglutinating antigens. Parainfluenza types 1 and 3 belong to the *Respirovirus* genus, and parainfluenza types 2, 4A, and 4B belong to the *Rubulavirus* genus. Parainfluenza virus type 5 causes disease in animals, and its role in humans remains controversial.[11]

Other viruses in this family include mumps, measles, Hendra, and Nipah viruses; New Castle disease virus; respiratory syncytial virus (RSV); and human metapneumovirus (HMPV).The HPIV serotypes and subtypes display substantial serologic cross-reactivity. The single-stranded, negative-sense, nonsegmented RNA genome (−ssRNA) of HPIV contains approximately 15,000 nucleotides that encode six common structural proteins.

The viral envelope is derived from the host cell and is covered with glycoprotein spikes. Two glycoproteins, the hemagglutinin-neuraminidase (HN) and fusion (F) proteins, play a major role in pathogenesis and are the major antigenic targets for neutralizing antibodies.[12] HN is coupled with the activated F protein to permit the virion entry into the cell. Activation of the F protein is mediated by cellular proteases. The specific localization of these proteases may influence specific-member HPIV cellular tropism.

Pathogenesis and Immunity

HPIVs replicate exclusively in cells of the respiratory epithelium, initially infecting epithelial cells of the nose and nasopharynx. Clinically, HPIVs most commonly affect the large airways of the lower respiratory tract, causing croup.[13] Viral tropism for this anatomic location seems to be related to the abundant ciliated epithelial cells.[14] In more severe cases, infection spreads to the distal airways and causes development of bronchiolitis or pneumonia.

The mechanism of airway and parenchymal injury and resulting symptoms probably are a combination of the host immune response and to a lesser extent the direct viral cytopathic effect. Significant viral replication is detected in the upper (i.e., nose) and lower (i.e., lungs) respiratory tract within 24 hours of infection, with peak viral replication occurring between days 2 to 5. Necrosis and occasionally proliferation of the bronchiolar epithelium accompany the destruction of ciliated epithelial cells in children with pneumonia and bronchiolitis.[15] A peribronchiolar infiltrate of lymphocytes, plasma cells, and macrophages appears along with edema and excessive mucus production, and if pneumonia is prominent, the alveoli are filled with fluid.[16]

Innate Immune Responses, Cytokines, and Chemokines.

By mechanisms that are not completely understood, HPIV-3 modifies the survival and functional properties of human antigen-presenting cells (i.e., monocytes and dendritic cells), which may prevent the development of efficient antiviral responses.[17] HPIVs induce the production of cytokines and chemokines in animal models, under in vitro conditions and in children with acute infections.[18,19] The magnitude of the cytokine response probably is related to the clinical syndrome and virus type.

Local production of interferon γ (IFNγ) was detected in 30% of children with HPIV lower respiratory tract disease, and nasal wash concentrations of interleukin-8 (IL-8) were significantly higher in children infected with HPIV-3 or HPV-1 compared with other HPIV types and in those with lower rather than upper respiratory tract infection.[19,20] A disruption in the mechanism that regulates metalloproteinases (MMPs) also has been associated with increased disease severity in infants with bronchiolitis caused by HPIVs or RSV.[21]

Cellular Immunity.

Host defense against HPIVs is mediated largely by humoral immunity and T-cell recognition of epitopes on the HN and F surface glycoproteins of the virus.[22] Animal models of acute HPIV infection suggest that CD8$^+$ T-lymphocyte–mediated immune responses are critical for viral clearance.[23] Infants with HPIV-induced croup have defective regulation of cell-mediated immune responses compared with children with uncomplicated URIs.[24] This and the prolonged viral shedding and severe disease manifestations observed in people with defective cell-mediated immunity indicate the important role of T lymphocytes in controlling infection.[5,25,26]

Humoral Immunity.

Mucosal immunity appears to play a key role in controlling disease. Studies of adults after an experimental challenge with HPIV-1 and HPIV-2 indicate that neutralizing antibody concentrations in secretions correlate better with protection than serum antibody concentrations.[27,28] In children, secretory antibodies appear 7 to 10 days after the onset of symptoms and peak at about 2 weeks after disease onset.[29] Most children are born with neutralizing antibodies to all four HPIV types, but titers fall sharply during the first 6 months of life.

Most HPIV antibody responses involve serum immunoglobulin G1 (IgG1), but levels of serum IgG3, IgG4, IgA, and IgM rise significantly in 30% of adults. Antigenic variations in HPIV viruses are related to the heterogeneity within the viruses rather than to antigenic viral drift. Reinfections, which occur many times throughout life, most likely reflect waning immunity. After several infections, antibodies may develop that cross-neutralize different parainfluenza virus strains (e.g., HPIV-1 and -3, HPIV-2 and -4).

In immunocompetent people, reinfections are more likely to cause only upper respiratory tract symptoms.[30] In epidemiologic studies, HPIV-3 was isolated from 143 children (i.e., 50% of all HPIV isolates) younger than 5 years of age. Of those, 9% had subsequent reinfections with isolation of the same virus type less than 1 month after the initial infection. Although reinfections are thought to induce increased resistance to LRIs by the infecting serotype, protection appears not to be based entirely on increased humoral immunity.[30,31] In these studies, the clinical manifestations of the reinfection episodes were not different from those of the initial episode. No reinfections were seen with HPIV-1 or HPIV-2.[7]

Epidemiology

The different serotypes of HPIV have distinct epidemiologic patterns that depend on the geographic location. However, overall HPIV seasonal patterns are predictable and cyclic except for tropical countries, where HPIVs do not exhibit seasonal variation.[32,33]

HPIV-1 causes the largest, most defined outbreaks of croup in the fall of odd-numbered years. Outbreaks of HPIV-2, although more erratic and milder, usually follow HPIV-1 outbreaks.[16] A major increase in the number of cases of croup in the autumn usually indicates an HPIV-1 or -2 outbreak.[34] HPIV-3 is the most frequently recovered strain. It is endemic, and infection most commonly occurs during the spring and summer and extends into autumn, especially when other HPIV outbreaks are absent.[7,30]

The use of molecular diagnostic tools is elucidating patterns of HPIV-4 infections. A large, retrospective study conducted in Colorado between 2009 and 2012 showed that HPIV-4 had year-round prevalence, with biennial peaks during the fall of odd-numbered years (Fig. 223.1).[35–37]

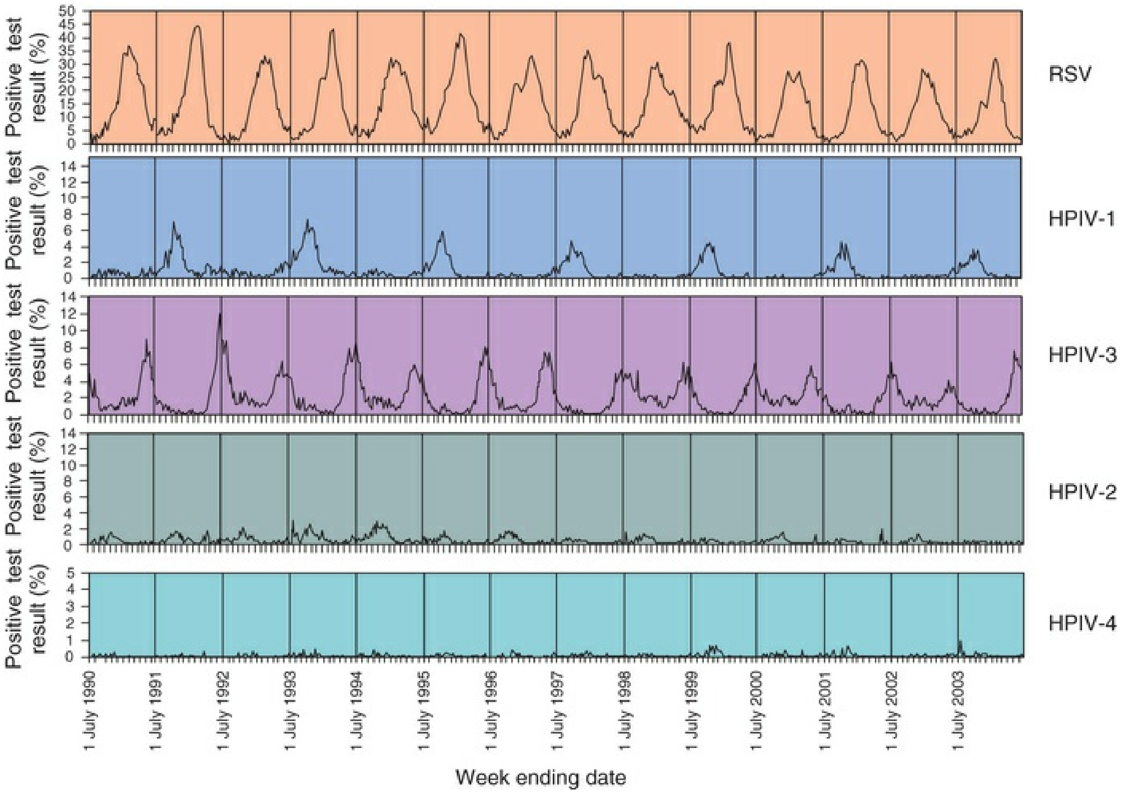

FIGURE 223.1 Seasonal trends of human parainfluenza virus (HPIV) infections are shown by the percentage of tests positive for serotypes 1, 3, 2, and 4 reported to the National Respiratory and Enteric Viruses Surveillance System (NREVSS) by week from July 1990 through June 2004. The percentage of antigen detection tests positive for respiratory syncytial virus (RSV) reported to NREVSS is shown for comparison. Notice that RSV and HPIV-4 have different axis scales than the other HPIV serotypes. (Modified from Fry AM, Curns AT, Harbour K, et al. Seasonal trends of human parainfluenza virus infections: United States, 1990–2004. Clin Infect Dis 2006;43:1016–1022.)

The age of primary infection varies by serotype. By 12 months of age, about 50% of infants have serologic evidence of HPIV-3 infection, and by 5 years of age, most children have been infected with HPIV-3.[35,38,39] In contrast, only 50% to 75% of 5-year-old children are seropositive for HPIV-1 and -2. Acquisition of HPIV-4 occurs during preschool years, following the pattern observed with HPIV-1 and -2.[40] A prospective surveillance study conducted in Houston, Texas, showed that rates of primary infection in the first and second year of life were 62 and 81 per 100 child-years, respectively.[30]

Infection with HPIV-3, the HPIV type that most closely resembles RSV, frequently occurs in young infants and is a prominent cause of bronchiolitis or pneumonia. Infections with HPIV-1 and HPIV-2 occur most commonly in children between 1 and 5 years of age. HPIV-4 infections are common in toddlers attending childcare centers and older children (mean age, 4 years) requiring hospitalization with more severe disease (Table 223.1).[35,36]

TABLE 223.1

Clinical and Epidemiologic Characteristics of Human Parainfluenza Virus Infections

Characteristic	HPIV-1	HPIV-2	HPIV-3	HPIV-4
Age	1–5 yr	2–6 yr	<6 mo	1–4 yr
Seasonality	Fall, odd-numbered years	Year-round, may follow HPIV-1	Endemic; spring/summer	Year-round with biennial peaks in the fall or winter of odd-numbered years
Most common clinical manifestation	Croup ++	Croup +	LRI (pneumonia, bronchiolitis)	URI ++ and LRI + (not croup)
Viral shedding[a]	2 wk	1 wk	3 wk	~1.5 wk
Hospitalization rates[3]	0.32–1.59/1000	0.1–0.86/1000	0.48–2.6/1000	Unknown

[a] In immunocompetent children.

HPIV, human parainfluenza virus; LRI, lower respiratory tract infection; URI, upper respiratory tract infection; +, less common; ++, more common.

Traditionally, HPIVs have been considered the second most common cause of hospitalization for respiratory disease in children.[3,41] HPIVs are associated with 30% to 40% of all acute respiratory tract infections in infants and children, and in the United States, they are responsible for 7% of all hospitalizations for fever or acute respiratory illness in children younger than 5 years of age.[3,7] Annual rates of HPIV-related hospitalization for children younger than 5 years of age vary from 1.0 to 5.1 per 1000 children.[7,8,42] Based on a 4-year longitudinal study, rates of hospitalization for US children younger than 5 years of age were similar for HPIVs, HMPV, and influenza virus: 1.02, 1.2, and 0.9 per 1000 children, respectively. Rates of hospitalization for RSV in the same population were threefold higher (3 of 1000).[3,43]

Rates of hospitalization for bronchiolitis, croup, and pneumonia due to HPIV infections in children younger than 5 years of age were estimated in a 12-year longitudinal study (1998–2010). The mean annual estimates were 0.2, 0.4, and 0.5 hospitalizations per 1000 children for bronchiolitis, croup, and pneumonia, respectively. The estimated annual costs attributed to these three conditions exceeded $250 million.[42] Most hospitalizations occurred for children younger than 2 years of age. Pneumococcal vaccination has been associated with a reduction in the incidence of pneumonia in infants with HPIV and other respiratory viruses, suggesting that pneumococcus is an important pathogen in the development of virus-associated pneumonia.[44]

HPIVs also cause acute respiratory illness with substantial morbidity and mortality rates in immunocompromised patients, those with underlying chronic cardiopulmonary conditions, and in the elderly.[5,6,45]

Transmission

HPIVs, particularly HPIV-3, are highly transmittable. Similar to RSV, HPIVs are transmitted from direct, close person-to-person contact through large respiratory tract droplets and by exposure to contaminated fomites. Climatologic factors may impact the shedding of HPIVs; in vitro studies have shown that aerosol particles of HPIV-3 survive longer when the relative humidity is 20% rather than 50% or 80%.

Infection most likely is transmitted by hands contaminated with secretions containing virus, followed by autoinoculation. An adult volunteer study demonstrated that HPIV was not transferable readily to the fingers of other volunteers after 20 minutes on contaminated hands.[46] If kept from drying, HPIVs survive on porous surfaces for up to 4 hours and on nonporous surfaces for as long as 10 hours.[47]

In closed settings, HPIV-3 infection occurs in virtually all exposed children. Secondary attack rates for HPIV-1 and HPIV-2 are 65% to

79%.[2] The usual incubation period for HPIV infection is 2 to 6 days.[22] Depending on the serotype, children with primary HPIV infection can shed virus from 1 week before the onset of symptoms to more than 3 weeks after symptoms resolve. Children with primary HPIV-1 infection shed cultivatable virus for 4 to 7 days and viral RNA, which is measured by polymerase chain reaction (PCR), for up to 2 weeks.[35] In the Houston Family Study, about 17% of children infected with HPIV-3 shed virus for as long as 3 to 4 weeks (see Table 223.1).

Nosocomial infections and outbreaks of HPIV-3 infection are associated with high attack rates. Outbreaks in neonatal nurseries and in bone marrow transplantation units have been reported.[48–53]

Clinical Manifestations

HPIVs cause a variety of upper and lower respiratory tract illnesses (Fig. 223.2), which vary by age, virus serotype, and season. Most primary infections are symptomatic, and disease prevalence is greater among outpatients than inpatients. In healthy children, most illnesses involve the upper respiratory tract, and up to 35% of cases are complicated with otitis media.[54,55]

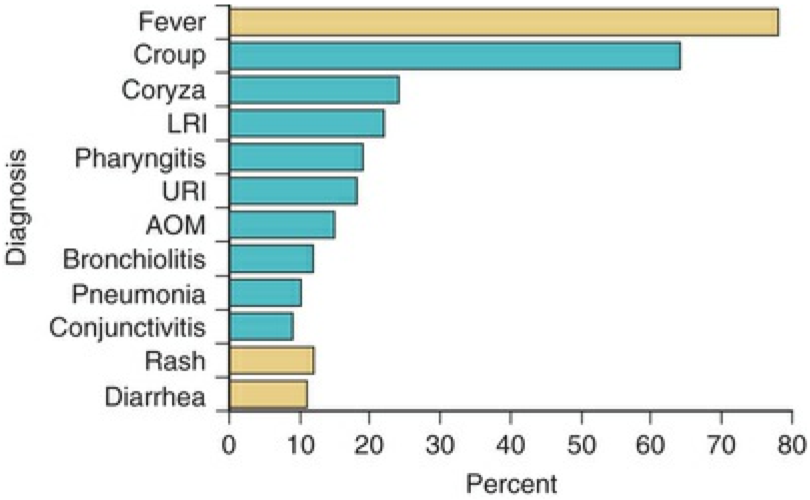

FIGURE 223.2 Clinical illnesses caused by parainfluenza viruses. *Orange* indicates systemic symptoms, and *blue* indicates respiratory symptoms. AOM: acute otitis media; LRI, lower respiratory tract infection; URI, upper respiratory tract infection. (Modified from Reed G, Jewett PH, Thompson J, et al. Epidemiology and clinical impact of

parainfluenza virus infections in otherwise healthy infants and young children <5 years old. J Infect Dis 1997;175:807–813; Frost HM, Robinson CC, Dominguez SR. Epidemiology and clinical presentation of parainfluenza type 4 in children: a 3-year comparative study to parainfluenza types 1–3. J Infect Dis 2014;209:695–702).

HPIV-1 and HPIV-2 typically are associated with croup, HPIV-3 with bronchiolitis and pneumonia, and HPIV-4 with mild URIs in children and adults. HPIV-4 has been associated with severe LRIs in patients with underlying medical conditions.[35,36,39,56] Croup is the most common HPIV-associated diagnosis.[13,57]

Upper Respiratory Tract Disease.

In children, HPIVs account for about 20 % of all URIs.[58–60] Infection typically starts with coryza, cough, rhinorrhea, pharyngitis without cervical lymphadenopathy, and low-grade fever. All four serotypes have been recovered from children and adults with the common cold.[33] URI is the typical manifestation of HPIV infection in immunocompetent adults.

Croup.

Croup (i.e., laryngotracheobronchitis) is a term used to encompass a heterogeneous group of illnesses that affect the larynx, the trachea, and the bronchi. Croup affects about 3% of children annually, with a peak incidence between ages 6 months and 3 years.[13,57] The incidence is 1.5 to 2 times higher among males than females.

HPIVs, especially HPIV-1, are the most frequent cause of croup, accounting for almost 75% of cases.[13,61,62] Croup is characterized by fever, laryngeal obstruction, dyspnea, inspiratory stridor, and a hoarse, barking cough. In mild to moderate cases, symptoms typically last 3 to 5 days. progression is unpredictable, however, and sudden respiratory failure can occur.

In cases with severe stridor, differentiation from epiglottitis can be facilitated by lateral neck radiography. The typical finding in children with croup is subglottic narrowing (i.e., steeple sign).[63] Repeated episodes of spasmodic croup can follow, and abnormalities in lung function can persist for several years in some children.[64] It is unclear whether disposition precedes or results from viral infection.

Bronchiolitis.

Historically, HPIVs have been considered the second in frequency to RSV as a cause of bronchiolitis. However, the use of molecular diagnostics has identified other respiratory viruses more frequently than HPIV as etiologic agents of bronchiolitis.[65,66] All four types of HPIV can cause bronchiolitis, but HPIV-1 and HPIV-3 have been reported most frequently.[3,8,42]

More than 80% of cases of bronchiolitis occur during the first year of life, and most affect infants are younger than 6 months of age. HPIV-1 and HPIV-3 cause 5% to 15% of bronchiolitis cases in children, respectively, and approximately 0.2 per 1000 children with HPIV bronchiolitis require hospitalization.[42] Most hospitalizations for bronchiolitis occur from November through April. Using US National Hospital Discharge Survey data over 18 years, HPIV-related bronchiolitis hospitalizations in children younger than 1 year of age peaked earlier during odd-numbered years than even-numbered years, resulting in a longer season.[8]

Predominant symptoms include fever, tachypnea, retractions, expiratory wheezing, rales, and air trapping. Bronchiolitis caused by HPIVs is clinically indistinguishable from that caused by other respiratory viruses.

Virus-induced asthma and asthma exacerbations are more commonly associated with respiratory viruses other than HPIVs in children and adults.[67,68] Nevertheless, asthma is diagnosed commonly in children older than 2 years of age with any type of HPIV infection.[3,36]

Pneumonia.

All HPIV types can cause pneumonia. HPIV-1, -2, and -3 are responsible for approximately 10% of pneumonia cases in the outpatient setting and 7% to 15% of cases in hospitalized children of all ages.[69–73] The percentage of hospitalized children diagnosed with HPIV pneumonia, including those requiring admission to a pediatric intensive care unit, is higher in the first year of life, and as with bronchiolitis, it most often is associated with HPIV-3 infection.[42,74]

HPIV pneumonia occurs more frequently and is more severe in chronically ill or immunocompromised children.[36,75] In hematopoietic stem cell transplant (HSCT) recepients, HPIV infection can result in refractory pneumonia with prolonged viral shedding, viral dissemination, and high mortality rates.[5,26,76]

Otitis Media.

In 10% to 35% of children with an HPIV URI, acute otitis media (AOM) follows 3 to 4 days after onset of the URI.[54,55,77–81] In a study conducted over 20 years among previously healthy children younger than 5 years of age using culture techniques, the rate of AOM was higher for HPIV-3 than for HPIV-1 and HPIV-2 infection.[7] Other data have confirmed these findings and also suggest that HPIV-4 is a common cause of AOM in children.[36]

Other Manifestations.

Neonates, particularly premature infants, infected with HPIV can have apnea.[3,52] Fever and febrile seizures have been reported in young infants with HPIV infections, and it is the most common finding in older children with HPIV infections regardless of the HPIV type.[36] A study conducted from 2000 to 2004 and enrolling 2798 children younger than 5 years of age showed that HPIVs accounted for 6.8% of all hospitalizations for fever or acute respiratory illness, or both.[3]

Conjunctivitis and gastroenteritis also occur frequently, with no HPIV type associations.[33,36] Cases of parotitis, myopericarditis, aseptic meningitis, encephalitis, and Guillain-Barré syndrome are reported, suggesting possible neurotropism of some strains.[82–84] Disseminated infection can occur in immunosuppressed people.[85]

Laboratory Findings and Diagnosis

Specific diagnosis requires identification of the virus in respiratory secretions. PCR is the preferred diagnostic test because of its high sensitivity and rapidity. Because HPIVs rarely are isolated in otherwise healthy asymptomatic children, detection of the virus in the context of an acute respiratory illness suggests causality.[86,87]

Respiratory specimens for viral diagnosis should be collected early in the course of illness. Nasopharyngeal aspirates or swabs are the preferred samples. Rates of HPIV detection may be similar with a nasopharyngeal swab or NP aspirate, and a paired nasopharyngeal and oropharyngeal swab may increase sensitivity.[88,89] Direct sampling by bronchoalveolar lavage or lung biopsy may be necessary to identify the virus and establish causality in immunocompromised hosts with lower respiratory tract disease.[90] For virus isolation, immediate placement of samples on ice (or refrigeration at 4°C) and transport to the laboratory for tissue culture inoculation are critical.

Reverse transcriptase PCR (RT-PCR) has replaced tissue culture and indirect immunofluorescence(IF) techniques for the identification of all HPIV types.[91,92] RT-PCR is especially useful for the diagnosis of HPIV infections in critically ill patients, especially those who are immunocompromised.[93–95] Rapid antigen diagnostic tests using IF techniques are available for HPIV-1, -2, and -3, and although specific, they are less sensitive than PCR.[96] Serologic assays based on hemagglutination inhibition or enzyme immunoassays can be used to detect serum IgM or IgG antibodies against HPIV, but they have limited value in disease management.

Treatment

No specific antiviral therapy is available for HPIV infection. Most HPIV infections are self-limited in immunocompetent hosts and do not require treatment. For the management of croup, dexamethasone and nebulized epinephrine have been associated with improved clinical outcomes.[57] Management of bronchiolitis is supportive.

Ribavirin has in vitro activity against HPIVs. The use of ribavirin (mostly inhaled) has been reported for immunocompromised children and adults with severe HPIV pneumonia with or without concomitant administration of immune globulin intravenous (IGIV); however, controlled studies are lacking.[26,97,98]

DAS181 is a sialidase fusion protein with activity against influenza and HPIV that removes sialic acid–containing receptors from the surface of respiratory epithelial cells, preventing virus binding. Use of DAS181 for the treatment of HPIV LRI in lung and HSCT patients, including children, has reduced viral loads and improved clinical symptoms.[99–103]

Other novel antiviral agents have activity against HPIV. The hemagglutinin-neuraminidase inhibitors (i.e., BCX 2855 and BCX

2798) appear promising. Although there are no data on use in humans, the agents have potent in vitro activity against HPIV and appear to be beneficial in animal models of infection.[104–106] Nitazoxanide, originally developed as an antiprotozoan agent, has broad antiviral activity. In a randomized, placebo-controlled clinical trial enrolling patients with laboratory-confirmed influenza, nitazoxanide treatment reduced viral shedding and duration of symptoms.[107] Its potential role in the treatment of HPIV infections is not known.[108] There are anecdotal reports of using interferon α-2b in HPIV-infected patients.[109]

During the acute infection, efforts should be aimed at decreasing healthcare-associated infections. In addition to standard precautions, contact precautions are recommended for hospitalized infants and young children for the duration of illness. Prevention of environmental contamination by respiratory tract secretions and careful hand hygiene should control healthcare-associated spread.

Special Considerations

Immunocompromised Hosts

Parainfluenza infections are associated with substantial morbidity and mortality for children and adults with congenital or acquired immunodeficiencies, including HSCT and solid-organ transplant (SOT) recipients, children with cancer undergoing chemotherapy, and children with severe T-lymphocyte deficiencies. Although nosocomial infections have been described, most HPIV outbreaks in transplantation units coincide with the peak incidence of these infections in the community.[110]

Hematologic Malignancies.

In children with leukemia or lymphoma, HPIV has been detected in 10% of cases and was the second most common respiratory viral infection identified. Ninety percent of infections were acquired in the community, and 61% were caused by HPIV-3. Neutropenia and lymphopenia at onset of infection were associated with progression to LRI.[111]

Hematopoietic Stem Cell and Solid-Organ Transplantation.

Among patients undergoing HSCT, the incidence of HPIV infections ranges from 4% to 7%, of which up to 40% progress to LRI.[90,106,112] In this setting, HPIV pneumonia is associated with prolonged viral shedding, viremia, and mortality rates of up to 40%. Most cases of HPIV pneumonia have been associated with HPIV-3.[26,48,113–116]

The most severe illnesses and 90% of the deaths related to HPIV pneumonia occur in the first 100 days after transplantation, when lymphopenia is most pronounced. Use of unrelated donors, myeloablative conditioning regimens, and high-dose corticosteroids for the treatment of graft-versus-host disease are identifiable risk factors for progression to pneumonia.[26,112,117] Other respiratory copathogens frequently are identified in patients with HPIV-3 pneumonia and may contribute to the significant morbidity and mortality rates.

Solid-organ transplant recipients, especially those undergoing lung transplantation, have increased HPIV-associated mortality rates and severe morbidity, including chronic rejection and development of bronchiolitis obliterans.[118–121] Airflow decline has been linked to HPIV pneumonia and HPIV URIs in HSCT recipients.[122]

Congenital or Acquired Immunodeficiencies.

Patients with primary immunodeficiencies can have prolonged HPIV shedding, particularly when infected with HPIV-3. Fatal giant cell pneumonia has been described in children with severe combined immunodeficiency and IFNγ receptor deficiency syndrome.[123,124]

In children infected with the human immunodeficiency virus type1 (HIV-1), HPIV infections have been associated with increased morbidity and mortality rates in developing countries.[75,125] Prolonged shedding occurs in HIV-infected children.[126,127]

Prevention

The lack of durable immunity and full understanding of the mechanisms responsible for immune protection have hampered the development of HPIV vaccines.[128] Formalin-inactivated vaccine preparations developed in the late 1960s were immunogenic in infants and did not cause enhanced disease, but they did not confer protection.[129] Subsequently, subunit vaccine candidates containing HN or F protein showed some protection in animals against LRI but failed to protect against URI and have not been evaluated in human clinical trials.[130]

Live, attenuated and subunit vaccine candidates are being studied in humans. Two strategies have been used for the development of live, attenuated HPIV-3 vaccines: use of an antigenically related strain (i.e., bovine PIV-3) or Sendai virus (murine PIV-3), and use of a cold-adapted HPIV-3 strain. These candidate vaccines have been safe and well tolerated in children and adults.[131–134] Improved seroconversion rates and immunogenicity have been demonstrated with live, attenuated candidate vaccines administered intranasally.[135,136]

Reverse genetics has allowed the development of recombinant rHPIV-1, -2 and -3 and chimeric bovine/human PIV-3 virus (rB/HPIV-3) candidate vaccines that are undergoing testing in seropositive and seronegative children. Early results are promising.[137–142] This technology allows rapid production of the vaccine with minimal risk for contamination.

Key Points

Diagnosis and Management of Human Parainfluenza Virus (HPIV) Infections

Microbiology

- Enveloped, negative-sense, single-stranded RNA paramyxovirus
- Five types: HPIV-1, -2, -3, -4A, and -4B

Epidemiology

- Different HPIVs have distinct epidemiologic patterns
  - HPIV-3 is endemic with peaks in the spring.
  - HPIV-1 and HPIV-2 cause outbreaks of croup.
  - HPIV-4 causes biennial peaks in the fall and winter.

- Age of primary infection varies for each serotype.
- By age 5 years, almost all children have been infected with all HPIVs.
- HPIV infection does not confer protective immunity, and reinfections are common throughout life.
- HPIVs are transmitted from person to person by direct contact and exposure to contaminated droplets and fomites.

Clinical Features

- HPIVs account for 18% to 45% of all upper respiratory tract illnesses in children.
- Acute otitis media occurs in 10% to 35% of children after HPIV upper respiratory tract infection.
- HPIV-1 and -2 are the most frequent causes of croup in children 1 to 5 years of age.
- HPIV-3 is associated predominantly with bronchiolitis and pneumonia (children <1 year old).
- HPIV-4 is mostly associated with upper respiratory infections in healthy children.
- HPIV infection can result in refractory pneumonia, with a mortality rate of approximately 40% for hematopoietic stem cell transplant patients.

Diagnosis

- Polymerase chain reaction (PCR), direct fluorescent antibody, or viral culture from respiratory secretions (nasopharyngeal swab or aspirate)
- PCR is the preferred method, especially for an HPIV-4 diagnosis and immunocompromised, critically ill children and elderly persons.

- Bronchoalveolar lavage or lung biopsy may be required to confirm the cause of infection in immunocompromised or hematopoietic stem cell transplant (HSCT) patients.

Treatment

- Most HPIV infections are self-limited in immunocompetent hosts and do not require treatment.

- Ribavirin (inhaled) with or without immune globulin intravenous (IGIV) has been used in immunocompromised patients with severe pneumonia.

- New antiviral therapies include DAS181 and hemagglutinin-neuraminidase inhibitors.

- Several vaccine candidates (i.e., recombinant and live, attenuated viruses) are being tested.

- Assiduous infection prevention measures are critical to prevent nosocomial transmission, especially for HSCT recipients.

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224

Mumps Virus

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Mumps (i.e., epidemic parotitis) is an acute, vaccine-preventable disease of childhood that typically involves swelling of one or both parotid glands, although many different organs can be infected.[1] Childhood mumps has become uncommon in the United States since the widespread implementation of measles-mumps-rubella (MMR) vaccination. Reports of mumps outbreaks involving highly vaccinated populations in the United States and other countries have prompted re-evaluation of current mumps vaccination strategies.[2–6]

Description of the Pathogen

Mumps virus (MuV) is a member of the *Rubulavirus* genus in the Paramyxoviridae family. MuV has a single-stranded, negative-sense, nonsegmented RNA genome of 15,384 nucleotides. The viral genome is contained in a helical nucleocapsid enclosed in a trilayered envelope studded with two surface glycoproteins possessing hemagglutinin and neuraminidase (HN protein) and cell fusion (F protein) activities.[7] MuV contains seven structural proteins, including a nucleocapsid protein, phosphoprotein, matrix protein, high-molecular-weight protein, small hydrophobic (SH) protein, HN protein, and F protein.

There is one serotype of the virus. The gene for the SH protein is the most variable part of the MuV genome. Based on the gene sequences for the SH and HN proteins, the MuV has been classified into 12 genotypes.[8,9]

MuV grows well in many human and monkey tissues, and in embryonated eggs. Cytopathic effects in cell culture include rounding and fusion of cells into giant multinucleated syncytia and the formation of intracytoplasmic inclusions.[10]

Epidemiology

Mumps occurs worldwide and affects only humans; there is no animal reservoir. In the absence of vaccination, most people acquire infection by young adulthood. Epidemic parotitis is caused solely by MuV. Endemic mumps is most common in winter and early spring in temperate climates. Although male and female infection rates are similar, males are more likely to have complications.

In the United States, the reported incidence of mumps declined after the introduction of mumps vaccine in 1967 and recommendation for routine childhood immunization in 1977. After expanded recommendations for a 2-dose MMR vaccine schedule for measles control in 1989, mumps cases declined further.[11] During the 2001–2003 period, fewer than 300 mumps cases (i.e., incidence of 0.1 case/100,000 people) were reported annually; this was a 99% decline from the 185,691 reported cases in 1968. However, an increase in cases occurred late in 2005 (Fig. 224.1).[12] From 2006 to 2010, several large-scale mumps outbreaks occurred in 2-dose vaccinated populations, especially among school-aged children and young adults in settings with high contact rates (e.g., college campuses).[12–19] These outbreaks highlight the importance of early detection and timely reporting of cases to health departments.[2] Transmission of mumps within hospital settings also can occur.[20]

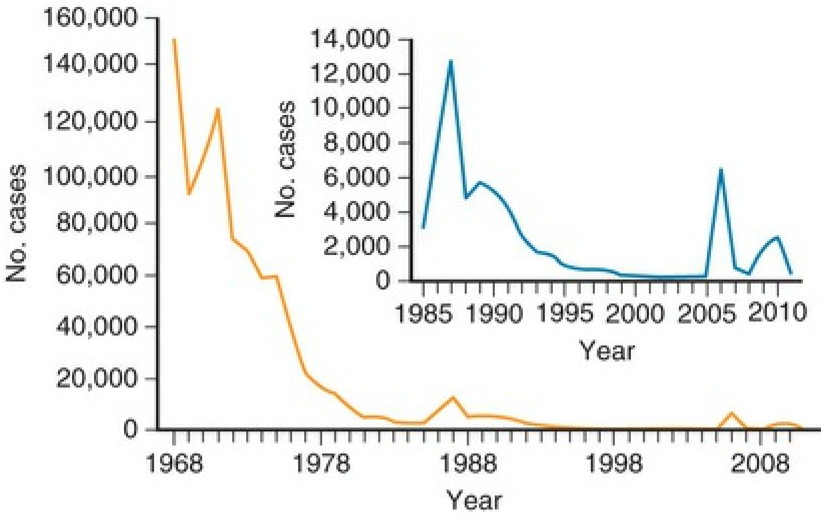

FIGURE 224.1 Number of reported cases of mumps by year in the United States, 1968 to 2011.

In 2006, a major mumps resurgence occurred in eight Midwestern states, resulting in 6584 cases (i.e., incidence of 2.2 cases/100,000 people) (Fig. 224.2). The MuV isolated was a genotype G strain. Almost 40% of patients were between 18 and 24 years of age and were mainly college students who had received 2 doses of MMR vaccine.[16] Most people had parotitis, and many had complications of orchitis, meningitis, encephalitis, deafness, oophoritis, mastitis, and pancreatitis.

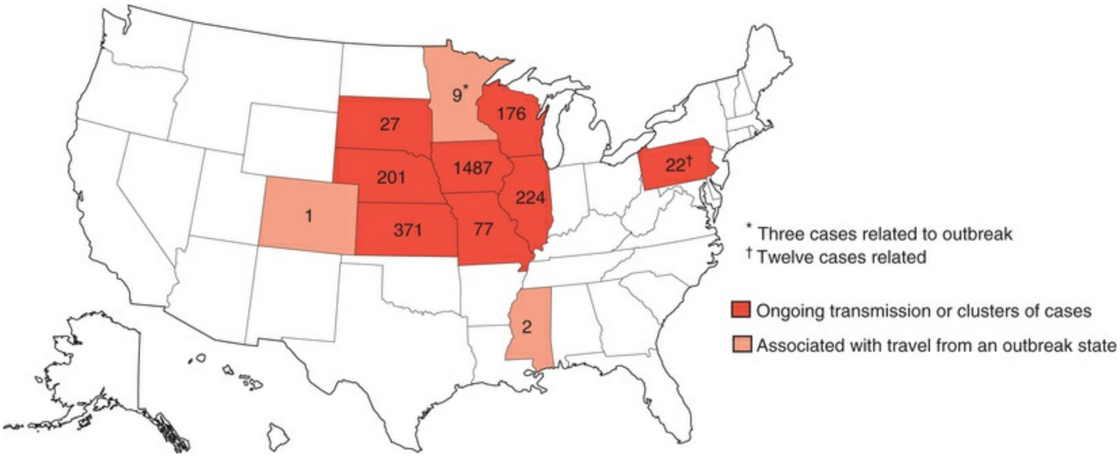
9*
176
27
201
1487
224
22†
1
371
77
2
* Three cases related to outbreak
† Twelve cases related
🟥 Ongoing transmission or clusters of cases
▨ Associated with travel from an outbreak state

FIGURE 224.2 Outbreak-related mumps cases by state, January 1 to May 2, 2006.

Between June 28, 2009 and June 27, 2010, a large outbreak of 3502 mumps cases occurred in the Northeast.[18] The source case was an 11-year-old US resident, who developed mumps while attending a summer camp in New York soon after his return from the United Kingdom.[17] The outbreak occurred primarily among 2-dose vaccinated school students between 13 and 17 years of age, who were members of the tradition-observant Jewish community.[18]

During 2010, another mumps outbreak (505 cases) occurred on the US territory of Guam in a highly vaccinated population; it primarily involved school-aged children.[15] In September of 2011, a mumps outbreak occurred on a university campus in California.[2] In August of 2011, the presumed source patient, a 21-year-old, unvaccinated man, developed mumps after his return from Western Europe, where mumps was circulating. Subsequently, 29 mumps cases occurred among university students; 22 (76%) students had received 2 doses of MMR vaccine.[2]

Mumps outbreaks among highly vaccinated adolescents also have occurred in the Netherlands, Spain, Israel, Korea, and Australia.[3,4,21] Strain change and waning immunity is hypothesized to play a role in mumps outbreaks among vaccinated people, and experts have proposed new mumps vaccine development.[6,22]

The incubation period of mumps is 16 to 18 days (range, 12–25 days).[23,24] An estimated 80% to 90% of nonimmune household contacts become infected.[25] Attack rates for development of clinically apparent disease have been substantially lower in recent outbreaks, especially for those who received 2 doses of MMR vaccine.[14] Patients are most contagious 1 to 2 days before symptom onset and for 5 days thereafter; MuV has been isolated from saliva 7 days before symptoms and up to 9 days after the appearance of parotitis. Clinical and subclinical infections provide lifelong immunity; reinfection occurs rarely. Children with subclinical disease are infectious.[26]

Pathogenesis and Immune Response

Mumps infection is acquired after contact with infected respiratory secretions. Viral replication in the nasopharyngeal mucosa and regional lymph nodes is followed by primary viremia, which results in spread of infection to multiple organs, including the central nervous system (CNS) and glandular epithelium.[7,27] Parotid gland pathology includes diffuse interstitial edema and serofibrinous exudate with infiltration of lymphocytes and macrophages. The ductal epithelium undergoes necrosis with intraluminal accumulation of lymphocytes and debris.[28]

Orchitis results from direct MuV infection of the testes; MuV has been isolated from testicular biopsy specimens of the affected gland within the first few days of symptoms.[29] Histologic changes within the testes include interstitial edema and lymphocytic infiltration.[30] Focal destruction of the germinal epithelium can occur.

MuV infection of the CNS is common.[7] The virus probably enters the CNS through the choroid plexus and infects the choroidal epithelium and ependymal cells lining the ventricles.[31] Enlargement of the lateral and third ventricle (i.e., hydrocephalus) has been observed in animal models and humans. The pathogenesis of virus-induced hydrocephalus is postulated to be accumulation of infected ependymal cell debris in the cerebrospinal fluid (CSF).[7] Mumps encephalitis occurs when infection spreads to the brain parenchyma along neuronal pathways.

Specific immunoglobulin M (IgM), IgA, and IgG antibodies are produced in response to mumps infection.[32–35] Virus-specific secretory IgA appears concurrently with the cessation of viral shedding in saliva. Intrathecal synthesis of mumps IgG and IgM antibodies has been demonstrated, along with production of interferon γ by activated cytotoxic T lymphocytes in the CSF.[36–39]

Clinical Manifestations

One third of patients with mumps infection have subclinical or mild respiratory tract illness.[40,41] The most common manifestation is painful parotid swelling (i.e., 95% of symptomatic patients),[41] which usually is unilateral at the onset of illness and later becomes bilateral in 70% of cases. Prodromal symptoms, including fever, malaise, headache, and anorexia, typically precede parotitis by 12 to 24 hours. Earache on the side of parotitis and discomfort with eating or drinking acidic foods are common.

The swollen parotid gland lifts the earlobe upward and outward, and the angle of the mandible is obscured (Fig. 224.3). The opening of the Stensen duct on the buccal mucosa is edematous and erythematous. Trismus can occur. About 10% of submandibular and sublingual glands can be affected.[1] Presternal edema can be prominent. Morbilliform rash has been reported.[42] Systemic symptoms, including fever, usually resolve within 3 to 5 days, and parotitis subsides within 7 to 10 days. Adolescents and adults have more severe disease than young children.

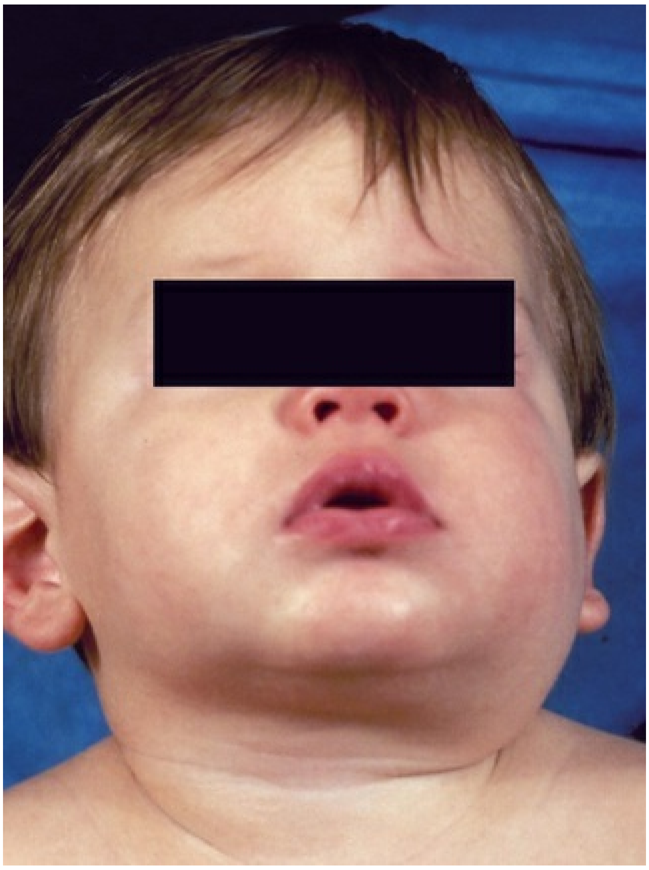
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FIGURE 224.3 Toddler with mumps parotitis. (Courtesy of A. Margileth.)

The differential diagnosis of parotitis is broad and includes bacterial (suppurative) parotitis, parotid duct stone, drug reactions, recurrent parotitis of childhood, parotid tumor, and Sjögren syndrome. Other viruses, such as Epstein-Barr virus, influenza, coxsackievirus A, echovirus, and parainfluenza virus types 1 and 3, can cause parotitis and are usually responsible for “recurrent mumps” (Fig. 224.4). Children with human immunodeficiency virus (HIV) infection can have chronic bilateral parotid swelling that is not caused by MuV infection. Failure to use a strict case definition of mumps infection based on clinical and laboratory criteria or confirmatory laboratory testing can lead to an overestimation of the number of mumps cases in a population.[43,44]

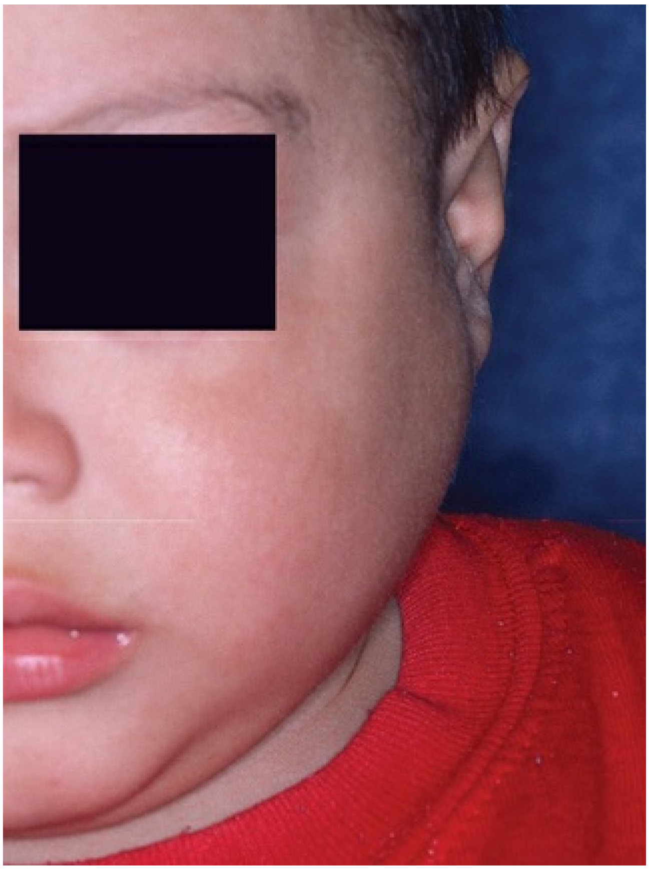

FIGURE 224.4 Boy with parotitis not due to mumps virus. (Courtesy of J.H. Briené.)

Complications

Central Nervous System Infection

MuV is highly neurotropic, and the degree of neuropathogenicity may depend on the virus genotype.[45] The molecular determinants of MuV neuropathogenesis are unclear.[46] Although CSF pleocytosis occurs in more than 50% of people with mumps parotitis, less than 10% have symptoms of meningitis.[1,47] Parotitis does not develop in about 50% of patients with mumps meningitis.[48] MuV can be isolated from CSF in 40% to 50% of patients with mumps meningitis.[49]

CNS disease due to MuV is threefold higher in males than females. Meningitis is more common than encephalitis.[23,50] Encephalitis may develop in 0.1% of infections.[1] Meningitis typically occurs 3 to 10 days after the onset of parotitis, but can precede or occur without parotitis. Patients have fever, headache, vomiting, lethargy, and nuchal rigidity; 20% of patients have seizures.[48] The CSF white blood cell count (WBC) usually is less than 1000 cells/mm^3, with lymphocytes predominating. The CSF protein level is normal or mildly elevated, and the CSF glucose concentration is decreased in 30% of cases.[51] CSF pleocytosis can persist for prolonged periods, suggesting persistent infection.[52]

In general, the course is self-limited with no sequelae, but ataxia, behavioral problems,[48,53] aqueductal stenosis with hydrocephalus,[54,55] and sensorineural deafness can occur.[56,57] In Japan, where mumps remains endemic because measles-rubella vaccine is used instead of MMR vaccine, the incidence of hearing loss among children with mumps is 1 case per 1000 people.[58] Other complications of mumps include paralysis[59] and neuroretinitis.[60] About 1.4% of people with encephalitis die.[61]

Orchitis

Orchitis develops in 14% to 35% of postpubertal males with mumps.[62,63] Males between 15 and 29 years of age are at highest risk. Orchitis is uncommon in prepubertal males.[25,41]

Symptoms begin 4 to 8 days after the onset of parotitis, but orchitis can occur before or in the absence of parotitis. Testicular involvement usually is unilateral, and epididymitis is associated with orchitis in most cases.[64] Clinical findings include fever, malaise, vomiting, lower abdominal pain, and testicular pain. The testicle typically is swollen and tender for 3 to 7 days. MuV has been isolated from seminal fluid, and viral RNA has been detected in semen several weeks after infection.[65] An elevated serum C-reactive protein level is common.[66]

Treatment of mumps orchitis is symptomatic, with bed rest and the use of scrotal support, ice packs, and anti-inflammatory agents.[64] Complete recovery occurs for about 50% of males with mumps orchitis; 50% have some testicular atrophy. Infertility rarely occurs, although a decrease in sperm count and sperm motility can occur in up to 25% of patients.[64,67]

Other Sites of Infection

Hematuria, proteinuria, and transient alterations in creatinine clearance can occur in children with mumps.[68] Glomerulonephritis usually is self-limited, and death from renal failure is unusual.[69]

Arthralgia, polyarticular migratory arthritis with effusion, and monoarticular arthritis are described.[70] Signs usually appear 1 to 3 weeks after the onset of parotitis, but they can occur before or in the absence of parotitis. Joint complaints are threefold to fourfold more common among males, and the average age of occurrence is 24 years.[70,71] Large joints (i.e., knee, hip, wrist, ankle, and shoulder) are affected most frequently. The duration of joint symptoms ranges from 2 days to 6 months. Recovery with no evidence of persistent or recurrent symptoms is usual.

Electrocardiographic abnormalities consistent with myocarditis are reported in up to 15% of patients (often adults) with mumps.[72] Abnormalities resolve within 2 to 4 weeks, although sequelae are reported.[73]

Pancreatitis can occur in about 4% of mumps infections and may cause mild epigastric pain[74]; severe hemorrhagic pancreatitis has been reported.[75] The role of MuV in the development of insulin-dependent diabetes mellitus is controversial. Cases have occurred after mumps outbreaks, but no causal relationship has been established.[76,77]

Oophoritis can occur in 5% of postpubertal women with mumps.[1] Other rare complications include mastitis,[25] thyroiditis,[78] thrombocytopenic purpura,[79] and hepatitis with acute cholecystitis.[80]

Mumps in Pregnancy

Compared with uninfected women, women with mumps during pregnancy have no increase in the risk of delivering an infant with congenital malformations.[81,82] The rate of spontaneous abortion among women who acquire mumps during the first trimester of pregnancy is increased in some studies but not in others.[82,83]

Gestational mumps infection has been implicated in the development of endocardial fibroelastosis (EFE) in offspring. Although many infants with EFE have had positive skin test responses to mumps antigen,[84,85] MuV has not been isolated from affected infants.[86,87] PCR has detected MuV genome in more than 70% of myocardial samples from 29 patients with autopsy-proven

EFE.[88] Perinatal mumps infection with parotid swelling, pneumonia, and pulmonary hypertension has been reported.[89–92]

Diagnosis

The diagnosis of mumps is suspected in patients with parotitis for 2 or more days and no other apparent cause. Laboratory findings include elevated serum amylase levels during the first week of illness and a low or normal WBC count with a relative lymphocytosis. Mumps infection can be confirmed by positive MuV culture result, detection of the viral genome by reverse transcriptase PCR (RT-PCR), positive serum mumps-specific IgM antibody test result for a single serum sample, or demonstration of a fourfold or greater rise in mumps-specific IgG antibody titers between acute and convalescent serum samples.[23,24,43,93]

Practitioners should consult their local health department for recommendations for optimal specimen collection and submission.[94] If a patient has clinical features compatible with mumps, buccal and oral swabs should be obtained, and blood should be drawn for serologic testing. Suitable specimens for MuV isolation include a throat swab or Stensen duct exudates, CSF, and urine. Samples for virus detection should be collected as soon as mumps is suspected. This is particularly important in immunized patients because the quantity and duration of virus shedding may be decreased.[95] Clinical specimens should be obtained within 1 to 3 days and not more than 8 days after the onset of parotitis.[23,24]

MuV can be isolated readily from saliva, throat, urine, and CSF.[1,23] MuV can be isolated from the oropharynx 7 days before and up to 9 days after symptom onset.[96] Virus is found in urine for up to 2 weeks and in CSF for 8 or 9 days after symptom onset.[97] Cell culture shows the typical cytopathic effect of cellular degeneration and syncytium formation, and virus is confirmed by hemagglutination inhibition assays or immunofluorescent antigen detection.[98,99]

More rapid and sensitive RT-PCR assays have replaced viral culture in routine practice.[24] PCR can detect viral RNA directly on clinical specimens and in CSF samples from children with aseptic meningitis.[100,101] RT-PCR also can detect MuV RNA in previously vaccinated children who develop mumps.[95]

Mumps-specific IgM and IgG antibodies can be measured by standard quantitative or semiquantitative serologic tests. The semiquantitative enzyme immunoassay (EIA) is the most frequently used test, and it is more sensitive than other labor-intensive serologic tests (e.g., hemagglutination inhibition, complement fixation, neutralization assays).[1,23,24,93,102,103]

The Centers for Disease Control and Prevention (CDC) test for mumps using a nonquantitative capture IgM EIA. A positive IgM test result indicates current or recent mumps infection. The optimal time for IgM testing may be 7 to 10 days after symptom onset.[102,103] Serologic confirmation can be challenging in vaccinated people.[1,24] Mumps IgM is less likely to be positive if the patient has previously received 1 (i.e., 50% positive)[102] or 2 doses of mumps vaccine (i.e., 13%–15% positive).[95] A positive IgG response indicates recent or past exposure to wild-type MuV or vaccine. A second serum sample should be obtained 2 to 3 weeks after symptom onset to verify IgG seroconversion.[104] In previously vaccinated people, mumps IgG levels already can be elevated in the acute phase sample. Mumps-specific IgM and IgG antibodies can be detected in CSF in cases of mumps meningitis.[105]

Treatment and Prevention

No specific antiviral therapy is available for mumps infection. Treatment is supportive.

Mumps Vaccine

The live, attenuated Jeryl Lynn strain (i.e., genotype A) of MuV vaccine currently used in the United States was licensed in 1967.[106,107] Mumps vaccine had been introduced globally in 120 countries by the end of 2013. Neutralizing antibodies develop in more than 90% of vaccine recipients after a single dose.[108] Concentrations of neutralizing antibody are considerably lower after vaccination than after natural infection,[109] but vaccine-induced immunity is long-lasting.[110] The correlate of protection induced by mumps vaccine is not well understood.[111,112]

Although the mumps vaccine was licensed for use in 1967, universal immunization was not recommended until 1977. Between

1985 and 1988, an increase in the number of mumps cases was observed (see Fig. 224.1), primarily in older school-aged children, college students, young adults, and children too young to be vaccinated.[19,113] The resurgence may be explained by failure to vaccinate all susceptible people during the 10 years after licensure of the mumps vaccine, resulting in a cohort of nonimmune older people.[114]

Mumps cases increased dramatically in England and Wales beginning in 2003 and 2004, and it peaked in 2005 with about 56,000 reported cases.[115,116] The highest attack rate was among adolescents and young adults born between 1983 and 1986. These people would not routinely have been offered MMR vaccination when introduced in 1988, and many in this age group could have received no vaccine or only 1 dose.[115] Declining immunization rates in the UK may account for an increase in mumps cases in younger children.[117]

Outbreaks of mumps have been reported in highly vaccinated US populations.[13–18] In some of these outbreaks, sustained transmission has occurred.[17,22] Outbreaks have been caused predominantly by genotypes not contained in the vaccine.[118] Partial vaccine failure due to strain change has been suggested to play a role,[6,119] but evidence is lacking from well-designed studies.[120,121] Infection also may result from waning immunity,[6,19,110,114,122,123] consistent with vaccine effectiveness estimates from the UK and serologic data from Finland.[124,125]

MuV induces low-avidity antibodies after vaccination and natural infection.[126] The protective efficacy of 1 dose of mumps vaccine based on postlicensure data is about 78% (range, 49%–92%); 2 doses provide an approximately 88% rate of protection (range, 66%–95%).[127,128] In the 2006 Midwestern outbreak, receipt of 2 doses of mumps vaccine was associated with substantially higher individual protection and a lower attack rate (2%) in one college with higher 2-dose vaccination coverage compared with an attack rate of 3.8% in another college with lower coverage.[12]

Outbreak analyses suggest that adolescents or young adults who receive 2 doses of vaccine but who reside in low-population rural communities, where opportunities for natural boosting by exposure to endemic disease is low, may be at higher risk for mumps infection when they move to more crowded living situations.[19] One hypothesis is that current population immunity of about 90% is lower than that needed to achieve community (herd) protection.[129] Higher rates of vaccination or newer, more effective mumps vaccine strategies may be required.[5,6,22]

Recommendations

Two doses of mumps vaccine are recommended and administered subcutaneously to children at 12 through 15 months of age and at 4 through 6 years of age[24,130] (Box 224.1). Mumps vaccine is given in combination products with measles and rubella immunization (i.e., MMR vaccine) or with measles, rubella, and varicella immunization (i.e., MMRV vaccine). Complete mumps immunization is particularly important for children approaching puberty. Children who have not received a second dose of vaccine should do so at a routine provider visit by 11 to 12 years of age. Routine use of mumps vaccine is not recommended for people born before 1957.[130] Immunization is not contraindicated in immune people.

Box 224.1

Recommendations for Mumps Vaccine

Evidence of Immunity to Mumps (Any of the Following)

- Documentation of age-appropriate vaccination with a live mumps virus–containing vaccine[a]
    - Preschool-aged children: 1 dose
    - School-aged children (i.e., grades K–12): 2 doses
    - Adults not at high risk: 1 dose
- Laboratory evidence of immunity
- Laboratory confirmation of disease
- People born before 1957

Routine Vaccination for Healthcare Personnel

- People born in or after 1957 without other evidence of immunity:

2 doses of measles-mumps-rubella (MMR) vaccine (>28 days apart)

- For unvaccinated personnel born before 1957 who lack laboratory evidence of mumps immunity or laboratory confirmation of disease, healthcare organizations should consider vaccinating personnel with 2 doses of MMR vaccine at the appropriate interval.

Outbreak Settings

- Children 1–4 years of age and adults at low risk; if affected by the outbreak, consider a second dose[b] of MMR vaccine
- Adults at high risk (i.e., international travelers and students at post–high school educational facilities) should be offered 2 doses of MMR vaccine
- Healthcare personnel born in or after 1957 who have received only 1 dose of MMR vaccine should be offered a second dose
- Healthcare personnel born before 1957 without other evidence of immunity should receive 2 doses of MMR vaccine during an outbreak of mumps

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[a] Measles-mumps-rubella-varicella (MMRV) vaccine is not licensed for use in children >12 years old.

[b] Minimal interval between doses is 28 days.

Data from Centers for Disease Control and Prevention. Prevention of measles, rubella, congenital rubella syndrome and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2013;62(RR-04):1–34.

Adverse Reactions

Allergic reactions, possibly due to the gelatin or neomycin component of the vaccine, are uncommon. Severe allergic reactions, including anaphylaxis, are rare.[24] Reported adverse events with a temporal association with the mumps component of MMR or MMRV vaccine, including fever, febrile seizures, aseptic meningitis, encephalitis, orchitis, and parotitis, are rare. Reported rates of all CNS reactions with the Jeryl Lynn vaccine strain range from 1 case in 50,000 to 1,000,000 doses of vaccine, a frequency lower than the background incidence observed in the general population.[131] An increase in the expected number of mumps vaccine–associated cases of meningitis occurred in Canada, Japan, and the UK during a period when the Urabe Am 9 strain of MuV was used in combination with a measles and rubella vaccine.[132–134]

Vaccine Contraindications

Vaccine virus has been isolated from the placenta of nonimmune women immunized 7 to 10 days before therapeutic abortion.[135] Virus has not been isolated from fetal tissue of immunized women, and no case of mumps vaccine–associated embryopathy has been reported. However, because of theoretical risks to the fetus, pregnant women should not be immunized, and conception should be avoided for 28 days after vaccination. Mumps vaccine is not transmitted from vaccinees to contacts and should be given when indicated to children whose mothers are pregnant.

Persons who are allergic to neomycin or gelatin should receive vaccine in a setting where they can be monitored and after consultation with an allergist. Most children with egg hypersensitivity can be immunized with MMR or MMRV. Skin testing of children allergic to eggs is not recommended because it is not predictive of reactions to MMR or MMRV vaccine.[24] Children with a significant hypersensitivity reaction after the first dose of MMR should be tested for immunity and, if immune, should not receive a second dose. Alternatively, they could be evaluated, possibly with skin testing, before receiving a second dose. Children with anaphylactic reactions to vaccine should not be reimmunized.

Immune globulin (IG) preparations interfere with the serologic response to live, attenuated virus vaccines. Mumps vaccine should be given during the 2 weeks before or 3 months after receipt of a standard dose of IG or blood transfusions and for longer periods after high-dose immune globulin intravenous (IGIV).

Children with compromised immunity should not receive mumps vaccine. The American Academy of Pediatrics (AAP) does not recommend MMR vaccine for children with most immunodeficiency diseases, including children receiving immunosuppressive therapy (e.g., corticosteroids, alkylating agents, antimetabolites, radiation), those with malignancy who are receiving immunosuppressive therapy, or those who have undergone bone marrow transplantation.[24] Children can receive mumps vaccine if they have not received immunosuppressive therapy for at least 3 months and their underlying disease is in remission. Patients with HIV should receive mumps vaccine as part of the MMR vaccine unless they are severely compromised.[24,136] The second dose of MMR vaccine can be administered as early as 4 weeks after the first dose to induce seroconversion as early as possible. Nonimmune contacts of immunosuppressed people should be immunized because vaccinated people do not transmit attenuated MuV.

Control Measures

The CDC and AAP recommend a 5-day isolation period after onset of parotitis under standard and droplet precautions.[137,138] IG does not offer effective postexposure prophylaxis, and mumps vaccine is not effective in preventing illness after exposure. Mumps outbreaks carry a high economic and resource burden.[139]

In college and university settings, prematriculation MMR completion may prevent the introduction of mumps and limit its spread.[2] During an outbreak, standard control measures include isolation, contact tracing, and catch-up immunization campaigns.[22] Vaccination programs during outbreaks are effective in preventing disease after subsequent exposures.

Data on the effectiveness of administration of a third dose of MMR vaccine to control outbreaks in highly 2-dose vaccinated populations are limited.[15,140] Practitioners should consult their local health department for guidance on the administration of a third dose of MMR in selected high-risk populations.[141] Ring vaccination may be an effective strategy to prevent mumps outbreaks in confined settings.[142]

Key Points

Diagnosis and Management of Mumps Infection

Microbiology

- Negative-sense, single-stranded RNA virus
- Member of *Rubulavirus* genus in the Paramyxoviridae family
- One serotype but at least 12 genotypes based on variability in the *SH* gene

Epidemiology

- Humans are the only known host.
- Virus is spread by respiratory secretions.
- In the prevaccine era, mumps infections were most common during winter and spring in children <10 years of age.
- Incubation period is 12 to 25 days.
- Patients are most contagious 1 to 2 days before and for 5 days after the onset of symptoms.

Clinical Findings

- One or more salivary glands can be swollen.
- In 30% of cases, the patient has only upper respiratory tract infection symptoms.
- Other manifestations of infection include

▪ Meningitis or encephalitis

▪ Orchitis

▪ Thyroiditis

▪ Myocarditis

▪ Sensorineural hearing loss

- Hepatitis
- Arthritis
- Oophoritis
- Glomerulonephritis
- Pancreatitis
- Transverse myelitis
- Thrombocytopenic purpura

Diagnosis

- Virus can be isolated from saliva, throat, urine, and CSF.
- Reverse transcriptase polymerase chain reaction (RT-PCR) is the preferred method for detecting mumps virus RNA in clinical specimens.
- Positive serum mumps IgM antibody result confirms acute infection but can be negative in previously immunized people.
- A fourfold or greater rise in mumps IgG levels between acute and convalescent serum samples also can be used to diagnose infection.

Prevention

- Mumps-containing vaccination at 12–15 months of age with a second dose at 4–6 years of age
- Mumps-containing vaccines are safe and very effective for immunocompetent children.

Isolation

- Hospitalized patients are cared for under standard and droplet precautions for 5 days after onset of symptoms.
- Children in school or childcare should be excluded from attending for 5 days after onset of symptoms.

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225

Respiratory Syncytial Virus

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Respiratory syncytial virus (RSV) is one of the last viral infections that continues to cause annual outbreaks and for which no safe and effective vaccine is available. RSV infects most children at least once in the first 2 years of life. RSV infection in the first 12 months of life is the leading cause of hospitalization, accounting for between 57,000 and 172,000 hospitalizations annually.[1,2] Globally, RSV is estimated to account for as many as 200,000 deaths of children younger than 5 years of age, with a disproportionate number occurring in resource-limited countries.[3,4]

The initial RSV infection induces cellular immunity and neutralizing antibodies. However, immunity is not complete, and RSV reinfections continue to occur throughout life. How RSV avoids or inhibits the immune response to cause reinfection is not well understood.[5] Most primary RSV infections are symptomatic, and most infections involve only the upper respiratory tract. Among the elderly, especially those with comorbidities, RSV is an important cause of morbidity and mortality.[6]

Description of the Pathogen

RSV is an enveloped, nonsegmented, negative-sense RNA virus. Human RSV is classified as a species in the genus *Orthopneumovirus* in the family *Pneumoviridae*.[7] Other members of the Paramyxoviridae family include measles, mumps, parainfluenza, Nipah, and Hendra viruses. The pleomorphic RSV virion contains a helical nucleocapsid surrounded by a viral envelope derived from the plasma membrane of the host cell.

The viral nucleocapsid is composed of viral proteins in complex with the RSV genome, which encodes 11 proteins. The entire RSV genome has been sequenced and consists of more than 15,000 nucleotides. Ten genes are transcribed into 10 separate mRNAs, except the gene for M2 mRNA, which encodes two viral proteins, resulting in a total of 11 distinct viral proteins.[7]

Viral encoded proteins include components of the nucleocapsid and RNA-dependent RNA polymerase complex (i.e., nucleoprotein [N], phosphoprotein [P], large polymerase protein [L], and two regulatory proteins involved in RNA transcription and processing [M2-1 and M2-2]); the matrix (M) protein, which is important for viral structure; and two nonstructural proteins, NS-1 and NS-2, which modulate the host response to infection, including inhibition of interferon induction.

Three transmembrane glycoproteins project as spikes from the lipid envelope. Glycoprotein G is heavily glycosylated, has highly variable domains, and mediates attachment of the virus to the ciliated epithelial cells of the respiratory tract. Glycoprotein F (i.e., fusion protein) mediates viral penetration of the host cell by facilitating fusion of the viral lipid envelope with the plasma membrane of the cell. After protein F binds to a cellular receptor, it undergoes a conformational and antigenic change that enables viral entry, cell-to-cell spread of the virus, and syncytia formation. The viral surface proteins F and G are the primary targets for host neutralizing antibodies. The third surface protein is a small hydrophobic protein (i.e., SH) that is structurally similar to viroporins, proteins that become inserted into the membrane of infected cells, increase membrane permeability, and disrupt the physiologic properties of the cell.[7]

All RSV strains belong to a single serotype. However, sufficient antigenic dimorphism exists in the G glycoprotein to allow assignment of strains to one of two antigenic subgroups, designated A and B, based on cross-neutralization studies. Two highly variable domains in G are separated by a conserved region that may have a role in suppressing the immune response of the host. A and B subtypes are quite divergent and show antigenic relatedness of about 25%. G protein antigenic relatedness between subgroups is only 1% to 7%, whereas the more highly conserved F protein exhibits 50% antigenic relatedness between subgroups.[7]

Molecular epidemiology studies show that viruses of RSV subgroup A and B may circulate simultaneously in the population and that temporally and geographically distinct RSV epidemics are caused by viruses of multiple subgroups and subtypes. The role of subgroup diversity in RSV epidemics and disease severity is not well understood, although some studies suggest that infection with a virus of the heterologous subgroup may be more common after primary infection.

In contrast to the continual antigenic drift of influenza antigens, the surface glycoproteins of RSV are more antigenically stable. Despite strain diversity, accumulation of new mutations that result in antigenic escape is less common with RSV than with influenza. Nonetheless, nucleotide substitutions in the F protein gene's coding region are recognized. RSV isolates that contain mutations in the F protein gene that confer resistance to palivizumab are detected in 5% to 10% of young children receiving monthly palivizumab prophylaxis. These children can experience a breakthrough RSV infection resulting in hospitalization.[8,9]

Epidemiology

RSV causes outbreaks of disease on a worldwide basis. Countries with a temperate climate tend to have seasonal outbreaks that begin in early winter, peak in January or February, and end by early spring[10] (Fig. 225.1). Countries with a tropical climate are more likely to experience disease throughout the year, with peaks occurring during the rainy season.[4] Efforts to relate RSV activity (including onset and end of yearly outbreaks) to climate conditions suggest a complex interaction with latitude, temperature, humidity, and ultraviolet radiation.[11]

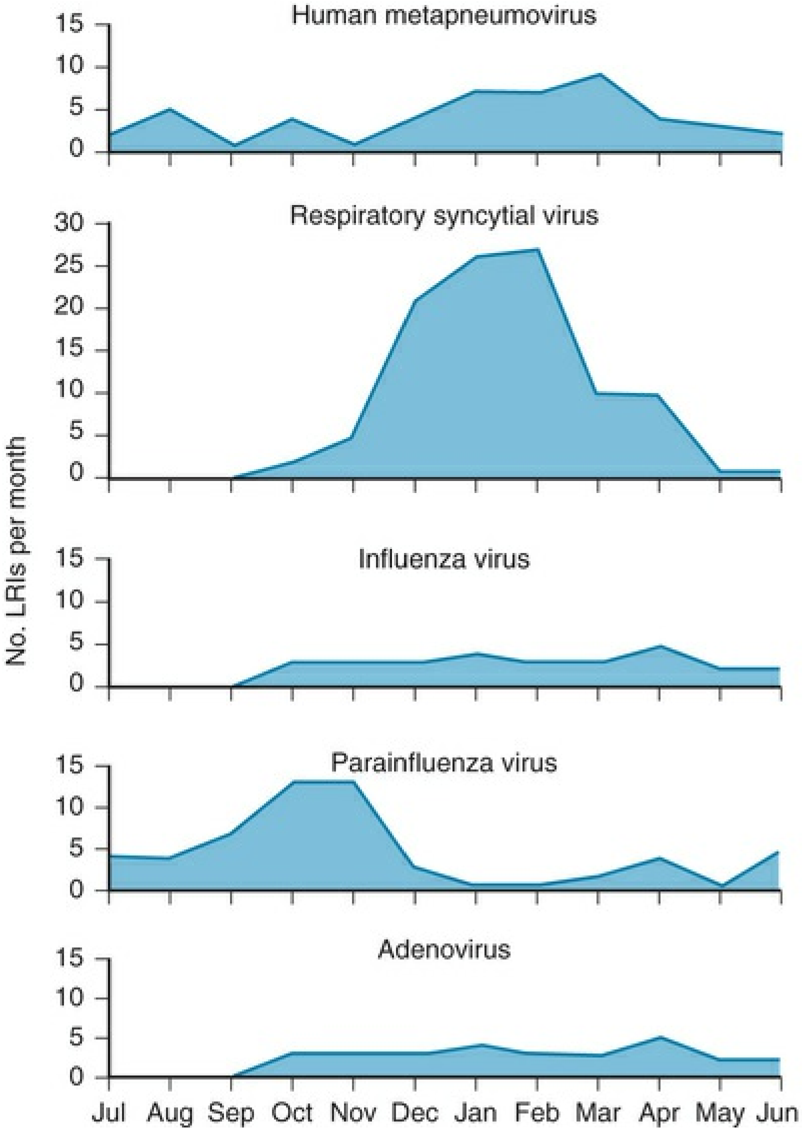

FIGURE 225.1 Epidemiologic pattern of lower respiratory tract illness (LRI) with respiratory syncytial virus and other viruses. (Data from 25 years of surveillance in the Vanderbilt Vaccine Evaluation Clinic.)

RSV is the leading viral pathogen associated with childhood respiratory tract illness requiring hospitalization. RSV hospitalization rates are consistently between 2 and –3 per 100 children younger than 1 year of age in industrialized countries.[1,2] Rates are two to four times higher among infants and young children in certain high-risk groups. During seasonal RSV outbreaks, approximately 75% of children hospitalized for acute lower respiratory tract illness have RSV infection.[1,2,12,13] Fewer than 100 children per year die of RSV-associated complications in the United States.[14] This number is similar to the number of annual pediatric deaths attributable to complications of influenza infection.

RSV is increasingly recognized as an important cause of death of adults and may be associated with 10% of all hospitalizations for pneumonia and 5% of hospitalizations for congestive heart failure among people 65 years of age or older.[6]

Young children at increased risk for severe RSV disease include premature infants (i.e., born before 29 weeks' gestation), infants with chronic lung disease of prematurity or hemodynamically significant congenital heart disease, and patients with an immunodeficiency[1,2,12,15] (Box 225.1). Numerous other factors have been associated with an increased risk of RSV hospitalization, including poverty, malnutrition, exposure to environmental pollutants such as second-hand tobacco smoke, maternal smoking during pregnancy, congenital malformation of the airways, neuromuscular impairment, Down syndrome, decreased cord blood vitamin D concentration, cystic fibrosis, household crowding, childcare attendance, size of the childcare facility, lower level of maternal education, altitude, and lack of breastfeeding.[16,17] However, most of these risk factors are inconsistent from study to study, and in most instances, the impact on increased hospitalization is small (see Box 225.1).

Box 225.1

Medical Conditions Associated With Increased Risk of Severe Respiratory Syncytial Virus Infection

Host factors

- Hemodynamically significant congenital heart disease
- Prematurity defined as <29 weeks' gestation
- Chronic lung disease of prematurity defined as <32 weeks' gestation and requirement for supplemental oxygen for 28 days after birth

Conditions associated with a small increased risk of severe infection

- Malnutrition
- Crowded household
- Childcare attendance

Viable RSV can survive on nonporous surfaces for more than 24 hours. Transmission occurs through contact with contaminated secretions and by large respiratory droplets.[18,19,20] Nasal and conjunctival mucous membrane inoculation are efficient means of transmission. The incubation period is about 5 days, and viral shedding can occur in healthy infants for up to 3 weeks after the onset of illness. Hospital infection control practices that limit RSV transmission include hand hygiene, contact and droplet precautions for patient isolation, use of gowns and gloves, cohorting of infected patients, and use of face masks and goggles.[21]

Rapid diagnosis by antigen or nucleic acid detection assays may enhance hospital infection control by identifying RSV-infected patients. Nonetheless, routine use of viral diagnostic assays is not recommended routinely by the American Academy of Pediatrics practice guidelines.[16,17] Symptomatic patients require isolation regardless of the viral cause.

Healthcare-associated transmission of RSV is an important, preventable cause of RSV disease in hospitalized patients. Failure to adhere strictly to hospital infection control procedures during RSV epidemics and hospital outbreaks can result in fatal healthcare-associated RSV infections.

RSV respiratory tract infection can be complicated by otitis media; other serious bacterial coinfections are uncommon. Antibiotic therapy does not alter the course of uncomplicated RSV bronchiolitis or pneumonia and should be minimized.[16] Routine chest radiography for children with bronchiolitis is not recommended.[16] Many infants with bronchiolitis have radiographic evidence of atelectasis and hyperinflation. When radiographs are obtained for an infant with uncomplicated bronchiolitis, antibiotics are more likely to be administered than when radiographs are not obtained, and there is no difference in outcome.[16]

Pathogenesis and the Immune Response

RSV replicates in cells of the nasopharynx, and infection is confined to the upper respiratory tract in most cases. However, in 30% to 40% of patients, infection spreads to the lower respiratory tract by aspiration of cells containing infectious virus or by cell-to-cell spread, causing bronchiolitis or pneumonia. The immune response induced by RSV may be both protective and pathogenic.[5]

Virus replicates in the ciliated epithelial cells of the mucosa of the bronchioles and pneumocytes of the alveoli, resulting in an inflammatory cell infiltration of the peribronchiolar tissue. Accompanying edema, increased mucus production, and impairment of ciliary action result in various degrees of intraluminal obstruction. Air trapping and hyperinflation result from partial airway obstruction and increased expiratory resistance.[22] Absorption of trapped air in the alveoli distal to the obstruction leads to localized atelectasis and further increases the work of breathing.

Innate and adaptive immune responses participate in viral clearance, although the relative importance of each in the pathogenesis is incompletely understood for primary and recurrent infections. Virus-induced direct cytotoxic injury and an exuberant host inflammatory response contribute to the pathogenesis of bronchiolitis.[23,24]

Young infants are susceptible to severe primary RSV bronchiolitis at an age when maternally acquired RSV-specific antibodies are present, and transplacentally derived RSV antibodies appear to have an ameliorating effect on disease severity. For example, some studies correlate milder RSV illness with higher levels of maternal RSV-specific immunoglobulin G for prematurely born infants. Long-term protection from RSV reinfection is incomplete, although subsequent RSV infections typically are less severe than the initial infection.

Neutralizing antibodies to viral surface glycoproteins are important for reducing the risk of RSV reinfection, and the T-cell–mediated immune response is important for control of established infection and termination of viral replication.[23,24] The roles of innate immunity, adaptive immunity, and toll-like receptors, interferons, surfactants, the inflammatory response, and viral immune evasion in RSV disease are areas of active investigation.

One postmortem study of children who died of acute RSV infection revealed a predominance of macrophages and neutrophils, relative absence of cytotoxic T lymphocytes, and low concentrations of cytokines released by $CD4^+$ and $CD8^+$ lymphocytes.[25] Abundant viral antigen suggests a direct virus-induced cytotoxicity, at least in seronegative infants who experience a primary infection. Other evidence suggests an exuberant host inflammatory response contributes to the pathogenesis of RSV bronchiolitis.

Clinical Manifestations

After an incubation period of 3 to 5 days, RSV-infected infants develop upper respiratory tract symptoms, including rhinorrhea and congestion, sometimes with fever (Box 225.2). Involvement of the lower respiratory tract is associated with nasal flaring, retractions (i.e., supracostal, intercostal, and subcostal), cough, tachypnea, wheezing, and increased work of breathing. Lower respiratory tract disease results in a spectrum of illness severity, ranging from mild disease to life-threatening respiratory failure and cyanosis. The course of bronchiolitis varies and may require serial observations to adequately assess illness acuity. Severe complications, such as a need for intensive care and need for intubation and mechanical ventilation, are uncommon in children with bronchiolitis.

Box 225.2

Common Clinical Manifestations of Respiratory Syncytial Virus Infection

Infancy

Upper respiratory tract infection

Bronchiolitis/pneumonia

Apnea

Older Children and Adults

Upper respiratory tract infection

Bronchitis

Pneumonia (elderly)

Exacerbation of asthma

The ability of the physical examination to predict disease progression is limited.[16] During the first few weeks of life, particularly among preterm infants, infection with RSV may produce minimal respiratory tract signs. Lethargy, irritability, and poor feeding, sometimes accompanied by apneic episodes, may be the presenting manifestations in these infants.

Numerous studies have documented that infants hospitalized with severe viral lower airway disease are more likely to have recurrent episodes of wheezing compared with infants who do not experience severe bronchiolitis. It is not clear whether bronchiolitis results in lung injury that alters normal lung development, predisposing the infant to wheezing, or infants have a preexisting aberration of the immune response or of airway function that predisposes to severe bronchiolitis and recurrent wheezing. Many studies suggest that lung function may be abnormal before the onset of bronchiolitis and that these infants are predisposed to asthma even if bronchiolitis does not develop.[26,27]

Laboratory Diagnosis

RSV can be detected in respiratory tract secretions by virus culture, by antigen detection assays using enzyme immunoassays or direct immunofluorescence assays, and by identification of the virus genome with nucleic acid multiplex assays. Improper specimen collection and handling can impact the performance of any test. RSV is labile, and specimens for virus culture should be kept cold and inoculated into tissue culture as quickly as possible. If virus is present, a characteristic syncytial cytopathic effect can be seen in cell culture within 3 to 7 days. Time to RSV detection in culture can be reduced by the use of shell vial cultures and immunostaining.

Rapid RSV diagnostic tests for antigen detection usually perform well during the peak of the RSV season but have limited usefulness before and after the seasonal peak because of the low predictive value of a positive result. Serologic studies have limited usefulness other than for research purposes.

Nucleic acid detection assays demonstrate viral coinfections in up to 30% of children hospitalized with bronchiolitis.[28] The clinical significance of coinfections is not clear. The results of studies evaluating the relationship between disease severity and viral load have been inconsistent. Results from studies using nuclear amplification techniques suggest that one or more viral pathogens may be isolated from the upper respiratory tract of more than 30% of asymptomatic young children.[29]

Treatment

No available treatment shortens the course of RSV bronchiolitis.[16] Chapter 33 should be consulted for specific guidance on the management of a child with bronchiolitis. Treatment of lower respiratory tract disease includes supplemental oxygen when needed, management of respiratory secretions that may block the upper airways, and maintenance of appropriate hydration. Advances in pediatric critical care are responsible for decreased morbidity and mortality rates attributable to RSV infection.

Ribavirin is a synthetic guanosine nucleoside analogue that inhibits RSV replication and is the only US Food and Drug Administration (FDA) approved antiviral agent for treatment of RSV infection. Aerosolized ribavirin therapy has been shown in small clinical trials of RSV-infected immunocompetent patients to provide a modest improvement in oxygenation, but decreases in mechanical ventilation and duration of hospitalization have not been consistently demonstrated.[30] Considering the conflicting results of clinical trials, high drug cost, cumbersome administration apparatus, and concern about toxicity to healthcare providers, ribavirin usually is not indicated for the treatment of RSV bronchiolitis in immunocompetent patients. The role of ribavirin therapy for the treatment of RSV disease in severely immunocompromised patients such as bone marrow transplant recipients remains controversial.

Prevention

Strict adherence to infection control policies is critical for protection of all patients, especially those who are anatomically and immunologically compromised. Reducing the burden of RSV disease must focus on education regarding the importance of decreasing exposure to and transmission of all respiratory viruses.

Palivizumab is a humanized murine monoclonal antibody produced by recombinant DNA technology. The antibody binds to a conserved epitope on protein F found on RSV subtypes A and B.[23] After intramuscular administration, the antibody is distributed hematogenously throughout the body, including to the lower respiratory tract. When RSV is encountered in the bronchioles, palivizumab binds to protein F and prevents the conformational change that is necessary for the viral lipid envelope to fuse with the plasma membrane. Without fusion, the virus is unable to enter the cell and is unable to replicate.

Palivizumab was licensed by the FDA in 1998, and the American Academy of Pediatrics (AAP) first provided guidance for use of this expensive intervention. Since then, additional information has become available about the small benefit of palivizumab prophylaxis on the risk of hospitalization of preterm infants, the absence of a statistically significant reduction in mortality rates or need for intensive care, the declining incidence of hospitalization for all-cause bronchiolitis, and the absence of reproducible data showing a reduction in subsequent wheezing among palivizumab recipients.[2,31–33]

A randomized, double-blind, placebo-controlled trial of motavizumab, a humanized monoclonal antibody, in healthy, term, Native American infants showed an 87% relative reduction in the hospitalization of those treated for RSV but no difference in the rates of medically attended wheezing in children between the ages of 1 and 3 years.[34] In a prospective, longitudinal birth cohort study of unselected, healthy, term infants in the Netherlands, lung function abnormalities at birth predisposed them to hospitalization for RSV infection and post-RSV wheezing.[35] However, the findings did not support a direct, generalizable causal association with RSV lower respiratory tract infection and subsequent long-term wheezing in term infants.[34]

AAP guidance has become increasingly restrictive based on the data. A summary of current recommendations for palivizumab prophylaxis during the first year of life includes the following groups[17]:

- Infants born before 29 weeks' gestation may receive up to a maximum of five monthly doses. Infants born at or after 29 weeks' gestation do not have a statistically significant greater rate of RSV hospitalization than term infants, and prophylaxis is not recommended.
- Infants with chronic lung disease of prematurity (defined as less than 32 weeks' gestation and a requirement for supplemental oxygen for the first 28 days of life) may benefit from prophylaxis.
- Infants born with hemodynamically significant congenital heart disease may benefit from prophylaxis.

Future Directions

Ultimate control of RSV disease will require development of a safe and effective vaccine. Subunit RSV protein vaccines containing F protein are problematic for use in seronegative infants because of the potential for disease enhancement. However, an RSV protein vaccine may be useful in boosting immunity in nonnaïve, RSV-experienced older children and adults who are at increased risk for severe RSV disease due to underlying disease or advanced age.

Efforts to develop a live, attenuated RSV vaccine have encountered difficulty in providing sufficient attenuation of the vaccine strain so that the vaccine retains immunogenicity but does not cause symptoms in the vaccinee. Additional attenuated vaccine candidates are being developed.[36] A nonreplicating vaccine administered during gestation to boost the maternal neutralizing antibodies that are passed transplacentally to protect the infant during the first few months of life offers particular promise.

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226

Human Metapneumovirus

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Description of Pathogen

Human metapneumovirus (MPV) was first described in 2001 by Dutch investigators who collected a number of unidentified virus isolates over a 20-year period.[1] Electron micrograph and biochemical studies of the virus showed that it was pleomorphic and had a lipid envelope (Fig. 226.1). Reverse transcription polymerase chain reaction (RT-PCR) and sequence analysis of the virus genome identified it as a member of the Pneumovirus subfamily of the Paramyxoviridae family, which includes respiratory syncytial virus (RSV).

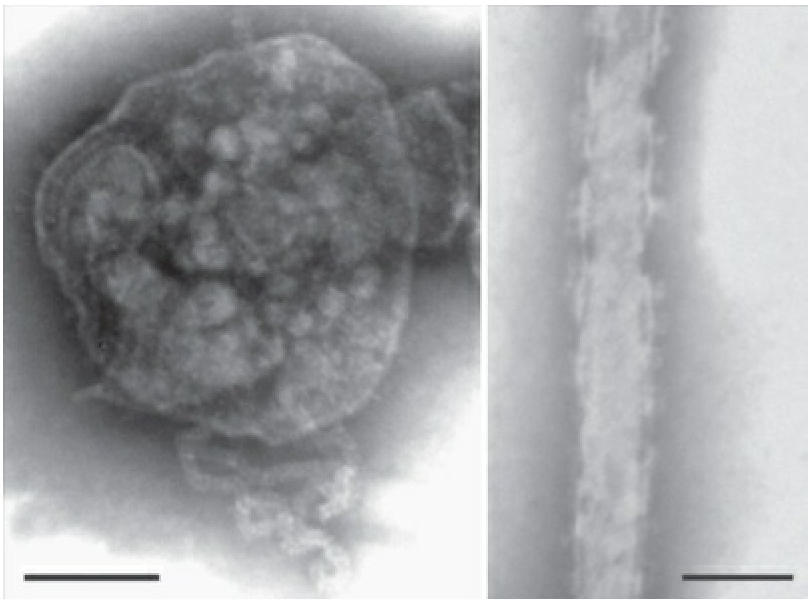

FIGURE 226.1 Electron micrographs of human metapneumovirus. In the whole virion *(left)*, glycoprotein spikes are visible in the viral membrane, and an extruded nucleocapsid is visible below. In the filamentous viral particle *(right)*, a herringbone pattern of the coiled nucleocapsid is visible within the virion. Bar = 100 nm.

MPV is most closely related by sequence homology to avian pneumovirus type C. Avian pneumovirus, discovered in 1979, is a major pathogen of poultry, causing severe respiratory disease in chickens and turkeys with consequent economic losses.[2] Evolutionary genetic analysis suggests that MPV diverged from avian pneumovirus C several hundred years ago.[3–5]

MPV has a negative-sense, single-stranded RNA genome like other paramyxoviruses. The MPV genome encodes nine proteins (Table 226.1 and Fig. 226.2). The fusion (F) protein has domains analogous to those of other paramyxovirus fusion proteins and mediates binding to integrins, internalization, and fusion of the virus and cell membranes.[6–12] Studies using animal models show that F is the major target for neutralizing antibodies.[13–16] The other major MPV membrane protein is G, a heavily glycosylated protein that may serve as an attachment protein for interaction with host cells.[17] In contrast to all other paramyxovirus accessory glycoproteins, the MPV G protein does not appear to be a protective antigen.[15,18,19] The matrix (M) protein augments immune response in candidate vaccines.[20] Analysis of the predicted amino acid sequences of the remaining MPV proteins suggests that they are similar in function to analogous proteins of other paramyxoviruses, although there is little directly conserved sequence.[11]

TABLE 226.1

Genes and Proteins of Human Metapneumovirus

Designation	Nucleotides (mRNA)	Molecular Weight (kd)	Function
N	1200	44	Nucleoprotein; structural protein, replication
P	885	33	Phosphoprotein; structural protein, replication
M	765	28	Matrix; structural protein
F	1620	59	Fusion; binds to integrins, mediates fusion of virus with the host cell membrane; target of neutralizing antibodies
M2-1	564	21	Regulates RNA transcription and replication
M2-2	204	8	Regulates RNA transcription and replication
SH	552	21	Short hydrophobic; function unknown
G	657–714	~75	Glycosylated protein; putative attachment to cells
L	6018	231	Large protein; the RNA polymerase

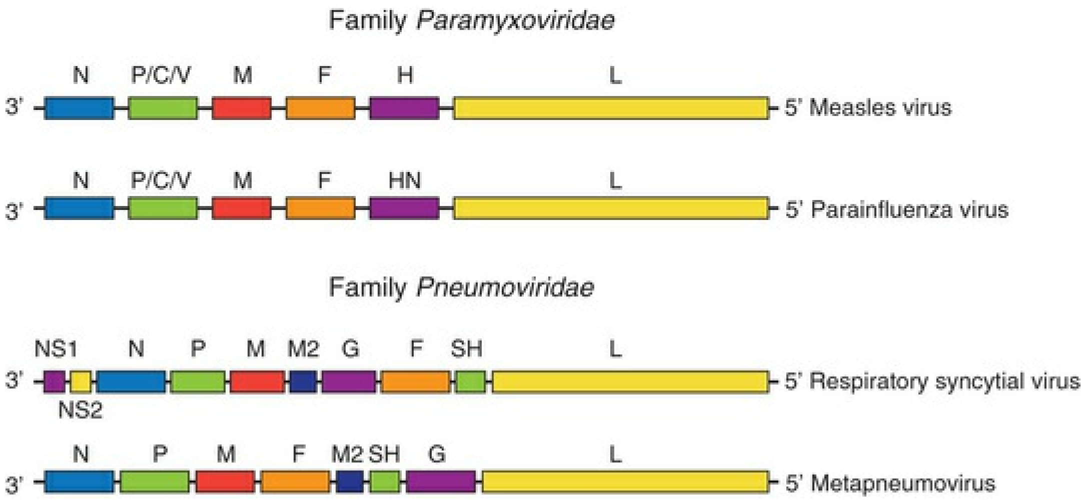

FIGURE 226.2 Schematic of the genomic organization of human metapneumovirus (MPV) compared with other paramyxoviruses. Gene segments are drawn roughly to scale. The MPV genome encodes nine proteins: fusion protein (F), glycosylated protein (G), large polymerase protein (L), matrix protein (M), nucleoprotein (N), phosphoprotein (P), RNA regulator protein (M2), and small hydrophobic protein (SH). H, hemagglutinin; HN, hemagglutinin-neuraminidase;

NS1, nonstructural 1; NS2, nonstructural 2; P/C/V, phosphoprotein.

Phylogenetic analysis of MPV genomes defines two major genetic subgroups of MPV, designated A and B, each with two minor subgroups.[3–5,21] The F protein is highly conserved, with 93% to 95% amino acid identity between major subgroups and about 97% amino acid identity within subgroups. In contrast, the G protein is only 30% to 35% conserved between major subgroups of MPV and 70% within subgroups.[3,21]

Reinfection with homologous or heterologous strains of MPV occurs readily, even during early childhood.[22–24] It is not clear whether the ability of MPV to reinfect humans results from infections with different subgroup viruses that are antigenically distinct, incomplete or waning immunity, or $CD8^+$ T-lymphocyte impairment induced by respiratory virus infections.[25] Longitudinal studies suggest that circulating subgroups alternate over time, indicating some antigenic pressure.[26] Serum neutralizing titers in adults appear to correlate with risk of reinfection.[27] There are no definitive human data determining the degree of cross-protection between different MPV subgroups. However, animal studies of the antigenic diversity between MPV subgroups suggest that there is cross-protective immunity in hamsters and primates.[15,21,28–30] These findings have important implications for the development of vaccines or antibodies against MPV.

There are few data describing the pathogenesis or histologic findings of MPV infection in humans. MPV has been isolated only from the respiratory tract, suggesting that replication is limited to respiratory tract epithelium. One study of lung transplant recipients infected with MPV described acute and organizing lung injury with diffuse alveolar damage, hyaline membrane formation, and cytoplasmic inclusion bodies.[31] Bronchoalveolar lavage fluid from MPV-infected patients contained sloughed, degenerated epithelial cells with eosinophilic cytoplasmic inclusions, multinucleated giant cells, and histiocytes.[32] A major limitation of these reports is that all patients had underlying diseases, and the findings may not reflect MPV infection in otherwise healthy humans.

Detailed analyses of the pathologic features of MPV infection have been described in mice, cotton rats, cynomolgus macaques, and chimpanzees.[33–37] Histopathologic changes included disruption of respiratory epithelium, sloughing of epithelial cells, loss of ciliation, inflammatory infiltrates in the lungs, and abundant fibrin and mucus. Histopathologic changes or evidence of infection were not detected in other tissues. Immunohistochemical staining for MPV in macaques and cotton rats revealed localization of viral antigen almost exclusively at the apical surface of ciliated respiratory epithelial cells.[35,36]

Preliminary studies in humans and animals show that MPV infection stimulates the production of various cytokines and chemokines and invokes T-lymphocyte responses; clearance is unaffected by the absence of natural killer cells.[33,38–43] MPV inhibits type I interferon responses, and because MPV lacks genes associated with this inhibition in other paramyxoviruses, the mechanism is not clear.[44]

Epidemiology

MPV infections occur in annual epidemics during the late winter and early spring months in temperate locations. The MPV season overlaps with those of RSV and influenza viruses, but the peak incidence of MPV usually occurs 1 to 2 months later than the peak of RSV. Prospective surveillance studies conducted over a 25-year period showed that MPV was present in every season, although the prevalence varied from year to year.[22,45]

Different lineages of MPV frequently circulate in a community during the same winter season, although one subgroup may predominate in a given year.[26,45] Viruses from each subgroup appear capable of causing severe lower respiratory tract disease, but different subgroups have not been associated convincingly with different levels of severity of disease.[46,47] In most studies of patients with acute respiratory tract infection, the percentage of MPV detection varies from 6% to 15%. MPV infection usually causes illness; MPV is infrequently detected in nasal specimens from asymptomatic children.[22,48–51]

Studies of hospitalized and outpatient children in many countries have found MPV to be associated with 6% to 40% of acute respiratory illnesses in a given season.[22,45,50,52–83] The average prevalence of infection is 5% to 10%, although it may be much higher during the peak months of MPV circulation. MPV prevalence usually is second to RSV in most studies and is comparable with that of influenza and parainfluenza virus infections.[60,83]

Hospitalization of children for MPV infection occurs primarily in the first year of life, although many studies report that the peak age of hospitalization for MPV is from 6 to 12 months of age and thus later than the peak age of hospitalization for RSV.[56,79,83–92] The biologic reasons for this are unknown. Males appear to be at greater risk of lower respiratory tract infection due to MPV compared with females, similar to sex difference in severity observed for other respiratory viruses. MPV infections are more severe in patients with underlying medical conditions such as asthma, prematurity, cardiopulmonary disease, or immunocompromised states.[50,53,54,69,73,74,93]

MPV infection has been associated with acute respiratory illness in adults. In several studies, MPV accounted for 5% to 15% of all hospitalizations for acute respiratory illness among older patients.[94–96] Most hospitalized adults have chronic underlying conditions such as asthma, chronic obstructive pulmonary disease, or cancer.[69,88–92,95–103] Overall, rates of hospitalization due to MPV infection in adults are similar to those for RSV and influenza infections.[104] The clinical manifestations of MPV infection are slightly different for younger and older patients (Box 226.1).

Box 226.1

Clinical Manifestations of Human Metapneumovirus Infection

Infancy

Bronchiolitis

Pneumonia

Croup

Exacerbation of asthma

Upper respiratory tract infection

Acute otitis media

Older Children and Adults

Upper respiratory tract infection

Croup

Laryngitis

Bronchitis

Asthma exacerbation

Pneumonia (elderly)

Exacerbation of chronic obstructive pulmonary disease (elderly)

Clinical Manifestations

MPV has been associated with a variety of respiratory symptoms and diagnoses (Table 226.2). Children with MPV infection typically have upper respiratory tract symptoms, including rhinorrhea, cough, and fever. Conjunctivitis, vomiting, diarrhea, and rash are reported only occasionally. Lower respiratory tract syndromes most frequently associated with MPV infection are bronchiolitis, croup, pneumonia, and asthma exacerbation. These illnesses are neither clinically nor radiographically distinct from the same clinical syndromes caused by other common respiratory viruses. Central nervous system manifestations rarely accompany MPV infections.[105–107]

TABLE 226.2

Presenting Signs and Symptoms and Diagnoses Associated with Pediatric Metapneumovirus Infection in Eight Clinical Studies[a]

Study Findings	**Boivin et al, 2003**[53]	**Laham et al, 2004**[56]	**van den Hoogen et al, 2003**[50]	**Esper et al, 2004**[54]	**Williams et al, 2004**[22]	**Williams et al, 2006**[45]	**Williams et al, 2010**[60]	**Dollner et al, 2004**[69]
Number of MPV-infected patients	12	32	25	53	49	118	29	50

Fever (%)	67	100	61	77	52	54	76	44
Rhinorrhea (%)	92	38	80	64	88	82	72	90
Cough (%)	100	90	72	68	90	66	86	90
Wheezing (%)	83	28	24	51	52	NA	38	56
Vomiting (%)	25	—	—	—	10	20	—	36
Diarrhea (%)	8	6	—	—	17	14	—	14
Rash (%)	0	12	—	—	4	3	—	—
Abnormal chest radiograph (%)	—	68	62	56	50	NA	—	
Bronchiolitis (%)	67	9	—	—	59	NA	38	48
Pneumonia (%)	17	38	—	—	8	NA	24	34
Croup (%)	0	—	—	—	18	NA	10	
Asthma (%)	—	19	—	—	14	NA	24	
Acute otitis media (%)	50	12	—	—	37	50	—	

[a] References 50, 53, 54, 56, and 69 include only hospitalized children. Reference 22 includes only children with lower respiratory illness. Reference 45 includes only children with upper respiratory illness.

MPV, metapneumovirus; NA, not applicable; —, not reported; (%), percent of patients in the study.

MPV has been associated with severe and fatal disease, especially in high-risk patients. Colonization with *Streptococcus pneumoniae* has been associated with MPV seroconversion in young children, and limited data suggest that pneumococcal superinfection occurs in some cases.[108–110] A substantial proportion of children infected with MPV develops acute otitis media (AOM), and viral RNA has been detected in middle ear fluid from patients with AOM.[46,83,111–113]

Similar to RSV, transmission of MPV probably occurs by respiratory droplets and secretions. Infectious MPV particles can persist in the environment for hours,[114] and numerous nosocomial outbreaks have been reported.[90,97,100,115–117] The duration of virus shedding in the nasopharynx is 1 to 2 weeks in otherwise healthy children, but it can last for weeks to months in immunocompromised patients.[22,45,50,70,118,119]

Laboratory Findings and Diagnosis

Traditional virus culture techniques are insensitive for the detection of MPV. The virus grows slowly in a limited number of cell types and requires trypsin for replication in culture – conditions that are not used routinely in clinical virology laboratories.[1,114,120–122] There is no commercial rapid antigen test for MPV, although immunofluorescent detection has been reported.

Reliable diagnosis of MPV currently depends on molecular techniques based on nucleic acid amplification assays. Several reverse transcriptase polymerase chain reaction (RT-PCR) methods are quite sensitive.[123–125] Numerous rapid multiplex PCR assays are commercially available that can detect up to 18 or more viruses simultaneously, including MPV.[126,127]

Treatment

Most children infected with MPV can be managed at home with supportive care. For infants and children who require hospitalization, the primary therapies are supplementary oxygen and intravenous hydration. Extracorporeal membrane oxygenation has been used in cases of respiratory failure refractory to mechanical ventilation.[128] Bronchodilators and corticosteroids have been used empirically, but there are no controlled trials of these medications for MPV and no data to support efficacy. Bronchodilator and corticosteroid treatments were effective in a cotton rat model of infection.[129]

Ribavirin and polyclonal human immunoglobulin have virus-inhibiting activity against MPV in vitro equivalent to activity against RSV.[130] However, there are no data supporting the benefits of these therapies beyond anecdotal reports in profoundly immunocompromised MPV-infected patients.[131–136]

Special Considerations

The relationship between MPV and asthma is not clear. MPV infection is associated with exacerbations of asthma in adults and children.[22,51,137–139] Two reports suggest that MPV infection during infancy is associated with asthma or impaired lung function later in life.[140,141] All such studies are complicated by the difficulty of assigning the diagnosis of asthma during infancy, when acute wheezing is frequently associated with viral infections.[104]

In some cohorts, high viral loads have been associated with disease severity.[142,143] Chronic medical conditions, including prematurity, have been associated with severe disease.[144,145] Infections caused by MPV can be fatal in immunocompromised hosts. Several studies suggest that MPV is a common cause of acute respiratory tract infection in children and adults with malignancy or undergoing hematopoietic stem cell transplantation (HSCT), in those with human immunodeficiency virus (HIV) infection, and in lung transplant recipients.[103,132,146–150] One fourth to one half of immunosuppressed patients with MPV infection had a lower respiratory tract infection, and as many as 5% died of pneumonia.[151–153] Mortality rates for MPV infected patients undergoing HSCT are as high as 40%.[154] Long-term prospective studies are needed to characterize fully the extent and severity of disease due to MPV in immunocompromised hosts.

Prevention

The molecular biology cloning technique called *reverse genetics* is used to generate recombinant live paramyxoviruses from DNA copies of virus genomes, allowing the incorporation of specific mutations or entire genes into recombinant viruses.

These techniques have been developed for MPV. Recombinant chimeric bovine/human parainfluenzae virus type 3 and bacille Calmette-Guérin vaccines expressing MPV were immunogenic and protective in small animals.[16,155] Investigators have generated recombinant MPV strains that lack various genes, including the genes that encode the small hydrophobic (SH), G, M2-1, and M2-2 proteins, or that possess avian metapneumovirus gene insertions.[156–159] Many of these recombinant viruses caused attenuated infection in rodents or nonhuman primates but were highly immunogenic, inducing neutralizing antibodies and protection against challenge with wild-type MPV. Virus-like particles are effective at inducing B-cell and T-cell responses in animal models and confer homologous and heterologous genotype protection.[160,161]

MPV-specific monoclonal antibodies similar to palivizumab have shown preventive and therapeutic efficacy in rodent models,[162,163] and some have broadly neutralizing activity against RSV.[164,165] A live, attenuated vaccine has been tested in humans, although only about one third of volunteers developed an antibody response.[166] Several potential vaccine candidates and prophylactic antibodies are in development within 9 years of the discovery of MPV, a remarkable achievement.

Key Points

Epidemiology, Clinical Features, Diagnosis, and Treatment of Human Metapneumovirus

Epidemiology

- Distributed worldwide
- Affects all age groups, but most serious disease is in young children or persons with underlying chronic respiratory diseases or immunosuppression
- Transmission: direct person-to-person contact, droplets, and contact with contaminated environmental surfaces

Clinical Features

- Acute upper and lower respiratory infections
- Disease characterized most frequently by
  - Rhinorrhea, cough, wheezing
  - Associated acute otitis media
- Bronchiolitis, pneumonia, croup, and asthma exacerbation common lower respiratory syndromes
- Hypoxemia is the most common complication in the young and elderly.
- Duration of viral shedding is 1–2 weeks.

Diagnosis

- Detection by nucleic acid testing of respiratory specimens

- Detection by fluorescent antibody testing of respiratory specimens

Treatment

- Supplemental oxygen
- No highly effective antiviral drugs or vaccine available

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Rubeola Virus

Measles and Subacute Sclerosing Panencephalitis

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Rubeola (i.e., measles) is an acute, highly contagious, vaccine-preventable viral disease of childhood.[1] In the prevaccination era, measles was an almost universal experience during childhood. After the licensure of a live measles vaccine in 1963, the incidence of measles declined markedly in the United States. Because of high rates of 2-dose measles-mumps-rubella (MMR) vaccine coverage, the United States declared elimination of endemic measles in 2000. Recent measles outbreaks due to importations and spread in communities with unvaccinated children highlights the importance of sustaining high levels of population immunity through immunization.[2,3]

Despite substantial progress made in global measles control, large outbreaks continue to occur in many countries due to low rates of vaccine coverage.[4] Measles remains a major cause of child mortality in low- and middle-income countries (LMICs).[5]

Description of the Pathogen

Measles virus (MV) is an enveloped, nonsegmented, negative-strand RNA virus belonging to the *Morbillivirus* genus in the

Paramyxoviridae family. MV is closely related to rinderpest virus, a cattle pathogen that was eradicated in 2011.[6] MV genome consists of 15,894 nucleotides and encodes eight proteins.[7] The surface envelope glycoproteins and the hemagglutinin (H) and fusion (F) proteins are the main targets for development of neutralizing antibodies.[8] The matrix (M) protein is important in virus assembly. The internal proteins, nucleoprotein (NP), polymerase phosphoprotein (P), and large protein (L), form the nucleocapsid. Two nonstructural proteins (C and V) regulate the cellular response to infection.[7]

The receptor binding H protein interacts with F protein and mediates virus attachment and host cell entry. The F protein enhances cell-to-cell spread of the virus. Neutralizing antibodies are primarily directed against the H protein and confer lifelong immunity.[8] There are three identified cellular entry receptors for MV. Human signaling lymphocyte activation molecule (i.e., hSLAM or CD150) is a common immune cell receptor for all MV strains, whereas membrane cofactor protein (i.e., MCP or CD46) is a receptor for vaccine strains.[9] A third receptor, poliovirus receptor–like 4 (i.e., PVRL4 or Nectin 4) is expressed on the adherens junctions of epithelial cells.[10]

Wild-type MV infects only primates. Although MV is a monotypic virus, minor genetic and antigenic variation occurs in some virus strains.[11] These antigenic variations have not compromised long-lasting immunity. MV is inactivated by lipid solvents, heat, and light.

Pathogenesis

Measles is transmitted by direct contact with respiratory droplets or, less commonly by airborne inhalation.[12] The incubation period is about 10 to 14 days from exposure to onset of symptoms. People with measles are contagious from 4 days before to 4 days after rash onset.[13] Measles is highly contagious, with a basic reproductive number (R_0) of 12 to 18.[14] Symptomatic infection develops in 90% of susceptible contacts.

Evidence from studies of nonhuman primates has corrected historically held ideas of pathogenesis.[1] Measles virus initially infects $CD150^+$ alveolar macrophages or dendritic cells, or both, rather than epithelial cells of the upper respiratory tract.[15,16] Infected cells cross the respiratory epithelium and migrate to the draining lymphatic tissue, where the virus preferentially infects CD150$^+$ memory T lymphocytes and B lymphocytes.[17] Infected lymphocytes then spread the virus to respiratory tract epithelial cells through the basolateral surface at later stages of disease by the alternative epithelial cell receptor PVRL4.[10,15]

Pathologic changes associated with viremia include lymphoid hyperplasia of the adenoids, tonsils, lymph nodes, spleen, and intestinal tract. Target infected cells include the epithelial or endothelial cells, B and T lymphocytes, monocytes or macrophages, and dendritic cells.[17,18] Multinucleated giant cells are found most commonly during the early stage of measles in the nasopharynx, tonsils, and bronchial mucosa.[19] Intranuclear inclusions and syncytial epithelial cells may be seen. Mononuclear infiltration with peribronchial inflammation occurs in the respiratory tract.

Immune Response

Adaptive immune responses are important in developing and maintaining lifelong immunity to measles.[18] The onset of rash coincides with development of measles-specific humoral and cellular immune responses and rapid clearance of infectious virus.[18] However, MV RNA can persist in peripheral blood mononuclear cells for several months, despite development of humoral immunity.[20]

Neutralizing antibodies confer lifelong immunity to measles.[21] Measles-specific serum immunoglobulin M (IgM) appears with the onset of rash, followed by a sustained production of measles-specific serum immunoglobulin G (IgG).[18] Neutralizing antibodies to the H and F proteins are necessary for protection.[8,18] People vaccinated with killed virus in whom atypical measles developed after exposure to MV had neutralizing antibodies to H protein but lacked neutralizing antibody to F protein.[22] In contrast, recipients of live, attenuated vaccine demonstrate neutralizing antibody to the H and F proteins and are immune to infection.

Whereas humoral immunity is important in preventing measles, the cellular immune response appears to be important in aborting symptoms during acute infection.[18] Children with agammaglobulinemia fully recover from measles in the absence of a specific antibody response, whereas deficiency in cellular immunity predisposes children and adults to severe or fatal infection.[23] During acute illness, the initial cellular immune response mediated by cytotoxic CD8$^+$ T lymphocytes and activated type 1 CD4$^+$ lymphocytes is important for MV clearance. Production of cytokines such as interferon γ, and interleukin-2 (IL-2) contribute to the generation of a predominant helper T lymphocyte subtype 1 (Th1) response. During recovery, as viral RNA persists, a shift to the Th2 response influenced by IL-4 and IL-10 likely promotes the development of MV-specific antibodies but can suppress Th1 responses and macrophage activation in response to intracellular microbes.[1,18]

A striking feature of the immune response to MV is the induction of transient cellular immunosuppression after infection. Reduced responsiveness to non-MV antigens can last for several weeks to months after acute infection, resulting in increased susceptibility to secondary infections and increased mortality rates.[18,24] Delayed-type hypersensitivity responses, such as reactivity to the tuberculin skin test, are transiently suppressed, and defects in mitogen-induced lymphocyte proliferation are observed in vitro.[25,26] Other abnormalities include lymphopenia, dominant Th2 responses, and T-cell nonresponsiveness.[18] The mechanisms of MV-induced immune suppression remain unclear.[27]

Epidemiology

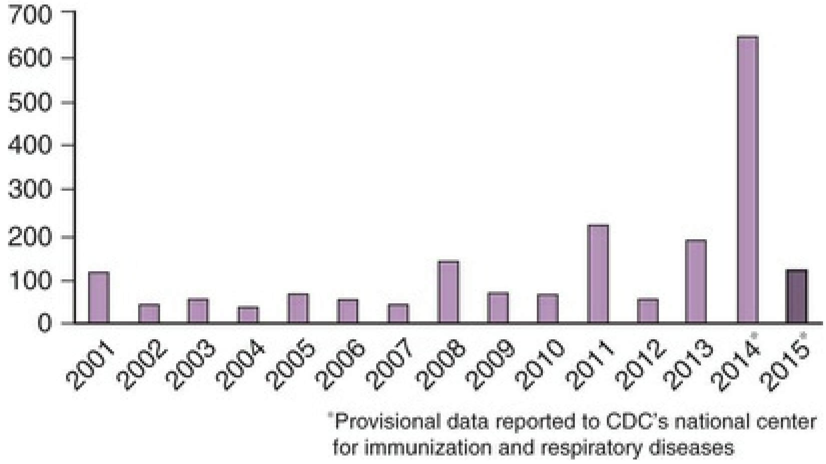
Measles affects only humans; there is no known animal reservoir.[1] The disease is endemic in many regions of the world, with an estimated 20 million cases annually.[28] In the prevaccine era, more than 90% of US children contracted infection by 15 years of age (highest attack rate at 5–9 years of age), and most adults therefore were not susceptible during cyclic epidemics.[29] Epidemics of measles occurred in 2- to 5-year cycles, reflecting the changing pool of susceptible people in the community.[1] In temperate climates, measles epidemics typically occur in late winter through early spring.[1]

In the vaccine era, infants and younger children are most susceptible to measles.[30] Protective transplacental immunity to measles is conferred to infants whose mothers had measles infection or received measles vaccine. Infants whose mothers had measles infection have passive measles antibody for longer periods than infants whose mothers received measles vaccine.[31] The morbidity and mortality rates for measles are highest among infants, immunocompromised (e.g., HIV infection, leukemia), and severely malnourished children, including those with vitamin A deficiency.[32,33] Measles also can be severe in secondary household cases.[34]

Since availability of the measles vaccine in the United States in 1963, a dramatic decline in measles incidence was seen through the 1980s until 1989–1991 period, when about 55,685 cases and 123 deaths were reported.[35] This major resurgence resulted from decreased measles vaccination rates among preschool-aged children, who often resided in crowded, urban areas,[36] and susceptibility of adolescents because of primary vaccine failure (i.e., failure to respond to a first dose).[37] Subsequently, the Advisory Committee on Immunization Practices (ACIP) recommended a second dose of measles-containing vaccine as a combined MMR vaccine.[38]

After high 2-dose vaccine coverage, reported measles cases declined rapidly to 309 cases in 1995.[35] In 2000, the United States declared elimination of endemic measles (i.e., absence of year-round transmission).[39,40] However, imported cases and limited spread occur each year. During the postelimination period (2001–2011), a total of 911 measles cases were reported (median, 61 cases/year; range, 37–220 cases), with a low annual population incidence (<1 case per million people).[41,42] There were about 33 importations/year and 4 outbreaks/year (range, 2–16 outbreaks); 25% of cases were hospitalized.[41,42]

In recent years, a slow but steady rise in measles cases (i.e., 140 in 2008, 220 in 2011, and 189 in 2013) have been reported to the Centers for Disease Control and Prevention (CDC), including a dramatic rise in 2014 (Fig. 227.1).[43,44] Reported cases originated predominantly from large outbreaks in Western Europe, Pakistan, Vietnam, and the Philippines.[43] During 2014, the United States had 668 measles cases reported from 27 states, including 23 outbreaks, representing the greatest number of measles cases since 1994.[44] One outbreak of 383 cases occurred in Ohio, primarily among unimmunized Amish missionaries returning from the Philippines, which experienced a large outbreak in 2014.[44]



*Provisional data reported to CDC's national center for immunization and respiratory diseases

FIGURE 227.1 Measles cases, by year—United States, 2001 to 2015. (Data from Centers for Disease Control and Prevention. Update: measles—United States, January-July 2008. MMWR 2008;57:893-896; Centers for Disease Control and Prevention. Measles (Rubeola). https://www.cdc.gov/measles/cases-outbreaks.html.)

Between January 4 and April 2, 2015, 159 measles cases (age range, 6 weeks–70 years) from 18 states and the District of Columbia were reported to the CDC; 16% of patients were younger than 12 months of age, and 14% required hospitalization. A total of 111 (70%) of these cases were associated with a 2014 multistate outbreak that began in a Disney theme park in California.[3,44,45] Of the 159 cases, more than 80% of cases were unvaccinated or had unknown vaccination status; 96% were import associated. Common sources of importations include unvaccinated US residents or travelers returning from abroad, with subsequent transmission among clusters of intentionally unvaccinated people[2,44–46] (Fig. 227.2). Measles outbreaks carry a substantial economic burden.[14]

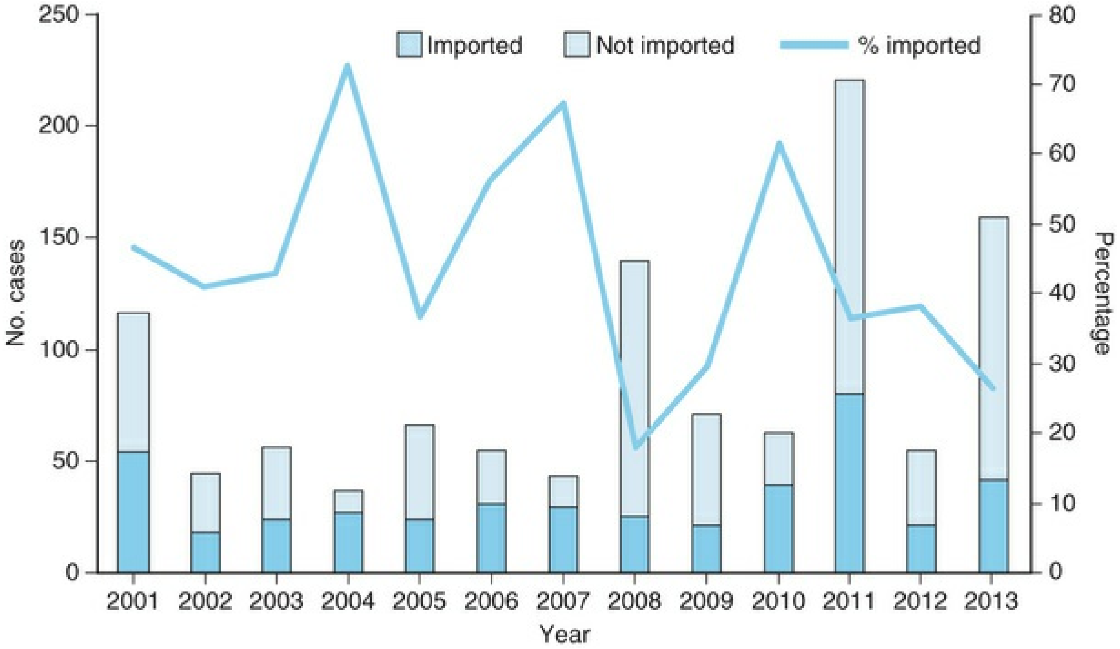


FIGURE 227.2 Measles cases (number and percent) that were directly imported and not directly imported in the United States for 2001 through 2013. Directly imported cases are infections occurring in patients who acquired measles outside the United States and brought the infection into the country. Cases not directly imported include infections that were acquired in the United States but linked to directly imported cases, imported virus, and cases with unknown sources. The 2013 data are for January 1 to August 24. (From Gastañaduy PA, Redd SB, Fiebelkorn AP, et al. Measles—United States, January 1–May 23, 2014. MMWR Morb Mortal Wkly Rep 2014;63:496–499.)

Given the high level of contagiousness, measles outbreaks can occur in communities where less than 10% are susceptible.[47] The growing number of parents hesitant to vaccinate their children is a major concern.[14] In the 2014–2015 outbreak, MMR vaccination rates in the community fell below the necessary threshold to sustain community immunity, resulting in spread to secondary cases.[48] Immunization rates of 96% to 99% are needed to maintain herd immunity and prevent outbreaks.[49]

Substantial progress has been made in global measles control and elimination.[50,51] In 1980, before widespread vaccination, measles accounted for an estimated 2.6 million deaths annually.[52] With improved measles-control strategies, estimated measles deaths worldwide decreased by 75%, from 544,200 in 2000 to 145,700 in

2013.[28] During the 2000–2013 period, measles vaccination prevented an estimated 15.6 million deaths, and there was a 72% decline in the annual reported measles incidence from 146 to 40 cases per million people. The reduction in childhood deaths from measles has accounted for an estimated 23% reduction in the all-cause mortality rate for children younger than 5 years of age.[53]

Measles was eliminated from the World Health Organization (WHO) Region of the Americas in 2002.[54] Elimination of measles is defined as absence of endemic transmission of MV in a defined geographic area for more than 12 months in the setting of a well-performing surveillance system.[55] The WHO Global Vaccine Action Plan has established measles elimination targets in at least five WHO regions by 2020.[56] However, the disease remains endemic in Europe, Asia, Africa, and the Middle East (Fig. 227.3).[57] Large outbreaks have involved broad age groups, including adults.[4,51] Importations of measles into the United States continue to occur, resulting in secondary cases and outbreaks.[2,3,58,59]

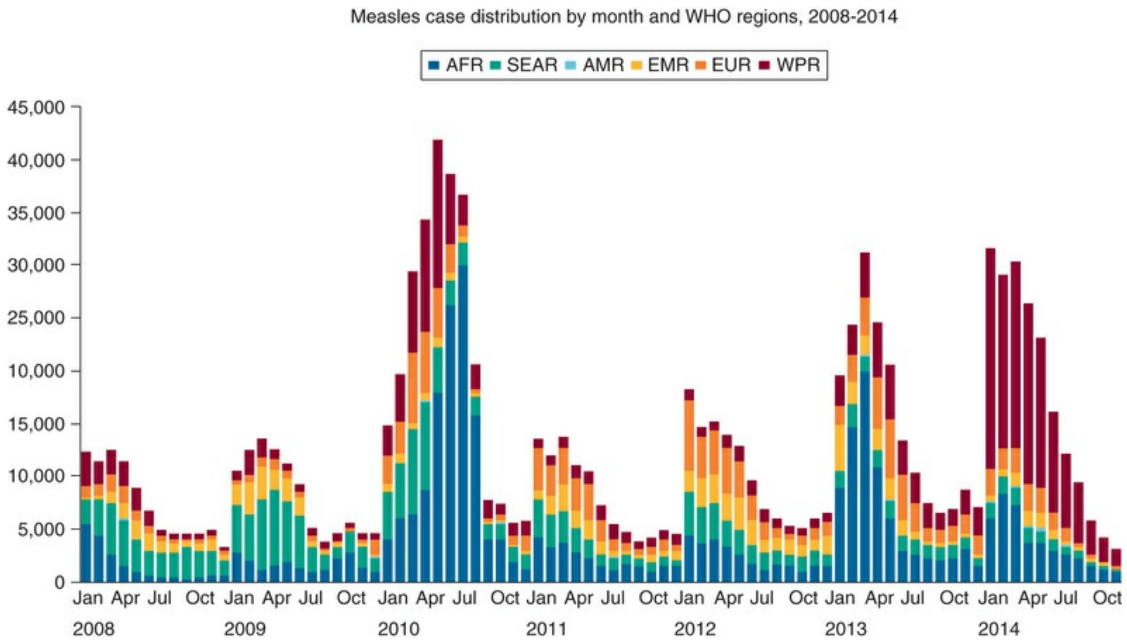


FIGURE 227.3 Measles cases reported to the World Health Organization for September 2014 through February 2015. (From World Health Organization. Measles Surveillance Data. http://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/active/mea

Measles eradication is biologically, programmatically, and operationally feasible, and it is cost-effective.[50,60–62] A 2-dose measles-containing vaccine schedule protects most immunocompetent children.[63] Challenges for global measles eradication include weak or conflict-affected health systems, inadequate surveillance of immunization campaigns, vaccine skepticism, and cultural and financial barriers.[51,60–62]

Clinical Manifestations

Typical Measles

After an 8- to 12-day incubation period, a prodromal illness characterized by fever, cough, nonpurulent conjunctivitis, and coryza develops.[1] During the 2- to 4-day prodrome, a pathognomonic enanthem called *Koplik spots*, which are bluish white, 1-mm lesions on a red base, may be visible on the buccal mucosa.[64,65] Koplik spots initially are discrete and appear anywhere on the buccal mucosa, including the hard and soft palate, but they characteristically are located opposite the lower premolars. Lesions eventually coalesce and spread rapidly throughout the buccal mucosa. After the enanthem is seen for 12 to 72 hours, it starts to slough with the appearance of the rash.

The rash typically begins at the peak of the respiratory symptoms, typically about 14 days after exposure and 2 to 3 days after appearance of the Koplik spots. The rash is erythematous and initially maculopapular, starts on the forehead or posterior occipital area, and spreads within 3 days to the trunk and extremities (Fig. 227.4). The rash is more likely to be confluent over the head and upper extremities than over the trunk and lower extremities (Fig. 227.5). The rash usually lasts for 3 to 5 days and fades from red to copper to brown in a cephalocaudal direction; fine desquamation follows. In malnourished children, a deeply pigmented rash with more extensive desquamation may occur.[1,66] The rash can become mildly hemorrhagic, and petechiae or purpura occasionally occurs.[67]

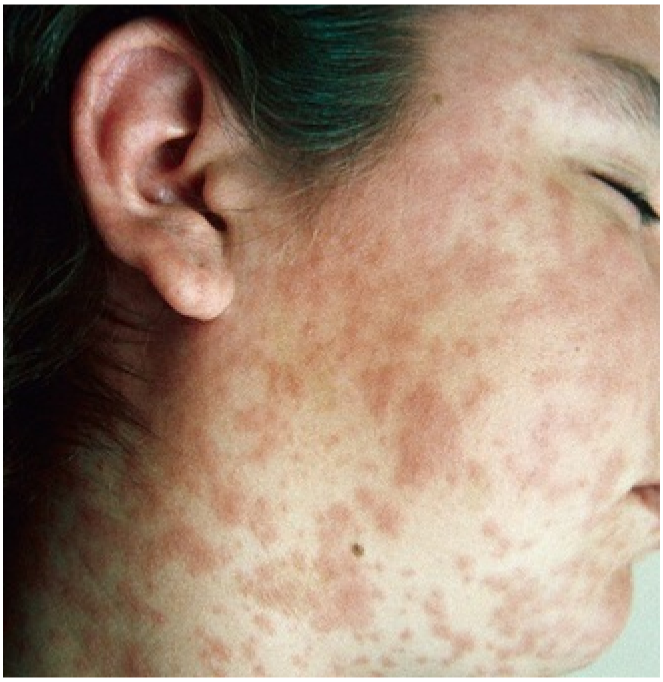


FIGURE 227.4 Typical rash on day 2 or 3 of measles. (Courtesy of J.H. Briené.)

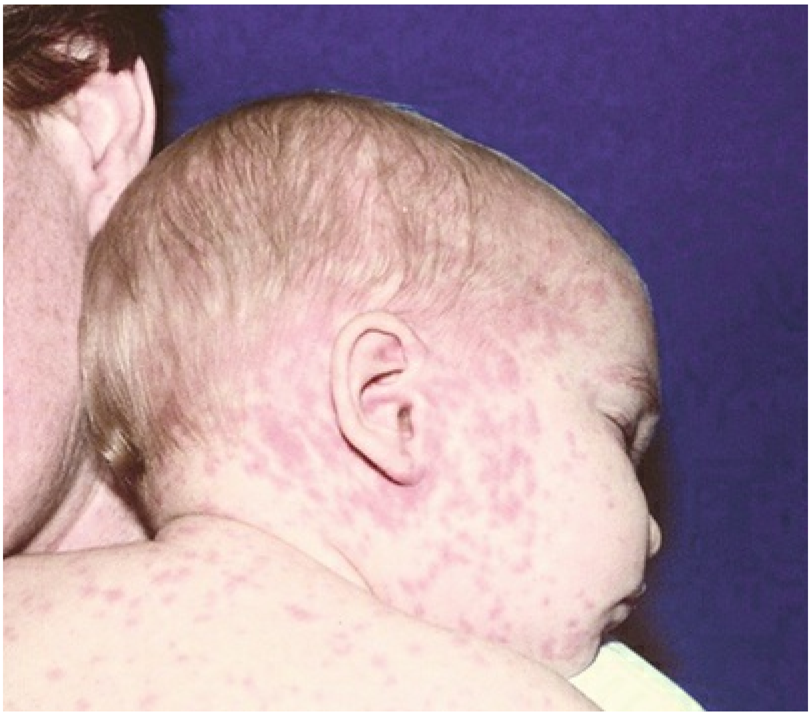


FIGURE 227.5 Measles rash on day 5, showing the typical confluence and density of lesions on the head and scattered lesions on the trunk. (Courtesy of J.H. Briené.)

Symptoms during the exanthematous phase include high fever (up to 40°C) that peaks 2 to 3 days after rash onset, continued respiratory symptoms, nonpurulent conjunctivitis, pharyngitis, and mild generalized lymphadenopathy. After the fever peaks, it usually resolves rapidly, followed by clinical recovery in uncomplicated measles. Persistent fever is a possible indication of secondary bacterial infection. Occasionally, diarrhea, vomiting, and abdominal pain may occur. In LMICs, diarrhea is a major complication of measles.[68]

Transient anicteric hepatitis has been reported in young adults with measles.[69] An atypical form of measles occurred in people infected with wild-type MV who had previously received formalin-inactivated (i.e., killed) measles vaccine in the United States between 1963 and 1968.[70] A severe disease that lacked many typical features of measles had a nonconfluent, caudocephalad progression of rash, which sometimes had a petechial and vesicular component. Pneumonia, hilar adenopathy, pleural effusion, and prolonged recovery (≥2 weeks) were common.

Hemorrhagic Measles

Severe hemorrhagic measles (i.e., black measles) is most common among infants in developing countries and is characterized by a sudden onset of high fever accompanied by seizures or altered mental status.[67] Other manifestations include pneumonia; an extensive hemorrhagic exanthem and enanthem; bleeding from the mouth, nose, and gastrointestinal tract; and disseminated intravascular coagulation. The prognosis is poor, and fatalities are common.[67]

Modified Measles

Modified measles is an attenuated form of infection that can occur in people who have received immune globulin after exposure to measles.[65] The clinical manifestations of modified measles are milder than those of typical infection, and the incubation period is prolonged (14–20 days). Complications are rare.

Laboratory Findings and Diagnosis

Laboratory abnormalities include leukopenia and lymphopenia.

The diagnosis of measles is confirmed by serology, virus isolation, or detection of measles virus RNA by reverse transcriptase polymerase chain reaction (RT-PCR) on clinical samples.[71] Serology (often by enzyme immunoassay) is the most widely used method to confirm the diagnosis.[72] A presumptive diagnosis can be made by detection of MV-specific immunoglobulin M (IgM) antibody on a single serum sample.[13] A fourfold or greater rise in the IgG antibody titer from paired acute and convalescent sera obtained at least 10 days apart also indicates recent infection.[13]

MV-specific IgM antibody usually is detectable 1 to 2 days after rash onset and persists for 30 to 60 days in unimmunized people.[73] The timing of specimen collection, vaccination history, and the type of assay can influence the sensitivity of measles IgM assays. False-negative IgM results occur for less than 20% of patients during the first 72 hours after rash onset; repeat testing is recommended if the generalized rash persists for more than 72 hours.[13,74] IgM antibody can be present transiently or absent in infected people who previously received 1 or 2 doses of measles vaccine. MV-specific IgM antibody testing therefore is not recommended to exclude measles infection in vaccinated people.[13]

In the United States and other countries with high MMR vaccine coverage, serology and RT-PCR assay are recommended to confirm the diagnosis.[13,71] Specimens from the throat or nasopharynx are preferred for RT-PCR assay, and sampling more than one site may increase detection.[13] MV sometimes can be isolated from blood, urine, and secretions of the throat and nasopharynx, but isolation is difficult and not recommended routinely.[13] MV genotyping may be beneficial for differentiating wild-type from vaccine virus strains and performing molecular epidemiologic studies to identify sources and transmission patterns of imported disease.[75,76]

In LMICs with a low incidence of measles, clinical diagnosis may be difficult.[1] The differential diagnosis of measles includes rubella, enteroviral infection, exanthem subitum, adenovirus, Epstein-Barr virus, parvovirus, and streptococcal or staphylococcal infections. Drug hypersensitivity, Rocky Mountain spotted fever, dengue, leptospirosis, and Kawasaki disease also can be confused with measles.

Treatment

No specific antiviral therapy is indicated for measles. Ribavirin is active against MV in vitro and has been used to treat immunocompromised patients with measles pneumonia and encephalitis.[77–79] Ribavirin has not been evaluated in controlled clinical trials and is not licensed for the treatment of measles.

In LMICs, administration of vitamin A to children with active measles decreases morbidity and mortality.[80,81] US studies have correlated low vitamin A levels in younger children with measles with increased morbidity rates.[82,83] The WHO recommends vitamin A administration to all children with measles.[84] The CDC also recommends vitamin A administration to all children with severe measles (e.g., hospitalized patients).[13,85] Vitamin A treatment for measles is administered once daily for 2 consecutive days as follows: 50,000 IU orally for infants younger than 6 months of age; 100,000 IU orally for infants between 6 and 11 months of age; and 200,000 IU orally for children aged 12 months of age or older. For children with clinical evidence of vitamin A deficiency, a third dose should be administered 2 to 4 weeks later.[1,86]

Special Considerations and Complications

Respiratory Tract Complications

Based on 1985–1992 US surveillance data, one or more complications occurs in about 30% of reported measles cases, and deaths were reported in about 0.2% of cases.[87] Children younger than 5 years of age, immunocompromised children, and malnourished children are at highest risk for adverse outcomes. Respiratory tract complications are common and reflect the intense inflammatory response to MV replication and disruptions of the epithelial cell integrity, possibly compounded by immunosuppression.[18,24,65,88]

The most common complication of childhood measles is acute otitis media (7% to 9%). Respiratory complications include bronchopneumonia, bronchiolitis, laryngotracheobronchitis, and pneumonia.[1,65,89,90] Pneumonia due to MV or secondary bacterial superinfection occurs in 1% to 6% of children with measles and accounts for 60% of deaths. Diarrhea occurs in about 8% of cases.[87] Rare complications include thrombocytopenic purpura, hepatitis, appendicitis, ileocolitis, pericarditis, myocarditis, glomerulonephritis, hypocalcemia, severe desquamation, and myositis.[65]

In LMICs, the case-fatality rate is 2% to 15%, compared with an estimated 0.2% to 0.3% in the United States.[91,92] Pneumonia and diarrhea are the most common life-threatening complications of measles, especially in malnourished children, and pneumonia accounts for 56% to 86% of measles-related deaths.[93] The most common secondary bacterial pathogens causing pneumonia are *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenza*.[91] Keratoconjunctivitis is a common complication after measles, especially in children with vitamin A deficiency, and it can result in blindness.[94]

Central Nervous System Complications

Central nervous system (CNS) complications of measles include acute encephalitis, subacute sclerosing panencephalitis (SSPE), and measles inclusion body encephalitis in immunocompromised hosts.[95–97]

Acute Encephalitis.

Acute encephalitis occurs in about 1 of 1000 measles cases and affects primarily older children and adults.[87,98] Fever, headache, altered mental status, seizures, and multifocal neurologic signs usually occur 6 days (range, 1–15 days) after appearance of the rash. Cerebrospinal fluid (CSF) shows mild to moderate lymphocytic pleocytosis, elevated protein levels, and normal glucose concentrations.[98]

The pathogenesis of measles encephalitis is ill defined, but it probably represents an autoimmune disorder,[99] although MV has been isolated from the CNS in some patients.[100] Neuropathology is characterized by perivenular inflammation, demyelination, and gliosis. Magnetic resonance imaging (MRI) findings may be compatible with acute disseminated encephalomyelitis. The case-fatality rate for primary measles encephalitis is about 15%; about one fourth of survivors have long-term sequelae such as seizures and mental retardation.[95,98]

Subacute Sclerosing Panencephalitis.

SSPE is a rare chronic complication of measles characterized by a slowly progressive, fatal neurologic disease due to persistent CNS infection.[101] The incidence of SSPE in the prevaccine era was 1 in 100,000 measles cases.[87] The disease is rare in the United States since universal measles vaccination was initiated.[102,103]

SSPE typically is associated with the acquisition of measles before age 2 years.[102] Travel of infants to measles-endemic countries before receipt of vaccine can be a clue to SSPE. The disease is two to three times more common among males, with onset usually occurring 7 to 10 years after asymptomatic, mild, or typical measles.[95]

Brain histopathology in SSPE cases demonstrates panencephalitis with lymphocytic and plasma cell infiltrate, demyelination, neuronal loss, and type A and type B intranuclear Cowdry inclusion bodies.[104] Electron microscopy of the inclusion bodies reveals paramyxovirus-like structures.

The pathogenesis of SSPE is unclear. An abnormal immune response to MV and the presence of defective or mutant MV strains in the brain may be important.[101] Although patients with SSPE have high CSF and serum measles antibody concentrations, cellular immune responses are limited. Defective MV strains can produce incomplete CNS infection and remain latent in host cells.[101,105] MV mutants possessing the fusion protein with enhanced fusion activity may promote neuronal cell entry and spread.[106]

Early symptoms of SSPE include subtle mood disturbances, hyperactivity, and cognitive decline. As the disease progresses, myoclonic seizures, motor disturbances, and ocular disease (necrotizing retinitis in 50%) may occur. Eventually, coma, autonomic instability, akinetic mutism, and vegetative state supervene. Death usually occurs within 1 to 3 years after symptom onset.[95]

The characteristic electroencephalographic (EEG) finding is a burst-suppression pattern with paroxysmal high-amplitude bursts and background suppression. Typical CSF findings include marked elevations in MV antibody titers (range, 1 : 8–1 : 64 or higher) and positive CSF oligoclonal bands. Serum MV antibody levels also are markedly elevated (>1 : 1280). Computed tomography demonstrates cortical brain atrophy. MRI findings for one patient are shown in Fig. 227.6. Brain biopsy is diagnostic, although the triad of clinical criteria, characteristic EEG pattern, and elevated CSF measles oligoclonal bands is sufficient to make the diagnosis.[101]

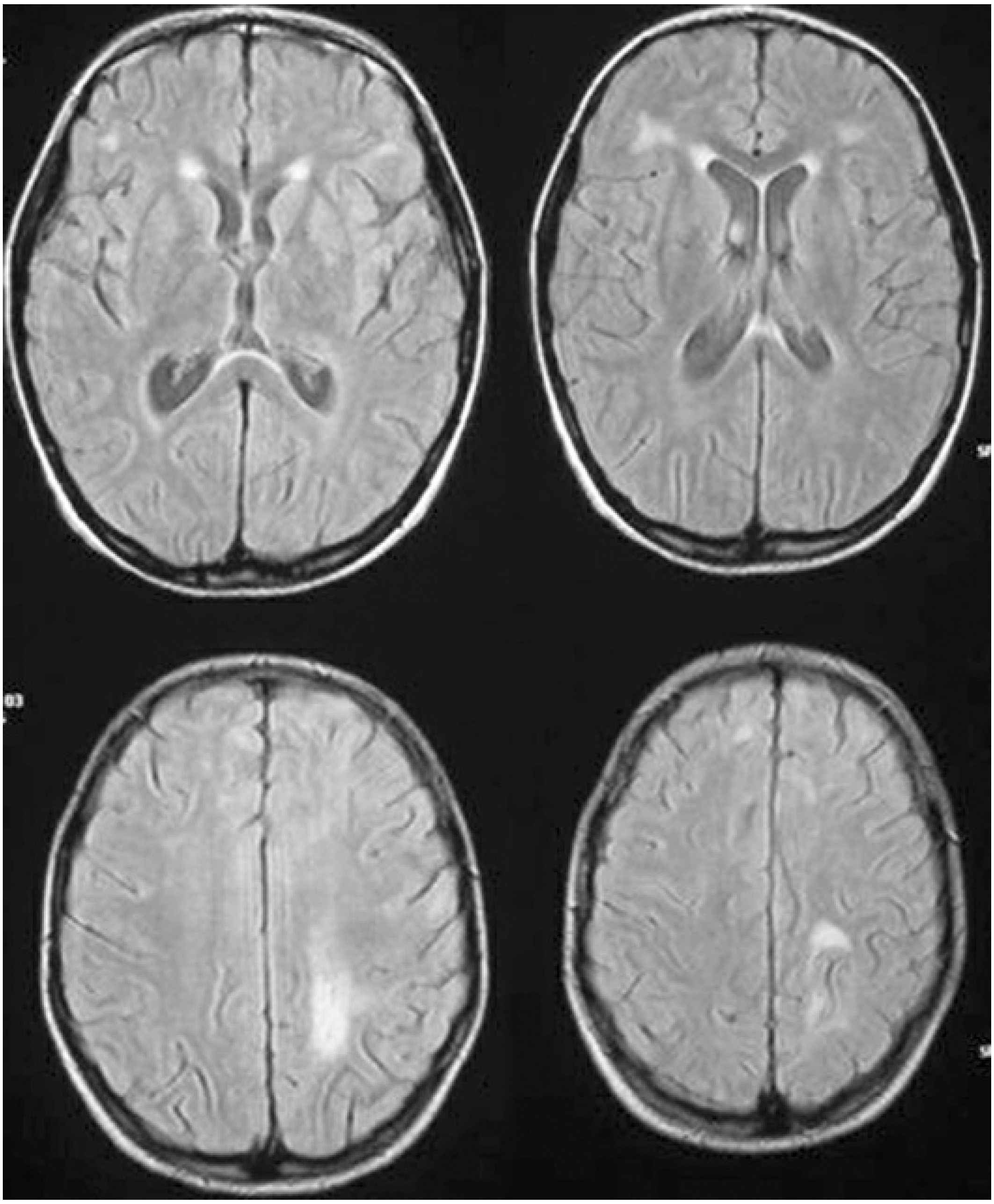


FIGURE 227.6 In 2006, an 8-year-old girl had clumsiness and decreased school performance that progressed over 13 weeks to weakness of the right face and extremities, hyperreflexia, jerking movements, decreased intellectual capacity and alertness, seizures, and death. Initially diagnosed and

treated as acute disseminated encephalomyelitis, evaluation of the clinical course and electroencephalogram showing slowing with burst suppression led to consideration of subacute sclerosing panencephalitis. The measles indirect fluorescent antibody titer was 1: 8192 in serum and 1: 512 in cerebrospinal fluid. The patient had visited Turkey from age 7 to 10 months and had a 1-day febrile exanthematous illness. Axial fluid-attenuated inversion recovery (FLAIR) magnetic resonance images show brain atrophy and white matter lesions in the frontal (bilateral), parietal, and temporal lobes. (Courtesy of E.N. Faerber, J.J. Melvin, and S.S. Long, St. Christopher's Hospital for Children, Philadelphia, PA.)

Therapy with corticosteroids, plasmapheresis, ribavirin, inosiplex, and immunomodulating therapy (e.g., intrathecal interferon α and β) have been used, but the responses have been poor.[107–109]

Measles in Immunocompromised Hosts

Primary viral pneumonia (i.e., giant cell pneumonia) and encephalitis are common in malnourished or immunosuppressed children with deficient cellular immunity (e.g., congenital immunodeficiency, receipt of chemotherapy for cancer, HIV infection).[23,110–115] Clinical diagnosis can be challenging because the typical rash may be absent.[110] MV can be isolated persistently from blood and the nasopharynx for up to 1 month after rash onset. The antibody response can be limited.

Death usually results from progressive pneumonia. In one study, the case-fatality rate for immunosuppressed patients with measles was 70% for cancer and 30% for HIV-infected patients. HIV-infected patients who had received measles vaccine had lower mortality rates than unvaccinated patients.[112]

Subacute measles inclusion body encephalitis in an immunocompromised host (typically with lymphoblastic leukemia) develops within 1 year after acute infection or vaccination.[95,97] Symptoms include seizures, altered level of consciousness, hemiparesis, hemiplegia, ataxia, aphasia, slurred speech, and visual effects. Fever usually is absent, and CSF findings typically are normal, although mild pleocytosis and elevated protein levels may be seen.[114] The EEG pattern shows nonspecific abnormalities, and neuroimaging is normal at presentation. Detection of MV RNA by brain biopsy is the only reliable method of diagnosing subacute measles encephalitis.[95]

The mortality rate is high, especially for those with T-lymphocyte deficiencies.[95] Anecdotal benefit with ribavirin therapy has been reported.[115]

Measles in pregnancy can be a serious disease, with the potential for complications, especially pneumonia resulting in fatal outcomes.[116] Data on the effect of measles on the outcome of pregnancy are limited, and reports of congenital measles are sporadic. Infants born to mothers who acquire measles late in pregnancy can develop a measles exanthem within the first 10 days of life. No distinct congenital measles syndrome has been described, but the severity of the systemic illness in pregnant women with measles infection can cause spontaneous abortion, premature labor, and low birth weight babies.[116,117]

Prevention

Active Immunization

Active immunization with measles-containing vaccine is the best method of preventing measles.[63,118] The isolation of MV in tissue culture by John Enders led to the development of the first live, attenuated measles vaccine, which was licensed in 1963 in the United States.[119] The more attenuated Moraten strain of live, attenuated measles is the exclusive measles vaccine currently licensed for use in the United States. The vaccine is prepared in chick embryo cell culture and produces a mild, noncommunicable infection. Measles vaccine is available in the United States only in combination form as MMR and measles-mumps-rubella-varicella (MMRV) vaccines.

Interference by transplacentally transferred passive antibodies against measles is the most important obstacle to early infant measles immunization. The optimal age of first immunization can vary from 6 to 15 months, depending on the country of residence and risk of acquiring measles.[1,61] In the United States, measles vaccines were given at 9 months of age until 1965, at 12 months between 1965 and 1976, at 15 months between 1977 and 1994, and at 12 through 15 months thereafter.[120] The increasing age at vaccination was based on low seroconversion rates in infants vaccinated when younger than 12 months of age. Increasing vaccine failure rates of up to 95% with decreasing age at vaccination below 12 months of age have been observed, and several studies have confirmed a correlation between vaccine failure with young age and high maternal measles antibody titer.[121,122] Measles vaccine efficacy rates of 95% are reported in populations that received vaccine when older than 12 months of age.[123]

Vaccine-induced immunity, now the case in most US women of reproductive age, is associated with low measles-specific antibody titers and lower titers and shorter duration of passive antibodies in offspring.[124–126] Most infants lose maternal antibody by 9 to 12 months of age.[124] An earlier loss of maternal antibodies against measles can result in increased susceptibility of infants younger than 12 months of age to infection.[31] Measles-specific T-lymphocyte immunity is induced after early measles vaccination despite the presence of antibody, and it may prime a balanced humoral and cellular response.[127] T-lymphocyte immunity can persist after early vaccination.[128] All infants older than 6 months of age who travel outside of the contiguous United States should be given MMR, which is repeated as a first valid dose at 12 to 15 months of age.[13]

Measles antibodies develop in about 85% of children vaccinated at age 9 months, 95% of those vaccinated at 12 months, and 98% of those vaccinated at 15 months.[1] The ACIP and the American Academy of Pediatrics (AAP) recommend the first dose of measles vaccination at 12 through 15 months of age and a second dose at 4 through 6 years of age before school entry.[13,63] The second dose is intended to provide immunity to children who have primary vaccine failure (≤5%) after the first dose.[42] The currently available measles vaccine is highly effective, with one dose. It is about 95% protective in children receiving the vaccine at 12 months of age or earlier; two doses provide more than 99% protection when administered at least 4 weeks apart.[63,118] All school children who have not received the 2-dose MMR vaccine must receive catch-up vaccination, including at the 11- to 12-year-old visit and beyond.[13]

Vaccine-induced immunity can last several decades or longer in healthy people.[129] Secondary vaccine failure is infrequent (~5%) at 10 to 15 years after vaccination, but it is likely lower when the age of first vaccination is 12 months or older.[130] Although antibody concentrations can wane, protective immunity may still be retained. A secondary immune response, typically not associated with symptoms, often occurs after re-exposure to MV, with a marked increase in antibody concentrations.[1]

Infants between the ages of 6 and 11 months should receive 1 dose of MMR vaccine during community-wide outbreaks or before travel to countries where measles is endemic or in epidemic situations; however, 2 subsequent valid doses should be given at 12 months of age or later.[13] Children 12 months of age or older should receive 2 doses of MMR vaccine before international travel that are separated by at least 28 days.[63]

Use of MMRV vaccine is recommended for children between the ages of 12 months and 12 years.[131] In two postlicensure studies, one additional febrile seizure per 2300 to 2600 children between the ages of 12 and 23 months was observed in those who had received MMRV compared with those who received MMR vaccine and V vaccine administered as separate injections at the same visit.[132,133] There was no increased risk of febrile seizures associated with the second dose of MMRV at 4 to 6 years of age.

Based on these data, the ACIP and AAP recommend the administration of MMR and V vaccine as two injections at a single visit at 12 to 47 months of age, unless the parent or caregiver expresses a preference for the MMRV vaccine. Use of the MMRV vaccine usually is preferred over separate injections for the second dose of measles, mumps, rubella, and varicella vaccines at any age (i.e., 15 months to 12 years) and for the first dose at 48 months of age or later.[131]

MMR vaccine is not recommended for pregnant women.[13] Measles vaccine is contraindicated in immunosuppressed children, except for asymptomatic HIV-infected children, who are at risk of severe or fatal disease after measles. HIV-infected children without severe immunodeficiency and their susceptible household contacts who themselves are not severely immunocompromised should receive the MMR vaccine, although primary vaccine failure is common in HIV-infected children.[110,134]

The available measles vaccines are safe in immunocompetent people. Adverse reactions to the MMR vaccine may include fever (<15%) and transient rash (5%) in recipients. Febrile reactions usually occur 7 to 12 days after vaccination and persist for 1 to 2 days.[63] Encephalitis after MMR vaccination is rare (<1 case/1 million doses). Allergic reactions related to allergies to egg or egg products or to neomycin are uncommon. Patients with a history of nonanaphylactic egg allergies or contact dermatitis from neomycin may receive measles vaccine. Those with a hypersensitivity reaction after the first dose should be tested for measles immunity, and if found to be nonimmune, they may require skin testing and desensitization before receiving the second dose of measles vaccine.[13] Vaccination is contraindicated for people with a history of immediate anaphylactic reactions to previous vaccine dose.[13] Hypothesized associations between measles vaccination and the development of Crohn disease, other inflammatory bowel diseases, and autism have not been supported by several rigorous studies.[135–137]

In countries with a high measles incidence, the WHO recommends routine measles vaccination at 9 months of age.[1] The second vaccine dose usually is administered in primary healthcare systems or during mass immunization campaigns. Efforts are ongoing to develop an ideal measles vaccine, which would be inexpensive, safe, immunogenic in young infants, heat stable, and be given as a single dose by needle-free administration.[1] Innovative approaches such as aerosolized measles vaccine measles could contribute to elimination efforts worldwide.[138,139] However, in a randomized, controlled trial published in 2015, the aerosolized measles vaccine was inferior to the subcutaneous vaccine, resulting in lower rates of seropositivity.[140] The WHO strategy for global elimination of measles is focused on achieving and maintaining high coverage with the 2-dose MMR vaccine coupled with effective laboratory-based surveillance.[141]

Passive Protection

Human immune globulin (IG) given intramuscularly (IGIM) or intravenously (IGIV) within 6 days of exposure can be used to prevent or modify measles in people without evidence of immunity.[13,63] IGIV at a dose of 400 mg/kg is recommended for people at high risk for severe, complicated measles, such as pregnant women without evidence of immunity and severely immunocompromised children, regardless of immunization or immunologic status.[13] IGIM at a dose of 0.5 mL/kg (maximum, 15 mL) should be given to all infants younger than 12 months of age who have been exposed to measles. Children with HIV/AIDS with severe immunosuppression or symptomatic disease or HIV-exposed infants with unknown infection status should receive IG prophylaxis after exposure to measles regardless of their measles immunization status.

To ensure immunogenicity, measles vaccine must be deferred after IG administration. The period of deferment depends on the dose and type of IG therapy.[13] Measles vaccination should be postponed for 3 to 6 months after the administration of IGIM for prophylaxis against tetanus, hepatitis A and B, rabies, measles, and varicella. When IGIV is used as replacement therapy or for the treatment of idiopathic thrombocytopenic purpura or Kawasaki disease, vaccination should be deferred for 8 to 11 months, and when blood or blood products are given, vaccination should be deferred for 3 to 7 months. No delay in vaccination is necessary after the administration of washed red blood cells. Children who receive monthly IGIV do not routinely require additional IG postexposure prophylaxis if the IGIV was given within 3 weeks.[13]

Public Health Measures and Outbreak Control

Healthcare personnel must immediately report suspected measles cases to their local health departments. Measles is a notifiable disease that requires reporting to the CDC within 24 hours. Control measures include initiation of outbreak investigation, patient follow-up, prioritization of contacts, voluntary isolation and quarantine, postexposure vaccination, and early MMR vaccine for infants between the ages of 6 and 11 months.[63,71,142]

Measles vaccine may provide protection against measles if given within 72 hours of exposure.[13,63] In institution-associated measles outbreaks (e.g., childcare centers, primary and secondary schools, colleges), all students and their siblings should be vaccinated unless they have documentation of immunity (i.e., receipt of ≥1 vaccine doses at or after age 12 months for preschool-aged children and 2 doses of measles vaccine for school-aged children, laboratory evidence of immunity, laboratory confirmation of disease, or born before 1957).[63] School personnel born in 1957 or later who have not had documented measles or 2-dose measles-containing vaccine also should be vaccinated.

For measles outbreaks in preschool-aged populations, vaccination efforts should focus on those who are not up to date with their measles vaccinations and on infants between 6 and 12 months of age who are not yet immunized.[13] Infants younger than 12 months who are vaccinated during an outbreak must be revaccinated at 12 to 15 months of age and again before school entry.

Healthcare personnel without documented immunization status or laboratory evidence of measles immunity must be vaccinated to prevent nosocomial transmission of measles. Exposed personnel should be relieved of direct patient contact for days 5 to 21 after exposure, regardless of their receipt of postexposure vaccine or IG.[13,13–145]

Isolation Procedures

Isolation of household or school contacts alone is not effective in preventing transmission because excretion of virus occurs before the onset of symptoms. Immunocompetent patients with measles should be isolated and placed on airborne transmission precautions until 5 days after the onset of rash. Immunocompromised people should be isolated for the duration of their illness.[146] Hospitalized patients exposed to measles should be isolated with airborne precautions for days 5 to 21 after exposure.[146]

Key Points

Epidemiology, Clinical Features, Diagnosis, and Prevention of Measles

Epidemiology

- Acute, vaccine-preventable viral disease of childhood; affects only humans

- Droplet and airborne transmission; highly contagious
- Natural infection results in lifelong immunity.
- Vaccination has resulted in dramatic declines in global incidence and mortality rates.
- Eliminated from the Americas; still endemic in many countries
- Importations into the United States continue to occur, resulting in cases and outbreaks, primarily involving unvaccinated people.
- Outbreak investigation carries a substantial economic burden.
- Eradication is biologically, programmatically, and operationally feasible.

Clinical Features

- All infections are symptomatic
- Incubation period of 8–12 days; patient contagious 4 days before until 4 days after rash onset
- Disease characterized most frequently by
  - Classic triad: cough, coryza, conjunctivitis with fever
  - Erythematous maculopapular rash that spreads in a cephalocaudal direction
  - Evanescent enanthem (i.e., Koplik spots) that appears on the lower buccal mucosa adjacent to the molars
- Complications include otitis media, pneumonia, and diarrhea; encephalitis occurs in 1 of 1000 cases; rare deaths from

pneumonia and neurologic complications.

- Rash can be absent in immunocompromised hosts.
- Case-fatality highest among infants

Diagnosis

- Serology (i.e., measles-specific immunoglobulin M) and virus RNA detection by reverse transcriptase polymerase chain reaction (RT-PCR) on clinical samples

Treatment

- Vitamin A treatment reduces risk of death for deficient children.
- No antiviral drugs are available.
- Antibiotic treatment for secondary bacterial complications (e.g., otitis media, pneumonia)

Prevention

- Measles vaccination remains a highly cost-effective public health intervention.
- Standard immunization at 12–15 months of age with a second dose at 4–6 years of age
- Measles-containing vaccines are safe and highly effective for immunocompetent children.
- High levels of population immunity through immunization are crucial for disease control and elimination.
- Human immune globulin is given to high-risk, exposed, susceptible contacts (e.g., infants <12 months of age, pregnant women, severely immunocompromised children).

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RNA Viruses: Rhabdoviridae

OUTLINE

228 Rabies Virus

228

Rabies Virus

Rodney E. Willoughby Jr.

The Virus

Rabies virus and 14 similar viruses, including Australian, European, Lagos, Mokola, Duvenhage, Bokeloh, Ikoma, and Lleida bat lyssaviruses, are members of the Rhabdoviridae family, genus *Lyssavirus,* which is derived from the Greek word *lyssa,* meaning "madness." *Rabies* derives from the Sanskrit word *rabhas,* which means "to do violence."[1] Rabies virus and many lyssaviruses cause human encephalitis through zoonotic infection.[2]

The lyssaviruses differ antigenically but are morphologically similar and neurotropic.[3] Rabies virus is an enveloped, bullet-shaped virus that is 180 nm long and 75 nm wide and composed of five structural proteins (Fig. 228.1). Rabies virus contains one copy of a single-stranded, nonsegmented, negative (noncoding) RNA of approximately 12,000 nucleotides. The virus envelope contains glycosylated G-protein spikes that bind to cells. The matrix (M) protein is located on the inner virus envelope, inside which the virus nucleoprotein (N) tightly binds the viral RNA to form the nucleocapsid core. This core, along with a large transcriptase protein (L) and a phosphorylated protein (P), is the rabies virus nucleocapsid (RNP).

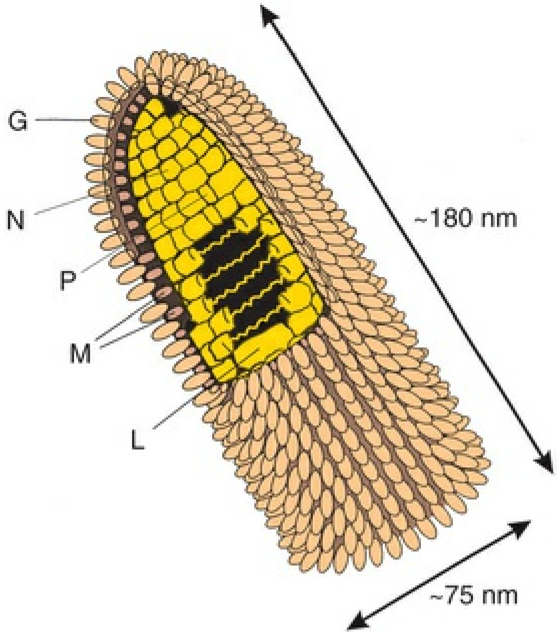

FIGURE 228.1 Hypothetical model of the rabies virion. The surface is covered by G glycoproteins (G) embedded in lipid membrane derived from the host cell. Matrix proteins (M) associate with the lipid membrane. Within this envelope is a ribonucleoprotein core composed of RNA closely associated with protective nucleoprotein (N), virion transcriptase (L), and phosphoprotein (P).

Pathogenesis

The incubation period after rabies virus inoculation begins with ill-defined local replication in muscle or skin for canine or bat rabies variants, respectively. This step in pathogenesis is the basis of the rationale for recommendations of local wound care and instillation of neutralizing antibody to reduce the rabies infectious inoculum. Neutralizing antibodies actually can penetrate the infected cells.[4] Response to the rabies vaccine then generates further neutralizing antibody.

After local tissue replication over weeks to months, the virus attaches to nicotinic acetylcholine receptors that provide access to the peripheral nervous system through neuromuscular spindles or muscle motor end plates. Sensory and autonomic nerves also are infected.[2] Other host receptors for rabies virus include specific carbohydrates, the neuronal cell adhesion molecule (NCAM), and the p75 neurotrophin receptor (p75NTR).[5]

Rabies virus moves centripetally along peripheral nerves, without virus replication, at rates of 100 mm/day or higher. After it is in the spinal cord, virus spreads rapidly to the brain, tracing neurons in retrograde fashion across synapses at a rate of one synapse per day. Centrifugal spread then occurs along motor, sensory, and autonomic axons into host body tissues (usually restricted to nerves innervating organs, including hair follicles) and particularly into the salivary and lacrimal glands.[6,7] Pathologic features are minimal. *Negri bodies* are rabies specific eosinophilic inclusions of RNPs and chaperonins in the cytoplasm of neurons that vary by brain region and may not be found in 30% of cases.[8] Histology shows perivenular lymphocytosis. Inflammation of the dorsal root ganglia correlates with focal neurologic prodromes.[9] In the less common paralytic form of rabies, axonal loss mimics acute motor axonal neuropathy and other polio-like diseases.[10] Minimal histologic damage is in stark contrast to the severity of clinical rabies. Rabies viremia and viruria are not mechanisms of virus spread.

Virulence and Immunity

Host factors that reduce the incubation period are (1) young age; (2) immunocompromised state, including corticosteroid use; (3) greater severity of the wound; (4) closeness of the wound to the central nervous system; and (5) large inoculum. Neuroinvasiveness is determined by the virus G protein. In animal models, a single-point mutation at position 333 of the G protein renders strains avirulent as a result of alteration in the ability of the virus to spread from cell to cell.[11] Overexpression of the G glycoprotein induces neuronal apoptosis and generates effective immunity.[12–14]

The G protein and the RNP are the major targets of the protective host response. The G glycoprotein is the major target of virus-neutralizing antibody and of cellular immunity.[15] Antigenicity of the G protein of rabies virus is broad enough to induce protective immunity to all rabies virus strains, but it may not protect against other lyssaviruses.[1]

Epidemiology

Rabies primarily is an animal infection. Humans become infected through exposure to infected animals. Worldwide data on the human burden of rabies are incomplete because of the hopelessness, stigma, and extreme poverty associated with populations at greatest risk for rabies. It is estimated that 50,000 to 60,000 people die annually of rabies. Most cases of rabies occur in males and children.[16]

The control of rabies requires knowledge of the endemic animal source of rabies and the geography of infection and an understanding of virus transmission in nature.[16,17] Any warm-blooded animal can become infected, but some animal species are more susceptible, and some rabies strains are more infectious than others.[18,19] Shedding of virus in saliva and the rapidity of death vary among animal species. Skunks shed virus for up to 18 days before death, whereas foxes succumb rapidly.

The dog remains the principal vector for transmission of rabies virus to humans in most parts of the world outside of North America and Europe. Cats usually are second in importance in these areas. In the Americas, with the waning of dog rabies and a broadening of the habitat of vampire bats, most rabies is transmitted by bats.[20] The source of rabies has shifted from domestic animals to wildlife (Fig. 228.2) in North America, where six separate rabies enzootics exist. Outside of North America, wildlife rabies enzootics involve other animals (Table 228.1). Other bat lyssaviruses have been isolated in Europe, Africa, and Australia and can cause sporadic human encephalitis with fatal outcomes.[21] Genetic sequencing and typing by monoclonal antibody panels can distinguish rabies enzootics and whether humans are infected with local or imported rabies virus strains.[22]

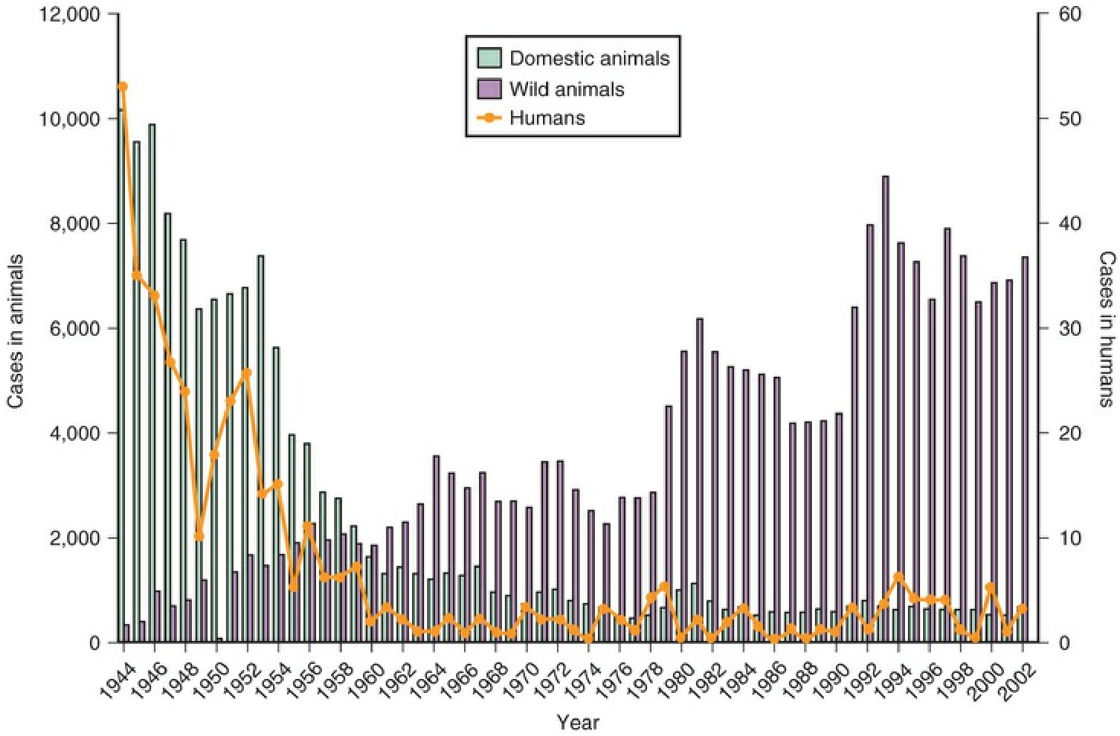

FIGURE 228.2 Temporal trends in animal and human rabies in the United States. (Modified from Rupprecht CE, Gibbons RV. Clinical practice: prophylaxis against rabies. N Engl J Med 2004;351:2626–2635.)

TABLE 228.1

Endemic Rabies in Wildlife

Geographic Region	Principal Species With Endemic Rabies[a]
United States and Canada	
Central United States and Canada	Striped skunk
Mid-Atlantic, southeast United States	Raccoon
New York, Quebec, Ontario	Red fox
Northwest territories	Arctic fox
Arizona	Grey fox
Texas	Grey fox
Caribbean	Mongoose
Europe	Red fox
Iran	Wolf
Africa	Jackal

[a] The bat is always considered endemically rabid. The dog is the principal vector for transmission of rabies around the world, except for North America and Europe.

The vehicle of virus transmission is infected animal saliva, which can be inoculated by a bite or scratch. Contact of infected animal saliva with human mucous membranes also can transmit infection.[23] Nine of 13 human cases of rabies reported in the United

States between 1980 and 1990 resulted from exposure to animals outside of the country.[22] In contrast, a history of animal exposure was absent in 78% of nontravelers and determined by molecular techniques to have been acquired from bats.[24] It is assumed that certain insectivorous bats inflict unperceived bites on sleeping persons.[23] In addition to animal transmission of rabies virus, there have been 4 outbreaks of solid-organ transplantation-associated rabies and 10 corneal implants transmitting rabies.[25,26]

Clinical Manifestations

Natural survivors of rabies are being increasingly reported, albeit with poor outcomes.[27,28] There also are reports of persons meeting laboratory definitions of rabies with milder disease[29–31] Serologic surveys document asymptomatic exposure in high-risk populations[32] The concept that rabies virus infection can cause a continuum of illness severity is being investigated.[33]

Clinical stages of human rabies correspond to steps in pathophysiology. The asymptomatic first phase is the virus incubation period, which usually lasts from 10 to 90 days but ranges from 4 days to 8 years.[34] The long incubation period lowers the yield of obtaining a history of an antecedent animal exposure. Retaking the history, focused on travel, immigration, occupations, and animal exposures, is critical.

The second, or prodromal, period lasts for 2 to 10 days and follows virus invasion into the central nervous system. Early symptoms, which occur in up to one half of patients, are nonspecific and include fever, dysphagia, and changes in behavior, sleep, and emotions. Local pruritus, pain, paresthesia, weakness, or myoclonic jerks occur at the site of inoculation in approximately 50% of cases and are most helpful in focusing the diagnosis on rabies. This stage correlates with virus infection of the dorsal root ganglia, spinal cord, brainstem, and limbic system.

The third stage is the development of central nervous system signs of disease. The *furious form* of rabies comprises aggressiveness (e.g., biting, hitting, yelling), excitement, hyperactivity, and hallucinations that last for brief periods and alternate with normal behavior, progressing to confusion or delirium. Fever can be intermittent but is invariably present. More than 50% of patients experience hydrophobia (with attempts to drink liquids) or aerophobia (when air is blown on the face). These reactions result from violent diaphragmatic contractions as an exaggerated respiratory protective reflex, and they are sufficient to cause pneumothorax. Hypersalivation and dysphagia increase the risk of aspiration. Status epilepticus, marked dystonia, parkinsonian signs, or opisthotonus are uncommon and should suggest other diagnoses. Clinical presentation at this stage can mimic that of intoxication, envenomation, meningitis, encephalitis, cerebral malaria, myoclonic epilepsy, tetanus, polio, or Guillain-Barré syndrome.

The *paralytic form* of rabies occurs in approximately 20% of patients and is slower to evolve. Flaccid paralysis progresses to quadriparesis, bulbar abnormalities, and respiratory insufficiency. Hypersalivation and hydrophobic spasms can occur. Guillain-Barré syndrome often is considered, but findings of fever, pain, sensory or sphincter disturbance, and more prominent involvement of proximal musculature are more suggestive of rabies.[9] In developing countries, where tissue-derived rabies vaccines are produced, vaccine-associated autoimmune encephalitis is a consideration. Other diagnostic possibilities include hysteria, botulism, and elapid snake bite.

Early deaths can result from respiratory arrest or cardiac dysrhythmias, including asystole. Recognized early, these events can respond to sedation.[35]

The fourth stage of rabies is coma, usually developing 6 to 8 days after hospitalization. Coma correlates with generalized spasm of the basilar arteries measured by transcranial Doppler ultrasonography and metabolic changes in cerebrospinal fluid (CSF) measured by nuclear magnetic resonance spectroscopy.[36,37] Examination results consistent with brainstem death are distinctively discordant with electroencephalographic (EEG) or magnetic resonance imaging (MRI) findings.[38–40]

The immune response to rabies usually is detected within 14 days after hospitalization. Complications associated with the immune response include complete heart block in dog rabies and cerebral edema in bat rabies. After 12 to 15 days, intracranial pressure and EEG activity drop acutely, and diabetes insipidus follows. Death usually occurs within 7 days of symptom onset in furious rabies and 21 days in paralytic rabies; critical care can prolong survival to a median of 18 days after hospitalization.

Laboratory Diagnosis

Rabies often is misdiagnosed clinically. CSF findings are typical of mild viral meningoencephalitis. CSF is normal in approximately one third of cases during the first week of illness. Electroencephalography, computed tomography, and MRI of the brain also can be normal.[41]

Specific laboratory tests that are not widely available are required for diagnosis. Aside from studies performed on brain tissue, virus-specific studies require tissue from sites reflecting the centrifugal movement of the virus. Detection of rabies virus antigen by immunofluorescence testing or culture of specimens obtained by skin-punch biopsies of the hair follicles at the nape of the neck has 50% to 94% sensitivity and almost 100% specificity. Reverse transcriptase polymerase chain reaction (RT-PCR) testing for rabies nucleic acid performed on the patient's saliva or skin has similarly high sensitivity and specificity.[42–44] Virus occasionally can be isolated from CSF, or its genome can be amplified from CSF or urine samples. Fluorescent immunohistology is a more sensitive method than histologic examination of brain tissue for Negri bodies and virus culture of brain tissue. Consideration should be given for brain biopsy at the time of placement of intracranial pressure-monitoring devices in patients with idiopathic encephalitis.

Rabies-specific antibodies in serum or CSF can be measured by indirect fluorescence assay (IFA) or enzyme immunoassay, and neutralizing antibody can be measured by the rapid fluorescent focus inhibition test (RFFIT) or fluorescent antibody virus neutralization (FAVN). Antibodies can be detected in serum as early as 6 days (and in CSF within 13 days) after the onset of symptoms.[24] Only clinical rabies, not rabies immunization, produces detectable rabies antibodies in the CSF.[24]

Treatment

Patients are intermittently alert until coma supervenes. Care should emphasize minimization of environmental stimuli that precipitate spasms, meticulous respiratory care, and control of pain and anxiety. Since the 1970s, intensive medical care has produced a few survivors. Two case series report an upper limit of 5% survival.[45,46] Recent case reports suggest a continuum of disease, which argues for greater survival benefit with intensive care.[29–32,47]

Limited animal experiments and human case reports suggest that inflammation is accentuated, paralytic disease precipitated, or death accelerated when persons with rabies receive rabies vaccine or rabies-specific immune globulin.[48–50] Use of broad-spectrum antiviral agents (e.g., vidarabine, ribavirin, interferon α) is unsuccessful and associated with massive brain necrosis.[51,52] A teenage girl survived rabies without prior receipt of postexposure prophylaxis (PEP). Her therapy included deep sedation to minimize dysautonomia. Administration of rabies vaccine and immune globulin were avoided.[53] Seven more survivors have been registered. An updated protocol and case registry of similarly treated patients are available at www.mcw.edu/rabies.

Prevention

Available Vaccines

Schedules and indications for administration of rabies vaccine and human-derived rabies immune globulin (HRIG) are shown in Tables 228.2 and 228.3. Three rabies vaccines are licensed in the United States: human diploid cell vaccine (HDCV), primary chick embryo cell vaccine (PCECV), and rhesus lung cell vaccine, absorbed (RVA), although RVA is no longer being produced. Outside of the United States, additional vaccines include purified Vero cell vaccine (PVRV) and purified duck embryo vaccine (PDEV). All of these vaccines can be used interchangeably, although it is preferable to use the same vaccine for the entire course of immunizations. In the United States, intramuscular administration is recommended.[54] In other countries, many of the cell culture vaccines are administered intradermally to reduce the dose volume to expense ratio.[55] Nerve tissue vaccines and suckling mouse brain vaccines are in declining use and should never be used if there is access to cell-culture–derived vaccines.[56]

TABLE 228.2

Rabies Immunization Schedules, United States[a]

Immunization Schedules	Dose	Route of Administration	Days
PRE-EXPOSURE PROPHYLAXIS			
Vaccine	1 mL	IM	0, 7, and 21–28
POSTEXPOSURE PROPHYLAXIS			
Vaccine	1 mL	IM	No previous immunization: 0, 3, 7, 14 Previously immunized: 0, 3
Human rabies immune globulin (HRIG)	20 IU/kg	Infiltrated at site of exposure	Immediately (if not immunized previously)

[a] International rabies immunization schedules conforming to World Health Organization recommendations are available at World Health Organization. WHO Guide for Rabies Pre and Post Exposure Prophylaxis in Humans. Updated 2013. http://www.who.int/rabies/PEP_Prophylaxis_guideline_15_11_2013.pdf.

TABLE 228.3

Schedule of Postexposure Prophylaxis for Rabies in the United States, 2015

Vaccination Status, Treatment	Regimen[a]
NOT PREVIOUSLY VACCINATED	
Wound cleansing	All postexposure treatment should begin with immediate, thorough cleansing of all wounds with soap and water. If available, a virucidal agent such as a povidone-iodine solution should be used to irrigate the wounds
Human RIG	Administer at a dose of 20 IU/kg of body weight. If anatomically feasible, a *full dose* should be infiltrated around the wounds; any remaining volume should be administered IM at an anatomic site distant from vaccine administration. RIG should not be administered in the same syringe as the vaccine. Because human RIG can partially suppress the active production of antibody, no more than the recommended dose should be given
Vaccine (HDCV or PCECV)	One 1-mL dose IM (deltoid area) on days 0, 3, 7, 14[b]
PREVIOUSLY VACCINATED[c]	
Wound cleansing	All postexposure treatment should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent such as a povidone-iodine solution should be used to irrigate the wounds
Human RIG	Should *not* be administered
Vaccine (HDCV or PCECV)	One 1-mL dose IM (deltoid area[d]) on days 0, 3[b]

[a] These regimens are applicable for all age groups, including children.

[b] Day 0 is the day on which the first dose of vaccine is administered.

[c] Any person with a history of pre-exposure vaccination with HDCV, RVA, or PCECV;

prior postexposure prophylaxis with HDCV, RVA, or PCECV; or previous vaccination with any other type of rabies vaccine and a documented history of antibody response to the prior vaccination.

[d] Deltoid area is the only acceptable site of vaccination for adults and older children. For younger children, the outer aspect of the thigh can be used. Vaccine should never be administered in the gluteal area.

HDCV, human diploid cell culture vaccine; IM, intramuscularly; PCECV, purified chick embryo cell culture vaccine; RIG, rabies immune globulin.

From Rupprecht CE, Briggs D, Brown CM, et al. Use of a reduced (4-dose) vaccine schedule for postexposure prophylaxis to prevent human rabies recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 2009;59(RR-2):1–9.

Pre-exposure Prophylaxis

Pre-exposure prophylaxis with vaccine should be offered to people in veterinary medicine, wildlife management, and rabies laboratory work; spelunkers; and selected people who travel to areas where canine rabies is endemic. There is increasing interest in rabies vaccine as part of routine childhood immunizations in rabies endemic countries.[57]

It is not necessary to measure the antibody response, except in immunosuppressed patients or if risk is ongoing.[54] Aside from local and systemic reactions, which are usually mild, side effects include immune complex–mediated reactions (e.g., hives, angioedema, arthritis), most often after booster doses. Cell culture–derived, vaccine-associated neurologic diseases are unproven.[58] Pregnancy is not a contraindication to rabies vaccine.[58] Chloroquine interferes with antibody production after HDCV administration.[23]

Postexposure Prophylaxis

Postexposure management of a patient wounded by an animal begins with aggressive care of animal-induced wounds, including tetanus prophylaxis. Complete and thorough washing and repeated flushing (especially of larger wounds) is accomplished with soap, detergent, or disinfectant and water or water alone/ Suturing and occlusive dressings are avoided. Definitive wound repair is best accomplished as a second, elective procedure after the risk of bacterial superinfection is past. Failure of PEP often is ascribed to wound closure or lack of administration of rabies immune globulin.

After disinfection, judgment regarding whether a rabies exposure has been likely must be made. Close communication with the local public health department is warranted to obtain information about the prevalence of infected animal species and to ensure proper examination of animals. Two thirds of PEP courses can be avoided by submission of the suspect animal for examination of the brain[58] Prophylaxis usually is not required for contact with a vaccinated animal or when contact with a rabid animal has not violated the individual's skin barrier or involved a mucous membrane. Because few cases of human rabies have occurred from small rodent bites, vaccination is not recommended after these exposures.[23] In developed countries, bites from dogs and cats that remain healthy after 10 days of observation do not warrant prophylaxis. However, in developing countries where the risk of animal rabies is higher, vaccination should be given immediately and should be discontinued only if the observed animal remains healthy.

Immediate administration of rabies immune globulin and commencement of immunization are required for persons who are bitten by wild carnivores and bats and by dogs or cats known or suspected to be rabid. Because bats have infected people in the absence of a recognized bite, rabies prophylaxis is recommended for persons who were asleep or unattended in a room with a bat and others for whom it is impossible to exclude direct contact with a bat.

Passive immunization should be administered as early as possible to exposed people not previously immunized. Human rabies immune globulin (HRIG) should be given at a dose of 20 IU/kg, with the entire dose infiltrated into the wound if feasible. The volume can be diluted if insufficient to infiltrate the entire wound. Unused immune globulin can be injected intramuscularly into the gluteal or anterolateral thigh muscle with a different syringe and injection site from those used for the vaccine. HRIG is safe and free from serious side effects. It should be given at the time of the first vaccine dose, but HRIG is not beneficial if given later than 7 days after the first vaccination. Equine rabies immune globulin in a dose of 40 IU/kg often is used outside of North America. Because the product is purified, it is well tolerated and equally as effective as HRIG.

Postexposure immunization for previously unimmunized people requires 4 doses given into the deltoid muscle (never in the gluteal region) over 14 days.[54] It is not necessary to measure the antibody response, except in immunosuppressed patients. Children produce an immune response equivalent to that of adults. The immunization series can be stopped if the brain of the suspected rabid animal tests negative for rabies virus on direct fluorescent antibody testing or if the domestic dog or cat remains healthy during 10 days of observation[58] Regimens for immunization are summarized in Table 228.3.

Theoretically, human-to-human transmission can occur, but transmission to healthcare personnel has not been documented.[59,60] The patient should be placed in an isolation room, and gowns, gloves, masks, and goggles should be worn by anyone who has direct contact with the patient. Healthcare personnel who experience mucous membrane or parenteral exposure to potentially infected tissues or saliva should be considered for PEP. When rabies is not considered antemortem, an average of 80 to 150 healthcare personnel receive prophylaxis.[61] There are no data to support chemoprophylaxis with oral ribavirin or amantadine.

Ultimately, improved rabies prevention depends on immunization of domestic animals and wildlife vectors of rabies. Wildlife exposures are increasing (see Fig. 228.2).[58] Rabies is increasing internationally where deforestation displaces bat colonies, affluence increases pet ownership, or there is an increase in feral dog packs. Wildlife can be efficiently immunized against rabies by the oral route through the use of baits containing live, attenuated strains or recombinant poxviruses that produce G glycoprotein.[62] There is a need for less expensive rabies vaccine and immune globulin, especially in countries with a high incidence of human rabies.[56] It reflects poorly on all nations when rabies has been vaccine preventable for more than 130 years but is economically inaccessible to more than 50,000 children and adults annually worldwide.

Key Points

Characteristics of Rabies Virus and Infection

Virology

- Single negative-stranded RNA viruses of the family Lyssaviridae

- Marked tropism for the nervous system

Epidemiology

- Emerging, major zoonosis causing encephalitis, with 55,000 deaths annually in Africa and Asia
- Dogs are the major vectors worldwide, with bats predominant in the Americas. Wild animal reservoirs vary geographically.
- Predilection for children and males
- Prolonged and variable incubation period

Clinical

- Major furious form is characterized by febrile encephalitis with focal myoclonus and paresthesias with characteristic hydrophobia and aerophobia (when present); intermittent consciousness until late in the disease.
- Minor paralytic form is often confused with Guillain-Barré syndrome, but rabies shows sphincter disturbances and more sensory phenomena.
- Prominent vascular and metabolic dysfunction contribute to rabies encephalitis.
- Milder forms of rabies disease can occur.

Diagnosis

- Requires sending skin biopsy, saliva, serum, and CSF specimens to a World Health Organization rabies reference laboratory

Treatment

- Conventional therapy is palliative.
- Milwaukee protocol (www.mcw.edu/rabies) consists of sedation to minimize dysautonomia, metabolic support, and critical care.

- Immunization and human rabies immune globulin (HRIG) are avoided after the patient becomes symptomatic.

Prevention

- Pre-exposure prophylaxis (3 doses over 21–28 days) is indicated for travel to rabies-endemic areas and for high-risk occupations. Boosters (2 doses) are then required after an exposure.

- Postexposure prophylaxis consists of aggressive washing of wound and 4 doses of vaccine over 14 days plus HRIG. Immunocompromised patients receive 5 doses and require serologic confirmation.

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RNA Viruses: Orthomyxoviridae

OUTLINE

229 Influenza Viruses

229

Influenza Viruses

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Influenza viruses cause annual winter epidemics of respiratory illness in temperate climates and have resulted in four influenza pandemics since 1900. The global burden of influenza and global variation in influenza virus circulation patterns are increasingly recognized.[1–3] In the United States, influenza is estimated to result in 3000 to 49,000 deaths and 55,000 to 431,000 hospitalizations annually.[4–6]

Among children, influenza virus infections are common, and influenza-associated hospitalization rates are highest for those younger than 2 years of age and those with underlying medical conditions.[7–14] Although more than 90% of seasonal influenza-associated deaths occur among persons 65 years of age or older, 40 to more than 200 influenza-associated deaths are estimated to have occurred annually among US children from 1977 through 2007.[4,15] During the 2009 A(H1N1)pdm09 pandemic, children were disproportionately affected and experienced the highest pandemic influenza attack rates and hospitalization rates.[16]

Influenza vaccination is the best method of influenza prevention. Influenza vaccines are currently approved for use in children at least 6 months of age.[17]

Microbiology

Three antigenic types of influenza virus (i.e., A, B, and C) are recognized. Influenza A viruses are further subdivided into multiple subtypes, and influenza B viruses are often divided into two lineages: influenza B/Yamagata and influenza B/Victoria.

Influenza A and B viruses contain eight segments of negative-sense, single-stranded RNA that code for 10 and 11 proteins, respectively.[18] Similar to other RNA viruses, influenza viruses replicate using RNA polymerases in a process that is error prone, leading to frequent mutations that give rise to genetically diverse virus populations or quasispecies.[19] In some instances, these quasispecies possess adaptive mutations and may persist and circulate. Adaptive mutations confer antigenic differences or resistance to influenza antiviral medications or allow transmission from one host species to another.[20]

Influenza viruses are irregular spherical (80 to 120 nm in diameter) or filamentous structures with surfaces that are studded with rod-shaped hemagglutinin (HA) and neuraminidase (NA) spikes (Fig. 229.1).[21] These surface glycoproteins are the major targets of the protective host immune response, and they form the basis for influenza A virus subtyping.[22–24] Influenza C virus lacks NA.[25]

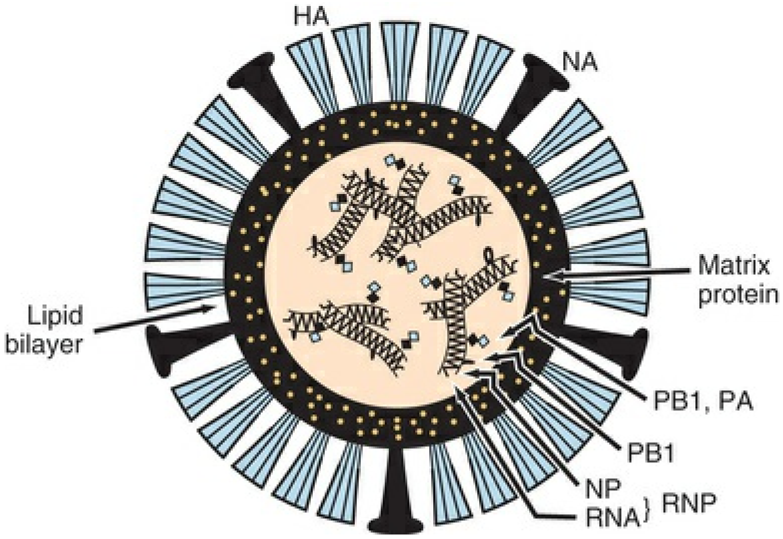

FIGURE 229.1 The influenza virus virion. HA, hemagglutinin; M, matrix protein; NA, neuraminidase; NP, nucleoprotein; PA, polymerase acidic protein; PB1, polymerase basic 1 protein; RNP, ribonucleoprotein. (Modified from Betts RF. Influenza virus. In: Mandell GL, Bennett JE, Dolin R [eds]. Principles and Practice of Infectious Disease, 4th ed. New York, Churchill Livingstone, 1995, p. 1546.)

HA is the attachment protein. It is synthesized as a single polypeptide chain that undergoes proteolytic cleavage to yield HA1 and HA2.[18,26] Cleavage of HA is required for infectivity, and increased cleavability is associated with excess virulence.[27,28] HA is expressed on the surface as a trimer, and it binds to sialic acid, which is the receptor for influenza viruses. Avian and human influenza A viruses preferentially bind to sialic acids with different oligosaccharide side chains.[29,30] NA is synthesized as a single polypeptide chain and is expressed on the surface as a tetramer.[31] This protein destroys sialic acid, the receptor recognized by HA, facilitating the release of progeny virions from the infected cell.

Aquatic birds are the natural hosts of influenza A viruses, and viruses bearing most subtypes of HA and NA have been isolated from birds.[32] Two influenza A subtypes that had not been previously isolated from birds and with evolutionarily distinct genomes were isolated from bat populations in Central America, suggesting that bats may be another reservoir for influenza A viruses.[33,34] Influenza A viruses also have been isolated from pigs, cattle, horses, dogs, cats, seals, whales, penguins, and nonhuman primates. Infections with influenza B viruses have been identified in seals.[35,36] Influenza C viruses infect only humans.

The standard convention for nomenclature of influenza viruses takes into account the variability in influenza surface proteins. Virus designations specify type, host (for strains of animal origin), geographic source, strain number, and year of isolation, followed by the HA and NA subtypes in the case of influenza A viruses (Box 229.1)[37]

Box 229.1

Standard Nomenclature for Influenza Viruses

Type/host species (if not human)/location where isolated/strain number/year of isolation and hemagglutinin and neuraminidase subtype for influenza A viruses

Examples

Influenza A/California/7/2004 (H3N2)

Influenza A/goose/Guangdong/1/96 (H5N1)

Influenza B/Hong Kong/20/2003

From Shinya K, Ebina M, Yamada S, et al. Avian flu: influenza virus receptors in the human airway. Nature 2006;440:435–436.

Antigenic Drift and Antigenic Shift

Genetic mutations that result in changes in viral HA and, to a lesser extent, in NA are responsible for the ability of influenza viruses to cause annual worldwide epidemics. Minor changes in the antigenic characteristics of the HA and NA of influenza A and B viruses, called *antigenic drift,* result from an accumulation of point mutations in the genes encoding these proteins. Antigenic variants responsible for annual epidemics arise continually when point mutations allow viruses to escape neutralization by antibodies directed against previously circulating strains.[38]

Antigenic shift is a major antigenic change that occurs when an influenza A virus that bears a novel HA (or novel HA and NA) emerges in the human population. Antigenic shift is a rare event that is responsible for worldwide epidemics (i.e., pandemics) and occurs solely in influenza A viruses. Antigenic shift occurs when a nonhuman influenza virus directly infects human hosts or when a new virus is generated by genetic reassortment between nonhuman and human influenza viruses.[38] The segmented genome of influenza viruses facilitates reassortment events.

Swine are thought of as mixing vessels for the emergence of novel recombinant viruses derived from human and avian viruses because swine possess the sialic acid α2,3-galactose–linked receptors to which avian influenza viruses preferentially bind and the sialic acid α2,6-galactose–linked receptors to which human influenza viruses bind preferentially.[39] However, reassortant viruses can be generated in any host that is coinfected with two influenza A viruses.

Influenza Pandemics of the 20th and 21st Centuries

Since 1900, four pandemics have occurred with the emergence of novel influenza A viruses: the 1918 H1N1 Spanish flu pandemic, the 1957 H2N2 Asian flu pandemic, the 1968 H3N2 Hong Kong flu pandemic, and the 2009 H1N1 pandemic. During the 1918, 1957, and 1968 pandemics, the strains that emerged were novel influenza A subtypes that replaced the previously circulating subtype and became established as the predominant circulating influenza A subtype.

In 1977, H1N1 viruses reappeared after a 20-year absence (since the 1957 H2N2 pandemic) and caused disease in children and young adults who lacked previous exposure to H1N1 viruses. H1N1 viruses subsequently began circulating in the human population but did not replace the H3N2 viruses. Instead, influenza A H1N1 and H3N2 viruses continue to cocirculate.

In April 2009, cases of human infection with a novel influenza A (H1N1) virus were identified. This novel virus possessed a unique combination of gene segments, including genes that originated from swine, avian, and human influenza viruses that were established in pigs in North America and Europe (Fig. 229.2). By June 2009, this virus, now referred to as A(H1N1)pdm09, was causing widespread illness throughout the world, and it continues to circulate worldwide as a seasonal influenza virus.[40,41]

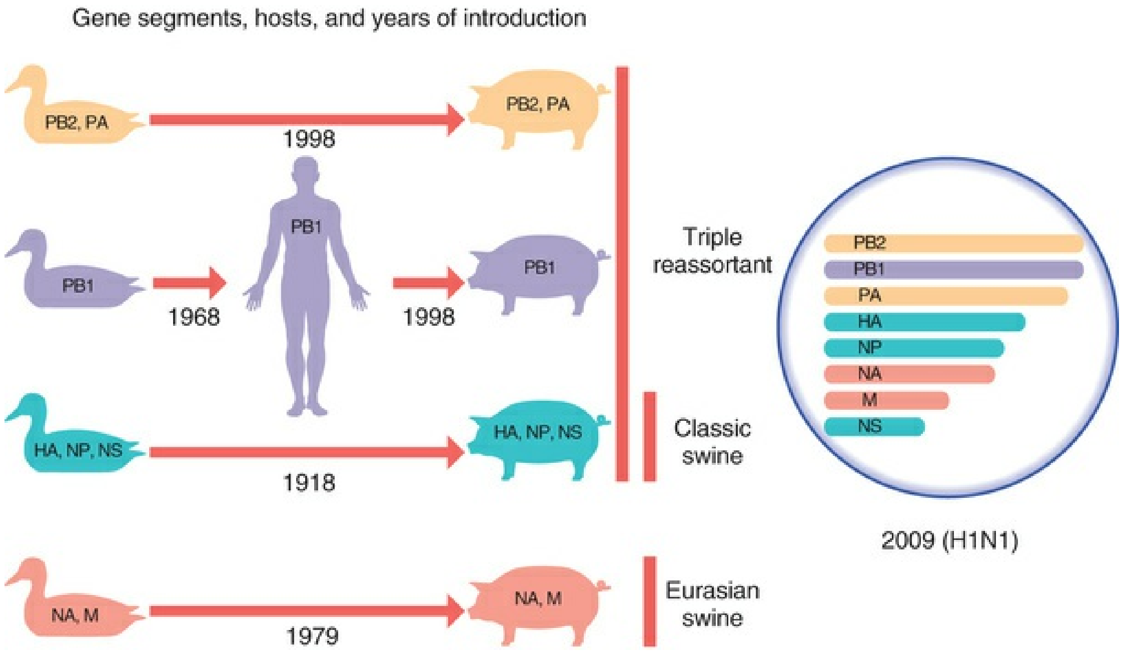

FIGURE 229.2 Host and lineage origins for the gene segments of the 2009 influenza A (H1N1) virus. HA, hemagglutinin; M, matrix; NA, neuraminidase; NP, nucleoprotein; NS, nonstructural; PA, polymerase acidic; PB1, polymerase basic 1; PB2, polymerase

basic 2. (Modified from Garten RJ, Davis CT, Russell CA, et al. Antigenic and genetic characteristics of swine-origin 2009 A(H1N1) influenza viruses circulating in humans. Science 2009;325:197–201.)

Sequence analysis of the 1918 pandemic influenza A (H1N1) viruses suggests they resulted from adaptation of avian H1N1 influenza A viruses to the human population.[42] The HA of avian influenza viruses exhibits receptor-binding specificity for sialic acid residues with α2,3 linkages expressed in the gastrointestinal tract of waterfowl and the lower respiratory tract of humans, whereas the HA of human influenza viruses exhibits receptor-binding specificity for sialic acid residues with α2,6 linkages expressed in the upper respiratory tract of humans. Some 1918 pandemic viruses possess dual binding specificity for sialic acid α2,3- and α2,6-galactose–linked receptors, but it is unclear whether this dual specificity accounts for the increased virulence attributed to the viruses.[43,44]

Pathogenesis

Influenza virus transmission is thought to occur primarily through large-particle respiratory droplets. Transmission by contact with contaminated surfaces also occurs, and limited data suggest a possible role for aerosol transmission of influenza virus by small-particle droplet nuclei.[45–51]

Influenza viruses infect the columnar epithelial cells of the respiratory tract. Peak virus replication occurs 1 to 3 days after inoculation. Virus shedding continues for 6 to 8 days in adults and can persist for more than 13 days in young children or immunocompromised people.[52–54] Necrosis of epithelial cells, edema, and inflammation occur rapidly.[55] Most infections are confined largely to the upper airways, but infection can spread to involve smaller airways such as the bronchioles and alveoli. In the absence of bacterial superinfection, epithelial cell recovery begins within 3 to 5 days, but complete restoration of ciliary function and mucus production takes about 2 weeks.

In experimental human influenza A virus infection in healthy adults, interleukin-6 (IL-6) and interferon α (IFNα) concentrations in nasal lavage fluid peak on day 2 and correlate directly with viral titers, temperature, mucus production, and symptom scores.[56] Tumor necrosis factor-α (TNF-α) responses peak later as viral shedding and symptoms are subsiding, and IL-8 responses peak late in the course of illness (i.e., days 4 to 6) and correlate only with lower respiratory symptoms. A study that enrolled patients with community-acquired influenza found that plasma and nasal lavage levels of IL-6 correlated best with symptoms, whereas TNF-α correlated with fever but not with other symptoms and peaked only after fever and other symptoms had already declined.[57]

Immunity

During influenza infection, death of virus-infected cells is mediated by antibody-dependent cellular cytotoxicity, antibody plus complement, cytotoxic T lymphocytes (CTLs), or apoptosis.[58,59] The development of influenza-specific CTLs is important for clearance of virus and recovery from illness. Clearance of virus is delayed in people with T-lymphocyte immunodeficiency states.[60] CD8$^+$ class I histocompatibility antigen-restricted CTL subsets recognize CTL epitopes in surface glycoproteins and internal proteins and confer subtype-specific and cross-reactive species immunity.[61] Subsets of lymphocytes with a CD4$^+$ class II histocompatibility antigen phenotype augment B-lymphocyte–mediated antibody production and CD8$^+$ cell proliferation.[61] Intracellular targeting of processed antigen or interaction with the major histocompatibility complex may lead to differential recognition by class I– and class II–restricted CTLs.

Influenza virus infection induces the production of local and humoral antibodies to HA and NA. Antibodies to HA are critical for virus neutralization, and those to NA reduce virus replication.[18,23] Although antibodies to nucleocapsid and matrix proteins are detectable, they do not appear to provide protection.[23] Protection afforded by CTLs or cross-reactive antibodies is limited. Subtype-specific, antibody-mediated protective immunity to influenza is durable over many years, but antigenic variation in HA and NA may compromise this immunity.[62]

Epidemiology

In temperate climates, influenza epidemics occur annually, typically during the winter months, whereas in some tropical climates, influenza viruses circulate year round or circulate more during rainy seasons.[63,64] Influenza A and B viruses can circulate at the same or different times, and the severity of influenza epidemics varies substantially from year to year, depending on the predominant circulating strains. In temperate climates, epidemics of influenza and respiratory syncytial virus (RSV) or other respiratory viruses often occur at about the same time during the winter.[65,66]

Influenza A H3N2 viruses usually cause the more severe influenza epidemics (as measured by overall mortality or hospitalization rates), whereas influenza A H1N1 and influenza B viruses often result in relatively milder epidemics.[67] Mortality and hospitalization rates may not reflect the full impact of influenza in some seasons. For example, during the 2009 A(H1N1)pdm09 pandemic, which disproportionately affected children and younger adults, overall severe morbidity and mortality rates were lower than in some influenza A (H3N2) predominant seasons, when most severe infections occur among older persons with comorbidities.[68]

Impact of Seasonal Influenza on Children

Influenza virus infection and illness occur most commonly among school-age children.[69–71] Children play an important role in sustaining community epidemics of influenza A and B because of the high attack rate of influenza among young children and because they shed infectious virus for longer periods and at higher titers than adults. Adults in homes with young children have a significantly higher risk of influenza illness than adults without child contact.[69] In a community outbreak, peaks of influenza among children typically precede peaks of influenza among adults, and early in an epidemic, school absenteeism precedes work absenteeism.[72] In a prospective survey of 313 schoolchildren, influenza accounted for an excess of 28 illness episodes, 63 missed school days, 22 secondary illnesses in families, and 20 days of missed parental work per 100 children.[73]

Influenza results in a substantial number of outpatient and inpatient visits for children. An estimated 89 to 620 emergency department visits and 2 to 16 hospitalizations per 10,000 children younger than 5 years of age occur due to influenza annually in the US.[74] Among infants younger than 6 months of age, an estimated 9 to 104 hospitalizations occur per 10,000 children, and hospitalization rates exceed hospitalization rates for healthy adults 65 years of age or older during some seasons.[7,10,11,14,75–77] Influenza-associated hospitalization rates are higher among children with cardiac and pulmonary conditions than among healthy children.[78,79] Children with neurologic and neuromuscular conditions are at increased risk for severe illness, respiratory failure, and prolonged hospitalization associated with influenza.[78,80–82]

Deaths of children attributed to laboratory-confirmed influenza became a nationally reportable disease in the US in 2004. Of laboratory-confirmed, influenza-associated deaths reported during the 2004–2012 period, almost one half occurred among previously healthy children and one third occurred among children with neurologic disorders.[83]

2009 A(H1N1)pdm09 Pandemic

During the spring of 2009, a novel influenza A (H1N1) virus that resulted in a pandemic was identified.[40] An estimated 61 million illnesses, 274,000 hospitalizations, and 12,500 deaths associated with the A(H1N1)pdm09 virus occurred in the US during the first year.[84] The highest estimated attack rates in the US occurred among children and young adults, and the highest estimated hospitalization rates occurred for children younger than 5 years of age.[16] Globally, an estimated 284,500 deaths associated with the novel virus occurred during the first year of A(H1N1)pdm09 circulation.[2]

Clinical Manifestations

Clinical manifestations of influenza virus infection vary according to the age of the host (Table 229.1). Infants with influenza virus infection can manifest irritability, difficulty feeding, or fever alone and can have clinical presentations that are difficult to distinguish from that of bacterial sepsis.[85] In neonates, influenza virus infection can result in apnea.[86]

TABLE 229.1

Common Manifestations of Influenza Illness in Children

Age	Manifestation	Frequency
Infant, toddler <5 years old	Afebrile URI	+
	Febrile URI	+++
	Acute otitis media	++
	Pneumonia	+
	Laryngotracheobronchitis	+
	Bronchiolitis	+
	Sepsis syndrome	+
Child ≥5 years old	Afebrile URI	+
	Flu-like syndrome[a]	+++
	Acute otitis media	++
	Pneumonia	+
	Myositis	+
	Myocarditis	Rare
	Encephalopathy	Rare

[a] Fever, cough, headache, myalgia, and malaise.

URI, upper respiratory tract infection; +++, most common manifestation; ++, common manifestation; +, infrequent manifestation.

Among preschool and school-age children, fever and signs of respiratory tract involvement, including laryngotracheobronchitis, are common. Gastrointestinal symptoms, including nausea, vomiting, and diarrhea, also can occur and are more common in preschool-aged children than in older age groups.[87,88] Older children and adults are more likely to have an abrupt onset of fever and chills accompanied by headache, sore throat, myalgia, malaise, anorexia, and a dry cough.[38]

The younger the child, the greater the overlap between influenza and syndromes caused by other viruses, particularly infections caused by RSV, adenovirus, and parainfluenza virus.[89,90] In a study of hospitalized children younger than 6 years of age, fever and cough together had a sensitivity of 54% for detecting influenza virus infection but a positive predictive value of only 16%, which increased to 25% when the analysis was limited to periods when at least one influenza virus infection was detected per week among study participants.[66] In another study that included children 17 years of age and younger, the triad of cough, headache, and pharyngitis as a predictor of laboratory-confirmed influenza in children during influenza season had a sensitivity of 80% and specificity of 78%.[91]

Upper respiratory tract illness caused by influenza is characterized by a dry, hacking cough that peaks after 3 to 4 days and persists for more than 1 week after other symptoms resolve. Sore throat occurs frequently, but it is not associated with exudative pharyngitis. Patients may complain of rhinorrhea and eye discomfort (i.e., tearing, photophobia, or burning). Croup syndrome associated with influenza tends to be more severe than that associated with parainfluenza virus; secretions are tenacious, and fever is typically higher. Airway compromise is often more severe and is sometimes complicated by bacterial superinfection.[92]

Most episodes of bronchopneumonia are mild and associated with complete recovery. A history of high fever (often >39°C), epidemic influenza in the community, and recent flu-like symptoms in other family members may help differentiate influenza pneumonia from infections caused by other respiratory viruses. Rarely, pneumonia due to influenza can be fatal in previously healthy individuals.[93–95]

Complications

Complications involving the upper and lower respiratory tract of influenza include acute otitis media (AOM), sinusitis, bronchiolitis, croup, and pneumonia. AOM was diagnosed in 35% of children 6 months through 3 years of age who had influenza-associated upper respiratory tract infections (URIs) in one prospective study.[96] In other studies, influenza virus was isolated from middle ear fluid in 3% of all children with AOM and accounted for 5% to 28% of all cases of viral otitis media.[97,98] AOM associated with viral URI typically manifests 3 to 4 days after the onset of the URI.[99]

Influenza-associated pneumonia has been reported for 8% to 15% of children hospitalized with influenza.[80,100,101] Radiographically confirmed pneumonia associated with influenza can be primary viral pneumonia or secondary bacterial pneumonia. Secondary bacterial pneumonia is characterized by the appearance of fever and a productive cough during convalescence, along with radiologic evidence of lobar consolidation.[38] *Streptococcus pneumoniae* and *Staphylococcus aureus* are the most frequent bacterial causes of pneumonia and other bacterial coinfections in children with influenza, and an increasing proportion of coinfections with *S. aureus* are methicillin resistant.[102–106] In addition to severe, progressive pneumonia, *S. aureus* superinfection has been associated with bacterial tracheitis and toxic shock syndrome.[92,107] Infection with *S. aureus* is thought to enhance cleavage of viral HA, increasing the virulence of influenza viruses.[108] Bacterial coinfections in children with influenza are associated with more severe illness and poorer outcomes.[105,109–111]

Myocarditis and evidence of cardiac muscle damage associated with electrocardiographic changes, disturbances in cardiac rhythm, and elevated levels of cardiac enzymes are rare complications after influenza A and B infection.[38] Febrile convulsions are associated with influenza infection in infants and young children and have been reported in up to 20% of children 6 months to 5 years of age who were hospitalized with influenza.[104,112,113] Encephalitis and encephalopathy are unusual complications of influenza virus infection. Sporadic cases of influenza-associated encephalitis or encephalopathy have been reported from several countries, including the US, but most reported cases have occurred in Japan.[114,115] In two large case series of patients with influenza-associated encephalitis or encephalopathy in Japan, most reported cases were for children younger than 5 years of age. Patients had a range of neuropsychiatric symptoms, including seizures, altered consciousness, and psychotic behavior. Up to 28% of patients had persistent neurologic sequelae, and 27% to 32% of patients died.[116,117] Other neurologic complications associated with influenza include transverse myelitis, Guillain-Barré syndrome, and Reye syndrome.[38] Reye syndrome (i.e., encephalopathy and fatty degeneration of the liver) has become uncommon since recognition of the association between Reye syndrome and concomitant aspirin use and influenza in children.[118–120]

Myositis, characterized by acute pain and tenderness in the gastrocnemius and soleus muscles that is severe enough to limit walking, can occur within 1 to 3 days of influenza symptom onset. Myositis has been observed more often with influenza B than with influenza A virus infection.[121] Serum creatine kinase concentrations often are elevated transiently. Complete recovery usually occurs in 3 to 4 days. Associated rhabdomyolysis and renal failure occur rarely. Acute parotitis associated with influenza virus infection has also been observed during some epidemics.[122]

Influenza virus infection can cause exacerbations of underlying illness, particularly in children with preexisting pulmonary disease such as asthma and cystic fibrosis.[123] Patients with cystic fibrosis who have influenza virus infection have lower expiratory flow rates than those with other nonbacterial infections.[124,125]

Laboratory Findings

The peripheral white blood cell count usually is normal. Relative lymphopenia is typical in older children, and neutrophilia with a left shift occasionally is observed in infants. The radiographic appearance of lower respiratory tract influenza infection is not distinguishable from that of infection caused by other respiratory viruses.[126] Peribronchial infiltrates, hyperexpansion, and segmental or lobar atelectasis are common; interstitial infiltrates and pleural effusions are uncommon. Influenza pneumonia can evolve from peribronchial infiltrates to a more diffuse alveolar process in cases of fatal disease.[94]

Diagnosis

Because of overlap with the clinical presentation of other respiratory tract infections, influenza cannot be diagnosed definitively on the basis of clinical signs and symptoms or epidemiologic patterns.[65] In one study, the diagnosis of influenza in children based on clinical signs and symptoms during the influenza season was 38% sensitive and 91% specific compared with laboratory confirmation of influenza virus infection.[127] Establishing the diagnosis of influenza through laboratory testing, especially in hospitalized patients and those at high risk for severe influenza, can limit inappropriate antibiotic use, guide antiviral therapy, and provide data for influenza surveillance purposes.

Influenza diagnostic tests based on examination of nasopharyngeal aspirates, nasopharyngeal swabs, or nasal swabs include tissue or cell culture, reverse transcriptase polymerase chain reaction (RT-PCR), rapid antigen detection tests, and immunofluorescence assays (Table 229.2).[128] Sensitivity of these diagnostic tests is affected by the quality of the respiratory specimen and the timing of specimen collection. Nasopharyngeal or nasal specimens are preferred to throat swab specimens. Diagnostic yield is highest when specimens are collected within the first few days of illness, when influenza virus shedding is at its peak.[52]

TABLE 229.2

Influenza Diagnostic Testing Options

Diagnostic Test	Advantages	Disadvantages
Rapid antigen test	Provides results in 30–60 minutes	Variable sensitivity
	Some may differentiate influenza types but not subtypes	
	High specificity (63%–100%)	
DFA and IFA stain	Provides results in 2–4 hours and has high specificity (>80%)	Sensitivity depends on technical skill of operator
Real-time RT-PCR	Considered the gold standard diagnostic test; can provide results in 6–8 hours	
	High sensitivity and specificity	
Virus culture	Yields isolates that can be typed, subtyped, and characterized antigenically and genetically	May take ≥3days to obtain results
	High sensitivity and specificity	
Serology	Useful during outbreak investigations and epidemiologic studies; can detect past infection	Requires acute and convalescent sera; results usually not available to inform clinical decision making in acute setting

DFA, direct fluorescence assay; IFA, immunofluorescence assay; RT-PCR, reverse transcriptase polymerase chain reaction.

Real-time RT-PCR is considered the gold standard for detection of influenza viruses. It provides results within 6 to 8 hours, can be combined with detection of other respiratory viruses in a multiplex format, and allows typing, subtyping, and strain identification by sequence analysis of influenza viruses.[129,130] Virus culture is less sensitive than real-time RT-PCR for detection of influenza viruses, but it yields isolates that can be typed, subtyped, and characterized antigenically and genetically. With conventional culture, results are not available for 3 or more days. The shell vial culture technique provides results sooner than conventional techniques, with results available in 18 to 48 hours.[128]

Rapid antigen diagnostic tests have highly variable sensitivities but high specificities for detecting influenza in specimens from children. In a meta-analysis of studies comparing rapid tests to real-time RT-PCR or virus culture for children, the overall sensitivity was 67%, and specificity was 98%.[131] Rapid tests can provide results within 30 to 60 minutes, and some can differentiate between influenza A and B viruses. There are no licensed rapid tests that differentiate influenza A virus subtypes.

Because of the potentially low sensitivity of influenza rapid tests, results must be interpreted in the context of local influenza surveillance data. If the influenza rapid test is negative, but the patient has symptoms consistent with influenza, the patient may still have influenza, and clinicians should use clinical judgment when deciding whether to obtain additional influenza testing (e.g., real-time RT-PCR, culture) or initiate antiviral therapy. Interpretation of a positive rapid influenza test result also is problematic when the prevalence of influenza among people with respiratory illness is low.[132]

Direct and indirect fluorescent antibody tests have a specificity of more than 80%, but they have highly variable sensitivities compared with virus culture.[133] Serologic testing of acute and convalescent specimens for the presence of antibodies to influenza viruses can be useful for clinical studies and outbreak investigations, but they do not provide timely data.

Treatment

Two classes of antiviral drugs are licensed for the treatment of influenza in the US: the adamantanes, which are ion channel inhibitors and are active against influenza A viruses but not against influenza B viruses, and the NA inhibitors, which are effective against influenza A and influenza B viruses. The adamantanes have not been recommended for treatment of influenza during most recent influenza seasons because of widespread resistance among the circulating influenza viruses.[134,135] A third class of antiviral drugs, RNA-dependent RNA polymerase inhibitors, is licensed for the treatment of influenza only in Japan.[136]

Adamantanes

The adamantanes include the oral medications amantadine and rimantadine. These drugs block the M2 ion channel on influenza A viruses that maintains the acidity of the Golgi microenvironment and permits virus uncoating.[137] Amantadine and rimantadine are approved by the US Food and Drug Administration (FDA) for prophylaxis of influenza in children 1 year of age or older, but only amantadine is approved for treatment of influenza in children.

In studies of the use of adamantanes for the treatment of influenza in adult patients, amantadine or rimantadine therapy begun within 48 hours of the onset of symptoms was associated with a rapid reduction in fever, systemic complaints, and virus shedding.[138–140] Data on the effectiveness of adamantane treatment of children are limited. Treatment with rimantadine appears to reduce viral shedding rapidly in most patients, but shedding of resistant virus late in therapy has been observed.[141,142]

Amantadine is excreted renally, and dosage adjustments must be made for patients in renal failure.[143] Rimantadine also is excreted renally and requires substantial hepatic metabolism before clearance, necessitating dosage adjustments for patients with hepatic dysfunction or renal failure.[143]

Neuraminidase Inhibitors

The NA inhibitors licensed for the treatment of influenza in children in the US include zanamivir, which is available as an inhalational agent, and oseltamivir, which is available as a liquid suspension or tablet. Peramivir, a NA inhibitor available as an intravenous agent, is licensed for the treatment of uncomplicated influenza in adults 18 years of age or older. The NA inhibitors bind to the influenza neuraminidase enzyme active site, inhibiting the release of virions from the infected cells.[137]

Inhaled zanamivir is FDA approved for treatment in children 7 years of age or older and for chemoprophylaxis in children 5 years of age or older. Oseltamivir is approved for chemoprophylaxis of influenza in children 1 year of age or older and for treatment in children 2 weeks of age or older. Intravenous zanamivir is being studied for use in the treatment of influenza.[144]

Inhaled zanamivir and oral oseltamivir reduce the duration of illness due to influenza in children when treatment is initiated early in the course of illness. In one randomized, placebo-controlled trial involving children 4 to 12 years of age and three trials involving adults and children 12 years of age or older, zanamivir shortened the duration and severity of influenza symptoms when initiated within 48 hours of illness onset.[145–147] In randomized, controlled trials of oseltamivir efficacy among children in the outpatient setting, oseltamivir treatment within 24 to 48 hours of illness onset reduced the duration of illness and virus shedding, overall illness severity defined by composite symptom scores, and the incidence of AOM.[148–150] In a randomized trial enrolling children with asthma and influenza, oseltamivir reduced the incidence of asthma exacerbations and improved pulmonary function during the illness period. A Cochrane review of randomized trials evaluating oseltamivir concluded that oseltamivir reduced illness duration by a mean difference of 1 day compared with placebo among previously healthy children but found no effect among children with asthma.

Data on the effectiveness of oseltamivir treatment of hospitalized children is limited largely to observational studies, in part because evaluating efficacy against severe outcomes in hospitalized children would require enrollment of prohibitive numbers of children due to the relative infrequency of severe outcomes in the pediatric population.[151–154] Although some observational studies of hospitalized children have found an association between oseltamivir treatment or early treatment and reductions in length of hospital stay, risk of mechanical ventilation, and death, others have found no treatment effect.[151–155] A potential limitation of these observational studies is bias if patients treated early with oseltamivir are substantially different from those who are untreated or treated late.

Peramivir treatment of uncomplicated influenza in adults reduces the duration of illness. Two randomized trials that evaluated a single intravenous dose of peramivir compared with placebo in adults in the outpatient setting found that peramivir reduced illness duration by 1 day.[156] However, a trial of a 5-day course of intravenous peramivir compared with standard of care that included hospitalized adults and children 6 years of age or older found no effect from treatment on length of hospitalization.[157]

Zanamivir is concentrated in the respiratory tract; 10% to 20% of the active compound reaches the lungs, and the remainder is deposited in the oropharynx. Only 5% to 15% of the total dose is absorbed and excreted in the urine. Therefore, zanamivir dosage adjustment is not required for patients with renal failure. The estimated concentration of the drug in the respiratory tract is more than 1000 times the 50% inhibitory concentration (IC_{50}) for NA, and the inhibitory effect begins within 10 seconds.

Nebulized zanamivir should not be used in intubated patients because it may lead to ventilator failure and subsequent death.[158] Postlicensure reports indicate that inhaled zanamivir can cause cough, bronchospasm, and a reversible decrease in pulmonary function.[136] If patients with pulmonary dysfunction receive zanamivir, they should have a fast-acting bronchodilator available and discontinue zanamivir if respiratory difficulty develops.

Oseltamivir is readily absorbed from the gastrointestinal tract and is converted by hepatic esterases to the active compound that is widely distributed in the body. The half-life of oseltamivir is 6 to 10 hours. Oseltamivir is excreted primarily through the kidneys, and the dosage must be modified in patients with renal insufficiency. The most commonly reported side effects are nausea, vomiting, and diarrhea.

Peramivir is excreted renally and requires dose adjustment for patients with renal insufficiency. The half-life of peramivir is 12 to 25 hours.[136,159] The most commonly reported side effects of peramivir are diarrhea, nausea, and vomiting; decreased neutrophil count also has been associated with treatment.[136] Data on peramivir use in children is limited largely to studies from Japan, where peramivir has been licensed since 2010, and to the 2009 H1N1 pandemic, when peramivir was approved for treatment of critically ill hospitalized patients in the US under an FDA Emergency Use Authorization. Available data indicate that intravenous peramivir usually is well tolerated in children.[160–162]

Antiviral Treatment in Infants

Oseltamivir is the only influenza antiviral medication licensed for the treatment of influenza in infants at least 2 weeks of age, and specific dosing guidelines are available for this age group.[163,164] Separate dosing is necessary for preterm infants because immature renal function may result in slower and variable drug clearance.[163–165] Of 72 children younger than 1 year of age who received 3 to 3.5 mg/kg/dose of oseltamivir carboxylate twice daily for 5 days in a prospective phase I/II study, none experienced moderate or severe adverse events.[166] In a randomized, placebo-controlled trial of oseltamivir treatment in hospitalized children, oseltamivir was well tolerated with no difference in adverse events between treatment groups, including among infants <1 year.[166a] Several observational studies of oseltamivir phosphate treatment for children younger than 1 year of age have documented symptom profiles during treatment similar to that reported for older children.[166–169]

Indications for Antiviral Treatment

Treatment of children with influenza virus infection should be based on the severity of disease, underlying medical conditions, and time since symptoms started. Empiric treatment is recommended for all people with suspected or confirmed influenza requiring hospitalization and for persons with progressive or complicated illness, regardless of previous health or vaccination status.[144,163] Empiric antiviral therapy also is recommended for people who are at a higher risk for influenza complications, such as children with underlying medical conditions, pregnant women, and children younger than 5 years of age (Box 229.2).[144]

Box 229.2

People at Higher Risk for Influenza Complications

Children <5 years of age, particularly children <2 years of age

Adults ≥65 years of age

Those with the following underlying medical conditions: chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematologic (including sickle cell disease), neurologic, neuromuscular, or metabolic (including diabetes mellitus) disorders

Those with immunosuppression caused by medications or underlying medical conditions (including HIV infection)

Women who are pregnant or within 2 weeks after delivery

Those <19 years of age who are receiving long-term aspirin therapy

American Indians and Alaskan Natives

Adults who are morbidly obese (body mass index ≥40)

Residents of nursing homes and other chronic care facilities

Antiviral treatment should be started as soon as possible after illness onset. Early initiation of treatment for severely ill children has been associated with reduced morbidity and mortality rates in some observational studies.[152,154] Empiric treatment often is necessary, and initiation should not be delayed while awaiting confirmatory diagnostic test results. Regardless of the initial test results, patients should continue to receive antiviral treatment until an alternative diagnosis can be established.[144] Treatment of severely ill patients, such as those who require hospitalization, is recommended regardless of illness duration. Several studies conducted among adults have shown that hospitalized patients benefit from treatment, even when it is initiated more than 48 hours after illness onset.[170,171]

Antiviral Resistance

Resistance to the adamantane compounds occurs as a result of mutations in the gene encoding the M2 protein, and resistance to the NA inhibitors occurs as a result of mutations in the HA or NA genes. Starting with the 2005–2006 influenza season, widespread adamantane resistance was observed among circulating influenza A (H3N2) viruses.[134] From the emergence of the 2009 H1N1 virus through May 2014, most influenza A and B viruses tested were resistant to the adamantanes but were sensitive to oseltamivir, zanamivir, and peramivir.[172] Oseltamivir-resistant 2009 H1N1 viruses have been detected sporadically, frequently in association with the *H275Y* mutation, and they have been associated with subtherapeutic treatment with oseltamivir in some instances.[173]

The emergence and rapid evolution of antiviral resistance among circulating influenza strains necessitates careful monitoring of local influenza surveillance data to determine which influenza strains are circulating and the prevalence of antiviral resistance among circulating strains. Influenza antiviral treatment strategies should be reassessed frequently based on local influenza virus circulation patterns.

Special Considerations

Immunocompromised Hosts

Immunocompromised hosts frequently acquire infection through nosocomial transmission, and they can shed virus for extended periods, especially if T-lymphocyte function is compromised.[60,174–177] Influenza A and B cause substantial morbidity and mortality rates for recipients of solid-organ and hematopoietic stem cell transplants; fatal pulmonary and neurologic syndromes have been reported.[176,178,179] Influenza-associated hemophagocytic syndrome has been reported for children with acute leukemias.[180] Guidelines for the prevention of influenza in hematopoietic stem cell transplant recipients have been published.[181]

Development of influenza viruses resistant to antiviral medications in immunocompromised patients exposed to antiviral medications is reported.[182,183] Influenza immunization is recommended by the American Society of Transplantation for recipients of solid-organ transplants before and after transplantation; if transplant recipients receive influenza vaccine soon after transplantation, revaccination 3 to 6 months after transplantation, when the immune response to vaccine is improved, may be warranted if still within the influenza season.[184]

Human Immunodeficiency Virus Coinfection

Some studies suggest that people infected with human immunodeficiency virus (HIV) have an increased susceptibility to influenza virus infection compared with the general population.[185,186] Children with HIV infection also may have prolonged virus shedding.[185] Influenza vaccination with trivalent inactivated vaccine (TIV) has a similar safety profile in HIV-infected children and HIV-uninfected children.[187] Vaccination with TIV produces adequate antibody responses in HIV-infected children receiving antiretroviral therapy, although antibody responses may be lower than those seen in healthy age-matched children, and responses are inversely correlated with the degree of immunosuppression.[187–191]

Annual influenza vaccination is recommended for all HIV-infected people in the US.[17] Because immune responses to influenza vaccination may be suboptimal in some children with HIV infection, influenza vaccination also is recommended for those who live with or care for HIV-infected children.[17]

Pregnancy

Although no evidence supports influenza as a teratogen or a cause of abortion, influenza during pregnancy may increase the risk of adverse infant outcomes, such as being born with a low birth weight and being small for gestational age.[193] Risk of hospitalization with influenza among pregnant women increases with gestational age, and women in the third trimester of pregnancy are hospitalized at a rate comparable with that of nonpregnant women with high-risk medical conditions.[194,195] Influenza pneumonia is associated with high morbidity and mortality rates for pregnant women.[196]

Influenza vaccination remains the primary strategy for reducing influenza complications among pregnant women.[17] Risk for influenza complications among pregnant and early postpartum women has emphasized the need for empiric antiviral treatment of any pregnant woman with suspected influenza.

Prevention

Vaccine

Two types of influenza vaccines are licensed for use in children in the US: an injectable inactivated influenza virus vaccine (IIV) and a live, attenuated inhaled vaccine (LAIV). A third type of vaccine, a recombinant protein vaccine (RIV) administered as an injection, also is FDA approved but not yet available for use in children. Inactivated virus vaccines are available as trivalent (IIV3) or quadrivalent (IIV4) preparations, whereas all live, attenuated vaccines in the US are now quadrivalent (LAIV). The IIV3s contain three vaccine strains selected to match the strains considered most likely to circulate in the upcoming influenza season: an influenza A (H1N1), an influenza A (H3N2), and an influenza B/Yamagata or influenza B/Victoria strain; quadrivalent preparations contain strains from both influenza B lineages.

In the US, influenza vaccines are made through three types of production technology: egg based, cell culture based, and recombinantly expressed proteins. The egg-based and cell culture–based technologies use vaccine strains initially grown in chicken eggs, whereas recombinant technology does not require egg-grown vaccine or use chicken eggs in the production process.

The US Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) recommends influenza immunization annually for all persons at least 6 months of age. Immunization is particularly important for people at increased risk for severe influenza, including children younger than 5 years of age, people 50 years of age or older, those with chronic underlying medical conditions or immunosuppressive conditions, children receiving chronic aspirin therapy, women who are or will be pregnant during the influenza season, residents of long-term care facilities, American Indians and Alaska Natives, and people who are morbidly obese.[17] Household contacts and caregivers (including healthcare personnel, homecare providers, and employees of assisted-living and long-term care facilities) of people at increased risk for severe influenza also should be vaccinated.[17]

Immunization of all healthcare personnel is recommended by the ACIP, and mandatory immunization of healthcare personnel is recommended by the Infectious Diseases Society of America and the American Academy of Pediatrics.[197,198] Immunization of close contacts of children younger than 6 months of age is particularly important because these children cannot be immunized with currently licensed vaccines. Coverage in all groups, including healthcare personnel and young children, remains below levels that are likely to reduce substantially the impact of annual influenza epidemics.[192]

School-aged children often have the highest attack rates of influenza and play a key role in the introduction and transmission of influenza viruses in communities.[71,199–201] Observational studies and several randomized trials in which immunization of children was associated with reductions in influenza or respiratory illness among their household contacts or those living in the same community provide support for a universal recommendation for immunization of children.[202–205]

The efficacy of influenza vaccines depends on the age of the vaccine recipient, closeness of antigenic match between the vaccine strains and epidemic strains, and the end points used for the measurement of efficacy. Clinical efficacy studies that use laboratory-confirmed influenza as an end point have higher estimates of protection than effectiveness studies that use clinical illness end points. Currently available influenza vaccines are challenging to manufacture quickly and do not provide reliable protection against strains that are antigenically different from the vaccine strain. The continuous antigenic changes that occur among influenza viruses result in the need for annual revaccination. Efforts to improve influenza vaccines are an active area of research, including development of more immunogenic vaccines that can be manufactured in shorter timeframes and universal influenza vaccines that can protect against drifted strains over multiple seasons.[206–208]

Vaccine for Children With Egg Allergies

Specific guidelines exist for giving influenza vaccine to children with a history of egg allergy.[17] Only IIVs are recommended for children with egg allergy because data on the use of LAIV in this population are limited. Children with any allergic reaction to eggs involving symptoms other than hives should be vaccinated under the supervision of a health care provider experienced in managing severe allergic conditions.

Inactivated Vaccine

Inactivated seasonal influenza vaccines available in the US are split virus or virus subunit vaccines, and they are considered interchangeable when given in the standard doses. The immunogenicity of IIV is inconsistent in infants younger than 6 months of age.[209–211] IIVs are licensed for use in people at least 6 months of age.

Seroresponse rates increase with increasing age, reaching 70% to 100% among adolescents. However, immunologic priming is important for a response to IIV, and a single dose of vaccine is ineffective in inducing immunity and protection in children lacking previous experience with the matching influenza type or subtype.[212] Young children require several years of exposure to influenza epidemics or two doses of vaccine to ensure a reliable response to all vaccine antigens after the administration of an inactivated vaccine.[213,214] Two doses of IIV administered 4 or more weeks apart are recommended for children younger than 9 years of age during their first season of influenza immunization.[17]

In a large, randomized, placebo-controlled trial that evaluated IIV in children 1 to 15 years of age, vaccine efficacy ranged from 77% to 91%.[215] Other observational studies have estimated lower vaccine effectiveness among children.[216–220] The incidence of AOM in two studies of IIV and one study of LAIV was lower among influenza vaccine recipients than among unimmunized children.[221–223] However, a randomized, placebo-controlled study of IIV in children 6 to 24 months of age failed to show decreases in the incidence of AOM or duration of middle ear effusion in vaccine recipients.[224]

Fewer data are available on vaccine efficacy and effectiveness in children with underlying chronic medical conditions. Among children with asthma, IIV has been safe and efficacious in preventing influenza, but studies of the effectiveness of influenza vaccination to prevent acute asthma exacerbations have produced mixed results.[225–230] Among children with HIV infection, data on IIV efficacy is limited largely to studies evaluating immunologic outcomes. Several studies have documented that IIV is at least moderately immunogenic in children with HIV infection, although immune responses to vaccine are inversely correlated with the degree of immunosuppression.[187,188,191] A randomized, placebo-controlled trial evaluating IIV efficacy against clinical influenza among South African children 6–59 months of age with HIV infection found that IIV was 18% efficacious during a year in which circulating influenza viruses had drifted from the vaccine strain.[190]

Vaccination of pregnant women with an IIV provides protection to their infants, presumably through passive transfer of antibodies against influenza.[231,232] Vaccination of pregnant women with IIV3 was 63% effective in preventing laboratory-confirmed influenza among infants of vaccinated women through 6 months of age in a randomized, controlled trial and resulted in a 41% reduction in laboratory-confirmed influenza among infants through 6 months of age in a prospective cohort study.[233,234]

In 2009, a higher-dose IIV (i.e., fourfold increase in vaccine antigen) was licensed in the US for people 65 years of age or older and has demonstrated superior immunogenicity and effectiveness.[17,235] In 2011, the FDA licensed a reduced-dose (i.e., 9-μg of HA per strain) intradermal, inactivated vaccine for use in people between the ages of 18 and 64 years.[17] The intradermal vaccine uses a 1.5-mm microneedle to deliver vaccine consistently into the dermis, which is heavily populated with dendritic cells involved with antigen presentation. In a randomized trial, reduced-dose intradermal vaccine elicited similar humoral and cell-mediated immune responses compared with intramuscular vaccine in healthy adults.[236]

Live, Attenuated Vaccines

Live, attenuated influenza vaccines in which six internal protein genes of a temperature-sensitive, attenuated, cold-adapted parent influenza virus are combined with wild-type HA and NA genes are licensed for use in healthy, nonpregnant people between 2 and 49 years of age.[17] However, observational studies found that LAIV had low to no effectiveness against the predominant circulating influenza strains among children 2 to 17 years in the US during the 2013 to 2016 influenza seasons. As a result, the ACIP recommended against the use of LAIV during the 2016 to 2017 influenza season.[17,236a,237]

Many studies have shown that LAIV is safe for healthy, school-age children and adolescents.[223] In the largest randomized, controlled trial conducted among children younger than 6 years of age, those with medically diagnosed or treated wheezing within 42 days before enrollment or with a history of severe asthma were excluded.[237a] Using a prespecified definition, the rate of medically significant wheezing was no greater among LAIV recipients than IIV recipients among children 24 to 59 months of age, but it occurred more frequently among LAIV recipients 6 to 23 months of age. However, a significantly increased risk of wheezing was observed among children 18 to 35 months of age in another study.[238]

In a pooled analysis of 20 studies evaluating LAIV compared with placebo or IIV in children 2 to 17 years of age, children 24 to 35 months of age who received LAIV did not have higher rates of wheezing.[239] Based on these observations, LAIV is not approved for use in children younger than 24 months old, and the ACIP recommends against the use of LAIV in children 2 to 4 years of age with a history of wheezing during the preceding 12 months or children of any age with asthma.[17]

Shedding of vaccine strain virus has been documented in children who have received LAIV; when genotype analysis was performed, shed virus retained the attenuated phenotype.[240–242] The frequency of transmission of LAIV from immunized young children to unimmunized contacts has been estimated to be less than 2%, and it is likely lower among older children and adults who shed less virus.[240,241] Transmission of vaccine virus from immunized people to unimmunized contacts has not been shown to cause significant illness.[241] LAIV virus is shed for a shorter duration and at lower titer than wild-type influenza virus.[243] LAIV should not be given while the recipient is receiving influenza antiviral medication because antivirals decrease influenza viral replication and may interfere with the immune response to LAIV. People who receive influenza antiviral medications during the 2 days before to 14 days after receiving the LAIV should be reimmunized after cessation of antiviral therapy.[17]

People who receive LAIV develop mucosal immunity, which is challenging to measure. Clinical studies have demonstrated that LAIV has excellent efficacy against influenza during most seasons, particularly among children. In one randomized, controlled trial comparing LAIV with placebo in children, two doses of LAIV were 94% effective against culture-confirmed influenza, and a single dose was 89% effective during a season when the vaccine strains were well matched against circulating strains and 86% effective during a season when the predominant circulating strain had drifted from the vaccine strain.[244,245] The efficacy of LAIV against laboratory-confirmed seasonal influenza in young children in other randomized trials has ranged from 52% to 89%.[244–246]

The safety, immunogenicity, and efficacy of LAIV and IIV have been compared in several studies.[237a,248–251] Both vaccines are well tolerated and effective but elicit substantially different immune responses.[250,251] In randomized, controlled comparative trials enrolling young children, vaccination with LAIV was more effective than IIV against laboratory-confirmed influenza, regardless of the match between circulating strains and vaccine strains, and it provided greater cross-protection during seasons when vaccine strains were not well matched against circulating influenza virus strains.[248]

In a study comparing immune responses to a 2-dose sequence of IIV, LAIV, or a combination of the two vaccines in children between 6 and 35 months of age, both vaccines induced similar humoral antibody responses, but only LAIV induced cell-mediated responses thought to be important for heterosubtypic immunity.[252] In contrast, in several randomized, placebo-controlled studies comparing LAIV and IIV in healthy young adults, IIV was more efficacious.[253–255] In a single study conducted among adults, LAIV was more effective in those who had never received influenza vaccine in the past.[256]

Chemoprophylaxis

If given before or shortly after influenza virus exposure, chemoprophylaxis with an influenza antiviral agent can effectively prevent symptomatic influenza virus infection. Oseltamivir postexposure chemoprophylaxis (PEP) in household contacts of those with influenza has been 68% to 89% effective in preventing laboratory-confirmed influenza when given soon after exposure.[257,258] Several studies have documented similar efficacy for zanamivir when it is given as PEP.[259,260]

In most situations, counseling patients about signs and symptoms of influenza and encouraging early treatment if signs or symptoms develop constitute a preferable alternative to chemoprophylaxis for people with a suspected exposure to influenza virus. Clinical judgment based on consideration of the patient's age, severity of underlying illness, ability to comply with a chemoprophylactic regimen, and access to medical care should be used when considering PEP. PEP is considered for those at high risk for severe influenza who have not been vaccinated or have received vaccine less than 14 days before exposure.[261]

Chemoprophylaxis should be given for 10 days and within 48 hours after the time of exposure.[261] Occasionally, extended periods of prophylaxis are indicated for patients who cannot be immunized.[262] The choice of antiviral agent used for chemoprophylaxis should be guided by local surveillance data on antiviral resistance when available. Influenza virus infection can occur in those receiving antiviral chemoprophylaxis, and sporadic cases of antiviral-resistant influenza virus infection have been identified in people taking chemoprophylaxis.[173,258,262,263] Clinicians should advise patients taking chemoprophylaxis to seek care at the first signs of respiratory illness, and providers should consider antiviral-resistant influenza virus as a potential cause in these instances.

Zoonotic Influenza

Influenza viruses infect many animal species in addition to humans. Interspecies transmission has been documented, including human infections with avian and swine influenza viruses. Human infection with novel or nonhuman influenza A virus strains, including influenza A viruses of animal origin, is a notifiable disease in the US.[264]

Sporadic cases and clusters of human infection with avian viruses with HA subtypes H5, H6, H7, H9, and H10 prove that avian influenza A viruses can be transmitted directly to humans without passage through an intermediate host and without acquiring human influenza gene segments by genetic reassortment.[265] The first case of human infection with an avian influenza A H5N1 virus was identified in 1997 in a child in Hong Kong, who died as a result of the infection.[266] A few months later, 17 additional cases occurred with 5 additional deaths.[267] The 1997 outbreak ended, but progenitors of the Hong Kong H5N1 viruses continued to circulate in avian species in the region. In late 2002, outbreaks of highly pathogenic H5N1 avian influenza were reported in 10 countries in Asia and human cases were reported in Vietnam and Thailand.[268,269] Since then, H5N1 viruses have spread to other countries in Asia, Europe, and Africa, and more than 800 cases of human infection and more than 400 deaths have been reported (http://www.who.int/csr/disease/avian_influenza/en).

Other avian influenza viruses have emerged and caused outbreaks among humans. Most notably, the avian H7N9 virus has led to more than 800 cases of human infection predominantly linked to bird exposure at live bird markets in China since 2013.[270,271] In 2015, outbreaks of several subtypes of avian influenza viruses, including H5N1, H5N2, and H5N8, among birds in the US were identified, highlighting the potential threat of human infection with avian influenza viruses in North America.[272,273] Guidance for infection control, testing, and influenza antiviral chemoprophylaxis for people in the US exposed to birds with suspected or confirmed avian influenza virus infection is available (http://www.cdc.gov/flu/avianflu).

The incubation period for human cases of avian influenza virus infections ranges from 2 to 6 days, but longer incubation periods have been reported.[271,274] Most patients with avian influenza virus infection have a history of contact with sick poultry, but there are instances of probable person-to-person transmission among family clusters with close contact.[271,275,276] Although most cases have febrile respiratory illnesses (sometimes with dyspnea), there have been reports of atypical infections, including infections in two children who had diarrhea and coma without respiratory tract symptoms.[277–279]

Laboratory findings include lymphopenia, thrombocytopenia, and in some cases, abnormal hepatic transaminase levels.[280–282] Reported complications include progression to acute respiratory distress syndrome, shock, and renal failure.[280,282–285] The diagnosis of avian influenza virus infections is based on molecular methods.[286]

In a review of 308 persons infected with H5N1, oseltamivir treatment initiated up through 6 to 8 days after symptom onset reduced the mortality rate by 49%.[287] Although treatment of avian influenza virus infection with oseltamivir provides a survival benefit, the case-fatality rate for treated patients remains high. Resistance to oseltamivir or amantadine has been reported for H5N1 viruses. H7N9 viruses are resistant to adamantanes, and sporadic resistance to oseltamivir and zanamivir has been reported.[270,288–291]

Sporadic cases and clusters of human infection with swine influenza viruses have been reported in the US and elsewhere since 1958. They include infection with classic swine influenza viruses and triple-reassortant swine influenza viruses containing genes from human, avian, and swine influenza viruses.[292] In 2011, sporadic cases of human infection with a newly identified swine-origin triple-reassortant influenza A (H3N2) virus containing genes from a swine-origin A (H3N2) virus known to be circulating in North American pigs and the matrix gene from the 2009 H1N1 virus were identified, including a case cluster in which limited human-to-human transmission might have occurred.[293,294] Most patients with swine influenza virus infection were exposed during participation at agricultural fairs and have had mild, self-limited illnesses that were clinically indistinguishable from seasonal influenza, although severe and fatal cases also have been reported.[292,295]

The incidence of human infection with swine influenza viruses is unknown because testing for influenza viruses is not always conducted for patients with influenza-like illness. However, serologic studies suggest that these infections might occur more frequently among persons with occupational exposure to swine and their close contacts.[296,297]

Swine influenza virus infections should be considered in the differential diagnosis of patients with respiratory illness and recent swine exposure.[298] Avian influenza virus infections should be considered in the differential diagnosis of those with respiratory illness and recent contact with sick or dead birds.[299] If swine or avian influenza virus infection is suspected, clinicians should obtain a nasopharyngeal swab, nasal aspirate or wash, or swabs from two sources combined into one tube of viral transport media from the patient and contact the local health department to facilitate testing.

Pandemic Influenza

The introduction with subsequent global spread in humans of a novel influenza A virus is referred to as *antigenic shift*. The prerequisites for a pandemic are isolation from humans of a novel influenza virus to which the general population has little or no immunity, ability of the virus to replicate and cause disease in humans, and sustained and efficient transmissibility of the virus from person to person.[300]

Novel influenza viruses with pandemic potential can arise through reassortment of gene segments among avian, swine, or human influenza viruses in humans or an intermediate host or can be wholly avian or swine influenza A viruses that cross the species barrier and directly infect humans.[301] As demonstrated in 2009, a pandemic can result if a virus emerges with antigenic characteristics that are novel to most humans; an entirely new HA gene is not necessarily required.[41]

The history and biology of influenza viruses indicate that future influenza pandemics are inevitable. However, the timing of a pandemic, the subtype that will cause it, and the impact of the pandemic cannot be predicted. Specific measures for the control of influenza pandemics include vaccines and antiviral drugs. Two inactivated avian influenza vaccines, including adjuvanted and unadjuvanted influenza A/H5N1 vaccines, are licensed in the US.[302] The US Department of Health and Human Services maintains a stockpile of avian influenza vaccines and the two currently licensed classes of antiviral drugs, adamantanes and NA inhibitors.[303] The US government pandemic preparedness plan is available at www.pandemicflu.gov.

Key Points

Influenza Virus Infections

Microbiology

- Three antigenic types of influenza viruses are recognized: A, B, and C.
- The surface proteins hemagglutinin (HA) and neuraminidase (NA) are the major targets of the protective immune response. Minor changes in these surface glycoproteins are responsible for the ability of influenza viruses to evade immunity acquired from infection in previous seasons and cause annual epidemics of respiratory illness.
- The emergence of influenza A viruses with novel HAs that are antigenically distinct from previously circulating influenza A viruses has resulted in four influenza pandemics in 1918, 1957,

1968, and 2009.

Epidemiology

- Among children, influenza-associated hospitalization rates are highest among young children, especially infants younger than 6 months of age.

- People at increased risk for severe seasonal influenza include children younger than 5 years of age, people 65 years of age or older, those with chronic medical conditions, pregnant women, residents of long-term care facilities, American Indians and Alaska Natives, and people who are morbidly obese.

- Annual influenza immunization is recommended in the US for all those 6 months or older. Infants younger than 6 months can be protected by vaccinating the pregnant mother and other members of the household.

Diagnosis

- Clinical signs and symptoms often are not distinctive; laboratory testing is the only reliable way to distinguish influenza from other respiratory infections.

- Real-time reverse transcription polymerase chain reaction (RT-PCR) is the gold standard for diagnosis. Virus culture is less sensitive but yields isolates that can be typed, subtyped, and characterized antigenically and genetically.

- Rapid diagnostic tests have various degrees of sensitivity and specificity. During periods when influenza viruses are known to be circulating in the community, a patient with a negative rapid test result still may have influenza, and clinicians should use clinical judgment to decide whether to initiate antiviral therapy or obtain additional diagnostic testing.

Treatment

- Immediate empiric treatment is recommended for those with suspected influenza requiring hospitalization or with progressive or complicated illness.

- Treatment is recommended for people with chronic medical conditions, pregnant women, and children younger than 5 years of age.

- Two classes of antiviral drugs are available: the adamantanes (i.e., rimantadine and amantadine) and the neuraminidase inhibitors (i.e., oseltamivir, zanamivir, and peramivir).

- In recent years, neuraminidase inhibitors are the mainstay of treatment.

- Local surveillance and prevalence of antiviral resistance should be used to guide antiviral treatment strategies.

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RNA Viruses: Arenaviridae and Filoviridae

OUTLINE

230 Filoviruses and Arenaviruses

230

Filoviruses and Arenaviruses

Margot Anderson, Daniel G. Bausch

The Viruses

Viruses of the families Filoviridae and Arenaviridae are composed of single-stranded RNA in lipid envelopes.[1–3] The Filoviridae comprise five pathogenic species of Ebola virus and one Marburg virus (Table 230.1). Arenaviruses are taxonomically divided into Old World (i.e., Africa) and New World (i.e., Americas) viruses.

TABLE 230.1

Filoviruses and Arenaviruses Known to Cause Human Disease

Virus	Disease	Principal Reservoir or Vector	Geographic Distribution of Disease	Annual Cases	Disease-to-Infectio Ratio
FILOVIRIDAE					
Ebola	Ebola virus disease or Ebola HF	Fruit bat?	Sub-Saharan Africa, Philippines[b]	—[a]	1 : 1
Marburg	Marburg virus disease or Marburg HF	Fruit bat (Egyptian fruit bat [*Rosettus aegyptiacus*])	Sub-Saharan Africa	—[a]	1 : 1
ARENAVIRIDAE[c]					
Old World					
Lassa	Lassa fever	Rodent (multimammate rat [*Mastomys*	West Africa	30,000–50,000	1 : 10

		natalensis])			
Lujo[d]	Lujo HF	Unknown; presumed rodent	Zambia	Unknown	Unknow
Lymphocytic choriomeningitis	Lymphocytic choriomeningitis	Rodent (house mouse [*Mus musculus*]); transmission from pet rodents also documented	Worldwide	Unknown; infection probably frequent but underrecognized	3 : 10
Dandenong[e]	Dandenong fever	Unknown: presumed rodent	Unknown: Balkan Peninsula?	Three cases recognized to date	Unknow
ARENAVIRIDAE					
New World					
Junin	Argentine HF	Rodent (corn mouse [*Calomys musculinus*])	Argentine pampas	<50	1 : 1.5
Machupo	Bolivian HF	Rodent (large vesper mouse [*Calomys callosus*])	Beni Department, Bolivia	<50	1 : 1.5
Guanarito	Venezuelan HF	Rodent (cane mouse [*Zygodontomys brevicauda*])	Portuguesa State, Venezuela	<50	1 : 1.5
Sabiá[f]	Brazilian HF	Unknown; presumed rodent	Rural area near Sao Paulo, Brazil?	—[e]	1 : 1.5
Chapare[g]	Chapare HF	Unknown; presumed rodent	Cochabamba, Bolivia	Unknown	Unknow

[a] Although some endemic transmission of the filoviruses (i.e., Ebola > Marburg) occurs, these viruses have most often been associated with outbreaks. Until the 2013–2016 Ebola virus outbreak in West Africa, in which more than 28,000 cases occurred, filovirus outbreaks typically had less than 100 cases, with 425 cases being the largest previous outbreak.

[b] Five species of Ebola virus are known, with the following mean case-fatality ratios: Ebola Zaire, 76%,;Ebola Sudan, 55%; Ebola Bundibugyo, 37%; Ebola Tai Forest, 0% (only 1 recognized case), and Ebola Reston, 0% (not pathogenic to humans).[89] All are endemic to sub-Saharan Africa, with the exception of Ebola Reston virus which is found in the Philippines.

[c] In addition to the arenaviruses listed in the table, Flexal, Pirital, and Tacaribe viruses have caused human disease as a result of laboratory accidents. Another arenavirus, Whitewater Arroyo, has been detected in sick people in California, but its role as a pathogen has not been clearly established.

[d] Discovered in 2008 in an outbreak of 5 cases (4 fatal) in South Africa. The index case came to South Africa from Zambia.

[e] Discovered in 2009 in a cluster of 3 fatal transplant-related cases that occurred in Australia. The donor died of cerebral hemorrhage 10 days after returning to Australia

from a 3-month visit to the former Yugoslavia, where he had traveled in rural areas.

[f] Discovered in 1990. Only 3 cases (1 fatal) of Sabiá virus infection have been identified, 2 of them from laboratory accidents.

[g] Discovered in 2003 in a small outbreak in Cochabamba, Bolivia. Chapare virus was isolated from a fatal case, but few other details from the outbreak have been reported.

HF, hemorrhagic fever.

Along with viruses from the Bunyaviridae and Flaviviridae families (see Chapters 218 and 219), filoviruses and arenaviruses are the principal causative agents of hemorrhagic fever (HF). Viral HF is an acute and sometimes severe systemic illness that classically involves fever, a constellation of initially nonspecific signs and symptoms, potentially severe volume loss through diarrhea and vomiting, and a propensity for shock and bleeding. The exception is lymphocytic choriomeningitis virus (LCMV), an Old World arenavirus that has become disseminated worldwide. LCMV infection is classically associated with febrile illness and central nervous system (CNS) disease.[4] A variant of LCMV, Dandenong virus, associated with severe disease in transplant recipients, was discovered in 2009.[4a] Many of these viruses are considered potential bioweapons.[5]

Epidemiology

Maintenance in Nature and Transmission to Humans

Filoviruses and arenaviruses are zoonotic, with the endemic area for each virus restricted by the distribution of its animal reservoir.[1,2,4] With the exception of Lassa virus and the 2013–2016 epidemic of Ebola virus in West Africa (>28,000 cases), human infection is uncommon.

Humans play no role in maintenance of the virus in nature. Fruit bats are thought to be the filovirus reservoir. Pathogenic arenaviruses are maintained in rodents, with strict pairing between the specific virus and animal reservoir (see Table 230.1).[4,6,7] Miners, spelunkers, forestry workers, and others with exposure to environments where bats typically roost are at risk of filovirus infection.[8–10] The rodents that transmit Lassa and Machupo viruses and LCMV commonly invade domestic environments, whereas the reservoirs for Junín and Guanarito viruses typically inhabit agricultural fields, wood lots, or other rural habitats.[4]

Transmission to humans usually occurs through inadvertent exposure to animal excreta or saliva or, in some cases, blood and other body fluids when the animals are hunted and butchered.[1–4] Nonhuman primates, especially gorillas and chimpanzees, and other wild animals can serve as intermediate hosts for filoviruses.[11–13] These animals are presumably infected by exposure to bats and develop severe and usually fatal disease similar to human HF. Because the HF viruses are rapidly inactivated by heating, infection likely occurs through exposure during preparation rather than by consumption of cooked meat. LCMV has been transmitted to humans through contact with infected laboratory mice and cell lines and by pet rodents, especially hamsters.[14]

Human-to-Human Transmission

Although attack rates usually are low (15% to 20%, even for Ebola Zaire virus, which probably is the most transmissible), secondary human-to-human transmission does occur (see Table 230.1), as seen most dramatically in the 2013–2016 Ebola Zaire virus outbreak in West Africa.[15–17] Large outbreaks typically are fueled by nosocomial transmission in resource-poor regions, where basic infection control practices cannot be maintained.[17a] Infectivity parallels the clinical state, and people are most infectious late in the course of severe disease.[18] There is no evidence of transmission during the incubation period.

Transmission occurs through direct contact with blood or body fluids and probably occurs through oral or mucous membrane exposure, most often in the context of providing care to a sick family member (i.e., community exposure) or patient (i.e., nosocomial transmission), or by participation in burial rituals that involve washing and touching corpses.[19] Transmission through breast milk and congenital transmission have been documented.[20] Infection through fomites cannot be excluded but is probably not common unless the object is obviously contaminated with blood or body fluids.[20,21] Sexual transmission from virus persistence in the semen has been identified more than 1 year after recovery from acute disease.[22]

Although infectious aerosols have been artificially produced in the laboratory, which is a concern because of the potential for their use in biowarfare, epidemiologic and limited laboratory-based data do not suggest aerosol transmission between humans in natural settings.[15,19,23–26]

Pathobiology

After inoculation onto mucous membranes or deposition in the lungs and initial replication in local tissues, virus migrates to regional lymph nodes and ultimately through the blood to a broad range of tissues.[1–3,27] The liver, endothelium, and adrenal glands appear to be particularly important targets. The CNS is especially affected in LCMV and New World arenavirus infections.[3]

Microvascular instability and impaired hemostasis are the hallmarks of viral HF.[1–3] Impaired hemostasis can entail endothelial cell, platelet, or coagulation factor dysfunction. Disseminated intravascular coagulopathy (DIC) may occur. Because bleeding has been seen in a minority of HF cases, renaming of some of the diseases has been suggested to de-emphasize the hemorrhagic component. For example, Ebola HF is now commonly referred to as Ebola virus disease (EVD). Rather than exsanguination, severe disease results from an inflammatory and vasoactive process consistent with the systemic inflammatory response syndrome (see Chapter 11) and severe fluid loss from diarrhea, vomiting, and fever resulting in insufficient effective circulating intravascular volume, cellular dysfunction, and multiorgan system failure.[27,28] Cardiac inotropy can be inhibited, especially in cases of Lassa fever, and pericardial and pleural effusions have been seen when radiographic equipment is available.[29,30] In severe disease, viremia remains unchecked, and there is little or no antibody response.[18] Inflammatory cell infiltrates at sites of infection also are mild.[31]

Immune cell activation is the fundamental process in the pathogenesis of LCMV, although without the same effects on endothelial cell function and hemostasis as in HF.[3] CNS involvement in LCMV typically occurs 1 or 2 weeks after disease onset, after virus has cleared from the bloodstream, and it is thought to be immune mediated, although virus can still be recovered from the cerebrospinal fluid (CSF) at this time.[3]

Clinical Manifestations

Viral Hemorrhagic Fever

Filovirus and arenavirus infections are seen in both sexes and all age groups, with a spectrum from asymptomatic infection (especially for arenaviruses) to rapidly fatal disease.[8,32–39] It is usually not possible, especially at disease onset, to distinguish the specific virus cause by clinical manifestations. The syndrome produced by the New World arenaviruses is usually collectively referred to as *South American HF*.

After an incubation period of 8 to 10 days (range, 3–21 days), patients typically have nonspecific signs and symptoms, including fever, general malaise, anorexia, headache, chest or retrosternal pain, sore throat, myalgia, arthralgia, lumbosacral pain, and dizziness. Hiccups can occur early in EVD. The pharynx may be erythematous or exudative in Lassa fever, sometimes leading to misdiagnosis of streptococcal pharyngitis. Gastrointestinal signs and symptoms ensue rapidly and include nausea, vomiting, epigastric and abdominal pain, abdominal tenderness, and diarrhea, which in EVD can be voluminous.[37,38,40,41] Misdiagnosis as acute appendicitis or another abdominal emergency sometimes occurs. A dry cough with a few scattered rales is common, but prominent pulmonary symptoms are uncommon early in the course of the disease. Jaundice is not typical and suggests a different diagnosis.

Clinical manifestations for a subset of patients, especially those with filovirus infections, progress to vascular instability marked by conjunctival injection (not accompanied by itching, discharge, or rhinitis), facial flushing, edema, bleeding, hypotension, shock, and proteinuria. The likelihood of clinically discernible hemorrhage is highest for filovirus infections and the South American HFs, although it still is seen in a minority of patients. Hematemesis, melena, hematochezia, metrorrhagia, petechiae, purpura, epistaxis, and bleeding from the gums and venipuncture sites can develop, but hemoptysis and hematuria are uncommon (Fig. 230.1). Bleeding rarely occurs in the first few days of illness. Swelling of the face and neck is sometimes seen in Lassa fever, and Lujo HF is relatively specific to these diseases (see Fig. 230.1).[36] Extensive edema attributed to massive vascular leakage (i.e., swollen baby syndrome) has been described in children with Lassa fever.[42]

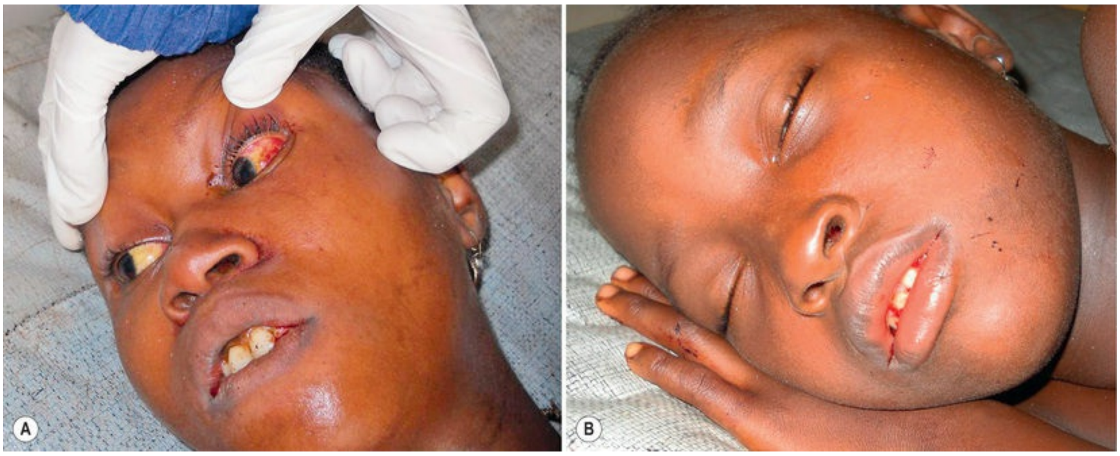

FIGURE 230.1 Subconjunctival hemorrhage, oral bleeding, and facial swelling in patients with Lassa fever. (Courtesy of Victor Lungay.)

Morbilliform, maculopapular, petechial, and ecchymotic rashes can occur. Maculopapular rash on the torso or face may be an early and relatively specific, although not sensitive, indicator of filovirus infection. For unclear reasons, rash typically occurs in light-skinned people with Lassa fever, but it is rare in dark-skinned people.

CNS manifestations, including disorientation, tremor, gait anomalies, convulsions, and hiccups, can occur in end-stage disease, especially in South American HF, particularly Argentine HF.[3] Renal insufficiency or failure is common. Pregnant women often come to medical attention because of spontaneous abortion and vaginal bleeding.[43–45] However, a few Ebola virus–infected pregnant women have had mild or atypical clinical manifestations, posing a diagnostic dilemma.[46]

Common clinical laboratory findings are summarized in Table 230.2. Radiographic and electrocardiographic findings usually are nonspecific and correlate with the physical examination findings.[47,48]

TABLE 230.2

Clinical Laboratory Tests and Characteristic Findings for Filovirus and Arenavirus Infections

Test	Characteristic Findings and Comments
Leukocyte count	Early: moderate leukopenia, sometimes with atypical lymphocytes Later: leukocytosis with left shift suggesting bacterial infection
Hemoglobin and hematocrit	Hemoconcentration
Platelet count	Mild to moderate thrombocytopenia
Electrolytes	Sodium, potassium, and acid-base perturbations, depending on fluid balance, renal function, and stage of disease
BUN and creatinine	Renal failure can occur late in disease.
Serum chemistries (AST, ALT, amylase, γ-glutamyl transferase, alkaline phosphatase, creatinine kinase, lactate dehydrogenase, lactate acid)	Usually increased, especially in severe disease; AST > ALT; lactate level >4 mmol/L (36 mg/dL) can indicate persistent hypoperfusion and sepsis
Sedimentation rate	Normal or decreased
Blood gas	Metabolic acidosis can indicate shock and hypoperfusion
Coagulation studies (PT, PTT, fibrinogen, fibrin split products, platelets, D-dimer)	DIC common in Ebola, Marburg, Lujo virus, and New World arenavirus infections
Urinalysis	Proteinuria common; hematuria seen occasionally; sediment can show hyaline-granular casts and round cells with cytoplasmic inclusions
Blood culture	Useful early to exclude viral HF if positive and later to evaluate for secondary bacterial infection; blood should be drawn before antibiotic therapy is instituted
Stool culture	Useful to exclude viral HF if positive for hemorrhagic bacillary dysentery
Thick and thin blood smears	Useful for the diagnosis of blood parasites (malaria and trypanosomes) and bacterial sepsis (meningococcus, *Capnocytophaga*, and anthrax); negative in viral HF unless coinfection
Rapid test, PCR, or other assay for malaria	Negative in viral HF unless coinfection with malaria
Febrile agglutinins or other assay for *Salmonella enterica* serotype Typhi	Negative in viral HF unless coinfection
Cerebrospinal fluid analysis	Usually normal in viral HF Lymphocytic choriomeningitis: protein moderately increased (50–150 mg dL); glucose normal or decreased; mononuclear pleocytosis up to 5000 cells/mm^3 (although neutrophils can comprise up to 25% of cells)

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; DIC, disseminated intravascular coagulation; HF, hemorrhagic fever; PCR, polymerase chain reaction; PT, prothrombin; PTT, partial thromboplastin time.

In fatal cases, death occurs about 8 to 10 days after onset of disease for the filoviruses and 10 to 14 days for arenaviruses. Shock, bleeding, neurologic manifestations, high levels of viremia, elevated levels of aspartate aminotransferase (>150 IU/L), and pregnancy, especially during the third trimester, are indicators of a poor prognosis. The mortality rate is especially high for children younger than 5 years of age.[36,38,40,49] Despite slightly improved survival of pregnant women during the 2013–2016 outbreak in West Africa, most pregnancies result in stillbirths or early neonatal death, with only one report of a child, who received various experimental therapies, surviving beyond the neonatal period.[45,45a] Rarely, women who were infected during pregnancy have survived acute EVD without aborting, only to experience a stillbirth of a macerated fetus in the subsequent weeks. The stillborn fetuses were confirmed to be positive for the virus by RT-PCR testing, despite no evidence of persistent Ebola virus in the mothers' blood. This finding is thought to result from the relative immune privilege of the intrauterine compartment during pregnancy and immaturity of the fetal immune system allowing viral persistence.

Lymphocytic Choriomeningitis Virus Infection

Many LCMV infections are asymptomatic or result in a nonspecific febrile illness, sometimes accompanied by photophobia.[50] After 7 to 14 days of illness and often after a brief period of defervescence, a spectrum of CNS manifestations ensue in some patients. They include aseptic meningitis (the most common) and fulminant encephalitis with cranial nerve palsies, abnormal reflexes, focal seizures, polyneuritis, flaccid paralysis, and papilledema. CNS symptoms also can occur without a recognized febrile illness. Rare manifestations and complications of LCMV infection include hydrocephalus, transverse myelitis, Guillain-Barré syndrome, hearing loss, arthritis, parotitis, orchitis, myocarditis, mucosal bleeding, and pneumonia.

Congenital infection has been associated with spontaneous abortion in early pregnancy and, when occurring later in pregnancy, with a variety of neurologic deficits, including psychomotor retardation, microcephaly and macrocephaly, ventriculomegaly, hydrocephalus, nonimmune hydrops fetalis, intracranial hemorrhage, chorioretinitis with visual loss, and seizures (Fig. 230.2).[51] Occasional LCMV and Dandenong virus infection in organ transplant recipients has resulted in a highly fatal syndrome, sometimes resembling viral HF.[52]

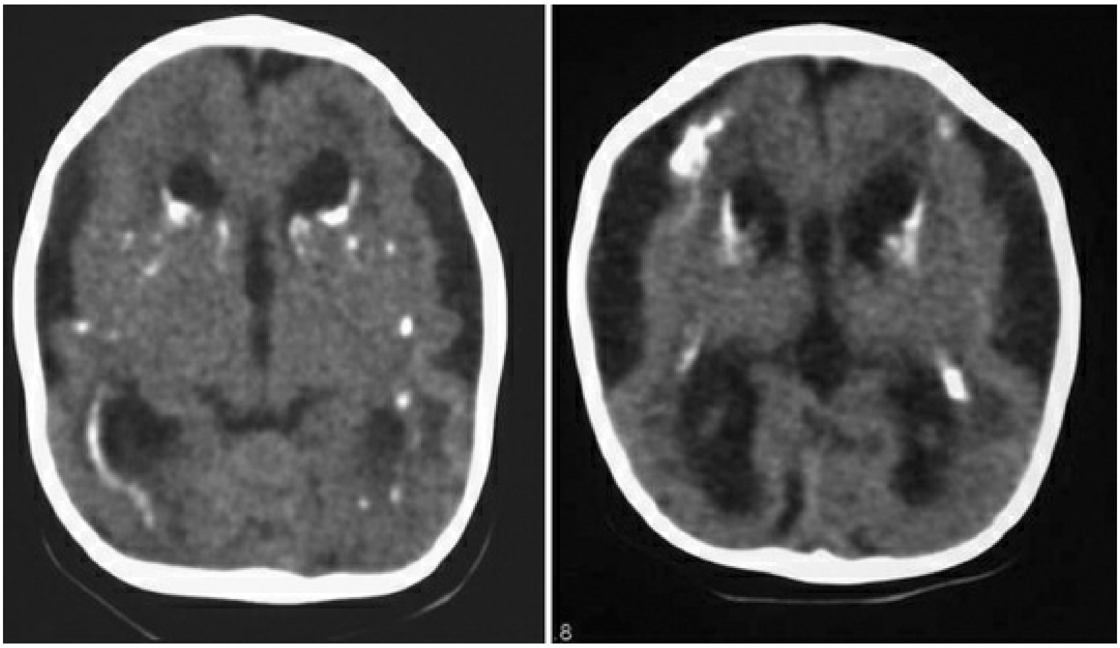

FIGURE 230.2 Computed tomography of a 5-month-old infant with profound developmental delay and chorioretinitis due to intrauterine lymphocytic choriomeningitis virus infection. Scans show microcephaly, lissencephaly, and calcifications that are periventricular, intracerebral, and over the convexities of the brain. The serum immunofluorescent antibody titer was greater than 1 : 1024. The mother had no known illness or exposure to rodents during pregnancy. (Courtesy of G.L. Rodgers and S.S. Long, St. Christopher's Hospital for Children, Philadelphia, PA.)

Differential Diagnosis

The nonspecific presentation of people with filovirus and arenavirus infections leads to an extremely broad differential diagnosis that varies by geographic region but often includes malaria, typhoid fever, leptospirosis, rickettsial disease, and many other systemic febrile illnesses.[1–3] Clinicians should focus on making the general diagnosis of viral HF and then quickly seek laboratory support to confirm the syndrome and specific infecting virus. For LCMV with neurologic manifestations, the arboviral meningitides and herpes encephalitis must be ruled out.

A diagnosis of viral HF should be considered in patients with a clinically compatible syndrome who within 3 weeks before disease onset had any of the following risk factors:

- Resided in or traveled to areas where a HF virus is known or suspected to be endemic
- Possibly had direct contact with blood or body fluids of someone with a suspected or confirmed viral HF during their acute illness (includes healthcare personnel and those caring for family members at home or touching corpses at a funeral)
- Had contact with live or recently killed wild animals (especially bats, nonhuman primates, and rodents) in or recently arriving from an area where a HF virus is endemic
- Worked in a laboratory or animal facility where HF viruses are handled
- Had sex with someone recovering from a viral HF in the past year

Because viral HF is rare even in people possessing one of the risk factors, alternative diagnoses always should be sought aggressively, especially malaria and typhoid fever. Acts of bioterrorism must be considered if viral HF is seen in a patient without any of the risk factors, especially if there are clusters of cases.[5] All confirmed cases should be reported immediately to local, state, and federal health authorities.

Laboratory Testing

Prompt laboratory diagnosis is imperative. RT-PCR is the mainstay of diagnosis, with sensitivities and specificities usually higher than 90%.[18,53–56] A few rapid dipstick tests have been developed, but because these tests await thorough validation, results should be confirmed with RT-PCR.[57] ELISA, IFA, and cell culture may play important roles in confirming current or past infection. Testing can be arranged through a few specialized laboratories, such as the US Centers for Disease Control and Prevention (404-639-1115).

Treatment

The overall clinical management of viral HF is the same as for septic shock.[1–3,58] Patients should be managed in an intensive care unit when possible, with maintenance of strict viral HF infection prevention and control procedures. The possibility of DIC should be assessed and treatment with appropriate blood products implemented. Intravenous access is usually indicated. Because of the risk of bleeding and hematomas at insertion sites and the risk of nosocomial contamination, caution should be exercised in the use of central intravascular catheters, intramuscular and subcutaneous injections, arterial puncture, and procoagulants (e.g., nonsteroidal anti-inflammatory drugs).

Although aggressive oral and intravenous hydration is the mainstay of supportive care, this may pose a challenge in infants and young children requiring constant encouragement and assistance to drink and supervision of intravenous catheters. Hydration by intraosseous or subcutaneous routes has also been employed.[58a]

Isotonic intravenous fluids (i.e., lactated Ringer solution or normal saline) with or without added dextrose are recommended based on the finding of marked hyponatremia in many patients with EVD.[37] Pain and fever should be treated with acetaminophen, tramadol, or narcotics as necessary, and vomiting should be treated with ondansetron. Gastric ulcer prophylaxis with a proton-pump inhibitor or H_2-blocking agent also is recommended.

Broad-spectrum antibacterial or antiparasitic therapy, or both, with specific consideration of antimalarial agents and doxycycline for tickborne rickettsial diseases, should be given until a diagnosis can be confirmed. If fever persists or begins anew after initially resolving, secondary bacterial infection should be suspected.

The massive 2013–2016 outbreak in West Africa prompted accelerated clinical trials and occasional compassionate use of various experimental therapeutic approaches to EVD, including the use of convalescent plasma, monoclonal antibodies, and various antiviral compounds.[59–61] Although early-phase clinical trials have demonstrated the safety of some of these approaches, efficacy has yet to be demonstrated definitively, perhaps in part because studies were started too late and enrolled too few patients to reach target enrollment and statistical endpoints. These products remain experimental and are not generally available.

The antiviral drug ribavirin reduces mortality of Lassa fever. The drug is administered intravenously for 10 days as a loading dose of 30 mg/kg (maximum, 2 g), followed by 15 mg/kg (maximum, 1 g) every 6 hours for 4 days, and then by 7.5 mg/kg (maximum, 500 mg) every 8 hours for another 6 days.[62] Ribavirin should be diluted in 0.9% saline and infused slowly, with the dose diminished in people with a creatinine clearance of less than 50 mL/min. Based on limited data, the drug also appears to be efficacious for the South American HFs.[63,64]

The main side effect of ribavirin is a dose-dependent, mild or moderate hemolytic anemia that infrequently necessitates transfusion and disappears with cessation of drug treatment. Rigors may occur when ribavirin is infused too rapidly.[62] Relative contraindications to use in the pediatric population include severe anemia or hemoglobinopathy, renal insufficiency, decompensated liver disease, and known hypersensitivity. Hemoglobin, hematocrit, and bilirubin levels should be monitored.

Transfusion of appropriately titered convalescent plasma within the first 8 days of illness reduces the mortality rate for Argentine HF.[63] However, this therapy has been associated with a convalescent-phase neurologic syndrome characterized by fever, cerebellar signs, and cranial nerve palsies in 10% of those treated. Direct comparison of the efficacy of convalescent plasma and ribavirin for Argentine HF has not been conducted. Animal studies show convalescent plasma to be efficacious for Lassa fever, but only if it contains a high titer of neutralizing antibody (which cannot be assumed uniformly) and there is a close antigenic match between the infecting viruses of the donor and recipient.[65] In most countries, no stockpile of immune serum is available for patients with viral HF.

The treatment of LCMV infection is supportive. Anti-inflammatory drugs such as corticosteroids may be considered for severe CNS disease. The single surviving patient in a cluster of LCMV cases related to transplanted organs received ribavirin and had a reduction of immunosuppressive therapy.[66]

Hospital Discharge and Management of Convalescence

Viremia usually clears rapidly in survivors, although clearance can be delayed for months or even years from a few immunologically protected sites, especially the testes and chambers of the eye.[22,67,68] It has become customary to require a negative RT-PCR test result for blood samples as a criterion for discharge, although experience over the years before this practice was adopted does not suggest virus shedding or any transmission risk after acute symptoms resolve, with the exception of sexual transmission.[18,69,70]

Convalescence from viral HF can be prolonged. A host of short-term and long-term problems have been reported. Persistent arthralgia and myalgia, general weakness and fatigue, headache, and visual problems are among the most prominent, sometimes lasting years after resolution of acute disease.[67,71–78] Post-EVD uveitis is a common problem that can result in significant loss of visual acuity, including complete blindness, if untreated. Sensorineural deafness occurs in up to 30% of patients after Lassa fever and has been reported after Venezuelan HF and EVD.[2,3,79] Although less easily measured, the mental health impacts of viral HF undoubtedly are often profound. Depression, anxiety, and posttraumatic stress disorder are common in these patients, who have survived severe illness with lasting sequelae, often have lost family members to the same disease, and have endured significant stigmatization on recovery.

Survivors of viral HF should be evaluated regularly after discharge by general history and physical and mental health examinations and referred for social services. For survivors of filovirus infection, eye examinations, including slit-lamp examinations to screen for uveitis, should be performed. Clinical management during convalescence usually is supportive. Sulfasalazine has been effective for arthralgia refractory to nonsteroidal anti-inflammatory drugs. Psychological counseling or pharmacotherapy often is warranted.

Prevention

All patients with a syndrome compatible with viral HF should be presumed infectious and kept isolated under standard HF precautions until a specific diagnosis is made. Placement in a negative-airflow room is prudent, but hermetically sealed isolation chambers are not required. Access to the patient should be limited to designated staff and family members with specific training on infection control guidelines and the use of personal protective equipment.

Personal Protection and Nursing Precautions

Specific viral HF isolation precautions (i.e., mask, double gloves, gown, protective apron, face shield, head covering, and shoe covers or rubber boots) are recommended.[80] Positive airway pressure masks and other small-particle aerosol precautions should be used when performing procedures that can generate aerosols, such as endotracheal intubation. Items that were in direct contact with a patient with a viral HF can be decontaminated using chlorine bleach or one of various commercially available lysis buffers.

Contact Tracing

People with unprotected direct contact with a patient during the symptomatic phase of illness should be monitored daily for evidence of disease for 21 days after the last contact. If possible, contacts should check their temperature daily and record the results in a log. Confinement of asymptomatic people is usually not warranted, but those who develop signs or symptoms compatible with a viral HF should be isolated immediately until the diagnosis can be excluded.

Fortunately, the low secondary attack rates of filoviruses and arenaviruses afford a measure of reassurance, even when cases go unrecognized, as long as proper barrier nursing is maintained. Because mild cases, which may be more difficult to recognize, usually have low infectiousness, missed or delayed diagnosis of these patients is unlikely to pose a problem from the standpoint of infection control.

Vaccines

Several experimental vaccine candidates show promise for filoviruses and arenaviruses, including a recombinant vesicular stomatitis virus-based vaccine for EVD that showed 100% efficacy in a phase III trial conducted during the 2013–2016 outbreak in West Africa.[81] The live, attenuated vaccine Candid #1 decreases morbidity and mortality rates for Argentine HF and may protect against Bolivian HF, although it does not appear to cross-protect against other arenaviruses.[82] However, the vaccine is not approved in the United States, and supplies are insufficient even for Argentina, where it is produced.

Postexposure Prophylaxis

Various experimental drugs and vaccines have been used as postexposure prophylaxis on the basis of compassionate use for people potentially exposed to Ebola virus, but the efficacy of these measures can not be determined.[83–85] For arenaviruses, postexposure prophylaxis with oral ribavirin (35 mg/kg loading dose [maximum 2.5 g], followed by 15 mg/kg [maximum 1 g] three times daily for 10 days) may be considered for people with direct unprotected contact with blood or body fluids (e.g., needle stick injury, splash of blood to mucous membranes).[86,87] Prophylaxis should not be given if the only exposure was during the incubation period. Convalescent plasma is efficacious as postexposure prophylaxis for Argentine HF.[63]

Reservoir and Vector Control

Effective and sustainable control measures usually entail avoidance of known reservoir habitats or, when this is not feasible, implementation of measures to prevent direct contact with virus vectors and reservoirs and their excreta.[88] Most successful prevention programs integrate biologic and chemical control measures with education and regulation to change human behaviors that put people at risk. Although it is not possible or even desirable to completely eliminate the various animal reservoirs, trapping rodents may occasionally be useful in outbreaks and more routinely for control of mice and LCMV inside homes.

Key Points

Filovirus and Arenavirus Hemorrhagic Fever

Diagnosis

- The nonspecific clinical manifestations of filovirus and arenavirus hemorrhagic fever (HF) make clinical diagnosis of single cases extremely difficult, especially early in the course of illness.

- Viral HF should be considered in febrile patients with a compatible clinical syndrome and history of travel and exposure, especially if the patient fails to respond to empiric treatment for the usual infectious diseases prevalent in the area.

- Despite the name, hemorrhage is seen in a minority of patients with viral HF, and its absence should not be used to exclude the diagnosis.

Management

- Treatment of viral HF usually is supportive and follows guidelines for the management of septic shock.

- Ribavirin and treatment with convalescent plasma have demonstrated efficacy in a few arenavirus HFs.

Prevention

- All patients with a syndrome compatible with filovirus or arenavirus HF should be presumed infectious and kept isolated under strict HF precautions until a specific diagnosis is made.

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RNA Viruses: Retroviridae

OUTLINE

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Introduction to Retroviridae

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The Retroviridae are a large family of enveloped RNA viruses that primarily infect vertebrates.[1] Retroviruses require the generation of a double-stranded DNA genome (i.e., provirus) and integration within host DNA for the production of viral progeny. Integration of proviral DNA can modify the host genome to produce transforming genes, or oncogenes, and research into this process has provided insights into the molecular basis of carcinogenesis. Retroviruses also have medical importance as potential vectors for gene transfer and gene therapy.[2]

Human endogenous retroviruses (HERVs) consist of proviral DNA or partial genomes that have been integrated into host genomes,[3] and they can constitute up to 8% of human genomic DNA. HERV proviral DNA in germline cells can be passed from parents to their offspring. Transcription of HERV elements does not result in the generation of infectious viruses, but it can produce functional proteins, which play a role in normal physiologic processes, including embryonic development. Although implicated in several diseases, the precise role of HERVs as etiologic or contributing agents of disease is unknown.[3,4]

Retroviruses that are passed horizontally through blood, sexual secretions, or breast milk are known as exogenous retroviruses. Human pathogens include human T-cell lymphotropic virus types 1 and 2 (HTLV-1 and HTLV-2), which are associated with T-lymphocyte lymphomas and neurologic disease, and human immunodeficiency virus types 1 and 2 (HIV-1 and HIV-2), the causative agents of acquired immunodeficiency syndrome.

Retroviruses are composed of lipid-enveloped particles that are 80 to 100 nm in diameter. They have a protein core that contains two linear, positive-sense, 7- to 11-kb, single-stranded RNA genomes and viral enzymes important for viral replication (i.e., protease, reverse transcriptase, and integrase). Glycoprotein spikes in the lipid membrane envelope determine the host range of retroviruses through their interaction with target cell surface receptors and coreceptors. After virus entry into the cell, linear, double-stranded, proviral DNA is made from the single-stranded RNA of the virus by the viral reverse transcriptase enzyme. Integration of the provirus into the host genome is mediated by the viral enzyme integrase and is necessary for the production of viral particles. The long-term stability of the integrated provirus and its transmission to the cell's progeny provide the basis for persistence of the retrovirus over the lifetime of the host.

Regulatory sequences (i.e., long terminal repeats) on either end of the proviral genome flank the coding regions for viral structural (gag) proteins, envelope (env) proteins, and enzymes (i.e., DNA polymerase [pol], reverse transcriptase, and integrase). Some retroviral genomes (including those of HIV) contain at least two additional genes, *tat* and *rev*, that are essential for virus replication. Retroviral genomes also can contain various accessory genes, which can modify the replication kinetics and pathogenicity of the viruses.

Recombination and errors in reverse transcription in retroviruses can generate genomic diversity. Various selective pressures (e.g., virus cell tropism and growth fitness, host immune responses, antiretroviral therapies) can drive the evolution of a genetically diverse group of viral variants (i.e., quasispecies) over the course of infection. The evolution of the quasispecies provides a mechanism by which retroviruses can evade mechanisms of control such as host immune responses and antiretroviral therapies.

Retroviruses use host cell machinery to synthesize and process viral genomes, messenger RNA, and proteins necessary for the generation of progeny viral particles. Virion assembly requires encapsidation of viral RNA and takes place primarily at the cell plasma membrane. As the virion buds through cellular membranes, it picks up a lipid bilayer along with the viral envelope glycoproteins and several host cell membrane proteins.

Key Points

Retroviridae Characteristics

- Enveloped RNA viruses
- Spikes of glycoprotein in the lipid envelope mediate host cell entry.
- Viral reverse transcriptase converts the single-stranded RNA genome into a double-stranded provirus, and viral integrase mediates integration into the host genome.
- Integration into the host genome is required for production of virus progeny and forms a barrier to cure.
- Errors in reverse transcription and recombination generate genomic diversity Human pathogens include human T-cell lymphotropic virus types 1 and 2 (HTLV-1 and HTLV-2) and human immunodeficiency virus types 1 and 2 (HIV-1 and HIV-2).

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Human T-Cell Lymphotropic Viruses

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Epidemiology

Human T-cell lymphotropic (or lymphoma) viruses (HTLVs) are deltaretroviruses. The two most clinically important HTLVs are HTLV type 1 (HTLV-1) and HTLV type 2 (HTLV-2).[1,2] Infections with HTLV-3 and HTLV-4 have been identified in central African populations, but their clinical significance is unclear.[3,4]

HTLV-1 and HTLV-2 are most prevalent in southwestern Japan, the Caribbean, Melanesia, and parts of Africa. Around the world, an estimated 5 to 10 million people are infected with HTLV-1, with disease manifesting in only 5% of cases.[5] In the United States, about 1 in 6250 volunteer blood donors has antibodies to HTLV-1 or HTLV-2. However, foci of HTLV-1 infection have been reported from the Gulf Coast states and from New York City among people who were born in the Caribbean or had sexual contact with people from that area. Endemic foci of HTLV-2 infection exist among the Guayani Indians of Panama and some Native Americans living in Florida and New Mexico. In the United States, Europe, South America, and Asia, HTLV-2 infection is four times more common than infection with HTLV-1 among injection drug users.

Genomic similarities between HTLV and simian T-lymphotropic viruses (STLVs) suggest that the human viruses are derived from viruses transmitted to humans from nonhuman primates. Human populations that are exposed to nonhuman primates through hunting, butchering, or keeping primates as pets appear to be at increased risk for HTLV infections. STLVs do not appear to be transmitted to humans through occupational exposure to nonhuman primates (e.g., employment in primate centers or laboratories). HTLVs are spread by three modes: sexual contact, infusion of blood or blood products, and breastfeeding. Parenteral exposure to HTLV-1–contaminated blood is an efficient route of transmission.

Since 1988, all US blood donors have been screened for HTLV-1 antibodies and excluded if seropositive. HTLV-3 and HTLV-4 appear to be serologically indistinguishable from HTLV-1 and HTLV-2.[4] Because the viruses are infectious only when present in lymphocytes, there is no risk of infection from serum or clotting factors, and people with hemophilia do not have high rates of seropositivity. HTLV-1 and HTLV-2s infection occur in childhood and appear to be associated principally with transmission through breast milk.[6]

Rates of 4% to 22% have been reported for mother-to-child transmission, and most cases are thought to occur through breastfeeding.[7] The risk of transplacental or perinatal transmission of viruses from an infected mother is about 5% for an infant who is not breastfed, whereas the risk of infection is about 25% for the breastfed child. Infected women should not breastfeed their infants.

HTLV-1 is not transmitted by casual contact. Medical workers are not at risk of contracting infection if they observe universal precautions.

Clinical Manifestations

HTLV-1

Infection with HTLV-1 can cause two diseases: adult T-cell leukemia/lymphoma (ATLL) and HTLV-1–associated myelopathy/tropical spastic paraparesis (HAM/TSP).[8] The cumulative lifetime risk of developing either disease is approximately 5% for infected people.[5]

ATLL is a clonal malignancy of well-differentiated CD4$^+$ T lymphocytes, occurring in about 2% to 4% of HTLV-1–infected people.[9] Although CD4$^+$ and CD8$^+$ T lymphocytes are infected, the leukemic cells are exclusively CD4$^+$.[10,11] The HTLV-1 DNA provirus is integrated into the genome of malignant cells. Infection appears to have a long latency period, usually manifesting clinically in persons 40 to 60 years of age after many years of asymptomatic infection. The disease typically is aggressive and rapidly fatal. It is associated with hypercalcemia and characteristic lytic lesions of bone, ascribed to the ability of virus-encoded *trans*-activating factor tax to activate genes for parathyroid hormone production.

HAM/TSP is a slowly progressive neurologic disease associated with permanent weakness in the legs, paresthesias, long tract neurologic abnormalities, and urinary incontinence.[12] Although these manifestations of infection are evident in less than 1% of all people infected with HTLV-1, they occur in about 20% of those infected by contaminated blood. Antibodies to HTLV-1 are found in the cerebrospinal fluid of patients with this disorder. Treatment with corticosteroid or other immunosuppressive agents is only modestly beneficial. HAM/TSP affects patients of all ethnic groups, but it is most prevalent in geographic regions where HTLV-1 has been endemic for a long time.[13]

HTLV-1 has been associated with isolated cases of uveitis, arthritis, polymyositis, and panbronchiolitis. HTLV-1–infected people commonly come to medical attention with skin lesions. Skin manifestations are observed in 43% to 72% of ATLL cases.[14] Children can manifest infective dermatitis associated with HTLV-1 (IDH), a severe form of chronic eczema associated with *Streptococcus pyogenes* and *Staphylococcus aureus* infections.[15]

HTLV-2

HTLV-2 appears to have originated in Africa several thousand years ago.[16] DNA provirus has been detected in breast milk, and maternal-child transmission, probably due to breastfeeding, is documented. Rare cases of mycosis fungoides and large granular lymphocytic leukemia have been detected in HTLV-2–infected individuals, but causality has not been proved. HTLV-2 does appear to be associated with an HAM/TSP-like neurodegenerative disease and other neurologic disorders.[17] Bacterial skin infections have been described in those coinfected with HTLV-2 and HIV-1.

Key Points

Characteristics of Human T-Cell Lymphotropic Viruses

Epidemiology

- Human T-cell lymphotropic virus types 1 and 2 (HTLV-1, HTLV-2) are most clinically important.
- Between 5 and 10 million people are infected worldwide.
- HTLV-1 and HTLV-2 are most prevalent in southwestern Japan, the Caribbean, Melanesia, and parts of Africa.
- HTLVs are spread by sexual contact, infusion of blood or blood products, and breastfeeding.
- Most mother-to-child transmission occurs through breastfeeding, and avoidance of breastfeeding limits new infections.

Clinical Manifestations

- Adult T-cell leukemia/lymphoma (ATLL) is a clonal malignancy of well-differentiated CD4$^+$ T lymphocytes, and it occurs in about 2% to 4% of HTLV-1–infected people.
- HTLV-1–associated myelopathy/tropical spastic paraparesis (HAM/TSP) is a slowly progressive neurologic disease.
- HTLV-1 infection can manifest with dermatitis, uveitis, arthritis, polymyositis, and panbronchiolitis.

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Human Immunodeficiency Virus

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Human immunodeficiency virus types 1 and 2 (HIV-1 and HIV-2) are members of the *Lentivirus* genus of the Retroviridae family.[1] HIV-1 and HIV-2 appear to have entered humans as a result of cross-species transmission of simian immunodeficiency viruses (SIVs). HIV-1 is similar to an SIV that infects chimpanzees (SIV_{cpz}; Table 233.1), and HIV-2 is similar to SIV strains that infect sooty mangabeys (SIV_{sm}). The simian viruses do not cause disease in their natural hosts. Comparative genomic analyses of SIV_{cpz} and HIV-1 have documented at least 3 independent transmissions of SIV_{cpz} strains to humans. The current HIV-1 pandemic likely resulted from 1 of these transmission events in the first half of the 20th century.[2,3] Similar analyses also suggest that HIV-2 resulted from the transmission of SIV_{sm} to humans in West Africa in the first half of the 20th century.[4]

TABLE 233.1

Comparison of Human Immunodeficiency Viruses Types 1 and 2

	HIV-1	HIV-2

Source virus	Chimpanzee simian immunodeficiency virus	Sooty mangabey simian immunodeficiency virus
Geographic distribution	Worldwide	West Africa; India
Transmission	Sexual; contaminated needles; blood transfusion; mother-to-child	Sexual; mother-to-child; blood transfusion; lower overall transmissibility than that of HIV-1
Mother-to-child transmission	25%–35%[a]	≤4%[a]
Clinical manifestations	Lymphadenopathy; wasting syndrome; central nervous system disease; $CD4^+$ lymphocyte depletion and immunodeficiency	Same as those of HIV-1 but generally less rapid disease progression

[a] Transmission rates without antiretroviral therapy.

Human Immunodeficiency Virus Type 1

Life Cycle

The mature HIV-1 virion is approximately 110 nm in diameter and is composed of a core surrounded by a lipid bilayer envelope. The virion core consists of a structural shell composed of a protein (p24) processed from the gag precursor polypeptide. Within this shell are 2 copies of single-stranded RNA, 2 transfer RNA primers of host cell origin, and multiple copies each of the virus-encoded reverse transcriptase, integrase, and RNAse H enzymes. Matrix protein (p17), another product of the gag polypeptide precursor, surrounds the virion core and is associated with the transmembrane glycoprotein of the viral envelope (gp41). At least 3 more virus-encoded proteins (vpr, vif, and nef) are packaged within the virion. These proteins are active early in the intracellular life cycle of HIV-1 and contribute to the efficiency of infection. Trimers of an external glycoprotein (gp120), anchored by gp41, protrude from the lipid bilayer envelope. The gp120 glycoproteins contain binding sites for the cell surface HIV-1 receptor (CD4 molecule) and coreceptors (chemokine receptors) and therefore are functionally important in virus attachment and entry.

Virus–cell membrane fusion begins with the interaction of gp120 with the first immunoglobulin-like domain of the $CD4^+$ molecule expressed on the cell surface. This interaction causes conformational changes in gp120 that allow binding of gp120 to the coreceptor. Binding results in exposure of a hydrophobic domain in gp41 that in turn leads to the insertion of this domain into the cell membrane and the initiation of viral envelope–cell membrane fusion.

The 9-kb HIV-1 genome is similar in organization to that of other retroviruses, but it has at least 6 other genes (*tat, rev, vpr, vpu, vif,* and *nef*) that are not found in nonprimate retroviruses. Each of these genes encodes a protein that has been implicated in virus replication and pathogenicity.[5]

After internalization and uncoating of the viral core, a new viral life cycle begins with the generation of a DNA transcript of viral RNA through the activity of the viral reverse transcriptase. As the linear, double-stranded DNA provirus is generated, it remains associated with RNA, matrix proteins, and the viral integrase enzyme as a preintegration complex. For completion of the viral replication cycle, the preintegration complex must be transported from the cytoplasm to the nucleus and integrated into host genomic DNA. The extent to which integration and subsequent virion synthesis occur appears to depend on the cell cycle stage and activation state of the infected cell.[6] Cells with integrated provirus represent long-lived reservoirs for viral persistence and barriers to eradication of the virus from infected people.

Virion assembly takes place primarily at the cell plasma membrane. Structural (*gag*, envelope) and viral enzyme genes encode precursor proteins that are processed and cleaved to produce multiple gene products. Cleavage of the gag structural proteins by the viral protease enzyme occurs during viral assembly and is essential for the proper assembly of infectious virions. As the virus buds through cellular membranes, it acquires a lipid bilayer along with viral envelope glycoproteins. Understanding of the viral life cycle has contributed to the development of antiretroviral agents that block viral entry or inhibit viral enzymes, including reverse transcriptase, protease, and integrase.

Early Infection Events

The CD4 molecule is the primary cellular receptor for HIV-1; cells that express this molecule on their cell surfaces ($CD4^+$ T lymphocytes and cells of monocyte or macrophage lineage) are major targets for HIV-1 infection. Members of the chemokine receptor family are coreceptors for HIV.[7] Cell surface chemokine receptors are 7-transmembrane, G-protein–coupled receptors that transduce chemokine binding into intracellular signals, which in turn lead to the activation and migration of leukocytes. The configuration of cysteine motifs in chemokines is the basis for structural groupings (C-C-C or CC-chemokines; C-X-C or CXC-chemokines) that determine differences in biologic activities. Most HIV-1 strains use the CCR5 or CXCR4 (also known as LESTR or fusin) coreceptors.

CCR5 appears to be important especially in the initial establishment of infection. HIV-1 infection is uncommon in people with a homozygous 32-bp deletion in CCR5; their lymphocytes do not express this chemokine receptor on cell surfaces and are relatively resistant to infection with primary HIV-1 isolates in vitro. Nonetheless, several HIV-1–infected people who are homozygous for this defect have been identified, a finding suggesting that under some circumstances, other coreceptors could be used in the establishment of infection. Although heterozygosity for the CCR5 deletion mutant does not appear to protect from the acquisition of infection, studies in both adults and children indicate that it may protect against disease progression.

Following virus entry, HIV-1 proteins can interact with multiple cellular proteins to enhance virus replication.[8] For example, HIV-1 Tat interacts with the cellular protein cyclin-T1 to increase the efficiency of proviral transcription; the interaction of HIV-1 Gag with tumor suppressor gene 101 (TSG-101) enhances virus budding from the plasma membrane. Several cellular proteins that restrict the replication of primate lentiviruses also have been identified. CEM-15 is a member of the APOBEC 3 family of proteins. These proteins are cytidine deaminases that are packaged into retroviruses; during reverse transcription, they introduce G to A hypermutations that alter the integrity of the proviral DNA. HIV-1 Vif restores HIV-1 infectivity by complexing with CEM-15 and targeting it for proteosomal degradation, thus preventing its incorporation into virions. TRIM-5α is a cellular restriction factor that appears to interfere with uncoating of the viral RNA following entry.

Mother-to-Child HIV Transmission

Mother-to-child HIV-1 transmission can occur during gestation (in utero), during delivery (intrapartum), or in the postpartum period through breastfeeding. Although admixture of maternal-fetal blood is a potential mechanism for in utero and intrapartum transmission, most infections are thought to occur on mucosal (ocular or gastrointestinal) exposure to maternal blood and cervicovaginal fluids during delivery or to breastmilk after birth. CD4$^+$ T lymphocytes are the likely major source of virus production and dissemination throughout the body. Regardless of the route of infection, the gastrointestinal tract appears to be a major site of viral replication, persistence, and CD4$^+$ T-lymphocyte depletion throughout infection.[9,10]

Early Infant Diagnosis and Therapy

HIV-1 DNA can be detected by means of polymerase chain reaction assay in peripheral blood mononuclear cells of infected infants at birth, a finding suggesting in utero infection. In infants who are not breastfed, results of polymerase chain reaction assay are negative in the majority of infected infants (≤75%) at birth, but they become positive at 2 to 4 weeks of age; this finding suggests intrapartum transmission of HIV-1. In breastfeeding cohorts, up to 40% of infants can acquire HIV-1 through breast milk transmission. The administration of antiretroviral therapies can markedly reduce the risk of mother-to-child HIV-1 transmission.[11]

Rapid increases in the plasma HIV-1 RNA copy number to 10^5 to 10^7 copies/mL have been documented in vertically infected infants during the first weeks of life. By contrast, plasma HIV-1 RNA levels gradually decrease in untreated infants after the first 1 to 2 years of life, but mean plasma HIV-1 RNA levels do not drop to less than 10^5 copies/mL until at least the third year of life. A continued reduction in plasma HIV-1 RNA (mean −0.2 to −0.3 log decline per year) has been observed in vertically infected children through 5 to 6 years of age. Plasma HIV-1 RNA levels during infancy do not appear to distinguish between infants with rapid and slow disease progression. However, after 3 to 4 years of age, plasma HIV-1 RNA levels are predictive of disease progression. Reductions in plasma HIV-1 RNA after antiretroviral therapy have been associated with clinical benefit. The initiation of antiretroviral therapy in early infancy can preserve immune function and reduce HIV-associated morbidity and mortality rates[12–14]; early diagnosis and treatment of infants are recommended routinely, irrespective of symptoms or CD4 counts.[15,16] Initiation of combination antiretroviral therapy within hours of birth can markedly limit the generation of a persistent HIV reservoir.[17]

Human Immunodeficiency Virus Type 2

HIV-2 was first isolated in the mid-1980s from people with acquired immunodeficiency syndrome (AIDS) in West Africa. Since then, most cases of HIV-2 infection have been reported from West Africa, although cases have also been reported from Zimbabwe and India.[18] The distribution of HIV-2 infections in West Africa coincides with the natural habitat of the sooty mangabey. HIV-2 is thought to be a zoonosis resulting from cross-species transmission of SIV_{sm}. HIV-2 and SIV_{sm} are genomically similar and share an accessory gene, *vpx,* not found in other primate lentiviruses.

To a lesser extent, HIV-2 also shares structural and genomic similarities with HIV-1. The HIV-2 *gag* and *pol* genes share approximately 60% homology with corresponding HIV-1 genes, whereas the *env* genes share only 30% to 40% homology. Viral genomic differences form the basis for molecular assays that distinguish between HIV-1 and HIV-2. Corresponding differences in viral proteins form the basis for antibody tests that distinguish between infections with these viruses.

Heterosexual and mother-to-child transmission of HIV-2 has been documented. Transmission through blood transfusion also occurs. Transmission through contaminated needles is postulated but not well documented. Heterosexual and mother-to-child transmissions of HIV-2 appear to occur less readily than transmission of HIV-1. Antiretroviral therapy can reduce the risk of mother-to-child transmission of HIV-2.

The clinical manifestations of HIV-2 infection are similar to those of HIV-1. Lymphadenopathy, wasting syndrome, central nervous system disease, and $CD4^+$ depletion are common findings.

Opportunistic infections and malignant diseases are common complications. The rate of CD4$^+$ depletion is much slower, and the median time from infection to the development of AIDS is longer after HIV-2 infection than after HIV-1 infection. HIV-1 and HIV-2 coinfection occurs and follows a clinical course similar to that in people infected with HIV-1 alone.

The cause of the reduced transmissibility and pathogenicity of HIV-2 is unclear. Peripheral blood proviral load in HIV-2 infection is similar to that in HIV-1 infection, but plasma RNA levels are much lower in HIV-2–infected people than in HIV-1–infected people. Improvements in molecular techniques to detect, quantify, and characterize HIV-2 should allow improved understanding of the pathogenesis of HIV-2 infections in humans.

Key Points

Human Immunodeficiency Virus

Human Immunodeficiency Virus Type 1

Life Cycle

- 9-kb genome encodes 3 structural and 6 regulatory genes.
- Viral integrase mediates production of double-stranded DNA; integration of this provirus into the host genome is required for completion of the virus life cycle and serves as a barrier to cure.
- Understanding of the virus life cycle has led to the development of antiretroviral agents that block viral entry or inhibit viral enzymes.

Early Infection Events

- Viral entry is mediated by interaction between viral surface glycoproteins and host cell surface molecules (CD4, chemokine receptors).
- Multiple host proteins can interact with viral proteins to enhance or inhibit viral replication.

Mother-to-Child Transmission

- Mother-to-child transmission can occur during gestation (in utero) or, more commonly, during delivery (intrapartum) or in the postpartum period through breastfeeding.

- Antiretroviral regimens effectively prevent this transmission.

Early Infant Diagnosis and Therapy

- Early infant diagnosis requires direct detection of the virus in peripheral blood samples.

- Early diagnosis and antiretroviral therapy are routinely recommended to reduce HIV-related morbidity and mortality.

- Very early therapy (within hours of birth) can restrict the size of long-lived HIV reservoirs.

Human Immunodeficiency Virus Type 2

- HIV-2 is transmitted through sexual contact and from mother to child but appears to be less readily transmitted than HIV-1.

- HIV-2 infection is associated with immunodeficiency, but the rate of $CD4^+$ depletion is slower and the median time from infection to the development of AIDS is longer than with HIV-1.

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RNA Viruses: Picornaviridae

OUTLINE

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Introduction to Picornaviridae

Kevin Messacar, John F. Modlin, Mark J. Abzug

The family Picornaviridae represents a large group of small, positive-stranded RNA viruses that infect a wide variety of hosts throughout the animal kingdom and are now classified by RNA sequence alignment (Table 234.1).[1] Included in the Picornaviridae family are 3 genera commonly associated with human infection: *Enterovirus, Parechovirus,* and *Hepatovirus*.

TABLE 234.1
Classification of the Human Picornaviruses

Genus	Species
Enterovirus	*Human enterovirus A*
	Human enterovirus B
	Human enterovirus C
	Human enterovirus D
	Human rhinovirus A
	Human rhinovirus B
	Human rhinovirus C
Parechovirus	*Human parechovirus*
Hepatovirus	*Hepatitis A virus*

Seven enterovirus species (*human enterovirus A* through *D* and *human rhinovirus A* through *C*), the human *parechovirus* species, and *hepatitis A virus*, the only member of the *Hepatovirus* genus (see Chapter 237), cause human infection. The enteroviruses, rhinoviruses, and parechoviruses each contain multiple serotypes, which are differentiated from one another both by RNA sequence and by neutralization with immune serum. Important clinical and epidemiologic characteristics are associated with viral serotype, and some biologic and genetic diversity also exists within each serotype.

Enteroviruses, rhinoviruses, and hepatitis A virus can be distinguished from one another on the basis of certain biophysical, clinical, and epidemiologic properties. Rhinoviruses replicate optimally at 33°C, thus reflecting their adaptation to the nasal mucosa. They are unstable at a pH <6 and can be recovered only from the respiratory tract. *Enterovirus D68* is unique among enteroviruses and shares similar optimal growth temperature and acid lability with rhinoviruses. Other enteroviruses and hepatitis A virus, which remain stable over a wide pH range, survive the acid environment of the stomach and are shed in the feces. Enteroviruses replicate in diverse tissues and cause many different diseases. Hepatitis A virus replication is limited to liver cells, and extrahepatic clinical manifestations of hepatitis A infection are rare. The physical, clinical, and epidemiologic properties of the parechoviruses are indistinguishable from those of the enteroviruses.

Biology

The major physical characteristics of picornaviruses are shown in Box 234.1. Picornavirus infection at the cellular level requires the presence of specific host cell membrane proteins that serve as receptors for viral attachment.[2] The receptors for many of the human picornaviruses have been identified and characterized.

Box 234.1

Major Physical Characteristics of the Picornaviridae

Size: 24–30 nm

Symmetry: icosahedral

Envelope: none

Genome: single-stranded RNA, $2.3–2.8 \times 10^6$ daltons (7.5 kb)

Penetration, uncoating, and release of the positive-stranded RNA genome into the cytoplasm occurs within minutes at 37°C. The RNA functions as a monocistronic messenger, the product of which is a large polyprotein that is cleaved in a series of steps into both structural and nonstructural regulatory proteins. Four capsid proteins (VP1, VP2, VP3, and VP4) are assembled in equimolar amounts into the capsid. Progeny RNA are copied from the genome by a negative-stranded RNA intermediary and are encapsidated to complete the replication cycle. In vitro infection produces approximately 10^4 to 10^5 particles/cell, but the number of infectious particles is 10- to 1000-fold lower. Host protein and RNA synthesis is compromised within 3 hours of cell infection, and cell lysis occurs within 8 hours, with release of the progeny virions.

Picornaviruses are resistant to ether, chloroform, and alcohol but are inactivated by formaldehyde, phenol, and irradiation. They are rapidly inactivated at temperatures in excess of 50°C.

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Polioviruses

Stephanie B. Troy, Yvonne A. Maldonado

Pathogen and Pathophysiology

Polioviruses are positive-stranded RNA viruses belonging to the Picornaviridae family. They have a naked protein capsid consisting of 4 structural proteins, VP1 to VP4. The genomic RNA is approximately 7440 to 7500 nucleotides in length. For genome replication, RNA-dependent RNA polymerase is encoded that lacks a proofreading mechanism. Consequently, poliovirus can mutate rapidly with replication. The 3 serotypes of poliovirus are antigenically distinct, but all 3 have 70% nucleotide identity.[1] Polioviruses can be stored indefinitely at −20°C, but they are inactivated by formaldehyde, chlorination, and ultraviolet light.

Humans are the only known natural hosts; however, poliovirus can replicate in other primates. The virus is propagated exclusively in cultured cells of primate origin because other cell lines lack a functional receptor molecule. Since identification and molecular cloning of the viral receptor, transgenic mice have been developed that are susceptible to all 3 serotypes of poliovirus.[2]

Poliovirus is transmitted primarily by the fecal-oral route and replicates in the pharynx and lower intestinal tract (Table 235.1). Only small amounts of infectious virus are needed to cause infection. Virus is typically shed in the pharynx for 1 to 3 weeks and in the gut for 4 to 8 weeks after primary infection. During reinfection, pharyngeal shedding is rare and fecal shedding is reduced to <3 weeks. The incubation period generally is 7 to 14 days but can be as short as 3 days and as long as 35 days. The virus spreads quickly from the alimentary tract to regional lymph nodes. After several days, minor viremia ensues, and certain sites (e.g., muscle, fat, liver, spleen, and bone marrow) become infected. If virus is contained at this point, subclinical infection occurs. Further replication of virus in these tissues leads to major viremia and the onset of clinical symptoms. The central nervous system is seeded in approximately 1% of infections. The virus also can infect the central nervous system through axonal transport from skeletal muscle[3]; such infection may correlate with the intense myalgia seen at the onset of paralysis in affected patients.

TABLE 235.1

Pathogenesis of Poliovirus Infection

Site of Virus Replication	Days After Acquisition	Clinical Illness
Pharynx and intestine	0–1	Asymptomatic
Regional lymph nodes	1–3	Asymptomatic
Blood (minor viremia), muscle, fat, liver, spleen, bone marrow	3–7	Minor illness
Blood (major viremia), central nervous system	7–21	Major illness

Poliovirus replicates within neurons; the anterior horn cells of the spinal cord are involved most often. Neurons in nuclei of the medulla, vermis of the cerebellum, midbrain, thalamus and hypothalamus, palladium, and motor cortex of the cerebrum also can be involved. Rarely, the posterior horn cells and dorsal root ganglia are infected. Although poliovirus infection usually destroys neurons, injury occasionally is reversible.

Serum neutralizing antibodies develop after approximately 1 week and protect against paralysis but not against reinfection. Immunity to poliovirus infection is serotype specific, without any cross-protection. Immunity persists for life. Local antibody appears 1 to 3 weeks after infection and limits virus replication at the mucosal level. Reinfection occurs; however, the duration of viral shedding is reduced, and viremia does not occur.

Epidemiology

Poliovirus infection occurs primarily in summer and fall in temperate climates and year round in tropical areas. Warm weather favors the spread of virus. Before the Industrial Revolution, poliomyelitis occurred predominantly in an endemic form, infecting most infants early in life. Most infections with poliovirus were inapparent; paralytic disease developed in a small proportion of infected people.

As hygiene and sanitation improved, especially in the more temperate countries, epidemics appeared. Change occurred because of lack of contact with the virus by the youngest populations, and large groups of older children and adults became susceptible. The first large epidemic of paralytic poliomyelitis in the United States occurred in Vermont in 1894 and involved approximately 130 people. Epidemics increased in size and frequency and peaked in 1952, when 57,879 cases were reported in the US. Introduction of the inactivated vaccine in 1955 led to a sharp decline in the number of cases.

In 1988, the World Health Assembly developed the goal of global eradication of poliomyelitis by the year 2000.[4] This objective was determined to be feasible because poliovirus has no animal reservoir, does not survive for long periods in the environment, and induces lifelong immunity after disease or vaccination. Global eradication strategies were developed and implemented, and although poliomyelitis has not been eradicated globally, remarkable progress has been made. Annual cases have dropped more than 99%, from 350,000 in 1988 to 416 in 2013.[5] Wild poliovirus serotype 2 was eradicated globally in 1999, and no wild poliovirus serotype 3 has been isolated since November 2012. Only 3 countries (Afghanistan, Nigeria, and Pakistan) continue to have uninterrupted wild poliovirus transmission. Unfortunately, wild poliovirus has been exported from endemic countries and has caused several large outbreaks in previously poliovirus-free countries, including Tajikistan and the Republic of Congo in 2010, Chad in 2011, and Somalia in 2013 (Fig. 235.1).[6] These outbreaks demonstrate that sustaining high levels of immunization coverage, even in poliovirus-free countries, is critical to eradication efforts.

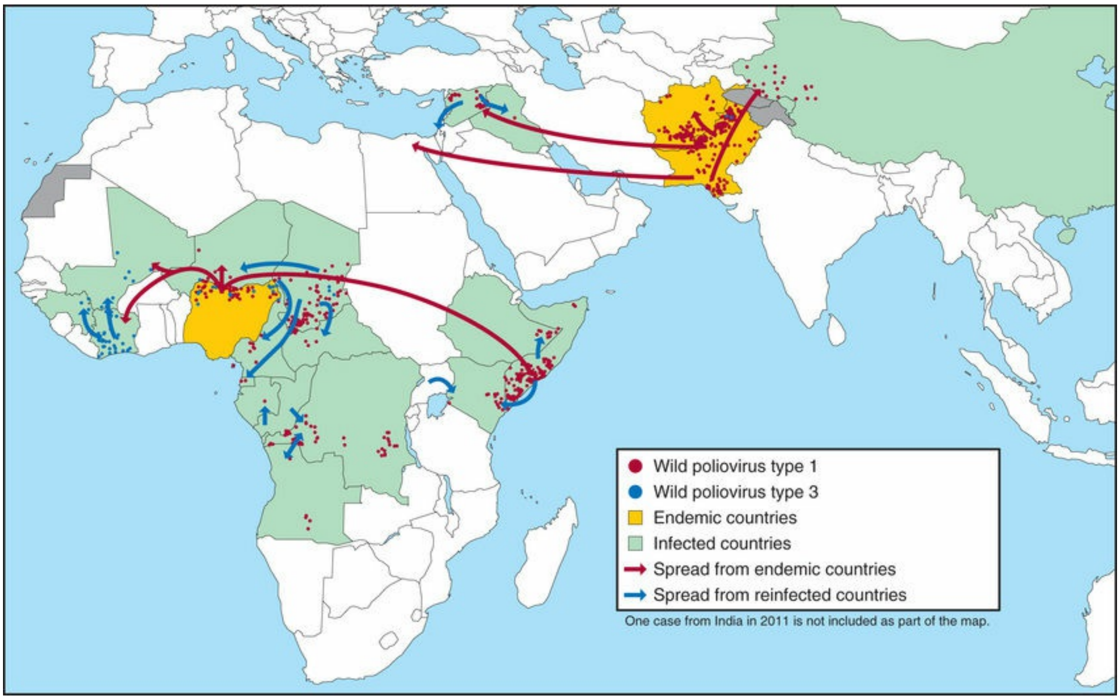
● Wild poliovirus type 1
● Wild poliovirus type 3
🟨 Endemic countries
🟩 Infected countries
→ Spread from endemic countries
→ Spread from reinfected countries
One case from India in 2011 is not included as part of the map.

FIGURE 235.1 **Global wild poliovirus distribution and international spread, 2011 to 2014.** (From World Health Organization; provided by Dr. Stephen Cochi.)

One complicating factor in global eradication is that oral poliovirus vaccine (OPV) can mutate and cause poliomyelitis. OPV can cause vaccine-associated paralytic poliomyelitis (VAPP) in vaccinees or their close contacts, at a rate of approximately 4.7 cases per million births.[7] Congenital humoral immunodeficiencies confer a 3000-fold higher risk of VAPP.[8] Of more concern was the discovery in 2000 that with prolonged replication, OPV can mutate to form vaccine-derived polioviruses (VDPVs), capable of causing poliomyelitis outbreaks.[9] VDPVs are defined as isolates with >1% VP1 sequence divergence from their parental OPV strain for serotypes 1 and 3 and >0.6% sequence divergence for serotype 2.[8] They can evolve from person-to-person OPV spread in undervaccinated communities (circulating VDPVs [cVDPVs]) or from prolonged (>1 year) intestinal OPV replication in patients with congenital humoral immunodeficiencies (immunodeficiency-associated VDPVs [iVDPVs]). Between 2000 and 2014, cVDPV outbreaks occurred in 22 countries and caused >750 cases of paralytic poliomyelitis (Fig. 235.2). The attack rates and severity of disease associated with cVDPV are similar to those seen with wild poliovirus.[10] OPV serotype 2 appears to circulate longer and be transmitted more readily in the community; this feature may explain why serotype 2 accounts for >85% of isolated cVDPVs.[11] The mortality rate was >60% in the >70 patients identified who were excreting iVDPV, but likely because most of the cases were in high- and middle-income countries with good sanitation and high levels of population immunity, iVDPV has not been known to cause an outbreak.[8,12]

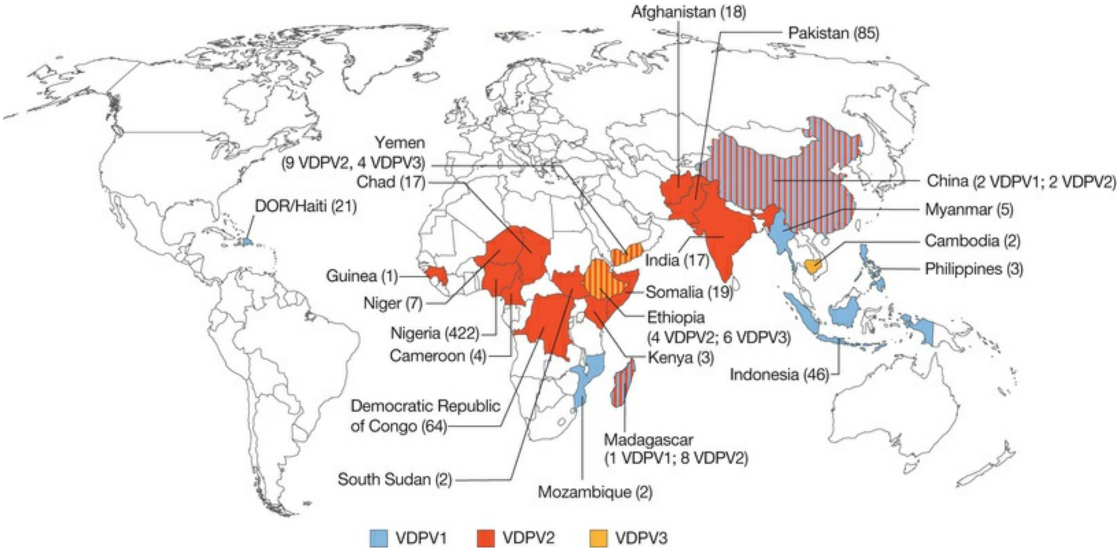

FIGURE 235.2 **Cases of paralytic poliomyelitis from circulating vaccine-derived poliovirus (VDPV), 2000 to 2014.** (Data from www.polioeradication.org.)

Clinical Manifestations

From 90% to 95% of poliovirus infections produce no symptoms or nonspecific minimal symptoms, such as fever, malaise, anorexia, and sore throat. Aseptic meningitis develops in 4% to 8% of infected children, but recovery usually is complete in 5 to 10 days; <1% of infections lead to paralytic disease. Known provocative events for developing paralytic disease include strenuous exercise during the first few days of major viremia and intramuscular injection 2 to 4 weeks before infection.[13,14]

Paralytic illness in children often is biphasic, with an initial self-resolving, minor illness. The child then experiences high fever and intense muscle pain accompanied by a decrease or loss of reflexes. The appearance of paralysis is sudden and progresses to complete loss of motor function in 1 or more extremities over a period of several hours. Maximal loss of function develops within 5 days of onset. The hallmark of poliomyelitis is spotty, asymmetric paresis or paralysis, with larger muscles involved more frequently than smaller muscles (e.g., of the hands and feet) and lower limbs more often affected than upper limbs. Bladder paralysis and bowel atony commonly occur but improve over a period of 1 to 3 days. Pain, spasticity, nuchal and spinal rigidity, and hypertonia occur early and result from lesions in the brainstem, spinal ganglia, and posterior columns. In general, paralysis tends to subside over time, with maximal improvement by 6 months. However, 60% of affected people exhibit some degree of residual deficit. Sensory abnormalities are rare except in patients with the most severe cases.

Bulbar (brainstem) poliomyelitis occurs in 5% to 35% of patients with paralytic cases, is the most severe form of the disease, and can result in respiratory compromise secondary to involvement of the respiratory center in the brainstem or infection of the 9th, 10th, and 12th cranial nerves. Cranial nerve involvement results in paralysis of the pharynx, soft palate, and vocal cords, with subsequent respiratory compromise. Currently, <7% of patients with spinal poliomyelitis die, usually as a result of respiratory failure from paralysis of the respiratory muscles. In contrast, as many as 60% of patients with bulbar paralysis died before modern methods of assisted ventilation became available.

Other diseases can mimic poliomyelitis. Nonpoliomyelitis enteroviruses, especially coxsackievirus A7, enterovirus 71, and more recently enterovirus 68 (by association), can cause sporadic cases, as well as small outbreaks of paralytic disease. Guillain-Barré syndrome causes ascending symmetric paralysis, and infant botulism causes descending symmetric paralysis. West Nile encephalitis can cause unilateral flaccid paralysis, and Lyme disease can cause neuropathy. Acute flaccid paralysis not caused by poliovirus generally occurs at a rate of 2 to 6 cases per 100,000 children <15 years old.[5]

Diagnosis

Results of routine laboratory studies are not distinctively abnormal. The complete blood cell count and differential cell count usually are unremarkable. Examination of cerebrospinal fluid demonstrates changes consistent with aseptic meningitis. Definitive diagnosis can be made when poliovirus is isolated from a clinical specimen in a patient with a compatible clinical syndrome. Poliovirus can be recovered readily from the throat and stool and rarely from the cerebrospinal fluid of infected people. The virus produces cytopathic effects in monolayers of monkey kidney cells, genetically engineered mouse cells with a poliovirus receptor, and human cells within 1 to 2 weeks. VDPVs and wild-type polioviruses, as well as other enteroviruses, cannot be distinguished without additional specific studies such as polymerase chain reaction or antiserum-based microneutralization assays. In the absence of virus isolation, a serologic diagnosis can be made by demonstrating an increase in poliovirus neutralizing antibodies against a specific serotype in paired acute and convalescent serum.

Treatment

Supportive care is the mainstay of treatment. Analgesics and bed rest are indicated. Manual decompression of the bladder, medication to relieve severe muscle spasms, intermittent catheterization, or the shortterm use of a parasympathetic stimulant can be necessary if bladder paralysis exists. Ventilator support can be necessary for patients with respiratory compromise. Although no approved antiviral treatments are currently available, several poliovirus antiviral compounds and antipoliovirus monoclonal antibodies are in clinical or preclinical testing.[15]

Special Considerations

Pregnant women have an increased risk of paralytic disease. Rarely, poliovirus causes an intrauterine infection resulting in abortion or premature delivery; malformations are not a consequence. Infection acquired from a mother incubating the virus at the time of delivery can result in paralytic disease in the newborn. Immunocompromised patients are prone to the development of progressive, often fatal disease. People with B-lymphocyte immunodeficiency are susceptible to chronic or disseminated infection from wild and attenuated vaccine virus.

New neurologic symptoms develop in approximately 25% to 35%

of patients with paralytic disease 25 to 35 years after infection.[16] This "postpolio syndrome" is characterized by muscle weakness, pain, atrophy, and fatigue. The muscles involved are the same as those involved in the original illness. The causes of these changes remain unclear; postulates include neuronal "fallout," slow infection, or immunopathologic mechanisms.

Prevention

Use and Efficacy of Salk and Sabin Vaccines

Poliomyelitis reached pandemic proportions in the US in the first half of the 20th century. During the early 1950s, paralytic disease developed in 10,000 to 20,000 people annually during the summer and fall. Considering that paralytic illness represented <1% of total infections, millions of infected people likely contributed to the spread of virus throughout communities.

The first inactivated poliovirus vaccine (IPV, Salk) was introduced in 1955, just 6 years after the virus had been successfully propagated in tissue culture of nonneurogenic origin.[17] Use of IPV was followed by an immediate decline in paralytic poliomyelitis from 37 to 0.8 cases per 100,000 population in 1961.[18] In 1961 to 1962, live OPV (Sabin) was introduced and quickly supplanted the use of IPV because it was easier to administer, induced lifelong immunity, provided mucosal immunity, and secondarily immunized contacts through fecal shedding of virus.

The initial use of OPV in the US and elsewhere resulted in a dramatic reduction in the global incidence of poliomyelitis. In most developing nations, OPV is still used for routine and mass immunization programs and has resulted in a dramatic decline in paralytic disease in these regions. However, outbreaks of poliomyelitis occurred in developing countries with relatively high rates of vaccine coverage because of suboptimal seroconversion rates, especially in tropical regions. Possible explanations include vaccine instability, vaccine formulation, concurrent enteric infections, malnutrition, and the presence of inhibitory substances in the intestine.[19,20]

To improve immunogenicity, the formulations of both IPV and

OPV were changed in 1987 and 1990, respectively. The newer, enhanced-potency IPV (eIPV) contains 40, 8, and 32 D-antigen units per dose of poliovirus types 1, 2, and 3, respectively, compared with 20, 2, and 4 D-antigen units per dose in the original Salk vaccine. In 1984, Finland experienced a unique epidemic that involved 9 cases of paralytic disease caused by serotype 3 virus. Investigation demonstrated an unexpectedly low rate of seropositivity (i.e., 60%) to type 3 poliovirus in the population. The decline in the seropositivity rate from earlier years was attributed to a decline in serotype 3 poliovirus content of vaccine and a slight change in the immunologic and molecular characteristics of the epidemic virus compared with the vaccine virus.[21] The increased antigenic content of eIPV is associated with a higher seroconversion rate after the administration of fewer doses.[22] Similarly, the newer formulation of OPV contains higher antigen content (10^6, 10^5, and 6×10^5 median tissue culture infective dose [$TCID_{50}$] of Sabin types 1 to 3, respectively, versus 10^6, 10^5, and 3×10^5 $TCID_{50}$ of Sabin types 1–3).[20] The OPV formulation change was made to increase seroconversion to serotype 3, which has historically had lower seroconversion rates than the other 2 serotypes. Both eIPV and OPV produce high serum neutralizing antibody titers after 3 doses, and poliovirus immunity lasts for decades after vaccination.[23–25]

Vaccine-Associated Paralytic Poliomyelitis

After the dramatic reduction in cases of poliomyelitis in the US, concern about VAPP increased. From 1980 through 1995, 132 cases of VAPP were reported in the US.[26] Of these cases, approximately 40% occurred in previously healthy vaccine recipients, 31% in healthy contacts of vaccine recipients, and 24% in immunodeficient people. Serotype 3 is most commonly isolated from patients with VAPP, followed by serotype 2.[7] Seventy-four percent of VAPP cases in OPV recipients occur following the first dose of OPV, and 52% of VAPP cases in contacts of OPV recipients occur in people who have never been vaccinated with OPV. Intramuscular injections within 30 days of immunization with OPV are associated with higher rates of VAPP.[27] The incidence of VAPP in the US remained steady at approximately 4 cases annually over a decade without wild-type paralytic poliovirus infection until the transition to the exclusive use of IPV in the US in 2000.

Alternative Vaccination Strategies

A combined schedule of eIPV and OPV has been used by several countries and has several advantages. First, most VAPP cases could be avoided using a schedule of eIPV followed by OPV because VAPP generally occurs in OPV recipients who have not been vaccinated previously. In addition, several studies have demonstrated that sequential dosing of both eIPV and OPV in either order provides better systemic and mucosal immunity than does administration of either vaccine alone.[23,28–30]

Monovalent OPV (mOPV) against serotype 1 or 3, and bivalent OPV (bOPV) against both serotypes 1 and 3, has been introduced for use in mass immunization campaigns in countries where wild poliovirus is endemic or has been imported. Immunization with mOPV leads to approximately 3 times more type-specific antibody concentrations than trivalent OPV.[10,31,32] However, mOPV1 and mOPV3 use in place of the trivalent vaccine may have contributed to an outbreak of circulating VDPV type 2 in Nigeria because fewer children were immune to serotype 2.[10]

Efforts have been made to make eIPV more affordable for developing countries. eIPV has been combined with other injectable vaccines into pentavalent and even hexavalent vaccines without decreasing immunogenicity.[33] Another strategy is to administer a factional dose of eIPV intradermally. Twenty percent of the standard eIPV dose given intradermally results in lower antibody titers than does the full dose intramuscular eIPV but, depending on vaccination timing, can achieve comparable seroprotection rates. One study evaluating a booster of 40% dose intradermal eIPV versus full-dose intramuscular eIPV showed comparable antibody titers and immunity levels.[25] Other strategies to reduce the cost of eIPV are being studied, including intradermal eIPV patches, adjuvanted eIPV, and optimization of the eIPV production process.[34]

Enhanced-Potency Inactivated Poliovirus Vaccine, Oral Poliovirus Vaccine, and the

Poliomyelitis Eradication End Game

The role of eIPV versus OPV for routine immunization is reassessed frequently. When given in a 3-dose schedule, both vaccines provide lifelong serologic immunity for a majority of recipients. OPV results in better mucosal immunity, a feature that could help prevent the spread of polioviruses in the community.[35] OPV also can boost immunity in contacts of recipients through spread of the vaccine virus. In addition, OPV is significantly less expensive than IPV, costing $0.15 versus $2.50 per dose.[34] However, OPV alone is less likely to provide adequate immunity in certain tropical countries. Furthermore, OPV carries an attendant risk of both VAPP and VDPV. In 2012, more cases of paralytic poliomyelitis were caused by VAPP and VDPV globally than were caused by wild polioviruses.[36] Consequently, to achieve poliomyelitis eradication, OPV will need to be phased out.

The *Polio Eradication and Endgame Strategic Plan 2013–2018* produced by the World Health Organization is a coordinated plan to phase out the use of OPV.[36,37] It first recommended universal eIPV introduction (≤1 dose in all countries) in the fall of 2015, followed by a synchronized transition from trivalent OPV to bivalent OPV (containing only serotypes 1 and 3) in April 2016. The eIPV dose is recommended to provide some level of serotype 2 immunity to protect against circulating serotype 2 vaccine viruses (serotype 2 wild poliovirus has been eradicated). The switch to bivalent OPV would help remove serotype 2 vaccine virus from circulation to prevent new VDPV cases because most VDPV has been serotype 2. The strategic plan then recommends cessation of the use of bivalent OPV 3 years after wild poliovirus is last detected.

Current Poliovirus Immunization Schedule in the United States

Because of the absence of indigenous transmission of wild-type poliovirus in the US and the rare but continued occurrence of VAPP in the 1990s, the US Public Health Service recommended a sequential 2-dose eIPV–2-dose OPV vaccination schedule from 1997 through 1999.[26] Since January 2000, immunization has consisted of a

4-dose series of eIPV exclusively: at 2, 4, and 6 to 18 months and 4 to 6 years (see Chapter 6). The change to eIPV resulted in the elimination of VAPP in the US, without a negative impact on vaccine coverage.

In the US, OPV has not been used since 2000, but it could be implemented by public health officials for mass vaccination in the event of a poliomyelitis outbreak. Travelers to countries where OPV is used, who are previously unimmunized, or who have not received a booster dose of IPV should be aware of the risk of VAPP in these settings and should consider IPV immunization. Travelers who have received an incomplete series should complete the series, not repeat it. For previously immunized adult travelers to poliomyelitis-endemic areas, vaccination with 1 dose of IPV is recommended; for adult travelers who have not previously been immunized, 3 doses of IPV should be given with intervals of at least 4 weeks between doses.[38] Available information suggests that only 1 lifetime booster dose of IPV is necessary. Current information regarding poliomyelitis-endemic areas can be obtained at www.polioeradication.org, and updated poliovirus immunization information can be obtained at www.cdc.gov.

Author Note

The content in this chapter solely represents the opinions of the authors and does not represent the opinion of the US Food and Drug Administration.

Key Points

Epidemiology, Diagnosis, and Management of Poliovirus Infections

Microbiology

- Positive-stranded RNA viruses belonging to the Picornaviridae family
- Three antigenically distinct serotypes

Epidemiology

- Humans are the only known natural host.

- Transmission is primarily by the fecal-oral route.

- Polioviruses are highly contagious.

- At its peak, 600,000 cases/year occurred, but vaccination has decreased the incidence by >99%, and global eradication is within reach.

Clinical Features

- Most infections are asymptomatic.

- In <1% of infections, paralysis ensues, characterized by asymmetric paralysis affecting proximal more than distal muscles and lower more than upper extremities.

- Bulbar paralysis, occurring in 5% to 35% of paralytic cases, is the most severe form; death usually results from respiratory compromise.

- Sensory abnormalities are rare.

Diagnosis

- Isolation of virus from a clinical specimen, usually stool.

Treatment/Prevention

- Treatment is supportive.

- Both a live, attenuated oral poliovirus vaccine (OPV) and an inactivated poliovirus vaccine (IPV) are used globally and are highly effective; IPV is used exclusively in the United States.

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Enteroviruses and Parechoviruses

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The human enteroviruses and parechoviruses are members of the Picornaviridae family that are commonly transmitted by enteric and respiratory routes and cause a wide spectrum of illnesses in people of all ages.

The enteroviruses are divided among 4 species within the genus *Enterovirus, human enterovirus A, B, C,* and *D,* based on RNA sequence relatedness. *Enterovirus species C* polioviruses and 3 additional genus *Enterovirus* species, *human rhinovirus A, B,* and *C,* are discussed in separate chapters. Before the availability of viral genome sequencing, the human enteroviruses were distinguished from the rhinoviruses by their relative acid stability and were subdivided into several classes based on differences in host range and into individually numbered serotypes within each class on the basis of differential neutralization by immune sera (Table 236.1). The 3 poliovirus serotypes are the prototypic enteroviruses that can be transmitted to nonhuman primates and replicate in primate cell culture. The coxsackieviruses originally were distinguished from polioviruses by their ability to cause paralysis and death in suckling mice. They are divided into groups A and B according to the type of disease produced in these animals (see Table 236.1). Group B coxsackieviruses are isolated readily in primate cell culture, whereas most group A coxsackieviruses grow poorly in cell culture. Echoviruses (enteric cytopathic human orphan viruses) are not pathogenic for mice and monkeys but are recovered readily in primate cell culture. All enterovirus serotypes identified since 1970 are designated simply as enterovirus and are numbered sequentially. More than 100 poliovirus, group A coxsackievirus, group B coxsackievirus, echovirus, and enterovirus serotypes are now distributed among the 4 *human enterovirus species A* through *D* (Table 236.2).

TABLE 236.1

Traditional Biologic Classification of the Human Enteroviruses

Subgroup	Serotypes	Experimental Host Range		Cell Culture
		Primates	Newborn Mice	
Polioviruses	1–3	++	–[a]	++
Coxsackievirus A	1–24[b]	–[c]	+++	±[d]
Coxsackievirus B	1–6	–	+++	++
Echoviruses	1–34[e]	–	–[f]	++
Enteroviruses	68–72[g]	Variable	Variable	+

[a] Rare strains (e.g., Lansing strain of poliovirus 2) have been adapted to mice.

[b] Coxsackievirus A23 has been reclassified as echovirus 9, which leaves 23 coxsackieviruses in group A. Antigenic interrelationships exist between coxsackievirus types A3 and A8, A11 and A15, and A13 and A18.

[c] Coxsackievirus A7 is pathogenic for the central nervous system of primates.

[d] Most coxsackievirus serotypes of group A are not readily isolated in cell cultures, but exceptions exist (e.g., types A9 and A16), and additional serotypes have been adapted to cell cultures.

[e] Echovirus 10 has been reclassified as reovirus 1 and echovirus 28 as rhinovirus 1A. Echovirus 34 is a variant of coxsackievirus A24; a total of 31 serotypes of echovirus therefore remain from the original 34. Antigenic interrelationships exist between echovirus types 1 and 8, 12 and 29, and 6 and 30. Echoviruses 22 and 23 are now reclassified in the genus *Parechovirus*.

[f] Except echovirus 21.

[g] Hepatitis A virus was designated as enterovirus 72 but now is classified as a separate Picornavirus genus.

TABLE 236.2

Classification of Human Enteroviruses by RNA Sequence

Enterovirus Species	Enterovirus Serotypes
A	Coxsackievirus A serotypes 2–8, 10, 12, 14, 16
	Enterovirus serotypes 71, 76, 89–91, 114, 119, 120, 121
B	Coxsackievirus A serotype 9

	Coxsackievirus B serotypes 1–6
	Echovirus serotypes 1–7, 9, 11–21, 24–27, 29–33
	Enterovirus serotypes 69, 73–75, 77–88, 93, 97, 98, 100, 101, 106, 107, 111
C	Coxsackievirus A serotypes 1, 11, 13, 17, 19–22, 24
	Poliovirus serotypes 1–3
	Enterovirus serotypes 95, 96, 99, 102, 104, 105, 109, 113, 116–118
D	Enterovirus serotypes 68, 70, 94, 111

Adapted from Picornavirus Taxa. http://www.picornastudygroup.com/taxa/taxa.htm.

Parechoviruses share many of the same biologic, clinical, and epidemiologic characteristics as enteroviruses, but they differ sufficiently in genomic sequence to be classified in a separate genus.[1] The prototypic parechovirus serotypes 1 and 2 originally were designated echovirus 22 and 23, respectively; 14 human parechovirus serotypes are recognized currently.

Pathogenesis

The pathogenesis of enterovirus infections has been investigated most extensively with poliovirus infection in monkeys and humans. Although comparable data are not available for the nonpolio enteroviruses, it is assumed that the pathogenic events are similar, although tissue and organ tropism is highly variable. Enterovirus D68 differs from other human enteroviruses in that it is primarily an agent of respiratory disease, sharing biologic and molecular properties with human rhinoviruses, and therefore is discussed separately at the end of this section.

Human enteroviruses are acquired directly or indirectly by the ingestion of virus that is shed in the feces or upper respiratory tract of infected contacts. Initial viral replication occurs in the upper respiratory tract and distal small bowel. Infectious virus is detectable in ileal lymphoid tissue 1 to 3 days after the ingestion of virus, and fecal shedding can be detectable for ≥6 weeks. Generally, enteroviruses are recovered from the gastrointestinal tract in greater density and for longer periods than from the upper respiratory tract, with the exception of enterovirus D68.

Viral replication in submucosal lymphoid tissue gives rise to a transient "minor" viremia that distributes virus to reticuloendothelial tissue in distant lymph nodes, liver, spleen, and bone marrow. Early viral replication does not cause histopathologic changes in the gastrointestinal tract or lymphoreticular tissue.

Further replication in these organs leads to a sustained “major” viremia and dissemination of virus to target organs such as the central nervous system (CNS), heart, and skin.

Many infected people control infection before major viremia and experience only transient symptoms or have asymptomatic infection. The onset of symptomatic disease including fever and other systemic manifestations coincides with major viremia, and organ-specific disease (i.e., poliomyelitis, myocarditis) is determined by tropism of the infecting serotype. Disease results from virus-induced cell necrosis and the accompanying inflammatory response. For example, animal models of myocarditis demonstrate initial viral replication in myocytes that results in scattered necrosis and focal infiltration with inflammatory cells that persists for weeks to months after disappearance of virus. The late phase of the inflammatory response is postulated to be caused by virus-induced, cytotoxic T-lymphocyte destruction of myocytes, development of a myocardial neoantigen,[2] or cross-reactivity between viral and myocardial cell antigens.[3] Healing is accompanied by interstitial fibrosis and loss of myocytes. Both experimental and clinical data suggest that certain host factors enhance the severity of enterovirus infection, including exercise during the incubation period, cold stress, malnutrition, and B-lymphocyte immunodeficiency.

Enterovirus D68 is isolated most frequently from respiratory specimens rather than fecal samples. Enterovirus D68 grows most efficiently at 33°C (rather than at 37°C, as do other enteroviruses) and is acid sensitive, a feature that can limit survival in the gastrointestinal tract.[4] Primarily spread through respiratory transmission, enterovirus D68 attaches to sialic acid receptors on epithelial cells of respiratory mucosal surfaces.[5] Enterovirus D68 has been detected in serum from children with pneumonia early in the course of illness,[6] as well as in the CNS in case reports.[7,8]

Immunity

Protective immunity to enterovirus infection is serotype specific. Infection leads to production of neutralizing humoral antibodies that protect against recurrent disease but not against asymptomatic reinfection. Passive antibody provided by immune globulin,[9] or by transplacental maternal antibody,[10] effectively prevents enterovirus disease. Secretory immunoglobulin A (IgA) antibodies appear in nasal and duodenal secretions 2 to 4 weeks after primary infection and persist for at least 15 years.[11] Secretion of IgA antibodies at each mucosal site depends on local virus replication.[12] On enterovirus re-exposure, secretory IgA antibodies prevent or substantially reduce subsequent replication. Secretory IgA antibodies also are found in colostrum and milk of immune women. Antibodies in human milk can interfere with the replication of attenuated polioviruses given to breastfed infants during the first month of life.[13]

Patients with isolated B-lymphocyte immunodeficiency syndromes develop persistent enterovirus infections, a finding suggesting that humoral antibodies are necessary for viral clearance.[14] Administration of intramuscular immune serum globulin does not affect the course of acute poliovirus poliomyelitis,[15] but few controlled trials of immune globulin intravenous (IGIV) in other CNS and non-CNS enterovirus infections have been performed. Studies in a well-characterized murine model showed that inhibition of T-lymphocyte function has little effect on the course of enterovirus infection, although T lymphocytes participate in immunopathologic events contributing to the cytotoxicity that accompanies infection.[16] These data may explain the observation that patients with T-lymphocyte immunodeficiency or immunosuppression appear to be at lesser risk for severe or prolonged enterovirus infection. In contrast, experimental studies suggested that macrophage function is critical to clearance of virus and recovery from infection.[17] Other host factors, including human leukocyte antigen (HLA) genes, immune response gene polymorphisms, and vitamin A deficiency are linked to susceptibility and severity of enterovirus A71 disease.

Epidemiology

Infections occur in all human populations, although rates of infection vary markedly by geography, season, age, and other host factors. Transmission occurs throughout the year in most locations, but at much higher rates in temperate climates in summer and fall.[18] Seasonal periodicity is more pronounced (i.e., higher density of infection during short seasons) with increasing latitudes in both hemispheres compared with tropical latitudes. Conversely, seasonal fluctuations diminish in tropical latitudes.

Although enterovirus infections and disease occur in all age groups, infants and young children have the highest rates. Infants <1 year of age are infected at severalfold higher rates than children and adults; and within the first year of life, enterovirus infections are recognized most often clinically in infants <3 months of age.[19–21] The risk of disease in boys exceeds that in girls by as much as 50%. Infants of low socioeconomic status have a higher risk of infection that is attributable to crowding and poor hygiene.

The contribution of different enterovirus serotypes to human infection and disease varies markedly. Thirty percent to 80% of adults have antibody to the more common enterovirus serotypes (e.g., group B coxsackieviruses 1 to 5 and some echoviruses). A few serotypes cause endemic disease with annual regional variation in the United States. Other serotypes (e.g., echoviruses 9, 11, and 30) are responsible for widespread outbreaks in which the epidemic strain accounts for >30% of all isolated enteroviruses, followed by several years of relative quiescence.[22] The reasons for the appearance and disappearance of particular serotypes are unknown, although accumulation of a “critical mass” of susceptible young children may be necessary to sustain epidemic transmission.[23] Periodic reappearance of the same serotype is marked by strain variation as measured by oligonucleotide fingerprinting or genomic sequencing.[21,24] Between 1970 and 2008, species B enteroviruses predominated among enterovirus isolates submitted from state and local public health laboratories to the National Enterovirus Surveillance System (NESS) of the Centers for Disease Control and Prevention.[25,26] From 2006 to 2008, 8 serotypes (all species B enteroviruses) represented 72% of all enteroviruses submitted to the NESS (Table 236.3).[25] In contrast, some enterovirus serotypes (e.g., echovirus 1, coxsackievirus B6, and enterovirus B69) rarely are recognized clinically and appear to have little epidemic potential.

TABLE 236.3

Most Common Enterovirus Serotypes Submitted by State and Local Public Health Laboratories to Centers for Disease Control and Prevention, 2006 to 2008

Enterovirus Serotype	Percentage
Coxsackievirus B1	16.5
Echovirus 6	10.7
Echovirus 9	10.7
Echovirus 18	8.8
Coxsackievirus A9	7.5
Coxsackievirus B4	6.7
Echovirus 11	5.8
Coxsackievirus B3	5.4
Total	72

From Centers for Disease Control and Prevention. Nonpolio enterovirus and human parechovirus surveillance—United States, 2006–2008. MMWR Morb Mortal Wkly Rep 2010;59:1577–1580.

Enterovirus A71 has caused large outbreaks of hand-foot-and-mouth (HFM) disease, aseptic meningitis, and serious CNS disease in young children.[27–37] Although sporadic cases and small outbreaks of enterovirus A71 infections occur globally, since the mid-1990s several genetic lineages, most recently genotype C4, have caused widespread disease in infants and young children throughout Asia.[38–46]

Enterovirus D68 was uncommonly reported to the NESS from 1970 to 2008. From 2008 to 2010, small regional outbreaks of enterovirus D68 were reported in Asia, Europe, and the US.[47] In 2014, the largest and most widespread outbreak of enterovirus D68 respiratory disease occurred in the US, with more than 1100 confirmed infections.[48]

Transmission

Enteroviruses are shed in the upper respiratory tract for 1 to 3 weeks and in the feces for 2 to 8 weeks after primary infection, findings suggesting both respiratory and fecal-oral routes of transmission. Studies of naturally occurring and attenuated polioviruses demonstrate that fecal (but not oropharyngeal) shedding also occurs during reinfection, albeit at lower titer and for a shorter duration. Both direct fecal-oral and indirect mechanisms of person-to-person transmission are postulated. Secondary infection rates exceed 50% in household contacts.[49] Infants, particularly those in diapers, appear to be the most efficient transmitters of infection. Indirect transmission is abetted by poor sanitary conditions and can occur by numerous routes, including contaminated water, food, and fomites. The relative roles of virus shedding by symptomatic and asymptomatic people are not known, but both are likely important. Notable exceptions to the importance of respiratory and fecal-oral transmission are enterovirus D70 and coxsackievirus A24, the agents of acute hemorrhagic conjunctivitis, which are shed in tears and spread by fingers and fomites.[50]

The incubation period for enteroviral infection is difficult to determine precisely and may vary according to the clinical syndrome. Brief febrile illnesses occur after an average incubation period of 3 to 5 days. Detailed studies of poliovirus infection have indicated that CNS manifestations (i.e., aseptic meningitis, poliomyelitis) usually are not observed until 9 to 12 days after exposure.[51] The incubation period of acute hemorrhagic conjunctivitis is 1 to 3 days.

Clinical Manifestations

Most enterovirus infections in children are asymptomatic. The proportion of infections that result in illness varies widely and is affected by numerous host factors. Table 236.4 shows clinical syndromes commonly associated with nonpolio enterovirus infections in children. Some enteroviral diseases (e.g., nonspecific febrile illness, pharyngitis, and aseptic meningitis) are associated with multiple serotypes of group B coxsackievirus and echovirus,[49,52] whereas others are associated with specific subgroups (e.g., myopericarditis with group B coxsackieviruses and herpangina with group A coxsackieviruses) or a limited number of serotypes (e.g., acute hemorrhagic conjunctivitis with coxsackievirus A24 or enterovirus D70).

TABLE 236.4

Spectrum of Illness Caused by the Enteroviruses

	Group A Coxsackieviruses	Group B Coxsackieviruses	Echoviruses	Newer Enteroviruses
EXANTHEMS AND ENANTHEMS				
Herpangina	+++	+	+	−
Hand-foot-and-mouth disease	+++	+	−	+++
Nonspecific rash	++	+	+++	++

CENTRAL NERVOUS SYSTEM INFECTIONS				
Aseptic meningitis	+	+++	+++	++
Encephalitis	+++	++	++	++
Motor paralysis	++	+	+	+++
RESPIRATORY INFECTIONS				
Pneumonia/Bronchospasm	−	−	−	+++
DISEASES OF MUSCLE				
Pleurodynia	+	+++	+	−
Myositis	++	++	++	−
Myopericarditis	+	+++	+	−
OPHTHALMIC INFECTIONS				
Acute hemorrhagic conjunctivitis	+++	−	−	+++
SYSTEMIC INFECTIONS				
Neonates	+	+++	+++	−
B-lymphocyte immunodeficiency	+	+	+++	−

+++, characteristic; ++, occasionally reported; +, rarely reported; −, no known association.

Nonspecific Acute Febrile Illnesses

Nonpolio enteroviruses are the most commonly identified causes of fever without an apparent focus in infants <3 months of age.[53,54] During the summer and fall, enteroviruses account for at least one half of cases.[20,21,55] Fever often occurs alone or in association with irritability, lethargy, poor feeding, vomiting, diarrhea, exanthems, or signs of upper respiratory tract infection.[56] Approximately one half of infants infected with an enterovirus have aseptic meningitis,[54,56] often in the absence of meningeal signs.[56] Most infants with fever or aseptic meningitis recover within 2 to 10 days without complications.

Exanthems and Enanthems

Enteroviruses are common causes of a broad array of acute cutaneous eruptions and mucous membrane lesions (Fig. 236.1). Exanthems can be maculopapular and resemble those of measles, rubella, or roseola, or they can be vesicular, petechial, purpuric, or urticarial. Exanthems are reported more commonly with echovirus infections than with infections with other enteroviruses.

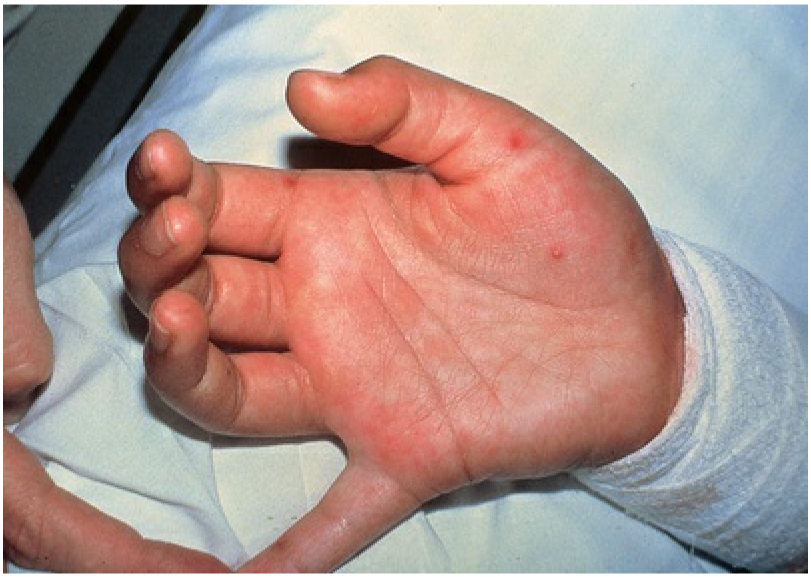
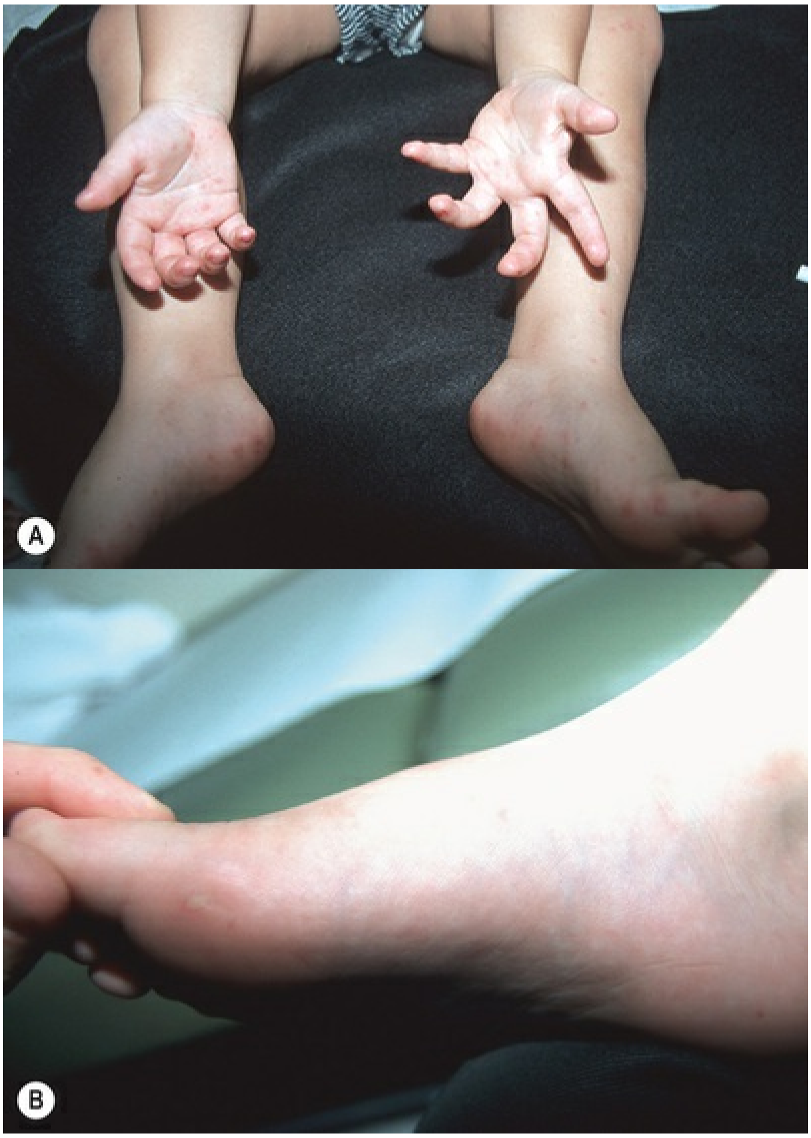


FIGURE 236.1 **Typical hand lesions of Coxsackie A virus in an infant with a febrile illness. No other exanthem was present.** (Courtesy of M. C. Fisher and S. S. Long, St. Christopher's Hospital for Children, Philadelphia.)

Herpangina is a distinctive enanthem characterized by painful vesicular lesions on the soft palate, uvula, tonsils, and posterior oropharynx, often accompanied by fever, headache, and sore throat. Mucosal lesions begin as punctate macules and evolve over a 24-hour period to 2- to 4-mm vesicular lesions that ultimately ulcerate centrally. Fever subsides in 2 to 4 days, but lesions can persist for a week.

Coxsackievirus A6 and coxsackievirus A16 (and less commonly other group A and group B coxsackieviruses) and enterovirus A71 cause *HFM disease*, a syndrome characterized by vesicular stomatitis and cutaneous lesions of the distal extremities (Fig. 236.2). Children <10 years of age are affected most commonly. Fever, sore throat, and refusal to eat are common complaints. Oral lesions occur chiefly on the buccal mucosa and tongue and can coalesce and ulcerate by the time of the initial examination. Cutaneous lesions occur in approximately 75% of cases and are found mainly on the hands, feet, wrists, ankles, and buttocks or genitalia. HFM disease associated with coxsackievirus A6 can be extensive and additionally can involve perioral, perianal, and dorsal hand and feet lesions.[57] The lesions of HFM disease typically are tender papules or vesicles with a surrounding zone of erythema; vesiculobullous, purpuric, and Gianotti-Crosti–like lesions and lesions accentuated in areas of eczematous dermatitis have been associated with coxsackievirus A6.[58] HFM disease generally is self-limited, with an average 7-day duration.[55] When caused by enterovirus A71, however, HFM disease can herald the onset of more serious CNS disease, including acute motor neuron disease and brainstem encephalitis.[38,59,60]



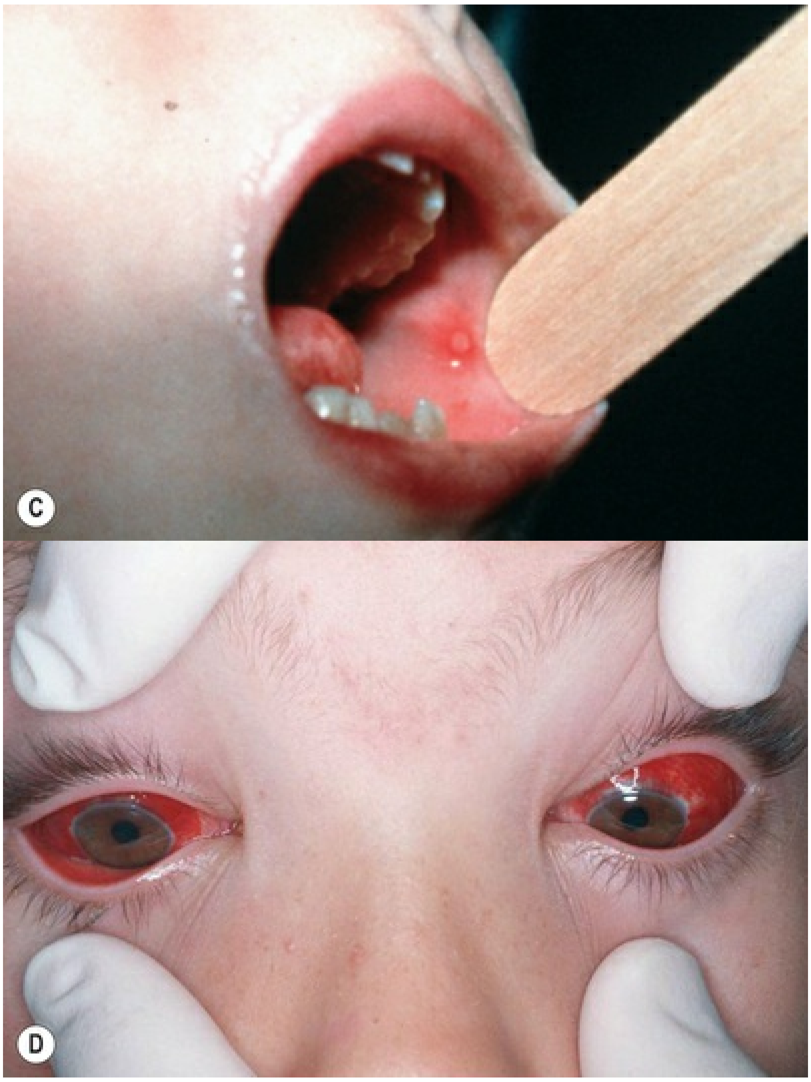


FIGURE 236.2 Characteristic findings of hand, foot and mouth disease include (A, B) petechial, maculopapular, or vesicular lesions on hands and feet and (C) ulcerative lesions with erythema on the oral mucosa. (D) Acute hemorrhagic conjunctivitis with hemorrhage and edema of the conjunctivae. (Copyright by J. H. Brien.)

Respiratory Infections

Sore throat and coryza are frequent upper respiratory tract symptoms associated with the early phase of many enterovirus infections. Acute parotitis occasionally is reported in association with herpangina caused by group A coxsackieviruses and also with group B coxsackieviruses and enterovirus D70 infections. Exudative pharyngitis, otitis media, croup, bronchiolitis, and pneumonia are other less common respiratory findings associated with some enteroviruses.

Enterovirus D68 is associated primarily with respiratory disease. Although most enterovirus D68 infections are associated with mild respiratory symptoms, severe lower respiratory disease leading to hospitalization, intubation, and death is reported. Among children hospitalized with enterovirus D68 respiratory infection, one half had a history of asthma. Most of these children presented with dyspnea, cough, wheezing, tachypnea, and hypoxia, and approximately 50% were febrile.

Central Nervous System Infections

Meningitis

Most cases of community-associated aseptic meningitis are caused by viruses, 90% of which are group B coxsackieviruses and echoviruses.[52] Although many serotypes cause meningitis, coxsackievirus serotypes B2 and B5 and echovirus serotypes 4, 6, 9, 11, 16, and 30 are most commonly reported. Not all enteroviruses that infect young infants are equally likely to cause meningitis. In 1 study, febrile infants infected with certain serotypes (e.g., the group B coxsackieviruses and echovirus serotypes 11 and 30) were more likely to have meningitis; group A coxsackieviruses caused <5% of cases.[56] Enterovirus D68 has been detected in cerebrospinal fluid (CSF) in case reports of aseptic meningitis.[61]

Infants <3 months of age appear to have the highest rate of aseptic meningitis, perhaps in part because lumbar puncture commonly is performed for evaluation of fever in this age group.[20] A few infants have clinical manifestations suggestive of neurologic disease.[20,55,56] The severity of meningeal symptoms and other signs of neurologic involvement in older children and adults with aseptic meningitis varies widely. Onset can be gradual or abrupt. Typically, the patient has a brief prodrome of fever, chills, and headache. Meningismus, when present, varies from mild to severe. Kernig and Brudzinski signs are present in only one third of older children and adults.

The CSF white blood cell (WBC) count can be normal or demonstrate mild pleocytosis (typically <500 WBCs/μL but occasionally >1000 WBCs/μL). Pleocytosis frequently is predominantly polymorphonuclear in the first 48 hours, then transitioning to mononuclear prominence. CSF glucose typically is normal (10% <40 mg/dL), and CSF protein is normal to mildly elevated (<100 mg/dL).

Most cases of enteroviral meningitis are uncomplicated. Fever and signs of meningeal irritation resolve in 2 to 7 days, but CSF pleocytosis can persist. A biphasic pattern of illness can occur, with fever in the initial phase followed by return of fever and meningeal signs after several days of an afebrile interlude. Adults compared with children appear to have more severe and prolonged symptoms.[62] Approximately 10% of infants hospitalized with aseptic meningitis experience acute CNS complications such as seizures, obtundation, or increased intracranial pressure.[20,63] Although some early reports suggested that infants with viral meningitis at an early age had a moderate risk of longterm neurologic and cognitive sequelae,[64] prospective studies have indicated no measurable effect,[65,66] including infants with neurologic findings during the acute illness.[20]

Encephalitis

Enteroviruses are among of the most commonly identified causes of infectious encephalitis; these viruses account for ≥10% to 20% of cases of known origin. Many nonpolio enterovirus serotypes have been identified in patients with encephalitis. Group A coxsackieviruses have been isolated from infants and children with focal enteroviral encephalitis.[67]

Clinical manifestations of enterovirus encephalitis range from mild, reversible changes in mental status to coma, decerebration, and death. Patients with focal encephalitis can have partial motor seizures, hemichorea, or acute cerebellar ataxia. Initial findings in some cases suggest a diagnosis of herpes simplex virus encephalitis.[67,68] Because CSF findings in enteroviral encephalitis are similar to those of aseptic meningitis, the term *meningoencephalitis* commonly is used interchangeably with *encephalitis.* Magnetic resonance brain imaging and electroencephalography usually reflect the extent and severity of disease. Encephalitis occurring as a manifestation of generalized neonatal infection (see the later section on infection in special hosts) often is fatal or results in permanent neurologic sequelae. The prognosis for older infants and children is better; although static neurologic sequelae and rare deaths occur, most patients recover fully.

Poliomyelitis-Like Illness

Nonpolio enteroviruses uncommonly cause a syndrome of acute motor weakness and acute flaccid paralysis (AFP) that is clinically and pathologically indistinguishable from poliomyelitis. Outbreaks of acute paralysis caused by enterovirus A71 have involved thousands of people, mostly children, in Eastern Europe and Asia, as well as smaller numbers of patients in Australia and parts of the US.[60,69–71] Coxsackievirus A7 has caused small outbreaks of AFP in Scotland and Russia, and AFP has been described in enterovirus D70 epidemics. Sporadic cases of AFP can be caused by numerous enteroviruses, most commonly the following: enterovirus A71; group A coxsackievirus types 7, 9, and 24; group B coxsackievirus types 1 to 5; and echovirus types 6 and 9. The myelitis caused by nonpolio enteroviruses tends to be less severe than that caused by polioviruses (i.e., less persistent muscle weakness and less common bulbar involvement).

Cases of acute flaccid weakness and cranial nerve dysfunction in children temporally associated with an outbreak of enterovirus D68 respiratory disease were noted in the US and, to a lesser extent, in Europe and Canada in 2014.[72–75] The term *acute flaccid myelitis* was used to describe the acute onset of limb weakness associated with neuroimaging lesions in the grey matter of the spinal cord.[76] Most children had abrupt onset of neurologic deficits approximately 1 week following an acute febrile respiratory illness. Preceding or concurrent headache, neck stiffness, photophobia, and pain in the affected limb, neck, or back were common. Cranial nerve dysfunction was seen in 34% of cases and was associated with focal lesions in cranial nerve nuclei in the brainstem. Limb weakness commonly was asymmetric and was associated with hyporreflexia and intact sensation of the affected limb, similar to findings in poliomyelitis. Mild improvements in neurologic deficits were reported, but residual weakness persisted in most cases. In some children with acute flaccid myelitis, enterovirus D68 was identified in respiratory samples, but not in the CSF, thus precluding causal attribution.

Brainstem Encephalitis

A distinctive, life-threatening form of brainstem encephalitis has been observed during epidemics of enterovirus A71 infection in Malaysia, Australia, Taiwan, China, and other locations.[38,39,60,71] Most cases occur in children <5 years of age and in association with HFM disease or herpangina. Affected children have myoclonus, vomiting, ataxia, nystagmus, and oculomotor palsies. The most severely affected patients die rapidly of noncardiogenic pulmonary edema, pulmonary hemorrhage, interstitial pneumonitis, or cardiac dysfunction, postulated to be caused by dysregulation of sympathetic outflow and overload of the pulmonary vascular bed.[60,77] High rates of neurologic sequelae occur among survivors of severe disease. Neuronal degeneration and mononuclear cell infiltration in the grey matter of the pons and medulla are found at postmortem examination; enterovirus A71 has been isolated from brainstem tissue, but uncommonly from CSF.[39,71] A few similar cases have occurred sporadically in the US.[27,78]

Other Neurologic Syndromes

Guillain-Barré syndrome is reported in a limited number of patients infected with group A coxsackievirus types 2, 5, and 9 and echovirus types 6 and 22. Acute transverse myelitis has been attributed to coxsackievirus A9, coxsackievirus B4, and echovirus 5.

Infections of Skeletal and Cardiac Muscle

The myotropic nature of the group A and group B coxsackieviruses has been recognized since their discovery. Group B coxsackievirus types 1 to 5 are the principal causes of myotropic diseases, although pleurodynia and myopericarditis rarely have been associated with some group A coxsackieviruses and echovirus types.

Pleurodynia (Epidemic Pleurodynia, Bornholm Disease)

Pleurodynia, an acute, communicable disease involving the intercostal and abdominal muscles, is characterized by fever and sharp, spasmodic pain in the chest wall or abdomen. Local outbreaks of pleurodynia with high attack rates within affected households have occurred, and major epidemics can take place every 10 to 20 years. The diagnosis of pleurodynia is more common in older children and adults. Involvement of the abdominal muscles is more common in younger children than in older children and adults, who most often have thoracic pain. The paroxysmal nature of the pain is a hallmark of the disease. Involvement of the intercostal and other muscles of respiration enhances pain with deep breathing and causes a sensation of “pleuritic” pain that can result in splinting of the chest and rapid, shallow breathing. Muscle inflammation can be detected by eliciting tenderness on direct palpation or, less commonly, by observing localized swelling. Fewer than 10% of patients have a pleural friction rub or pleural fluid evident on chest radiographs. Pain is most severe initially and typically diminishes over 4 to 6 days, although pain can persist up to 3 weeks. Illness can be biphasic. Analgesic medications and limitation of physical activity are helpful in reducing pain.

Myositis

Involvement of other muscles is less common; sporadic cases are caused by coxsackieviruses A9, B2, and B6 and by echoviruses 9 and 11. Both focal and generalized myositis can occur. Focal myositis often involves the thigh muscles. Generalized myositis frequently manifests as polymyositis syndrome with an abrupt onset of fever, chills, and weakness, tenderness, and edema of the involved muscle groups. Myoglobinemia, myoglobinuria, and elevated serum levels of skeletal muscle enzymes are characteristic. Most cases occur in adults, who recover rapidly.

Myopericarditis

Enteroviruses are major causes of acute infection of cardiac muscle and pericardium. Although most patients have symptoms and signs of either pericarditis or myocarditis, the term *myopericarditis* is preferred because pathologic studies reveal that both the pericardium and the myocardium usually are involved. Group B coxsackievirus types 2 to 5 account for one third to one half of sporadic cases,[79,80] and for almost all epidemic cases of myopericarditis,[81] but many other enterovirus serotypes have been implicated. Enteroviral myopericarditis is indistinguishable clinically from disease caused by other cardiotropic viruses.

Enteroviruses cause myopericarditis in all age groups. Physically active adolescents and young adults may have the highest risk, and male patients have at least twice the risk of female patients.[82] Approximately two thirds of patients have a febrile upper respiratory tract illness preceding symptoms of substernal chest pain, exercise intolerance, and dyspnea.[83] Auscultation reveals a pericardial friction rub in 35% to 80% of patients and a gallop rhythm or other signs of ventricular failure in ~20%. Electrocardiographic (ECG) abnormalities, including ST-segment changes, T-wave abnormalities, or arrhythmias, invariably are present. Echocardiography may confirm acute ventricular dilatation, diminished cardiac ejection fraction, or pericardial effusion. Serum levels of myocardial enzymes frequently are elevated. Although the acute course of myopericarditis often is complicated by congestive heart failure or cardiac arrhythmia, most children recover uneventfully. The mortality rate during the acute illness is <5%. However, ECG or echocardiographic abnormalities persist in 10% to 30% of patients, and similar proportions of patients have persistent or recurrent congestive heart failure.

Chronic dilated cardiomyopathy is the final result of multiple infectious and noninfectious cardiac insults,[84] including up to one third of cases of acute myopericarditis and, in some instances, unrecognized past enteroviral infection.[80,85,86] A case-control study of idiopathic dilated cardiomyopathy in adults in the United Kingdom and Italy suggested a possible association with group B coxsackieviruses.[87] Enteroviral RNA has been detected in cardiac tissue months to years after the onset of dilated cardiomyopathy in some studies,[88,89] but not in others using similar methods.[90–93]

Ophthalmic Infections

Acute hemorrhagic conjunctivitis is a highly contagious infection characterized by eye pain, eyelid swelling, and subconjunctival hemorrhage (see Fig. 236.2D). Widespread epidemics of acute hemorrhagic conjunctivitis have occurred in many parts of the world, particularly in the tropics. Two enterovirus serotypes have been responsible for almost all cases. Enterovirus D70 was the cause of the original pandemic in 1969 that spread globally during the early 1970s.[94] Since 1970, the epidemiology of disease caused by a variant of coxsackievirus A24 has intertwined with that of enterovirus D70.[95] Both viruses have caused epidemics throughout Southeast Asia and the Indian subcontinent. Disease in the West has been confined to seasonal outbreaks in the Caribbean, Central America, and southern Florida.[96]

Acute hemorrhagic conjunctivitis is transmitted directly from person to person by fingers and fomites. Both enterovirus D70 and coxsackievirus A24 are readily isolated from tears, but only infrequently from other sites. Contagion is favored by crowding and poor sanitation; reuse of water for bathing and sharing of towels contribute to the spread of infection. After an incubation period of 1 to 2 days, symptoms of ocular pain, photophobia, watery discharge, and swelling of the eyelids appear abruptly. Fever and headache occur in 20% of cases. The distinctive physical finding is subconjunctival hemorrhage, found in 70% to 90% of enterovirus D70 cases but in fewer coxsackievirus A24 cases. Conjunctival edema and follicle formation, punctate epithelial keratitis, and preauricular lymphadenopathy are present commonly. Symptoms and signs peak on the first day of illness and resolve within a few days without residual eye complications. Unusual cases of concomitant motor paralysis have been reported during some enterovirus D70 outbreaks.

Other Infections

The role of enteroviruses in gastrointestinal disease is unsettled but probably is minor. Conflicting data comparing rates of enterovirus isolation from children with acute diarrheal illness and matched healthy control subjects are reported. Some echoviruses, particularly types 11, 14 and 18, have been implicated in outbreaks of diarrhea in young infants. Enteroviral hepatitis beyond the neonatal period occurs rarely.[97,98] Pancreatitis is reported in patients infected with group B coxsackievirus types 1 to 5 and echovirus types 6, 11, 22, and 30. Prospective studies of acute pancreatitis have demonstrated concurrent enterovirus infection in 2% to 20% of patients.[99,100] Orchitis can occur in adolescents during infection with coxsackievirus A9, group B coxsackieviruses 2, 4, and 5, and echovirus 6.

Enteroviruses and Diabetes Mellitus

Although the role of genetic susceptibility is clearly established, enterovirus infection may initiate and possibly maintain an inflammatory insult to pancreatic islet cells and thereby contribute to the development of type 1 diabetes mellitus.[101] Evidence for the involvement of group B coxsackieviruses is most abundant, but other species B and C enteroviruses also are implicated.[102–105] Cases of new onset diabetes occur in seasonal patterns,[106,107] and sometimes in clusters or small outbreaks, often peaking 1 to 2 months after peak enterovirus activity.[108,109]

Two major theories of the pathophysiology of enterovirus-induced diabetes have been proposed. The “direct hit” hypothesis posits destruction of pancreatic islets by direct viral infection. A second theory focuses on acute viral infection as a trigger for an autoimmune response to pancreatic islet cells because of the similarity between the antigens of the virus and islet cells.[110] Although persistent enterovirus infection also is considered a possible mechanism of islet cell damage, evidence of persisting infection in immunocompetent humans is inconsistent and controversial.[101,109,111,112]

Infection in Special Hosts

Infections in Pregnancy

Nonpolio enterovirus infections do not appear to be more serious in pregnant women, although a distinctive syndrome of fever and severe abdominal pain (probably secondary to mesenteric lymphadenitis) is described in late pregnancy in association with perinatal transmission to neonates.[113,114] Although enterovirus infection during pregnancy undoubtedly is common, documented intrauterine infection is rare, perhaps because of an effective placental barrier.[10,115] Rare cases of fetal hydrops and stillbirth are reported,[116] but evidence that fetal infection is associated with congenital malformation is speculative.

Neonatal Infections

Neonates are at risk of serious, often fatal disease resulting from enterovirus infections acquired during the perinatal period. The echoviruses and group B coxsackieviruses are responsible for most neonatal infections, especially echovirus serotypes 6, 9, and 11 and group B coxsackievirus serotypes 1 to 5. Serious neonatal group B coxsackievirus serotype 1 disease was widely reported during 2007 and 2008 when this serotype circulated prominently in the US.[117] Parechoviruses, especially parechovirus serotype 3, are reported to cause neonatal encephalitis, severe hepatitis, rash with fever, and other neonatal syndromes identical to those caused by enteroviruses.[118]

Neonates who acquire enterovirus infections perinatally as a result of vertical transmission from infected mothers develop illness within the first week of life. Onset of serious infection beyond 10 days of age is rare. During seasonal outbreaks, approximately 3% of pregnant women excrete enteroviruses at term.[10] The outcome of neonatal infection is strongly influenced by the presence or absence of passively acquired maternal antibody specific for the infecting enterovirus serotype.[10,119,120] Thus the timing of maternal infection in relation to delivery is probably the most critical factor in the outcome of neonatal enterovirus infection.

Horizontal transmission from family members and nosocomial postnatal infection occur less frequently.[114,121,122] Infant-to-infant spread within nurseries occurs via the hands of healthcare personnel engaged in mouth care, gavage feeding, and other activities affording close direct contact.[123]

Although a wide range of clinical disease has been reported in neonates, including benign nonspecific febrile illnesses, exanthems, and aseptic meningitis, the most severe manifestations include myocarditis, hepatitis, encephalitis, and pneumonia.

Myocarditis

Neonatal myocarditis is most frequently caused by group B coxsackievirus serotypes 2 to 5. The onset often is abrupt, with respiratory distress, tachycardia, cyanosis, jaundice, and diarrhea. Initial examination frequently reveals temperature instability, tachycardia, arrhythmia, hepatomegaly, and signs of poor peripheral circulation. ECG tracings can show low-voltage and other electrophysiologic abnormalities, and echocardiograms often indicate poor left ventricular or biventricular function.

Approximately one third of illnesses are biphasic, with lethargy, poor feeding, or mild respiratory distress preceding the onset of cardiac manifestations by 2 to 5 days.

Infants with group B coxsackievirus myocarditis often have concomitant meningoencephalitis, pneumonia, hepatitis, pancreatitis, or adrenalitis. Although a limited number of organs can be involved pathologically, the degree of involvement often is severe, thus giving rise to terms such as *disseminated, systemic,* or *overwhelming* group B coxsackievirus disease in the neonatal period. The mortality rate in infants with myocarditis alone is generally reported to be 30% to 50%, but it is higher when other organs are involved. Survivors may have gradual improvement in cardiac function, whereas others have chronic impairment.

Hepatitis

Neonatal hepatitis can occur as the sole manifestation of infection or can accompany myocarditis and other manifestations of neonatal group B coxsackievirus disease. Echovirus 11 has been implicated most frequently,[114] but cases caused by echovirus serotypes 6, 7, 9, 14, 17, 19, and 21 and group B coxsackieviruses are described. The degree of hepatic involvement varies, but a severe form of hepatitis unique to this age group is characterized by extensive necrosis of the liver and fulminant hepatic failure. Initial signs and symptoms of severe hepatitis resemble those of septicemia, with lethargy, poor feeding, apnea, and jaundice. Within 2 to 3 days, evidence of hypocoagulability appears, along with ecchymoses and prolonged bleeding at puncture sites. Anemia, marked prolongation of the prothrombin time and partial thromboplastin time, and extreme elevations of serum transaminase levels occur.[113,114] Marked hypocoagulability, more attributable to hepatic failure than to disseminated intravascular coagulation, causes spontaneous hemorrhage into the skin, lungs, gastrointestinal tract, kidneys, and brain. The mortality rate is high. Infants dying of hepatitis have massive hepatic necrosis (Fig. 236.3) and may have extensive hemorrhage into the cerebral ventricles, pericardial sac, renal medulla, and interstitial spaces of many solid organs. Necrosis commonly is limited to the liver and adrenal glands and spares the heart, brain, meninges, and other organs. Cirrhosis and chronic hepatic insufficiency can develop in some survivors, whereas other survivors recover hepatic function.

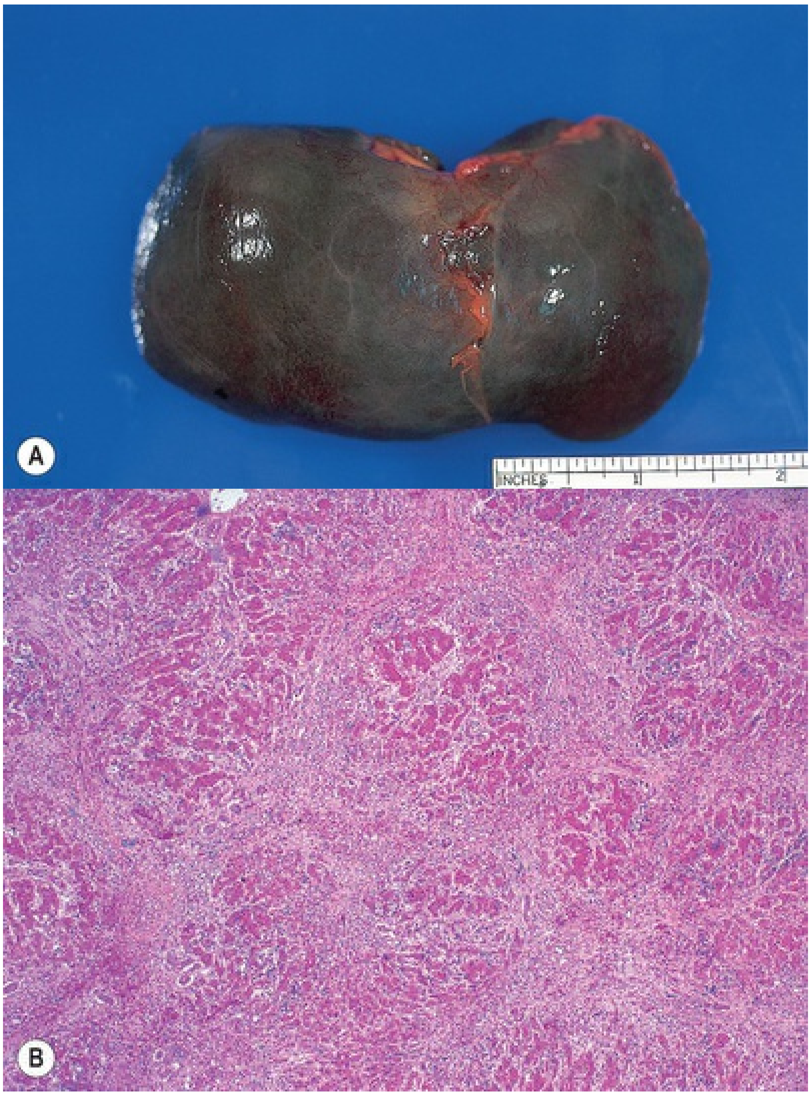


FIGURE 236.3 **A term infant whose mother had a respiratory illness at delivery had onset of “overwhelming sepsis” at 3 days of age, with (A) a small, hemorrhagic liver that (B) on microscopic examination (×400) revealed extensive hepatocellular necrosis.** (Courtesy of S. S. Long.)

Central Nervous System Infection

Extreme lethargy, seizures, hemiparesis, flaccid paralysis, and coma herald the more serious form of meningoencephalitis that occurs in the neonate as isolated CNS disease or accompanying myocarditis or hepatitis. Inflammation of the brain or spinal cord is found in approximately two thirds of infants dying of myocarditis.[124] Distinctive periventricular white matter lesions have been observed by magnetic resonance imaging in many neonates with enterovirus (and parechovirus) encephalitis, and postmortem microscopic examination demonstrates diffuse or scattered perivascular inflammation with lesions in the cerebrum, cerebellum, pons, medulla, and spinal cord.[125,126] Survivors can have residual cognitive and motor deficits.

Pneumonia

Echovirus serotypes 6, 9, and 11 have been associated with a few reported cases of perinatal pneumonitis.[127] Some cases characterized by the onset of symptoms within hours of birth suggest prenatal exposure and have a high mortality rate. Less severe neonatal pneumonitis has been described with echovirus serotypes 7 and 22.[128] Pathologic evidence of pneumonitis can be seen with group B coxsackievirus myocarditis in newborns, but generally it is limited to focal areas of interstitial inflammation.[124]

Infections in Patients With Immunodeficiency

Enteroviruses cause persistent, sometimes fatal infections of the CNS, gastrointestinal tract, and skeletal muscle in patients with hereditary or acquired defects in B-lymphocyte function. Most reported patients are children with X-linked agammaglobulinemia or severe combined immunodeficiency syndrome[14] or adults with common variable immunodeficiency. Cases of chronic meningoencephalitis as a complication of X-linked hyper-IgM syndrome and in children treated with anti-CD20 monoclonal antibody have been reported.[129] Severe multisystem or chronic infections also occur in recipients of bone marrow and solid organ transplants.[130] Echoviruses are responsible for most of these infections; individual cases caused by group A coxsackievirus types 4, 11, and 15 and by group B coxsackievirus types 2 and 3 have been reported.[14]

Chronic meningoencephalitis, the most common clinical syndrome, typically begins insidiously with headache, lethargy, mild meningismus, motor dysfunction, or seizures; abnormalities fluctuate in severity, disappear, or slowly progress. Persistent CSF pleocytosis and a high CSF protein concentration are characteristic. Virus is recovered persistently in high titer from the CSF of many patients.[14] Subtle abnormalities such as developmental arrest or regression are not uncommon, especially in IGIV-treated patients, and polymerase chain reaction (PCR) rather than culture can be necessary to confirm the presence of virus in CSF in such patients.[129,131]

Chronic myositis in a subset of hypogammaglobulinemic patients produces an illness similar to dermatomyositis. Recovery of virus from muscle tissue in at least 1 case suggested ongoing viral replication.[132] Isolation of enteroviruses from other tissues such as the brain, lung, liver, spleen, kidney, and bone marrow has suggested that infection is widely disseminated in at least some cases.

The prognosis for immunodeficient children who are persistently infected is poor. The efficacy of IGIV in the treatment of chronic enterovirus meningitis has been inconsistent. Some patients have experienced clinical improvement when IGIV was injected directly into the ventricles,[132] but relapse of infection occurs even after longterm intraventricular IGIV therapy. Pleconaril therapy has been used under compassionate release.[133,134]

Parechovirus Infections

Of the 14 parechovirus serotypes recognized to infect humans[135]; serotypes 1 and 3 are most commonly associated with disease.[136] The manifestations of parechovirus infections in infants are similar to those of enterovirus infections and are difficult to differentiate based on clinical presentation.[118] Parechoviruses commonly cause high persistent fevers in infants less than 5 months of age,[137,138] and they can be associated with a sepsis-like presentation.[139–141] Maculopapular exanthem is common, and a distinctive rash involving the extremities with palmar and plantar erythema has been noted with parechovirus 3 infection.[142,143] CNS infection, including aseptic meningitis and encephalitis associated with white matter changes, has been described in neonates.[125,126] Mild elevation in liver enzymes is common, and frank hepatitis with hepatic necrosis in newborns has been reported.[139] Absolute leukopenia can be a distinctive laboratory feature.[138] Parechoviruses follow a seasonal distribution similar to that of enteroviruses in temperate climates, predominating in the late summer to early fall.[144] A biannual pattern of parechovirus 3 infection has been noted in Europe since 1988.[144]

Laboratory Diagnosis

Polymerase Chain Reaction Testing

PCR detection of enteroviruses using primers that identify conserved sequences in the 5′ noncoding region of the enterovirus genome is more sensitive than culture in CSF, respiratory tract secretions, serum, and urine.[21,145,146] PCR also has been used to detect enteroviral RNA in cardiac tissue from patients with myocarditis,[89] although the relative sensitivity and specificity of the technique in these patients are not defined. PCR testing of fecal specimens can be adversely affected by polymerization inhibitors in stool. Many multiplex PCR assays commercially available for evaluation of respiratory specimens cannot differentiate rhinoviruses from enteroviruses because of their genetic similarities. Type-specific major capsid protein VP1 seminested PCR amplification and sequencing[147] or type-specific real-time (RT-PCR) can be used to identify specific enterovirus serotypes (e.g., enterovirus serotypes D68 and A71).[148]

Diagnosis of enterovirus meningitis by PCR of CSF has been shown to be more sensitive than cell culture and produces a faster result, thus enabling a shorter length of hospital stay.[149,150] PCR testing of serum, pharyngeal, and rectal specimens increases sensitivity,[151] but testing of pharyngeal and rectal specimens decreases specificity because it may detect asymptomatic shedding. The diagnosis of enterovirus A71 CNS disease often relies on virus detection by PCR in respiratory secretions or feces (or isolation of virus from these sites in cell culture) because the virus is uncommonly detected in CSF.[152]

Parechoviruses are not detected by PCR using typical enterovirus primers. However, PCR detection of all known human parechoviruses is possible using primers that identify conserved sequences in the 5′ untranslated region of the parechovirus genome. Parechovirus serotypes can be determined by nested or seminested PCR amplification and sequencing of the VP1 region[153] Because of similarities in clinical presentations requiring testing, combined human parechovirus-enterovirus RT-PCR assays have been developed.[154]

Virus Isolation

Isolation of viruses in cell culture remains an important method of laboratory diagnosis. Success of isolation varies widely between enterovirus classes and among serotypes within a class. Overall, sensitivity ranges between 50% and 75%. Generally, 3 or 4 primate cell lines must be used to support isolation of most enteroviruses. A cytopathic effect usually is evident between 2 and 5 days after the inoculation of cell monolayers. Once isolated, the virus serotype can be identified for most of the common enteroviruses with use of the Lim Benyesh–Melnick intersecting equine antiserum pools or by RNA sequencing. Group A coxsackieviruses do not grow in cell culture as readily as other enteroviruses; the optimal method for their isolation is newborn mouse inoculation.

An etiologic diagnosis is confirmed by isolation of virus from CSF, pericardial fluid, tissue, or blood. The opportunity to recover a virus in cell culture is optimized by sampling multiple sites. Isolation of virus from stool is less definitive because unrelated intercurrent asymptomatic infections and prolonged shedding can occur. However, because the background rate of shedding from the gastrointestinal tract is relatively low in the population, isolation of enterovirus from any site is presumptive evidence of disease causation.

Serologic Examination

The microneutralization test is the method used most widely for determining enterovirus antibodies. This serotype-specific assay has limited usefulness in the routine diagnosis of nonpolio enterovirus infections because it is not feasible to incorporate all relevant viral antigens into the assay, and methods based on neutralization are relatively insensitive, poorly standardized, and labor intensive. Type-specific immunoassays now are available commercially for measuring antibodies against the more common enterovirus serotypes, but they often are not well standardized. Serum IgM antibody has been detected early in the course of infection with group B coxsackieviruses, echovirus 30, and enterovirus D70. However, enteroviral IgM assays are not generally serotype specific,[151,155] and they appear to lack sensitivity.[156]

Antigen detection assays using monoclonal antibodies have been developed to identify specific serotypes such as enterovirus A71.

Treatment

Immune serum immunoglobulin and IGIV are reported to suppress or eradicate persistent enterovirus infections in some, but not all, patients with immunoglobulin deficiency or other immunodeficiencies.[14] However, the efficacy of immunoglobulin has not been demonstrated in the treatment of other serious or acute enterovirus infections. A prospective, randomized trial of IGIV (750 mg/kg) for treatment of enterovirus infections in newborn infants did not demonstrate significant clinical benefit, nor did this treatment reduce the daily incidence of viremia or viruria overall; however, viremia and viruria remitted faster among subjects who received IGIV that contained a neutralization titer of ≥1 : 800 to the subject's infecting virus.[157] IGIV (with or without corticosteroids) has been used for patients with enterovirus A71 brainstem encephalitis; modulation of cytokine profiles has been shown, but data proving clinical efficacy are lacking.[158] High-titer enterovirus A71 immune globulin is being evaluated. IGIV may have beneficial immunomodulatory effects in enteroviral myopericarditis.[159] In a study using historical controls, improved cardiac function and a trend toward increased survival was found in children with acute myopericarditis who were treated with IGIV.[160] However, randomized controlled trials have not been reported. Although corticosteroid and other immunosuppressive therapies have been used for myocarditis,[161,162] experimental evidence suggested adverse rather than beneficial effects,[163] and a large prospective randomized trial of prednisone combined with either cyclosporine or azathioprine versus supportive treatment showed no differences in outcome.[164]

Antiviral compounds in clinical development include agents that bind avidly to a pocket in the viral capsid, thereby preventing virus attachment and uncoating.[165] One compound, pleconaril, an orally administered drug with a favorable pharmacokinetic and toxicity profile, was studied in clinical trials and was shown to have a modest benefit in adults and children with enterovirus meningitis and picornavirus upper respiratory tract infections.[166–169] Uncontrolled experience in immunocompromised patients with persistent enterovirus infections and patients with serious, potentially fatal infections also indicated possible clinical benefit.[62,133,170] A randomized, placebo-controlled, phase II trial of pleconaril orally for treatment of neonates with enteroviral sepsis syndrome suggested possible virologic and clinical efficacy.[171] Unfortunately, although new drugs are in development, no antiviral agents are currently available in the US.[172]

Prevention

Because pre-exposure administration of immune serum globulin reduces the risk of paralytic poliomyelitis, it is possible that nonpolio enterovirus infections could be prevented in the same manner. Although commercial preparations of IGIV contain variable concentrations of antibody against some enterovirus serotypes, no data are available regarding the protective efficacy of these preparations. Prophylactic administration of immune globulin (or convalescent plasma) has been attempted in the setting of nursery epidemics, but the use of infection control strategies confounds interpretation of efficacy. Maintenance administration of IGIV in hypogammaglobulinemic patients has reduced the incidence of chronic enteroviral meningoencephalitis, although breakthrough infections occur. Active immunization against the nonpolio enteroviruses as a group is not practical because of the large number of serotypes. However, several candidate enterovirus A71 vaccines have been developed that were effective against HFM disease and herpangina in clinical trials, with suggested protection against neurologic disease.[173,174]

Simple hygienic measures such as handwashing, careful disposal of soiled diapers, and avoidance of shared eating utensils and drinking containers should reduce transmission. It is prudent to advise pregnant women and children who are immunocompromised to avoid contact, whenever possible, with people suspected of having enterovirus infection.

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Hepatitis A Virus

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Pathogen

Hepatitis A virus (HAV) is a nonenveloped RNA virus and a member of the Picornaviridae family.[1] The single-stranded RNA genome is approximately 7500 nucleotides long and contains a single, long, open reading frame. The encoded polyprotein includes structural proteins for the 27- to 28-nm diameter capsid, nonstructural proteins with protease or polymerase activities, and other proteins with functions that have not been fully determined.[2,3]

Among infected people, HAV replicates in the liver, is excreted in bile, and is found in high concentrations in stool. The incubation period averages 28 days (range, 15–50 days). Peak viral concentrations in stool and greatest infectivity are during the 2 weeks before the onset of symptoms. Virus concentrations in stool diminish markedly within 1 week after the onset of symptoms. However, polymerase chain reaction assays have been used to demonstrate low levels of viral RNA in stools of infected neonates for up to 6 months after infection.[4] In older children, HAV RNA can be detected in stools for as long as 10 weeks after symptoms begin, but the clinical significance of these findings is uncertain.[5] Viremia occurs soon after infection and persists at least through the period of elevation of hepatic enzymes in serum.[6,7]

The pathogenesis of HAV infection is not completely understood. However, the absence of cytopathic changes in cell culture and the demonstration of HAV-directed natural killer and lymphokine-activated killer cells in vitro suggest that cell-mediated immunity is responsible for hepatocellular damage.[8]

HAV is a single serotype.[9] Seven HAV genotypes have been identified with unique geographic distribution; 4 genotypes are found in humans (I, II, II, IV).[3] Genotype IA is the most commonly identified genotype in US HAV cases (88%), followed by IB (11%) and IIIA (0.7%).[10]

Immunity resulting from HAV infection is lifelong. In contrast to infection with hepatitis B and hepatitis C viruses, HAV infection does not result in chronic infection or chronic liver disease.

Epidemiology

The principal mode of HAV transmission is from person to person, by the fecal-oral route. Transmission occurs most commonly among close contacts, including household and sexual contacts of people infected with HAV. HAV also is transmitted by contaminated food, most often from an infected food handler, but also in association with food contaminated before retail distribution (e.g., produce contaminated during growing or processing).[11–13] Common-source food exposures are of increasing concern. Several outbreaks of hepatitis A virus genotype IB illness associated with food from the Middle East have been reported, including frozen strawberries from Egypt and Morocco in Europe, frozen pomegranate seeds from Egypt in Canada, semidried tomatoes from Turkey in Europe and Australia, and pomegranate arils from Turkey in the United States.[14–19] Transmission by contaminated water is rare. Because transient viremia occurs in HAV infection, bloodborne HAV transmission can occur, such as among injection drug users.[20] On rare occasions, HAV infection has been transmitted by transfusion of blood or blood products collected from donors during the viremic phase of infection.[21] In addition, outbreaks have been reported in Europe and the US among patients who received factor VIII and factor IX concentrates prepared with the use of solvent detergent treatment.[22] However, changes in viral inactivation procedures, introduction of hepatitis A vaccine, and improved donor screening have nearly eliminated the risk for HAV transmission from clotting factors.[23] Vertical transmission to children from pregnant women who develop hepatitis A during the third trimester of pregnancy has been reported, but the risk appears to be low. In approximately 50% of people with sporadic, community-acquired hepatitis A, no source of infection is identified.[24] When a risk factor is identified, international travel is the most commonly reported.[10,25]

Because most young children have asymptomatic or unrecognized infections, they play an important role in the epidemiology of hepatitis A and often serve as sources of infection for others. In several studies using serologic testing of household contacts, 25% to 40% of contacts <6 years of age had serologic evidence of acute HAV infection.[26,27] In 1 US study, 52% of households of adults without an identified source of infection included a child <6 years of age, and the presence of a young child was associated with HAV transmission in the household. In this study, transmission chains were identified that involved as many as 6 generations and >20 cases.[26]

The relationship between risk of infection and likelihood of asymptomatic infection during childhood is important to understanding HAV transmission patterns worldwide and to developing prevention strategies. Level of economic development, as indicated by hygienic and sanitary conditions, is correlated with global HAV transmission patterns (Fig. 237.1). In areas where seroprevalence of antibody to HAV (anti-HAV) is high even among young children (e.g., parts of Asia, Africa, Central and South America), the lifetime risk of infection is greater than 90%, and infection occurs primarily in early childhood.[27,28] Asymptomatic infection predominates, and nearly the entire population is infected before reaching adolescence. The high rates of HAV transmission during childhood may not be recognized because typical clinical manifestations of hepatitis A are uncommon in children. The incidence of clinical hepatitis A generally is low, and outbreaks are rare because most adults are immune. However, adults who remain susceptible to infection in these areas are at high risk for HAV infection. Travelers to highly endemic areas from the developed world also are at high risk. In areas of moderate endemicity (e.g., Eastern Europe), HAV is not transmitted as readily because of better sanitation and living conditions, and the average age of infection is older than in areas of high endemicity. However, transmission among young children remains relatively common. Paradoxically, the potential for large outbreaks can be increased (compared with highly endemic areas) because of the relatively larger pool of susceptible older children and adults who are at high risk for infection and who, when infected with HAV, are likely to develop symptomatic illness.[29] Unimmunized travelers from the developed world to these areas also are at risk.[30] In some instances, countries undergoing rapid development accompanied by improvement in sanitation standards and clean water supplies have experienced changes in the epidemiologic pattern of HAV. In these countries, HAV is likely to become a more serious problem.[31] Declines in childhood and adolescent HAV seroprevalence lead to susceptibility at a later age, with greater associated morbidity and mortality. In most developed countries without universal vaccination policies, the incidence of both HAV infection and hepatitis A clinical disease is low. Most cases occur in the context of cyclic, community-wide outbreaks that feature transmission among preschool and school-aged children and their adult contacts.[31] As endemicity continues to decline in some parts of the developed world, most cases are identified in defined risk groups, such as travelers returning from endemic areas, international adoptees from endemic countries, and injection drug users.[29,32]

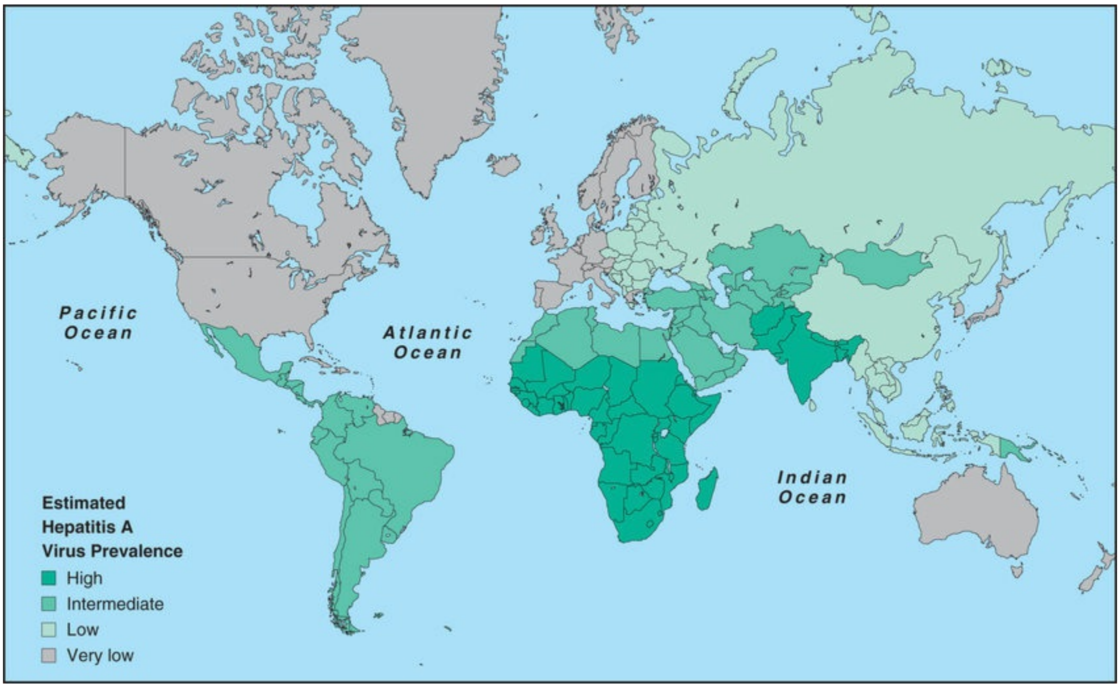

FIGURE 237.1 **Prevalence of antibody to hepatitis A virus, 2006. Geographic distribution of hepatitis A virus (HAV) infection endemicity. For multiple countries, estimates of prevalence of antibody to hepatitis A virus (anti-HAV), a marker of previous HAV**

infection, are based on limited data and may not reflect actual prevalence. In addition, anti-HAV prevalence rates could vary within countries by subpopulation and locality. (Adapted from Jacobsen KH, Wiersma ST. Hepatitis A virus seroprevalence by age and world region, 1990 and 2005. Vaccine 2010;28:6653–6657.)

In the US, before hepatitis A vaccine was widely available, hepatitis A occurred in large, nationwide epidemics approximately every decade.[25] Until 2001, the highest rates of HAV infection in the US were observed among children 5 to 14 years of age, with approximately one third of reported cases involving children <15 years of age.[33–35] The highest rates and the majority of cases occurred in the western and southwestern states.[34–36]

Since licensure of the first hepatitis A vaccines in 1995, incidence rates have declined sharply (Figs. 237.2 and 237.3).[25] Declines have been especially prominent since implementation of targeted recommendations made in 1996 to 1999 for childhood vaccination in states with high hepatitis A rates.[33,34] In 2006, universal vaccination was recommended in all states.[28] The number of reported cases in the US reached an all-time low of 1398 cases in 2011, thus representing a 96% decline in reported cases since vaccine recommendation. The first increases in cases since 1995 occurred in 2012 (1562 total cases) and again in 2013 (1781 total cases), coincident with the 2013 multistate outbreak of hepatitis A.[19,25,37] The number of cases increased slightly in 2014 (1239 cases). Hepatitis A rates declined since vaccine introduction from 11.7 cases per 100,000 population in 1996 to 0.4 cases per 100,000 population in 2011, with a slight increase to 0.5 and 0.6 cases per 100,000 population in 2012 and 2013, respectively, and declined in 2014 back to 0.4 cases per 100,000 population.[25,37] Since the mid-2000s, age, regional, ethnic, and racial differences in incidence rates of hepatitis A have been eliminated, thereby indicating fundamental shifts in hepatitis A epidemiology (see Fig. 237.3).[24,38,39] Moreover, with the lack of circulating HAV after massive declines in HAV infections among children, the seroprevalence rates have dropped for adults as the average ages of hepatitis A hospitalizations and deaths have increased.[40] The likely reason for this finding is that the adults who were infected in childhood with subsequent immunity are aging out of the population, to be replaced by adults who were too old to be vaccinated as children but who did not have the opportunity to be exposed to the virus and develop disease at an earlier age. The 2013 multistate outbreak of hepatitis A occurred largely in adults, with few cases in unvaccinated children.[38] This finding illustrates that future problems with imported food contaminated with HAV may pose a risk to this large, susceptible, adult population.

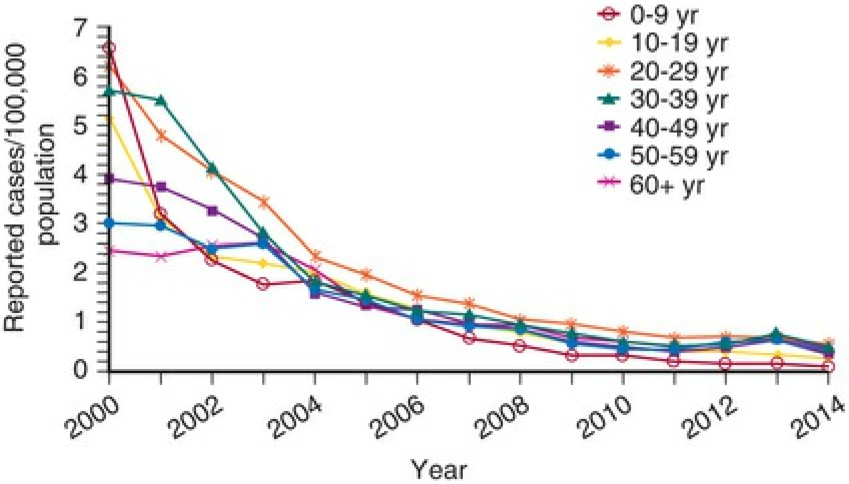

FIGURE 237.2 **Incidence of acute hepatitis A, by age group and year, United States, 2000 to 2014. Incidence rates are per 100,000 population and were reported by the National Notifiable Diseases Surveillance System in 2014.** (From Centers for Disease Control and Prevention. Incidence of acute hepatitis A, by age group—United States, 2000–2014. https://www.cdc.gov/hepatitis/statistics/2014surveillance/index.htm#tabs-1170596-5.)

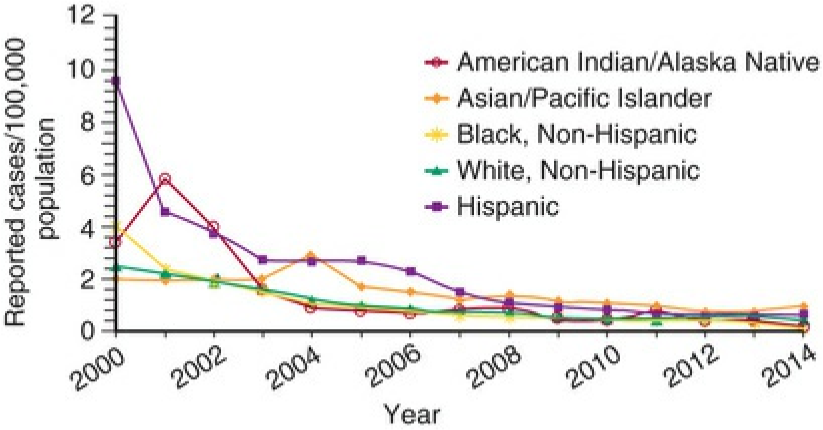

FIGURE 237.3 **Cases of acute hepatitis A, by race or ethnicity in the United States, 2000 to 2014. Incidence rates are per 100,000 population and were reported by the National Notifiable Diseases Surveillance System in 2014.** (From Centers for Disease Control and Prevention. Incidence of acute hepatitis A, by race/ethnicity—United States 2000–2014. https://www.cdc.gov/hepatitis/statistics/2014surveillance/index.htm#tabs-1170596-5.)

Methods to isolate and sequence HAV from sera of infected people and to define the genetic variation of HAV are advancing understanding of the epidemiology.[41] The resulting database of HAV genome sequences has been useful in investigations of foodborne outbreaks by demonstrating links among apparently sporadic cases and suggesting possible sources of contamination.[11,38,42]

Clinical Manifestations

HAV infection can be inapparent (the patient is asymptomatic with no elevation in serum hepatic enzymes), subclinical (asymptomatic with elevation of hepatic enzymes), anicteric (symptomatic without jaundice), or icteric (symptomatic with jaundice). The likelihood of having symptoms with HAV infection is related directly to age. Most children <6 years of age have asymptomatic infection or mild, nonspecific symptoms with hepatitis A; <10% of children in this age group have jaundice.[43] Among older children and adults, 76% to 97% have symptoms when they are infected with HAV, and 40% to 70% of patients with symptoms are icteric.[44]

When symptoms occur, most patients have an onset of low-grade fever, myalgia, anorexia, malaise, nausea, and vomiting. These symptoms are followed several days later by specific symptoms and signs of hepatic dysfunction, including dark urine, light-colored stools, jaundice, and scleral icterus.[44] Many children (60%) and some adults (20%) have diarrhea. Some children (<20%) have upper respiratory tract symptoms (e.g., cough, coryza, sore throat). Urticaria can occur at the onset of illness.[45] Physical findings are variable and can include jaundice, scleral icterus, hepatomegaly, right upper quadrant tenderness, and splenomegaly. Abdominal ultrasonography showed edema of the gallbladder wall in approximately 50% of children with uncomplicated hepatitis A who were studied prospectively; transient ascites occurred in a few patients.[46] The symptoms of hepatitis A last for several weeks on average and usually not longer than 2 months, although some people can have prolonged or relapsing signs and symptoms for up to 6 months.

Laboratory Findings and Diagnosis

During HAV infection, inflammation of the liver is accompanied by abnormalities in serum hepatic enzymes, with increases in serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and γ-glutamyltranspeptidase. Usually in acute hepatitis A, ALT and AST values are between 200 and 5000 IU/L; the ALT value is higher than the AST value; and alkaline phosphatase levels are only mildly elevated. Elevations in ALT and AST can precede symptoms by a week or more and generally peak 3 to 10 days after the onset of symptoms (Fig. 237.4).

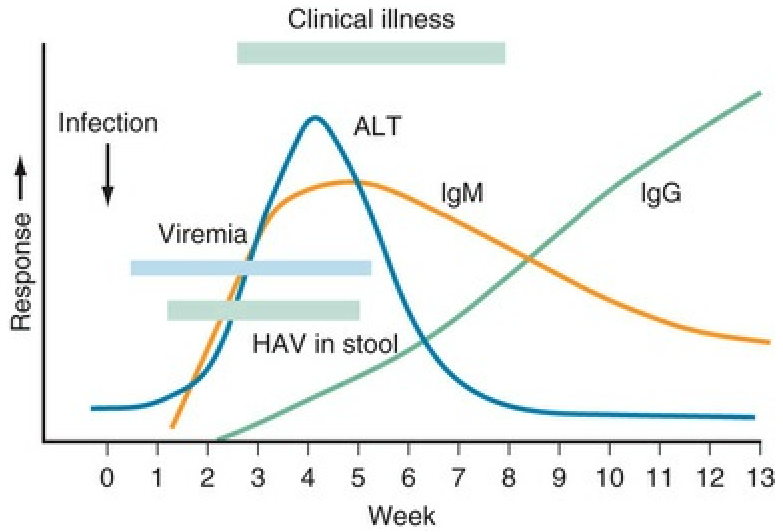

FIGURE 237.4 **Typical serologic profile of hepatitis A virus (HAV) infection. ALT, serum alanine aminotransferase level; Ig, immunoglobulin.**

The specific diagnosis of hepatitis A relies on serologic testing in addition to the presence of symptoms. Virtually all people with acute hepatitis A have detectable immunoglobulin (Ig) M anti-HAV during the acute or early convalescent phase of infection (see Fig. 237.4).[47] IgM anti-HAV generally disappears within 6 months after the onset of symptoms, although people who test positive for IgM anti-HAV >1 year after infection or with no known history of infection have been reported.[48,49] IgG anti-HAV, which appears in the convalescent phase of infection, remains detectable in serum for the person's lifetime and confers protection against disease. Commercial enzyme immunoassays are available for detection of

IgM and total anti-HAVs in serum. Because the test for total anti-HAVs frequently is performed first in laboratories, and results are positive for anyone who has been vaccinated or infected in the past, IgM anti-HAV detection is necessary to make the diagnosis of HAV hepatitis.

Polymerase chain reaction assays can be used to detect HAV RNA in stool specimens and sera of people with HAV infection, although these tests are available only in a few research laboratories.[3,6] To date, polymerase chain reaction assays cannot determine whether a person is infectious because incomplete virus particles can be detected. On the basis of epidemiologic studies, peak infectivity occurs during the 2 weeks before the onset of symptoms. For practical purposes, people with hepatitis A can be assumed to be noninfectious 1 week after the onset of jaundice.

Light microscopic examination of liver specimens in acute hepatitis A reveals pathologic features common to all forms of viral hepatitis, including hepatocellular necrosis, inflammatory infiltration of lymphocytes and other mononuclear cells, and regeneration of hepatocytes. The extent of involvement varies with the stage and severity of hepatitis and age of the patient. Liver biopsy typically is not indicated for the diagnosis or management of hepatitis A.

Treatment

Treatment generally is supportive. Hospitalization may be necessary for patients who are dehydrated from nausea and vomiting or who have fulminant hepatitis A. No specific diet or restriction of activity is necessary. Medications that can cause hepatic damage or that are metabolized by the liver should be used with caution. For the infrequent presentations of cholestatic or relapsing hepatitis A, a short course of corticosteroid therapy has been reported as effective in limiting symptoms and hastening recovery, but no controlled trials have evaluated this approach.[50,51]

Liver transplantation is successful in some people with acute liver failure. Criteria for choosing patients for liver transplantation are difficult to establish because survival without transplantation is high (50%–70%), even for patients in a coma, and no single factor is predictive of a poor outcome.[52]

Special Considerations

HAV infection occasionally results in fulminant hepatitis and death. In addition, hepatitis A has several atypical manifestations, including relapsing hepatitis A, cholestatic hepatitis, autoimmune hepatitis, and extrahepatic symptoms.

Fulminant hepatitis A, characterized by the onset of severe liver injury and hepatic encephalopathy in patients with no known preexisting liver disease, is an infrequent occurrence.[53] The case-fatality rate among reported cases of hepatitis A in all age groups is approximately 0.6%.[25] Host factors associated with a higher risk for fulminant hepatitis A include older age (>50 years old) and underlying chronic liver disease.[54] Molecular studies have not shown an association between fulminant hepatitis A and any type of viral variant. Of 348 children with acute liver failure from the US, Canada, and the United Kingdom who were entered into a registry, only 3 (0.9%) had acute hepatitis A.[55] Spontaneous recovery occurs in 30% to 60% of people with fulminant HAV infection, and survivors generally regain full liver function. Prognosis is influenced by age, clotting factor level, stage of coma, and presence of renal disease.[24] In approximately 10% to 15% of patients with hepatitis A, relapsing hepatitis occurs, and approximately 20% of these patients have multiple relapses.[24,51] These patients typically have another episode of hepatitis 1 to 4 months after the initial acute hepatitis. The relapse is accompanied by elevation of serum hepatic enzymes and persistence of IgM anti-HAV. Molecular studies have demonstrated the presence of HAV in stool specimens during relapse. Most patients recover completely within several weeks.

Cholestatic hepatitis occurs rarely following infection with HAV.[50] Patients with this disorder have substantially elevated concentrations (>10 mg/dL) of bilirubin in serum and jaundice persisting for an extended period (in some cases >3 months). This syndrome can be distinguished from obstructive jaundice by normal abdominal ultrasonographic findings. A short course of corticosteroids can reduce symptoms and hasten disease resolution.[24]

Several case series have been described in which HAV infection is followed by autoimmune chronic active hepatitis, in some instances requiring longterm corticosteroid therapy.[56] Extrahepatic manifestations of hepatitis A include pruritus, arthralgia, cutaneous vasculitis, cryoglobulinemia, and hemophagocytic syndrome (anemia and thrombocytopenia, with hemophagocytosis apparent on biopsy of bone marrow). These manifestations are rare and resolve with resolution of hepatitis.

Prevention

The methods of prevention of hepatitis A include the following: (1) general measures of good personal hygiene (with an emphasis on hand hygiene), provision of safe drinking water, and adequate disposal of sanitary waste; and (2) pre-exposure or postexposure prophylaxis with immune globulin (IG) or hepatitis A vaccine.

Immune Globulin

IG is a solution of antibodies prepared from human plasma by serial ethanol precipitation for intramuscular administration. In the US, GamaSTAN (Grifols Therapeutics, Inc., Research Triangle Park, NC) is the only available hepatitis A immune globulin (IgG anti-HAV) product. The manufacturing process removes model enveloped and nonenveloped viruses, including human immunodeficiency virus, hepatitis B virus, and hepatitis C virus, as well as low levels of Creutzfeldt-Jakob disease (CJD)/variant CJD agent infectivity.[57] The efficacy of IG (0.02 mL/kg intramuscularly) in preventing hepatitis A is 80% to 90% when IG is administered before exposure to HAV or within 2 weeks after exposure.[58,59] Seroprotective anti-HAVs (i.e., 10–20 mIU/mL) appear rapidly after pre-exposure intramuscular injection and reach peak levels in approximately 2 days after injection.[59] No information exists regarding the efficacy of IG or vaccine if it is administered >2 weeks after exposure.[36] The prevalence of anti-HAV in the population has been declining; however, no clinical or epidemiologic evidence of decreased protection from IG has been observed, though decreased potency of IG has been found.[60,60a] IG is indicated in patients for whom the vaccine is contraindicated, and in certain situations for international travel and postexposure prophylaxis.[61]

IG should be administered intramuscularly only, preferably in the deltoid muscle of the upper arm or the anterolateral aspects of the upper thigh in children <24 months of age.[61] Serious adverse events from IG are rare. IG is contraindicated for patients with IgA deficiency because of reports of anaphylaxis in these people, as well as for patients who have severe thrombocytopenia or any coagulation disorder.[62] IG can be administered at the same time as most inactivated vaccines; however, IG can interfere with the response to live, attenuated virus vaccines (e.g., measles, mumps, and rubella vaccine and varicella virus vaccine) when administered either as individual or combination vaccines.[36,62,63]

Vaccine

Hepatitis A vaccine is preferred over IG for pre-exposure and postexposure prophylaxis because of induction of active immunity and longer protection, greater ease of administration, and often greater acceptability. In the US, HAVRIX (GlaxoSmithKline Biologicals, Philadelphia) was approved by the Food and Drug Administration in 1995 and VAQTA (Merck & Co. Inc., Whitehouse Station, NJ) was approved in 1996; both vaccines are licensed for people ≥12 months of age. In 2001, a combination hepatitis A and hepatitis B vaccine (TWINRIX, GlaxoSmithKline) was approved for patients 18 years old or older. Inactivated hepatitis A vaccines are prepared by methods including growth in cell culture, purification by ultrafiltration or other methods, inactivation with formalin, and adsorption to an aluminum hydroxide adjuvant.[64,65] HAVRIX and VAQTA are available in pediatric and adult formulations and are licensed in a 2-dose series, with the second dose scheduled 6 to 18 months after the first. However, if the second dose is given >18 months after the first dose, no additional doses are required.[63] The route of administration is intramuscular, in the anterolateral thigh for children aged <2 years and the deltoid muscle for children and adults. TWINRIX is licensed in a 3-dose series or a 4-dose alternate series.[66–68] Monovalent hepatitis A vaccine may be used to complete hepatitis A vaccination begun with TWINRIX and vice versa.[69]

Inactivated hepatitis A vaccines have been studied extensively in children and adults. In general, within 4 weeks after one dose of vaccine, ≥90% of children aged ≥1 year and adults respond with levels of antibody considered to be protective; a second dose is necessary 6 to 18 months later to boost antibody levels for longterm protection.[70,71] Nearly 100% of patients will develop protective antibodies after receiving 2 doses. Response to vaccine may be lower in patients >40 years of age, immunosuppressed patients, patients with advanced liver disease or recipients of liver transplants, and infants with passively acquired maternal antibody. Delayed administration of the second dose beyond 18 months does not appear to reduce immunogenicity.[72] Available data indicate that the vaccines are safe and immunogenic in children <12 months of age who do not have passively acquired maternal antibody.[73] However, final antibody concentrations in infants with passively acquired maternal antibody are one third to one tenth of those of anti-HAV–negative infants who are vaccinated according to the same schedule, and fewer infants with passively acquired maternal antibody have detectable anti-HAV 6 years after vaccination compared with children vaccinated as infants who did not have passively acquired maternal antibody.[73,74] The immunogenicity of TWINRIX is considered equivalent to that of the single antigen hepatitis vaccine when it is administered in a 3-dose series.[36]

Inactivated hepatitis A vaccine is highly efficacious in preventing clinical hepatitis A. In a large study conducted in Thailand among children 1 to 16 years of age, efficacy of the vaccine was 94% after 2 doses of vaccine administered 1 month apart.[75] In another study conducted in New York among children 2 to 16 years of age and with a different inactivated vaccine, efficacy was 100% starting 17 days after administration of 1 dose.[76]

The duration of protection after vaccination is unknown; however, anti-HAVs have been shown to persist in vaccine recipients for at least 20 years.[77–80] Detectable antibodies are estimated to persist for 20 to 25 years or longer, based on mathematical modeling and anti-HAV kinetic studies.[81,82]

In prelicensure clinical trials among children, the most frequently reported local reaction following hepatitis A vaccination was soreness at the injection site (15%–19%).[71,72] Systemic reactions that include fatigue, fever, diarrhea, and vomiting occurred in <5% of vaccine recipients.[36] No serious adverse events among children or adults that could be attributed definitively to the vaccine and no increases in serious adverse events among vaccinated people compared with baseline rates have been identified.[33,83,84]

In 1996, targeted hepatitis A vaccine was initially recommended by the Advisory Committee on Immunization Practices (ACIP) for children at 2 years of age and adolescents in communities with high rates of HAV disease or for outbreak control.[33] In 1999, the ACIP recommended vaccination in counties, communities, and 11 states with hepatitis A rates ≥20 cases per 100,000 population and consideration of vaccination in 6 additional states with rates of ≥10 cases but <20 cases per 100,000 population.[34] By 2004, first-dose coverage rates among children 24 to 35 months of age who were living in these states had reached 25% to 50%.[85] The impact of even limited routine vaccination of children on hepatitis A incidence was evidenced by historic reductions in incidence rates.[35,40] In 2006, the ACIP extended recommendations to routine vaccination of children 12 to 23 months of age and for anyone wishing to obtain immunity (Table 237.1).[36] Vaccination of people at increased risk for hepatitis A also is recommended (see Table 237.1 and Fig. 237.1).[36] In 2007, the ACIP updated recommendations for prevention of hepatitis A for international travel and postexposure prophylaxis.[61]

TABLE 237.1

Advisory Committee on Immunization Practices Recommendations for Routine Pre-Exposure Use of Hepatitis A Vaccine

Group	Comments
All children at 12–23 mo of age[a]	Integrate into routine childhood immunization schedule; children who are not vaccinated by 2 yr of age can be vaccinated at subsequent visits
Children 12–18 yr of age	Maintain existing programs[b]; can be considered in areas without existing programs
International travelers	Except people traveling to Canada, Western Europe, Japan, Australia, or New Zealand, who are at no greater risk than in the United States
Men who have sex with men	Includes adolescents
Illicit drug users	Includes adolescents
People with chronic liver disease	Increased risk of fulminant hepatitis A
People receiving clotting factor concentrates	
People who work with HAV in research settings	
Anyone wishing to obtain immunity	
People who anticipate close, personal contact (e.g.,	

household or regular babysitting) with an international adoptee during the first 60 days after arrival in the United States from a country with high or intermediate endemicity[c]	

[a]Hepatitis A vaccine is not licensed for children <12 months of age.

[b]Areas covered by 1999 Advisory Committee on Immunization Practices recommendations (Alaska, Arizona, Arkansas, California, Colorado, Idaho, Missouri, Montana, Nevada, New Mexico, Oklahoma, Oregon, South Dakota, Texas, Utah, Washington, Wyoming, and selected areas in other states).[34]

[c]The first dose should be administered as soon as the adoption is planned, ideally 2 or more weeks before the arrival of the adoptee.[88]

HAV, hepatitis A virus.

From Centers for Disease Control and Prevention. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 2006;55(RR-07):1–23.

In 2009, the ACIP updated guidance by recommending hepatitis A vaccination for all previously unvaccinated people who anticipate close personal contact with an international adoptee from a country of high or intermediate endemicity during the first 60 days following arrival of the adoptee in the US.[86]

The use of vaccine largely is responsible for the >95% decrease in hepatitis A cases since vaccine introduction from 1996 to 2011.[37] Geographic variability and most disparities in nationally reported acute hepatitis A disease by race or ethnicity have been eliminated.[35] However, 2-dose vaccine coverage remains low. Hepatitis A vaccine coverage for children 19 to 35 months of age in 2015 was 86% and 60% for ≥1 and ≥2 doses, respectively.[87] Coverage for children 13 to 17 years of age in 2012 was 60% and 48% for 1- and ≥2-dose coverage, respectively.[88] Among adults 19 to 49 years of age in 2014, a group for which vaccine is recommended only for those at high risk of HAV infection, the total ≥2-dose coverage was 12%; coverage was 19% for travelers outside the US and 18% for adults with chronic liver conditions.[89] Reduced exposure to HAV early in life, significant decreases in anti-HAV seroprevalence in older adults, and low 2-dose vaccination rates are causing an increasing proportion of susceptible adults.[19,89]

Sustained reduction in disease incidence in the US should be achieved through vaccination of successive cohorts of children and should provide the opportunity to eliminate HAV transmission. To achieve this goal, however, higher population vaccination coverage throughout the US must be achieved; rapid identification and control of outbreaks, including common-source food exposures, must continue; and expanded recommendations for single- or double-dose vaccination could be considered.

International Travel (Pre-exposure)

All susceptible people traveling to or working in countries that have high or intermediate hepatitis A endemicity should receive pre-exposure prophylaxis. Hepatitis A vaccine at the age-appropriate dose is preferred to IG for children and adults 1 to 40 years of age. One dose of a monovalent hepatitis A vaccine administered any time before departure protects most healthy people 1 to 40 years of age. No data on single dose hepatitis A vaccine efficacy are available for TWINRIX. For optimal protection, adults >40 years of age, immunocompromised people, and patients with chronic liver disease or other chronic medical conditions who are planning to depart to an area in <2 weeks should receive the initial dose of vaccine along with IG (0.02 mL/kg) administered at a separate injection site. Travelers who are <12 months of age, who are allergic to a vaccine component, or who otherwise elect not to receive vaccine should receive a single dose of IG (0.02 mL/kg), which provides effective protection against HAV infection for up to 3 months. Those who do not receive vaccination and who plan to travel for >2 months should receive an IG dose of 0.06 mL/kg, which must be repeated if the duration of travel is >5 months.[61]

Postexposure Prophylaxis

Hepatitis A vaccination has shown efficacy compared with placebo when it is given up to 14 days after exposure to a person with HAV infection.[61,90,91] A controlled study that compared the efficacy of hepatitis A vaccine with that of IG when given after exposure showed the performance of vaccine to be similar to that of IG in healthy children and adults 12 months through 40 years of age.[61,91] People who recently have been exposed to HAV and who previously have not received hepatitis A vaccine should be administered 1 dose of monovalent hepatitis A vaccine or IG (0.02 mL/kg) as soon as possible, ideally within 2 weeks of exposure. The relative efficacy of vaccine is comparable to that of IG for postexposure prophylaxis among people 1 to 40 years of age. For healthy people 1 to 40 years of age, a dose of monovalent hepatitis A vaccine is recommended. For people >40 years of age, IG is preferred, but vaccine can be used if IG is unavailable. IG is recommended for infants <12 months of age, people who are immunocompromised, patients with chronic liver disease, and people for whom vaccine is contraindicated.[61] TWINRIX is not approved for use as postexposure prophylaxis.

Key Points

Diagnosis and Management of Hepatitis A Virus Infection

Microbiology

- Nonenveloped RNA virus and member of the Picornaviridae family
- Replicates in the liver, is excreted in bile, and is found in high concentrations in stool
- Average incubation period of 28 days (range, 15–50 days)
- Greatest infectivity 2 weeks before onset of symptoms

Epidemiology

- Primarily fecal-oral transmission by person-to-person contact or consumption of contaminated food or water
- Endemic in many developing countries; infection occurs mainly in childhood.
- Low prevalence in developed countries; infection occurs typically among adolescents and adults.
- In the United States, international travel is the most frequently reported risk factor.
- International adoption is a risk factor.

Clinical Features

- Symptoms range from none to acute debilitating disease
- Symptomatic infection generally is characterized by acute onset and

- ▪ Early symptoms: low-grade fever, myalgia, anorexia, malaise, and vomiting.
- ▪ Later symptoms or signs: hepatic dysfunction, dark urine, light-colored stools, jaundice, and scleral icterus.

- Likelihood of developing symptoms increases with patient's age
- Average duration is 2 months; overall case-fatality rate is 0.3% to 0.6%

Diagnosis

- Presence of serum antibodies to HAV: IgM detectable 5 to 10 days before onset of symptoms; IgG appears in convalescent phase and is lifelong
- Polymerase chain reaction assay can be used to detect viral RNA in blood or stool but is not widely available and typically is used only in outbreak investigations.

Treatment

- Supportive care

Prevention

- General measures of good personal hygiene, provision of safe drinking water, and adequate waste disposal
- Pre-exposure or postexposure prophylaxis with hepatitis vaccine

or immune globulin

HAV, hepatitis A virus; Ig, immunoglobulin.

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Rhinoviruses

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Rhinoviruses (*rhino*, nose) are the most common causes of the common cold, and they account for at least 50% of upper respiratory tract infections in children and adults. Rhinoviruses are difficult to detect, but the development of sensitive polymerase chain reaction (PCR)–based assays has led to the identification of 3 distinct groups of rhinovirus (*Human rhinovirus A* [HRV-A], *Human rhinovirus B* [HRV-B], and *Human rhinovirus C* [HRV-C]).[1] Although infection results in serotype-specific lasting immunity, rhinovirus infections are common because >100 different serotypes exist.

Description of Pathogen and Epidemiology

Rhinovirus belongs to the Picornaviridae family. The virus is composed of single-stranded RNA within a capsid with icosahedral symmetry. Canyons on the surface of the virus provide an attachment site for receptors on the surface of susceptible target cells. The attachment site for most rhinoviruses is the intercellular adhesion molecule-1 on human respiratory tract epithelium. Viral infectivity is neutralized when host immunoglobulin G binds to the surface of the virus, thereby blocking interaction between the host cell receptor and the receptor binding site located at the base of the canyon.[2]

Rhinovirus is found worldwide and causes infection throughout the year. In temperate climates, a sharp increase in the number of rhinovirus infections occurs in September after the return of children to school,[3] and the incidence of detections per person-weeks in households is related to the number of children.[4] Schoolchildren frequently transfer rhinovirus to family members; in 1 study, 73% of infections in the home could be traced by serotype to infection in a child.[5] A smaller peak of rhinovirus infections occurs in the spring.

Rhinovirus infection of humans is restricted to respiratory tract epithelium, primarily the nose and nasopharynx, and it does not appear to extend to the submucosa. The temperature of normal nasal mucosa is 33°C to 35°C, the optimal temperature for growth of rhinovirus in vitro. Rhinovirus also can infect the lower respiratory tract.[6–8] Rhinovirus RNA has been detected in blood, but rhinoviremia has not been demonstrated by culture.[9] The virus has not been detected in stool. Human rhinovirus has not been recovered from domestic animals (dogs and cats); the only animal model of infection is in primates.

Rhinovirus transmission occurs by small-particle aerosol, large-particle aerosol, or direct contact.[10] To cause infection, virus must be deposited on the nasal mucosa or conjunctiva; oral inoculation is not sufficient.[11,12] In studies of experimental[13,14] and naturally acquired[11,15] rhinovirus infections, virus often can be recovered from the hands of infected people, as well as from objects touched by infected people, including toys in a physician's waiting room.[13,15,16] Studies of young adults showed efficient transfer during brief hand contact and inoculation by finger onto conjunctival or nasal epithelium.[13] Sneezing and coughing were inefficient methods of transfer.[15] In a different experimental model, it appeared that infection could be transmitted by aerosol.[17,18] Transmission routes under natural conditions have not been established definitively, but in 1 study, interruption of hand transmission alone reduced secondary attack rates in mothers after introduction of virus by a family member.[10]

Clinical Manifestations

The symptoms of a rhinovirus cold largely are subjective; nasal congestion or discharge, sore or scratchy throat, and cough are typical complaints. In adults, physical findings can be limited to mild erythema of the nasal mucosa and pharynx. In addition, children also can have fever during the first 2 to 3 days and moderate enlargement of the anterior cervical lymph nodes. Illness generally lasts 5 to 7 days in adults, but it can persist for 10 to 14 days in children.

Both in vivo and in vitro studies have demonstrated that the respiratory tract epithelium remains intact during infection. Nasal biopsy specimens taken during and after illness showed no histologic change in the nasal mucosa other than an influx of neutrophils early in the course of infection.[19,20] Similarly, rhinovirus replication in vitro produced no apparent damage to a monolayer of nasal epithelial cells.[21]

Infection with rhinovirus begins with inoculation of the nasal mucosa. Studies using in situ hybridization techniques show that viral replication occurs in only a small number of epithelial cells at any point in time.[22,23] Infected epithelial cells initiate an inflammatory cascade by release of cytokines and chemokines, including interleukin-8 a potent chemoattractant for neutrophils. Vascular leakage allows plasma containing albumin and other serum proteins to flood the nasal mucosa. Evaluation of nasal washings has shown that viral titers and concentrations of serum albumin, neutrophils, interleukin-8, and kinins all peak approximately 48 hours after inoculation and then decline, thus paralleling the course and severity of symptoms (Fig. 238.1).[24] Localized inflammatory response limits viral replication, and symptoms improve. Between 2 and 3 weeks, sufficient neutralizing antibody is produced to block viral replication, and the infection ends.

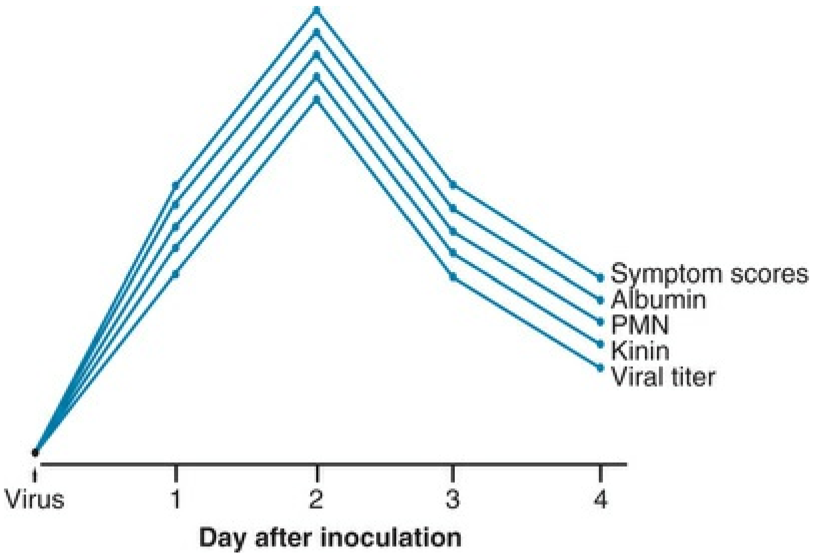

FIGURE 238.1 **Schematic composite of kinetics of average symptom scores compared with concentrations of markers of inflammation and virus in nasal washes after inoculation of rhinovirus. PMN, polymorphonuclear leukocyte.** (Redrawn from Hendley JO. Clinical virology of rhinoviruses. Adv Virus Res 1999;54:463.)

Laboratory Findings and Diagnosis

Diagnosis can be confirmed by detection of rhinovirus in cell culture; nasal wash samples are superior to nasal swab specimens.[25,26] Optimally, 2 sensitive cell lines (WI-38 human embryonic lung fibroblasts and susceptible HeLa cells) are inoculated. Using either cell line alone misses 20% to 35% of culture-positive samples[25]; use of both cell lines increases sensitivity from 76% to 82%.[27,28] Using detection by cell culture, rhinovirus was associated with approximately 30% of symptomatic colds. Reverse transcriptase PCR (RT-PCR) technology detects rhinovirus with a sensitivity of 98% to 100%. Studies using both cell culture and RT-PCR for detection of rhinovirus from nasopharyngeal secretions of adults and children with naturally acquired colds have shown that rhinovirus is associated with 50% of all colds during year-round surveillance,[27,29] as well as 80% of colds occurring in the fall.[28] The group C rhinoviruses detected with RT-PCR have not been grown in available cell lines. The long duration of shedding of rhinoviruses can confound interpretation of a causal role in clinical settings.[4] In a prospective study in children, however, sequential detections of rhinoviruses usually represented acquisition of new strains. Moreover, febrile illnesses were significantly associated with group B rhinoviruses.[30]

Treatment

No effective treatment is available for rhinovirus colds. The capsid-binding agent pleconaril had activity,[31] and interferon α is under investigation.[32] Antihistamines, decongestants, and antitussives have not been shown to be effective in children with colds. *Echinacea* preparations are commonly believed to be effective, but a placebo-controlled, double-blind study showed no significant effect on the rate of rhinovirus infection or its symptoms.[33]

Special Considerations

Although rhinovirus infections are considered benign, self-limited infections, certain populations can experience more serious consequences. In 1 study, preterm infants with rhinovirus infection were severely compromised, and all required respiratory support.[34] In another study, rhinovirus (predominantly HRV-C) was identified in young infants admitted with a diagnosis of apparently life-threatening event.[35] Rhinovirus-associated wheezing early in life is strongly associated with recurrent wheezing and a later diagnosis of asthma. One study suggested that a subset of young children with a rhinovirus-associated first episode of wheezing, namely those with a high viral load, benefited from a 3-day course of oral prednisolone such that they experienced decreased respiratory symptoms in the short term and fewer recurrent wheezing episodes over the next 12 months.[36] Children with underlying medical conditions such as chronic pulmonary or neurologic disease also can experience more severe disease manifestations.[37,38] In symptomatic patients before hematopoietic cell transplantation, rhinovirus detection was associated with reduced 100-day survival.[39]

Prevention

Development of a vaccine is thwarted by the large number of serotypes and the serotype specificity of immunity. Transmission can be interrupted, at least in part, by the simple physical removal of virus on fingers by handwashing before inoculation of nasal or conjunctival mucosa.

Acknowledgment

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[†] Deceased.

RNA Viruses: Caliciviridae

OUTLINE

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Caliciviruses

Aron J. Hall

Pathogens and Pathogenesis

The first calicivirus was discovered in 1972 by electron microscopic examination of stool samples from children affected by an outbreak of gastroenteritis in a school in Norwalk, Ohio, several years previously.[1] This discovery of the subsequently named Norwalk virus marked the first identification of a virus as a cause of gastroenteritis. Norwalk virus and other viruses with similar morphologic features are now classified in the genus *Norovirus* of the family Caliciviridae (Fig. 239.1). Caliciviruses are small, nonenveloped, single-stranded RNA viruses that can be divided into at least 5 genera: *Norovirus, Sapovirus, Nebovirus, Lagovirus,* and *Vesivirus*.[2] Main characteristics of noroviruses and sapoviruses, also referred to as human caliciviruses, are summarized in Table 239.1. Neboviruses, lagoviruses, and vesiviruses are strictly animal pathogens and have not been detected in naturally occurring human illnesses.

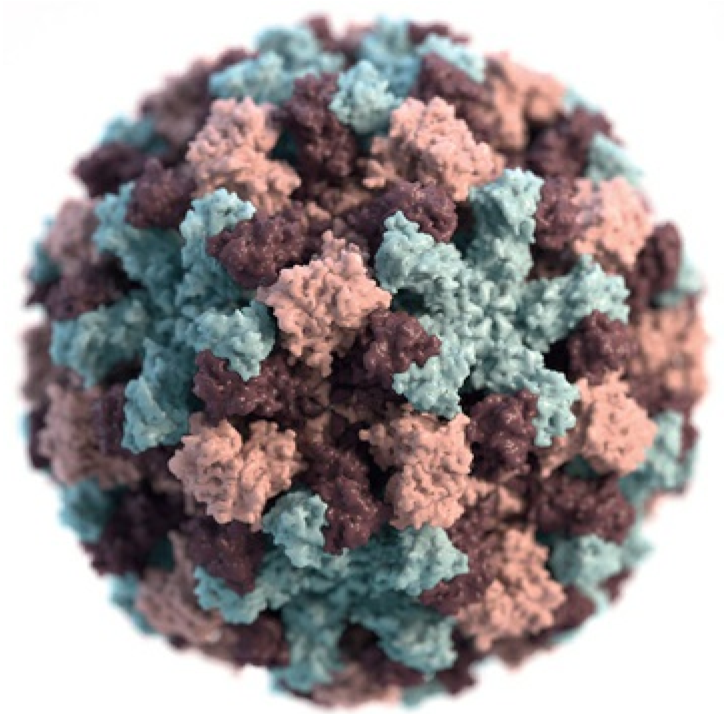

FIGURE 239.1 Three-dimensional graphic representation of a norovirus virion with different colors representing different regions of the viral capsid. (Courtesy of Alissa Eckert, Centers for Disease Control and Prevention, Atlanta, Ga.)

TABLE 239.1

Comparison of Main Characteristics of Noroviruses and Sapoviruses

Characteristic	Noroviruses	Sapoviruses
Appearance by electron microscopy	27–35 nm virus with appearance of cup-like indentations in capsid (Fig. 239.1)	27–35 nm virus with striking cup-like depressions with hollow in middle leading to "star of David" configuration
Other names	Small round structured viruses, "Norwalk-like" viruses	"Classical" caliciviruses, "Sapporo-like" viruses
Name of prototype virus	Norwalk virus	Sapporo virus
Genogroups (G)	I–VII (GIII exclusively bovine viruses, GV exclusively murine viruses, GVI–VII exclusively canine viruses)	GI–V (GIII exclusively porcine viruses)
Immunity	Shortterm (6 mo–8 yr) homologous acquired immunity; genetic resistance or susceptibility factors	Largely unknown
Affected age groups	All ages	Mainly children
Clinical symptoms	Vomiting and diarrhea	Mild gastroenteritis with less vomiting
Asymptomatic infections	30% in volunteer studies	Common (possibly ≤75% of infections among children in

		childcare outbreaks)
Percentage of diarrheal hospitalizations among children <5 yr of age	10%–25%	<5%
Outbreak potential	High	Moderate
Modes of transmission	Fecal-oral: direct person-to-person spread; contaminated food, water or fomites; droplet spread from vomitus	Fecal-oral: person-to-person spread likely the predominant mode; occasionally contaminated food

Noroviruses are classified into 7 genogroups (G): viruses of GI, GII, and GIV cause human disease, whereas GIII, GV, GVI, and GVII contain viruses only found in animals.[3] These 7 genogroups are further subdivided into 40 genotypes,[3] among which GII.4 viruses have emerged as the leading cause of norovirus outbreaks worldwide.[4] Sapoviruses similarly are divided into 7 genogroups, 4 of which (I, II, IV, and V) contain viruses affecting humans.[5] Humans are considered the primary reservoirs for human caliciviruses, but serologic evidence of infection with bovine and canine noroviruses suggests the potential for rare zoonotic transmission.[6,7] Additionally, some evidence suggests possible infection of dogs and cats with human strains of norovirus and sapovirus.[8,9]

Noroviruses and sapoviruses infect villi of the small intestine and likely cause diarrhea by a variety of mechanisms, including both disruption of the epithelial barrier and active anion secretion.[10] Mechanisms of immunity to norovirus infection remain unclear. Immunity to 1 infecting strain does not appear to confer broad cross-protection and may be only temporary. In experimental challenge studies using high doses of Norwalk (GI.1) virus, people became susceptible to reinfection with the same strain after 6 months or less.[11,12] Modeling of community transmission based on observed disease incidence rates suggests that immunity can last 4 to 8 years.[13] High levels of antibody seem to be markers for susceptibility, rather than protection, whereas some people can be entirely refractory to infection with a particular strain.[12] This apparent paradox has been explained in part by studies demonstrating genetic factors related to susceptibility and resistance to norovirus infection. Innate resistance has been associated with mutations in the genes for the secretor enzyme, 1,2-fucosyltransferase (FUT2), leading to lack of expression of histo

–blood group antigens.[14–17] These antigens are expressed on the surface of intestinal cells and in body fluids such as saliva and serve as binding ligands for norovirus. People who express histo–blood group antigens (i.e., secretors) are susceptible to most, but not all, norovirus genotypes and typically have higher antibody levels.[14,15,17–20]

Epidemiology

Caliciviruses, specifically noroviruses, are the most common infectious causes of acute gastroenteritis in people worldwide and are second only to rotavirus among children <5 years of age.[21] In a systematic review and meta-analysis of 175 studies conducted in 48 different countries, noroviruses were detected in 18% of acute gastroenteritis cases.[21] In the United States, noroviruses are estimated to cause on average 19 million to 21 million illnesses, 56,000 to 71,000 hospitalizations, and 570 to 800 deaths annually.[22] With the implementation of universal rotavirus vaccination in the US, norovirus has surpassed rotavirus to become the leading cause of severe pediatric gastroenteritis.[23] With the introduction of rotavirus immunization in many other countries and the consequent reduction of the burden of rotavirus disease, the relative importance of noroviruses in severe pediatric gastroenteritis is similarly expected to increase in these settings.[24]

Noroviruses are highly infectious and are transmitted primarily through the fecal-oral route, either directly from person to person or indirectly by contaminated food and water (Fig. 239.2).[25] Droplet spread from vomitus also can infect people in the vicinity or can contaminate environmental surfaces, where norovirus can persist and remain infectious for several days.[26–28] These characteristics help make noroviruses the leading causes of acute gastroenteritis outbreaks in the US and Europe, responsible for approximately 50% of all reported outbreaks.[29,30] Although outbreaks occur year round, they are more common in colder months.[30,31] Periodic increases in norovirus outbreaks also have occurred in association with the emergence of new viral strains, particularly those within GII.4, resulting in seasons with increased norovirus activity.[32,33] Although the emergence of new GII.4 strains typically results in replacement of the previously predominant strain, it does not always result in an increased number of outbreaks, as observed with the most recent GII.4 New Orleans and GII.4 Sydney strains.[34,35] Fig. 239.3 shows the settings of 3243 outbreaks suspected or confirmed resulting from norovirus reported to the Centers for Disease Control and Prevention during 2009 to 2012.[36] The most common setting of reported US norovirus outbreaks is longterm care facilities, in which the predominant transmission route is direct person-to-person contact.

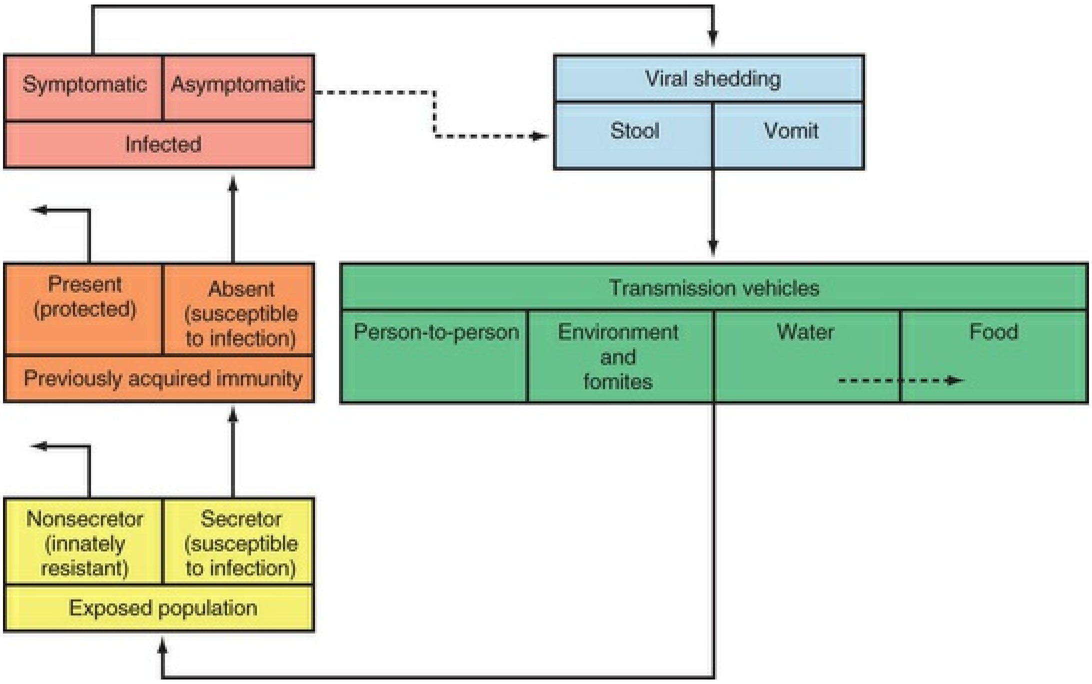

FIGURE 239.2 Transmission cycle of norovirus. Transmission is shown beginning with infected people (red box), including both symptomatic and asymptomatic infections. Virus is shed in stool and vomit of symptomatic people (blue box), as well as in the stool of asymptomatic people (dashed arrow). Subsequent transmission vehicles can include raw or ready to eat foods, drinking or recreational water, contaminated fomites or environments, and direct person-to-person contact (green box). Cross-contamination can occur among these vehicles, such as contamination of fresh produce with irrigation water or shellfish with wastewater. People exposed to contaminated vehicles include both innately susceptible and resistant people, as conferred in part by secretor status (yellow box). Among exposed people without innate resistance, some will have previously acquired immunity and therefore will be protected from infection (orange box). People without innate or acquired immunity then become infected, and the cycle begins again.

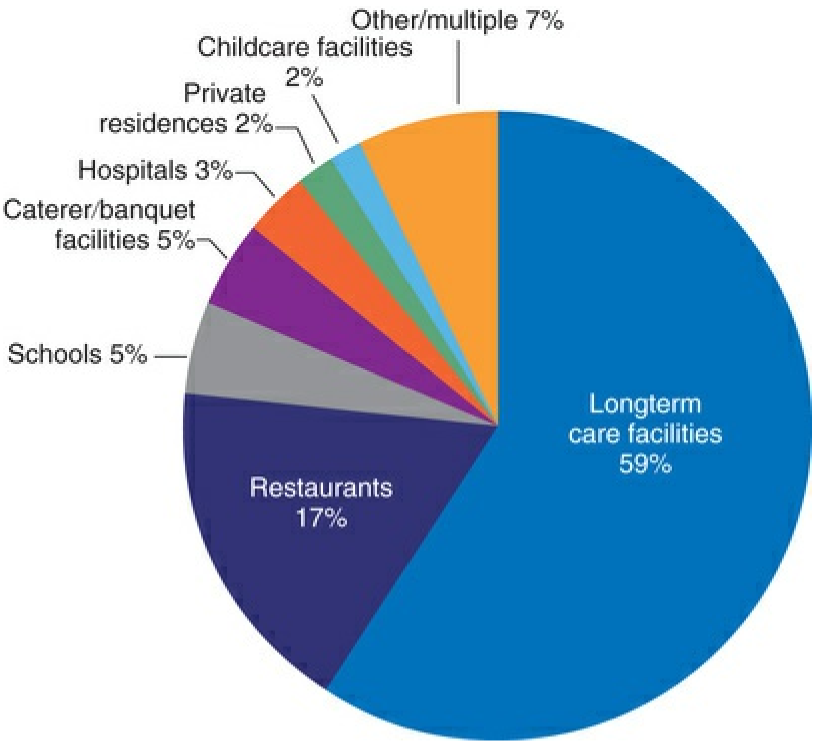

FIGURE 239.3 **Settings of 3243 outbreaks suspected or confirmed resulting from norovirus and reported to the Centers for Disease Control and Prevention through the National Outbreak Reporting System from 2009 to 2012.** (Data from Hall AJ, Wikswo ME, Pringle K, et al. Vital signs: foodborne norovirus outbreaks—United States, 2009–2012. MMWR Morb Mortal Wkly Rep 2014;63:491–495.)

Noroviruses also are the leading causes of foodborne disease outbreaks in the US. During 2009 to 2012, noroviruses accounted for 48% of all foodborne disease outbreaks with a single suspected or confirmed cause reported to the Centers for Disease Control and Prevention.[36] Outbreaks have been associated with consumption of oysters that concentrate viruses from contaminated waters, raspberries presumed to be contaminated in fields, and delicatessen meat contaminated during processing; however, outbreaks are usually linked to prepared foods (e.g., salads, sandwiches) contaminated during final preparation by an infected food worker.[36–41]

The epidemiology of sapoviruses is less well studied. A study in the US estimated 9 sapovirus cases in the community and 1 sapovirus-associated outpatient visit each year per 1000 population, representing 2% of all cases of acute gastroenteritis across the age spectrum.[42] A prospective study in the United Kingdom found similar results of 26 community cases and 2 cases in patients presenting to general practice per 1000 person-years attributable to sapovirus.[43] Although sapoviruses are a common causes of infection of infants, with seroprevalence similar to that of GII noroviruses, infections are often mild or asymptomatic.[44–46] Outbreaks of sapovirus illness are much less common than are outbreaks of norovirus, but they have been reported in schools, childcare facilities, adult longterm care facilities, and hospitals, as well as occasional foodborne outbreaks.[47–51] The broad age range of people affected in these outbreaks suggests that sapovirus infection may not be restricted to young children. Furthermore, an emergent genotype of sapovirus (GI.2) has been associated with an increased number of outbreaks in Europe that primarily affected older adults.[52]

Clinical Manifestations

Norovirus and sapovirus infections usually manifest as acute-onset vomiting with watery, nonbloody diarrhea, after an incubation period of 12 to 48 hours. Other symptoms include abdominal cramps, nausea, and occasionally low-grade fever; the term “stomach flu” is therefore commonly used to describe the illness, although the infection is not related to influenza. Although illness is generally self-limiting and full recovery can usually be expected in 1 to 4 days, symptoms can be debilitating and lead to dehydration and its sequelae requiring medical attention, especially in children <5 years of age and older adults ≥65 years of age.[18,22] Norovirus outbreaks in nursing homes also have been associated with increased rates of all-cause hospitalization and death, thus underscoring the severe impacts that norovirus infection can have in these populations.[53] Norovirus infections do not appear to result in longterm sequelae, although secondary features that have been reported include necrotizing enterocolitis in neonates, chronic diarrhea in immunosuppressed patients, postinfectious irritable bowel syndrome, and neurologic manifestations such as infantile seizures and encephalopathy.[54–58] More data are needed to confirm these observations and determine their relative frequency.

Generally, norovirus illness is less severe than is rotavirus disease, although medically attended pediatric cases of acute gastroenteritis associated with either virus have similar severity scores.[59] Clinical sapovirus infection manifests with similar but milder symptoms than does norovirus infection and with less vomiting.[46,60] Volunteer studies suggested that 30% of norovirus infections can be asymptomatic.[61] Importantly, norovirus and sapovirus can be shed in stools for 2 to 4 weeks after infection, although peak shedding occurs 2 to 5 days after infection.[50,62,63] Children and people with suppressed immune systems have been reported to shed virus for longer periods.[18] The point at which an infected person ceases to represent a significant risk of contagion is unclear.

Laboratory Findings and Diagnostic Tests

Human caliciviruses are refractory to growth in vitro, a feature that has hampered the development of diagnostic tests. In the 1990s, reverse transcriptase polymerase chain reaction (RT-PCR) became the preferred tool for diagnosing calicivirus infection; RT-PCR replaced electron microscopy and serologic tests that were insensitive, nonspecific, and generally difficult to perform.[64,65] RT-PCR platforms using TaqMan probes that allow for simultaneous detection and quantification largely have replaced conventional RT-PCR assays for laboratory diagnosis, and assays approved for use by the Food and Drug Administration are in the pipeline.[66,67] Enzyme immunoassays for norovirus antigen detection also have been developed, and at least 1 assay has been cleared for use by the Food and Drug Administration. However, because of poor sensitivity, enzyme immunoassays are not recommended for clinical diagnosis of sporadic gastroenteritis cases, although they can have utility in rapid diagnosis during outbreak investigations when multiple specimens are available.[68,69] Multipathogen molecular-based diagnostic platforms have been developed for simultaneous detection of common bacterial, parasitic, and viral causes of gastroenteritis, including noroviruses.[3]

Treatment

Treatment is supportive for dehydration and electrolyte imbalances. First-line therapy for uncomplicated viral gastroenteritis should be oral rehydration, whereas severe dehydration or shock warrants intravenous fluid therapy.[70] Antiemetics, antimotility agents, and antibiotics are not recommended.[71,72] Research and development of potential antiviral agents against noroviruses are ongoing, although no clinical trial has yet been conducted.[73,74]

Prevention

Prevention of infection should focus on standard hygienic precautions, including frequent hand hygiene, environmental disinfection, proper disposal of fecal or vomit-soiled materials, and limited contact with ill people.[75] Washing with soap and water is the preferred method of hand hygiene to prevent calicivirus transmission, with alcohol-based hand sanitizers useful only as adjuncts when hands are not visibly soiled.[76] Whenever possible, contact with ill people should be limited during the period of peak infectiousness (acute illness through 72 hours after recovery). Ill staff members in healthcare facilities and food handlers should be excluded from work until at least 48 hours after symptom resolution. Potentially contaminated environmental surfaces should be disinfected using a chlorine bleach solution with a concentration of 1000 to 5000 ppm (1 : 50–1 : 10 dilution of household bleach [5.25%]) or other approved disinfectant.[77] Current vaccine development efforts using virus-like particles have shown promise, although no vaccine against human caliciviruses has yet been licensed.[78,79]

Key Points

Epidemiology, Clinical Features, Diagnosis, and Management of Norovirus Gastroenteritis

Epidemiology

- Present throughout the world
- Affects all age groups, though greatest burden of more severe illness among young children (<5 years) and older adults (>65 years)
- Multiple modes of transmission

- Direct person-to-person contact
- Consumption of contaminated food or water
- Ingestion of airborne droplets of vomitus
- Contact with contaminated environmental surfaces

- Infectious dose: as few as 18 to 2800 virus particles
- High outbreak potential

Clinical Features

- 30% of infections can be asymptomatic
- Incubation period: 12 to 48 hours
- Disease characterized by
  - Acute-onset vomiting
  - Watery, nonbloody diarrhea
  - One or more of the following: abdominal cramps, nausea, fever, headache
- Dehydration most common complication in young patients and older adults
- Duration of illness: 12 to 60 hours

Diagnosis

- Limited availability of clinical assays for individual cases, so generally based on symptoms
- In outbreaks or for research studies, detection of norovirus by

reverse transcription polymerase chain reaction testing of stool specimens; sequencing of norovirus for genotype and cluster identification

Treatment

- Replacement of fluid and electrolytes by oral rehydration solutions or intravenous fluids
- No antiviral drug or vaccine currently available

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Astroviruses

Jacqueline E. Tate

Astroviruses were first described in 1975 when they were detected by electron microscopic examination in stool specimens of infants with gastroenteritis.[1,2] Since 1990, with development of sensitive and specific diagnostic methods, including enzyme immunoassays (EIAs) and reverse transcriptase polymerase chain reaction (RT-PCR), astroviruses have been identified as relatively common causes of community-acquired and hospital-acquired gastroenteritis.[2a–2d] Astroviruses are among the most common viral causes of gastroenteritis among children after rotaviruses and noroviruses.[3]

Description of Pathogen

Astroviruses are nonenveloped, positive-sense, single-stranded RNA viruses in the family Astroviridae.[4,5] By electron microscopic examination, astroviruses are 28 to 30 nm in diameter with a smooth edge, and they sometimes have a characteristic star-like appearance in the center (Greek, *astron* meaning "star") (Fig. 240.1).[5a,5b] At least 8 distinct serotypes (HAstV 1–8) of human astrovirus are recognized, defined both antigenically and by genetic sequence differences, with several novel species described since 2008.[6–8] Serotype 1 viruses are detected most commonly, but more than 1 serotype may circulate in communities during each season.[7,9] Non–serotype 1 viruses can predominate in a season, and greater serotype diversity can be found in developing countries.[7,10–14]

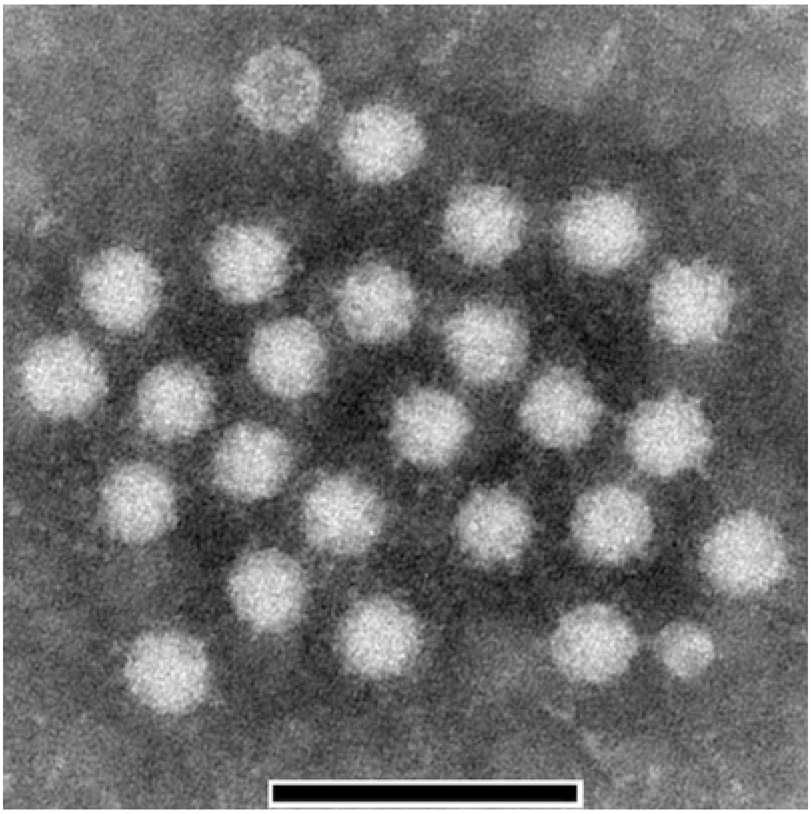

FIGURE 240.1 Astroviruses are 28 to 30 nm, have a smooth edge, and have a distinctive 5- or 6-pointed star on some particles when fecal suspension–derived virus is viewed. The smooth surface is not always present on astroviruses grown in culture and can resemble miniature versions of noroviruses. (Scale bar = 100 nm.) (Courtesy of Charles D. Humphrey, PhD, Centers for Disease Control and Prevention, Atlanta, Ga.)

Epidemiology

Like rotaviruses and caliciviruses, astroviruses have worldwide distribution and have been detected as causes of sporadic gastroenteritis and of outbreaks.[15–19] In both economically developed and developing countries, astroviruses have been detected in 2% to 9% of children treated for acute, nonbacterial diarrhea.[20] The lower proportions reported from some studies (<1%–3%) may reflect insensitive detection methods rather than true prevalence.[3,19,21–27] The mean prevalence of astroviruses globally is 11%, with detection usually higher in developing countries and in rural areas (23%) compared with urban areas (7%).[28] Since the 1990s a decreasing trend in astrovirus detection has been observed, but methodologic differences over time make such longitudinal comparisons difficult.[28]

Outbreaks of astrovirus gastroenteritis have been reported in closed settings such as schools, childcare centers, hospitals, nursing homes, and households, and they can be associated with high attack rates.[16,18,29–36] Astroviruses have been reported to be responsible for 5% to 16% of cases of nosocomial gastroenteritis in children's hospitals.[32,37,38]

Although astroviruses have been detected in all age groups, most infections occur in children <2 years of age.[15,16,23,39] Most adults have serum antibodies against astroviruses that are acquired early in life.[40] Disease in adults is uncommon. In volunteer studies, most adults challenged with virus did not become infected or develop diarrhea.[41] However, illness among teachers during school outbreaks has been described, perhaps as a result of a large dose of virus in this type of setting or a different mechanism of spread.[29,30] Outbreaks among older adults may reflect waning immunity associated with increasing age.[33–35] Astroviruses also have been associated with disease in immunocompromised adults.[42] Astroviruses have been found in stool from asymptomatic people. Further studies are needed to define the role of these viruses as pathogens more clearly.

Transmission is by the fecal-oral route, generally through person-to-person contact, but transmission occasionally can occur by contaminated food, water, or fomites.[29,30,43,44] The infectious dose has not been established. In temperate climates, astrovirus shows a seasonal distribution similar to that of rotavirus with a peak in winter; seasonality is less clear in tropical settings but tends to peak during the rainy season.[12,19,21,22,39,45,46]

Clinical Manifestations

The mean incubation period for astrovirus infections is 4.5 days.[47] Symptomatic illness occurs more commonly and with increased symptoms in infants and young children, although asymptomatic infections can occur at all ages.[17,18] Clinical symptoms generally are milder but similar to symptoms caused by rotavirus, with 2 to 5 days of watery diarrhea, often accompanied by vomiting and less often by high fever and abdominal pain.[23,32,39,48] Illness generally is mild and self-limited, but malabsorption and lactose intolerance have been reported following infection.[23,39,49] In highly immunocompromised children, astroviruses can spread systemically and cause severe, disseminated, lethal infections.[50] Stools do not contain blood or mucus. Children can shed virus 1 to 2 days before illness and for a median of 5 days after the onset of symptoms.[18,31,32] Prolonged diarrhea has been reported among children with malnutrition and in immunocompromised patients. Asymptomatic viral excretion among healthy children has been reported for 3 weeks when more sensitive detection methods have been used.[18] Persistent excretion occurs in immunocompromised patients.[51] Because illness is largely confined to young children and older adults, infection probably confers protection that is relatively durable. Astroviruses have been identified as potential, but uncommon, risk factors for intussusception in young children in several studies.[52–54]

Laboratory Findings and Diagnosis

Since 1990, many improvements have been made in diagnostic methods for astroviruses, including adaptation to grow in continuous cell lines, sequencing and elucidation of the structure of the genome, and development of improved methods of detection, including EIAs and RT-PCR.[3] Commercial EIAs to detect viral antigen in stool are available in many countries and offer sensitive and specific methods to diagnose infections; none of these EIAs are available in the United States.[2b,2d,3] Commercial monoplex and multiplex real-time RT-PCR kits are available. Other diagnostic methods include serum EIA for astrovirus antibodies and electron microscopic examination; these methods are used primarily in research settings.[3] Next-generation technologies (e.g., such as whole-genome sequencing and viral metagenomics) are becoming available and can help improve understanding of the basis of viral pathogenesis and identify emerging strains.

Treatment

The mainstays of management are rapid assessment, correction of fluid loss and electrolyte disturbances, and maintenance of adequate hydration. Oral rehydration therapy with appropriate glucose and electrolyte solutions is sufficient for most patients. Intravenous rehydration is required for children severe dehydration, shock, or intractable vomiting. Children should maintain caloric intake as best as possible, with maintenance of diet.[55] Breastfed infants should continue to nurse on demand, and formula-fed infants should continue formula immediately on rehydration. Children receiving semisolid or solid foods should continue to receive their usual diet during episodes of diarrhea, although substantial amounts of foods high in simple sugars (carbonated soft drinks, juice, gelatin desserts) should be avoided because the osmotic load could worsen diarrhea. No specific antiviral therapy exists.

Prevention

No vaccine is available, and none is in clinical trial. Prevention of astrovirus infections is best accomplished through good hygiene, including attention to appropriate hand hygiene practices.

Key Points

Astroviruses

Epidemiology

- Worldwide distribution.
- Causes of sporadic gastroenteritis and outbreaks
- Detected in all age groups, but most infections occur in children <2 years of age
- Transmission by the fecal-oral route, generally through person-to-person contact, but transmission occasionally can occur by contaminated food, water, or fomites

Clinical Manifestations

- Mean incubation period is 4.5 days.

- Symptomatic illness is more common, and symptoms are exaggerated in infants and young children.

- Clinical symptoms generally are mild and self-limiting.

- 2 to 5 days of watery diarrhea, often accompanied by vomiting and less often by high fever and abdominal pain

- Children can shed virus 1 to 2 days before illness and for a median of 5 days after onset of symptoms.

- Persistent excretion occurs in immunocompromised patients

Diagnosis

- Commercial enzyme immunoassays detect viral antigen in stool.

- Sensitive and specific method to diagnose infections

- None available in the United States

- Commercial monoplex and multiplex real-time reverse transcriptase polymerase chain reaction kits are available.

Management

- No specific therapies available

- Mainstays of management

- Rapid assessment

- Correction of fluid loss and electrolyte disturbances

- Maintenance of adequate hydration

Prevention

- Good hygiene
- Attention to appropriate hand hygiene practices

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Hepatitis E Virus

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Hepatitis E virus (HEV), the major etiologic agent of enterically transmitted non-A hepatitis worldwide, is a spherical, nonenveloped, single-stranded, positive-sense RNA virus that is approximately 32 to 34 nm in diameter.[1] HEV is the sole member of the family Hepeviridae, genus *Hepevirus*.[2] The HEV genome, which is approximately 7.2 kilobases, consists of 3 open reading frames (ORF 1, ORF 2, and ORF3). HEV is classified into 4 major genotypes, which represent a single serotype.[3] Genotype 1 includes Asian and African strains; genotype 2 includes Mexican and some African strains. Both genotypes 1 and 2 are associated with large epidemics. Genotype 3 includes strains from sporadic human cases from industrialized countries including the United States, Japan, and countries in Europe, as well as animal strains from swine. Genotype 4 includes strains from human cases in Asia (mainly Taiwan and China) and animal strains from swine.

Following HEV infection, both immunoglobulin (Ig) M and IgG antibodies to HEV (anti-HEV) are elicited (Fig. 241.1). IgM anti-HEV generally is detectable at the time of symptom onset or liver enzyme elevations; levels decline during early convalescence.[4] IgG anti-HEV persists and appears to provide protection against disease,[5] but the duration of immunity after infection has not been determined. One study demonstrated persistence of IgG anti-HEV in approximately 50% of people studied at least 14 years after infection.[6]

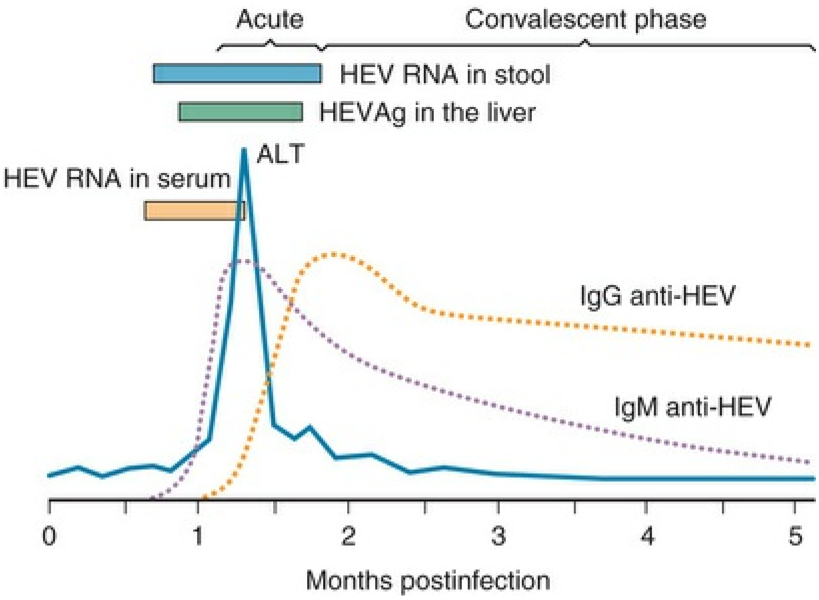

FIGURE 241.1 **Typical serologic and biochemical response to hepatitis E virus infection. ALT, alanine aminotransferase; anti-HEV, antibodies to hepatitis E virus; HEV, hepatitis E virus; HEVAg, hepatitis E virus antigen; Ig, immunoglobulin;** (Courtesy of Dr. K. Krawczynski.)

Histopathologic features of HEV infection include both classic acute viral hepatitis, with focal hepatocellular necrosis, ballooned hepatocytes, and acidophilic degeneration of hepatocytes, and cholestatic hepatitis, with bile stasis in canaliculi and gland-like transformation of hepatocytes.[7,8]

Epidemiology

HEV infection manifests in 2 distinct clinicoepidemiologic patterns mainly related to viral genotype.[9] In hepatitis E epidemics, HEV (genotype 1 or 2) is transmitted primarily by the fecal-oral route. Fecally contaminated drinking water is the most commonly documented vehicle of transmission, and outbreaks usually occur during the rainy season and sometimes affect thousands of people.[5,7,10] HEV infection also accounts for most cases of acute sporadic hepatitis in both children and adults in endemic countries.[11–13] Risk factors for sporadic hepatitis E have not been well defined.

Many of the hepatitis E cases in the US and Western Europe have been reported among travelers returning from HEV genotype 1–endemic areas.[14–16] Although outbreaks of hepatitis E do not commonly occur in the US and Western Europe, increasing numbers of autochthonous cases unrelated to travel are being reported.[17,18] The HEV strains isolated from patients with autochthonous hepatitis E belong to HEV genotype 3 and 4 and have close genetic resemblance to the swine HEV strains isolated from local farms, a finding suggesting that swine could serve as zoonotic source for human disease. However, the mechanism of transmission from swine to humans in these autochthonous cases is unknown. The worldwide distribution of hepatitis E has not been determined fully, in part because of a lack of well-standardized serodiagnostic tests and a lack of surveillance for hepatitis E.[19,20] However, HEV appears to be endemic globally, given the high seroprevalence of anti-HEV in different populations, the high seroprevalence in animals, the frequent occurrence of outbreaks, and the finding that a significant proportion of sporadic acute viral hepatitis is caused by HEV.[21–24] Large outbreaks of HEV have been documented over a wide geographic area, primarily in developing countries with inadequate environmental sanitation (Fig. 241.2).[10,25–30]

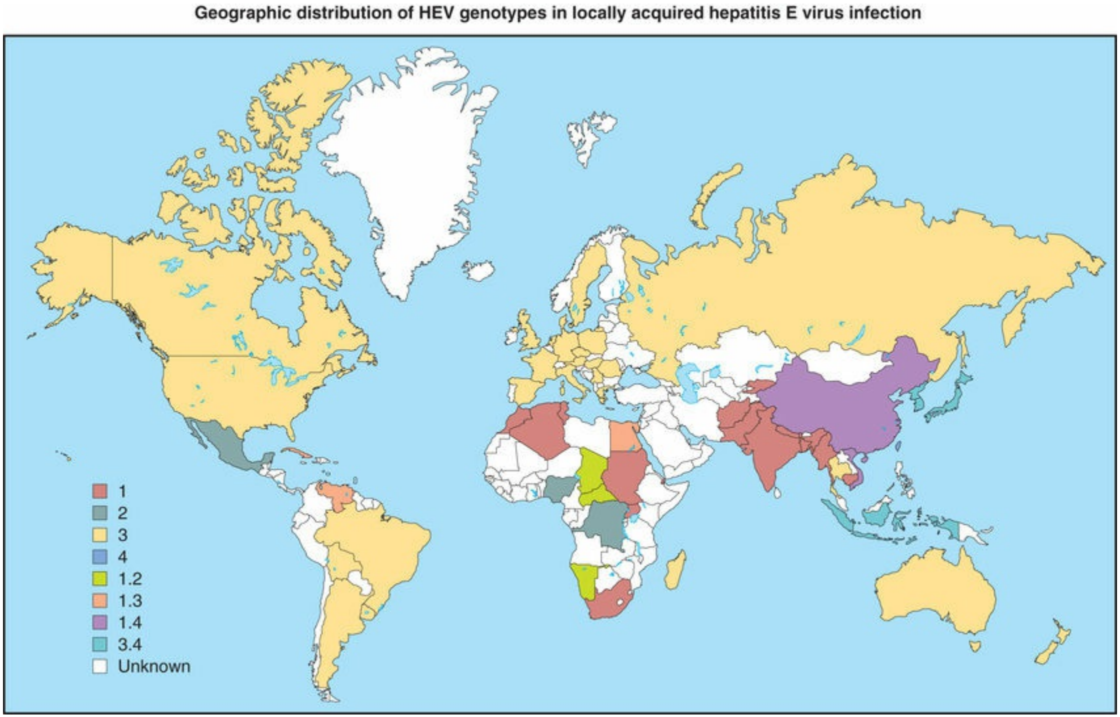
Geographic distribution of HEV genotypes in locally acquired hepatitis E virus infection
1
2
3
4
1.2
1.3
1.4
3.4
Unknown

FIGURE 241.2 **The global pattern of hepatitis E virus infection.** (From Centers for Disease Control and Prevention. https://www.ncbi.nlm.nih.gov/pubmed/25738664.)

Identification of IgG anti-HEV in animal species in many regions of the world provides credence to the speculation that HEV is a zoonotic agent.[31,32] HEV can be transmitted by food, as evidenced by disease following consumption of uncooked offal meat from wild boar and sika deer in Germany and Japan and after consumption of raw figatellu, a traditional pig liver sausage in France.[33–35] Vertical transmission of HEV from infected mother to fetus is common.[36] In epidemic settings, person-to-person transmission can contribute to significant transmissions.[37] Nosocomial transmission, presumably by person-to-person contact and by transmission through blood transfusion, has been reported.[38,39]

Clinical Manifestations

Infection can be asymptomatic, it can be clinically inapparent, or can result in clinically evident disease. The incubation period ranges from 15 to 60 days (mean, 40 days). Typical acute clinical signs and symptoms are indistinguishable from those of other types of viral hepatitis and consist of jaundice, malaise, anorexia, nausea, vomiting, abdominal pain, dark urine, fever, and hepatomegaly.[10,12,13,40,41] Other less common signs and symptoms are diarrhea, arthralgia, pruritus, and urticarial rash. The period of infectivity after acute infection has not been determined, but virus excretion in stool has been demonstrated beginning approximately 2 weeks before elevation of serum hepatic enzyme levels and ending by the time liver enzyme levels return to normal.[42,43] In most outbreaks, the highest rates of clinically evident disease have occurred in young to middle-aged adults; lower disease rates in younger age groups could be the result of anicteric or subclinical infections.[5,19,25,28] In contrast, most autochthonous HEV infection occurs among older men (usually >40 years of age).[44] No evidence of chronic HEV infection has been detected in longterm follow-up of otherwise healthy people.[45] However, chronic HEV infection occurs among adult recipients of solid organ transplants, people with acquired immunodeficiency syndrome, and people with hematologic malignant diseases.[46–48] Association of autochthonous HEV infection with neurologic signs and symptoms including Guillain-Barré syndrome is recognized increasingly, as is cirrhosis in immunosuppressed populations.[49,50] Cases of chronic HEV infection that rapidly progressed to cirrhosis have been reported among children who received bone marrow transplants for hematologic malignant diseases and among liver transplant recepients.[51,52] HEV also causes severe hepatic decompensation in patients with preexisting chronic liver disease.[53,54]

The mortality rate observed during epidemics of HEV infection is approximately 0.1% to 4%.[55] However, fulminant hepatitis occurs more frequently among pregnant women, particularly in the third trimester, and case-fatality rates can reach 25%.[56–58] Mortality rates in young children can be high.[55,59] The reason for the high mortality rates among pregnant women is unknown; causes of death include hepatic encephalopathy and disseminated intravascular coagulation.[60,61] In a prospective study of 26 pregnant women with HEV infection, 15 patients had fulminant hepatic failure and 11 patients had nonfulminant disease. Five mothers died undelivered, 2 aborted, 4 had premature delivery, and 15 delivered full-term infants. Fifteen (79%) of the 19 live born infants had evidence of HEV infection at birth (12 had IgM anti-HEV and 10 had HEV RNA detected). Neonates had icteric hepatitis (7), anicteric hepatitis (5), and jaundice with normal hepatic enzymes (3). In the first week of life 7 infants died, 1 of prematurity and 6 of HEV infection; 5 of 6 mothers of infants who died had fulminant hepatic failure. Vertical transmission of HEV to the fetus with poor perinatal outcome has occurred in 30% to 100% of mothers with HEV infection.[62]

Laboratory Findings and Diagnosis

Laboratory findings are similar to those of other types of viral hepatitis and include elevated serum levels of bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and γ-glutamyltransferase.[8,9,41] Resolution of hyperbilirubinemia and serum aminotransferase elevations generally occurs within 1 to 6 weeks after onset of illness.

Enzyme immunoassays to detect IgM and IgG anti-HEV in serum are available commercially, but none is cleared for clinical use in the US by the Food and Drug Administration. The sensitivity and specificity of these tests vary significantly.[20] Reverse transcriptase polymerase chain reaction can be used to detect HEV RNA in serum and stool but is not available routinely in diagnostic laboratories. Other tests initially used to detect HEV infection are the immunohistochemistry test to identify HEV antigen in liver tissue and the fluorescent antibody-blocking assay to identify the anti-HEV reaction to HEV antigen in serum. However, both these assays have limited sensitivity and are available only in a few research laboratories. Western blot assays can detect IgM and IgG anti-HEV in serum but are less sensitive. Interpretation of test results can be difficult, and in low-endemic regions a definitive diagnosis generally requires use of multiple tests, consideration of risk factors, and exclusion of other causes of acute hepatitis (Table 241.1).

TABLE 241.1

Interpretation of Hepatitis E Test Results in Patients With Clinical Hepatitis

		Result	
Specimen	**Assay**	**Positive**	**Negative**
Serum	IgM anti-HEV	Consistent with current or recent HEV infection; in most cases, IgG anti-HEV also detected	Consider other causes of hepatitis; if acute hepatitis E suspected, test for IgG anti-HEV, HEV RNA
	IgG anti-HEV	Consistent with past or current HEV infection; test for IgM anti-HEV or HEV RNA to confirm current or recent infection	If acute hepatitis E suspected, test for IgM anti-HEV or HEV RNA
Serum or stool	HEV RNA	Current infection	Cannot exclude current infection

anti-HEV, antibodies to hepatitis E virus; HEV, hepatitis E virus; Ig, immunoglobulin.

Modified from Ticehurst JR. Hepatitis E virus. In: Murray PR, Baron EJ, Pfaller MA, et al. (eds). Manual of Microbiology, 7th ed. Washington, DC, American Society for Microbiology, 1999.

Treatment

Treatment is supportive. Data are not available to evaluate the efficacy of antiviral agents or other specific therapies. In solid organ transplant recipients with chronic hepatitis E, discontinuation of immune suppressor drugs is associated with sustained virologic response.[63] In some instances, pegylated interferon and ribavirin were used successfully to treat chronic HEV infection.[64,65]

Prevention

Prevention relies primarily on providing clean drinking water and avoiding contamination of drinking water stored in home. Prudent hygienic practices when traveling to developing countries consist of avoiding drinking water (and beverages with ice) of unknown purity and eating uncooked fruits and vegetables that are not peeled and prepared by the traveler.

Studies conducted during outbreaks have demonstrated that anti-HEV from previous exposure protects against clinical disease.[5] Passive immunoprophylaxis with convalescent serum in nonhuman primates has been shown to prevent disease but not infection.[66] However, immune globulin prepared from plasma collected in low-endemic areas is not effective in preventing clinical disease in humans.[39] The efficacy of immune globulin prepared from plasma collected in high-endemic areas is unclear.[39,67,68] In studies of prototype recombinant vaccines, animals were protected against disease but not against infection, as indicated by detectable viremia and viral excretion.[69,70] In a large phase III trial, a recombinant protein vaccine (truncated ORF-2 protein) was found to be safe and effective in preventing hepatitis E.[71] This vaccine is now approved for use in China but is not widely available. This vaccine could be a powerful new tool for prevention of hepatitis E and may have a role in preventing outbreaks in regions and settings where outbreaks commonly occur.[72]

Newly Identified Viruses

Patients with acute hepatitis in whom recognized viral and nonviral causes have been excluded are considered to have non–A through E (non–A-E) hepatitis.[73] Since 2000, new viruses, which include GB virus (GBV) agents (previously known as hepatitis G virus),[74] transfusion transmitted virus, and Sendai virus, have been identified as possible causes of non–A-E hepatitis.[75–77] However, their role in the origin of non–A-E hepatitis has not been established, and their pathogenic role is not clear. Studies have shown that GBV does not replicate in the liver of people coinfected with hepatitis C virus and GBV, a finding suggesting that GBV is not a hepatotropic virus.[78,79] Although a viral origin of non–A-E hepatitis possibly exists, efforts to find the potential etiologic agent have not yet succeeded.

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C

Fungi

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Classification of Fungi

Thomas F. Patterson, Deanna A. Sutton

Fungal disease contributes significantly to patients' morbidity and mortality in certain clinical settings. Extensive medical interventions, immunosuppression, and a heightened awareness of fungal disease, particularly opportunistic mycoses in the setting of immune compromise, have all necessitated an increased understanding of fungal etiologic agents and their classification, identification, and clinical manifestations.

The Agents

Definition.

Fungi are heterotrophic (lacking chlorophyll) eukaryotic organisms surrounded by a rigid cell wall composed mostly of chitin, glucan, chitosan, mannan, and glycoproteins. They have a nucleus surrounded by a membrane, and their replication is by both mitosis (asexual) and meiosis (sexual). Fungi range from simple, single-celled organisms, mostly yeasts, to complex filamentous mold species and basidiocarps (mushrooms).[1] Yeasts typically are round to oval with budding cells (blastoconidia). Yeasts mostly are small, white to cream-colored colonies on Sabouraud dextrose agar, although some species can be pink to salmon colored. The term *black yeast* is applied loosely to the yeast form of the mold genus

Exophiala and other closely related genera. Molds are multicellular, produce an extensive mycelium (filamentous), are variously colored, and have several modes of reproduction that may be asexual (conidiogenesis yielding conidia), sexual (sporogenesis yielding spores), or both. The classic primary mold pathogens such as *Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatitidis,* and *Paracoccidioides brasiliensis* are thermally dimorphic in that they can exhibit both a yeast stage (spherules for *Coccidioides* spp.) and a filamentous phase, depending on their growth in the host or under laboratory conditions. Other molds can be referred to as pleomorphic (i.e., can demonstrate multiple morphologic forms under laboratory conditions). This pleomorphism is discussed further when considering appropriate naming of molds (taxonomy and nomenclature).

Classification.

The Kingdom Fungi is arranged in a hierarchical classification system with each rank denoted by a particular ending: phylum, -mycota; subphylum, -mycotina; class, -mycetes; order, -ales; family, -aceae. Most of the clinically significant genera in the kingdom Fungi are within the phyla Ascomycota, Basidiomycota, subphylum Mucoromycotina, and subphylum Entomophthoromycotina.[2] Herein are contained members of the order Mucorales, which includes most genera inciting mucormycosis, as well as the Entomophthorales, inciting entomophthoramycosis. An example of an abbreviated classification for the fungus *Microascus cirrosus* would be as follows: kingdom Fungi, subkingdom Dikarya, phylum Ascomycota, order Microascales, family Microascacaea, genus *Microascus*, species *Microascus cirrosus*. Closely related parafungal organisms in the genera *Pythium* and *Lagenidium* are in the kingdom Streminipila (Stramenopila), phylum oomycota, whereas *Rhinosporidium* is in the supergroup Opisthokonta, division Holozoa.[3]

Taxonomy and Nomenclature.

Taxonomy refers to the classification of fungi in a very systematic way, and nomenclature refers to the assigning of names. These tasks now are under the auspices of the International Code of Nomenclature for algae, fungi, and plants. The Melbourne Code, implemented on January 1, 2013, introduced sweeping changes into the naming of fungi and resulted in the elimination of multiple names for the same organism that produces various morphologic forms (dimorphism or pleomorphism).[4] Thus, for example, the use of both the teleomorph (sexual) name *Pseudallescheria boydii* and its anamorph name *Scedosporium boydii* (previously thought to be *Scedosporium apiospermum*) no longer is permitted.[5] Going forward, the accepted name is *Scedosporium,* and similar changes are noted for various genera. The preferred name is no longer the teleomorph state, as was previously designated, but the oldest validly published name, which may be either the anamorph or teleomorph.

Laboratory Findings and Diagnosis

Collection and Examination of Specimens

The 2012 publication by the Clinical and Laboratory Standards Institute entitled *Principles and Procedures for Detection of Fungi in Clinical Specimens—Direct Examination and Culture: Approved Guideline,* is an excellent source for ensuring that the specimen being examined or cultured is appropriate for the etiologic agent being sought.[6] Consultation with the laboratory before specimen collection, however, is always recommended when the clinical history suggests potentially uncommon, unusual, or atypical organisms. Specimen types, rejection criteria, and specimen processing are well defined in this document, including blood culture for fungal organisms. Although the use of homogenization or grinding of specimens often facilitates the recovery of *Histoplasma capsulatum,* this method should never be used for member of Mucorales and for most other filamentous fungi because it is deleterious to fragile fungal hyphae. Direct examination of specimens with various stains such as the Gram stain, 10% potassium hydroxide preparations, calcofluor white fluorescent stain, India ink, and others is always recommended. Histopathologic stains such as hematoxylin and eosin and Gomori methenamine silver stain should be routine for tissue specimens, and additional special stains should be added when indicated (e.g., Fontana-Masson stain for melanin, mucicarmine for *Cryptococcus*). A comprehensive review of the histopathologic diagnosis of fungal infections is available.[7]

Culture and Identification

Phenotypic Identification.

The recovery of etiologic agents, both yeasts and molds, requires the appropriate media, incubation temperatures, and length of incubation. Several resources are available defining these parameters, including a document published by the Clinical and Laboratory Standards Institute.[6] Several systems are available for yeast recovery and identification, both manual and automated, and these systems often are determined by the laboratory's size and the population of patients served. Mold recovery and identification can be more problematic, so a few salient comments are included here regarding their identification. Although Sabouraud dextrose agar may be useful in recovery, the morphologic features of many molds are atypical on this medium, and a plant-based medium such as potato dextrose agar always should be incorporated into the battery of mold recovery and identification media. Other plant-based media and extended periods of incubation also may be required for the development of diagnostics structures for some opportunistic mold pathogens.

Molecular Identification.

Many larger or reference facilities have begun to incorporate molecular identification of both yeast and molds, either on a routine basis or for individual isolates. The method most commonly used is Sanger sequencing with identification by comparative sequence analysis.[8] This method compares sequence data for the isolate in question against a database of organisms to determine the percentage of similarity to known, credible deposits in the database, preferably compared with type strains. Identification by molecular sequencing always should be compatible with phenotypic identification.

Protein Analysis.

An additional tool for fungal identification is matrix-assisted laser desorption/ionization–time of flight mass spectrometry. This technique has not been used extensively because of the cost of the equipment, the need for more effective protein extraction methods for some genera, and less than robust databases, particularly for molds. These limitations are being overcome, however; yeast identification is becoming more common, and mold databases are being improved significantly.[9]

Clinical Manifestations

Both the functional integrity of the host's immune system and an intact skin barrier are major determinants of disease expression. Table 242.1 contains specific risk factors. The spectrum and severity of infections, as well as the pathologic entities, often overlap, however (see Table 242.2). For example, invasive candidiasis and cryptococcosis are frequent infections in immunocompromised hosts. However, superficial candidal infections occur in healthy infants, and cryptococcal infections can occur in otherwise healthy people. Similarly, various hyaline and phaeoid molds, as well as member of Mucorales, can cause clinical and pathologic entities that may be indistinguishable, and clinical entities that normally are superficial subsequently can become invasive. Thus, with the foregoing limitations and the difficulty of precise placement taken into account, the manifestations of fungal disease can be divided broadly into 3 main categories: primary systemic infections, opportunistic infections, and superficial/inoculation mycoses (see Table 242.2). This simple categorization also does not take into account community versus healthcare acquisition or the sometimes broad, overarching clinical presentations of an increasingly diverse number of fungal infections. The concept, however, is useful.

TABLE 242.1

Specific Predisposing Risk Factors Associated With the Development of Fungal Infections

Predisposing Factor	**Etiologic Agent(s)**
Barrier disruption: intravenous catheters, mucositis, trauma, burns	*Candida* spp. *Aspergillus* (lung transplant) Other molds

Exposures: inoculation, aerosols	Endemic mycoses *Aspergillus* and other molds
Metabolic: ketoacidosis, hyperglycemia	*Candida* spp. Mucorales
Quantitative or qualitative neutrophil dysfunction	Candida spp.
Inherited (chronic granulomatous disease), acquired (chemotherapy induced neutropenia)	*Aspergillus* and other molds
Deficits in cell-mediated immunity: acquired immunodeficiency syndrome, corticosteroids, tumor necrosis factor-α, other biologic agents	Endemic mycoses *Cryptococcus* spp.

TABLE 242.2

Classification of Human Infections Caused by the Medically Important Fungi

Clinical Category	Principal or Representative Causes
PRIMARY SYSTEMIC MYCOSES	
Histoplasmosis	*Histoplasma capsulatum*
Coccidioidomycosis	*Coccidioides immitis/posadasii*
Blastomycosis	*Blastomyces dermatitidis*
Paracoccidioidomycosis[a,b]	*Paracoccidioides brasiliensis*
OPPORTUNISTIC MYCOSES[c]	
Invasive candidiasis	*Candida* spp.
Invasive aspergillosis	*Aspergillus* spp.
Cryptococcosis	*Cryptococcus neoformans*
Agents of mucormycosis[a,d]	*Lichtheimia* spp., *Mucor* spp., *Rhizomucor* spp., *Rhizopus* spp., *Mortierella* spp., *Cunninghamella* spp., etc.[e]
Hyalohyphomycosis[f]	*Penicillium* spp., *Acremonium* spp., *Fusarium* spp.
INOCULATION OR CONTAMINATION MYCOSES	
Superficial mycoses (dermatophytosis)[a,g]	*Microsporum* spp., *Trichophyton* spp., *Epidermophyton* spp.
Pityriasis (tinea) versicolor	*Malassezia furfur*
Sporotrichosis	*Sporothrix schenckii* complex
Chromoblastomycosis[a,h]	
Phaeohyphomycosis[a,i]	Dematiaceous fungi[j]
Mycetoma[a,k]	
Scedosporiosis[a,l]	*Scedosporium apiospermum/S. boydii*[l]

[a] Synonymous, obsolete, overlapping, or incomplete terminology for the clinical entities.

[b] South American blastomycosis.

[c] A complete list of agents is encyclopedic (see text).

[d] Phycomycosis, zygomycosis.

[e] *Saksenaea* spp., *Cokeromyces* spp., *Syncephalostrum* spp., *Conidiobolus* spp., *Basidiobolus* spp.

[f] Many nondematiaceous molds; colorless cell walls in hematoxylin and eosin–stained

sections.

[g] Ringworm (tinea).

[h] Chromomycosis.

[i] Cerebral chromomycosis, chromoblastomycosis, chromomycosis, cladosporiosis, phaeomycotic cyst, pheosporotrichosis, subcutaneous mycotic cyst.

[j] Group of fungi that are pale brown to black in the cell walls of vegetative cells, conidia, or both; ubiquitous saprophytes of soil and plants. Examples include *Alternaria* spp., *Bipolaris* spp., *Cladosporium* spp., *Curvularia* spp., *Fonsecaea* spp., *Phialophora* spp., *Rhinocladiella* spp., and *Wangiella* spp.

[k] Madura foot, maduromycosis.

[l] Allescheriasis, allescheriosis, petriellidosis, pseudallescheriosis, pseudoallerscheriasis; *Pseudallescheriai* boydii and a distinct species from S. *apiospermum* (telomorph) now recognized as *Scedosporium boydii.*

Primary Systemic Mycosis.

The primary systemic mycoses (histoplasmosis, blastomycosis, coccidioidomycosis, and paracoccidioidomycosis) are caused by the thermally dimorphic, endemic pathogens *Histoplasma capsulatum, Blastomyces dermatitidis or Blastomyces gilchristii, Coccidioides immitis or Coccidioides posadasii* and *Paracoccidioides brasiliensis or Paracoccidioides lutzii*. These agents are capable of causing disease in immunologically competent hosts. Sometimes also included are the genera *Emmonsia* and *Sporothrix*, the agents of adiaspiromycosis and sporotrichosis.[10]

Opportunistic Mycoses.

Opportunistic mycoses are caused by less virulent agents, and invasive disease with these agents almost always occurs in immunocompromised people or those with indwelling foreign bodies. Many such infections are nosocomial. Examples include invasive candidiasis, aspergillosis, cryptococcosis, and mucormycosis.

Superficial or Inoculation Mycoses.

These infections may be superficial or subcutaneous, and they can result from skin contamination or inoculation through compromised integumentary barriers. An example of superficial infection is dermatophytosis. Examples of subcutaneous infection include mycetoma and the cutaneous manifestations of mucormycosis. Mycetoma, a chronic, destructive localized infection of skin, soft tissue, fascia, and bone, can be caused by a variety of true fungi (eumycotic mycetoma), as well as by several aerobic actinomycetes (actinomycotic mycetoma).

Key Points

Overview of Fungi and Fungal Infections

Microbiology

- Agents of hyalohyphomycosis: molds that are hyaline in tissue; variously colored or lightly pigmented in culture and associated with soil, water, and decomposing vegetation. Species include *Aspergillus* spp. and other genera including *Fusarium,* the *Pseudallescheria boydii* species complex, *Paecilomyces, Chrysosporium, Penicillium,* and others.

- Agents of phaeohyphomycosis: melanized or dematiaceous (darkly pigmented) molds or yeast-like fungi associated with soil, water, decomposing vegetation. More than 150 species and 70 genera, including *Bipolaris, Alternaria, Scedosporium prolificans, Exophiala, Exserohilum, Cladosporium, Curvularia, Cladophialophora, Scopulariopsis,* and others

- Many fungi now referred to as a species complex because of phylogenetic, phenotypic, and physiologic differences in strains

Epidemiology

- Infections occur worldwide, most commonly in severely immunocompromised children, usually following inhalation of conidia.

- Infections can follow direct inoculation from trauma or localized infection (keratitis, sinusitis, otitis).

- Specific exposures are associated with some organisms (water aerosols for *Fusarium;* or near-drowning for *Pseudallescheria boydii* species complex; outbreaks caused by contaminated solutions, e.g., *Fusarium* keratitis).

Clinical Features

- Cutaneous infection: follows trauma in immunocompetent or compromised children; slowly increasing nodular or ulcerative lesions; also can reflect disseminated infection (fusariosis)

- Pulmonary infection: follows inhalation; symptoms including productive cough, fever, weight loss, shortness of breath, hemoptysis; nonspecific radiographic infiltrates

- Disseminated infection: severely immunocompromised children; neurotropism with brain abscess common for some organisms (agents of phaeohyphomycosis such as *Cladophialophora bantiana*)

Diagnosis

- Recovery of organism in culture from specimens of body fluids or tissue

- Microscopic examination of pathologic material: nonspecific histopathologic features for agents of hyalohyphomycosis; beaded irregular appearance of pigmented hyphae for agents of phaeohyphomycosis

- Melanin staining by Masson-Fontana method useful for agents of phaeohyphomycosis

Treatment

- Traditionally amphotericin B (or lipid formulation), but many species resistant to polyenes

- Activity and clinical use of voriconazole or posaconazole reported in case series; itraconazole limited to less seriously ill

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243

Candida Species

P. Brian Smith, William J. Steinbach

Advances in medical therapy have allowed for the improved survival of increasingly immunocompromised and critically ill patients. These improvements have augmented the frequency as well as the morbidity and mortality associated with *Candida* infection in infants and children.

Epidemiology

Although more than 200 identified species of *Candida* have been identified, only approximately a dozen appear to cause disease in children, including *C. albicans, C. parapsilosis, C. tropicalis, C. glabrata, C. krusei, C. lusitaniae, C. stellatoidea, C. kefyr, C. pseudotropicalis, C. dubliniensis, C. intermedia,* and *C. guilliermondii.*[1–4]

C. albicans is the most commonly isolated species in children.[1,5,6] In a prospective study of neonatal candidiasis, *C. albicans* was isolated as the causative organism in 66% (38 of 58) of cases.[1] Similarly, *C. albicans* was isolated in 54% (31 of 57) of pediatric patients in the first year following hematopoietic stem cell transplantation.[7] However, the epidemiology of invasive candidiasis is changing, and the percentage of cases caused by *C. albicans* has declined from more than 80% to as low as 29% in some centers.[5,8] Despite these trends, *C. albicans* continues to be associated with increased rates of end-organ damage and a higher attributable mortality rate relative to other *Candida* species.[9,10]

C. parapsilosis is of particular importance as a cause of invasive candidiasis in neonatal and pediatric patients.[1,11] In a cohort of infants of <1000 g birth weight who had invasive *Candida* infections, 43% (132 of 307) of cases were caused by *C. parapsilosis*.[10] *C. parapsilosis* also is the most common species found colonizing the hands of healthcare personnel,[12] a finding suggesting a possible vehicle of transmission. In animal models of infection, *C. parapsilosis* is less virulent than other *Candida* species and is associated with lower mortality rates.[1,10,13] *C. parapsilosis* is important to distinguish from other species because of its occasional lower susceptibility to the echinocandin antifungal agents.

C. glabrata and *C. krusei* are less commonly isolated species but are important because they often are resistant to fluconazole.[14] In adults, in whom the use of fluconazole for prophylaxis is more widespread, *C. glabrata* is increasing in incidence and is the second or third most common cause of candidiasis.[15,16] *C. tropicalis* is considered to be the second most virulent species behind *C. albicans* and has increasingly been isolated.[8] *C. lusitaniae,* which is resistant to amphotericin B formulations, is less frequently isolated but is important given its unique resistance pattern. *C. dubliniensis*, once thought to be an "atypical" *C. albicans*, is a separate species often found in human immunodeficiency (HIV)–infected patients.[17] *C. guilliermondii* has been reported as a cause of bloodstream infections (BSIs) in patients with cancer, and *C. kefyr* is a reported cause of esophagitis.[18,19]

Candida species are the third most common pathogens in nosocomial BSIs among premature infants.[20–22] A prospective study of 2847 infants admitted to 6 neonatal intensive care units (NICUs) revealed a cumulative incidence of 0.3% (3 of 1139) in infants weighing more than 2500 g, 3% among very low birth weight (VLBW; <1500 g birth weight) infants, and 7% among extremely low birth weight (ELBW; <1000 g birth weight) infants.[10,23] The mean age at diagnosis was 15 to 33 days of life.[6,24] However, the incidence of invasive candidiasis among premature infants has declined since the 1990s.[25–27] Among infants discharged from 322 NICUs, the incidence of invasive candidiasis decreased from 3.6 episodes per 1000 infants in 1997 to 1.4 episodes per 1000 infants in 2010.[27]

The mortality rate from all *Candida* species in premature infants has been reported consistently at 20% from large multicenter studies.[10,13,21,22] In addition to a high mortality rate, invasive candidiasis in infants is associated with significant morbidities in survivors, including poor neurodevelopmental outcome, periventricular leukomalacia, chronic lung disease, and severe retinopathy of prematurity.[28–31]

Candida also is isolated commonly in hospitalized older pediatric patients. In an examination of more than 3400 BSIs in patients 16 years of age or younger, *Candida* was the third most commonly isolated organism.[32] A study of more than 500 patients in 35 pediatric ICUs (PICUs) revealed *Candida* to be the second most common cause of nosocomial infections.[33] Mortality rates also are substantial in pediatric patients. Candidemia was associated with a mortality rate of 16% in 1108 pediatric cases diagnosed outside the neonatal period,[34] and the mortality rate in another cohort of 64 PICU patients with candidemia cases (70% of which were caused by non-*albicans* species) was 28%.[35]

Clinical Manifestations

Superficial and Mucosal Infections

Oropharyngeal Candidiasis (Thrush).

Thrush, commonly found in infants and immunocompromised children, is characterized by pearly, white, curd-like, material visible on the buccal and gingival mucosa.[36] The underlying mucosa can appear erythematous or normal in color. Often painful, thrush can lead to inadequate nutritional intake and subsequent dehydration. Thrush occasionally progresses to esophagitis, laryngitis (Fig. 243.1), or invasive disease in severely immunocompromised patients. Newborn infants often are colonized from the mother's genital tract. In hospitalized neonates, the median age of onset is 9 to 10 days. Consistently, *C. albicans* is the species most commonly isolated.[37]

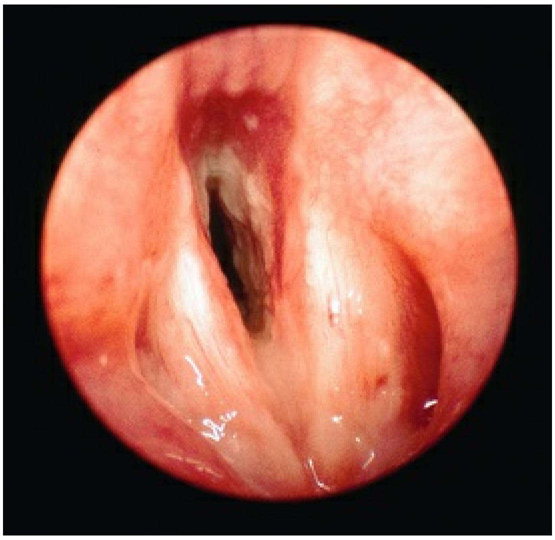

FIGURE 243.1 Endoscopic view of *Candida albicans* laryngitis in a 12-year-old girl with systemic lupus erythematous who was receiving high-dose glucocorticoid therapy and antibiotics. She did not have oral candidiasis. (Courtesy of S. S. Long.)

Diaper Dermatitis.

Candida diaper dermatitis is characterized by a confluent erythematous rash with satellite pustules.[38] Among term infants, diaper dermatitis is most common from 7 to 9 months of age, but it manifests earlier in premature infants. Diaper dermatitis in term infants is rarely associated with systemic disease. However, in a prospective study of VLBW infants, 32% of infants with mucocutaneous involvement (largely diaper dermatitis) developed invasive candidiasis.[39]

Esophagitis.

Candida esophagitis occurs most often in severely immunocompromised people such as HIV-infected patients. Esophagitis can occur in the absence of thrush.[40] Patients commonly present with dysphagia or odynophagia. Definitive diagnosis requires endoscopy for biopsy, but often the diagnosis can be made by clinical presentation or observation of mucosal irregularities on barium esophagram. In immunocompromised patients, including people with acquired immunodeficiency syndrome (AIDS), *Candida* esophagitis can occur simultaneously with cytomegalovirus and herpes simplex infection or reactivation.

Chronic Mucocutaneous Candidiasis.

Persistent or recurrent *Candida* infections of the skin, mucous membranes, and nails is termed *chronic mucocutaneous candidiasis*.[41] Affected patients have heterogeneous defects in T-lymphocyte–mediated immunity and poor proliferative responses specifically to *Candida* species. Although often phenotypically similar, the diverse group of underlying disorders and conditions predisposing patients to chronic mucocutaneous candidiasis includes HIV, inhaled corticosteroid use, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, and Job syndrome.[42,43]

Vulvovaginitis.

Although vulvovaginitis occurs in 75% of healthy women over the course of their lifetimes, certain conditions are associated with increased risk, including HIV infection, pregnancy, diabetes mellitus, and exposure to broad-spectrum antibiotic agents.[44] More than 80% of cases of vulvovaginitis are caused by *C. albicans*.[45] Symptoms of infection are nonspecific but include pruritus, vaginal discharge, and dysuria.

Unique Neonatal Manifestations.

Congenital cutaneous candidiasis is an uncommon clinical condition caused by an ascending infection into the uterus before birth. The infant at birth has a diffusely erythematous papular rash (Fig. 243.2).[46] The papular rash becomes pustular, followed by the development of vesicles and bullae. The rash also can manifest as bright red, "burn-like" dermatitis, and usually it is associated with positive cerebrospinal fluid (CSF), blood, and urine cultures. Infants weighing >1500 g most often have a benign clinical course. Systemic involvement is more likely in premature infants and frequently is associated with markedly elevated white blood cell counts (>100,000/mm^3). Risk factors for congenital cutaneous candidiasis include the presence of a maternal intrauterine device or cerclage placement.[47]

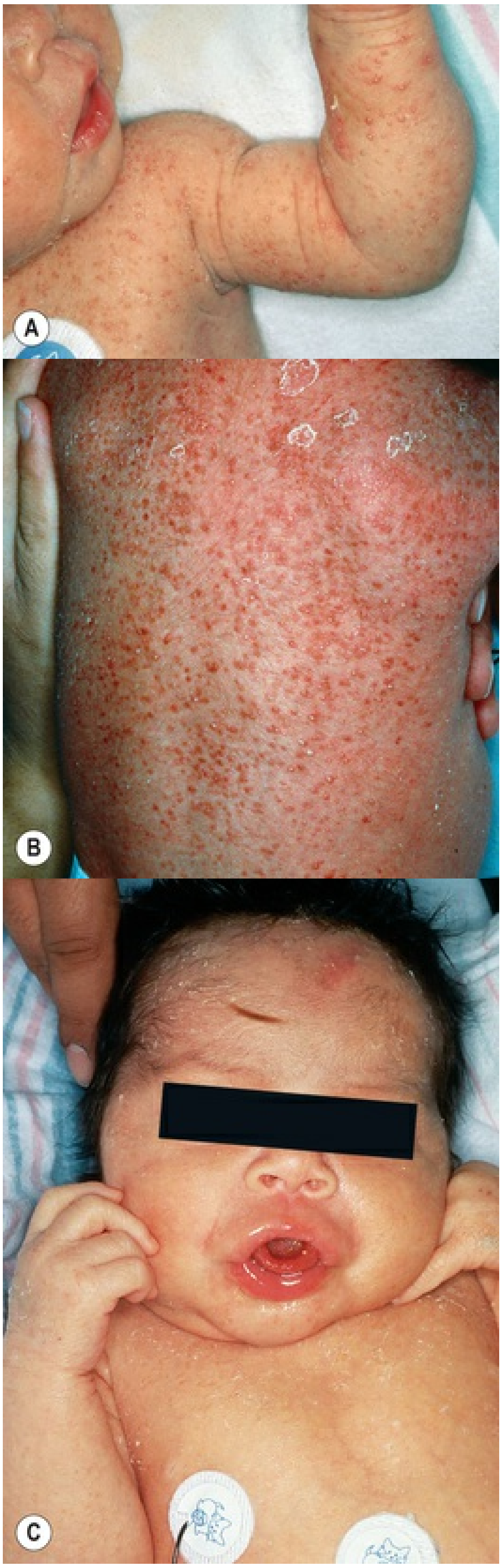

FIGURE 243.2 (A) and (B) Term neonate with the typical exanthem of congenital cutaneous candidiasis on the first day of life.. Note superficial papulopustules with erythema. (C) Clearing within a few days is expected. This infant was treated with amphotericin B.

(Copyright by J. H. Brien.)

A second dermatologic manifestation in infants is invasive fungal dermatitis. Unlike congenital cutaneous candidiasis, lesions develop after birth but within the first 2 weeks of life (Fig. 243.3).[47] The skin is the point of entry for the organism, and risk factors for development include extreme prematurity, vaginal birth, hyperglycemia, and postnatal corticosteroid administration. The rash of invasive fungal dermatitis is erosive and crusting and is associated with a high incidence of positive blood cultures. Definitive diagnosis is made by biopsy.

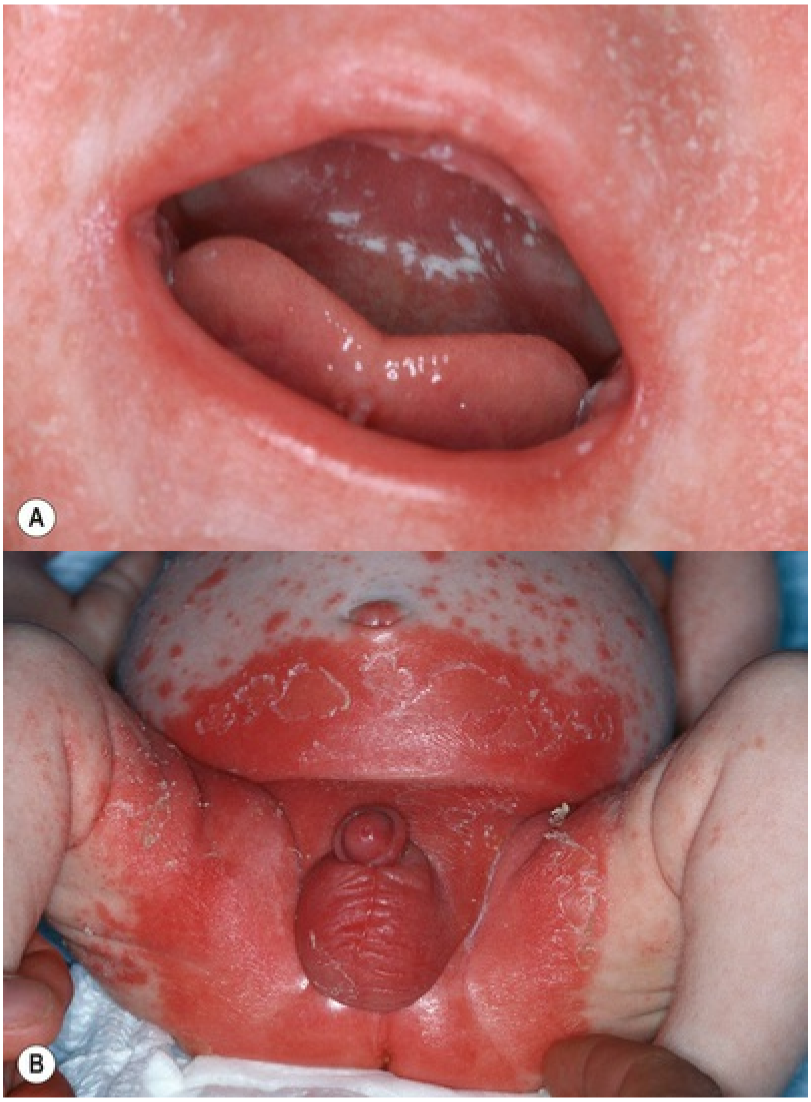

FIGURE 243.3 One-week-old infant with cutaneous dissemination of *Candida albicans* infection associated with (A) oral thrush and (B) extensive diaper dermatitis.

(Copyright by J. H. Brien)

Invasive *Candida* Infections

Candidemia or *Candida* BSI is defined as isolation of *Candida* from blood culture. Candidiasis describes all deep-seated *Candida* infections, including candidemia, as well as infections of single organs (e.g., liver, spleen, bone, brain). Candidiasis is rare in immunocompetent children. Infants with candidiasis typically are extremely premature, and children with candidiasis often are immunocompromised as a result of hematologic malignant disease, transplantation, or other primary or secondary immunodeficiency conditions. In addition to poor immunologic status, these patients commonly have multiple risk factors.

Signs and symptoms of *Candida* BSI often are nonspecific and subtle, especially in infants, and can include temperature instability, lethargy, apnea, hypotension, respiratory distress, abdominal distention, hyperglycemia, and feeding intolerance.[11,48] The presentation of candidemia cannot be readily distinguished from bacterial BSI. In immunocompromised children, *Candida* BSI often manifests as persistent fever despite antibiotic therapy. Presenting signs and symptoms can result from end-organ (central nervous system [CNS], renal, hepatic) dissemination following periods of BSI. Although prolonged candidemia is associated with increased risk of dissemination, dissemination can occur in the setting of only a single positive blood culture result.[11,49]

Meningoencephalitis.

Meningitis occurs in approximately 15% of infants with candidemia; this percentage represents a decrease since the 1980s, but it still is an excessive rate compared with adults with candidemia.[9] The decreased rate may reflect more aggressive use of empiric antifungal therapy. The incidence of meningitis in pediatric patients with cancer and candidemia also is higher than in their adult counterparts (11% vs. 1%).[50] This finding has important implications for diagnostic evaluation and therapeutic approaches because clinicians cannot assume a lack of CNS involvement in patients with seemingly simple candidemia.

Candidiasis of the CNS is more accurately described as meningoencephalitis because infection often results in granulomas, parenchymal abscesses, and vasculitis (Fig. 243.4). As a result, unremarkable CSF examination in the presence of CNS infection is common.[6,31] In 1 study, only 25% of infants with *Candida* meningitis had abnormal CSF.[28] Complications of CNS infections include obstructive hydrocephalus, calcifications, and thrombosis.[51] If CNS involvement is suspected or confirmed, imaging (ultrasonography, computed tomography, or magnetic resonance imaging) should be considered.

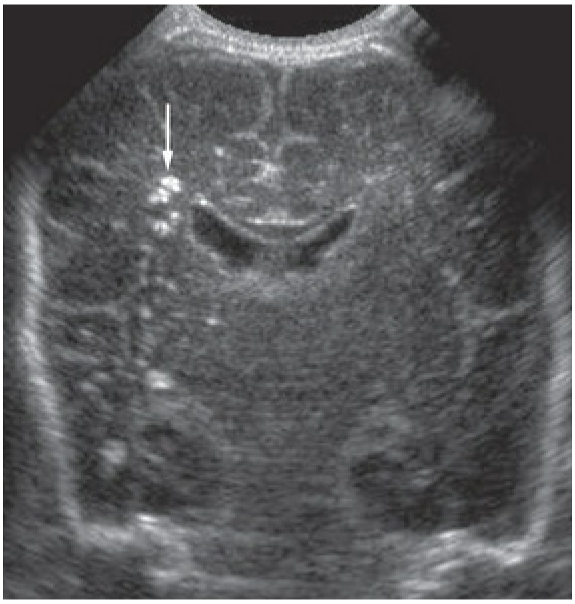

FIGURE 243.4 Cranial ultrasound scan showing fungal abscesses (*arrow*) seen as hyperechoic regions in a 22-day-old ex–25-week neonate with *Candida albicans* candidemia.

Renal and Urinary Tract Infections.

Renal *Candida* infections include candiduria, fungal debris within the renal collecting system, and renal parenchymal involvement (Fig. 243.5).[52] Renal disease can manifest as pyelonephritis, rising creatinine concentrations, hypertension, a flank mass, or acute urinary obstruction from fungal mycetoma.[53,54] In addition to severely immunocompromised patients, children with anatomic obstructions, congenital malformations of the urinary tract, or neurogenic bladder causing urinary stasis are at increased risk for *Candida* urinary tract infection.[52]

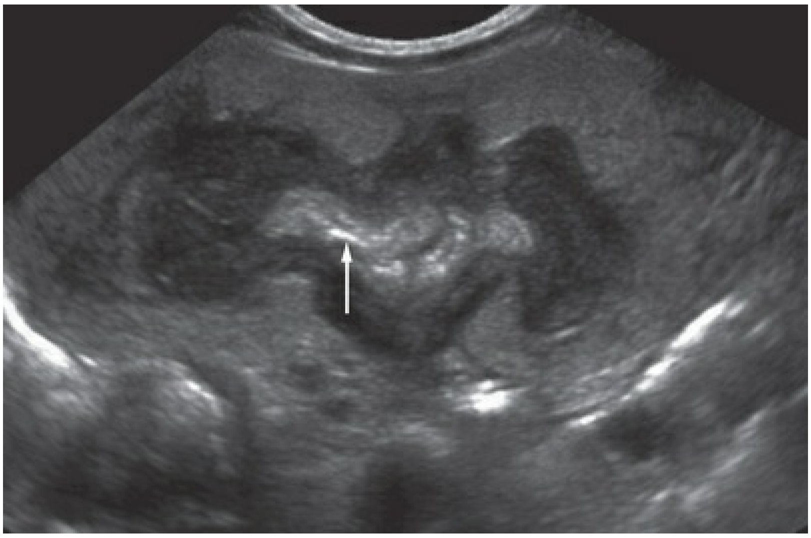

FIGURE 243.5 Renal ultrasound scan showing fungal abscess (*arrow*) seen as echogenic material within the renal collecting system of a 7-year-old child with acute myelogenous leukemia who was undergoing induction chemotherapy.

Patients with candiduria should have a renal ultrasound scan performed to evaluate for the 2 types of renal involvement: nonshadowing echogenic foci and parenchymal infiltration.[53] Findings can persist despite proper therapy, negative culture results, and clinical recovery.[55] However, caution must be used in interpreting ultrasound examination results because blood clots and renal stones also can resemble collections of infected material.[52,53] Fortunately, systemic antifungal therapy usually is sufficient treatment for renal involvement. Surgical intervention is indicated in patients with complete urinary obstruction.[53] Nonneutropenic patients with uncomplicated candiduria who have a Foley catheter in place should have the catheter removed or replaced and do not need systemic antifungal therapy.[56]

Optic Complications.

Optic infections can result in chorioretinal infections or, more rarely, lens abscesses.[57,58] The incidence of chorioretinal lesions complicating candidemia is decreasing.[59,60] Although chorioretinal lesions were found in 28% of adults with candidemia in 1 series,[61] only 1 patient with optic involvement was found among 123 VLBW infants with candidemia who were similarly studied.[59] In another study, no ocular findings were discovered in 30 children with candidemia.[62]

Infants with candidemia without direct optic infection are at increased risk for the development of severe retinopathy of prematurity.[29–31,57,63] Although the reason for this association is unclear, cytokines produced in reaction to the infection may play a role.[57] Because of the risk of endophthalmitis and the increased risk of severe retinopathy of prematurity, ophthalmologic examination should be considered in all infants with candidemia. Ophthalmologic examination for term and near-term infants with candidemia is especially important because they are not followed routinely for retinopathy of prematurity. Systemic antifungal therapy usually is sufficient for chorioretinal infections, but infections of the lens, an avascular structure, can require surgical treatment.[57,64]

Hepatosplenic Candidiasis.

Hepatosplenic candidiasis (also known as chronic disseminated candidiasis) (Figs. 243.6 and 243.7) occurs predominantly in patients with leukemia but can occur in any patient with candidemia. Children can come to medical attention with nausea and vomiting, right upper quadrant pain, hepatomegaly, or splenomegaly, often after recovery of immune function.[65] Blood culture results are positive in as few as 20% of patients with chronic disseminated candidiasis, and biopsy is considered the gold standard for diagnosis.[66] Treatment often lasts for months.

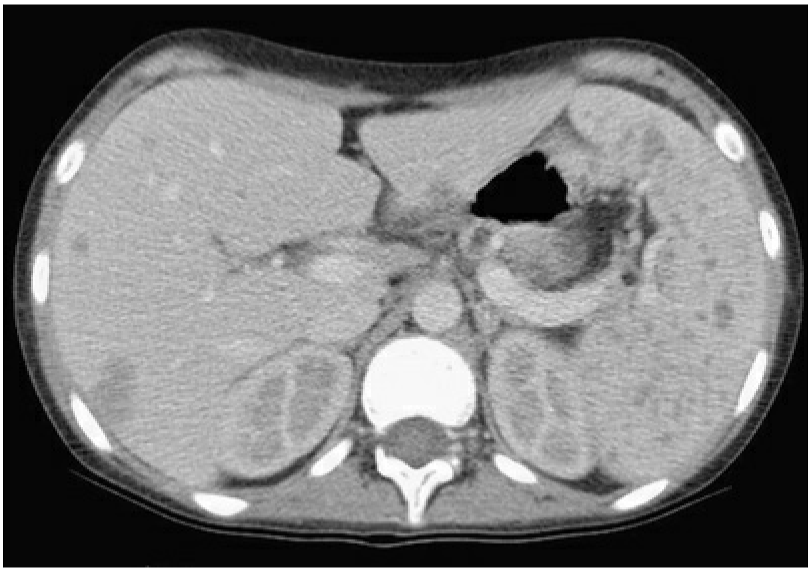

FIGURE 243.6 Abdominal computed tomography without contrast showing multiple hypodense areas in the spleen and liver caused by a disseminated *Candida albicans* infection in a 12-year-old child who underwent an unrelated cord blood transplant for acute lymphoblastic leukemia.

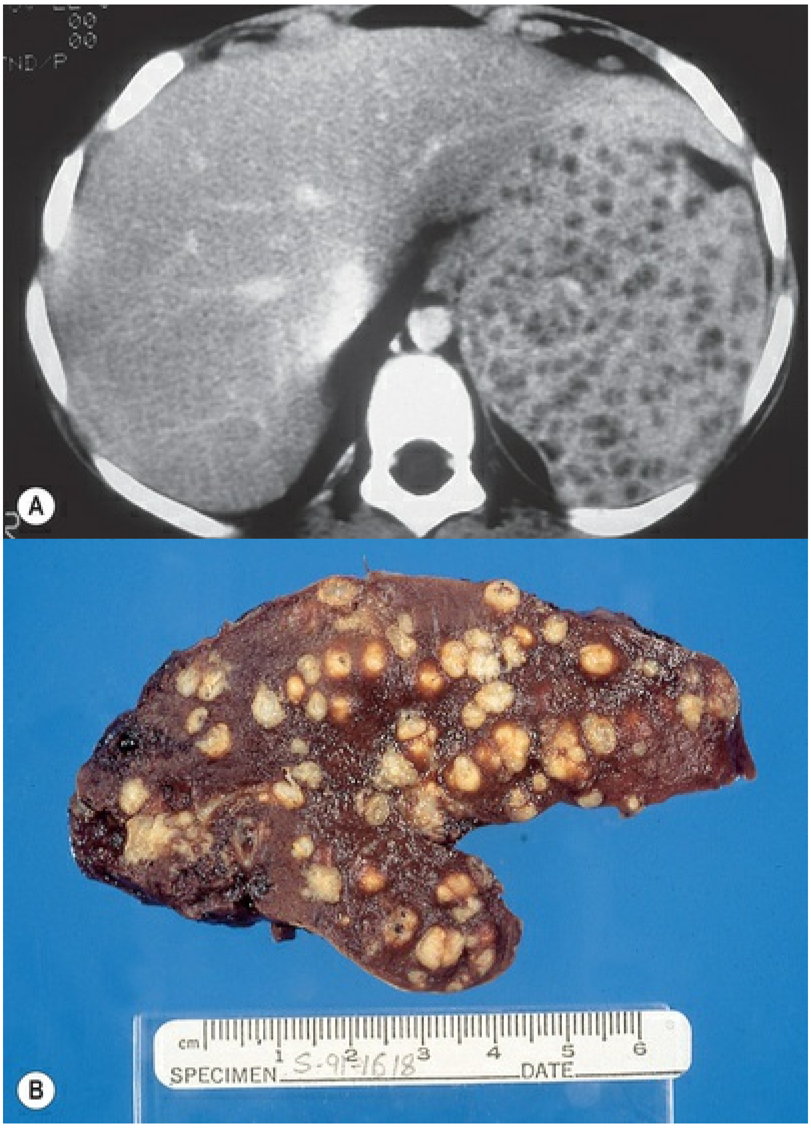

FIGURE 243.7 (A) Computed tomography and (B) gross specimen showing multiple granulomatous lesions of *Candida albicans* in the liver and spleen in a 5-year-old boy with acute lymphoblastic leukemia, prolonged granulocytopenia, and fever despite amphotericin B therapy. (Courtesy of S. S. Long.)

Other Affected Organs.

Endocarditis is documented in ≤5% patients with candidemia. Central vascular catheters can cause localized damage to the endocardium and increase the risk for endocarditis, especially in infants.[67,68] Other risk factors for *Candida* endocarditis in children include immunosuppression, congenital heart disease, and corrective surgical procedures for congenital heart disease.[68]

Candidemia also can result in infections of bones and joints, which can become evident days to weeks after control of BSI. Assessment of end-organ damage in the presence of neonatal candidemia should include an ultrasonogram of the head and abdomen, lumbar puncture, ophthalmologic examination, and an echocardiogram. Candidemia in a child should prompt a careful CNS examination, echocardiogram, and ophthalmologic examination.

Laboratory Findings and Diagnosis

Routine Tests.

Although white blood cell counts often are used as markers for systemic infections, only 60% of infants with candidiasis have abnormal counts.[5] Thrombocytopenia is a more sensitive marker, found in 84% of VLBW infants with candidemia.[69] However, the specificity of thrombocytopenia is low because other infections often cause thrombocytopenia.[69] Unexpected hyperglycemia can be associated with candidemia in neonates receiving parenteral alimentation.

Blood Culture.

The sensitivity of a standard bacterial culture typically is equivalent to that of a fungal culture. However, the sensitivity of either type of culture is lower for fungal compared with bacterial pathogens.[70–72] *Candida* species exhibit tissue tropism that often leads to deep organ involvement in the absence of prolonged candidemia. Blood culture sensitivity increases with increasing numbers of infected deep organs. In an adult autopsy study, sensitivity of blood culture was <30% with a single infected site but increased to 80% when 4 or more organs were involved.[71] Sensitivity of blood culture in pediatric patients is further compromised by the small amount of blood collected (as little as 0.5 mL in preterm infants vs. >10 mL in adult patients). Although sensitivity is poor, blood culture specificity approaches 100%. Isolation of *Candida* from a blood culture should not be considered a contaminant.

Polymerase chain reaction (PCR) allows for earlier identification of *Candida* species from positive blood cultures. Available PCR-based assays can identify certain yeast species from positive blood cultures with sensitivity and specificity >98%.[73–75]

Serologic Testing.

Serologic testing is seldom used for diagnosis of *Candida* infections.[76] Sensitivity is compromised in profoundly immunocompromised children with limited antibody production. Specificity also is low because colonized patients often produce antibodies.

Antigen Detection.

Limitations to antigen assays include rapid antigen removal by the immune system, use of polyclonal antibodies causing variability in results among assays, and poor assay sensitivity.[76] Moreover, several assays require the antigen to undergo processing by the immune system, and this processing may not occur reliably in immunocompromised patients. The 2 antigens used to detect *Candida* are (1,3)-β-D-glucan and mannan.

(1,3)-β-D-glucan is a cell wall component found in most species of *Candida* and can be detected in elevated amounts in serum of patients with invasive disease. When investigators used a cutoff value of 60 pg/mL, the assay demonstrated a sensitivity and specificity of 70% and 87%, respectively, in a series of 333 adult patients.[77] A meta-analysis including 19 studies found that (1-3)-β-D-glucan assays had a sensitivity of 81% and a specificity of 81% for diagnosis of invasive candidiasis, although most of the data were obtained from adults.[78] A retrospective examination of (1-3)-β-D-glucan levels in 61 infants with clinically suspected fungal infection found that the mean 1-3-β-D-glucan level was 364 pg/mL (range, 131–976 pg/mL) compared with 89 pg/mL (range, 30–127 pg/mL) among uninfected control infants.[79] However, the assay can produce many false-positive results.[80] False-positive test results can occur in patients receiving hemodialysis with a cellulose membrane and in samples exposed to gauze.[81,82]

Increasing numbers of patients are being evaluated with these newer molecular diagnostic tools, but to date no large pediatric or neonatal series have been conducted.[76,83] A second fungal antigen, mannan, has been found to correlate with invasive disease, but assays have limitations of low sensitivity and specificity. Assay sensitivity can be improved by testing at multiple time points. No pediatric studies have been conducted using *Candida* mannan antigen or antimannan antibody assays.

Fungal Metabolites.

D-Arabinitol, a sugar alcohol, is produced by *C. albicans, C. parapsilosis*, and *C. tropicalis*. D- and L-arabinitol are present in normal human urine and serum.[84] Ratios of serum D-arabinitol to creatinine were shown to correlate with antifungal treatment response in 10 of 10 adults with cancer.[85] In children with confirmed invasive candidiasis, the ratio of urinary D-arabinitol to L-arabinitol (DA/LA ratio) was elevated.[86] In a separate study, the urine DA/LA ratio was elevated in 6 infants infected with *C. albicans* compared with that of 40 healthy control infants.[84] Limitations of D-arabinitol as a diagnostic test include low specificity because colonized patients are known to have elevated D-arabinitol and creatinine levels, the need for gas chromatography mass spectrophotometry, and little or no D-arabinitol production by several pathogenic species of *Candida*.[87] At present, this test is not commercially available.

DNA Polymerase Chain Reaction.

PCR was both sensitive and specific for *Candida* in clinical specimens of adults as a qualitative diagnostic test in preliminary studies,[88] in which detected 1 colony-forming unit per milliliter of specimen.[89,90] Sensitivity of PCR as a diagnostic test is optimized by targeting ribosomal DNA genes, which contain highly conserved areas (18s, 5.8s, and 28s) separated by internal transcribed sequences (ITS1 and ITS2) containing variable, species-specific regions. These genes are present in multiple copies within the *Candida* genome and are an attractive target for amplification because the number of copies improves PCR assay sensitivity.[90]

Real-time PCR offers several advantages over conventional PCR techniques, including faster detection of amplicon as detection occurs during cycling and minimization of contamination because reaction vials do not have to be opened. Additionally, real-time PCR allows for the quantitation of the amount of starting DNA in the clinical sample, a feature that could aid assessment of response to antifungal therapy.[91]

Treatment

Thrush typically is treated with oral nystatin suspension. Azole antifungal agents (fluconazole, voriconazole) are alternatives. *Candida* dermatitis is treated with topical nystatin or miconazole. Candida vulvovaginitis is treated with topical antifungal formulations or oral azoles.

If a diagnosis of *Candida* BSI is confirmed in a patient with a central venous catheter (CVC) (tunneled, nontunneled, subcutaneously implanted, or peripherally inserted), the catheter should be removed as soon as possible and within 24 hours.[92] Delayed removal of CVCs consistently has been associated with increased mortality rates as well as morbidities, including poor neurodevelopmental outcome in infants.[10] Timely CVC removal is a critical tenet of management. Because of the extremely rapid development of *Candida* biofilms on catheters, a strategy to treat invasive candidiasis with a colonized catheter still in place is incorrect.

Few well-powered, randomized controlled trials have been conducted to establish treatment of candidiasis in children. A comparison of micafungin (2 mg/kg/day) with liposomal amphotericin B (3 mg/kg/day) found no difference in treatment success (i.e., 73% [35 of 48] for micafungin and 76% [38 of 50] for liposomal amphotericin B groups).[93] The incidence of adverse events was lower in the micafungin group (4%) compared with the liposomal amphotericin B group (17%). Length of therapy generally should be at least 3 weeks for infants because CNS involvement should be assumed. In older children, therapy should last at least 2 weeks following documented sterilization of the bloodstream.

Most clinically important species of *Candida* are susceptible to amphotericin B deoxycholate, with the exception of *C. lusitaniae* and occasionally *C. glabrata* and *C. krusei*.[94] Amphotericin B deoxycholate generally is better tolerated in infants compared with older children and adults.[95] Because immediate hypersensitivity reactions are less common in infants, test doses of the drug are not indicated in this population.[96] Lipid preparations of amphotericin B often are used because of renal insufficiency or in patients unable to tolerate amphotericin B deoxycholate; relatively increased doses of the parent drug can be administered with less associated toxicity. In the 1 randomized controlled trial of amphotericin B products in infants for the treatment of candidemia, 56 infants (including 36 ELBW infants) were given amphotericin B deoxycholate if their serum creatinine concentration was <1.2 mg/dL (n = 34) or either of 2 liposomal formulations (n = 22).[97] No statistically significant difference in mortality rates was noted among the 3 cohorts.

Flucytosine ([5-FC] Ancobon) is not an option as monotherapy for candidiasis because resistance develops rapidly. Use of 5-FC for candidiasis is further limited by adverse gut and bone marrow effects and by the lack of a parenteral formulation in the United States. The use of 5-FC in preterm infants is not recommended because of the immaturity of the preterm infant's kidney function and the need to monitor serum levels.[98] However, 5-FC occasionally is administered in combination with other agents for *Candida* meningoencephalitis because of its excellent CSF penetration and fungicidal activity.[99] In a cohort of 17 cases of *Candida* meningitis (including 11 infants), improvement was noted in 15 patients receiving combination therapy with amphotericin B deoxycholate and 5-FC.[100]

Fluconazole is commonly used to treat candidiasis in infants and pediatric patients.[101] The 2 most common species of *Candida* found in infants and pediatric patients, *C. albicans* and *C. parapsilosis*, are almost always susceptible to fluconazole. However, 50% of *C. glabrata* and 100% of *C. krusei* isolates are resistant to fluconazole.[102] Children >3 months of age require 12 mg/kg/day to achieve comparable adult treatment dose exposures, and they should likely receive a 25 mg/kg loading dose on the first day. In premature infants, a regimen of 12 mg/kg/day is necessary to achieve exposures similar to those in older children and adults,[103] and a loading dose of 25 mg/kg has been shown to achieve steady-state concentrations sooner than the traditional dosing scheme.[104,105]

Voriconazole has a wider spectrum of activity against *Candida* species than fluconazole and is active in vitro against some isolates of *C. glabrata* and *C. krusei* that are resistant to fluconazole. The pharmacokinetics of voriconazole has been described in children as young as 2 years of age (Table 243.1).[106–108]

TABLE 243.1

Dosing of Pediatric Antifungal Agents for Candidiasis

Drug	Formulation	Pediatric Dose	Infant Dose
POLYENES			
Amphotericin B deoxycholate	IV	0.5–1 mg/kg/day	1 mg/kg/day
TRIAZOLES			
Fluconazole	IV, PO	6–12 mg/kg/day	12 mg/kg/day (loading dose of 25 mg/kg)
Voriconazole	IV, PO	16 mg/kg/day divided q12h (9 mg/kg loading dose)	NA
ECHINOCANDINS			
Caspofungin	IV	50 mg/m^2/day (70 mg/m^2/day loading dose)	25 mg/m^2/day
Micafungin	IV	2–4 mg/kg/day	10 mg/kg/day
Anidulafungin	IV	1.5 mg/kg/day (3 mg/kg loading dose)	1.5 mg/kg/day (loading dose 3 mg/kg)

IV: intravenous; NA: not available; PO: oral.

Echinocandins (micafungin, anidulafungin, and caspofungin) are fungicidal for all clinically significant *Candida* species. Side effects are minimal in older patients, and the tolerability to this drug is superior to that of amphotericin B deoxycholate.[109] Studies have examined the pharmacokinetics of the echinocandins in children (see Table 243.1).[110–115] Although micafungin levels are undetectable in CSF,[116] the drug penetrates and cures invasive fungal infections in CNS tissue in animal models.[109] Higher systemic exposures in premature infants are thought to be important to drive the antifungal agent into the CNS.[117]

Special Considerations

Development of invasive candidiasis is the result of interactions among virulence factors of the *Candida* species, colonization burden, and host immunologic function. Specific risk factors for invasive disease tend to fall into 1 of 2 categories: those that increase colonization of mucosal surfaces or those that disrupt or impair immune function.[118]

Risk Factors Increasing Colonization

Infants initially are colonized by vertical transmission during birth or horizontally by parents or caregivers.[119,120] On admission to the NICU, 5% to 10% of all infants in 1 report were found to be colonized with *Candida* when cultures were taken from the oropharyx, skin, endotracheal tube aspirate, and rectum.[121] VLBW infants were found to be colonized at slightly higher rates. By 7 days of life, colonization rates increased to 50%, and they later rose to 64% by 1 month of age.[120,122,123]

After *Candida* colonization of the gastrointestinal tract and skin, any penetration of the mucosa, epithelial barrier through immature neonatal skin, or a device allows for hematogenous dissemination.[120,123,124] In a study of VLBW infants, invasive disease developed in 8% (3 of 39) with *Candida* colonization and in none of the noncolonized infants.[121] Endotracheal colonization has been associated with a sixfold increased risk of candidiasis.[122] In another neonatal study, a threefold increased risk of invasive disease was observed with each additional skin site of *Candida* colonization.[125] A study of pediatric liver transplant recipients also identified colonization as a risk factor for candidiasis.[126]

The use of broad-spectrum antibiotics enhances *Candida* colonization by eliminating competing bacterial flora.[6] In a cohort of more than 6000 infants, expanded-spectrum cephalosporin or carbapenem use in the previous 7 days was associated with candidiasis.[127]

High serum glucose levels provide substrate for fungal growth and are a reported risk factor for candidiasis in infants.[128] Hyperglycemia also can lead to upregulation of genes for adhesion proteins and proteins, thereby impairing the ability of complement to opsonize fungi.[129] Gastric acidity is considered protective against candidiasis by suppressing growth of *Candida* in the upper gastrointestinal tract. Acid-reducing drugs such as histamine-2 (H_2)–blocking and proton pump–inhibiting agents increase overgrowth of *Candida* in the gastrointestinal tract.[130] The use of H_2-blocking agents is linked to a risk of candidemia in infants,[23] and it also can increase the risk of infection by inhibiting neutrophil function.[131]

Risk Factors That Disrupt or Impair Immune Function

In almost every instance, candidiasis affects patients whose immune function is compromised. Prematurity is the strongest risk factor for invasive disease in infants. The immune system of the preterm infant has defects in chemotaxis, cytokine and antibody production, and phagocytosis.[49,132] In addition, the need for invasive medical devices such as a CVC and endotracheal tube further compromise the underdeveloped layer of skin.

Defects in neutrophil function or number are important risk factors for candidiasis in older children.[133,134] These neutrophil defects can be the result of primary immune defects (chronic granulomatous disease) or secondary defects (cytotoxic chemotherapy). The role of neutrophils in controlling *Candida* infections includes phagocytosis of organisms, as well as the elaboration of cytokines that stimulate other components of the immune system.[135]

The presence of a CVC, commonly used in immunocompromised patients, facilitates formation of a thrombin sheath to which *Candida* can adhere and replicate and that protects the growing fungus from host immune defenses. The presence of a CVC is associated with *Candida* BSI in both infants and children.[5,136] In addition, some *Candida* organisms., especially non-*albicans* species such as *C. parapsilosis* and C. *tropicalis*, produce a biofilm that provides additional protection from immunologic attack and antifungal drug activity.[137] Persistence of candidemia can be related to biofilm development. In 1 study, 100% (22 of 22) of *C. parapsilosis* isolates from adults with multiple positive blood culture results produced biofilms, compared with 62% (8 of 13) of isolates from patients with only 1 positive culture result.[137]

The use of corticosteroids such as hydrocortisone and dexamethasone is associated with an increased risk of candidiasis in infants and children.[50,138–140] Corticosteroids, in addition to suppressing immune function, can upregulate *Candida* virulence genes,[141] and corticosteroid-induced hyperglycemia also can predispose patients to infection.[20]

Among adult ICU patients, patients in surgical ICUs are at the greatest risk of candidiasis.[142] Abdominal surgical procedures that compromise the intestinal mucosal barrier can allow translocation of *Candida* into the bloodstream.[23,48,143] Surgical patients also are at heightened risk because of exposure to broad-spectrum antibiotics and the use of CVCs.[143]

Prevention

Nonabsorbable Oral Agents.

The use of nonabsorbable oral agents for the prevention of neonatal *Candida* BSI is controversial. A randomized controlled trial of 65 infants who were given nystatin or placebo demonstrated a significant decrease in both colonization rates and invasive *Candida* infections (6% in the nystatin group vs. 32% in the placebo group).[144] However, no difference in mortality rates or duration of hospitalization was noted, and interpretation of findings is confounded by the extremely high rate of *Candida* infection in the control group.[10,13] No decrease in candidiasis was observed in a placebo-controlled trial of 600 infants of <1750 g birth weight who were given oral miconazole gel.[145] In an analysis of >1700 infants weighing <1500 g at birth, the incidence of candidiasis was decreased with use of nystatin or miconazole therapy compared with placebo (4% vs. 23%; 95% confidence interval, 0.14–0.27).[146]

Fluconazole.

The pharmacokinetics of fluconazole makes it an attractive drug for prophylaxis. Fluconazole has good enteral absorption, excellent CSF penetration, and a long half-life allowing for long dosing intervals.[104] The drug is metabolized by the kidney and is excreted 80% unchanged in the urine.[147]

Several placebo-controlled trials have evaluated fluconazole prophylaxis in preterm infants. The first study enrolled 103 VLBW infants and demonstrated decreased rates of colonization but no difference in invasive disease.[123] The second study of 100 ELBW infants found a significant decrease in the incidence of candidiasis.[125] The placebo arm of this study had one of the highest rates (26%) of invasive candidiasis reported in ELBW infants, thus making the results and generalizability difficult to interpret. Neither study demonstrated a statistically significant survival benefit. A randomized multicenter study of 322 VLBW infants showed significant reductions in invasive candidiasis in fluconazole versus placebo recipients but no difference in all-cause mortality.[148] Again, the rate of candidiasis (13%) in the control group was much higher than reported generally. In a more recent placebo-controlled trial of 361 infants of <750 g birth weight, fluconazole (6 mg/kg twice weekly) decreased the incidence of candidiasis 3% versus 9% (P = 0.02).[149] No difference was observed in death or neurodevelopmental outcome between the 2 groups.

Studies of benefit of fluconazole (for prophylaxis in older children) also have shown mixed results. In a randomized study in children comparing oral fluconazole with oral nystatin in 50 children undergoing cancer chemotherapy,[150] 1 patient in the fluconazole group developed *Candida* colitis, and 1 patient in the fluconazole group and 2 patients in the nystatin group required empiric antifungal therapy.[150] A second, nonrandomized study of fluconazole prophylaxis in afebrile neutropenic pediatric patients demonstrated 3 breakthrough fungal infections among the 24 treated patients,[151] including 2 infections with fluconazole-resistant *Candida* species and 1 *Aspergillus* infection.

Key Points

Diagnosis and Management of *Candida* Infection

Epidemiology

- *Candida albicans* is the most common infecting species.
- Non-*albicans Candida* species are increasing as infecting species.

Clinical Features

- Certain patient populations (surgical intensive care, neutropenia) are at highest risk of invasive candidiasis.
- *Candida* meningoencephalitis is underdiagnosed in the neonatal population.

- Known neonatal risk factors for invasive candidiasis include cephalosporin or carbapenem use.

Diagnosis

- Blood cultures are the standard for diagnosis, but they are insensitive, especially in neonates because of low volume of samples.

- Negative culture results do not rule out disease definitively.

- Polymerase chain reaction and other molecular tests are in development.

Treatment

- Antifungal resistance is increasing, especially in non-*albicans Candida* species.

- Optimizing dosing of antifungal agents for pediatric patients is crucial.

- *Candida*-contaminated central venous catheters should be removed as soon as possible; biofilm formation begins rapidly.

Duration of Therapy

- Treatment for candidemia is at least for 21 days after first negative culture result in neonates and 14 days in children.

- Evaluation for dissemination to focal sites is prudent (see text).

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Aspergillus Species

William J. Steinbach

Although yeasts such as *Candida* species are the most common causes of invasive fungal infections in children, *Aspergillus* infections are increasing and have a dismal mortality rate.[1–3] Invasive aspergillosis likely is gaining prominence because of more intensive chemotherapies for certain malignant diseases, immunosuppressive therapies for graft-versus-host disease (GvHD), increased use of mismatched or unrelated donor transplantations, newer preparative regimens to avoid graft rejection or disease relapse, and increases in early posttransplantation survival rates resulting from better control of bacterial and cytomegalovirus infections.[1,4]

Microbiology

The genus *Aspergillus* contains nearly 200 species, only approximately 2 dozen of which are known to cause human disease. Human disease is primarily caused by *A. fumigatus, A. flavus, A. niger, A. terreus*, and *A. nidulans*, with each species at times causing unique clinical infections. *A. fumigatus* is responsible for most cases of invasive and chronic aspergillosis,[5] specifically pulmonary, sinus, and central nervous system infection. Isolated sinus disease also can be caused by *A. niger* and *A. flavus*,[6] and ear disease in immunocompetent children often can result from infection with *A. niger*. A review of *Aspergillus* cultures found that amphotericin B–resistant *A. terreus* accounted for only 3% of cases of invasive aspergillosis, but it was found exclusively in cases of invasive disease and not in patients with colonization alone.[6]

The ecologic niche of *Aspergillus* species is the soil; the organisms especially thrive in compost, where they function as saprophytes growing on organic debris and recycling carbon and nitrogen throughout the environment.[7] Unlike the major pathogenic species *A. fumigatus*, *A. nidulans* is easily traceable genetically and often is studied as a laboratory model, yet translation of pathogenesis to *A. fumigatus* is unclear. Asexual reproduction in all *Aspergillus* species is abundant and is characterized by the production of green pigmented asexual conidia (spores). The conidia are produced in long chains radiating from phialides, and this reproductive structure is the derivation of the genus name *Aspergillus,* from the aspergillum used to spread holy water during the Roman Catholic Mass.

Aspergillus organisms aerosolize conidia, which immunocompetent people breathe harmlessly every day; it is estimated that most people inhale several hundred *A. fumigatus* conidia daily. Invasive infection in severely immunocompromised patients, or allergic or chronic infection in immunocompetent and less immunocompromised patients, usually is acquired through inhalation of airborne conidia. Two lines of host defense against *Aspergillus* exist, macrophages and neutrophils, and both are apparently required for resistance to invasive disease. The first defense is formed by alveolar macrophages; in vitro murine studies suggested that resident pulmonary macrophages are responsible for eliminating inhaled *Aspergillus* conidia from the lung.[8,9] If inhaled conidia escape, conidia germinate in the invasive *Aspergillus* hyphae and become susceptible to neutrophil release of toxic reactive oxygen species that are fungicidal.[10] The host can develop disease because of neutropenia, high challenge doses of conidia overcoming macrophages, or corticosteroid suppression of macrophage conidiacidal activity.[11]

A. fumigatus, in particular, is highly successful in colonization and invasion in immunocompromised patients. *A. fumigatus* has several characteristics that allow it to be a successful saprophyte and opportunistic pathogen. The ability to grow at 37°C is crucial for the development of human disease, and *A. fumigatus* is thermotolerant and thrives at human body temperature. Conidia are small (2.5–3 µm in diameter), thus permitting buoyancy in the air for prolonged periods and inhalation deep into the lung alveoli. When inhaled by an immunocompetent person, conidia rarely have deleterious effects because they are cleared by the phagocytic cells of the innate immune system. However, severe allergic disease can occur with repeated exposure to large doses of conidia.

Whole-genome sequencing of several *Aspergillus* species, coupled with newer proteomic techniques, has advanced understanding of pathogenesis. Various suspected putative *Aspergillus* virulence factors have been exhaustively reviewed,[12] and gene disruption studies have examined numerous varied gene products with little insight into true pathogenesis. Species of *Aspergillus* also are well known for their production of secondary metabolites, including the carcinogen aflatoxin produced by some strains of *A. flavus,* which plays an unclear role in human invasive fungal disease. The true virulence of *A. fumigatus* likely is multifactorial, and it likely also weighs heavily on the host's condition. Non-*fumigatus Aspergillus* species (e.g., *A. calidoustus, A. lentulus*, others) are increasing in incidence and carry worrisome antifungal resistance patterns.

Clinical Manifestations

Aspergillus produces a spectrum of disease, including allergic bronchopulmonary aspergillosis (ABPA), aspergilloma, chronic aspergillosis, and various forms of invasive aspergillosis.[12] The most common forms of invasive aspergillosis are acute pulmonary aspergillosis, acute invasive rhinosinusitis, cerebral aspergillosis, and disseminated disease. As with most invasive mold infections, the clinical signs and symptoms are nonspecific. Unfortunately, the most severely immunocompromised patients are those least likely to have symptoms, and in these patients diseases progresses most rapidly, whereas less severely immunocompromised patients (e.g., patients with diabetes mellitus or longterm corticosteroid use) usually have more indolent symptoms.[5]

Pulmonary Infection

Clinical manifestations in different patient populations have been reviewed,[5] but disease in most immunocompromised patients often is characterized by bilateral diffuse pulmonary infection (Fig. 244.1). The most common presentation is unremitting fever in a high-risk patient,[3] but high fever can be absent in patients receiving corticosteroid therapy.[13] Other early symptoms of pulmonary disease include a dry cough and possibly chest pain. Dyspnea is more common is patients with diffuse disease, and the presentation in some patients is similar to that of pulmonary embolism. Hemoptysis can occur and can be fatal as the first presenting episode,[14] whereas in neutropenic patients, pneumothorax also is an occasional presenting feature.[5]

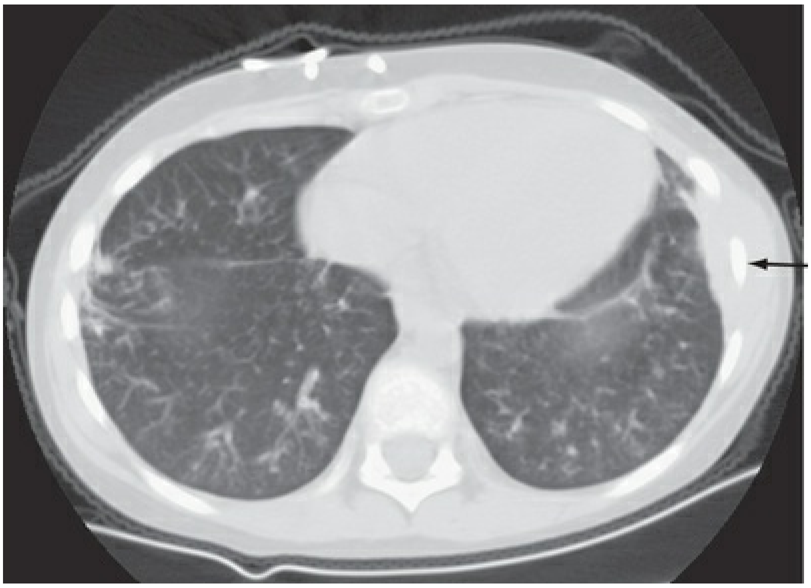

FIGURE 244.1 **Axial computed tomography of the chest (lung window) in a 12-year-old child with a history of acute myelobastic leukemia and cord blood transplantation. The scan shows diffuse interstitial disease, with pleural thickening and soft tissue involvement on the left (arrow). Bronchoalveolar lavage culture grew *Aspergillus terreus.***

Invasive pulmonary aspergillosis is the leading cause of death in patients with chronic granulomatous disease (CGD), and it can be the first manifestation of CGD. Invasive aspergillosis in patients with CGD usually manifests within the first 20 years of life. Invasive aspergillosis in a child or adult without a known predisposing risk factor should prompt an evaluation for CGD. Patients with CGD can lack typical clinical symptoms (including being completely asymptomatic), or they can be afebrile and have only an elevated erythrocyte sedimentation rate. In a review of clinical findings at diagnosis of invasive aspergillosis in 23 patients with CGD, only one third of these patients were symptomatic, only one fifth were febrile; one half had a white blood count <10,000 cells/mm^3, and almost one half had an erythrocyte sedimentation rate <40 mm/hr.[15]

In early disease in a patient with CGD an acute neutrophilic response occurs, and neutrophils surround hyphae. However, hyphae remain intact as a result of impaired neutrophil-mediated killing. In this setting, pulmonary aspergillosis is a chronic progressive infection that can spread locally to involve pleura, vertebrae, and the chest wall (Fig. 244.2). In contrast to patients with neutropenia, in patients with CGD hyphal angioinvasion is not a feature of disease. The halo sign (angioinvasion with surrounding tissue ischemia), cavitated lesions, and pulmonary infarcts seen in neutropenic patients are not seen typically in CGD. Areas of tissue destruction are secondary to a reactive acute and granulomatous inflammatory process rather than directly related to growth of the hyphae.[16] Infection with *A. nidulans* is more common in patients with CGD; pulmonary disease is more likely to involve adjacent bone, more likely to cause disseminated disease, generally refractory to intensive antifungal therapy, and more likely to require surgical intervention in patients with CGD than in patients who do not have CGD.[17]

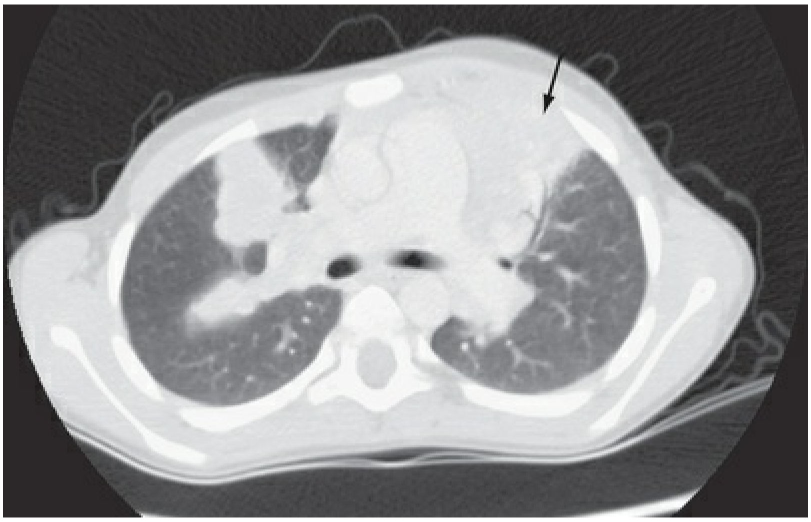

FIGURE 244.2 Axial computed tomography of the chest (lung window) after contrast in an 11-year-old child with chronic granulomatous disease and cord blood transplantation. The scan shows chest mass extending to soft tissues (arrow), bilateral consolidations, and lymphadenopathy. Chest mass biopsy culture grew *Aspergillus fumigatus.*

Invasive Sinusitis

Invasive *Aspergillus* sinusitis likely is underdiagnosed for lack of detailed examination, but patients can come to medical attention with ear pain or discharge, facial pain or swelling, localized pallor of the nasal septum or turbinate mucosa, epistaxis, orbital swelling, or headache.[5,13] The maxillary sinus is involved most commonly (Fig. 244.3), followed by the ethmoid, sphenoid, and frontal sinuses.[18] A careful rhinoscopic examination is needed to look for insensitive areas with decreased blood flow, frank crusting or ulceration, or blackened, necrotic foci. One study reviewed 11 patients with invasive fungal sinusitis after bone marrow transplantation, including 8 patients with *Aspergillus* infection. The mean interval from bone marrow transplantation to the diagnosis of fungal sinusitis was 22 days, and all patients had maxillary sinus involvement, one half also had ethmoid sinusitis involvement, and most patients had extension of the infection into the orbits, bone, or brain.[18] One major difficulty is the critically important diagnostic distinction between mucormycosis and aspergillosis, given the divergent therapeutic approaches. In a study evaluating pulmonary aspergillosis and pulmonary mucormycosis, concomitant sinusitis was significantly associated with mucormycosis and not aspergillosis in patients with radiographic evidence of pulmonary disease.[19]

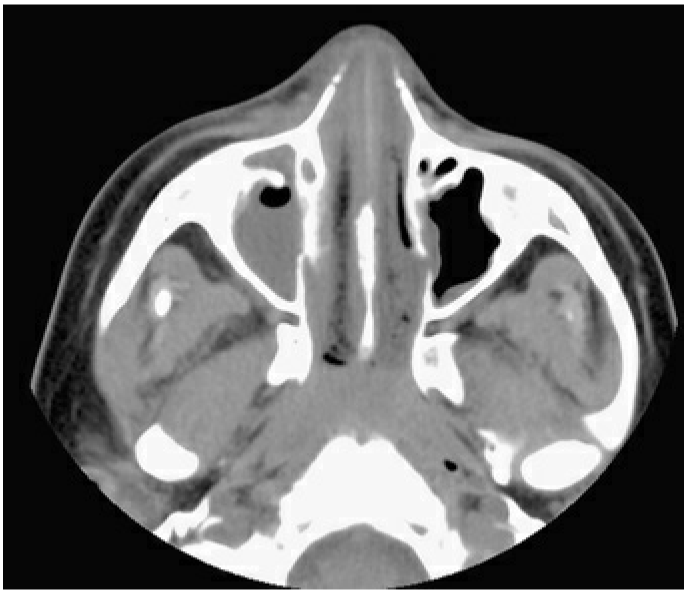

FIGURE 244.3 Axial computed tomography of the sinuses in a 17-year-old patient with combined variable immunodeficiency. The scan shows opacification of the right maxillary sinus and minor thickening of the left maxillary sinus. Sinus aspirate culture grew *Aspergillus fumigatus.*

Cerebral Infection

Cerebral involvement occurs in up to 40% of patients with invasive aspergillosis.[3,20] The pathogenesis is thought to involve hematogenous dissemination from an extracranial focus, most commonly the lung, or direct extension through the sinuses. *Aspergillus* hyphae are angioinvasive and thrombose arteries to create hemorrhagic infarcts, which then become abscesses (Fig. 244.4). Cerebral aspergillosis is the most common brain abscess type in hematopoietic stem cell transplant (HSCT) recipients; in 1 study 58% of brain abscesses were caused by *Aspergillus*, and 87% of these patients had concomitant pulmonary infection.[21] In another report of 18 patients with invasive aspergillosis, 10 patients had cerebral involvement, including 3 patients who presented with neurologic signs and no pulmonary symptoms.[22] The classic features of abscesses such as headache, nausea, and vomiting can be present in <10% of cases, with more prevalent features including altered mental status, confusion, hemiparesis, and cranial nerve palsies. Multiple lesions in the corticomedullary junction are consistent with infarct secondary to *Aspergillus* vasculopathy; dilated cortical vessels located in the central portion of the lesions in the corticomedullary junction are often distinctive signs of cerebral aspergillosis.[23] Definitive diagnosis requires a brain biopsy, but these patients often are too coagulopathic for the diagnostic operation.

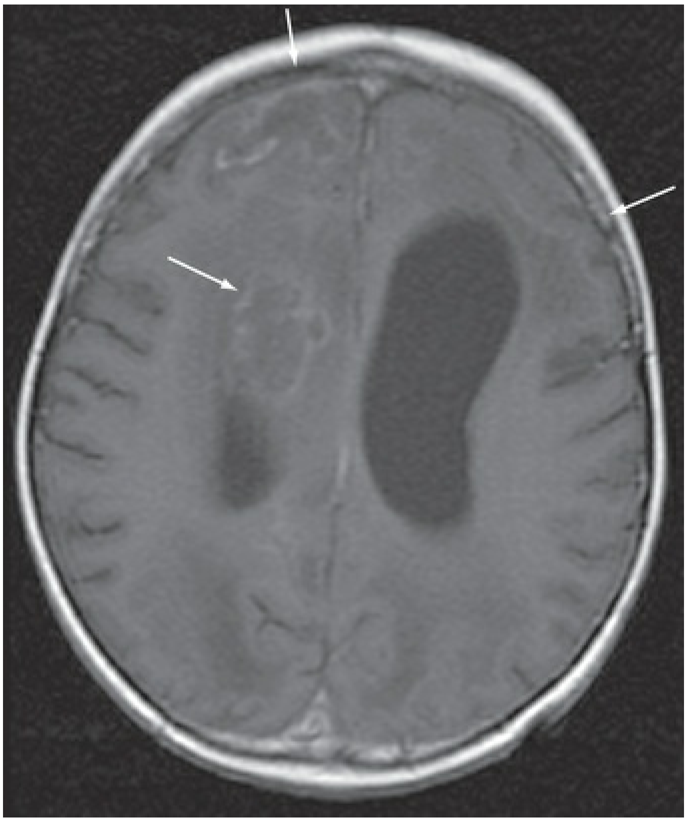

FIGURE 244.4 Axial contrast-enhanced magnetic resonance imaging in a 3-year-old child with a history of medulloblastoma. The scan shows ventricular dilatation and multifocal abscesses (arrows). Brain biopsy culture grew *Aspergillus fumigatus.*

Cutaneous Infection

Cutaneous aspergillosis can be either primary, usually from skin injury or traumatic inoculation, or secondary, from contiguous extension of hematogenous dissemination. In general, burn victims, neonates, and solid-organ transplant recipients develop cutaneous inoculation after prolonged local skin injury. HSCT recipients often develop secondary disease from contiguous extension of infected structures under the skin or from hematogenously disseminated embolic lesions.[24] In a review of >4000 patients with malignant disease, 15 had documented *Aspergillus* cutaneous infection,[25] whereas in another review, embolic skin lesions were present in approximately 11% of patients with disseminated aspergillosis.[26]

Cutaneous aspergillosis often begins as an area of raised erythema that progresses to include pain; skin involvement can be the first presenting sign of invasive infection.[27] The center of the lesion changes from red to purple, and then to black, and it can ulcerate.[5] Infections arising at the site of an intravenous catheter puncture typically begin with erythema and induration and progress to necrosis that extends radially.[28] Compared with wound mucormycosis, patients with primary cutaneous aspergillosis appear to present with significantly less local necrosis and systemic toxicity.[24]

Chronic Pulmonary Aspergillosis

Acute invasive aspergillosis occurs almost exclusively in patients with profound immunosuppression and displays rapid progression with poor outcome. However, some patients clearly have a more chronic *Aspergillus* infection. Chronic aspergillosis previously was known by several different terms, most notably *semi-invasive aspergillosis, chronic invasive pulmonary aspergillosis,* and *symptomatic pulmonary aspergilloma.* The blurred entity of chronic aspergillosis has been reclassified to include the following[29]: chronic cavitary pulmonary aspergillosis, in which imaging findings consist of the formation and expansion of multiple cavities, with some containing fungus balls; chronic fibrosing pulmonary aspergillosis, which denotes progress to marked and extensive pulmonary fibrosis; and chronic necrotizing pulmonary aspergillosis, or subacute invasive pulmonary aspergillosis. These patients have a mild or moderate defect in immune function, and their course is unlike that of patients with the other 2 chronic aspergillosis classifications in which a slow and progressive enlargement of an *Aspergillus*-containing cavity is noted. The diagnosis requires at least 3 months of pulmonary symptoms of chronic illness, radiologic abnormalities, and elevated *Aspergillus* immunoglobulin G (IgG) antibody or other microbiologic data. Surgery appears to play a smaller role in managing chronic aspergillosis, and the mainstay of treatment is longterm antifungal therapy to halt the progression of disease. Although no randomized clinical trial has been conducted to demonstrate the benefit of antifungal therapy in chronic aspergillosis, anecdotal evidence suggests slow improvement.[29]

Pulmonary Aspergilloma

Aspergilloma is considered a saprophytic, or noninvasive, form of infection in which *Aspergillus* colonizes preexisting pulmonary cavities caused by tuberculosis, sarcoidosis, bullous emphysema, bronchiectasis, or other conditions. Aspergilloma develops in approximately 15% to 25% of patients with cavitating lung disease resulting from tuberculosis.[30] Disease can be divided into simple and complex aspergillomas based on radiographic criteria. The simple aspergilloma can be differentiated from the complex aspergilloma by the absence of constitutional symptoms, paracystic lung opacities, cyst expansion, or progressive pleural thickening.[31] In a study of 62 cases of pulmonary aspergilloma, chest radiograph showed a "fungus ball" in the cavities of 42 (67%) and thickening of the cavity wall in 16 (26%) cases.[32] Patients with aspergilloma can be asymptomatic, but many patients have persistent and productive cough, hemoptysis, and weight loss. Surgical management to extricate the aspergilloma completely is the preferred treatment. Although the postoperative morbidity rate is higher in complex aspergilloma, in a series of 88 patients, surgical management led to nearly equivalent (80%) survival rates in patients with either simple or complex aspergilloma.[33] Medical management often is unsuccessful because penetrance of the antifungal agent into the cavity is poor. Percutaneous intracavitary instillation of antifungal therapy designed to fill the cavity and create an anaerobic environment for the *Aspergillus* has led to some success,[34] but it should be reserved for patients with inoperable cases.[35]

Allergic Bronchopulmonary Aspergillosis

ABPA is a hypersensitivity lung disease resulting from sensitization to environmental exposure to allergens of *A. fumigatus*. In this condition, *A. fumigatus* grows saprophytically to colonize the bronchial lumen and results in persistent bronchial inflammation. Conidia trigger an IgE-mediated allergic inflammatory response in the bronchial airways that leads to bronchial obstruction. ABPA is primarily a disease of patients with asthma (occurring in 1%–2%) or cystic fibrosis (1%–15%). Disease manifestations result from immunologic responses to the *A. fumigatus* antigens and include wheezing, pulmonary infiltrates, bronchiectasis, and fibrosis. Immunologic manifestations include peripheral blood eosinophilia, immediate cutaneous reactivity to *A. fumigatus* antigen, elevated total levels of serum IgE, presence of precipitating antibody to *A.*

fumigatus, and elevated specific serum IgE and IgG antibodies to *A. fumigatus*.[36]

The mainstay of therapy for ABPA is corticosteroid therapy for attenuation of the inflammation and immunologic activity, whereas antifungal therapy is used to decrease the fungal burden and therefore the antigen load. In a randomized, double-blind study, itraconazole was found to be superior to placebo for treatment of ABPA.[37] Although data are questionably sufficient to recommend itraconazole for initial therapy for ABPA exacerbation, itraconazole should be added to the therapeutic regimen if the patient has a slow or poor response to corticosteroids,[36] as part of a 2-armed approach to optimize therapy.

Epidemiology and Risk Factors

In a review of more than 5500 patients who underwent HSCT during a 15-year period, >7% had mold infections, including 342 patients with proven or probable *Aspergillus,* 31 patients with *Fusarium,* 29 with *Zygomycetes* (mucormycosis), and 10 with *Scedosporium* infections.[1] Aspergillosis is the leading cause of infectious death in HSCT recipients, and 1 study showed that 36% of all cases of confirmed nosocomial pneumonia in these patients were caused by *Aspergillus,* with an attendant crude mortality rate of 95%.[38] The incidence of *Aspergillus* infection in HSCT recipients has ranged from 3% to 7%,[14,20] but the true incidence likely depends on the follow-up duration of individual studies. In a retrospective review of 409 patients, 13% had invasive aspergillosis; *Aspergillus* accounted for 17% of all isolated pathogens in allogeneic transplant recipients and for nearly 4% in autologous transplant recipients.[39] A review of patients found an increasing incidence of invasive aspergillosis in both allogeneic transplant recipients (5% increasing to 12%) and autologous transplant recipients (1% increasing to 5%). The incidence of *Aspergillus* non-*fumigatus* species as the cause of invasive pulmonary disease also increased dramatically after 1995 (18% increasing to 34%).[1] In another study of HSCT recipients with invasive aspergillosis, the risk of developing the disease was 12.8 times higher among recipients of allogeneic than autologous HSCT.[40] The incidence of invasive aspergillosis is possibly higher in unrelated donors because of the more complicated immunobiology and more immunosuppressive treatment regimens required.

Aspergillosis in HSCT recipients has a well-characterized bimodal distribution that correlates with (1) pre-engraftment neutropenia with a median of 16 days and (2) the peak of GvHD with a median of 96 days.[41] This distribution likely relates to the 2 major mechanisms of protection against invasive aspergillosis: alveolar macrophages and neutrophils. Most patients with autologous transplants had a diagnosis of invasive aspergillosis while they were neutropenic, whereas patients with allogeneic transplants are at greatest risk of invasive aspergillosis after engraftment or during impairment of cell-mediated immunity secondary to cytomegalovirus or GvHD.[41] As early posttransplant management and survival improve, the peak of invasive aspergillosis appears to be shifting to the outpatient setting. In large reviews of patients undergoing allogeneic HSCT, invasive aspergillosis was diagnosed at a mean of 88 to 115 days after transplantation,[3,22,40,42] with a mortality rate exceeding 80%. In some studies, most cases were diagnosed after posttransplant day 30,[40,42] and in another study, no cases of invasive aspergillosis were diagnosed during the neutropenic period following transplantation.[43]

The risk of invasive aspergillosis is calculated to increase from 1%/day after the first 3 weeks of neutropenia to 4% to 5%/day after 5 weeks,[44] with a 70% incidence after neutropenia exceeding 34 days.[45] Risk associated with prolonged or marked macrophage dysfunctions leads to occurrence of invasive aspergillosis with advanced underlying disease, transplantation during relapse of malignant disease or chemotherapeutic rescue therapy, GvHD, or concurrent infection such as with cytomegalovirus.[44] In a survey of 24 medical centers with 148 patients who had invasive aspergillosis, 30% of these patients also had a bacterial infection, 20% also had a viral infection, and 19% also had another fungal infection.[6]

Numerous studies associate invasive aspergillosis with receipt of HSCT from a human leukocyte antigen (HLA)–mismatched or unrelated donor, as well as with underlying disease.[1,41] Corticosteroids are a well-known major risk factor and can suppress the ability of monocytes and macrophages to kill conidia through inhibition of nonoxidative processes and impairment of lysosomal activity. Corticosteroids also inhibit chemotaxis of polymorphonuclear neutrophils, oxidative bursts, and activity against hyphae.[46] Generally, corticosteroids suppress macrophages, whereas cytotoxic chemotherapies decrease neutrophil number and function. Corticosteroids also greatly accelerate the growth of *A. fumigatus;* in 1 study these drugs decreased the doubling time of this organism to only 48 minutes.[47]

In several studies of HSCT risk factors, only moderate to severe GvHD and corticosteroid prophylaxis for GvHD,[3,42,48,49] and total body irradiation,[48] were significant variables in the multivariate analyses. In 1 study, numerous factors in the period from HSCT to diagnosis of fungal infection influenced survival, and all these factors were related to the cumulative dose of prednisolone. In multivariate analysis, the relative risk of death from invasive aspergillosis was 8.8 in patients with acute active GvHD (≥grade 2) or extensive chronic GvHD combined with a cumulative total prednisolone dose of >7 mg/kg dose in the week before diagnosis.[3]

Few pediatric studies have examined risk factors for invasive aspergillosis. In 1 study, the highest incidence of invasive aspergillosis was seen in children who had undergone allogeneic bone marrow transplantation (4.5% occurrence rate) and in children with acute myelogenous leukemia (4% occurrence rate). Specifically, the incidence of invasive aspergillosis was significantly higher in patients with acute myelogenous leukemia than in those with lymphoblastic leukemia (relative risk, 5.6; 95% confidence interval, 4.6–7.0).[50]

Diagnosis

Culture

A definitive diagnosis of aspergillosis requires isolation of the mold from culture in addition to histologic demonstration.[51] The gold standard of tissue biopsy often is considered too invasive and can be complicated by bleeding or secondary infection in HSCT recipients. In a prospective study of 3857 clinical specimens from 230 patients, a mold was isolated from 86 patients, and 95% of these molds were *Aspergillus* species.[48] A 1-year retrospective study found that 12% of patients with positive culture results for *Aspergillus* met criteria for invasive aspergillosis. Among high-risk patients a positive culture result was associated with invasive aspergillosis in 50% to 65% of cases and among intermediate-risk patients in 8% to 28%, whereas patients with low risk rarely had invasive aspergillosis.[6]

In 1 study the predictive value of positive respiratory tract culture results was 40% to 100% for invasive pulmonary aspergillosis.[52] Even in patients with an established diagnosis, sputum specimen results commonly are negative,[13,53] likely because invasive pulmonary aspergillosis is predominantly infiltrative and does not have aerial growth in the bronchial tree.[13] Colonization with *Aspergillus* species has been a marker for reduced shortterm survival because 12% of colonized patients died within 3 months. Invasive pulmonary aspergillosis was diagnosed in 12% of patients with respiratory tract colonization, but this finding is likely an underestimate because the diagnosis often was made by radiographic imaging, and culture specimens were not always obtained.[6]

Aspergillosis rarely is diagnosed by blood culture. Investigators have speculated that only 32 cases of true *Aspergillus* fungemia have been correctly documented in patients with hematologic disease.[54] In a study of 1477 separate positive *Aspergillus* culture results, fewer than 20 blood culture results were positive, and most of these were associated with pseudofungemia or terminal events noted at autopsy.[6] In general, the *Aspergillus* hyphal mass that develops in the lumen during angioinvasion remains in place until the force of blood flow causes hyphal breakage, which then allows the mass to circulate. The likelihood is small that a blood culture would capture these irregularly and infrequently discharged units. This difficulty in detection of *A. fumigatus* in blood culture stands in contrast to other angioinvasive filamentous fungi (e.g., *Fusarium* species, *Paecilomyces lilacinus, Scedosporium prolificans, Acremonium* species) that can discharge into the bloodstream a steady series of unicellular spores, which are more likely to be captured in a blood sample. This ability to sporulate in tissue and blood has been termed *adventitious sporulation*.[55] Because *A. terreus* also displays adventitious sporulation, histopathologic and potassium hydroxide examination of these spores also can allow rapid, presumptive identification of *A. terreus*. Therefore a positive blood culture result with *A. terreus* or another fungus that demonstrates adventitious sporulation should not be ignored.

Imaging

A review of 27 pediatric patients showed that radiographic changes that developed after HSCT but before the diagnosis of pulmonary fungal infection included unilateral infiltrates (52%) slightly more often than bilateral infiltrates. At the onset, infiltrates were interstitial (41%), alveolar (41%), and mixed (18%). Hilar or mediastinal lymphadenopathy or pleural effusion or thickening was rare. By the time of diagnosis of pulmonary fungal infection the infiltrates usually were bilateral (66%) and alveolar or nodular (74%), including 22% of patients having cavitary lesions.[56] Invasive pulmonary aspergillosis characteristically manifests on radiographs as multiple, ill-defined, 1- to 3-cm peripheral nodules that gradually coalesce into larger masses or areas of subsegmental and segmental consolidation. Lobar or diffuse pulmonary consolidation is a common finding.[57] Although chest radiographs usually are abnormal, in 1 series radiographs were normal in approximately 30% of patients in the week preceding death.[58]

Invasive pulmonary aspergillosis has 2 classic radiologic signs. The halo sign occurs in neutropenic patients with a hemorrhagic nodule resulting from angioinvasion. An early computed tomography (CT) finding of the halo sign is a rim of ground-glass opacity surrounding the nodule. In 1 study, the halo sign was seen in all patients with biopsy-proven invasive pulmonary aspergillosis, but this sign is nonspecific and also is seen in patients with mucormycosis or entomophthoramycosis (formerly zygomycosis), organizing pneumonia, or pulmonary hemorrhage.[59] These early lesions subsequently change into a cavitary lesion or lesion with an air crescent sign 2 to 3 weeks after recovery of neutrophils.[57,60] In 1 study, the air crescent sign was seen in 48% of patients 3 to 10 days after recovery from neutropenia.[22] The appearance of the air crescent sign had no relationship with the duration of neutropenia, and it showed a tendency to appear in large lesions such as a consolidation or a mass rather than in small lesions such as nodules.[61] Cavitation of the nodules or masses occurs in approximately 40% of patients and is characterized by an intracavitary mass composed of sloughed lung and a surrounding rim of air. The use of CT has increased the sensitivity of radiologic diagnosis. In a study of 37 cases with invasive pulmonary aspergillosis the mean time to diagnosis in HSCT recipients was reduced from 7 days to 1.9 days by using chest CT.[62]

Radiologic differences for invasive aspergillosis can exist between adults and children. In adult series of pulmonary aspergillosis, approximately 50% of cases show cavitation, and 40% show air crescent formation.[63] In a 10-year review of pediatric patients (mean age, 5 years), central cavitation of small nodules occurred in only 25% of children, and no evidence of air crescent formation was noted within any area of consolidation.[64] In another pediatric report, the rate of cavitation on chest radiography[56] was 22% (6 of 27), and in another report the rate of cavitation by CT was 43% (6 of 14).[65] In these last 2 pediatric series, mean ages were older than in the other report of lower rates of cavitation and an absence of air crescent formation. This finding suggests a spectrum of radiologic findings related to age.

Findings by thoracic magnetic resonance imaging (MRI) are not as characteristic as CT findings, and the typical MRI sign is the target sign, a nodular lesion with a lower signal in the center compared with higher, contrast-enhancing signal intensity in the rim on T1-weighted images. This sign is highly suggestive of late-stage disease.[66] MRI is the modality of choice for diagnosing cerebral aspergillosis, and it is more sensitive than CT. Findings often show multiple lesions located in the basal ganglia that include an intermediate signal intensity, lack of contrast enhancement, and an absence of mass effect.[67] CT examination of the head often reveals 1 or multiple hypodense, well-demarcated lesions. Hemorrhage and mass effect are unusual, but for patients with adequate neutrophil counts ring enhancement and surrounding edema are more frequent.[5] In evaluating sinus disease, T2-weighted MRI images show markedly decreased signal intensity compared with images of bacterial sinusitis, which show increased signal intensity.[5]

Bronchoalveolar Lavage

The value of bronchoalveolar lavage (BAL) was analyzed in 23 consecutive patients with histologically proven invasive aspergillosis; only 7 patients (30%) had BAL specimens diagnostic for invasive aspergillosis. In the BAL-positive group, 71% had multiple changes on thoracic CT compared with 25% of patients with a negative BAL result. The diagnostic yield of BAL was not associated with clinical symptoms or the duration of neutropenia. A thorough review of the diagnostic yield of BAL specimens in histologically proven invasive aspergillosis yielded sensitivities of approximately 40% (range, 0%–67%),[68] but in 1 study BAL had a sensitivity of only 50% even in patients with focal invasive aspergillosis.[69] The sensitivity of respiratory tract culture specimens in general has ranged from 15% to 69%,[6] and in 1 study it increased to 50% to 70% in high-risk invasive aspergillosis groups. Therefore a negative BAL or respiratory culture result in a high-risk patient does not exclude the possibility of invasive aspergillosis.

Serologic Testing

Antibody Testing

Serologic testing for antibodies to *Aspergillus* antigens is helpful to diagnosis aspergilloma or ABPA in immunocompetent people, but unfortunately serologic testing plays little role in the immunocompromised patient because *Aspergillus* growth does not correlate with an increase in anti-*Aspergillus* antibody titers.[12] Serologic examination of 18 patients with invasive aspergillosis showed that anti-*Aspergillus* antibody detection was negative in all cases, likely as a result of profound immunosuppression.[22]

Galactomannan Antigen Testing

Galactomannan (GM) is a major cell wall component of *Aspergillus*. Highest serum concentrations of GM are released in terminal phases of the disease.[12] An enzyme immunosorbent assay (EIA) was introduced using a rat anti-GM monoclonal antibody, EB-A2, which recognizes the 1→5-β-D-galactofuranoside side chains of the GM molecule.[70] A sandwich EIA was introduced in 1995,[71] and by using the same antibody as both a capture and a detector antibody in the sandwich EIA (Platelia *Aspergillus*, Bio-Rad, Hercules, Calif), the threshold for detection can be lowered to 1 ng/mL. This sandwich EIA is the current commercially available assay.

The GM assay is positioned to detect only *Aspergillus*, but over the years reports have noted fungal cross-reactivity, more commonly with *Fusarium*, *Paecilomyces, Blastomyces, Histoplasma, Cryptococcus, Trichosporon*, *Penicillium*, and others. The GM cutoff value in serum adopted by the current international guidelines is an optical density index (ODI) of 0.5, and a meta-analysis found that the GM assay possesses an overall sensitivity of 71% and a specificity of 89% for invasive aspergillosis, highest in patients with hematologic malignant disease and HSCT recipients, but sensitivity drops to only 22% in solid-organ transplant recipients.[72] The GM assay is consistently most useful in patients with hematologic malignant disease who are undergoing chemotherapy and patients after HSCT, but it has high false-negative results in patients with CGD.[73] Sensitivity is greater in neutropenic patients, likely because of a more angioinvasive pathogenesis, and unfortunately it is low in the setting of mold-active antifungal therapy.[74] Previously, piperacillin-tazobactam was found to yield false-positive reactions with the GM assay; however, as a result of manufacturing changes, cross-reaction no longer occurs.

Serial testing at least twice a week during periods of high risk has been recommended.[75] In 1 study an increase in value during the first week of observation was predictive of progressive disease in allogeneic HSCT recipients.[76] In a large prospective study of hematology patients and HSCT recipients with confirmed or probable invasive aspergillosis, GM was detected in 65% of patients an average of 8.4 days before positive CT or culture results, and GM was detected in 40% of patients a mean of 6.9 days before the onset of clinical symptoms.

Diagnosis of pediatric invasive aspergillosis with the GM assay was once deemed impossible because earlier studies repeatedly showed a higher rate of false-positive results in children.[77,78] Theories to explain increased false positivity in children ranged from the presence of *Bifidobacterium bifidum* in the gut microflora that could mimic the epitope recognized by the EB-A2 in the EIA test[79] to GM-positive infant formula used in children.[80] However, more recent studies showed that the GM assay is very effective in children and has a low (1%–2%) false-positivity rate.[81,82]

The GM assay in BAL fluid seems to be more predictive of disease than the biomarker in serum. A large retrospective study of BAL GM found increased sensitivity with a cutoff value of 1, compared with the lower cutoff value of 0.5 in serum. This study also found that mean BAL GM was not different in neutropenic versus nonneutropenic patients, unlike the assay in sera.[83] A meta-analysis of BAL GM found an overall sensitivity of 90% and specificity of 94%. Additionally, antifungal therapy did not significantly affect BAL sensitivity, as is the case with serum samples.[84] In pediatric patients, a similar BAL GM cutoff value was established and suggested that a BAL GM >1 and a concurrent serum GM >0.5 yielded the overall best predictive value for disease.[85]

(1,3)-β-D-Glucan Testing

(1,3)-β-D-glucan is an integral cell wall component and, in contrast to GM, normally is not released from the fungal cell.[12] Factor G, a coagulation factor of the horseshoe crab, is a highly sensitive natural detector of (1,3)-β-D-glucan[86] through a modified limulus endotoxin assay. This assay is more nonspecific than the GM assay and detects several different fungi, including *Aspergillus* spp., *Candida* spp., *Fusarium* spp., *Trichosporon* spp., *Saccharomyces cerevisiae, Acremonium, Coccidioides immitis, Histoplasma capsulatum, Sporothrix schenckii*, and *Pneumocystis jirovecii*. The (1,3)-β-D-glucan assay does not detect *Cryptococcus* and the yeast form of *Blastomyces dermatitidis* (which produce low levels of [1,3]-β-D-glucan) or *Absidia*, *Mucor*, and *Rhizopus* (which produce no [1,3]-β-D-glucan). This assay does not identify the genus of the fungi detected, only the presence of the fungal call wall component. A meta-analysis of adult hematology and oncology patients determined that the sensitivity and specificity of 2 consecutive tests were 49.6% and 98.9%, respectively.[87]

In a study comparing (1,3)-β-D-glucan with GM, the sensitivity, specificity, and positive and negative predictive values for GM and β-glucan were identical. False-positive reactions occurred at a rate of 10.3% in both tests, but the patients showing false-positive results were different in each test. Both tests anticipated the clinical diagnosis and CT abnormalities, but the β-D-glucan test tended to become positive earlier than the GM test. A combination of the 2 tests improved the specificity (to 100%) and the positive predictive value (to 100%) of each individual test without affecting the sensitivity and negative predictive values.[88]

Another study compared GM, polymerase chain reaction (PCR), and (1,3)-β-D-glucan in patients with hematologic disorders; the receiver-operating characteristic analysis showed that the area under the curve was greatest for the GM assay, by using 2 consecutive positive results.[89] Unfortunately, (1,3)-β-D-glucan assay experience in children is limited to case series, so full operating characteristics of the assay in pediatric patients is not known.

Polymerase Chain Reaction

Efforts are focused on defining an optimal primer sequence for a PCR detection method for *Aspergillus*. No PCR assay is available commercially, and reports of performance can be difficult to interpret because of the lack of standardization among centers. Given the ubiquitous nature of the mold, the value of this test likely will be its high negative predictive value. Issues remaining unresolved in the use of PCR are the best source of material (e.g., whole blood, serum, plasma, BAL specimens), the amplification protocol (e.g., real-time, sample volume, extraction methods), and primer selection (e.g., "panfungal," 18S rRNA, 28S rRNA, mitochondrial DNA).[90] Using PCR for BAL specimens compared with blood samples seems less promising because of the high number of false-positive BAL results. Real-time PCR assays seem to decrease the risk of false-positive results and have better reliability than conventional PCR assays.[91] A meta-analysis of blood-based *Aspergillus* PCR in high-risk adult hematology patients found a sensitivity of 84% and a specificity of 76%, with specificity increasing to 94% with at least 2 positive PCR results.[92] In a subsequent meta-analysis of screening such patients by PCR and GM assays, the negative predictive value for invasive aspergillosis for both tests negative was 100%, and the positive predictive value of both tests positive was 88%.[93]

Treatment

For decades, the clinical response rate for invasive aspergillosis was only approximately 30% by using either amphotericin B or itraconazole treatment.[94] In a pivotal study comparing voriconazole with amphotericin B deoxycholate for initial therapy,[95] voriconazole had a statistically superior response rate (53%) versus amphotericin B (32%), with improved patient survival (71% vs. 58%). Although some investigators criticized this study for the use of other licensed antifungal agents after initial randomization to voriconazole or amphotericin B deoxycholate, a subsequent analysis revealed that the strategy of initial therapy with voriconazole also was superior to subsequent use of liposomal amphotericin B.[96] An additional open-label study confirmed the benefit of voriconazole as primary therapy versus salvage therapy,[97] thus highlighting the importance of using optimal antifungal therapy first.

Voriconazole now is the guideline-recommended primary therapy for all forms of invasive aspergillosis.[98] However, no defined optimal alternative is available in the case of recalcitrant disease or in the event of voriconazole side effects. If "salvage" therapy is required after the first agent fails clinically or unacceptable toxicities develop, options include therapeutic drug monitoring of voriconazole levels to document adequate exposure to the guideline-approved first agent, change of antifungal therapy likely to include a different class of agent, or the addition of another antifungal agent to use combination antifungal therapy. Above all, the correct diagnosis must be established.

Voriconazole trough levels do not correlate exactly with clinical outcome, and no universally accepted minimum standards exist. Although most experts would agree that a serum level should exceed the expected minimum inhibitory concentration for voriconazole of the infecting *Aspergillus* isolate (generally 0.5 μg/mL), different studies report the need for levels of at least 1.0 or 2.0 μg/mL. Because voriconazole pharmacokinetics clearly shows great interpatient variability, dosing and levels cannot be extrapolated easily among patients. However, individual patient consistency is reasonable, so therapeutic drug monitoring and trending in an individual patient are clinically helpful. The dosing of voriconazole in pediatric patients uses fundamentally different pharmacokinetics (linear in children vs. nonlinear in adults), and therefore dosing is increased in children (see Chapter 293).

Posaconazole is another triazole with excellent activity against *Aspergillus,* and a study demonstrated excellent activity as salvage therapy,[99] yet pediatric dosing has not been finalized. One option for failed voriconazole therapy is to change to a different class of agent; an amphotericin B agent or an echinocandin is an excellent option. A study comparing 2 doses of liposomal amphotericin B (3 mg/kg/day vs. 10 mg/kg/day) found no difference in clinical outcome, yet greater toxicity was associated with the higher amphotericin B dose.[100] The echinocandin antifungal agents appear to act primarily on the growing hyphal tip of the *Aspergillus*.[101] In the large open trial examining caspofungin as salvage therapy for invasive aspergillosis, a 45% (37 of 83) favorable response rate was reported,[102] suggesting an option for salvage therapy if initial antifungal therapy should fail. Micafungin also has been studied as an agent for invasive aspergillosis, with similar results.[103] Echinocandins, given their limited, fungistatic activity against *Aspergillus*, should not be used as primary monotherapy for invasive aspergillosis.

In the past, combination antifungal therapy for invasive aspergillosis was of little consequence because only a handful of possible agents or combinations was available, including the use of other agents such as rifampin and flucytosine, which are no longer recommended. However, the surge of newer antifungal drugs has created numerous potential combinations.[104] Although historical concerns of antagonism have been expressed, especially with the polyene-azole interaction, these concerns generally have not been clinically relevant.[94,104] Reports of both success and failure with combination antifungal therapy for invasive aspergillosis are myriad, mirroring the conflicting laboratory data ranging from antagonism to synergy. A combination trial with 454 patients comparing voriconazole versus voriconazole plus anidulafungin revealed that combination therapy, with the echinocandin delivered for the first 2 weeks of 6 weeks of total therapy, led to greater survival in certain subsets of patients.[105] Although the difference in mortality rate (19.3% vs. 27.5%) did not achieve the prespecified threshold for statistical superiority, secondary analyses tended to favor combination therapy. Whether the effect reflects that a second agent used immediately is therapeutic while the azole is reaching therapeutic levels (that often take a week) or represents a true antifungal synergy is unclear.

Surgery has value for treatment of local pulmonary aspergillosis, for patients with significant hemoptysis, and for lesions impinging on great vessels or major airways.[5,106,107] Bone marrow recovery induces cavitation, which creates a major risk of massive hemorrhage when the *Aspergillus* lesion is located near a main pulmonary artery or branch.[107] When marrow recovery occurs, the increased granulocytes release proteolytic enzymes at the site of infection, thus potentially damaging lung tissue. Radical debridement also is a crucial adjunct in sinusitis, and it can contribute to improved survival.

Prognosis

That the outcome of invasive aspergillosis absent immune reconstitution generally is poor highlights the paramount importance of recovery of immune function to survive. In parallel, decreasing immunosuppression (removing or lowering corticosteroids) is considered to be a helpful adjunct. The mortality rate associated with untreated invasive aspergillosis is nearly 100% in most patient groups, and the overall survival among patients treated with amphotericin B consistently had been approximately 34%,[108,109] but now generally it has improved to approximately 50%.[110] Cerebral disease is rapidly and almost uniformly fatal irrespective of treatment.[21] The prognosis for focal pulmonary aspergillosis is more favorable than that for diffuse bilateral disease because as focal disease tends to progress more slowly. However, focal disease carries an increased risk of hemoptysis, which often is life-threatening.[5] In 1 series, the median duration of survival of patients diagnosed with invasive aspergillosis was 29 days.[1] In another series median survival after invasive aspergillosis diagnosis was 36 days, with a 1-year survival rate estimated to be 22%, whereas mean survival for 11 patients with central nervous system disease was only 19 days.[3]

Key Points

Diagnosis and Management of *Aspergillus* Infection

Epidemiology

- *Aspergillus fumigatus* is the most common species causing infection.

- It is a ubiquitous mold in the soil.

Clinical Features

- Bimodal peak incidence of disease in stem cell transplant recipients: during periods of neutropenia and periods of graft-versus-host disease

- Increasing number of cases of invasive aspergillosis in nonclassically immunocompromised patients (e.g., chronic obstructive pulmonary disease, patients in intensive care)

- Pulmonary disease the most common clinical manifestation

- Pulmonary disease common and more indolent in patients with chronic granulomatous disease

Diagnosis

- High-resolution computed tomography is the imaging standard for pulmonary disease; magnetic resonance imaging is necessary for central nervous system disease.

- Serum galactomannan assay is the ideal noninvasive method; performance is best when patients are screened twice weekly during periods of greatest risk; bronchoalveolar lavage galactomannan assay is valuable and likely preferred over serum galactomannan assay if obtainable.

- Negative culture result on a bronchoalveolar lavage specimen does not exclude disease.

Treatment

- Voriconazole is the preferred antifungal agent for primary therapy.

- For salvage therapy, options consist of changing antifungal classes of therapeutic agent or adding another antifungal agent.

- Azole resistance is developing slowly.

- Optimal antifungal dosing is crucial in pediatric patients;

physicians should strongly consider measuring voriconazole levels.

Duration of Therapy

- Absent defined recommendations, at least 6 to 12 weeks is advisable.
- Therapy should be continued during periods of immunosuppression.

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Agents of Hyalohyphomycosis and Phaeohyphomycosis

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Agents of hyalohyphomycosis and phaeohyphomycosis are ubiquitous filamentous molds. (Moulds is the preferred spelling by many mycologists.) These molds are soil saprophytes and plant pathogens that have gained notoriety as emerging pathogens in immunocompromised hosts, including children. The pathogenesis of infections with these organisms is not clearly established because many of these organisms are minimally pathogenic in humans. However, these fungal conidia can cause infection in severely immunocompromised children, frequently in the paranasal sinuses or lungs, as a result of inhalation of aerosolized conidia.[1,2] Some of these organisms (e.g., *Fusarium* spp.) also can gain entry through the gastrointestinal tract, central venous catheters, or skin.[3,4] Direct inoculation of these organisms into tissues following trauma can lead to infection in both immunocompromised as well as immunocompetent children.[5–7]

Agents of Hyalohyphomycosis (*Fusarium, Scedosporium Boydii* Complex, *Paecilomyces,* and *Penicillium* Species)

Agents of hyalohyphomycosis are a diverse group of molds whose tissue form is hyaline. Colonies can be of various colors or lightly pigmented. The most important of these organisms is *Aspergillus* (see Chapter 244), but other molds, such as *Fusarium* species, the *Scedosporium boydii* species complex, *Chrysosporium* species, *Penicillium* species, *Paecilomyces,* and others, also cause infection in severely immunosuppressed children. These organisms resemble each other and *Aspergillus* in tissue, so cultures are needed to confirm the specific agent causing the disease.[8,9] As with other fungi, molecular and phenotypic studies have resulted in taxonomic changes in these molds; as a result, many molds are reported clinically as a species complex (e.g., *S. boydii* species complex and *Fusarium solani* species complex), which can contain a large number of distinct species.[10,11] The risk factors for these infections include significant immunosuppression such as immunosuppression associated with hematopoietic stem cell transplantation or bone marrow transplantation, profound neutropenia, malignant disease, and inherited immunodeficiencies.[12,13]

Epidemiology

Increasing numbers of agents of hyalohyphomycosis have been reported to cause invasive mycoses in severely immunosuppressed children.[14,15] The epidemiology and risk factors for infection with these agents are similar to those associated with *Aspergillus,* and the clinical presentations of these infections are similar to manifestations of invasive aspergillosis.[1,13] Clinical presentations include sinusitis, pulmonary infection, localized abscesses, cutaneous infection, and disseminated infection. Some of these infections have characteristic epidemiologic features, including infection with *Fusarium* species, which has been associated with inhalation of contaminated aerosols from hospital water as well as infection following a primary paronychial or skin infection.[1,3,16] In 2006, 164 confirmed cases of *Fusarium* keratitis were reported in wearers of soft contact lenses, and these infections led to corneal transplantation in 34%.[17,18] In a case-control study, cases were associated with use of a contact lens solution, although *Fusarium* was not found in unopened bottles.[17] *S. boydii* (*S. apiospermum*) infection has been reported in patients after an episode of near-drowning.[10,19,20]

Clinical Manifestations

Fusarium infections are among the most common of these agents, and they cause a spectrum of disease: toxin-mediated (mycotoxin syndrome), locally invasive, catheter-related, allergic bronchopulmonary, and disseminated infection. Toxin-mediated disease results from ingestion of contaminated grains. Symptoms range from mild gastroenteritis to bone marrow suppression resulting in aplasia and eventual death. Locally invasive diseases include mycotic keratitis, endophthalmitis, sinusitis, brain abscess, cystitis, cutaneous and subcutaneous infections, and paronychial and ungual infections.[12,13,21–23] Penetrating trauma has been associated with osteomyelitis and pyogenic arthritis. Locally invasive infections can occur in immunocompetent and immunocompromised hosts.[24–26]

Disseminated fusariosis, which is limited to immunocompromised hosts, especially hosts with a hematologic malignant disease or hematopoietic stem cell transplantation, is characterized by fungemia, skin lesions, and multiple organ involvement. Fungemia is detected in 50% to 60% of patients with a diagnosis of disseminated infection, and *Fusarium* is the only mold commonly associated with fungemia.[12] Skin lesions are macular or papular, often with a necrotic center, and they occur predominantly on extremities and are characteristic of this infection (Fig. 245.1).[3,23] Disseminated fusarial infection often is fatal; mortality rates between 60% and 100% are reported despite antifungal therapy, although improved rates of mortality have been reported since 2005.[13,27,28]

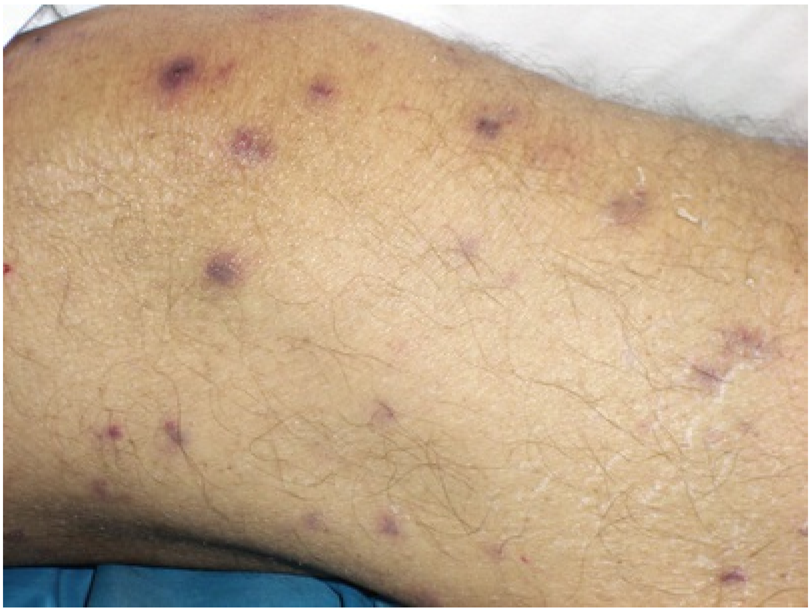


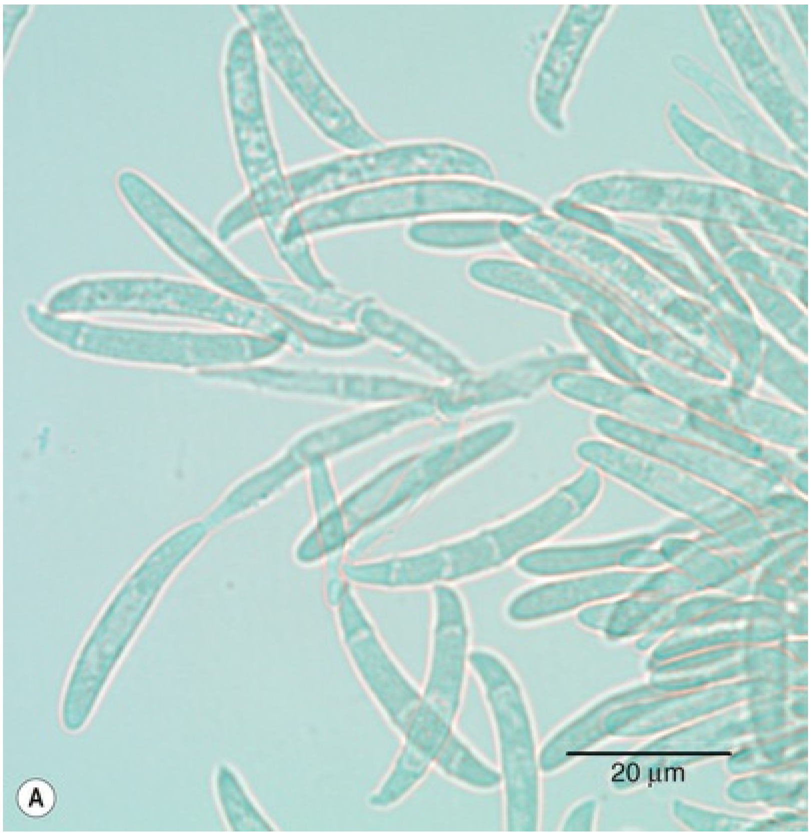
FIGURE 245.1 **Typical necrotic-appearing skin lesions of *Fusarium* infection on the arm of a patient with disseminated disease.**

The *Scedosporium apiospermum* species complex consists of the closely related species *S. apiospermum* and *S. boydii*. These two species were previously considered to be the same species, with *S. apiospermum* being the asexual form (anamorph) and *Pseudallescheria boydii* being the sexual form (teleomorph). However, through phylogenetic analysis, it is now recognized that *S. apiospermum* and *S. boydii* (previously also referred to by the teleomorph name *P. boydii*) are indeed distinct species. Other sibling or cryptic species that are morphologically identical include *S. aurantiacum, S. dehoogii, S. minutispora,* and *S. desertorum*. In tissue, hylane, septate hyphae of *Scedosporium* resemble *Aspergillus* species. In immunocompetent hosts, these are major causes of fungal mycetoma, but in immunosuppressed hosts, widely disseminated infection occurs, including involvement of brain. These organisms can be resistant to amphotericin B, with variable activity of extended spectrum azoles, voriconazole and posaconazole, shown in adults and children.

Clinical manifestations of other hyalohyphomycoses are not distinctive and mimic those of invasive aspergillosis, including pulmonary infection, sinus infection, central nervous system disease, osteomyelitis, and locally invasive infections (e.g., keratitis and skin and soft tissue infections).

Laboratory Evaluation and Diagnosis

In tissue, all these organisms appear as branched, septated hyphae that are indistinguishable from hyphae of *Aspergillus* and other hyaline molds. Specific diagnosis requires isolation of the organism from culture of tissue (Fig. 245.2A). Some of these organisms are resistant to amphotericin B clinically and in vitro, including *Fusarium* and *S. boydii,* with better susceptibility reported to the newer azoles, voriconazole and posaconazole.[32,33] Blood cultures can be useful in *Fusarium,* but results are rarely positive with infection caused by other agents of hyalohyphomycosis. Serologic testing and non–culture-based methods such as polymerase chain reaction for these agents are not available commercially.



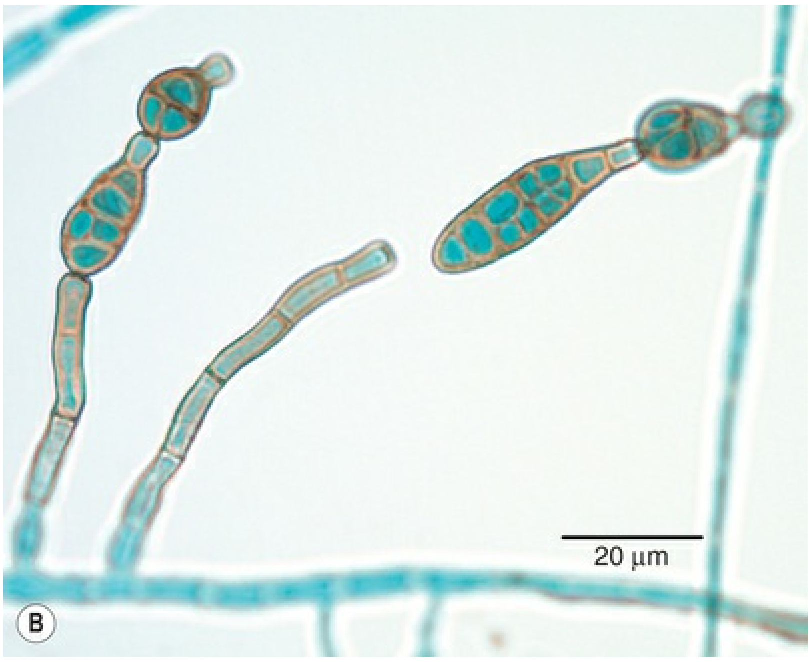


FIGURE 245.2 (A) Crescent-shaped macroconidia of *Fusarium* spp. (B) Club-shaped conidia of *Alternaria* spp.

Therapy and Prevention

Because some of these organisms, including *Fusarium* and *S. boydii,* are resistant to amphotericin B, responses to amphotericin B are poor, although successful outcomes with the use of lipid formulations of amphotericin B have been reported.[27,34,35] Posaconazole and voriconazole have been used with success in the treatment of both *S. boydii* and *Fusarium* infections and are the likely drugs of choice for the agents of hyalohyphomycosis.[4,31,32,36–38] With the use of voriconazole and liposomal amphotericin, better survival rates are being reported.[27] Similar responses have been reported with the salvage use of posaconazole. Itraconazole also has activity against many of these organisms, but because of variable bioavailability, the role of itraconazole is limited to children with less severe infection. Antifungal agents to prevent these mycoses are not specifically indicated because infection is rare, although prophylaxis with posaconazole has been shown to reduce *Aspergillus* infections and would presumably prevent the emergence of infections with these mycoses as well.[39,40]

Agents of Phaeohyphomycosis (*Bipolaris, Alternaria, Exophiala, Exoserohilum, Cladophialophora* Species, and *Scedosporium Prolificans*)

Agents of phaeohyphomycosis comprise a group of opportunistic molds that are dematiaceous (i.e., darkly pigmented in both tissue and culture).[7,9] Although phenotypic characteristics traditionally have been used to identify these organisms, molecular techniques have resulted in reclassification of many of these organisms, as well as the recognition of species complexes of distinct separate species. Examples of genera in this group include *Bipolaris, Alternaria, Scedosporium prolificans, Exophiala, Exserohilum, Cladosporium, Curvularia, Cladophialophora, Scopulariopsis,* and many others.[2,5,7,41–52] These emerging molds rarely are reported to cause infection in children.

Epidemiology

More than 150 and 70 genera of dematiaceous fungi have been implicated in human and animal disease, respectively; some of these fungi have been considered relatively nonpathogenic but can cause serious, even fatal, infection in severely immunocompromised children.[7] Some infections are associated with specific characteristics (e.g., *Cladophialophora bantiana* with a predilection for causing central nervous system infection), but generally these fungi do not cause syndromes specific to children.[2,4,7,53]

As with other molds, infection usually occurs by inhalation of conidia and generally starts in the sinuses or the lungs. Alternatively, infection can follow percutaneous inoculation and was associated with a large, multistate outbreak of *Exserohilum* meningitis caused by contaminated steroids.[2,6,54] Fungemia also can occur, although is less common compared with fusariosis.[55]

The organisms are found in decaying vegetation and are abundant in nature but of sufficiently low virulence that only scattered infections occur. These fungi thrive best in an acidic, glucose-rich environment and are killed by neutrophils. Neutropenia and uncontrolled diabetes are risk factors for infection. Traumatic inoculation from soil or plants is a major mode of infection.

Clinical Manifestations

The pathogenicity of agents of phaeohyphomycosis and the resulting clinical manifestations are quite variable. In immunocompetent children or children with minimal host defense abnormalities, phaeohyphomycosis can be associated with the development of sinusitis or pneumonia that can follow a subacute course developing over months to years, and direct invasion of brain from the sinuses can occur.[2,7,53] Infections can also have a significant component of hypersensitivity, with eosinophils and Charcot-Leyden crystals in sinus aspirates.

Locally invasive diseases include mycotic keratitis, paranasal sinusitis, osteomyelitis, and cutaneous infections. The paranasal sinuses are the most commonly infected sites, particularly in immunocompromised hosts with malignant disease. Characteristic lesions associated with sinonasal infections appear as superficial ulcers of the nasal septum, plaque-like necrotic lesions, and hemorrhagic crusts that are indistinguishable from lesions of aspergillosis or other fungi. Cutaneous lesions appear as nonhealing ulcerative or papular lesions with dry crusts. Subcutaneous lesions can enlarge gradually over months. Some organisms, such as *Cladophialophora, Verruconus* (previously known as *Ochroconis*) *gallopava, Rhinocladiella,* and others are neurotropic and cause brain abscesses.[7,55–57] Disseminated disease, including infection of the central nervous system, has been reported in severely compromised hosts, including children undergoing hematopoietic stem cell transplantation.

Laboratory Findings and Diagnosis

Agents of phaeohyphomycosis are characterized by the production of black melanin pigment, which can be seen histopathologically and in gross lesions. They are a diverse group of organisms characterized by septate, dematiaceous, branched, or unbranched fungal elements in tissue that can appear moniliform, bead-like, or swollen.[8,9] Species identification is made by examining conidia in culture (see Fig. 245.2B). Unfortunately, these mycoses can manifest in culture as *mycelia sterilia,* a mold culture that does not readily sporulate and thus does not allow identification. Masson-Fontana staining of tissue specimens is useful for staining the melanin in the hyphae and allows specific diagnosis of an agent of phaeohyphomycosis. Culture specimens are best obtained from normally sterile sites (e.g., biopsy of a subcutaneous lesion or sinus aspirate). These organisms can be found as commensals colonizing the respiratory tract from sputum samples, so a tissue biopsy may be needed to establish a diagnosis of invasive infection. Although blood culture results are rarely positive as compared with infections caused by *Fusarium,* fungemia can occur.[57]

Treatment and Prevention

Amphotericin B has been the common therapy for these infections. However, in vitro and in vivo activity of itraconazole and the extended-spectrum azoles, posaconazole and voriconazole, has been demonstrated against many of the agents of phaeohyphomycosis, so these drugs are possible alternatives, especially for longterm suppressive therapy.[4,58–60]

Although many of the black molds are susceptible to the extended-spectrum azoles, *S. prolificans* is a resistant pathogen.[2,31] The darkly pigmented *S. prolificans* (previously known as *S. inflatum*) is distinguished from the usually lightly pigmented *S. boydii* by the lack of sexual structures and the characteristic inflated conidiophore in the former. *S. prolificans* causes bone and soft tissue infections, as well as disseminated disease.[2] Outcomes are poor, even with treatment with the newer antifungal agents, thus often prompting attempts at combination therapy or local debridement.[61]

Voriconazole and posaconazole (usually used as salvage therapy) have been effective clinically in a few patients.[53,56,62] Itraconazole usually is reserved for patients with less severe infection.[63] Although pediatric doses of voriconazole or posaconazole are not established, voriconazole doses of 7 to 8 mg/kg every 12 hours intravenously have been suggested to give exposures similar to that of the usual adult dose (4 mg/kg every 12 hours). Posaconazole suspension typically has been started at 12 mg/kg/day in 2 to 4 divided doses but has largely been replaced by the extended-release tablet formulation, which is administered at doses of 300 mg/day following a 1-day loading dose of 300 mg times 2 doses for children 13 years of age and older. Therapeutic drug monitoring of both drugs should be useful to guide therapy. The echinocandins also have activity in vitro against some agents of phaeohyphomycosis, but clinical experience is limited, and these drugs are not recommended as single agents for therapy for these infections.[64,65]

No known ways exist to prevent infection with these unusual mycoses, although infection control efforts similar to those used to reduce risk of invasive aspergillosis are likely to reduce nosocomial airborne acquisition.

Key Points

Diagnosis and Management of Agents of Hyalohyphomycosis and Phaeohyphomycosis

Microbiology

- Agents of hyalohyphomycosis: molds that are hyaline in tissue; variously colored or light pigmented in culture, associated with soil, water, decomposing vegetation.

- Species include Aspergillus and other genera including *Fusarium, the Scedosporium boydii species complex, Paecilomyces, Chrysosporium, Penicillium,* and others

- Agents of phaeohyphomycosis: melanized or dematiaceous (darkly pigmented) molds or yeast-like fungi, associated with soil, water, decomposing vegetation.

- More than 150 species and 70 genera including *Bipolaris, Alternaria, Scedosporium prolificans, Exophiala, Exserohilum, Cladosporium, Curvularia, Cladophialophora, Scopulariopsis,* and others

- Many now referred to as a species complex because of the phylogenetic, phenotypic, and physiologic differences in strains

Epidemiology

- Occur worldwide, most commonly in severely immunocompromised children usually following inhalation of conidia

- Can follow direct inoculation from trauma or localized infection (keratitis, sinusitis, otitis)

- Specific exposures associated with some organisms (water aerosols for *Fusarium;* or near-drowning for *Pseudallescheria boydii* species complex; outbreaks caused by contaminated solutions: *Fusarium* keratitis and *Exserohilum* meningitis following injection of contaminated steroids)

Clinical Features

- Cutaneous infection: follows trauma in immunocompetent or compromised children; slowly increasing nodular or ulcerative lesions; also can reflect disseminated infection (fusariosis)

- Pulmonary: follows inhalation; including productive cough, fever, weight loss, shortness of breath, hemoptysis; nonspecific radiographic infiltrates

- Disseminated: severely immunocompromised children; neurotropism with brain abscess common for some organisms (agents of phaeohyphomycosis, e.g., *Cladophialophora bantiana*)

Diagnosis

- Recovery of organism from body fluids or tissue

- Microscopic examination of pathologic material: nonspecific histopathologic features for agents of hyalohyphomycosis; beaded irregular appearance of pigmented hyphae for agents of phaeohyphomycosis

- Melanin staining by Masson-Fontana method useful for agents of phaeohyphomycosis

Treatment

- Traditionally amphotericin B (or lipid formulation), but many species resistant to polyenes
- Activity and clinical use of voriconazole or posaconazole reported in case series; itraconazole reserved for less seriously ill patients

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Agents of Mucormycosis

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Mucormycosis (formerly zygomycosis) is an uncommon but emerging infection that occurs in immunocompromised patients, including children and neonates.[1–6] Previously, the term *zygomycosis* was used to refer to syndromes of mucormycosis and entomophthoramycosis, but updates in taxonomy determined that the class name Zygomycota is invalid.[7] Because the class Zygomycota no longer exists, the term *zygomycosis* has become obsolete.[1,7] Molds causing these infections are now in phylum Glomeromycota, subphyla Mucoromycotina and Entomophthoromycotina, respectively.[1,7] Infectious agents in the order Entomophthorales (e.g., *Conidiobolus* and *Basidiobolus*) produce distinct cutaneous and subcutaneous disease syndromes that are not discussed in this chapter.[8–11] Because clinically significant genera are in the subphylum Mucoromycotina, order Mucorales, the term *mucormycosis* is a useful clinical and valid mycologic reference.[1,7] Organisms in this order are characterized by the formation of broad, aseptate, or rarely septate hyphae and by sexual reproduction with formation of zygospores. The Mucorales are divided into 6 families of significance in human or animal disease, although most cases of human infection are caused by members of the family Mucoraceae. These families have undergone taxonomic revisions based on molecular, physiologic, and phylogenetic studies, including the reclassification of the family

Absidiaceae to Lichtheimiaceae for pathogenic species that are able to survive at temperatures of ≥37°C.[7,12] The family Mucoraceae produces *sporangiospores* (asexual spores) in a closed, sac-like structure called a *sporangium* that are released when the wall ruptures. The sporangium is attached to the hyphal substratum with a stalk-like structure, the *sporangiophore.* Different species are distinguished by the microscopic appearance of the sporangiophores, sporangia, and sporangiospores, as well as by the presence or absence of rhizoids (root-like structures) that anchor sporangiophores to the substratum.[13] In the family Mucoraceae, members of the genera *Rhizopus, Mucor, Actinomucor, Rhizomucor,* and *Apophysomyces* all have been implicated in human disease. Less frequently reported species in human disease in other families include *Cunninghamella, Saksenaea, Syncephalastrum, Cokermyces,* and *Lichtheimia*.[1]

The species isolated from cases of human infection are ubiquitous in decomposing organic matter such as spoiled bread, fruit, and other food items, as well as in soil. The most commonly encountered human pathogen is *Rhizopus ahhrizus* (*R. oryzae*), but many other species have been implicated.[3,6] All these organisms cause similar syndromes in children and neonates.[3–5]

Mucormycosis generally is acquired through inhalation of spores; the lungs and sinuses are the most common initial sites of infection. Less commonly, disease can arise after ingestion of contaminated foods or by direct inoculation following trauma or through vascular catheters, an important route of nosocomial transmission in neonates.[3,14] In an immunocompetent host, pulmonary macrophages ingest and kill inhaled sporangiospores.[15,16] In diabetic hosts and other immunosuppressed patients, macrophages fail to suppress spore germination.[17] Once infection is established, neutrophils have a pivotal role in killing hyphae. Severe neutropenia increases the risk of invasive infection, as does ketoacidosis in diabetic patients because of abnormal neutrophil function.[18]

Epidemiology

The spores of Mucorales are ubiquitous in the environment, but they only rarely cause infection without predisposing host factors.[6]

Certain predisposing conditions are associated with specific clinical manifestations of disease. For example, patients who have diabetic ketoacidosis typically have rhinocerebral mucormycosis. In patients with leukemia and other causes of neutropenia who are receiving cytotoxic chemotherapy, rhinocerebral, pulmonary, or disseminated disease can develop. Infants and children with severe malnutrition can have gastrointestinal tract mucormycosis.[5,19] Patients receiving deferoxamine for iron overload states also are at increased risk for mucormycosis.[6,15]

Prolonged neutropenia is well recognized as an important risk factor for mucormycosis among patients with leukemia and recipients of bone marrow or hematopoietic stem cell transplants.[20] Other contributing factors in these patients are the use of corticosteroids and broad-spectrum antibacterial agents.[3,5,21,22] Prolonged use of antifungal agents without activity against Mucorales (especially voriconazole, but also the echinocandins and fluconazole) in severely immunosuppressed patients has been reported as a risk factor for mucormycosis.[23–26]

In children, mucormycosis often develops in settings similar to those seen in adults, including neutropenia, solid-organ transplantation, hematopoietic stem cell or bone marrow transplantation, burns, and deferoxamine treatment for management of iron overload.[3,6] Infection occurs in distinct settings in children and neonates as well. These conditions include diabetes mellitus in children, particularly with uncontrolled diabetic ketoacidosis, and cutaneous infection in neonates.[3,14]

Nosocomial outbreaks of mucormycosis have been linked to construction work, as well as to contaminated air conditioning systems.[27] Nosocomial clusters of cutaneous infections, especially in neonates, have been traced to the use of contaminated biomedical devices (e.g., wooden tongue depressors) or have been associated with various adhesive bandages used in the hospital setting (e.g., elastic bandages or tape) and hospital linens.[28,29] However, because most cases of mucormycosis in hospitalized patients are sporadic, determining the site of inoculation or source of infection is difficult.[3,6]

Clinical Manifestations

Mucormycosis has several clinical presentations. Rhinocerebral and pulmonary infections are by far the most common. Other common clinical manifestations are gastrointestinal, cutaneous, and disseminated infection, which can include central nervous system involvement. Similar to other angioinvasive molds, a characteristic feature of mucormycosis is vascular invasion, which results in thrombosis, infarction, and necrosis of surrounding tissue. Mucormycosis often is characterized by the rapid onset of a necrotic lesion, followed by a fulminant course that requires rapid and aggressive medical and surgical therapy.

Rhinocerebral Infection

Rhinocerebral mucormycosis often begins with a necrotic lesion in the paranasal sinuses that then spreads to involve the orbit, face, palate, and brain. The disease classically occurs in patients with diabetic ketoacidosis, but it also can occur in patients with neutropenia and other immunocompromising conditions. Most commonly, rhinocerebral mucormycosis progresses rapidly and requires extensive surgical debridement combined with antifungal therapy.

Initial symptoms can include nasal or sinus congestion or pain, and epistaxis, along with fever. Black, necrotic lesions on the nasal or palatine mucosa are characteristic diagnostic signs, but the diagnosis often is not established early in infection. Infection can spread into the orbits and the periorbital or perinasal tissues and is associated with induration, necrosis, and edema. Ptosis, proptosis, dilation and fixation of the pupil, and loss of vision can occur. Infection can spread into the cavernous sinus and brain, with resulting abscess formation and necrosis of the frontal lobes.

Studies using computed tomography or magnetic resonance imaging are needed to assess the anatomic extent of suspected infection. The results of cerebrospinal fluid examination are nonspecific and do not assist in diagnosis.

Pulmonary Infection

Pulmonary mucormycosis is most common in severely neutropenic and other severely immunocompromised children, including children undergoing bone marrow or hematopoietic stem cell transplantation, particularly in the setting of graft-versus-host disease.[3,6,20,30] The clinical presentation usually is nonspecific and is similar to that of pneumonia caused by other angioinvasive molds (*Aspergillus*), and it can include pleuritic chest pain, cough, fever, and hemoptysis. The radiologic signs also can be nonspecific but include nodular lesions, cavitation, and a reversed halo sign which is characterized by a nodule with a central ground-glass attenuation encircled by a ring of denser consolidation that can be used to distinguish pulmonary mucormycosis radiologically from invasive pulmonary aspergillosis.[31] The mortality rate is high because of the unsuspected diagnosis in many patients, as well as the persistence of the underlying severe immunosuppression that predisposed the patient to infection.

Gastrointestinal Tract Infection

Mucormycosis of the gastrointestinal tract is rare but occurs in malnourished infants and children. In 1 review, 19 of 34 children with this condition were <1 year of age.[3,32] All segments of the gastrointestinal tract can be involved, but the most commonly affected sites are the stomach, large and small intestine, and esophagus.

Symptoms reflect the site affected but are not specific and include abdominal pain and hematemesis or gastrointestinal tract bleeding. Gastrointestinal mucormycosis can be complicated by perforation, perirenal abscess, and renal infarction. The course of the disease can be rapid, and survival is rare because of severe immunocompromise in the host and the difficulty in making the diagnosis.

Cutaneous Infection

Traumatic implantation of spores from soil can lead to extensive necrotic cutaneous infections.[33–37] Cutaneous mucormycosis has developed at the sites of surgical incisions and infected burn wounds.[2,3] *Rhizopus* spp. and other Mucorales organisms have caused necrotizing cellulitis in premature infants and children with leukemia in whom contaminated biomedical devices or adhesive products were applied to the skin near sites of catheter insertion or wounds.[29,30,35,38–40] Cutaneous infection with the emerging molds *Apophysomyces elegans* and *Saksenaea vasiformis* have been reported increasingly following traumatic inoculation in otherwise immunocompetent people, including children, especially following natural disasters (e.g., tornados) or from combat wounds.[3,36,37] These infections can be difficult to diagnose and identify because of the lack of growth from homogenized tissues and poor sporulation on routine media.[33,41–44] Children with leukemia also can have cutaneous lesions that result from hematogenous dissemination from another site.[3]

Cutaneous lesions typically begin with erythema and edema and progress to raised, indurated lesions with a black, necrotic center. Lesions are painful and are indistinguishable from those caused by *Aspergillus* or other molds, and they can resemble ecthyma gangrenosum. Cutaneous mucormycosis can progress rapidly, requiring extensive surgical debridement as well as optimal antifungal therapy.[2]

Disseminated Infection

Dissemination can follow any primary site of mucormycosis but usually is seen in severely neutropenic children after pulmonary infection.[3] The most frequent and feared site of dissemination is the brain, but metastatic necrotic lesions can occur in any organ. Cutaneous lesions can be an initial site of diagnosis that actually reflects disseminated infection.

Focal cerebral infection usually occurs in children as a result of disseminated infection, but in adults it also can occur as an isolated event in association with injecting drug abuse. The diagnosis of central nervous system mucormycosis is difficult but should be considered in a severely immunocompromised child with systemic mucormycosis who becomes lethargic, confused, or obtunded and is found to have a focal brain lesion on an imaging study.

Diagnosis

Early diagnosis of mucormycosis is essential for successful treatment. Unfortunately, the diagnosis of these infections is difficult because infection often is not suspected early in the course, blood culture results rarely are positive, and cultures of infected tissues are undertaken reluctantly. Non–culture-based methods are not available commercially, although various molecular tests are undergoing evaluation.[2] Agents of mucormycosis usually can be distinguished from other molds (e.g., *Aspergillus*) by their characteristic broad, rarely septate, or aseptate hyphae with right-angled branching. However, in histopathologic samples with only hyphal fragments identified, specific distinction can be difficult. Moreover, homogenization of tissue samples can render culture results for Mucorales negative. In patients suspected of having mucormycosis, communication between the clinician and the microbiologist to inoculate a nonhomogenized sample can increase the diagnostic yield.

Treatment

If treatment of mucormycosis is to be successful, the underlying immunologic or metabolic defects that precipitated the infection must be corrected, infected necrotic tissue must be debrided, and aggressive antifungal therapy must be administered.[2,3] Amphotericin B has consistent activity against Mucorales, but the toxicity of amphotericin B deoxycholate limits the drug's usefulness. Lipid formulations of amphotericin B and introduction of posaconazole, the first extended-spectrum azole with activity against these fungi, may reduce toxicity and improve outcomes of patients with mucormycoses.[45] Adjunctive measures should include surgical excision of infected tissues and discontinuation or reduction in immunosuppressive therapies or iron chelation treatment if possible. Hyperbaric oxygen therapy has been advocated by some investigators, but its efficacy remains unproven.[46–49]

Lipid formulations of amphotericin B (in doses ≥5 mg/kg/day) are less toxic than amphotericin B deoxycholate and are recommended as primary therapy in most patients.[1–3,45,49–53] Posaconazole has been shown to have activity in salvage therapy of mucormycosis and offers the advantage of longterm oral therapy, although previous oral solution formulations have very limited bioavailability.[54,55] Newer extended-release tablets are approved by the Food and Drug

Administration (FDA) for children >13 years of age at doses of 300 mg/day following a 1-day 300-mg loading dose for 2 doses, as indicated in adults.[56] An intravenous formulation has also been developed, although its safety and efficacy in pediatric patients have not been established. Additionally, isavuconazole, an extended-spectrum triazole with activity against many agents of mucormycosis as well as aspergillosis, has been released and is FDA approved for used in this infection in adults, although very limited evaluation has occurred in children.[57]

The duration of therapy depends on the clinical response, the extent of surgical excision, and the persistence of the underlying immunosuppression. Longterm oral therapy with posaconazole has been associated with a good response.[54,55]

The mortality rate of mucormycosis among patients with cancer remains high, despite faster diagnosis and aggressive surgical and antifungal treatment.[1,3,31,58] Although rates of successful salvage therapy with either posaconazole or liposomal amphotericin B are as high as 80%, the selection of patients to receive these agents likely influences these reported favorable response rates.[52,54,55] Better responses also occur in patients with infection that is surgically excised or debrided (e.g., isolated renal, cerebral, or cutaneous infection).

Prevention

Preventive measures should focus on reducing underlying risk factors that lead to the development of mucormycosis. These preventive measures include control of diabetes mellitus, the use of iron chelating agents other than deferoxamine, and limiting the use of aluminum-containing buffers in dialysis.[2,6,15] Limiting exposure of severely immunosuppressed patients to soil and plants, as well as the use of laminar air filtration and limitation of exposure to hospital construction, have been recommended to reduce the occurrence of aerosolization of molds, which include Mucorales.[59] The use of nonsterile items (which often become contaminated with environmental molds) on skin and mucous membranes in low birth weight infants and other immunocompromised patients should be avoided or initiated with caution.[30,39,60] In addition, reports of mucormycosis in patients receiving longterm prophylactic therapy with voriconazole raise concerns about the extended use of this drug in high-risk patients.[61] Although prophylaxis studies with posaconazole were not powered to show reduction in mucormycosis, consideration of posaconazole prophylaxis as a means of reducing mucormycosis and other mold infections in high-risk patients may be reasonable.[62,63]

Key Points

Diagnosis and Management of Mucormycosis

Microbiology

- Agents of mucormycosis: broad, aseptate, or rarely septate ribbon-like hyphae with right-angle branching
- Organisms now classified in the phylum Glomeromycota (which has replaced Zygomycota), subphylum Mucoromycotina; predominately in the order Mucorales so that mucormycosis is useful clinically and mycologically
- Order Mucorales with 6 families contains most agents of human disease. Taxonomic revisions reflect phylogenetic, phenotypic, and physiologic differences in strains including the reclassification of the family Absidiaceae to Lichtheimiaceae for pathogenic species that are able to survive at ≥37°C.
- Family Mucoraceae members (*Rhizopus, Mucor, Actinomucor, Rhizomucor,* and *Apophysomyces*) all implicated in human disease. Species in other families (*Cunninghamella, Saksenaea, Syncephalastrum, Cokermyces,* and *Lichtheimia*) less frequently reported in human disease

Epidemiology

- Spores of Mucorales are ubiquitous in the environment but usually cause infection only with predisposing host risk factors.
- Risk factors for infection include neutropenia, diabetes mellitus, ketoacidosis, iron overload, iron chelation, severe malnutrition, transplantation, corticosteroids, antifungal drugs without activity against agents of mucormycosis, burns, contaminated traumatic

wounds, and intravenous catheters.

Clinical INFECTIONS

- Cutaneous: associated with intravenous catheters and wound dressings; burns; traumatic implantation into normal children, especially with *Apophysomyces elegans* and *Saksenaea vasiformis*

- Pulmonary: usually in severely neutropenic children; nonspecific presentation following inhalation of organism including productive cough, fever, shortness of breath, hemoptysis; nonspecific infiltrates including reversed halo sign, which can help distinguish from invasive pulmonary aspergillosis

- Gastrointestinal: rare but occurs in malnourished infants and children; can affect any area of gastrointestinal tract with symptoms including perforation and abscess

- Rhinocerebral: classically associated with diabetic ketoacidosis, but occurs with prolonged neutropenia and immunocompromise; requires aggressive medical or surgical treatment

- Disseminated: in severely immunosuppressed children with prolonged neutropenia and in solid-organ or stem cell transplantation; high mortality rates, especially with central nervous system involvement

Diagnosis

- Recovery of organism from body fluids, tissue; no commercial non–culture-based methods; polymerase chain reaction methods in development

- Microscopic examination of pathologic material: broad, ribbon-like hyphae with few or no septations

- Cultures of nonhomogenized tissue can increase yield.

Treatment

- Polyenes (lipid formulations of amphotericin B) the drugs of choice; activity of posaconazole demonstrated in salvage trials and for longterm therapy; isavuconazole approved by the Food and Drug Administration but not studied in children

- Adjunctive therapy: echinocandins (can increase host responses, especially in combination therapy), hyperbaric oxygen, immune modulation, white blood cell infusion (all anecdotal)

- Preventive therapy: posaconazole presumed to have activity but not completely protective

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Malassezia Species

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Microbiology

Malassezia (formerly called *Pityrosporum*)[1] is a genus of lipophilic, basidiomycetous yeasts lacking ballistospores and classified in the order Malasseziales. Its phylogenetic placement within the Ustilaginomycotina (Basidiomycota) appears to be highly supported[2–5]; however, Hibbert's recent taxonomic treatment placing the order in the Ustilaginomycotina *incertae sedis* highlights its still somewhat unresolved phylogenetic placement.[6] *Malassezia* increasingly is recognized as an opportunist affecting both humans and animals.[7,8] Newer identification methods have made the characterization of several new species possible and also have enhanced our understanding of the ecology and clinical associations of the genus.[9] The genus is responsible for various superficial skin infections of humans, including pityriasis (tinea) versicolor (PV),[7,10,11] and *Malassezia* folliculitis (MF).[11] The association of *Malassezia* with seborrheic eczema/dermatitis also has been reconfirmed, although the implication of the immune system in this disease is critical.[7,12,13] Less commonly, members of the genus cause invasive disease in premature infants and other immunocompromised and debilitated individuals.[1] *Malassezia* species also have been implicated in atopic dermatitis, confluent and reticulate papillomatosis,[11] and neonatal cephalic pustulosis.[7,14,15] Various species of *Malassezia* form part of the normal microbial flora of the skin of humans and other warm-blooded animals, and most infections are endogenous in origin.

Until the 1990s only three *Malassezia* species were recognized: two lipid-dependent species, *M. furfur* and *M. sympodialis,* and one nonobligate lipophile, *M. pachydermatis.* After genomic and ribosomal sequence comparisons of a large number of human and animal isolates, the genus *Malassezia* was enlarged to seven species, consisting of the three former taxa (*M. furfur, M. pachydermatis,* and *M. sympodialis*) and four new taxa (*M. globosa, M. obtusa, M. restricta,* and *M. slooffiae*).[16] More recently, six new species have been described and reported: *M. dermatis,*[17] *M. japonica,*[18] *M. nana,*[19] *M. yamatoensis,*[20] *M. caprae,*[21] and *M. equina*[21,22], and *M. cuniculi*.[7] With the exception of *M. pachydermatis,* 13 of the 14 *Malassezia* species are lipid dependent. Their isolation in culture requires the use of a lipid-enriched culture medium. If a conventional medium is used (e.g., Sabouraud dextrose agar), the surface must be covered with a thin layer of sterile olive oil; however, this method yields recovery only of *M. furfur, M. pachydermatis,* and *M. yamatoensis*. Other selective media useful for a wider range of species include Dixon, modified Dixon, and Leeming and Notman agars.[23] *M. pachydermatis, which most commonly is not lipid dependent,* usually can be isolated on Sabouraud dextrose agar. The incubation temperature also is an important consideration because for many cutaneous species, the optimum growth temperature is 32°C to 34°C, rather than 37°C. Methods have been developed to separate the species of *Malassezia* on the basis of morphologic and physiologic differences; however, these are somewhat cumbersome, and species identification can be difficult. Commonly used physiologic tests include urease, catalase, and β-glucosidase activities, growth at 37°C and 40°C, and evaluation of growth in four water-soluble lipid supplements (Tweens 20, 40, 60, 80) and in Cremophor EL (castor oil) using a diffusion method in Sabouraud glucose agar.[24–27] The dependence on lipid precludes the use of conventional assimilation tests.

Molecular methods used to detect and characterize *Malassezia* species in humans and animals include biotyping using enzymatic methods, pulsed-field gel electrophoresis (PFGE), random amplification of polymorphic DNA (RAPD), DNA sequence analysis, restriction analysis of polymerase chain reaction (PCR) amplicon of ribosomal sequences, amplified fragment length polymorphism (AFLP), denaturing gradient gel electrophoresis

(DGGE), and terminal fragment length polymorphism (tFLP). These methods have confirmed the robustness of the new classification of *Malassezia* species, all species having their own characteristic karyotype.[28–31] DNA-based culture-independent methods, such as quantitative real-time PCR methods, can detect as few as 10 copies of *Malassezia* DNA and currently are the most reliable methods for detecting *Malassezia*.[31]

Although 14 species of *Malassezia* thus far have been recovered from humans and animals,[5] they do not appear to have equal clinical importance. Although many clinicians previously have considered all clinical isolates to be *M. furfur*, this assumption is no longer valid because the host, sources of infection, and routes of transmission vary by species.

Epidemiology

Malassezia species form part of the normal cutaneous flora of humans and other warm-blooded animals. The prevalence of skin colonization depends on age, anatomic site and, to a lesser extent, race. Cutaneous *Malassezia* is found immediately after birth. In a British study of skin swabs from 245 neonates, 31% were positive for *Malassezia*[32]; in 195 neonates from Iran, 68% tested positive, with a distribution of *M. furfur* and *M. globosa* of 60% and 7%, respectively.[33]

The incidence of skin colonization with *Malassezia* species increases with age, rising from about 25% in children to almost 100% in adolescents and adults.[34,35] The density of colonization in postpubertal people is greater in anatomic sites that contain pilosebaceous glands; *Malassezia* species have been isolated from 100% of samples taken from the back of adults, but from only 75% taken from the face and scalp. Studies have shown that the degree of colonization with *Malassezia* species is closely aligned with age-related changes in sebaceous gland activity,[34,36] and increased fatty acid concentration occurs primarily at puberty. PV is worldwide in distribution but most prevalent in hot, humid, tropical and subtropical climates, where 30% to 40% of the adult population can be affected.[8] In temperate climates the disease affects 1% to 4% of adults and is most common during the hot summer months. *Malassezia* folliculitis also is more prevalent in tropical countries and more common during the summer months in temperate regions.[8]

The precise conditions that lead to the development of PV and other forms of superficial *Malassezia* infection have not been defined, but host-specific adaptations are important factors because the transition from commensal to pathogenic states appears to be a continuum rather than a discrete entity.[7,37] The lesions of PV and seborrheic dermatitis have a predilection for anatomic sites that are well supplied with sebaceous glands, and patients with the latter condition have been shown to have higher concentrations of lipids on their skin than other individuals.[8] Instances in which members of the same family who are not cohabiting have demonstrated PV suggest a genetic predisposition. The higher incidence of *Malassezia* folliculitis and seborrheic dermatitis in people with immunosuppressive disorders, including AIDS, and in patients undergoing corticosteroid or other immunosuppressive treatment suggests that the relationship between *Malassezia* species and the immune system is important.

Exposure to lipid-rich intravenous infusions through a central venous catheter is the single most important risk factor for systemic *Malassezia* infection in both adults and infants.[38–46] Among neonates, other risk factors include low birth weight (LBW), early gestational age, and length of hospitalization. An investigation of one outbreak of *M. furfur* infection among LBW infants, most of whom received intravenous lipids, identified long duration of antimicrobial treatment as an additional risk factor for disease.[42]

Human-to-human transmission of *Malassezia* species is possible, either through direct contact or via contaminated clothing or bedding. In practice, however, cutaneous infection is endogenous in most cases, and spread from person to person is uncommon. No cases of occupational infection among healthcare personnel (HCP) have been reported.

Although most infections appear to be sporadic, healthcare-associated (HA) outbreaks of systemic *Malassezia* infection have been reported since the late 1980s in LBW infants and debilitated adults and children who were receiving parenteral lipid nutrition through indwelling vascular catheters.[40–44] An investigation of one outbreak of *M. furfur* infection among LBW infants provided evidence that the organism can be transmitted from an infected or a colonized infant to other infants by the hands of HCP.[42] HA outbreaks of *M. pachydermatis* infection also have been reported.[22–24] In one outbreak, patient-to-patient transmission of the organism was documented in a neonatal intensive care unit (NICU), but the source of the outbreak was not identified.[45] In another outbreak involving 15 infants in a NICU, *M. pachydermatis* was introduced into the unit on the hands of HCP who were colonized from pet dogs at home.[46] The organism persisted in the unit through patient-to-patient transmission.

Clinical Manifestations

Superficial Skin Disorders

Pityriasis Versicolor

A disfiguring but otherwise harmless condition, PV most commonly affects the trunk, neck, and upper portions of the arms. Although commonly ascribed to *M. furfur* under the old taxonomic classification, molecular studies have shown that most cases in northern countries are attributed to *M. globosa,* which is present in the yeast state on healthy adult skin but produces clinical lesions of PV after developing into the pseudohyphal state.[11] In tropical and subtropical climates, lesions more often are localized on the face and attributed to *M. furfur*. The characteristic lesions consist of patches of fine brown scaling that may become confluent and progress to cover large areas of the skin of the trunk and proximal extremities. Pruritus, which occurs in less than one third of adolescents and adults with PV, can be a prominent feature in young children. The disease is exacerbated by sunlight and sweating. Occasionally the rash has an inflammatory component, manifesting as erythema and fine vesicles. In light-skinned people, lesions are hyperpigmented and range in color from red to brown. In dark-skinned or tanned people, the lesions are hypopigmented and white. In contrast to adults, who seldom have facial involvement, prepubescent children with PV often have hypopigmented nummular lesions with fine scaling on the face.

In most cases the diagnosis of PV is made clinically. Hyperpigmented lesions must be distinguished from a number of conditions, including erythrasma, nevi, seborrheic dermatitis, and tinea corporis. Hypopigmented lesions can be confused with pityriasis alba and vitiligo. Wood light examination can be useful if the diagnosis is uncertain. On exposure to ultraviolet light, infected skin, particularly the scaly borders of the most recent lesions, emit a pale yellow fluorescence. If the diagnosis is in question, material for direct microscopic examination can be obtained by taking scrapings from the affected skin or by gently pressing transparent tape to the skin and then removing and examining the tape.

Malassezia Folliculitis

MF is a chronic disorder that primarily affects adults with a chronic debilitating disease and immunosuppressed people.[11,47] A minor outbreak of 11 cases of MF over 4 months was reported in an intensive care unit among cardiac transplant recipients.[48] MF also is seen quite often in people with AIDS. Little information is available about MF in infants and children. The typical lesions are small, erythematous, follicular papules that slowly enlarge and often become pustular. The condition often is associated with troublesome pruritus. Lesions occur on the back, chest, upper arms, and sometimes the neck, but seldom on the face. Pruritus and lack of comedones differentiate the condition from acne vulgaris. However, the two diseases often coexist, with nonitching acne lesions on the face and itching lesions of MF on the trunk and upper arms. It is sometimes necessary to perform a skin biopsy to make a definitive diagnosis. As with PV, *M. globosa* appears to be the predominant causative agent.[11]

Seborrheic Eczema/Dermatitis

The role of *Malassezia* species in seborrheic eczema (SE) or seborrheic dermatitis (SD) has previously been questioned; however, recent studies have reaffirmed its association.[12,49,50]

The clinical forms of seborrheic dermatitis include infantile seborrheic eczema on the scalp and trunk, and adult seborrheic eczema with an erythematous rash with scaling on the scalp, face, ears, chest, and upper part of the back. Dandruff is the mildest manifestation of the disease. Scaling of the eyelid margins and around the nasolabial folds is a common presentation. Itching is common on the scalp. The course of the disease is chronic, with regular flare-ups. In temperate climates the disease often improves during the summer months. The most common species associated with SE/SD include *M. globosa* and *M. restricta,* followed by *M. sympodialis, M. furfur,* and *M. slooffiae.*[26,51]

Systemic Infections

Systemic *Malassezia* infection has become a well-recognized complication of lipid-supplemented parenteral alimentation, and most cases occur in LBW infants younger than 1 month. Life-threatening systemic *Malassezia* infections have also been reported in older children and adults, all of whom received lipid emulsions through indwelling central venous catheters for periods ranging from a few days to many months. Predisposing diseases in this setting include Crohn disease, continuous ambulatory peritoneal dialysis, other chronic illnesses, invasive procedures, intensive care, and long-term antibiotic administration. Reported systemic infections range from localized organ infections to fulminant fungemia and death.

In infants, *Malassezia* fungemia can manifest with fever, apnea, or both, and bradycardia; interstitial pneumonia and thrombocytopenia are common. The most common symptoms of systemic infection are fever and respiratory distress with or without apnea. Less common symptoms and signs are poor feeding and hepatosplenomegaly. No signs of infection have been noted at catheter insertion sites, nor has rash been seen in infants with systemic *Malassezia* infection.

Predominant pathologic changes in patients with systemic *Malassezia* infection involve the heart and lungs and include mycotic thrombi around the tips of indwelling catheters, vegetations on the endocardium, vasculitis, and inflammation of alveoli, bronchi, and bronchioles. Predominant organisms in invasive disease include *M. furfur* and *M. pachydermatis.*

Diagnosis

Superficial Infections

Direct microscopic examination of scrapings from lesions usually is sufficient to permit the diagnosis of PV if clusters of round or oval budding yeast cells and short, seldom-branching pseudohyphae are seen. Because *Malassezia* species are part of the normal cutaneous flora, their isolation in culture must be correlated with clinical findings. Additionally, with the exception of most strains of *M. pachydermatis*, these organisms cannot be isolated on routine mycologic media unless lipid is added. In MF, microscopic examination of biopsy specimens reveals inflammatory cell infiltration of the pilosebaceous apparatus, keratin plugging, and round, budding yeast cells in the dilated hair follicles.

DNA-based, culture-independent molecular methods (e.g., quantitative real-time PCR methods) are the most reliable for detecting *Malassezia* in skin samples.[31] Isolates from nosocomial outbreaks can be analyzed by molecular tools to confirm strain identity.[38,39]

Systemic Infections

The diagnosis of *Malassezia* septicemia should be considered in any febrile patient (particularly with clinical and radiologic evidence of pneumonia) receiving lipid-containing alimentation through a central venous catheter, especially if the results of routine blood cultures are sterile. If the catheter can be removed, the tip of the catheter should be inoculated onto Sabouraud dextrose agar overlaid with olive oil or another medium supplemented with long-chain lipids. When catheter removal is not feasible, blood for culture is obtained through it. The lipid concentration of conventional broth and agar media usually is insufficient to support the growth of *Malassezia* species (with the exception of *M. pachydermatis*), but it would appear that the blood of patients receiving parenteral alimentation often contains sufficient lipids to support initial growth of these organisms in culture. Although the yield is low, microscopic examination of Giemsa-stained smears of blood obtained through the catheter may be helpful.

Treatment

Skin Infections

In most patients, PV responds to topical treatment, but more than 50% experience relapse within 12 months. Selenium sulfide lotion (2.5%) should be applied to the lesions for 15 to 30 minutes nightly for 1 to 2 weeks and then once monthly to prevent recurrences. Ketoconazole shampoo is applied for 3 to 5 minutes once daily for 5 days. For extensive involvement in adolescents, or in infections unresponsive to topical therapy, both itraconazole (200 mg once daily for 1 week) and ketoconazole (200 mg once daily for 1 week) are effective oral treatments, although oral ketoconazole cannot be recommended because of its greater potential for severe toxicity.

Treatment with a topical imidazole or selenium sulfide often is effective in MF, but oral treatment with ketoconazole (in doses of 200 mg/day for 1 to 2 weeks) may be required in patients with extensive or recalcitrant lesions. To prevent recurrence, maintenance treatment should be given once or twice a week. Ketoconazole shampoo, used twice a week for 2 to 4 weeks, is an effective treatment for seborrheic dermatitis and dandruff of the scalp. Thereafter, it should be used at 1- or 2-week intervals to prevent recurrence. Oral azole therapy for 1 to 2 weeks should be reserved for cases that do not respond to topical treatment. Ciclopirox olamine 1% shampoo also appears to be a safe agent for treatment of scalp SD.[52]

Systemic Infections

The most important factor in successful management of *Malassezia* fungemia in preterm infants and in older children is prompt removal of the colonized vascular catheter. Lipid supplements should be discontinued in almost all patients, and an antifungal azole agent, such as parenteral fluconazole (in doses of 5 mg/kg/day) or amphotericin B, should be administered to those with more serious infection.[38] The extended spectrum azoles, voriconazole and posaconazole, have in vitro activity, but clinical data on their efficacy are extremely limited. No data support the activity of echinocandins against these basidiomycetous yeasts. Oral fluconazole or itraconazole may be adequate therapy for less ill patients. The duration of therapy depends on persistence of the fungemia, the presence of metastatic foci of infection, and removal of the catheter. In vitro antifungal susceptibility testing of *Malassezia* species is unstandardized because of its dependency on lipid for growth; however, several methods have been published.[38,53–55] These methods, which test a variety of species (*M. furfur, M. dermatis, M. globosa, M. obtuse, M. restricta, M. slooffiae, M. sympodialis,* and *M. pachydermatis)* against several antifungal agents (amphotericin B, itraconazole, ketoconazole, fluconazole, voriconazole, posaconazole, and terbinafine), demonstrate species-dependent in vitro data, reporting higher minimal inhibitory concentrations (MICs) for fluconazole for some *M. pachydermatis* isolates.

Key Points

Diagnosis and Management of *Malassezia* Infections

Microbiology

- Lipophilic, basidiomycetous yeasts in the order Malasseziales
- Genus includes 14 species, 13 of which require lipid-enriched culture medium for growth.
- *M. pachydermatis* is not lipid dependent.

Epidemiology

- *Malassezia* is part of the normal flora of humans and warm-blooded animals.
- Skin colonization begins at birth, increases to 25% in children, and reaches almost 100% in adults.
- Degree of colonization is related to sebaceous gland activity at puberty.
- Lipid-rich intravenous infusions are an important risk factor for systemic disease.
- Most infections are sporadic, although nosocomial systemic outbreaks have been reported.

Clinical Features

- Superficial skin disorders

  - Pityriasis versicolor: commonly affects trunk, neck, upper arms; lesions are hyperpigmented in light-skinned people and hypopigmented in dark-skinned people.

  - *Malassezia* folliculitis: primarily affects adults with debilitating disease; lesions are small, erythematous, follicular papules that often enlarge and become pustular.

  - Seborrheic eczema/dermatitis: clinical forms include infantile and adult seborrheic eczema; dandruff is the mildest manifestation.

- Systemic infections: severity ranges from localized organ infection to fulminant fungemia.

Diagnosis

- Superficial infections – direct microscopic examination of lesions, culture with special media and/or lipid overlay, molecular methods, including matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) mass spectrometry analysis

- Systemic infections – cultures of central venous catheter and blood (require lipid supplementation and may require long incubation times [up to 2 weeks]), and molecular methods

Treatment

- Skin infections

  - Pityriasis versicolor: topical selenium sulfide lotion 2.5% or oral azole

  - *Malassezia* folliculitis: topical imidazole or selenium sulfide; oral azole may be required; maintenance treatment may be required to prevent recurrence.

- Seborrheic dermatitis: ketoconazole shampoo or ciclopirox olamine 1% shampoo usually is effective; oral azole for recalcitrant infections.

- Systemic infections

- Remove vascular catheter promptly in preterm infants with fungemia; discontinue lipid supplements; fluconazole is the preferred antifungal, and amphotericin B is reserved for more severe disease.

- In vitro activity of various antifungal agents is species dependent; higher minimal inhibitory concentrations (MICs) for fluconazole for *M. pachydermatis*.

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Sporothrix schenckii Complex (Sporotrichosis)

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Sporotrichosis is a chronic subcutaneous fungal infection caused by thermally dimorphic fungal species in the *Sporothrix schenckii* complex. This species complex is found worldwide in soil, on decomposing vegetation, and on plant material, such as sphagnum moss, hay bales, rosebushes, and wood. In nature, *S. schenckii* grows as a filamentous mold, but in tissue it forms small budding yeast cells. Sporotrichosis has a worldwide distribution but is most common in warm, temperate, or tropical regions where the temperature ranges between 16°C and 22°C.

Phylogenetic, phenotypic, and physiologic differences have been identified among strains previously referred to as *Sporothrix schenckii;* therefore, isolates now are reported as members of the *S. schenckii* complex.[1,2] In addition to *S. schenckii,* other distinct species in the complex include *S. mexicana, S. globosa, S. luriei, S. albicans, S. inflata,* and *S. brasiliensis.*[1,2,3] The typical rosettes produced by these species are mostly indistinguishable; however, the sessile conidia display varying morphologies. *S. luriei* lacks sessile conidia and has a thick-walled budding yeast form.[3] Calmodulin gene sequences are the most informative for species identification.[3] Varied in vitro susceptibility may be responsible for varying clinical responses.[4]

Epidemiology

Cutaneous infection, the most common manifestation in children and adults, usually follows traumatic implantation of *S. schenckii.*[5] Minor trauma from thorns or wood splinters is a typical route of exposure. Lesions usually appear 1 to 4 weeks after inoculation. Pulmonary disease is less common but is acquired by inhalation. Animal-to-human transmission, usually from cats with lesions, can occur but is not common, although large outbreaks associated with cats have occurred; transmission from other animals, including armadillos, also has been reported.[6–8]

Infection with *S. schenckii* complex occurs in all age groups, independent of race and gender, although some studies report a male predominance, possibly because of a higher number of exposures. Infections often are sporadic, occurring after outdoor exposures, although common-source outbreaks are described and can be traced to activities that result in contact with contaminated moss, hay, or wood.[9–12] Ongoing zoonotic transmission from cats has been associated with epidemics of sporotrichosis in Brazil, Malaysia, and other regions.[7,8,13–15] Investigation of outbreaks has led to insights into the epidemiology of sporotrichosis in the epidemic setting, but less information is available about the disease in areas where sporotrichosis is hyperendemic.[16] Pappas and colleagues described 238 cases that occurred in a remote region of the central highlands of Peru.[16] The incidence of disease ranged from 48 to 60 cases per 100,000 population and was highest among children 7 to 14 years of age, approaching 1 case per 1000. This report indicates that sporotrichosis in children is more common than is recognized, particularly in economically developing countries. Risk factors for sporotrichosis among children living in Peru included increased skin trauma (e.g., living in homes with dirt floors) and having contact with cats.

Clinical Manifestations

Most cases of sporotrichosis are localized to skin and lymphatic tissues. In contrast to sporotrichosis in adults, which can occur at any anatomic site, in children the disease most commonly affects the face and limbs, particularly the hands and fingers.[16–18]

Pulmonary and extrapulmonary infection occurs, including in joints, bones, the central nervous system, and other tissues, but it is less common. Systemic infection is more likely to occur in patients with altered host defenses, including people with diabetes, alcoholism, injection drug use, and other immunocompromising conditions, including those with AIDS. Systemic forms of sporotrichosis are rare in children.[16]

After inoculation the fungus replicates at the site of infection and then invades the regional lymphatics. In 25% of cases, infection remains confined to the initial site of inoculation, as it commonly does in facial lesions. Such “fixed” infections are more common in children than in adults.[5,19] Cutaneous sporotrichosis develops as a small, firm, painless papule or vesicle that initially is mobile but later becomes fixed. The lesion slowly enlarges over several weeks, and the skin and subcutaneous tissues surrounding the lesion become indurated and red. Within 10 days to 2 weeks after the appearance of the lesion, skin necrosis occurs, leaving a minimally painful superficial ulcer with irregular borders. In most cases the infection spreads to the regional lymph nodes that drain the site of the primary infection. The resulting ascending chain of nontender, mobile, subcutaneous nodules with overlying erythematous skin is the classic manifestation of sporotrichosis. Left untreated, the nodules enlarge slowly, soften, and can evolve into draining ulcers, even though the involved skin may not be painful (see Fig. 20.4).

In disseminated cutaneous sporotrichosis (which occurs in <1% of patients), numerous small papules or vesicles progress to necrotic, ulcerated nodules over the trunk and limbs. This form generally follows lymphatic or hematogenous spread from an initial cutaneous or pulmonary site of infection, but it also can be due to multiple cutaneous inoculations. The diagnosis of cutaneous or lymphocutaneous sporotrichosis should be suspected in any patient with papulovesicular or ulcerative lesions of the skin that are unresponsive to antibacterial treatment. Sporotrichosis should be suspected with the triad of painless skin ulcer, nodules along ascending lymphatics, and lack of response to antibacterial treatment. Other infectious etiologies that should be considered, in the appropriate epidemiologic setting, include blastomycosis, chromoblastomycosis, paracoccidioidomycosis, and leishmaniasis. “Fixed” cutaneous infections without lymphangitic spread are difficult to differentiate clinically from actinomycosis, nocardiosis, and nontuberculous mycobacterial disease.

Pulmonary sporotrichosis usually manifests as subacute or chronic pneumonia, which can be indistinguishable clinically from other chronic pulmonary infections. The symptoms, which are nonspecific, include a productive cough, fever, weight loss, anorexia, shortness of breath, and hemoptysis, which can be massive. Radiographic findings are nonspecific and can mimic tuberculosis parenchymal lesions, usually involving the upper lobes, which can cavitate. Hilar adenopathy and pleural involvement can occur. Disseminated sporotrichosis, which is uncommon in children, generally develops after lymphatic or hematogenous spread from an initial cutaneous infection or after pulmonary infection.[5] Skeletal involvement has been reported in up to 80% of patients with extracutaneous disease. A chronic destructive arthritis of the knee and other large weight-bearing joints is the most typical presentation, although the small joints of the hand and wrist can be involved. Meningitis is a rare but severe manifestation of disseminated sporotrichosis.

Diagnosis

Laboratory diagnosis of sporotrichosis can be difficult and depends on direct microscopy and culture of pathologic material. The results of direct microscopic examination can be negative because of the paucity of organisms in clinical samples (e.g., skin scrapings or exudates). Detection of the typical oval or cigar-shaped cells or asteroid bodies of *S. schenckii* complex in stained histologic sections confirms the diagnosis. Immunofluorescence is a sensitive and specific method but is not widely available for clinical use; molecular diagnostics methods also are undergoing evaluation.[20]

The diagnosis of sporotrichosis depends on isolation of the organism in culture from a specimen of soft tissue exudate or tissue biopsy. With visceral organ or osteoarticular infection, the yield is increased with cultures of tissue, rather than sputum, synovial, or other body fluids. Cultures incubated at room temperature usually are positive within a week.

Serology has not proved to be useful for the diagnosis of sporotrichosis, and tests that are not based on culture are not available.

Treatment

Guidelines for the treatment of sporotrichosis have been published.[21] Lymphocutaneous sporotrichosis uncommonly resolves without treatment.[13] Permanent scarring and disfigurement are common, as is bacterial superinfection. Oral itraconazole (in doses of 6 to 10 mg/kg/day, maximum 400 mg/day) is recommended for children with cutaneous or lymphocutaneous sporotrichosis, although lower doses (100 mg/day) also have been effective.[21,22] Therapy should be continued for 2 to 4 weeks after the lesions have resolved. In most patients, therapy is required for 3 to 6 months and is successful in more than 90%.[21,23] Fluconazole is less effective and should be regarded as a second-line agent for children who cannot tolerate other therapies or who do not absorb itraconazole.[21,24] Ketoconazole has less efficacy and more toxicity and should not be used. Data on the use of posaconazole or voriconazole for sporotrichosis are limited, but *Sporothrix* species frequently are resistant in vitro to voriconazole, which should not be used.[4,25] Oral terbinafine (up to 500 mg twice daily) has been effective for lymphocutaneous disease in small clinical studies in adults, but data in children are very limited.[26,27] Saturated solution of potassium iodide (SSKI) is the least costly option for lymphocutaneous infection and can be administered to children, but SSKI is associated with many side effects and thus is poorly tolerated by children and adults. Dose-limiting side effects include a strong metallic taste, gastrointestinal tract intolerance, salivary gland swelling, rash, and fever.[28] In children a dose of 50 mg or 1 drop 3 times daily in water or juice is given initially and increased as tolerated by 1 drop per dose per day (maximum of 1 drop/kg or 40 to 50 drops 3 times daily, whichever is *lower*).[21,29] Local application of heat, using a variety of warming devices or baths, has been reported as an effective alternative treatment for fixed cutaneous lesions but should be reserved for patients in whom antifungal drugs are contraindicated or not tolerated.[30]

For patients with life-threatening systemic or pulmonary sporotrichosis, amphotericin B (0.7 to 1 mg/kg/day) or liposomal amphotericin B (3 to 5 mg/kg/day) is recommended.[21] Itraconazole can be used for less seriously ill patients and as oral sequential therapy after an initial response to therapy with amphotericin B. Surgical resection, when possible, combined with antifungal therapy may improve outcome. Osteoarticular sporotrichosis usually is treated with itraconazole, which should be continued for 1 to 2 years.[21] Unfortunately, joint function uncommonly returns to normal. SSKI and terbinafine should not be used for osteoarticular sporotrichosis.[21]

Prevention

Sporotrichosis can be prevented by reducing skin trauma in high-risk settings (e.g., working with hay bales, moss, plants, rosebushes, and trees) by wearing protective clothing (e.g., long sleeves and gloves); by limiting animal exposures in specific epidemiologic settings (e.g., epidemic transmission from cats); or by avoiding exposure completely.[7,10,16]

Key Points

Diagnosis and Management of Sporotrichosis

Microbiology

- Thermally dimorphic fungus: grows as a mold in nature, with small budding yeast cells in tissue; grows within a week on routine microbiologic media

- Isolated in soil, decomposing vegetation: sphagnum moss, hay, rosebushes, wood

- Currently referred to as *Sporothrix schenckii* complex because of phylogenetic, phenotypic, and physiologic differences in strains; additional distinct species include *S. mexicana, S. globosa, S. luriei,* and *S. brasiliensis*

Epidemiology

- Occurs worldwide, most commonly as a cutaneous or lymphocutaneous infection

- Typically associated with minor trauma from thorns or wood splinters

- Zoonotic transmission: uncommon, usually from cats (which has led to current epidemic in Brazil and other regions globally); other animals (e.g., armadillos) also have been implicated

Clinical INFECTIONS

- Cutaneous or lymphocutaneous: especially common in children, including on the face and eyelids, perhaps as a result of autoinoculation

- Fixed lesion: painless papule with erythema and induration

- Lymphocutaneous lesion (more common): superficial ulcer with ascending lymphangitic chain of nontender, mobile, subcutaneous nodules or ulcers over erythematous skin

- Pulmonary infection: subacute or chronic pneumonia after inhalation of organism; nonspecific presentation, including productive cough, fever, weight loss, shortness of breath, and hemoptysis; nonspecific parenchymal infiltrates

- Disseminated infection: uncommon, especially in children; can involve bone and central nervous system

Diagnosis

- Recovery of organism in culture from body fluids or tissue specimens

- Microscopic examination of pathologic material can show oval or cigar-shaped cells or asteroid bodies.

- Immunofluorescent tissue stain is sensitive and specific but may not be available widely; molecular tools are in development.

Treatment

- Lymphocutaneous or cutaneous infection: itraconazole is the preferred therapy, usually for 3 to 6 months.

- Life-threatening disseminated or pulmonary infection: amphotericin B or liposomal amphotericin B, followed by itraconazole

- Osteoarticular or extrapulmonary infection: extended course of itraconazole

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Cryptococcus Species

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Most human cryptococcal infections are caused by one of two species, *Cryptococcus neoformans* or *C. gattii*.[1,2] These species previously were divided into three entities, *C. neoformans* var. *neoformans*, *C. neoformans* var. *grubii*, and *C. neoformans* var. *gattii*, which were classified into eight molecular genotypes and five serotypes based on capsular polysaccharide antigens. Serotypes A and D and the hybrid diploid AD strains belong to *C. neoformans;* serotypes B and C strains are classified as *C. gattii* (Table 249.1). Currently serotype A strains are designated *C. neoformans* var. *grubii*, and serotype D strains are designated *C. neoformans* var. *neoformans*, although these may soon be given species designation.[3–6] *C. neoformans* var. *grubii* has a worldwide distribution and is the most common causative agent of cryptococcosis in people with acquired immunodeficiency syndrome (AIDS) and other immunocompromised people, accounting for more than 95% of cases of cryptococcal infection.[4,7] In contrast, *C. gattii* usually affects immunocompetent people living in the tropics and subtropics. It has been associated with eucalyptus trees, which were considered its major environmental niche. As reported in 2004, *C. gattii* caused a substantial outbreak of cryptococcal infections on Vancouver Island, British Columbia, expanding its geographic boundaries and demonstrating its association with other trees as well.[8]

TABLE 249.1

Characteristics of the Genus *Cryptococcus*

	***Cryptococcus* Species**		
Characteristic	***Cryptococcus neoformans***		*Cryptococcus gattii*
Varieties	*grubii*	*neoformans*	—
Serotypes	A[a]	D[a]	B, C[b]
Genotypes (VN system)	VNI (AFLP1), VNII (AFLP1A)	VNIV (AFLP2)	VGI (AFLP4), VGII (AFLP6), VGIII (AFLP5), and VGIV (AFLP7)
Sexual state	*Filobasidiella neoformans*	*Filobasidiella neoformans*	*Filobasidiella bacillispora*
Geographic distribution	Worldwide (95% of cryptococcal cases)	Northern Europe	Tropics and subtropics; recent outbreak on Vancouver Island
Natural sources	Avian guano	Avian guano	Eucalyptus trees; other trees
Isolation from AIDS patients	Common	Common	Uncommon

[a] Hybrid diploid AD serotype comprises VNIII (AFLP3).

[b] *C. gattii* serotypes B and C can be any of the *C. gattii* mole ulcer types.

AIDS, acquired immunodeficiency syndrome; AFLP, amplified fragment-length polymorphism analysis.

Several factors contribute to the virulence of *C. neoformans*, including the ability to grow in the environment and at 37°C, production of a polysaccharide capsule, and the ability to produce melanin. Acapsular strains of *Cryptococcus* exhibit a marked decrease in virulence. The ability to produce melanin is thought to play a role in both the virulence and the neurotropism of *C. neoformans* because melanin-deficient mutants are less virulent in mice, and the central nervous system (CNS) is rich in precursors for the production of melanin.[9] Primary infection with cryptococci usually occurs after the organism is inhaled into the lungs. Cryptococci are controlled principally by cell-mediated immunity in conjunction with phagocytosis.[10] Initially, neutrophils play a role in containing the yeast in the lungs, followed by monocyte activity. $CD4^+$ T lymphocytes have been shown to be essential in containing CNS infection, which may account for the much higher incidence of cryptococcosis in people with AIDS. Although antibody and complement cannot kill cryptococci directly, both enhance opsonization.[7]

Epidemiology

C. neoformans and *C. gattii* differ in their natural habitat and geographic distribution. *C. gattii* causes infection in tropical and subtropical regions of the world and is associated with several species of eucalyptus trees, which are its ecologic niche. However, the outbreak of *C. gattii* infections on Vancouver Island demonstrated an association with other trees, including firs and oaks, and an expanded geographic range.[8] For *C. neoformans*, both *C. neoformans* var. *grubii* (serotype A) and *C. neoformans* var. *neoformans* (serotype D) are isolated most frequently from soil contaminated with pigeon or other bird guano.[11] The two varieties differ in their geographic distribution; serotype A has been isolated throughout the world and usually infects people with AIDS or other immunocompromising conditions, whereas serotype D infections are more prevalent in certain geographic areas, such as northern Europe.[7]

Although *Cryptococcus* species can be isolated from pigeon droppings, documentation of infection after this type of exposure is limited.[12] Molecular strain typing has not yet linked a specific environmental source to cryptococcosis, but it has demonstrated that some clinical and environmental isolates are indistinguishable.[13] Host factors are important in determining the risk of developing cryptococcosis. HIV infection is now the most common immunocompromising illness in patients with cryptococcosis, although the incidence of cryptococcosis has decreased with the institution of active antiretroviral therapy (ART). However, in areas worldwide where ART is not available, cryptococcosis remains the most common life-threatening fungal infection.[7] In people with HIV infection, cryptococcosis usually occurs in patients with CD4$^+$ lymphocyte counts below 100 cells/mm^3.[14] Other immunocompromised people with cell-mediated immunologic defects, such as patients with lymphoma and sarcoidosis, and people receiving corticosteroid treatment, also have an increased risk of both *C. neoformans* and *C. gattii* infections.[15] No association between cryptococcosis and ethnicity has been detected.[14]

Until the AIDS epidemic began, cryptococcosis was rare. Population-based active surveillance conducted in four areas of the United States between 1992 and 1994 showed that cryptococcosis developed in 2% to 5% of people with AIDS per year.[14] The rate of cryptococcal infection in HIV-infected people declined dramatically after the introduction of ART; it decreased by 46% in one study, and in another study dropped from an incidence as high as 66 per 1000 to 2 to 7 per 1000.[16,17] Also noteworthy is the fact that of the 1083 cases of cryptococcosis detected during a population-based surveillance study before ART, only 4 cases occurred in people younger than 18 years of age, 2 of whom were infected with HIV.[14] These data were confirmed by other studies showing that cryptococcal infection was less common in HIV-infected children than in HIV-infected adults, with occurrence rates of 1% and 1.4%, respectively.[18,19] Most pediatric cases of cryptococcosis occurred in children 6 to 12 years of age; 9 of 13 cases diagnosed after 1990 occurred in children with vertical HIV infection. Similarly *C. gattii* infection is uncommon in children; only three confirmed cases have been reported (all pulmonary and all in patients who were not infected with HIV).[20]

Occasional cases of cryptococcosis occur in children without HIV infection, the most common underlying conditions being lymphoproliferative disorders and immunosuppressive treatment.[21] Rare cases occur in apparently healthy children. The reasons for the lower incidence reported in children is unknown but may relate to differences in environmental exposures or immunologic factors.

Clinical Manifestations

Cryptococcosis is acquired by inhalation of infectious airborne particles. The incubation period is unknown and could be weeks, months, or even longer. Whether the infectious particles are desiccated acapsular yeast cells or basidiospores of the sexual state of the fungus is unclear, but the encapsulated yeast cells are thought to be too large to penetrate the defenses of the upper respiratory tract. After inhalation organisms disseminate in immunocompromised patients from the lungs to other sites, with or without evident pulmonary infection. Any organ can be affected, including bone and soft tissue, but the most serious form of the disease is meningitis or meningoencephalitis, which is fatal if untreated.[7]

The clinical manifestations of cryptococcosis in children with AIDS are similar to those in HIV-infected adults.[18,19,21] The presentation of cryptococcosis in patients with AIDS more commonly involves extrapulmonary disease, including cryptococcemia, and extensive CNS infection with a high burden of organisms, as manifested by positive results on India ink examinations and antigen titers, in addition to a limited cerebrospinal fluid (CSF) inflammatory response.[22]

Pulmonary Manifestations

Primary cryptococcosis is asymptomatic in up to one third of immunocompetent people after inhalation of *C. neoformans*.[23] Even in immunocompromised patients, including people with AIDS, primary pulmonary infection may not be diagnosed until extrapulmonary dissemination occurs, particularly meningitis.[24] More persistent pulmonary cryptococcosis often develops in people with HIV infection. Most patients come to medical attention with headache, fever, cough, dyspnea, and weight loss, and some have pleuritic chest pain and hemoptysis. The most frequent radiographic findings are focal or diffuse interstitial infiltrates and hilar lymphadenopathy. Unlike in patients with filamentous fungal infections, nodular and alveolar infiltrates are rare, as are large mass lesions and pleural effusions.[23,25]

Neurologic Manifestations

Infection of the CNS is the most common clinical presentation of cryptococcosis and the complication most frequently associated with mortality. Although cryptococcal meningitis can be acute, it most often follows an indolent course, with asymptomatic periods. In people with AIDS, the most common symptoms are headache, fever, and altered mental status; meningeal signs are uncommon. Focal neurologic signs are initially uncommon and occur in about 10% of patients. If focal lesions are detected, especially in patients with AIDS, another diagnosis, such as brain abscess arising from another infectious cause (e.g., toxoplasmosis, tuberculosis, bacterial abscess) or malignancy (primary CNS lymphoma) should be considered because CNS mass lesions (cryptococcomas) have not been reported in HIV-infected children.[26] Increased intracranial pressure is common in patients with CNS cryptococcosis, especially those with AIDS, and represents a life-threatening complication. These patients present with severe headache, abnormal mental status, visual disturbance, and frequently hearing loss.[27,28] The underlying mechanism is unclear, but it is thought to be partly the result of interference with CSF reabsorption in the arachnoid villi due to accumulation of fungal polysaccharide. Aggressive management of elevated intracranial pressure by means of repeated lumbar CSF drainage is perhaps the most important factor in reducing mortality and minimizing the morbidity of acute cryptococcal meningitis.[27]

About 90% of patients with cryptococcal meningitis who are not infected with HIV have abnormal CSF findings, including increased opening pressure (65%), elevated protein concentration (90%), lowered glucose concentration (75%), and a lymphocytic pleocytosis. In people with AIDS, the CSF can appear normal, having normal protein and glucose concentrations and minimal or absent pleocytosis.[29]

Skin Manifestations

Cryptococcal skin lesions occur in 10% to 15% of patients with disseminated disease as a result of hematogenous spread. Direct extension from a bone lesion can also occur. Single or multiple pustules or papules are most common and sometimes progress to ulcers or abscesses. These lesions typically are described as resembling molluscum contagiosum, and without a biopsy and culture they cannot be distinguished from lesions caused by other infectious agents, such as *Histoplasma capsulatum, Coccidioides immitis,* and *Talaromyces* (formerly *Penicillium*) *marneffei.*[30] Although the most common sites of cryptococcal skin lesions are the face and scalp, the trunk or limbs also can be involved.

Other Sites

Bone infection occurs in about 5% to 10% of patients with disseminated cryptococcosis. Pain and swelling can be present, but bone lesions often are found incidentally. Radiographs reveal well-defined osteolytic lesions without marginal sclerosis or periosteal change. Joint involvement is rare. Eye involvement with cryptococcal meningitis can occur and manifests as retinitis. Cryptococcosis can involve any organ system, including the adrenal glands, heart, liver, spleen, and prostate.

Diagnosis

Diagnosis is not usually difficult; it requires isolation of *Cryptococcus* organisms in culture or detection of cryptococcal capsular antigen in the blood, CSF, or urine.

Encapsulated *C. neoformans* often can be seen on direct microscopic examination of CSF or other body fluids and secretions mounted in India ink, mucicarmine, or other stains, such as nigrosin. In people with AIDS, *C. neoformans* cells usually are plentiful in the CSF, although care must be taken not to confuse organisms with lymphocytes in CSF. Budding of the organism can be useful for that distinction.

C. neoformans can be isolated from CSF in 75% to 90% of cases of cryptococcal meningitis, and a culture is even more likely to be positive in patients with AIDS because of the high burden of organisms.[29] In patients with negative cultures, periodic high-volume CSF samples (>10 mL) may increase the yield. The organism grows well on standard microbiologic media and fungal media (e.g., Sabouraud dextrose agar), but it is inhibited in media containing cycloheximide. *C. gattii* grows as deep blue colonies on a canavanine-glycine-bromothymol (CGB) culture medium, but *C. neoformans* does not induce a color change on this medium (Fig. 249.1). Growth is enhanced at 30°C to 35°C, and incubation should be extended for up to 2 weeks in suspected cases. Blood and urine cultures also can be positive. Isolation of *Cryptococcus* organisms from respiratory tract samples, including sputum, bronchoalveolar lavage fluid, or lung tissue, may be useful in pulmonary infection. Immunocompromised patients with pulmonary cryptococcosis should be evaluated for CNS disease.

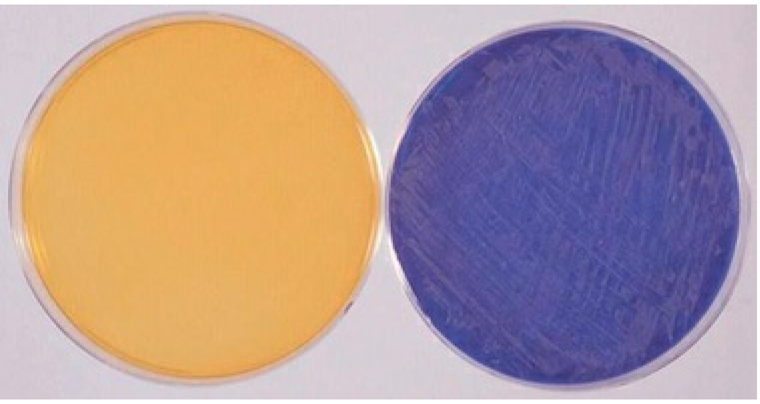

FIGURE 249.1 *Cryptococcus gattii* causes a cobalt blue color change when grown on canavanine-glycine-bromothymol (CGB) culture media *(right)*, whereas *C. neoformans* does not *(left).*

Testing for cryptococcal capsular antigen in serum, CSF, urine, or bronchoalveolar lavage specimens is one of the most reliable nonculture methods of fungal diagnosis. The antigen test is positive in more than 90% of patients with untreated cryptococcal meningitis, but it is somewhat less sensitive in patients without CNS disease. The test is highly specific, and false-positive results are seen primarily in other basidiomycetous yeast infections, such as those caused by *Trichosporon* spp. False-negative test results can occur if the organism burden is low or if the organisms are not well encapsulated. Tests to detect serum antibodies to *C. neoformans* have been less helpful because such antibodies are seldom found in patients with untreated meningeal or disseminated infection, although their presence may indicate a favorable prognosis.[31]

Antigen tests should be performed on all CSF specimens at the time of initial diagnosis, and the results can be measured on subsequent CSF specimens to evaluate the response to treatment, although serial CSF antigen titers have a limited role in management.[32] Serum antigen levels are even less useful for monitoring the response to treatment, likely because of the persistence of polysaccharide capsules. Various commercial tests are available for detection of cryptococcal antigen, and these now use the enzyme immunoassay rather than the original latex agglutination assay.

Treatment

Left untreated, cryptococcal meningitis is fatal.[33] Because treatment for cryptococcal disease has not been studied in a controlled manner in pediatric patients, data from adult trials have been used to formulate recommendations for treating cryptococcal infection in children.[34,35] For most patients with severe cryptococcosis and cryptococcal meningitis, combination therapy with amphotericin B and flucytosine for 2 weeks, then 8 weeks of therapy with fluconazole, is recommended.[35,36] This approach is associated with a mortality rate of less than 10% and a mycologic response greater than 70%.[34,37]

Amphotericin B deoxycholate remains the standard agent for treating other serious cryptococcal infections, even though it must be administered parenterally and is associated with dose-limiting toxicities.[36] Amphotericin B usually is given at a dose of 0.7 to 1 mg/kg/day in combination with flucytosine at 100 mg/kg/day, in 4 divided doses for 2 weeks, followed by therapy with fluconazole or itraconazole for 8 weeks or until cultures are sterile.[35,36] Lipid-based formulations of amphotericin B reduce the toxicities of this drug. Although the optimal doses of these agents have not been established, a dose of 3 to 5 mg/kg/day has been effective.[38,39] Cost remains a serious obstacle to their routine use.

Flucytosine is an orally bioavailable antifungal agent with potent activity against *C. neoformans,* but resistance develops rapidly when the drug is used as a single agent. When flucytosine is given in combination with amphotericin B, relapses are reduced and cultures become negative more quickly[37]; more recent studies have shown a survival benefit to this approach.[40] Flucytosine has the potential for considerable toxicities, including bone marrow suppression, nausea and vomiting, and skin and kidney toxicities, especially in patients with abnormal renal function.

The triazole antifungal agents, including fluconazole and itraconazole, and the extended spectrum triazoles, voriconazole and posaconazole, have excellent activity against *C. neoformans.*[41] Because fluconazole crosses the blood-brain barrier, achieves good CSF concentrations, and is well tolerated, it has become the primary azole used in cryptococcal meningitis. For children with mild to moderate cryptococcosis that does not involve the CNS or that is confined to the lungs, fluconazole alone can be considered for primary therapy. However, higher failure and mortality rates are associated with the use of fluconazole as the primary therapy of cryptococcal meningitis; therefore, use of this drug as a single agent is not recommended in most patients with more severe infection or meningitis.[36]

For children with cryptococcal meningitis who are completing a 2-week induction course of amphotericin B combined with flucytosine, fluconazole (10 to 12 mg/kg/day divided into 2 doses daily, given either intravenously or orally) then is recommended for a minimum of 8 weeks.[35] Itraconazole is an alternative, but it does not penetrate well into the CSF, and it is associated with significant drug interactions and gastrointestinal tract intolerance.[35]

Refractory infection can occur and usually is related to the severe immunocompromised condition of the person, more than to antifungal resistance, which is uncommon.[41] Susceptibility testing of *Cryptococcus* organisms has limited clinical value. Clinically the more important course is to confirm the diagnosis and to establish drug compliance and lack of interactions that limit drug exposure. Alternative agents are available, including voriconazole and posaconazole, both of which have been shown in anecdotal series to have activity, although overall responses are not favorable because of their use almost exclusively as late salvage therapy in very immunosuppressed patients.[42,43] The echinocandins do not have activity against *Cryptococcus* species because of a difference in the fungal cell wall; therefore, these drugs should not be used.[44]

Prevention of relapse after successful treatment requires long-term suppressive treatment.[35] After 10 weeks the dosage of fluconazole can be reduced to an adolescent or adult dose of 200 mg/day, depending on the patient's clinical status. The safety of discontinuing secondary prophylaxis in children infected with HIV after immune reconstitution with ART has not been studied extensively, but cases in adults and adolescents appear to indicate that the risk of relapse is low once the $CD4^+$ lymphocyte count has risen above 200 cells/mm^3.[34] Suppressive therapy should be reinstated if later the $CD4^+$ lymphocyte count drops below 200 cells/mm.[3]

Special Management Considerations

In all cases of cryptococcal meningitis careful attention to the management of intracranial pressure is essential to ensure an optimal clinical outcome.[27,28] The principal intervention for reducing elevated intracranial pressure is percutaneous lumbar drainage of CSF. Radiographic imaging of the brain is recommended before the initial lumbar puncture to rule out a space-occupying lesion.[36] Enough CSF should be removed to reduce the opening pressure by 50%. If repeated lumbar punctures or use of a lumbar drain fails to control the symptoms of elevated pressure, or when persistent or progressive neurologic deficits are present, a ventriculoperitoneal shunt is indicated.[36] Adjunctive treatment with corticosteroid therapy is not recommended in patients with HIV infection.[36] Also, the use of acetazolamide therapy is associated with increased toxicity, including severe acidosis in one trial in adults, and is not recommended.[45]

ART has significantly improved the long-term outcomes associated with cryptococcal infection in patients infected with HIV and has reduced the incidence of disease. However, in the past decade an immune reconstitution inflammatory syndrome (IRIS) has been reported after initiation of ART in the acute treatment phase of opportunistic diseases in both adults and children.[46,47] Symptoms include elevated intracranial pressure, CSF pleocytosis, fever, headache, and meningismus, which can make it difficult to distinguish IRIS from relapse or progression of disease.[48,49] IRIS (which also can occur in patients without HIV infection who have a rapidly recovering immune system, such as after stopping immunosuppressive therapy) generally occurs within the first 1 to 2 months after the start of ART; for this reason, delaying ART until the patient has completed 5 weeks of antifungal therapy for cryptococcal infection should be considered. This approach is associated with a survival benefit.[50]

Prevention

Guidelines have been published for the prevention of opportunistic infections, including cryptococcosis, in people with HIV infection.[51] Several studies have demonstrated that prophylactic administration of fluconazole to people with HIV infection who are at high risk for cryptococcosis can significantly reduce the risk of development of the disease.[52,53] In selected countries with limited resources, screening of asymptomatic patients for serum cryptococcal antigen is recommended.[54] However, the use of fluconazole to prevent cryptococcal infection in the U.S. is not recommended because of the relative infrequency of infection and the unfavorable cost-benefit ratio of this approach.[55] No vaccine is available.

Key Points

Diagnosis and Management of Cryptococcal Infections

Microbiology

- Encapsulated, basidiomycetous yeasts; grow well on routine microbiologic media
- Two species (*C. neoformans* and *C. gattii*) account for most of invasive infections.
- *C. gattii* grows as deep blue colonies on canavanine-glycine-bromothymol blue media, whereas *C. neoformans* is unable to induce a color change on this media.

Epidemiology

- Occurs worldwide but only rarely causes disseminated infection in immunocompetent people
- Estimated 1 million cases in adults and children worldwide per year, and 700,000 deaths
- Major risk factors: AIDS, prolonged glucocorticoid treatment, organ transplantation, hematologic malignancy, sarcoidosis, or use of other immunosuppressive medications
- Cryptococcosis is uncommon in children (even those with AIDS) compared with adults, for unknown reasons.

Clinical Features

- Central nervous system: often indolent, with headache, fever, and altered mental status most common; focal neurologic deficits present in 10%; increased intracranial pressure very common

- Pulmonary: cough, pleuritic chest pain, hemoptysis, and focal or diffuse interstitial infiltrates with hilar lymphadenopathy
- Cutaneous: typically seen in those with disseminated disease; can mimic molluscum contagiosum
- Other: any organ system can be affected, including adrenals, heart, liver, spleen, and prostate

Diagnosis

- Recovery of organism from body fluids or tissue
- Microscopic examination of cerebrospinal fluid (CSF) on wet mounts stained with India ink
- Detection of cryptococcal capsular antigen in blood, CSF, or urine

Treatment

- CNS: combination amphotericin B and flucytosine for 2 weeks, then fluconazole for 8 weeks. Fluconazole should be continued until immune reconstitution is observed (CD4$^+$ lymphocyte count >200 cells/mm^3 for at least 6 months)
- CNS: attention to intracranial pressure and attempt to reduce urgently if elevated
- Immune reconstitution inflammatory syndrome (IRIS): can occur after recovery of immunologic responsiveness; complicates management

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250

Histoplasma capsulatum (Histoplasmosis)

John C. Christenson, Martin B. Kleiman

Histoplasmosis is the most common primary systemic mycosis in the Americas, affecting hundred of thousands of people living in urban and rural areas of the Ohio and Mississippi River valleys and some mideastern states, and parts of Central and South America.[1,2] The fungus is also endemic to Australia, Africa, and eastern Asia.[3–5]

The Pathogen

Microbiology

Histoplasmosis is caused by the dimorphic fungus *Histoplasma capsulatum* var. *capsulatum*. Another variant, *H. capsulatum* var. *duboisii*, is known to cause disease in Africa. A common soil saprophyte, *H. capsulatum* grows as a spore-bearing mold below 35°C and as a yeast-like organism at 37°C. In its mold form, tuberculate macroconidia 8 to 14 μm in diameter are an identifying morphologic feature (Fig. 250.1A). Morphologic methods of identifying *H. capsulatum* isolates are slow, laborious, and hazardous; DNA probe technology shortens the time required for identification.[6] The infectious particles are the microconidia, spores

2 to 5 μm in diameter that are produced by the mold form. Yeast-like forms are 2 to 3 μm by 3 to 4 μm in diameter and typically are found in infected tissues (Fig. 250.1B and C).

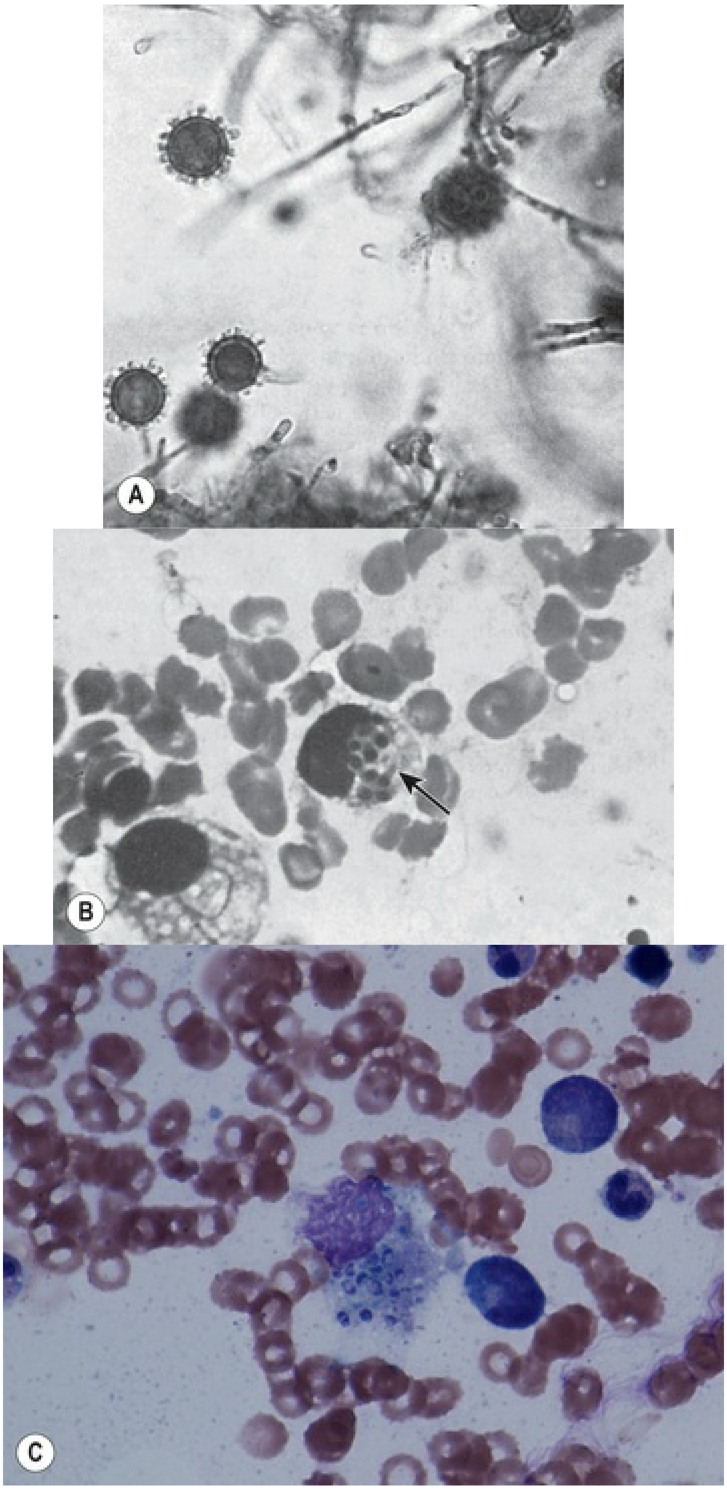

FIGURE 250.1 (A) Characteristic appearance of the tuberculate macroconidia of the mold form of *Histoplasma capsulatum.* Lactophenol cotton blue

stain, ×400. (B) Yeast-like forms of *H. capsulatum* in tissue. Yeast-like forms typically are found phagocytosed by histiocytes *(arrow)* and are 2 to 3 μm in diameter. Giemsa stain, ×400. (C) Bone marrow smear demonstrating yeast-like forms of *H. capsulatum.*

Pathogenesis

After inhalation, microconidia germinate within distal bronchioles and pulmonary alveoli, where they undergo transition to yeast-like forms. Acute inflammatory changes ensue. Lymphohematogenous fungal dissemination occurs early in infection, even in self-limited disease.[7] The successful pathogenesis of *H. capsulatum* results from the organism's transition to the yeast phase, entry into and proliferation within macrophages, and ability to survive and retain its ability to reactivate.[8–12] In healthy people, specific T-lymphocyte immunity develops after 1 month and interleukin-12 (IL-12) and interferon γ (IFNγ) stimulate macrophages to kill the fungus, thereby controlling disease. Tumor necrosis factor-α (TNF-α) is also critical for effective host immunity.[13] Histopathologic changes include granulomas with Langerhans giant cells, typical yeast-like forms, and caseous necrosis.[14] Lesions heal by fibrous encapsulation and can calcify. In some patients, albeit rarely in children, an exuberant fibrous reaction destroys or obstructs major vessels, bronchi, or lung parenchyma, and/or critical mediastinal structures. In immunocompromised people or those with progressive disseminated infection, granulomas can be poorly formed and the large fungal burden can overwhelm the reticuloendothelial system.[15,16] Findings compatible with macrophage activation syndrome can occur in this setting.[17]

Immunity

Antibodies against the organism are measurable about 1 month after infection, but these play no major role in controlling infection. In healthy people the cell-mediated immune response is the key to controlling fungal growth and provides a degree of protection against reinfection.[18] *H. capsulatum* replicates within macrophages until T lymphocytes are activated.[13] Granuloma formation occurs in response to infection of macrophages.[19] The release of proinflammatory cytokines and chemokines is required for the development of a protective immune response that not only controls the infection, but also provides protection against recurrent infection.[20] Reinfection usually results from reexposure; recurrences have shorter incubation periods and are generally milder than primary infections. Recrudescence of latent infection has been well documented in people infected with HIV,[21] in recipients of organs transplanted from infected donors,[22] and in people receiving corticosteroids[23] or TNF-α inhibitors[13,24–27]; however, the frequency of reactivation, versus reexposure-induced infection, is the subject of debate. Progressive disseminated infections that occur in otherwise immunocompetent people, especially infants, can cause a transient T-lymphocyte deficiency that resolves after eradication of the organism.[15,16]

Epidemiology

Areas of high incidence include the Mississippi and Ohio River valleys (Fig. 250.2), where skin test reactivity in hyperendemic areas can develop in as many as 80% of people by 18 years of age.[2,28] Infections can occur sporadically or in clusters.[29–34] A single epidemic of more than 100,000 cases of infection has been described in Indianapolis.[1] Bird and bat excrement promote fungal growth in the environment. Inhalation of aerosols generated when contaminated areas are disturbed are risk factors for infection. Box 250.1 presents a summary of activities and point sources that most often predispose to infection. Contaminated air in closed spaces can cause intense exposure and serious illness. Large outbreaks have been reported in industrial settings and in a school.[30,33,34] Infections increasingly are reported among travelers returning from endemic areas.[31,35–41] Vertically acquired, disseminated histoplasmosis and HIV infection have been reported in a 5-week-old infant.[42]

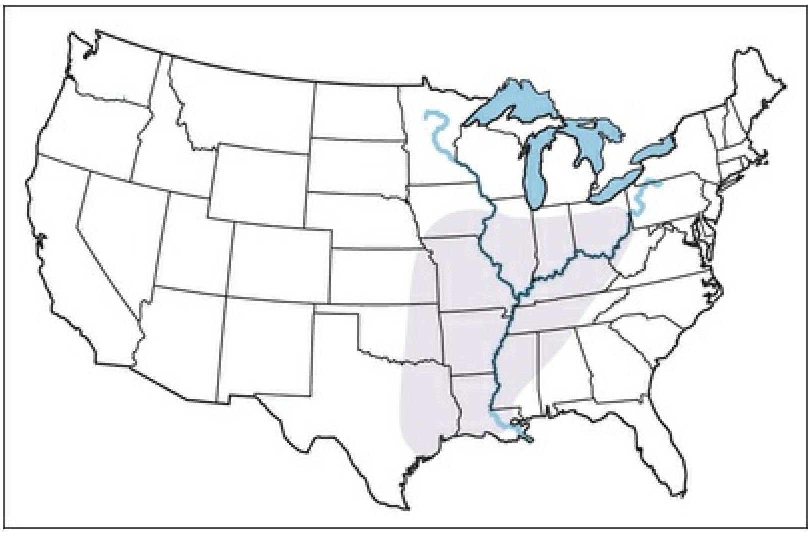

FIGURE 250.2 United States map showing the most highly endemic regions for *Histoplasma capsulatum*, the Ohio and Mississippi river valleys.

Box 250.1

Point Sources and Activities Associated With Sporadic Childhood Histoplasmosis

Cleaning/renovating basements, attics, wall insulation of older homes, barns, and silos

Cleaning under bird feeders

Cutting firewood/tree stumps

Cleaning abandoned building

Digging at sites of former bird roosts

Gardening

Playing and working in barns

Playing in hollow trees

Exploring caves

Being downwind of excavation/demolition of contaminated sites

Rototilling

Exposure to bonfires

Clinical Manifestations

In settings other than outbreaks, symptomatic infection occurs in less than 5% of infected individuals, and clinical manifestations vary widely. The outcome of exposure to *H. capsulatum* is influenced by (1) inoculum size; (2) the functional integrity of the person's cellular immunity; (3) strain-specific virulence factors; and (4) preexisting immunity.

Immunocompetent People

The spectrum of common clinical manifestations of histoplasmosis in childhood is summarized in Box 250.2. In a single-source, high-inoculum outbreak at a high school, 523 people developed serologic evidence of recent infection, and 355 (68%) developed symptoms compatible with acute pulmonary histoplasmosis.[30] Most became symptomatic 2 to 3 weeks after exposure. Common complaints were headache (95%), fatigue (79%), fever (79%), cough (73%), myalgias (71%), chills (67%), nonpleuritic chest pain (66%), and arthralgias (52%).

Box 250.2

Principal Clinical Manifestations of Histoplasmosis in Children

Respiratory Tract

Mediastinal lymphadenopathy

Pulmonary infarction

Cavitary pneumonia

Asthma-like illness

Pleural effusion

Acute/chronic bronchial obstruction

Isolated cervical/supraclavicular lymphadenopathy

Superior vena cava syndrome

Mediastinal granuloma/fibrosis

Vocal cord granuloma

Vocal cord paralysis

Hemoptysis

Broncholithiasis with lithoptysis

Chylothorax

Diaphragmatic weakness/paralysis

Other

Esophageal diverticulum/fistula

Pericarditis

Erythema nodosum

Meningitis/focal cerebritis

Arthritis

Parotitis

Interstitial nephritis

Nephrocalcinosis

Hypercalcemia

Gastrointestinal tract ulceration/hemorrhage

Gastrointestinal tract pseudomalignancy

Crohn disease–like illness

Biliary obstruction

Cutaneous or conjunctival inoculation and regional adenitis

Choroiditis

Endocarditis

Adrenal mass

Symptoms of histoplasmosis in children usually last 2 or 3 days. In about 5% of children, symptoms are subacute, persist longer than 2 weeks, and include lethargy, poor appetite, and weight loss. Rheumatologic manifestations can occur, including erythema nodosum (Fig. 250.3), arthralgia, or both, often in adolescents.[41] In about 10% of symptomatic children, pericardial effusion develops and, albeit infrequently, can become large enough to impair diastolic filling.[43,44] Pericardial fluid is almost always sterile and usually results from inflammation caused by infected contiguous lymph nodes. Hypercalcemia, occasionally seen with other granulomatous infections, can occur in histoplasmosis.[45] Many mediastinal and abdominal manifestations result from irritation, compression, or destruction of structures adjacent to infected lymph nodes and granulomas.[46,47] Other manifestations include chylothorax,[48] pleural effusion,[49,50] multifocal choroiditis,[51] cystic duct obstruction,[52] and traction esophageal diverticulum.[53] Osteomyelitis[54] and central nervous system infections[55,56] are unusual manifestations of histoplasmosis in healthy older children. Except in cases of massive exposure, fatality is rare in otherwise healthy older children.

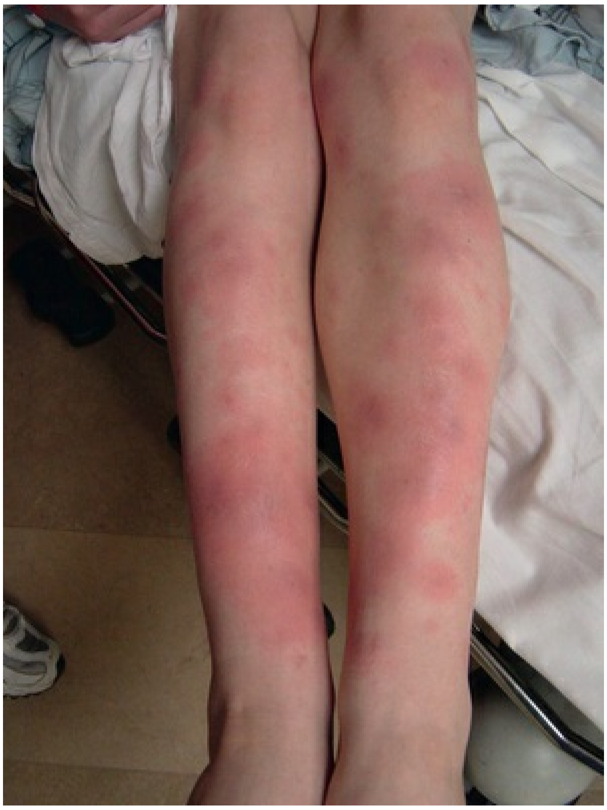

FIGURE 250.3 Erythema nodosum in an adolescent male with acute pulmonary histoplasmosis.

Fungal dissemination that occurs early in infection almost always is self-limited in healthy people. The term *progressive disseminated histoplasmosis* is applied to instances of continued and overwhelming reticuloendothelial infection, which is fatal if left untreated.[16,46] This manifestation often suppresses cellular immune function in previously immunocompetent people, and it is a common opportunistic infection in individuals with acquired or congenital cellular immune dysfunction.[15] An infrequent manifestation of progressive dissemination occurs in otherwise healthy infants. Termed *progressive disseminated histoplasmosis of infancy*, its initial symptoms are subacute, sometimes lasting several weeks, although progressive.[16,46] Complaints and signs include fever, weight loss, and progressive hepatosplenomegaly (Fig. 250.4). Meningitis occurs in about 60% of affected infants. Pancytopenia and disseminated intravascular coagulation (DIC) are ominous signs; the infection is fatal if it goes untreated. Interestingly, a recent report describes a case of disseminated histoplasmosis in one of infant twins.[57]

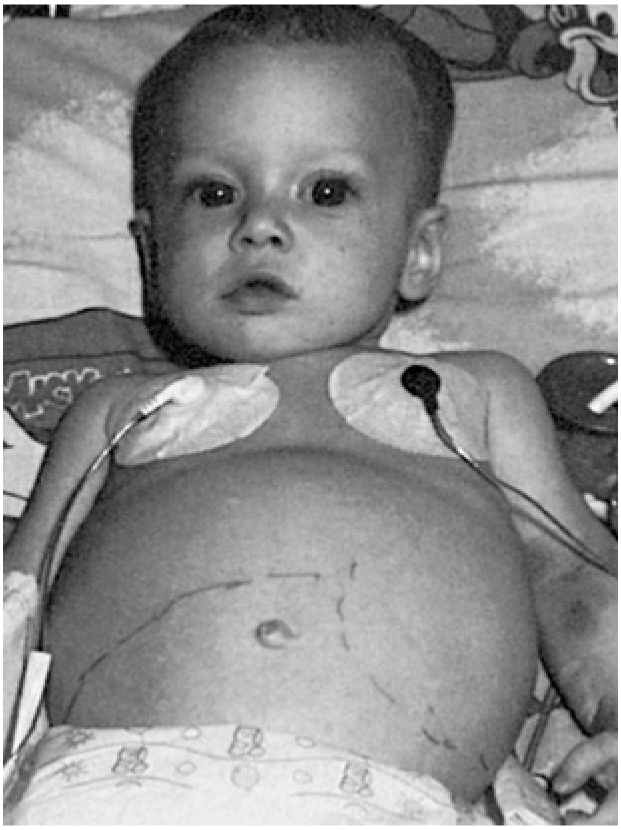

FIGURE 250.4 Six-month-old boy with disseminated histoplasmosis. He had a 1-month history of failing to thrive and a “swollen abdomen.” Note the characteristic appearance with massive hepatosplenomegaly and early signs of cachexia, yet the baby has a bright, responsive facial appearance.

Immunocompromised People

Impaired cellular immunity markedly increases the risk of progressive dissemination and life-threatening infection.[21,58–60] In addition to immunosuppressive therapy for malignancies or transplantation,[22,61,62] increased risk has been associated with the use of TNF antagonists used to treat inflammatory conditions.[24–27] Illness usually begins with fever, and then cough, diffuse pulmonary infiltrates and, ultimately, hypoxia occur. Patients with HIV infection may have only a prolonged fever and weight loss, and no pulmonary findings.[63,64] Occasionally, large necrotic masses of infected lymph nodes can develop. Data for children are lacking; however, in adults with HIV infection complicated by histoplasmosis, multiorgan dysfunction, DIC, elevated serum levels of lactic dehydrogenase, shock, and respiratory failure are predictive of death.[64] In patients receiving combination antiretroviral therapy (cART), immune reconstitution can cause recurrence of symptoms to develop.[65,66]

Laboratory Findings and Diagnosis

Nonspecific Tests

In self-limited histoplasmosis in an immunocompetent person, a hemogram may show only mild anemia. The erythrocyte sedimentation rate almost always is elevated. Pancytopenia and DIC often are seen in untreated, progressive disseminated histoplasmosis. Hemophagocytosis can occur in disseminated infections in immunocompromised people.[67] For an immunocompetent person with histoplasmosis, histopathologic examination shows well-formed, necrotizing, granulomatous inflammation. In immunocompromised patients, the histologic findings are poorly formed granulomas with sheets of histiocytes containing typical yeasts.[19,68]

A chest radiograph in a person with an acute infection can be normal, or it can show a middle mediastinal mass and lymphadenopathy, or localized pulmonary infiltrates, or both (Fig. 250.5).[69] Some clinical, laboratory, and imaging findings help distinguish a benign mediastinal mass (e.g., caused by histoplasmosis) from a malignancy.[69a] CT of the chest is more sensitive than plain radiography (Fig. 250.6). In a high-inoculum exposure or in immunocompromised people, a diffuse reticulonodular infiltrate can be observed (Fig. 250.7). Radiographs or CT scans of asymptomatic residents of endemic regions often reveal single or multiple calcified nodules in the lungs and hilar lymph nodes and, occasionally, calcifications in the spleen or liver (Fig. 250.8). These findings usually are the result of previous, often unrecognized infections.

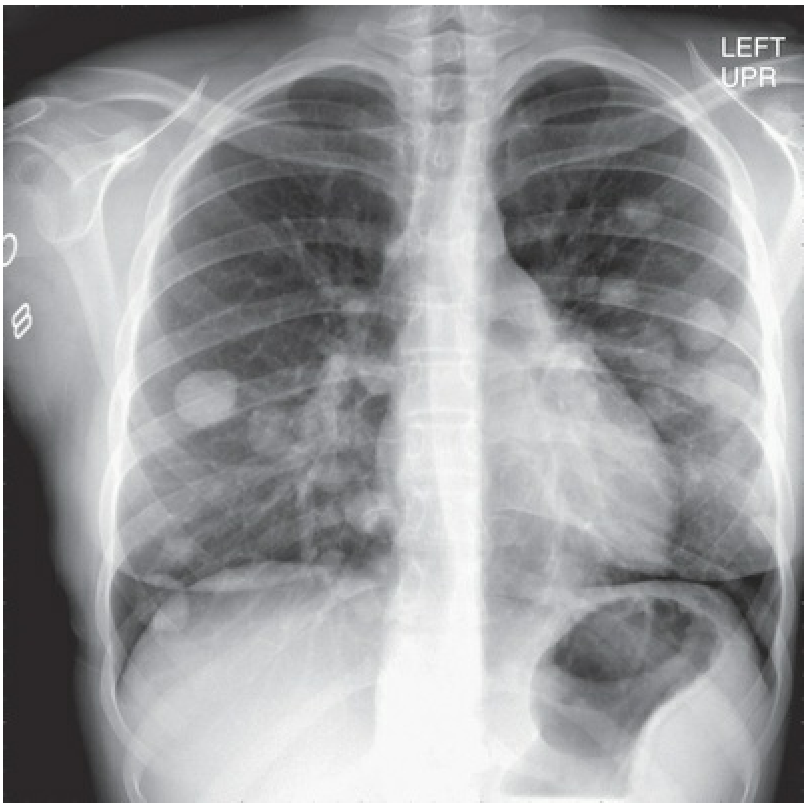

FIGURE 250.5 Chest radiograph demonstrating pulmonary nodules caused by histoplasmosis in an adolescent female with type 1 diabetes mellitus. The girl was brought for medical treatment for chest pain.

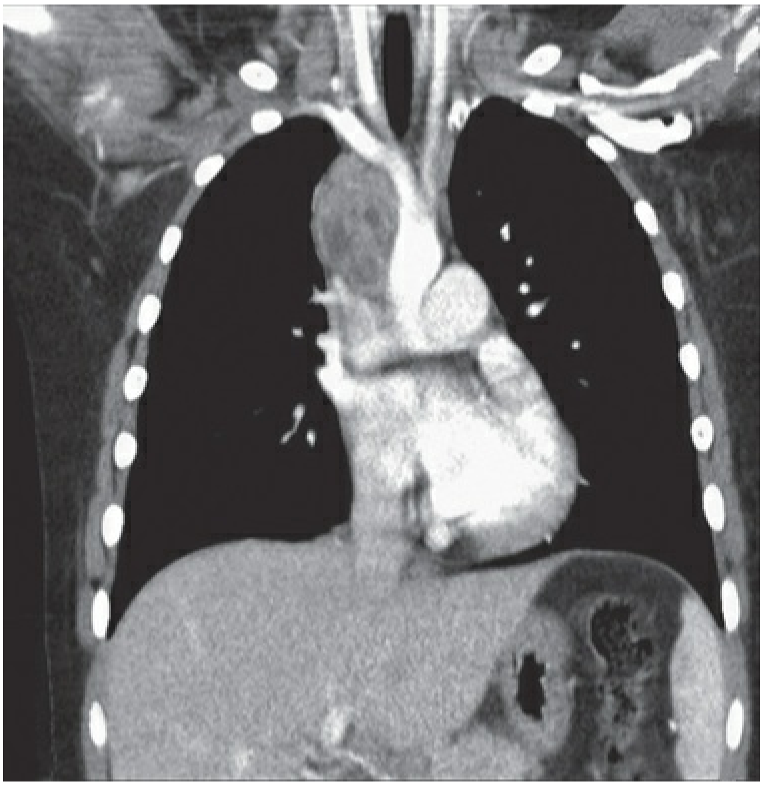

FIGURE 250.6 CT scan of a 5-year-old girl who had a fever, chest pain, and cough caused by histoplasmosis. Note the large mediastinal mass on the right side.

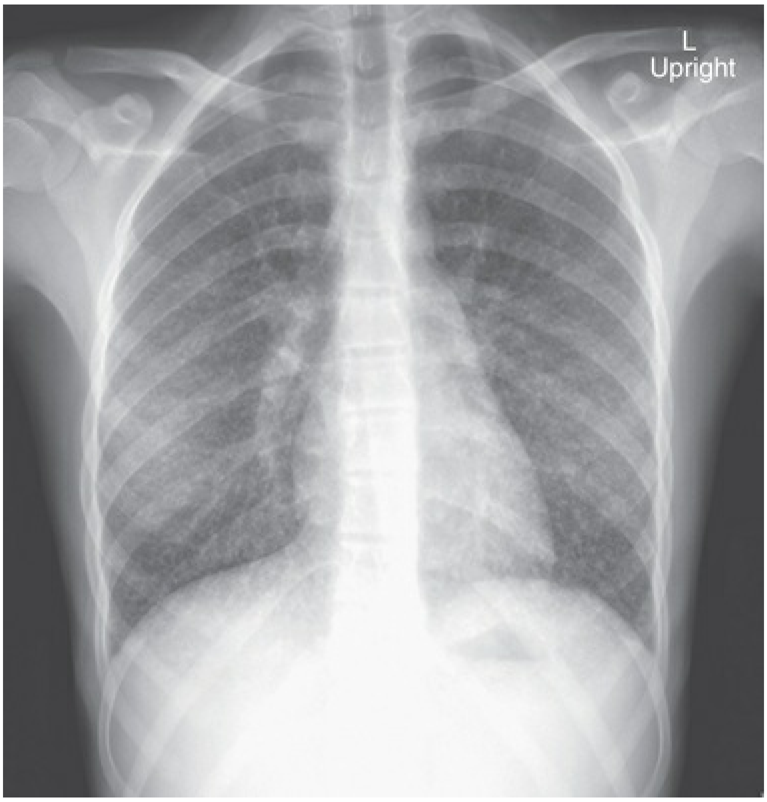

FIGURE 250.7 Chest radiograph of a severely ill immunocompromised adolescent exposed to *Histoplasma capsulatum* spores while working in a barn. Note the diffuse reticulonodular infiltrate. The girl presented with a hemophagocytic syndrome–like illness. Her bone marrow smear is shown in Fig. 250.1C.

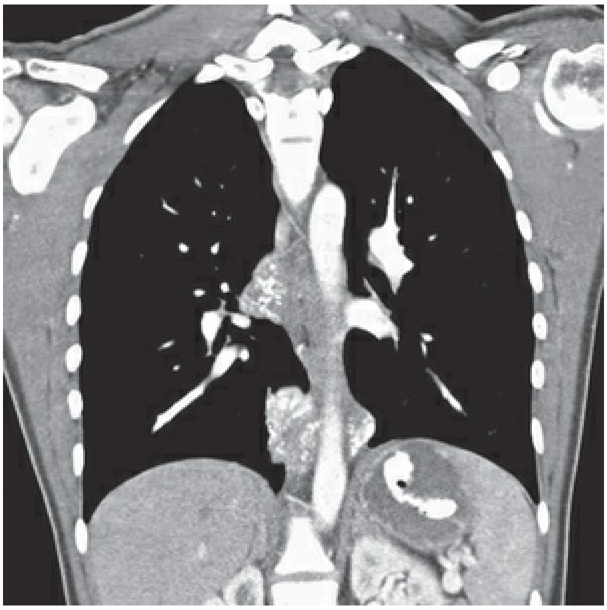

FIGURE 250.8 CT scan demonstrating calcified nodules in an asymptomatic adolescent female evaluated for scoliosis.

Specific Laboratory Tests

The principal laboratory tests for diagnosis of histoplasmosis are serologic tests, culture, and tissue and body fluid examinations, along with quantitative enzyme immunoassay (EIA) for *Histoplasma* antigen in the urine, serum, cerebrospinal fluid, and bronchoalveolar lavage fluid.[70–74] Table 250.1 provides an interpretive guide to laboratory test results in children with histoplasmosis. Multiple positive test results, especially in children with clinically compatible illnesses, increase the positive predictive value of marginally positive serologic results.

TABLE 250.1

Laboratory Test Results in Children With Histoplasmosis According to Clinical Manifestations

Clinical Manifestation	Antigen[a]	Complement Fixation Antibody	Immunodiffusion Antibody	Culture	Comments
Acute histoplasmosis with severe pulmonary disease (high inoculum)	++[b]	++++	+++	+[c]	Antigen assays are likely to be positive early in the disease.
Acute histoplasmosis with mild pulmonary disease	++	++++	+++	–	Antigen assays are likely to be positive early in the disease.
Acute histoplasmosis with fever >1 mo	+++	++++	+++	–	
Mediastinal granulomas with/without associated symptoms and signs of compression	–	++	++	–	
Disseminated disease, infant	++++	++++	++++	+++[c]	
Disseminated disease, immunocompromised patient	++++	+++	++	+++[c]	
CNS histoplasmosis	+	+++[d]	++	–	CSF specimens
Pericarditis, erythema nodosum (other rheumatologic manifestations)	–	++	++	–	
Asymptomatic history of histoplasmosis and/or presence of mediastinal calcified nodules, calcified hepatic/splenic nodules	–	+	+	–	

[a] Negative antigen; progressive disseminated infection is unlikely.

[b] Serum/urine, bronchoalveolar lavage fluid or bronchial washings.

[c] Bone marrow and blood specimens.

[d] Antibody detection in cerebrospinal fluid.

++++, expected to be positive; +++, frequently positive; ++, sometimes positive; +, rarely positive; –, expected to be negative.

CNS, Central nervous system; CSF, cerebrospinal fluid.

Immunodiffusion and complement fixation assays that detect *Histoplasma*-specific antibody are positive in about 90% of infections in immunocompetent patients.[70] The titer of antibody by the complement fixation test is directly proportional to the severity of the illness and the degree of exposure.[30,75] In acute, self-limited infections, measurable antibody appears 4 to 6 weeks after infection and can revert to negative after 12 to 18 months. Although more sensitive than the immunodiffusion test, the complement fixation test is less specific, showing 18% cross-reactivity with antigens of *Blastomyces, Paracoccidioides,* and *Coccidioides,* in addition to other fungi.[76] The clinical features, exposure and travel histories, and results of other diagnostic tests aid in differentiating these entities. In the immunodiffusion precipitin test, H bands are found in only 23% of patients with an acute pulmonary infection but are more highly suggestive of active infection than are M bands; M bands are found in 76%. The immunodiffusion assay is quite specific, showing cross-reactions in only 5%.

A positive culture is confirmatory, but growth may take up to 6 weeks. The sensitivity of culture is low in all but severe, progressive dissemination and chronic pulmonary infection. The organism can be isolated in blood from patients with disseminated disease by using lysis centrifugation blood culture methods.[77] In the presence of a compatible illness and the probability of exposure, observation by an experienced examiner of yeast-like forms compatible with *H. capsulatum* in tissue, bone marrow, bronchoalveolar lavage fluid, or peripheral blood often is diagnostic (see Fig. 250.1B and C). Exceptions can include instances in which typical, though nonviable, organisms are observed within granulomas in patients with past infections.[78] Although progress has been made in molecular methodology that can detect *H. capsulatum* in tissue specimens, assays are not commercially available.[79–81]

A rapid EIA that quantifies *Histoplasma* antigen in urine, serum, bronchoalveolar lavage, and cerebrospinal fluid is available for diagnosis.[74,82–85] The EIA demonstrates high sensitivity in serious manifestations of infection, including early primary pulmonary infection and serious and life-threatening histoplasmosis. EIA is especially useful for immunocompromised patients in whom serologic tests can be falsely negative. In a highly endemic region, antigenuria was detected in 100% of children with progressive, disseminated histoplasmosis. Because the assay reflects the fungal burden, it also is used both to monitor the effectiveness of treatment and thereafter to detect relapse.[57] Serum specimens (in which simultaneously measured concentrations are substantially lower than those of urine) should be used to monitor the effectiveness of treatment in individuals whose urine concentrations are very high. When antigen becomes undetectable in the serum, urine specimens can be used for follow-up. After therapy is completed, EIA on urine samples can be used to detect early relapse in individuals at high risk for recurrence.[72,73] Although reasonably specific, the *Histoplasma* antigen assay can cross-react with *P. brasiliensis, B. dermatitidis, C. immitis* and *C. posadasii,* and *Penicillium marneffei.*[85] However, differentiation of these endemic mycoses usually is straightforward when clinical manifestations, serologic tests, and geographic considerations are evaluated. Low-positive *Histoplasma* urine antigen results (<0.6 ng/mL) must be interpreted with caution. Although they may represent histoplasmosis infection, they also can indicate cross-reaction with another fungal antigen.[86–88] False-positive results occur in 1% of specimens.

Differential Diagnosis

The differential diagnosis of symptomatic pulmonary histoplasmosis usually includes tuberculosis, with which clinical and radiographic findings often overlap. Other subacute infections that cause similar findings include blastomycosis and coccidioidomycosis. When middle mediastinal/hilar lymphadenopathy is disproportionate to the degree of pulmonary infiltrates, histoplasmosis can mimic lymphoma, particularly in patients with fever and weight loss. In a series of patients residing in an endemic area, all children with middle mediastinal adenopathy and complement fixation titers of 1 : 32 or higher were diagnosed accurately with histoplasmosis.[69] Progressive disseminated forms of histoplasmosis can mimic septicemia, leukemia, or a reticuloendothelial or primary gastrointestinal tract neoplasm, if the initial signs include hepatosplenomegaly, anemia, thrombocytopenia, leukopenia, coagulopathy, hemorrhage from gastrointestinal ulceration, or any combination of these conditions.[59,89]

Because severe, disseminated, or recurrent histoplasmosis can represent an opportunistic infection, evaluation should include screening for a previously unrecognized acquired or congenital immunodeficiency disorder.[65,66,90,91]

Treatment

Key factors used to determine whether antifungal therapy for histoplasmosis is needed are the clinical manifestations, severity of symptoms, and functional integrity of the immune system. Recommendations for the treatment of children with histoplasmosis are reviewed in Table 250.2. Inasmuch as controlled trials have not been performed in children, most recommendations for treatment are derived from the results of trials conducted in adults and the opinions of experts.[92]

TABLE 250.2

Summary of Treatment Recommendations for Children With Histoplasmosis

Manifestation	Moderately Severe or Severe Illness	Mild to Moderate Illness
Acute pulmonary type	AMB[a] for 1–2 wk, then ITR[b] for 12 wk Corticosteroids appear to be beneficial in patients with high-inoculum disease	Symptoms <4 wk: none Persistent symptoms >4 wk: ITR for 6–12 wk[b]
Disseminated disease (non-HIV)	AMB[a] for 1–2 wk, then ITR for at least 6 mo[c]	ITR for 6–18 mo or the same as for severe illness[b]
Disseminated disease (HIV)	LAB for 1–2 wk, then ITR for life[d]	
CNS histoplasmosis	LAB for 4–6 wk, then ITR for 12 mo[b]	
Granulomatous mediastinitis	AMB[a] for 1–2 wk, then ITR for 6 mo	ITR for 6–12 mo
Fibrosing mediastinitis	ITR for 3 mo[e]	Same as for severe illness
Pericarditis	Pericardial drainage for severe tamponade plus an NSAID for 2–12 wk[f]	NSAID for 2–12 wk
Rheumatologic	NSAID for 2–12 wks	Same as for severe illness
Compression of contiguous structures by granulomatous lymphadenopathy.	Symptoms <4 wk: none Persistent symptoms >4 wk: ITR for 6–12 wk[g]	

[a] Liposomal amphotericin B (LAB) or deoxycholate AMB. Many clinicians prefer the use of LAB because it has a lower frequency of infusion-related adverse reactions and nephrotoxicity.

[b] Itraconazole drug level monitoring is needed. Itraconazole suspension has higher

bioavailability than the capsule form and is the preferred agent for follow-up itraconazole treatment.

[c] Therapy should continue until the *Histoplasma* antigen concentration in serum is undetectable and the *Histoplasma* urine antigen concentration is less than 2 μg/mL and stable. (Low urine concentrations can be present for extended periods after successful therapy.)

[d] See text regarding discontinuation of secondary prophylaxis after combination antiretroviral therapy.[97]

[e] Probably ineffective if fibrotic. When granulomatous mediastinitis could be present, ITR may be considered.

[f] Indomethacin is the preferred NSAID.

[g] Corticosteroids may be beneficial in reducing the effect of compression. If used, ITR also should be used.

AMB, amphotericin B; CNS, central nervous system; FLU, fluconazole; HIV, human immunodeficiency virus; ITR, itraconazole; LAB, liposomal amphotericin B; NSAID, nonsteroidal anti-inflammatory agent.

Healthy children whose chest radiographs show findings compatible with previous histoplasmosis require no therapy. Symptomatic histoplasmosis in immunocompetent children usually is self-limited, and few children benefit from antifungal treatment. Disease manifestations that uniformly require therapy in otherwise immunocompetent children are progressive disseminated infection and serious respiratory infections resulting from high-inoculum exposure. Other infections for which antifungal therapy often is used are pulmonary infection with clinical symptoms that last longer than 4 weeks and granulomatous adenitis that obstructs or occludes blood vessels, bronchi, the esophagus, or other critical structures. The lymphocytolytic effect of corticosteroids can provide prompt relief of obstruction; in these instances, concomitant antifungal treatment is needed to prevent progressive dissemination.[47,53,92] Neither antifungal nor corticosteroid therapy is beneficial if inflammation has progressed to fibrosis.[93] Presumed ocular disease, rheumatologic syndromes, and isolated pericarditis do not require antifungal therapy. Patients with *Histoplasma* pericarditis usually improve, sometimes dramatically, with indomethacin.[43,44]

Immunocompromised people with any manifestation of active histoplasmosis should be treated with an antifungal agent because the risk for progressive dissemination is high. Asymptomatic patients in whom a biopsied pulmonary nodule reveals granulomatous inflammation, sometimes containing typical yeast-like organisms, do not benefit from treatment.[78]

Amphotericin B is the preferred agent for initial treatment of severely ill patients because it induces a faster clinical response than the azole agents.[94] However, the effectiveness, convenience of administration, and lesser toxicity of the azoles have established their important therapeutic roles.[95] Azoles can be used either as consolidation therapy after induction with amphotericin B, or as monotherapy in mildly or moderately ill patients.[92] In patients with progressive, disseminated infection, antigenuria should be monitored at monthly intervals to ensure that the urine antigen level decreases. Low-level antigenuria (<2 ng/mL) can persist in asymptomatic infants for several weeks after adequate treatment for disseminated histoplasmosis.[57] In these instances, antifungal therapy can be stopped safely, provided the infant is clinically well and the recommended duration of treatment has been completed. Such patients should be followed to ensure that antigenuria resolves.

Liposomal amphotericin B has been shown to reduce the duration of fungemia and antigenemia more quickly than itraconazole.[94] A controlled clinical trial in adults with AIDS complicated by disseminated histoplasmosis found that liposomal amphotericin B was associated with improved survival compared with amphotericin B deoxycholate.[96]

Before cART became available, a microbiologic cure could not be achieved reliably in people with HIV infection. Because relapse often occurs after the cessation of antifungal treatment, long-term antifungal suppressive therapy with itraconazole is recommended (see Table 250.2).[92,97] Fluconazole, although not recommended for the treatment of acute infections, can be used for suppression if the patient cannot tolerate itraconazole.[98] Itraconazole results in more rapid sterilization of blood cultures than fluconazole, despite no demonstrable difference in urine antigen clearance. Fluconazole resistance has been reported to develop during therapy.[99] Other azoles (e.g., voriconazole and posaconazole) have been shown to be effective as salvage therapy in a small number of patients. Ketoconazole is not effective.[100–103]

In adult patients who received cART therapy, a controlled trial found that discontinuation of secondary prophylaxis was safe under five conditions: if cART was given for at least 6 months; the CD4$^+$ T-lymphocyte count was higher than 150 cells/mm^3; antifungal therapy had been given for 1 year; fungal blood cultures were negative; and serum and urine *Histoplasma* antigen levels were below 4.1 units.[104] Candidates for long-term antifungal suppression include patients with histoplasmosis who have cellular immune disorders not induced by HIV and in whom antigenuria persists or relapse occurs after adequate therapy.

Echinocandins (e.g., caspofungin and micafungin) lack adequate activity against *H. capsulatum*.[105,106]

Large necrotic masses that do not diminish with medical treatment should be drained only if they obstruct critical structures.[107] Excision of densely fibrotic lesions involving the lung parenchyma, blood vessels, and/or bronchi is rarely helpful and is associated with a high risk of uncontrolled hemorrhage.[108]

Special Considerations

Adrenal insufficiency, nephrocalcinosis, and hypercalcemia (perhaps caused by hypersensitivity to vitamin D) have been associated with disseminated infections. Gastrointestinal tract ulcerations can cause bleeding, mimic neoplastic disorders, or obstruct the gastrointestinal or biliary tracts. Transplacental infection was reported in an infant born to a mother infected with HIV who had disseminated histoplasmosis during pregnancy.[109] Presumed ocular histoplasmosis is a destructive retinal lesion; evidence that this disorder is caused by histoplasmosis is weak.[110,111] Presumed ocular histoplasmosis, mediastinal fibrosis,[112] chronic histoplasmosis, osteomyelitis,[54] central nervous system infection,[55,56,113–115] and endocarditis[116] are manifestations that occur almost exclusively in adults. Cavitary pulmonary lesions are observed in adults with preexisting lung disease (e.g., emphysema) but are seen rarely in immunocompetent, previously healthy children. A superior vena cava syndrome that occurred secondary to mediastinal fibrosis and required placement of an intravascular stent was described in a young child with T-lymphocyte deficiency.[117]

Prevention

In endemic regions, patients with cellular immunodeficiencies or HIV infection and people who receive immunosuppressive drugs should be counseled about high-risk activities (see Box 250.1).[97] If such activities are unavoidable, the person should wear a protective mask. Advances in vaccine development have been reviewed in other sources.[118,119]

Key Points

Microbiology, Epidemiology, and Clinical Aspects of Histoplasmosis

Microbiology and Acquisition

- The spore-bearing, mycelial form of *Histoplasma capsulatum* grows in the environment; bird and bat excreta stimulate growth. Inhaled spores convert to the yeast-like (parasitic) form that replicates at 37°C and is recovered from sites of infection.

- Infection results from inhalation of microconidia (spores) produced by the mycelial form of the endemic, dimorphic fungus *H. capsulatum* var. *capsulatum.*

Epidemiology

- Distributed worldwide; highly endemic in the Ohio and Mississippi River valleys of the U.S.

- Infections occur both sporadically and when contaminated sites are disturbed.

Clinical Features

- Severity is proportionate to inoculum size and the degree of functional impairment of cellular immune function; 90% of infections in healthy hosts are subclinical.

- High-inoculum infection may lead to severe pulmonary disease and respiratory failure.

- Common symptoms include low-grade fever, chest pain, weight loss, headache, myalgias, and erythema nodosum (in adolescents).

- Life-threatening, progressive disseminated infection can occur during infancy or in children with acquired or congenital cellular immune dysfunction.

Diagnosis

- In patients who live in or have visited endemic regions, focal pulmonary infiltrates with middle mediastinal lymphadenopathy with or without calcifications is highly suggestive of histoplasmosis.

- Strongly compatible laboratory findings:

▪ Complement fixation antibody titer ≥1 : 32 to yeast or mycelial phase for individuals who reside in an endemic area

▪ Detection of antigen in urine and/or serum

▪ Histopathologic demonstration of granulomatous inflammation associated with yeast-like forms characteristic of *H. capsulatum*

Treatment

- Most mild infections in healthy children resolve without antifungal treatment.

- Nondisseminated infections associated with persistent symptoms can be treated with itraconazole.

- Seriously ill patients, including those with signs of progressive dissemination, require induction therapy with amphotericin B followed by itraconazole.

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251

Pneumocystis jirovecii

Francis Gigliotti, Terry W. Wright

Description of Pathogen

Pneumocystis jirovecii (formerly called *P. carinii*) is an opportunistic parasite that has some of the common features of protozoa, but in which molecular studies have shown greater genetic homology to fungi.[1] *Pneumocystis* organisms have a high degree of host-species specificity; the organisms that infect humans is designated *P. jirovecii*.[2] Alternative acceptable nomenclature retains the use of *P. carinii* but uses the annotation *forma specialis* or *f. sp.* to identify the host of origin; therefore, *P. carinii* that infects humans, rats, or mice would carry the *f. sp.* designation *hominis, ratti,* or *muris*, respectively. Clinicians should be aware that any of these variations may appear in the medical literature.

To date, reliable axenic culture of *Pneumocystis* from any mammalian host has not been achieved. However, specific developmental life forms of *Pneumocystis* have been identified in infected tissue. The 5- to 7-µm cyst contains up to 8 pleomorphic intracystic bodies (sporozoites). Once excysted, sporozoites are believed to become trophic forms (trophozoites). All these forms reside in the alveoli of the lung. Most immunocompetent children have acquired the infection asymptomatically by the age of 4 years. *Pneumocystis* pneumonia (PCP) occurs almost exclusively in severely compromised people, and with rare exceptions the infection remains localized to the lungs. Although pneumonia in immunocompromised patients was presumed to represent reactivation of a latent infection, animal studies have called into question the capacity of *Pneumocystis* to persist as a latent infection.[3]

Epidemiology

Animal-to-animal transmission of *Pneumocystis* by the airborne route has been demonstrated, and DNA sequences identical to those of *Pneumocystis* have been detected in samples of ambient air. Human-to-human transmission has not been proved, but clusters of cases of pneumonia have been reported in immunocompromised patients. Animal-to-human transmission is unlikely because of the well-established genetic and antigenic diversity of the organism related to the host of origin. A natural habitat has not been found, but the infection has a worldwide distribution. Serologic studies have demonstrated that a high proportion of the population has evidence of infection and that seroconversion occurred during childhood. A prospective longitudinal study demonstrated that seroconversion began in the first few months of life and by 20 months of age, 85% of the infants had seroconverted.[4] Animal studies have demonstrated that *Pneumocystis* can be transmitted from healthy host to healthy host, producing very mild disease in the process.[5] This finding, along with the observation of early seroconversion in children, provides a potential explanation of how *Pneumocystis* is maintained in the human population.

Overt disease in the form of pneumonia develops only in immunocompromised people. The occurrence of PCP is related to the extent of immunosuppression, especially impairment of cell-mediated immunity.[6] For example, PCP occurs in about 40% to 50% of infants and children with acquired immunodeficiency syndrome (AIDS) or severe combined immunodeficiency syndrome (SCIDS), in 12% of children with acute lymphocytic leukemia, and in 6% of organ transplant recipients if no prophylaxis is given.

Clinical Manifestations

The signs and symptoms of PCP are directly related to the organisms and to the inflammatory response in the alveolar lumen, septum, or both. Two somewhat different clinical patterns have been observed, which differ only in the intensity of expression.

The endemic infantile form of PCP, originally described in outbreaks in European nursing homes for infants, is an interstitial plasma cell pneumonitis.[7] Its onset is subtle, and it is seen largely in debilitated infants at 4 to 6 months of age. A bronchiolitis-like illness can occur, with prominent tachypnea and dyspnea in the absence of fever. Intercostal retractions are marked, and as the course progresses, flaring of the nasal alae and cyanosis can be observed and crackles are heard bilaterally. In untreated cases the course of the illness is prolonged over many days to a few weeks, and at least half of these patients die.

In older children and adults with an underlying immunodeficiency disorder that is not related to AIDS (e.g., cancer or organ transplantation), PCP begins abruptly with fever, tachypnea, and cough. Intercostal retractions and flaring of the nasal alae can occur, but breath sounds are normal and rales are not heard. The untreated course is progressive, and these patients all die within a month.

The spectrum of clinical manifestations in patients with AIDS can vary from the subtle variety seen in the infantile type to the acute fulminating type. Without treatment the course ends in fatality in almost all patients.

Clinical observations in humans suggest that a poor prognosis in PCP correlates with evidence of inflammation. For example, an elevated level of neutrophils or interleukin-8 in bronchoalveolar lavage fluid correlates with poorer oxygenation and a lower survival rate. Some insight into these observations comes from animal models. Physiologic studies of mice with SCIDS demonstrate that lung injury (decreased compliance, hypoxia, and surfactant dysfunction) is directly related to the *Pneumocystis*-specific inflammatory response rather than to the organism burden per se.[8] In addition, $CD8^+$ T lymphocytes appear to be critical to causing injury in the absence of effective $CD4^+$ T-lymphocyte–mediated immunity. Therefore, developing better means of controlling the inflammatory response could result in an improved outcome for patients with PCP.

Laboratory Findings and Diagnosis

In all clinical types of PCP the arterial oxygen tension (PaO_2) is decreased and reflects the severity of the disease. In moderately severe cases the PaO_2 is below 70 mm Hg and the alveolar-arterial oxygen gradient is above 35 mm Hg. The white blood cell count is unaffected by the infection. In patients with AIDS-related PCP, the $CD4^+$ T-lymphocyte count is usually below the normal range and often is below 200 cells/mm^3 in patients older than 6 years of age. In patients taking immunosuppressive medicines, determining the risk of PCP based on $CD4^+$ T-lymphocyte counts is complicated by the fact that the $CD4^+$ cells present may not be fully functional.

The role of antibody in the control of *Pneumocystis* has been underappreciated. Early descriptions of patients with PCP included patients with primary antibody deficiencies.[9] Patients with hyper-IgM syndrome now are known to be at high risk for PCP.[10,11] These patients lack the CD40 ligand on their T lymphocytes; consequently, these cells are unable to interact properly with B lymphocytes for the production of specific IgG. Mouse models have confirmed the importance of antibody. For example, blocking the CD40 ligand in mice prevents resolution of PCP, a finding consistent with observations in patients with hyper-IgM syndrome.[12] B-lymphocyte–deficient mice (MuMT), which are incapable of normal antibody production but largely have preserved T-lymphocyte function, are naturally susceptible to *Pneumocystis*.[13] Passive administration of *Pneumocystis*-specific antibody to immunosuppressed mice limits the extent of infection.[14]

The chest radiograph typically shows bilateral alveolar disease, which first appears in the perihilar area and then progresses peripherally, often sparing the apical areas (Fig. 251.1). In some cases no radiographic abnormality is detectable at the onset of symptoms. Definitive diagnosis requires demonstration of *Pneumocystis* in the pulmonary parenchyma or in fluid from the lower respiratory tract.[15] The least invasive method for obtaining diagnostic specimens is to induce sputum. This procedure requires the cooperation of the patient and usually is limited to children 5 years of age or older. Typically, 20 to 30 minutes of inhaling a nebulized mist of 3% saline from an ultrasonic nebulizer is required to stimulate adequate expectoration. The sputum specimen is diluted 1 : 1 in sterile saline, treated with dithiothreitol, and processed for cytologic examination and culture. About 20% to 40% of specimens reveal organisms in patients with PCP (Table 251.1). The organism is more likely to be found in the sputum of PCP patients who have AIDS than in those who do not have AIDS because of the greater infectious burden in the former condition.

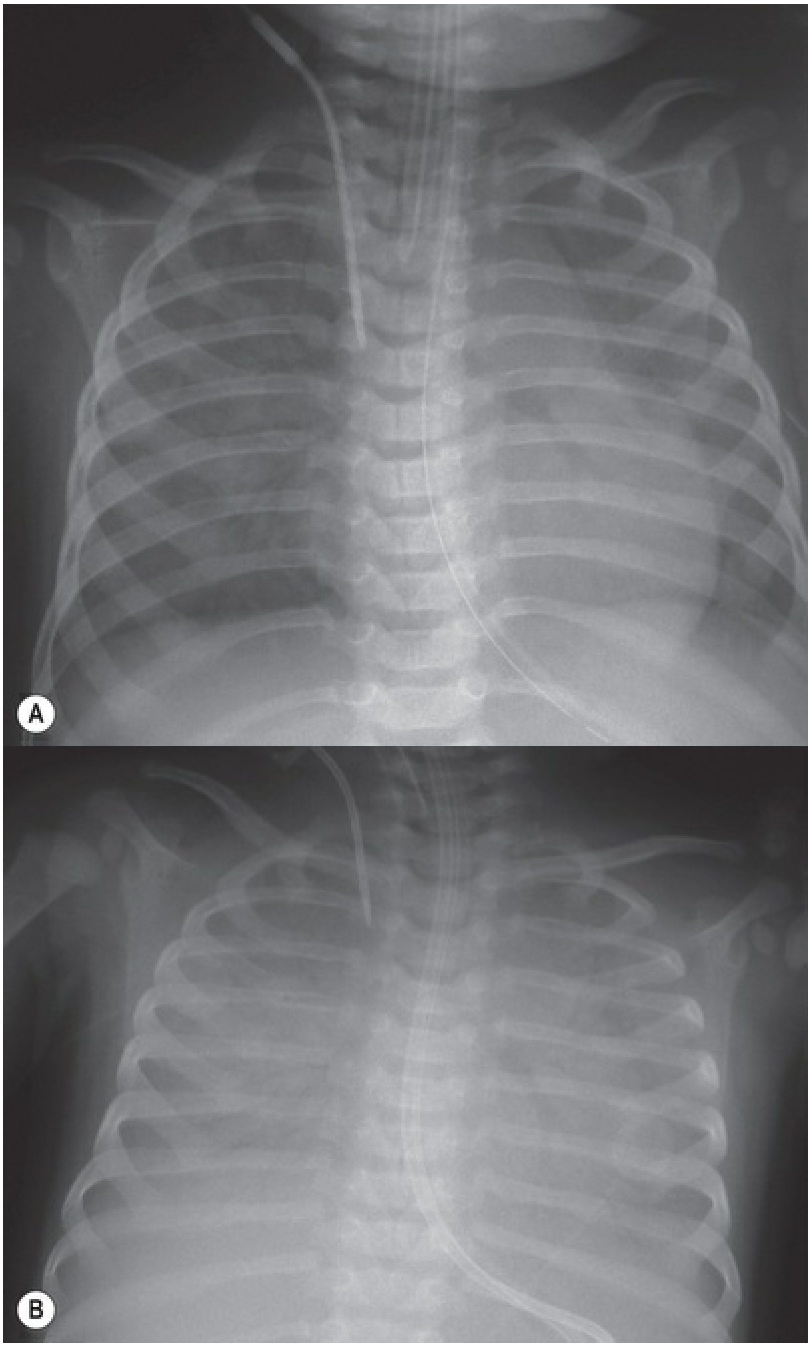

FIGURE 251.1 Typical findings for *Pneumocystis* pneumonia as the presenting manifestation of HIV infection in a 6-month-old infant with a 5-day history of

fever and congestion. The physical examination revealed tachypnea, retractions, flaring, and hypoxia but no rales. A plain radiograph shows bilateral diffuse air-space lung disease (A), which progressed peripherally over 2 days (B). Note apical sparing. (Courtesy E.N. Faerber, J. Chen, and J. Foster, St. Christopher's Hospital for Children, Philadelphia, PA.)

TABLE 251.1

Specimens Tested to Aid Identification of *Pneumocystis* Infection

Method	Sensitivity (%)[a]	Comments
Induced sputum	20–40	≥5 yr
Tracheal aspirate	50–60	First step in intubated patients
Fiberoptic bronchoscopy bronchoalveolar lavage	75–95	Procedure of choice in most patients; both bronchoalveolar lavage and biopsy procedures are preferred
Transbronchial biopsy	75–95	
Open-lung biopsy	90–100	Most sensitive and informative specimen

[a] Estimates of the percentage of specimens expected to be positive in cases of *Pneumocystis* pneumonia.

Bronchoalveolar lavage (BAL) is the method of choice for most patients because it can be performed through a flexible fiberoptic bronchoscope using topical 1% lidocaine anesthesia. A transbronchial lung biopsy also can be performed at the time of bronchoscopy. A successful biopsy should provide at least 20 alveoli for study. With the use of these two procedures, PCP can be identified in nearly 100% of cases.

Open-lung biopsy provides a larger specimen for evaluation of the histopathology of the disease process and for identification of viruses, bacteria, and fungi. However, open biopsy has the disadvantage of requiring general anesthesia and can be complicated by pneumothorax and bleeding.

Specimens should be stained with Giemsa, Grocott-Gomori, or fluorescein-labeled antibody stains (Fig. 251.2). Other useful stains include toluidine blue O and Gram-Weigert stains. Specimens also should be inoculated onto culture media for bacteria and fungi and onto shell viral culture for viruses (especially cytomegalovirus). Many research laboratories are performing polymerase chain reaction testing to identify *Pneumocystis* in a sputum or BAL sample. These investigations may lead to diagnostic assays that can be adapted to clinical laboratories.

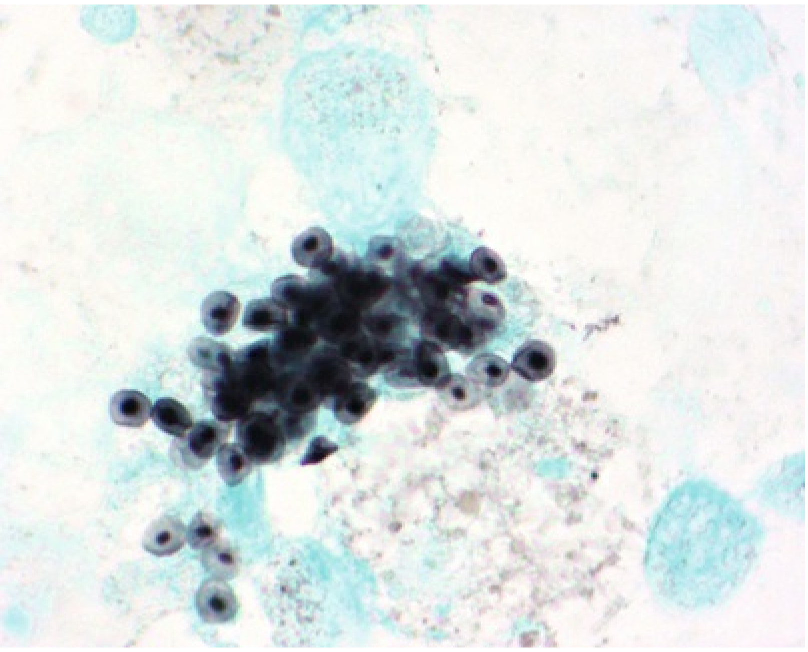

FIGURE 251.2 A bronchoalveolar lavage specimen, stained using the Grocott-Gomori method, shows the dark staining (brown to black) of *Pneumocystis* cysts. These cysts measure 5 to 6 μm in diameter. This method stains background tissue light green.

Special Considerations

Under certain circumstances, forgoing an invasive diagnostic procedure and treating the patient on the basis of a presumptive diagnosis of PCP may be prudent, such as in children with terminal stages of untreatable cancer and patients with uncontrollable bleeding disorders. When an invasive diagnostic procedure is planned, knowing that *Pneumocystis* persists in the lungs for many days after the onset of specific therapy is useful; therapy can be initiated immediately and the procedure performed hours later under optimal circumstances.

Treatment

Table 251.2 presents the drugs and dosage schedules used in the treatment of PCP. Trimethoprim-sulfamethoxazole (TMP-SMX), the drug of choice, is available both for oral and for intravenous therapy. The oral route of administration can be used in mild cases if the patient can take and retain oral medication dependably. However, most patients require at least initial treatment by the intravenous route. The course of treatment is 2 to 3 weeks for most children. Because all immunocompromised patients require posttreatment prophylaxis, the dose of TMP-SMX is reduced to the prophylaxis dose after recovery and continued indefinitely or until the immunodeficiency has resolved.

TABLE 251.2

Recommended Treatments for Infants, Children, and Adolescents With *Pneumocystis* Pneumonia[a]

Drug	Infant and Child Dosage	Adolescent and Adult Dosage
Trimethoprim-sulfamethoxazole (TMP-SMX) (drug of choice)	**TMP**	**TMP**
	15–20 mg/kg/day, PO or IV, divided into 4 doses	15–20 mg/kg/day, PO or IV, divided into 4 doses
	SMX	**SMX**
	75–100 mg/kg/day, PO or IV, divided into 4 doses	75–100 mg/kg per day, PO or IV, divided into 4 doses
Pentamidine (alternate of choice)	4 mg/kg/day, IV (infused over ≥60 min), once daily	4 mg/kg/day, IV (infused over ≥60 min), once daily
Atovaquone	3–24 mo of age: 45 mg/kg/day, PO, divided into 2 doses 1–3 mo and >24 mo of age: 30 mg/kg/day, PO, divided into 2 doses (maximum daily dose, 1500 mg)	1500 mg/day, PO, divided into 2 doses, with food
Dapsone plus trimethoprim	**Dapsone**	**Dapsone**
	2 mg/kg per day (maximum 100 mg), PO, once daily	100 mg per day, PO, once daily
	Trimethoprim	**Trimethoprim**
	15 mg/kg per day, PO, divided into 3 doses	15 mg/kg per day, PO, divided into 3 doses
Primaquine plus clindamycin	**Primaquine**	**Primaquine**
	0.3 mg/kg/day (maximum, 30 mg), PO, once daily	15–30 mg, PO, once daily
	Clindamycin	**Clindamycin**
	40 mg/kg/day, IV, divided into 4 doses (no pediatric data for this regimen)	800 mg/day, IV, divided into doses every 8 hr
Trimetrexate plus leucovorin	**Trimetrexate**	**Trimetrexate**
	45 $mg/m^2/day$, IV or PO, once daily	45 $mg/m^2/day$, once daily *OR* <50 kg: 1.5 mg/kg/day, IV, once daily 50–80 kg: 1.2 mg/kg/day, IV, once daily

		>80 kg: 1 mg/kg/day, IV, once daily
	Leucovorin	**Leucovorin**
	20 mg/m^2/day, IV or PO, divided into doses every 6 hr (continue 3 days beyond trimetrexate)	<50 kg: 0.8 mg/kg/day, IV or PO, divided into doses every 6 hr >50 kg: 0.5 mg/kg/day, IV or PO, divided into doses every 6 hr (continue 3 days beyond trimetrexate)

[a] General duration of therapy is 3 weeks in patients with AIDS and 2 weeks in other immunosuppressed patients. Prednisone is recommended as adjunctive therapy to any antimicrobial therapy for moderate or severe *Pneumocystis* pneumonia (room air arterial oxygen tension ≤70 mmHg or an alveolar-arterial gradient ≤35 mmHg).

IV, intravenous; PO, orally; TMP-SMX, trimethoprim-sulfamethoxazole.

Adverse reactions to TMP-SMX are uncommon in patients without AIDS (~5%) but occur frequently in children with AIDS (~40%). An erythematous, maculopapular rash is the most common adverse effect. The rash often is transient and may clear without withdrawal of the drug; however, progressive intensive rashes, especially urticaria, require discontinuation of the drug. In rare cases, Stevens-Johnson syndrome can occur secondary to the sulfonamide and can have serious consequences. Other adverse effects include neutropenia, megaloblastic or aplastic anemia, renal dysfunction, nausea, vomiting, and diarrhea.

Patients who cannot tolerate or who fail to respond to TMP-SMX should be treated with intravenous pentamidine isethionate. If intravenous access is not available, the drug can be given by deep intramuscular injection, but serious reactions at the injection site are common (e.g., soft tissue necrosis and abscess). Other adverse reactions, which occur in up to 70% of cases, include renal and hepatic dysfunction, thrombocytopenia, anemia, hypotension, abnormally high or low blood glucose concentrations, and rash.

Several other drugs have been shown to have activity against *Pneumocystis* but have not been studied extensively in children. They include atovaquone, an oral hydroxynaphthoquinone; trimetrexate, a drug for intravenous use that must be given concomitantly with leucovorin; TMP-dapsone, given orally; pyrimethamine-sulfadoxine (Fansidar), given orally; clindamycin plus primaquine, given orally; and aerosolized pentamidine.

Supportive measures are important in the management of PCP. The PaO_2 should be maintained above 70 mm Hg; in addition, if possible, the inspired oxygen fraction (FiO_2) should be kept below

50 vol%. If the PaO_2 cannot be maintained at 60 mm Hg or higher, assisted ventilation usually is indicated. Anemia should be corrected with a packed red blood cell transfusion.

Several studies in adults suggest that administration of a corticosteroid in severe and moderately severe cases of PCP improves survival. Limited data in children indicate similar effects.[16] It is reasonable to consider corticosteroid administration at the onset of treatment in patients with a PaO_2 below 70 mm Hg or an alveolar-arterial gradient of 35 mm Hg or greater. Methylprednisolone (2 mg/kg/day) has been used in children. The dose should be tapered and the corticosteroid discontinued in the recovery stage of the pneumonia. The corticosteroid's effect in this setting probably is modulation of the inflammatory response.

The animal data[8] linking pulmonary morbidity with the *Pneumocystis*-induced inflammatory response suggest that better means of controlling this inflammatory response could result in improved outcomes in patients with PCP.

Prevention

Four drugs are available for the prevention of PCP (Table 251.3). TMP-SMX or aerosolized pentamidine is used most frequently, but only TMP-SMX has been studied in children. Comparative studies in adults show that TMP-SMX is superior to aerosolized pentamidine for preventing PCP in patients with AIDS, although the frequency of adverse reactions is greater with TMP-SMX. The prophylactic dose is 5 mg TMP and 25 mg SMX/kg/day in 2 divided doses. The drug can be given daily or only 3 days per week. The 3-day schedule should be on consecutive days, such as Monday, Tuesday, and Wednesday.[17] Some evidence suggests that TMP-SMX may prevent certain bacterial infections in addition to *Pneumocystis*. If this effect is sought, the daily dosage schedule should be used.

TABLE 251.3

Recommended Prophylaxis for Recurrence of *Pneumocystis* Pneumonia After Treatment in HIV-Infected Infants, Children, and Adolescents

Age Category	First Choice	Alternatives

Infants and children	TMP-SMX orally	Dapsone orally *or* Aerosolized pentamidine *or* Pentamidine intravenously
Adolescents	TMP-SMX orally	Dapsone orally *or* Dapsone + pyrimethamine + folinic acid orally *or* Aerosolized pentamidine *or* Atovaquone orally

TMP-SMX, Trimethoprim-sulfamethoxazole.

For patients who cannot tolerate TMP-SMX, aerosolized pentamidine can be tried in children who are old enough and able to cooperate with administration.[18] Most children age 5 years or older can tolerate treatment with aerosolized pentamidine. A dosage has not been established, but 300 mg delivered in a Respirgard II nebulizer once monthly is reasonable and well tolerated. The main adverse effects are cough and bronchospasm. For patients ≤5 years of age and those who cannot tolerate aerosolized pentamidine or TMP-SMX, dapsone given orally at a dosage of 2 mg/kg/day or 4 mg/kg once weekly can be used. Dapsone is effective in preventing PCP, but adverse reactions similar to those caused by sulfonamides can occur. The total dosage should not exceed 100 mg per day, or 200 mg weekly. Atovaquone at a dose of 1500 mg given orally once daily appears to be equal to pentamidine and dapsone for preventing PCP in adults. Atovaquone has not been well studied in children; however, a dosage of 30 mg/kg once daily is suggested for children 1 to 3 months of age, and for those older than 24 months of age; a dosage of 45 mg/kg once daily is suggested for children 4 to 24 months of age.[19]

Several risk factors for PCP have been recognized, and these guide the selection of candidates for prophylaxis. Prophylaxis is important for immunosuppressed patients who have had one episode of PCP; children with severe cell-mediated immunodeficiency, such as occurs with SCIDS, organ transplantation, and AIDS; and children with lymphoproliferative malignancies and other types of malignancy that require intensive chemotherapy.

In infants and children with AIDS, the CD4$^+$ T-lymphocyte count or percentage can be used as the criterion for primary prophylaxis.[19] However, approximately one half of the cases of PCP in infants with AIDS occur as the initial manifestation of AIDS, with a high mortality. All infants exposed to or infected with HIV should receive PCP prophylaxis between 1 month and 1 year of age, or until HIV infection has been ruled out, because of the high risk of pneumonia in this age group. After 1 year of age the CD4$^+$ lymphocyte count and percentage serve as the guide (Table 251.4).

TABLE 251.4

Recommended Primary Prophylaxis for *Pneumocystis* Pneumonia in HIV-Infected Infants and Children by Age and CD4$^+$ Count or CD4$^+$ Percentage

Age	CD4$^+$ Count	CD4$^+$ %
1–12 mo	All infants	All infants
12–23 mo	<750/mm^3	<15
24 mo–5 yr	<500/mm^3	<15
≥6 yr	<200/mm^3	<15

Chemoprophylaxis does not ensure complete protection from PCP. Breakthrough infections occur in at least 6% of those treated with TMP-SMX and in about 12% of those receiving aerosolized pentamidine or oral dapsone. For children who have adverse reactions to TMP-SMX, desensitization can be attempted by escalating from extremely small doses to full doses.[20] This approach has been applied successfully in patients with AIDS. Prophylaxis is effective only during the intervals when the patient is taking the drug; therefore, an effort must be made to ensure adherence in high-risk patients and to continue prophylaxis when patients are hospitalized.

In adults with HIV infection who are receiving combination antiretroviral therapy, primary and secondary prophylaxis against PCP can be discontinued safely after the CD4$^+$ lymphocyte count has been 200/mm^3 or higher for longer than 3 months.[21] A similar approach is recommended for children who have received at least 6 months of combination antiretroviral therapy and whose CD4$^+$ lymphocyte counts have returned to normal levels for age.[19]

Key Points

Diagnosis and Management of *Pneumocystis* Pneumonia

Microbiology

- Fungal organism that cannot be grown in culture
- Displays tight host-species specificity

Epidemiology

- Acquired by inhalation
- Key risk factor is decreased lymphocyte number or function or both.

Diagnosis

- Hypoxia is the pathognomonic feature.
- Based on demonstration of *Pneumocystis* organisms in a pulmonary specimen

Treatment

- Trimethoprim-sulfamethoxazole is the drug of choice.
- Response to treatment is slow, typically 4–5 days.

Duration of Therapy

- Three weeks for patients who have AIDS or other forms of severe immunosuppression
- Two weeks for other patients

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252

Blastomyces dermatitidis (Blastomycosis)

Gregory M. Gauthier, Bruce S. Klein

Blastomyces dermatitidis, the etiologic agent of blastomycosis, can infect both people with healthy immune systems and those with impaired immune defenses. Most infections are sporadic; however, 16 outbreaks have been reported, of which 13 involved pediatric patients.[1–16] An estimated 2% to 13% cases of blastomycosis occur in patients 18 years old or younger.[17–23] Clinical manifestations of blastomycosis range from asymptomatic infection to acute pneumonia, chronic pulmonary infection, disseminated disease, and acute respiratory distress syndrome[1,24,25]

Microbiology

B. dermatitidis belongs to a group of human pathogenic fungi that undergo a temperature-dependent conversion between two distinct morphologic forms, mycelia and yeast.[26] In the soil (22°C to 25°C), *B. dermatitidis* grows as septated mycelia (1 to 2 μm in diameter) that produce infectious spores (4 to 5 μm in diameter).[27,28] Soil disruption by human activities (e.g., construction) aerosolizes mycelial fragments and spores, which convert to yeast when inhaled into the lungs of a human host (37°C).[26] *B. dermatitidis* yeast, which are 8 to 15 μm in size, have a distinct morphologic appearance characterized by a broad-based bud and a refractile (i.e., double-contoured) cell wall (Fig. 252.1).[27,28]

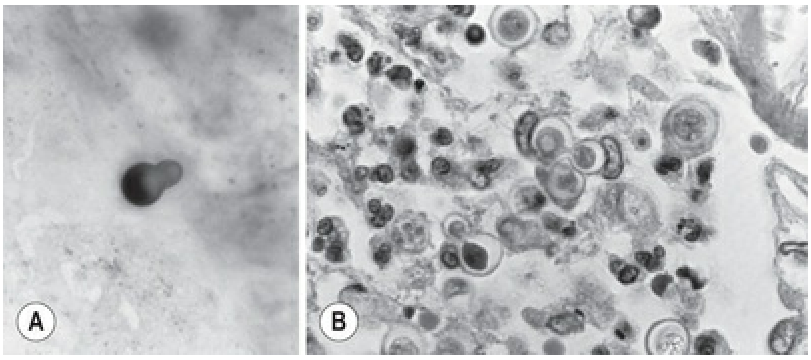

FIGURE 252.1 (A) Cutaneous blastomycosis. Touch preparation of a skin biopsy showing a single *Blastomyces dermatitidis* yeast-like cell with a broad-based bud. Gomori methenamine silver nitrate stain, ×1000. (B) Acute pulmonary blastomycosis. Single yeast-like cells with doubly contoured walls and two prominent, budding yeast-like cells of *B. dermatitidis* seen in a suppurative exudate. In histopathologic sections of involved tissues, finding yeasts 8 to 15 μm in diameter with single, broad-based buds is considered diagnostic. The inflammatory reaction can be acute, suppurative, or granulomatous. Hematoxylin and eosin, ×1000.

In addition to growing as mycelia or yeast, *Blastomyces* organisms exist in an asexual (imperfect, anamorphic) state or a sexual (perfect, teleomorphic) state. *B. dermatitidis* is the name for the asexual state, and *Ajellomyces dermatitidis* is the name for the teleomorphic state.[29] Sexual reproduction in *B. dermatitidis* occurs in the mycelial phase when hyphae with different mating-type loci (e.g., MAT1-1 and MAT1-2) fuse and form specialized reproduction structures.[29] Although mating contributes to genetic diversity, its impact on virulence is unknown.[29,30] Recent molecular analysis of clinical and environmental isolates suggests that *Blastomyces* can be divided into two phylogenetic species, *B. dermatitidis* and *B. gilchristii* sp. nov.[31]

Pathogenesis and Immunity

The reversible switch between mycelial and yeast morphologies is critical to the biology and life cycle of *B. dermatitidis* and those of other thermally dimorphic fungi.[30] Growth as mycelia (22°C to 25°C) promotes environmental survival and transmission to new hosts by infectious spores, in addition to genetic diversity through sexual reproduction.[30] Growth in the yeast phase (37°C) facilitates evasion of hosts' immune defenses.[30] Inhaled spores are phagocytosed by pulmonary macrophages and converted to yeast organisms, which survive and replicate within macrophages during the early stages of *Blastomyces* infection.[32] Extrapulmonary dissemination occurs by lymphohematogenous spread, and in children this most commonly affects the skin and bones.[33]

Genetic regulation of the morphologic switch between mycelial and yeast forms has been the focus of intense research, given the importance of this event on pathogenesis. The discovery of dimorphism-regulating kinase-1 (*DRK1),* which encodes a histidine kinase, provided the first genetic proof (by deletion experiments in the mouse model) that the conversion from mycelia (or spores) to yeast was essential for virulence.[34] The function of *DRK1* also is conserved in other dimorphic fungi, such as *Histoplasma capsulatum* and *Talaromyces marneffei* (formerly *Penicillium marneffei*).[34,35] The reverse morphologic switch, from yeast to mycelia, is regulated by a transcription factor encoded by *SREB* (siderophore biosynthesis repressor in *Blastomyces*) and is influenced by N-acetylglucosamine transporters *NGT1* and *NGT2*.[36,37]

In the yeast phase an immunogenic protein encoded by *Blastomyces* adhesin-1 (*BAD1,* formerly *WI-1*) is upregulated and is essential for virulence in the mouse model; also, its structure has been defined.[38–41] BAD1 functions as an adhesin that binds yeast cells to host tissue and acts as an immune evasin to downregulate host immune defenses.[40] The core tandem repeats bind heparin sulfate in host tissues to promote adherence of yeast.[40] Soluble and cell wall–bound BAD1 bind CR3 and CD14 receptors, impairing production of tumor necrosis factor-α (TNF-α) by macrophages and neutrophils.[42–44] BAD1 also inhibits activation of CD4$^+$ T lymphocytes, reducing production of interferon γ (INFγ) and interleukin-17 (IL-17).[40] The ability of BAD1 to induce a humoral immune response has been used to develop a new sensitive and specific serologic test for diagnosis of blastomycosis.[45]

The cells of the innate and adaptive immune system are critical for host defense against *B. dermatitidis* infection, whereas humoral immunity is dispensible.[46] Alveolar macrophages and neutrophils are capable of killing some, but not all, spores inhaled into the lungs. Spores that survive the initial host response germinate as yeast organisms, which are relatively resistant to reactive oxygen species, suppress nitric oxide production, inhibit cytokine production, and impede CD4$^+$ T-lymphocyte activation.[40,43,44,47–49] Despite the ability of *B. dermatitidis* to modulate host immune responses, Th1 and Th17 T lymphocytes can activate macrophage fungicidal activity to successfully combat infection in some patients.[50,51] Approximately 50% of those infected with *B. dermatitidis* develop asymptomatic or subclinical infections.[1] After recovery from blastomycosis, children and adults develop T-lymphocyte–mediated immunity against *B. dermatitidis* that can last for at least 2 years.[52]

Epidemiology

The lack of reliable skin and serologic tests, difficulty in isolating the fungus from the environment, and reliance on passive surveillance and retrospective studies have hampered the development of in-depth epidemiologic knowledge about *B. dermatitidis*.[53] Currently blastomycosis is reportable in only 6 of the United States and in 2 Canadian provinces. Although underestimated, the incidence of blastomycosis ranges from 0.2 to 1.94 cases per 100,000 population annually.[18,20,54–59] The geographic range of *B. dermatitidis* in North America includes the Mississippi River and Ohio River basins, areas along the St. Lawrence River in New York, the southeastern U.S., and 4 Canadian provinces (Fig. 252.2). In the endemic region *B. dermatitidis* grows in an ecologic niche near freshwater sources (rivers, streams, lakes) that have sandy soils with an acidic pH and decaying vegetation or rotting wood.[1,12,60–63] Although rare, autochthonous cases of human blastomycosis have been reported from Africa (approximately 100 cases) and India (fewer than 10 cases).[64–69]

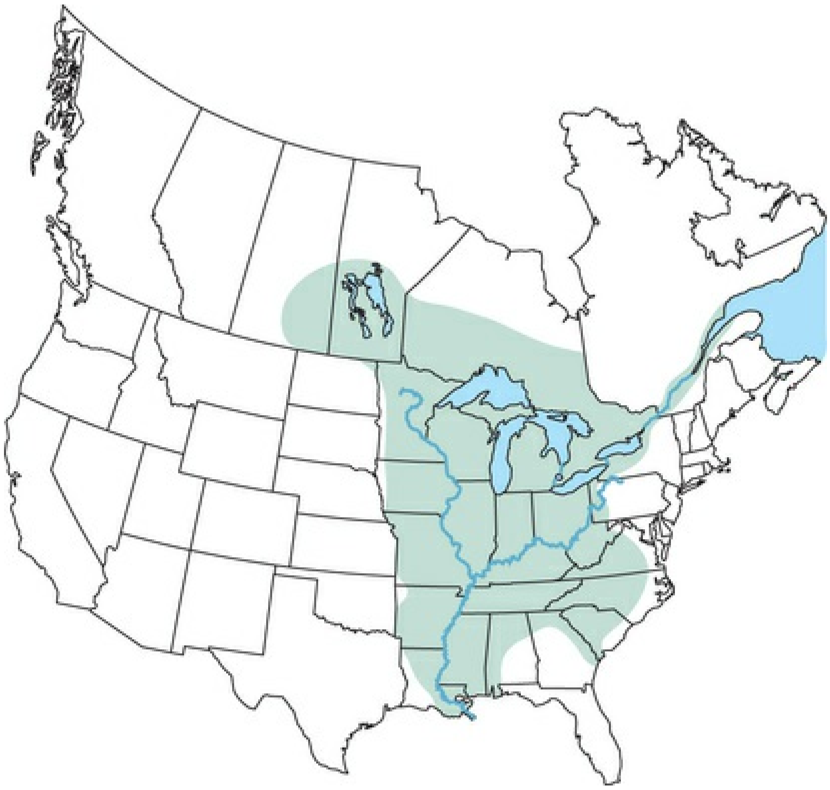

FIGURE 252.2 Map of North America showing the endemic region for infection. Shaded area on the map represents the endemic region. (From Gauthier GM. *Blastomyces dermatitidis* and blastomycosis. In: Sullivan DJ, Moran GP [eds]. Human Pathogenic Fungi. Caister Academic Press, Norfolk, U.K., 2014.)

The vast majority of patients with blastomycosis acquire the infection by inhaling spores and mycelial fragments after disruption of the soil. Activities associated with acquisition in sporadic or outbreak settings include home remodeling, road construction, hunting, clearing brush and cutting trees, using a community compost pile, exploration of underground forts and beaver dams, and canoeing or fishing in endemic regions.[1–16,55] In rare cases, *B. dermatitidis* infection can result from cutaneous trauma (e.g., laboratory accident, bite of an infected dog) or perinatal exposure.[62] Although most cases of blastomycosis are sporadic, 16 well-described outbreaks have been reported.[1–16]

Clinical Manifestations

The incubation period for blastomycosis ranges from 3 weeks to 3.5 months.[1,17,70] The average age of pediatric patients with blastomycosis is 9 to 12 years (range, 18 days to 18 years).[24,33,71–74]

Blastomycosis is rare in neonates and infants.[75] In most studies the gender distribution is skewed toward males.[24,33,71,72,74]

Clinical manifestations of pulmonary infection are variable and include nonspecific symptoms, such as headache, cough, chest pain, weight loss, fever, abdominal pain, and night sweats (Table 252.1)[17,24,71] In two recent case series, 38% to 53% of patients with sporadic blastomycosis had disseminated disease.[24,71] The skin, bone, and central nervous system (CNS) were the most common sites of extrapulmonary infection (Table 252.1). In contrast, disseminated disease in children infected in an outbreak setting is rare (Table 252.1).[1,17] Pulmonary blastomycosis can be complicated by respiratory failure, acute respiratory distress syndrome, and death. The full clinical spectrum of blastomycosis is summarized in Fig. 252.3.[76]

TABLE 252.1

Clinical Manifestations of Blastomycosis in Case Series of Pediatric Patients

	Wisconsin[a,1,17]	Manitoba[b,71]	Wisconsin[b,24]
Number of patients	46	34	17
Average age	NR	10 ± 5 yr	12.2 ± 4.4 yr
Age range	NR	0.4–18 yr	2–18 yr
Fever	30%	68%	65%
Shortness of breath	15%	74%	12%
Cough	50%	32%	71%
Weight loss	33%	29%	47%
Headache	37%	24%	24%
Fatigue, weakness, or malaise	NR	53%	35%
Chest pain	35%	NR	24%
Abdominal pain, nausea, or vomiting	28%	NR	18%
Night sweats	28%	NR	29%
Extrapulmonary blastomycosis	0%	38%	53%
Cutaneous blastomycosis	0%	29%	35%
Skeletal blastomycosis	0%	21%	41%
Central nervous system blastomycosis	0%	15%	18%

[a] Outbreak of blastomycosis in northern Wisconsin in 1984.

[b] Single center, retrospective study of sporadic blastomycosis.

NR, Data not reported

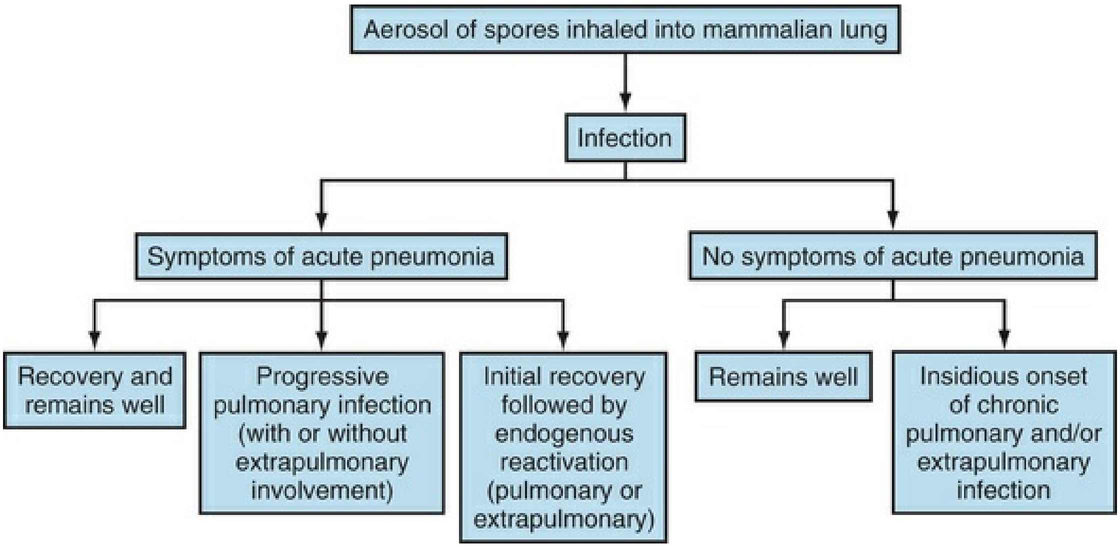
Aerosol of spores inhaled into mammalian lung
Infection
Symptoms of acute pneumonia
No symptoms of acute pneumonia
Recovery and remains well
Progressive pulmonary infection (with or without extrapulmonary involvement)
Initial recovery followed by endogenous reactivation (pulmonary or extrapulmonary)
Remains well
Insidious onset of chronic pulmonary and/or extrapulmonary infection

FIGURE 252.3 Spectrum of clinical illness in blastomycosis. (Redrawn from Sarosi GA, Davies SF. Blastomycosis. Am Rev Respir Dis 1979;120:911–938.)

Acute and Chronic Pulmonary Infection.

Acute pulmonary infection is the most common manifestation of blastomycosis in children.[24,33,71–74,77] The spectrum of severity ranges from mild or no illness (Fig. 252.4) to respiratory failure, including acute respiratory distress syndrome.[25,75,77] Symptoms often mimic community-acquired pneumonia and include fever, chills, a productive cough with or without hemoptysis, shortness of breath, chest pain, and malaise.[17,24,71,73,78] Cutaneous findings (e.g., plaques, nodules, or ulcers) in a patient with pneumonia are highly suggestive of fungal pneumonia, including blastomycosis. Immune-mediated cutaneous findings (e.g., erythema nodosum or erythema multiforme), which can be observed in patients with histoplasmosis or coccidioidomycosis, are rare with blastomycosis.[78,79] Unrecognized or untreated acute pulmonary blastomycosis can lead to chronic pneumonia, characterized by fever, night sweats, weight loss, cough, and chest pain. Chronic pulmonary blastomycosis mimics tuberculosis, other mycoses, and neoplasms.

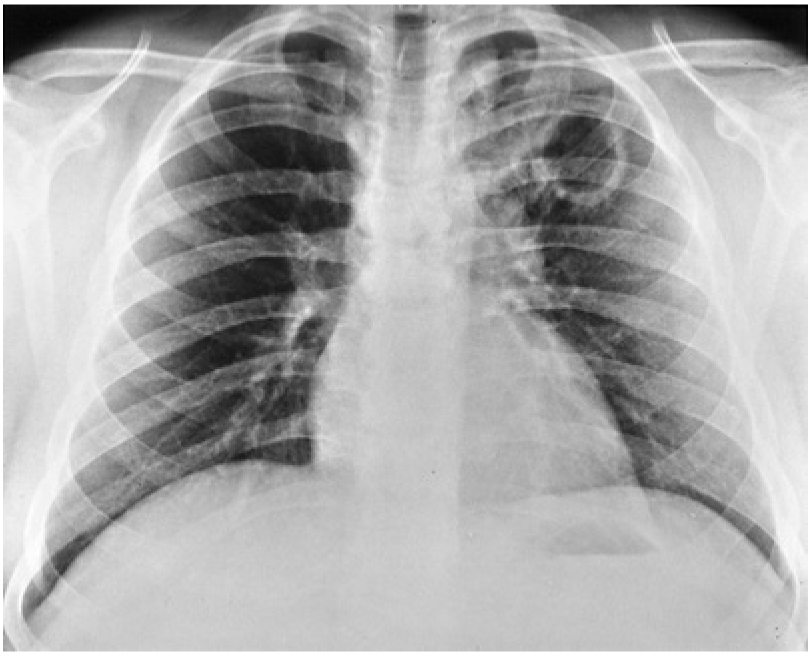

FIGURE 252.4 Chest radiograph of an 18-year-old man with insulin-dependent diabetes mellitus who had hemoptysis of 2 days' duration; he described no fever and no antecedent respiratory symptoms. The radiograph shows a large cavitary lesion in the left upper lobe and enlargement of a left hilar lymph node (hilar lymphadenopathy is uncommon in pulmonary blastomycosis).

Radiographic manifestations are heterogeneous and nonspecific. The most frequent radiographic pattern is consolidation, which is indistinguishable from that seen in community-acquired pneumonia.[71,80,81] Nodular and interstitial infiltrates also are common. Masses and cavities, which mimic malignancy and tuberculosis, are infrequent in children.[71,80,81] Hilar lymphadenopathy and calcification are rare in blastomycosis. Pleural effusion is uncommon. In patients with severe disease, radiographic findings can be slow to resolve; however, most patients recover without long-term pulmonary sequellae.[81,82]

Extrapulmonary Manifestations.

Extrapulmonary blastomycosis occurs in more than one half of pediatric patients and can involve any organ. The duration of infection (i.e., time from symptom onset to diagnosis), rather than age, is thought to influence the rate of dissemination.[17,33,71] Most patients with disseminated disease have concurrent pulmonary symptoms or chest radiographic abnormalities; however, pulmonary disease can resolve before disseminated blastomycosis is diagnosed.[24,75]

Cutaneous Manifestations.

Skin lesions are common in disseminated infections, observed most often in sporadic cases and infrequently in outbreak settings.[1,17,83] Cutaneous disease often begins as minimally tender papules that evolve into verrucous or ulcerative lesions; both types can be present simultaneously. Verrucous lesions have raised irregular borders, crusting, and purulent drainage (Fig. 252.5A). In ulcerative forms, borders are sharp and heaped up and granulation tissue and exudate are seen centrally (Fig. 252.5B). Chronic disseminated cutaneous blastomycosis has been reported rarely.[84] Histopathologic findings characteristic of blastomycosis include pseudoepitheliomatous hyperplasia with neutrophilic and granulomatous inflammation (i.e., pyogranulomatous inflammation).[85]

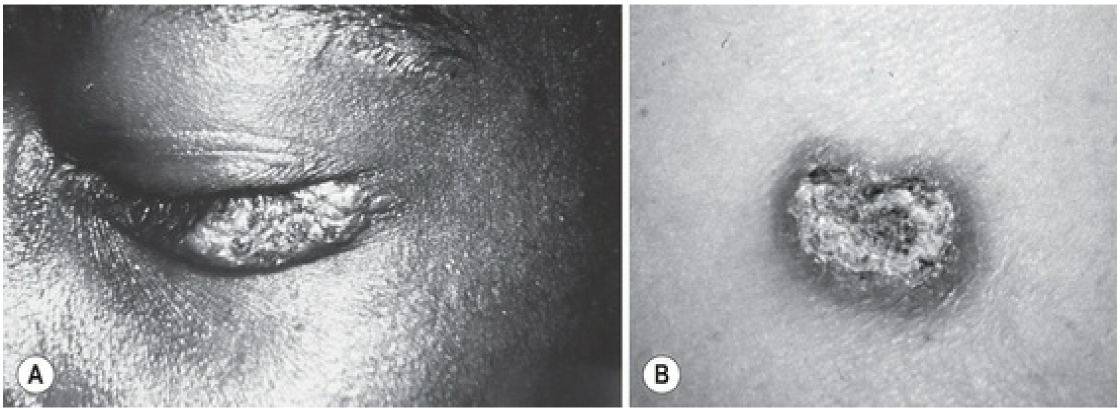

FIGURE 252.5 **Cutaneous lesions of blastomycosis. (A) Verrucous lesion characterized by crusting and induration. (B) Ulcerated lesion.**

Osseous Manifestations.

Acute or subacute suppurative osteomyelitis occurs in 21% to 50% of children with sporadic blastomycosis.[24,33,71] The most commonly affected bones are the long bones (e.g., tibia, femur), vertebral bodies, ribs, and skull (Fig. 252.6).[21,71,74,86–89] Blastomycotic osteomyelitis is characterized by lytic bone destruction with associated bone pain. Complications include pathologic fracture;

vertebral body collapse; soft tissue abscess with or without sinus tract formation; and extension into the joint space, causing septic arthritis.[72,88]

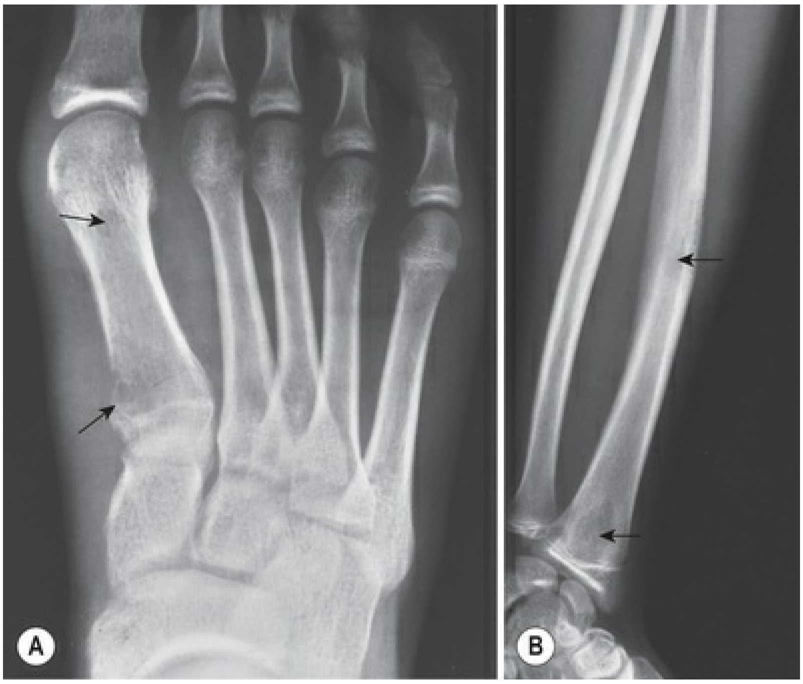

FIGURE 252.6 Radiographs from a 16-year-old boy who complained of pain of 2 months' duration in his right foot and right forearm. He had no fever, but he had lost 5.9 kg (13 lb). (A) Radiolucent areas in the proximal and distal first metatarsal *(arrows).* (B) Lucent areas of the distal metaphysis and midshaft of the radius *(arrows).*

Central Nervous System Manifestations.

Dissemination of blastomycosis into the CNS is uncommon; however, 15% to 18% of patients in two recent case series from the U.S. and Canada had CNS blastomycosis.[24,71] Typically, CNS dissemination occurs in less than 5% to 10% of immunocompetent patients.[21,90] Clinical manifestations include meningitis and abscess, which can be complicated by hydrocephalus, cerebral herniation, mass effect, seizures, and panhypopituitarism.[71,90] Cerebrospinal fluid (CSF) findings include lymphocytic or neutrophilic pleocytosis, an elevated protein level, and a low glucose level.[90] The sensitivity of CSF fungal culture is a suboptimal 45%.[90] In patients with obstructive hydrocephalus, ventricular fluid is more likely to be diagnostic than CSF obtained by lumbar puncture.[91]

Unusual Manifestations.

Rare sites of dissemination include the middle ear, peritoneum, spleen, heart, kidney, larynx, and oral cavity.[72–74,77] Otitis media is frequently due to extension into the middle ear from an extra-auditory site of infection.[92–94] Infections of the prostate gland or epididymis, which occur in adults, have not been reported in prepubescent children.[74]

Laboratory Findings and Diagnosis

The most important "diagnostic test" is to include *B. dermatitidis* as part of the differential diagnosis in patients with pneumonia, cutaneous lesions, or osteomyelitis. Because blastomycosis can mimic infection with neoplasms and either bacteria or mycobacteria, correct diagnosis and initiation of antifungal therapy often are delayed.[21,71,95] Lack of response to therapy for community-acquired pneumonia should raise suspicion. The combination of pneumonia and cutaneous lesions is highly suggestive. Blastomycosis in a family pet provides a diagnostic clue and points to a common-source exposure.[6,96] A detailed history that focuses on determining potential exposures is important; these include residential location, travel, disruption of soil (e.g., home remodeling, road or building construction), outdoor activities (e.g., hunting, fishing, canoeing), logging or tree cutting, and use of community compost.

Mild anemia, leukocytosis (with a mild increase in band forms), and an elevated erythrocyte sedimentation rate are common but nonspecific findings.

Direct Examination and Culture.

A rapid diagnosis can be established through identification of yeast with a broad-based budding pattern in specimens of sputum, bronchial washings, body fluids, or tissue.[53] *B. dermatitidis* is never a commensal. Potassium hydroxide (10% KOH) and calcofluor are used to stain yeast in sputum and body fluids, whereas Gomori methenamine silver (GMS) and periodic acid-Schiff (PAS) are used to stain tissue (see Fig. 252.1).[53] *B. dermatitidis* yeast can be difficult to visualize using hematoxylin and eosin staining. Tissue specimens showing neutrophilic infiltration and granulomas should be examined thoroughly for broad-based budding yeast using GMS or PAS stains.

Culture of *B. dermatitidis* from sputum, tissue, or body fluids provides a definitive diagnosis, but growth can take 1 to 4 weeks. In most mycology laboratories, *B. dermatitidis* is incubated at 25°C to 30°C on Sabouraud dextrose agar, brain-heart infusion, or potato dextrose agar.[53] At this temperature, *B. dermatitidis* grows as mycelia and requires confirmatory testing by a chemiluminescent DNA probe assay or exoantigen test, or by conversion to the yeast form at 37°C.[53,97] The latter test is rarely performed because mycelia-to-yeast conversion is slow in vitro. Protocols for reverse transcriptase polymerase chain reaction amplification of BAD1 and *DRK1* have been developed but are not available commercially.[98,99]

Serologic Tests.

Serologic testing by complement fixation or immunodiffusion has poor sensitivity and specificity.[70] In a large outbreak investigation the complement fixation, immunodiffusion, and enzyme immunoassay were positive in 9%, 28%, and 77% of cases, respectively.[1,70] A commercial antibody test based on BAD1 has a sensitivity of 87% and a specificity of 94% to 99%.[45] When this test is used in combination with antigen testing (see next section), the sensitivity increases to 97%.[45]

Antigen Tests.

An antigen assay that detects a galactomannan from the cell wall of *B. dermatitidis* was developed in 2004[100] and has supplanted antibody tests. Appropriate specimens for antigen testing are urine, blood, bronchoalveolar lavage fluid, and cerebrospinal fluid.[100–103] The sensitivity of the antigen test, which is 85% to 93% on urine and 57% to 82% on serum,[101,102] is influenced by the burden of infection. The sensitivity of the urine antigen test is only 50% in localized pulmonary disease.[101] Moreover, cross-reactions are common with *Histoplasma* (96%) and occur rarely with *Aspergillus* and *Cryptococcus*.[100] The BAD1 serologic test has the potential to differentiate blastomycosis from histoplasmosis.[45] Major cross-reactions with *Paracoccidioides* (100%) or *T. marneffei* (70%) are problematic if the patient has traveled or resided in Central or South America, or Southeast Asia, respectively. Although clinical data are limited, antigen levels in the urine or serum can be used to monitor the response to antifungal therapy.[104]

Treatment

Antifungal therapy is recommended for all pediatric patients with blastomycosis. The antifungal selection is based on the severity of the disease, immunocompromise, CNS involvement, and pregnancy.[105] Amphotericin B deoxycholate or lipid products (liposomal amphotericin, ABLC, ABCD) are used in patients with moderate to severe pneumonia, disseminated infection, immunocompromise, or pregnancy.[105] Azole drugs are used as initial therapy for mild disease or as consolidation therapy after 1 to 2 weeks of amphotericin B. Itraconazole is the preferred oral therapy for both children and adults.[105] In a trial of itraconazole 90% of 48 adults with a nonmeningeal, non-life-threatening infection who received doses of 200 to 400 mg/day for 6 months were cured.[106] Voriconazole and posaconazole show good activity in vitro against *B. dermatitidis.*[107] Voriconazole, owing to its excellent penetration into the CNS, has been used successfully in patients with CNS disease who either failed to respond, had a recurrence after treatment, or were intolerant of recommended regimens.[108–111] Posaconazole also has been used successfully to treat blastomycosis.[112] Fluconazole and ketoconazole no longer are recommended for routine therapy because of the high rates of relapse seen with these drugs.[105] Drug interactions, absorption, distribution, and toxicity of the azoles are complex, and knowledge of these issues is essential for successful therapy (see Chapter 293). For example, absorption of itraconazole capsules is optimal if they are taken with food and an acidic beverage, whereas itraconazole solution is administered without food, and is ideal for patients receiving histamine-2 blocking agents or proton pump inhibitors, because gastric acidity is not required for absorption. Itraconazole, voriconazole, and posaconazole require therapeutic drug monitoring and periodic assessment of serum hepatic enzyme levels.[105,113]

Recommendations for treating blastomycosis are derived from clinical trials in adults and the clinical experience of experts. Current clinical practice guidelines for the management of blastomycosis are summarized in Table 252.2 and include recommendations for the treatment of children.[105] In all instances, long-term follow-up is required to identify late dissemination or relapse. The likelihood of adherence to therapy should be assessed before the start of treatment with any oral antifungal agent and should be reassessed if a patient fails to improve.[105]

TABLE 252.2

Summary of Recommendations for Treatment of Blastomycosis

Manifestation/Patient Population	Preferred Treatment	Comments
Moderately severe to severe pulmonary disease	Lipid AMB, 3–5 mg/kg/day, or deoxycholate AMB, 0.7–1 mg/kg/day, for 1–2 wk; then itraconazole,[a] 5–10 mg/kg/day divided twice daily for 6–12 mo	Most clinicians prefer to use azole step-down therapy after clinical improvement; however, the entire course can be given with AMB deoxycholate to a total of 2 g. Lipid AMB formulations have fewer side effects, and duration is not based on total dose received. Perform pregnancy testing for female adolescents before administration of azole. Maximum daily dose of itraconazole is 400 mg.
Mild to moderate pulmonary disease	Itraconazole,[a] 5–10 mg/kg/day divided twice daily for 6–12 mo	Perform pregnancy testing for female adolescents before administration of azole. Maximum daily dose of itraconazole is 400 mg.
Moderately severe to severe disseminated disease	Lipid AMB, 3–5 mg/kg/day, or deoxycholate AMB, 0.7–1 mg/kg/day, for 1–2 wk; then itraconazole,[a] 5–10 mg/kg/day divided twice daily for 6–12 mo	Most clinicians prefer to use azole step-down therapy after clinical improvement; however, the entire course can be given with AMB deoxycholate to a total of 2 g. Lipid AMB formulations have fewer side effects, and duration is not based on total dose received. Treat osteoarticular disease for 12 months. Perform pregnancy testing for female adolescents before administration of azole. Maximum daily dose of itraconazole is 400 mg.
Mild to moderate disseminated disease	Itraconazole,[a] 5–10 mg/kg/day divided twice daily for 6–12 mo	Perform pregnancy testing for female adolescents before administration of azole. Treat osteoarticular disease for 12 months.
Central nervous system disease	Lipid AMB, 5 mg/kg/day for 4–6 wk is preferred[b]; then an oral azole for at least 1 yr	Step-down therapy: *Children 2–12 yr:* fluconazole, 12 mg/kg/day; itraconazole,[a] 10 mg/kg/day; or voriconazole,[c] 9 mg/kg IV every 12 hr (maximum dose, 350 mg every 12 hr) *Children ≥12 yr:* 6 mg/kg every 12 hr loading for 1 day, then 4 mg/kg every 12 hr. Longer treatment

		may be required for immunosuppressed patients.
Disease in immunosuppressed patients	Lipid AMB, 3–5 mg/kg/day, or deoxycholate AMB, 0.7–1 mg/kg/day, for 1–2 wk; then itraconazole,[a] 5–10 mg/kg/day divided twice daily for 12 mo	Lifelong suppressive therapy should be determined on a case-by-case basis. Perform pregnancy testing for female adolescents before administration of azole. Maximum daily dose of itraconazole is 400 mg.
Disease in pregnant women	Lipid AMB, 3–5 mg/kg/day	Azoles should not be used during pregnancy

[a] In any regimen for which itraconazole is used, a random serum concentration should be obtained after 2 weeks of treatment and, if needed, the dosage adjusted to ensure adequate drug exposure. Serum itraconazole level = Itraconazole + Hydroxyitraconazole. Limited information is available about its use in newborns. Adults receive a loading dose of 200 mg orally 3 times a day for 3 days; however, this regimen has not been studied in children.

[b] In animal models of fungal meningitis, liposomal AMB achieves higher CNS levels than other lipid formulations. Hence, many infectious diseases experts recommend liposomal AMB as the preferred lipid formulation for the treatment of CNS fungal infections.

[c] Serum voriconazole trough levels should be obtained to guide proper dosage.

AMB, Amphotericin B; IV, intravenous.

Moderately severe to severe pulmonary disease and/or dissemination in children is treated with a full dosage of either amphotericin B deoxycholate or a lipid formulation for 1 to 2 weeks or longer until improvement occurs.[105] Thereafter, itraconazole is used for 12 months. For these manifestations and any manifestation of blastomycosis for which itraconazole is used, the maximum dose is 400 mg/day; serum concentrations should be determined after 2 weeks of treatment and the dosage adjusted to ensure adequate drug exposure. Children with mild to moderate pulmonary infection can be treated with oral itraconazole for 6 to 12 months.[105] When blastomycosis is diagnosed and treated during pregnancy, the newborn should receive therapy if there is evidence of infection.[105] Although data are limited, amphotericin B should be used for treatment in neonates. Consultation with experts may be needed for unusual or severe cases.

Liposomal amphotericin B is preferred for treating CNS infections because studies in animal models have shown that liposomal formulations attain higher CNS concentrations than other amphotericin B formulations. Treatment should be at full dosage for 4 to 6 weeks, followed by treatment with an azole (fluconazole, itraconazole, or voriconazole) for at least 1 year.[105] A multicenter review of 22 adults concluded that initial treatment with a lipid formulation of amphotericin B and then a prolonged course of an azole, including voriconazole, was effective.[90,114] Most experts recommend voriconazole as consolidation therapy for CNS disease because of its excellent penetration into the CSF compared with itraconazole and its lower minimum inhibitory concentration against *B. dermatitidis* compared with fluconazole. For patients with osteomyelitis, a combination of surgical debridement plus 12 months of antifungal therapy is needed. Surgical drainage also is needed for large abscesses and empyemas because antifungal therapy alone may not be curative.

The echinocandins (e.g., caspofungin, micafungin, anidulafungin) have poor activity against *B. dermatitidis* in vitro because there is minimal biosynthesis of β-(1,3)-glucan in the yeast phase.[115,116] Echinocandins should not be used to treat blastomycosis.[105,117]

Special Considerations

Blastomycosis in pregnancy or in the neonate is uncommon, and clinical data are based on a limited number of case reports.[118–121] Blastomycosis is most frequently diagnosed in the second and third trimesters, and disseminated infection occurs in 62% of pregnant patients.[118] Transmission to the neonate during the peripartum period is poorly understood, and potential routes include transplacental dissemination or aspiration of infected vaginal secretions during delivery.[118–121] All female adolescents diagnosed with blastomycosis must undergo assessment for pregnancy because use of azole agents can result in congenital malformations (fluconazole, voriconazole, posaconazole) and spontaneous abortion (itraconazole).[122–124] In pregnant women and neonates, amphotericin B formulations are the drugs of choice.[105]

B. dermatitidis is considered a primary fungal pathogen because it causes disease in patients with normal and impaired immune systems.[125–129] In an immunosuppressed person, blastomycosis can be newly acquired or can be due to reactivation of latent infection. Most clinical data for blastomycosis in immunocompromised patients is based on case reports and case series in adults. Although blastomycosis is uncommon in patients infected with HIV, severe pulmonary disease and a propensity to disseminate to the CNS occur.[125] For patients immunosuppressed as a result of solid-organ transplantation (SOT), blastomycosis typically manifests as pneumonia, which often is complicated by respiratory failure, acute respiratory distress syndrome, and coinfection with other opportunistic pathogens (most commonly cytomegalovirus).[127,128] Respiratory failure and acute respiratory distress syndrome are associated with high mortality rates, ranging from 33% to 67%.[127,128] Disseminated disease in SOT recipients occurs in 33% to 50% but rarely involves the CNS.[127,128] Blastomycosis also can occur in patients receiving tumor necrosis factor-α inhibiting agents and those with malignancy.[126,129] Antifungal therapy for immunosuppressed patients should consist of an amphotericin B lipid formulation or deoxycholate and then consolidation therapy with an azole (itraconazole, voriconazole, posaconazole) for a total of 12 months. Longterm suppressive therapy should be determined on a case-by-case basis.[105] For SOT recipients, relapse after a proper course of antifungal therapy (e.g., 12 months) is uncommon.[127,128]

Prevention

Immunodeficient patients should be advised of the importance of avoiding exposure to environmental habitats associated with blastomycosis outbreaks when they are counseled about reducing their risk of acquiring opportunistic infections.

Progress in vaccine development has included the generation of a live, attenuated recombinant strain of *B. dermatitidis* that is deficient in BAD1.[130] In a murine model the BAD1-null strain, when administered subcutaneously, induced protective immunity against a lethal pulmonary challenge with *B. dermatitidis*.[130] Moreover, the BAD1-null strain has been used to establish T-lymphocyte–dependent mechanisms and to identify the conserved antigen (calnexin) in the vaccine that promotes protective immunity against *B. dermatitidis* and other thermally dimorphic fungi, including *H. capsulatum* and *Coccidioides* species.[130,131] Currently no vaccine is available.

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Key Points

Blastomyces dermatitidis Infection

Microbiology

- Thermally dimorphic fungus that converts between mycelia and yeast
- Mycelial form, which produces spores, is the infectious form.
- Growth as yeast facilitates evasion of the immune system and infection in human tissues.
- *BAD1*, an essential yeast phase–specific gene, encodes a multifunctional protein that facilitates adhesion to host cells and suppression of the host's immune defenses.

Epidemiology

- Ecologic niche: sandy soils with an acidic pH that are near freshwater and decaying vegetation
- Activities that disrupt soil, aerosolizing spores that can be inhaled and can convert into yeast, causing pneumonia in healthy and immunocompromised patients
- Blastomycosis can be sporadic or associated with outbreaks.

Clinical Features

- Infections can mimic bacterial and mycobacterial infections and also malignancy.
- Pneumonia is the most common clinical manifestation.
- Dissemination is common and frequently involves the skin and

bone.

Diagnosis

- The most important "diagnostic test" is to include blastomycosis in the differential diagnosis:

▪ Pneumonia that fails to respond to antibiotics

▪ Patients with respiratory failure or acute respiratory distress syndrome who live in or visit endemic regions

▪ Pneumonia with skin lesions

▪ Osteomyelitis involving the spine, ribs, or long bones

▪ Verrucous or ulcerative skin lesions

- A positive travel or exposure history or a pet with blastomycosis

- Tests to establish the diagnosis of blastomycosis

▪ Fungal staining and fungal culture of clinical specimens

▪ *Blastomyces* antigen test of urine, serum, bronchoalveolar lavage specimen, or cerebrospinal fluid

Treatment

- Amphotericin B deoxycholate or lipid formulations

- Azole antifungal agents (itraconazole, voriconazole, posaconazole)

- Pregnancy testing should be performed for all adolescent females before azole administration.

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Coccidioides immitis and *Coccidioides posadasii* (Coccidioidomycosis)

George R. Thompson III

Coccidioidomycosis is an infection caused by the dimorphic fungi *Coccidioides immitis* and *C. posadasii*. These fungi are endemic to the southwestern United States, Mexico, Guatemala, and sporadic regions in Central and South America. Infection is caused by inhalation of highly infectious and environmentally resistant spores after disruption of the soil causes aerosolization of the organisms. Primary infection often is manifested as an acute respiratory illness, although the spectrum of disease ranges from asymptomatic exposure to severe and life-threatening disseminated disease.[1]

The Pathogen

Microbiology

Coccidioides spp. are dimorphic fungi; in soil they exist as spore-forming saprophytic molds, and in vivo they exist in a spherule-endospore (SE) phase (yeast-like phase) (Fig. 253.1). Two species have been identified through phylogenomic characterization. Although these genomic differences clearly delineate two separate species, no phenotypic, antigenic, virulence, or morphologic differences have been described to date. *C. immitis* is found in California and Washington, whereas *C. posadasii* is found in Mexico and areas of Central and South America.[2]

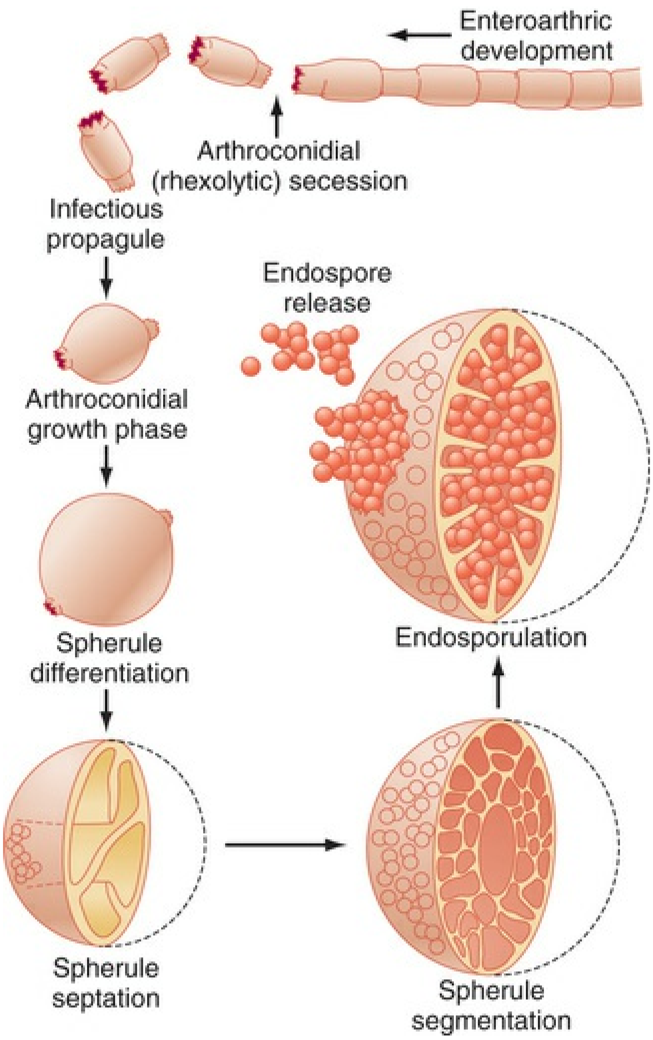


FIGURE 253.1 Life cycle of *Coccidioides immitis.*

(Redrawn from Cole GT, Sun SH. Arthroconidium-spherule-endospore transformation in *Coccidioides immitis.* In: Szaniszlo PJ [ed]. Fungal Dimorphism: with Emphasis on Fungi Pathogenic for Humans. New York, Plenum Press, 1985, p. 281.)

The infectious form of *Coccidioides* consists of desiccated spores (arthroconidia), which are boxcar–shaped structures with thick, hydrophobic walls. Spores are released from the mold when the thin-walled intervening cells disarticulate. After inhalation the spores germinate in the lung and, over 3 to 4 days, become spherules 10 to 80 µm in diameter. Inhalation of only a few spores can cause infection in humans. Spherules undergo internal cleavage and septation and eventually release large numbers of endospores 2 to 5 µm in diameter (Fig. 253.2). The endospores then enlarge, forming spherules, thereby completing the life cycle.[3] Growth of *Coccidioides* is stimulated by progesterone, 17β-estradiol, and testosterone and may significantly affect in vivo growth in the host.[4] The mold form is rarely found in human tissue.

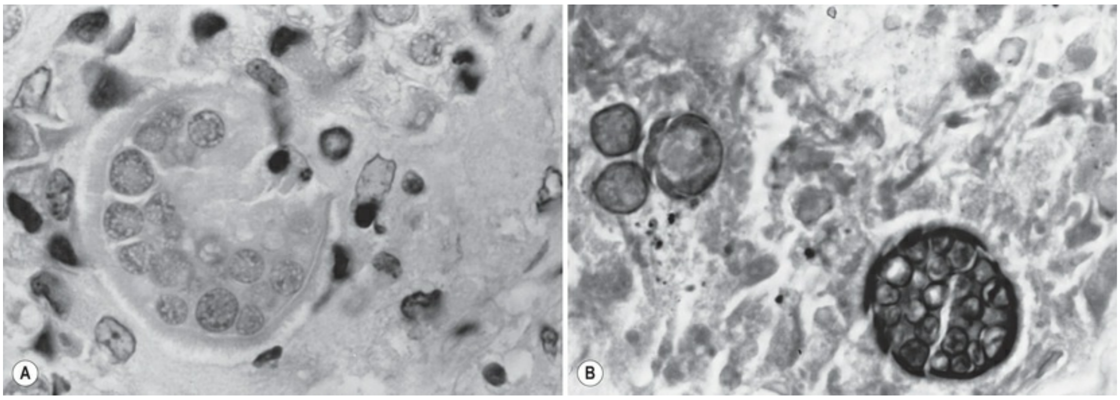


FIGURE 253.2 Specimens from a patient with AIDS who also had pneumonia caused by *Coccidioides immitis.* (A) Ruptured endosporulating spherule containing endospores 2 to 5 µm in diameter. Hematoxylin and eosin stain, ×1250. (B) Typical intact, large endosporulating spherule and three immature spherules. Gomori methenamine silver nitrate stain, ×1000.

Pathogenesis

Primary infection occurs in the lungs. Neutrophils, lymphocytes, and monocytes influence fungal dimorphism toward the spherule phase. A fungal enzyme with elastase activity may facilitate the spread of infection and increase inflammation.[5] *C. posadasii* perturbs pulmonary surfactant proteins, potentially enabling disease progression.[6] Molecular techniques have been used to examine (1) specific genes that affect virulence and (2) a cell surface glycoprotein that is produced early in spherule development, acts as an adhesin, and has been found to be a major contributor to pathogenicity.[7] An initial neutrophilic inflammatory response does not control infection despite rapid phagocytosis of *Coccidioides* particles,[8] and granulomatous inflammation eventually predominates. A characteristic histologic finding is granulomatous inflammation containing spherules and endospores (see Fig. 253.2).

Primary pulmonary infection, whether clinically apparent or asymptomatic, often is accompanied by dissemination of the fungus. Symptoms of extrapulmonary infection occur in about 1% of infected patients, and virtually any organ system can be involved, although the central nervous system (CNS), skin, and bone are most often affected in cases of disseminated infection.

Immunity

Despite complement-dependent chemotaxis induced by fungal elements, neutrophils and macrophages have a diminished capacity to kill *Coccidioides* forms intracellularly. Phagocytosis of spherules is physically difficult because of the size of these forms (≤80 μm).[8] A metalloproteinase produced during endosporulation interferes with host recognition, thereby impairing phagocytosis when these fungal elements are most susceptible.[9] Fibrillar surface matrices also prevent effective leukocyte contact with spherules and isolate endospores from phagocytic fungicidal mechanisms.[10]

Natural infection results in lifelong immunity. Polyclonal B-lymphocyte activation and increased serum complement fixation (CF) antibody titers develop in cases of severe infection, especially when coupled with loss of skin test reactivity, but humoral immunity is not completely protective. Protection has been firmly related to induction of Th1-associated immune responses. Coccidioidal antigens are processed and presented to T lymphocytes by macrophages and dendritic cells. This induces the production of interferon γ (IFNγ) and other Th1 cytokines that act by recruiting and activating immune effector cells.[11] Stimulated coccidioidal-immune T lymphocytes interact with and activate macrophages and enhance phagosome-lysosome fusion and killing. A diminished Th1 response to *C. immitis* antigens has been demonstrated in patients with disseminated infections, compared with Th1 responses in otherwise healthy subjects.[12] A variety of factors may contribute to this weaker response, including high concentrations of fungal antigen, circulating immune complexes, and direct suppression of immunity by fungal products or effectors.[13] Congenital or acquired impairment of cellular immunity is a major risk factor for serious primary infection or relapse of past infection.

Epidemiology

Coccidioidomycosis occurs in arid regions of the southwestern United States and is endemic to southern California, Washington, Utah, Arizona, western and southern Texas, and New Mexico (Fig. 253.3).[2] Infection also occurs in regions of Mexico and Central and South America where biogeographic distribution probably resulted from a codispersal of the human host population and its pathogen. Environments with hot summers, infrequent freezes, alkaline soil, and alternating periods of rain and drought support fungal growth and aerosolization of arthroconidia. Analyses of epidemic strains have shown that outbreaks result from environmental distribution rather than from the emergence of a pathogenic subtype.[14,15]

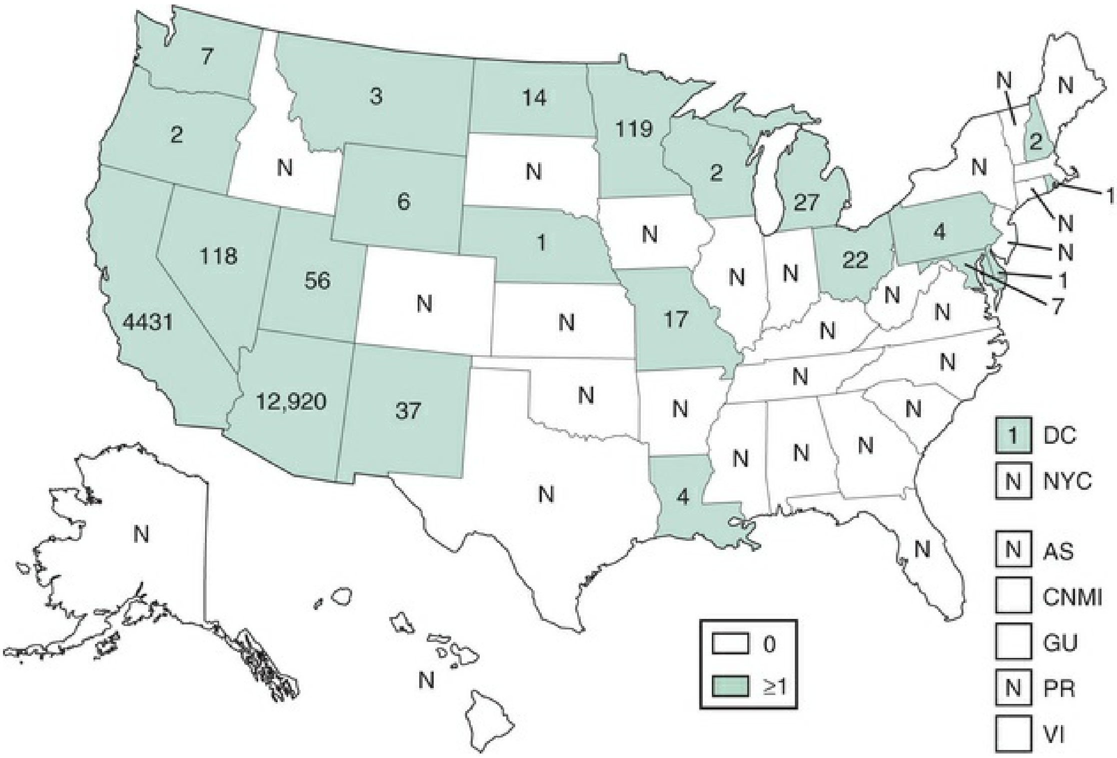


FIGURE 253.3 Coccidioidomycosis reported cases: United States and U.S. territories, 2012. N, not

notifiable; DC, Washington, DC; NYC, New York City; AS, American Samoa; CNMI, Commonwealth of the Northern Mariana Islands; GU, Guam; PR, Puerto Rico; VI, Virgin Islands. (Data from Centers for Disease Control and Prevention. Summary of notifiable diseases: United States, 2012. MMWR Morb Mortal Wkly Rep 2014;61[No. 53]:58.)

Infection usually is acquired during recreational or occupational activities that increase the likelihood of exposure to aerosolized arthroconidia. Examples of such activities include construction work, military exercises, archeological investigations, and recreational events. Outbreaks also can happen after earthquakes, such as occurred in 1994 after the Northridge earthquake.[2] A fourfold increase in the incidence of infections was seen in both Arizona and California between 2000 and 2007.[2] Infections can be difficult to diagnose when a traveler returns to a nonendemic area where practitioners have little experience with the diagnosis and care of coccidioidomycosis. Outbreaks also have occurred among travelers returning from regions not previously known to be endemic.[16] Fomites, such as dusty clothing or agricultural products, also have been implicated as sources of infection and may account for cases well outside the established endemic region.[17,18] Person-to-person spread of coccidioidomycosis has not been documented by the respiratory route; however, bandages contaminated by purulent drainage on which arthroconidia had grown have been implicated in transmission.[18]

An estimated 150,000 new infections occur annually in the U.S.[19] Rates are highest in the fall and early winter. Coccidioidomycosis has become increasingly important as migration to the Sunbelt states (and accompanying construction) has grown, as have the numbers of elderly and immunosuppressed people in the endemic region.[2] Skin test positivity was found in 17% of children who had lived in a highly endemic area for up to 1 year and in 77% of those who had lived in an endemic area for 10 years or longer. The return of skin testing reagents (Spherusol) to the commercial market has allowed the epidemiology of coccidioidomycosis to be updated.[20,21]

Clinical Manifestations

Infection is subclinical in roughly 60% of those exposed, and most other cases are self-limited, primary pulmonary infections. Of those infected, pulmonary complications occur in less than 5% and disseminated infections in less than 1%. Pulmonary complications and extrapulmonary infections can occur without recognized antecedent illness. In 2005 to 2006, illnesses in children that required hospitalization mirrored the increased incidence of disease in the general population; these illnesses also were more common among patients with comorbid conditions. Surgical drainage was required in 41% of the cases.[22]

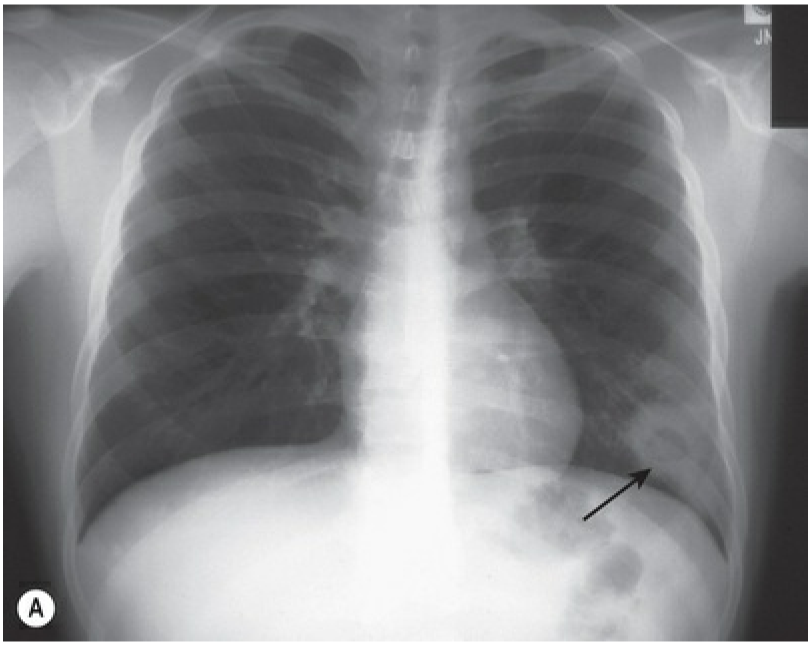
Primary Pulmonary Infection

The incubation period is 10 to 16 days (range, 1–4 weeks). Malaise, chest pain, and fever are common symptoms.[3] Cough is variable, and hemoptysis is unusual in children. An acute, diffuse, erythematous rash and erythema multiforme are common. Erythema nodosum and fever can follow the onset of symptoms by 3 to 18 days. Erythema nodosum and transient arthritic complaints (desert rheumatism) are mediated by the cellular immune response. Occasionally, pulmonary symptoms are absent and only hypersensitivity manifestations occur.[23]

Symptoms usually improve without treatment in a few weeks to several months. In adults 5% to 10% of infections result in residual pulmonary nodules or thin-walled cavities, and patient education in these circumstances is paramount to avoid an inappropriate oncologic workup in the future.[24] In rare cases primary pulmonary infections that result from exposure to large inocula are severe and progress to involve multiple areas of the lungs; they also can cause symptoms of adult respiratory distress syndrome.[3]

Chronic Pulmonary Complications

Chronic pulmonary complications are uncommon in children and usually occur in adults with diabetes mellitus or an immunocompromising condition. Chronic progressive pneumonia, lung cavities, and pulmonary nodules are the most common manifestations (Fig. 253.4). Peripheral thin-walled cavities sometimes rupture into the pleural space and cause pyopneumothoraces.



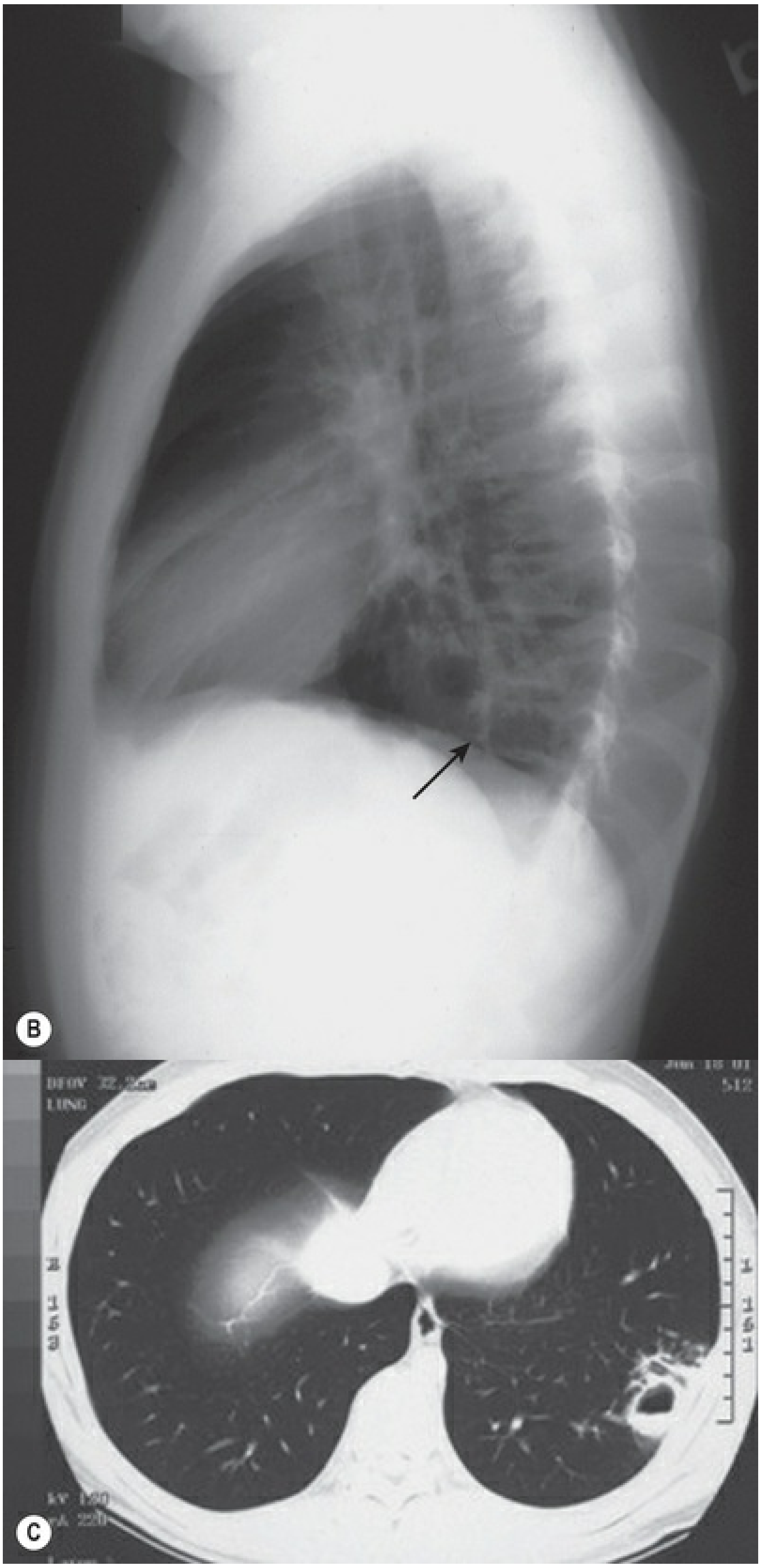


FIGURE 253.4 Imaging studies from a 14-year-old boy with type 2 diabetes mellitus who had a 6-month history of occasional chest pain and a 13.6 kg (30 lb) weight loss. Chest radiographs (A and B) show peripheral left lower-lobe lung abscess *(arrows).* (C)

CT (lung window) shows the air-fluid level. Aspirate yielded growth of *Coccidioides immitis.* (Courtesy of J.H. Brien.)

Extrapulmonary Manifestations (Dissemination)

Clinical manifestations of dissemination to extrapulmonary sites occur in about 0.5% to 1% of patients, usually within several months of the primary pulmonary infection and rarely after 1 year. Dissemination is less frequent in children than in adults.[24] Persistent fever is common, and frequently affected sites include the skin, bones, joints, and CNS.[25] Those at highest risk are neonates and young infants, immunosuppressed patients, Filipinos, African Americans,[26] Native Americans, pregnant women, and women in the early postpartum period. Patients receiving tumor necrosis factor-α (TNF-α) antagonists[27] also are at risk (Box 253.1).

Box 253.1

Risk Factors for a Poor Outcome in Patients With Active Coccidioidomycosis

Primary Infection

Severe, prolonged (≥6 wk) or progressive infection

Extrapulmonary Infection (Risk Factors for Dissemination)

Primary or acquired cellular immune dysfunction (including receipt of tumor necrosis factor-α antagonists, immunosuppressive agents; recipient of bone marrow or solid-organ transplant; HIV infection)

Neonates, infants, and the elderly

Male (adult)

Filipino, African American, Native American

Skin test anergy

Pregnancy

Standardized complement fixation antibody titer ≥1 : 32, or increasing titer with persistent symptoms

Osteomyelitis and Arthritis.

Osteomyelitis is subacute or chronic, and it occasionally is associated with extension into adjacent soft tissues.[28] Common sites are the hands and feet, ribs, skull, and vertebrae. Vertebral involvement can result in collapse, instability, paraspinal abscess or,[29] in some instances, meningitis. Monoarticular arthritis, often of the knee or ankle, occurs in 20% of adults with disseminated infection and can be chronic. Isolated osseous lesions can resemble neoplasms.[30]

Cutaneous Disease.

Most skin infections represent extrapulmonary manifestations caused by bloodstream spread from a primary pulmonary focus. Lesions begin as papules or pustules that enlarge and can ulcerate. Verrucous plaques, subcutaneous cold abscesses, and wart-like lesions also occur (Fig. 253.5). Lesions can occur anywhere but are common on the face. Cutaneous lesions accompanied by regional adenitis rarely occur after accidental inoculation.[31,32]

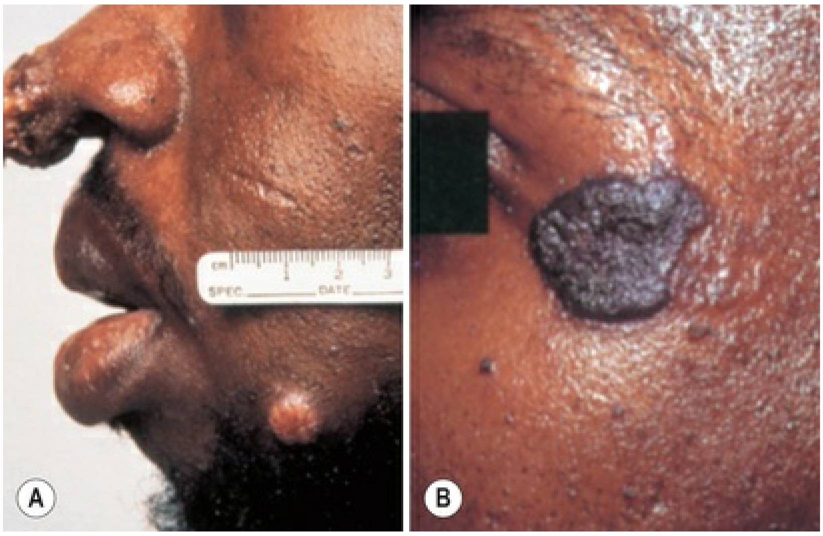


FIGURE 253.5 Cutaneous manifestations of disseminated coccidioidomycosis. (A) Raised nodules on the nose and cheek. (B) Hyperpigmented verrucoid

plaque lateral to outer canthus. (From Sanders CV, Nesbitt LT Jr. The Skin and Infection. Philadelphia, Williams & Wilkins, 1995.)

Meningitis.

Meningitis can occur acutely but often is subacute with transient periods of remission. Symptoms often include headache, altered sensorium, ataxia, vomiting, and focal neurologic deficits. Fever is variable, and meningismus occurs in only 50% of patients.[33] CNS vasculitis, often associated with cerebral infarction, is recognized increasingly; a retrospective review reported a mortality rate of 70%.[34] Basilar meningeal reaction can interfere with cerebrospinal fluid (CSF) resorption and cause obstructive or communicating hydrocephalus. If left untreated, meningitis is fatal within 1 to 2 years. Lifelong therapy is required to prevent relapse.[35]

Diagnosis

Symptoms of coccidioidomycosis are protean. A careful history of travel to endemic areas and inquiry about high-risk activities often prompts consideration of the diagnosis, particularly for patients living in nonendemic regions.[16,36]

Nonspecific Tests

The erythrocyte sedimentation rate usually is increased, and mild peripheral eosinophilia occurs in 5% to 10% of patients with primary infection. The chest radiograph can be normal or can show parenchymal infiltrates, hilar lymphadenopathy, thin-walled cavities, or parapneumonic effusion.[3] In patients with meningitis, the CSF shows pleocytosis with a predominance of lymphocytes or neutrophils, moderate hypoglycorrhachia, and an elevated protein concentration; eosinophilia is reported in 15% of cases.[33,37] Specific antibody is present in the CSF of patients with meningitis. Osseous lesions usually are lytic, but CT scans and MRI are more sensitive than plain radiography.[38] MRI is useful for demonstrating the bone marrow signal abnormalities of osteomyelitis and sites of decompression into soft tissue or joints.

Direct Examination and Culture

Observation of spherules containing endospores 2 to 5 µm in diameter is diagnostic. Spherules do not take up Gram stain but can be identified in infected body fluids with potassium hydroxide preparations or the calcofluor white stain. Stains of infected CSF usually are negative. In tissue samples, pyogranulomatous inflammation with endosporulating spherules is seen readily with hematoxylin and eosin stain or periodic acid-Schiff stain. Spherules also stain well with Gomori methenamine silver nitrate (see Fig. 253.2). Mold forms are rarely seen in body fluid or tissue specimens and typically only in the presence of foreign material (e.g., ventriculoperitoneal shunts).[39]

If organisms are not visualized in body fluid specimens or tissue, the diagnosis can be confirmed by culture. The mold form is a hazard to laboratory personnel; therefore, the clinical laboratory should be informed if coccidioidomycosis is suspected. The growth of *Coccidioides* spp. is supported by many conventional laboratory media at either 30°C or 37°C. Yield from respiratory tract secretions can be enhanced by chemical digestion of purulent specimens, and polymerase chain reaction protocols have been developed for direct detection in sputum samples.[40] Cultures of blood infrequently are positive except in highly immunocompromised people with disseminated infection. Culture of purulent material from other infected sites can be positive, although urine, peritoneal fluid, and CSF cultures are often negative despite infection at these sites. The fungus is isolated in culture in its mycelial phase and can be confirmed as *Coccidioides* spp. using exoantigens or nucleic acid probes.[41] Progress in development of molecular diagnostic techniques that can identify *Coccidioides* spp. in clinical specimens has been reviewed.[42] Polymerase chain reaction testing in a clinical setting has been shown to identify negative results accurately with a sensitivity similar to that of fungal culture.[40]

Skin Test

Four weeks after exposure, almost all infected individuals have a positive intradermal skin test result (induration ≥5 mm) to coccidioidal antigen prepared from spherule forms (Spherulin).[43] Although recent conversion of skin test reactivity is diagnostic, reactivity persists after infection, which relegates the skin test to use primarily as an epidemiologic tool. Cutaneous anergy in infected, symptomatic patients suggests the presence of a poor immunologic response and is a poor prognostic sign.[44] Conversely, conversion to skin test positivity correlates with improvement. The return of skin testing in a new formulation (Spherusol) has renewed interest in this test.[21]

Serologic Tests

Assays for coccidioidal antibody are valuable diagnostic and prognostic tools and are the mainstay of diagnosis and management.[45] False-negative test results can occur early in the course of infection, before the development of an immune response, and in highly compromised people, who are unable to manifest a robust antibody response. Cross-reactions with *Histoplasma capsulatum, Blastomyces dermatitidis,* and *Talaromyces marneffei* (formerly *Penicillium marneffei*) can occur in some assays.[46,47]

The use of enzyme immunoassay (EIA) kits for antibody detection is associated with false-positive test results but is useful for screening when followed up with a more specific assay. Circulating antigen is detected in patients with extensively disseminated infection and also in sequestered sites (e.g., CSF), but this finding is not useful in the routine management of most patients. Antigen detection also can result in cross-reaction with other endemic mycoses.

Specific IgM anti-*Coccidioides* antibody is detectable in 75% of patients 1 to 3 weeks after the onset of symptoms and is usually absent after 6 to 9 months. IgM historically was detected by the tube precipitin test, but current methodologies use the more sensitive immunodiffusion tube precipitin (IDTP) technique. Latex particle and EIA methods also are available as screening tests for IgM anti-*Coccidioides* antibody, but positive results should be confirmed using more specific methods.[48]

The CF assay detects IgG-specific antibody; it is positive in about 50% of patients at 4 weeks and in 83% at 3 months after infection. CF titers become undetectable within several months if the infection resolves, although a small minority of patients appear to be serofast. CF titers greater than 1 : 16 correlate with the presence and severity of disease. A quantitative immunodiffusion complement fixation (IDCF) test for detecting IgG antibody also is available and should not be confused with the IDTP test. The IDCF method is useful for sera that are anticomplementary.

Coccidioidal antibody is present in the CSF of 95% of patients with coccidioidal meningitis, although serial samples may be required. Titers decline during effective therapy. A parameningeal focus of coccidioidal infection also can cause a positive CF result in cerebrospinal fluid.

Treatment

The decision to treat is based on specific features and the severity of the initial illness, risk factors for severe infection or poor outcomes, or both[24] (see Box 253.1). Treatment is required for patients with primary or acquired immunodeficiency, including those receiving TNF-α blocking agents, and for patients with fulminant infections, extrapulmonary manifestations, or prolonged symptoms. In an observational study of patients with primary pulmonary coccidioidomycosis, complications of infections were observed only in those who initially received antifungal therapy. This was not a randomized controlled trial, but it does illustrate that complicated disease or dissemination can develop even in those treated for the initial infection.[49]

Published reports of the results of amphotericin B treatment (the first antifungal agent used) are limited to nonrandomized, open-label studies of chronic pulmonary infections and extrapulmonary disease. Accumulated experience with intrathecal and intracisternal instillation of amphotericin B for the treatment of meningitis also has been reported.[50] Because of the toxicity and inconvenience of amphotericin B, use of alternative agents has become desirable, and the effectiveness and relative safety and convenience of the oral azoles are now very attractive. Amphotericin B generally is reserved for use in the management of severe or rapidly progressive disease. Amphotericin B also is used for women during pregnancy because the azole agents have the potential for teratogenicity.[51] Some experts reserve amphotericin for use as salvage therapy.[52] No clinical evidence supports greater efficacy of lipid formulations of amphotericin B; however, the lower rate of nephrotoxicity observed with lipid formulations provides a substantial advantage over amphotericin B deoxycholate.

Fluconazole and itraconazole are the principal agents used for treatment.[24] Selection of an azole is based on proven efficacy for the disease manifestation, tolerability, and cost.[53] Although better tolerated than amphotericin B, these agents also have adverse effects, pharmacokinetic properties, and drug interactions that must be considered (see Chapter 293). Voriconazole and posaconazole have shown efficacy in the treatment of coccidioidomycosis,[54–56] although their use is limited to patients with chronic or disseminated infection who are intolerant of or refractory to first-line agents. Recommendations for children are derived from published experience in adults; however, extrapolation of treatment and outcomes disregards the potential differences in host factors and tolerance of therapy. Physicians who treat children with coccidioidomycosis should consider seeking consultation with experts.

Primary Infection

Immunocompetent patients without risk factors (see Box 253.1) who have mild respiratory symptoms usually do not require treatment. However, they should be assessed at 3- to 6-month intervals for up to 2 years to ensure that both symptoms and radiographic abnormalities have resolved.[24] Severe, prolonged, or progressive primary respiratory tract infections require antifungal therapy. Firm criteria for severity have not been established yet for children; useful indicators in adults include loss of more than 10% of body weight; symptoms that persist for 3 weeks or longer; pulmonary infiltrates that involve more than one half of one lung or that occur bilaterally; prominent hilar lymphadenopathy; chest pain; and CF titers of 1 : 16 or higher.

Itraconazole or fluconazole is used most often for the treatment of primary infection. The duration of treatment typically is 3 to 6 months. Important determinants of improvement include resolution of respiratory and constitutional symptoms, a decrease in CF antibody titers, and radiographic improvement. Periodic reassessment is needed for at least 1 to 2 years thereafter. Patients with pulmonary infiltrates should be followed to resolution, or as a pulmonary nodule forms so that the knowledge avoids a later oncologic evaluation.

Nonmeningeal Extrapulmonary Infection

Treatment is indicated for all extrapulmonary infections and in all immunocompromised patients, including pregnant women.[24] In patients with severe illness or rapid progression of disease, amphotericin B formulations are used initially. The dose and duration of amphotericin B therapy depend on the severity of the symptoms, rapidity of response, and host-related risk factors. The remainder of the course of treatment can be completed with an oral azole, except during pregnancy, when amphotericin should be continued. The total duration of therapy should be at least 1 year and should extend for 3 months beyond complete resolution of symptoms. Because late relapse can occur, usually within 2 years of apparently successful treatment, long-term follow-up is required. Treatment for meningitis and spinal disease should be lifelong.

The azole agents have been evaluated in the treatment of extrapulmonary manifestations of coccidioidomycosis in adults. Fluconazole (800–1200 mg/day)[57–60] and itraconazole[61,62] (200 mg twice daily) are effective and have been compared in a randomized trial.[63] The primary endpoint did not show superiority of either compound, but itraconazole showed more favorable outcomes in patients with osseous disease. Relapse rates after cessation of a 12-month course of therapy were 18% for itraconazole and 28% for fluconazole (a difference not statistically significant). The dose range for itraconazole in children is 5 to 10 mg/kg/day; the suspension form is better absorbed and is preferred (adult dose, 100–200 mg twice daily).

Meningeal Infection

Amphotericin B, given both systemically and either intrathecally or directly instilled into the cerebral ventricles or cisterna magna,[50] was the mainstay of therapy for coccidioidal meningitis before the azoles became available. The inconvenience and toxic effects of amphotericin, in addition to the irritating arachnoiditis resulting from intrathecal instillation, have relegated amphotericin formulations to second-line therapy (i.e., used only if the response to an azole is suboptimal). Fluconazole shows favorable CSF pharmacokinetics for CNS disease. Doses effective in adults are 400 mg/day, but some experts begin therapy with 800 to 1000 mg/day and increase as tolerated by the patient.[33] Response rates to fluconazole range from 67% to 80%. Children should be treated with fluconazole at doses in the upper end of the recommended range (12 mg/kg/day).[64] Indicators of improvement are a reduction in the CSF cell count and protein level and a decrease in the CF titer of the cerebrospinal fluid.

Despite excellent response rates to azoles, relapse of infection after the cessation of therapy was reported in 14 of 18 patients treated with an azole.[65] Relapses occurred 2 weeks to 30 months after the cessation of treatment courses that lasted 8 to 101 months. Because no clinical or laboratory factors predictive of relapse have been identified yet, fluconazole therapy should be continued indefinitely.

Patients who fail to respond to treatment with an azole may improve with systemic therapy and direct instillation of amphotericin B into the intrathecal, ventricular, or intracisternal spaces, with or without continuation of azole treatment. The optimal management of CNS vasculitis is unclear.

The persistent basilar inflammation resulting from meningitis caused by *Coccidioides* can result in obstructive hydrocephalus, necessitating placement of a CSF shunting device. In these cases, the abnormal dynamics of CSF flow interferes with the distribution of intrathecally administered amphotericin B; fluconazole, which crosses the blood-brain barrier more readily, simplifies the management of such patients. The development of hydrocephalus is not necessarily indicative of treatment failure and does not itself require any alteration in antifungal management unless it is accompanied by other findings suggestive of treatment failure.

Special Considerations

Acquired or inherited cellular immune dysfunction is a risk factor for aggressive and disseminated coccidioidomycosis. In this setting diagnosis often rests on clinical suspicion, histopathologic findings, and culture. Skin test anergy and seronegativity do not exclude the diagnosis in an immunocompromised person. Although the incidence of coccidioidomycosis is highest in residents of endemic areas, infections can occur in residents of nonendemic areas[36] as a result of exposure during travel or from recrudescence of past infection. HIV-positive patients are at high risk for active coccidioidomycosis if the CD4$^+$ lymphocyte count is lower than 250/mm^3.[66,67] People with no apparent symptoms of active infection but who have elevated coccidioidal antibody titers also are at risk for having active coccidioidomycosis. Treatment strategies are similar to those for patients who are not immunocompromised; they include amphotericin B for severe or diffuse pulmonary disease, then fluconazole or itraconazole. For mild disease monotherapy with fluconazole or itraconazole is recommended. After treatment, if immune reconstitution is not possible, lifelong antifungal suppression with fluconazole or itraconazole is needed to prevent relapse.[67]

Recrudescence of coccidioidomycosis is common in patients who receive organ or hematopoietic stem cell transplants.[68] Seropositive transplant recipients and/or people with previous clinical coccidioidomycosis should receive prophylactic antifungal therapy, and fluconazole has been used successfully for this purpose.[69,70] Severe coccidioidomycosis has been reported in recipients of organs from donors with unrecognized infections. In these instances diagnosis can be delayed if transplantation is performed in nonendemic regions using organs procured from patients from endemic areas.[71]

Limited clinical information is available for newer therapeutic agents. Posaconazole, an extended spectrum triazole with activity against *Coccidioides* spp., has been shown to be effective in patients with pulmonary and disseminated infection, and despite the absence of detectable CSF levels, it has shown efficacy in the treatment of meningitis. Similarly, voriconazole has been proven effective in the treatment of pulmonary, disseminated, and meningeal forms of coccidioidomycosis.[55,56] These agents currently have limited use, primarily because of cost concerns.

The echinocandins should not be used as monotherapy in the treatment of coccidioidomycosis because of a lack of inherent activity. However, echinocandins used in combination with other agents can be useful in the salvage setting. This “indirect” efficacy is likely a product of an immunopharmacologic mechanism, as is seen in the treatment of other fungi.[72]

Prevention

Substantial evidence supports the feasibility and usefulness of an effective vaccine for coccidioidomycosis.[73] Attempts to immunize with a killed spherule vaccine were unsuccessful, and candidate immunizing agents and approaches remain under development. Primary prophylaxis with an azole is not recommended for patients with HIV infection, although secondary prophylaxis may be indicated in recipients of solid-organ or bone marrow transplants who have a history of coccidioidomycosis or positive skin tests/serologic testing. In endemic areas exposure to activities that may aerosolize spores in heavily contaminated sites should be avoided, especially by immunosuppressed people. If such an activity is unavoidable, respiratory filtration devices should be used.

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Key Points

Coccidioides immitis and *Coccidioides posadasii*

Microbiology

- *Coccidioides* spp. are endemic, dimorphic fungi that exist as saprophytic molds in the environment and as endosporulating spherules in parasitic forms.
- Multinucleate spores (arthroconidia) released from the mold result in a primary respiratory tract infection after inhalation.
- Conversion to spherules in the host releases large numbers of endospores that amplify infection.

Epidemiology

- *C. immitis* is found in California and Washington state; *C. posadasii* is found primarily in Arizona, Mexico, and regions of Central and South America.

- Hot summers, alkaline soil, infrequent freezes, and alternating rain and drought favor growth.

- Isolated and epidemic outbreaks can result from activities and environmental conditions that favor fungal growth and aerosolization of spores.

Diagnosis

- Diagnosis is confirmed by culture or observation of endosporulating spherules in tissue specimens.

- In immunocompetent individuals, immunoglobulin M (IgM)–specific antibody is found in 75% within 1 to 3 weeks of symptom emergence; IgG-specific antibody is present in 50% by 4 weeks and in 83% by 3 months.

- Standardized complement fixation titers greater than 1 : 16 correlate with the presence and severity of extrapulmonary disease.

- Complement fixation antibody is present in the cerebrospinal fluid of 95% of patients with meningitis.

Treatment

- For all patients, follow-up is required for 2 years to ensure resolution.

- Antifungal therapy is required for severe, prolonged (>6 weeks) primary infection, all extrapulmonary infections, and in patients with risk factors for poor outcomes.

- Fluconazole and itraconazole are effective; itraconazole is preferred for bone infections; fluconazole achieves effective levels in cerebrospinal fluid and is preferred for central nervous system infections.

- Amphotericin B is preferred for severe, rapidly progressive, nonmeningeal infections; after induction, azole agents are used to complete therapy.
- Management of meningeal infections is complex, and consultation with experts is recommended.

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Dermatophytes and Other Superficial Fungi

Tanya Greywal, Sheila Fallon Friedlander

Dermatophytes are aerobic fungi that can invade and infect keratinized layers of the skin, hair, and nails, mediated by both keratinases and proteases. Originally thought to derive from parasites transmitted from cats or dogs, infection was referred to as *tinea* (from the Latin word for worm), followed by a modifying term (e.g., *capitis*) that described the affected body site. Most dermatophyte infections involve three genera of fungi: *Trichophyton, Microsporum,* and *Epidermophyton*. These fungi are found worldwide; infection is acquired from contact with affected humans or animals, or from exposure to contaminated soil or fomites (e.g., combs, brushes). Dermatophytes often are classified by their host preferences—anthropophilic and zoophilic species primarily infect human and animal species, respectively, whereas geophilic species reside in soil. Direct contact can result in transmission of zoophilic or geophilic dermatophytes to humans. Dermatophytes do not cause invasive disease, except when they invade the dermis and subcutis locally (Majocchi granuloma) or infect immunocompromised hosts. The clinical disease attributed to dermatophytes varies by organism, site of infection, and host immunologic responses.

Tinea Capitis

Key Points

Diagnosis and Management of Tinea Capitis

Microbiology

- *Trichophyton tonsurans*, an anthropophilic dermatophyte, is the most common cause of tinea capitis in North America.
- Other causes: *Microsporum canis* (usually from pets), *Microsporum audouinii, Trichophyton mentagrophytes, Trichophyton violaceum*

Epidemiology

- Highest prevalence in children 3 to 10 years of age; family members at risk; can occur in postmenopausal child caretakers
- More common in urban settings
- *T. tonsurans* is transmitted from human to human.
- *M. canis* is transmitted from pets (dogs, cats).

Diagnosis

- Direct microscopy with KOH examination
- Fungal culture
- Wood light for *M. canis* and *M. audouinii*: fluoresce bright yellow

Treatment

- Oral griseofulvin (20–25 mg/kg/day, micronized, maximum dose of 1g) often used; should be taken with a fatty meal to increase drug absorption.
- Terbinafine is an FDA-approved alternative that often requires a shorter duration of therapy, but may be more expensive; see dosing in text.

- Second-line therapies: itraconazole or fluconazole
- Adjunctive antifungal shampoo: selenium sulfide 2%, ketoconazole, or ciclopirox; twice a week use decreases infectivity

Duration of Therapy

- For griseofulvin, 6 to 8 weeks of therapy is recommended (with treatment 2 weeks beyond clinical resolution of disease).
- For other agents, shorter courses can be used (e.g., terbinafine, 5–8 mg/kg/day for 4 weeks).

Microbiology and Epidemiology

Tinea capitis is the most common pediatric dermatophyte infection in temperate climates worldwide and is a common cause of hair loss in prepubertal children.[1] The precise incidence is unknown; however, infection is most common in younger elementary school-aged children, and it occasionally affects postpubertal individuals.[2,3] Prepubertal prevalence may relate to the absence of sebum fatty acids, which possess fungistatic properties.[4]

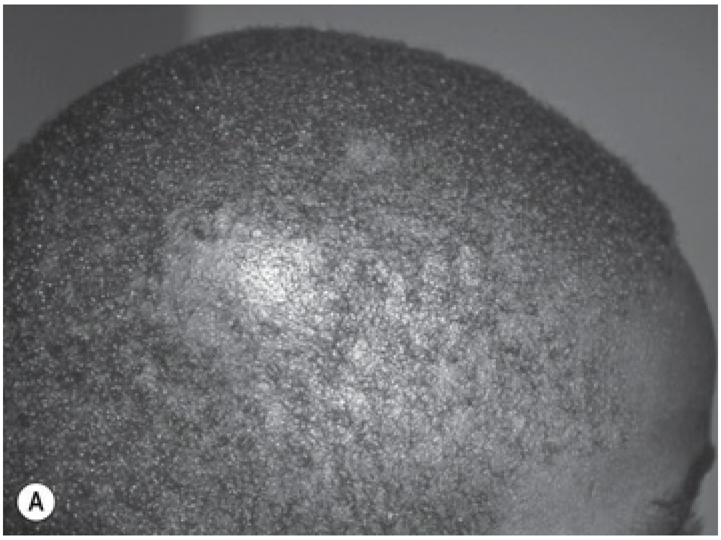
Prevalence and pathogens vary widely.[5] *Trichophyton tonsurans* is most common in the United States, whereas *Microsporum canis* is usually seen in South America and around the Mediterranean.[6] *Trichophyton soudanense* and *Trichophyton violaceum* are the major causes of disease in many parts of Africa and have also been found in immigrant populations in Scandinavia and other European countries.[6]

T. tonsurans is the predominant cause of tinea capitis in North America and Central America, accounting for >90% of cases.[7] In a survey of elementary school-aged children in Alabama, the incidence of *T. tonsurans*–positive scalp cultures was approximately 11%, with symptomatic disease in only 3%. In another study of >10,000 US children, approximately 6% were culture positive.[8,9] However, a retrospective study using the International Classification of Diseases, ninth revision codes for symptomatic tinea capitis identified a much lower rate of infection (0.1%).[10]

T. tonsurans is transmitted from human to human, whereas animals are the typical vectors of *M. canis*. Of note, *M. canis*, *Microsporum audouinii, Trichophyton mentagrophytes,* and *T. violaceum* less frequently cause infection in North America. Overall, these infections can be insidious, with frequently asymptomatic scalp colonization in endemic regions. *T. tonsurans* often is isolated from symptom-free family members of infected individuals, who play an important role in the spread of infection.[11,12] One small study found that siblings had a 46% risk for infection, owing to reservoirs such as shared hair brushes and combs.[13] There is no evidence that hair care practices (e.g., use of pomades, braiding) facilitate infection. There have been recent outbreaks of *T. tonsurans* infection in group childcare, which can last several months and are difficult to clear.[14]

Clinical Manifestations

Tinea capitis can present with myriad findings—from a spectrum of subtle, almost imperceptible diffuse hair loss to severe boggy, scaling abscess-like nodules. The more common findings include patchy areas of scaling and hair loss (Fig. 254.1). Involved areas can show scattered broken hairs of various lengths or areas of discrete hair loss with broken stubs of hair (black dot ringworm). Occipital or posterior cervical lymphadenopathy is a clue to diagnosis.[15]



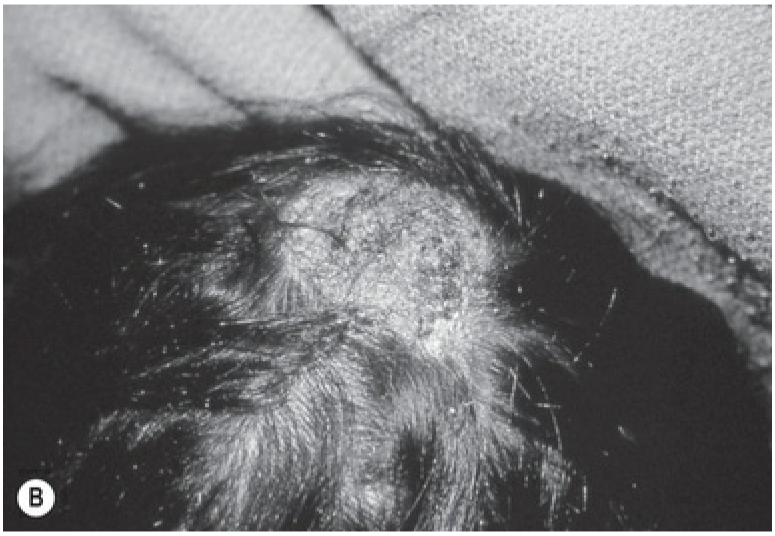


FIGURE 254.1 (A) Tinea capitis. Note the focal alopecia and scaling. (B) Kerion associated with tinea capitis from Trichophyton tonsurans.

In more severe inflammatory disease, a boggy, indurated mass, often with superimposed vesicles and pustules, can be present (Fig. 254.2). Known as *kerion celsi,* the lesion represents an extreme local immunologic response to infection.[16] When associated with fever, lymphadenopathy, leukocytosis, and purulent drainage, a kerion can be misdiagnosed as a bacterial infection or abscess, and the patient might be exposed to unnecessary surgical procedures or antibiotic therapy.[17] In addition, patients can have a dermatophytid ("id") immunologic response to dermatophytosis, which is characterized by pruritic, papulovesicular, or eczematous eruptions involving the face, trunk, or extremities.[18] This eruption, which sometimes occurs following initiation of therapy, is a hypersensitivity response to the infecting fungus and should not be confused with a drug reaction.

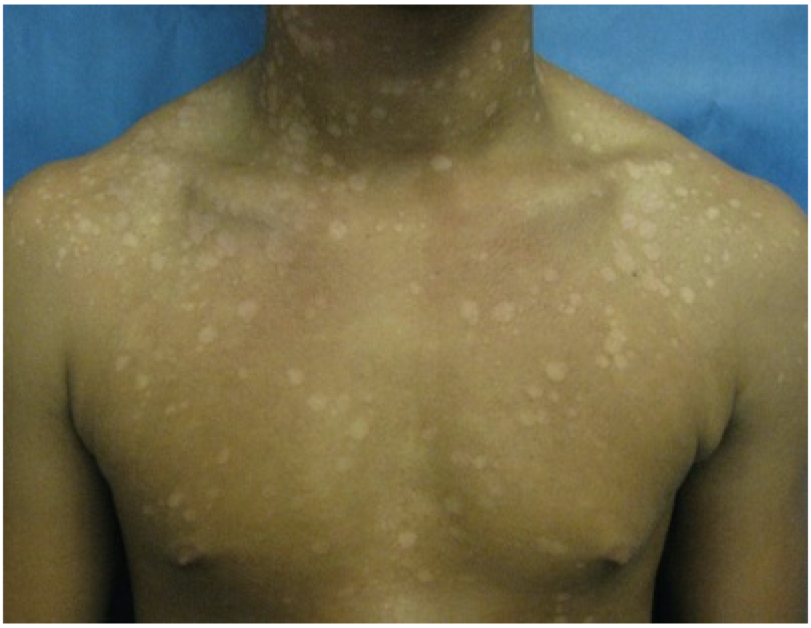


FIGURE 254.2 Tinea versicolor. Hypopigmented patches with fine scale.

Tinea capitis should be suspected in any prepubescent child with unexplained hair loss, particularly if the hair loss is focal, patchy, and accompanied by scaling or lymphadenopathy. Although a presumptive diagnosis can be made clinically, confirmation should be attempted whenever possible. Wood light examination of the area of hair loss can establish the presence of a *M. canis* or *M. audouinii* infection. Because these dermatophytes invade the outer hair shaft (ectothrix), they will fluoresce yellowish-green when exposed to ultraviolet light. By contrast, the more common *T. tonsurans* invades the inner core (endothrix) of the hair shaft and cannot be detected using ultraviolet light. Potassium hydroxide (KOH) preparation of affected hairs or scale and culture are standard evaluations. Samples are obtained by scraping or plucking hair in the affected area, followed by a KOH examination that may reveal arthroconidia or spores within or around the hair shaft, or hyphae. A specimen for culture is obtained by rubbing a moistened cotton-tipped applicator or toothbrush over the involved scalp and then placing the sample in a culturette transport system.[19] Family members should be queried regarding symptoms, and many experts recommend treating all family members empirically with twice-weekly topical ketoconazole or selenium sulfide antifungal shampoo.

The differential diagnosis for tinea capitis includes alopecia areata, atopic dermatitis, folliculitis, impetigo, lupus erythematosus, psoriasis, seborrheic dermatitis, traction alopecia, and trichotillomania.[20] Alopecia areata usually manifests as focal hair loss without inflammation or scaling; careful examination often reveals the presence of exclamation point hairs, which are broader at the tip of the hair with a diminution in the diameter of the hair closest to the scalp. Fractured hairs of different length, unusual patterns of hair loss, and excoriations of the scalp are hallmarks of trichotillomania; patchy hair loss of eyebrows and eyelashes also is seen more commonly in both trichotillomania and alopecia areata than in dermatophytosis. Seborrheic dermatitis, atopic dermatitis, and psoriasis typically are not associated with alopecia, although scratching can cause secondary scalp and hair changes that mimic tinea capitis.

Treatment

Standard treatment previously consisted of griseofulvin, 20 mg/kg daily (maximum of 1 g) in micronized form (available in suspension), or 10 to 15 mg/kg daily (maximum of 750 mg) in ultramicronized form. Because it is frequently the only agent covered by insurance plans, griseofulvin remains a popular, widely used treatment. The duration of treatment generally is 6 to 8 weeks. In recent years, many providers have found that higher doses of micronized griseofulvin (up to 25 mg/kg daily) and longer durations of treatment are sometimes required for cure.[21] *M. canis* disease often is more difficult to treat than *T. tonsurans*, and higher dose and longer duration of therapy often are required to achieve complete resolution.[22,23] Administration of griseofulvin with a fatty meal (e.g., milk, ice cream, peanut butter) enhances drug absorption; laboratory tests to monitor for adverse effects are not required unless therapy exceeds 8 weeks. A prospective trial using micronized griseofulvin (20 mg/kg/day) and topical therapy with twice-weekly selenium sulfide shampoo for 6 weeks showed mycologic, clinical, and complete cure rates of 89%, 66%, and 49%, respectively.[24] Common side effects of griseofulvin include nausea, headache, and photosensitivity reactions.

Many experts now consider terbinafine the better option for treating *T. tonsurans*. Terbinafine was approved by the US Food and

Drug Administration (FDA) for children, and because a 2- to 4-week course can results in cure, adherence is more likely.[25] A large, multinational randomized controlled trial of >1500 children compared oral griseofulvin (10–20 mg/kg/day) with terbinafine oral granules (5–8 mg/kg/day) for 4 weeks.[26] Complete clinical and mycologic cure was significantly higher in those treated with terbinafine, particularly for *T. tonsurans* infections.[26] Other studies have shown high cure rates with 2-week courses of terbinafine using a weight-based sliding scale dosing system with standard 250-mg terbinafine tablets: ¼ tablet (62.5 mg) to ½ tablet (125 mg) for patients weighing 20 to 40 kg, and 1 full tablet (250 mg) for patients >40 kg.[27] For *Microsporum* spp. and other inflammatory *Trichophyton* spp. infections, griseofulvin is superior to terbafine.[28,29] When choosing treatment, one must keep in mind that *T. tonsurans* accounts for more than 90% of US scalp infections.

Treatment with oral fluconazole or itraconazole, using daily or pulse regimens, can be effective for tinea capitis, and shorter duration of therapy also appears efficacious; however, limited data are available in children.[21,25,30] In addition, all of these agents, as well as terbinafine, rarely cause hepatic inflammation. Therefore most experts recommend obtaining baseline measurements of serum hepatic enzymes, with repeat testing if clinical symptoms or signs suggest possible hepatotoxicity.

In conjunction with oral therapy, topical agents such as selenium sulfide shampoo (1% or 2.5%), ciclopirox shampoo (1%), and ketoconazole shampoo may reduce the number of surface fungi and thus overall infectivity. A study comparing selenium sulfide shampoo 1% and ciclopirox shampoo 1% as adjunctive agents showed equivalency.[31] Topical therapies alone are not sufficient for treatment.[5,31–33]

Other therapies such as systemic corticosteroid, antibiotic, or surgery generally are not indicated.[34–37] Studies of use of systemic corticosteroids do not show consistent benefit for accelerated healing or reduction of postinflammatory scarring.[34–36] Nonetheless, in cases of severe inflammation that do not respond rapidly to systemic antifungal therapy, many experts use a short (10–14 day) course of oral prednisone in an effort to decrease scarring.

Tinea Pedis (Athlete's Foot)

Microbiology and Clinical Manifestations

Tinea pedis is a superficial fungal infection of the epidermis commonly caused by *Trichophyton mentagrophytes* var. *interdigitale, T. rubrum, Epidermophyton floccosum*, or *T. tonsurans*.[38] Infection is spread by contact with arthrospores from infected individuals, which can be present in pool, locker room, or bathroom areas. Tinea pedis is less common in prepubertal individuals, but some studies have reported prevalence of 2% to 4% in school-aged children.[39] Data from a human volunteer study suggest that the fungi responsible for tinea pedis do not invade normal skin.[40] A moist environment and maceration of the skin appear to be important predisposing factors. The role of bacteria in tinea pedis is poorly defined; however, some evidence indicates that subclinical bacterial infection may permit pathogenic fungi to invade the cornified epithelium.

There are three clinical forms of tinea pedis in children. The most common form is due to a variety of dermatophyte infections, including *T. rubrum*, and manifests as maceration, peeling, and fissuring of the intertriginous areas of the toes. Pruritus is the most prominent symptom. The second form of tinea pedis is due to *T. mentagrophytes* and manifests as vesicles, small bullae, and occasionally erosions, particularly on the instep of the plantar surface of the foot and interdigital web spaces. This inflammatory condition is subacute and can be associated with an eczematous rash or vesicles on the hands (*dermatophytid* or *id reaction*). In general, as the lesions heal, plaques and scales form. The third and probably least common form is usually caused by *T. rubrum* and is characterized by chronic, diffuse scaling and hyperkeratosis of the plantar surface of the feet and heels, referred to as *moccasin foot*.

Although some providers clinically diagnose and empirically treat patients, it is important to obtain KOH with or without cultures from children who have resistant or atypical disease. Common conditions mimicking tinea pedis in children include dyshydrosis, juvenile plantar dermatosis, allergic contact dermatitis, and irritant dermatitis. Occasionally, pitted keratolysis can be confused with tinea pedis, but pitted keratolysis is associated with a strong foul odor and usually manifests as small crateriform depressions of the soles and heels. In adolescents and adults, tinea pedis must be differentiated from bacterial infection, erythrasma, plaque or pustular psoriasis, and primary irritant dermatitis. Erythrasma can be diagnosed by using a Wood lamp that reveals a coral-red fluorescence; the axillae and groin are typically affected in erythrasma. Irritant and contact dermatitis generally spare the intertriginous areas of the toes. Also, the vesiculobullous form of tinea pedis can be confused with scabies or dyshidrosis.

Treatment

Topical antifungal agents are effective against most forms of tinea pedis. Common and effective topical agents include allylamines and imidazoles, including econazole, luliconazole, naftifine, and terbinafine.[41–45] A meta-analysis of 11 randomized trials comparing azoles with terbinafine and naftifine showed a slightly higher cure rate with terbinafine and naftifine.[46] Vesicular forms may benefit from wet compresses applied for short periods 2 to 3 times a day. Systemic therapy with griseofulvin or terbinafine may be necessary for treatment of a diffuse moccasin-foot type of infection. Alternatively, 40% urea cream in conjunction with a topical antifungal agent is thought to help loosen thick plantar scale, thus allowing increased absorption of the antifungal agent.[47,48]

Tinea Corporis (Ringworm)

Key Points

Diagnosis and Management of Tinea Corporis

Epidemiology

- 50% of cases in the US occur in children younger than 15 years.
- More commonly affects males than females
- Most infections result from human-to-human transmission.
- Outbreaks among wrestlers can occur, termed *tinea gladiatorum.*

Clinical Features

- Papulosquamous (most common): annular plaque with ring of scale and central clearing, classically termed “ringworm”
- Inflammatory or vesicular: plaques with vesicles at the advancing edge
- Granulomatous (Majocchi granuloma): nontender skin nodules with overlying crust, plaques; perifollicular distribution can occur
- Manifestations can be atypical (“tinea incognito”) if erroneously treated with topical corticosteroids.

Diagnosis

- Direct microscopy with KOH examination reveals hyphae; culture and biopsy with periodic acid–Schiff stain if necessary.

Treatment

- Topical triazoles: ketoconazole, clotrimazole or econazole once or twice a day
- Allylamines: terbinafine, naftifine
- Unresponsive cases, especially Majocchi granuloma, may require an adjunctive oral antifungal agent (e.g., fluconazole, griseofulvin, or terbinafine).

Duration of Therapy

- 14 to 21 days for topical therapy
- Duration of oral antifungal therapy depends on the agent chosen (e.g., ~2 weeks for fluconazole).

Microbiology and Clinical Manifestations

Tinea corporis is a superficial skin infection that occurs worldwide and affects all age groups. There is a predilection for males, and about 50% of cases in the US occur in children <15 years of age.[49] Any dermatophyte can cause disease, but the predominant pathogen varies geographically. *T. rubrum, T. tonsurans, T. mentagrophytes, M. canis*, and *E. floccosum* are the most common causes of tinea corporis in the US. Acquisition occurs through direct contact with infected humans or animals (primarily dogs and cats) and, less commonly, through exposure to contaminated fomites. The infectivity and inflammatory potential vary by species. Outbreaks among wrestlers are common and have been termed *tinea gladiatorum* (tinea capitis also can be present in affected individuals).[50] *T. tonsurans* is the most common cause of tinea gladiatorum in the US.[51]

Three clinical forms of disease occur: papulosquamous, inflammatory/vesicular, and granulomatous. Papulosquamous disease is the most common and manifests as an erythematous papule or plaque that evolves into an annular ring lesion with well-defined margins—the classic "ringworm." Infection spreads to involve surrounding healthy skin, often with a central area of clearing. Inflammatory or vesicular tinea corporis frequently occurs with *M. canis* infection and commonly has fine vesicular lesions at the plaque's advancing edge. Generally, remaining discrete lesions may coalesce. Granulomatous tinea corporis, often referred to as *Majocchi granuloma,* is the least common form of disease and often occurs in children whose initial infection was misdiagnosed and treated with topical corticosteroid agents, in immunocompromised hosts, or in females who have reinoculated the fungus while shaving their legs.[52] The granulomas form when dermatophytes within hair follicles rupture into the dermis and cause an inflammatory response. The infection is subacute or chronic and manifests as firm, nontender skin nodules with an overlying crust or plaque; lesions associated with leg shaving are follicular or perifollicular and often have a circumferential scale on an erythematous base.

Isolated lesions of nummular eczema can mimic tinea corporis, as can the herald patch of pityriasis rosea. Granuloma annulare and psoriasis often are mistaken for tinea corporis. If tinea corporis is erroneously treated with topical corticosteroids, the classical features of ringworm may not be evident. In such cases, the term *tinea incognito* is used, and KOH examination often aids in identifying the dermatophyte. Granuloma annulare can be mistaken for tinea corporis, and often is the true cause of "resistant tinea corporis." Granuloma annulare is distinguished by the absence of scale.

Diagnosis of *T. corporis* is optimized by making a KOH preparation from the active or leading edge scraping. Culture or biopsy with periodic acid–Schiff (PAS) staining is useful in equivocal cases.

Treatment

Most forms of tinea corporis can be treated with once- or twice-daily topical antifungal therapy for 14 to 21 days. Optimal duration of therapy and comparative efficacy of topical agents have not been evaluated extensively. Patients with widespread cutaneous lesions or a granulomatous reaction sometimes are treated systemically with terbinafine, griseofulvin, or alternative antifungal agents. Most recommend treatment with oral agents, and in a study using fluconazole 200 mg weekly, 100% of affected individuals were culture negative by the third week.[53] Several studies have documented a slight superiority and less side effects using newer agents, such as terbinafine and fluconazole, compared with griseofulvin.[54,55]

Tinea gladiatorum raises particular concern of spread to other athletes. It is unclear how long infected individuals should avoid contact with others, but many experts recommend 10 to 15 days after commencement of therapy.

Tinea Cruris (Jock Itch)

Tinea cruris is an acute or subacute superficial fungal infection of the perineum and groin that occurs primarily in males in warm, humid environments. There is an increasing incidence in postpubertal females who wear tight-fitting exercise garments or panty hose and in adolescents who are obese or diabetic.[56]

T. rubrum, T. mentagrophytes, and *E. floccosum* are the most common pathogens. The incidence of *T. rubrum* is increasing in the US.[7]

Tinea cruris typically manifests as red to reddish-brown, scaly lesions that usually are symmetric and have well-demarcated borders or fine, oozing vesicles or both. Local pruritus is a very common symptom. Chronically involved skin can manifest with brownish discoloration and well-defined borders.

The differential diagnosis includes allergic or irritant contact dermatitis, candida intertrigo, erythrasma (*Corynebacterium minutissimum* infection), psoriasis, and seborrheic dermatitis. Secondary infection with *Candida albicans* can develop in obese individuals with chronic tinea cruris. KOH examination of a specimen from the advancing edge of the lesion may show hyphae. Erythrasma can be identified and differentiated by its coral-red fluorescence when evaluated with a Wood lamp.

Treatment of tinea cruris depends on the clinical findings. Oozing areas should be treated with Burow solution compresses and the application of topical antifungal agents such as terbinafine, naftifine, and luliconazole.[57–59] For those with a *C. albicans* superinfection, the addition of nystatin powder is recommended because of its antifungal and drying properties. However, nystatin powder should not be mixed with the antifungal cream because this can form a gritty, irritating mixture. Also, when tinea cruris occurs with a concurrent dermatophyte infection of the fingernails or toenails (onychomycosis), treatment of both disorders may be required for cure.

Tinea Favosa

Tinea favosa (favus) is a chronic fungal infection of the scalp most commonly caused by *Trichophyton schoenleinii*. Tinea favosa does not occur in the US, except in recent immigrants or residents of a few well-localized, endemic areas. Favus generally is less contagious than other dermatophytoses, and intrafamilial infection is less prominent.[60]

Tinea favosa typically occurs in children and is classified into three clinical stages.[60] The first stage involves erythema of the scalp, with perifollicular involvement primarily. In the second stage, friable yellowish-brown crusts have a peculiar cup-shaped configuration (scutulum) and are associated with some hair loss. The last stage is most severe and affects large areas of the scalp with edema, oozing, focal ulceration, extensive hair loss, and eventually scarring alopecia. The differential diagnosis and treatment of tinea favosa are similar to tinea capitis.

Tinea Unguium (Onychomycosis)

Tinea unguium is a dermatophytic infection of the nails that is commonly associated with tinea pedis. Prevalence increases with age and is uncommon in prepubertal children. Worldwide prevalence ranges from 0.1% to 1%.[61] Adults have a higher prevalence at 2% to 14%, and prevalence in elderly people approaches 40%.[61] In addition, children with onychomycosis often have older affected family members.[62]

T. rubrum, T. mentagrophytes, and *E. floccosum* are the primary pathogens of tinea unguium.[63,64] Although clinical presentation can vary, most commonly the fungus directly invades keratin along the distal and lateral aspects of the nail and slowly spreads proximally along the nail.[39] The nail becomes "soft" and disfigured with subungual debris and nail discoloration. A more superficial infection creates focal, irregular opaque lesions on the nail.

Onychomycosis must be differentiated from congenital and acquired conditions that cause nail changes, such as alopecia areata, atopic dermatitis, bacterial infection, *Candida* infection, lichen planus, pachyonychia congenita, paronychia, psoriasis, trauma, twenty-nail dystrophy, and yellow nail syndrome.[65] *Candida* infection often has an associated paronychia and rarely causes subungual deposits. However, chronic mucocutaneous candidiasis should be considered in the differential diagnosis of any child with candidal onychomycosis.

Nail clippings and subungual debris should be obtained for diagnosis by direct microscopy and culture. Fungal elements can be visualized by direct microscopy of KOH-treated scrapings, but the sensitivity of this test is highly operator dependent.[66] A more reliable technique involves direct microscopic evaluation of paraffin-embedded nail clippings stained with PAS.[66] Relatively inexpensive, rapid PCR evaluation kits are now available at some research centers.

Treatment of onychomycosis includes oral and topical therapies. Griseofulvin is often used in children, but it has repeatedly been documented in adults that terbinafine leads to higher cure rates in onychomycosis than does griseofulvin. Most experts use terbinafine if financial and medical considerations do not contraindicate use. Alternatives therapies include itraconazole and fluconazole. The duration of griseofulvin therapy is prolonged (6–12 months), and recurrence is common. Terbinafine and the triazoles typically are administered for shorter durations (3 months) or as pulse regimens; however, they are not approved by the FDA for the treatment of pediatric onychomycosis.[62,67] In addition, mechanical debridement with 40% urea ointment applied daily for 10 days is sometimes used in cases recalcitrant to systemic therapy or when systemic therapy is contraindicated.

Classically, topical antifungal therapy has included ciclopirox and amorolfine. Newer agents that have been shown to be safe and effective include efinaconazole and tavaborole.[65,68–70] In general, topical agents also require a prolonged course of treatment (6–12 months) but may be less effective than oral medications because of inability to penetrate to the lowest portions of the nail bed. Therefore topical therapy generally is used only if there is no nail matrix (lunular) involvement. Young children have thin, fast-growing nails that may allow for enhanced drug penetration, and trials are underway to evaluate the new topical agents' efficacy in childhood disease.[71] Carbon dioxide laser treatment may increase penetration and efficacy in combination with topical antifungal therapy but has not proven to be highly efficacious.[72]

Tinea Versicolor (Pityriasis Versicolor)

Key Points

Epidemiology, Clinical Features, Diagnosis, and Treatment of Tinea Versicolor

Epidemiology

- Distributed throughout the US; more common in warm, humid climates

- Commonly affects adolescents and young adults.

Microbiology

- *Malassezia* (formerly *Pityrosporum)* spp. are causative organism; usually a benign commensal, but can assume an invasive form.

Clinical Features

- Often comes to medical attention during summer months with complaint of skin not tanning normally

- Pink, hypopigmented, or hyperpigmented patches and plaques with fine white scale

- Commonly distributed on neck, trunk, and proximal upper extremities; may occur on the face, particularly the temples, in young children

- Pruritus is minimal or absent.

Diagnosis

- Direct microscopy of KOH preparation shows spaghetti and meatballs appearance of blastoconidia and pseudomycelium; Wood lamp may show golden fluorescence.

- Modified Dixon agar or olive oil overlay on routine fungal media is used for culture.

Treatment and Duration of Therapy

- Topical antifungal cream and/or shampoo is generally sufficient treatment; should be used for at least 2 weeks; recurrence is common.

- Discoloration can persist for months despite clearance of infection.

- Oral antifungal agents (e.g., fluconazole, taken once and then repeated in 1 week) for resistant cases

Tinea versicolor is a common superficial yeast infection most frequently caused by *Malassezia furur* or *M. globosa. Malassezia* (formerly *Pityrosporum*) spp. are saphrophytic yeasts that are normal skin commensals in >90% of adults; however, under the right environmental circumstances, the dimorphic organism can invade the superficial epidermis and occasionally can cause invasive disease or sepsis in neonates and immunosuppressed individuals.[73] *Malassezia* thrives in environments rich in sebum and humidity and is therefore more common in older children and in tropical areas. Clinical findings include asymptomatic tan, pink, or hypopigmented macules or patches on the neck and upper trunk. Lesions often coalesce, leading to the presence of scalloped borders. Facial involvement, particularly on the temples, can be seen in children. Fine white (furfuraceous) scale may also be noted (Fig. 254.2). KOH preparation from skin scrapings reveals a spaghetti and meatball appearance of blastoconidia and pseudomycelium, confirming the diagnosis. Wood lamp examination reveals yellow fluorescence. Differential diagnosis includes pityriasis alba (particularly when occurring on the face), vitiligo, postinflammatory hypopigmentation, progressive macular hypomelanosis, tinea corporis, and, rarely, hypopigmented cutaneous T-cell lymphoma.

First-line therapy generally consists of topical imidazole or allylamine antifungal cream, particularly if involvement is localized to a small area. Unfortunately, involvement usually is more generalized, and antifungal shampoos, including ketoconazole and selenium sulfide, are often a cost-effective, simple way to treat larger areas. Ketoconazole shampoo can be applied in the shower and left on for a few minutes nightly for three consecutive nights, and then used monthly to help prevent recurrence. Patients should be advised that it may take months for the skin to repigment and that recurrence is common. Effective treatment of resistant or extensive cases includes oral fluconazole 400 mg in adolescents, given once and then repeated in 1 week.[74,75] Vigorous physical activity (causing sweating) within a few hours after taking the medicine increases penetration into the skin.[75] *Malassezia* (formerly *Pityrosporum*) spp. also can cause folliculitis, which is most concentrated in sebum-bearing areas (face, chest, back), and resembles acne but lacks comedones. It occurs most often in adolescents, particularly those who have been treated with long-term oral antibiotics, and in immunosuppressed patients. Oral antifungal agents are often required, although immunocompetent patients may respond adequately to topical antifungal therapies.

Tinea Nigra

Tinea nigra is a superficial mold infection of the stratum corneum that manifests as black, dark brown, or grey patches on the palms and soles; it is relatively uncommon in the US. Scale can be present, but it is typically minimal. Patients with hyperhidrosis or those living in humid climates are more commonly affected. Tinea nigra is occasionally confused with a melanocytic lesion because of its dark color. The two entities can be differentiated visually using dermoscopy, which shows brown strands or "pigmented spicules" in tinea nigra.[76,77] It is caused by a mold with a multitude of labels, including *Phaeoannellomyces* and *Hortaea* or *Exophiala werneckii*, which can be visualized using KOH preparation, revealing grey-brown to green hyphae and budding yeast cells. Topical antifungal agents such as miconazole, clotrimazole, and terbinafine are useful, as are drying solutions (e.g., aluminum chloride 20% solution).[78] Treatment of hyperhidrosis alone sometimes can lead to cure. Topical keratolytics (e.g., 3% topical salicylic acid) are also helpful in some cases.[78]

Piedra

White and black piedra are superficial fungal infections of the hair caused by *Trichosporon beigelii* and *Piedraia hortae,* respectively. They more commonly occur in tropical climates and manifest as soft concretions attached to scalp hair, but they also can occur in the axilla, pubis, and beard areas. These concretions can easily be confused with nits, hair casts, and other hair disorders; but on KOH examination, masses of septate hyphae (pigmented in black piedra) are seen within these concretions.[78] The differential diagnosis of piedra includes chronic intertrigo, hair casts, monilethrix, nits, pediculosis capitis, pediculosis pubis, tinea capitis, trichomycosis axillaris, trichoptilosis, and trichorrhexis nodosa.[79]

Treatment for both white and black piedra includes clipping or shaving hair in the affected area, along with topical antifungal therapy.[80] Ketoconazole 2% shampoo and topical keratolytics also can be effective.[78,79,81,82] Oral itraconazole (white piedra) or terbinafine (black piedra) may help to treat refractory or disseminated cases, which can occur in immunocompromised individuals. *T. beigelii* sepsis and organ dissemination can occur in low birth weight neonates and immunocompromised individuals.

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Agents of Eumycotic Mycetoma

Pseudallescheria boydii (Anamorph *Scedosporium apiospermum*)

Elaine G. Cox, John Manaloor

A mycetoma (maduromycosis, Madura foot) is a noncontagious, localized chronic infection that affects skin, subcutaneous tissue, fascia, muscle, and bone. Characteristic clinical features of mycetomas include localized swelling, fistulous tracts, and suppurative drainage containing dense colonies (called *granules, sclerotia*) of the offending pathogen. Mycetomas can be divided into two general categories based on the causative agent: *eumycotic mycetoma* caused by one of the filamentous fungi, and *actinomycotic mycetoma* caused by *Actinomycetes.* Striking geographic differences occur in the proportion of mycetomas caused by each.[1] Agents of eumycotic mycetoma are considered in this chapter, and agents of actinomycotic mycetoma are considered in Chapter 195).

Microbiology

At least 32 species of filamentous fungi (Eumycetes) are recognized as causes of eumycotic mycetoma[2] (Box 255.1). All are common saprophytes of soil and vegetable matter. *Madurella mycetomatis,* the most common cause worldwide, accounts for 70% of eumycotic mycetoma infections, and *Pseudallescheria boydii* (anamorph *Scedosporium apiospermum*) and *Leptosphaeria senegalensis* each account for 10% of infections.[2] *P. boydii, Fusarium falciforme, M. mycetomatis, Madurella grisea,* and *Exophilia jeanselmei,* in decreasing order of frequency, are the most common causes of eumycotic mycetoma in the United States. Within these groups, additional species have been recognized that are distinct phylogenetically and clinically, and have distinct antifungal susceptibilities.[3] *Scedosporium aurantiacum, Pseudallescheria minutispora,* and *Madurella pseudomycetomatis* are among those recognized most recently.[4]

Box 255.1

Etiologic Agents of Eumycotic Mycetoma

Ascomycota

Emericella nidulans (anamorph *Aspergillus nidulans*)

Leptosphaeria senegalensis[a]

Leptosphaeria tompkinsii

Neotestudina rosatii[a]

Pseudallescheria boydii (anamorph *Scedosporium apiospermum*)[a]

Mitosporic Fungi (Fungi Imperfecti)

Acremonium kiliense

Acremonium recifei

Aspergillus flavus

Aspergillus nidulans

Curvularia geniculata[a]

Curvularia lunata[a]

Corynespora cassiicola

Cylindrocarpon cyanescens

Cylindrocarpon destructans

Exophilia jeanselmei[a]

Fusarium falciforme[a]

Fusarium solani var. *coeruleum*

Fusarium solani var. *minus*

Fusarium verticillioides

Madurella grisea[a]

Madurella mycetomatis[a]

Phaeoacremonium spp.

Phialophora verrucosa

Plenodomus avramii

Polycytella hominis

Pseudochaetosphaeronema larense

Pyrenochaeta mackinnonii[a]

Pyrenochaeta romeroi[a]

Rhinocladiella atrovirens

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[a] Among the causative agents described most commonly.

Adapted from De Hoog GS, Ahmed AOA, McGinnis MR, Padhye AA. Fungi causing eumycotic mycetoma. In: Murray PR, Baron EJ, Pfaller MA (eds). Manual of Clinical Microbiology, 9th ed. Washington, DC, American Society of Microbiology, 2007, p. 1919.

The agents of eumycotic mycetoma grow on Sabouraud dextrose agar, with optimal growth occurring between 25°C and 37°C.

Isolation is facilitated by agar containing chloramphenicol to inhibit growth of bacteria and cycloheximide to inhibit growth of extraneous molds, although cycloheximide also can inhibit growth of *P. boydii.* Incubation may be required for up to 6 weeks for growth. Identification of isolates is based on morphology and pigmentation of colonies, mechanisms of conidia production, and morphology of conidiophores and conidia. *Madurella* spp., *Neotestudina rosatii,* and *Pyrenochaeta* spp. do not sporulate readily, so special sporulation media and physiologic tests for carbohydrate and nitrate utilization may be needed for identification.

Virulence and Immunity

The agents of eumycotic mycetoma are relatively avirulent, opportunistic pathogens that do not invade intact skin. Infection results from direct fungal inoculation or contamination of wounds. Factors that predispose an exposed person to mycetoma have not been determined. Impaired cellular immunity may contribute, but has not been observed consistently. Fungal agents act as chemoattractants that stimulate the complement system to induce chemotaxis, leading to the accumulation of neutrophils around granules and in the centers of abscesses and sinus tracts. However, this immune response appears to be ineffective for inhibiting fungal replication.[5]

Antibodies to some antigens of the offending agent are produced after established infections and can be measured by counter-immunoelectrophoresis, immunodiffusion, and immunoblot methods.[6,7] Specific immunoglobulin G (IgG) and IgM antibody directed against the causative organism also can be measured by enzyme immunoassay (EIA).[6,7] In endemic regions, antibodies to fungi that cause mycetoma can be detected by EIA in both infected and uninfected people, confounding a serologic approach to diagnosis.[6,8] The effect of specific antibody on the course of infection has not been established. Antibody titers decrease in some patients after appropriate treatment. In some endemic regions, resolution of precipitation arcs identified with counter-immunoelectrophoresis techniques are used to guide therapy.[5]

Pathogenesis

Infection usually begins with a skin wound caused by a thorn contaminated with the causative fungus. Organisms proliferate, with development of localized skin and subcutaneous infection appearing as a papular lesion. Often unrecognized, the lesion enlarges slowly and painlessly over weeks to months. Inflammation can advance along fascial planes; hematogenous dissemination does not occur, although lymphatic spread has been described and is estimated to occur in about 2% of cases.[9]

The process slowly destroys contiguous soft tissues and has a predilection for infecting and permanently damaging bone (Fig. 255.1). Multiple sinus tracts are common, and exuded drainage contains granules consisting largely of densely packed fungal colonies. Some matrix substances found in granules in vivo are not found in cultures grown in vitro and may represent antigenic material derived from the fungus or the host. The size, shape, and color of fungal filaments and presence or absence of matrix material within granules vary with the offending agent.

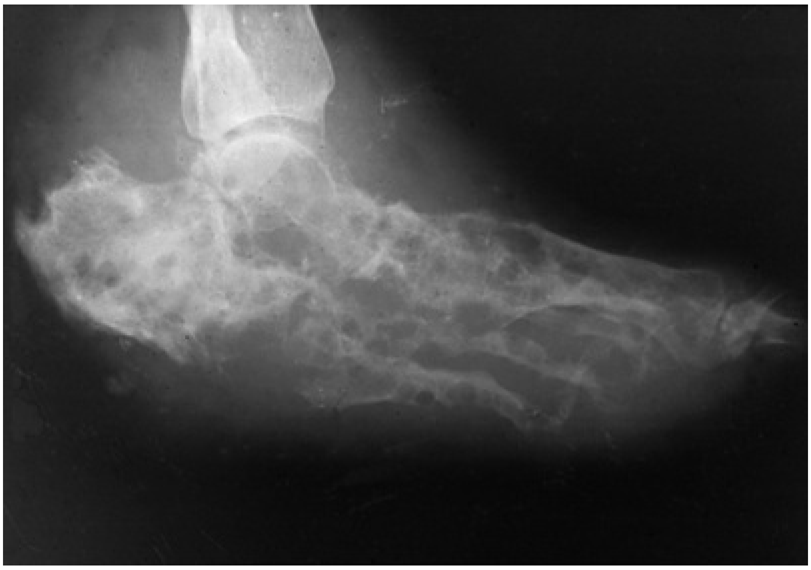

FIGURE 255.1 Radiograph of the foot of a 43-year-old farm worker with an 8-year history of foot swelling and fistulous drainage of suppurative material. *Madurella mycetomatis* was isolated from exuded granules. The radiograph shows extensive destruction of all bones of the foot with characteristic multiple lytic cavities and almost complete loss of normal bony architecture.

Except for the granules, histopathologic findings in mycetoma are nonspecific. Localized abscesses containing neutrophils and necrotic material surround granules. A subacute and chronic inflammatory response consisting of plasma cells, lymphocytes, multinucleated giant cells, and epithelioid cells surrounds the abscess (Fig. 255.2). An eosinophilic deposit (the Splendore-Hoeppli reaction) surrounds the granule and is thought to represent an immunologic response. Fibrosis ensues eventually and contributes to the gross anatomic deformities.[10]

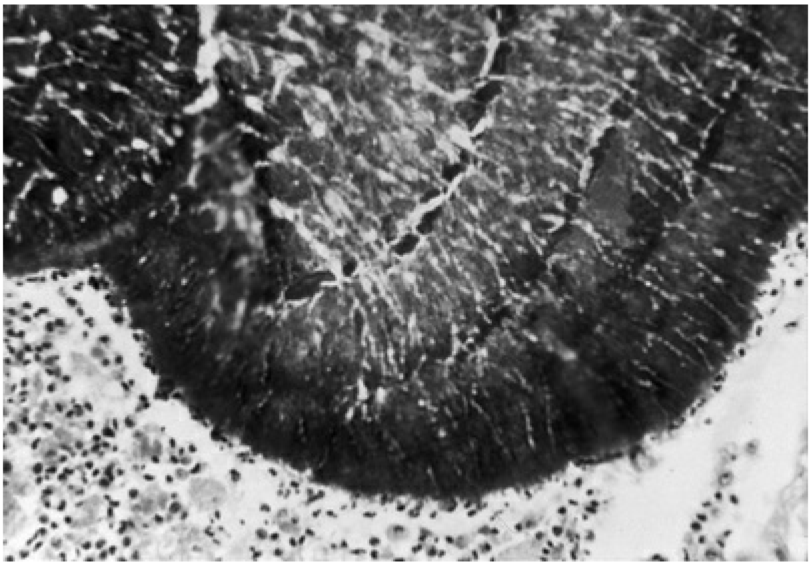

FIGURE 255.2 Hematoxylin and eosin−stained section of a brownish granule of *Madurella mycetomatis* containing radially oriented hyphae within a matrix of cement-like material. The granule is located within an abscess and is surrounded by acute inflammatory cells (original magnification, ×200).

Epidemiology

Most mycetomas occur in tropical or subtropical regions, mainly in areas where rainy seasons alternate with lengthy dry periods. Mexico,[11] India, Sudan,[12] Brazil, and Argentina have the highest incidence of reported infections. Eumycotic mycetomas are rare in the most temperate regions of the world, including the United States. Clinical diagnosis is becoming more common in individuals who travel to endemic regions.[6,13]

In endemic areas, the agents of eumycotic mycetoma commonly inhabit soil and plants. Thorn injuries, abrasions, and occupational activities that predispose to skin trauma and soil contamination lead to infection. A variety of pathogens have been reported among immunocompetent individuals.[14,15] Infection occurs most frequently in men 21 to 50 years of age, with a male-to-female ratio of 4 : 1,[13,16] and is infrequent among children. School-aged children younger than 11 years are most likely affected.[12] Poor nutrition or concomitant infections, often seen in resource-limited rural areas, are thought to increase the likelihood that exposure will lead to infection.

Clinical Manifestations

The initial lesion usually is a small subcutaneous nodule attached to the overlying skin. Fistulous tracts and sinus formation begin within several months to 1 year after infection. The purulent drainage contains granules. Subcutaneous nodules slowly enlarge, additional nodules appear, and new sinuses form as old sinus tracts heal. The progress of infection is slow, and medical attention frequently is not sought for many months or years. Extension contiguously and along fascial planes can lead to chronic bone infection. Systemic symptoms are absent unless secondary bacterial infection intervenes. Pain is not characteristic, and its presence often is associated with secondary bacterial infection of bone or progression of fistulous tracts.

Although infection can begin at any superficial anatomic site, mycetomas usually occur on extremities. About 70% affect feet, and 12% to 15% involve hands; other sites on extremities and the head and neck account for most of the remaining cases.[13] Chronic changes and destruction eventually affect most underlying structures[17] (Table 255.1). The result is a disfigured, scarred, swollen site with draining sinuses and functional impairment.

TABLE 255.1

Anatomic Alterations Attributable to Mycetoma

Tissue	Abnormality

Skin and subcutaneous fatty tissue	Fistulas, granulomas, change in color, zones of fibrosis
Muscle	Degenerative myositis
Tendon	Few alterations because of resistance
Nerve sheath	Hypertrophy
Lymphatics	Inflammatory reaction; embolization of granules possible
Lymphatic ganglia	Hypertrophy; dissemination rare
Bone	Periostitis, osteolysis, osteofibrosis
Peripheral nerve	Altered by sclerosis

From Magana M. Mycetoma. Int J Dermatol 1984;24:221–236.

Laboratory Findings and Diagnosis

In the presence of a lesion with tumefaction (indurated swelling), fistulous sinus tracts, and drainage that contains granules, the clinical diagnosis of mycetoma is straightforward. However, because treatment and prognosis differ for mycetomas caused by *Actinomyces* spp. or filamentous fungi, a specific diagnosis is necessary, and biopsy is required. Histopathologic findings in mycetoma are nonspecific and consist of acute and chronic inflammation, granulomatous changes, and fibrosis. On biopsy specimen, “grains” may or may not be observed because they are scattered along sinus tracts and vulnerable to sampling error. When present, they are large and surrounded by neutrophils. Careful examination of granules in tissue (see Fig. 255.2) or purulent material suggests the causative agent. Accurate confirmation requires fungal culture. Granules range in size from 0.2 to 5 µm and are often visible to the unaided eye. The color, texture, size, and shape of the granules provide important clues to the etiologic agent. Eumycotic mycetomas have granules that are black or white and soft or hard, with a cement-like matrix. Gomori methenamine silver nitrate staining of eumycotic granules shows wide, interwoven septate hyphae 2 to 5 µm in diameter; large swollen cells up to 15 µm in diameter also may be present at the periphery of granules. Actinomycotic infections have gram-positive, interlaced, thin filaments 0.5 to 1 µm in diameter, with coccoid and bacillary forms.[10]

To facilitate recovery of fungus, granules obtained from purulent material or tissue should be washed in normal saline that contains antimicrobial agents to inhibit growth of contaminating bacteria. Sabouraud dextrose agar is inoculated and incubated at 25°C and

37°C and examined for growth at 2-day intervals for 6 weeks. A secure etiologic diagnosis is established when a single agent is isolated from several granules.

Diagnostic modalities such as polymerase chain reaction[18] and matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) mass spectrometry are becoming available to assist in identification of an isolated pathogen.[19–21]

Radiographic abnormalities can be seen in soft tissue and bone and include areas of increased soft tissue density (caused by granulomas) adjacent to normal soft tissue. Osseous lesions have a variable appearance (see Fig. 255.1); most are lytic cavities in bone that can contain large numbers of granules. Cortical bone also can be eroded by extrinsic irritation from contiguous soft tissue inflammation. Periosteal new bone formation can be seen as spicules oriented perpendicular to the long axes of long bones. Osteopenia results from disuse or impairment of perfusion. The "dot in circle" sign finding on magnetic resonance imaging is suggestive of mycetoma.[22,23] Ultrasonography can distinguish between the eumycotic mycetoma and actinomycetoma by appearance of their macrogranular characteristics.[24]

Although serologic tests have been investigated for use in diagnosis and to monitor therapy, standardized reagents are not available commercially.

Treatment and Special Considerations

Eumycotic mycetoma has a low cure rate overall, responding less favorably to treatment than do mycetomas caused by *Actinomyces* spp. Optimal management includes medical and surgical interventions. Initial surgical debulking generally is necessary, although medical therapy is a beneficial adjunct in an attempt to avoid amputation.[25,26] In general, response to antifungal agents is poor, perhaps because of changes within fungal cell walls that enable them to act as barriers to penetration of drug. These cell wall alterations also impair leukocyte adhesion to make the cell less penetrable to the respiratory burst products of inflammatory cells.

Most clinical experience with antifungal therapy has been with mycetomas caused by *M. mycetomatis.* Antifungal susceptibility testing might be helpful because there is considerable strain-to-strain variation in susceptibility. However, testing is not available widely, and standard cutoff values have not been well established.[5] Treatment with amphotericin B often is ineffective because of inherent resistance. Limited efficacy has been observed in a few patients treated with liposomal amphotericin formulations.[27] Fluconazole is ineffective largely, but newer azoles have demonstrated clinical efficacy in the treatment of eumycotic mycetoma.[9,28,29] Ketoconazole (200 mg per dose given twice daily in adults) historically was the most frequently used agent and was successful in about 70% of cases.[30] However, ketoconazole was not successful in treating eumycetomas caused by *M. grisea, P. boydii (S. apiospermum),* and *Acremonium* spp.[31] Griseofulvin (500 mg per dose given three times daily in adults) used for patients who did not respond to ketoconazole was infrequently successful. Itraconazole initially showed a favorable response in only 40% of patients; more recent experience demonstrates good tolerability and efficacy.[30,32–34] Voriconazole has been used successfully for treatment of subcutaneous infections with *S. apiospermum* when administered intravenously followed by orally, as an adjunct to debridement.[26,35] In clinical studies, posaconazole was more effective than voriconazole in treating *P. boydii* in certain clinical scenarios.[9,16,20,29,36–39] The echinocandin class appears to have little to no therapeutic potential in early clinical studies, although there is some evidence of activity of caspofungin against *P. boydii* in vitro.[40] Agents under investigation, such as ravuconazole and isavuconazole, show promise for superior efficacy.[28,29,41] Additional strategies, such as combination therapy, show little promise except for possible synergy between ciprofloxacin and posaconazole.[42,43]

Although there are no controlled studies of duration of treatment, antifungal therapy should be continued for at least 10 months or at least 3 months after resolution of inflammation. Decreasing antibody titer may be a marker of effective therapy[5]; however, standardized serologic tests are not available.

Incision and drainage of abscesses, debulking of large masses, and excision of sinus tracts facilitate healing, reduce pain, and may mitigate need for amputation. Length of antifungal therapy often can be reduced with adequate debulking procedures. Excision can be curative if performed when lesions are small and have not involved bone; a wide margin of uninfected tissue should be removed in such cases.[19,30] Without antifungal therapy, relapse after resection occurs in more than half of cases. Other treatment modalities, such as topical negative pressure, have minimal success.[25]

Prevention

In endemic areas, prevention requires protection from injuries prone to contamination by soil or vegetable matter. Improvements in hygienic standards, reduction of occupational injuries, and use of adequate footwear and protective clothing should reduce the frequency of mycetoma. Education of people at risk to seek medical intervention early, when cure is more likely and loss of limb can be avoided, is essential. New strategies of education have included point-of-care attempts at integrated management.[12]

Pseudallescheria boydii (Scedosporium apiospermum)

P. boydii (S. apiospermum) is a saprophytic fungus with worldwide distribution in soil, water, and feces of domesticated animals. *P. boydii* is an opportunistic pathogen that rarely causes infection in healthy, immunocompetent hosts. *P. boydii* causes about 10% of eumycotic mycetoma and also is responsible for a variety of other infections, especially in immunocompromised people.[2,44] Nonmycetomatous infections caused by *P. boydii* are termed *pseudallescheriasis.*

Microbiology

P. boydii is a member of the class Ascomycetae and, in contrast to most pathogenic fungi, exists in tissue in its teleomorphic (sexual) form. The anamorph (asexual form) is termed *S. apiospermum* and can cause infection that is clinically indistinguishable from infection caused by the teleomorph. The mold grows on Sabouraud and most standard media, and matures in 7 days. Growth can be inhibited by cycloheximide contained in some selective agars used for primary isolation. On oatmeal agar, white colonies grow rapidly at 25°C and later turn to grey. Hyphae are yellow-brown and 2 to 3 μm in diameter. Asci are 12 to 18 μm × 9 to 13 μm in diameter and contain 8 ascospores. Two morphologic types of asexual conidia are produced, the most common being *Scedosporium* type and a smaller *Graphium* type. In tissue sections, the hyphae of *P. boydii* are branched, septate, hyaline, and hematoxylin stain positive. Morphologic distinction of *P. boydii* hyphae from hyphae of *Aspergillus* and other hyaline molds is not possible, and direct immunofluorescent testing is needed. *P. boydii* likely does not represent a single entity but rather is a complex with at least 6 known species.

Epidemiology

P. boydii is a common inhabitant of water, soil, and manure and usually gains entry to a host through accidental trauma or aspiration. Although worldwide in distribution, considerable regional differences occur in the frequency of isolation of *P. boydii* from people with clinical illnesses.[45] This discrepancy may be attributable to differences in strain virulence.[37,46]

Clinical Manifestations

Almost 99% of infections caused by *P. boydii* are mycetomas. The presence of granules (sclerotia) is a distinguishing feature of true mycetomas. Infections caused by traumatic implantation of *P. boydii,* but which do not contain granules, are termed *pseudallescheriasis.*[47]

P. boydii is found occasionally as a commensal in preexisting lung cavities and in paranasal sinuses. Respiratory tract illnesses attributed to *P. boydii* follow inhalation of contaminated material and include pneumonitis as well as fungus balls in lung cavities and paranasal sinuses.[15,48] Infections that occur in immunocompetent children usually are localized and result from contaminated puncture injuries. Eyes and periorbital structures, skin and subcutaneous tissue, and osteoarticular structures are affected most commonly.[49]

Infections in an immunocompromised host can be localized but are increasingly reported to result in invasive and disseminated disease. Life-threatening manifestations occur most often in patients with solid-organ transplants,[50] hematologic stem cell transplants,[51] hematologic malignancies,[52] HIV infection, or chronic granulomatous disease and in people receiving immunosuppressive therapy.[20,53] In these groups of patients, systemic infection, meningitis, brain abscess, keratitis and endophthalmitis, otomycosis, endocarditis, indwelling device-related infection, central nervous system infections, and other invasive infections are common.[54] Mortality rates as high as 75% are reported in patients with central nervous system and progressive disseminated infections.[44,55–57] Clinical findings in these settings often mimic findings caused by *Aspergillus* or *Fusarium* infections.

Diagnosis

Diagnosis is confirmed by isolating the offending agent from a normally sterile site. Culture has been the gold standard, but identification by polymerase chain reaction is increasingly important and used more widely.[18,58] Because antifungal susceptibility patterns differ for these organisms, laboratory confirmation is needed.[59] Rare instances of coinfection have been identified.

Treatment

P. boydii often is resistant to amphotericin B,[60] and its use in these infections has been associated with poor clinical response as well as recurrence after seemingly effective therapy.

Development of the first triazoles provided new, but limited, therapeutic options. Fluconazole has no activity against *P. boydii*.[53] Itraconazole[61–63] and ketoconazole[64] have been used clinically with mixed results. Both voriconazole and posaconazole have activity in vitro.[39,41,60,65–70] Voriconazole has been used successfully in cutaneous infections,[26,35] disseminated disease,[55,57] and pulmonary infections.[15] Voriconazole appears to have good penetration into the cerebrospinal fluid and has been used in treating central nervous system disease.[55,57,69,71–75] Because of the wide spectrum of disease manifestations that appear to respond favorably, voriconazole is considered by most experts to be the drug of choice.[9] Posaconazole also has good activity in vitro against *S. apiospermum*[56] but also has adequate penetration into the central nervous system. Posaconazole has been used successfully to treat brain abscesses in immunocompromised hosts who were refractory to treatment with other agents.[1,16,69,76,77] An isolated report suggests a potential role for potassium iodide.[78] Drainage or excision of infected tissue, when possible, is an important adjunct to therapy.[1,57] Mortality in invasive infections is high if operative management is not feasible.

The optimal duration of antifungal therapy has not been established and must be individualized. In immunocompetent hosts in whom lesions can be excised, antifungal treatment may be discontinued after 6 months.[1] Patients with underlying conditions that make clearance of the fungus unlikely may require treatment indefinitely. Consultation with experts is recommended in managing such patients.

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Key Points

Eumycotic Mycetoma (Maduramycosis, Madura Foot)

Definition

- Noncontagious, chronic infection of skin, subcutaneous tissue, fascia, muscle, and bone caused by a variety of filamentous fungi

Microbiology

- *Madurella mycetomatis* (70%); *Pseudallescheria boydii* (anamorph *Scedosporium apiospermum*) (10%); *Leptosphaeria senegalensis* (10%)

- At least 32 species of filamentous fungi (see Box 255.1)

Epidemiology

- Tropical, subtropical areas with rainy seasons and dry seasons. Mexico, India, large regions of Africa, Central and South

America. Rare in temperate regions; infrequent among children

- Skin injury predisposes to inoculation of contaminated wounds

Clinical Features

- Lesions often affect feet (70%) and sometimes hands (15%).
- Subcutaneous nodule(s) early; fistulous tracts in weeks to months
- Purulent drainage contains granules.
- Lesions usually are painless, and systemic symptoms are absent unless secondarily infected with bacteria.
- Slow progression along fascial planes often leads to bone infection.

Diagnosis

- Tumefaction, fistulous sinus tracts, and drainage containing granules often are present.
- Clinical, radiographic, and histopathologic findings are similar in actinomycotic mycetoma.
- Examination and culture help to distinguish between entities and informs appropriate antimicrobial therapy.
- Polymerase chain reaction and matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) can assist in final characterization of agents causing mycetoma.

Treatment

- Eumycotic mycetomas respond less favorably than infection caused by *Actinomyces.*
- Surgical debulking and drainage of abscesses is needed in association with antifungal therapy.

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D

Human Parasites and Vectors

OUTLINE

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Protozoa
Nematodes
Cestodes
Trematodes

256

Classification of Parasites

Peter J. Hotez

Although all infectious agents of humans are parasites, by convention, parasitic diseases often are defined as diseases caused by protozoa or helminths. Parasitic protozoa and helminths sometimes are referred to as animal parasites to distinguish them from bacteria, fungi, and viruses. This distinction has a historical basis. Parasitology (the study of animal parasites) emerged as a separate discipline from microbiology as a result of nineteenth-century scientific investigations conducted outside the mainstream of science in Europe. Animal parasites were considered "exotic" because many initially were described by European investigators working in the tropics. The life cycle of filariasis was elucidated by Manson (British) in China, malaria by Ross (British) in India, ancylostomiasis by Looss (German) in Egypt, and schistosomiasis by Bilharz (German) in Egypt.

The animal parasites of humans and their vectors constitute a diverse array of eukaryotic organisms that span many phyla (Box 256.1).[1] The major endoparasitic helminths of humans belong to the phyla Platyhelminthes (flatworms) and Nematoda (roundworms). The endoparasitic protozoa are a diverse group of several thousand eukaryotic unicellular animals.[2] Together, the parasites exert an enormous toll on human life and health. The Global Burden of Disease Study estimated that 854,600 people died from malaria in 2013, with most of those deaths from *Plasmodium falciparum* among children.[3] In that same year, an estimated 62,500 people died from visceral leishmaniasis, 10,600 died from American trypanosomiasis (Chagas disease), and 6900 deaths were due to African trypanosomiasis. Intestinal parasites were also major childhood killers, with cryptosporidiosis causing an estimated 41,900 deaths and amoebiasis 11,300 deaths among children younger than 5 years.

Box 256.1

Major Kingdoms and Phyla of Animal Parasites With Representative Genera

Kingdom Archeozoa

Phylum Metamonada *(Giardia)*

Phylum Microspora *(Enterocytozoon)*

Kingdom Protozoa

Phylum Parabasala *(Trichomonas)*

Phylum Euglenozoa *(Leishmania)*

Phylum Ciliophora *(Balantidium)*

Phylum Apicomplexa *(Toxoplasma)*

Phylum Rhizopoda *(Entamoeba)*

Kingdom Animalia

Phylum Platyhelminthes *(Schistosoma)*

Phylum Nematoda *(Ascaris)*

In contrast, the helminth infections caused many fewer deaths but a high degree of disability. The Global Burden of Disease Study estimated that more than 1 billion people were infected with helminth infections in 2010, including ascariasis (819 million people), trichuriasis (465 million), hookworm disease (439 million), and schistosomiasis (252 million).[4] These helminth infections were responsible for an estimated loss of 8.5 million disability-adjusted life years.

Despite their public health importance, most of the human parasitic diseases have been neglected by the scientific, medical, and public health communities.[5,6] Their neglect stems from the observations that parasitic diseases generally occur among the poor and more often than not occur in remote and rural areas where they are hidden from view. In addition, because they result in chronic disability, they are themselves poverty promoting. In some cases, parasitic diseases have stigmas attached. Hence the major chronic parasitic infections of humans often are referred to as *neglected tropical diseases*.[5–7] Since 2006, global efforts have been implemented to provide low-cost or drug company–donated treatments for 7 of the most common neglected tropical diseases (i.e., ascariasis, trichuriasis, hookworm, schistosomiasis, lymphatic filariasis, onchocerciasis, and trachoma) in programs of mass drug administration.[5–7] The United States Agency for International Development (USAID) recently estimated that more than 1 billion people have received access to essential neglected tropical disease medicines through its programs of mass drug administration. However, the commercial markets for new drugs, vaccines, and diagnostics are extremely small, and there have been few incentives for pharmaceutical companies to undertake drug discovery and development programs for parasitic and neglected tropical diseases. As a result, many of the drugs still in use today for parasitic infections were first discovered in the middle of the twentieth century.[6] There is some optimism that the recent creation of new nonprofit product development will accelerate development and clinical testing of new drugs and vaccines for neglected tropical disease.[6]

Parasitic Archeozoa and Protozoa

Some investigators are of the opinion that the old classification, in which a single phylum of protozoa encompassed all unicellular eukaryotic microorganisms, is not validated by the wealth of new ultrastructural and molecular taxonomic data. Armed with newly developed molecular probes, tools, and approaches to cladistic analysis, biologists are re-examining the classification of these organisms. For instance, the parasite *Giardia lamblia* has been shown to lack mitochondria and to contain ribosomal RNA sequences that more closely resemble those of bacteria.[8,9] It has been proposed that this organism represents an evolutionary transition between prokaryotic and eukaryotic microorganisms.[10] Similarly, the obligate intracellular microsporidia have ultrastructural features, such as ribosomes and a unique complex extrusion apparatus, that are distinctly different from those found ordinarily in protozoa. Some experts think that these parasites are different enough to justify exclusion from Protozoa. Corliss reclassifies them as Archeozoa, a term that reflects their evolutionary transitional nature.[1] Typically, members of Archeozoa primitively lack certain organelles, such as mitochondria, peroxisomes, and typical Golgi bodies. In contrast, one or more of these organelles is present characteristically in Protozoa. In response to these observations, some microbiologists have elevated both the Archeozoa and Protozoa to the status of a taxonomic kingdom to more accurately describe the diversity of these two groups (Box 256.2). In this classification, the former subphyla of protozoa, specifically, Apicomplexa, Ciliophora, and Rhizopoda, are raised to independent phyla within the kingdom of Protozoa. Clinicians prefer to identify unicellular eukaryotic microorganisms on the basis of their mode of transmission (e.g., enteric, arthropod-borne) or site of parasitism within humans (e.g., blood, gastrointestinal tract) (Table 256.1). However, a sound taxonomic understanding of these microorganisms fosters an understanding of their pathophysiology and predicts the activity of antiparasitic agents. For instance, albendazole might be useful for treatment of Microspora but not for more conventional protozoa.

Box 256.2

Representative Human Parasite Genera of the Kingdoms Protozoa and Archeozoa

Kingdom Archeozoa

Phylum Archamoebae

Phylum Metamonada

Giardia

Chilomastix

Phylum Microspora

Enterocytozoon

Nosema

Kingdom Protozoa

Phylum Percolozoa

Phylum Parabasala

Dientamoeba

Trichomonas

Phylum Euglenozoa

Leishmania

Trypanosoma

Phylum Opalozoa

Phylum Mycetozoa

Phylum Choanozoa

Phylum Dinozoa

Phylum Ciliophora

Balantidium

Phylum Apicomplexa

Babesia

Cryptosporidium

Cyclospora

Plasmodium

Toxoplasma

Phylum Rizopoda

Acanthamoeba

Entamoeba

Phylum Heliozoa

Phylum Radiozoa

TABLE 256.1

Classification of Representative Archeozoa and Protozoa According to Modes of Transmission

Mode of Transmission	Representative Genera
Enteric	*Balantidium*
	Cryptosporidium
	Cyclospora
	Dientamoeba
	Entamoeba
	Giardia
	Sexual *Trichomonas*
Arthropod	*Babesia*
	Leishmania
	Plasmodium
	Trypanosoma

Almost certainly our knowledge about classification and biology of the Archeozoa and Protozoa will increase substantially in the coming decade. The new knowledge will be derived from the dozen or more protozoan genome projects completed within the decade.

The projects include completion of genomes for some of the most important protozoan pathogens.[11] In every case, these genome projects are revealing promising drug targets and new insights into evolution of parasitic protists.

Parasitic Animalia

The endoparasitic worms of humans belong to the phyla Nematoda and Platyhelminthes. Nematodes are nonsegmented cylindroid roundworms that predominantly are free-living forms inhabiting the soil and water. Many species of nematodes also are plant parasites of enormous agricultural and economic importance. Almost every vertebrate can harbor one or more species of endoparasitic nematodes. Humans are no exception, and nearly one fourth of the world's population is infected with at least one species of nematode (e.g., *Ascaris lumbricoides, Trichuris trichiura,* and the hookworm *Necator americanus*).[3,12]

Human parasitic nematodes vary enormously in length from just over 200 µm (microfilariae) to more than 120 cm *(Dracunculus)*. Their size, however, does not correlate with pathogenicity. One of the smallest nematodes, *Strongyloides stercoralis,* is among the most virulent of human pathogens. Nematodes are surrounded by a resistant cuticle and move by means of a complex muscular system; their digestive system is divided into an oral (buccal) cavity, esophagus, midgut, hindgut, and anus. Frequently, these structures are modified in the parasitic forms. For instance, the oral cavity of hookworms is enlarged and armed with teeth or cutting plates to ingest intestinal mucosa, and the esophagus is equipped with large exocrine glands that may contain hydrolytic enzymes for exodigestion.[12] The reproductive organs are highly developed in parasitic nematodes, particularly in females, and reflect their capacity to give rise to progeny. An adult female ascarid can release 200,000 eggs per day. Most nematodes have one or more life cycle stages, such as an egg or larva, that develop outside the host. It is convenient to categorize nematodes on the basis of their site of external development and the mechanism of entry into their definitive human host. Therefore we frequently group endoparasitic nematodes according to whether they are transmitted through contact with soil *(Ascaris)*; have an invertebrate intermediate host such as an insect *(Wuchereria)*, crustacean *(Dracunculus)*, or mollusk *(Angiostrongylus)*; or have another vertebrate host with acquisition by the ingestion of undercooked meat *(Trichinella)* (Table 256.2). Several new genome projects for human nematode parasites are underway (http://www.nematodes.net and http://www.nematodes.org), which should add considerably to our fundamental knowledge.

TABLE 256.2

Major Human Parasitic Nematodes Classified by Mode of Transmission

Mode of Transmission	Common Mode of Acquisition
SOIL TRANSMITTED	
Ancylostoma duodenale (hookworm)	Skin penetration by or ingestion of larvae
Ascaris lumbricoides (human roundworm)	Ingestion of embryonated egg
Necator americanus (hookworm)	Skin penetration of larvae
Strongyloides stercoralis (threadworm)	Skin penetration of larvae
Toxocara canis (dog roundworm)	Ingestion of embryonated egg
Trichuris trichiura (whipworm)	Ingestion of embryonated egg
PARATENIC	
Anisakis spp.	Ingestion of fish
Trichinella spiralis	Ingestion of pork
ARTHROPOD-BORNE	
Brugia malayi	Bite of mosquito
Dracunculus medinensis	Ingestion of cyclops (crustacean)
Loa loa	Bite of mango fly (*Chrysops* spp.)
Onchocerca volvulus	Bite of blackfly
Wuchereria bancrofti	Bite of mosquito

Two endoparasitic classes of the phylum *Platyhelminthes* are important medically: trematodes and cestodes (Table 256.3). Human trematodes include blood flukes (schistosomes), intestinal flukes, and tissue flukes. Each species of human trematode also has external life cycle stages in one or more intermediate hosts. At least one intermediate host is always a mollusk. The adult fluke is either monoecious, having both sexes (hermaphroditic), or diecious, having separate sexes. Monoecious flukes reproduce by self- or cross-fertilization, whereas diecious trematodes live in copula as separate sexes. Except for the schistosomes, all human trematodes are monoecious. Eggs released by adult flukes typically hatch in water and give rise to free-living ciliated miracidia that seek their molluscan intermediate host. Miracidia are pluripotent and, when inside the snail, ultimately generate large numbers of cercariae.

Cercariae exit the snail and enter their definitive human host by direct skin penetration (schistosomes) or encyst as metacercariae in a second intermediate host such as fish (*Clonorchis*) or vegetation *(Fasciola)* before ingestion. In terms of prevalence and chronic disease burden, the two most important trematodes are *Schistosoma haematobium* and *S. mansoni.* More than 200 million people are infected with either of these two parasites, most in Africa, although some estimates suggest that this number could be two or more times higher.[3,13,14] Two schistosome genome projects have been completed.[15]

TABLE 256.3

Major Human Parasitic Platyhelminths Classified by Mode of Transmission

Parasite	Common Mode of Acquisition
DIGENETIC TREMATODES (FLUKES)	
Clonorchis sinensis	Ingestion of EMc in fish
Fasciola hepatica	Ingestion of EMc in vegetation
Fasciolopsis buski	Ingestion of EMc in vegetation
Paragonimus spp.	Ingestion of EMc in crustaceans
Schistosoma spp.	Skin penetration of cercaria
CESTODES (TAPEWORMS)	
Diphyllobothrium latum	Ingestion of pleurocercoids in fish
Dipylidium caninum	Ingestion of cysticercoids in fleas
Hymenolepis diminuta	Ingestion of cysticercoids in insects
Hymenolepis nana	Ingestion of embryonated eggs
Taenia saginata	Ingestion of cysticerci in beef
Taenia solium	Ingestion of cysticerci in pork
INFECTIONS BY LARVAL CESTODES	
Cysticercosis	Ingestion of *Taenia solium* eggs
Hydatid disease	Ingestion of *Echinococcus granulosus* eggs

EMc, encysted metacercariae.

In their definitive vertebrate host, cestodes are parasitic tapeworms with a gastrointestinal tract attachment apparatus (scolex) and a series of proglottid segments (strobila). Each proglottid segment contains both male and female reproductive organs and typically fills with eggs before detachment in feces. Ingestion of eggs by an intermediate host results in the liberation of larvae that frequently migrate to muscle as a final destination. Humans acquire tapeworms when they ingest the larval stage contained within arthropods or uncooked meat. Much more severe disease results when humans serve as the “accidental” intermediate host for cestodes by ingesting tapeworm eggs. Such intake can result in cysticercosis after ingestion of the eggs of *Taenia solium* or in hydatid disease after ingestion of the eggs of *Echinococcus granulosus.* Cysticercosis is emerging as an important cause of epilepsy in children, including children living in North America.

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Ectoparasites (Lice and Scabies)

Dirk M. Elston

Pediculosis

The Parasites, Virulence, and Pathogenesis

Pediculosis is an infestation by one of several species of sucking lice of the phylum Arthropoda, class Insecta, order Phthiraptera, suborder Anoplura, family Pediculidae or family Pthiridae. The three types of lice that infest humans are *Pediculus humanus capitis* (the head louse), *Pediculus humanus humanus* (the body louse), and *Phthirus pubis* (the crab louse).

Louse infestation spreads readily, and the host response offers little protection against reinfestation. Resistance to chemical pediculicides is widespread, especially knockdown resistance to permethrin related to a double gene mutation (*T929I* and *L932F*). Glutathione-*S*-transferase–based resistance also has been implicated in pyrethroid resistance. Mono-oxygenase–based resistance is common but can be overcome by synergistic agents such as piperonyl butoxide.

Transfer of lice is optimal when hairs are parallel and slow moving, as when two individuals are sleeping or napping. Except in very humid climates, head lice lay nits very close to the scalp (within 1 to 2 mm), and adult head lice can survive for about 24 hours off of the scalp.

Epidemiology

Head louse infestation affects about 6 to 12 million people per year in the United States alone, with highest prevalence among children between the ages of 3 and 12 years. Transmission occurs by means of direct contact or through fomites such as hats and scarves. Crab lice usually are spread sexually. Adolescents with pubic lice are roughly twice as likely as uninfested adolescents to have chlamydial or gonococcal infection. Among the homeless, body lice serve as vectors for *Bartonella quintana* endocarditis, epidemic typhus, louse-borne relapsing fever, and trench fever.

Clinical Manifestations and Diagnosis

Head louse infestation manifests with pruritus of the scalp and posterior cervical lymphadenopathy. Body louse infestation produces a widespread dermatitis that can mimic a viral exanthem. The finding of characteristic bluish hued to copper-colored skin discoloration, *maculae cerulea*) should prompt a search for body lice or nits in the seams of clothing. Crab louse infestation involves pubic hairs as well as hair on the chest, abdomen, and legs. Patients can present with generalized pruritus. Maculae cerulea (Fig. 257.1) identical to those seen in body louse infestation can be present in crab louse infestation, and underwear commonly is stained with bloody louse excrement.

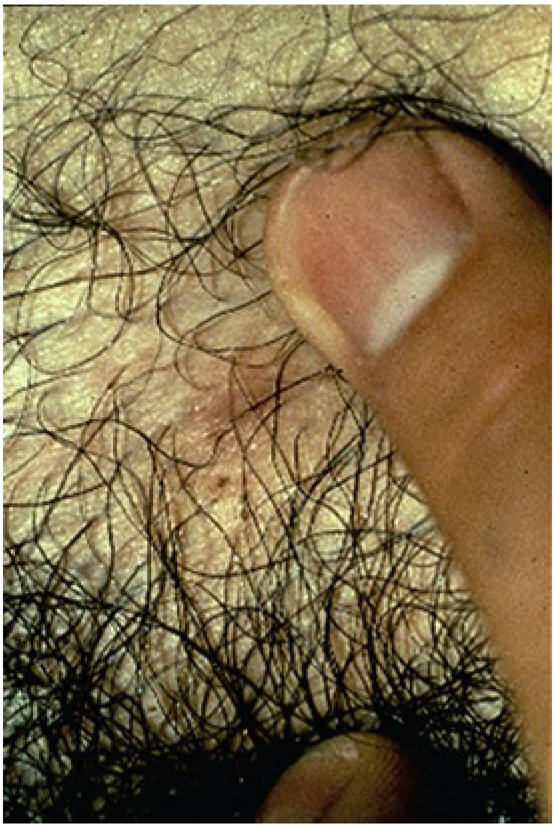

FIGURE 257.1 Maculae cerulae caused by bite of the body louse.

The diagnosis is made by finding lice or nits in the hair or seams of clothing (Figs. 257.2 to 257.5).

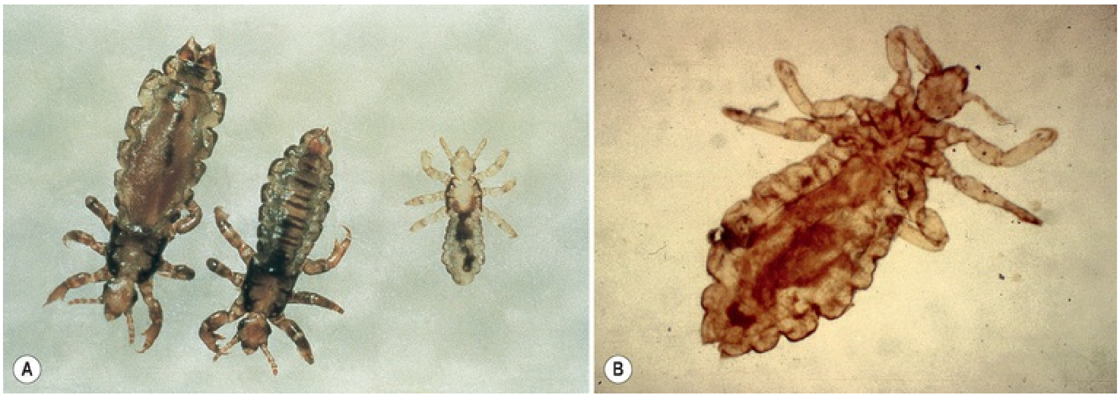

FIGURE 257.2 (A and B) *Pediculus humanus* (head and body louse).

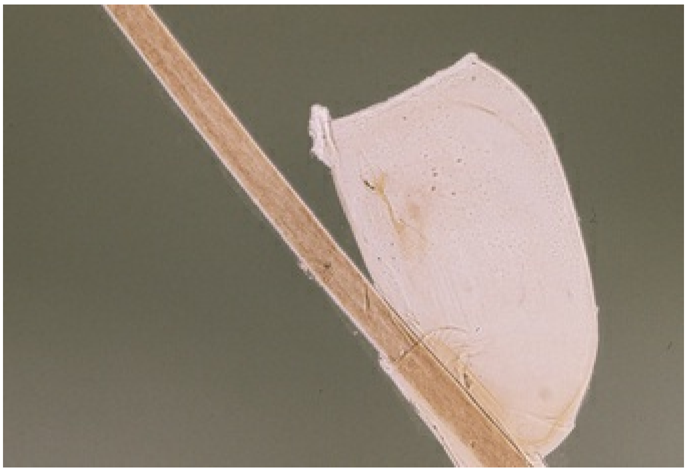

FIGURE 257.3 Empty egg case on shaft of hair.

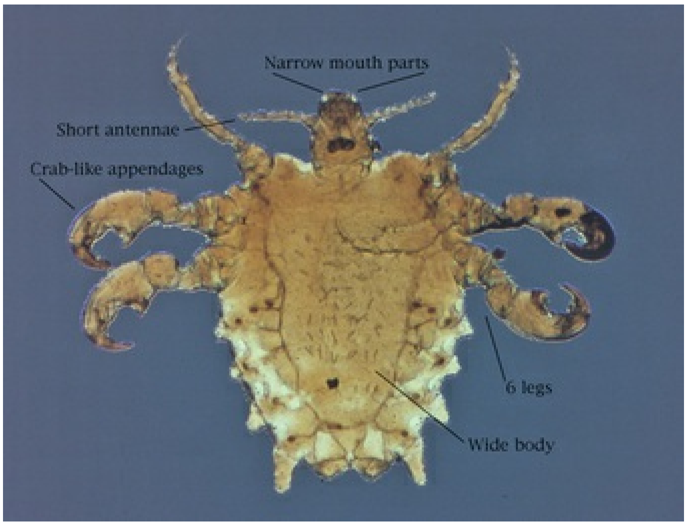

FIGURE 257.4 *Phthirus pubis* (crab louse).

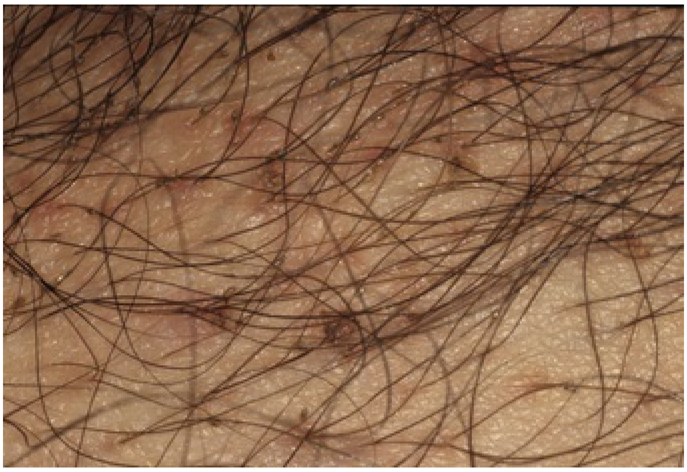

FIGURE 257.5 Crab lice in pubic hair.

Treatment

Shaving of all parasitized hair will eradicate head and pubic lice but is not cosmetically acceptable in most societies. Mechanical removal by wet-combing is labor intensive, and compliance is poor. Dilute solutions of vinegar or formic acid are not capable of dissolving nit cement but can facilitate combing by flattening the hair cuticle.

Topical products (Table 257.1) are recommended treatment for louse infestations. Considerations for choosing therapy include over-the-counter availability, toxicity, cost, and resistance patterns of lice.[1] Repeat application of topical agents at 7 days is generally recommended for all agents except lindane, but recent evidence suggests that ova can take as long as 13 days to hatch, suggesting that 3 applications a week apart may be optimal timing.[2] Lindane is no longer recommended for treatment of lice.

TABLE 257.1

Treatments for Pediculosis and Scabies

Name	Evidence[a]	Instructions for Use	Precautions
TOPICAL TREATMENTS LABELED FOR THE TREATMENT OF PEDICULOSIS[b]			
First Line			
Benzyl alcohol	IB	Apply topically to dry scalp for 10 minutes, then rinse off	Allergic/irritant dermatitis
Second Line			
Spinosad	IB	Apply topically to dry scalp for 10 minutes, then rinse off	Irritant dermatitis/eye irritation
Topical ivermectin	IB	Apply topically to dry scalp for 10 minutes, then rinse off	Irritant dermatitis/eye irritation
Permethrin 1%	IA	Apply topically to dry scalp for 10 minutes, then rinse off	Allergic/irritant dermatitis
Pyrethrins	IIB	Apply topically to body or dry scalp for 5–10 minutes, then rinse off	Allergic/irritant dermatitis
Malathion	IB	Application schedule varies by vehicle	Respiratory depression
TREATMENTS FOR SCABIES			
First Line			
Permethrin 5%	IA	Apply topically[c]	Risk for leukemia
Precipitated sulfur	IIB	Apply topically[c]	Offensive odor
Benzyl benzoate	IB	Apply topically[c]	Neurotoxicity
Ivermectin	IB	200 μg/kg orally	Neurotoxicity; safety has not been proved in children <15 kg (33 lb)

Second Line			
Crotamiton	IIA	Apply topically[c]	Marginal efficacy

[a] Levels of evidence: IA, meta-analysis of randomized controlled trials; IB, at least one randomized controlled trial; IIA, at least one controlled study without randomization; IIB, at least one other type of quasi-experimental study.

[b] Most labels suggest repeat application in 1 week, but an extra application at 2 weeks may be needed in many patients

[c] The cream should be applied to the entire body, including the head in infants. Care should be taken to apply a thick coat under the nails, in the umbilicus, axillae, web spaces, wrists, ankles, and genitalia. Close contacts should be treated concurrently.

Topical Agents

Benzyl Alcohol 5% (Ulesfia Lotion).

Benzyl alcohol lotion is approved by the US Food and Drug Administration (FDA) for children 6 months and older and may be the treatment of choice. The quantity applied must be sufficient to saturate the hair completely for 10 minutes. FDA phase 3 drug trials comparing the product to vehicle placebo for two 10-minute applications showed it to be safe and effective ($P < 0.001$).[3] Toxicity has been reported with intravenous exposure to benzyl alcohol in neonates and low birth weight infants. The “gasping syndrome” (characterized by central nervous system depression, metabolic acidosis, and gasping respirations) has been associated with benzyl alcohol dosages of >99 mg/kg/day. The product label indicates that benzyl alcohol was quantified in a single plasma sample in 4 out of 19 subjects (21%) after topical application, including 3 subjects in the 6 months to 3 years age group at 0.5 hour after treatment. The level ranged from 1.97 to 2.99 µg/mL—levels unlikely to produce toxicity. With topical use, benzyl alcohol can induce histamine release and produce scalp itching and eye irritation.

Permethrin 1% Lotion (Nix).

Permethrin is a synthetic pyrethroid neurotoxin available over the counter as a 1% cream rinse and is approved for use in children 2 months and older. Permethrin acts on sodium-gated channels resulting in paralysis (knockdown) and subsequent death of the louse. Knockdown resistance is now widespread and identified readily by gene mutation or lack of initial immobilization.

Resistance to permethrin commonly crosses over to pyrethrins as well as to the other pyrethroids.[4]

Pyrethrin/Piperonyl Butoxide (Rid, A200).

Pyrethrins are botanically derived, over-the-counter pediculicides that act as neurotoxins. Piperonyl butoxide typically is added to potentiate the insecticidal effect. Allergic contact dermatitis can occur in people who are sensitive to Compositae plants and ragweed. It should only be used in children older than 2 years.

Spinosad 0.9% Suspension (Natroba).

Spinosad topical suspension is a novel neurotoxin indicated for the treatment of head lice in children 6 months and older. It contains a mixture of spinosyn A and spinosyn D in a ratio of approximately 5 : 1. The active ingredient is derived from the fermentation of a soil actinomycete bacterium, *Saccharopolyspora spinosa.* The suspension is applied for 10 minutes. The suspension contains benzyl alcohol that may contribute to the product's efficacy.[5] The product label indicates that benzyl alcohol was quantifiable (>1 µg/mL) after application in 6 out of 26 subjects (25%), including 4 out of 12 subjects in the 6 months to <2 years age group. The highest observed concentration was 2.37 µg/mL, a range similar to that observed after topical Ulesfia application.

Ivermectin 0.5% Lotion (Sklice Lotion).

Topical ivermectin lotion is indicated for the topical treatment of lice in children 6 months and older, with a single 10-minute application, and compares favorably with oral ivermectin.[6] Adverse effects include skin and eye irritation. Ivermectin is derived from the fermentation of a soil-dwelling actinomycete, *Streptomyces avermitilis*. Absorption of ivermectin was evaluated in 20 lice-infested subjects (13 weighing 15 kg or less). The mean plasma maximal concentration (0.24 ± 0.23 ng/mL) is much lower than that observed after oral administration.

Malathion 0.5% (Ovide).

Malathion is a weak organophosphate cholinesterase inhibitor that acts as a neurotoxin. Currently, malathion resistance is rare in the

United States but is more common in the United Kingdom. Although malathion is labeled for use in children 6 years and older, recent studies showed no cholinesterase inhibition in children 2 to 6 years of age. Flammability of malathion preparations compounded in isopropyl alcohol has resulted in human injury about once in >1 million prescriptions filled. Efficacy for eradication of louse infestation in the US is 97% to 98%.[7]

Carbaryl.

Carbaryl is a carbamate insecticide once used commonly in the UK, where over-the-counter sales have been restricted because of concerns about carcinogenicity. Acetylcholinesterase-based resistance is emerging.

Alternative Agents

Oral Ivermectin.

Ivermectin may have some potential for neurotoxicity, and safety and efficacy in the setting of pediculosis remain to be established. Safety has not been proved in children <15 kg (33 lb). A study comparing oral ivermectin (at a dose of 400 μg/kg of body weight) with 0.5% malathion lotion, each given on days 1 and 8, found ivermectin to be more effective. It should be noted that the dose of ivermectin used was twice that typically prescribed for this indication.[8,9]

Others.

Dimeticones kill head lice by physical means and appear promising as an alternative to neurotoxins. Isopropyl myristate, 1,2-octanediol, and various plant-based products also demonstrate some efficacy. A combination product containing 50% isopropyl myristate and 50% cyclomethicone was approved in Canada in 2006 and marketed under the name Resultz. At least 3 botanical shampoos have shown greater efficacy compared with carbaryl—*Zanthoxylum limonella* Alston, *Acorus calamus* Linn., and *Phyllanthus emblica* Linn.—and several compare favorably with malathion.[10,11] Crotamiton (Eurax) is better known as a second-line antiscabetic agent but also has some activity as a pediculicide. Trimethoprim-sulfamethoxazole once was thought to act on lice by killing bacterial flora necessary for the synthesis of B vitamins in the louse's gut, but recent evidence suggests limited efficacy. Lice in clothing can be killed by ironing or machine laundering at 50°C and machine drying on a hot cycle.

Special Considerations

Variations in cerebral p-glycoprotein, cytochrome P450 monooxygenases, esterases, and alcohol and aldehyde dehydrogenases make some individuals more susceptible to toxic effects of pesticides.[12] Reports suggesting a possible association between pesticides and childhood leukemia have raised concern about the use of pediculicides in children, particularly pyrethroids.[13] Congenital leukemia with a *11q23/MLL* rearrangement has been reported in a child whose mother had heavily abused aerosolized permethrin during pregnancy, and laboratory evidence that incubation of a BV173 cell line with permethrin can induce MLL cleavage suggests a possible causal association.[14]

Prevention

“No-nit” policies have not been shown to reduce the incidence of louse infestation but exclude many children from school. A better approach is through community education and louse inspections during outbreaks. Piperonal is a pediculicide that also exhibits repellent effects.

Key Points

Diagnosis and Management of Louse Infestation

Microbiology

- Bloodsucking lice of the phylum Arthropoda, family Pediculidae or family Pthiridae.

Epidemiology

- Transmission occurs by direct contact or through fomites such as hats and scarves.

- Crab lice usually are spread sexually.

Treatment

- Benzyl alcohol lotion 5% (Ulesfia) is the first US Food and Drug Administration (FDA)-approved nonneurotoxic louse treatment available in the United States.

- Other topical treatments include a number of neurotoxic agents such as spinosad, topical ivermectin, pyrethrins with piperonyl butoxide, permethrin, malathion, and carbaryl.

- Alternative agents include oral ivermectin, dimeticones, botanicals, crotamiton, and isopropyl myristate/cyclomethicone.

Duration of Therapy

- Most topical products are labeled to be applied twice, but off-label treatment with 3 applications 7 days apart may target late-hatching ova more effectively.

Scabies

The Parasites, Virulence, and Pathogenesis

Human scabies usually is caused by the mite *Sarcoptes scabiei* var. *hominis,* an obligate human parasite and member of the class Arachnida, subclass Acari, order Astigmata, and family Sarcoptidae.[15] Animal mange mites occasionally can produce symptoms in humans.

Sarcoptes scabiei elicits a mixed type I/type IV hypersensitivity reaction. Cross-reactivity occurs between the scabies mite and the house dust mite. During infestation, there is marked increase in the secretion of interleukin-6 (IL-6) and vascular endothelial growth factor. IL-6 activates Th1 CD4$^+$ lymphocytes to secrete IL-2, promoting lymphocyte proliferation and differentiation.

Direct skin-to-skin contact for 15 to 20 minutes is required for transfer of mites. The average person harbors only 5 to 12 mites, but those with crusted scabies can shed mites by the thousands.

Epidemiology

Roughly 300 million cases of scabies occur in the world each year. Risk factors include overcrowding, immigration, poor hygiene, poor nutritional status, homelessness, dementia, and sexual contact. In developing countries, scabies infestation and associated impetigo appear to be important risk factors for chronic kidney disease.

Clinical Manifestations and Diagnosis

The diagnosis should be suspected in anyone with intense, intractable, generalized pruritus. Often, multiple family members are affected, and the itch typically is worse at night. The eruption has a predilection for anterior axillary folds, periumbilical skin, the nipple area in females, volar surface of the wrists, interdigital web spaces, the belt line, penis, scrotum, and ankles (Figs. 257.6 to 257.8). Mite burrows are serpiginous 1- to 4-mm keratotic lines, often punctuated by a small vesicle at one end, which houses the mite. In infants and young children, scalp, face, and neck can be heavily involved. Pustules on the palms and soles are typical in infantile scabies. After puberty, genital nodules are common. In endemic areas, widespread impetigo generally is presumed to indicate scabies infestation. Crusted scabies in children with Down syndrome appears with whitish flaky crusts with striking involvement of the hands and ears. In infants and young children, a dense Langerhans cell infiltrate can result in misdiagnosis as Langerhans cell histiocytosis.

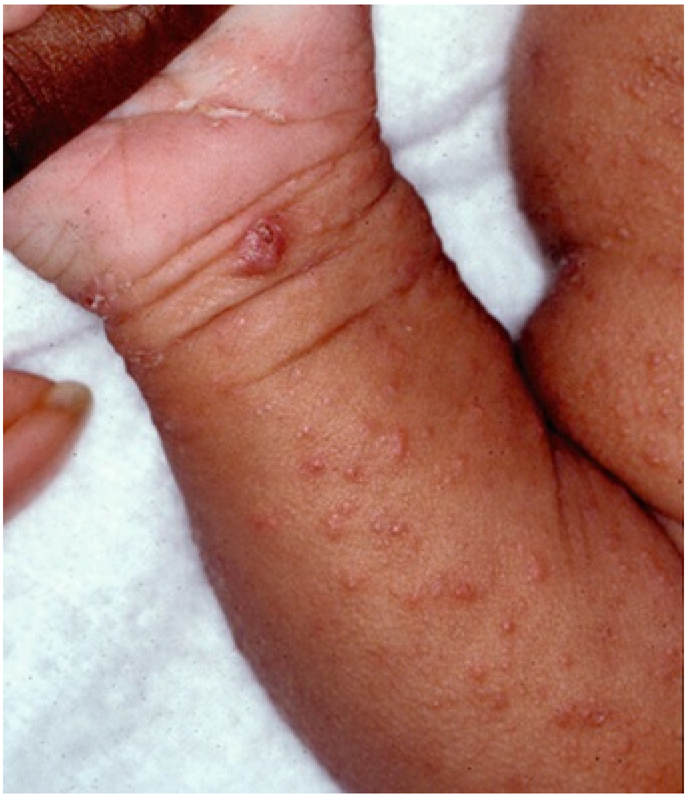

FIGURE 257.6 Scabies in an infant.

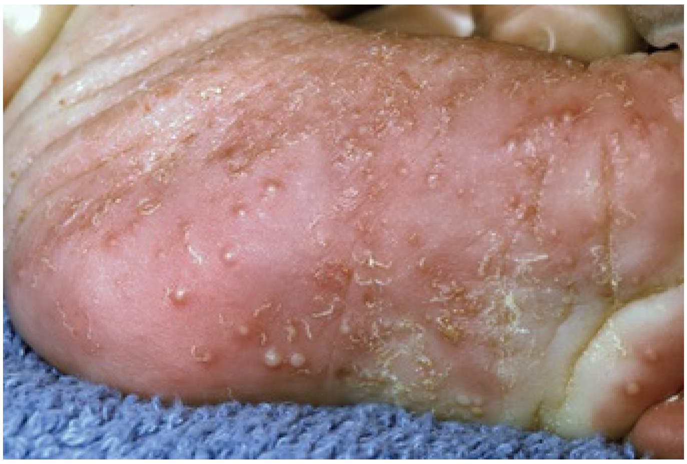

FIGURE 257.7 Acral pustules of scabies.

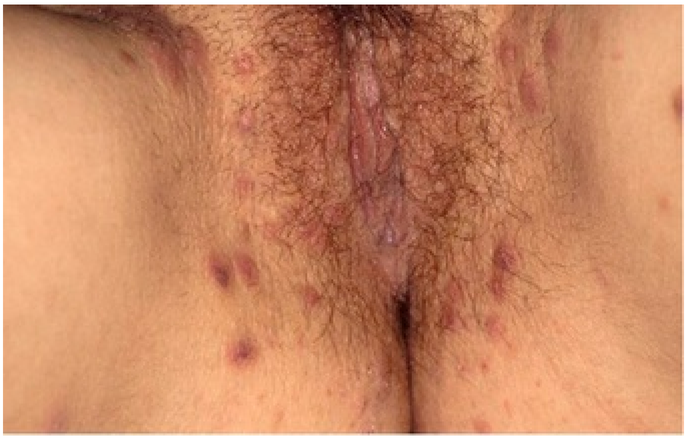

FIGURE 257.8 Scabies nodules.

The diagnosis is confirmed by identification of the mites, eggs, or fecal pellets in scrapings from burrows (Fig. 257.9). Fluorescent microscopy can be used to highlight fecal debris and fragments of ova. *S. scabiei* DNA polymerase chain reaction assays exist but are rarely used in clinical practice.

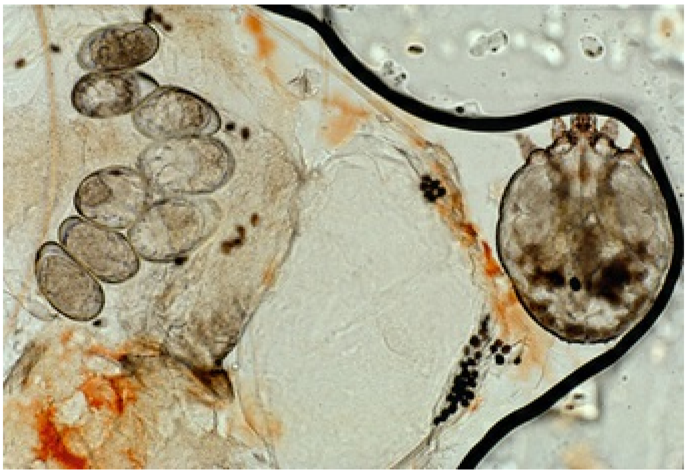

FIGURE 257.9 Microscopic appearance of mites, ova, and feces of scabies.

Treatment (Table 257.1)

First-Line Treatments

Permethrin 5%.

Permethrin cream 5% should be applied to the entire body, including the head in infants, left on for at least 8 hours and repeated in 7 to 10 days. A Cochrane group review of interventions for scabies concluded the following: topical permethrin remains the most effective treatment for scabies, ivermectin appears to be an effective oral alternative; more research is needed on the effectiveness of malathion.

Precipitated Sulfur 6% to 10% in Petrolatum.

Sulfur is the oldest recorded treatment modality for scabies and remains in common use worldwide. Despite a lack of controlled clinical trials, sulfur generally is acknowledged to have a high degree of efficacy, even in the setting of crusted scabies.

Benzyl Benzoate 10% to 25%.

Benzyl benzoate remains one of the most commonly prescribed agents for scabies in many parts of the world and compares favorably with other topical agents and oral ivermectin. Benzyl benzoate is not available in the US or Canada. The 25% emulsion is applied below the neck, with 3 applications during a 24-hour period. In young adults or children, the concentration can be reduced to 12.5%. Use can be complicated by allergic contact dermatitis, and benzyl benzoate should not be used during pregnancy, in lactating women, in infants, or in children younger than 2 years because of the risk for neurotoxicity.

Oral Ivermectin.

For the off-label treatment of scabies, ivermectin is given orally as a single dose of 200 μg/kg repeated in 7 to 10 days. High doses can cause embryotoxicity in animals, and some have suggested it should not be used during pregnancy, although ivermectin often has been used in this setting in the treatment of onchocerciasis. Safety has not been proved in children <15 kg (33 lb). Comparisons with permethrin, benzyl benzoate, and lindane have shown mixed results. In scabies-endemic areas, ivermectin has been shown to reduce the incidence of streptococcal disease and renal damage in children.[16,17]

Second-Line Treatments

Crotamiton 10%.

Crotamiton 10% is applied twice daily for 2 to 5 consecutive days. Although efficacy is low, crotamiton sometimes is used as an adjunctive agent because of its inherent antipruritic effect.

Special Considerations

Treatment of close contacts is strongly recommended; unfortunately, randomized controlled trials of treatment for contacts are lacking.[18] Crusted scabies may require treatment with both oral ivermectin and a topical agent. The author has found 10% precipitated sulfur to be most effective. Keratolytics should be used to improve penetration of treatment agents. The nails should be trimmed and brushed with a scabicidal agent. Patients with crusted scabies are highly infectious and require isolation.

Prevention

In some countries, soaps containing monosulfiram have been used for prophylaxis in communities with high rates of infestation.

Key Points

Diagnosis and Management of Scabies Infestation

Microbiology

- *Sarcoptes scabiei* var. *hominis* is an obligate human parasite and the usual agent of scabies.

Epidemiology

- Transmission occurs through close physical contact.
- Fomites such as bed sheets are an important means of spread in the setting of crusted scabies.

Treatment

- First-line treatments include permethrin, precipitated sulfur, benzyl benzoate, and oral ivermectin.
- Second-line treatments include crotamiton.

Duration of Therapy

- Most topical products should be applied twice, with a 7- to 10-day interval between treatments.

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Protozoa

OUTLINE

258 Babesia Species (Babesiosis)
259 Balantioides coli (Formerly Balantidium coli)
260 Blastocystis
261 Cryptosporidium Species
262 Endolimax nana
263 Entamoeba histolytica (Amebiasis)
264 Other Entamoeba, Amebas, and Intestinal Flagellates
265 Giardia intestinalis (Giardiasis)
266 Cystoisospora (Isospora) and Cyclospora Species
267 Leishmania Species (Leishmaniasis)
268 Microsporidia
269 Naegleria fowleri
270 Acanthamoeba Species
271 Plasmodium Species (Malaria)
272 Sarcocystis Species
273 Toxoplasma gondii (Toxoplasmosis)
274 Trichomonas vaginalis
275 Trypanosoma Species (Trypanosomiasis)

258

Babesia Species (Babesiosis)

Kristina N. Feja

Babesiosis is an emerging tickborne zoonotic disease, clinically similar to malaria, that is caused by intraerythrocytic protozoa in the genus *Babesia*.[1–10] Symptomatic infection is more frequently diagnosed and reported in asplenic adults,[11] those older than 50 years,[8] and immunocompromised hosts,[3,8] but neonates[12] and infants[13,14] also are infected in endemic areas after a tick bite, blood product transfusion,[14] and vertical transmission.[12,13] Although as many as 7 species of *Babesia* have been implicated in human babesiosis,[3] *B. microti* is most common in the northeastern and upper midwestern United States,[1] *B. duncani* in the western US,[15] and *B. divergens* in Europe.[2] Fever, malaise, and hemolytic anemia typify clinical disease,[16] which tends to be milder in *B. microti* infection[5] and more severe in *B. divergens* infection.[7] Clinical diagnosis is confirmed by identification of the parasite in a blood smear or detection of *Babesia* DNA in serum by polymerase chain reaction (PCR).[17] Atovaquone and azithromycin are considered the treatment of choice for mild to moderate disease.[18] Avoidance of exposure to the tick vector is the best measure to prevent babesiosis.[1]

Description of the Pathogen

Babesia spp. belong to the phylum Apicomplexa along with *Cryptosporidium, Plasmodium,* and *Toxoplasma*.[5] *Babesia* organisms require both a tick vector and a vertebrate host to complete their complex life cycle.[19] The parasites directly infect erythrocytes (without the pre-erythrocytic–hepatic stage that some plasmodia exhibit), where trophozoites divide by sporogony (budding) into two or four merozoites, depending on the species.[3,19,20] Egress of the merozoites occurs with lysis of the erythrocytes, leading to invasion of further red blood cells and clinical symptoms.[19,20] A more detailed description of the life cycle is presented at http://www.cdc.gov/parasites/babesiosis/biology.html.

Recent analyses of 18S ribosomal RNA sequence data[21] support division of human *Babesia* spp. into four clinically relevant clades.[3,6,20,21] Clade 1 contains *B. microti* and *B. microti*−like parasites; clade 2 includes *B. duncani*[15] (initially named WA1, WA2, CA5, and CA6) and *B. duncani*−like (CA1, CA3, CA4) organisms. Clade 3 comprises *B. divergens, B. venatorum* (previously designated EU1),[2,22,23] and *B. divergens*−like[4] cases. Clade 4 organisms are rarely transmitted to humans but include the human isolate from Korea (KO1).[24] Each *Babesia* sp. is transmitted by a certain *Ixodes* tick and has a primary vertebrate reservoir, whereas humans are accidental hosts. Nymphal ticks are the primary vector because of their small size and summer feeding activity,[5,25] but transmission of *B. microti* requires 36 to 72 hours of tick attachment.[26] Because these ticks also transmit *Borrelia burgdorferi* and *Anaplasma phagocytophilum,* coinfections occur.[27,28] The tick vector for *B. microti* in the eastern US is *Ixodes scapularis,* and the primary reservoir is the white-footed mouse.[3,5,20] Adult ticks feed on white-tailed deer, ensuring their survival, but the deer are not a reservoir for *B. microti*.[25] *B. divergens* and *B. venatorium* are both transmitted in Europe by *Ixodes ricinus*, and the primary reservoirs are cattle and roe deer, respectively.[3,5,20] The exact tick vectors for *B. duncani*, *B. duncani*−like, and *B. divergens*−like species are not established.[3] Transmission also occurs without the tick vector in congenital and perinatal[12,13,29–31] cases and during transfusion of blood from parasitemic donors.[14,32–34]

Epidemiology

Initially described as the cause of febrile hemoglobinuria in cattle in

1888,[35] *Babesia* are responsible for significant disease burden in livestock and animals.[3,19] The first human case was reported in a splenectomized male in 1957 in Europe,[36] and the first case in a healthy individual was reported in 1970 from Nantucket Island, Massachusetts (called *Nantucket fever*).[37] In the 1970s and 1980s, *B. microti* was found to be endemic in Massachusetts (Nantucket Island, Martha's Vineyard, Elizabeth Islands, and Cape Cod), Rhode Island (Block Island), southeastern Connecticut, and New York (Shelter Island, Fire Island, and eastern Long Island).[38] During the same period *B. divergens* caused sporadic but more severe disease in splenectomized adults in Europe.[7,39] During the past five decades the incidence of babesiosis in the US has increased substantially,[3,20,40–42] and with the recent use of molecular studies,[21] newly recognized species continue to emerge in ever-expanding geographic areas.[3,6,15,43]

National surveillance for human babesiosis in the US started in 2011, with required reporting in 18 states and New York City, and expanded to 27 states reporting in 2013.[44,45] A total of 1124 confirmed and probable cases of babesiosis were reported in 2011, 911 in 2012, and 1762 cases in 2013.[44–46] There appears to be underreporting in areas of emerging babesiosis, likely owing to lack of specific clinical signs (such as erythema migrans rash in Lyme disease) and low index of suspicion among medical providers.[47] In a study in New York state, 29% of patients serologically confirmed to have Lyme disease also were seropositive for *B. microti* compared with 7% without Lyme seropositivity, suggesting common co-infections.[48] Babesiosis is mostly seasonal, with about 85% of cases having symptom onset between June and August, when nymphal ticks are most actively feeding.[3,25] However, only 45% of patients recall a tick bite in the 8 weeks before symptom onset.[45] The mean age of reported US cases is consistently 62 years, and >60% are males.[44–46]

Currently, *B. microti* infection is endemic in the northeastern[38,40,49–53] and upper midwestern (Wisconsin[54] and Minnesota[55]) US, with >95% of cases consistently reported from 7 states (Connecticut, Massachusetts, Minnesota, New Jersey, New York, Rhode Island, and Wisconsin).[44–46] Community-based serosurveys in endemic areas of northeastern US performed in late 1970s to 1990s reveal antibodies to *B. microti* in 2% to 10% of residents,[41,42,56,57] whereas testing of blood-donor specimens from 2000 to 2012 in these same areas found antibodies in 1% to 1.4% of samples.[58,59] The incidence of babesiosis was 1620/100,000 on Block Island between 1991 and 2000 and 1250/100,000 on Nantucket Island in 2010.[41,47] The seroprevalence incidence in children (aged 0–19 years) on Block Island was 1632/100,000, slightly higher than the incidence among adults aged 20 to 89 years (1618/100,000).[41] In recent years, the spread of *B. microti* continues, with increased number of cases within endemic areas[41,50,60,61] and appearance of cases in contiguous areas such as Pennsylvania[62] and Canada[63,64] (Fig. 258.1) Although *B. microti* is the most common species in the US, rarely, *B. duncani* and *B. duncani*–type infections have been reported in Washington and California.[15,43,65] *B. divergens*–like infections have occurred in Missouri,[66] Kentucky,[67] and Washington State.[4,68]

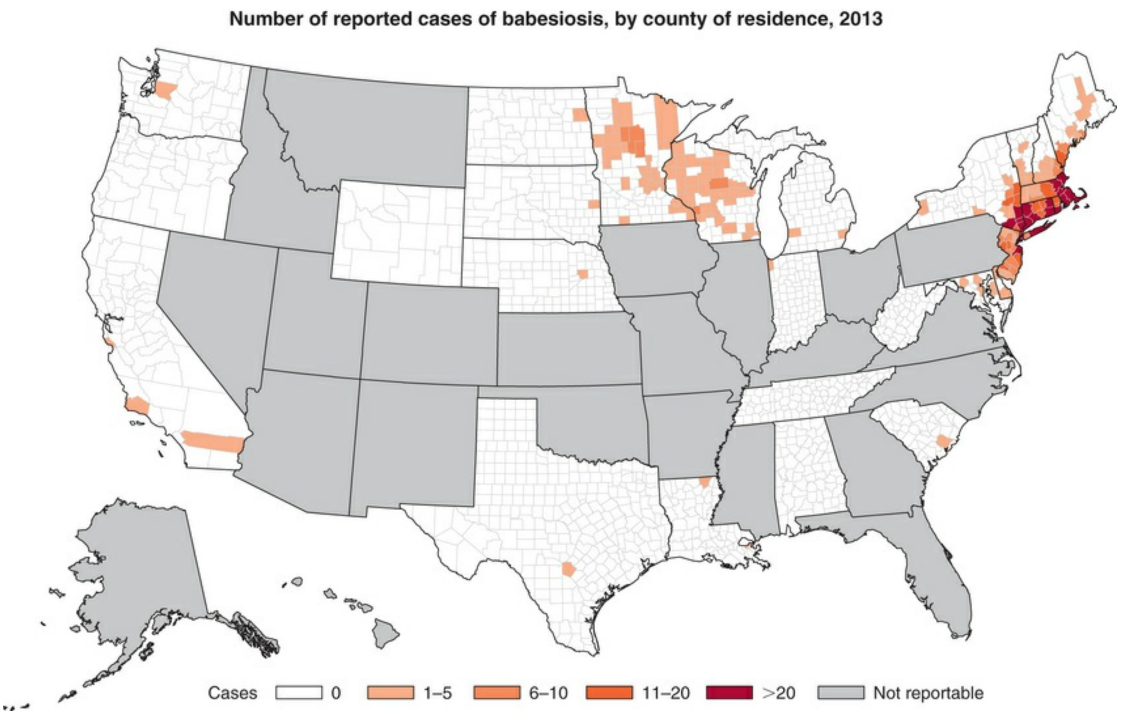
Number of reported cases of babesiosis, by county of residence, 2013
Cases
0
1–5
6–10
11–20
>20
Not reportable

FIGURE 258.1 Number of reported cases of babesiosis by county of residence in 2013 from 27 states that required reporting. (Source: Centers for Disease Control and Prevention.)

In Europe, human babesiosis is much less common than in the US, with reported cases totaling <100.[2] Most cases result from *B. divergens* infection in asplenic individuals,[2,7,39,69] although cases in healthy persons have been reported.[70] Babesiosis has been reported in Croatia,[36] other eastern European countries, and western Europe,[71–75] including the United Kingdom, Ireland, and Scandinavia.[22,76–78] Few cases of disease due to *B. venatorum* (EU1) have been described.[23,73] Indigenous *B. microti* was first reported in Switzerland[22] and Germany,[79] but the disease likely is underrecognized and underreported owing to its less fulminant course and lack of cross-reactivity with serologic tests for *B. divergens*.[22] In Asia, cases of *B. microti*,[80,81] *B. venatorum*,[82] and a new strain (KO1) have been reported.[24] Human babesiosis also has been reported in Africa, Australia, and South America.[10,20,39,83,84] Further increase in the number of cases is expected with growing number of immunocompromised patients[3] and with the increase in tick vector populations linked to expanding deer populations[25,41,85,86] and climate change.[87]

Clinical Manifestations

Clinical manifestations of babesiosis vary from asymptomatic infection, to mild to moderate disease, to severe disease that can be fatal.[4] The incubation period following a tick bite is 1 to 4 weeks,[3] and 1 to 9 weeks (as long as 6 months) following transfusion.[25,88] Between 32% and 62% of infections are asymptomatic.[41,56,57,89] Infections can become symptomatic after many months of asymptomatic parasitemia.[89]

Clinical infection most often is a nonspecific, influenza-like illness, and the diagnosis is rarely made.[1,41] A gradual onset of malaise and fatigue is followed by fever as high as 40.5°C (105°F).[20] The most common symptoms of *B. microti* infection are summarized in Table 258.1. Additional symptoms reported in two series totaling 84 patients included emotional lability in 50%, neck stiffness in 48%, sore throat in 31%, vomiting in 20%, joint swelling in 11%, and conjunctivitis in 11%.[90,91] Individuals noted an average of 9 separate symptoms lasting 10 weeks.[90] Persistent parasitemia, as detected by PCR, can last for several months to >1 year, even with treatment.[89]

TABLE 258.1

Common Symptoms of *Babesia microti* Infection

Symptom	Percentage of All Patients ($N = 299$)
Fever	87
Fatigue	82
Chills	68
Sweats	57
Headache	50
Myalgia	46
Anorexia	38
Cough	29
Arthralgia	26
Nausea	24

Modified from Vannier E, Krause PJ. Update on babesiosis. Interdiscip Perspect Infect Dis 2009;2009:984568; Krause PJ, McKay K, Thompson CA, et al. Disease-specific diagnosis of coinfecting tickborne zoonoses: babesiosis, human granulocytic ehrlichiosis, and Lyme disease. Clin Infect Dis 2002;34:1184–1191; and Krause PJ, Lepore T, Sikand VK, et al. Atovaquone and azithromycin for the treatment of babesiosis. N Engl J Med 2000;343:1454–1458.

Physical findings often are limited to fever in mild cases, although jaundice, pallor, mild hepatosplenomegaly, dark urine, and occasionally pharyngeal erythema can be present.[1,16,20] Noncardiac pulmonary edema[91] and ocular manifestations, such as retinal splinter hemorrhages, have been described.[92]

Typically, *B. divergens* and *B. divergens*–like infection is more fulminant,[7,20,39] resulting in a case-fatality rate of 42%.[3] However, *B. microti* also can cause severe disease, especially in those with risk factors, but mortality is <1%.[44] Risk factors for severe babesiosis, in addition to infection with *B. divergens,* include: age >50 years; male sex; asplenia[11]; and immune-compromising conditions,[93] including AIDS,[94] and malignancy.[1] Coinfection with *Borrelia* or *Anaplasma* spp., or both, appears to cause more severe disease[27,28,90,95]; therefore, any patient with prolonged or severe symptoms also should be tested for these pathogens.[1] About 45% of US patients with babesiosis require hospitalization for a median of 4 to 5 days.[44-46] Most hospitalized *B. microti*–infected patients have comorbidity, such as asplenia, heart disease, hypertension, chronic obstruction pulmonary disease, alcoholism, and diabetes.[16] Children aged 0 to 19 years have significantly fewer symptoms (40% are symptom free), have significantly shorter duration of illness, and are hospitalized infrequently, particularly compared with people older than 50 years.[41] Patients with anemia (hemoglobin concentration <10 g/dL) or parasitemia (>10%) are more likely to have complications,[16] such as acute respiratory distress syndrome, disseminated intravascular coagulopathy, congestive heart failure, acute renal failure, myocardial infarction,[16] splenic infarction,[96] splenic rupture,[97] septic shock,[98] and death.[75,77]

Laboratory Findings and Diagnosis

Laboratory findings can be normal or nonspecifically abnormal in asymptomatic or mild cases. Thrombocytopenia (mean around 90,000 cells/dL) and anemia (mean 10 g/dL) occur in >60% of patients.[16,45] Evidence of hemolysis (such as low hemoglobin and haptoglobin, elevated lactate dehydrogenase, and reticulocyte count), elevated serum hepatic transaminases (mean, 100−120 U/L), elevated blood urea level and creatinine, and variable leukocyte count can be present.[16,20,25]

Laboratory diagnosis of human babesiosis primarily employs Giemsa- or Wright-stained thin blood smear, PCR,[99] and species-specific serology.[17,100,101] Characteristic findings on blood smear are shown in Fig. 258.2. The tetrad of merozoites ("Maltese cross") is pathognomonic for *B. microti* and *B. duncani*, but is not seen commonly.[5,15] Blood smear findings for *Babesia* and *Plasmodium* are contrasted in Table 258.2. At least 300 microscopic fields should be reviewed because parasitemia levels can be <1% early in disease.[20] PCR testing is available in commercial laboratories, is more sensitive than blood smears, and is needed for accurate speciation.[1] Serologic testing most commonly is species-specific indirect immunofluorescence antibody assay and often is positive at the time parasitemia becomes detectable.[100] An enzyme immunoassay[58,102] and immunoblot testing[103] also are described. A fourfold increase of immunoglobulin G titers in acute and convalescent sera confirms recent infection.[25] A single positive titer supports the diagnosis, but is not confirmatory.[100] Diagnostic techniques are compared in Table 258.3.[104]

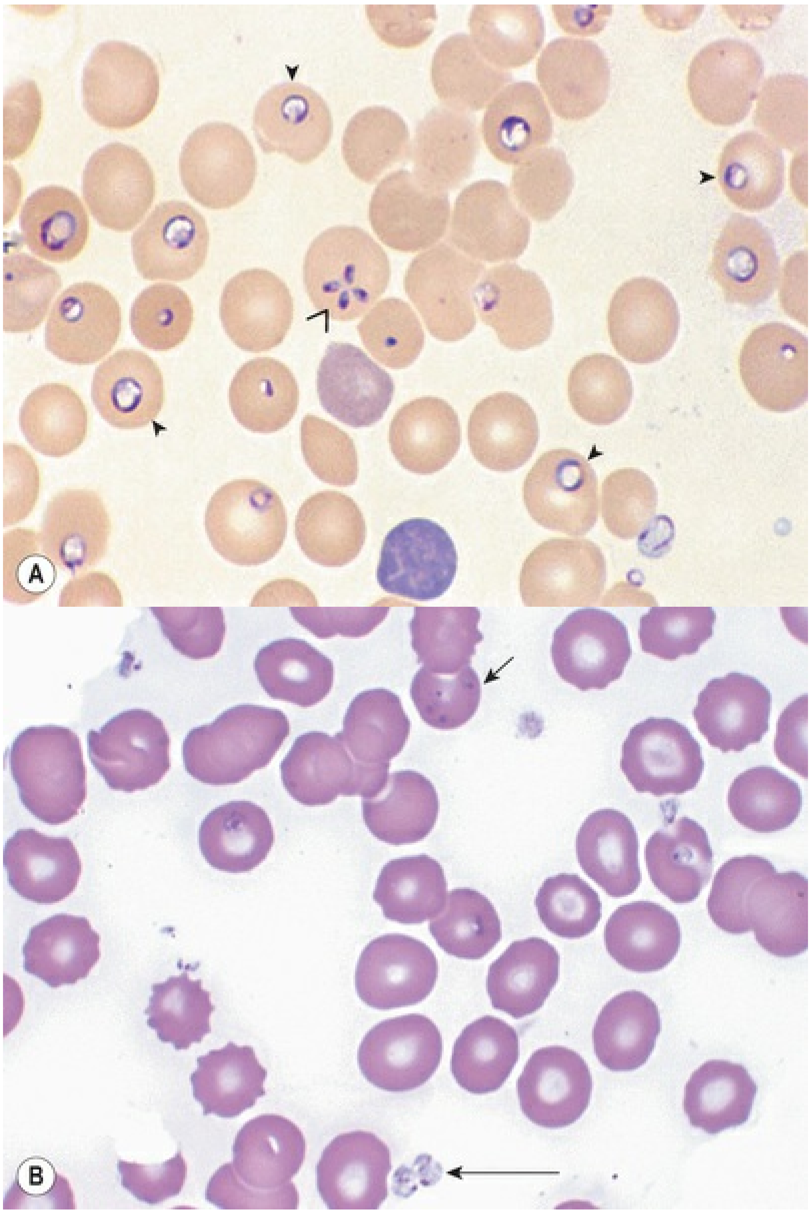

FIGURE 258.2 Wright- (A) and Giemsa-stained (B) peripheral blood smear from a 26-day-old infant with transplacentally acquired babesiosis and ~15% parasitemia.[12] The smear demonstrates typical features, including thrombocytopenia, parasites of variable size and morphology, and absence of hemozoin pigment. A pathognomonic tetrad *(open arrowhead)* and typical basket cells (*arrowheads* and throughout) are seen in image A, whereas image B demonstrates an extracellular syncytium *(long arrow)* and multiple parasites per erythrocyte *(short arrow)*. Original magnification, ×1000. (Courtesy of Robert W. Tolan.)

TABLE 258.2

Comparison of Findings on Thin Blood Smear Between *Babesia* and Plasmodium Infections

Finding	*Babesia* Species	*Plasmodium* Species
Ring appearance	Pleomorphic more common[a]	Monomorphic more common
Morphology present	Only ring forms[a]	Ring forms and/or schizonts and gametocytes
Intracellular parasites	Polyparasitism common (may have ≥4)[b]	Rarely >4 intracellular parasites per erythrocyte
Food vacuole	Refractory white vacuole often present[a]	Rare (in early trophozoite stages)
Chromatin dots	1–3 present[a]	1–2 present in ring forms
Tetrads (Maltese cross)	Present (*B. microti*)[a]	Absent
Red blood cell morphology	Normal[c]	Can be normal, unchanged, small, enlarged, or fimbriated
Erythrocyte stippling	Absent[c]	Maurer,[e] Schüffner,[f] or Ziemann[g] stippling
Hemozoin (partially digested hemoglobin)	Absent[c]	Present
Extracellular parasites	Common[d]	Uncommon

[a] Demonstrated in Fig. 258.2A.

[b] Demonstrated in Fig. 258.2B, *short arrow.*

[c] Demonstrated in Fig. 258.2A and B.

[d] Demonstrated in Fig. 258.2B, long arrow.

[e] Irregular mauve/red dots in *Plasmodium falciparum*−infected erythrocytes.

[f] Pink- or red-staining dots in *Plasmodium ovale*− or *Plasmodium vivax*−infected erythrocytes.

[g] Eosinophilic dots in *Plasmodium malariae*−infected erythrocytes.

Modified from Pantanowitz L, Ballesteros E, De Girolami P. Laboratory diagnosis of babesiosis. Lab Med 2001;32:184–187.

TABLE 258.3

Overview of Diagnostic Approaches for Human Babesiosis

Diagnostic Method	Advantages	Disadvantages
Blood smear	Inexpensive, rapid; reliable with high parasitemia	Can be confused with malaria, especially by inexperienced reader; can be negative with low-level parasitemia
Immunofluorescent antibody assay (serology)	The only commercially available serology	Expensive; requires reference laboratory confirmation; cross-reactivity; species specific
Enzyme immunoassay (serology)	Less cross-reactivity	Not commercially available (investigational)
Hamster inoculation	Effective for low-parasitemia disease	Slow, labor intensive; can be negative with fastidious organisms
Microaerophilous	Effective for low-	Impractical for human disease diagnosis

stationary phase in vitro culture	parasitemia disease	
Polymerase chain reaction assay	Reliable; accurate if assay is standardized and performed well	Expensive

Modified from Schuster FL. Cultivation of *Babesia* and *Babesia*-like blood parasites: agents of an emerging zoonotic disease. Clin Microbiol Rev 2002;15:365–373.

Treatment

Asymptomatic patients with parasitemia (on blood smear or by PCR testing) do not need treatment unless they are parasitemic for >3 months.[1] Patients with mild to moderate disease should be treated with a 7- to 10-day course of atovaquone and azithromycin.[1,25,100] A randomized trial of quinine *plus* clindamycin therapy compared with atovaquone *plus* azithromycin therapy demonstrated equivalent cure rates, with significantly fewer toxicities in the latter group (15% vs. 72%).[105] Symptoms should improve after 48 hours of treatment.[1] Atovaquone and azithromycin therapy generally is well tolerated and successful in the treatment of infants,[12,106] but there are reports of drug resistance in immunocompromised persons (Table 258.4).[107]

TABLE 258.4

Treatment Regimens for Human Babesiosis

Drug	Adult Dose	Pediatric Dose[a]
ATOVAQUONE *PLUS* AZITHROMYCIN		
Atovaquone (oral)	750 mg every 12 hr	20 mg/kg/dose every 12 hr
Azithromycin (oral)[b]	500–1000 mg once on day 1, then 250 mg daily	10 mg/kg/dose once on day 1, then 5 mg/kg/dose once daily
CLINDAMYCIN *PLUS* QUININE		
Clindamycin (intravenous)	300–600 mg every 6 hr	7–10 mg/kg/dose every 6–8 hr
Clindamycin (oral)	600 mg every 8 hr	7–10 mg/kg/dose every 6–8 hr
Quinine (oral)[c]	650 mg every 6–8 hr	8 mg/kg/dose every 8 hr

[a] Maximal pediatric doses should not exceed adult doses

[b] In immunocompromised patients higher doses of 600−1000 mg/day may be used.[1]

[c] Intravenous quinidine can be used in place of oral quinine if patient is monitored in hospital for possible QT prolongation.[25]

Severe illness should be treated with 7 to 10 days of quinine *plus* clindamycin intravenously.[1] In addition to supportive care, exchange transfusion (which greatly reduces the level of parasitemia) is indicated in severe cases with high-grade parasitemia (≥10%), significant hemolysis, or renal, hepatic, or pulmonary compromise.[1] Although routine screening of healthy individuals for posttreatment relapse is not recommended, those found to have positive thin blood smears or PCR positivity for >3 months after completing therapy should be retreated, irrespective of symptoms.[1] Immunocompromised patients can develop persistent or relapsing disease; therefore these patients should be monitored for recurrence of symptoms and have thin blood smears or PCR checked only if symptoms arise.[93] Other agents used in this population, often in combination, for multiple and prolonged courses, include atovaquone, azithromycin, clindamycin (intravenous route is preferred[1]), doxycycline, proguanil, pentamidine, quinine, and trimethoprim-sulfamethoxazole.[93] Continuation of treatment for at least 6 weeks total and for at least 2 weeks beyond clearance of parasitemia by thin blood smear is associated with more frequent cure.[93,108] No adjunctive immunomodulating therapies have been identified.

Special Considerations

Immunocompromised hosts, such as asplenic individuals, are at particular risk for severe *Babesia* infection, mostly due to *B. divergens*, but also to *B. microti,* although the disease usually is less severe than with *B. divergens*.[3,7,11,93] In those with AIDS, babesiosis can manifest as fever of unknown origin as well as persistent or relapsing disease.[94] An underlying immunodeficiency should be considered in any patient with severe or prolonged babesiosis.[1] Transfusion-associated babesiosis is an emerging problem[32–34] and currently is the most frequent transfusion-transmitted infection, with >170 cases reported since 1980.[25,109] Transplant recipients[95] and neonates[14,32,110–112] are frequently affected. There is no US Food and Drug Administration–approved method for laboratory screening of the blood supply. Instead, potential donors with a history of babesiosis are permanently denied from (and should decline) donating. Preliminary data from the first laboratory-based blood donor screening program using immunofluorescence antibody and

PCR eliminated transmission to neonates and pediatric hemoglobinopathy patients.[113] Enzyme immunoassay appears best suited for efficient high-throughput blood donor screening.[58] Although two cases of tick-transmitted babesiosis in neonates were reported from Long Island,[114] most cases in neonates are transfusion associated.[14] To date, 5 cases of congenital or perinatal babesiosis have been reported.[12,13,29–31]

Prevention

The best way to prevent babesiosis is to avoid exposure to ixodid ticks.[1] If exposure to the vector is unavoidable, wearing protective clothing (long pants, tucked into socks or boots, and long sleeves), use of tick repellants, daily careful examination of the entire body for ticks, and prompt removal of ticks can decrease the likelihood of being bitten or having infection transmitted during a bite.[1] Careful observation for development of symptoms for a month or so after tick removal is prudent, but there is no role for antibiotic prophylaxis, examination of removed ticks for parasites, or laboratory testing of asymptomatic individuals after tick removal.[1] Screening the blood supply and decreasing infections during pregnancy also can prevent babesiosis.[17] Although animal vaccines exist, there is no role for passive or active immunoprophylaxis in humans. Aside from transfusion-associated (and, potentially, organ-associated)[95] transmission, no human-to-human transmission has been documented, and no particular infection prevention measures are necessary.

Acknowledgment

The author acknowledges the substantial use of Robert W. Tolan's work from the previous edition and expresses sadness of the infectious diseases community over his untimely loss.

Key Points

Diagnosis and Management of *Babesia* species (Babesiosis) Infection

Microbiology

- Apicomplexan intraerythrocytic parasite transmitted to humans by ixodid tick bites
- The same vector transmits *Borrelia burgdorferi* and *Anaplasma phagocytophilum*.
- *Babesia microti* most common in United States; *Babesia divergens* in Europe; other species much less common

Epidemiology

- Most case of *B. microti* in the US occur in CT, MA, MN, NJ, NY, RI, WI.
- Sporadic cases in CA, IN, KY, MD, MO, VT, WA in the US as well as in Europe and worldwide
- Range of endemicity is expanding rapidly.
- Chief risk factors are age >50 years, asplenia, male sex, and immunocompromising conditions.
- Transfusion-transmitted infection is recognized increasingly.
- Congenital/perinatal transmission is rare but is well documented.

Diagnosis

- Thin blood smear microscopy is rapid, inexpensive, and diagnostic with appropriate expertise.
- Speciation requires polymerase chain reaction (PCR) testing.
- Serology can support clinical suspicion but is suboptimal for management decisions.

Treatment

- Asymptomatic infection requires no treatment unless parasitemia lasts >3 months.

- Atovaquone *plus* azithromycin combination is preferred treatment for most cases.

- Quinine *plus* intravenous clindamycin along with exchange transfusion is preferred treatment for severe cases

Duration of Therapy

- Prolonged parasitemia (>7 days) can occur despite clinical improvement.

- Duration of therapy typically is 7 to 10 days for the immunocompetent host.

- In the compromised host, therapy should continue for 2 weeks after negative thin blood smears and negative PCR, or for 6 weeks (whichever is longer).

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259

Balantioides coli (Formerly *Balantidium coli*)

Kateřina Jirků-Pomajbíková, Christen R. Stensvold

Balantioides coli originally was called *Balantidium coli*, syn. *Neobalantidium coli*, but recently has been renamed based on new phylogenetic observations.[1,2] This cosmopolitan ciliate inhabits the intestine of several mammalian species, and it is the only ciliate known to infect humans.[3] Balantiosis is considered a neglected zoonotic disease, and human clinical cases are typically associated with close contact with domestic pigs.[3] Infected people can be symptom free or may develop symptoms, ranging from mild diarrhea to fulminating dysentery.[4]

Life Cycle and Description

The life cycle of *B. coli* comprises two stages: the motile trophozoite that inhabits the host's hindgut and causes disease, and the cyst that is environmentally resistant and is responsible for transmission (Fig. 259.1).[3] Trophozoites are large and ovoid, measuring 50 to 150 µm. The cytostome is visible at the anterior end of the body, and a kidney-shaped macronucleus and longitudinal cilia rows on the surface are often visible.[3–5] The cytoplasm may contain ingested particles in contractile vacuoles (Fig. 259.2).[5] The cyst is spherical and thick-walled, with a size ranging between 40 and 60 μm and with a visible trophozoite inside.[3–5] The cyst stage is commonly detected in pig feces, but rarely in human or nonhuman primate feces (Fig. 259.3).[3,6,7]

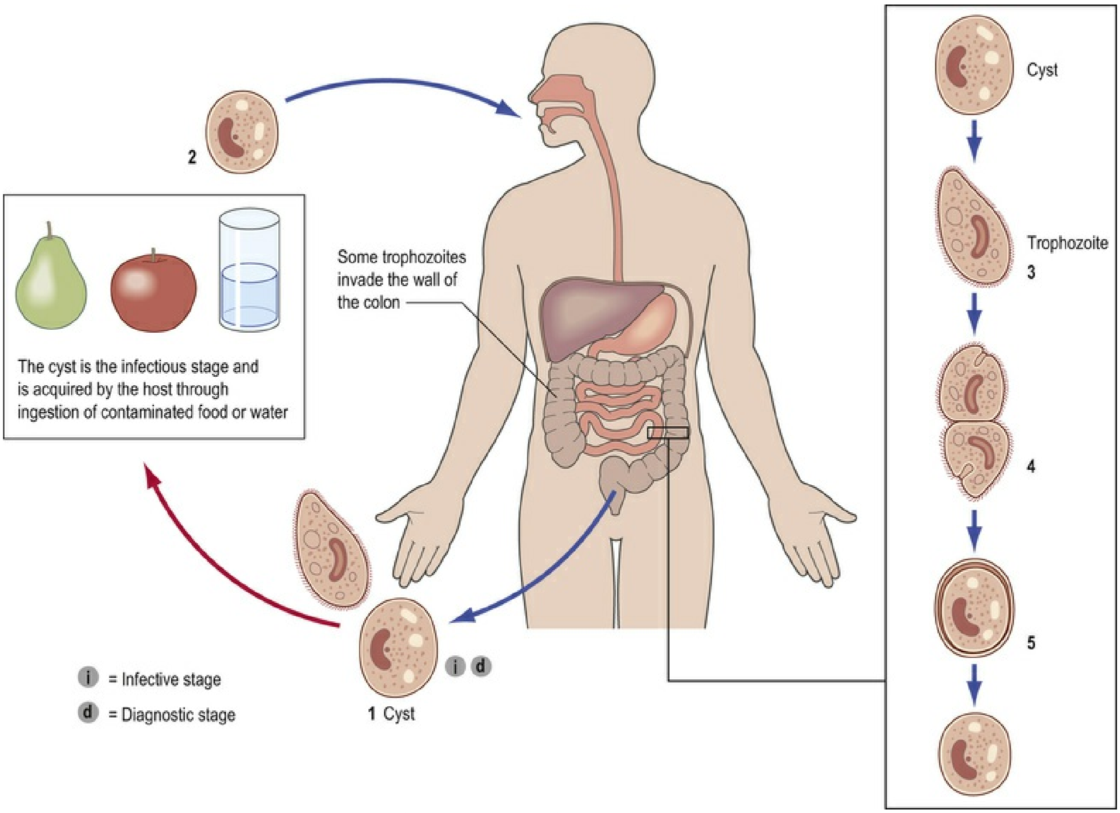
2
The cyst is the infectious stage and is acquired by the host through ingestion of contaminated food or water
Some trophozoites invade the wall of the colon
i d
1 Cyst
i = Infective stage
d = Diagnostic stage
Cyst
Trophozoite
3
4
5

FIGURE 259.1 Life cycle of *Balantioides coli* and pathogenesis of balantidiasis. (Courtesy of the Centers for Disease Control and Prevention.)

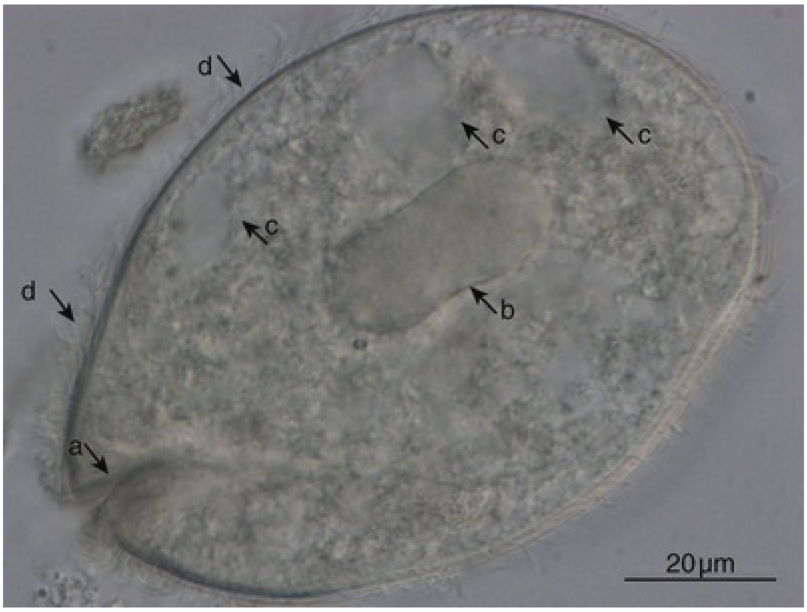

FIGURE 259.2 Pear-shaped trophozoite stage of *Balantioides coli* detected in stool specimen using merthiolate-iodine-formaldehyde (MIF) sedimentation. Its characteristic morphologic features, facilitating diagnosis, are visible: (*a*) a cytostome, (*b*) a kidney-shaped macronucleus, (*c*) contractile vacuoles, and (*d*) cilia on the surface. (Courtesy of K. Jirků-Pomajbíková, adapted from Pomajbíková K, Petrželková KJ, Profousová I, et al. Discrepancies in the occurrence of *Balantidium coli* between wild and captive African great apes. J Parasitol 2010;96:1139–1144.)

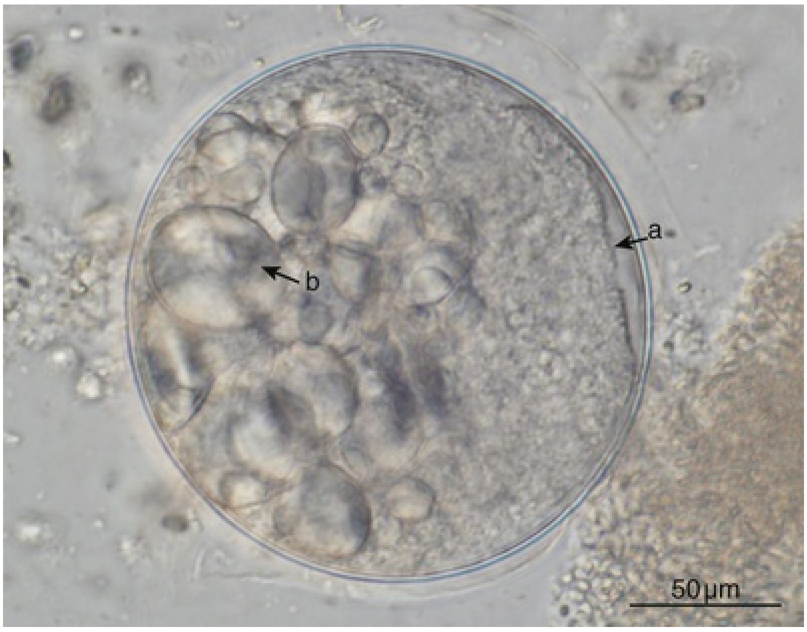

FIGURE 259.3 Round, thick-walled cyst stage of *Balantioides coli* detected in pig fecal specimen using

merthiolate-iodine-formaldehyde (MIF) sedimentation. The trophozoite stage (*a*) filled with starch grains (*b*) is visible inside the cyst (K. Jirků-Pomajbíková, adapted from Pomajbíková K, Petrželková KJ, Profousová I, et al. Discrepancies in the occurrence of *Balantidium coli* between wild and captive African great apes. J Parasitol 2010;96:1139–1144.)

Epidemiology

B. coli is zoonotic, occurs worldwide, and has been found in several mammalian hosts such as humans, captive African great apes, domestic pigs, and wild boars.[1,3,4] Suid infections are usually not linked to any pathologic manifestations, and suids are considered reservoir hosts, being a source of infection for humans.[3,8] It is not unusual for the prevalence of *B. coli* in populations of suids to reach 100%.[3,9] Balantiosis is considered a waterborne and foodborne disease, which means that water and food contaminated with cysts can be a source of infection.[3,10,11]

Although human infections have been reported from most parts of the world, there is high prevalence in some tropical and subtropical areas, including New Guinea, southern Iran, South and Central America, central Asia, the Philippines, and some Pacific islands.[3,12] In Papua New Guinea, where common domestic animals include pigs, the prevalence in humans may be up to 28%.[13,14] In Peru, 6% of a study cohort was found to be infected with *B. coli,*[15] and in 11 of 22 Bolivian Altiplano communities surveyed, *B. coli* prevalence ranged between 1% and 5%.[16] In the United States and other economically developed countries, sporadic infections have been reported in disabled people living in institutions where poor conditions of personal hygiene prevail.[17] Human infection is rare in industrialized countries but can occur in susceptible (e.g. immunocompromised) individuals.[18,19]

Clinical Manifestations

Humans infected with *B. coli* can be symptom free, but under certain circumstances, *B. coli* trophozoites can invade the mucosa of the cecum and colon, causing balantiosis. In such cases, clinical manifestations take two main forms: diarrhea and dysentery (Fig. 259.4).[3] The disease usually is chronic with intermittent episodes of diarrhea of varying severity and constipation associated with abdominal pain, anorexia, weight loss, and weakness.[3] Sometimes, symptoms in the cecal region mimic appendicitis. The differential diagnosis includes amebic and bacterial dysentery as well as noninfectious disorders (e.g., inflammatory bowel disease).[5] Rarely, *B. coli* trophozoites perforate the intestinal wall by penetrating through the muscular layers into the peritoneal cavity.[18–21] Extraintestinal infections of the liver, lungs, and genitourinary tract have been reported.[18,22,23] In most people, recovery occurs without treatment, but in malnourished or immunosuppressed hosts, the disease course can be fulminant and fatal.[18,24] *B. coli* should be considered in immunocompromised people with diarrhea.[18,22–24] Factors predisposing to clinical illness include malnutrition, alcoholism, hypochlorhydria, and other causes of immunosuppression (e.g., malignancies or HIV).[3] Moreover, recently it was revealed that a diet rich in starch might predispose hosts to developing balantiosis.[25]

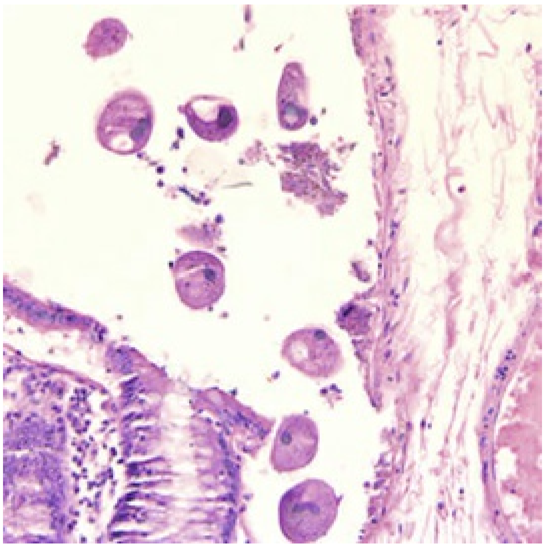

FIGURE 259.4 Biopsy of colon shows excystation of *Balantioides coli* with emergence of trophozoites.
(Courtesy of DPDx image library, Centers for Disease Control and Prevention.)

Diagnosis

The diagnosis usually is made by visualizing cysts or trophozoites, or both, in a fecal specimen, in scrapings obtained from inflamed gut mucosa, or in an endoscopic biopsy collected from the periphery of ulcers. *B. coli* is commonly diagnosed by coprologic methods (e.g., wet mounts, flotation, concentration, or staining techniques), but merthiolate-iodine-formaldehyde sedimentation is recommended as the gold standard because of its high sensitivity for both trophozoites and cysts.[3,4] Samples usually are examined using light microscopy; a phase contrast microscope can be used to help identify *B. coli* morphologic features.[3] The cyst stage is detected in the feces of suids, whereas the trophozoite stage typically is found in human and ape feces.[4] Because trophozoites disintegrate rapidly in feces, fecal samples must be examined as soon as possible after collection or be placed in fixation medium such as 4% formaldehyde (only for coprologic examination) or 96% ethanol (also for molecular analyses).[1,3,4]

Treatment and Prevention

Tetracycline, which should not be given to pregnant women and children younger than 8 years, is the drug of choice.[26,27] Tetracycline (for adults 500 mg orally 4 times daily for 10 days; contraindicated for children younger than 8 yrs and for pregnant women) is effective. Alternative therapies include metronidazole (for adults, 500–750 mg orally 3 times daily for 5 days; for children, 35–50 mg/kg/day orally in 3 dosage for 5 days), or iodoquinol for adults, 650 mg orally 3 times daily for 20 days; for children, 30–40 mg/kg/day [maximum, 2 g] orally for 20 days).[26,27] For more information on the treatment of balantidiasis, see the Centers for Disease Control and Prevention web page https://www.cdc.gov/dpdx/balantidiasis/tx.html.

To reduce transmission, prevention of contamination of the environment with pig feces is important. Reducing human contact with infected pigs and with contaminated food and water and improving conditions of personal hygiene and nutrition are additional methods of control.

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2013.

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Blastocystis

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Blastocystis is a protist parasitizing the lower intestine of humans and a vast range of animals. Although *Blastocystis* has been implicated as a cause of various gastrointestinal tract symptoms, its role as a pathogen, mechanism of transmission, and life cycle have been subject to much debate.[1–4] A clinical syndrome of self-limited intestinal symptoms has been described in several series of predominantly adult patients, with infection intensity possibly accounting for differences in clinical presentation.[5] Extraintestinal manifestations, such as urticaria, also have been described.[6,7] *Blastocystis* spp. from humans, other mammals, and birds are classified into subtypes, but because non–DNA-based laboratory methods do not enable distinction between subtypes, the organism should be reported as *Blastocystis* sp. not as *Blastocystis hominis*.[8]

Organism

Blastocystis is a protist belonging to the Stramenopiles.[9] It has been isolated from a wide variety of animals and has been reported in human populations from most parts of the world.[10] A total of 9 subtypes (arguably species) have been identified in humans to date, with humans colonized most commonly by subtypes 1, 2, 3, and 4, depending on geographic region.[8,10,11] Several morphologic stages have been described, including the vacuolar, avacuolar, multivacuolar, granular, ameboid, and cystic stages. The vacuolar form is observed most frequently in clinical samples and in fecal cultures; it is spherical and usually ranges in size from 4 to 15 μm in diameter[12]; much larger cells may be seen in cultures. The cyst (2–5 μm) is the transmissible form and is able to survive in water at room temperature for up to 19 days but is fragile at extremes of heat and cold and when exposed to common disinfectants.[13–16] After ingestion of an infectious cyst, the organism excysts in the lumen of the cecum and proximal colon, developing into vacuolar forms and undergoing encystation before being excreted as the cyst form, which, if eaten, completes the cycle.

Epidemiology

Blastocystis has a global distribution. Surveys of intestinal parasites in population groups in developing countries documented prevalence rates of 54% in Papua New Guinea and 33% among travelers and foreign residents with diarrhea in Nepal.[17,18] In a study of fecal specimens from 48 states and the District of Columbia, *Blastocystis* was identified in 23% of 5792 stool specimens.[19]

There are few reports of *Blastocystis* infection in children. A study surveying 1042 internationally adopted children submitting at least one stool specimen for ova and parasite testing within 120 days after arrival to the United States saw a prevalence of *Blastocystis* of 10%.[20] A community-based survey northeast of Mexico City reported a frequency of 7% in children younger than 14 years.[21] A study of the prevalence of enteroparasites in a facility for orphaned and homeless children in Argentina found *Blastocystis* in 44% of stool samples.[22] A similar study of children living in residential institutions and street communities in metropolitan Manila, Philippines found *Blastocystis* in 41% of children examined.[23] A community-based study in Papua New Guinea found that >65% of children younger than 18 years had *Blastocystis.*[17] Meanwhile, the use of DNA-based diagnostic methods recently led to identification of a 100% prevalence in Senegalese children with gastrointestinal symptoms.[24]

Infection has been associated with recent travel to the tropics and consumption of untreated water.[25,26] *Blastocystis* has been detected in cases of nosocomial diarrhea and in children attending childcare centers.[27,28] Sexually active homosexual men have *Blastocystis* infection rates as high as 52%, a finding consistent with person-to-person transmission.[29] Limited data suggest that illness due to *Blastocystis* can be more severe in patients with AIDS and other immunocompromising disorders.[30,31] Working with animals may increase the risk for becoming infected with *Blastocystis*.[32]

Clinical Manifestations

Whether *Blastocystis* causes disease is controversial, and potential mechanisms of pathogenicity is unclear. Symptoms described in *Blastocystis*-positive individuals include abdominal pain, diarrhea, nausea, anorexia, bloating, and flatulence. Means to differentiate infection from colonization do not exist.[1] Differences in clinical presentation might be due to one or more of the following factors: subtype virulence factors, immune status of the host, host genotype, parasite load, host response, and dysbiosis.[1] Nevertheless, the presence of this organism in stool suggests that the host was exposed to fecally contaminated food or drink. *Blastocystis* does not appear to be more common in patients with inflammatory or functional bowel diseases than in healthy individuals, although conflicting data exist.[33–35]

Attempts to infect germ-free guinea pigs did not provide convincing evidence of pathogenicity, except when large numbers of organisms were inoculated with normal enteric flora, with gross pathologic effects being limited to mild intestinal hyperemia.[36] Microscopic examination revealed a slight increase in cellularity and intraepithelial penetration by *Blastocystis.* A case-control study examining the association between acquisition of *Blastocystis* and presence of mucosal lesions by upper gastrointestinal endoscopy and sigmoidoscopy failed to demonstrate intestinal pathology.[37] Studies on *Blastocystis* in a gut microbiota context are emerging, and it is possible that such studies hold the key to unraveling the clinical significance of *Blastocystis*.[38]

Diagnosis

Diagnosis most often is made by staining of a fixed fecal specimen with iron hematoxylin or trichrome stain (Fig. 260.1), which is superior to iodine staining of wet mounts and microscopy of fecal concentrates.[39,40] Recognition of the organism can be difficult because of large variation in size and form. *Blastocystis* can be grown readily in culture using Jones medium, with relatively high diagnostic sensitivity.[39,41] Polymerase chain reaction testing is both highly sensitive and specific, but is used primarily for research.[41,42] Studies using serology are scarce, and it is not known whether serology could be a useful tool to distinguish infection from colonization.

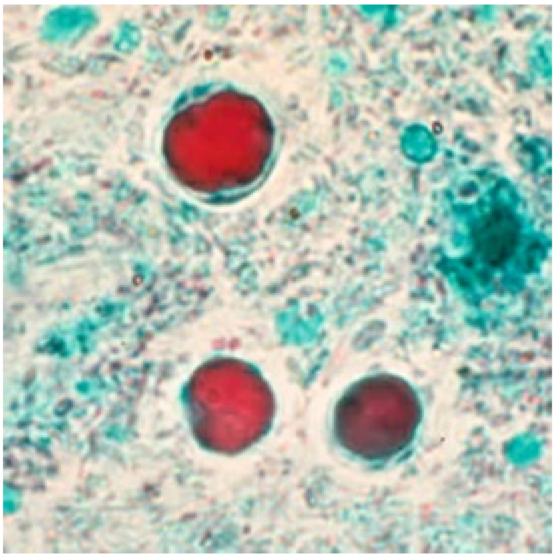

FIGURE 260.1 Vacuolar forms of *Blastocystis* in a fixed fecal smear stained with trichrome stain (Courtesy of DPDx image library, Centers for Disease Control and Prevention).

Treatment and Prevention

Detection of the organism in feces should not lead automatically to administration of antimicrobial therapy because clinical significance is controversial and carriage is common; most children in whom *Blastocystis* is detected should not be treated. Therapy should be considered in cases of persistent intestinal symptoms and when no other cause is found. Metronidazole alone, which often is used for *Blastocystis* eradication, appears to have very limited effect, whereas other drugs, such as paromomycin, nitazoxanide, and so-called triple therapy (diloxanide furoate, trimethoprim-sulfamethoxazole, and secnidazole) might be somewhat efficacious.[43–45]

Prevention of *Blastocystis* infection involves adequate sanitation, careful handwashing, avoidance of untreated water, and use of enteric precautions to interrupt person-to-person spread.

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Cryptosporidium Species

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Human disease caused by *Cryptosporidium* was first described in 1976 and became recognized increasingly during the human immunodeficiency virus (HIV) epidemic. Improved detection of oocysts in feces has shown *Cryptosporidium* to be a common cause of diarrhea in both immunocompetent and immunocompromised hosts.[1,2] In developing countries, *Cryptosporidium* is among the four most common causes of moderate to severe diarrhea and diarrhea-associated deaths in young children.[3]

The Pathogen

Organisms of the genus *Cryptosporidium* are 2- to 6-µm coccidian parasites that infect epithelial cells lining the digestive and respiratory tracts of vertebrates, including fish, birds, reptiles, and mammals as well as humans. The organism lacks host specificity; however, most human infections are caused by *Cryptosporidium hominis* or *C. parvum*.[4–6] The life cycle of *Cryptosporidium* is similar to that of other true coccidia that infect mammals. Infectious oocysts excyst within the lumen of the intestine and release sporozoites. The released sporozoites penetrate host cells, where they develop into trophozoites. Trophozoites can undergo asexual division resulting in autoinfection in adjacent cells or undergo sexual reproduction resulting in formation of oocysts. After fertilization of gametes, a thick-walled oocyst is formed. The oocysts of *Cryptosporidium* undergo sporogony within the host cells and are infectious when released in feces.[4]

Epidemiology

Oocysts of *Cryptosporidium* withstand adverse environmental conditions and can survive for long periods if stored moist and cold.[7] Oocysts are resistant to common disinfectants, including disinfectants recommended for hospital use. One study found that ammonia concentrations of >50% and formalin concentrations of ≥10% were necessary to kill the organism.[8]

Infection occurs after ingestion or, possibly, inhalation of infectious spores.[9] In healthy adult volunteers with no serologic evidence of past infection with *C. parvum,* the median infective dose was 132 oocysts.[10] Spread to humans occurs through person-to-person transmission and from ingestion of environmentally contaminated water or contaminated food.[4,11–13] An increase in cases reported in 2007–2008 is attributable partially to multiple large recreational water-associated outbreaks.[14] Transmission also has been linked with close association with infected animals.[15,16] Person-to-person transmission is responsible for cryptosporidiosis outbreaks in childcare centers and hospitals and is most often caused by *C. hominis*.[17] *Cryptosporidium* also causes traveler's diarrhea.[4] In the United States, reported cases of cryptosporidiosis are highest among young children (ages 1-4 years) with an estimated incidence rate of 6.6 per 100,000 population during 2011–2012. Symptoms peak in the summer and early fall (June through October), coinciding with the summer recreational water season.[18,19]

Zoonotic transmission from calves has been well documented, and other animals such as rodents, puppies, and kittens probably also serve as reservoir hosts.[4,20] Zoonotic transmission occurs in people living and working in close association with animals and is most often caused by *C. parvum*. A recent review of the waterborne parasitic outbreaks reported worldwide between 2004 and 2010 found that *Cryptosporidium* spp. were the etiologic agent in 60% of the outbreaks.[21]

Outbreaks of cryptosporidial infection have been associated with contaminated community water supplies in several US states and the United Kingdom.[22,23] In 1993, a waterborne outbreak in Milwaukee, Wisconsin caused approximately 400,000 cases of diarrhea.[23] Consumption of untreated surface water or inadequate water filtration has occurred in some waterborne outbreaks. Swimming pool water and water from decorative fountains have been linked to outbreaks.[18] An accidental fecal spillage into a community swimming pool resulted in 44 persons contracting diarrhea in one outbreak. Attack rates in different groups of swimmers ranged from 47% to 100% of exposed group members, with the highest rate in people with prolonged water exposure.[22] Waste water in the form of raw sewage and runoff from dairies and grazing lands can contaminate drinking and recreational water.[4,18] Molecular techniques allow specific linkages of outbreaks of *Cryptosporidium* disease to human versus animal contamination of water.[5]

Cryptosporidiosis is associated with diarrheal illness worldwide but is more prevalent in underdeveloped countries and in children younger than 2 years.[2,4,24–26] Surveys of selected populations have shown that infection rates in developed countries range from 0.6% to 20% compared with rates as high as 32% in less developed countries.[27] Seroprevalence studies confirm that cryptosporidiosis is more common in developing countries. In Europe and North America, approximately 25% to 35% of people have antibodies against *Cryptosporidium,* compared with 64% in Peru and Venezuela.[4] Increased infection rate probably is due to poor sanitation, lack of clean water, crowded living conditions, and close association with animals.[4]

Clinical Manifestations

Cryptosporidiosis is characterized by profuse watery diarrhea that can contain mucus but rarely contains white or red blood cells. Fifty percent of affected people have crampy abdominal pain, nausea, and vomiting. Nonspecific symptoms such as myalgia, fatigue, weakness, headache, anorexia, weight loss, and low-grade fever also may occur as well as asymptomatic infection.[4,7,17,27–29] Severity of symptoms correlates with density of oocyst shedding, which can be intermittent. Symptoms may vary based on the species of infecting *Cryptosporidium*.[30] Malabsorption, lactose intolerance, dehydration, and malnutrition often occur in severe cases. Radiographic findings are nonspecific and include prominent mucosal folds and thickening of intestinal walls.[7]

The incubation period is 2 to 14 days. Infection can be asymptomatic, self-limited, or protracted with severity linked to immunosuppression. Most immunocompetent hosts have a self-limited diarrheal illness that usually resolves within 10 to 14 days, although diarrhea can persist for as long as 5 weeks.[31] Oocyst shedding can continue for up to 2 weeks after clinical improvement.[23] Prolonged, debilitating disease can occur in immunocompromised hosts, including people with HIV infection, malignancy, CD40 ligand deficiency, severe combined immunodeficiency syndrome, other T-lymphocyte abnormalities, or selective immunoglobulin A deficiency and in solid-organ or stem cell transplant recipients, patients with end-stage renal disease undergoing hemodialysis, or people who are undernourished.[6,32]

Biliary tract disease is well documented in immunocompromised hosts and is characterized by fever, right upper quadrant pain, nausea, vomiting, and diarrhea. Jaundice and elevated serum levels of alkaline phosphatase, γ-glutamyltranspeptidase, and bilirubin can occur. The gallbladder can appear dilated and thick-walled on radiography and ultrasonography. If stenosis of the common bile duct occurs, the extrahepatic ducts usually are dilated.[33] Approximately 15% of patients with the acquired immunodeficiency syndrome (AIDS) who have cryptosporidiosis have biliary tract involvement. *Cryptosporidium* also has been detected in the pancreatic duct of a child with AIDS and has been associated with pancreatitis and sclerosing cholangitis in an immunocompetent host.[4,7,27,33,34]

Cryptosporidium has been detected in people with respiratory tract symptoms including cough, shortness of breath, wheezing, croup, and hoarseness. These symptoms can occur with and without diarrhea. Oocysts have been identified in sputum and bronchoalveolar lavage specimens. Not all respiratory tract symptoms can be attributed to cryptosporidiosis because other pathogens often are present, especially in HIV-infected patients. Further study of respiratory tract disease, including the potential for airborne spread of the organism, is warranted.[4,9,35]

Laboratory Diagnosis

Most clinical laboratories use enzyme immunoassays or immunofluorescence assays to detect *Cryptosporidium* antigens in stool specimens. Polymerase chain reaction analysis also has been reported to have an increased sensitivity over light microscopy and is now considered the diagnostic method of choice.[36–38] In addition, polymerase chain reaction may be beneficial as an epidemiologic tool.

The definitive diagnosis of cryptosporidial infection relies on identifying oocysts in feces or body fluids, or along the epithelial surface of biopsy tissue (Fig. 261.1). On sections stained with hematoxylin and eosin, oocysts appear as small, spherical, basophilic bodies located along the microvilli of the epithelium lining of the gastrointestinal tract. Because not all areas of the intestinal tract may be affected, sampling errors can occur. An indirect immunofluorescence assay can be used to detect oocysts in embedded tissue.[4] Histologic sections reveal villous atrophy and blunting, epithelial flattening, and inflammation of the lamina propria.

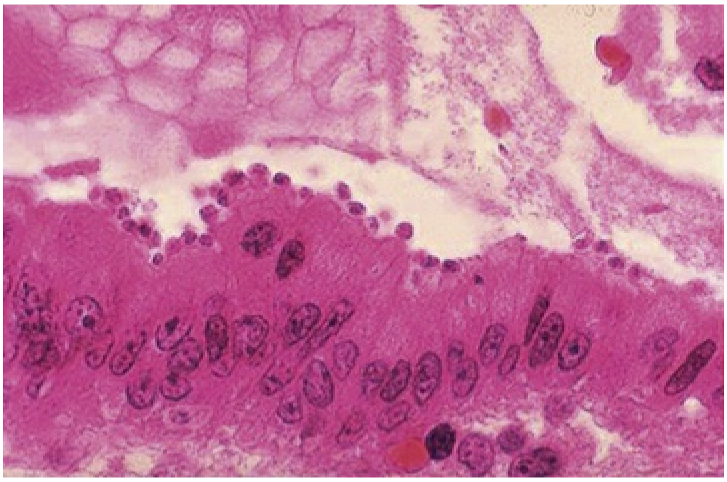

FIGURE 261.1 Cryptosporidia can be seen along the luminal border of the small bowel.

Fresh stool specimens should be placed in a fixative before submission to the laboratory, to prevent infection of laboratory workers. At least three specimens should be examined in immunocompetent hosts and two specimens in immunocompromised hosts.[39] Serodiagnostic assays are available for epidemiologic study; however, the role of serodiagnosis in acute diarrheal disease is undefined.[4]

Treatment

In most immunocompetent hosts, cryptosporidiosis is self-limited and requires no therapy except maintenance of adequate hydration. In severe cases, including immunocompromised hosts, a variety of antimicrobial agents have been used with no consistent success. Nitazoxanide is the only approved therapy for cryptosporidiosis and is approved for this condition in children. Clinical trials have demonstrated reductions in duration of diarrhea and oocyst shedding after treatment.[40–43] However, in studies of HIV-infected children in Zambia, nitazoxanide, including prolonged high-dose therapy, did not appear to be beneficial.[42,44] The recommended dose is 200 mg twice a day for 3 days for children 4 through 11 years of age, and 100 mg twice a day for children 12 through 47 months of age. The dose of nitazoxanide in people ≥12 years of age is 500 mg twice a day for 3 days.

Clarithromycin, azithromycin, roxithromycin, and paromomycin, a nonabsorbable aminoglycoside, have been reported to be successful in managing cryptosporidial diarrhea in immunocompromised patients.[45–53] However, randomized trials show conflicting results.[49,52,53] Combination therapy with paromomycin and azithromycin has been proposed, but limited clinical experiences preclude recommendations.[54]

Immunologic therapy may be beneficial in patients with cryptosporidiosis. Breastfeeding may be protective.[55] Oral administration of hyperimmune bovine colostrum, dialyzable leukocyte extract (a cell-free supernatant from the lymph nodes of immunized cows), and human serum immune globulin have all been reported to attenuate diarrhea and other symptoms associated with cryptosporidiosis.[28,56,57]

In addition to specific antiparasitic agents, use of nonspecific antidiarrheal agents such as kaolin plus pectin, loperamide, diphenoxylate, bismuth subsalicylate, or opiates have been helpful in management of symptoms, as well as the long-acting parenteral somatostatin analogue octreotide acetate.[28]

Special Considerations

HIV-infected people have high rates of cryptosporidial infection. Before the availability of combination antiretroviral therapy (cART), about 10% to 15% of AIDS patients in the US had reported cryptosporidiosis, whereas the prevalence in developing countries, such as in Haiti and countries in central Africa, is as high as 50%. Infections in HIV-infected people can be self-limited or chronic; rarely, asymptomatic infection can occur. A retrospective review indicated that patients with CD4$^+$ T-lymphocyte counts of >180 cells/mm^3 often have spontaneous resolution of infection. In patients with more severe immunosuppression, chronic disease is likely to develop.[58] Improvements in symptoms and clearance of shedding of oocysts can occur after treatment with cART, and most experts recommend starting cART in treatment-naïve patients with *Cryptosporidium* infections.[35,59] This may be due to improvement in the immune system as well as some effect of protease inhibitors on the parasite's life cycle.[60]

Outbreaks of *Cryptosporidium* infection in childcare centers are reported with increasing frequency.[61–63] Childcare centers with toddlers most often are involved, and the attack rate can be as high as 67%.[62] In addition, family members have been infected by attendees.[64] Transmission of infection within closed pediatric hospital units also has been documented.[65]

Prevention

Because the organism most commonly is spread by person-to-person transfer, handwashing helps prevent infection. Alcohol-based hand cleaners are not effective against *Cryptosporidium* spp.[18] Universal precautions should be used for hospitalized patients older than 6 years; diapered or incontinent children younger than 6 years should be managed with contact precautions. Infected people in hospitals can be cohorted to limit the spread of disease. Children with diarrhea should not attend group childcare. Immunocompromised people should take special precautions around animals. People should avoid swallowing recreational water; avoid drinking water from shallow wells, lakes, rivers, streams, ponds, and springs; and avoid drinking untreated water during community-wide outbreaks caused by contaminated drinking water.[16]

Key Points

Diagnosis, Clinical Features, and Treatment of Cryptosporidiosis

Microbiology

- Most infections are caused by *Cryptosporidium hominis* or *C. parvum*, 2- to 6-µm coccidian parasites that infect epithelial cells lining the intestinal and respiratory tracts.
- Oocysts are infectious when released from the infected host.

Epidemiology

- Infection occurs through person-to-person transmission, from ingestion of environmentally contaminated water or contaminated food, and through zoonotic transmission.
- Outbreaks have been associated with contaminated community water supplies, swimming pool and recreational water exposure, and childcare center attendance.

Clinical Features

- Profuse watery diarrhea without white or red blood cells is most common.
- Infection also can be associated with myalgia, fatigue, weakness, headache, anorexia, weight loss, and low-grade fever; asymptomatic infection can occur.
- Symptoms are more severe in immunocompromised hosts.

Diagnosis

- Polymerase chain reaction, enzyme immunoassays, or immunofluorescence assays on stool specimens, or identification of oocysts in feces

- Multiple samples improve sensitivity of testing.

Treatment

- Self-limited in immunocompetent hosts
- Nitazoxanide is the only approved therapy.
- In HIV-infected patients, treatment of HIV with combination antiretroviral therapy may improve clinical symptoms.

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262

Endolimax nana

Casper S. Poulsen, Christen R. Stensvold

Endolimax nana is a single-celled parasite of the colon. Although considered nonpathogenic, infection with *E. nana* is an indicator of exposure to fecal contamination and often is seen in fecal samples positive for other common parasitic intestinal protists.

Description of *Endolimax nana*

E. nana is an intestinal parasitic ameba, which appears to be most closely related to *Iodamoeba*.[1,2] *E. nana* has a monoxenous life cycle (Fig. 262.1), with trophozoite stages (8–10 μm) found in the colon where they move by pseudopodia, feeding exclusively on bacteria.[3,4] The trophozoite nucleus is vesicular and spherical with a polymorphic karyosome (Fig. 262.2). After encystation, the oval cyst (6–9 μm × 5–7 μm) is excreted in feces, and when mature, it contains four nuclei (Fig. 262.3). Mature cysts may excyst and colonize the colon when ingested.[3–5] When established, the ameba may persist in the colon for up to at least 17 years.[4]

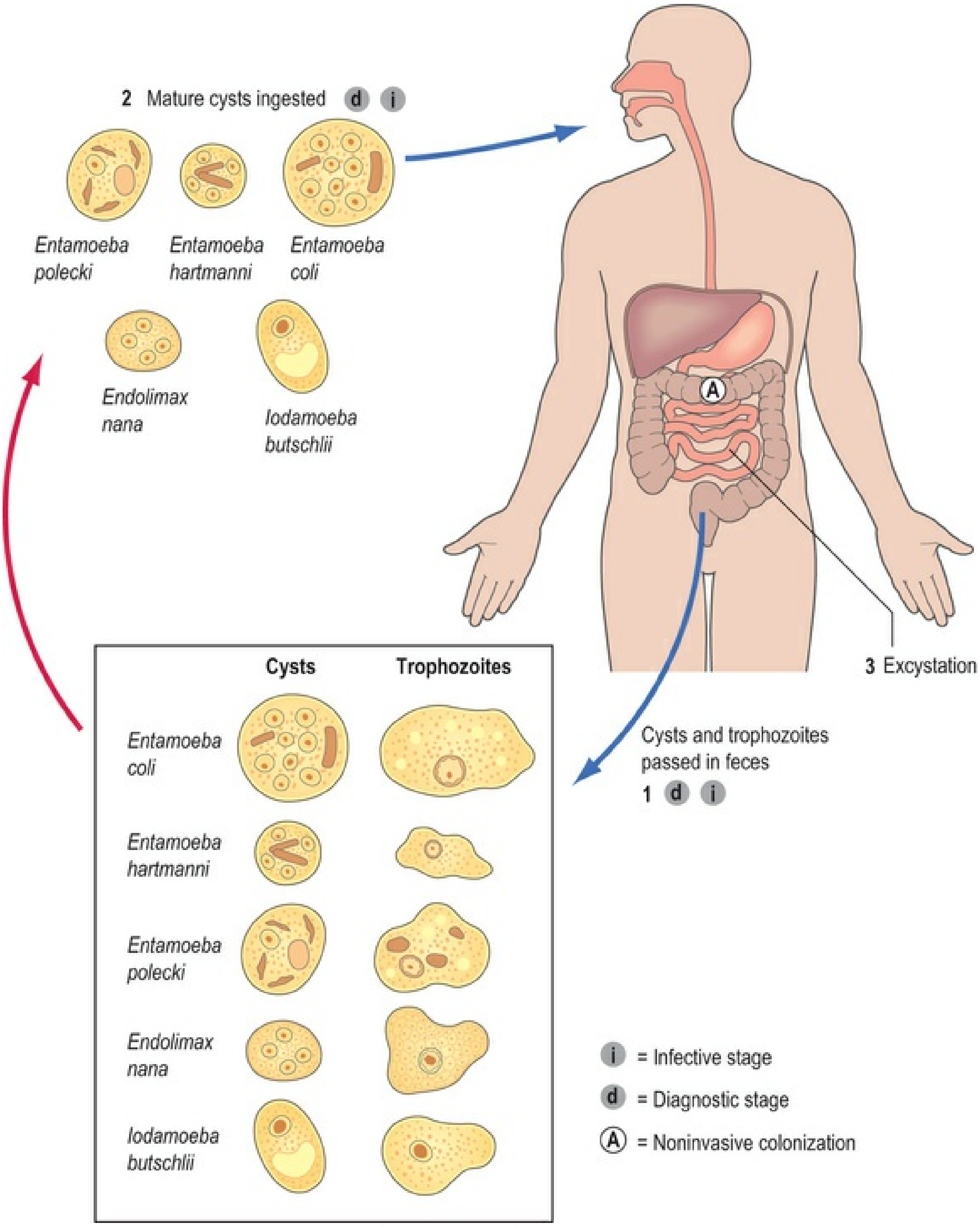

FIGURE 262.1 Life cycle of *Endolimax nana, Entamoeba coli, Entamoeba hartmanni, Entamoeba polecki,* and *Iodamoeba bütschlii*. (Courtesy of DPDx image library, Centers for Disease Control and Prevention).

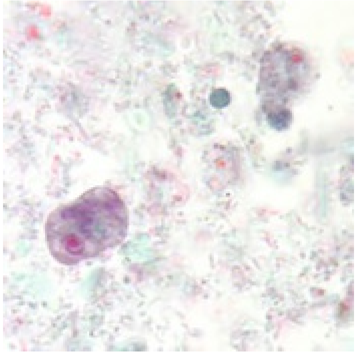

FIGURE 262.2 Trophozoites of *Endolimax nana* in stool specimen. (Courtesy of DPDx image library, Centers for Disease Control and Prevention).

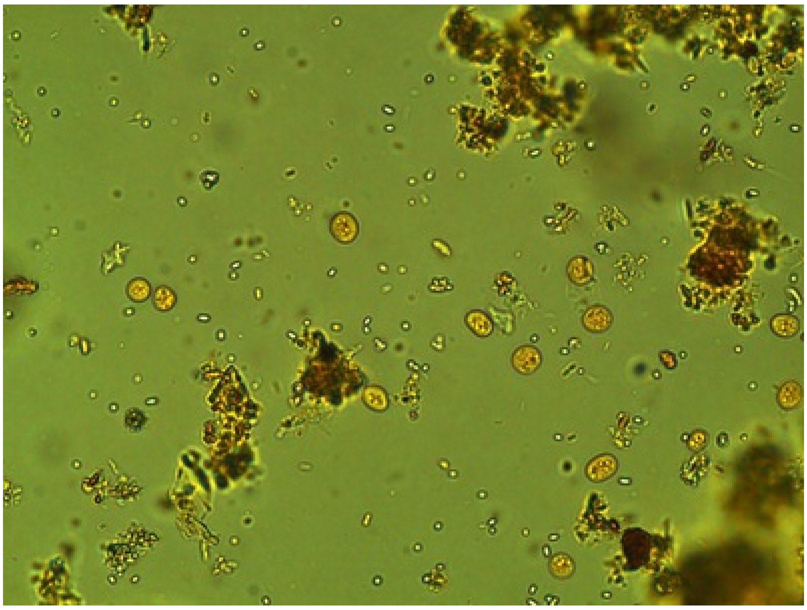

FIGURE 262.3 Mature cysts of *Endolimax nana* in fecal concentrate. (Courtesy of Dr. Marianne Lebbad, Public Health Agency of Sweden.)

Epidemiology and Clinical Manifestations

E. nana has a worldwide distribution and has commonly been associated with cases of diarrhea in children; this association may be explained in part by *E. nana* being an indicator of fecal contamination of food or water.[6–8] In general, *E. nana* is highly prevalent in children from developing countries such as Cote d'Ivoire (83%), Brazil (43%), Nicaragua (35%), and Thailand (8%).[9–12] A lower prevalence (1.5%) was reported in a survey from Germany (2%).[13]

Diagnosis and Treatment

Detection of *Endolimax* traditionally relies on microscopy, with trophozoites and cysts being identifiable by direct examination. The formalin-ether concentration method is routinely used, and when stained with iodine, the oval cysts may appear gibbous with the four nuclei paired and located at each end.[4] However, cysts and trophozoites are difficult to differentiate from other amebas, such as *Entamoeba histolytica, Entamoeba hartmanni*, and *Dientamoeba fragilis*. It is especially difficult to differentiate between cysts of *E. hartmanni* and *E. nana* because they are similar in size and have four nuclei; however, *E. nana* nuclei have a larger punctuate karyosome and lack peripheral chromatin, but high magnification (oil lens; original magnification, ×1000) is needed to discern these features with confidence. Because *E. nana* is considered a commensal, treatment usually is not recommended.

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Entamoeba histolytica (Amebiasis)

Joanna Nelson, Upinder Singh

Entamoeba histolytica is a tissue-lysing ameba that typically causes colitis or liver abscess. It was first discovered in 1875 by Fedor Aleksandrovich Lösch, who described amebic trophozoites in the stool and colonic ulcerations in a farmer with a fatal case of dysentery.[1] In 1993, what was once thought to be a fairly ubiquitous parasite was reclassified into two morphologically identical but genetically distinct species: the pathogenic *Entamoeba histolytica*, an invasive disease-causing parasite; and the commensal *Entamoeba dispar*, a noninvasive parasite.[2]

Description of the Pathogen

E. histolytica is a pseudopod-forming, nonflagellated protozoan parasite. Historically, it was considered the only invasive species of parasites in the *Entamoeba* genus infecting humans (including *E. histolytica, E. dispar, E. moshkovskii, E. hartmanni, E. polecki, E. coli, E. gingivalis, E. chattoni,* and *E. bangladeshi*). However, recently *E. moshkovskii* and the newly discovered *E. bangladeshi* have been associated with diarrhea in children.[3–5] Molecular phylogeny of eukaryotic organisms based on small subunit ribosomal RNA places *Entamoeba* on the lowermost branches of the eukaryotic tree, closest to the social ameba *Dictyostelium discoideum,* whereas analysis of elongation factor 1α shows that *E. histolytica* is likely an outgroup of *Euglena* and higher eukaryotes.[6–8] However, the organism most closely resembles lower eukaryotes in structure. The life cycle of *E. histolytica* consists of an infectious cyst and an invasive trophozoite (Fig. 263.1). The infectious cyst is 10 to 16 μm in diameter, contains four nuclei, and is surrounded by a refractile wall (Fig. 263.2A). Trophozoites are 10 to 60 μm in diameter and have one nucleus with a central karyosome or endosome (Fig. 263.2B). The quadrinucleate cyst is highly resilient and can survive in the environment for weeks to months. *E. histolytica* infection occurs when cysts are ingested in contaminated food or water. Excystation occurs in the small or large bowel, giving rise to eight daughter trophozoites. Trophozoites can colonize or invade the large bowel, but cysts are never found in tissue. About 10% of colonized individuals develop invasive disease characterized by flask-shaped colonic ulcers due to disruption of the intestinal mucosal barrier by the trophozoite. Trophozoites can also enter the bloodstream through the portal venous system and spread to other organs. Interaction of the amebic strain with bacterial flora as well as host factors (malnutrition, diet, sex, age, immune status) may influence whether infection results in colonization or invasive disease. Trophozoites reproduce by binary fission and encyst within the colon, excrete cysts into the environment in the stool, and thus perpetuate the life cycle.

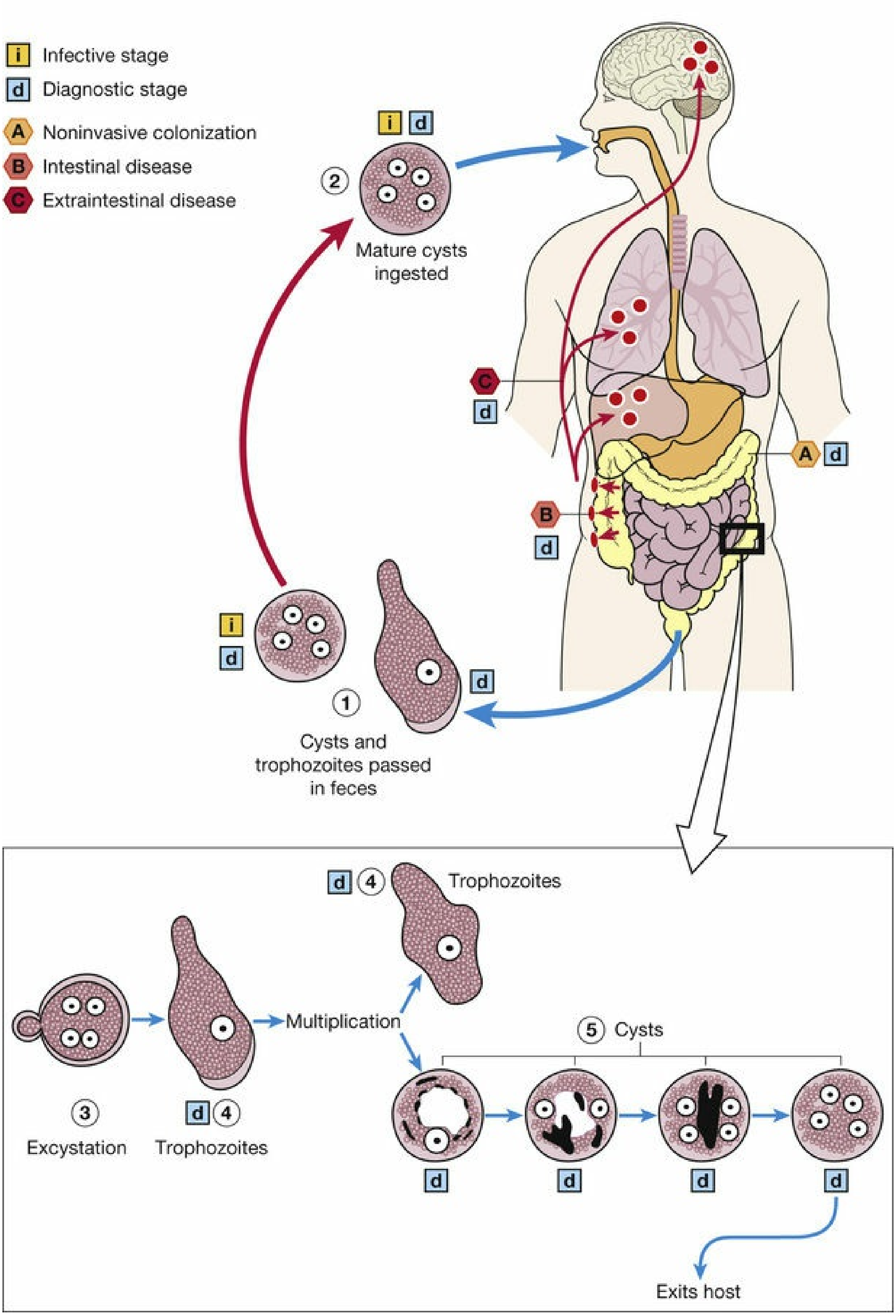

FIGURE 263.1 Life cycle of *Entamoeba histolytica*. Cysts and trophozoites are passed in feces (*1*). Cysts are typically found in formed stool, whereas trophozoites are typically found in diarrheal stool. Infection by *E. histolytica* occurs by ingestion of mature cysts (*2*) in fecally contaminated food, water, or hands.

Excystation (*3*) occurs in the small intestine, and trophozoites (*4*) are released, which migrate to the large intestine. The trophozoites multiply by binary fission and produce cysts (*5*), and both stages are passed in the feces. Because of the protection conferred by their walls, the cysts can survive days to weeks in the external environment and are responsible for transmission. Trophozoites passed in the stool are rapidly destroyed when outside the body, and if ingested would not survive exposure to the gastric environment. In many cases, the trophozoites remain confined to the intestinal lumen (*A:* noninvasive infection) of individuals who are asymptomatic carriers, passing cysts in their stool. In some patients the trophozoites invade the intestinal mucosa (*B:* intestinal disease), or, through the bloodstream, extraintestinal sites such as the liver, brain, and lungs (*C:* extraintestinal disease), with resultant pathologic manifestations. It has been established that the invasive and noninvasive forms represent two separate species, respectively *E. histolytica* and *E. dispar*. These two species are morphologically indistinguishable unless *E. histolytica* is observed with ingested red blood cells (erythrophagocystosis). Transmission can also occur through exposure to fecal matter during sexual contact (in which case not only cysts, but also trophozoites could prove infective). (Courtesy of the DPDx image library, Centers for Disease Control and Prevention.)

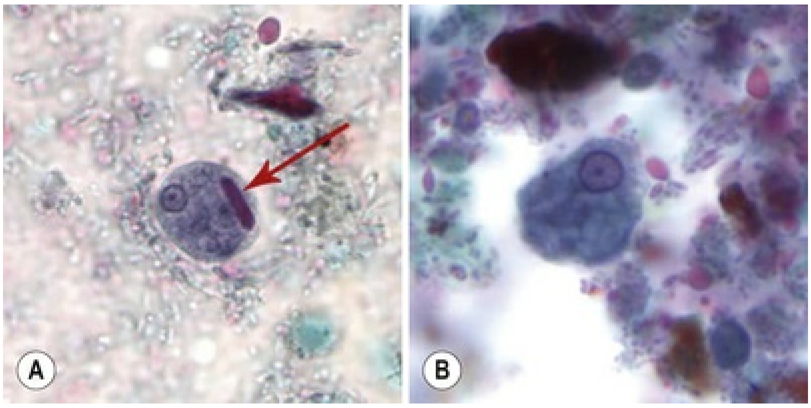

FIGURE 263.2 Light microscopy of *Entamoeba histolytica* in stool. (A) Cyst of *E. histolytica*/*E. dispar* stained with trichrome. Notice the chromatoid body

with blunt, rounded ends *(arrow)*. (B) Trophozoite of *E. histolytica*. The specimen was preserved in polyvinyl alcohol (PVA) and stained in trichrome. PCR was performed on this specimen to differentiate between *E. histolytica* and *E. dispar* (Courtesy of DPDx image library, Centers for Disease Control and Prevention.)

Pathogenesis

A well-defined sequence of events occurs during amebic invasion of the colonic mucosa.[9–11] First, trophozoites adhere to colonic mucins and epithelial cells through interaction of an amebic galactose/*N*-acetyl-D-galactosamine (Gal/GalNAc) inhibitable adherence lectin to host glycoconjugates.[12,13] Then, secreted proteolytic enzymes disrupt the intestinal barrier and facilitate tissue penetration by trophozoites.[14–16] Trophozoites kill host epithelial and immune cells, resulting in tissue destruction. This process was described as a three-part process in vitro that includes adherence, cytolysis, and phagocytosis. Target cell killing is contact dependent and mediated by the amebic Gal/GalNAc inhibitable lectin.[17,18] The heavy subunit of lectin is encoded by a multigene family, is highly expressed in trophozoites, and is highly conserved in *E. histolytica* isolates worldwide, thus having important implications for vaccine development.[19,20] Lectin also mediates serum resistance by inhibiting assembly of the membrane attack complex of human complement on the surface of the ameba.[21]

The mechanism of cytolysis has been the subject of intense investigation. In lymphocytes killed in vitro by *E. histolytica*, compaction of nuclear chromatin, cytoplasmic condensation, and membrane blebbing occur, suggesting an apoptotic mechanism of cell killing.[22] Furthermore, activation of host cell caspases occurs within minutes of contact by trophozoites, and caspase 3 activation specifically by *E. histolytica* leads to activation of apoptosis.[23] Amebapore is a 5-kd polypeptide with pore-forming activity that may be a major effector molecule in mediating cytolytic activity but does so by mechanisms other than inducing apoptosis.[24,25] Amebapore may coact with other virulence factors, perhaps by facilitating entry of amebic proteases into host cells analogous to perforin/granzyme-mediated cell killing by cytotoxic T lymphocytes. Finally, within seconds of contact by an amebic trophozoite, the target cell's cytoplasmic calcium level rises about 20-fold, and cell death occurs in 5 to 15 minutes.[26] On incubation of Chinese hamster ovary cells with purified amebic Gal/GalNAc lectin, a nonlethal, reversible rise in intracellular calcium concentration occurs, suggesting that amebic adherence lectin may be cytotoxic directly.[26,27] Recently, the three-part process of adherence, cytolysis, and phagocytosis has been called into question. It has been demonstrated that *E. histolytica* ingests distinct pieces of living human cells, resulting in intracellular calcium elevation and eventual cell death. This process is called trogocytosis (from the Greek *trogo,* which means “to nibble”).[28]

Immunity

Innate Immunity.

Amebas encounter natural barriers in the intestine and systemic circulation after extraintestinal invasion. In the gut, innate barriers prevent potential pathogens and antigens from gaining access to the underlying epithelium, a process called *nonimmune exclusion*. Gastrointestinal tract mucins are the first line of host defense against *E. histolytica*. Binding sites of mucins have been shown to compete with binding sites of underlying epithelium, preventing attachment of pathogens to the intestinal wall.[29]

The nutritional hormone leptin has been shown to have an important role in neutrophil recruitment. Children with mutation in the leptin receptor (Q223R) were found to have increased susceptibility to amebiasis.[30] Similarly, mice with the 223R mutation had delayed clearance of ameba from bowel and diminished neutrophil recruitment to the site of infection. This suggests that leptin plays an important role in neutrophil chemotaxis.[31]

The human complement system is an important early host defense against bloodstream dissemination of *E. histolytica.* The major *E. histolytica* extracellular proteinase, a 56-kd neutral cysteine proteinase, activates complement in the fluid phase.[32]

Acquired Immunity.

Tissue invasion results in rapid development of acquired immune responses. In a prospective cohort study in Bangladesh, children with immunoglobulin A (IgA) anti-Gal/GalNAc lectin in stool on enrollment developed 64% fewer *E. histolytica* infections during the first 5 months of follow-up compared with antibody-negative children.[33] Apart from serum and secretory IgA, the dominant class of antibodies produced against *E. histolytica* appears to be IgG.[34]

In one study, higher median interferon γ (IFNγ) levels in children was associated with >50% reduction in risk for *E. histolytica* diarrhea and longer survival without *E. histolytica* diarrhea.[35] IFNγ production was lower in malnourished children, which has been associated with *E. histolytica* infections. Innate and acquired IFNγ responses were not distinguished.[35]

Epidemiology

The greatest morbidity and mortality due to *E. histolytica* occurs in developing nations, where sanitary conditions are poor, particularly in the Indian subcontinent, Africa, and Central and South America.[36] Disease is more severe in elderly, young, or malnourished individuals, individuals on immunosuppression, and pregnant women. Reports have documented the bidirectional relationship between malnutrition and morbidity associated with diarrhea.[37–45] Intestinal amebiasis occurs equally in males and females; however, 90% of amebic liver abscesses in adults (but not children) occur in males.[46–48] Recently, a molecular mechanism to explain this discrepancy was found. In a mouse model, testosterone levels were found to influence activation of natural killer T cells, with higher testosterone levels resulting in lower IFNγ produced from natural killer T cells and thus larger liver abscesses.[49]

E. histolytica and *E. dispar* infect about 500 million people worldwide. Fortunately, most people previously believed to be infected with *E. histolytica* carry *E. dispar*, which does not cause human disease.[2] With the discovery and new understanding of *E. bangladeshi* and *E. moshkovskii*, there is an expanding spectrum of *Entamoeba* that can be pathogenic in humans. The best estimate is that approximately 40 to 50 million symptomatic *E. histolytica* infections occur worldwide annually.[50] In Hue City, Vietnam, the annual incidence of amebic liver abscess was 21 cases per 100,000.[51]

Studies in Mexico demonstrated 8.4% seroprevalence. Similarly, in Fortaleza, Brazil, high rates of *E. histolytica* antibodies were detected. In Bangladesh, seroprevalence is about 50% by age 5 years.[52] Worldwide, approximately 100,000 deaths occur from amebiasis annually, making it the third leading cause of death from parasitic disease.[53,54]

Most individuals with amebiasis are infected by ingestion of food or water contaminated with feces containing cysts, but other modes of transmission, including oral anal sex and contaminated enema apparatus, have been reported.[55,56] Groups at increased risk in developed nations include immigrants from endemic areas, long-term visitors to endemic areas, people in group homes and institutions for mentally disabled, men who have sex with men (MSM), and people with AIDS.[36,57,58] Over the past few decades, there has been an increase in sexually transmitted *E. histolytica* in Australia and East Asian developed nations such as Japan, Taiwan, and Korea, concurrent with an increase in men who MSM and in people with HIV infection. In Japan, nearly 80% of amebic cases diagnosed are in MSM, and positive serology for *E. histolytica* was seen in 21% of roughly 1300 HIV patients screened.[59–62]

In the United States, amebiasis is the third most common cause of parasitic infections, with combined prevalence of *E. histolytica* and *E. dispar* estimated at 4%.[36,63] High prevalence (40% to 50%) was described in MSM in New York City and San Francisco during the late 1970s, although invasive disease seemed uncommon (likely owing to predominant species *E. dispar*).[64] A retrospective review of more than 34,000 patients with HIV infection in the US from 1990 to 1998 showed a lower incidence of 13.5 cases per 10,000 person-years.[57] Approximately 2900 cases of amebiasis were reported to the Centers for Disease Control and Prevention in 1993 and 1994. In 1993, 33% of patients reported were Hispanic, and 17% were either Asians or Pacific Islanders.[65] Since 1994, amebiasis is no longer a US nationally notifiable disease.

Clinical Manifestations

Noninvasive Intestinal Infection.

Noninvasive intestinal infection with an ameba identified morphologically as *E. histolytica* could be due to nonpathogenic *E. dispar*, although asymptomatic colonization can be seen with *E. histolytica* as well. In noninvasive infection, examination of stool samples typically reveals no occult blood or amebic trophozoites containing ingested red blood cells. In rural Mexico, a study using polymerase chain reaction (PCR) showed that *E. histolytica* caused a higher rate of asymptomatic infection than *E. dispar* (14% vs. 10%), suggesting a predominant distribution of *E. histolytica* strains of low invasive potential in that community.[66] Similarly, a study in Brazil showed that 11% of the population studied was colonized with *E. histolytica*, and 85% of study participants cleared the infection within 45 days without treatment.[67] Of individuals with asymptomatic colonization, 10% can go on to develop invasive disease within 1 year.[68]

Amebic Colitis (Intestinal Amebiasis).

Patients with *E. histolytica* colitis typically have a 1- to 3-week history of worsening diarrhea progressing to grossly bloody dysenteric stools with abdominal pain and discomfort. Children can have rectal bleeding without diarrhea.[69] Illness lasts >4 weeks in about 20% of patients. Constitutional symptoms frequently are mild. Whereas fever is present in only one third of patients, weight loss is common. Fecal leukocytes may not be present, but virtually all patients have heme-positive stools (Table 263.1; Fig. 263.3).[70–72] Patients with chronic, nondysenteric intestinal amebiasis may complain for months to years of abdominal pain, flatulence, intermittent diarrhea, mucus in stools, and weight loss. One third of patients with amebic colitis in central Virginia reported symptoms for >1 year. Amebic colitis can be confused with inflammatory bowel disease (IBD) in children, potentially leading to a fulminant course if amebic colitis is treated mistakenly with corticosteroid therapy. Amebic colitis also can also exacerbate IBD. A high index of suspicion should be maintained in children from endemic regions, travelers, and those with compromised immune systems.[73] The differential diagnosis in patients with bloody diarrhea include infectious causes *(Entamoeba, Shigella, Salmonella,* and *Campylobacter* spp., *Clostridium difficile,* enteroinvasive and enterohemorrhagic *Escherichia coli,* and *Balantidium coli)* and noninfectious diseases (IBD and gastrointestinal tract bleeding due to diverticulitis). Often the diagnosis of amebic colitis is difficult because manifestations can be insidious or chronic, bleeding can occur without diarrhea, fever is an unusual finding, a single stool examination for parasites is insensitive, histopathologic confirmation of infection in biopsy specimens can be difficult, and serologic tests have limited utility in the acute setting.

TABLE 263.1

Clinical and Epidemiologic Characteristics of Amebic Colitis

Characteristic	Percentage of Patients Affected
Symptoms >1 wk	80
Diarrhea	94–100
Dysentery	94–100
Abdominal pain	12–80
Weight loss	44
Fever >38°C	10
Heme-positive stools	100
Immigrant from or traveler to endemic area	>50
Prevalence (male/female)	50/50

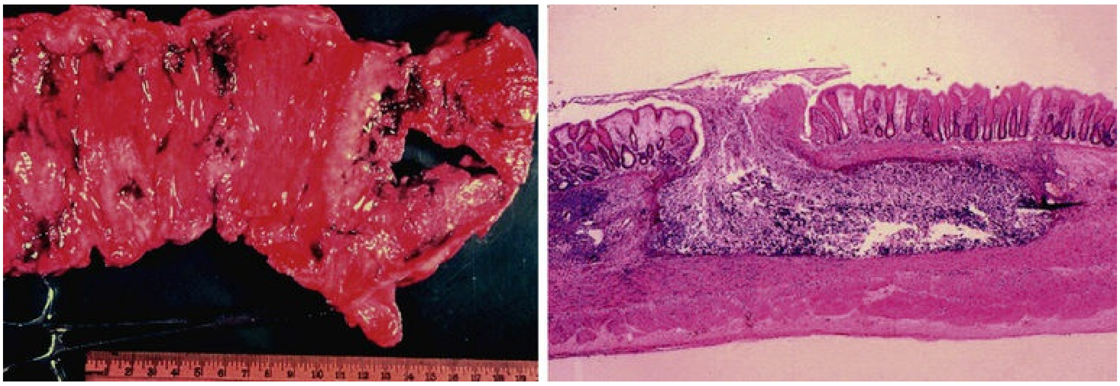

FIGURE 263.3 Ulceration in amebic colitis: (A) Gross pathology of amebic colitis showing multiple ulcers. (B) Classical flask-shaped ulcer of amebiasis, mucosal ulceration with widespread submucosal invasion. (From Stanley SL. Amoebiasis. Lancet 2003;361:1025−1034.)

Acute Fulminant or Necrotizing Colitis.

Fulminant or necrotizing amebic colitis (see Fig. 263.3) is an unusual (about 0.5% of cases) and severe complication of amebic colitis occurring more frequently in patients inappropriately treated with corticosteroid therapy; surgical intervention usually is required, and mortality exceeds 40%.[74,75] With full colonic involvement, mortality rates may be >90% in children and adults.[76] Abdominal pain, distention, and rebound tenderness are present in most patients with fulminant colitis, although frank guarding is uncommon. Indications for surgery include failure to respond to antiamebic therapy (e.g., localized abscess formation from perforation or persistence of abdominal distention and tenderness despite therapy) and toxic megacolon. Early diagnosis and surgical intervention is associated with improved prognosis. Poor prognostic indicators include prolonged duration of symptoms, invasion of trophozoites into the bowel wall, and a low peripheral white blood cell count.[76] Partial colectomy with colostomy is recommended over primary anastomosis for localized colonic disease as the friable bowel wall predisposes to incompetent anastomoses. For extensive disease, total colectomy has achieved better results.[74,75]

Ameboma.

Ameboma, a segmented mass of granulation tissue in the cecum or ascending colon, represents the hyperplastic granuloma related to amebic abscess in the bowel wall. Ameboma occurs in 0.5% to 1.5% of adults and children with intestinal amebiasis. Presentation usually is with a tender, palpable, abdominal mass. At diagnosis, amebic dysentery is present concurrently in two thirds of patients. An ameboma typically appears as single or multiple "apple core" lesions on a barium enema study, with irregular margins and distortion of the folds; the diagnosis is established with colonoscopy and biopsy. Lesions usually resolve with antiamebic therapy and do not require surgery.[70–72] In a case report of surgery performed for intussusception with a lead mass expected to be a lymphoma, an ameboma was found.[73]

Intestinal stricture occurs in the colon in <1% of patients with amebic dysentery; *E. histolytica* can be identified in the granulation tissue. Strictures usually respond to antiamebic therapy without surgical intervention.

Liver Abscess.

Amebic liver abscess (ALA) is considered one of the most common extraintestinal manifestations of amebiasis; 5% occur in children.

Even in endemic regions, ALA in neonates and in infants younger than 1 year is exceptionally rare. Adults and young children typically have fever, abdominal pain, and tender hepatomegaly; neonates tend to have fulminant onset of symptoms that mimic sepsis.[49,77] Infants with ALA are more likely than adults to have colitis concurrently despite negative stool examinations for ova and parasites.[49] In adults (but not in children), ALA occurs predominantly in males and can manifest as an acute or chronic illness. In one study, 85% of patients who had symptoms for <10 days had fever and abdominal pain. Chronic illness (2−12 weeks of symptoms) is more common and manifests with hepatomegaly and weight loss. Hepatic tenderness is common, but peritoneal signs and jaundice are unusual. Eighty percent of abscesses are singular and found in right lobe of liver, and thus pain is typically in right upper quadrant, although it can be located in the epigastric region or left upper quadrant, or referred to the right shoulder. Atelectasis, elevation of the right hemidiaphragm, and serous pleural effusion occur in 75% of patients with ALA and alone do not represent primary thoracic disease (Table 263.2).[47–49,71,78–82]

TABLE 263.2

Clinical and Epidemiologic Characteristics of Amebic Liver Abscess

Characteristic	Percentage of Patients Affected
Symptoms >4 wk	21–51
Fever	85–90
Weight loss	33–50
Diarrhea	20–33
Cough	10–30
Jaundice	6–10
Abdominal tenderness	84–90
Hepatomegaly	30–50
Immigrant from or traveler to endemic area	>50
Prevalence (male/female)	50/50 in children; 90/10 in adults

Pleuropulmonary amebiasis is the most common complication of ALA and occurs in up to 35% of patients. Other, less common extraintestinal manifestations include empyema and pericardial effusions resulting from direct extension from a hepatic abscess and producing fluid that is often described as looking like anchovy paste on thoracentesis. Amebic abscess of the brain usually is detected at autopsy. Cutaneous amebiasis has been described perianally from an enterocutaneous fistula or as an amebic ulceration of the penis or cervix. Genitourinary amebiasis and splenic abscesses also can occur secondary to hematogenous spread of amebic trophozoites.[71,78,83,84]

Growth and Cognitive Complications.

Diarrheal illness significantly influences morbidity of children in developing nations. Among 298 Bangladeshi children aged 2 to 5 years observed prospectively for 8.2 years, *E. histolytica* infection occurred at least once in 90%, and repeat infection occurred in 68%. *E. histolytica* infection had a significant effect on growth, and stunting was more frequent with *E. histolytica* infection compared with cryptosporidia, enterotoxigenic *E. coli*, and *Giardia*-associated diarrheal illness. Moreover, the relative risk for diarrheal illness also was higher in malnourished children.[85,86] Children with *E. histolytica* dysentery, compared with other etiologies, had lower Wechsler Abbreviated Scale of Intelligence scores after adjusting for environmental factors.[87]

Laboratory Findings and Diagnosis

Microscopy-based methods are not capable of differentiating pathogenic *E. histolytica* from *E. dispar* and *E. moshkovskii;* therefore microscopy should not be used solely to make the diagnosis of amebiasis. The possible exception is visualization of trophozoites containing ingested red blood cells, which does favor *E. histolytica* infection over *E. dispar* colonization.[88–90]

Among several antigen detection assays for diagnosis of human amebiasis, a commercially available enzyme immunoassay (EIA) (TechLab *E. histolytica* II test, TechLab, Blacksburg, VA) is the best available test for specific diagnosis in clinical settings. By detecting the Gal/GalNAc adherence lectin of *E. histolytica* on stool sample specimen, it can distinguish *E. histolytica* from *E. dispar* and *E. moshkovskii*. The sensitivity and specificity of this assay on stool in dysentery disease is >96%.[91] Rapid point-of-care antigen tests are also available for use in developing nations with similar sensitivity and specificity. One such assay, the *E. histolytica* Quik Chek assay (TechLab), was found to have a sensitivity of 98% and specificity of

100% when studied in populations in South Africa and Bangladesh.[92]

Colonoscopy can aid in diagnosis and remains important to evaluate other potential causes of disease. Of note, cathartic or enema preparation of the patient can interfere with visualization of trophozoites. The colonic mucosa appears hemorrhagic in patients with amebic colitis, with discrete, shallow ulcers with raised edges. Wet preparations aspirated or scraped from the ulcer base should be examined for trophozoites. Biopsy should be confined to the ulcer margins; special stains, such as periodic acid–Schiff stain, facilitate identification of *E. histolytica*.[93–95]

Serologic tests for antiamebic antibodies are an important adjunct to diagnosis. These tests can be falsely negative early in the course of disease but generally become positive within 7 to 10 days of illness.[46] More than 90% of patients develop antibodies to *E. histolytica,* which can be detected by indirect hemagglutination (IHA), EIA, counter-immunoelectrophoresis, or agar gel diffusion. IHA is positive in 88% of patients with amebic dysentery, in 70% to 80% of patients with ALA, and in only 5% of the general population in developed nations. Because antibody persists for years after infection, presence cannot be used to distinguish current from prior infection. In endemic areas, 5% to 30% of the population may have antibodies by IHA; thus serology is not as helpful for diagnosis in this population.[96] An EIA for *E. histolytica* galactose inhibitable lectin antigen and salivary IgG antibodies to a recombinant cysteine-rich lectin-derived protein (LC3) is more sensitive and specific for acute amebic colitis compared with EIA for serum anti-LC3 IgG antibodies.[97] Other serologic methods, including dot-EIA and rapid dipstick assay, have been used for diagnosis of different forms of human disease and also can be used for the diagnosis of amebiasis.[98]

Molecular methods have been used to diagnose human amebiasis and to differentiate pathogenic *E. histolytica* from *E. dispar, E. moshkovskii,* and newly discovered *E. bangladeshi.* In stool samples, PCR is more sensitive than the best currently available EIA kit for detection of *E. histolytica* antigens.[99] PCR testing for short tandem of transfer RNA–linked gene repeats also can separate genotypes and has been used for virulence and epidemiologic studies.[100] Real-time PCR assay has been used to diagnose intestinal infection and liver abscess in Bangladeshi patients.[101] The sensitivity of real-time PCR was higher than both traditional PCR and the antigen detection test.

Diagnosis of ALA is made by imaging findings plus serologic testing as stool tests and abscess aspirate frequently are unrevealing.[102] *E. histolytica* antibody can be detected in serum with IHA assay in 70% to 80% of cases, and, before treatment, the TechLab *E. histolytica* II EIA can detect amebic antigen in serum of approximately 96% of patients with ALA.[91] Ultrasonography, computed tomography, and magnetic resonance imaging studies of the liver are equally sensitive for detecting ALA (Fig. 263.4). However, none differentiates amebic from pyogenic abscess.[103–106] Six months after therapy, resolution of liver lesions by ultrasonography occurs only in one third to two thirds of cases, and thus follow-up studies are not helpful in evaluating response to treatment.

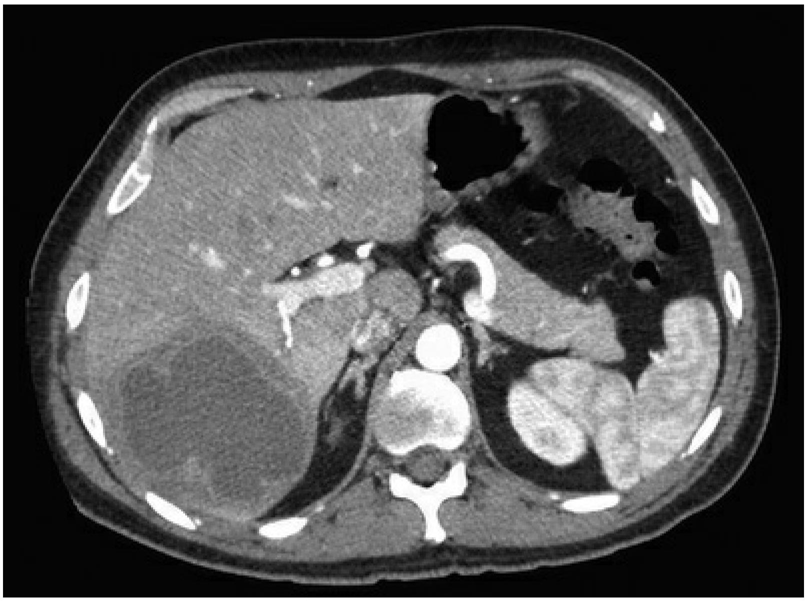

FIGURE 263.4 Computed tomographic image of hepatic amebic abscess.

Treatment

Asymptomatic infection with *E. histolytica* should be treated with an intestinal luminal agent alone because of concern for progression to active disease as well as public health consequence (Box 263.1).

Drugs effective against luminal infection are paromomycin, iodoquinol, and diloxanide furoate (which is not readily available in the US).[107–109] Metronidazole should not be used as sole therapy to treat asymptomatic people because this drug often fails to eradicate organisms from the lumen.

Box 263.1

Treatment of *Entamoeba histolytica* Infections

Asymptomatic Amebiasis

Treat with a luminal agent:

Paromomycin	25–35 mg/kg/day by mouth in 3 divided doses for 7 days
Diloxanide furoate	20 mg/kg/day by mouth (maximum, 1.5 g) in 3 divided doses for 10 days
Iodoquinol	30–40 mg/kg/day (maximum, 2 g) by mouth in 3 divided doses for 20 days

Amebic Colitis/Amebic Liver Abscess

Treat with one of the following *plus* a luminal agent:

Metronidazole	35–50 mg/kg/day (maximum, 750 mg) by mouth in 3 divided doses for 10 days
Tinidazole (≥3 years old)	50 mg/kg/day (maximum, 2 g) by mouth once daily for 5 days

Invasive amebiasis should be treated with metronidazole or tinidazole, plus a luminal agent. Metronidazole does not cure intestinal infection in up to 50% of patients with invasive amebiasis unless therapy is given for a minimum of 10 days. Shorter courses of metronidazole therapy are associated with relapse of invasive infection months later.[110,111] Tinidazole appears to be as effective as metronidazole and better tolerated.[112] If children cannot tolerate pills, the pill can be crushed and made into a suspension.[113] Auranofin, an oral gold-containing compound used to treat rheumatoid arthritis in adults, was shown to have activity against *E. histolytica* in vitro and in vivo. It is currently in clinical trials for treatment of amebiasis in adults.[114] After treatment is complete, repeated stool EIA studies should be performed to document eradication.

Fever from ALA is expected to be reduced after 3 to 4 days of treatment with metronidazole. Chloroquine, dehydroemetine, and percutaneous drainage of the liver abscess each has been used successfully in addition to metronidazole for the unusual case not responding to metronidazole alone.[109–111,115,116] Percutaneous drainage is not required for most ALAs and does not speed recovery.[115] Definitive indications for ALA aspiration are controversial, but in general consideration should be given in patients where diagnosis is uncertain (if concern for pyogenic abscess or superinfection), those who have failed to respond to metronidazole therapy after 4 days of treatment, individuals with large left lobe abscesses (because of risk for rupture into pericardium), and severely ill patients when rupture seems imminent.[55]

Prevention

Prevention of *E. histolytica* requires disruption of the fecal-oral spread of amebic cysts. People should be advised of the risk associated with traveling to endemic areas, safeguards to prevent ingesting colonic organisms, and the risk involved in sexual practices that include oral-anal contact. Because humans and primates are the only known reservoirs of *E. histolytica,* a successful vaccine potentially could eliminate amebiasis.[2,117]

Key Points

Epidemiology, Clinical Features, and Diagnosis of *Entamoeba histolytica* Infection

Microbiology and Histopathology

- Pseudopod-forming, nonflagellated protozoan parasite
- Life cycle involves a quadrinucleate cyst and invasive trophozoite.
- Flask-shaped colonic ulcers can be found in invasive disease.

Epidemiology

- Approximately 40 to 50 million symptomatic infections and up to 100,000 deaths occur annually worldwide.

- Amebiasis is the third most common cause of parasitic death worldwide.

- Increased risk for severity in elderly, young, or malnourished individuals, immunosuppressed patients, and pregnant women

- *Entamoeba moshkovskii* and *Entamoeba bangladeshi,* which appear morphologically similar to *Entamoeba histolytica,* also can cause symptomatic disease with diarrhea.

Clinical Features

- Asymptomatic colonization

- Intestinal amebiasis and associated complications

- Amebic colitis

- Acute fulminant or necrotizing colitis

- Ameboma

- Liver abscess

- Growth and cognitive complications

- Other uncommon manifestations include pleuropulmonary disease, empyema and pericardial effusions, amebic brain abscess, and cutaneous amebiasis.

Diagnosis

- Microscopic identification of the parasite in stool, liver abscess, or biopsy is not sensitive.

- Stool antigen detection is highly sensitive and specific (>96%).

- Real-time polymerase chain reaction assay is a highly sensitive, research-based test for the diagnosis of intestinal and liver infections.

- Serum antibody testing before the institution of treatment can detect infection in 70% to 96% depending on assay used.

- Colonoscopy is an important tool to evaluate for other diseases. Wet preparation of material from the ulcer base and special stains such as periodic acid–Schiff stain should be performed for diagnosis.

- Imaging with ultrasound, computed tomography, and magnetic resonance imaging cannot differentiate pyogenic from amebic abscesses and are equally sensitive for detecting amebic liver abscess.

Treatment

- Amebic colitis or amebic liver abscesses should be treated with metronidazole or tinidazole plus a luminal agent.

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Other *Entamoeba*, Amebas, and Intestinal Flagellates

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In addition to *Entamoeba histolytica*, other pseudopod-forming nonflagellated protozoan parasites that infect the human intestinal tract include *E. dispar, E. hartmanni, E. polecki, E. chattoni, E. coli, E. moshkovskii, E. gingivalis,* and *E. bangladeshi. E. invadens* does not infect humans but is of great value as a laboratory model in human research of amebiasis. The highly virulent species *E. histolytica* is distinguished from the other, mostly nonpathogenic, intestinal pseudopod-forming protozoa by morphologic appearances of the cyst and trophozoite forms or by differences in antigens or DNA sequences (see Chapter 263).

Entamoeba dispar

E. dispar is a nonpathogenic intestinal commensal protozoan that is indistinguishable morphologically from *E. histolytica* on light microscopy. About 90% of the infections previously attributed to *E. histolytica* actually were due to *E. dispar*. Symptomatic *E. dispar* infection has not been demonstrated in humans.[1] The prevalence of amebic intestinal colonization in some male homosexual populations is as high as 33%, and *E. dispar* commonly is found in stool specimens from patients with acquired immunodeficiency syndrome.[2] A stool antigen detection test that differentiates nonpathogenic *E. dispar* from pathogenic *E. histolytica* is available commercially (TechLab E. histolytica II test, TechLab, Blacksburg, VA).[3]

Entamoeba moshkovskii

E. moshkovskii is morphologically identical to *E. histolytica;* however, improved diagnostic techniques have allowed for its identification in human specimens.[4] Although earlier studies of *E. moshkovskii* failed to show an association with clinical illness, studies from Asia and Australia suggest a potential role in symptomatic gastrointestinal tract illness and disease in a mouse model of colitis.[5–8] Future studies will be important in defining the pathogenic potential of this *Entamoeba* spp.

Entamoeba bangladeshi

E. bangladeshi is morphologically identical to *E. histolytica.* It was first described when polymerase chain reaction testing was performed on both diarrheal and surveillance samples from patients in Bangladesh and a novel sequence was discovered.[9] Further investigation is required to determine the clinical significance of *E. bangladeshi.*

Entamoeba polecki

E. polecki is a common parasite of pigs, wild boars, and monkeys in the tropics and subtropics.[10] Humans acquire infections accidentally, and whether this organism can produce disease in humans is unknown. In Papua New Guinea, where pigs are the main domestic animals, up to 30% of people can be colonized.[11] The trophozoite stage of *E. polecki* has a frothy cytoplasm and resembles that of *E. histolytica;* the cyst, however, contains a single nucleus and may contain inclusion bodies and abundant fragmented chromatoidal bars. *E. polecki* has been treated successfully with metronidazole, ornidazole, and furamide, with metronidazole given in a regimen similar to that used for *E. histolytica* infection.[12]

Entamoeba chattoni

E. chattoni is a parasite of nonhuman primates, although accidental human infections have been reported on rare occasions, mainly related to contact with monkeys.[13] There is no evidence that this species produces clinical disease in humans; however, its uninucleated cysts have been confused with cysts of *E. histolytica*.[14]

Entamoeba invadens

E. invadens is a pathogenic species in snakes, producing symptoms similar to human amebiasis.[15] *E. invadens* is not important medically but has been used extensively as a laboratory model in the study of *E. histolytica* encystation.[16,17]

Entamoeba gingivalis

E. gingivalis is found in the mouth and is associated with poor dental hygiene.[18] In patients infected with human immunodeficiency virus, *E. gingivalis* infection is associated with periodontal disease, although a causal relationship has not been established.[19,20] *E. gingivalis* has no cyst form and can be confused with *E. histolytica* when sputum is examined in patients with suspected pulmonary amebic or pyogenic abscess.[19] On rare occasions, *E. gingivalis* has been recovered from other sites, including neck nodules and the uterus.[21–23] Treatment with metronidazole has been reported to be effective.[20]

Entamoeba hartmanni

E. hartmanni is a nonpathogenic organism also found in the colon. This organism is identical morphologically to *E. histolytica*, except for its smaller size (trophozoites <12 μm and cysts <10 μm in diameter).[19]

Entamoeba coli

E. coli is nonpathogenic and the most prevalent human ameba. This organism can be distinguished from *E. histolytica* because of the larger cyst (>15 µm in diameter), the presence of 5 to 8 nuclei, and an eccentric karyosome. The presence of this organism in stool is not an indication for treatment but is a useful indicator of fecal-oral exposure.[19]

Dientamoeba fragilis

D. fragilis trophozoites are binucleated and variable in size (5 to 12 µm in diameter). The prevalence of *D. fragilis* is 0.4% to 42% worldwide[24] and is up to 50% in groups at high risk for fecal-oral transmission, including children, people in institutional settings, and people in settings with inadequate hygiene.[25] Previously isolated only from animal models, cyst and precystic forms of *D. fragilis* have now been isolated from human stool specimens. Cysts have a distinct wall; they are binucleate with a large central karyosome. Precysts range in size from 4 to 5 µm and contain darkly staining cytoplasm.[26]

The mode of transmission for *D. fragilis* remains unclear. Several studies have shown an association of concurrent pinworm *Enterobius vermicularis* with *D. fragilis* parasitosis; others have not.[25,27–30] Symptoms have been observed in 20% to 58% of people infected with *D. fragilis*[25] and can include abdominal pain, loose stools, nausea, anorexia, vomiting, bloating, flatulence, weight loss, and fever.[24,25] Chronic symptoms have been reported, with up to 32% of patients having persistent diarrhea.[29] There have been reports of associations of *D. fragilis* with irritable bowel syndrome, appendicitis, and marked eosinophilia.[31–33]

The diagnosis of *D. fragilis* is based on microscopic examination of stool. Multiple fresh samples should be examined with a permanent stain such as hematoxylin, trichrome, or celestine blue B. Molecular methods also have been used to identify the parasite directly in stool.[4,34] Treatment is recommended when significant symptoms occur. Iodoquinol, metronidazole, tetracycline, paromomycin, and secnidazole have been effective in eradicating the parasite in the limited number of patients studied.[30,35–38]

However, a recent randomized control trial showed that a course of metronidazole was no better than placebo in improving symptoms.[39]

Chilomastix mesnili

The most prevalent nonpathogenic flagellate, *C. mesnili* can be distinguished from *Giardia intestinalis* on the basis of its lemon-shaped cyst and a single nucleus. Some identical forms have been found in other animals, but it is not clear that these animals have any role in the epidemiology of human infections.[10]

Iodamoeba butschlii

I. bütschlii, a nonpathogenic commensal of the colon, can be distinguished from *E. histolytica* in trophozoite form because of its smaller size and sluggish motility, and in the cyst form because of its characteristic large glycogen vacuole, which stains with iodine on a wet preparation.[19]

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Giardia intestinalis (Giardiasis)

Matthew Washam, Robert W. Frenck Jr.

Giardia intestinalis is a flagellated protozoan that infects the duodenum and upper small intestine. *Giardia* is the most commonly identified enteric parasite in the United States and Canada. Infection can be asymptomatic or associated with a variety of intestinal manifestations. Factors contributing to this variation include genotype of the *Giardia* strain, the number of cysts ingested, the age of the host, and the status of the host's immune system. Diagnosis is made by detection of cysts or trophozoites in stool specimens, duodenal fluid, or small bowel biopsy or by detection of *Giardia* antigens in stool specimens. Several drugs are effective in treating people infected with *Giardia*. Prevention occurs by use of appropriate hand hygiene and prevention of ingestion of contaminated food and water, including contaminated recreational water.

Pathogen and Pathogenesis

Giardia, an intestinal flagellate in the division Protozoa, is distributed globally and has been detected in nearly all classes of vertebrates, including domestic animals and wildlife. Six *Giardia* species are currently recognized, and *Giardia intestinalis* (also known as *Giardia duodenalis* and *Giardia lamblia*) is the only species found in humans.[1] Molecular typing of *G. intestinalis* strains reveal that human strains are placed in two of eight specialized genetic groups referred to as *assemblages* (A to H), which are species specific.[1–5] Assemblages A and B infect primarily humans and primates, although other mammalian hosts can be infected as well. Assemblages C through H do not appear to infect humans. These findings suggest that *G. intestinalis* does not have as high a level of potential transmission as a zoonotic disease as thought previously.[4–7]

Giardia has two major stages in its life cycle: the trophozoite is the replicative stage within the host, and the cyst is the relatively inert infectious stage allowing for prolonged survival to a variety of environmental stimuli.[8,9] After ingestion, excystation of *Giardia* cysts occurs in the proximal small intestine, releasing trophozoites that undergo repeated mitotic division and form environmentally resistant cysts in response to bile salts and other conditions.[10] Trophozoites are 10 to 20 μm in length and 5 to 15 μm in width, with a convex dorsal surface, two nuclei, four symmetrically placed flagella originating at the anterior pole of the nucleus, and a ventrally located adhesive disk (Fig. 265.1). The disk is composed of microtubules, microribbons, and cross-bridges consisting of proteins referred to as *giardins* and is responsible for attachment to the intestinal epithelium and subsequent colonization.[11] Rotavirus coinfection may act synergistically to enhance pathogenicity by allowing for more successful attachment.[12,13] Trophozoites divide by longitudinal binary fission, with a doubling time of 6 to 12 hours in vitro. *Giardia* undergoes frequent antigenic variations during infection of humans and animals during encystations and during culture in vitro.[14–16]

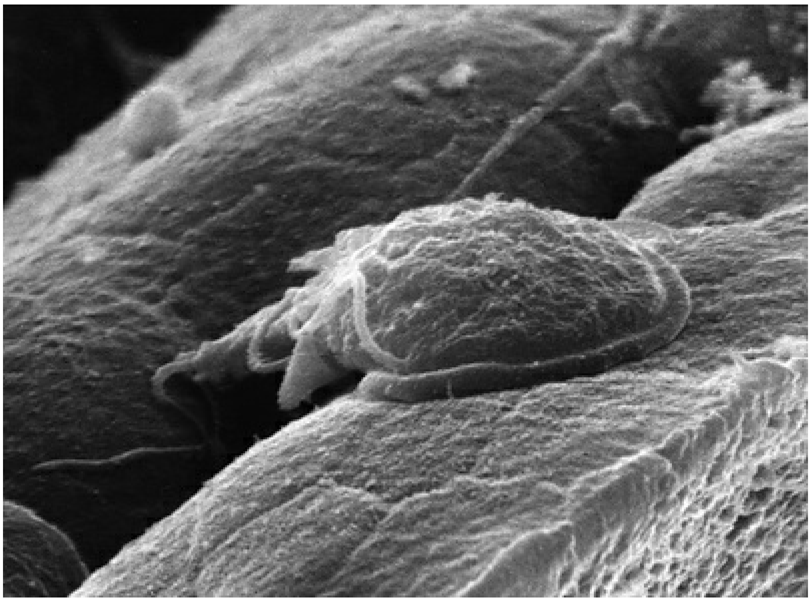

FIGURE 265.1 Scanning electron micrograph of a *Giardia* intestinalis trophozoite attached to the microvillous border of the small intestine (original magnification, ×1680). (Courtesy of Stanley Erlandsen, MD.)

As detached trophozoites pass through the intestinal tract, they encyst to form smooth, oval-shaped, thin-walled cysts that measure 8 to 12 μm in length and 8 to 10 μm in width and are passed in feces.[1] In patients with watery diarrhea and rapid transit time, trophozoites may be found in stool specimens but are not stable once passed. After ingestion of *G. intestinalis* cysts, an incubation period of 3 to 25 days (median, 7–10 days) ensues before onset of symptoms.

The pathogenesis of diarrhea in giardiasis is thought to be related to several factors, including (1) the number of organisms ingested, (2) the specific infecting strain, (3) nonantibody protective factors in the gastrointestinal tract, and (4) the immune response of the host.[17]

Studies in adults show that ingestion of as few as 10 to 100 fecally derived cysts is sufficient to initiate infection, and studies in children document person-to-person transmission in childcare centers.[18] *Giardia* cysts are infectious immediately on being excreted in feces and remain viable for 3 months in water at 4°C.[5,19] Freezing decreases infectivity, whereas heating, drying, and seawater appear to eliminate the ability of the organism to infect.[19–21] The exact mechanisms used by *Giardia* to cause diarrhea have not been fully elucidated.[22,23] Morphologic damage to intestinal epithelial cells and their brush borders can occur after colonization, with the degree of mucosal abnormality correlating with severity of diarrhea.[16,24] Varying degrees of villous atrophy have been observed in intestinal biopsy specimens from people with giardiasis, with most having normal or relatively mild villus shortening.[25,26] This microvilli disorganization may explain some of the physiologic changes with giardiasis. Disaccharidase deficiencies, usually of lactase, in the microvillous membrane have been documented in humans and in the mouse model of *G. muris* infection.[27,28] Protein, fat-soluble vitamins, and D-xylose malabsorption also are associated with *Giardia* infection in humans.[29,30] Decreased intestinal absorption of oral antimicrobial agents can occur and lead to treatment failure of other infections.[31] Simultaneous colonization of the small intestine with *Giardia* and Enterobacteriaceae may contribute to malabsorption by deconjugation of bile salts in some patients.[32] Production of enterotoxin has not been demonstrated.

Relatively little is known about protective responses in human giardiasis. Both B and T lymphocytes appear to play a role in protective immunity, as shown by the predisposition to giardiasis in patients with common variable immunodeficiency and in children with X-linked agammaglobulinemia.[10,33–36] Anti-*Giardia* immunoglobulin G (IgG) can be found in >80% of patients during symptomatic infection.[17,37,38] IgG antibody tends to persist, thus limiting usefulness in distinguishing current from past infection in individual patients.[38] An association between the presence of IgG anti-*Giardia* and protective immunity is not clear. Serum IgM antibodies increase early in infection and decrease rapidly after 2 to 3 weeks.[38,39] Serum IgA antibodies can be absent in symptomatic people; measurement has limited diagnostic value. Secretory IgA (sIgA) is presumed to be important in host protection.[17] Human milk is protective against giardiasis in infants; this protection correlates with the amount of specific sIgA anti-*Giardia*.[40–43] Human milk is lethal to *Giardia* trophozoites through action of free fatty acids, which are liberated from milk triglycerides by bile salt −stimulated lipase.[44–46] Long-term CD4 T-lymphocyte−driven cellular immunity may occur variably after *Giardia* infection, with cross-reactivity between assemblages A and B.[47]

Epidemiology

Giardiasis occurs worldwide and is the most commonly identified human intestinal parasite in the US and Canada.[48–53] Giardiasis has been a nationally notifiable gastrointestinal tract illness in the US since 2002. Reporting of giardiasis occurs in 44 states (exclusions are Tennessee, Oklahoma, Kentucky, Mississippi, North Carolina, and Texas).[48,50] Age-specific prevalence rates are highest in children 1 to 9 years of age, followed by people 35 to 49 years of age. Giardiasis incidence rates have remained relatively stable in the US since 2002 at 7.2 to 8.7 cases per 100,000 population, with 19,927 cases reported in 2010 (7.6 cases per 100,000 population).[50,51] There are regional variations in incidence with the Midwest and Northwest reporting the highest rates of giardiasis.[50] Most cases were reported between May and September (Fig. 265.2) and were associated with the summer recreational water season and with camping. Males accounted for approximately 56% of reported cases from 2006 to 2010. Although reporting of giardiasis is required by 44 states, because diarrheal diseases often are underreported, these rates underestimate the disease burden attributable to *Giardia*.

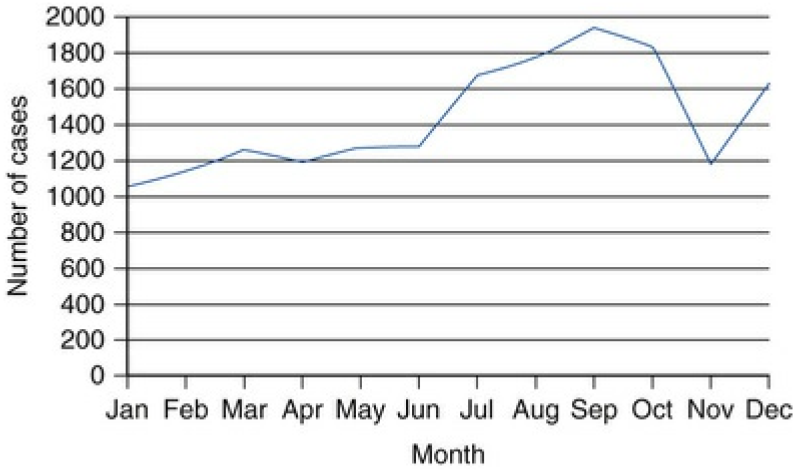

FIGURE 265.2 Number of reported giardiasis cases occurring by month, National Notifiable Disease Surveillance System, United States, 2010 to 2012.[51-53]

Transmission of *G. intestinalis* is more common in certain groups, including (1) children and employees in childcare centers, (2) travelers to disease-endemic areas of the world, (3) close contacts of infected people, (4) people who swallow contaminated drinking water or recreational water, (5) people exposed to infected domestic and wild animals (dogs, cats, cattle, deer, and beaver), (6) people who take part in outdoor activities (e.g., camping or backpacking) who consume unfiltered or untreated water, and (7) men who have sex with men.[48] The relative contribution of person-to-person, animal-to-person, and foodborne and waterborne transmission to sporadic human giardiasis is not well understood.[54–65] Ingestion of surface water treated by faulty or inadequate purification systems has been a commonality of waterborne outbreaks. In addition, drinking untreated mountain stream water is a major risk for hikers. From 2009 to 2010, *Giardia* was identified as the causal agent of 1 (1%) of 81 reported recreational water associated outbreaks and of 5 (11%) of 45 reported drinking water and other nonrecreational water source–associated outbreaks of gastroenteritis in the US.[66,67] Although *Giardia* is one of the most frequently identified parasites associated with waterborne disease outbreaks in the US, foodborne outbreaks of giardiasis are reported rarely.[56,59,63,68,69] During 1998 to 2010, only 18 (0.2%) of 9020 of foodborne outbreaks with a known etiology were associated with *Giardia*.[70,71] Because the infectious dose in adults is only 10 to 100 cysts,[18] person-to-person spread also occurs, particularly in areas of low hygienic standards, crowding, and frequent fecal-oral contact. Person-to-person spread occurs frequently in childcare centers and in families of children with diarrhea.[72–74] As with other enteropathogens, individual susceptibility, lack of toilet training, crowding, and fecal contamination of the environment all contribute to transmission of *Giardia* in childcare centers.[74]

Clinical Manifestations

After excystation and colonization, a broad spectrum of clinical manifestations can occur: (1) asymptomatic excretion of organisms, (2) acute infectious diarrhea, or (3) chronic diarrhea with failure to thrive or persistent gastrointestinal tract symptoms (Table 265.1). Symptoms vary by age, with symptomatic infections more frequent in children than in adults.[75,76] Short-lasting, acute diarrheal disease with or without low-grade fever, nausea, and anorexia is usual; an intermittent or more protracted course occurs occasionally and is characterized by diarrhea, abdominal cramps, bloating, malaise, flatulence, nausea, anorexia, and weight loss.[45,54,75,76] Stools can be profuse and watery initially and later become greasy, foul smelling, and buoyant. Blood, mucus, and fecal leukocytes are absent. Varying degrees of malabsorption can occur, and abnormal stool patterns can alternate with periods of constipation and normal bowel movements. Giardiasis should be considered in any patient with a history of contact with an index case or a young child who attends a childcare center, has traveled recently to an endemic area, or has gastrointestinal tract symptoms, including persistent or intermittent diarrhea and constipation, malabsorption, crampy abdominal pain, abdominal bloating, unexplained gastrointestinal tract symptoms, failure to thrive, or weight loss. Extraintestinal involvement is unusual, but trophozoites occasionally migrate into bile or pancreatic ducts. Infrequently associated conditions with giardiasis include reactive arthritis, urticaria, and retinal changes.[77–80]

TABLE 265.1

Clinical Symptoms of Giardiasis

Symptom	Percent Range
Diarrhea	64–100
Malaise, weakness	72–97
Abdominal distention	42–97
Flatulence	35–97
Abdominal cramps	44–81
Nausea	14–79
Foul-smelling, greasy stools	15–79
Anorexia	41–73
Weight loss	53–73
Vomiting	14–35
Fever	0–28
Constipation	0–17

Data from references 54, 75, and 76.

The asymptomatic carrier rate of *G. intestinalis* is estimated to be 3% to 7% in the US and as high as 20% in southern regions. In prevalence studies of children younger than 36 months enrolled in childcare centers, *Giardia* cysts have been found in 21% and 26% of asymptomatic children.[81,82] Longitudinal studies have shown that asymptomatic infections are well tolerated.[81,83] Thus neither testing of case contacts nor treatment of asymptomatically infected people is indicated routinely.

Humoral immunodeficiencies, including common variable hypogammaglobulinemia and X-linked agammaglobulinemia, predispose humans to chronic symptomatic giardiasis.[10,34–36] People with sIgA deficiency appear to have an increased risk for *Giardia* infection.[84,85] Children with severe T-lymphocyte deficiencies from thymic dysplasia (DiGeorge syndrome) and patients with acquired immunodeficiency syndrome with a low $CD4^+$ T-lymphocyte count do not have persistent or severe diarrheal episodes from *Giardia.*[17] People with cystic fibrosis have a higher incidence of *Giardia* infection, probably as a result of local factors such as an increased amount of mucus, which may protect the organism in the duodenum.[86]

Diagnosis

A definitive diagnosis is established by detection of *Giardia* trophozoites or cysts in stool specimens, duodenal fluid, or small bowel tissue by microscopic examination using staining methods such as trichrome or direct fluorescent antibody (DFA) assays; by detecting soluble stool antigens using enzyme immunoassays (EIA); or by using molecular techniques including polymerase chain reaction (PCR).[87–90] The traditional method used was identification of trophozoites and cysts on direct smears or concentrated specimens of stool. Identification of *Giardia* in the stool can be difficult because of intermittent excretion of cysts and three stool samples collected on separate days increases sensitivity.[91] Trophozoites are fragile and are more likely to be present in unformed stool as a result of rapid intestinal transit time. Medications, including antimicrobial agents, antacids, antidiarrheal compounds, and certain enema and laxative preparations, can interfere with identification of *Giardia* by altering morphology or by causing a temporary disappearance of parasites from stool specimens. Such compounds should be withheld for 48 to 72 hours before collection of stool for identification of *Giardia.* Contrast material, such as barium used for imaging studies, also masks the presence of parasites, and stools should be examined before performing tests with these materials.

Giardia detection is improved through use of antigen testing and molecular techniques. Antigens shared by trophozoites and cysts excreted in stool specimens include the 65-kd antigen used in commercial diagnostic assays.[87,88,92,93] DFA testing is a sensitive and specific method and is considered the gold standard by many laboratories.[94–102] Commercially available rapid immunochromatogenic cartridge assays and EIAs are alternative antigen-based tests that have variable sensitivity and that can be performed rapidly in laboratories without access to fluorescent microscopy.[91] Molecular testing with PCR offers improved sensitivity over microscopy and can be used for genotype differentiation.[90]

When giardiasis is suspected and stool specimens are negative, the string test, duodenal aspiration, or biopsy can be performed.[96] In a fresh specimen, trophozoites usually can be visualized on direct wet mount. Duodenal biopsy is the optimal method for diagnosis. The biopsy sample can be used to make touch preparations for identifying *Giardia* in tissue sections and for histologic examination, and to identify abnormalities not associated with *Giardia*. Small intestinal biopsy should be considered in patients with characteristic clinical symptoms, negative stool and duodenal fluid specimens, and one of the following: abnormal radiographic findings (such as edema and segmentation in the small intestine), abnormal lactose tolerance test, absent sIgA, hypogammaglobulinemia, or achlorhydria.

Specific antibodies to *Giardia* have been detected and quantified by immunodiffusion, hemagglutination, immunofluorescence, and EIA. Although not typically used in routine diagnosis, serology may serve as a useful indicator of levels of infection within a community.[103] Radiographic studies of the small intestine can show nonspecific findings such as irregular thickening of mucosal folds. The peripheral blood leukocyte count usually is normal; giardiasis is not associated with eosinophilia.

Treatment

Children with acute or chronic diarrhea with failure to thrive, malabsorption, or other gastrointestinal tract symptoms should be treated with an antiprotozoal agent if *Giardia* is identified in stool or a duodenal specimen. Several drugs are available in the US for treatment of giardiasis (Table 265.2).[104–113] Tinidazole, nitazoxanide, and metronidazole are the drugs of choice.[105] Tinidazole and metronidazole are members of the nitroimidazole family. Tinidazole, which is used as single-dose therapy, was approved by the US Food and Drug Administration (FDA) in 2004 for adults and children 3 years and older for treatment of giardiasis.[106–110] Nitazoxanide was approved by FDA in 2003 for use in children with giardiasis and cryptosporidiosis, and more recently for giardiasis treatment in adults.[104–106,112,113] Quinacrine and furazolidone are not available from any US manufacturer, although the drugs can be obtained from several US compounding pharmacies. Paromomycin, a luminally active aminoglycoside that is not absorbed, is less effective than other agents but can be used for treatment of pregnant women.[108] Albendazole is effective against many helminths, making it useful for treatment when multiple intestinal parasites are identified or suspected.[104,105]

TABLE 265.2

Oral Antimicrobial Therapy for Giardiasis

Antimicrobial Agent[a]	Pediatric Dose	Adult Dose
Albendazole (Albenza)	10 mg/kg once daily for 5 days (max., 400 mg/day)	400 mg once daily for 5 days
Furazolidone (Furoxone)	6 mg/kg/day divided into 3–4 doses for 7 to 10 days	100 mg 4 times a day for 7 to 10 days
Metronidazole (Flagyl)	15 mg/kg/day divided into 3 doses for 5 days	250 mg 3 times a day for 5–7 days
Nitazoxanide (Alinia)	12 through 47 months: 200 mg/day divided into 2 doses with food for 3 days 4 through 11 years: 400 mg/day divided into 2 doses with food for 3 days	500 mg twice daily with food for 3 days
Paromomycin[b]	Not recommended	500 mg 3 times a day for 7 days
Quinacrine[c] **(Atabrine)**	6 mg/kg/day divided into 3 doses for 5 days (max., 300 mg/day)	100 mg 3 times a day for 5 days
Tinidazole (Tindamax)	≥3 years of age, 50 mg/kg as a single dose (max., 2 g) with food	2 g as a single dose with food

[a] For refractory cases, metronidazole and quinacrine for 14 days.

[b] Not absorbed; may be useful for treatment of giardiasis in pregnancy.

[c] Not available commercially but can be compounded (contact Professional Compounding Centers of America 800-331-2498 or www.pccarx.com).

A review of comparative trials on treatment of giardiasis reported that cure rates for patients treated with metronidazole (201 of 219, 92%) were higher than for patients treated with furazolidone (126 of 150, 84%; $P < 0.001$).[114] Approximately 7% of metronidazole-treated patients and 10% of furazolidone-treated patients had side effects that were adverse enough to report. A meta-analysis of 31 publications on treatment of giardiasis also showed that metronidazole administered for more than 3 days appears to achieve a better parasitologic cure than do other long-term treatment regimens.[107] Single-dose tinidazole was as effective as longer-term treatments.[107] The clinical response rate of tinidazole was 85%, compared with 80% for metronidazole. One study of furazolidone, which is available in a pediatric liquid formulation, showed a cure rate of 92% after a 10-day course. Metronidazole can be formulated into liquid preparations by special request. Asymptomatic excreters generally are not treated except in specific instances, such as repeated antibiotic treatment failures (possibly related to decreased antibiotic absorption), outbreak control, and prevention of household transmission by toddlers to pregnant women or people with hypogammaglobulinemia or cystic fibrosis.[32,115]

Symptomatic giardiasis recurs in some immunologically normal people despite appropriate therapy and in cases in which reinfection cannot be documented. The ability to isolate trophozoites axenically in culture permits in vitro susceptibility testing of *Giardia* strains, although testing is not standardized, and study of mechanisms of resistance.[116–120] Variable strain susceptibility, as well as resistance, has been demonstrated. Switch to a drug of a different class or combined therapy may be considered for patients whose infection persists after single-drug therapy (assuming that the medication was taken as prescribed and that reinfection is unlikely).[117,118,121–123] Combination therapy with standard doses of metronidazole and quinacrine given for 3 weeks has been effective when studied in a small number of refractory infections.[122]

Prevention

Prevention of giardiasis involves good hygiene and avoidance of water and food that might be contaminated.[48] Infected people and people at risk especially should adhere to strict hand-hygiene techniques after contact with feces, notably caregivers of diapered infants in childcare centers where diarrhea is common and carrier rates are high. People with diarrhea, especially children in diapers, should avoid all swimming venues until diarrhea subsides. Information about recreational water illnesses and control measures is available at www.cdc.gov/healthyswimming/ and www.cdc.gov/healthywater/hygiene/.

Methods adequate to purify public water supplies include chlorination, sedimentation, and filtration. Inactivation of *Giardia* cysts by chlorine requires attention to multiple variables such as the chlorine concentration, water pH, turbidity, temperature, and contact time. These variables cannot be controlled appropriately in all municipalities and are almost impossible to control in swimming pools and other water venues.[124–127] People should avoid swallowing recreational water; drinking water from shallow wells, lakes, rivers, streams, ponds, and springs; and drinking untreated water during community-wide outbreaks caused by contaminated drinking water. Travelers to endemic areas are advised to avoid drinking untreated water and uncooked foods that might have been grown, washed, or prepared with water that potentially was contaminated.

Purification of drinking water can be achieved by heating the water to a brisk boil for at least 1 minute or by using a filter that has been tested and rated by the National Safety Foundation (NSF) standard 53 or NSF standard 58 for cyst removal. Filtered water will need additional treatment to kill or inactivate bacteria or virus. Treatment with halazone for at least 30 minutes, saturated crystalline iodine, or similar chlorine and iodine preparations may be less effective against *Giardia* than boiling or filtering because they are affected by temperature, pH, and cloudiness of the water.[124,127] Additional information about water purification including use of water filters can be found at www.cdc.gov/travel/foodwater.html/ or at www.cdc.gov/crypto/gen_info/filters.html/.

Key Points

Diagnosis and Management of Infections With *Giardia intestinalis*

Microbiology

- Flagellated protozoan

- Humans strains are included in 2 of 8 specialized genetic groups called *assemblages.*
- After ingestion of infectious cysts, excystation occurs in the proximal small intestine, releasing trophozoites that attach to intestinal epithelium.

Epidemiology

- Distributed globally
- Detected in all classes of vertebrates including domestic and wild animals
- Most commonly diagnosed enteric parasite in the United States
- Person-to-person, foodborne, and waterborne transmission occur
- Nationally notifiable disease

Clinical Features

- Infection can be asymptomatic, acute, or chronic with failure to thrive or persistent intestinal symptoms.
- Chronic symptomatic giardiasis can occur in people with certain immune deficiencies.

Diagnosis

- Detection of cysts or trophozoites in stools or duodenal fluid by microscopy
- Detection of soluble stool antigen by direct fluorescent antibody testing, enzyme immunoassay, or immunochromatogenic assay
- Polymerase chain reaction can be used to subtype *Giardia.*
- Serologic tests not used in routine diagnosis

Treatment

- Several drugs are available in the US, but tinidazole, nitazoxanide, and metronidazole are the drugs of choice.

Prevention

- Avoidance of water and food that might be contaminated, use of appropriate hand hygiene, and avoidance of swimming venues by children (and others) with diarrhea

- Purification of drinking water when hiking

- A vaccine is not available.

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Cystoisospora (*Isospora*) and *Cyclospora* Species

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Cystoisospora belli (formerly *Isospora belli*) has been renamed and included in the *Cystoisospora* genus. Both *C. belli* and *Cyclospora* spp. infect the small intestine and have been implicated in diarrheal disease. *C. belli*, which first was linked with disease in 1915, is believed to infect only humans.[1] Prior reports of diarrhea associated with "Cyanobacteria-like" or "coccidian-like" bodies in stools are now thought to have been caused by *Cyclospora* spp.[2,3] Interest in *C. belli* and *Cyclospora* has increased because of their association with the human immunodeficiency virus (HIV) epidemic and identification in waterborne and foodborne outbreaks, respectively.

Pathogens

Both *C. belli* and *Cyclospora cayetanensis* are intestinal coccidia of the phylum Apicomplexa. Noninfectious, unsporulated oocysts are passed in stools. Sporulation outside the host usually occurs within 7 to 15 days under ideal conditions (23°–27°C). When sporulation occurs, oocysts presumably become infectious to a susceptible host. *C. belli* can be distinguished from *Cyclospora* spp. by their size and the number of sporozoites in each sporocyst; *C. belli* have four sporozoites per sporocyst, compared with two sporozoites per sporocyst in *Cyclospora* spp.[1,2]

Epidemiology

C. belli infection is endemic in developing countries, especially in South America and Africa, because of poor sanitation, and in tropical and subtropical climates.[1] The organism has been reported as an etiologic agent of traveler's diarrhea in visitors to endemic areas and has been implicated in outbreaks in facilities for handicapped people.[1,4–8] Cystoisosporiasis has been documented in 15% of patients with the acquired immunodeficiency syndrome (AIDS) in Haiti but in <0.2% of patients with AIDS in the United States.[1] The presence of the organism almost always is associated with symptoms, and in the United States, reports of *C. belli* usually involve persons with AIDS. Infection in other immunocompromised populations, such as patients with cancer or patients receiving immunosuppressive medications, also has been reported.[9–11]

C. cayetanensis infections have been documented in both immunocompetent and immunocompromised hosts worldwide.[9–15] Epidemiologic studies in Peru and Nepal have demonstrated seasonal variation in the number of infections. In Peru, infections peaked between April and June.[2] In Nepal, no infections were diagnosed in the cooler, dry months between December and April.[12] Asymptomatic carriage of the organism has been noted in Peruvian natives.[2] However, in studies of tourists and foreign residents in Nepal, identification of the organism was always associated with diarrhea.[12]

Infection with *C. belli* and *Cyclospora* follows ingestion of mature oocysts.[6] Because sporulation occurs outside of the host, direct person-to-person transmission does not occur. Both *Cystoisospora* and *Cyclospora* have been linked to contaminated food and water, although *Cyclospora* is more frequently associated with food and waterborne sources. The first reported outbreaks of diarrheal illness associated with *Cyclospora* in the US occurred among employees and physicians in a Chicago hospital in 1990; stagnant water supplied to the physicians' dormitory was implicated.[16] Multiple outbreaks associated with contaminated foods, including berries, lettuce, snow peas, and basil, and water have been reported.[17–26]

Clinical Manifestations

Clinical signs and symptoms associated with either organism usually are evident within 1 week (range, 3–14 days) of infection. Diarrhea is the hallmark of infection for both organisms but may not be the presenting or predominant symptom for patients with *Cyclospora* infection.[1–3,6,19,27] Described as profuse, foul-smelling, and watery, diarrhea can result in dehydration or weight loss. Affected people can have intermittent, crampy abdominal pain, flatulence, nausea, vomiting, and anorexia. Biliary tract disease also has been reported.[28–30] Diarrhea can alternate with constipation in cyclosporiasis.[3] Fever is more common in cystoisosporiasis. In immunocompetent hosts, both organisms produce a self-limited infection, although diarrhea can persist for several weeks. Chronic diarrhea is common in HIV-infected patients, and onset of diarrhea can be more insidious than in immunocompetent hosts.[1,27] In patients with HIV infection, symptoms and shedding of oocysts can continue indefinitely. In immunocompetent hosts with self-limited disease, shedding can persist for several weeks after resolution of symptoms. Bouts of acute and relapsing diarrhea also are described.[16]

Laboratory Findings and Diagnosis

Infection with either organism is best diagnosed through identification of oocysts in stained smears of stool. Although staining frequently is variable, both organisms can be identified with use of a modified acid-fast stain.[15] *Cyclospora* also are detectable with phenosafranine stain and through autofluorescence.[2] Oocysts are round and resemble *Cryptosporidium*, but *Cyclospora* are twice the size of *Cryptosporidium* (Fig. 266.1). *Cyclospora* do not stain with the monoclonal antibody specific for *Cryptosporidium* spp.[2,18] *C. belli* oocysts are oval, measuring 23 to 33 µm long by 10 to 19 µm wide (Fig. 266.2).[1] Polymerase chain reaction and flow cytometry have been used to detect both

Cyclospora and *C. belli* in clinical and environmental samples, but these tests are not available commercially.[31–35] Serologic assays are not available for detection of antibody to either organism.

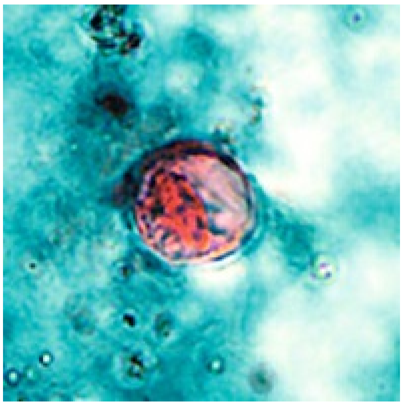

FIGURE 266.1 Oocysts of *Cyclospora* spp. (From Centers for Disease Control and Prevention, Atlanta, GA).

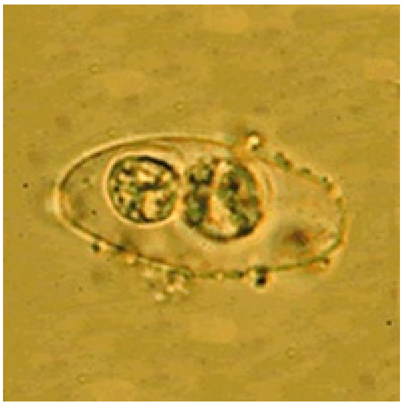

FIGURE 266.2 Unconcentrated fresh stool demonstrating *Isospora belli.* (From Centers for Disease Control and Prevention, Atlanta, GA).

Small bowel biopsy reveals pathologic changes, including blunting and atrophy of villi, acute and chronic inflammation, and hyperplasia of crypts.[6,7] The extent of histopathologic changes correlates with severity of clinical symptoms, including malabsorption.[2] Finally, peripheral eosinophilia is commonly seen in association with cystoisosporiasis and can indicate the possibility of this infection in the right settings.[36]

Treatment

C. belli is effectively treated with trimethoprim-sulfamethoxazole (TMP-SMX).[37] In a study of administration of oral TMP (160 mg) and SMX (800 mg) four times daily for 10 days and then twice daily for 3 weeks to adults who were HIV-infected, diarrhea ceased within 2 days in all patients; however, relapse occurred in 47%.[27] In another study, initial therapy with TMP (160 mg) and SMX (800 mg) four times daily for 10 days, followed by prophylaxis with either TMP (160 mg) and SMX (800 mg) three times a week or sulfadoxine (500 mg) and pyrimethamine (25 mg) given weekly was equally effective in eliminating diarrhea and preventing relapse in patients infected with HIV.[38] The recommended dose of TMP-SMX for children is 5 mg of TMP/kg/dose given twice daily for 10 days. In another study in adults, daily pyrimethamine (75 mg), alone or with folinic acid, followed by daily pyrimethamine at the reduced dose of 25 mg was effective in patients with adverse reactions to sulfonamide drugs.[39] An acceptable dosing regimen for children who are unable to tolerate TMP-SMX would include pyrimethamine 1 mg/kg plus folinic acid 10 to 25 mg by mouth once daily for 14 days. Nitazoxanide and ciprofloxacin also have been reported to be effective.[40,41] Additionally, immune reconstitution associated with initiating combination antiretroviral therapy in HIV-infected patients with cystoisosporiasis is indicated.[37]

Similar success with TMP-SMX treatment has been reported in *Cyclospora* infections.[19,37,42–44] Patients with HIV were treated successfully with a regimen of 160 mg TMP plus 800 mg SMX, given four times a day for 10 days; diarrhea resolved in all patients within 2.5 days. Recurrence was prevented with secondary prophylaxis consisting of TMP-SMX administered thrice weekly.[44] Treatment with 160 mg TMP plus 800 mg SMX, administered twice daily for 7 days, successfully eradicated the organism from immunocompetent hosts in Nepal.[43] There are few studies of treatment in children; TMP-SMX, 5 mg of TMP/kg/dose given twice daily for 10 days, would be an acceptable regimen. Ciprofloxacin is acceptable therapy for patients who cannot tolerate TMP-SMX.[29,40] Nitazoxanide also has been proposed as effective therapy in patients with sulfa intolerance.[29,45]

As with all causes of diarrhea, supportive care, including replenishment of fluids and electrolytes, is essential.

Prevention

To date, nosocomial spread has not been reported. Nonetheless, careful handwashing by both the caregiver and the patient is recommended. Travelers to endemic areas should avoid untreated water as well as consumption of unpeeled fruits and vegetables, all of which can be contaminated.

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267

Leishmania Species (Leishmaniasis)

Moshe Ephros, Naomi E. Aronson

Description of the Pathogen

The genus *Leishmania* comprises vector-borne protozoan parasites that cycle asexually between the digestive tract of the sand fly as a motile flagellated promastigote and, in a wide range of vertebrate hosts (e.g., rodents, canids, hyrax, humans), as an immotile intracellular amastigote (Fig. 267.1). Infection can therefore be either zoonotic or anthroponotic (when humans serve as reservoir) and occurs when a female sand fly (Fig. 267.2) takes a blood meal and introduces infective metacyclic promastigotes into a vertebrate's skin, where they are phagocytosed by macrophages and dendritic cells. Parasites replicate in the reticuloendothelial system in phagolysosomes while evading or disabling host defenses; host cells ultimately rupture and release amastigotes, which infect other phagocytic cells (Fig. 267.3). In addition, parasites disseminate through regional lymphatics and vascular channels.

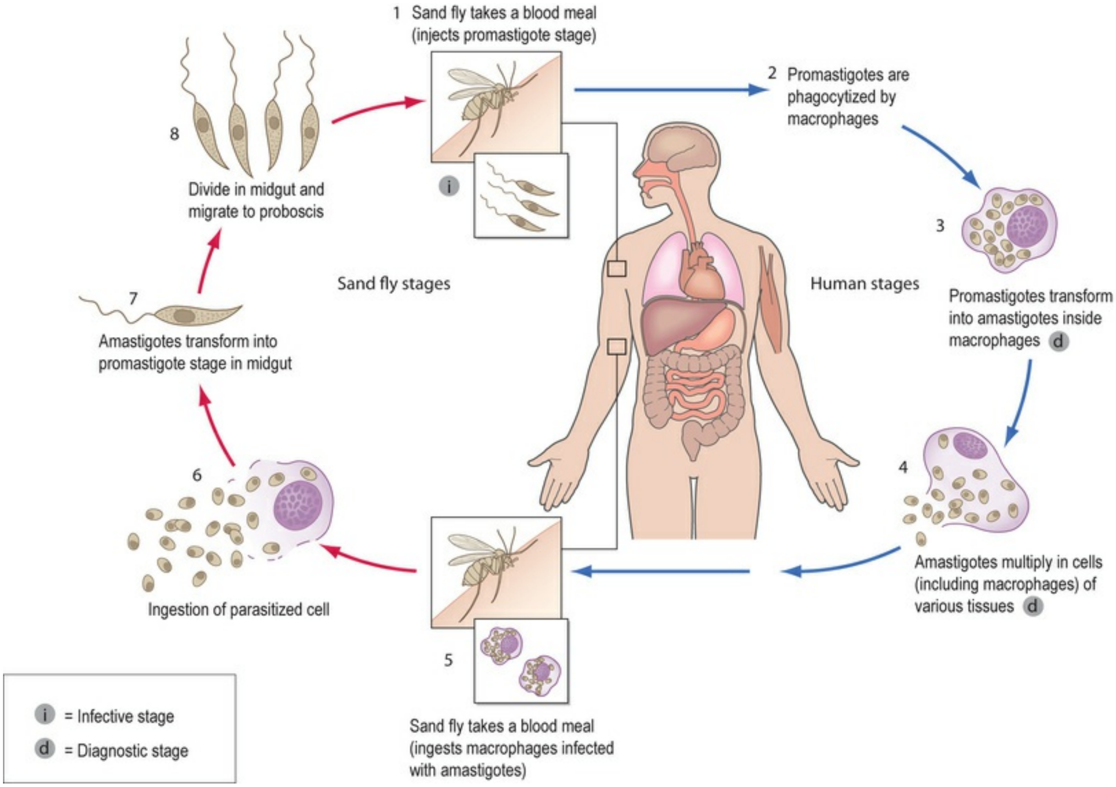

1 Sand fly takes a blood meal (injects promastigote stage)
2 Promastigotes are phagocytized by macrophages
3 Promastigotes transform into amastigotes inside macrophages d
4 Amastigotes multiply in cells (including macrophages) of various tissues d
5 Sand fly takes a blood meal (ingests macrophages infected with amastigotes)
6 Ingestion of parasitized cell
7 Amastigotes transform into promastigote stage in midgut
8 Divide in midgut and migrate to proboscis
i
Sand fly stages
Human stages
i = Infective stage
d = Diagnostic stage

FIGURE 267.1 Life cycle of *Leishmania* spp. showing the sand fly stage and the human stage. (Courtesy of the Centers for Disease Control and Prevention.)

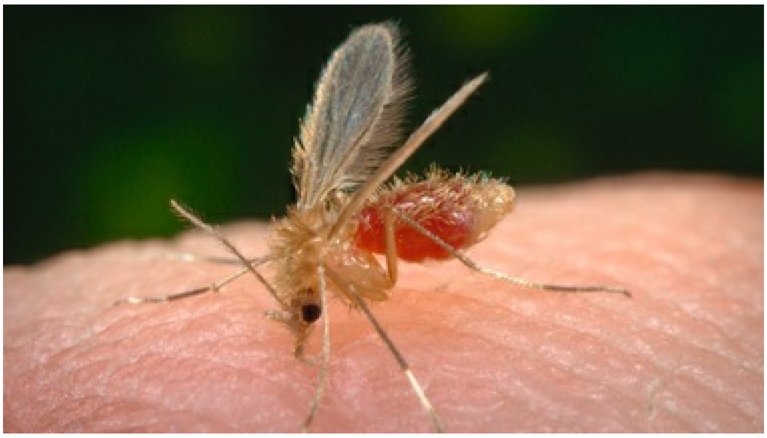


FIGURE 267.2 *Phlebotomus papatasi* sand fly after a blood meal. (Courtesy of James Gathany, Centers for Disease Control and Prevention.)

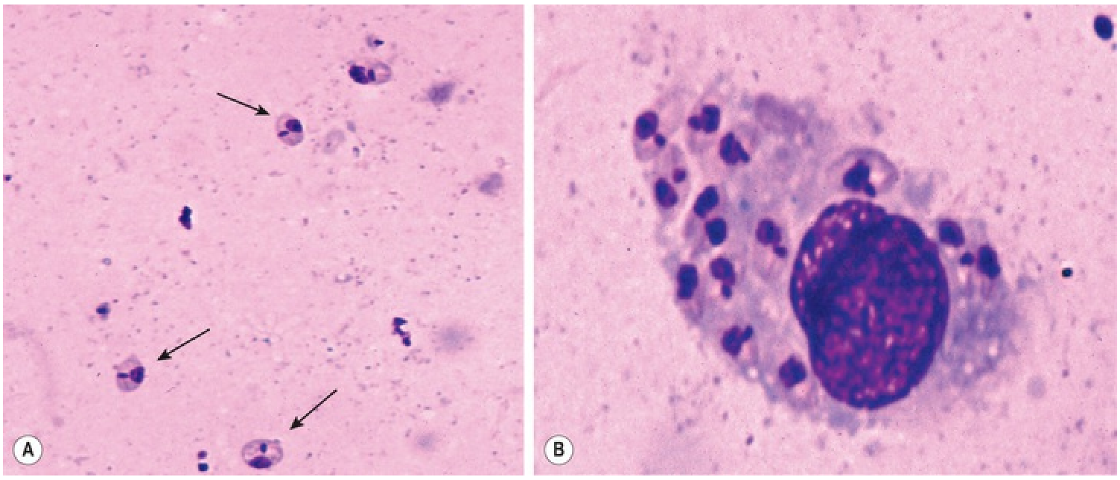


FIGURE 267.3 (A) Numerous extracellular *Leishmania* amastigotes *(arrows)*, demonstrating characteristic dot-dash morphology. Skin scraping stained with Diff Quick; original magnification ×300. (B) *Leishmania* amastigotes inside a mononuclear cell. Skin scraping, Diff Quick stain; original magnification, ×300. (Courtesy of Dr. Peter McEvoy, Armed Forces Institute of Pathology.)

The genus *Leishmania* is divided into two subgenera: *Leishmania*, distributed worldwide, and *Viannia*, limited to Central and South America (Table 267.1). Species can be categorized by parasite isoenzymes (zymodemes),[1] but current taxonomy increasingly relies on molecular analysis with species-specific oligonucleotide primers or mass spectrometry.[2]

TABLE 267.1

Leishmania Species That Cause Human Disease[a]

	Species	Sand Fly Vector Species	Mammalian Reservoir[b]	Main Geographic Locations	Main Clinical Manifestations	Other
OLD WORLD						
Subgenus						
Leishmania	*L. major*	*Phlebotomus*	Many sylvatic animals, including *Psammomys obesus, Rhombomys optimus, Gerbillus* spp.	India, Pakistan, Central and Southwest Asia, Turkey, Areas in Africa, Middle East	Cutaneous leishmaniasis (CL)	
	L. tropica	*Phlebotomus*	Human, rock hyrax, dog	Central and Southwest Asia, Middle	CL	Leishmar recidivan occasiona

				East, Turkey, Greece, India, Pakistan, Yemen, Northern Africa, Ethiopia, Kenya		viscerotro leishmani
	L. aethiopica	*Phlebotomus*	Rock hyrax,bush hyrax, southern tree hyrax, pouched rat	Ethiopia, Kenya, Uganda	CL	Diffuse cutaneou leishmani (DCL)
	L. infantum (syn. *L. chagasi*)	*Phlebotomus*	Dog, various other canids, hare	Mediterranean, Northern Africa, Middle East, Central and Southwest Asia, Balkans, China, sporadic in sub-Saharan Africa	Visceral leishmaniasis (VL)	CL
	L. donovani	*Phlebotomus*	Human	India, China, Pakistan, Southwest Asia, Horn of Africa (Ethiopia, Kenya, Somalia, Sudan, Uganda)	VL	Post–kala azar dern leishmani occasiona
NEW WORLD						
Leishmania	*L. mexicana*	*Lutzomyia*	Sylvatic rodents, spiny pocket mouse, various rats	Central and South America, Mexico, sporadic in Texas and Oklahoma	CL	DCL
	L. amazonensis	*Lutzomyia*	Rats, red-nosed mouse, bushy tail squirrel	Panama, South America (esp. Amazon basin)	CL	DCL, occasiona VL or mucosal leishmani (ML)
	L. infantum (syn. *L. chagas*i)	*Lutzomyia*	Dog, hoary fox, crab-eating fox, opossum	Central and South America	VL	Occasiona CL
Viannia	*L. braziliensis*	*Lutzomyia*	Various mice and rats, opossum	Central and South America	CL and ML	ML (esp. Bolivia, Brazil, Pe dissemina CL (Brazi
	L. peruviana	*Lutzomyia*	Opossum, various	Peru and Argentina	CL	Infrequer ML

			mice	(Western Andes slope)		
	L. guyanensis	*Lutzomyia*	Sloth, opossum, anteater, spiny rat	South America (esp. Northern Amazon basin, Guyana, French Guiana)	CL	Occasiona ML
	L. panamensis	*Lutzomyia*	Sloth, opossum, mice, anteater, red squirrel	Panama, Costa Rica, Colombia, Ecuador, Peru, Venezuela	CL	Occasiona ML

[a] Not all-inclusive; major species only.

[b] Not all-inclusive; see World Health Organization. Control of the leishmaniases. WHO technical report series: 949. 2010: pp. 91−104. http://apps.who.int/iris/bitstream/10665/44412/1/WHO_TRS_949_eng.pdf.

From Aronson N. Cutaneous leishmaniasis: Epidemiology and control. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Copyright © 2016 UpToDate, Inc. For more information visit www.uptodate.com..

Pathogenesis and Immunity

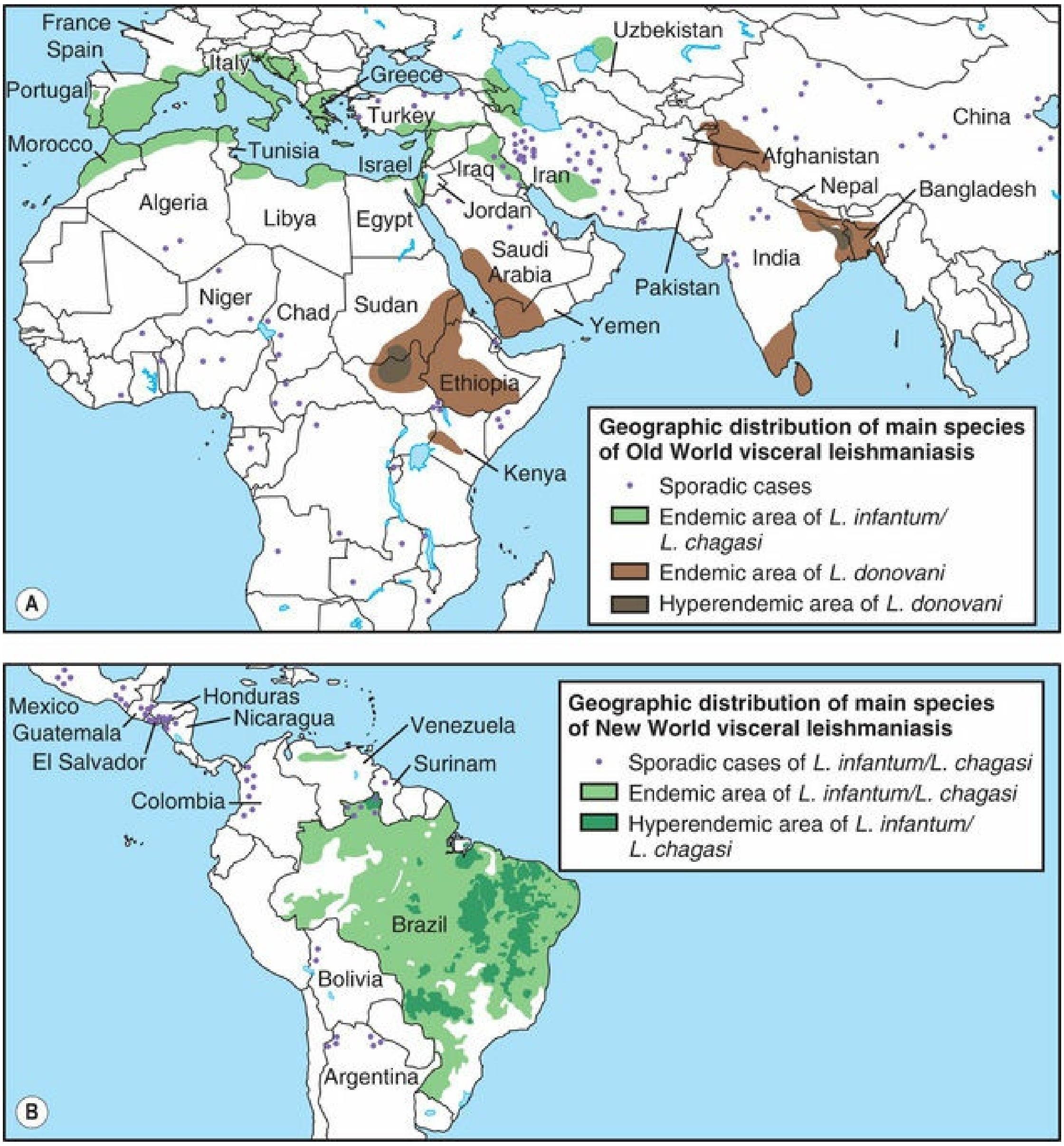
The virulence of a specific parasite for a specific host depends on a large number of interacting variables.[3] Parasite factors include inoculum size, genetically determined subspecies or strain variability that influences pathogenicity, and tissue tropism (e.g., risk for mucosal leishmaniasis, [ML] with *L.V. braziliensis*), which varies geographically.[4–6] Host factors include immune defects, nutritional status, extremes of age, and comorbidities.[7–11] Sand fly factors such as the maxadilan content of *Lutzomyia* saliva, a vasodilatory protein that also otherwise facilitates infection, are also associated with pathogenicity. Host immune responses acquired before infection directed against sand fly saliva impede *Leishmania* infection.[12,13]

Despite the fact that each *Leishmania* sp. usually causes a specific clinical syndrome (i.e., visceral leishmaniasis [VL], cutaneous leishmaniasis [CL], or ML), any species can cause other clinical syndromes. Infection occurs when the parasite is able to overcome or inhibit protective host cell−mediated immunity, expressed predominantly by a Th1 response driven by interferon γ (IFNγ), interleukin-2 (IL-2), and IL-12.[14] At the cellular level, IFNγ induces macrophage L-arginine−dependent nitric oxide and superoxide production.[3] A predominantly Th2 host response or *Leishmania* inhibition of host Th1 response usually facilitates infection. Abnormal host cell−mediated immunity response increases infection rates, disease severity, and atypical manifestations. Histopathology of affected tissue will show mixed acute and chronic infection and granulomas with epithelioid giant cells, with or without parasites. With clinical cure, the host develops species-specific immunity dependent, in part, on lifelong persistence of viable intracellular parasites and a Th1 cellular response. Memory T lymphocytes, even in the absence of persistent parasites, and $CD8^+$ T lymphocytes also may play a role.[15–17] In VL, a positive skin test response is present concomitantly with clinical cure. Antibodies directed against the parasite are not protective, although their presence may aid in diagnosis.[18–20]

Epidemiology

Leishmaniasis is a complex of diseases transmitted by a sand fly bite. Human infection is caused by more than 23 species of *Leishmania* with >90 sand fly subspecies that are proven or likely vectors.[20a] Proven vectors of human disease are the genus *Phlebotomus* in the Old World and *Lutzomyia* in the New World (see Table 267.1). Leishmaniasis generally is a zoonosis with ecologic links between a specific animal reservoir and sand fly subspecies. Anthroponotic transmission is seen in urban *L. tropica* cutaneous infections in Afghanistan.[21] Anthroponotic transmission of *L. donovani* visceral infection occurs in India, Nepal, and Bangladesh, whereas mixed zoonotic and anthroponotic *L. donovani* transmission occurs in East Africa.[22–28] Female sand flies are usually nocturnal feeders, but if disturbed, they may feed during the day. Transmission is seasonal, and sand flies are poor fliers, so hyperendemic transmission areas occur close to mammalian reservoirs. Other uncommon modes of transmission include intravenous drug use, blood transfusion, organ transplantation, occupational needle stick, laboratory accident, maternal-fetal transmission, and sexual transmission.

Leishmaniasis affects about 12 to 15 million people worldwide, 75% of cases being cutaneous disease. Leishmaniasis is a neglected tropical disease; globally it is strongly associated with social determinants of poverty, and limited resources are available for disease control, diagnosis, and treatment. The World Health Organization estimates an annual incidence of 1.3 million cases of CL and 200,000 to 400,000 new VL cases, with 20,000 to 40,000 VL deaths per year.[28] VL is second only to malaria as a parasitic cause of death in the world. A disproportionate number of children compared with immunocompetent adults are infected with VL (>50% cases) and Old World CL.[29] Contributing factors include higher rates of malnutrition, lack of prior exposure and acquired immunity to parasite and sand fly saliva, and a less mature immune system. Worldwide migration, poverty, lack of adequate control measures, and immunosuppressing conditions (e.g., HIV, transplantation, cancer chemotherapy, and biologic immunomodulator therapy) are driving an increasing incidence of VL.[30] Eighty percent of *L. donovani* VL occurs in northeastern India, southeastern Nepal, and Bangladesh (Fig. 267.4).[28] VL due to *L. infantum* occurs primarily in the Mediterranean, Middle East, Afghanistan, Iran, Pakistan, Iraq, and Brazil.[20a,23] More than 70% of CL cases are reported from 10 countries: Syria, Peru, North Sudan, Iran, Ethiopia, Costa Rica, Colombia, Brazil, Algeria, and Afghanistan (see Fig. 267.4C and D).[28]


France
Spain
Portugal
Italy
Greece
Turkey
Morocco
Tunisia
Israel
Iraq
Iran
Uzbekistan
China
Afghanistan
Nepal
Bangladesh
Algeria
Libya
Egypt
Jordan
Saudi Arabia
India
Pakistan
Niger
Chad
Sudan
Yemen
Ethiopia
Kenya
Geographic distribution of main species of Old World visceral leishmaniasis
Sporadic cases
Endemic area of L. infantum/ L. chagasi
Endemic area of L. donovani
Hyperendemic area of L. donovani
A
Mexico
Guatemala
El Salvador
Honduras
Nicaragua
Venezuela
Surinam
Colombia
Brazil
Bolivia
Argentina
Geographic distribution of main species of New World visceral leishmaniasis
Sporadic cases of L. infantum/L. chagasi
Endemic area of L. infantum/L. chagasi
Hyperendemic area of L. infantum/ L. chagasi
B

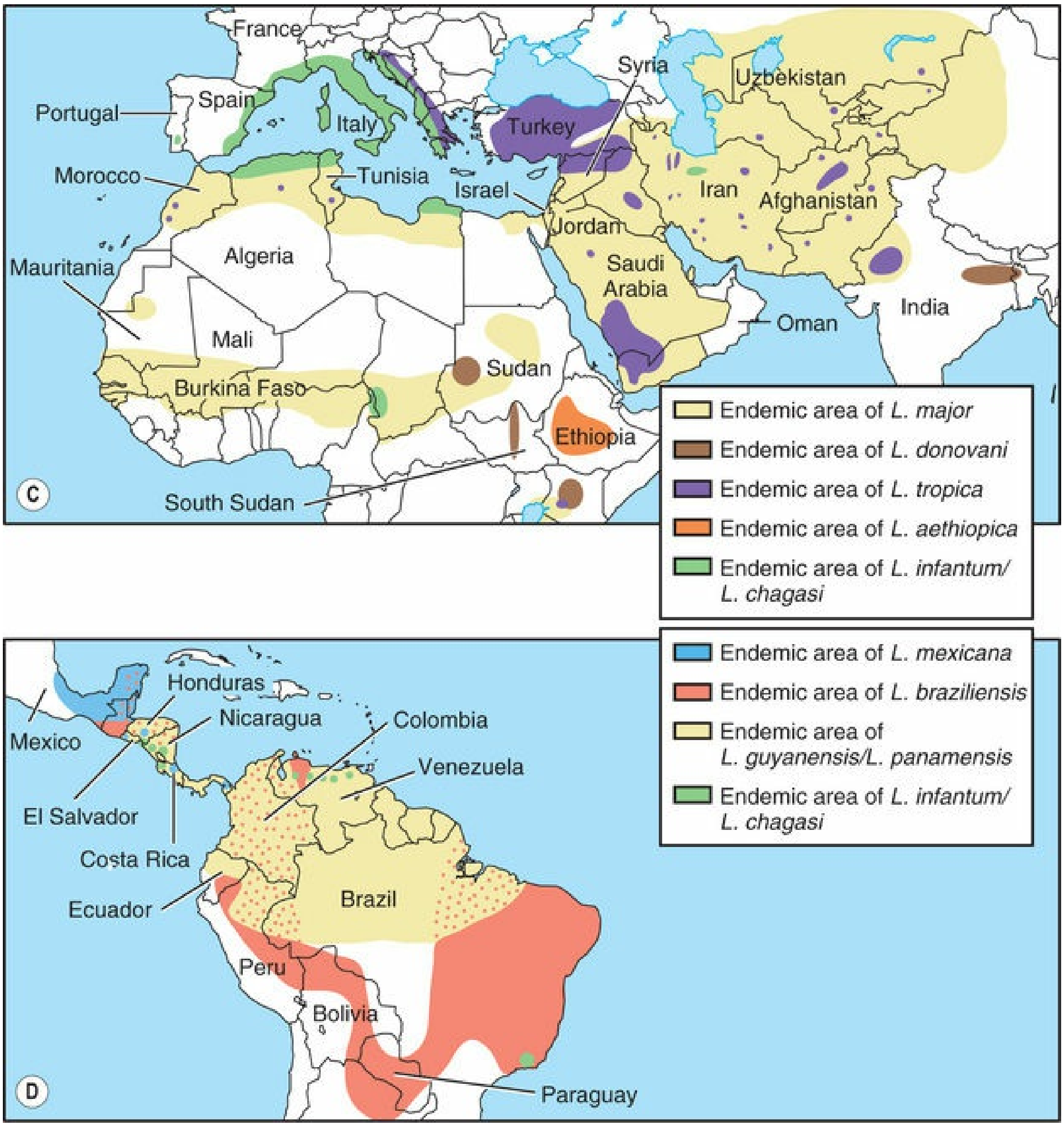


FIGURE 267.4 (A) Map of Old World visceral leishmaniasis distribution. (B) Map of New World visceral leishmaniasis distribution. (C) Map of Old World cutaneous leishmaniasis distribution. (D) Map of New World cutaneous leishmaniasis distribution (From Aronson N, Herwaldt B, Libman M et al. Diagnosis and treatment of leishmaniasis: clinical practice guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). Clin Infect Dis 2016;63:1539–1557.)

Sporadic leishmaniasis can affect people of all ages and can occur when susceptible people (i.e., tourists, migrants) enter an endemic area. Outbreaks have been associated with movement of large numbers of susceptible people (i.e., agricultural or refugee settlements, military personnel) into endemic areas or may be related to population upsurges of reservoir hosts.[31,31a] Among travelers, imported CL cases have increased since the mid-2000s. CL is one of the most common dermatologic conditions (18% of skin diseases) in returning travelers from Central and South America, especially Bolivia, Costa Rica, and Peru.[32,33] In a British report, Old World CL was associated with Mediterranean coastal travel and mainly *L. infantum* CL; New World CL was primarily due to *Viannia* spp. in backpackers or soldiers.[34]

Clinical Manifestations

Cutaneous Leishmaniasis

CL should be suspected when a person has a chronic, usually painless, nodular or ulcerative lesion on exposed skin and a history of residence in or travel to an endemic area. Nuances of childhood cases are shown in Box 267.1. The incubation period after sand fly bite is between 2 weeks and many months, sometimes even years. An erythematous macule appears first, gradually becoming an inflammatory papule with progressive induration (with or without superficial scaling). As inflammation increases the papule becomes nodular, often ulcerating, and with a raised border. Lesion morphology is highly variable and also includes plaques and psoriasiform or verrucous lesions. Size can vary from <1 cm to 10 cm. Satellite lesions, hyperkeratotic eschars, fibrinous exudates, sporotrichoid (lymphangitic) spread, and regional lymphadenopathy also occur. Lesions usually are painless unless secondarily infected.[35,36] Resolution with scarring (usually described as paper-like with thin skin) is the rule, taking from months to years. Facial lesions can be quite disfiguring and may involve mucosae contiguous with skin (sometimes resembling ML). Lesions overlying joints may heal poorly.

Box 267.1

Pediatrics-Specific Leishmaniasis Points

General

Children comprise a disproportionately larger part of the total disease burden, including visceral leishmaniasis (VL) due to *L. infantum* (syn. *chagasi*), and some cutaneous leishmaniasis (e.g., Old World cutaneous leishmaniasis [CL]).

Children have fewer comorbidities and tolerate systemic therapy better than adults, with fewer and milder adverse effects.

Systemic treatment of children's leishmaniasis may yield lower cure rates than adults due to pharmacokinetic differences (e.g., increased drug clearance).

Scarring and disfigurement can result in social stigmatization that may be highly damaging, especially but not exclusively, for young women and girls.

For prevention of sand fly bites, use recommended insect repellents and permethrin-treated fine-mesh bed nets and clothes.

Cutaneous Leishmaniasis

Children have more facial lesions than do adults.

Most children in Old World-endemic areas are infected at 2–3 years of age.

Local therapy (e.g. thermotherapy, intralesional injection) often is painful or traumatic and may require multiple sessions; anesthesia or sedation may be required.

Visceral Leishmaniasis

Mortality of treated VL in endemic countries ranges from 3% to 10%, with a somewhat better prognosis for children. However, children younger than 6 months and adults 65 years and older have the highest mortality rates.

Asymptomatic or oligosymptomatic infections (which can mimic many other pediatric diseases) occur variably by location and may or may not progress to overt disease.

Congenital infection occurs rarely.

Hemophagocytic lymphohistiocytosis (HLH) can be induced by VL, and VL should be considered in any patient with HLH residing in or having visited a VL-endemic area.

The sensitivity of bone marrow aspiration for diagnosing VL in children is approximately 90%, better than for adults (40%–70%).

Amphotericin B products may have a need for pediatric specific dosing regimens in VL.

Miltefosine is problematic for young children because it is only available as capsules, weight-based dosing for small children may be insufficient, and it is not yet approved by the US Food and Drug Administration for children younger than 12 years.

CL in the normal host most often is localized, but the interplay between host and parasite can lead to a wide spectrum of manifestations, such as inflammatory oligoparasitic lesions (e.g., leishmaniasis recidivans) or hyperparasitic, less inflammatory lesions (e.g., diffuse CL) (Fig. 267.5). CL in immunocompromised people, especially in those with abnormal cell-mediated immunity, may have an especially prolonged course, more severe or unusual cutaneous lesions, or occasionally become visceralized.[37,38]

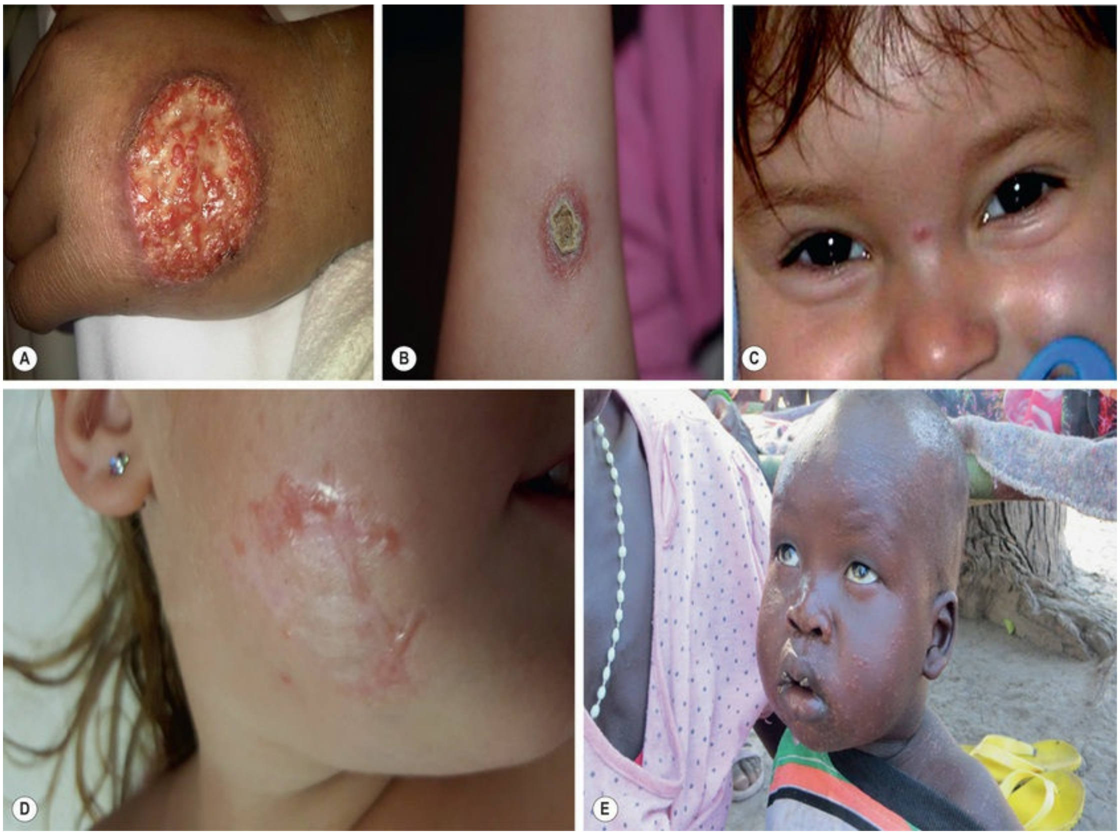


FIGURE 267.5 Composite of clinical photographs of

leishmaniasis. (A) Ulcer due to *L.V. braziliensis* acquired in Colombia. (B) Typical *L. major* lesion. (C) Nodular lesion due to *L. infantum* acquired in Majorca. (D) Leishmaniasis recidivans due to *L. tropica*, showing active lesions surrounding a scar, acquired in Israel. (E) Post−kala-azar dermal leishmaniasis after treatment for visceral leishmaniasis due to *L. donovani* in Sudan. (A, Courtesy of Dr. Peter Weina, Walter Reed National Military Medical Center. C, Courtesy of Dr. Dick MacLean (dec.), McGill University. E, Courtesy of the World Health Organization.)

The multiple clinical syndromes associated with the many geographically diverse species of *Leishmania* are listed in Table 267.1. Old World CL occurs widely in the Middle East, the Mediterranean, Asia, Africa, and the Indian subcontinent. The parasites responsible usually are *L. major, L. tropica,* and *L. aethiopica,* but also *L. infantum* and *L. donovani*. Leishmaniasis recidivans is almost always due to *L. tropica*, mostly on the face, usually at the edge of a healed CL scar. The lesions include nodules, papules, and shallow ulcers and can wax and wane over years, are difficult to treat, and are oligoparasitic and inflammatory.[39] ML associated with Old World CL and VL in the Sudan due to *L. major* or *L. donovani* or due to *L. infantum* in immunocompromised people has been reported.[40]

New World CL is widespread in Latin America and is caused by a number of species from both *Viannia* and *Leishmania* subgenera (see Table 267.1). In addition, *L. infantum* (syn. *chagasi*) can also cause cutaneous disease. As in Old World CL, the primary manifestation is localized CL, but diffuse CL does occur (*L. mexicana* and *L. amazonensis*).[41] *L. V. braziliensis*, especially south of Costa Rica, is associated with ML, particularly in Bolivia, Brazil, and Peru. To a lesser extent, *L. V. panamensis, L.V. guyanensis,* and *L. amazonensis* also are associated with ML.

Mucosal Leishmaniasis

ML generally occurs in 1% to 5% of people with New World CL due to species associated with ML. Months to years after New World CL, a patient can experience symptoms related to metastatic mucosal involvement of the nose, mouth, pharynx, and larynx, including nasal stuffiness, epistaxis, septal perforation or nasal collapse, palatal dysfunction or vocal cord involvement, and airway compromise or obstruction. Otolaryngologic examination may be required to aid in diagnosis.

ML local changes can be predominantly hypertrophic (espundia, or sponge-like) or ulcerative (destructive), with oligoparasitic, highly inflammatory lesions. Risk factors include male sex, young adulthood, severe malnutrition, and original CL lesion duration of >4 months.[42–45]

CL and ML must be included in the differential diagnosis of any persistent or progressive skin or mucosal lesion in someone having been in an endemic area. Diseases to be considered in the differential diagnosis of CL include cutaneous tuberculosis, nontuberculous mycobacteria (i.e., leprosy, syphilis, yaws, tropical pyoderma), fungal infections (e.g., blastomycosis, chromoblastomycosis, lobomycosis, sporotrichosis), sarcoid, lupus vulgaris, and skin neoplasia. For ML, consider *Mycobacterium tuberculosis,* syphilis, yaws, paracoccidiomycosis, histoplasmosis, sarcoid, lethal midline granuloma, certain lymphomas, skin neoplasia, and rhinosporidiosis.

Visceral Leishmaniasis

VL (also known as *kala-azar*) is caused by *L. donovani* in East Africa and northeastern India, Nepal, and Bangladesh (see Fig. 267.4). *L. donovani* causes the most severe VL syndrome with high mortality when untreated and often manifests as the pentad of fever, weight loss, hepatosplenomegaly, pancytopenia, and hypergammaglobulinemia. In the Mediterranean, South America (mainly Brazil), Middle East, and South West Asia, *L. infantum* (syn. *chagasi*) causes VL in children and immunocompromised hosts. Much less commonly, other *Leishmania* spp. associated with VL include *L. tropica* and *L. amazonensis*.[46,47]

Parasites persist inside macrophages throughout the reticuloendothelial system, regardless of treatment. This allows for later reactivation in situations in which cell-mediated immunity is attenuated. Overt symptomatic VL is unlikely to resolve without treatment, and mortality is 75% to 95%; however, mortality is reduced to 3% to 10% with treatment. Asymptomatic and subclinical infections are common, reflecting an appropriate host immune response to *Leishmania*. The ratio of asymptomatic to symptomatic VL varies depending on the region, ranging from 30 : 1 to 100 : 1 in Western Europe and North America, to 6 : 1 in Brazil, and to 4 : 1 in Bangladesh.[48–51] Most of these subclinical or asymptomatic infections seem to be self-resolving, but in India and Nepal risk for progression to overt VL was seen.[52]

The onset of nonspecific VL symptoms is insidious with an incubation period that is usually 3 to 8 months but can range from weeks to years.[53] In imported VL, adults are more likely than children to have a long duration of symptoms before treatment is initiated.[54] Occasionally, a small macule, papule, or ulcer may precede VL symptoms. These lesions show amastigotes on analysis but may be resolved by the time symptomatic VL develops.[55] The signs and symptoms of children and adults with VL do not significantly differ.[56–59]

Fever is common (95%−100%) and can be constant, intermittent, or recurrent. Classically, a twice-daily fever pattern has been associated with VL. Other frequent symptoms are lethargy, anorexia, weight loss, and abdominal distention. Less common symptoms include rigors, cough, diarrhea, jaundice, bleeding, and bruising.[30,58,60–69] Splenomegaly occurs in 95% to 100% of patients and can be massive. Generally the spleen is described as nontender, firm, or even hard in texture, although in rapidly progressive cases it may feel soft. HIV patients have a somewhat lower frequency of splenomegaly (80%).[70] Hepatomegaly is less frequently observed (66%−95%), and enlargement is less than the spleen. Lymphadenopathy is reported in East African VL but is seen less commonly in other geographic settings.[27] In Indian *L. donovani* infection specifically, hyperpigmentation (darkening in light-skinned persons) of the hands, feet, forehead, and abdomen led to the Hindi name *kala-azar* (black fever). Other less common findings are pallor, edema, bleeding, ascites, malnourishment, and intercurrent infections (bacteremia, bronchopneumonia, gastroenteritis, otitis media, skin infections). Immunocompromised patients may have additional unusual presenting signs in the gastrointestinal tract (chronic diarrhea, esophageal constricting lesions, tongue lesions), disseminated skin lesions, and mucosal or lung (pleural effusion) involvement.[71]

Clinical laboratory abnormalities vary among the published pediatric clinical series but include pancytopenia, anemia (usually normocytic-normochromic), leukopenia, neutropenia, eosinopenia, thrombocytopenia, low serum albumin, and hypergammaglobulinemia. Renal involvement has been reported and includes urinary concentrating defects, immune complex interstitial nephritis, minimal change glomerulonephritis, white and red blood cells in urine, proteinuria, and decreased glomerular filtration rate.[72–74] Mildly elevated serum hepatic transaminases and sometimes hyperbilirubinemia may be seen. The sedimentation rate often is 50 to 60 mm/hr.

The differential diagnosis of VL is broad, essentially that of chronic fever and splenomegaly. A more acute clinical course can suggest typhoid fever, malaria, acute schistosomiasis, cytomegalovirus, hepatitis, American trypanosomiasis, and amebic liver abscess. Chronic diseases to consider include leukemia and lymphoma, brucellosis, miliary tuberculosis, subacute bacterial endocarditis, histoplasmosis and other disseminated endemic fungal infections, tularemia, hyperreactive malarial splenomegaly syndrome, portal hypertension (e.g., schistosomiasis), and Felty syndrome.

Hemophagocytic lymphohistiocytosis (HLH) is a complication of VL, especially in children, and leads to diagnostic confusion. VL always should be considered in patients with HLH who may have been exposed in VL endemic regions. Treatment of VL usually will resolve signs and symptoms and permit avoidance of potentially harmful HLH treatments and investigation.[75–78]

Risk factors associated with a poor outcome or death include prolonged illness, jaundice, severe anemia, malnutrition, age <1 year, mucosal bleeding, neutropenia <500/mm^3, platelets <50,000/mm^3, concomitant infections, gastrointestinal symptoms.[27,79–81] A prognostic scoring system for children with VL has been published.[82] Death is generally due to complications of concomitant infections (during neutropenia), bleeding, malnutrition, and occasionally hepatic failure. HIV-infected patients have poor response to treatment, higher relapse rate, and higher mortality. Tuberculosis increases the risk for mortality from VL, even in the absence of HIV infection.[79,83]

Congenital VL is reported infrequently, when a mother has traveled to an endemic area during pregnancy. In one case, the placenta revealed amastigotes, but VL usually was diagnosed in the infant 7 to 16 months after birth.[84,85]

Diagnosis

When leishmaniasis is suspected clinically, diagnosis should be attempted by a variety of parasitologic and adjunctive immunologic tests. Tissue from lesions or potentially infected organs should be tested for parasites by smear, histopathology, parasite culture, or molecular testing.[86] Biopsy (as opposed to aspirate or scraping) is not required often but may be particularly useful when the diagnosis is not clear or when atypical disease is encountered, thus allowing for pathologic evaluation as well for culture and molecular testing. More information about testing at reference laboratories is available at http://www.cdc.gov/parasites/leishmaniasis/health_professionals/in

Under oil immersion, hematoxylin-eosin and Wright-Giemsa stains show intracellular amastigotes with their characteristic rod-shaped kinetoplast (see Fig. 267.3). In vitro culture (using Schneider or Novy-MacNeal-Nicolle media) should be attempted despite a relatively lengthy time to positive culture (i.e., days to weeks). Molecular testing for parasitic DNA is sensitive (~95%) and permits determination of species.[21,87–90]

For CL, the ulcer should be clean or debrided, and tissue should be obtained by scraping or brushing the base or edge. If there is no ulcer, tissue should be obtained by aspirate, skin snip, punch, or shave biopsy. Speciation by isoenzyme analysis of cultured parasites or by molecular analysis of infecting *Leishmania* is important for therapeutic decision making, particularly in CL (e.g., differentiating *L. mexicana* and *L. braziliensis* or *L. tropica* from *L. major*).[86] For ML, specimens are obtained similarly as for CL except that tissue may need to be obtained by an otolaryngologist. In addition to histopathology, polymerase chain reaction (PCR) and culture should be performed.

For VL, tissue aspirate or biopsy should be performed. Although a splenic aspirate provides high sensitivity (~95%), this usually is not performed in North America because of the risk for hemorrhage.[86,91] Bone marrow aspiration usually is performed but is less sensitive overall (40%–90%), although sensitivity in children is 90%.[29,63,64,68] Sampling of liver, enlarged lymph nodes, whole blood, or buffy coat also should be considered.

In the severely immunocompromised patient, parasites can be located in atypical sites such as intestinal mucosa, lung, and buffy coat.[71,92–94] In addition, quantitative PCR may prove helpful in monitoring response to therapy or diagnosing relapse of disease.[89,95]

When VL is suspected, testing for antileishmanial antibodies (e.g., rK39) by enzyme immunoassay, immunofluorescence assay, or agglutination assay can be helpful. Rarely, with strong clinical suspicion, antibodies alone might be considered sufficient to make a presumptive diagnosis and to initiate therapy. Antibody tests generally are not useful in the diagnosis of CL or ML.[96–98]

Treatment

There is no single, effective treatment that can cover all *Leishmania* spp. and syndromes. Additionally, clinical healing, even with treatment, is not always associated with a sterile cure. The goals of treating CL and ML are to accelerate healing and to prevent metastatic infection, scarring, and relapse; the goal of treating VL is to prevent mortality. Treatment should be tailored to the individual patient, including considerations of parasite species, the geographic region where infection was acquired, host comorbid conditions and immune status, and patient preferences. US clinical practice diagnostic and treatment guidelines are available.[98a]

Cutaneous Leishmaniasis

Self-healing is typical for CL after a variable number of months depending on species (e.g., *L. major*, 2–6 months; *L. mexicana*, 3–9 months; other species, 6–24 months).[99] The patient should be involved in decisions about watchful waiting for spontaneous healing of lesions with frequent follow-up and reassessment as well as local wound care. In general, CL is treated with local therapy *except* when the following complicating factors are present: (1) infection with species that can cause ML *(L.V. braziliensis, L.V. guyanensis, L.V. panamensis),* especially if acquired in the mucosal belt of Peru, Bolivia, and Brazil; (2) immunocompromised host; (3) complicated forms of CL such as leishmaniasis recidivans, diffuse cutaneous leishmaniasis, disseminated cutaneous leishmaniasis, and *L. aethiopica*; (4) clinical failure of initial local therapy; (5) size, location, or number of lesions not feasible for local therapy; (6) more than four lesions >1 cm; (7) an individual lesion ≥5 cm; (8) lesions in cosmetically sensitive locations (i.e., face, ear, finger, genital region, toes); and (9) subcutaneous nodules in lymphatic drainage route or large regional adenopathy. The treatment of CL with complicating factors generally is systemic oral or parenteral therapy.

All CL that is ulcerative is a wound. Secondary infection (purulence or surrounding cellulitis) should be treated; debridement of overlying crust or necrotic debris should be performed down to a clean base if any purulence is noted. Ulcerative lesions should be washed with mild soap and water daily, then covered with a thin layer of petrolatum-based ointment after bathing. Cosmetic surgery and skin grafts should be postponed for 12 months after successful CL healing to avoid reactivation (including at sites remote from the initial lesion).[100]

Local therapy is preferred for Old World CL and may be useful in some New World CL caused by *Leishmania* spp. unlikely to be associated with dissemination. This recommendation is because local therapy generally is sufficient in these circumstances, speeds healing, is less toxic, and is less expensive compared with systemic therapies. Local therapy includes modalities of heat and cryotherapy, intralesional amphotericin or pentavalent antimonial drugs, photodynamic treatment, and paromomycin-based topical cream or ointment.[101,102] For young children, some treatments can be painful and may require general anesthesia.

Topical paromomycin is a local therapy mainly studied in ulcerative lesions due to *L. major* or non−ML-associated Central American *Leishmania* spp. In Israel, topical 15% paromomycin with 12% methylbenzethonium chloride (Leshcutan ointment) was associated with healing in only 35% to 40% of *L. tropica* lesions. The vehicle appears to be important for efficacy, and not all preparations are equivalent.[103] WR 279,396 (a cream of 15% paromomycin and 0.5% gentamicin) is in development; efficacies of 81% to 94% were seen in randomized controlled trials.[104–106]

Systemic therapy includes both oral and parenterally administered drugs. The oral drugs used for CL include miltefosine and the azoles (fluconazole and ketoconazole). Miltefosine was approved by the US Food and Drug Administration (FDA) in 2014 for the treatment of CL due to *L.V. braziliensis*, *L. V. guyanensis*, and *L.V. panamensis*. A recent review summarizes the evidence base for miltefosine, but salient facts include regional differences in efficacy for CL, especially with *L. V. braziliensis*; resistance has been described; and it is teratogenic.[107] The target dosage is 2.5 mg/kg/day for 28 days (Table 267.2). The azole drugs have limited efficacy, and treatment failure is common. Azoles may be active for *L. major*, *L. mexicana*, and some *L.V. panamensis* infections.[108,109]

TABLE 267.2

Leishmaniasis Treatment Approaches (North America) and Common Toxicities

Route of Administration	Treatment	Dose/Regimen	Where to Get It (if Not Commercially Available)	Adverse Events
CUTANEOUS LEISHMANIASIS				
Physical methods	Thermotherapy (heat)	Thermomed (Thermosurgery Technologies Inc.) Apply to skin under local anesthesia in grid over lesion, 30-sec intervals of heat, 1 session	Device available in some dermatology offices (multiple indications)	Blistering, secondary infection
	Cryotherapy (liquid nitrogen)	Multiple regimens, freeze 15–20 sec, thaw for 60 sec, refreeze, repeat every 3 wk for up to 3 times or until healed if sooner		May have hypopigmentation if dark skinned, hyperpigmentation if light skinned, scar, keloid, vesicles, erythema, pain immediately after treatment
Intralesional (IL)	Pentavalent antimony (SbV)[a]	Multiple regimens 0.2–5 mL per session every 3–7 days up to 3 wk or until healed if sooner (undiluted sodium stibogluconate [SSG] or meglumine antimoniate [MA])	Intralesional SbV is not covered by the CDC sponsored protocol	Occasional redness, pain, rare urticaria, angioedema
	Cryotherapy + IL SbV	SbV +/- cryotherapy (superficial freeze, thaw, inject) for 5–8 sessions		
Topical	Topical paromomycin	Paromomycin 15% and methylbenzethonium	Compounding pharmacy,	Local Inflammation at

		12% in paraffin, apply to lesions twice daily for 10 days, rest for 10 days, repeat	international mail order pharmacy (Leshcutan)[b]	treatment site
Topical	WR 279,396	Paromomycin 15% and gentamicin 0.5%, apply once daily for 20 days (the 0.5% gentamicin has been removed from the formulation as of Nov 2016)	Compounding pharmacy,[c] US military healthcare beneficiaries may obtain from USAMMDA[d]	Local inflammation at treatment site
Oral	Miltefosine	Approved only for patients ≥12 yr of age who weigh ≥30 kg (66 lb). Dosage: 2.5 mg/kg/day (max., 150 mg) for 28 days; 30–44 kg: 50 mg PO twice daily for 28 days; ≥45 kg: 50 mg capsule 3 times daily for 28 days. Take with food.	Contact Profounda, the US marketer	Gastrointestinal symptoms, motion sickness, hepatotoxicity, scrotal pain, nephrotoxicity, teratogenic
Oral	Fluconazole	200 mg PO daily for 6 wk, or 400 mg PO daily for 4 wk (adults); 6–12 mg/kg/day (young children)		Gastrointestinal symptoms, headache, hepatotoxicity, reversible hair loss, rare agranulocytosis
Oral	Ketoconazole	600 mg daily for 28 days (adults)		Black box warning, gastrointestinal symptoms, headache, hepatotoxicity, decreased secretion of adrenal corticosteroids, reversible low testosterone
Parenteral	Pentavalent Antimonial (SbV)	SSG, 20 mg SbV/kg/ day IV or IM for 20 days	Contact CDC Drug Services[e]	Myalgia, arthralgia, headache, hepatotoxicity, fatigue, abdominal symptoms, elevated serum transaminases, amylase, lipase; mild cytopenias, nonspecific ST changes on ECG, QT prolongation, reactivated herpes viruses
Parenteral		MA, 20 mg SbV/kg/day IV or IM for 20 days	Apply to FDA for IND	Same as SSG, considered fairly

				interchangeable
Parenteral	Liposomal amphotericin (L-AmB)	Liposomal amphotericin B (AmBisome) Immunocompetent host: 3 mg/kg/day IV on days 1–5, 10; or days 1–7 (total dose 21 mg) Immunocompromised host: 4 mg/kg/day IV on days 1–5, 10, 17, 24, 31, 38 (total dose, 40 mg) HIV: add antiretrovirals		Renal, infusion-related reactions such as rash, chest or back pain, hypotension, hypertension, low magnesium, low potassium, chills, gastrointestinal symptoms
MUCOSAL LEISHMANIASIS				
Oral	Miltefosine *(L. braziliensis)*	Approved only for patients ≥12 yr of age who weigh ≥30 kg (66 lb). Dosage: 2.5 mg/kg/day (max., 150 mg) for 28 days; 30–44 kg: 50 mg PO twice daily for 28 days; ≥45 kg: 50 mg capsule PO 3 times daily for 28 days. Take with food.	Contact Profounda, the US marketer	Gastrointestinal symptoms, motion sickness, hepatotoxicity, scrotal pain, nephrotoxicity, teratogenic
Parenteral	SbV	SSG, 20 mg SbV/kg/day for 28 days	Contact CDC Drug Services for SSG[e]; apply to FDA for IND for MA	Myalgia, arthralgia, headache, hepatotoxicity, fatigue, abdominal symptoms, elevated transaminases, amylase, lipase, mild cytopenias, nonspecific ST changes on ECG, QT prolongation, reactivated herpes viruses
Parenteral	L-AmB	2.5–3 mg/kg/day for cumulative dose of 30–60 mg/kg		Renal, infusion-related reactions such as rash, chest or back pain, hypotension, hypertension, low magnesium, low potassium, chills, gastrointestinal symptoms
VISCERAL LEISHMANIASIS				
Oral	Miltefosine (Indian *L. donovani)*	Approved only for patients ≥12 yr of age who weigh ≥30 kg (66 lb). Dosage: 2.5	Contact Profounda, the US marketer	Gastrointestinal symptoms, motion sickness, hepatotoxicity,

		mg/kg/day (max., 150 mg) for 28 days; 30–44 kg: 50 mg PO twice daily for 28 days; ≥45 kg: 50 mg capsule PO 3 times daily for 28 days. Take with food.		scrotal pain, nephrotoxicity, teratogenic
Parenteral	L-Amb	Immunocompetent host:		
		3 mg/kg/day IV days 1–5, boost days 14, 21 Immunocompromised host: 4 mg/kg/day IV days 1–5, boost days 10, 17, 24, 31, 38 HIV: add antiretrovirals, secondary prophylaxis[f]		Renal, infusion-related reactions such as rash, chest or back pain, hypotension, hypertension, low magnesium, low potassium, chills, gastrointestinal symptoms
Parenteral	SbV	SSG, 20 mg SbV/kg/day IV or IM for 28 days	Contact CDC Drug Services for sodium stibogluconate[e]	Myalgia, arthralgia, headache, hepatotoxicity, fatigue, abdominal symptoms, elevated serum transaminases, amylase, lipase; mild cytopenias, nonspecific ST changes on ECG, QT prolongation, reactivated herpes viruses
		MA, 20 mg SbV/kg/day IV or IM for 28 days	Apply to FDA for IND for MA	Same as SSG

[a] Two pentavalent antimonial drugs that have different concentrations but are dosed at the same SbV. Sodium stibogluconate is 100 mg/mL, and meglumine antimoniate is 81 mg/mL.

[b] Compound 15% paromomycin and 12% methylbenzethonium in soft white paraffin.

[c] Compound paromomycin sulfate 15% w/w with gentamicin sulfate ointment, 0.5%, Aquaphilic ointment base with 10% carbamide (available from MEDCO Lab Inc., Sioux City, IA) 67.8% and water 16.67%. An alternative compound would be Unibase cream, paromomycin sulfate 15% (based on free base), gentamicin 0.5%, urea 6.75%, purified water 42.2%.

[d] usarmy.detrick.medcom - usammda.list.leishmania-tx-protocol@mail.mil,

[e] CDC Drug Services at (404) 639-3670, drugservice@cdc.gov.

[f] There is no preferred secondary prophylaxis regimen. Options include L-AmB, 3−5 mg/kg every 3−4 weeks; alternate is pentamidine, 4 mg/kg (no more than 300 mg) every 3−4 weeks.

CDC, Centers for Disease Control and Prevention; ECG, electrocardiogram; FDA, US Food and Drug Administration; IM, intramuscular; IND, investigational new drug (application); IV, intravenous; MA, meglumine antimoniate; PO, oral; SSG, sodium stibogluconate; USAMMDA, US Army Medical Materiel Development Activity.

Parenteral therapies include amphotericin products (deoxycholate and lipid compounds) and the pentavalent antimonial drugs (i.e., sodium stibogluconate and meglumine antimoniate). Sodium stibogluconate is not approved by the FDA but is available through an investigational new drug protocol from the Centers for Disease Control and Prevention. Meglumine antimoniate can be obtained by investigator sponsored investigational new drug request. Pentavalent antimonial drugs generally have good efficacy in the treatment of CL, but there is known clinical nonresponsiveness in CL cases acquired in Madidi National Park, Bolivia and Manu National Park and Porto Maldonado, Peru. Amphotericin B deoxycholate is effective treatment for CL, but its use is constrained by toxicity and duration of treatment; off-label use of liposomal amphotericin circumvents this, and several case series suggest 70% to 80% efficacy using the FDA-approved VL regimen total dose.[110–112]

Mucosal Leishmaniasis

The longstanding treatment of ML has been pentavalent antimonial drugs (20 mg/kg/day given intravenously or intramuscularly) for 28 days with or without pentoxifylline.[113] A recently published case series suggested that liposomal amphotericin at a total dose of 30 mg/kg was associated with 88% efficacy.[114] Miltefosine is indicated for the treatment of ML at the oral dose of 2.5 mg/kg/day (maximum, 150 mg/day in divided doses) for 28 days; however, miltefosine only has been studied in Bolivian ML, and further clinical experience will elucidate whether it has broad geographic efficacy.

Visceral Leishmaniasis

All patients with symptomatic VL should be treated because untreated VL is associated with fatality, usually due to bleeding or bacterial infections. Treatment includes antiparasitic therapy as well as nutrition, control of bleeding, antibiotics for secondary infection, and blood transfusion for severe anemia. All VL patients should be assessed for immunocompromising conditions (e.g., HIV infection) because this can affect treatment and management.

Drugs for the treatment of VL include liposomal amphotericin, sodium stibogluconate, meglumine antimoniate, parenteral paromomycin, and oral miltefosine. In North America, the treatment of choice is liposomal amphotericin B administered to immunocompetent patients at a dose of 3 mg/kg on days 1 to 5, 14, and 21. Immunocompromised hosts and VL from East Africa need higher doses and longer durations of treatment.

Clinical response using various systemic drugs varies by geographic area, with clinical resistance to pentavalent antimonial drugs frequent in north India and Nepal.[115,116] For VL acquired in India, Nepal, Bangladesh, or Bhutan, miltefosine or liposomal amphotericin is used at the FDA-approved regimen for *L. donovani*; however, several studies have suggested lower total doses may suffice for Indian VL.[117,118]

In contrast, higher doses of liposomal amphotericin are needed in East African *L. donovani* VL. Liposomal amphotericin doses of 30 mg/kg total dose were required, even higher in relapsed VL, and the World Health Organization now recommends an liposomal amphotericin total dose of 40 mg/kg in Africa.[119,120] In non–HIV-infected patients in East Africa, pentavalent antimonial drugs still perform well. The combination of parenteral pentavalent antimonials (20 mg/kg/day) and paromomycin (15 mg/kg/day) for 17 days showed similar efficacy to 30 days of pentavalent antimonial drugs.[121]

In Mediterranean and Brazilian *L. infantum* (syn. *chagasi*), liposomal amphotericin is effective and has less toxicity, has a shorter treatment duration, and is approved by the FDA for VL, compared with the stalwart treatment of pentavalent antimonials, which has been used for decades but is now relegated to second-line therapy. In Greek children, an abbreviated regimen of liposomal amphotericin (10 mg/kg/day for 2 days) was as effective as 30 days of pentavalent antimonials. However, the daily dose of 10 mg/kg carries some risk for severe hypotension.[122,123] Miltefosine has not been well studied in *L. infantum* VL.

Young children may have lower response rates to pentavalent antimonial treatment compared with older children and adults, possibly explained by an increased clearance rate and lower plasma exposure.[124,125] Children tend to tolerate pentavalent antimonials and amphotericin better than adults, with less side effects, perhaps owing to fewer medical comorbid conditions. Miltefosine is approved by the FDA only for children 12 years or older who weigh at least 30 kg. In addition, the smaller capsule of 10 mg was not approved, only the 50-mg capsule. The approved drug regimens are listed in Table 267.2. Studies of miltefosine in young children in South Asia and South America showed lower response rates, particularly persons receiving <2.5 mg/kg/day.[126,127]

Most VL relapses occur in the first 6 months of follow-up. Clinical findings are sufficient to assess relapse and correlate well with parasitologic responses. The patient's temperature should be monitored with defervescence expected within 1 week of treatment initiation. The spleen and liver decrease in size over a period of 3 to 6 months. Leukopenia and thrombocytopenia usually normalize within a month, but anemia may take 6 to 12 months to resolve.[123,128–130] Antibodies remain detectable for prolonged periods and are not useful for following; if symptoms do not resolve or relapse, then parasitologic confirmation should be sought.

Immunocompromised Host

Immunocompromised patients with CL generally are treated with systemic therapy, although there are limited reports to support treatment recommendations (see Table 267.2). Secondary prophylaxis is not used, and antiretroviral therapy should be initiated or maintained in HIV-infected patients.

In VL, liposomal amphotericin at a higher dose of 4 mg/kg given intravenously on days 1 to 5, 10, 17, 24, 31, and 38, for a total dose of 40 mg/kg, is recommended. In persons with HIV/AIDS, antiretroviral therapy should be optimized, and secondary prophylaxis (chronic maintenance therapy) should be given for $CD4^+$ cell counts until 6 months of immune reconstitution has occurred.[131] Immune reconstitution inflammatory syndrome occurs but appears to be uncommon. Combination treatment with miltefosine and liposomal amphotericin in India shows promise.[132] The pentavalent antimonial drugs are less well tolerated in HIV-infected patients, and mortality was higher than with liposomal amphotericin.[133]

In transplant recipients with VL, doses of immunosuppressive drugs should be decreased, and a recent case-control study suggested benefit from secondary prophylaxis[134] During treatment of CL and VL in patients receiving drug-induced immunosuppression (such as the TNFα-inhibiting drugs) decreased dosing or withdrawing (if possible) the immunosuppressing drug is recommended.[71,135] Persons with VL and other immunocompromising situations (e.g., hematologic malignancies, chemotherapies, biologic immunomodulators, or corticosteroids) should also receive systemic therapy, although data are restricted to case reports and small case series.[71]

Prevention and Control

Preventing leishmaniasis has not yet proved successful. There is no effective human vaccine or chemoprophylaxis.[14] Leishmanization, the purposeful infection with pathogenic *Leishmania* of noncritical body sites (e.g., buttocks) to achieve immunity in CL, thereby preventing destructive facial scarring, has been performed but is not recommended. Other approaches vary by the setting (e.g., endemic area vs. traveler, areas with zoonotic or anthroponotic transmission, animal reservoir, and vector type).[136–141]

For travelers, personal protection measures include use of insect repellents and insecticide-impregnated clothing and fine-mesh bed nets. In endemic areas, vector control using residual insecticides potentially is ecologically and individually deleterious (e.g., DDT), requires repeated spraying, leads to vector resistance, and is ineffective if transmission occurs in areas other than in and around buildings.[142] Destruction of sand fly eco-niches is usually environmentally unacceptable and, given their focal nature, is rarely effective.[136] Biologic sand fly control may have a role.

Proactive blood banking practices can prevent transfusion-related leishmaniasis, a rare but probably underestimated occurrence. Routine screening, especially in endemic areas, with the exclusion of positive blood, as well as instructing those with a history of visceral leishmaniasis (treated or not) to not donate blood may be appropriate. Using leukodepletion filters when administering blood products should exclude most intracellular parasites.[143] Routine serologic screening of organ donors from *Leishmania*-endemic areas is not recommended currently.[144]

In anthroponotic visceral leishmaniasis, case finding and treatment are very important yet probably insufficient because the parasite burden of undiagnosed asymptomatic persons and those with post–kala-azar dermal leishmaniasis will impede progress toward diminishing the overall local disease burden and the disruption of transmission. Where domestic dogs are reservoirs, immunization, when available, will help disrupt the life cycle. Until then, culling and use of collars or other topically applied insecticides or repellents are important tools.[136] When sylvatic canids are the reservoir, these modalities are impracticable other than attempting wild animal culling (not usually acceptable ecologically).

Until an effective vaccine is developed, a multidisciplinary approach may yield the best, yet still modest, results in the prevention and control of leishmaniasis.

Key Points

Leishmaniasis

Definitions, Pathogenesis and Epidemiology

- Sand fly–transmitted protozoan infection (1 genus, 2 subgenera, >23 species) causing a pleomorphic spectrum of clinical disease, with wide geographic distribution, multiple vectors, and mammalian reservoirs
- Major clinical syndromes include visceral (VL), cutaneous (CL), and mucosal (ML) leishmaniasis.
- Infection usually is lifelong; cure, either spontaneous (CL) or by treatment (CL, VL, ML), is clinically, not parasitologically, defined.
- Persons with defective cell-mediated immunity may have a higher risk for late reactivation and dissemination and may demonstrate atypical manifestations.
- Worldwide, ~350 million people are at risk in ~90 countries, with 12–15 million affected and 1–2 million new cases annually (~75% CL); proportionally more cases occur in children.

- VL is associated with significant mortality despite treatment (~10%); CL and ML cause significant morbidity (scarring and destructive naso-oropharyngeal lesions).

Diagnosis

- Consider leishmaniasis in people residing in or having visited an endemic area, with:
  - CL: persistent, usually painless, cutaneous nodules or ulcers
  - ML: inflammatory/destructive naso-oropharyngeal-laryngeal lesions, which can occur years after CL lesion healed
  - VL: febrile systemic illness, hepatosplenomegaly, and progressive pancytopenia
- Laboratory testing:
  - CL, ML: microscopy, culture, or PCR of lesion aspirate, scraping, or biopsy
  - VL: microscopy, culture, or PCR of bone marrow, liver, blood, buffy coat or lymph node; splenic aspirate is highly sensitive but carries risk for hemorrhage; serology may be useful adjunct

Management

Cutaneous

- Scarring, self-resolving infection, which usually heals over months to years and does not always require therapy

- Wound care for ulcerative CL lesions
- Treat to improve cosmetic and functional outcomes when lesions are large, numerous, or on sensitive areas, or the patient is immunocompromised or at risk for metastatic complications.
- Therapy can be local or systemic; some local methods may require sedation or anesthesia for children.

Mucosal

- Treat systemically to prevent mortality and tissue destruction
- Use pentavalent antimony, liposomal amphotericin B, or miltefosine

Visceral

- Treat systemically to prevent mortality
- Use pentavalent antimony, liposomal amphotericin B, or miltefosine
- Adjunctive therapy for secondary infections or bleeding
- Immunocompromised hosts may require posttreatment suppressive therapy.

Prevention

- No vaccine or prophylactic drug
- Sand flies usually bite dusk to dawn.

▪ Wear clothing that covers body

▪ Sleep indoors

▪ Use air conditioning

- Use insect repellents and permethrin-impregnated clothing and bed nets

- Vector and reservoir control may be used but are not highly effective in areas of anthroponotic leishmaniasis; active case finding and treatment are the basis for disease control.

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Microsporidia

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Before 1985, few human microsporidial infections had been reported. Since then, the number of cases has increased dramatically because of recognition of this pathogen in patients infected with human immunodeficiency virus (HIV). Although most reported infections have occurred in HIV-infected people, the organism is recognized increasingly as pathogenic in other immunocompromised populations (e.g., organ transplant recipients), as well as in immunocompetent hosts.[1–3]

Pathogen

Microsporidia are obligate, intracellular, spore-forming parasites that have been reclassified from protozoa to fungi (Fig. 268.1).[4] They are ubiquitous and infect most animal groups, including humans (Table 268.1). At least 15 species of microsporidia have been reported to be pathogenic in humans.[5,6] Microsporidia are characterized by spore size, nuclear configuration, and relationship between the organism and its host cell. Replication occurs within the cytoplasm of the host cell by both binary fission (merogony) and multiple fission (schizogony), and it culminates in spore production (sporogony). Maturing spores accumulate within a vacuole that eventually ruptures and releases the spores.[7] All microsporidial spores contain a complex tubular extrusion mechanism that injects the infectious substance (sporoplasm) from an infected cell into an uninfected host cell.[7]

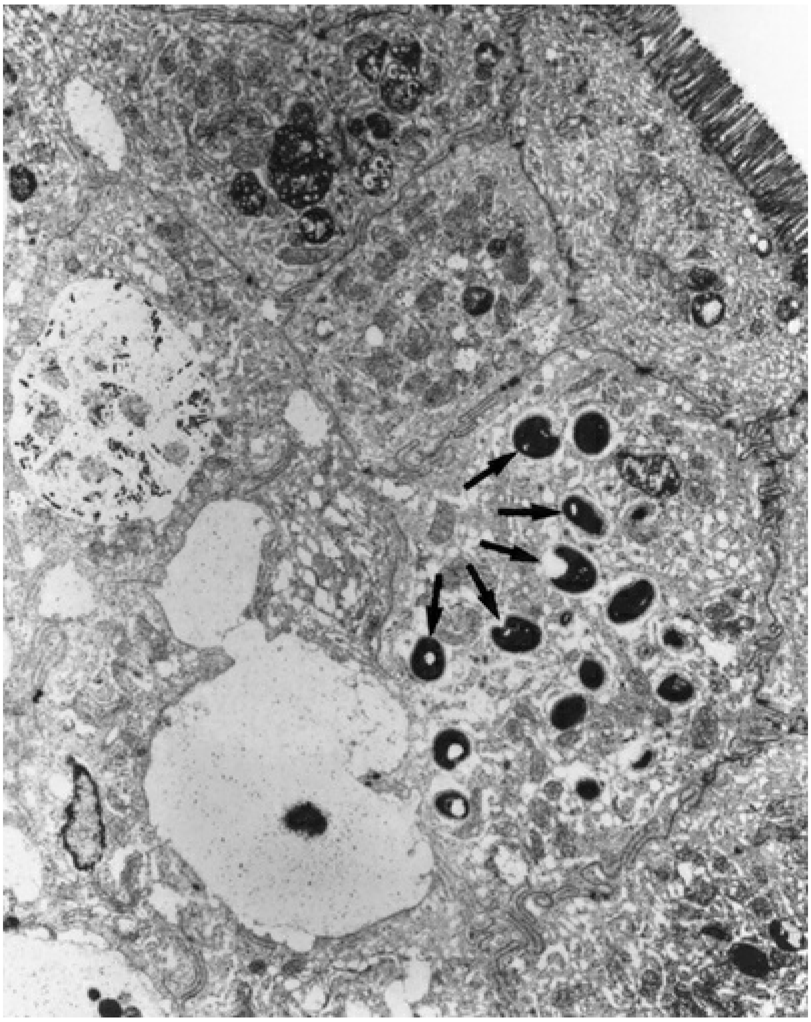

FIGURE 268.1 **Electron micrograph of mature spores (*arrows*) of *Enterocytozoon bieneusi* in a duodenal biopsy specimen (original magnification, ×10,000).** (Reproduced with permission from Gyorkey F, Genta RM, et al. The role of microsporidia in the pathogenesis of HIV-related chronic diarrhea. Ann Intern Med 1993;119:895.)

TABLE 268.1

Clinical Diseases Associated With Microsporidia

Organism	Disease
Anncaliia algerae	Myositis, disseminated disease, keratopathy, skin infection
Anncaliia connori	Disseminated disease, keratopathy
Anncaliia vesicularum	Myositis
Encephalitozoon cuniculi	Encephalitis, hepatitis, peritonitis, keratopathy, sinusitis, osteomyelitis, pulmonary disease, disseminated disease
Encephalitozoon hellem	Keratopathy, disseminated disease, sinusitis, pneumonitis, nephritis, urethritis, cystitis
Encephalitozoon intestinalis	Diarrhea, cholangitis, disseminated disease, nodular skin lesions, keratopathy
Enterocytozoon bieneusi	Diarrhea, cholangitis, pulmonary disease
Microsporidium africanum	Keratopathy

Microsporidium ceylonensis	Keratopathy
Nosema ocularum	Keratopathy
Pleistophora ronneafiei	Myositis, disseminated disease, sinusitis
Trachipleistophora hominis	Myositis, disseminated disease
Trachipleistophora anthropophthera	Disseminated disease, encephalitis
Tubulinosema acridophagus	Disseminated disease
Vittaforma corneae	Keratopathy, urinary tract infection, diarrhea

Epidemiology

The epidemiology of microsporidial disease is not defined clearly. Antibodies against *Encephalitozoon cuniculi* are relatively common in selected human populations, a finding suggesting that latent human infection may occur.[8]

Transmission is thought to occur from person to person and through ingestion of contaminated water and food.[4] Following ingestion, infectious spores travel to the intestine, where their contents are injected into cytoplasm of host cells. Intracellular division produces new spores that can spread to nearby cells, disseminate to other host tissues, or be passed into the environment through feces. Spores also have been detected in urine and respiratory tract epithelium, thus suggesting that related body fluids also can be infectious and that transmission also can be airborne.[4,9] Once in the environment, microsporidial spores remain infectious for up to 4 months.[9] Zoonotic transmission has been proposed, as has vector-borne transmission.[4,10] The potential for vertical transmission of infection from an infected mother has not been documented in humans, but it occurs in other mammals.[4]

Clinical Manifestations

Microsporidial infection can be caused by several different organisms and can affect multiple organ systems (see Table 268.1). *Anncaliia* species were formerly *Brachiola* species.[1–19] Corneal infections in HIV-infected patients are characterized by conjunctival irritation, photophobia, foreign body sensation, and decreased visual acuity. Slit-lamp examination reveals conjunctival hyperemia, mixed follicular-papillary tarsal conjunctival reaction, and punctate epithelial keratopathy.[9] In immunocompetent hosts, keratopathy is mainly associated with the use of contact lenses and is reported to extend deeper into the cornea than in HIV-infected patients.[16]

Microsporidia-associated diarrhea is intermittent; stools are copious, watery, and nonbloody and contain no fecal leukocytes. Clinical symptoms include crampy abdominal pain and weight loss; fever is not usually present. Because microsporidia have been found in the bile, ductal biliary cells, and gallbladder tissue of several HIV-infected patients with cholangitis, these organisms have been suggested to have a causal role in cholangitis.[11,13] Disseminated disease has been shown to involve liver, kidneys, brain, bladder, lung, bone, and sinuses.

Laboratory Findings and Diagnosis

Microsporidial infection is diagnosed by microscopic demonstration of the organism in tissue or body fluids. All microsporidia range in size from 1.5 to 5 μm in width and 2 to 7 μm in length.[6] The organism can be detected with hematoxylin and eosin, Giemsa, acid-fast, fluorescent brightening (e.g., calcofluor white, Fungi-Fluor [Polysciences, Inc., Warrington, Pa]); Gram, modified trichrome, and periodic acid–Schiff stains and with immunofluorescence assay.[4,20,21] Nonetheless, the organism can be overlooked because of its small size, variable staining, and lack of an inflammatory response. Polymerase chain reaction has been reported to be a sensitive and specific diagnostic tool.[22–25] Testing is available through the Centers for Disease Control and Prevention for *Enterocytozoon bieneusi, Encephalitozoon intestinalis, Encephalitozoon hellem,* and *Encephalitozoon cuniculi.* Identification of species can be made by electron microscopic examination, immunofluorescence, or polymerase chain reaction.[2,3,22] Current serologic tests are not helpful in diagnosis.

Treatment

Albendazole has activity against many species of microsporidia and is recommended as initial therapy.[26–31] However, albendazole is not effective against *E. bieneusi* or *Vittaforma corneae* infections. In a small, placebo-controlled trial of fumagillin (60 mg/day for 2 weeks), therapy was effective in patients with advanced HIV infection and *E. bieneusi* infection; neutropenia and thrombocytopenia were frequent adverse events.[32,33] Successful treatment of *E. bieneusi* infections also has been reported with TNP-470, a synthetic analogue of fumagillin.[33] Topical fumagillin, often in conjunction with oral albendazole, can be used to treat ocular infections.[34] Metronidazole, atovaquone, nitazoxanide, and fluoroquinolones have been reported to decrease diarrhea and other symptoms but not to eradicate the organism.[26,35–37] Topical voriconazole 1% has also been reported to be effective in cases of superficial keratitis.[38] In patients with HIV infection, immune reconstitution resulting from the initiation of effective combination antiretroviral therapy is considered the primary initial therapy, and symptoms may resolve without additional treatment.[39]

Prevention

Because transmission probably occurs by passage of infectious spores in feces, isolation precautions should be considered for hospitalized patients. Patients and caregivers should perform careful handwashing. Immunocompromised people should avoid untreated water as well as unpeeled fruits and vegetables, all of which can be contaminated.[3]

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Naegleria fowleri

Joanna Nelson, Upinder Singh

Description of the Pathogen

Naegleria fowleri is a free-living ameba, and it is the only known pathogenic species of the genus *Naegleria,* which causes primary amebic meningoencephalitis (PAM) in humans and animals.[1,2] Some 30 other species have been identified according to sequencing data, some of which, like *N. australiensis* and *N. italica,* are known to cause death of experimental animals.[3,4] The organism is a facultative pathogen that occurs worldwide in soil and warm freshwater ponds, hot springs, streams, rivers, pools, and tap water. Notably, it is not found in salt water. The parasite is thermophilic and thermotolerant, proliferates in naturally and artificially warmed waters, and has an optimum activity at 37°C, but it can grow at temperatures as high as 45°C.

The life cycle includes 3 phases: trophozoite (the infective stage), flagellate, and cyst phases (Fig. 269.1). The trophozoite measures 10 to 30 µm, has a distinctive limacine (slug-like) pattern of locomotion, and has ≥1 ectoplasmic pseudopods (Fig. 269.2). *Naegleria* is the only free-living ameba that can transform into a nonreproductive, nonfeeding flagellate form in response to unfavorable environmental conditions.[5] The flagellate can in turn spontaneously revert to the trophozoite. Cysts are resistant to environmental stresses, double-walled, and approximately 9 µm in diameter, with a central nucleus and pores through which the trophozoites excyst.[5] Most remarkable feature of the molecular biology of *Naegleria* species is that the ribosomal RNA genes are carried on a 14-kb plasmid that is present as a multicopy (4000) episome.[6] The free-living *Naegleria* feed on bacteria, and unlike other pathogenic protozoa, they have no known intermediate hosts.[7]

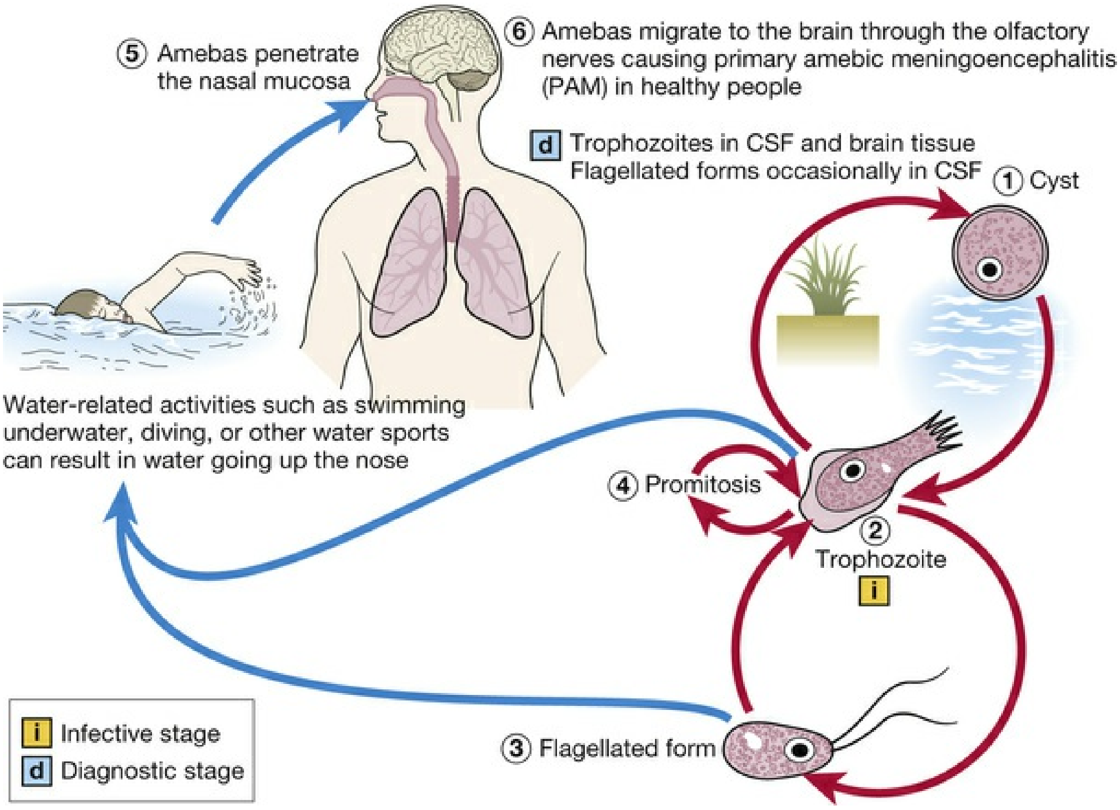
⑤ Amebas penetrate the nasal mucosa
⑥ Amebas migrate to the brain through the olfactory nerves causing primary amebic meningoencephalitis (PAM) in healthy people
d Trophozoites in CSF and brain tissue
Flagellated forms occasionally in CSF
① Cyst
Water-related activities such as swimming underwater, diving, or other water sports can result in water going up the nose
④ Promitosis
② Trophozoite
i
③ Flagellated form
i Infective stage
d Diagnostic stage

FIGURE 269.1 Life cycle of *Naegleria fowleri. Naegleria fowleri* has 3 stages in its life cycle: (*1*) cysts, (*2*) trophozoites, and (*3*) flagellated forms. The trophozoites replicate by (*4*) promitosis (nuclear membrane remains intact). *N. fowleri* is found in freshwater, soil, thermal discharges of power plants, heated swimming pools, hydrotherapy and medicinal pools, aquariums, and sewage. Trophozoites can turn into temporary nonfeeding flagellated forms, which usually revert back to the trophozoite stage. Trophozoites infect humans or animals by (*5*) penetrating the nasal mucosa and (*6*) migrating to the brain through the olfactory nerves, thus causing primary amebic meningoencephalitis. *N. fowleri* trophozoites are found in cerebrospinal fluid and tissue, whereas flagellated forms occasionally are found in cerebrospinal fluid. Cysts are not seen in brain tissue. (From the Centers for Disease Control and Prevention DPDx. [https://www.cdc.gov/dpdx/].)

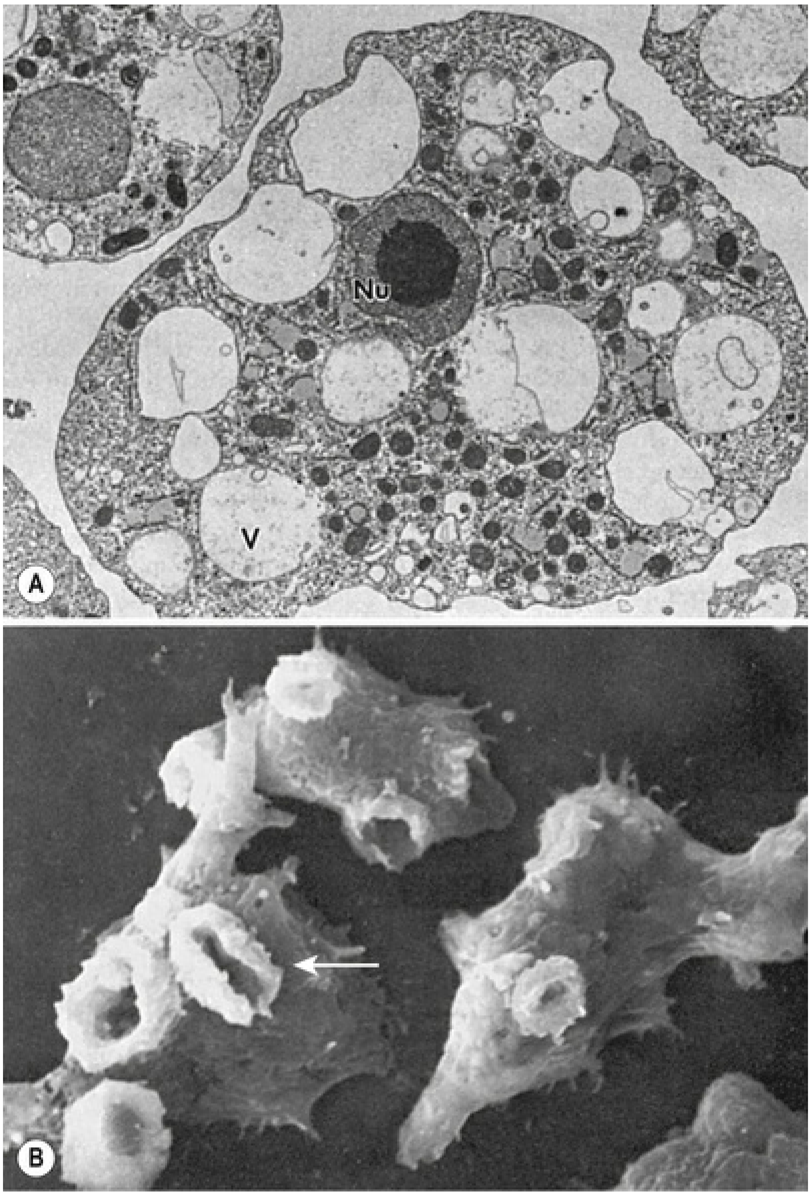

FIGURE 269.2 (A) Transmission and (B) scanning electron micrographs of *Naegleria fowleri.* Trophozoites of a pathogenic *N. fowleri* (LEE strain) ameba, isolated from a human case of primary amebic meningoencephalitis in 1968, were grown axenically in Cline medium at 37°C. Food-cup surface structures (arrow in B) are abundant on the surface of the amebas. These structures are used to ingest bacteria, yeast, or mammalian cells. Nu, nucleus; V, vacuole.

(Courtesy of Francine Marciano-Cabral, MD.)

When causing human infection, amebas enter the nasal cavity, are phagocytosed by sustentacular cells of the olfactory neuroepithelium, and migrate along the unmyelinated axonal fibers of the olfactory nerve, through the cribriform plate, and into the subarachnoid space. The incubation period varies from 2 to 7 days but can be as long as 15 days after exposure. The olfactory bulbs, the base of the frontal and temporal lobes, and the cerebellum primarily are involved in a hemorrhagic, necrotizing process.[8–10]

Epidemiology

In 1965, Fowler and Carter demonstrated that free-living amebas can invade the human brain and cause rapidly fatal meningitis. Worldwide prevalence cannot be estimated reliably; however, more than 16 countries have reported cases of PAM since the 1960s.[11] In the United States from 1937 to 2007, 121 cases were reported. Most (87%) cases occurred in the summer months in the setting of recreational warm freshwater exposure; all cases occurred in southern states.[12] More than 50% of PAM cases have occurred in Florida and Texas.[11] The first reported case of PAM in Minnesota, in 2012, raised concern that ongoing climate change could contribute to a wider geographic distribution of PAM.[13] In the US, the age of patients has ranged from 8 months to 66 years, with a median age of 12 years. Among the cases where sex of the patients was documented, 78% were male.[11,12] In general, the predilection for young, healthy people may reflect behavior (e.g., more likely to remain in the water for longer periods of time, more active in the water, and more prone to diving and underwater swimming) that stirs bottom sediment that may contain amebas. In addition to freshwater, disease has been acquired through exposure to underchlorinated swimming pools.[7] Reported clusters have also been related to nasal irrigation or other exposures with infected tap water.[14–16] Similarly, examination of treated water drinking systems worldwide has also shown the presence of *Naegleria fowleri*.[17] A few cases have not followed exposure to water and were attributed to inhalation of cysts.

Clinical Manifestations

Because of the rapid progression and significant mortality rates associated with PAM, a high degree of clinical suspicion should be maintained in the setting of children and young adults presenting with acute neurologic symptoms and a history of recent freshwater exposure. The initial presentation of patients with PAM can be indistinguishable from that seen in acute bacterial or pyogenic meningoencephalitis.[18] In 94% to 100% of patients, initial symptoms of PAM consist of severe, bifrontal headaches not responsive to analgesics, fever ranging from 38°C to 41°C, pharyngitis, nasal congestion or discharge, nausea, vomiting, and altered mental status.[1,19] Some people initially notice an altered sense of smell and taste. Somnolence, confusion, signs of meningeal irritation, and convulsions are followed by coma in approximately two thirds of patients, although PAM often progresses so rapidly that focal neurologic signs do not develop. Intracranial pressure is increased terminally and commonly causes herniation of the uncus and cerebellar tonsils. The mortality rate is >95%, and death usually occurs within 3 to 10 days after the onset of symptoms.[1,20] Diffuse or focal subclinical myocarditis has been identified in approximately one half of patients at autopsy, as evidenced by neutrophils in myocardium but importantly have lacked isolation of ameba in heart tissue. In a few cases, amebas were found in extra–central nervous system tissue after death, as noted either on histologic examination or by polymerase chain reaction (PCR). Whether cross-contamination through formalin media or leakage of *Naegleria* debris over a compromised blood-brain barrier contributed to these findings is not clear, however. One report noted no transmission of PAM to 21 transplant recipients from organ donors who died of PAM.[21]

Laboratory Findings and Diagnosis

Because human naegleriasis is an acute disease, early diagnosis is essential so that appropriate antimicrobial therapy can be initiated to limit extensive amebic damage. Patients with PAM typically have leukocytosis with neutrophilia.[18] Computed tomography or magnetic resonance imaging demonstrates cerebral edema and obliteration of the subarachnoid space. Images obtained after intravenous infusion of contrast material can show marked meningeal enhancement, particularly in the basilar areas.[10,18,22]

The cerebrospinal fluid (CSF) pressure can be markedly increased (≤300–600 mm Hg), and the fluid is cloudy and slightly hemorrhagic.[18] CSF pleocytosis can be modest initially, but it increases to 400 to 26,000 cells/mm^3, with a predominance of neutrophils. The CSF glucose concentration is normal or decreased (mean, 43 mg/dL; low, 2 mg/dL), and the protein concentration usually is increased (mean, 413 mg/dL; high, 1170 mg/dL). Rapid diagnosis is made by microscopic examination, preferably using phase-contrast techniques, of freshly drawn CSF, to visualize motile amebas. Amebas can be seen on Wright- or Giemsa-stained CSF preparations. Trophozoites have a clear nucleus with a prominent, dark-staining central nucleolus that aids in distinguishing them from macrophages. The amebic cytoplasm usually contains phagocytosed material, including erythrocytes and myelin fragments. Fresh CSF preparations collected within 30 minutes of evaluation and centrifuged at slow speeds (250 times gravity) also should be examined for motile trophozoites.[1,23,24] *Naegleria* organisms are destroyed by refrigeration. Suspending amebas in 1 mL of distilled water can further confirm the identity of the amebas as *Naegleria*, by watching for the development of actively swimming flagellate forms in 1 to 2 hours.[1,25] Brain biopsy of grey matter can reveal trophozoites localized around blood vessels. Indirect immunofluorescence or immunoperoxidase staining can be used to speciate amebas in formalin-fixed, paraffin-embedded tissue sections. *Naegleria* cysts rarely are present in tissue, and identification of cysts should raise suspicion of another infective ameba, such as *Acanthamoeba* (Table 269.1).[26] CSF PCR testing has been proposed as a means of rapid diagnosis of PAM; however, PCR is not available widely.[27] Serologic tests generally are not helpful because the acutely infected patient usually dies before mounting a significant antibody response. In addition, antibody can be present in the healthy population, a finding suggesting the possibility of subclinical infection. Further corroboration can be obtained by isolation of the amebas from CSF or macerated brain tissue on a nonnutrient agar plate that has been spread with a lawn of *Escherichia coli* and incubated overnight at 37°C. The amebas grow in large numbers and feed on the bacteria. Tissue culture, especially on monkey kidney cells, also has been used to cultivate *Naegleria*.[28]

TABLE 269.1

Characteristics of *Naegleria* and *Acanthamoeba*

	Naegleria	*Acanthamoeba*
Disease	Primary amebic meningoencephalitis	Granulomatous amebic encephalitis (also causes *Acanthamoeba* keratitis)
Agent	*N. fowleri*	>20 implicated *Acanthamoeba* species
Protozoology	Trophozoite 10–15 µm in diameter Round cyst with pores Transient flagellate form	Trophozoite 14–40 µm in diameter Double-walled cyst
Epidemiology	History of recreational water sports Previous good health	History of poor health Immunocompromised (AIDS)
Incubation period	2–7 days, ≤15 days	Uncertain, >10 days
Clinical course	Acute, fulminant	Chronic
Portal of entry	Olfactory neuroepithelium	Lung, skin, eyes
CSF findings	Active trophozoites present Neutrophils predominant	Organism rarely isolated from CSF Lymphocytes predominant, neutrophils increased
Pathology	Acute purulent leptomeningitis Only trophozoites in brain tissue	Chronic granulomatous encephalitis Cysts and trophozoites in brain tissue

AIDS, acquired immunodeficiency syndrome; CSF, cerebrospinal fluid.

Treatment

Survival from PAM is rare, with only a few well-documented published cases. In the absence of clear guidelines, amphotericin B is the most widely accepted drug for the treatment of PAM.[29] Amphotericin B intrathecal therapy also has been used as an adjunct to intravenous amphotericin with reported success.[30,31] Amphotericin targets the parasite's plasma membrane by binding to ergosterol in the membrane, thus producing pores and causing loss of small molecules. From in vivo and in vitro evaluations, *N. fowleri* appears to be highly sensitive to amphotericin B, but delay in diagnosis and the fulminant nature of the disease result in few survivors,[32] and even with appropriate treatment selection, disease relapses have occurred.[33]

Numerous anecdotal case reports have noted success in treating *Naegleria* infections with combination therapy. These regimens have included amphotericin B in combination with rifampin or amphotericin B in combination chloramphenicol, fluconazole, or ketoconazole.[32,34–36] Miltefosine is an investigational drug now available through the Centers for Disease Control and Prevention with in vitro activity against free-living amebas.[37] One case report described a 12-year-old girl who survived after receiving miltefosine in combination with amphotericin B, fluconazole, rifampin, and azithromycin.[38] Regimens including amphotericin and azithromycin also have been suggested as possible synergistic agents in vitro and in mouse models of PAM.[39] The optimal duration of therapy is not known, but a course of at least 10 days of treatment has been used in survivors.[30,31]

Prevention

Avoidance of the free-living amebas is virtually impossible because these organisms are ubiquitous in the environment, as evidenced by the presence of antibodies in screened human populations.[40] *N. fowleri* is so common in the environment that surveillance is not indicated unless several people are infected after a common exposure.[28,41,42] The incidence of PAM is low despite populations of amebas >1 organism/25 mL of water (as found in water tested in late summer in Florida) and despite millions of exposures to recreational waters. Protective factors are unknown. *N. fowleri* is susceptible to ≤1 mg/L chlorine.[1] Proper chlorine disinfection of water in swimming pools and whirlpools and avoidance of diving and of introduction of water into the nostrils appear to be reasonable measures to avoid development of amebic encephalitis.[1] Recommendations include use of chlorine in swimming pools at 1 mg/L if the water temperature is <26°C, at least 2 mg/L if the temperature is >26°C, and 3 mg/L for temperatures >28°C.[1] Cysts are destroyed after 1 hour of exposure to pool or tap water at these concentrations.

Key Points

Epidemiology, Clinical Features, and Diagnosis of *Naegleria fowleri* Infection

Microbiology and Histopathology

- Free-living ameba

- Life cycle involves trophozoite, flagellate, and cyst forms.
- Causes hemorrhagic necrosis of central nervous system

Epidemiology

- Rare disease; 120 reported cases from 1937 to 2007 in the United States
- Exposure to warm recreational freshwater or contaminated tap water
- Primarily young, healthy people affected

Clinical Features

- Rapidly progressive fulminant meningoencephalitis
- >95% fatal

Diagnosis

- CSF findings similar to bacterial meningitis
- Microscopic identification of trophozoite in CSF

Treatment

- Therapeutic regimens are not well defined. Limited data suggests amphotericin B is the treatment of choice.

CSF, cerebrospinal fluid.

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Acanthamoeba Species

Joanna Nelson, Upinder Singh

Description of Pathogen

Nearly 25 named species and 15 genotypes of *Acanthamoeba* have been identified worldwide. Previously these groups were distinguished based on morphologic features into 3 groups (I, II, III); however, molecular techniques have led to species identification based on genetic similarities.[1] *Acanthamoeba* are classified as free-living amebas because of their lack of dependence on animals to complete their life cycle. The organism has 2 phases in its life cycle: a motile trophozoite phase and a resilient infective cyst stage (Fig. 270.1). Trophozoites are 25 to 50 μm in diameter and have distinctive slender, spine-like projections of the plasma membrane called acanthopodia (Fig. 270.2). The cysts have a double-layered wall and are 15 to 30 μm in diameter. Both forms have a wide distribution in nature. Several species of *Acanthamoeba* are known pathogens in humans. *A. castellanii, A. culbertsoni, A. polyphagia, A. astronyxis, A. palestinensis, A. healyi*, and *A. divionensis* usually cause fatal, subacute disseminated disease with granulomatous amebic encephalitis in immunocompromised hosts.[2,3] Additionally, *A. polyphagia, A. castellanii, A. culbertsoni, A. hatchetti, A. rhysodes, A. quina, A. lugdunensis*, and *A. griffini* can cause amebic keratitis, a vision-threatening disorder predominantly seen in immunocompetent contact lens wearers.[2]

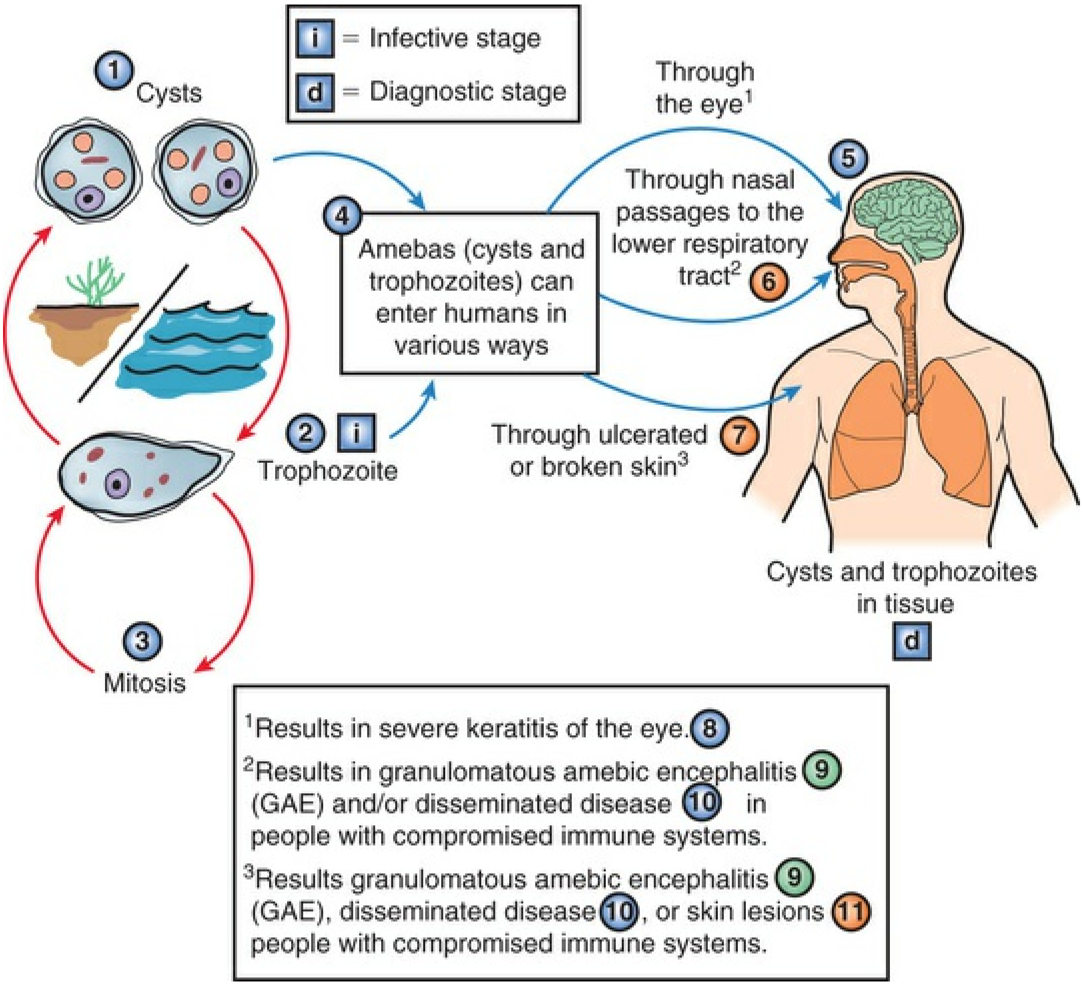
i = Infective stage
d = Diagnostic stage
① Cysts
② i Trophozoite
③ Mitosis
④ Amebas (cysts and trophozoites) can enter humans in various ways
⑤ Through the eye¹
Through nasal passages to the lower respiratory tract² ⑥
Through ulcerated or broken skin³ ⑦
Cysts and trophozoites in tissue d
¹Results in severe keratitis of the eye. ⑧
²Results in granulomatous amebic encephalitis ⑨ (GAE) and/or disseminated disease ⑩ in people with compromised immune systems.
³Results granulomatous amebic encephalitis ⑨ (GAE), disseminated disease ⑩, or skin lesions ⑪ people with compromised immune systems.

FIGURE 270.1 **Life cycle of *Acanthamoeba. Acanthamoeba* has 2 stages, (*1*) cysts and (*2*) trophozoites, in its life cycle. The trophozoites replicate by (*3*) mitosis. The trophozoites are the infective forms, although both cysts and trophozoites gain entry into the body (*4*) through various means. Entry can occur (*5*) through the eye and lead to severe keratitis in otherwise healthy people, particularly contact lens users. Entry can also occur (*6*) through the nasal passages, or (*7*) broken skin, and *Acanthamoeba* can spread through hematogenous dissemination to cause granulomatous amebic encephalitis, skin lesions, or disseminated disease in people with compromised immune systems.** (From the Centers for Disease Control and Prevention DPDx. [https://www.cdc.gov/dpdx/].)

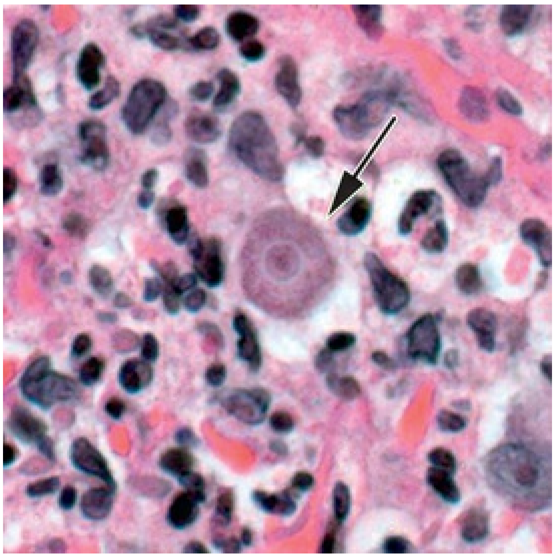

FIGURE 270.2 ***Acanthamoeba* trophozoite (*arrow*) in a biopsy tissue (hematoxylin and eosin stain; original magnification, ×1000).** (From the Centers for Disease Control and Prevention DPDx. [https://www.cdc.gov/dpdx/].)

Epidemiology

Acanthamoeba species have been isolated readily from water (including treated water; brackish water; seawater; swimming pools; sewage; domestic tap water; bottled mineral water; cooling, heating, and humidifying units; hot tubs; hospitals and dialysis units; dental irrigation units; eyewash stations; and contact lenses and associated paraphernalia), soil, dust, air, and sediments and as contaminants in cell cultures.[2–4] Limited seroprevalence surveys of healthy people have demonstrated antibodies from immunoglobulin M (IgM) and IgG classes to *Acanthamoeba* species, a finding indicating that asymptomatic infections likely occur.[5,6] People with compromised immune systems such as those with diabetes mellitus, chronic liver disease, renal failure, or systemic lupus erythematosus, transplant recipients, patients receiving chemotherapy or corticosteroids on a longterm basis, pregnant women, and human immunodeficiency virus (HIV)–infected people are at risk for severe manifestations of *Acanthamoeba* infections such as disseminated disease and granulomatous amebic encephalitis.[7–13] Difficulties in diagnosing amebic encephalitis limits the ability to capture the true incidence of disease. Although central nervous system (CNS) disease with *Acanthamoeba* occurs predominantly in immunocompromised people, cases have been reported in both adults and children with intact immune systems.[14–22]

Amebic keratitis most commonly occurs in immunocompetent contact lens wearers, but it can also be related to corneal trauma. In a multicenter review of 116 cases in the United States, 96% of cases were associated with contact lens use.[23] The estimated annual incidence ranges from 1.7 to 19.5 cases per 1,000,000 contact lens wearers.[24] Previous outbreaks were related to the use of nonsterile, homemade saline solution in the 1980s and the use of a specific contact lens solution in 2007 that was later recalled.[25,26] Poor lens hygiene, water contamination, and ineffectiveness of disinfectant solutions against *Acanthamoeba* likely play roles in ongoing infections.[24,25,27]

Clinical Manifestations

Acanthamebic encephalitis usually is termed *granulomatous amebic encephalitis* because of its pathologic appearance. The disease generally occurs after infection at other sites, thus implying that trophozoites reach the CNS by hematogenous dissemination.[8] The route of infection is thought to be by inhalation of amebae through the nasal passages and lungs or introduction through skin lesions. Although the incubation period for *Acanthamoeba* infections is unknown, it can be several weeks or months. The neurologic symptoms of granulomatous amebic encephalitis have an insidious onset and include focal deficits such as hemiparesis, diplopia, cranial nerve palsies (especially of cranial nerves III and VI), and cerebellar ataxia. Nonfocal neurologic manifestations include personality changes, seizures, headache, meningismus, nausea, stiff neck, lethargy, altered mental status, signs of increased intracranial pressure, and coma.[28] Low-grade intermittent fever, nausea, and vomiting also can occur. The disease usually is fatal after an average of 39 days of illness (range, 7–120 days).

The symptoms of *Acanthamoeba* keratitis often begin with the sensation of a foreign body in the eye, followed by severe (usually unilateral) ocular pain, redness, photophobia, tearing, blurred vision, and eyelid edema. Clinical findings during early disease (within the first 4 weeks) are characterized as epitheliopathy, with perineural infiltrates pathognomonic. Late disease (after 4 weeks) is characterized by ring infiltrates, ulceration, and secondary sterile anterior uveitis, sometimes with hypopyon (Fig. 270.3). Limbitis can be seen in both early and late disease. Waxing and waning of symptoms and physical signs are common and often result in delayed diagnosis, and bacterial superinfection is not uncommon.[24] Blindness can result if disease progresses without treatment. In rare circumstances, *Acanthamoeba* can spread from the cornea to the retina, thereby causing chorioretinitis. On these occasions, the spread of *Acanthamoeba* has been postulated to have been facilitated by combined keratoplasty, extracapsular cataract extraction, and intraocular lens insertion.[29]

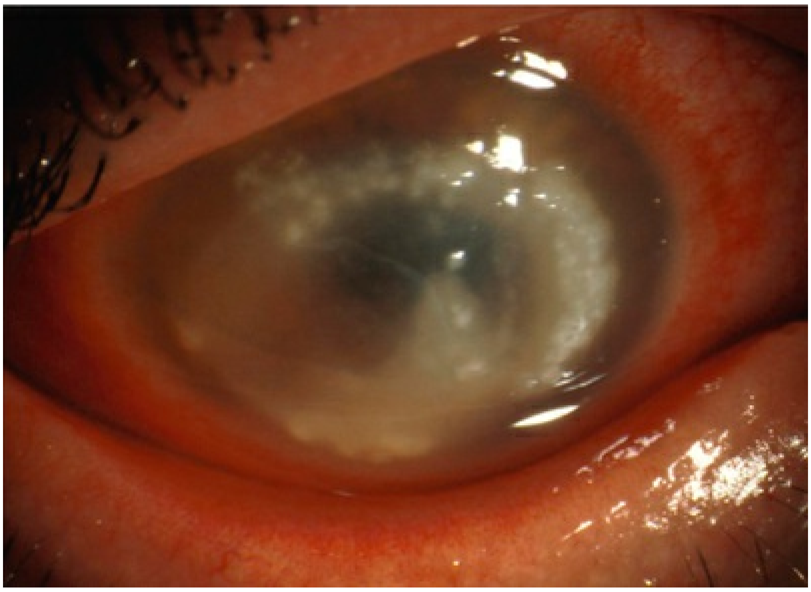

FIGURE 270.3 Ring infiltrate and severe scleritis in advanced *Acanthamoeba* keratitis. (From Dart JK, Saw V, Kilvington S. *Acanthamoeba* keratitis: diagnosis and treatment update 2009. Am J Ophthalmol 2009;148:487.e2–499.e2.)

Cutaneous infections often are a reflection of disseminated disease caused by *Acanthamoeba* and are most common in patients with acquired immunodeficiency syndrome (AIDS), but they can also be seen in other immunosuppressed patients such as organ transplant recipients or patients with malignant disease who are receiving chemotherapy.[30–34] The cutaneous form of the disease is characterized by the presence of hard erythematous nodules or skin ulcers.[35] Early manifestations include the presence of firm papulonodules that become abscesses, drain purulent material, and then develop into nonhealing, indurated ulcerations.[2,36,37] The mortality rate in patients with cutaneous infection in patients without CNS involvement is approximately 73%, whereas the mortality rate in patients with cutaneous infection accompanied by CNS disease is 100%.[30] Other manifestations of *Acanthamoeba* infections in HIV-infected patients include sinus infection, which manifests with the typical symptoms of sinusitis.[38]

Laboratory Findings and Diagnosis

The diagnosis of granulomatous amebic encephalitis depends on isolation or histologic demonstration of *Acanthamoeba* from a brain biopsy specimen (see Fig. 270.2). Various stains (e.g., hematoxylin and eosin, Wright, Giemsa, periodic acid–Schiff, and calcofluor white) highlight the trophozoites or cysts in tissue, which in the brain often localize to the perivascular spaces. Indirect immunofluorescent and immunoperoxidase staining methods can be used to confirm the diagnosis. Polymerase chain reaction of brain tissue can also aid in the diagnosis.[39] Computed tomography of the head has shown mass lesions that resemble abscesses, tumors, or hemorrhage.[2,40] These lesions often are multifocal and occasionally nonenhancing and occur throughout the cortex, brainstem, and spinal cord. Lumbar puncture can be contraindicated because of these space-occupying lesions, but when it is performed, the cerebrospinal fluid (CSF) has elevated opening pressure, lymphocytic pleocytosis, moderately elevated protein concentrations, and low glucose concentrations. Although the CSF traditionally has been considered sterile, reports have noted motile trophozoites and positive culture results from CSF samples from children.[14,21] Culture requires that tissue be inoculated onto nonnutrient agar overlaid with *Escherichia coli* or *Enterobacter aerogenes,* which serve as food sources for the ameba.[26,41] The organism also can be isolated from culture of skin lesion swabs, and in suspected cases biopsy should be performed on skin lesions.

In vivo confocal microscopy for the diagnosis of amebic keratitis has emerged as a useful noninvasive diagnostic tool, with sensitivity and specificity reported at greater than 90%, although these numbers can be operator dependent.[25,28] A suspected diagnosis based on this technique should then be confirmed by isolation or demonstration of *Acanthamoeba* in corneal scrapings or corneal biopsy specimens by culture or histopathologic examination. Scrapings should be examined for motile trophozoites or cysts as a wet mount before drying or fixation. Polymerase chain reaction can be used for diagnosis and has a specificity of 84% compared with 53% for culture in 1 study.[42] Staphylococci, streptococci, and other bacteria have been isolated concurrently in some cases and can confound the diagnosis. *Acanthamoeba* has also been isolated from contact lenses, lens cases, lens-cleaning solutions, and corneal tissues.[26]

Treatment

Central Nervous System Infections

Treatment of granulomatous amebic encephalitis rarely is successful, probably because of a combination of late diagnosis and antimicrobial failure. Although no standard regimen exists, anecdotally successful regimens have involved combination therapy including pentamidine, sulfadiazine, trimethoprim-sulfamethoxazole, flucytosine, and fluconazole, ketoconazole, or itraconazole.[3,43] Treatment of granulomatous amebic encephalitis in immunocompromised hosts can be particularly challenging; however, treatment success has been reported with combination therapy using fluconazole, pyrimethamine, and sulfadiazine along with surgical resection of the CNS lesion.[44] Oral regimens including a combination of trimethoprim-sulfamethoxazole, rifampin, and ketoconazole have been used successfully to treat children with chronic *Acanthamoeba* meningitis.[14] A small retrospective analysis suggested that adding miltefosine to treatment regimen may increase survival, but more data are needed to make definitive conclusions.[45] Miltefosine is currently available through the Centers for Disease Control and Prevention as an investigational drug to treat free-living ameba infections.

Cutaneous Disease

Patients with cutaneous acanthamebiasis have been treated with various drugs. Successful treatment of a patient with AIDS with cutaneous and sinus lesions by using 40 mg/kg of 5-fluorocytosine orally for 2 weeks was reported.[46] Topical therapy with miltefosine also is a consideration in the immunocompromised host.[47] Some treatment regimens that can be successful in 1 patient can yield a poor outcome in another. For instance, intravenous pentamidine in combination with topical chlorhexidine and 2% ketoconazole cream, followed by itraconazole orally, has been used successfully,[48] although failure of a similar regimen was reported in another patient.[49] *Acanthamoeba* isolates have shown varied susceptibility patterns among species and among strains of the same species; thus susceptibility testing is recommended to guide therapy.[50]

Keratitis

Treatment of amebic keratitis can be effective, particularly when therapy is initiated early. Treatment entails use of topical antiamebic agents and, in more severe cases, surgical debridement. No clear guidelines are available for treatment of this disease; however, combination therapy with either topical chlorhexidine or polyhexamethylen biguanide (PHMB), plus dibromopropamidine, are commonly used successfully.[2,26] Adjunctive oral and topical therapies such as ketoconazole and itraconazole can be considered.[25] The use of adjunctive topical corticosteroids is controversial. Although some reports of corticosteroid therapy controlling inflammation, pain, and ulceration exist,[51] the use of these drugs has been complicated by crystalline keratopathy caused by infection with viridans streptococci (including *Streptococcus oralis*) and *Staphylococcus aureus.*[52] When medical therapy with debridement has failed, penetrating keratoplasty, corneal transplantation, and even enucleation have been required.[26]

Prevention

The ubiquitous nature of *Acanthamoeba* argues against complete prevention of granulomatous amebic encephalitis in highly immunocompromised people. *Acanthamoeba* keratitis, however, is largely a preventable disease if proper contact lens care techniques are followed and swimming with contact lenses is avoided. Additional appropriate prevention measures include thermal disinfection of contact lenses, use of hydrogen peroxide–containing solutions (2-step processes are better than 1-step), good lens case care, and the use of an amebicidal storage solution (a combination of PHMB and chlorhexidine appears to be ideal).[53,54] Sterile saline containing benzalkonium preservatives (chlorine-based solutions are not effective against *Acanthamoeba*) should be used for lens storage.

Key Points

Epidemiology, Clinical Features, and Diagnosis of *Acanthamoeba* Infection

Microbiology and Histopathology

- Free-living ameba with 2 stages: trophozoite and cyst
- Trophozoite has characteristic acanthopodia: spine-like projections of plasma membrane.
- Brain biopsy shows edema, multinucleated giant cells, hemorrhagic necrosis; both cysts and trophozoites can be found in tissue.

Epidemiology

- Found ubiquitously in water and soil
- Causes disseminated disease and granulomatous amebic encephalitis in immunocompromised patients
- Amebic keratitis most common in contact lens wearers

Clinical Features

- Granulomatous amebic encephalitis manifests as insidious onset of focal neurologic deficits, personality changes, altered mental status, fever, progressing to seizure, increased intracranial pressure, coma, and death.
- Cutaneous lesions are firm papulonodules that become abscesses, drain purulent material, and then develop into nonhealing indurated ulcerations.
- Keratitis manifests with foreign body sensation, ocular pain, and

redness.

Diagnosis

- Biopsy of affected tissue for culture, histopathologic examination, immunohistochemical staining, or polymerase chain reaction

Treatment

- Therapeutic regimens are not well defined; surgical debridement may play an adjunctive role.

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271

Plasmodium Species (Malaria)

Julie Gutman, Paul M. Arguin

Although malaria is a major cause of morbidity and mortality in the world, most cases in the United States and Europe occur in people who have traveled to or emigrated from endemic areas.[1] Obtaining a travel history from all patients who present with fever and having a high index of suspicion for malaria in people who have recently traveled to a malaria-endemic area are important because infection can be rapidly fatal. In addition, malaria rarely is acquired from blood transfusion, through congenital transmission, or through transmission from an imported case. This chapter focuses on malaria as it is likely to be encountered in nonendemic settings.

Description of the Pathogen

Five species of malarial parasites can naturally infect humans. Humans are the natural hosts for 4: *Plasmodium falciparum, P. vivax, P. ovale,* and *P. malariae,* whereas the fifth, *P. knowlesi,* typically infects macaques. Although all species of malaria can cause severe infections, *P. falciparum* is the most lethal and the most drug resistant. Of the human species, *P. vivax* was previously the most widely distributed geographically and the best adapted to survive in temperate climates. However, successful malaria control programs in the US and Europe essentially eliminated *P. vivax* from these regions. *P. falciparum* is the most prevalent species in sub-Saharan Africa. *P. ovale* mainly occurs in the western areas of sub-Saharan Africa. *P. knowlesi* normally infects macaques in Southeast Asia; however, it has been implicated in human cases throughout Southeast Asia and is responsible for approximately 50% of cases in Malaysia. Different stages of *P. knowlesi* closely resemble *P. malariae,* thus making it difficult to diagnose by microscopy. In contrast to the usually benign infections with *P. malariae,* infection with *P. knowlesi* can be rapidly fatal, so considering this possibility when treating patients who could have acquired malaria in this region is important, to minimize severe morbidity and mortality.[2]

The life cycles of all human malarial parasites are illustrated in Fig. 271.1. Sporozoites are inoculated into humans by the bite of an *Anopheles* species mosquito and invade hepatic parenchymal cells within minutes. The parasites undergo asexual multiplication, or schizogony, in this tissue phase of their life cycle, also called exoerythrocytic schizogony. After a period of development and multiplication (7–10 days for *P. falciparum, P. ovale,* and *P. vivax* and 10–14 days for *P. malariae* and *P. knowlesi*), merozoites emerge to invade erythrocytes and begin what will become the symptomatic phase of the illness. Parasites of the 2 relapsing species, *P. ovale* and *P. vivax,* also can differentiate into a quiescent stage, the hypnozoite, which later can enter into schizogony and reemerge to invade erythrocytes. *P. malariae* has the potential to persist at very low levels in the circulation for decades if it is not recognized and treated.

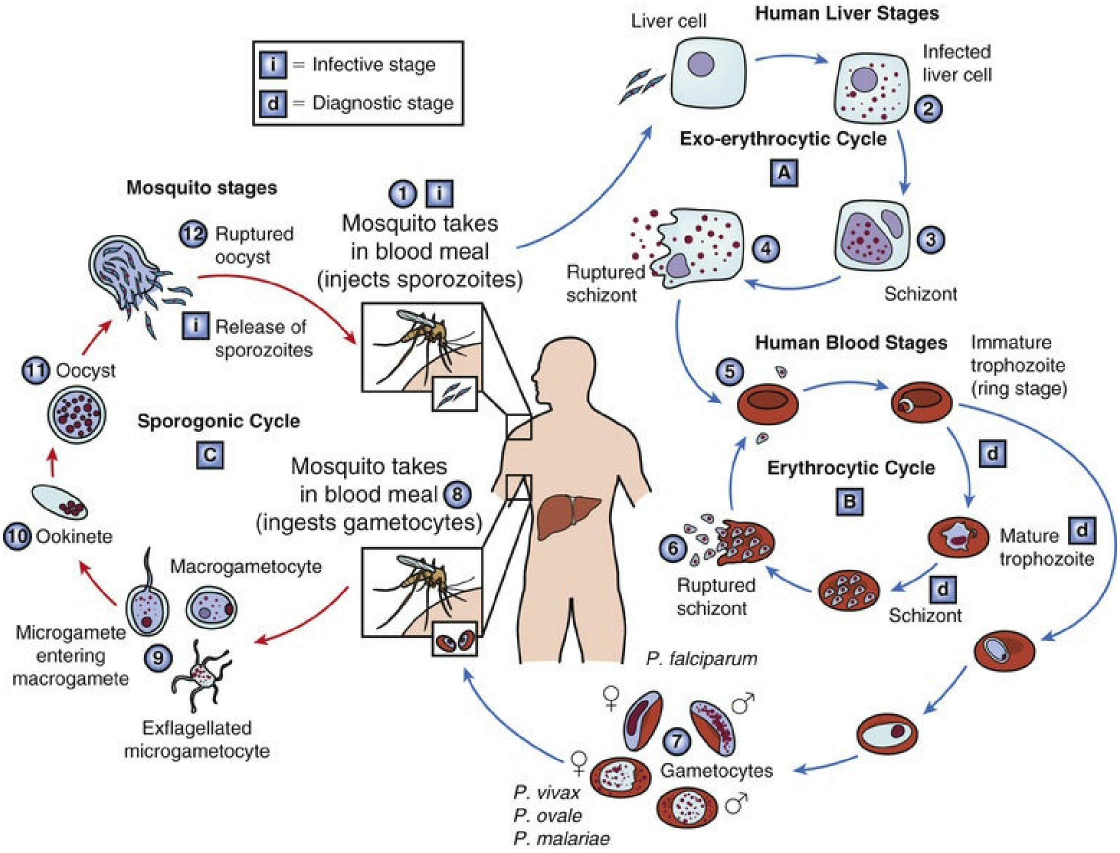

FIGURE 271.1 Generalized life cycle of malarial parasites in the anopheline mosquito vector and in humans. **(From the Centers for Disease Control and Prevention.)**

Each species has developed an efficient strategy for erythrocyte invasion that relies on a specific, complex interaction of certain surface proteins or glycoproteins on the erythrocyte and a specific ligand of the parasite. For example, *P. vivax* preferentially invades erythrocytes bearing the Duffy blood group antigen, an antigen that is rarely found on erythrocytes in people from West and central Africa[3]; consequently *P. vivax* malaria is uncommon throughout most of West Africa. *P. falciparum* invades erythrocytes of all ages, while *P. vivax* and *P. ovale* preferentially invade reticulocytes, and *P. malariae* and *P. knowlesi* preferentially invade mature erythrocytes. Once inside the erythrocyte, parasites can undergo either asexual schizogony or sexual differentiation to produce gametocytes.

During asexual schizogony, the parasites are known as trophozoites once they are established inside the erythrocyte; the early trophozoite forms often are called rings because of their apparent lack of central cytoplasmic staining. Parasites in this stage ferment homolactate and actively digest the host cell hemoglobin, which they use as a source of amino acids and energy.[4] This activity is accomplished through a set of highly adapted proteinases in a singularly adapted organelle, the food vacuole.[5] The residue of hemoglobin degradation is an intact tetrapyrrole ring, ferriprotoporphyrin IX, which the parasites detoxify through polymerization and can be seen microscopically as malarial pigment, hemozoin.[6] This polymerization step is thought to be the site of action of quinoline-containing antimalarial compounds, including chloroquine.[7,8]

The actual replicative phase, when the parasite is called a schizont, comprises the last few hours of the erythrocytic stage of the parasite's life cycle, during which the parasite undergoes mitosis and subdivides and differentiates into merozoites. The subsequent rupture and release of merozoites lead to fever and other malarial symptoms. In synchronized infections, which typically occur only after the infection is well established, the periodicity of symptoms is 48 hours in *P. ovale* and *P. vivax* malaria, 72 hours in *P. malariae* infections, and 24 hours in *P. knowlesi* infections.[9] Although periodicity can be every 48 hours in *P. falciparum* infections, it often is irregular. The absence of periodicity does not rule out malaria (any species) as a diagnosis for a febrile illness in a person with an appropriate travel history.

Parasites in the erythrocytic stages also can undergo sexual differentiation, a step that is necessary for transmission. Male and female gametocytes, which are produced by each *Plasmodium* species, remain inside the erythrocyte until they are ingested by the mosquito. At this point, they undergo further differentiation and join to form a zygote, which differentiates into an ookinete and invades the mosquito midgut to form the reproductive oocyst. Sporozoites emerge from the oocyst and migrate to the salivary gland, where they can reinfect a human during a subsequent blood meal.

In general, all the erythrocytic asexual and sexual developmental stages of *P. ovale, P. vivax, P. malariae,* and *P. knowlesi* occur in circulating blood and can be visualized in the peripheral blood smear. The late trophozoite stages of *P. falciparum* rarely are seen in the peripheral circulation because of the development of “knobs” on infected erythrocytes that lead to adherence of the parasitized erythrocytes to the capillary endothelium.[10] Sequestration of parasites in various organs is believed to be responsible for the clinical manifestations of *P. falciparum* infections, such as central nervous system and pulmonary complications.

No strict immunity per se develops to malaria, but rather an acquired ability to tolerate *Plasmodium* spp. infections occurs that is a selective process related to the degree of exposure to a variety of strains.[11] Most deaths caused by malaria in malaria-endemic areas with high transmission of *P. falciparum* occur in children <5 years of age. Although *P. falciparum* can cause lethal infection in young children or nonimmune people, asymptomatic parasitemia is common in older age groups in highly endemic areas. In the US, most malaria cases occur among first- and second-generation immigrants returning to their countries of origin to visit friends and relatives and who either do not believe that malaria prophylaxis is necessary or are unaware of the need to take prophylaxis while traveling, despite their loss of immunity.[1] Malaria deaths in the US occur among all age groups.

Epidemiology

The epidemiology of malarial infections is intricately linked to the distribution and habits of the anopheline vectors in any particular region. In highly endemic areas, mosquito breeding can take place nearly year round, and reproductive capacity in the mosquito is maximized by a tropical climate.[12] In areas of seasonal transmission, prevalence is particularly related to rainfall or other ecologic events that affect the mosquito population. Malaria also can be related to occupation when only certain segments of the population are exposed to the vectors (e.g., in places where cases occur in men whose jobs require them to enter the forests where the vectors live). In nonendemic countries such as the US, the epidemiology of malaria is most closely linked to international travel patterns.

The estimated worldwide incidence of malaria is 212 million (uncertainty range, 148 million to 304 million) clinical malaria episodes per year, with an estimated 429,000 deaths (uncertainty range, 235,000 to 639,000) in 2015, most of which occurred in children <5 years of age.[13] Almost all deaths are caused by *P. falciparum*, with more than 80% occurring in sub-Saharan Africa. Before the 1950s, malaria was endemic in the US. During the late 1940s, a combination of improved housing and socioeconomic conditions, water management, vector-control efforts, and case management was successful in interrupting malaria transmission. In the US today, an average of 1500 cases and 5 deaths occur each year; almost all cases are in people who have traveled to or are emigrating from malarious areas,[1] although transmission occasionally occurs congenitally or through transfusion or transplantation. From 1963 to 2012, 97 cases of malaria acquired through transfusion were reported in the US.[14] From 1966 to 2005, 81 cases of congenital malaria were reported in the US.[15] Anopheline vectors still are present in most areas of the US, and, infrequently, localized instances of malaria have occurred because of transmission from imported human cases.[16]

Clinical Manifestations

The clinical features of malaria depend on the malaria-specific immune status of the host and the infecting species of *Plasmodium.* Nonimmune people (e.g., those who have not resided in an endemic area or have moved away from an endemic area) generally develop symptomatic illness. Infections with *P. falciparum* are more likely to become severe than are infections with the other 4 species that naturally infect humans.

The febrile paroxysm is the hallmark of malaria and typically lasts from 10 to 12 hours. It consists of a period of intense rigors or chills, followed by high fever that can induce a febrile seizure; profuse sweating occurs with defervescence. Other nonspecific symptoms at the time of fever include headache, malaise, myalgia, and arthralgia. Gastrointestinal tract symptoms, including abdominal pain, vomiting, and diarrhea, can occur. Although prostrated during febrile episodes, people otherwise can be remarkably asymptomatic between episodes.

Given the variable and nonspecific clinical findings and the potential for rapidly fatal disease, a high index of suspicion for malaria is necessary in ill travelers who have returned from an endemic area. Another complicating factor is that nonimmune people can have clinical symptoms despite low levels of parasitemia. Thus 3 thick and thin blood smears separated by 12 to 24 hours are recommended to exclude a diagnosis of malaria.

Significant morbidity and mortality rates from *P. falciparum* infections result from cerebral effects.[17] Delirium and confusion can occur with the high fever of malaria, but declining mental status is more ominous and indicates the need for urgent treatment. Symptoms can progress rapidly to coma. Whereas meningismus, generalized seizures, and symmetric upper motor neuron dysfunction can be seen, focal seizures or localizing neurologic signs are uncommon in malaria. The rapid recovery of central nervous system function with antimalarial treatment and the general lack of sequelae suggest metabolic encephalopathy as the probable mechanism of dysfunction. The highest risk for neurologic sequelae is in patients with multiple seizures, prolonged coma, hypoglycemia, and clinical features of intracranial hypertension.[18,19]

The combination of respiratory compromise and renal dysfunction with *P. falciparum* infection also is associated with increased mortality rates.[20] Respiratory distress syndrome can occur after initiation of appropriate therapy with clearance of parasitemia and should not be considered a failure of therapy. Renal dysfunction most commonly occurs as acute tubular necrosis, probably secondary to hypoperfusion from hypotension or hypovolemia. Although reported in children, this complication is observed more frequently in nonimmune adults. Nephrotic syndrome and glomerulonephritis have been associated with chronic infections with *P. malariae* in children, but these findings are not common.

Hyperparasitemia (≥5% red blood cells [RBCs] infected) is an independent marker of severe disease. It occurs with *P. falciparum* infection in nonimmune people and frequently is associated with hypotension, metabolic acidosis, and hypoglycemia.[17,20] These signs all can be attributed to parasitemia and associated cytokine disturbances, although concomitant gram-negative bacillary septicemia has been reported, particularly in association with severe gastrointestinal tract symptoms.[20] Hypoglycemia must be managed aggressively and monitored carefully, particularly during quinine or quinidine therapy.

Anemia is an expected consequence of malaria, especially in patients with hyperparasitemia. Hemolysis from erythrocytic parasitosis, sequestration and RBC destruction resulting in hypersplenism, and dyserythropoiesis have been identified as mechanisms contributing to anemia.[21] Thrombocytopenia is extremely common in malaria, including very low platelet counts, but it rarely leads to bleeding diathesis. Evidence of consumptive coagulopathy is rare but can occur with *P. falciparum* infection in nonimmune people, and it usually develops in the setting of “algid” malaria, a septic shock–like syndrome. Brisk hemolysis with hemoglobinuria, called blackwater fever, can occur with hyperparasitemia in nonimmune people. However, this condition is more common as an epiphenomenon in people residing in endemic areas and is associated with prolonged quinine intake (which is no longer recommended) or in glucose-6-phosphate dehydrogenase (G6PD)–deficient people who are using oxidant antimalarial drugs.

Although complications of malaria are generally limited to the acute illness, prolonged convalescence is common. In general, full recovery from any pulmonary, renal, or central nervous system compromise is the rule. The exception occurs in children with cerebral malaria, up to 10% of whom may have residual neurologic deficits.[19]

Laboratory Findings and Diagnosis

The most important step in making the diagnosis of malaria is including it in the differential diagnosis. Many of the deaths caused by malaria in the US are related to a delay in diagnosis.[22] Malaria should be considered the primary diagnosis until proven otherwise in any febrile patient who has traveled to or emigrated from an endemic area. Malaria also should be considered in patients who develop fever within days to a few months after blood transfusion.

The diagnosis of malaria is made by identifying parasites in thick or thin blood films stained with common hematologic stains, most typically Giemsa-based stains. The thick film preparation is the more sensitive technique, but it is more difficult to interpret by inexperienced examiners. Speciation and quantification are performed with a thin smear. For initial clinical management, identifying the presence or absence of malaria parasites is most important. If the parasites are present, determining the percentage of parasitemia is essential for management because patients with ≥5% infected RBCs have a greater incidence of complications and require immediate therapy intravenously. To quantify malaria parasites, between 500 and 2000 RBCs should be examined.

Erythrocytes infected with multiple parasites are counted as a single infected RBC. Gametocytes should not be counted in the evaluation of parasitemia (Fig. 271.2).

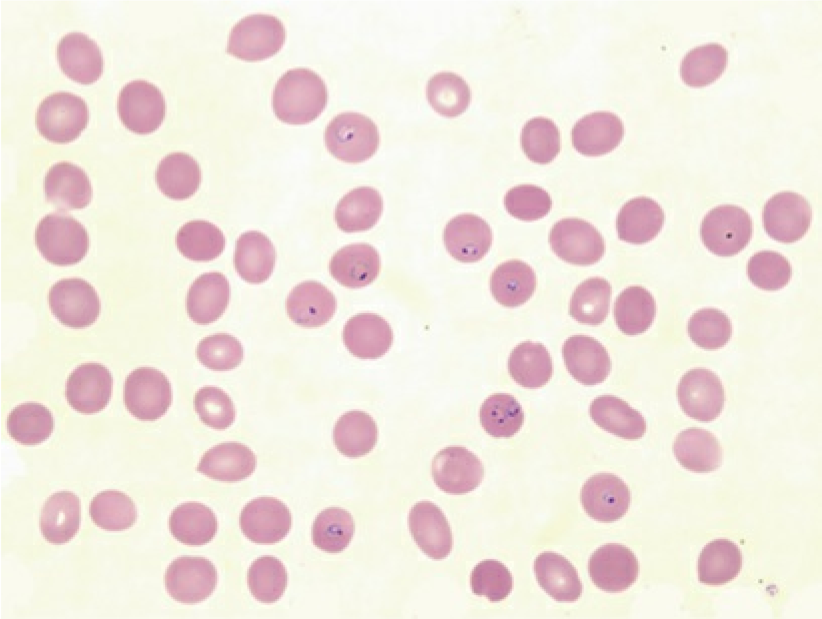

FIGURE 271.2 Calculation of parasitemia on a thin blood film. This image shows 59 red blood cells. Eight of the red blood cells have malaria parasites. Note that 1 of the red blood cells has 2 parasites. For the purposes of parasitemia calculation, this counts as 1 infected red blood cell. Between 500 and 2000 red blood cells should be counted, thus requiring the viewing of multiple fields. Parasitemia is the number of infected red blood cells divided by the total number of red blood cells counted.

P. falciparum is strongly suggested by RBC parasitemia >2%, RBCs containing multiple parasites, the exclusive presence of ring forms, and a lack of schizonts. *P. falciparum* is identified pathognomonically by the banana-shaped gametocyte form; the presence of this form is helpful, but its absence does not exclude the diagnosis. Late trophozoite stages of *P. falciparum* rarely are seen except in the setting of high-level parasitemia. A quantitative assessment of the initial parasitemia also is useful in assessing the patient's response to therapy.

Various test kits are available to detect antigens derived from malaria parasites. Such tests most often use a dipstick or cassette format, and they provide results in 15 to 20 minutes. These rapid diagnostic tests (RDTs) offer useful alternatives to microscopic examination when reliable microscopic diagnosis is not available. One RDT for malaria (Binax NOW Malaria, Alere, Waltham, Mass) was approved for use by the US Food and Drug Administration (FDA) in 2007. This RDT detects the histidine-rich protein 2 (HRP2) of *P. falciparum* malaria, as well as a panmalarial aldolase produced by all malaria species. The sensitivity of this test to detect *P. falciparum* malaria is reported to be 95%, whereas the sensitivity for *P. vivax* is only approximately 69%.[23] Sensitivity is lower in patients with low-level parasitemia (<200 parasites/mm^3). World Health Organization product testing of Binax NOW detected 91% of *P. falciparum* isolates at 200 parasites/mm^3 but only 10% of *P. vivax* isolates at 200 parasites/mm^3.[24] Although RDTs can be useful in making a rapid diagnosis, all Binax NOW tests, whether results are negative or positive, must be followed by microscopic evaluation of a blood smear.

Parasite nucleic acids can be amplified and detected by polymerase chain reaction, which can be a useful complement to microscopic examination. It is now recommended that all cases of malaria diagnosed in the US undergo species confirmation by polymerase chain reaction.[25] In addition, the Centers for Disease Control and Prevention (CDC) conduct surveillance for drug resistance mutations for malaria cases diagnosed in the US. By so doing, emerging resistance patterns in endemic countries can be detected more rapidly, thus leading to improved treatment strategies in those endemic countries as well as improvements in prevention guidelines for travelers. All laboratories in the US that diagnose malaria are encouraged to send blood samples from all cases to the CDC for surveillance. Testing is free of charge, and details can be found on the CDC website.[26] Currently, polymerase chain reaction is not sufficiently widely available with a rapid enough turnaround time to make it a viable choice for primary malaria diagnosis.

Serologic testing (immunofluorescence assay) detects antibodies against malaria parasites. Because of the time required for development of antibody and also the persistence of antibodies, however, serologic testing is not useful for routine diagnosis of acute malaria infection or illness.

Although no other laboratory findings are diagnostic for malaria, several laboratory findings support the diagnosis and can be useful to assess the severity of infection. Generally, patients have normocytic, hemolytic anemia with a variable white blood cell count and differential count. Thrombocytopenia often is present, and platelet counts are frequently lower than 50,000/mm^3. In the setting of cerebral malaria, when meningitis also must be excluded, lumbar puncture can reveal raised opening pressure, and cerebrospinal fluid analysis can show mildly elevated protein level and mild lymphocytic pleocytosis. Electrolyte disturbances, including acidosis and mild hyponatremia, are common in severe malaria and usually are multifactorial in origin, including dehydration, vomiting, renal failure, and tissue hypoxia. Hypoglycemia can occur and can be exacerbated by treatment with quinidine. Urinalysis results generally are normal except for proteinuria during high fever. Urinalysis also can reveal hemoglobinuria in the setting of brisk hemolysis, proteinuria associated with nephrotic syndrome, or RBCs with glomerulonephritis. Mildly elevated serum hepatic transaminase levels and indirect hyperbilirubinemia can be present; hepatic failure is uncommon and should prompt evaluation for other causes.

Treatment

Once the diagnosis of malaria is made, multiple factors must be assessed to establish an appropriate strategy for treatment. The first factor to consider is whether the patient has uncomplicated or severe malaria (Box 271.1). Other factors that affect therapy are the likelihood of antimalarial drug resistance (usually based on the geographic region in which malaria was acquired) and the use of antimalarial chemoprophylaxis[27,28] (see also Chapter 296).

Box 271.1

Manifestations of Severe Malaria

Cerebral malaria, defined as unarousable coma not attributable to any other cause in a patient with *Plasmodium falciparum* malaria

Seizures

Severe normocytic anemia with hematocrit <15%

Hypoglycemia

Metabolic acidosis with respiratory distress

Fluid and electrolyte disturbances

Acute kidney injury

Acute respiratory distress syndrome

Hypotension, shock, septicemia (“algid malaria”)

Abnormal coagulation

Hemoglobinuria

Hyperparasitemia (>5% of red blood cells infected)

Patients with *P. falciparum* malaria and those in whom *P. falciparum* cannot be excluded because the species has not been determined at the time of diagnosis should be hospitalized for therapy and monitored because of the rapid clinical deterioration that can occur even if the patient initially appears stable (see Box 272.1). Therapy should be started immediately and supportive care given as necessary. If the patient has severe malaria or is unable to tolerate oral therapy, intravenous quinidine in combination with doxycycline, tetracycline, or clindamycin should be used in a setting in which cardiovascular status and hypoglycemia can be monitored closely and managed urgently (Table 271.1, Box 271.2).[29] As newer antiarrhythmic drugs have replaced quinidine for many cardiac indications, some hospitals and other healthcare facilities have dropped quinidine gluconate from their formularies. Clinicians providing care for patients with malaria should be aware of the inpatient availability of quinidine to avoid delays in treatment.

TABLE 271.1

Guidelines for the Treatment of Malaria in the United States

Indication	Recommended Drug and Adult Dose	Recommended Drug and Pediatric Dose *Pediatric Dose Should* NEVER *Exceed Adult Dose*
Severe malaria,	A. **Quinidine gluconate** *plus* **1 of the**	A. **Quinidine gluconate**

all species	**following: doxycycline, tetracycline, or clindamycin** **Quinidine gluconate:** 10 mg (salt)/kg loading dose IV over 1–2 hr, then 0.02 mg (salt)/kg/min continuous infusion for at least 24 hr. An alternative regimen is 24 mg (salt)/kg loading dose IV infused over 4 hr, followed by 12 mg (salt)/kg infused over 4 hr every 8 hr, starting 8 hr after the loading dose. Once parasite density is <1% and patient can take oral medication, complete treatment with an oral regimen, dosed as below. Quinidine/quinine course = 7-day course for Southeast Asia; = 3-day course for all other regions of acquisition **Doxycycline:** 100 mg PO bid × 7 days. If patient is not able to take oral medication, give 100 mg IV every 12 hr and then give oral doxycycline as soon as patient can tolerate oral medication. Treatment course = 7 days **Tetracycline:** 250 mg PO qid × 7 days **Clindamycin:** 20 mg/kg/day PO divided tid × 7 days. If patient is not able to take oral medication, give 10 mg base/kg loading dose IV followed by 5 mg base/kg IV every 8 hr. Give oral clindamycin (oral dose as above) as soon as patient can tolerate oral medication. Treatment course = 7 days	***plus* 1 of the following: doxycycline, tetracycline,[a] or clindamycin** **Quinidine gluconate:** Same mg/kg dosing and recommendations as for adults **Doxycycline**[a]: 4 mg/kg/day PO divided bid × 7 days. Can be used in children ≥8 yr old. If patient is not able to take oral medication, can give IV. For children <45 kg, give 2.2 mg/kg IV every 12 hr and then give oral doxycycline (dose as above) as soon as patient can take oral medication. For children ≥45 kg, use same dosing as for adults **Tetracycline[a]:** 25 mg/kg/day PO divided qid × 7 days **Clindamycin:** 20 mg base/kg/day PO divided tid × 7 days. If patient is not able to take oral medication, give 10 mg/kg loading dose IV followed by 5 mg/kg IV every 8 hr. Switch to oral clindamycin (oral dose as above) a soon as patient can take oral medication
	B. **Investigational new drug: Contact CDC for more information**	B. **Investigational new drug: Contact CDC for more information**
	Artesunate 2.4 mg/kg/dose at time 0, 12, 24, and 48 hr, followed by 1 of the following: **atovaquone-proguanil (Malarone), doxycycline, clindamycin**, or **mefloquine**	**Artesunate** 2.4 mg/kg/dose at time 0, 12, 24, and 48 hr, followed by 1 of the following: **atovaquone-proguanil (Malarone), doxycycline, clindamycin**, or **mefloquine**
Uncomplicated malaria that is likely chloroquine sensitive	A. **Chloroquine phosphate (Aralen and generic formulations)** 1000 mg (salt) PO immediately, followed by 500 mg (salt) PO at 6, 24, and 48 hr Total dose: 2500 mg (salt)	A. **Chloroquine phosphate (Aralen and generic formulations)** 16.7 mg (salt)/kg PO immediately, followed by 8.3 mg (salt)/kg PO at 6, 24, and 48 hr Total dose: 41.7 mg (salt)/kg
	B. **Hydroxychloroquine** 800 mg (salt) PO immediately, followed by 400 mg (salt) PO at 6, 24, and 48 hr Total dose: 2000 mg (salt)	B. **Hydroxychloroquine** 12.9 mg (salt)/kg PO immediately, followed by 6.5 mg (salt)/kg PO at 6, 24, and 48 hr Total dose: 32.5 mg (salt)/kg
Uncomplicated	A. **Atovaquone-proguanil (Malarone) Adult**	A. **Atovaquone-proguanil**

malaria that is likely chloroquine resistant[b,c]	**tablet = 250 mg atovaquone and 100 mg proguanil** 4 adult tablets PO qd × 3 days	**(Malarone)** **Adult tablet =250 mg atovaquone and 100 mg proguanil** **Pediatric tablet = 62.5 mg atovaquone and 25 mg proguanil** 5–8 kg: 2 pediatric tablets PO qd × 3 days 9–10 kg: 3 pediatric tablets PO qd × 3 days 11–20 kg: 1 adult tablet PO qd × 3 days 21–30 kg: 2 adult tablets PO qd × 3 days
	B. **Artemether-lumefantrine** **1 tablet = 20 mg artemether and 120 mg lumefantrine** 3-day weight-based treatment course = 1 tablet initially followed by 1 tablet after 8 hr; then 1 tablet PO bid × 2 days 5–<15 kg = 1 tablet per dose 15–25 kg = 2 tablets per dose 25–<35 kg = 3 tablets per dose >35 kg = 4 tablets per dose	B. **Artemether-lumefantrine** **1 tablet = 20 mg artemether and 120 mg lumefantrine** 3-day weight-based treatment course = 1 tablet initially followed by 1 tablet after 8 hr; then 1 tablet PO bid × 2 days 5–<15 kg = 1 tablet per dose 15–25 kg = 2 tablets per dose 25–<35 kg = 3 tablets per dose >35 kg = 4 tablets per dose
	C. **Quinine sulfate**[d] ***plus*** **1 of the following: doxycycline, tetracycline, or clindamycin** **Quinine sulfate:** 650 mg (salt) PO tid × 3–7 days **Doxycycline:** Treatment as above **Tetracycline:** Treatment as above **Clindamycin:** Treatment as above	C. **Quinine sulfate**[d] ***plus*** **1 of the following: doxycycline**[a]**, tetracycline**[a] **or clindamycin** **Quinine sulfate**[d]**:** 10 mg (salt)/kg PO tid × 3–7 days **Doxycycline**[a]**:** Treatment as above (patients ≥8 yr) **Tetracycline**[a]**:**Treatment as above (patients ≥8 yr) **Clindamycin:** Treatment as above
	D. **Mefloquine (Lariam and generic formulations)**	D. **Mefloquine (Lariam and generics)**
	750 mg (salt) PO as initial dose, followed by 500 mg (salt) PO given 6–12 hr after initial dose	15 mg (salt)/kg) PO as initial dose, followed by 10 mg (salt)/kg PO given 6–12 hr after initial dose
Relapse prevention of *Plasmodium vivax* or *Plasmodium ovale* infection	**In addition to 1 of the regimens above for the treatment of the acute malaria infection:** **Primaquine phosphate:** 52.6 mg (salt) PO qd × 14 days	**In addition to 1 of the regimens above for the treatment of the acute malaria infection:** **Primaquine phosphate:** 0.8 mg (salt)/kg PO qd × 14 days

[a] Doxycycline and tetracycline are not indicated for use in children less than 8 years old.

[b] Four options are available for treatment of uncomplicated malaria caused by chloroquine-resistant *P. falciparum.* Atovaquone-proguanil and artemether-lumefantrine are equally recommended because of their ease of dosing and low

rates of side effects compared with the other 2 options, which have greater side effects or a more complex dosing regimen, but all 4 options are equally effective.

[c] These regimens are also acceptable options for likely chloroquine-sensitive malaria infections.

[d] For infections acquired in Southeast Asia, quinine treatment should continue for 7 days. For infections acquired elsewhere, quinine treatment should continue for 3 days.

bid, twice daily; CDC, Centers for Disease Control and Prevention; IV, intravenously; PO, orally; qd, once daily; qid, 4 times daily; tid, 3 times daily.

Box 271.2

Management of Patients With Severe Malaria

Hospitalize the patient.

Initiate intravenous antimalarial therapy immediately.

Correct fluid balance and electrolyte abnormalities cautiously.

Monitor, prevent, and correct hypoglycemia.

Correct anemia as needed.

Provide antipyretic therapy.

Protect the airway in patients with altered mental status.

Avoid harmful adjuvant therapies.

Patients with severe malaria should be given an intravenous loading dose of quinidine unless they have received >40 mg/kg of quinine in the preceding 48 hours or if they have received mefloquine within the preceding 12 hours. Consultation with a cardiologist and a physician with experience in treating malaria is advised when using quinidine to treat patients with malaria. An electrocardiogram should be performed before initiation of quinidine therapy to determine a baseline QTc interval. During administration of quinidine, monitoring of blood pressure (for hypotension) and continuous cardiac monitoring (for widening of the QRS complex or lengthening of the QTc interval) are required, and blood glucose concentrations should be evaluated (for hypoglycemia) periodically.[29] Cardiac complications, if serious, may warrant temporary discontinuation of the drug or slowing of the intravenous infusion. Exchange transfusion is no longer recommended by the CDC. Although exchange transfusion can rapidly reduce parasitemia, decades of use have not demonstrated an impact on survival.[30]

Clinical deterioration can occur in the first 24 hours despite appropriate therapy, particularly in patients with high-level parasitemia. Supportive care during this period is critical and should include careful monitoring for hypoglycemia and anemia, careful management of fluid and electrolyte disturbances, monitoring for respiratory and renal compromise, and protection of the patient's airway if declining mental status is evident. Adjunctive therapies such as corticosteroids, heparin, epinephrine, desferrioxamine, cyclosporine, prostacyclin, or osmotic agents for cerebral edema have not proven effective for severe malaria, and considerable evidence suggests potential harm from some of these treatments.

When intravenous quinidine is unavailable, contraindicated, or not tolerated, intravenous artesunate, an investigational drug available through the CDC, can be provided. Artesunate is not FDA approved but has been accepted widely for the treatment of malaria in other countries.[31–33] The CDC should be contacted through the Malaria Hotline (770-488-7788 during working hours; 770-488-7100 after hours and weekends) for any cases for which use of this investigational drug can be indicated. Parenteral artesunate has been associated in rare cases with delayed hemolysis, which occurs 1 to 3 weeks after initiation of treatment with artemisinin-based antimalarial agents, primarily among European travelers who received intravenous artesunate. The phenomenon is thought to be the result of delayed clearance of previously infected erythrocytes, which continue to circulate after the parenteral artesunate has been cleared, rather than a toxic effect of the drug.[34] Although the hemolysis can cause a significant drop in hemoglobin (median reduction, 6 g/dL), no associated fatalities have been reported.[35] Parasitemia should decrease substantially after the first 48 hours of effective antimalarial therapy. Parasites generally clear by 72 hours, and the persistence of parasites should prompt evaluation of possible causes, including inadequate dosage or possible drug resistance. Gametocytes of *Plasmodium* spp. are not killed by most therapies and can be seen for weeks after the initiation of treatment; this finding should not be considered a sign of drug failure, and no additional antimalarial therapy is required. Gametocytes should not be counted in the evaluation of parasitemia level.

Oral chloroquine can be used in patients with uncomplicated malaria caused by *P. falciparum* if infection was acquired in parts of the world free of widespread chloroquine resistance (see http://www.cdc.gov/malaria/travelers/country_table/a.html) and if the patient is able to take oral medication (see Table 271.1). Patients with *P. falciparum* malaria acquired in all other geographic areas should be treated with artemether-lumefantrine (Coartem), atovaquone-proguanil (Malarone), mefloquine, or with a combination of oral quinine sulfate *plus* tetracycline, doxycycline, or clindamycin. Because of the ease of dosing and low rates of side effects, artemether-lumefantrine or atovaquone-proguanil may be preferred, but all 4 options should be considered equally effective. Beginning an effective antimalarial medicine as soon as possible is of paramount importance. For patients with *P. falciparum* acquired in border areas of Southeast Asia, treatment with quinine should be continued for 7 days (instead of 3–7 days) because of evidence of declining efficacy. Doxycycline, tetracycline, or clindamycin should not be used alone for malaria therapy because of the delayed onset (48 hours) of action of these drugs. Mefloquine should not be used in patients who have acquired infection in Southeast Asia because of the high levels of resistance, nor should this drug be used in patients with a history of psychiatric illness.

Patients who do not have *P. falciparum* infection and who have no signs of severe disease can be treated with chloroquine or hydroxychloroquine (Plaquenil) as outpatients, depending on their overall clinical status, and if they are monitored for symptomatic improvement (see Table 271.1). Chloroquine treatment failure rates are high among patients with *P. vivax* infections acquired in Papua New Guinea and Indonesia, and thus patients with *P. vivax* infections acquired in these areas should not be treated with chloroquine or hydroxychloroquine.[36] If the patient cannot take oral medication, intravenous quinidine is the drug of choice. If the patient does not respond to treatment with chloroquine, the treatment should be changed to a regimen effective against chloroquine-resistant *P. vivax;* any regimen effective against chloroquine-resistant *P. falciparum* is suitable.

If the infecting species is identified as *P. vivax* or *P. ovale,* treatment with primaquine also is necessary to prevent relapse from latent hypnozoite forms in the liver (see Table 271.1). G6PD deficiency must be excluded before primaquine is administered. Ideally, primaquine therapy should be initiated concomitantly with the blood schizonticide because evidence indicates that this regimen results in greater efficacy in eradicating hypnozoites. However, if a delay occurs in determining the species or in obtaining G6PD testing results, primaquine still should be given even if shortterm treatment has been completed. Patients with G6PD deficiency who are not able to take primaquine should be retreated with chloroquine if relapses occur, or they should be given weekly chloroquine prophylaxis for 1 to 2 years. The recommended course of primaquine is 0.5 mg/kg daily for 14 days with a target total dose of >6 mg/kg. Patients weighing >70 kg can require treatment for >14 days to achieve the target total dose. Failure of primaquine to eradicate hypnozoites is very unusual if this total dose is attained. However, in many cases adherence to treatment cannot be ensured. If relapse occurs, the patient should be retreated with chloroquine and primaquine. Primaquine should not be used during pregnancy. People with decreased activity of hepatic isoenzyme 2D6 may not produce a sufficient quantity of the active metabolite of primaquine, thus resulting in occasional instances of primaquine failure.[37]

Physicians desiring consultation regarding the management of patients with malaria can call the Malaria Branch of the CDC at 770-488-7788 during working hours or at 770-488-7100 during nights and weekends. Up-to-date treatment recommendations also are available on the CDC website at https://www.cdc.gov/malaria/diagnosis_treatment/index.html.

Prevention

Travelers to endemic areas can prevent malaria through the use of chemoprophylaxis and personal protective measures such as insect repellents. The risk of acquiring malaria is highest in sub-Saharan Africa and Oceania and is more variable for other regions. The evolving picture of drug resistance complicates recommendations for chemoprophylaxis. Malaria prophylaxis recommendations are available in the biannual publication *Health Information for International Travel* and at the CDC malaria website at www.cdc.gov/malaria. Breastfed infants should receive appropriate malaria prophylaxis because they will not receive enough drug in milk to protect them.

Chloroquine (or hydroxychloroquine) can be used for prophylaxis in areas where chloroquine resistance has not been reported. Primaquine is the drug of choice for areas where *P. vivax* is the predominant malaria species (Table 271.2). Chloroquine is available only in tablet form in the US, and it tastes bitter when crushed. Reported side effects include gastrointestinal disturbance, headache, dizziness, blurred vision, insomnia, and pruritus, but often these effects do not require that the drug be discontinued. Chloroquine has been reported to exacerbate psoriasis.

TABLE 271.2

Drugs Used in the Prophylaxis of Malaria

Drug	Usage	Adult Dose	Pediatric Dose	Comments
Atovaquone-proguanil (Malarone)	Prophylaxis in all areas	Adult tablets contain 250 mg atovaquone and 100 mg proguanil hydrochloride 1 adult tablet orally, daily	Pediatric tablets contain 62.5 mg atovaquone and 25 mg proguanil hydrochloride 5–8 kg: ½ pediatric tablet daily 9–10 kg: ¾ pediatric tablet daily 11–20 kg: 1 pediatric tablet daily 21–30 kg: 2 pediatric tablets daily 31–40 kg: 3 pediatric tablets daily 41 kg or more: 1 adult tablet daily	Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious area and for 7 days after leaving such areas. Atovaquone-proguanil is contraindicated in patients with significant renal impairment (creatinine clearance <30 mL/min). Atovaquone-proguanil should be taken with food or a milky drink. Atovaquone-proguanil is recommended for children weighing 5 kg, pregnant women, and women breastfeeding infants weighing <5 kg

Chloroquine phosphate (Aralen and generic)	Prophylaxis only in areas with chloroquine-sensitive *Plasmodium falciparum*	500 mg (salt) orally, once/wk	8.3 mg(salt)/kg orally, once/wk, up to maximum adult dose of 500 mg (salt)	Begin 1–2 wk before travel to malarious areas. Take weekly on the same day of the week while in the malarious area and for 4 wk after leaving such areas. Chloroquine can exacerbate psoriasis
Hydroxychloroquine sulfate (Plaquenil)	An alternative to chloroquine for prophylaxis only in areas with chloroquine-sensitive malaria	400 mg (salt) orally, once/wk	6.5 mg(salt)/kg orally, once/wk. Maximum dose = adult 400 mg salt	Begin 1–2 wk before travel to malarious region. Take weekly on the same day of the week while in malarious area and for 4 wk after leaving malaria endemic area
Doxycycline (many brand names and generic formulations)	Prophylaxis in all areas	100 mg orally, daily	≥8 yr of age: 2.2 mg/kg up to adult dose of 100 mg/day	Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious area and for 4 wk after leaving such areas. Doxycycline is contraindicated in children <8 yr of age and in pregnant women
Mefloquine (Lariam and generic formulations)	Prophylaxis in all areas	250 mg (salt) orally, once/wk	≤9 kg: 5 mg(salt)/kg orally, once/wk 10–19 kg: ¼ tablet once/wk 20–30 kg: ½ tablet once/wk 31–45 kg: ¾ tablet once/week ≥46 kg: 1 tablet once/wk	Begin at least 2 wk before travel to malarious areas. Take weekly on the same day of the week while in the malarious area and for 4 wk after leaving such areas. Mefloquine is contraindicated in patients allergic to mefloquine or related compounds (e.g., quinine and quinidine) and in patients with active depression, recent history of depression, generalized anxiety disorder, psychosis, schizophrenia, other major psychiatric disorders, or seizures. Use with caution in patients with psychiatric disturbances, or a previous history of depression. Use is not recommended for patients with cardiac conduction abnormalities
Primaquine	Prophylaxis in areas with	52.6 mg (salt) orally, daily	0.8 mg(salt)/kg up to adult	Begin 1–2 days before travel to malarious areas.

	mainly *P. vivax* malaria		dose orally, daily	Take daily at the same time each day while in the malarious area and for 7 days after leaving such areas. Contraindicated in patients with G6PD deficiency. Also contraindicated during pregnancy and lactation unless the infant being breastfed has a documented normal G6PD level

G6PD, glucose-6-phosphate dehydrogenase.

For people traveling to areas with malaria transmission where drug resistance other than chloroquine resistance is not a concern, atovaquone-proguanil, doxycycline, and mefloquine are equally recommended prophylactic options (see Table 271.2).

Atovaquone-proguanil should be taken daily with food to improve absorption. Because atovaquone-proguanil is considered a causal prophylactic agent (i.e., kills the initial hepatic stage of parasites), it must be given for only 7 days after leaving a malarious area. The most common adverse effects reported in people using atovaquone-proguanil for prophylaxis include abdominal pain, nausea, vomiting, and headache. Atovaquone-proguanil should not be used in children weighing <5 kg, pregnant women, women breastfeeding infants who weigh <5 kg, or patients with significant renal impairment (creatinine clearance <30 mL/min). Daily doxycycline is another option for travelers who are ≥8 years old (see Table 271.2). Gastrointestinal complaints, photosensitivity, and candidal vaginitis are reported adverse effects. Doxycycline should be taken with an ample amount of fluid and should not be taken before sleep to minimize the risk of esophagitis. Photosensitivity associated with the use of doxycycline can be lessened with sunscreen use. Doxycycline is contraindicated during pregnancy.

Mefloquine can be used in children of any weight (see Table 271.2). It is taken weekly. Nausea and vomiting have been problematic in children. Other reported side effects include headache, insomnia, abnormal dreams, visual disturbances, depression, anxiety disorder, and dizziness. Rare serious adverse reactions include acute reversible neuropsychiatric reactions, seizures, and cardiac conduction abnormalities. Mefloquine is safe to use in pregnancy (FDA pregnancy category B). Mefloquine is contraindicated in patients with active depression, a recent history of depression, generalized anxiety disorder, psychosis, schizophrenia, other major psychiatric disorders, or seizures (but not including typical febrile seizures). Mefloquine should be used with caution in patients with previous psychiatric disturbances or a previous history of depression. The drug is not recommended for patients with cardiac conduction abnormalities. Resistance to mefloquine has been reported in Southeast Asia, where doxycycline or atovaquone-proguanil should be used for prophylaxis.[38]

Travelers who reject the advice to take prophylaxis, who choose a suboptimal drug regimen (e.g., chloroquine in an area with chloroquine-resistant *P. falciparum*), or who require a less than optimal drug regimen for medical reasons are at greater risk for acquiring malaria. In addition, some travelers who are taking effective prophylaxis but who will be in very remote areas can decide, in consultation with healthcare personnel, to carry a reliable supply of a full course of an approved malaria treatment regimen. In the event that these travelers are diagnosed with malaria, they will have immediate access to this appropriate treatment regimen, which, if acquired in a developed country, is unlikely to be counterfeit and will not deplete local resources. In rare instances when access to medical care is not available and the traveler develops a febrile illness consistent with malaria, the reliable supply medication can be self-administered empirically. Travelers should be advised that this self-treatment of a possible malarial infection is only a temporary measure and that prompt medical evaluation is imperative.

Two malaria treatment regimens can be prescribed as a reliable supply: atovaquone-proguanil and artemether-lumefantrine. The use of the same or related drugs that have been taken for prophylaxis are not recommended to treat malaria. For example, atovaquone-proguanil can be used for treatment by travelers not taking atovaquone-proguanil for prophylaxis.

Avoidance of mosquitoes and barrier protection are critical aspects of malaria prophylaxis given that no chemoprophylaxis guarantees complete protection. Anopheline mosquitoes feed from dusk to dawn. Avoiding nighttime exposure by staying in screened-in or air conditioned areas, using protective clothing, sleeping under insecticide-treated bed nets, and using insect repellents all are helpful. Topical mosquito repellents that contain *N*-*N*-diethyl-*m*-toluamide (DEET) or picaridin are the most effective in preventing malaria.[39] Permethrin-impregnated bed nets are effective, and permethrin sprays are available for use on clothing.

None of these measures is 100% effective, and therefore the diagnosis of malaria should be considered in anyone with a fever who has been in an endemic area. Most travelers in whom malaria is diagnosed manifest symptoms within a few weeks to months after return from the malaria-endemic area, particularly with *P. falciparum* infection. Infections with the other species of malaria can appear months later. For people emigrating from malaria-endemic areas, manifestations of *P. falciparum* infection rarely occur after 1 year, whereas manifestations of infection with the other species of *Plasmodium* can occur years later.

Pregnancy increases the risk of complications from malaria in both nonimmune and partially immune women. The clinical course of the disease in these women can be more severe, and malaria during pregnancy carries an increased risk of premature birth or pregnancy loss. Pregnant women should avoid travel to malaria-endemic areas. If they must travel, chloroquine or mefloquine prophylaxis can be used during pregnancy. Atovaquone-proguanil, doxycycline, and primaquine are not recommended for use during pregnancy. Human data on atovaquone-proguanil are insufficient to recommend the use of this drug combination in pregnancy (pregnancy category C), whereas doxycycline is a known teratogen (pregnancy category D). Primaquine is contraindicated because of the theoretical risk of hemolysis in the fetus, if the fetus is G6PD deficient.

Traveling with children requires special preparation. In the US, antimalarial drugs are available only in tablet form, and most taste bitter. Compounding pharmacies can pulverize tablets, weigh out the precise dose, and place the dose in a gelatin capsule; sufficient time will be needed before travel to allow preparation of appropriate dosages. The capsule can be opened at the time of administration, and the medication can be mixed with sweet food items (e.g., applesauce, chocolate syrup, or jelly) to disguise the taste.[39]

Key Points

Epidemiology, Clinical Features, Diagnosis and Treatment of Malaria

Epidemiology

- Parasitic disease transmitted by anopheline mosquitoes
- Predominately in tropical climates
- 198 million cases/year
- 584,000 deaths/year, mostly in children <5 years of age
- Most deaths are caused by *Plasmodium falciparum,* and 90% occur in sub-Saharan Africa.
- In the US, most cases occur in people who have traveled to or emigrated from endemic areas.

Clinical Features

- High fevers and rigors
- Nonspecific symptoms such as myalgia, headache, arthralgia, fatigue
- Abdominal pain, diarrhea, vomiting
- Declining mental status a possible sign of cerebral malaria

Diagnosis

- Malaria should be suspected in anyone with fever who was in an endemic area within the past year.
- Microscopic examination of thick or thin blood films detects parasites.
- Rapid diagnostic tests should be available if microscopy is not available on site.

- Polymerase chain reaction can be used to aid in speciation.

- Thrombocytopenia is very common.

Treatment

- Severe malaria (acquired in any region)
  - Quinidine IV followed by tetracycline, clindamycin, or doxycycline; *or*
  - Artesunate IV (investigational drug available by consultation with the CDC), followed by atovaquone-proguanil, mefloquine, or doxycycline
  - See Table 271.1 for doses, duration, and age specifications
- Uncomplicated malaria
  - Consider prophylaxis regimen taken
  - Consider area of travel and resistance patterns
  - Consider species of *Plasmodium* identified
  - Consider age of patient and pregnancy status
  - See Table 271.1 to tailor therapy to the foregoing specifications

CDC, Centers for Disease Control and Prevention; IV, intravenously.

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272

Sarcocystis Species

Douglas H. Esposito

Sarcocystis species are zoonotic protozoan parasites of the phylum Apicomplexa. Since it was first described in 1843, >150 species have been reported from a range of wild and domestic mammals, birds, and reptiles.[1] The organism requires a definitive host and an intermediate host to complete its life cycle.[1,2] Definitive-host infection is limited to the gastrointestinal tract (intestinal sarcocystosis), whereas intermediate-host infection leads to the formation of characteristic intramyocytic cysts (sarcocysts) for which the organism was named (Fig. 272.1). Although this infection was once considered rare in humans, outbreaks of symptomatic intermediate-host disease (muscular sarcocystosis) among tourists in Malaysia suggest that *Sarcocystis* species infection may be of increasing public health importance.[1]

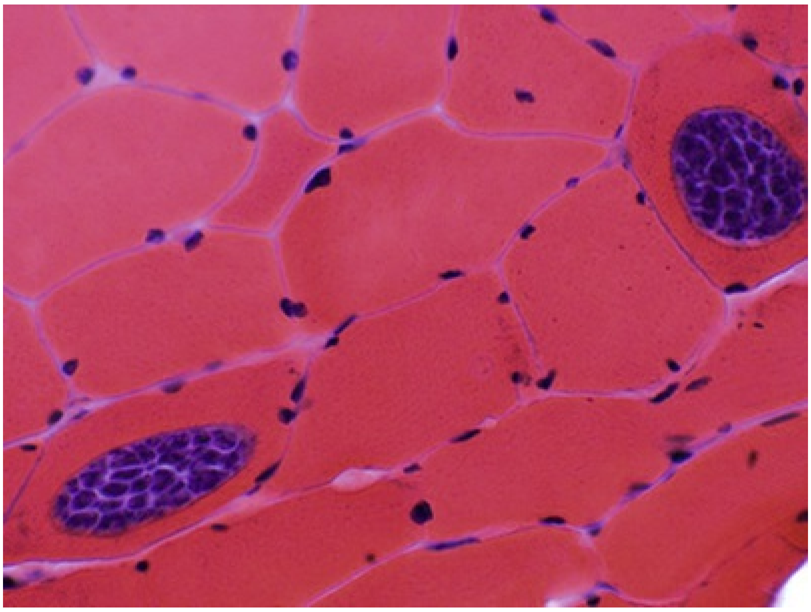

FIGURE 272.1 ***Sarcocystis*** **species in muscle tissue (hematoxylin and eosin stain). Notice the bradyzoites within each sarcocyst. (From the Centers for Disease Control and Prevention DPDx. [https://www.cdc.gov/dpdx/].)**

Pathogen

Humans are the natural definitive hosts for 2 known *Sarcocystis* spp., *S. hominis* and *S. suihominis*, of which cattle and pigs, respectively, are the natural intermediate hosts (Fig. 272.2).[1,2] Humans acquire infection by eating raw or undercooked sarcocyst-containing meat. Only sexual stage parasites are found in definitive-host infections. In the small intestine, motile bradyzoites released from sarcocysts enter cells of the mucosa, where they transform into either a macrogamont (female) or a microgamont (male). Once fertilized, each macrogamont develops into an oocyst that sporulates, to form a pair of sporocysts, each containing 4 sporozoites (Fig. 272.3). Oocysts enter the intestinal lumen and fracture into individual sporocysts, either before or after being shed in the feces.

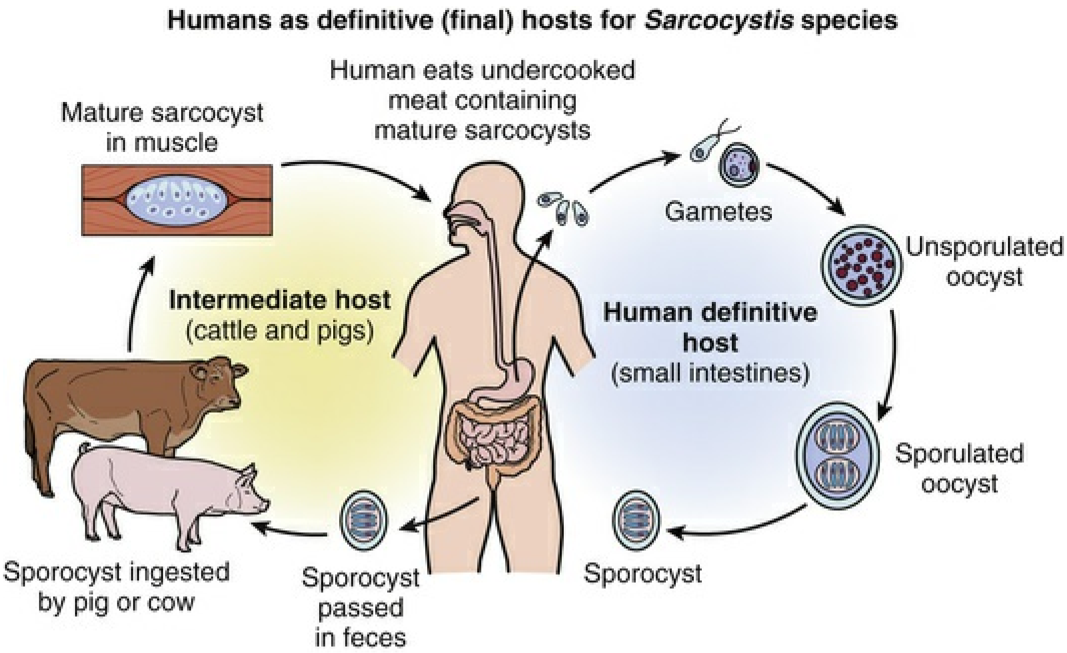
Humans as definitive (final) hosts for *Sarcocystis* species
Mature sarcocyst in muscle
Human eats undercooked meat containing mature sarcocysts
Gametes
Unsporulated oocyst
Intermediate host (cattle and pigs)
Human definitive host (small intestines)
Sporulated oocyst
Sporocyst ingested by pig or cow
Sporocyst passed in feces
Sporocyst

FIGURE 272.2 Human as definitive host for *Sarcocystis* species. (From Fayer R, Esposito DH, Dubey JP. Human infections with *Sarcocystis* species. Clin Microbiol Rev 2015;28:295–311. Copyright by the American Society for Microbiology.)

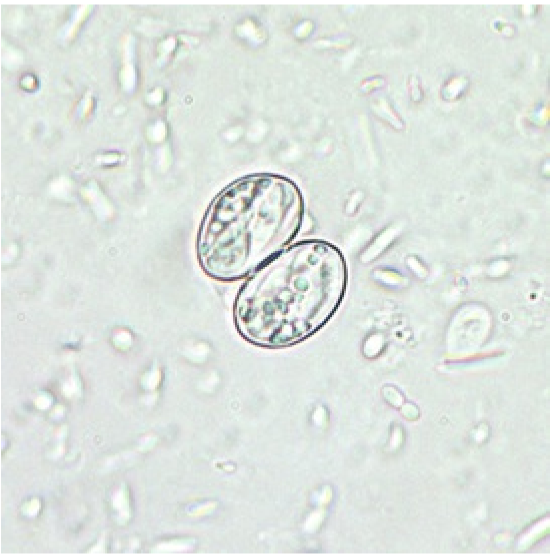

FIGURE 272.3 Sporulated oocyst of *Sarcocystis* species (unstained wet mount; original magnification, ×400). (From the Centers for Disease Control and Prevention DPDx. [https://www.cdc.gov/dpdx/].)

Humans are aberrant intermediate hosts for *S. nesbitti* (a species with a reptile as its likely definitive host) and possibly for other, unidentified *Sarcocystis* spp. (Fig. 272.4).[1,3–7] In intermediate-host infections, only asexual stage parasites are found.[1,2] Infection is acquired by ingesting food or water contaminated with feces from a sporocyst-shedding definitive host. In the small intestine, sporocysts excyst, releasing their 4 motile sporozoites, which penetrate the gut wall and enter the vasculature. There the sporozoites disseminate and undergo cycles of asexual development (merogony or schizogony) within the vascular endothelium of all parts of the body, first in small arterioles, then in capillaries, and finally in veins. Ultimately, the parasite enters myocytes of skeletal, smooth, or cardiac muscle where it forms bradyzoite-containing sarcocysts.

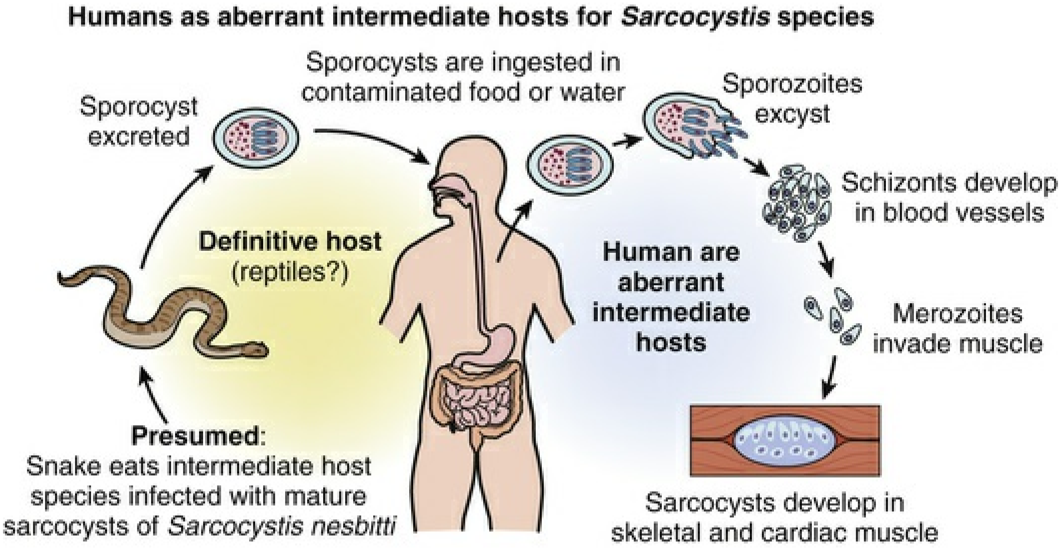
Humans as aberrant intermediate hosts for *Sarcocystis* species
Sporocyst excreted
Sporocysts are ingested in contaminated food or water
Sporozoites excyst
Schizonts develop in blood vessels
Definitive host (reptiles?)
Human are aberrant intermediate hosts
Merozoites invade muscle
Presumed: Snake eats intermediate host species infected with mature sarcocysts of *Sarcocystis nesbitti*
Sarcocysts develop in skeletal and cardiac muscle

FIGURE 272.4 Human as aberrant intermediate host for *Sarcocystis* species. (From Fayer R, Esposito DH, Dubey JP. Human infections with *Sarcocystis* species. Clin Microbiol Rev 2015;28:295–311. Copyright by the American Society for Microbiology.)

Epidemiology

Human intestinal sarcocystosis is distributed worldwide, but prevalence is not well characterized and may vary regionally.[1,8] Infection rates of >90% have been reported in cattle and pigs, the intermediate hosts for human infection, a finding suggesting high burdens of infection among people living in certain areas.

Before the 21st century, <100 cases of human muscular sarcocystosis had been reported in the literature, and most of these cases were diagnosed incidentally in asymptomatic people.[1,9] Distribution was worldwide, although most cases were from tropical and subtropical zones, nearly one half from Malaysia alone. No more than 10 cases were reported to be symptomatic intermediate-host infections.[1,4]

More recently, 2 large, unrelated outbreaks of symptomatic muscular sarcocystosis were reported among tourists to Pangkor and Tioman Islands in Malaysia.[4,10,11] Investigators identified *S. nesbitti* as the causative species in both outbreaks[3,4]; previously, all infections in humans were of unknown species.[1,2] Consumption of contaminated water was the likely source of infection for both outbreaks.[4,10,12,13]

Clinical Manifestations

Most people with intestinal sarcocystosis are asymptomatic or only mildly symptomatic, although severe illness can occur.[1,14] Symptoms can include fever, nausea, vomiting, abdominal cramping and distention, and diarrhea. The nature and severity of illness can depend on the number and species of sporocysts ingested.[1,2] Severe or disseminated infections among immunocompromised people can occur.[15]

Because so few symptomatic cases have been reported, characterization of the clinical manifestations of human muscular sarcocystosis is incomplete. Although infection can be asymptomatic or subclinical, severe, debilitating illness lasting weeks to months, and rarely years, has been reported.[1,9,16–18] Clinical variability can depend on many factors, including the infecting species, the infectious load, and host factors such as immunity and immune status.[1] Overall, the most common symptoms reported include fever, fatigue, myalgia, headache, cough, and arthralgia.[4,10,17] Less frequent are wheezing, nausea, vomiting, diarrhea, rash, lymphadenopathy, and symptoms reflecting cardiac involvement such as palpitations. Fever and muscle pain, sometimes relapsing, can occur in 2 distinct phases: early (beginning during the second week) and late (beginning during the sixth week) after infection.[4] Early-phase disease is characterized by nonspecific symptoms and laboratory abnormalities (e.g., lymphocyte count, liver functions, and lactate dehydrogenase),[4,10,11] and it may reflect generalized vasculitis associated with migration and development of the parasite within the vasculature.[1,4] Later, development of muscle tenderness, eosinophilia, and elevated serum creatinine phosphokinase levels can coincide with the onset of diffuse focal myositis.[4]

Diagnosis

Intestinal sarcocystosis should be considered in patients with enteritis and a history of having eaten raw or undercooked meat.[1] Confirmation relies on light or fluorescence microscopic observation of oocysts or sporocysts in stool; polymerase chain reaction is not widely available.[1,8]

The diagnosis of muscular sarcocystosis during the early phase of infection is made difficult by the lack of specificity of symptoms and clinical and laboratory findings, but it should be considered in patients with myalgia, with or without fever, and a history of travel to a tropical or subtropical region, especially Malaysia.[1,4,8] In the absence of alternate diagnoses such as influenza, dengue, or malaria, serial clinical and laboratory investigations for evidence of developing myositis and eosinophilia should be considered.[1,4] In patients with myositis, trichinellosis should be excluded. Confirmation of muscular sarcocystosis requires histologic observation of sarcocysts in muscle. Polymerase chain reaction is not widely available, and standardized serologic assays validated for use in humans do not currently exist.[1]

Treatment and Prevention

Human intestinal sarcocystosis is largely self-limited, and no specific treatment is available. No proven treatment exists for human muscular sarcocystosis. One patient treated with albendazole was reported to have improved, but whether this improvement was related to treatment or to the natural course of infection was not clear.[17] Co-trimoxazole, a drug with known antiprotozoal activity, may have activity against schizonts in the early phase of infection.[1,18] Glucocorticoids and nonsteroidal anti-inflammatory medications may improve symptoms associated with myositis.[4,10,11]

Thorough cooking or freezing of meat kills bradyzoites and prevents intestinal sarcocystosis.[1,2] To prevent muscular sarcocystosis, ingestion of sporocysts must be avoided.[1]

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Toxoplasma gondii (Toxoplasmosis)

Despina Contopoulos-Ioannidis, José G. Montoya

Toxoplasma gondii is a parasite with worldwide distribution. Although frequently subclinical, *primary* infection can result in a spectrum of manifestations from a mononucleosis-like syndrome to severe ocular disease in immunocompetent people, in significant neurologic and ocular sequelae in congenitally infected fetuses and children, and, in certain tropical areas, in pneumonia, disseminated disease, and even death among otherwise healthy people.[1,2] In addition, *reactivation* of chronic infection can occur in severely immunosuppressed people and can cause life-threatening disease. Patients with profound T-lymphocyte–mediated immune compromise are at higher risk, including patients with acquired immunodeficiency syndrome (AIDS),[3] hematopoietic stem cell transplant (HSCT) recipients,[4] seronegative solid-organ transplant recipients in whom a seropositive allograft is implanted,[5] patients receiving high doses of corticosteroids and, likely, monoclonal antibodies such as alemtuzumab, adalimumab, or infliximab.[6–8] Chronic infection can have more longterm consequences than thought previously; several investigators are addressing the possible impact of latent infection on psychiatric disorders and abnormal behaviors.[9]

The term *T. gondii infection* is used when referring to asymptomatic primary or chronic infection, and *toxoplasmosis* is used when primary infection or reactivation of chronic infection causes signs or symptoms.

Pathogen and Life Cycle

T. gondii is an obligate intracellular parasite with the capacity to infect almost any warm-blooded animal. The parasite has 3 infectious stages: *tachyzoites,* which are responsible for rapid spread of the parasite between cells and tissues and for the clinical manifestations of toxoplasmosis; *bradyzoites,* which are contained within tissue cysts, maintain chronic infection, and stay dormant for the life of the host unless the immune system is severely compromised; and *sporozoites,* which are contained within oocysts, are shed by members of the felid family, and widely disseminate the agent in the environment.[10] A sexual cycle takes place only in the small intestine of felids, thus allowing for the exchange of genetic material among strains and potentially generating variant strains in geographic areas where wild and large cats can travel long distances.[11,12]

The genome of *T. gondii* is available at http://toxodb.org. Genotyping studies have allowed the identification of several clonal lineages in Europe, North America, and South America. Clonal lineages I, II, and III appear to be the most common strains observed in these areas; lineage II is predominantly seen in Europe, whereas in North America lineages I, II and III are implicated in human disease, and an additional new clonal lineage IV (type 12) has been identified[13]; in South America lineages I and III are reported predominantly.[14] In addition, atypical strains that do not fall within the 3 main clonage lineages are observed more commonly in North and South America. Strains from clonage lineage I and IV and atypical strains have been implicated in more aggressive disease in humans.

Investigators have suggested that differences in *T. gondii* strains may at least partially explain the observed differences in the clinical spectrum of infection, particularly among Europe, North America, and South America. Atypical *T. gondii* strains have been reported from several additional areas of the world including Central and South America, Australia, and Africa. This finding should be taken into consideration when clinical syndromes consistent with severe toxoplasmosis are encountered in people returning from these areas. Significant differences in the prevalence and severity of major manifestations (e.g., chorioretinitis, brain calcifications, and hydrocephalus) have been observed in the United States, France, other Western European countries, and South America. For example, the ocular manifestations of congenital toxoplasmosis in children in Brazil are more severe than those in children in Europe.[15–18] Primary infections in adults have resulted in pneumonia, acute hepatitis, fever of unknown origin, and death in human immunodeficiency virus (HIV)–negative and immunocompetent people in South America.[1]

Cats, both domestic and wild, are the definitive hosts, host the complete life cycle, and are responsible for widespread existence of the parasite throughout the world. Most cats are asymptomatic during *T. gondii* oocyst shedding. Cats shed oocysts following the ingestion of any of the infectious stages of the parasite, tissue cysts, and oocysts. As many as 10 million oocysts can be shed in a single day in the cat's feces, for periods varying from 7 to 20 days. Oocysts can remain viable in moist soil for as long as 18 months. Other felids and intermediate hosts including humans can acquire infection from this environmental source. Eating meat of infected rodents, birds, or other animals also can infect cats, and the consumption of infected meat can infect humans.

Epidemiology

Population seroprevalence of *T. gondii* varies by geographic locale, thus reflecting the likelihood of having been exposed to oocysts in soil, untreated water, vegetables, raw shellfish, and other food items and to tissue cysts in uncooked or raw meat.[19–21] The age-adjusted seroprevalence of *T. gondii* infection in the US according to the most recent national survey (2009–2010) was 12% for people >6 years of age and 9% for women of childbearing age (15–44 years)[22]; however, even in the US, seroprevalence can be as high as 20% to 25% within certain socioeconomic and racial or ethnic subgroups. Seroprevalence in other parts of the world can be 60% to 80% (e.g., in Central and South America).[23–25] In most countries, including the US, prevalence is declining, whereas in certain areas of the world prevalence is stable or increasing. In all areas, seroprevalence increases with age (reflecting additive exposure) and usually is associated inversely with socioeconomic status, a reflection of a strong influence of hygienic and alimentary habits in transmission.

Humans and other vertebrates are incidental hosts and become infected primarily by the oral route through ingestion of environmental oocysts or infected meat containing tissue cysts (Fig. 273.1). Vertical transmission occurs during gestation. Humans also can acquire infection through receipt of an organ transplant from an infected donor and, more rarely, during a laboratory accident. Main risk factors for acute *T. gondii* infection in the US identified in a study published in 2009 were as follows: eating raw ground beef, rare lamb, or locally produced cured, dried, or smoked meat; working with meat; drinking unpasteurized goat milk; or living with ≥3 kittens.[20] An additional novel risk factor identified in this study was eating raw oysters, clams, or mussels. Drinking untreated water also showed increased risk but was not statistically significant.[20] Untreated water has been reported to be the source of major community outbreaks of acute toxoplasmosis in Canada and Brazil.[26,27] Family clusters of acute toxoplasma infections have also been documented in the US.[28,29] In up to 50% of patients with confirmed acute *T. gondii* infection, no known risk factors are identified.[30,31]

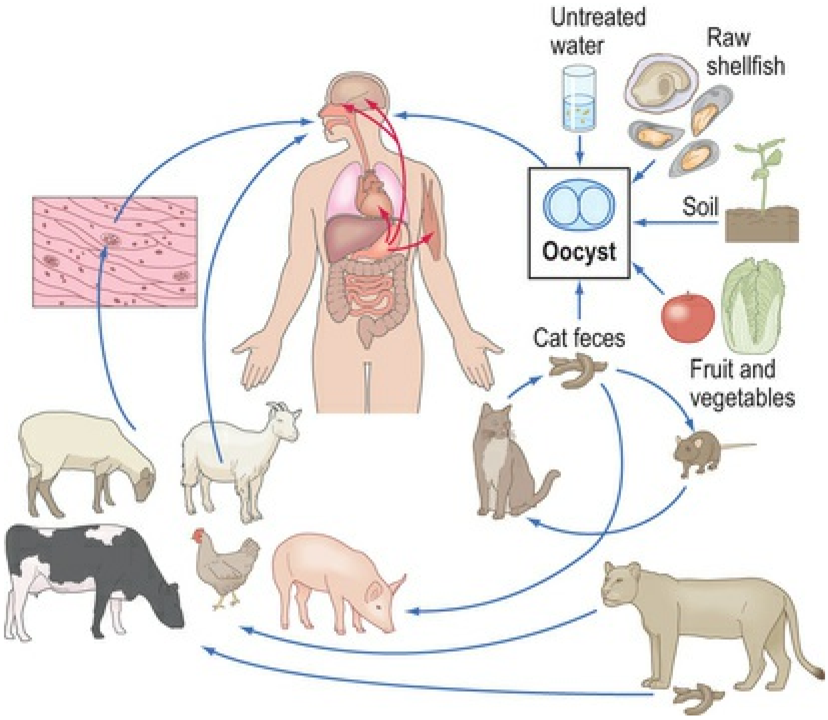

FIGURE 273.1 Life cycle of *Toxoplasma gondii.*

Congenital infection usually is the result of a woman's acquiring primary infection during gestation or within 3 months before conception. If significantly immunocompromised (e.g., by AIDS), previously infected women can reactivate infection during gestation and transmit the parasite to their children.[32–34] Rare but well-documented cases are reported of previously infected healthy women who acquired a more virulent strain of *T. gondii* during gestation and gave birth to an infected infant.

The incidence of acute primary *T. gondii* infections during gestation in the US in the early 1960s was estimated to be 1.1 in 1000 pregnant women.[35] More recent surveillance data in the US are not available, but the overall decrease in seroprevalence suggests that the current incidence of acute *T. gondii* infections during pregnancy is likely to be much lower. Most Western European countries report rates of seroconversion during pregnancy between 0.5 and 2.1 in 1000 pregnant women,[36] whereas in other parts of the world these rates remain high (e.g., 4.8 in 1000 women in South America[37]).

The overall rate of transmission to the fetus in women who seroconvert during gestation has been reported to be between 50% and 60% before the introduction of spiramycin and 25% to 30% thereafter.[2] The rate of vertical transmission increases and the severity of disease decreases with advancing gestational age at the time of maternal infection (Fig. 273.2).[38] In treated women, vertical transmission rates can be as low as 6% at 13 weeks of gestation, 40% at 26 weeks, and 72% at 36 weeks (see Fig. 273.2A).[38] More recently reported rates of mother-to-child transmission from France (where spiramycin therapy was begun in the 1970s) are similar (11%, 47%, and 64%, respectively).[39] In treated women, the risk of clinical signs in their infected fetus has been estimated at 56% if infection was acquired at 12 weeks of gestation, 17% if acquired at 24 weeks, and 9% if acquired at 36 weeks[39] (see Fig. 273.2B).[38]

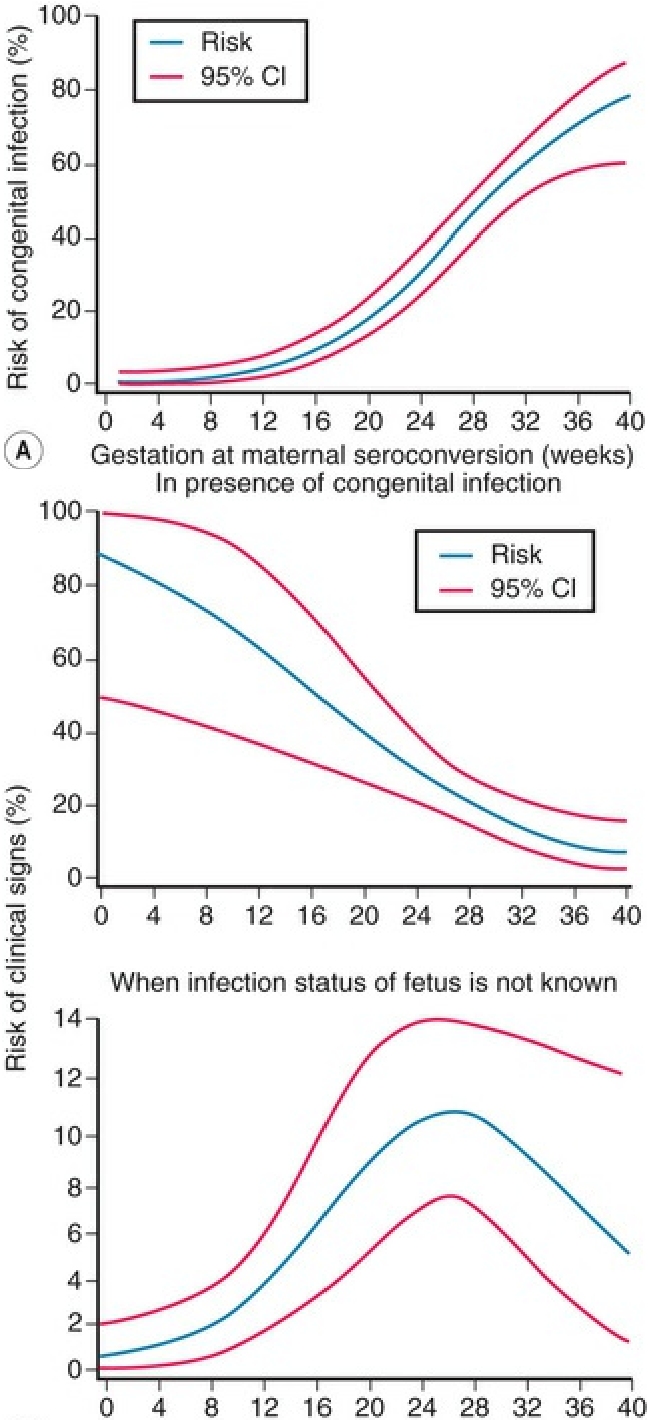

FIGURE 273.2 (A) Risk of congenital infection by age at gestational maternal seroconversion. (B) Risk of developing clinical signs (not necessarily symptomatic) before the age of 3 years, according to gestational age at maternal seroconversion. CI, confidence interval.

(From Dunn D, Wallon M, Peyron F, et al. Mother-to-child transmission of toxoplasmosis: risk estimates for clinical counselling. Lancet 1999;353:1829–1833, with permission.)

The incidence of congenital toxoplasmosis in the US, according to early reports from the New England newborn Screening Program (1986–1992), was estimated to be 0.82 cases in 10,000 live births,[40] and from 2006 to 2014 the incidence decreased to approximately 0.23 cases in 10,000 live births (Hsu Ho-Wen, personal communication from the Massachusetts Department of Public Health, 2015). However, the true incidence of congenital infection may be higher because the sensitivity of the newborn screening test (filter paper blot spot anti-*Toxoplasma* immunoglobulin M [IgM]) used is only 50% to 75%, and fetal losses were not counted.[40,41]

The incidence of congenital toxoplasmosis at birth in France in 2007 was 2.9 cases in 10,000 live births,[42] whereas the prevalence was 3.3 cases in 10,000 live births, and the incidence of symptomatic congenital toxoplasmosis was 0.34 cases in 10,000 live births. The global burden, however, is estimated to be 190,000 cases of congenital toxoplasmosis annually, with an overall incidence of 15 cases in 10,000 live births. The incidence of congenital toxoplasmosis in certain world regions (e.g., South America) is as high as 18 to 34 cases in 10,000 live births.[43] The severity of disease also is higher in these regions.[44]

Pathogenesis and Immune Response

Following oral ingestion of tissue cysts (e.g., in infected meat) or oocysts (e.g., from contaminated soil, water, or food), gastric juices disrupt cyst walls and release bradyzoites (from tissue cysts) and sporozoites (from oocysts), which are converted to tachyzoites. Because of their capacity to move by gliding, flexing, undulating, and rotating, tachyzoites easily infect contiguous cells. Tachyzoites also can infect distant tissues by hematogenous or lymphatic spread. Tachyzoites likely infect Peyer patches and the spleen first, followed by the lungs and liver. Parasitemia can be detected for several days during the early stages of acute infection and probably lasts for approximately 14 days before IgG antibodies are detected. Tachyzoites ultimately arrive at sites such as the brain, eye, heart, and skeletal muscle where, under the pressure of the immune system and other factors, they convert to bradyzoites.

In immunocompetent hosts, an effective immune response controls the proliferation of the rapidly replicating tachyzoite, induces conversion to the metabolically slower bradyzoite, and facilitates formation of tissue cysts (chronic infection). Tissue cysts likely persist for the life of the host, most commonly in the brain, retina, and cardiac and skeletal muscles. Innate, humoral, and cellular immune responses are required to prevent the uncontrolled proliferation of tachyzoites, including the activation of the following: the monocyte-macrophage system, dendritic cells, natural killer cells, and *T. gondii*–specific and cytotoxic $CD4^+$ and $CD8^+$ T lymphocytes; and interferon γ, interleukin-12, tumor necrosis factor-α, interleukin-10 and other cytokines, transforming growth factor-β, costimulatory molecules (e.g., CD28, CD40 ligand), and, to a lesser degree, immunoglobulins.[45]

In immunocompromised patients previously infected with *T. gondii,* significant depletion of T-lymphocyte–mediated immune responses can facilitate reactivation of infection.

Clinical Manifestations

Toxoplasmosis should be considered in the differential diagnosis of several clinical syndromes in immunocompetent children, congenitally infected infants, and immunocompromised children. Signs and symptoms result from primary infection or reactivation. In both forms, the rapid proliferation of the tachyzoite and its corresponding inflammatory immune response are responsible for clinical manifestations. Primary infection can be asymptomatic in many infants and children, and conventional risk factors for the acute infection may not be present in a particular patient.[30] If the goal is to detect each case of primary *T. gondii* infection in a given population of patients (e.g., pregnant women) or to diagnose toxoplasmosis in an ill patient, laboratory testing is necessary. Testing of only symptomatic patients or patients with conventional epidemiologic risk factors misses a substantial portion of acute cases (~50%).[30,31]

The severity of toxoplasmosis during primary infection or reactivation can be influenced by the genetics of the infecting strain,[46] inoculum size, infectious form (e.g., oocyst vs. tissue cyst), immunocompetence, genetics of the host (e.g., presence of human leukocyte antigen [HLA]-DQ3), and, particularly for congenital toxoplasmosis, the absence of prenatal or postnatal treatment.[16,18,39,47–50] Reports from several large observational studies provide supportive evidence for the efficacy of prenatal screening and treatment programs in reducing the mother-to-child-transmission risk and the severity of congenital toxoplasmosis.[39,44,47–50]

Primary Infection in Immunocompetent Children, Adults, and Pregnant Women

Although most children and adults are asymptomatic at the time of primary infection, in ~10% of patients, the following symptoms or syndromes, alone or in various combinations, have been reported: mononucleosis-like illness, fever (≤104°F or ≤40°C), lymphadenopathy, headache, myalgia, arthralgia, sore throat, stiff neck, nausea, abdominal pain, anorexia, confusion, eye symptoms including eye pain, general malaise, and fatigue; occasionally, skin rash and earache can occur. In community outbreak settings or in certain tropical areas, as many as 82% of infected people are symptomatic, and up to 19% can have eye disease.[26]

Lymphadenopathy can be localized or generalized. A solitary, occipital, and painlessly enlarged lymph node can be the sole manifestation of toxoplasmosis in a child, pregnant woman, or adult. However, more generalized lymphadenopathy (cervical, occipital, axillary, inguinal, mediastinal, and abdominal) can occur. Lymph nodes usually are 1 to 3 cm, nonsuppurative, and nontender, and the lymphadenopathy usually regresses within 3 months. Mild relapse of lymphadenopathy can occur between 3 and 6 months, but lymphadenopathy beyond then is rare and should suggest an alternate diagnosis.

Ocular toxoplasmosis as a manifestation of primary, postnatally acquired infection is more common than previously thought.[26,52] Chorioretinitis resulting in blurred vision, eye pain, decreased visual acuity, “floaters,” scotoma, photophobia, or epiphora can occur. People with postnatally acquired *T. gondii* also can develop chorioretinitis as a result of reactivation of previous infection. The morphologic features of *T. gondii* retinal lesions on funduscopic examination often are characteristic. An active whitish infiltrate usually is attached to the darkly pigmented border of an older scar. However, retinal lesions tend to be less typical in older and immunocompromised patients.

Other syndromes such as hepatitis, pneumonitis, myocarditis, and myositis are described. Disseminated disease, pneumonitis, and even death can occur in immunocompetent people infected with high parasite load and/or atypical strains of *T. gondii,* such as in Latin America.

Congenital Toxoplasmosis

In countries where serologic screening and prenatal treatment are offered systematically to pregnant women, most fetuses and newborns infected with *T. gondii* do not exhibit any clinical signs of disease on initial evaluation.[18] However, clinical manifestations of toxoplasmosis can be discovered years later. In cohorts of prenatally treated infants in France, initial eye lesions were detected at >7 months of age in 75% of affected children and at >3 years of age in 50% of congenitally infected children[53] (Fig. 273.3). In 34% of children, recurrences of eye disease or new eye lesions occurred up to 12 years after the first eye lesion.[53] In the US, among congenitally infected children whose mothers did not receive treatment during pregnancy, most fetuses and newborns are symptomatic,[15,17,18] and among infants who were not treated during their first year of life, >70% develop new chorioretinal lesions by 10 years of age.[54]

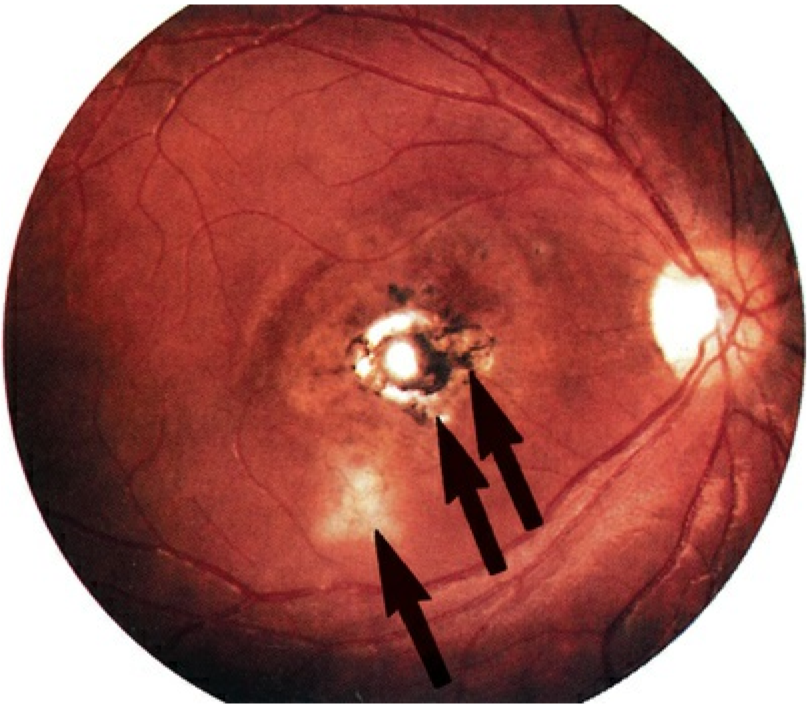

FIGURE 273.3 Toxoplasmic chorioretinitis in a

congenitally infected child. The sharply demarcated quiescent scar is pigmented (*double arrows*). Contiguous to this older lesion is a fluffy, active new lesion (*single arrow*). (From Mets MB, Toxoplasmic Collaborative Study Group. Ophthalmologic findings in congenital toxoplasmosis. Invest Ophthalmol Vis Sci 1992;33:1094, with permission.)

Congenital infection can result in fetal death or a wide variety of central nervous system and other organ abnormalities evident on fetal ultrasonography (Box 273.1). Clinical manifestations ascribed to congenital toxoplasmosis are shown in Box 273.2. Newborns can be asymptomatic or have any of the following clinical manifestations, alone or in combination: chorioretinitis, strabismus, blindness, hydrocephalus or microcephaly, seizures, encephalitis, hepatosplenomegaly, pneumonitis, hypothermia, jaundice, petechiae, skin rash, hearing loss.[2,17,55–57] Neurologic manifestation range from subtle signs to massive, acute encephalopathy. Intracranial calcifications can be present in brain imaging studies.

Box 273.1

Fetal Ultrasound Findings of Congenital Toxoplasmosis[a]

Ascites

Echogenic bowel

Fetal death

Hydrocephalus

Hydrops fetalis

Hepatosplenomegaly

Intracranial densities/calcifications

Intrahepatic densities/calcifications

Intrauterine growth retardation

Pericardial or pleural effusions

Placenta hyperdensities or increased thickness of the placenta

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[a] Listed alphabetically.

Box 273.2

Clinical Manifestations of Congenital Toxoplasmosis[a]

Ophthalmologic Findings

Amblyopia

Cataract

Chorioretinitis, chorioretinal edema

Chorioretinal scars

Choroidal neovascular membranes (vision threatening)

Detachment of posterior hyaloid membrane

Iritis (if associated with posterior pole lesions)

Leukocoria

Macular or peripheral retinal lesions

Microphthalmia or microcornea

Nystagmus

Necrotizing retinitis

Papilledema

Optic nerve atrophy

Retinal detachment

Strabismus

Visual impairment

Vitritis

Neurologic Findings

Brain masses

Cerebrospinal fluid pleocytosis, lymphocytosis (mild/moderate), eosinophilia, elevated protein, hypoglycorrhachia

Delay in developmental milestones (psychomotor retardation)

Hydrocephalus (obstructive)

Hypotonia (or abnormal muscle tone/spasticity)

Intracranial calcifications

Microcephaly or macrocephaly

Palsies

Sensorineural hearing loss

Seizures

Other Findings

Anemia

Disseminated intravascular coagulation

Hepatitis or cholestasis

Hepatic calcifications

Hepatomegaly or hepatosplenomegaly

Jaundice

Lymphadenopathy

Myocarditis

Pneumonitis

Preterm birth

Rash (petechial; blueberry muffin rash; purpura, maculopapular)

Sepsis-like illness (disseminated disease with multiple organ failure, acute respiratory distress syndrome, disseminated intravascular coagulation) (rare)

Splenomegaly

Temperature instability (hypothermia or hyperthermia/fever)

Thrombocytopenia

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[a] Listed alphabetically.

The classic triad of chorioretinitis, hydrocephalus, and brain calcifications is highly suggestive of toxoplasmosis and primarily is seen in neonates whose mothers were not treated during pregnancy.[15] More severe ocular disease is apparent in infants from certain parts of the world. For example, congenitally infected children in Brazil, compared with Europe, more frequently have chorioretinitis, multiple and larger eye lesions, and lesions located in the posterior pole that cause visual impairment and threaten vision.[16] These differences may be attributed to more virulent indigenous strains and/or infections with higher parasite load, and a lack of universal prenatal screening and treatment of pregnant women, or both.

Chronic Infection in Immunocompetent Children

During the chronic stage of infection, *T. gondii* does not appear to cause overt symptoms in most immunocompetent people. However, toxoplasmic chorioretinitis can develop in previously infected, immunocompetent people, most likely because of reactivation of the parasite and subsequent host immune response. Reactivation can occur in congenitally or postnatally infected people. Reactivation of congenital infection appears to occur more commonly between 10 and 30 years of age and is more likely to involve the macula bilaterally. In contrast, ocular disease resulting from reactivation of a postnatally acquired and latent infection appears to occur in people >50 years of age and is more likely to cause peripheral and unilateral retinal lesions.

Reactivation of Chronic Infections in Immunocompromised Patients

Reactivation of chronic infection in immunocompromised people can manifest as multiple brain abscesses, diffuse encephalitis, seizures, chorioretinitis, fever of unknown origin, pneumonitis, myocarditis, hepatosplenomegaly, lymphadenopathy, and skin rash. Some immunocompromised patients also can develop disseminated disease with a severe septic shock– like picture and multiorgan failure. Fever or pneumonia, or both, can occur as the only manifestation. Significant T-lymphocyte or B-lymphocyte deficiency must be present for children to reactivate infection secondary to immunosuppression, and it occurs in patients with AIDS or in allogeneic HSCT recipients. Use of monoclonal antibodies such as alemtuzumab, adalimumab, or infliximab[6–8] has been associated with symptomatic reactivation of latent infection (e.g., toxoplasmic encephalitis or chorioretinitis).

Diagnosis

Laboratory tests for the diagnosis of *T. gondii* infection and toxoplasmosis include serologic studies, polymerase chain reaction (PCR), histologic and cytologic examination of tissue and body fluids, and attempts to isolate the parasite in mice. Regardless of the presence or absence of symptoms, serologic tests can establish whether a patient is infected, and if infected, whether acutely or chronically. Clinically available serologic tools include methods to detect *T. gondii*–specific IgG, IgM, IgA, and IgE antibodies, the IgG-avidity, and differential agglutination (AC/HS) test.[58]

Acute and Chronic Infection

With the use of commercial kits for the detection of IgG and IgM, most laboratories can reliably diagnose the absence of *T. gondii* infection (negative IgG/negative IgM) or the presence of chronic infection (positive IgG/negative IgM). In contrast, the diagnosis of an acute infection cannot rest solely on a positive IgM test result. IgM antibodies are observed during acute infection but can remain positive for months to years without apparent clinical relevance. In addition, commercial IgM kits may not be specific.[59,60]

Of patients with positive IgM results at commercial laboratories, only 40% were confirmed to have a recent infection when their serum was tested at the National Reference Laboratory for the diagnosis of toxoplasmosis in the US Palo Alto Medical Foundation Toxoplasma Serology Laboratory (PAMF-TSL, Palo Alto, Calif; www.pamf.org/serology/; 650-853-4828; toxolab@pamf.org) with an additional comprehensive panel of tests. The remaining 60% of these patients were considered to have had a past infection.[59] At PAMF-TSL, a panel of confirmatory tests (IgG avidity, differential agglutination AC/HS test, IgM, IgA, IgE) is available in addition to the gold standard dye test for IgG and the IgM immunosorbent agglutination assay [ISAGA]. Currently, some commercial laboratories in the US offer the US Food and Drug Administration (FDA)–approved *Toxoplasma* IgG-avidity test and *Toxoplasma* IgA ELISA test. The tests at the National Reference Laboratory are used in various combinations (panels of tests), depending on the clinical situation and the specific clinical question. Serum with a positive IgM test result can be sent to the PAMF-TSL for confirmatory testing involving various combinations of the following tests: IgG dye test, IgG-avidity test, differential AC/HS agglutination test, IgM, IgA, and IgE. The appropriate choice of tests depends on the clinical situation and questions posed by the clinician. Final results at the PAMF-TSL can yield 3 interpretations : (1) *acute infection,* when results are consistent with a recently acquired infection; (2) *chronic infection,* when results are consistent with an infection acquired in the distant past (for older children this could also indicate a congenitally acquired infection); and (3) *unclear,* when results cannot exclude a recently acquired infection (in which case an earlier or subsequent sample is required to attempt to establish whether the infection is acute or chronic). For serologic test results consistent with an acute infection, an attempt should be made to establish the approximate date of infection to help determine whether a patient's clinical symptoms can be attributed to toxoplasmosis.

Definitive Diagnosis

The diagnosis of toxoplasmosis (caused by primary *T. gondii* infection or reactivation of chronic infection) requires the identification of tachyzoites in tissues or body fluids, the amplification of parasite DNA in any body fluid, or the visualization of tissue cysts surrounded by a pathologic inflammatory response. Tachyzoites can be visualized in histologic sections stained with hematoxylin and eosin or in cytologic preparations without any special staining, but are they best visualized with Wright-Giemsa and *T. gondii*–specific immunoperoxidase stains. Real-time PCR has become a useful method for the diagnosis of toxoplasmosis; a positive test result in amniotic fluid (AF) during gestation is diagnostic of fetal infection, in cerebrospinal fluid (CSF) of toxoplasmic encephalitis or congenital toxoplasmosis with central nervous system disease, in bronchoalveolar fluid of toxoplasmic pneumonia, in vitreous fluid of toxoplasmic chorioretinitis, and in peripheral blood, CSF, and urine of disseminated toxoplasmosis or of congenital toxoplasmosis. (However, a negative neonatal *T. gondii* PCR from blood, CSF, and/or urine does not exclude congenital toxoplasmosis.) Identification of the parasite in any body fluid is diagnostic of toxoplasmosis.

In certain clinical settings the diagnosis of toxoplasmosis can be made presumptively by positive results of *T. gondii*–specific serologic test along with characteristic histologic findings in a lymph node biopsy or retinal findings suggestive of ocular toxoplasmosis. Results of *T. gondii* PCR and parasite isolation can be falsely negative in patients receiving anti-*Toxoplasma* treatment. Particularly in cases of eye disease, reactivation (e.g., from congenitally or postnatally acquired infections), serologic testing may be nonspecific or not indicative of acute infection (e.g., positive *Toxoplasma* IgG antibody only). Reactivation of latent *T. gondii* infection in an immunocompromised patient (e.g., already known to be *T. gondii* seropositive) sometimes cannot be diagnosed serologically. Serologic test results in the posttransplant period are unreliable (antibody titers can remain the same, increase, or decrease) and are not helpful in excluding or establishing the diagnosis of reactivation. In these cases, PCR testing of body fluids/tissues (blood, bronchoalveolar lavage, CSF, urine, or other fluid/tissue) or histopathologic examination of stained tissue specimens for identification of tachyzoites can be diagnostic.

Diagnosis in Pregnancy

The diagnosis of toxoplasmosis during pregnancy is primarily accomplished by serologic testing for diagnosis of maternal infection, as well as AF PCR testing and fetal ultrasound examination for diagnosis of fetal infection. For appropriate interpretation of results, clinical information on the mother is required, including postconception age at testing, the presence of clinical signs and symptoms after or shortly before conception, and the presence of immunosuppression including HIV infection.

Maternal Serologic Tests

In countries where routine prenatal screening has been implemented, *Toxoplasma*-seronegative women are identified on their first prenatal visit and are screened monthly (e.g., France) or every 3 months (e.g., Austria, Germany, Italy) until delivery. Seroconversion during gestation is diagnostic of acquisition during pregnancy and is defined as a change from undetectable to detectable anti-*Toxoplasma* IgG.[2] In patients who seroconvert, the IgM test result becomes positive first, usually with a high level. In contrast, in countries where no routine prenatal screening is used, prenatal diagnosis of *T. gondii* infection or toxoplasmosis is based on a single serum sample tested during gestation.

In commercial laboratories, IgG-positive or IgG-negative results and IgM-negative results are reliable. If a pregnant woman has the ability to produce immunoglobulins and has negative IgG and IgM test results, no evidence of previous *T. gondii* infection exists; testing for *Toxoplasma* IgG and IgM every 4 to 8 weeks for the duration of the pregnancy is prudent. If the IgG test result is positive but at a low titer (e.g., near the cutoff of positivity for the IgG test or a dye test result at PAMF-TSL ≤1 : 512) and the IgM test result is negative, the patient most likely was infected at least 6 months before the date of testing. IgG-positive test results at high titers (e.g., IgG-dye test result ≥1 : 1024 at PAMF-TSL) even with negative IgM test results should be interpreted with caution with the assistance of medical consultants at reference laboratories and with performance of an additional panel of tests or follow-up serologic testing.

In pregnant women with positive toxoplasma IgG and IgM test results, the positive IgM test result alone cannot be used to confirm acute *T. gondii* infection or toxoplasmosis; additional confirmatory tests should be performed. The battery of tests used varies with the gestational age at which the serum sample was obtained. For women screened at <16 weeks of gestation, the more cost-effective panel contains the IgG dye test, IgM enzyme immunoassay (EIA), and IgG-avidity test. For women screened at >16 weeks of gestation, the AC/HS test is used in the panel instead for the IgG-avidity test. In most cases, results in these tests yield either of 2 interpretations: (1) infection acquired during or shortly before gestation or (2) infection acquired in the distant past before gestation. Sometimes when timing of infection cannot be accurately estimated by these tests, additional or follow-up testing is recommended. Follow-up testing could include IgG dye test, IgG avidity, AC/HS, IgM, IgA, or IgE.

If a pregnant woman has a negative IgG dye test result but a positive IgM test result, she may have been infected recently or may have a false-positive IgM result. Sera should be submitted to a reference laboratory for confirmatory testing; follow-up testing 2 to 4 weeks later may be required. Follow-up IgG dye test positivity would be diagnostic of seroconversion and of very recently acquired infection. In contrast, persistent IgG-dye test negativity (even if the IgM remains positive) suggests a false-positive IgM result.

Results of serologic test that are performed late (>20 weeks) in gestation can be difficult to interpret unless the woman is seronegative or the serologic test results clearly suggest an infection acquired in the distant past (before gestation). Assays sophisticated enough to make this distinction are limited to highly specialized laboratories such as the PAMF-TSL. With late maternal initial testing (unless the woman has clear serologic evidence of an acute *T. gondii* infection acquired late in gestation), usually it is not possible to exclude the possibility of an acute primary infection acquired early in gestation (unless a maternal serum obtained earlier in gestation is available for comparative serologic testing).

Polymerase Chain Reaction Testing on Amniotic Fluid

Once the diagnosis of acute *Toxoplasma* infection during pregnancy has been confirmed or highly suspected, the next step is to determine whether the fetus has been infected. AF PCR is the laboratory method of choice. The diagnostic accuracy of AF PCR varies according to the trimester of pregnancy during which maternal infection occurred (not the trimester during which amniocentesis was performed). A negative AF PCR result for an acute maternal infection that was likely acquired early in gestation can exclude fetal infection because the negative predictive value of AF PCR for such early maternal infections is high.[61] However, a negative AF PCR result for acute maternal infection likely acquired late in gestation should be interpreted with caution because the negative predictive value of AF PCR for such late infections is lower.[61] Nevertheless, a positive AF PCR result at any time during gestation is diagnostic of fetal infection and can be used to recommend treatment for fetal infection; the positive predictive value of AF PCR is essentially 100% in all trimesters, assuming that laboratory error is excluded.[61]

Independent of AF PCR results, all infants whose mothers were diagnosed with acute primary infection during gestation should undergo a postnatal evaluation to exclude congenital toxoplasmosis.

Diagnosis in the Neonate

The approach to evaluation for congenital infection is shown in Box 273.3. In the newborn, congenital toxoplasmosis can be diagnosed by the following: positive *Toxoplasma* IgG in addition to IgA or IgM antibodies; positive *T. gondii* PCR results on blood, urine, or CSF specimens; or parasite isolation from any body fluid (now rarely used). *Toxoplasma* IgE is not included in the routine neonatal panel of tests at the PAMF-TSL because it does not provide diagnostic information beyond what is already provided by the IgG, IgM (ISAGA) and IgA testing.

Box 273.3

Evaluation of Infants With Suspected Congenital Toxoplasmosis

Serologic Screening

- **Toxoplasma IgG antibodies:** IgG dye test at PAMF-TSL, the national reference laboratory for toxoplasmosis in the US [gold standard]; IgG ELISA done in commercial laboratories

- **Toxoplasma IgM antibodies:** IgM ISAGA done at PAMF-TSL and toxoplasmosis reference laboratories is more sensitive than IgM ELISA, which is done at commercial laboratories; IgM ISAGA recommended for infants <6 months of age; a negative IgM ELISA result cannot exclude the diagnosis of congenital toxoplasmosis even if IgA antibodies are also negative

- **Toxoplasma IgA antibodies:** by ELISA or ISAGA

Toxoplasma Gondii Polymerase Chain Reaction Testing

- **PCR on sample of peripheral blood, urine, and CSF:** CSF examination should be considered in the following cases:

  - Infants with positive *T. gondii* IgG, IgM ISAGA, or IgA

  - Infants born to mothers with recently acquired *T. gondii* infection during pregnancy who had positive *T. gondii* AF PCR or abnormal fetal ultrasound findings suggestive of CT independently of whether antepartum treatment was received or not

  - Infants born to mothers with recently acquired *T. gondii* infection during pregnancy who have not received any antepartum anti-*Toxoplasma* treatment during pregnancy, and particularly those who likely had acquired the infection in the second or third trimester- (even if *T. gondii* AF PCR or fetal ultrasound results were negative)

- CSF PCR can sometimes be helpful in making the diagnosis of CT, even earlier than serologic testing alone (e.g., in cases of maternal infections acquired late in gestation), and in some instances it may be the only positive test result.

Cerebrospinal Fluid Analysis (Cell Count, Differential, Protein, and Glucose)

- Based on data from PAMF-TSL, there is no evidence to suggest that CSF serologic testing (CSF *Toxoplasma* IgG and IgM) could offer any incremental benefit from the information already gained from neonatal serology *plus* CSF cell count, differential, protein, and glucose *plus* CSF *T. gondii* PCR *plus* CNS imaging.

- CSF examination could be deferred in infants with very low suspicion of CT such as asymptomatic infants at birth who fulfill all the following criteria: their mothers had a diagnosis of acute *T. gondii* infection in the first trimester; their mothers had received prenatal treatment throughout gestation; AF PCR results were negative; monthly fetal ultrasound scans were normal; *and* the infants had negative *Toxoplasma* IgM ISAGA and IgA findings at birth.

Other Laboratory Tests

- Complete blood count and liver function tests

Clinical Evaluation

- Detailed physical examination at birth; every 2 to 3 months during the first year of life and every 4 to 6 months afterward

- Pediatric neurologic evaluation at birth; every 2 to 3 months during the first year of life and every 4 to 6 months afterward

- Pediatric ophthalmologic examination at birth and every 3 to 4 months (preferably by a retinal specialist) during the first year of life; every 4 to 6 months during the second year of life, and every 6 months during the third year of life for infants with CT (close ophthalmologic follow-up is indicated for infants with CT because the diagnosis of the onset of the first eye lesion can be delayed)

Imaging

- Head computed tomography (to evaluate for, e.g., intracranial calcifications, ventriculomegaly, hydrocephalus). Head MRI could also be considered, given the absence of radiation risk. (Head ultrasonography has been used mainly in European cohorts where the rate of symptomatic CT cases is very low compared with the United States)

- Abdominal ultrasound for intrahepatic calcifications or hepatosplenomegaly

Auditory Brainstem Responses

- Shortly after birth and yearly audiologic evaluation afterward for the first 3 years of life

AF, amniotic fluid; CNS, central nervous system; CSF, cerebrospinal fluid; CT, congenital toxoplasmosis; ELISA, enzyme-linked immunosorbent assay; Ig, immunoglobulin; ISAGA, immunosorbent agglutination assay; PAMF-TSL, Palo Alto Medical Foundation Toxoplasma Serology Laboratory; PCR, polymerase chain reaction.

The preferred method for the detection of IgM antibodies in the newborn is the IgM ISAGA, and for IgA it is the enzyme immunoassay (EIA) or ISAGA technique.[62] The serum sample for serologic testing should be obtained from peripheral blood and not from cord blood because of the high rate of maternal blood contamination. Maternal blood contamination of the newborn's peripheral blood can occur during labor and maternal IgM and IgA antibodies can be detected in the neonatal blood the first 5 and 10 days of life, respectively. Thus a positive IgM ISAGA (after 5 days of life) or IgA ELISA (after 10 days) is diagnostic of congenital disease. Congenitally infected babies can be positive for both, positive for either, or occasionally negative for both. False-positive IgM ISAGA test results, particularly at low titers, can be seen in infants who have received transfusion of blood products. A positive anti–*T. gondii* IgM result in CSF is diagnostic of congenital disease, but testing of the CSF by PCR is strongly recommended because of its higher sensitivity.[63]

The diagnosis of congenital toxoplasmosis also can be made by a positive PCR test result in peripheral blood, CSF, urine, or other body fluid/tissue. The CSF also should be sent for CSF cell count, differential of white cells, and protein and glucose analysis. CSF of congenitally infected infants can have high levels of protein (up to 1000 mg/dL), hypoglycorrhachia, and eosinophilia in addition to mild to moderate lymphocytosis. Brain imaging studies can reveal calcifications, ventriculomegaly, or hydrocephalus; computed tomography is superior to ultrasonography for detection of central nervous system calcifications. Head MRI could also be considered for the initial evaluation, because it obviates the risk of radiation; however, empirical comparative data versus other imaging studies are lacking. Calcifications also can be detected in the liver by abdominal ultrasound.

Persistence of *Toxoplasma* IgG in a child ≥12 months of age is diagnostic of congenital toxoplasmosis and is considered the gold standard for definitive laboratory diagnosis. Maternal transplacentally transferred IgG antibodies usually disappear after 6 to 12 months of life. Initially, the titer of the IgG antibody in the infant should be similar to that of the mother. Then, the noninfected infant's IgG titers decrease according to the half-life of the IgG (~4 weeks); *Toxoplasma* IgG titer should decrease by at least 50% every month. Quantification of enzyme immunoassay values is less reliable. In performing serial testing, the infant's specimens should be tested in parallel, and expert consultation should be sought at reference laboratories. The kinetics of the child's IgG may be affected by treatment for toxoplasmosis. Disappearance of *Toxoplasma* IgG at <12 months of age, in the absence of anti-*Toxoplasma* treatment in an infant capable of producing normal levels of IgG, excludes the diagnosis of congenital toxoplasmosis.

Diagnosis in Immunocompetent Children

Systemic Disease

If an immunocompetent patient with suspected toxoplasmosis has negative IgG and IgM test results, symptoms or signs should not be attributed to infection with *T. gondii*. If the serologic test results are consistent with a chronic infection, use of a reference laboratory can help to determine a minimum window of timing of infection to establish relevance to clinical manifestations. Most immunocompetent children do not have clinically apparent reactivation of chronic infection. Ocular disease is an exception and can reactivate in immunocompetent children up to early adulthood. In addition, chronic *T. gondii* infection has been hypothesized to play a role in mental illness and behavior in infected animals and humans. Further investigation is required.

Lymphadenopathy caused by to toxoplasmosis can result in a virtually pathognomonic histologic pattern of findings, including reactive follicular hyperplasia, irregular clusters of epithelioid histiocytes encroaching on and blurring the margins of the germinal centers, and focal distention of sinuses with monocytoid cells.[64]

Ocular Disease

The diagnosis of acute postnatally acquired ocular disease can be made if *Toxoplasma* IgG and IgM antibodies are present in the serum and ocular symptoms started approximately at the same time as the infection was acquired. If serologic test results are consistent with distantly acquired infection, ocular symptoms can be ascribed presumptively to reactivation of *T. gondii* infection (acquired either congenitally or postnatally in the distant past), assuming that the morphologic features of the retinal lesions are characteristic (see Fig. 273.3) and the response to therapy for toxoplasmosis is adequate. In patients whose lesions are not typical of toxoplasmosis or who have a suboptimal response to therapy, sampling of ocular fluids for diagnosis should be considered.

Sampling of the aqueous humor, rather than vitreous fluid, has a lower risk of adverse events. The immune load (Goldmann-Witmer coefficient analysis of aqueous humor) is calculated as anti–*Toxoplasma*-specific IgG in aqueous humor compared with total IgG in aqueous humor divided by anti–*Toxoplasma*-specific

IgG in serum compared with total IgG in serum. A value of ≥2 or ≥ 3 depending on expert opinion is considered diagnostic of ocular toxoplasmosis. Vitreous fluid sampling, despite the greater risk of damage to the eye and retina, can be indicated when significant vitreal inflammation is observed, retinal lesions are difficult to visualize, or the patient is not responding to anti-*Toxoplasma* therapy. For vitreal samples, detection of the parasite by DNA amplification (PCR) is preferred.

Diagnosis in Immunocompromised Children

Clinicians should establish whether immunocompromised patients, or patients about to become so, are at risk of reactivating latent *T. gondii* infection (*Toxoplasma* IgG seropositive) or acquiring primary infection through the oral route or from a transplanted organ (*Toxoplasma* IgG seronegative). All patients whose cell-mediated immunity will be significantly compromised should be tested ahead of time for anti-*Toxoplasma* IgG and IgM antibodies (e.g., before transplantation). Serologic testing following transplantation is unreliable; in the posttransplant period, serologic results in previously seropositive individuals can be negative, can be unchanged, or can rise without clinical relevance.

Establishing that an immunocompromised patient is chronically infected with *T. gondii* (*Toxoplasma* IgG positive and IgM negative) also facilitates the decision for anti-*Toxoplasma* prophylaxis. *T. gondii*–seropositive patients with AIDS, patients who receive allogeneic HSCTs, or patients who receive drugs that target T- or B-lymphocyte immune responses should be followed closely and offered anti-*Toxoplasma* prophylaxis or preemptive therapy (should they become *Toxoplasma* PCR positive). Recipients of solid-organ transplants and the organ donors should be tested before transplantation procedures; donor-positive, recipient-negative patients are at high risk of developing life-threatening toxoplasmosis.

Methods of choice to diagnose toxoplasmosis in immunocompromised patients (due to reactivation of latent infection or acutely acquired primary infection) are testing of body fluids by PCR, examination of biopsy tissue by hematoxylin/eosin, Wright-Giemsa or *T. gondii*-specific immunoperoxidase stains, and isolation of the parasite. Real-time PCR (RT-PCR) testing is the diagnostic test of choice for *Toxoplasma* encephalitis (on CSF), pneumonia (on bronchoalveolar lavage fluid), disseminated disease (peripheral blood or urine), and chorioretinitis (vitreous fluid). Visualization of tachyzoites in any body fluid or tissue or isolation from body fluids (reference laboratories) also is diagnostic of toxoplasmosis.

Treatment

Treatment requires the combination of 2 drugs known to be active against *T. gondii;* pyrimethamine is the most effective drug and always should be prescribed in conjunction with folinic acid to prevent bone marrow toxicity. Other effective drugs include sulfadiazine, clindamycin, atovaquone, and trimethoprim-sulfamethoxazole (TMP-SMX) (Tables 273.1 and 273.2).

TABLE 273.1

Treatment for Pregnant Women Likely to Have Acquired *T. gondii* Infection During Gestation and Infants Suspected or Confirmed to Have Congenital Toxoplasmosis

Drugs	During Pregnancy	For Congenital Disease in the Fetus
Spiramycin	Recommended for pregnant women suspected or confirmed as having acquired their infection at <18 wk of gestation Spiramycin should be administered **until delivery** in patients with negative amniotic fluid PCR test results and negative follow-up ultrasonography or low suspicion of fetal infection Spiramycin is not teratogenic and is available in the US only through the Investigational New Drug process at the US Food and Drug Administration (301-796-1600) Consultation with experts in diagnosing or treating toxoplasmosis is strongly recommended[a]	Spiramycin is not recommended during pregnancy if the fetus is documented or suspected to be infected; in the setting of documented/suspected fetal infection, pregnant women should receive pyrimethamine, sulfadiazine, and folinic acid (see later in this table)
	Dose: 1 g (3 million U) every 8 hours orally; (should be continued until the end of gestation even if fetal infection is excluded; however, if fetal infection is suspected or confirmed, treatment	

	should be changed (see recommended treatment below)	
Pyrimethamine ***plus*** **Sulfadiazine** ***plus*** **Folinic acid**[b]	Recommended for women ≥18 wk of gestation suspected or confirmed to have acquired acute infection ≥18 wk of gestation *or* who have a positive amniotic fluid PCR test result or abnormal ultrasonogram suggestive of congenital toxoplasmosis in the fetus Pyrimethamine is potentially teratogenic and should not be used during pregnancy before week 18 (or week 14 in some centers in Europe); sulfadiazine should not be used alone **Doses:** Pyrimethamine: 50 mg every 12 hr orally for 2 days; followed by 50 mg once daily (until delivery) *Plus* Sulfadiazine: 75 mg/kg (first dose); followed by 50 mg/kg every 12 hr orally (maximum dose, 4 g/day) (until delivery) *Plus* Folinic acid (leucovorin)[b]: 10–20 mg daily (during and for 1 wk after pyrimethamine therapy)	**Infant with congenital toxoplasmosis**[c] (treatment regimen usually is recommended for 1 yr): **Doses:** Pyrimethamine: 1 mg/kg every 12 hr orally for 2 days; followed by 1 mg/kg once/day orally for 2 or 6 months (6 months can be considered for symptomatic cases); followed by 1 mg/kg once/day every Monday, Wednesday, and Friday to complete a total course of 12 mo. *Plus* Sulfadiazine: 50 mg/kg every 12 hr orally for 12 mo *Plus* Folinic acid (leucovorin)[b]: 10 mg 3 times/wk orally (up to 1 wk after completing pyrimethamine) Prednisone (if CSF protein ≥1 g/dL or severe chorioretinitis): 0.5 mg/kg every 12 hr orally (until CFS protein <1 g/dL or resolution of severe chorioretinitis); if corticosteroids are to be used, they should be initiated after 72 hours of anti-*Toxoplasma* therapy
		Older children with active eye disease (treatment is usually given for 1–2 wk beyond resolution of clinical manifestations and for ~4-6 weeks) **Doses:** Pyrimethamine: 1 mg/kg once every 12 hr orally (maximum, 50 mg/day) for 1–2 days; followed by 1 mg/kg once/day orally (maximum, 25 mg/day) *Plus* Sulfadiazine: 75 mg/kg (first dose); followed by 50 mg/kg every 12 hr orally (max 4 g/day) *Plus* Folinic acid (leucovorin)[b]: 10–20 mg daily orally (during and for 1 week after pyrimethamine therapy) Prednisone (for severe chorioretinitis): 0.5 mg/kg every 12 hr orally (maximum 40 mg/day); rapid

	taper

[a] Palo Alto Medical Foundation Toxoplasma Serology Laboratory (PAMF-TSL), Palo Alto, Calif (www.pamf.org/serology/; 650-853-4828; toxolab@pamf.org); or US (Chicago) National Collaborative Treatment Trial Study (NCCTS) (773-834-4152).

[b] Folic acid should not be used as a substitute for folinic acid (leucovorin).

[c] In some centers in Europe, the regimen of pyrimethamine and sulfadoxine (Fansidar) is also used for subclinical or mild forms of congenital toxoplasmosis or for difficulties in compliance or frequent hematologic adverse effects; after the first 2 months of therapy with pyrimethamine and sulfadiazine.

CSF, cerebrospinal fluid; PCR, polymerase chain reaction.

TABLE 273.2

Treatment Regimens[a] for Children With Severe Primary Toxoplasmosis[b] and Immunocompromised Children With Toxoplasmosis Resulting From Reactivation

Drugs	**Dose**
• Pyrimethamine[a] (PO)	1 mg/kg every 12 hr (max, 100 mg/day) for 1–2 days, followed by 1 mg/kg once/day (max, 25 mg/day; up to 50 mg/day [if <60 Kg] or up to 75 mg/day [if ≥ 60 Kg] can be given in older children with severe disease)
Plus	
Folinic acid[c] (PO)	10–20 mg daily (max, 50 mg/day; during and 1 wk after pyrimethamine therapy)
Plus	
Sulfadiazine (PO);	100–200 mg/kg/day divided every 6 hr (max, 4–6 g/day for severe disease[d])
• Pyrimethamine *plus* folinic acid (PO)	
Plus	
Clindamycin[e] (PO or IV)	
Or	
• Atovaquone[e] (PO)	
Preferrred Alternative Regimen	
• Trimethoprim-sulfamethoxazole[e] (PO or IV)	
Other Regimens	
• Pyrimethamine *plus* folinic acid	Same doses as above
Plus	
Clarithromycin[e] (PO)	
Or	
Dapsone[e] (PO)	
Or	
Azithromycin[e] (PO)	
• Sulfadiazine[e]	

(PO)	
Plus	
Atovaquone[e] (PO)	

[a]Preferred regimens: pyrimethamine plus sulfadiazine, and folinic acid or, alternatively, trimethoprim-sulfamethoxazole. (Supportive data for other regimens are limited.)

[b]Includes immunocompetent children with severe acute infection, particularly in the setting of myocarditis, myositis, hepatitis, pneumonia, brain or skin lesions, and lymphadenopathy accompanied by severe or persisting symptoms. Treatment also indicated for patients with active ocular disease caused by primary infection or reactivation. (For drug dosing for ocular toxoplasmosis, please see Table 273.1). For toxoplasmic encephalitis in HIV patients, treatment should be continued for 3–6 weeks (or more, for severely ill patients who did not achieve complete response), followed by suppressive therapy.

[c]Folinic acid is leucovorin; folic acid must not be used as a substitute for folinic acid.

[d]Guidelines for the Prevention and Treatment of Opportunistic Infections among HIV-exposed and HIV-infected children (AIDSinfo): https://aidsinfo.nih.gov/contentfiles/lvguidelines/PedOIDosingTables.pdf).

[e]Pediatric doses for these drugs have not been studied in the context of toxoplasmosis. Highest possible doses probably are needed in disseminated or severe cases.

Assistance is available for the diagnosis and management of patients with toxoplasmosis at the US (Chicago, IL) National Collaborative Treatment Trial Study [NCCTS] (773-834-4152) and the Palo Alto Medical Foundation Toxoplasma Serology Laboratory (PAMF-TSL), Palo Alto, Calif (www.pamf.org/serology/; 650-853-4828; toxolab@pamf.org).

PO, orally; IV, intravenously.

Pregnant Women

Treatment of acute *Toxoplasma* infection during pregnancy is aimed at preventing fetal infection or treating the infected fetus (Fig. 273.4). If results of serologic testing suggest acquisition of the infection during the first 18 weeks of gestation or shortly before conception, maternal treatment with spiramycin is indicated[65] (see Table 273.1). Spiramycin is not available commercially in the US. However, it can be obtained at no cost (drug compassionately provided by Sanofi-Aventis) and after consultation with the PAMF-TSL (650-853-4828), through the National Collaborative Treatment Trial Study (NCCTS) (773-834-4152), or through the FDA (301-796-1600). Therapy should be continued throughout pregnancy even if results of AF PCR obtained at ≥18 weeks of gestation are negative. If fetal infection is confirmed at ≥18 weeks, treatment with pyrimethamine, sulfadiazine, and folinic acid is recommended because of the high transmission rates after 18 weeks of gestation. If the patient already is receiving spiramycin, combination therapy should replace spiramycin. In some centers in Europe, the change to combination therapy takes place as early as weeks 14 to 16. Pyrimethamine should be avoided earlier in gestation because it is potentially teratogenic. Combination therapy also is recommended when results of AF PCR for *T. gondii* DNA are positive or when fetal ultrasound changes are highly suggestive of congenital toxoplasmosis.

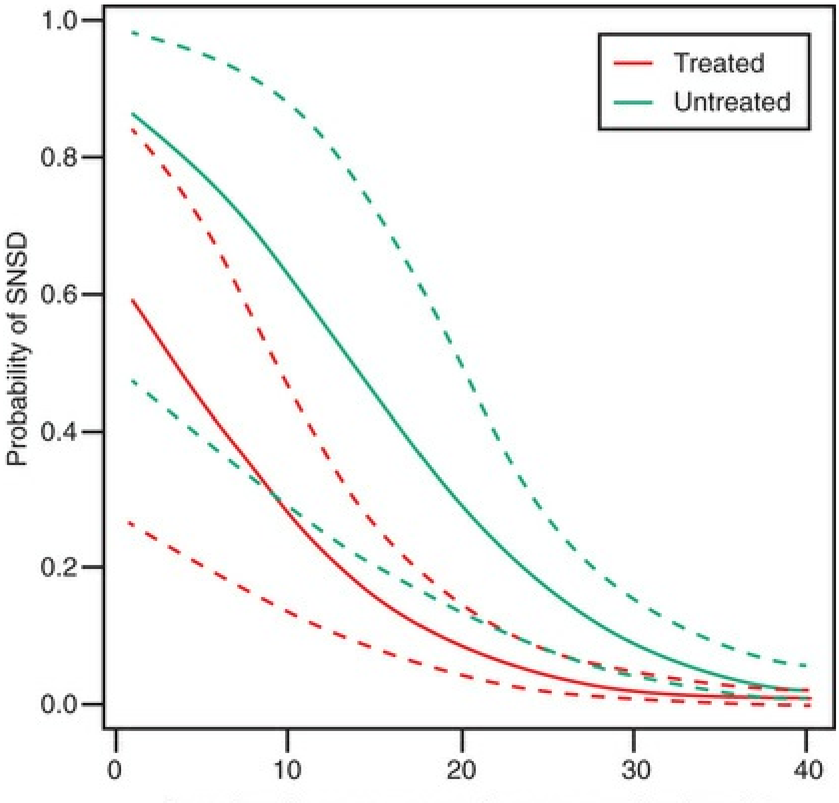
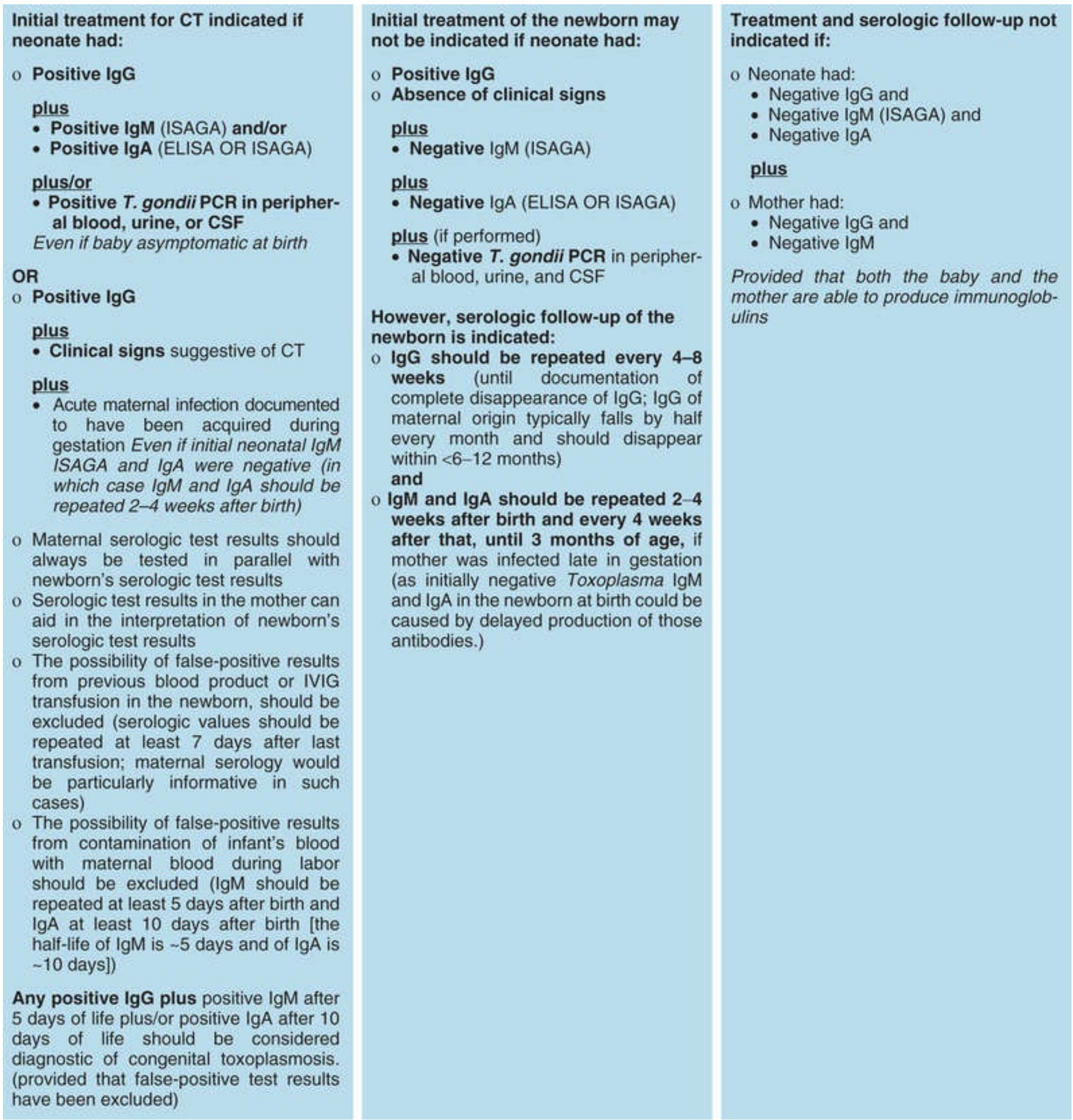


FIGURE 273.4 Probability of severe neurologic sequelae or death (SNSD) according to maternal treatment status (imputed gestational age at seroconversion [*solid lines*] and 95% Bayesian credible limits [*dashed lines*]). (From Cortina-Borja M, Tan HK, Wallon M, et al. Prenatal treatment for serious neurological sequelae of congenital toxoplasmosis: an observational prospective cohort study. PLoS Med 2010;7:e1000351. © 2010; made available through CCAL.)

Although no randomized clinical trials have been conducted on the efficacy of prenatal treatment, accumulated evidence from several observational cohort studies provides strong support for the benefit of prenatal screening and treatment in decreasing both the mother-to-child-transmission risk and the severity of congenital toxoplasmosis. The Systematic Review on Congenital Toxoplasmosis (SYROCOT)[44] revealed that when prenatal treatment was promptly initiated within 3 weeks of maternal seroconversion, the likelihood of mother-to-child-transmission was 52% lower, compared with delayed treatment initiation.[44] The lowest rates of mother-to-child-transmission have been observed in Germany,[49] where spiramycin is given until the 16th week of gestation in women with acute primary infection during pregnancy followed by at least 4 weeks of pyrimethamine-sulfadiazine plus folinic acid, independently of the fetal infection status (4.8% [33 cases in 685 pregnant women]) (The treatment for the rest of the pregnancy was determined based on the AF PCR and fetal ultrasound results.). Investigators from France reported that when monthly prenatal screening became mandatory in 1992, the delay between infection and treatment was reduced, and the risk of fetal infection decreased, for example, from 59.6% to 46.6% ($P = 0.038$) for maternal infections at the 26th week of gestation.[39] When AF PCR testing was introduced in France in 1995, earlier treatment of infected fetuses with the combination of pyrimethamine and sulfadiazine ensued, and the risk of developing clinical signs in children who were followed up for 3 years dropped significantly (odds ratio, 0.59; 95% confidence interval: 0.4–0.89; $P = 0.012$).[39] In Austria the risk of mother-to-child-transmission was sixfold lower in women who received prenatal treatment compared with untreated women, taking into account the gestational age at maternal infection (9% [87 cases in 1007 women] vs. 51% [32 cases in 63 women]).[47] An analysis of 293 infants from 14 European centers showed that antepartum treatment of toxoplasmosis was associated with 76% lower odds of severe neurologic sequelae or death.[50] In summary, early diagnosis and treatment of acute *Toxoplasma* infection should be offered to each pregnant woman.

Neonates

The approach to treatment and follow-up based on diagnostic test results is shown in Fig. 273.5. Pyrimethamine, sulfadiazine, and folinic acid therapy is recommended in infants <1 year of age when congenital toxoplasmosis is highly suspected or confirmed[2] (see Table 273.1). Data on the effectiveness of other regimens such as TMP-SMX or pyrimethamine plus clindamycin plus folinic acid in this context are insufficient.



Initial treatment for CT indicated if neonate had:

- **Positive IgG**

  plus
  - **Positive IgM** (ISAGA) **and/or**
  - **Positive IgA** (ELISA OR ISAGA)

  plus/or
  - **Positive *T. gondii* PCR in peripheral blood, urine, or CSF**

  Even if baby asymptomatic at birth

OR

- **Positive IgG**

  plus
  - **Clinical signs** suggestive of CT

  plus
  - Acute maternal infection documented to have been acquired during gestation *Even if initial neonatal IgM ISAGA and IgA were negative (in which case IgM and IgA should be repeated 2–4 weeks after birth)*

- Maternal serologic test results should always be tested in parallel with newborn's serologic test results
- Serologic test results in the mother can aid in the interpretation of newborn's serologic test results
- The possibility of false-positive results from previous blood product or IVIG transfusion in the newborn, should be excluded (serologic values should be repeated at least 7 days after last transfusion; maternal serology would be particularly informative in such cases)
- The possibility of false-positive results from contamination of infant's blood with maternal blood during labor should be excluded (IgM should be repeated at least 5 days after birth and IgA at least 10 days after birth [the half-life of IgM is ~5 days and of IgA is ~10 days])

Any positive IgG plus positive IgM after 5 days of life plus/or positive IgA after 10 days of life should be considered diagnostic of congenital toxoplasmosis. (provided that false-positive test results have been excluded)

Initial treatment of the newborn may not be indicated if neonate had:

- **Positive IgG**
- **Absence of clinical signs**

  plus
  - **Negative** IgM (ISAGA)

  plus
  - **Negative** IgA (ELISA OR ISAGA)

  plus (if performed)
  - **Negative *T. gondii* PCR** in peripheral blood, urine, and CSF

However, serologic follow-up of the newborn is indicated:

- **IgG should be repeated every 4–8 weeks** (until documentation of complete disappearance of IgG; IgG of maternal origin typically falls by half every month and should disappear within <6–12 months)

  and
- **IgM and IgA should be repeated 2–4 weeks after birth and every 4 weeks after that, until 3 months of age,** if mother was infected late in gestation (as initially negative *Toxoplasma* IgM and IgA in the newborn at birth could be caused by delayed production of those antibodies.)

Treatment and serologic follow-up not indicated if:

- Neonate had:
  - Negative IgG and
  - Negative IgM (ISAGA) and
  - Negative IgA

  plus
- Mother had:
  - Negative IgG and
  - Negative IgM

Provided that both the baby and the mother are able to produce immunoglobulins

FIGURE 273.5 Management algorithm for infants with suspected or confirmed congenital toxoplasmosis (CT). CSF, cerebrospinal fluid; Ig, immunoglobulin; IVIG, intravenous immune globulin; ISAGA, immunosorbent agglutination assay; PCR, polymerase chain reaction.

Immunocompetent and Immunocompromised Children

Treatment is indicated for immunocompetent children with severe acute *Toxoplasma* infection who have clinically significant syndromes including myocarditis, myositis, hepatitis, pneumonia, brain lesions, or skin lesions[66] (see Table 273.2). Although *Toxoplasma* lymphadenitis usually is considered a self-limited disease, treatment is indicated in patients who have severe or persisting symptoms. Treatment also is indicated in patients with active ocular disease (see Table 273.1).

The optimal duration of treatment for chorioretinitis in children has not been studied. Based on experience in adults, anti-*Toxoplasma* treatment usually is continued for at least 1 to 2 weeks after resolution of clinical signs and symptoms of acute chorioretinitis and for approximately 4 to 6 weeks total, whichever is longer.[67,68] Although acute eye disease often resolves within 10 to 14 days after initiation of treatment, some cases resolve more slowly. Longer treatment durations with pyrimethamine plus sulfadiazine have been proposed, for up to 3 months in children[53,69] and 4 months in adults.[70] Close ophthalmologic follow-up every 2 to 3 weeks is necessary in all cases of active toxoplasmic chorioretinitis to determine response and optimal duration of treatment. The drug regimen of choice is pyrimethamine plus sulfadiazine plus folinic acid. The use of alternative regimens such as TMP-SMX or a combination of pyrimethamine, clindamycin, and folinic acid (see Table 273.2) in these patients is supported by adult trials; such data are not available in children.

Prevention

Primary Infection

Seronegative pregnant women and immunocompromised patients should be educated on the known risks factors for the acquisition of *T. gondii* and avoidance strategies (Table 273.3). All pregnant women and immunocompromised patients should be screened for *Toxoplasma* IgG and IgM antibodies regardless of clinical or epidemiologic history. Seronegative pregnant women should be tested serially during gestation to detect seroconversion at the earliest time possible. Universal screening for *T. gondii* infection during pregnancy and monthly monitoring of seronegative women (as currently done in France) is not mandatory currently in the US. However, a decision analysis in the US showed that the implementation of a universal monthly antepartum screening program, including antepartum treatment, fetal ultrasound scans, AF PCR, and infant follow-up and treatment, was a cost-saving strategy, (with results remaining robust in several sensitivity analyses).[71] The role of prenatal screening and treatment for congenital toxoplasmosis in the US may need reevaluation, considering the abundance of favorable observational studies.[18,39,44,47–50]

TABLE 273.3

Recommendations for the Primary Prevention of *Toxoplasma gondii* Infection in Seronegative People[a]

Vehicle of Transmission	Recommendation
Meat and other edibles	Meat should not be "pink" in the center Cook meat thoroughly up to ≥63°C (145°F) for whole cut meat (excluding poultry); up to ≥71°C (160°F) for ground meat (excluding poultry), and up to ≥74°C (165°F) for all poultry (whole cuts and ground)[75]
	Freezing and thawing can kill *T. gondii* tissue cysts; freeze meat to −20°C for at least 24 hr
	Infected meat that has been smoked, cured in brine, or dried still can be infectious
	Wash hands carefully after contact with raw meat
	Avoid mucous membrane contact when handling raw meat
	While wearing gloves, wash kitchen surfaces and utensils that have come in contact with raw meat
	Abstain from skinning or butchering animals without wearing gloves
	Avoid drinking unpasteurized goat milk
	Avoid eating raw oysters, clams, or mussels
	Carefully wash fruits, vegetables, or any organic edibles
Untreated water	Refrain from drinking untreated water including that from wells or reservoirs that have not been secured from potential contamination by feces from wild or domestic cats
Cat feces and soil exposure[75]	**Pregnant women** Avoid contact with soil potentially contaminated with cat feces, especially handling of cat litter or gardening
	Wearing gloves is recommended during gardening or any contact with soil or sand because it could be contaminated with cat feces that contain *T. gondii* oocysts; if these activities cannot be avoided, wash hands with soap after gardening or contact with soil or sand **Nonpregnant people** Wash hands with soap after gardening or contact with soil or sand Change cat litter box daily (if own a cat); *T. gondii* becomes infectious after 5

	days from shedding in cat feces Keep outdoor sandboxes covered Keep cats indoor Do not feed cats raw or undercooked meats

[a] Up to 50% of people can become infected with *T. gondii* even without recalling behaviors associated with the acute infection.[30,31]

Recommendations for prevention of acute infections, particularly in seronegative pregnant women and immunocompromised children, are summarized in Table 273.3.

Seronegative recipients of noncardiac solid-organ transplants who receive an allograft from a seropositive donor should receive TMP-SMX prophylaxis for at least 6 months. Cardiac transplant recipients can also be given pyrimethamine prophylaxis for at least 6 weeks. These regimens have been reported to be effective in the prevention of primary infection in newly immunosuppressed patients at risk for toxoplasmosis.

Reactivation of Latent Infection

TMP-SMX and atovaquone have been used to prevent reactivation of latent infection in immunosuppressed adults. Dapsone plus pyrimethamine, and pyrimethamine plus sulfadiazine, also have been reported to be effective, but use of these drugs is limited by potential hematologic toxicity. Prophylaxis against reactivation of latent infection has been successful in patients infected with *T. gondii* who have AIDS and $CD4^+$ T lymphocyte counts <200 cells/mm^3. *Toxoplasma*-seropositive recipients of an allogeneic HSCT who develop graft-versus-host disease represent a unique challenge. Reactivation of *T. gondii* in immunocompromised persons can manifest as nonspecific illness (e.g., fever or pneumonia) yet be life-threatening; disease often is not recognized. Atovaquone prophylaxis has been proposed as an alternative regimen in these patients given the potential toxicity of TMP-SMX. Some investigators have proposed a preemptive strategy in which *Toxoplasma*-seropositive patients who receive an allogeneic HSCT and develop graft-versus-host disease are monitored routinely (e.g., weekly for the first 100 days) with blood *T. gondii* PCR. Patients with positive PCR results are given TMP-SMX or atovaquone preemptively. Discontinuation of prophylaxis against *Toxoplasma* encephalitis has proved safe in patients with AIDS who are receiving combination antiretroviral therapy, who have $CD4^+$ T-lymphocyte counts ≥200 cells/mm^3, and whose viral load has been undetectable for at least 6 months.

In patients with *Toxoplasma* chorioretinitis who experience frequent recurrences (e.g., >2 episodes/year), oral TMP-SMX for at least 12 months has been reported to be effective in the prevention of relapses in adults.[72,73] Eye disease recurrences vary according to whether the patient received antepartum treatment or postnatal treatment or both.[16,54,74]

Key Points

Toxoplasma gondii

Epidemiology

- *Toxoplasma* infection occurs by ingestion of viable tissue cysts in meat or oocysts in food or water.
- Congenital infection occurs almost exclusively when the mother becomes acutely infected during gestation (or within 3 months before conception).
- Chorioretinitis occurs after congenital infection, with reactivation of congenital infection, or with postnatally acquired acute infection.
- Organ transplant recipients can acquire the infection from the transplanted organ or can have reactivation of latent infection following immunosuppression.

Clinical Features

- *Congenital toxoplasmosis findings in the fetus:* asymptomatic *or* intrauterine growth retardation, hydrocephalus, intracranial calcifications, intrahepatic calcifications, echogenic bowel, hydrops fetalis, pericardial/pleural effusions, fetal death
- *Congenital toxoplasmosis findings in the newborn/infant:* asymptomatic *or* chorioretinitis, macular or peripheral retinal lesions, strabismus, visual impairment, hydrocephalus, macrocephaly or microcephaly, intracranial or intrahepatic

calcifications, preterm birth, psychomotor or mental retardation, abnormal muscle tone, seizures, nerve palsies, hepatosplenomegaly, jaundice, rash, sensorineural hearing loss, rarely sepsis-like illness, cerebrospinal fluid (CSF) abnormalities (pleocytosis, elevated protein, eosinophilia, hypoglycorrhachia), thrombocytopenia, anemia, hepatitis

- *Postnatally acquired acute infections in immunocompetent children:* asymptomatic *or* flu-like or mononucleosis-like illness, lymphadenopathy; occasionally severe disease

- *Toxoplasmosis in immunocompromised children* (reactivation of past infection): severe disseminated disease with multiorgan involvement; sepsis-like illness; fever; pneumonitis; myocarditis; hepatitis; encephalitis; seizures; myositis

- Toxoplasmosis should be in the differential diagnosis when compatible clinical signs and symptoms are present, independent of risk factors (50% of acutely infected patients do not recall known risk factors).

Diagnosis

- Evaluation for suspected congenital toxoplasmosis in the fetus: maternal serology; amniotic fluid *T. gondii* PCR, and fetal ultrasound

- Evaluation for suspected congenital toxoplasmosis in the newborn:

- Maternal serology and anti–*Toxoplasma*-specific immunoglobulin G (IgG), plus IgM (by immunosorbent agglutination assay, [ISAGA]) plus IgA (by enzyme-linked immunosorbent assay [ELISA] or ISAGA)

- *Toxoplasma* polymerase chain reaction in CSF, peripheral blood, and urine

- Testing of infants with suspected congenital toxoplasmosis should be performed at a reference laboratory because of the availability of the highly sensitive IgM-ISAGA test and PCR testing of blood/CSF and urine.

- Previous transfusion of blood products or IGIV may cause false-positive results.

- CSF analysis, complete blood count, and liver function tests

- Detailed pediatric, neurologic, and ophthalmologic evaluation (ideally by retinal specialist)

- Head computed tomography or head MRI or head ultrasound; abdominal ultrasound, and auditory brainstem responses

- Beyond the neonatal period, serologic assays can distinguish acute from chronic infection.

- Positive *Toxoplasma* IgM results at commercial laboratories should be confirmed at a reference laboratory (where comprehensive panel of tests are offered according to clinical situations).

- *In transplant recipients* diagnosis of acute *Toxoplasma* infection relies on positive polymerase chain reaction results from peripheral blood, CSF, urine, or other body tissues or body fluids or histopathologic examination with immunoperoxidase staining. Pretransplant serologic findings in the donor and recipient can assist in the diagnosis. Serologic findings in the posttransplant period frequently are not helpful.

Treatment

- *Congenital toxoplasmosis:* pyrimethamine plus sulfadiazine plus folinic acid

- *Severe toxoplasmosis in immunocompetent or immunocompromised children*: pyrimethamine plus sulfadiazine plus folinic acid or alternatively, trimethoprim-sulfamethoxazole.

Prevention and Prophylaxis

- Avoid undercooked meat and food/water potentially contaminated with *T. gondii*–infected soil and contact with *T. gondii*–infected soil

- Severely immunocompromised children should receive anti-*Toxoplasma* prophylaxis according to their *T. gondii* serologic status.

- Posttransplant recipients should receive prophylaxis according to the *T. gondii* pretransplant serologic status in the donor and recipient.

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Trichomonas vaginalis

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Trichomonas vaginalis can infect both men and women and is recognized as the most common nonviral sexually transmitted infection in the world.[1]

Description of the Pathogen

T. vaginalis, a flagellated protozoan parasite, was first described in 1836 by French physician Alfred François Donné, who observed these "animalculi" in vaginal fluid under a light microscope.[2] *T. vaginalis* eukaryotic parasites are typically oval or fusiform, 7 to 32 µm long, and 5 to 12 µm wide (Fig. 274.1).[3] Each has 4 anterior flagella that appear to arise from a single stalk, a central axostyle, and an undulating membrane that extends across the organism. The microbe contains a large anterior nucleus and well-developed Golgi bodies. The organism generates metabolic energy in membrane-bound chromatic granules called hydrogenosomes.[3] All areas of the cell surface are capable of phagocytosis and can ingest bacteria, leukocytes, and other particles. *T. vaginalis* is facultatively anaerobic, uses a variety of carbohydrate sources, has limited biosynthetic capabilities, and grows in various liquid and semisolid media or in cell culture, especially in low-pH environments (i.e., pH 4.9–7.5).[3,4] The organism reproduces by binary fission every 4 to 6 hours.

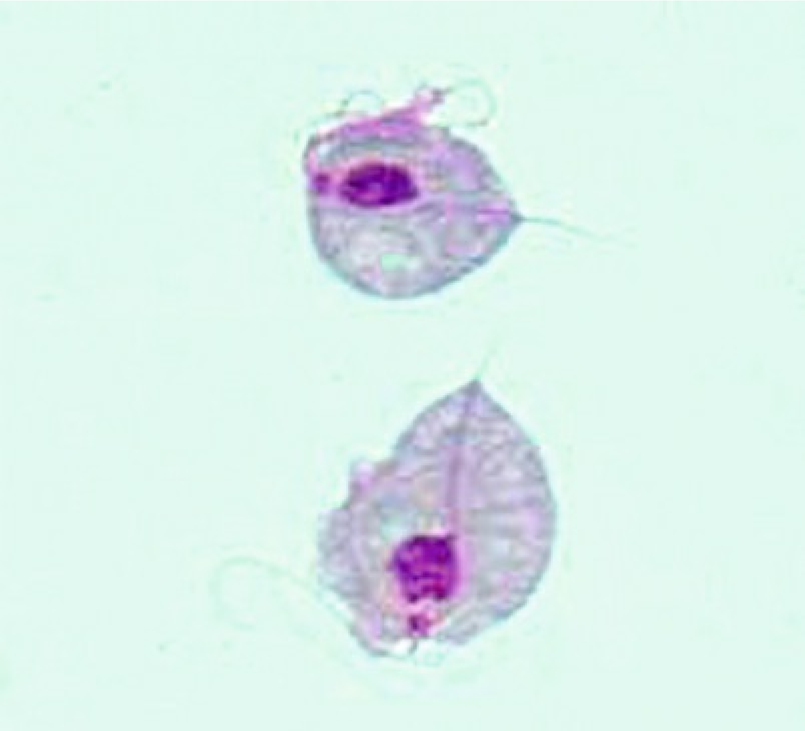

FIGURE 274.1 **Two trophozoites of *Trichomonas vaginalis* obtained from in vitro culture (Giemsa stain).** (From Centers for Disease Control and Prevention.)

T. vaginalis parasites exist only in trophozoite form, and humans are the only hosts.[3] Parasites readily attach to mucous membranes by adhesion proteins and can damage epithelial cells by direct contact.[5,6] Epithelial damage also can be caused by contact-independent mechanisms, including soluble and membrane-associated enzymes associated with phospholipase A activity, which can lyse nucleated cells in vitro and contribute to tissue damage and inflammation.[7–9] *T. vaginalis* can induce both humoral and cell-mediated immune inflammatory responses, but these responses are not protective because repeated and persistent infections can occur.[3]

Epidemiology

T. vaginalis infection is the most prevalent nonviral sexually transmitted infection. It causes an estimated 3.7 million infections annually in the United States, including 2.3 million infections among women and 1.4 million infections among men.[10] Neither trichomoniasis nor *T. vaginalis* infection is a nationally notifiable condition or reportable in any US state, and prevalence estimates are based on nationally representative studies. Among adolescents in school grades 7 to 12, an estimated 2.8% of girls and 1.7% of boys are infected with *T. vaginalis*.[11]

Health disparities by race or ethnicity are substantial. In a nationally representative study in the US, the prevalence of infection among non-Hispanic black women was 13%, significantly higher than the 1.8% prevalence among Mexican-American women and 1.3% among non-Hispanic white women.[12] Prevalence also increases with age, peaking at more than 11% among women ≥40 years of age.[12,13]

High-risk groups include incarcerated populations, with prevalences of 9% to 32% among incarcerated women and 2% to 9% among incarcerated men.[13–20] The prevalence of infection is also high among sexually transmitted disease clinic patients, at 17% of men and 26% of women tested.[21,22] Among women using drugs, the prevalence of *T. vaginalis* infection ranges from 13% to 38%.[23–25]

Transmission results almost exclusively from sexual contact during penile-vaginal sexual intercourse. *T. vaginalis* does not commonly cause oral or rectal infections.[26] Perinatal transmission of trichomoniasis can occur; the presence of *T. vaginalis* in a child beyond the perinatal period is considered suggestive of sexual abuse.[27,28]

Clinical Manifestations

Approximately 70% to 85% of *T. vaginalis* infections are asymptomatic.[12,29] Initial symptoms, when present, may develop within 5 to 28 days after infection. Untreated infections can last for months to years.[30,31]

Women

Women can develop signs and symptoms including vaginal discharge, vulvovaginal irritation, dysuria, and dyspareunia. Lower abdominal pain is less common. Associated vulvar and vaginal erythema with copious frothy discharge pooling in the posterior vaginal fornix can be present. Punctate hemorrhagic lesions in the genital epithelium can result in colpitis macularis ("strawberry cervix"), a finding specific for trichomoniasis. Discharge ranges in appearance but can be yellow green, malodorous, and diffuse.[32,33] The differential diagnosis of vaginal discharge can include bacterial vaginosis, candidal vulvovaginitis, and cervicitis related to other sexually transmitted diseases such as *Chlamydia* infection or gonorrhea. *T. vaginalis* infection is associated with preterm delivery as well as an increased risk of human immunodeficiency virus (HIV) infection.[34–38]

Men

Men may develop symptoms of urethritis, epididymitis, or prostatitis. Urethral discharge is common, and dysuria and pruritus can occur. *T. vaginalis* is responsible for 1% to 15% of cases of nongonococcal urethritis in men.[11,21,39,40] *T. vaginalis* urethritis cannot be distinguished clinically from nongonococcal urethritis caused by other pathogens, such as *Mycoplasma genitalium* or *Chlamydia trachomatis*. In areas where *T. vaginalis* is highly prevalent, men who have sex with women and have persistent or recurrent urethritis should be presumptively treated.[41]

Children

A few cases of trichomoniasis have been reported in premature newborns infected during vaginal deliveries.[42–44] Neonatal symptoms have included self-limited vaginal discharge, urinary tract infection, or respiratory tract symptoms. Such infections are self-limited and are expected to resolve within weeks.

Laboratory Findings and Diagnostic Tests

Although trichomoniasis is a clinical diagnosis, various laboratory assays are used to detect the presence of *T. vaginalis* parasites in vaginal or endocervical fluid from women, semen or urethral swabs from men, or urine specimens. Traditionally, screening and testing for this parasite have focused on women, and newer molecular tests may not be approved by the US Food and Drug Administration for use in male specimens given limited available data.

The most common test is microscopic evaluation of genital secretions (“wet mount”). This test is often performed by swabbing the anterior and posterior vaginal fornices, agitating the swab in 1 mL of saline solution, and examining a drop of the fluid on a microscope slide. Characteristic twitching of motile parasites can be seen under low (×100) or medium (×400) magnification. However, nonmotile parasites can be overlooked or mistaken for similarly sized leukocytes. Sensitivity of wet mount is poor (51%− 65%) and operator dependent, and it declines rapidly as microscopy is delayed.[45–48] To increase sensitivity, various algorithms have been suggested in which initial negative wet mount results are followed by a more highly sensitive test.[47]

Culture has a sensitivity of 75% to 96% and a specificity of up to 100%.[46,47] A commercially available culture system (InPouch TV, BioMed Diagnostics, White City, Ore) appears to be comparable to traditional Diamond media while permitting easier transport and storage.

Sensitive same-day rapid tests can be performed at the point of care. The OSOM Trichomonas Rapid Test (Sekisui Diagnostics, Framingham, Mass) is a Clinical Laboratory Improvement Amendments (CLIA)–waived immunochromatographic dipstick (sensitivity, 82%–95%; specificity, 97%−100%) with results in 10 minutes.[46,49–51] The Affirm VP III (BD Diagnostics, Sparks, Md) is a nucleic acid probe-hybridization test that evaluates for 3 causes of vaginitis: *Gardnerella vaginalis*, *Candida albicans,* and *T. vaginalis* (sensitivity of ≥63% specificity of 99.9%) with results in 45 minutes.[52,53]

Highly sensitive nucleic acid amplification tests that are now cleared by the Food and Drug Administration include the BD Probe Tec TV Q^x Amplified DNA assay (BD Diagnostics) and the APTIMA *Trichomonas vaginalis* assay (Hologic, San Diego, Calif) (sensitivity, 95.2%−100%; specificity, 95.3%−100.0%).[46,52,54,55]

Papanicolaou (Pap) smears are neither sensitive nor specific tests for trichomoniasis, although *T. vaginalis* parasites can be incidental findings.[48]

Treatment

The only medications approved in the US for treating trichomoniasis are metronidazole and tinidazole, both 5-nitroimidazole antibiotic medications. Sexually transmitted disease treatment guidelines from the Centers for Disease Control and Prevention recommend therapy with a single 2-g dose of either metronidazole or tinidazole orally; additional doses or longer treatment courses have been used successfully in patients with recurrent or persistent infections.[41] Randomized controlled trials demonstrated that tinidazole had efficacy equal to or superior to that of metronidazole, with cure rates of 86% to 100%.[56–60] In case of medication allergy, desensitization according to a published regimen can be considered.[61] Treatment of all sexual partners prevents recurrences in the index case, reduces transmission, and prevents new cases in the community.[41]

Most strains of *T. vaginalis* are susceptible to metronidazole, although antimicrobial resistance is an emerging issue. Among specimens from women diagnosed with trichomoniasis at sexually transmitted disease clinics in 6 cities, 4.3% exhibited low-level metronidazole resistance in vitro, and none demonstrated tinidazole resistance.[62] However, in a study of *T. vaginalis* isolates from 175 women with persistent trichomoniasis whose clinicians consulted the Centers for Disease Control and Prevention for susceptibility testing after standard therapy failed at least twice, 115 (66%) demonstrated some level of metronidazole resistance.[63] Treatment failure resulting from antimicrobial-resistant *T. vaginalis* should be distinguished from the possibility of reinfection from an untreated sexual partner.[41]

Special Considerations

Pregnancy and Lactation

Maternal *T. vaginalis* infection is associated with adverse pregnancy outcomes, including premature rupture of membranes, preterm delivery, and delivery of a low birth weight infant.[36,64] However, no clear evidence indicates that metronidazole treatment results in a reduction in perinatal morbidity.[37,65] For asymptomatic women, screening can be considered at the discretion of the treating clinician. Symptomatic pregnant women should be tested for *T. vaginalis* infection and considered for treatment with metronidazole.[41]

For lactating women, some clinicians recommend deferring breastfeeding for 12 to 24 hours following a 2-g dose of metronidazole and for 72 hours following a 2-g dose of tinidazole.[41,66–68]

Human Immunodeficiency Virus Infection

T. vaginalis infection is associated with both acquisition and transmission of HIV.[34,35,69–72] Up to 53% of women with HIV infection have been found to be coinfected with *T. vaginalis*; prevalence among HIV-infected men is unknown.[25,73] Women infected with both HIV and *T. vaginalis* should receive metronidazole 500-mg orally twice daily for 7 days because this regimen significantly improved cure rates in a randomized trial.[74]

Prevention

Treatment of all sexual partners can prevent recurrences, reduce transmission, and prevent new cases of trichomoniasis. Among sexually active people, the risk of trichomoniasis and other sexually transmitted infections can be reduced by using condoms consistently and correctly.[75] Periodic presumptive nitroimidazole treatment for people at high risk such as sex workers can effectively reduce the occurrence of trichomoniasis.[76,77] Male circumcision may reduce the risk of *T. vaginalis* infections for circumcised men and their female sexual partners.[78,79] Data are needed on effective intervention strategies to reduce associated health disparities.

Key Points

Trichomonas Vaginalis Infections

Epidemiology

- *Trichomonas vaginalis* is the most prevalent nonviral sexually transmitted infection, causing 3.7 million infections annually among men and women in the United States.

- Among adolescents, an estimated 2.8% of girls and 1.7% of boys are infected.

- Prevalence of infection increases with age, and the infection affects a disproportionately high percentage of black women.

- High-risk groups include incarcerated populations and sexually transmitted disease clinic patients.

- *T. vaginalis* infection is associated with preterm delivery and an increased risk of human immunodeficiency virus (HIV) infection.

Clinical Features

- 70% to 85% of *T. vaginalis* infections are asymptomatic.

- Women can develop vaginal discharge, vulvovaginal irritation, dysuria, and dyspareunia; punctate hemorrhagic lesions can cause colpitis macularis (“strawberry cervix”), which is specific for trichomoniasis.

- Men can develop symptoms of urethritis, epididymitis, or prostatitis.

- Neonates can develop self-limited vaginal discharge, urinary tract infection, or respiratory tract symptoms.

Diagnosis

- Traditional diagnostic tests: wet mount microscopic evaluation (poor sensitivity) or culture

- Same-day point-of-care tests: OSOM Trichomonas Rapid Test (Sekisui Diagnostics, Framingham, Mass), Affirm VP III (BD Diagnostics, Sparks, Md)

- Nucleic acid amplification tests (high sensitivity): BD Probe Tec TV Q^x Amplified DNA assay (BD Diagnostics), APTIMA *Trichomonas vaginalis* assay (Hologic, San Diego, Calif)

Treatment

- A single 2-g dose of either metronidazole or tinidazole orally usually is sufficient for cure.

- HIV-infected patients should receive a 500-mg dose of metronidazole twice daily for 7 days to improve cure rates.

- Antimicrobial resistance is an emerging concern given lack of treatment alternatives.

Prevention

- All sex partners should be treated to prevent recurrent and new cases.

- Risk of sexually transmitted infections can be reduced by abstaining from sex or using condoms.

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Trypanosoma Species (Trypanosomiasis)

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Organisms of the genus *Trypanosoma* are flagellated protozoan parasites that inhabit the blood and tissue of a wide variety of vertebrate hosts, including birds, reptiles, and mammals. The name is derived from the Greek, *trypano* (meaning auger, a helical shaped tool) and *soma* (meaning body). The trypanosomes that infect humans in Africa *(T. brucei)* are transmitted by the bite of *Glossina* flies, whereas human trypanosomiasis in the Americas *(T. cruzi)* is transmitted by feces of triatomid insects.[1–3] In combination, African trypanosomiasis and American trypanosomiasis cause significant morbidity and death throughout the world, thus calling for expansion of prevention efforts, with improved diagnostic methods and treatment strategies.

Human African Trypanosomiasis

Human African trypanosomiasis, also known as sleeping sickness, is a vector-borne parasitic disease caused by 2 subspecies of the *Trypanosoma brucei* complex: *Trypanosoma brucei gambiense (T. b. gambiense)* and *Trypanosoma brucei rhodesiense (T. b. rhodesiense)*.[1–8] They are both transmitted by male and female *Glossina* flies (“tsetse flies”), but they cause entities with significant epidemiologic and treatment differences.[1,9]

Description of the Pathogen

The African trypanosomes are extracellular hemoflagellate parasites that are members of the Trypanosomatidae family, genus *Trypanosoma,* and subgenus *Trypanozoon.*[1] The life cycle includes both insect vector and mammalian host. After inoculation of infective metacyclic trypomastigotes into subcutaneous tissue by an infected tsetse fly, trypanosomes are converted to the pleomorphic bloodstream trypomastigotes, which are infective for the tsetse fly (Fig. 275.1). In the vertebrate host, African *Trypanosoma* organisms always occur in the trypomastigote form, where they live and multiply in blood, cerebrospinal fluid (CSF), interstitial space of the lymph nodes, spleen, and brain. The tsetse fly ingests bloodstream forms when taking a blood meal from an infected animal. Procyclic trypomastigotes eventually migrate through the fly's esophagus toward the hypopharynx in the proboscis and into the salivary glands. In the salivary glands, the procyclic trypomastigotes transform into epimastigotes, attach to the epithelium, and finally become infective metacyclic trypomastigotes that are inoculated into the vertebrate host during a new blood meal (Fig. 275.2).[1,4]

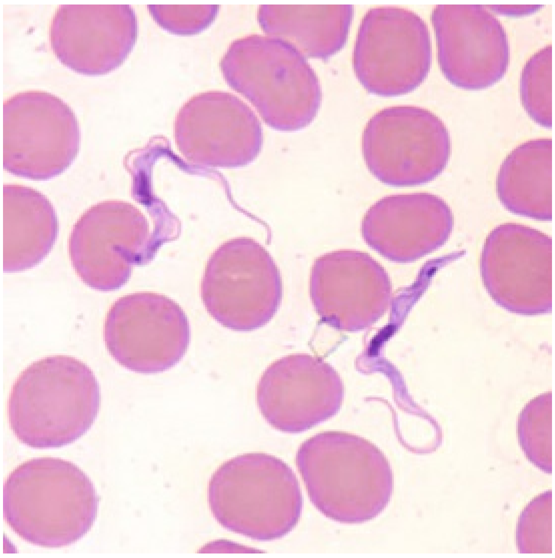

FIGURE 275.1 ***Trypanosoma brucei* in a thin blood smear (Giemsa stain).** (From Centers for Disease Control and Prevention. DPDx. [https://www.cdc.gov/dpdx].)

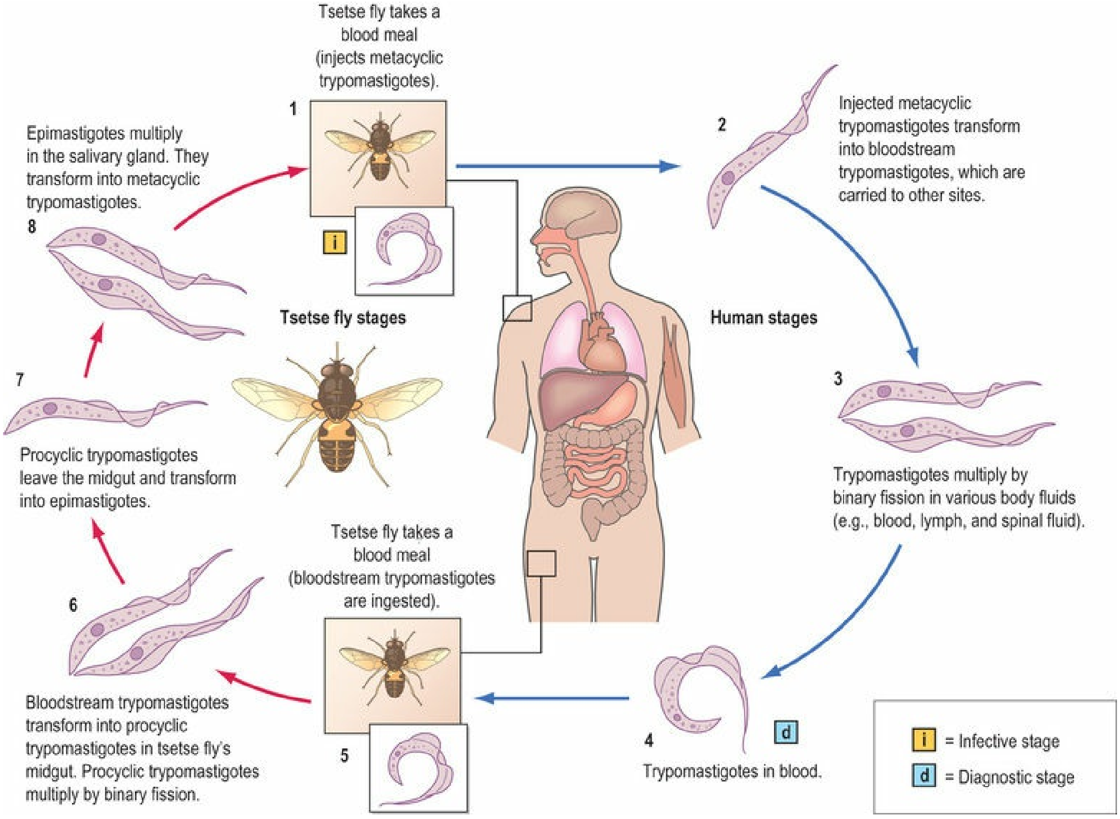
Tsetse fly takes a blood meal (injects metacyclic trypomastigotes).
1
2
Injected metacyclic trypomastigotes transform into bloodstream trypomastigotes, which are carried to other sites.
Epimastigotes multiply in the salivary gland. They transform into metacyclic trypomastigotes.
8
i
Tsetse fly stages
Human stages
7
3
Procyclic trypomastigotes leave the midgut and transform into epimastigotes.
Trypomastigotes multiply by binary fission in various body fluids (e.g., blood, lymph, and spinal fluid).
Tsetse fly takes a blood meal (bloodstream trypomastigotes are ingested).
6
Bloodstream trypomastigotes transform into procyclic trypomastigotes in tsetse fly's midgut. Procyclic trypomastigotes multiply by binary fission.
5
4
d
Trypomastigotes in blood.
i = Infective stage
d = Diagnostic stage

FIGURE 275.2 **Life cycle of *Trypanosoma brucei* (cause of African trypanosomiasis, African sleeping sickness).** (From Centers for Disease Control and Prevention.)

Epidemiology

T. b. gambiense occurs in West and Central Africa and accounts for more than 98% of all cases of human African trypanosomiasis. *T. b. rhodesiense* is found in East and south-central Africa.[5,6] The geographic gap between the 2 forms has been decreasing in Tanzania, the Democratic Republic of Congo, and Uganda.[1,7,8] This finding is of clinical significance because the laboratory differentiation between the 2 species is difficult, and treatment varies by species.[1] Estimates have shown that approximately 57 million people living over a geographic area of 1.4 million km^2 are at risk of *T. b. gambiense* infection, and 12.3 million people living over an area of 0.2 million km^2 are at risk of infection with *T. b. rhodesiense*.[8] Significant control efforts, including improvements in surveillance, vector and reservoir control, and wider accessibility to diagnostic methods and treatment, have resulted in a significant decline in the reported cases, with incident cases dropping to fewer than 10,000 for the first time in 2009 and reaching a record low of

6314 in 2013.[9]

Tsetse flies flourish at temperatures between 20°C and 30°C, in high humidity, and at an altitude lower than 1800 m. The development period of the parasite in the tsetse fly takes approximately 3 weeks; infection is lifelong (≤11 months) but is not passed to the fly's progeny. *Glossina palpalis* and *G. tachinoides,* which inhabit dense vegetation along river banks, are the most common vectors of *T. b. gambiense*, whereas *T. b. rhodesiense* is transmitted to humans by *G. morsitans* and less frequently by *G. swynnertoni* and *G. pallidipes,* which inhabit savannas and lake shores.[6] The main reservoir for *T. b. gambiense* is humans; however, animal reservoirs play important roles in human transmission of *T. b. rhodesiense,* with natural infections occurring in domestic animals, including cattle, sheep, and goats, and in some wild animals such as lions, hyenas, and several species of antelope.[6] The incubation period ranges from 5 days to a few weeks in *T. b. rhodesiense* infection and up to years in *T. b. gambiense* infection.[10] Humans primarily acquire *T. brucei* infections through the bite of infected tsetse flies. Rarely, humans can be infected transplacentally or by blood transfusion. The disease attacks all age groups and is equally frequent in female and male patients; however, children are infected rarely, mainly because of a decreased risk of exposure. The disease is invariably fatal if untreated.[1,6]

Pathogenesis and Pathology

After organisms are injected into the mammalian host with the saliva of the tsetse fly, they enter the lymphatics and then the bloodstream (see Fig. 275.2). Protective factors isolated from normal human plasma include trypanosome lytic factors 1 and 2 (TLF-1 and TLF-2), which destroy trypanosomes that are pathogenic in animals, but not *T. b. gambiense* and *T. b. rhodesiense,* as a result of acquired resistance mechanisms.[1] The TLFs have 2 components: apolipoprotein A1 (APOL1), which can form pores in lysosomes and elicit apoptotic pathways; and haptoglobin-related protein (HPR), which targets TLF-1 to the parasite. Together, APOL1 and HPR assemble into a single high-density lipoprotein to attack the parasite.[11–17]

Each subspecies has evolved and developed mechanisms to evade these protective responses. *T. b. rhodesiense* expresses a serum resistance-associated (SRA) gene that confers resistance to APOL1 by preventing its membrane insertion and enabling its degradation by proteases.[18–20] *T. b. gambiense* expresses a *T. b. gambiense*–specific glycoprotein (TgsGP) that prevents APOL1 insertion into endolysosomal membranes.[16,21,22] Inhibition of the *T. brucei* receptor for haptoglobin-hemoglobin also reduces the uptake of APOL1, thereby allowing for protease-mediated digestion of APOL1 in *T. b. gambiense*.[23] Both subspecies also use antigenic variation of the cell surface glycoproteins (variant surface glycoproteins) to avoid antibody-mediated clearance.[4,24]

Once these trypanosomes are able to avoid destruction by the immune system, they infect mammalian hosts and enter the lymphatic system where they cause lymph node enlargement with lymphocyte and mononuclear cell population expansion. Subsequently, the trypanosomes enter the bloodstream where they can disseminate to any organ (see Fig. 275.2). After a variable period, depending on the species, the organism enters the central nervous system (CNS) where it causes meningoencephalitis. The severity of symptoms is related directly to parasite burden. Histopathologic examination of the CNS reveals infiltration of plasma cells, macrophages, and lymphocytes, with perivascular proliferation of endothelial and neuroglia cells, severe cerebral edema, and punctate hemorrhage. Demyelination and neuronal damage have been observed and can extend deeply into white matter. Chronic meningoencephalitis can also occur. Vasculitis associated with increased permeability of the capillary vessels is considered to be the essential factor in pathogenesis and is suspected to be of immunopathogenic origin.[1,4,25]

Clinical Manifestations

Human African trypanosomiasis appears in 2 stages: the hemolymphatic stage and the meningoencephalitis stage. Infection caused by *T. b. rhodesiense* causes acute and severe disease with few CNS symptoms and death within weeks or months. *T. b. gambiense* infection is characterized by a milder, chronic, progressive course with involvement of the lymph nodes, CNS invasion, and a fatal outcome after several years.[4,25]

Within a few days, but up to 2 weeks after infection, an indurated, erythematous, painful, warm, circumscribed, rubbery lesion (trypanosomal chancre) can develop at the site of the tsetse fly bite. This lesion is seen in up to 20% of patients infected with *T. b. rhodesiense* and is much less common in *T. b. gambiense* infection. The lesion usually resolves within 3 weeks but with residual scarring and depigmentation.[1] The differential diagnosis includes cutaneous anthrax (in which marked swelling occurs around the eschar), syphilis, and African tick bite fever, caused by *Rickettsia africae* and *R. conorii*.

The early parasitemic phase of infection is accompanied by high fever, headache, and general malaise interspersed with relatively asymptomatic periods. As infection progresses, fever is intermittent, and a papular rash and generalized enlargement of lymph nodes occur, especially in the posterior cervical triangle (Winterbottom sign) and in the submaxillary, inguinal, and femoral regions. The nodes are discrete, soft, and nontender and contain abundant parasites.[26] The spleen and liver can be mildly enlarged. Over time, the patient develops dyspnea, chest pain, and loss of strength and becomes extremely emaciated.[25] Endocrine abnormalities include increased or decreased thyroid function, decreased sexual function, and, in women, amenorrhea. Arthralgia, weakness, and painful local edema of the hands, feet, and joints can be present. Deep hyperesthesia (Kerandel sign) is often reported in non-Africans; delayed, intense pain occurs when soft tissue is compressed.[26,27]

The most common laboratory abnormalities include hemolytic anemia, elevation of serum hepatic enzymes, coagulation abnormalities, thrombocytopenia, and hypocomplementemia. The sedimentation rate is markedly elevated.[4,28] The differential diagnosis during the first stage of the disease includes other causes of febrile illness occurring in the area, namely, malaria, typhoid fever, tuberculosis, brucellosis, syphilis, leptospirosis, hepatitis, borrelial relapsing fever, viral hemorrhagic fevers, and acute human immunodeficiency virus (HIV) infection.

In the second stage, sleep disturbance and neuropsychiatric disorders become more apparent. Meningoencephalitis can involve the spinal cord as well as the brain. The white matter of the brain shows pathognomonic cells called morula or Mott cells, which are plasma cells containing large concentrations of immunoglobulin M (IgM).[4] With CNS invasion, the chronic or sleeping sickness stage of infection is initiated.[25] Headache is severe, and irritability, personality and behavior changes, and gradual loss of cognitive function are common. Muscle spasms, ataxia, incoordination, tremor, alteration of reflexes, stiffness in the neck, papilledema, and flaccid paralysis occur. Psychiatric manifestations include hallucinations, delusional states, and overt psychoses. Choreiform or oscillatory movements of the arms, head, neck, and trunk are frequent.[4,6,29] Sleep disorders with diurnal somnolence, inappropriate episodes of sleeping, and nocturnal insomnia are prominent symptoms of the second stage.[4,25] Progressive somnolence and convulsions develop and lead to deep coma and death. Cardiac involvement can lead to congestive heart failure, pericardial effusion, and electrocardiographic changes.[30] Death results from meningitis, heart failure, or complications such as bacterial pneumonia. The differential diagnosis during the second stage of the disease includes other causes of chronic meningoencephalitis, especially tuberculosis, cryptococcal infection, and syphilis.

Congenital African trypanosomiasis, defined as the development of human African trypanosomiasis within the first 5 days of life,[31] has been described in a few case series.[31] In this form, progression to the second stage of the disease is faster. Transmission risk remains unknown.[31–33]

Diagnosis

The initial symptoms of human African trypanosomiasis are nonspecific. Therefore a combination of clinical signs in the correct epidemiologic setting should raise suspicion for this diagnosis.

Screening

In asymptomatic patients, screening can be performed for *T. b. gambiense* infection with a card agglutination test for trypanosomiasis (CATT), which uses a finger-prick drop of blood mixed on the card with a drop of reagent containing a freeze-dried trypanosomal antigen. If infection is present, agglutination occurs within 5 minutes.[6,26] This test can be performed in the field and has a sensitivity of 87% to 98% and a specificity of 93% to 95%.[26] False-negative results may occur in areas where the parasite does not express the specific antigen used in the test and as a result of a prozone phenomenon. Other serologic tests include immunofluorescent assay and enzyme immunoassay tests, which cannot be performed readily in the field.[34,35] No screening test is available for *T. b. rhodesiense* at this time.[1]

Symptomatic Disease

Diagnostic testing in a suspected case depends on visualizing the organism in blood, lymph node aspirate, bone marrow, or CSF by microscopic examination.[25] The miniature anion exchange centrifugation technique (mAECT) is the most sensitive technique available. In this assay, 350 μL of blood or CSF is obtained; the trypanosomes are isolated by anion exchange chromatography, concentrated by centrifugation, and then seen on microscopic examination. Fewer than 50 trypanosomes/mL of blood may be detected using this assay.[36] Additional techniques include the use of light-emitting diode fluorescence microscopy on lysed blood to visualize the trypanosomes and or loop-mediated isothermal amplification (LAMP), which uses a DNA amplification technique on a blood specimen.[37,38]

Older testing methods are less reliable because of the periodicity of parasitemia. Thick and thin Giemsa-stained smears of buffy coat preparations are more sensitive in *T. b. rhodesiense* infection, in which the degree of parasitemia is higher. This test has a lower limit of detection of approximately 5000 parasites/mL of blood. Concentration methods can increase the sensitivity. The microhematocrit centrifugation technique (Woo test), in which 6 to 8 sealed microhematocrit tubes are centrifuged and the buffy coat is examined using a long-distance objective lens for motile parasites, has a lower limit of detection of ~500 parasites/mL.[25] The quantitative buffy coat test, in which blood, ethylenediaminetetraacetic acid, and acridine orange stain are mixed and centrifuged, shows motile parasites with the use of fluorescence microscopy. Examination of wet preparations of lymph node aspirates has a sensitivity of 40% to 80%, similar to the sensitivity of blood examinations.[35,39] Several polymerase chain reaction tests for rapid detection of trypanosomes in human blood samples have been developed with sensitivities up to 100%.[6,40,41] However, molecular diagnostics have not been routinely used because of factors such as cost and the need for skilled personnel.[42]

Once the diagnosis of human African trypanosomiasis is made, CSF testing for staging purposes should be performed because the stage has important implications for therapy.[35] World Health Organization criteria for evidence of CNS infection are >5 leukocytes/mm^3 or visualization of trypanosomes. However, some clinicians use higher white blood cell count cutoffs such as >10 or >20 cells/mm^3. The presence of IgM in the CSF is an early and specific marker of CNS invasion.[25,26,43] A monoclonal antibody–based enzyme immunoassay for detection of *Trypanosoma* antigens in serum and CSF has high specificity (>99%) and sensitivity (*T. b. gambiense,* 95%; *T. b. rhodesiense,* 92%).[5]

Treatment

Few drugs are available to treat human African trypanosomiasis, with selection based mainly on the stage of disease and the specific pathogen. Early treatment is essential because the prognosis is poor once CNS involvement has occurred. In the absence of CNS disease, pentamidine and suramin are the drugs of choice.[1,6,44–46] These drugs do not cross the blood-brain barrier because of their poor lipophilic properties and are not considered when treating stage 2 disease.[45,47] Eflornithine alone or in combination with nifurtimox is used for treating stage 2 *T. b. gambiense* disease, and melarsoprol is used for stage 2 *T. b. rhodesiense* disease. Two newer drugs, fexnidazole and an oxaborole named SCYX-7158 have been developed, but they are still being tested in clinical trials.[46] Therapy is summarized in Table 275.1. Doses and side effects can be found in Chapter 296.

TABLE 275.1

Antimicrobial Therapy for Patients With African Trypanosomiasis[a]

Stage	**Category of Recommendation**	***Trypanosoma brucei gambiense***	***Trypanosoma brucei rhodesiense***
Hemolymphatic	Drug of choice	Pentamidine	Suramin
	Alternative	Suramin	None
Late-stage disease with CNS involvement	Drug of choice	Eflornithine *Or*	Melarsoprol
		Eflornithine plus	

		nifurtimox *Or* Melarsoprol	
	Alternative	None	None

[a]For doses, see Chapter 296.

CNS, central nervous system.

Prevention

In 2011, the World Health Organization Strategic and Technical Advisory Group on Neglected Tropical Diseases established an elimination goal for human African trypanosomiasis as a public health problem and created a roadmap toward this goal by 2020.[48,49] Routine preventive measures include avoiding known foci of tsetse infestation, avoiding endemic areas, wearing wrist- and ankle-length dark clothing, and use of insect repellents and mosquito bed nets. Clearing of vegetation around human settlements, limited destruction of game animals and potential wild reservoirs, prophylactic treatment of cattle and domestic animals, and spraying of insecticides have resulted in local eradication of the insect vector and a reduced incidence of human infection.[50] Refined vector control technologies may serve as potential, cost-effective strategies that could halt human African trypanosomiasis transmission.[51,52] Chemoprophylaxis is no longer available because of the poor risk-to-benefit ratio caused by adverse effects of the drugs.

American Trypanosomiasis

Chagas disease or American trypanosomiasis was discovered in 1909 by Dr. Carlos Chagas and is the result of infection by *T. cruzi*. Chagas disease is a systemic, lifelong infection that affects approximately 6 million people annually throughout the Americas.[2,53] This zoonotic infection is transmitted to humans by large, blood-sucking insects of the family Reduviidae. Three clinical stages are recognized in Chagas disease: a short acute stage; a long, clinically asymptomatic indeterminate stage; and a long-lasting chronic stage.[2,3] Large-scale vector control programs and screening of blood donors have reduced the incidence and prevalence of this disease.[54]

Description of the Pathogen

T. cruzi belongs to the genus *Trypanosoma,* subgenus *Schizotrypanum.* Members of this group develop in the lower gut and rectum of the triatomid vector (reduviid or kissing bug) (Fig. 275.3). The developmental cycle of *T. cruzi* includes 3 morphologic forms: amastigotes, epimastigotes, and trypomastigotes. The trypomastigote (Fig. 275.4) is found in the tissue and bloodstream (the only stage found in blood) of infected mammals and is responsible for the spread of infection from cell to cell and for transmission of the infection to the insect vector. The reduviid bug feeds on the vertebrate host and excretes the infectious forms (metacyclic trypomastigote) in its feces, which are rubbed or scratched into the bite wounds. The organisms can also enter the host through mucous membranes.

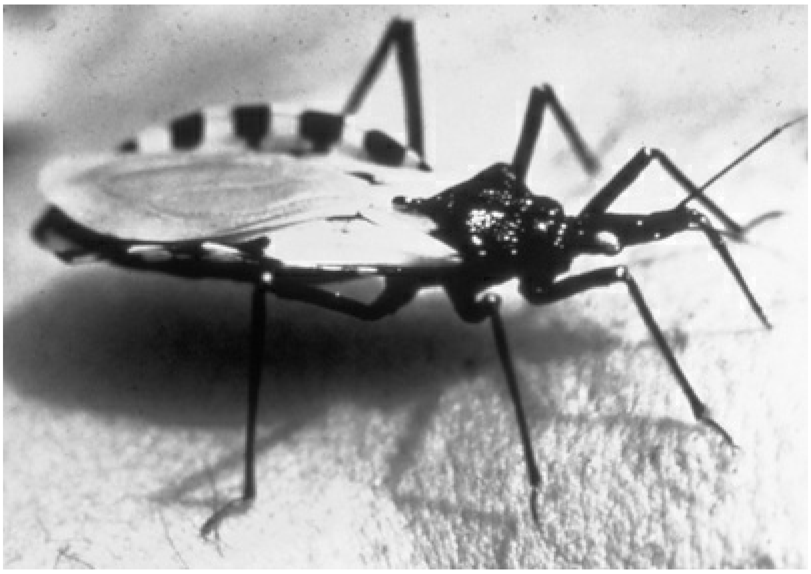

FIGURE 275.3 **A triatomine bug *(Dipetalogaster maximus)* feeding on human skin.** (From World Health Organization Tropical Disease Research Library.)

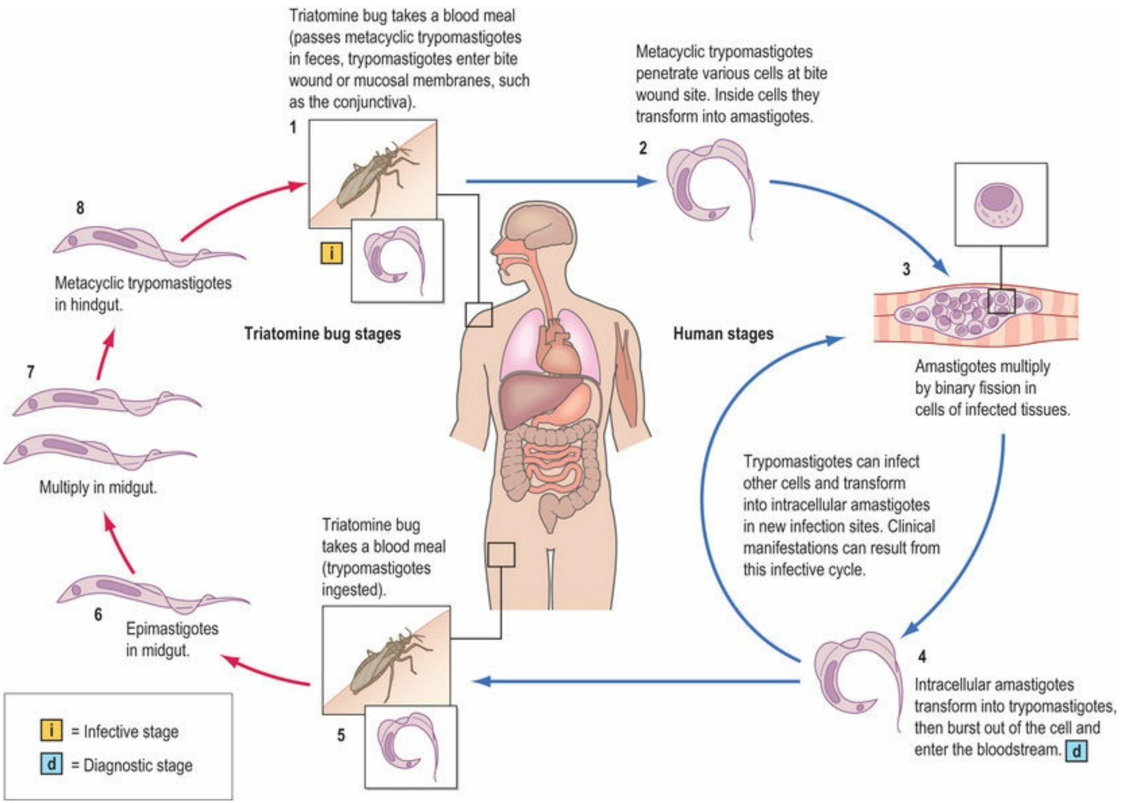
Triatomine bug takes a blood meal (passes metacyclic trypomastigotes in feces, trypomastigotes enter bite wound or mucosal membranes, such as the conjunctiva).
1
i
Metacyclic trypomastigotes penetrate various cells at bite wound site. Inside cells they transform into amastigotes.
2
3
Amastigotes multiply by binary fission in cells of infected tissues.
Trypomastigotes can infect other cells and transform into intracellular amastigotes in new infection sites. Clinical manifestations can result from this infective cycle.
4
Intracellular amastigotes transform into trypomastigotes, then burst out of the cell and enter the bloodstream. d
Human stages
Triatomine bug stages
Triatomine bug takes a blood meal (trypomastigotes ingested).
5
6
Epimastigotes in midgut.
Multiply in midgut.
7
8
Metacyclic trypomastigotes in hindgut.
i = Infective stage
d = Diagnostic stage

FIGURE 275.4 **Life cycle of *Trypanosoma cruzi* (cause of American trypanosomiasis, Chagas disease).** (From Centers for Disease Control and Prevention.)

T. cruzi is classified into 6 discrete typing units based on genomic sequencing: TcI to TcVI.[55] TcI, TcII, TcV, and TcVI are most frequently isolated from domestic cycles and are responsible for most human infections. TcI strains have been more commonly associated with cardiac disease, whereas TcII to TcVI strains are more commonly associated with gastrointestinal disease.[56] A genetically divergent lineage with the potential to infect humans, TcBat, has been isolated across Panama, Brazil, and Colombia.[57–59]

Epidemiology

The World Health Organization has estimated that approximately 70 million people are at risk of acquiring *T. cruzi* infection.[53] However, since the 1990s, improvements in vector control programs and compulsory blood bank screening have significantly reduced the incidence of disease.[2,3] In 2010, more than 5.7 million people in 21 Latin American countries had a diagnosis of Chagas disease; 62% of these people were from Argentina, Brazil, and Mexico.[53] In endemic areas, the incidence of Chagas disease has decreased from 700,000 new cases/year to approximately

30,000/year. Mortality rates also have decreased from approximately 45,000 deaths/year to 12,500/year.[2,3,53] The country with the highest incidence rate is Bolivia, followed by Mexico and Colombia. Since the 1990s, *Triatoma infestans,* the primary vector species, has been eliminated in Uruguay, Chile, and Brazil, in addition to parts of Argentina and Paraguay.[2,3] Transmission routes include vector borne (most common), congenital acquisition (almost 9000 infections/year), bloodborne, organ derived, and oral transmission by contaminated fruit or sugar cane juice.[60–77]

In the United States, approximately 300,000 people are infected with *T. cruzi*, most of whom acquired the disease from endemic countries. However, 7 autochthonous insect-borne human cases of Chagas disease have occurred in the US, as well as other cases of acute Chagas disease acquired through laboratory accidents.[78,79] Routine screening of the US blood supply began in 2007, and a study conducted by the Red Cross in 2006 to 2007 revealed that 1 in 4655 donations was positive for *T. cruzi* antibodies.[54] Increased immigration from endemic countries, particularly Mexico, has caused Chagas disease to become an important health issue in the US, Canada, and parts of Europe.[2,3,80]

More than 130 species of Triatominae are recognized, and although more than 50 of these species are known to transmit *T. cruzi*, relatively few of them feed on humans. Certain species show a considerable degree of adaptation to human habitation and are important vectors in transmission of Chagas disease, including *Triatoma infestans* (Argentina, Paraguay, southern Peru), *Rhodnius prolixus (*Colombia, El Salvador, Guatemala, Honduras, southern Mexico, Nicaragua, Venezuela), *Triatoma dimidiata* (Belize, Colombia, Costa Rica, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua), *Panstrongylus megistus* (Argentina, Brazil, Paraguay, Uruguay), and *Triatoma brasiliensis* (northeastern Brazil).[2,81] The domesticated species are large (2–3 cm or longer), obligate hematophagous insects that hide in crevices in walls, dark corners, windows, and door frames or in the thatch of roofs and take their blood meals at night. They require a blood meal at each stage of development to grow and mature. Infection lasts for the life of the vector, which can be up to 2 years. Species of *Triatoma* vary from one geographic area to another. In the US, several southern states have host vectors and reservoirs for *T. cruzi*, including opossums, armadillos, and canines.[78,79,82]

Pathogenesis and Pathology

During the acute phase, the lesion at the portal of entry shows a local inflammatory response with infiltration of lymphocytes, monocytes, and giant cells. Parasites are distributed widely throughout tissues, but they have a preference for the following: cardiac, skeletal, and smooth muscle cells; neural cells; and cells of the reticuloendothelial system (Fig. 275.5). The heart becomes enlarged, with interstitial inflammation of the endocardium and myocardium, edema, and focal necrosis in the contractile and conducting system. The cellular infiltrates consist of lymphocytes, monocytes, and plasma cells, as well as parasitized muscle cells.[83]

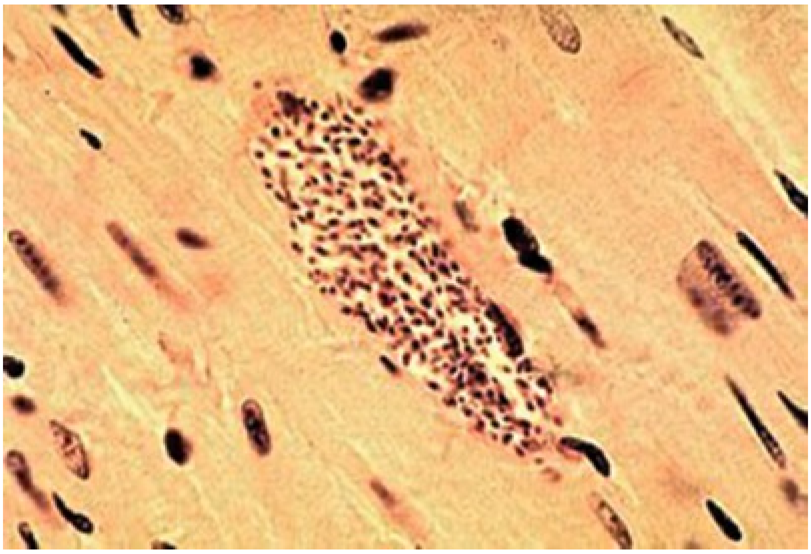

FIGURE 275.5 **Cardiac muscle with a pseudocyst containing amastigotes of *Trypanosoma cruzi*.** (From World Health Organization Tropical Disease Research Library/Stammers.)

During the chronic phase, ganglion cells are progressively destroyed, and the affected organs show variable tolerance to denervation. The heart becomes markedly enlarged, with characteristic thinning of the muscle wall, particularly the right atrium. Mural endocardial thrombosis and aneurysm can occur at the apex of the left ventricle. The myocardium is edematous and congested, myocardial fibers are degenerated, and dense foci of fibrosis can be seen in the interstitial space, but parasites are rarely found (15%–30% of cases). Inflammatory, fibrotic, and vascular changes occur in conductive tissue. The right bundle branch is the most commonly affected, and alterations in the atrioventricular conduction system are frequent. In people with digestive disease, the esophagus and colon are affected most commonly. Fibrosis is present in the myenteric plexus, as well as a considerable reduction in the number of neurons. Dysfunction is related directly to peristaltic abnormalities, which can lead to arrest in transit, extreme dilation of the organ, and hypertrophy of the muscle.[2,83]

Different hypotheses have been proposed to explain the mechanism of organ damage. These include direct cellular destruction by the parasite, cellular damage resulting from exposure to parasite-specific or nonspecific immune responses, microvasculopathy leading to ischemia or inflammation, inflammatory reactions resulting from allergic responses to parasitic antigens absorbed by host cells, or autoimmune reactions to antigens shared by the host and the parasite.[83–85] A clear understanding of the pathogenesis can be complicated by the finding that infections commonly involve a mixture of parasites (polyparasitism), each having distinct pathogenic potential.[86]

The immune system develops specific responses against *T. cruzi* that involve CD4$^+$ and CD8$^+$ T lymphocytes, B lymphocytes, and antibody production. However, complete eradication of the parasite is not achieved, a finding suggesting the development of escape mechanisms by *T. cruzi*. These escape mechanisms involve complement-regulatory molecules on the parasite surface, the ability to escape the phagocytic vacuole, poor pattern recognition receptors, poor development and a narrow recognition scope of *T. cruzi*–specific CD8$^+$ effector cells, and the development of senescence and exhaustion of CD4$^+$ and CD8$^+$ T lymphocytes, respectively.[87–92]

Clinical Manifestations

Clinically, Chagas disease occurs in 3 phases: acute, intermediate, and chronic. The acute phase (4–8 weeks) is often asymptomatic, but it can manifest with prolonged fever, headache, irritability, and fatigue. Infection often goes unrecognized and is diagnosed in only 1% to 2% of all patients. Lymphadenopathy and hepatosplenomegaly are observed frequently, and meningoencephalitis occurs occasionally. Depending on the site of entry, parasites can elicit a local inflammatory reaction of the skin (chagoma) or the eye (Romaña sign) with unilateral periorbital edema, conjunctivitis, and preauricular lymphadenitis (Fig. 275.6).[2,93] The most common (30% of cases) and severe manifestations are cardiovascular disturbances, including cardiac enlargement, functional heart murmurs, conduction blocks, and, occasionally, heart failure. Death caused by acute myocarditis occurs in 2% to 3% of cases, but in patients with meningoencephalitis, the mortality rate can be as high as 50%.[29]

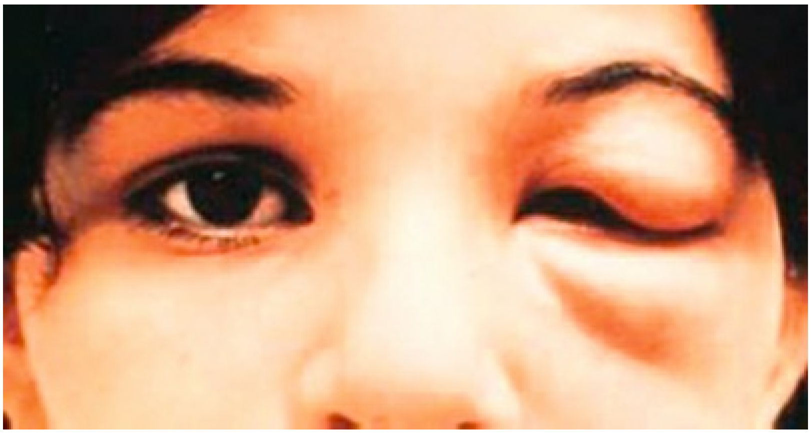

FIGURE 275.6 **Child with acute Chagas disease demonstrating the Romaña sign.** (From World Health Organization Tropical Disease Research Library.)

People who survive enter the indeterminate or chronic asymptomatic phase of the disease. This phase can persist for years, even for the life of the patient, or it can progress 10 to 20 years later to a chronic phase in up to 30% of the people. In the chronic phase, the patient has cardiac, digestive, or neurologic damage. The cardiac manifestations are the most common and include palpitations, dizziness, syncope, dyspnea, and chest pain.[2,3,94] The most important complications are pulmonary embolism and sudden death, usually resulting from ventricular fibrillation. In many cases, a typical aneurysm develops at the apex of the left ventricle.

The digestive form of the disease occurs in 10% to 15% of patients and varies from minor changes in motility of the esophagus or intestine to 2 main syndromes of megaesophagus and megacolon. Patients have difficulty swallowing and regurgitation, severe constipation, and abdominal pain. Esophagitis and esophageal cancer are the most common complications of megaesophagus, whereas fecaloma and volvulus can complicate megacolon.[2,3]

The prognosis depends on clinical staging. The acute phase is most serious in children <2 years of age and is almost always fatal if heart failure or meningoencephalitis develops. In patients with chronic disease and pronounced cardiac manifestations, the prognosis is poor, and death usually occurs within 5 years as a result of heart failure or pulmonary embolism. The prognosis in patients with the digestive form of the disease is usually good.[2,3]

Acute Chagas disease should be considered in any child who has been in an endemic area and in whom myocarditis and an acute febrile illness with lymphadenopathy develop. The acute phase must be differentiated from typhoid fever, visceral leishmaniasis, tuberculosis, toxoplasmosis, malaria, schistosomiasis, cytomegalovirus infection, infectious mononucleosis, and brucellosis. Chronic disease must be distinguished from endomyocardial fibrosis, viral myocarditis, rheumatic heart disease, and carcinoma of the esophagus or colon.

Immunosuppression after organ transplantation or secondary to HIV infection can lead to reactivation of infection and can result in severe systemic disease, which can have manifestations that differ from those in otherwise normal hosts. Transplant recipients often have subcutaneous nodules, panniculitis, and myocarditis, whereas patients with uncontrolled HIV infection can present with meningoencephalitis or focal brain lesions resembling those caused by cerebral toxoplasmosis.[2,93]

Congenital Infection

Congenital transmission of *T. cruzi* can be seen in both endemic and nonendemic countries as a result of immigration and lack of screening. Intrauterine infection can occur at any time during pregnancy and usually is asymptomatic.[64–66,68] Transplacental transmission is the only documented route of transmission, with no significant identification of *T. cruzi* in amniotic fluid or breast milk.[95,96] The risk for vertical transmission is highest in infants born to immunocompromised mothers, with rates as high as 100%.[97] In immunocompetent patients, maternal transmission rates can be as high as 50% in acute Chagas disease, whereas the rate decreases to

2% to 5% in chronic disease. In a study of 530 mothers in Bolivia, 154 (29%) had serologic evidence of chronic *T. cruzi* infection, and the infants of 10 (6%) of these mothers were infected.[68] Studies of infection during 2 periods in Bolivia found a rate of congenital infection of 5%.[64] However, a study in central Brazil showed a transmission rate of 2%, a finding suggesting geographic differences in the rates of transmission that could be directly associated with regional types.[98] In the US, an estimated 130,000 women 15 to 44 years of age were infected in the year 2000, and 170 to 640 cases of congenital infection occurred.[82]

Clinical illness can be present at birth or can develop within the first few weeks of life. The most common findings of congenital infection are prematurity, low birth weight, hepatosplenomegaly, fever, neurologic abnormalities (seizures, hypotonia, hyporeflexia, and tremors), anasarca, and petechiae.[3,64–66,68] Some patients have metastatic hemorrhagic chagomas in the skin or mucosa. Occasionally, intracranial calcifications and ocular lesions can occur. Cardiac involvement is rare and can manifest as heart failure. Megaesophagus and pneumonitis are reported.[3] Laboratory findings can include anemia, thrombocytopenia, lymphocytosis, jaundice, and hyperglobulinemia. CSF studies may reveal pleocytosis with lymphocytic predominance and an elevated protein concentration. Death frequently occurs during the first week of life. Most survivors have severe neurologic sequelae with mental deficiency or behavioral and learning disabilities.[3] Infants of seropositive mothers should be tested as soon as possible for the presence of circulating parasites and specific IgM antibody and should be monitored for a year after birth. A positive serologic test result for specific IgG at 6 and 12 months of age is an indication for treatment. Approximately 30% of congenitally infected patients will develop chronic Chagas disease with the characteristic cardiac and digestive system manifestations.[99]

The differential diagnosis includes TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, and herpes simplex) infections, enteroviral myocarditis, disseminated histoplasmosis, and HIV infection. Other diseases, such as erythroblastosis fetalis and hemophagocytic syndrome, should also be considered. In addition to methods used to diagnose postnatally acquired Chagas disease, examination of the umbilical cord can show parasites. Infection of the placenta does not necessarily indicate infection of the baby.

Diagnosis

Microscopic visualization of the organism in blood smears is the optimal method of diagnosis during the acute phase (including early congenital infection), but it is not sensitive in the chronic stage because of low-level parasitemia. Besides examination of stained thick and thin blood smears, examination of fresh blood for motile trypomastigotes can be performed. Concentration methods increase sensitivity. When smears are made, the angle of the "smearing" glass slide should be high, to avoid damaging the trypanosomes, which are delicate. The parasite can be isolated in special culture media.[2,3] Xenodiagnosis entails allowing laboratory-raised triatome bugs, previously fed on birds (which are not susceptible to the infection), to feed on the suspected case, with examination of the feces performed 20 to 25 days afterward. Polymerase chain reaction, where available, may become the optimal method for testing for acute infection, including chronic and congenital infections.[100–102] However, polymerase chain reaction is not currently standardized, and it is not sensitive in the chronic stage of the infection.[2,3] Serologic tests, including enzyme immunoassay, immunofluorescent assay, and indirect hemagglutination methods, are used for screening and diagnosing chronic infection. The diagnosis requires positive results of 2 different tests. If no exposure to vector-borne or blood-transmitted infection occurred, seropositivity after the age of 9 months, by which age maternal antibodies would have disappeared, indicates congenital infection.[2,3]

Treatment

Antitrypanosomal treatment is recommended for all patients with acute and congenital Chagas disease or reactivated infection and for chronic *T. cruzi* infection in children <18 years of age.[103] Drug therapy should be offered to adults 19 to 50 years of age who do not have advanced Chagas heart disease. Drug therapy should not be given during pregnancy, because the drugs are mutagenic, or to patients with severe renal or hepatic disease. Therapeutic options are limited to benznidazole and nifurtimox, neither of which is licensed for use in the US.[104–113]

Treatment is prolonged (60–90 days), with success rates of 60% to 85% in the acute stage of infection, >90% in congenital infection, and 60% (as measured by seroreversion) in early chronic disease in children.[114] Both benznidazole and nifurtimox are well absorbed from the gastrointestinal tract and are active against trypomastigotes and amastigotes. Before initiation of therapy, patients should have complete blood count and serum chemistry studies performed. The blood count should be monitored every 2 to 3 weeks during therapy, and the patient should be examined for dermatologic side effects and peripheral neuropathy. Benznidazole must be compounded in a liquid form for children.[104] Patients with congenital cases have been treated with nifurtimox.[10]

Clinical trials to evaluate alternatives to benznidazole and nifurtimox have not had promising results. The Clinical Trial for the Treatment of Chronic Chagas Disease With Posaconazole and Benznidazole (CHAGASAZOL) compared benznidazole with posaconazole. Although both posaconazole and benznidazole cleared the parasite during the acute phase, significantly more patients who received posaconazole had treatment failure on follow-up.[115] The Proof-of-Concept Study of E1224 to Treat Adult Patients With Chagas Disease tested the efficacy of ravuconazole in comparison with placebo and benznidazole in adults.[11] Although the E1224 trial also showed clearance of the parasite, the rate of treatment failure at 1 year was also higher when compared with the benznidazole arm of the trial. Finally, the Study of the Use of Oral Posaconazole in the Treatment of Asymptomatic Chronic Chagas Disease (STOP CHAGAS), a trial evaluating the combination of benznidazole with posaconazole compared with monotherapy using posaconazole, benznidazole, or placebo, was completed in 2015.[113,116]

For assistance in diagnosis, management, and obtaining drugs for trypanosomiasis in the US, contact the US Centers for Disease Control and Prevention at 404-718-4745 during normal business hours or 770-488-7100 for after-hours emergencies.

Prevention

Improved rates in the diagnosis of disease in acute and asymptomatic stages, screening of blood and of pregnant women from endemic areas, and vector control will help in controlling transmission of disease in humans.

Key Points

Comparison of African and American Trypanosomiasis

	African Trypanosomiasis	**American Trypanosomiasis**
Alternative name	African sleeping sickness	Chagas disease
Etiology	*Trypanosoma brucei* complex	*Trypanosoma cruzi*
Geography	*T. b. gambiense:* West Africa; *T. b. rhodesiense:* East Africa	*T. cruzi:* Mexico, Central and South America
Vector	Tsetse fly (*Glossina* spp.)	Triatome ("kissing") bug
Infectious vector fluid	Saliva	Feces
Location in host	Extracellular	Intracellular (pseudocyst), extracellular
Target organs		
Early	Systemic	Systemic
Late	Brain	Heart, esophagus, colon
Diagnosis	Visualization of parasite, serology, polymerase chain reaction	Visualization (early), serology, polymerase chain reaction
Outcome (untreated)	Fatal *T. b. gambiense:* months to years *T. b. rhodesiense:* weeks to months	Chronic heart or intestinal disease in 30%–40%

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Nematodes

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Intestinal Nematodes

Julie R. Harris, Peter J. Hotez

Intestinal nematode infections, sometimes referred to as soil-transmitted nematode, soil-transmitted helminth, or geohelminth infections, are among the most common parasitic infections in humans and affect more than one fourth of the world's population.[1] Studies have affirmed the negative health impact of intestinal nematodes, particularly *Ascaris lumbricoides, Trichuris trichiura*, and the hookworms *Necator americanus* and *Ancylostoma duodenale*, which affect child health and development, including causing physical growth delay, cognitive delay, and malnutrition throughout much of the developing world.[2–4] Studies have questioned the degree of morbidity caused by intestinal nematodes, particularly with low-intensity infections.[5–8] However, multiple studies have demonstrated that chronic intestinal nematode infections during childhood adversely affect school performance and attendance, as well as future economic productivity.[9,10] Information from the Global Burden of Disease Study 2010 indicated that intestinal nematode infections are the leading neglected tropical diseases in terms of disability-adjusted life-years.[11] Infection with these helminths also can have an impact on susceptibility to or clinical progression of other infectious diseases, including human immunodeficiency virus infection, tuberculosis, and malaria.[12–14] In most endemic populations, children are affected disproportionately by intestinal nematodes and often acquire infections of high intensity relative to their adult counterparts living under similar conditions.[1,2] Furthermore, accurate interpretation of clinical studies of nematode infections in children is often complicated by simultaneous infection with several different intestinal parasites.[1,15]

Intestinal nematode infections are encountered occasionally by pediatricians in the developed world.[16] In addition to travelers, children at elevated risk include recent immigrants, refugees, and international adoptees.[17–19] Because *A. lumbricoides, Enterobius vermicularis,* and *Strongyloides stercoralis* are endemic to selected regions of the United States, including the South and Appalachia, infection can also be acquired in the absence of foreign exposure.[20] However, few recent data exist on such infections in the US.[21,22] Intestinal nematode infections are still reported from Eastern Europe.[23,24]

Infection with intestinal nematodes generally occurs by 1 of 2 routes. For *A. lumbricoides, T. trichiura,* and *E. vermicularis,* infection results from ingestion of eggs, sometimes contained in food inadvertently contaminated with human feces. For *Strongyloides (S. stercoralis* and *S. fuelleborni)* and hookworms *(A. duodenale, Ancylostoma ceylanicum, Ancylostoma caninum,* and *N. americanus),* infective third-stage larvae, usually found in soil, penetrate host skin to begin the infective process. Infection with the larvae of *Ancylostoma* and *S. fuelleborni* also can be acquired orally, and these organisms have even been linked to neonatal helminth infections associated with larval ingestion in breast milk. The clinical findings associated with intestinal nematode infections in children are summarized in Box 276.1. Recognized syndromes caused by perinatal infection with *A. lumbricoides, A. duodenale,* and *Strongyloides* are listed in Table 276.1.

Box 276.1

Major Clinical Features of Intestinal Nematode Infections in Children

Ascaris lumbricoides

Löeffler pneumonia

Intestinal obstruction

Extraintestinal migration

Malabsorption

Eosinophilia

Trichuris trichiura

Chronic colitis

Dysentery

Intussusception

Rectal prolapse

Anemia

Ancylostoma duodenale and *Necator americanus*

Iron deficiency anemia

Hypoproteinemia

Chlorosis

Eosinophilia

Developmental delay

Ancylostoma caninum

Eosinophilic enteritis

Aphthous ileitis

Ancylostoma ceylanicum

Enteritis

Eosinophilia

Strongyloides stercoralis

Eosinophilia

Epigastric pain

Autoinfection

Hyperinfection and disseminated disease

Enterobius vermicularis

Pruritus ani

Vaginitis

Extraintestinal migration

TABLE 276.1

Neonatal Syndromes Caused by Intestinal Nematodes

Syndrome	Nematode Species	Speculated Routes of Transmission
Neonatal ascariasis	*Ascaris lumbricoides*	Transplacental
Infantile ancylostomiasis	*Ancylostoma duodenale*	Transmammary, perinatal
Infantile strongyloidiasis (swollen belly syndrome)	*Strongyloides fuelleborni* and *Strongyloides stercoralis*	Transmammary, perinatal

The diagnosis of *Ascaris*, hookworm, and *Trichuris* infection is established most frequently by identification of characteristic eggs in feces (Fig. 276.1). Pinworm eggs are found deposited on the perianal skin. In contrast, *Strongyloides* first-stage larvae, not eggs, are excreted routinely in feces. Serologic testing also can be useful in the diagnosis of strongyloidiasis, especially in lightly infected or asymptomatic people.[25]

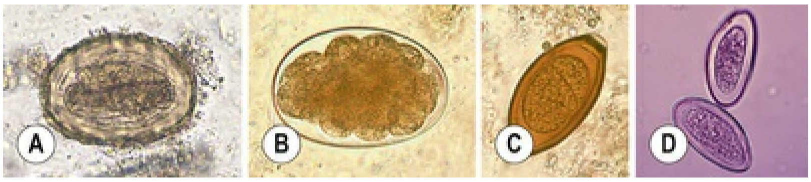

FIGURE 276.1 **Photomicrographs showing the morphologic features of intestinal nematode eggs. (A) *Ascaris lumbricoides*, (B) hookworm, and (C) *Trichuris trichiura* infections routinely are diagnosed by fecal egg examination using light microscopy. (D) *Enterobius vermicularis* eggs are deposited on the perianal skin, and can be removed with adhesive tape and viewed under light microscopy.** (From Centers for Disease Control and Prevention. DPDx. http://dpd.cdc.gov/dpdx/HTML/Image_Library.htm.)

Benzimidazole anthelmintics remain the cornerstone of therapy for most intestinal nematode infections, including infections caused by *Ascaris*, hookworm, *Trichuris,* and pinworm.[26] Nitazoxanide is also sometimes effective, but it is considered a second-line drug.[27–29] Reductions in morbidity can be achieved even in the absence of complete removal of parasites from the gastrointestinal tract. This observation has catalyzed global efforts to reduce the morbidity from intestinal helminths through widespread use of these agents, efforts that included a resolution passed at the 2001 World Health Assembly to deworm 75% of all at-risk children by the year 2010.[30,31] More recently, the World Health Organization estimated that only one third of the world's 876 million children at risk for intestinal helminth infections receive deworming medication on a regular basis.[32] Moreover, reinfection is common in children in endemic areas, thus necessitating repeated courses of therapy.[33] In addition, high treatment failure rates with mebendazole for human hookworm infection, decreasing efficacy with frequent and periodic use, and the possible emergence of drug resistance in human nematode infections raise important concerns about the widespread use of these agents.[31,34,35] However, in the absence of effective human vaccines or improved global sanitation, targeted chemotherapeutic interventions represent the best current options for control of the major health-related morbidity and mortality associated with intestinal nematode infections.[2]

Ascaris lumbricoides

Epidemiology

Ascariasis is the most common helminthic infection in humans, with an estimated 819 million people infected worldwide.[3,36] As many as 400 million children are infected, and an estimated 51 million children have severe morbidity resulting from heavy infections. Ideally suited to warmer climates, *A. lumbricoides* eggs are resistant to a wide array of environmental stresses. For that reason, ascariasis frequently has both urban and rural distributions and commonly affects children living in economically disadvantaged communities.[37] Ascariasis still occurs in the US as an imported infection, usually in recent immigrants from Latin America and Asia and in internationally adopted children.[18,19,38] Ascariasis likely remains an autochthonous infection in the southeastern US, where the rate of infection in children has historically ranged from 0.8% to 67%; however, more recent estimates are lacking.[16,17,39]

Chronic ascariasis in childhood can be associated with impaired physical growth and intellectual development, which in some cases can be linked to vitamin A and other micronutrient malabsorption as well as protein-calorie malnutrition.[40–43] Young children also are more susceptible to life-threatening complications such as intestinal obstruction, perforation, and peritonitis. Globally, intestinal and biliary tract obstruction caused by *Ascaris* accounts for 10,000 to 100,000 deaths a year, mostly in children.[44,45] In the developing world, the rate of complications secondary to ascariasis ranges from 11% to 67%, with intestinal or biliary tract obstruction the most common serious sequela.[45] Transplacentally acquired neonatal ascariasis also has been described, and its global incidence may be underestimated.[46,47]

The life cycle of *A. lumbricoides* in humans begins with ingestion of embryonated eggs that have been deposited in moist soil. Bile salts and the alkaline pH of the small intestine cause the eggs to hatch. Emerging second-stage larvae penetrate the bowel wall and ultimately invade the microcirculation of the lamina propria. Once in the circulatory system, larvae are carried to the liver through the portal veins and eventually are swept into the pulmonary vasculature, where they lodge in capillaries and rupture into the alveolar space. After ascending the bronchi to the trachea, larvae are swallowed and again migrate to the small intestine. *Ascaris* larvae mature into sexually differentiated adults in the lumen of the small bowel, mate, and begin laying eggs. If egg laying precedes mating, infertile eggs are produced.

Clinical Manifestations

Illness associated with ascariasis can be attributed to the migration of both larvae and adult worms. As larvae migrate through the lung parenchyma, they cause both mechanical and immune-mediated damage. Pulmonary microhemorrhages from ruptured alveolar capillaries result in inflammation and exudation of fluid. Neutrophils and eosinophils are recruited to the lung, perhaps in response to secretory products released by the migrating larvae. Pulmonary infiltrates in association with cough, dyspnea, wheezing, and mild hemoptysis (Löeffler pneumonia) can occur and last up to 2 weeks. In some regions of the world, this so-called verminous pneumonia, which can resemble asthma, is seasonal, occurring among cohorts of children following spring rains.[48] The intensity of illness caused by migrating larvae is proportional to larval numbers, with lightly infected people often having few if any pulmonary symptoms. In rare instances, migrating adult worms can obstruct the airway and cause respiratory distress.[49]

Symptoms associated with the presence of adult *Ascaris* worms in the small bowel include epigastric pain and diffuse abdominal discomfort. Because adult worms can grow to 40 cm in length, heavy infestations can result in acute intestinal obstruction and perforation, especially in the region of the ileum, that require emergency medical or surgical intervention (Fig. 276.2). Migration of adult worms into the biliary tree and then to the liver or pancreas, sometimes elicited by ingestion of certain irritants, can precipitate acute cholecystitis, hepatitis, or pancreatitis. Hepatic abscess can occur if the intrahepatic ducts are obstructed.[45,50]

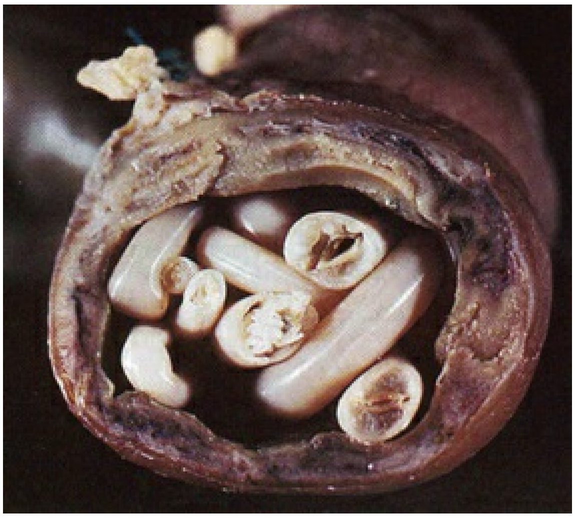

FIGURE 276.2 Surgical specimen showing adult *Ascaris lumbricoides* obstructing the small intestine. (From Meyers WM, Neafie RC, Marty AM, et al. Pathology of Infectious Diseases, vol 1: Helminthiases. Washington, DC, American Registry of Pathology, 2000.)

Chronic ascariasis has been associated with malnutrition, which is caused by malabsorption of dietary protein, fat, and vitamin A. The pathogenesis of malabsorption probably is multifactorial.[40,51] Investigators have postulated that adult worms successfully compete for nutrients by secreting a variety of enzymes and protease inhibitors into the environment of the proximal part of the small intestine. Whether the physical and mental growth retardation syndromes associated with chronic ascariasis in childhood have a purely nutritional basis remains unknown. Furthermore, *Ascaris* infection frequently occurs in the setting of infection with other intestinal nematodes, especially *Trichuris* and hookworm, thus making it difficult to ascribe longterm sequelae to an individual parasitic species.

Laboratory Findings and Diagnosis

The diagnosis of *Ascaris* infection is best established by examination of stool for characteristic ova (see Fig. 276.1). Each adult female produces so many eggs that a single stool specimen usually is adequate. The presence of unfertilized eggs (more elongated than fertilized eggs) still mandates treatment because even a single adult worm represents a risk for serious illness associated with migration.

When migration of *Ascaris* larvae through the lungs is associated with peripheral blood eosinophilia and pulmonary infiltrates on a chest radiograph, examination of sputum can reveal eosinophils and Charcot-Leyden crystals. The differential diagnosis includes other causes of verminous pneumonia, including strongyloidiasis, toxocariasis (visceral larva migrans), and hookworm infection.

In areas endemic for *A. lumbricoides,* any child manifesting acute abdominal symptoms consistent with intestinal obstruction or perforation should be evaluated for ascariasis. Occasionally, an adult worm is present in vomitus. Abdominal radiographs after barium administration can reveal the nature of the intestinal obstruction caused by *A. lumbricoides,* whereas computed tomography with oral contrast can demonstrate cylindric filling defects.[52] Endoscopic retrograde cholangiopancreatography and ultrasonography can be helpful in identifying adult *Ascaris* worms in the intestinal tract or hepatobiliary tree.[53–56] Occasionally, however, the diagnosis of intestinal ascariasis is made at laparotomy.

Treatment

Benzimidazoles, such as mebendazole (100 mg twice a day for 3 days or 500 mg once) and albendazole (400 mg in a single dose), are effective for treatment of intestinal ascariasis, with cure rates >90%.[2,57] Because of their teratogenic and tumorigenic potential, benzimidazoles generally are not given to children <2 years of age. However, wide experience with the use of these agents in children suggests that at a reduced dose (200 mg), administration of albendazole to children 12 to 24 months of age or even children <12 months of age is not problematic. For this reason, benzimidazoles increasingly are being distributed in low- and middle-income countries with heavy disease burdens.[58–60] Ivermectin (150–200 μg/kg once) is also highly effective[61]; however, the safety of ivermectin has not been studied children <15 kg, nor is it approved by the US Food and Drug Administration for ascariasis. Nitazoxanide is comparable to albendazole for treatment of *Ascaris* infections and is approved for use in children ≥12 months of age.[27,28,62–64] The recommended dose is 100 mg (5 mL) twice a day for children 12 to 47 months of age, 200 mg (10 mL) twice a day for children 4 to 11 years of age, and 500 mg twice a day for older children and adults, to complete a 3-day course. Pyrantel pamoate (11 mg/kg up to maximum 1 g/day for 3 days) is a suitable alternative.[31] In some heavily infected children, malnutrition, steatorrhea, and growth retardation are partially reversible with treatment.[64]

In cases of partial small bowel obstruction caused by *Ascaris,* some physicians recommend alternative therapy with piperazine citrate, which paralyzes the worms and can abrogate the need for surgical intervention. However, this drug is no longer available in the US. Piperazine and pyrantel pamoate are antagonistic and should not be given concurrently. Mineral oil or Gastrografin (a solution of diatrizoate meglumine and diatrizoate sodium) given orally or by nasogastric tube also can cause relaxation of the obstructing bolus of worms.

Standard supportive measures for treatment of small bowel obstruction also should be administered, including intravenous hydration, nasogastric suctioning, and monitoring of electrolyte status. Laparotomy to remove the adult worm bolus should be undertaken in patients who do not respond to therapy with anthelmintic drugs.

Prevention

Prevention of ascariasis requires elimination of contact with soil contaminated by egg-containing feces. Although *Ascaris* eggs are killed by prolonged exposure to sunlight or temperatures >40°C, they can survive in extremely cold temperatures for many months and are resistant to many chemical disinfectants. *Ascaris* eggs survive in temperate climates and urban environments.

Diagnosis and effective treatment with improved sanitation practices are the most reliable means of preventing the spread of *Ascaris*.[65,66] In endemic areas where the prevalence of infection with soil-transmitted helminths, including *A. lumbricoides*, is >50%, the recommendation is to administer anthelmintic agents to school-aged children twice yearly as part of a targeted deworming program; prevalences of 20% to 49% indicate annual treatment.[67,68] However, the effects of a single intervention are likely to be shortterm given the inevitability of reinfection. Because ascariasis is an infection that is associated with poverty and poor sanitation, improved water, sanitation, and hygiene, together with sustained economic growth, are requirements for longterm parasite control.

Hookworm (*Ancylostoma duodenale, Ancylostoma caninum, Ancylostoma ceylanicum,* and *Necator americanus*)

Epidemiology

Approximately 439 million people harbor hookworms in their gastrointestinal tracts, and hookworm infection remains a leading cause of iron deficiency, iron deficiency anemia, and protein malnutrition in the developing world.[3,36,69] Children and women of reproductive age (especially pregnant women) are particularly vulnerable to the morbid effects of hookworm infection, often because dietary intake fails to compensate for intestinal losses of iron and serum proteins.[70,71] Although once highly endemic in the southeastern US, hookworm infection was essentially eradicated in the US by the 1920s.[72,73] Pockets of autochthonous hookworm infection still may be present in parts of the rural south, although hookworm is no longer a public health problem in the US.[20]

The 2 most common species of hookworm that infect humans are *A. duodenale* and *N. americanus*, with estimates from the 1940s suggesting that *N. americanus* was responsible for more than 80% of human infections worldwide.[74] *N. americanus* is significantly more common in the Western Hemisphere, Southeast Asia, and Africa, although *A. duodenale* infection and mixed infections occur commonly. Other species that cause intestinal disease in humans include *A. ceylanicum* (Southeast Asia and India) and *A. caninum* (the dog hookworm), which has been implicated as a zoonotic cause of eosinophilic enteritis in Australia and the US.[75–77]

The external life cycle of the hookworm begins when eggs are deposited in moist soil. Eggs develop optimally at ambient temperatures of 20° to 30°C in the absence of direct sunlight. These conditions generally are achieved in association with cultivation of certain crops, such as mulberry leaves and sweet potatoes in China, tea in India, and coffee in Latin America. Thus, unlike ascariasis and trichuriasis, which can occur in urban slums, hookworm infection occurs primarily in rural areas.[37] On hatching, the emerging larvae molt twice to nonfeeding, infective third-stage larvae, which can migrate vertically in the soil in response to changing conditions of moisture. Infection occurs by 1 of 2 routes, depending on the species of hookworm. Whereas both *Ancylostoma* and *Necator* can penetrate the skin, *Ancylostoma* larvae also are infective orally, and in some areas the oral route of infection predominates. Once in the host, third-stage larvae resume development while migrating through the lymphatics and venules to the pulmonary circulation. After traversing the alveolar capillaries into the alveoli, larvae ascend the airways, are swallowed, and travel to the small intestine. Epidemiologic evidence indicates that some hookworm larvae of *A. duodenale* undergo developmental arrest within the host, where they await environmental or hormonal cues before resuming migration to the gut. This phenomenon may explain seasonal variations in fecal egg concentrations, as well as possible transmammary hookworm infection in newborn infants.[78,79]

Once in the small bowel, adult hookworms attach by their mouths to the intestinal mucosa and begin to feed (Fig. 276.3). Equipped with teeth, cutting plates, or both, as well as powerful esophageal muscles and hydrolytic enzymes, the hookworm digests the plug of tissue within its buccal capsule.[80,81] At the same time, potent anticoagulants and inhibitors of platelet function are released and cause profound bleeding from lacerated capillaries in the lamina propria (Fig. 276.4).[82–84] The ingested blood is acted on by hemoglobin-digesting proteases lining the parasite gut.[85,86] Adult worms mate in the small intestine, and the females deposit fertilized eggs in the lumen. A period of approximately 5 to 9 weeks is required after infection for eggs to appear in the feces, or longer in the case of developmentally arrested larvae.

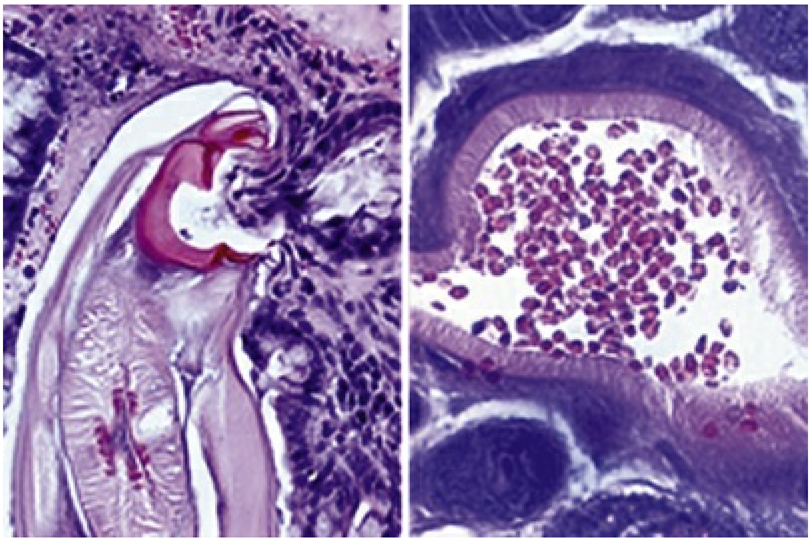

FIGURE 276.3 (*Left*) Photomicrograph showing a sagittal section of an adult *Ancylostoma* hookworm attached to the intestinal mucosa. (*Right*) Cross section of an adult worm showing ingested host red blood cells within the parasite's intestine. (Courtesy of R. Bungiro.)

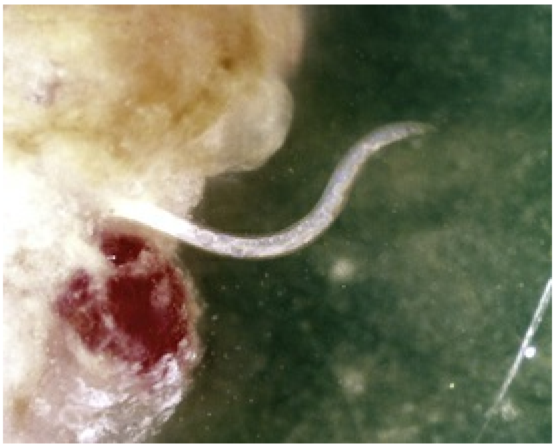

FIGURE 276.4 **Photograph of an adult hookworm attached to the intestine of an experimentally infected animal. Note the area of hemorrhage adjacent to the site of attachment.** (Courtesy of R. Bungiro.)

Clinical Manifestations

Skin penetration by third-stage larvae can be associated with an intensely pruritic form of dermatitis called ground itch, which usually is localized to the site of hookworm entry.[87] Ground itch is followed within a week by cough, which occurs when hookworm larvae enter the lungs. Hookworm pneumonitis usually is less severe than the verminous pneumonitis resulting from ascariasis, although it can last for several weeks. Wakana disease, a severe, immediate hypersensitivity-like syndrome characterized by nausea, vomiting, dyspnea, and eosinophilia, can occur after oral ingestion of a large number of infective *A. duodenale* larvae.[88]

The presence of adult hookworms in the small intestine can cause nonspecific gastrointestinal tract symptoms including abdominal pain, even before the onset of anemia. Blood loss secondary to hookworm infection generally is proportional to the worm burden and develops approximately 10 to 20 weeks after infection. *A. duodenale* infection usually is associated with greater blood loss than occurs with *N. americanus*.[89] Hookworm disease and anemia result when blood loss exceeds the host's iron reserves and dietary intake. Longstanding moderate or heavy hookworm infection causes serious iron deficiency anemia associated with pallor, chlorosis (a greenish yellow skin discoloration), dyspnea on exertion, and fatigue.

Children in the developing world are particularly vulnerable to the effects of hookworm anemia because of increased iron requirements and underlying nutritional deficiencies.[90] Growth and developmental delay, as well as learning disabilities, are common in chronically infected children.[91] Many of these effects can be attributed to iron deficiency, but hookworm-associated plasma protein loss and malabsorption also contribute to the clinical manifestations.[92,93] At least some of the malabsorption associated with hookworm infection may result from the secretion by the adult parasite of a potent inhibitor of digestive enzymes.[94,95] Hookworm disease also is an important problem among pregnant women in the developing world and can result in severe maternal anemia, low birth weight in infants, and reduced infant survival rates.[69,71,96]

A fulminant form of gastrointestinal tract hemorrhage related to acute hookworm infection has been described in newborn infants. These children, often <2 months of age, have melena, abdominal distention, and hypotension, with hematocrit values as low as 2% to 3%.[79,97] This condition is seen primarily in children infected with hookworms of the genus *Ancylostoma,* and investigators have speculated that larvae can be transmitted through the milk of chronically infected mothers. A similar route of vertical transmission has been shown to occur in infants in Papua New Guinea who are infected with *S. fuelleborni.*

Infection of humans with the dog hookworm *A. caninum* has been implicated as a cause of eosinophilic enteritis, particularly in northeastern Australia.[76,77] This condition, characterized by intense abdominal pain and peripheral blood eosinophilia, can mimic appendicitis or intestinal perforation. Laparotomy often reveals only a single adult canine hookworm attached to the intestinal mucosa. In addition, asymptomatic aphthous ileitis with eosinophilia has been reported in association with zoonotic infection with *A. caninum.*[98]

Laboratory Findings and Diagnosis

Acute infection, characterized by symptoms associated with migration of infective hookworm larvae, is diagnosed on the basis of clinical findings. The characteristic rash of ground itch occurs on any skin surface and can be erythematous, papular, or vesicular.[87] Intense pruritus can lead to scratching, excoriation, and secondary bacterial infection. In contrast to *Ascaris* pneumonia, the pulmonary symptoms of hookworm pneumonia usually are not severe.

Eosinophilia, which generally is mild, coincides with development of adult hookworms in the intestine.[99] Intestinal hookworm infection is detected by identifying the characteristic eggs in feces (see Fig. 276.1). Because most symptomatic people excrete large numbers of eggs, stool-concentrating techniques usually are not necessary to detect clinically relevant infections. Although hookworm secretory antigens can be detected in feces of infected laboratory animals,[100] fecal antigen tests are not available for diagnosing human infections. The eggs of *Ancylostoma* and *N. americanus* are similar under light microscopic examination and cannot be distinguished easily on the basis of morphologic features.

Treatment

Single doses of mebendazole are inadequate for treatment of human hookworm infection; higher cure rates have been reported after multiple doses of mebendazole (100 mg twice a day for 3 days) or albendazole (400 mg once).[31] Although the safety of benzimidazoles in children has not been established definitively, these compounds are the drugs of choice for children with intestinal helminth infections. Nitazoxanide may be effective in treatment of hookworm infections,[101] but comparative data with albendazole are lacking. An alternative treatment is pyrantel pamoate (11 mg/kg/day, not to exceed 1 g/day, for 3 days), which has been reported to be effective in treatment of infantile ancylostomiasis. Unfortunately, reports suggest the possibility of anthelmintic drug resistance among human hookworm isolates, based either on drug failure or diminishing efficacy with increasing drug use.[34,35]

Mebendazole is absorbed poorly and thus may not eradicate developmentally arrested *Ancylostoma* larvae residing in extraintestinal tissues. Therefore periodic follow-up stool examinations can be necessary to detect latent infection. Moreover, reinfection in endemic areas occurs so commonly that the effect of a single course of an anthelmintic drug is of questionable benefit. Iron supplementation reverses mild to moderate hookworm anemia and can lead to improvement in growth and intellectual development.[56] Severe and acute gastrointestinal tract hemorrhage caused by hookworm rarely can lead to hemodynamic compromise necessitating blood transfusion.

Prevention

Use of shoes can be protective under some circumstances for hookworm and other neglected tropical diseases.[66,102] However, compliance is often difficult, and both major hookworm species can penetrate all aspects of the skin, including the legs, buttocks, abdomen, hands, and arms.[103] At least shortterm benefits in iron status have been demonstrated in heavily infected children treated with albendazole or mebendazole.[2,104,105] However, no evidence of naturally acquired resistance to hookworm infection has been reported, and children in endemic areas are constantly exposed to infective third-stage larvae. In addition, arrested larvae within the host can be resistant to currently available anthelmintic agents. For these 2 reasons, mass or targeted chemotherapy programs alone may not control hookworm infection in many parts of the developing world. As a result, renewed interest has been shown in the development of vaccines.[106] To date, the most promising vaccine candidates are recombinant forms of 2 enzymes involved in parasite blood feeding, with a series of clinical trials planned in coming years.[107–111]

Trichuris trichiura

Epidemiology

Approximately 465 million people worldwide are infected with the whipworm *T. trichiura,*[36] which is distributed throughout the tropics and subtropics.[1,112] Named for its characteristic shape (Fig. 276.5), the adult stage of *T. trichiura* is an important cause of inflammatory bowel disease in children from the developing world. Children with trichuriasis usually have greater numbers of whipworms than their adult counterparts and suffer disproportionately from clinical trichuriasis.

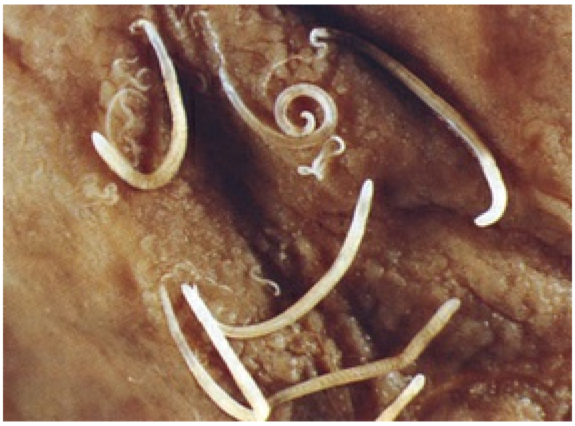

FIGURE 276.5 **Photograph of adult *Trichuris trichiura* attached to the colonic mucosa.** (From Meyers WM, Neafie RC, Marty AM, et al. Pathology of Infectious Diseases, vol 1: Helminthiases. Washington, DC, American Registry of Pathology, 2000.)

Fertilized *Trichuris* eggs require 3 to 4 weeks in a warm, moist environment to embryonate and become infectious. After ingestion, second-stage larvae hatch and penetrate mucosal epithelial cells of the cecum or colon. The worm expands intracellularly and ultimately creates tunnels within the epithelium to accommodate growth (Fig. 276.6). The thickened posterior portion of the worm eventually ruptures the cell membrane and protrudes into the lumen of the large intestine. In this manner, *Trichuris* can disrupt the normal colonic architecture. However, a large component of the pathogenesis of trichuriasis results from the host inflammatory response mediated by cytokines produced by T lymphocytes and macrophages.[113,114]

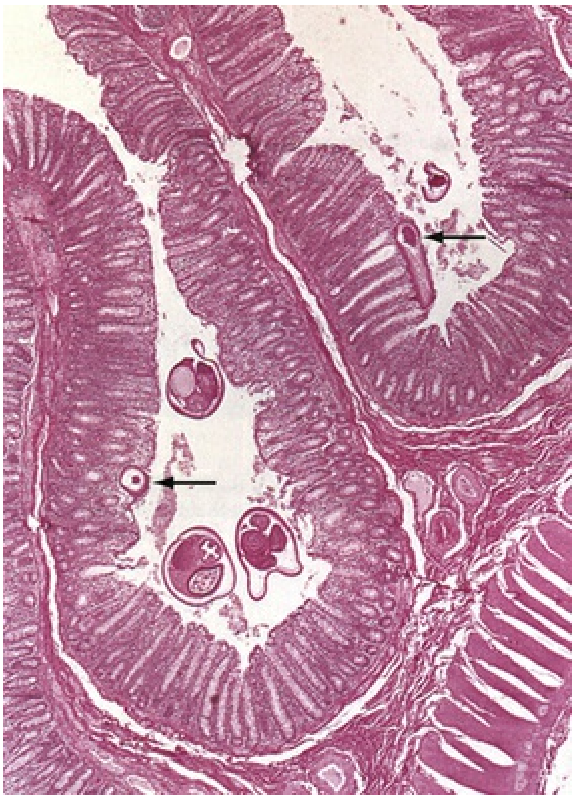

FIGURE 276.6 **Photomicrograph of an intestinal biopsy specimen showing sections of *Trichuris trichiura* in the colon. Note the anterior portions of adult worm within the colonic mucosa (*arrows*) and the thicker posterior portion in the lumen.** (From Meyers WM, Neafie RC, Marty AM, et al. Pathology of Infectious Diseases, vol 1: Helminthiases. Washington, DC, American Registry of Pathology, 2000.)

Adult whipworms mate, and females lay eggs in the colon, with approximately 5000 eggs deposited per day. A period of approximately 90 days is required to complete the life cycle of the parasite in humans from ingestion of eggs to development of mature egg-laying adult worms.

Clinical Manifestations

Although most whipworm infections are asymptomatic, 2 well-defined clinical entities are associated with heavy infection. The first, *Trichuris* dysentery, is an acute diarrheal disease associated with the passage of blood and mucus in stool.[112] Bleeding is probably secondary to the mucosal damage and inflammation caused by the attachment of adult worms to the colonic epithelium. No evidence shows that *T. trichiura* feeds on blood. The profound mucosal edema associated with *Trichuris* dysentery leads to tenesmus and, in protracted cases, can cause rectal prolapse or even colonic obstruction.[115]

Whipworm infection also can result in chronic colitis that shares many clinical features with other inflammatory bowel diseases such as Crohn disease and ulcerative colitis. In particular, the factors that mediate delay of growth appear to be similar to those found in children with other causes of inflammatory bowel disease.[116] In patients with heavy infections, worms also can spread proximally and cause ileitis. In some cases, trichuriasis works in synergy with infection caused by *Campylobacter jejuni* to produce more severe disease.[117]

Diagnosis

Unlike *Ascaris* and hookworms, *Trichuris* commonly is associated with diarrhea. *Trichuris* dysentery can resemble dysentery caused by other pathogens, including enteric bacteria and *Entamoeba histolytica.* Examination of stool for characteristic *T. trichiura* eggs is the most reliable means of diagnosis (see Fig. 276.1). Stool concentration techniques usually are not necessary to detect most symptomatic cases. If stool examination reveals the presence of Charcot-Leyden crystals, *Trichuris* infection is likely.

Important histologic findings distinguish *Trichuris* colitis from other types of inflammatory bowel disease. First, the pathologic changes in the colon resulting from whipworm infection are confined primarily to mucosal epithelium, with little involvement of the submucosa and muscularis layers. In addition, the dramatic symptoms of *Trichuris* colitis are characteristically out of proportion to the modest inflammatory response seen histologically.

Blood tests rarely are helpful in making the diagnosis of trichuriasis. Iron deficiency is a common finding and can be acute (caused by gastrointestinal hemorrhage) or chronic, as occurs in longstanding cases of colitis. The erythrocyte sedimentation rate, which often is elevated in inflammatory bowel diseases, is usually normal in children with whipworm infection.[112]

Treatment

Trichuriasis is considered less responsive to anthelmintic therapy than are other intestinal nematode infections.[31] Longer courses of albendazole (400 mg for 3–7 days) and mebendazole (100 mg 2 times a day for 3–7 days) are recommended for treatment.[57,118] Data are mixed on the efficacy of nitazoxanide against *Trichuris* infections; multiple-day doses can also be required for effectiveness of this drug.[28,101,119,120]An alternative regimen for the treatment of trichuriasis is a combination of albendazole (400 mg) and ivermectin (200 µg/kg), both given in a single dose orally.[60,121] A study of 155 children in Sri Lanka showed a cure rate of 79% after combination therapy, thus making the combination almost twice as effective as with albendazole alone.[122] Although the benzimidazoles generally are considered safe in children, one study in asymptomatic children with trichuriasis demonstrated that these drugs may be associated with growth delay.[123] Other studies, however, have not supported this observation. Oxantel is an alternative drug for trichuriasis and frequently is formulated in a liquid suspension with pyrantel pamoate, which is suitable for young children. This preparation is generally not available in the US. One study has shown a combination of oxantel pamoate and albendazole to be superior to albendazole plus ivermectin, albendazole plus mebendazole, or mebendazole alone against *Trichuris trichiura.*[124] Retreatment of *Trichuris* infections can be necessary, especially for children who remain in endemic areas. Iron supplementation may help resolve the anemia of trichuriasis, as well as speed the rate of catch-up growth. Although treatment speeds physical catch-up growth dramatically, recovery of cognitive skills can be much less pronounced in heavily infected children.[125]

Prevention

Improved water, sanitation, and hygiene measures necessary to reduce the spread of other geohelminthic infections also have an impact on trichuriasis. However, the benzimidazoles used in chemotherapy control programs may have less activity (especially in a single dose) against *Trichuris* than against other intestinal nematodes, thereby necessitating the addition of ivermectin. In addition, raw fruits and vegetables grown in endemic areas where irrigation water is contaminated can harbor and transmit infective eggs.

Enterobius vermicularis

Epidemiology

Along with toxocariasis, infection with the human pinworm *E. vermicularis* may be the most common helminthiasis in the US and other developed countries.[20] Most infections occur in children, with high rates of transmission documented in group childcare facilities, nursery schools, and elementary schools.[17,126] Although enterobiasis is seldom if ever a cause of serious morbidity in children, it often is distressing for parents and guardians. Reassurance by healthcare personnel is an important component in management of pinworm infection.

Infection with *E. vermicularis* occurs after ingestion of embryonated eggs that have been deposited by the adult female worm. Eggs frequently are identified on the perianal skin, thus implicating fecal-oral contamination as the most common route of infection in young children. However, infection by airborne eggs or contaminated fomites also has been described, as well as retroinfection, in which eggs deposited on the perianal skin hatch and give rise to motile larvae that migrate back into the rectum and develop into adults.

After ingestion, pinworm eggs hatch intraluminally, and the emerging larvae descend the small intestine and develop into mature adults on reaching the cecum. Adult female worms live primarily in the colon and migrate out onto the perianal skin, where they lay eggs. Worm migration frequently occurs at night. A female adult pinworm releases up to 10,000 fertilized eggs every 24 hours that embryonate and become infective within 6 hours. Although most eggs remain at the site of deposition, some can be dispersed into the air and contaminate environmental surfaces, or scratching can lead to transmission from contaminated fingers. Eggs can survive several days under conditions of high temperature and humidity. The complete life cycle of *E. vermicularis* can be completed in 4 to 6 weeks.

Clinical Manifestations

The most common symptom of people infected with pinworms is localized pruritus, probably caused by an allergic response elicited against the migrating adult pinworm as it lays its eggs on the perianal skin. Intense itching can result in scratching and excoriation of the area, occasionally leading to secondary bacterial cellulitis. In young girls and women, migrating pinworms can enter the vagina and cause mild vaginitis or even enter the urethra and introduce intestinal bacteria that can lead to lower urinary tract infection. In 1 study, young girls with urinary tract infection were almost twice as likely to have pinworm infection (36% vs. 16%) as were girls with no previous history of urinary tract infection.[127] Rarely, other sites of aberrant pinworm migration have been described, including the fallopian tubes, ovaries, and peritoneum.[128–130] Pinworms also have been associated with perianal cellulitis and granuloma or abscess formation.[131,132] Whether pinworm migration into the appendix is a common cause of acute appendicitis is controversial (Fig. 276.7), but the incidence of pinworm-associated disease appears to be low even in highly endemic areas.[126,133,134]

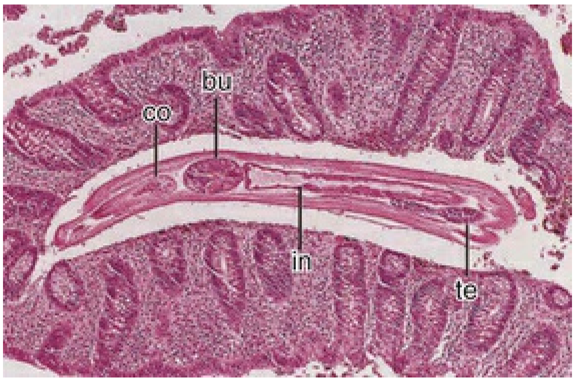

FIGURE 276.7 **Photomicrograph of an intestinal biopsy specimen showing the anterior region of an adult pinworm (*Enterobius vermicularis*) lodged in the lumen of the appendix. Note the parasite's corpus (*co*), esophageal bulb (*bu*), intestine (*in*), and testis (te) visible by hematoxylin and eosin stain.** (From Meyers WM, Neafie RC, Marty AM, et al. Pathology of Infectious Diseases, vol 1: Helminthiases. Washington, DC, American Registry of Pathology, 2000.)

The host-mediated inflammatory response to the intestinal stages of *E. vermicularis* is minimal, although eosinophilic ileocolitis has been reported.[135] However, the lack of prominent gastrointestinal tract complaints in the setting of this infection suggests that significant intestinal disease is rare.

Laboratory Findings and Diagnosis

The most reliable means of diagnosing pinworm infection is examination of transparent adhesive tape that has been applied to the perianal skin. The tape is then removed, placed on a microscope slide, and viewed for the presence of eggs (see Fig. 276.1). This procedure is best performed when the patient arises in the morning or before bathing, and it may have to be repeated on subsequent days to detect infection. *E. vermicularis* eggs are not excreted in the stool, so examination of feces is not helpful.

Serologic tests are not available to detect pinworm infection. Eosinophilia, which has been reported occasionally, is an unusual finding and therefore is not useful in the diagnosis. Adult pinworms, which are sometimes found in tissue specimens, are identified readily by the presence of bilateral cuticular ridges known as alae, which distinguish *E. vermicularis* from other intestinal nematodes of humans.

Treatment

Single-dose therapy with either mebendazole (100 mg), pyrantel pamoate (11 mg/kg, not to exceed 1 g), or albendazole (400 mg) is adequate treatment for pinworm infection.[57] Because none of these drugs is completely effective against eggs or developing larvae, a second treatment 2 weeks after the first is recommended. To date, resistance of *Enterobius* to benzimidazoles has not been reported.

Prevention

Because pinworm eggs can survive for days outside the host, all clothes and bed linens should be washed at the time of treatment. All family members should be treated as a group when multiple or repeated symptomatic infections occur. Within 1 institutional setting, a substantial reduction in the prevalence of pinworm was achieved through targeted chemotherapy of infected people and all potential contacts.[136] In this study, treating all infected people and their contacts with 2 doses of mebendazole 14 days apart reduced the prevalence of *E. vermicularis* infection from 24% to 1% over a 3-year period.

Strongyloides stercoralis and *Strongyloides fuelleborni*

Epidemiology

S. stercoralis can be found throughout both tropical and temperate climates, including parts of the US, particularly eastern Tennessee, Kentucky, and West Virginia.[20,137–140] The prevalence of strongyloidiasis probably is underestimated because of the relative difficulty in detecting subclinical infection. However, groups known to be at particularly high risk of harboring *Strongyloides* include veterans of World War II and Vietnam, refugees from Southeast Asia, and other immigrants to the US.[19,137,141] Epidemiologic studies have demonstrated an increased prevalence of strongyloidiasis in people who also are seropositive for human T- lymphotropic virus type I (HTLV-1).[142–144] Dogs and other mammals also can harbor *S. stercoralis* and can serve as reservoir hosts inasmuch as zoonotic infections in animal handlers have occurred.[145] A distinct and fulminant form of neonatal strongyloidiasis caused by *S. fuelleborni,* called swollen belly syndrome, has been described in neonates from Papua New Guinea.[146]

The life cycle of *Strongyloides* is complex and consists of both a parasitic (homogonic) cycle and a free-living (heterogonic) cycle. Human parasitism occurs initially when soil-borne third-stage filariform larvae penetrate the skin. Some, if not most, of the infective larvae migrate through the lymphatics and venules to the pulmonary circulation, penetrate the alveolar space, and migrate up the pulmonary tree, where they are swallowed and make their way to the small intestine. All parasitic adults found in the small bowel probably are female, and therefore reproduction within the host is likely to occur by parthenogenesis. Eggs deposited into the intestinal lumen release first-stage rhabditiform larvae that are passed in the feces (Fig. 276.8).

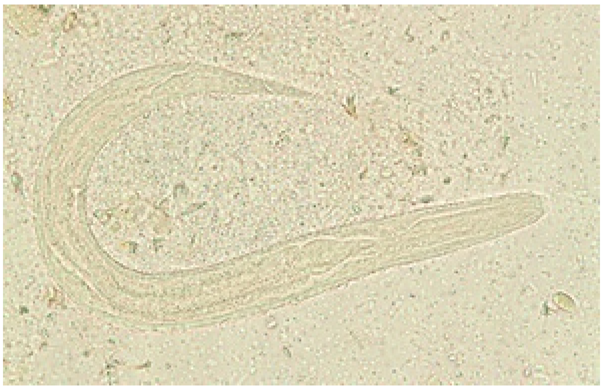

FIGURE 276.8 **Photomicrograph of a *Strongyloides stercoralis* first-stage (rhabditiform) larva excreted in feces. Unlike in most intestinal nematodes, *S. stercoralis* eggs typically are not detected in fecal samples.** (From Centers for Disease Control and Prevention. DPDx. http://dpd.cdc.gov/dpdx/HTML/Image_Library.htm.)

Under certain conditions, larvae do not exit the host in feces but instead molt intraluminally to the filariform stage during transit in the gut. These third-stage larvae can penetrate the intestinal mucosa or possibly the perianal skin and begin the infective cycle anew. This phenomenon, called internal autoinfection, allows *Strongyloides* to be maintained within the host for years after the initial infection. An important point is that the autoinfective cycle can be accelerated in an immunocompromised host and result in an often fatal condition known as hyperinfection.[144]

When first-stage larvae are deposited with feces, they develop in the soil into male or female adults, which mate and lay eggs. Eggs hatch, and larvae either can continue this free-living cycle for 1 or more generations or develop into parasitic filariform larvae and infect a suitable host.

Clinical Manifestations

Acute infection with *Strongyloides* larvae can elicit a cutaneous eruption at the site of skin penetration. This serpiginous urticarial rash, known as larva currens, is thought to represent an allergic response to migrating filariform larvae.[147–149] In chronic infections, such an eruption can be caused when autoinfective larvae penetrate the perianal skin or buttocks.

In immunocompetent patients, strongyloidiasis is an important cause of irritable bowel–like syndrome with intermittent abdominal cramping and diarrhea alternating with constipation.[150] In children, strongyloidiasis is associated with chronic diarrhea, fever, cachexia, and failure to thrive.[138,151] Malabsorption of both fat and protein can lead to a celiac-like syndrome characterized by steatorrhea, hypoalbuminemia, and peripheral edema. Deficiencies of vitamin B_{12} and folate also are common in patients with heavy infections.

A syndrome of infantile strongyloidiasis caused by *S. fuelleborni* has been described in Papua New Guinea.[146,152] Beginning in the first months of life, infected children often have diarrhea that becomes protracted, failure to thrive, protein malnutrition, and a kwashiorkor-like appearance attributable to hypoalbuminemia. Similar syndromes of infantile strongyloidiasis have been reported from parts of Africa. *Strongyloides* larvae have been detected in the milk of mothers with chronic infection, thus suggesting vertical transmission as a possible mode of neonatal disease.[153] Whether *S. stercoralis* also can be transmitted through human milk is not known, although this species has similarly been isolated from very young children.

The most serious complications of strongyloidiasis, hyperinfection and disseminated disease, occur during amplification of the autoinfective life cycle. Several well-defined risk factors for the development of hyperinfection syndrome have been recognized.[150] Most commonly, severe disease develops in patients who are chronically infected with *S. stercoralis* after the initiation of immunosuppressive agents for a variety of underlying conditions. Severe strongyloidiasis has been reported most commonly in patients being treated for hematologic malignant diseases or after solid-organ transplantation.[154] Most of these patients were receiving corticosteroids as part of their antineoplastic or immunosuppressive regimens; this finding raises the possibility that glucocorticoid therapy, even in the absence of malignant disease, can be the primary risk factor for hyperinfection syndrome.[155,156] *Strongyloides* hyperinfection also can occur in patients with generalized inanition and malnutrition, as well as in patients infected with HTLV-1.[143,144] In children with *Strongyloides* hyperinfection, the massive numbers of larvae migrating through the lungs can cause pulmonary infiltrates, dyspnea, and even respiratory collapse. These larvae often migrate aberrantly to distant organs, including the skin, brain, liver, heart, skeletal muscle, and lymph nodes, where they can elicit a vigorous immune response. Disseminated strongyloidiasis can be complicated by pyogenic abscess or meningitis caused by enteric bacteria transported from the colon by migrating worms.[157,158] Eosinophilia, found routinely in people with chronic strongyloidiasis, usually is absent in hyperinfection and disseminated disease. Untreated, *Strongyloides* hyperinfection has high mortality rate.[159]

Laboratory Findings and Diagnosis

Definitive diagnosis of *Strongyloides* infection relies on identification of first-stage rhabditiform larvae in the feces of an infected person (see Fig. 276.8). However, because female *S. stercoralis* nematodes release as few as 50 eggs a day, multiple stool specimens concentrated with the use of various techniques can be required to detect light or chronic infections. As a result, in most cases of uncomplicated strongyloidiasis a single fecal examination misses up to 70% of cases.[160] Several techniques, including an agar culture method, have been developed to increase the sensitivity of larval detection in the stools.[160–162] Alternatively, the number of larvae recovered from feces can be amplified by allowing them to undergo the heterogonic life cycle in Baermann cultures.[156] In patients with hyperinfective and disseminated strongyloidiasis, larvae can be recovered from extraintestinal sites, including sputum, bronchoalveolar lavage fluid, and, in some cases, cerebrospinal fluid (Fig. 276.9).[157]

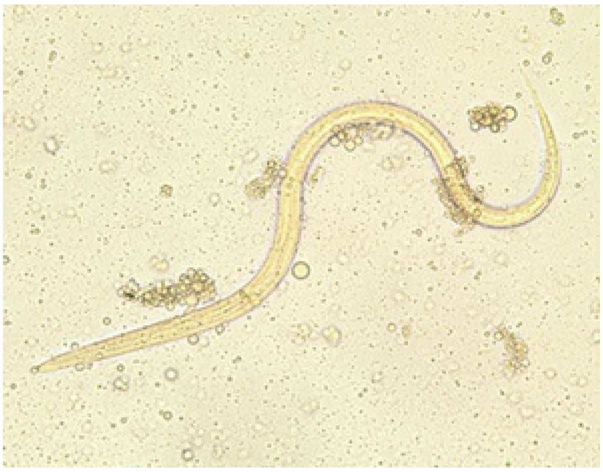

FIGURE 276.9 **Photomicrograph of a *Strongyloides stercoralis* third-stage (filariform) larva.** (From Centers for Disease Control and Prevention. DPDx. http://dpd.cdc.gov/dpdx/HTML/Image_Library.htm.)

Peripheral blood eosinophilia often is the only laboratory abnormality in chronic strongyloidiasis and probably represents an immune response to larvae migrating through host tissues. Eosinophilia frequently is absent in people with hyperinfection. Serologic assays can detect subclinical *S. stercoralis* infection.[163,164] These assays can aid in diagnosis in people from endemic areas who have unexplained eosinophilia.

Treatment

Because of the risk of hyperinfection, all people found to harbor *Strongyloides* should be treated, even in the absence of symptoms. The agent of choice is orally administered ivermectin (200 µg/kg/day for 2 days).[150] Cure rates are up to 97%.[165–169] Ivermectin has not been studied extensively in children and should not be given to children <15 kg. As an alternative, thiabendazole can be administered at a dose of 25 mg/kg twice a day (maximum, 3 g/day) for 3 days. Cure rates >80% have been reported, even in immunocompromised people with intestinal disease.[170] Unlike mebendazole, thiabendazole is well absorbed and has been associated with various side effects, including dizziness, nausea, and anorexia. Albendazole (400 mg, twice a day for up to 14 days) also has been used for treatment of strongyloidiasis,[118] as have combinations of ivermectin together with albendazole.[164]

The mortality rate from disseminated strongyloidiasis approaches 60%, even with aggressive treatment and supportive care. Therapy with ivermectin or ivermectin with albendazole should be continued for at least 7 to 14 days, preferably until the parasite can no longer be identified in clinical specimens.[118] In some cases, prolonged or repeated therapies with ivermectin can be required, and veterinary parenteral or enema formulations have been used in severely ill patients.[171] Concomitant bacterial infections should be treated aggressively with appropriate antibiotics, and exogenous corticosteroid and other immunosuppressive therapy should be tapered quickly. Documenting cure can be difficult because the production of eggs usually is low before treatment. Monitoring the serologic response to treatment, as well as peripheral blood eosinophil counts, can be useful.[172]

Prevention

As with other helminths transmitted in soil, proper sanitation practices as part of a full program of improved water, sanitation, and hygiene can help reduce the spread of *Strongyloides* infection in endemic areas. Attention to the importance of targeting strongyloidiasis, in addition to ascariasis, hookworm infection, and trichuriasis, may alter public health control for this disease through periodic deworming.[173] Prompt diagnosis and treatment of mild or asymptomatic infections should reduce the incidence of disseminated disease. People with unexplained eosinophilia, especially if they have lived in endemic areas, should be evaluated for strongyloidiasis before treatment with immunosuppressive therapy, especially glucocorticoids, is administered.

Key Points

Diagnosis and Management of Intestinal Nematode Infections

Microbiology

- Intestinal nematodes (roundworms) are multicellular parasites with complex life cycles.

- Infection is acquired by ingesting eggs or through skin contact by larvae.

- Adult worms reside in the small intestine (*Ascaris,* hookworm, *Strongyloides)* or large intestine (*Trichuris, Enterobius*).

Epidemiology

- More than 2 billion people living in tropical and subtropical regions are infected with ≥1 intestinal nematode.

- In the developed world, groups at significant risk for infection include immigrants, refugees, and children adopted from endemic regions.

- Most infections acquired in the United States are caused by *Strongyloides stercoralis* or *Ascaris lumbricoides,* which are endemic in the Southeast, or *Enterobius vermicularis* (pinworm), which is widespread and occurs in childcare and preschool settings.

Diagnosis

- Fecal microscopy is the diagnostic test of choice for most intestinal nematodes. In the case of *Strongyloides,* first-stage larvae, not eggs, are excreted in the feces.
- Pinworm *(Enterobius vermicularis)* infection is diagnosed most commonly by visual inspection of the perianal area for evidence of adult worms or by applying adhesive tape to the skin to recover eggs.

Treatment

- Screening and treatment for intestinal nematode infections in immigrants and international adoptees are recommended, even in the absence of symptoms.
- Benzimidazole anthelmintics (albendazole, mebendazole) remain the drugs of choice for treating *Ascaris,* hookworm, *Enterobius,* and *Trichuris* infections; however, anthelmintics are generally poorly effective against *Trichuris*.
- Ivermectin is the most effective treatment for *Strongyloides* infection, but only oral preparations are available routinely.
- Nitazoxanide is a broad-spectrum agent for treatment of parasitic infections and is effective against several intestinal nematodes.

Duration of Therapy

- Most infections are cured with 1 to 3 days of treatment.
- Follow-up stool evaluations are recommended to establish cure or the need for additional treatment.
- Despite therapy, disseminated strongyloidiasis in the compromised host is associated with significant mortality rates.

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Tissue Nematodes

Daniel Griffin, Dickson D. Despommier

Parasitic roundworms capable of invasion of human tissues are classified as tissue nematodes. They are found in a variety of ecologic niches that allow for human exposure. Many are present in outdoor environments and are transmitted to children through the ingestion of nonfood substances. The infectious stages of many of these tissue parasites often involve an animal host and can be classified as zoonotic infections. Many of these zoonotic parasitic tissue nematodes can permanently affect the cognitive ability, development, and vision of an infected child. This chapter focuses on some of the most medically relevant tissue nematodes.

Visceral Larva Migrans and Ocular Larva Migrans Caused by *Toxocara Canis*, *Toxocara Cati*, and *Baylisascaris Procyonis*

Besides *Enterobius vermicularis* (pinworm), toxocariasis may be the most common helminth infection in the United States, with seroprevalence in many areas exceeding 10%; however, the true burden of disease resulting from this large number of infections is poorly characterized.[1] Several clinical manifestations can follow exposure to the infectious larval forms of these tissue nematodes. Infected people can develop covert toxocariasis, which is a clinical manifestation of toxocariasis involving wheezing and eosinophilia that can manifest similar to and be misdiagnosed as asthma. Covert toxocariasis is believed to be caused by chronic exposure.[2] Perhaps the most commonly recognized clinical syndrome is visceral larva migrans, which manifests as a febrile illness characterized by multisystem involvement and eosinophilia.[1] Patients can also present with devastating neurologic manifestations (neurologic toxocariasis) or ocular larva migrans, which can be severe with irreversible visual loss resulting from scarring of the retina and in some cases retinal detachment secondary to larval migration to the eye.[3] *Toxocara* spp. infections identified through serologic testing may be associated with longterm cognitive consequences. Measurable reductions in scores on cognitive tests have been demonstrated when comparing children with serologic evidence of *Toxocara* spp. infection with children without such evidence.[4] Longitudinal studies to confirm these findings are still needed, but concern has been raised that the impact of this disease goes far beyond the cases brought to medical attention by symptoms.

Human infection with these tissue nematodes was first described in the 1950s, when a larva was detected in the eye of a child, and a series of children presenting with eosinophilia and severe multisystem disease was reported to be infected with *Toxocara canis* and *Toxocara cati* larva.[5,6] *T. canis* and *T. cati* are common causes of infections of dogs and cats, respectively, whereas *Baylisascaris procyonis,* a third important nematode in this group, commonly infects raccoons.[7] The life cycles and morphologic features of these tissue nematodes share similarities with *Ascaris lumbricoides* in humans, yet the adults of these 3 species have a shorter length than the adult *Ascaris* (Fig. 277.1).

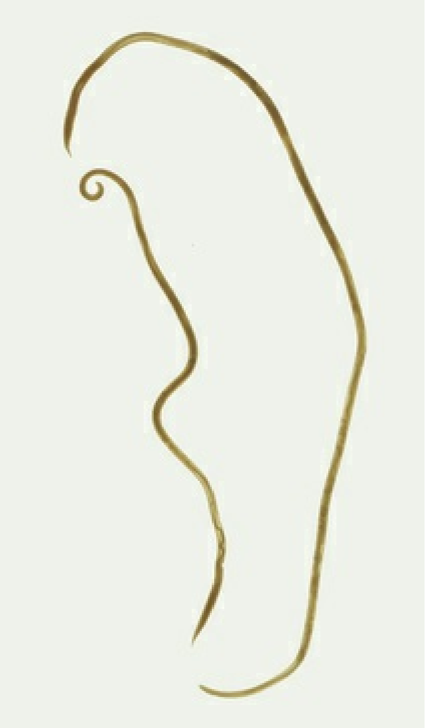

FIGURE 277.1 **Adults of *Toxocara canis.* The male measures 6 cm and the female measures 9 cm in length.**

Life Cycle

Human infection with *T. canis*, *T. cati*, or *B. procyonis* is initiated after embryonated eggs are ingested by humans. Humans come into contact with these eggs accidentally when their environment is contaminated by fecal material from dogs, cats, or raccoons that harbor the adult worms (Fig. 277.2).[8,9] After ingestion, the eggs are triggered to hatch, thereby releasing larvae that penetrate the wall of the small intestine and enter the circulation. In humans, the larvae migrate through various tissues, unable to complete their life cycle, and end up dying in the tissues they invade (Fig. 277.3).

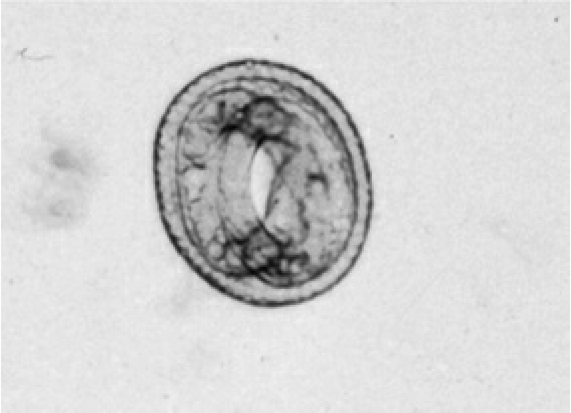

FIGURE 277.2 Embryonated egg of *Toxocara* species (65 μm).

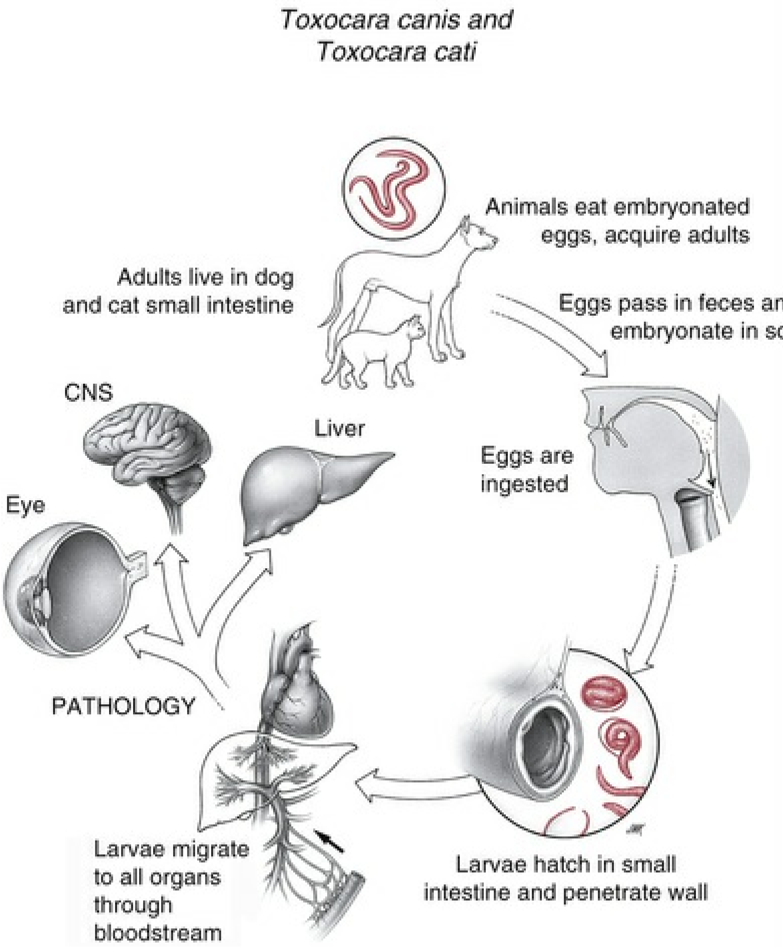
Toxocara canis and
Toxocara cati
Animals eat embryonated eggs, acquire adults
Adults live in dog and cat small intestine
Eggs pass in feces and embryonate in soil
Eggs are ingested
CNS
Liver
Eye
PATHOLOGY
Larvae migrate to all organs through bloodstream
Larvae hatch in small intestine and penetrate wall

FIGURE 277.3 Life cycle of *Toxocara canis* and *T. cati.* CNS, central nervous system. (Redrawn from Despommier DD, Gwadz RW, Hotez PJ, Knirsch CA [eds]. Parasitic Diseases, 5th ed. New York, Apple Trees Productions, 2005.)

When these embryonated eggs are ingested by their definitive host, they undergo the classic ascarid life cycle, including hatching, penetrating the intestinal, and entering the circulation. In the definitive zoonotic host, they migrate to the lungs and are coughed up and swallowed. Then they return to the intestinal tract, where they mature into adult worms after a period of 60 to 90 days from time of egg ingestion.[10] The adult worms produce eggs that are released into the environment and become infective after 2 to 4 weeks of maturation in the soil.[11] Infection can occur through ingestion of eggs, transplacentally, or through breast milk.[12] Although adult worms live for only 4 to 6 months, embryonated eggs can survive for several years in warm, moist soils.

Clinical Features

Toxocariasis is a disease that consistently affects the young, with visceral larva migrans occurring mainly in children <7 years of age and ocular larva migrans in children 8 to 16 years of age.[13] Although these diseases disproportionately affect the young, these helminths also are a recognized and perhaps underdiagnosed cause of disease in travelers.[3] The clustering of infection in children is believed to reflect their frequent exposure to fecally contaminated play environments (e.g., playgrounds, yards, and sandboxes). In addition to young age, risk factors for infection include male sex, pet ownership, low level of education, psychiatric disease, foreign birth, and play in public parks.[1]

With the introduction of larval forms into humans after ingestion of embryonated eggs, a range of pathologic features can occur that largely depends on which tissues are invaded. The clinical presentation appears to vary based on host factors such as the age of the person infected and whether the person is immunologically naïve, as well as pathogen-related aspects such as inoculum size, number of exposures, and tropism of particular strains.[11,14] The pathologic findings are believed to be caused by the host's immune response to dead and dying larvae in the viscera (Fig. 277.4). Patients with visceral larva migrans may present with a febrile illness including eosinophilia, hepatosplenomegaly, bronchospasm, and a myriad of other symptoms depending on localization of the nematode larva. The spectrum of disease that can result includes subclinical infections, less severe covert toxocariasis, and fully symptomatic visceral larva migrans with inflammation and disease in multiple organs. Before liver biopsy was replaced by serologic testing, the liver was a common site for isolating nematode larvae in eosinophilic granulomas.[6] Pulmonary symptoms, potentially confused with asthma, may be accompanied by infiltrates apparent on chest imaging.[2] Myocarditis as well as nephritis can develop. If larvae invade the central nervous system (CNS), then encephalopathy, seizures, and functional intestinal disorders can develop in infected patients.[15–19]

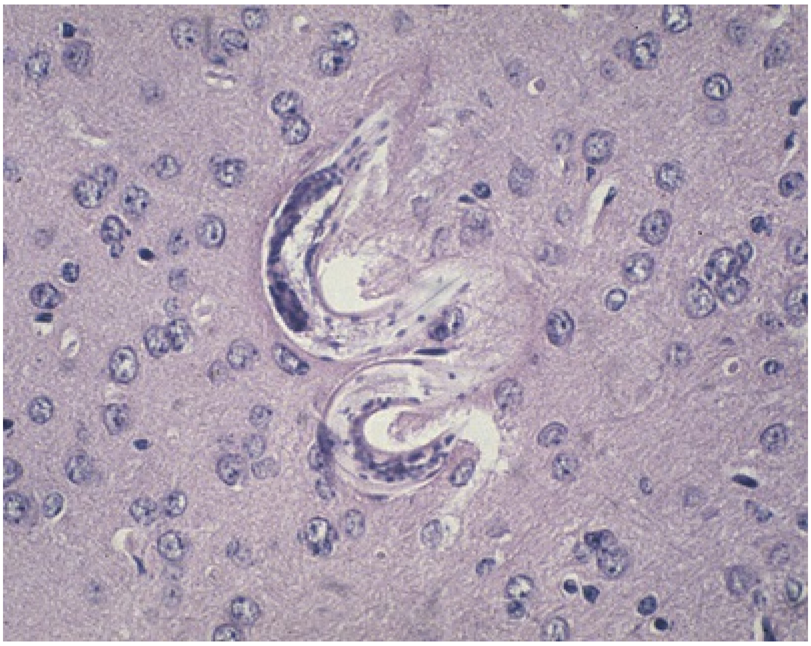

FIGURE 277.4 **The third-stage larva of *Toxocara canis* in the brain of an experimentally infected mouse.**

Ocular larva migrans is a devastating manifestation that tends to occur in people at a slightly older age; it generally manifests in adolescents as visual impairment isolated to a single eye. Larvae that have invaded the retina trigger an immune response as the larvae start to die. This immune response leads to granuloma formation that can result in deformation of the retina and detachment of the macula. In some cases these lesions have been visualized on ophthalmic examination, and because of their visual similarities to retinoblastoma, the risk of unnecessary enucleation of the infected eye exists.[20–23]

Although *Toxocara* spp. infections can be fatal in puppies, death is rare in human infection. When death occurs in humans, it is attributed to involvement of the myocardium or CNS,, along with an overly exuberant immune response when infection is with *T. canis* and *T. cati*. In contrast, infection with *B. procyonis,* a common infection of raccoons, can have high mortality rates.

Humans are exposed to *B. procyonis* through ingestion of embryonated eggs deposited in the environment by raccoons. The increased severity of disease and high mortality rate are attributed to unique features of this tissue nematode. *B. procyonis* larvae are larger, up to 2 mm compared with 0.5 mm for *T. canis* and *T. cati*, and have the unique ability to continue to grow inside the infected human.[24] *B. procyonis* is known as a pathogen to include in the differential diagnosis of eosinophilic meningitis and presents a public health problem because raccoons often enter human environments.[25]

Diagnosis

T. canis, T. cati, and B. *procyonis* infection should be included in the differential diagnosis in a child, adolescent, or returning traveler presenting with an unexplained febrile illness with eosinophilia and a compatible history. A combination of clinical presentation, appropriate risk factors, and a positive serologic test result supports the diagnosis. The recommended test for toxocariasis detects immunoglobulin G against excretory-secretory antigens derived from *Toxocara* spp. larvae. This *Toxocara* enzyme immunosorbent assay is available through the US Centers for Disease Control and Prevention and is estimated to be 78% sensitive and 92% sensitive when the appropriate cutoff is used.[26] One of the challenges of using serologic testing in the diagnosis is that the test detects an immune response to the larval form of the nematode and does not necessarily confirm current active infection. Although a biopsy demonstrating larvae is definitive, this is rarely indicated. The diagnosis of ocular larva migrans also incorporates a consistent ophthalmologic examination (Fig. 277.5). Stool examination of infected people is not helpful because these tissue nematodes are unable to complete their life cycle in humans, and thus adult egg-producing worms are never present in the human gastrointestinal tract. Although a serologic test has been developed for *B. procyonis* that has high sensitivity and specificity, many human cases are not diagnosed until autopsy (Fig. 277.6).

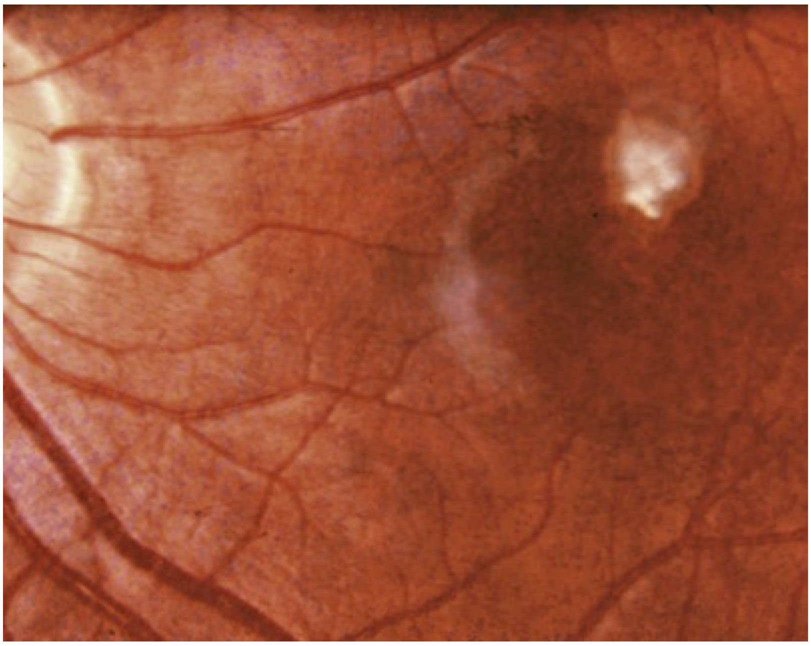

FIGURE 277.5 Larva of *Toxocara* in retina that manifests as a granuloma.

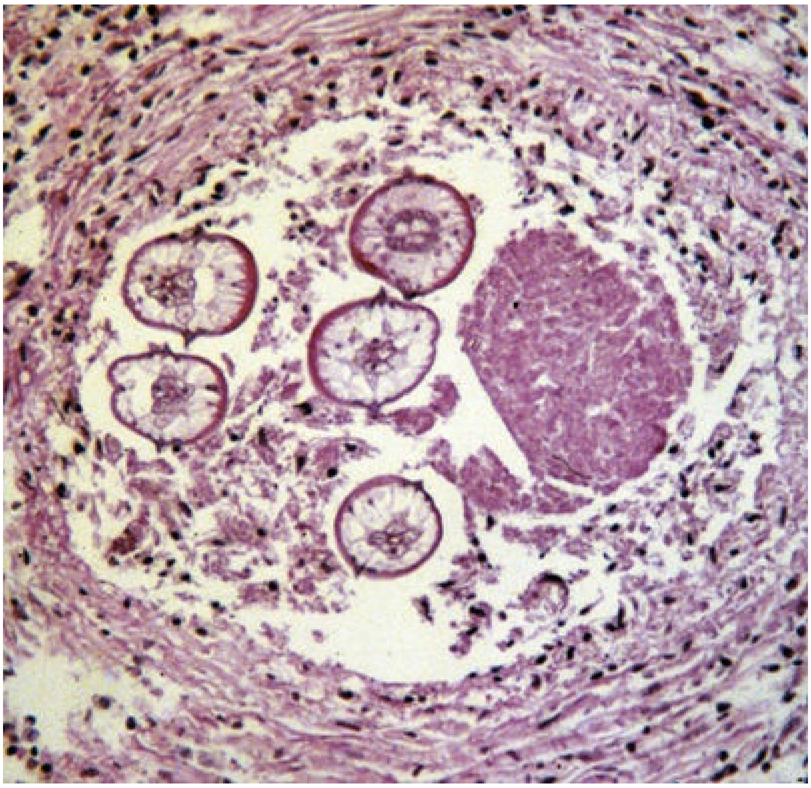

FIGURE 277.6 Larvae of *Baylisascaris procyonis* in brain of a child who died of the infection.

Treatment

Although evidence-based guidance with regard to treatment is limited, patients with *T. canis* and *T. cati* infections can be treated with oral albendazole, 400 mg twice daily for 5 days.[27] In the case of active ocular inflammation, topical and systemic corticosteroids can be used, whereas the role of anthelmintic therapy is unclear because of the lack of knowledge regarding the intraophthalmic pharmacokinetics and pharmacodynamics. The best treatment for *B. procyonis* infection is unclear, but good outcomes have been reported with high-dose albendazole, 25 mg to 50 mg/kg/day in divided doses started promptly and continued for 10 to 20 days, with concomitant corticosteroids.[25,28]

Prevention and Medical Ecology

Limiting human exposure to infective embryonated eggs in the environment is a critical aspect of decreasing the disease burden of these tissue nematodes. Once introduced into the environment, the infective ascarid eggs can remain viable for months to years because of their resistant acellular outer shell that allows them to withstand extreme temperature changes, various degrees of desiccation, and even harsh chemicals.[29,30] Any strategies to rid contaminated soil of these hardy eggs must overcome this barrier.

Once introduced into the soil by the indiscriminate deposition of fecal material by dogs, cats, or raccoons, eggs can be distributed through the environment. The common earthworm is efficient at redistributing fecal material back up to the surface even with eggs initially buried up to 2 feet below the surface.[29] Various domestic animals distribute contaminated soil on their paws, whereas ground-feeding birds such as pigeons, starlings, and sparrows can carry eggs farther afield on their feet and beaks.[10,31]

Eggs also can enter municipal drinking water supplies and end up in waters used for recreational purposes, where inadvertent water ingestion can infect a swimmer.[10] When infected animals deposit these eggs in an environment that allows for their maturation into an embryonated and infective state, the opportunity for continued transmission exists. In this particular public health challenge, veterinarians can have the most striking impact by encouraging pet owners to maintain dewormed pets.

Visceral Larva Migrans Caused by *Angiostrongylus* Spp.

The 2 major *Angiostrongylus* spp. of medical importance are *Angiostrongylus cantonensis* and *A. costaricensis*. *A. cantonensis* is the major cause of visceral larva migrans throughout China, Southeast Asia, and many areas of the Pacific and South Pacific, including Hawaii. *A. costaricensis* is found in Central and South America.

Life Cycle.

Rats are the definitive hosts for *Angiostrongylus* spp. The worms infect several rat species and live and lay eggs in the pulmonary arteries of rats. The released eggs move through the capillaries in the lung and then penetrate the alveolar spaces. From the alveolar spaces, the larvae migrate up the respiratory tree and are swallowed down into gastrointestinal tract ultimately to pass out of the rat in feces.[32] *A. cantonensis* larvae incubate in the soil before being consumed by a variety of mollusks and crustaceans.[33–36] Humans are infected when they inadvertently consume the larval stages of *A. cantonensis* present in uncooked snails, slugs, or raw vegetables contaminated with secretions of these invertebrates.

A. costaricensis larvae generally are restricted to infecting only 1 invertebrate host, the slug, and in most cases the specific slug known as *Vaginulus plebeius* Human infection results when humans accidently ingest these slugs or food contaminated with its secretions.

Clinical Features.

In most cases, human infection with *Angiostrongylus* spp. results in failure of the worm to complete its life cycle. Once in a human host the larvae often migrate to the brain or, rarely, to the lungs as has been observed in infants and small children. Then, the larvae die surrounded by an eosinophil-rich inflammatory infiltrate.[37] The pattern of clinical presentation varies with each species of this nematode. *A. cantonensis* third-stage larvae usually migrate to the meningeal capillaries, where the dying larvae trigger eosinophilic inflammation and resulting eosinophilic meningoencephalitis. Part of the disease can involve vascular thrombosis and aneurysms. *A.*

cantonensis is the most common cause of eosinophilic meningitis outside the developed world and should be considered in the differential diagnosis in travelers returning from endemic areas.[37]

Patients infected with *A. costaricensis* present with fever, bitemporal or frontal headache, and meningismus. Vomiting is reported in most cases, as are migrating painful paresthesias.[38] Investigators have suggested that migrating painful paresthesias often persist for weeks to months along with headaches. Although eosinophilic meningitis is characteristic on cerebral spinal fluid examination, focal lesions are usually not present on head computed tomography or magnetic resonance imaging, and this can finding be useful in distinguishing the disease from other disorders such as *Gnathostoma spinigerum* infection and neurocysticercosis.[39] The natural course of the disease without treatment is for resolution of symptoms in 1 to 2 weeks. Unfortunately, in children disease duration may be longer and severity may be worse.

Diagnosis.

The diagnosis of *Angiostrongylus* spp. is usually based on clinical presentation because serologic testing is not widely available. Confirmation of suspected cases has been achieved using posttreatment serologic testing in concert with research laboratories.[38]

Treatment.

With the self-limiting nature of this disease, treatment options often have focused on symptomatic features rather than on anthelmintic medications. Although animal models have supported the use of anthelmintic therapy trials, efficacy in human infection has not been demonstrated, and reports have noted that anthelmintic therapy may lead to disease exacerbation.[40–42] Serial lumbar punctures and analgesics are the usual approaches to therapy.

Visceral Larva Migrans Caused by *Gnathostoma Spinigerum*

G spinigerum is a parasite that infects a variety of mammals including cats, dogs, and mongooses; its intermediate hosts are copepods, snakes, fish, and birds. The disease is endemic in Southeast Asia and is increasingly recognized in Mexico and Central and South America.[43]

Life Cycle.

G. spinigerum adults live coiled in the wall of the small intestine of their definitive hosts. Eggs are passed out into the environment in the feces and hatch in freshwater. Larvae are released and are ingested by copepods of the genus *Cyclops*. Snakes, fish, and birds then ingest these infected crustaceans. In these intermediate hosts, the larvae mature into a stage infective for humans. When humans ingest infected crustaceans, the larvae are able to exit the gastrointestinal tract and then invade various tissues.[44–46]

Clinical Features.

The clinical features of *G. spinigerum* infection, or gnathostomiasis, are caused by the invasion of deep tissue by these larvae. Although these larvae fail to mature in the human host, they are aggressive migrators and cause direct destruction as well as the host inflammatory reaction.[47] Skin manifestations can include cutaneous larva migrans, panniculitis, and subcutaneous swellings. Invasion of the CNS can occur with peripheral eosinophilia, as well as eosinophilic meningitis with radicular pain and paresthesias caused by larval migration. *G. spinigerum* also can invade the eye and result in intraocular disease.[48]

Diagnosis.

Although previously the diagnosis of gnathostomiasis was limited to an appropriate travel history, clinical presentation, and eosinophilia, diagnostic tests have become available. Enzyme-linked immunosorbent assay and Western blot are now aiding diagnosis, but these tests are not available in the US, and definitive diagnosis is often not possible.[49]

Treatment.

Although this disease can be self-limited, therapy includes a 21-day oral course of albendazole at a dose of 400 mg once daily.[50]

Ivermectin has also been shown to be effective in several trials and can serve as an alternate agent. The role of anthelmintic therapy remains unclear for ocular and neurologic disease, in which this therapy can worsen symptoms. In some cases, corticosteroids have been used in the treatment of patients with CNS manifestations. Unfortunately, relapses have been reported with either therapy.[38]

Cutaneous Larva Migrans Caused by *Ancylostoma Braziliense*

Cutaneous larva migrans is a zoonotic hookworm infection with worldwide distribution that is most often caused by larvae of a dog or cat hookworm, such as *Ancylostoma braziliense, Ancylostoma caninum* (Fig. 277.7), or *Uncinaria stenocephala*. *A. braziliense* is the most common causative organism. These larvae are unable to mature, but on occasion *A. caninum* larvae can migrate to the small intestines in humans and cause eosinophilic enteritis or, rarely, subacute neuroretinitis, rather than cutaneous larva migrans. Other less common nematodes also can cause cutaneous larva migrans, including raccoon-transmitted *Strongyloides procyonis,* which results in "duck hunter's itch."

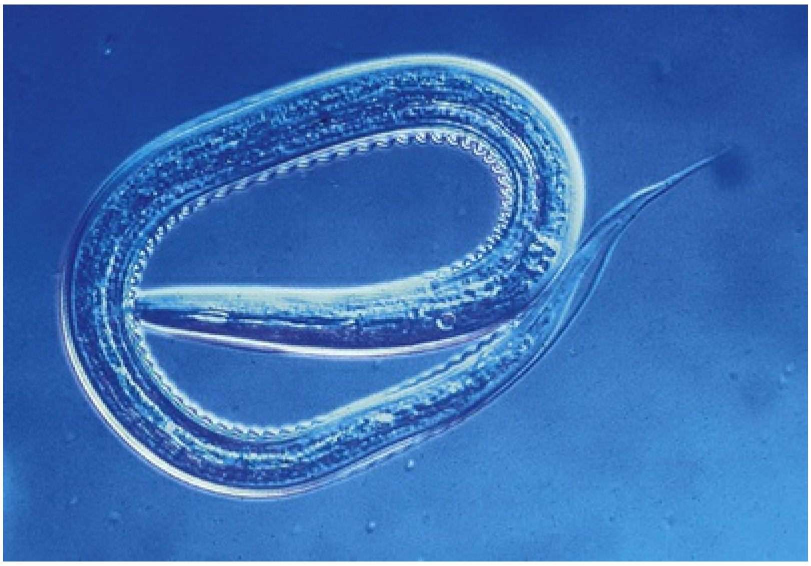

FIGURE 277.7 **Third-stage larva of *Ancylostoma caninum*.** (Courtesy of E. Gravé.)

Life Cycle.

The filariform larvae of these zoonotic hookworms survive in sandy, moist soils for several days. Larvae of zoonotic hookworms are especially common in India and Southeast Asia, Brazil, the Caribbean, and Puerto Rico, where dogs and cats are permitted to defecate.[51] In the human host, infection begins when the filariform larvae penetrate unbroken skin but then fail to receive the proper environmental cues. Instead of going farther in the life cycle, larvae migrate laterally through the deeper layers of the epidermis and can survive there for approximately 10 days.[52] An intense inflammatory reaction, associated with itching in the affected areas, develops within days after larvae enter the dermis and is provoked by hydrolytic enzymes secreted by the larvae.

Clinical Features.

The serpiginous lesions known as “creeping eruption” are evident after an incubation period of 1 week (Fig. 277.8). Secondary bacterial infection caused by scratching is common. In a review of 98 patients with cutaneous larva migrans seen at a travelers' clinic in Munich, 73% of the lesions were found on the lower extremities, with the buttocks and anogenital region (13%) and trunk and upper extremities (7% each) affected less frequently.[53]

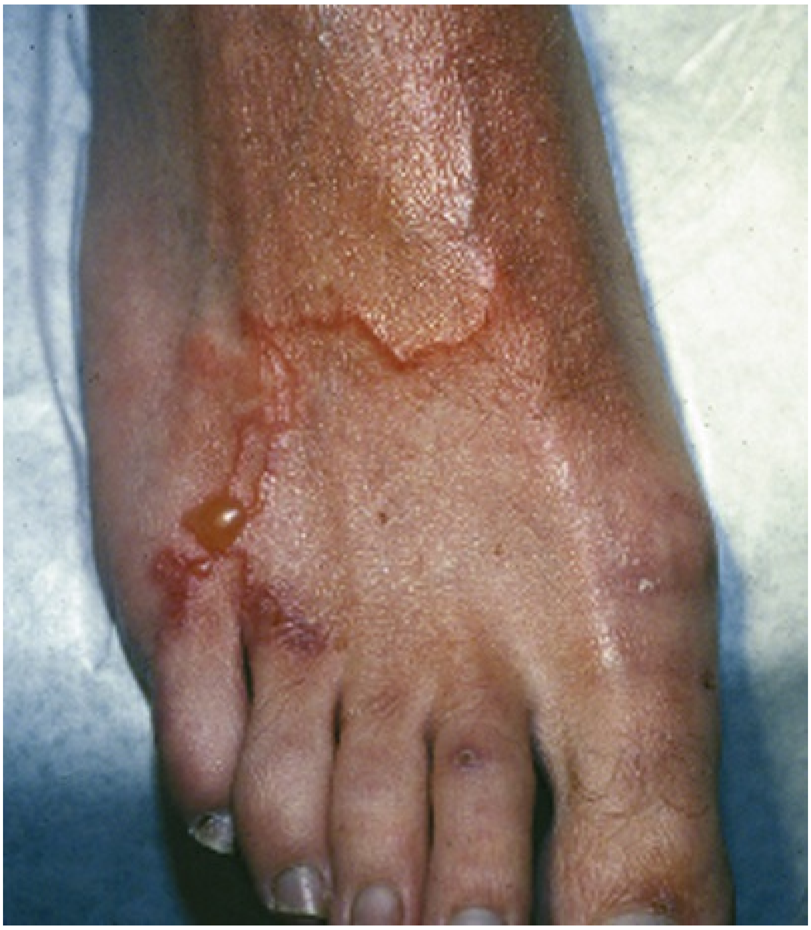

FIGURE 277.8 “Creeping eruption” caused by a larva of *Ancylostoma caninum.* (Courtesy of G. Zalar.)

Diagnosis.

The diagnosis is almost always purely clinical unless one surgically extracts the worm. Some patients have peripheral blood eosinophilia or an elevated serum immunoglobulin E level, but laboratory findings generally play little or no role in establishing a diagnosis.[53]

Treatment.

The treatment of choice is oral therapy with anthelmintic medication. A single dose of ivermectin (200 μg/kg once, sometimes repeated) is considered more effective than a single dose of albendazole, but repeated treatments of albendazole (400 mg daily for 5–7 days) are comparable. Some investigators recommend a 3-day course of albendazole (400 mg daily). Topical thiabendazole in a concentration of 10% to 15% applied 3 times daily for 5 to 7 days is an alternative treatment, but patients' compliance is an issue.

Cryotherapy with liquid nitrogen can cause blistering and ulceration of the skin and should not be performed.[54]

Visceral Larva Migrans Caused by Ascarids of Marine Mammals

Anisakiasis in humans is caused by various species of nematodes belonging to the genera *Anisakis, Phocanema, Terranova,* and *Contracoecum.* The adults of these parasites live in the lumen of the intestinal tract and infect sea mammals, particularly dolphins, whales, sea lions, and seals. Anasakid first-stage larvae infect several crustacean species. Second-, third-, or fourth-stage larvae infect a wide variety of teleosts (bony fish).[55]

Life Cycle.

The adult worms of marine mammal ascarids embed in the gastric mucosa and pass unembryonated eggs out into the environment in the feces. The eggs embryonate, and larvae mature inside the eggs until free-swimming larvae are released. Free-swimming larvae are ingested by crustaceans, and in this host they mature into the stage infective for fish as well as squid. Rather than staying in the intestine of the cold-blooded vertebrate host, larvae migrate to the peritoneal cavity, where they grow up to 3 cm in length. On the death of the vertebrate host, larvae migrate to muscles where they can be ingested by marine predators and develop into adult worms. After embedding into the mucosa, adult female worms begin laying eggs, and the life cycle is complete.[56]

Humans are accidental and dead end hosts for marine ascarids. Humans can become infected when they ingest raw or undercooked marine fish. In humans, the ingested larvae mature and quickly attempt to penetrate the gastric or intestinal mucosa.[57]

Clinical Features.

Infected people often present with abdominal pain that can be severe. The time from ingestion of parasites to the onset of symptoms is usually a matter of minutes to hours. Nausea, vomiting, abdominal distention, mild fever, and diarrhea with blood and mucus in the stool can be part of the presentation.[58] If larvae are able to penetrate the mucosa, then angioedema, urticarial, and allergic symptoms can dominate the clinical presentation.[59]

Diagnosis.

Definitive diagnosis and treatment are accomplished by removal of the parasite. Sometimes the worms are expelled through coughing or vomiting, but at other times endoscopic removal or surgical intervention for extraintestinal manifestations is necessary. Serologic tests using an antigen capture enzyme-linked immunosorbent assay are available in some countries and have a sensitivity reported to be nearly 100%.[60] Polymerase chain reaction (PCR)–based tests have been developed but are not commercially available.[61]

Treatment and Prevention.

Currently, no anthelmintic therapy is approved by the US Food and Drug Administration for the treatment of marine ascarid infection, but successful treatment has been reported with oral albendazole 400 mg twice daily for 6 to 21 days.[62,63] Thorough cooking or freezing of seafood before ingestion can prevent infection by anisakid nematodes. Most sushi restaurants in the US and elsewhere now inspect pieces of raw fish carefully before serving them, and the Food and Drug Administration requires freezing before raw fish are served. Flash freezing in liquid nitrogen has become a popular way of processing fish destined for sushi restaurants. After a peak in the 1980s, the incidence of anisakid visceral larva migrans in Europe and North America from the consumption of raw fish has been reduced to a few sporadic cases annually.[64]

Trichinella Spiralis (Trichinellosis)

The genus *Trichinella* has undergone revision since the advent of reliable DNA probes. Eight species and 11 genotypes are now recognized, all capable of infecting humans.[65–67] Members of the genus *Trichinella* can infect a broad spectrum of mammalian hosts, thus making these organisms the cause of one of the world's most widely distributed nematode infections. *Trichinella* spp. are genetically related to *Trichuris trichiura* and *Capillaria* spp.; all belong to the family Trichurata. These roundworms constitute an unusual group of organisms in the phylum Nematoda in that they all live their lives as intracellular parasites.

Diseases caused by *Trichinella* spp. are referred to collectively as trichinellosis. Currently, the prevalence of trichinellosis is low in the US, with infections occurring mostly as scattered outbreaks, less often involving pork consumption and more often involving poorly cooked game.[68,69] Most human cases are caused by *Trichinella spiralis,* and the information that follows concentrates on this species.

The domestic pig is the main reservoir host for *T. spiralis. T. spiralis* is significantly more prevalent in parts of Europe, Asia, and Southeast Asia than in the US. In Europe, and especially in Eastern Europe, the rise of trichinellosis has been associated with certain political and socioeconomic changes that resulted in a breakdown of the human and veterinary public health infrastructure.[70] Trichinellosis is considered endemic in Japan and China, and a large outbreak occurred in Lebanon in 1997 that infected more than 200 people.[71] In contrast, *Trichinella* spp. infections in wildlife in the US are now thought to be caused largely by the T5 strain, tentatively designated *T. murrelli.*[72]

Life Cycle

Infection is initiated by ingesting raw or undercooked meats harboring the nurse cell–larva complex (Figs. 277.9 and 277.10). Larvae are released from muscle tissue by digestive enzymes in the stomach and then locate to the upper two thirds of the small intestine. The outermost cuticular layer (epicuticle) becomes partially digested, thereby enabling the parasite to receive environmental cues and to select an infection site within the small intestine. Immature parasites penetrate the columnar epithelium at the base of the villus, where they live in a row and are considered intra-multicellular organisms.[73–75]

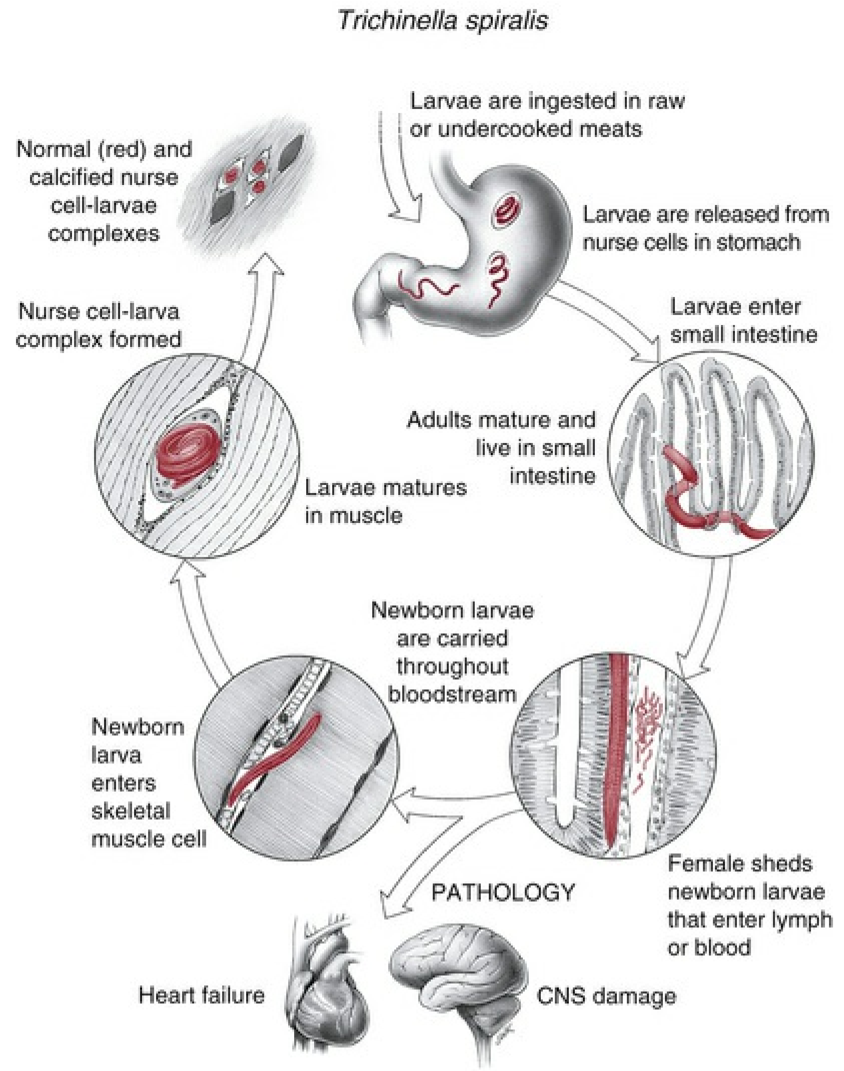
Trichinella spiralis
Larvae are ingested in raw or undercooked meats
Larvae are released from nurse cells in stomach
Larvae enter small intestine
Adults mature and live in small intestine
Female sheds newborn larvae that enter lymph or blood
Newborn larvae are carried throughout bloodstream
Newborn larva enters skeletal muscle cell
Larvae matures in muscle
Nurse cell-larva complex formed
Normal (red) and calcified nurse cell-larvae complexes
PATHOLOGY
Heart failure
CNS damage

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FIGURE 277.9 **Life cycle of *Trichinella spiralis.* CNS, central nervous system.** **(Redrawn from Despommier DD, Gwadz RW, Hotez PJ, Knirsch CA [eds]. Parasitic Diseases, 5th ed. New York, Apple Trees Productions, 2005.)**

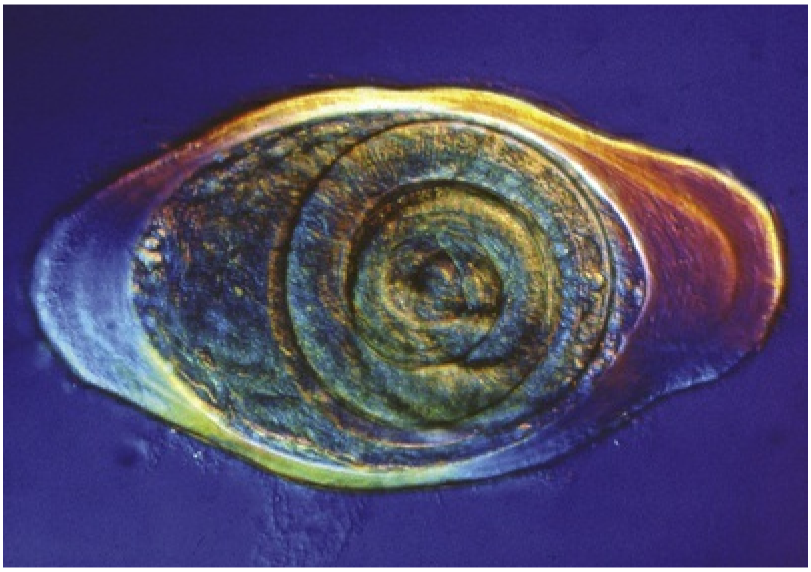

FIGURE 277.10 **Nurse cell–larva complex of *Trichinella spiralis*.**

Larvae molt 4 times in rapid succession over a 30-hour period and develop into adults. The female measures 3 mm in length by 36 µm in diameter, whereas the male measures 1.5 mm in length by 36 µm in diameter. Patency occurs within 5 days after mating. Adult females produce live offspring—newborn larvae, which measure 0.08 mm in length by 7 µm in diameter (Fig. 277.11). The female produces offspring as long as host immunity does not develop. Eventually, the host acquires protective responses that interfere with the overall process of embryogenesis and create physiologic conditions in the local area of infection that force the adult parasites to egress and relocate further down the intestinal tract. Expulsion of worms from the host is the final expression of immunity and can take several weeks.

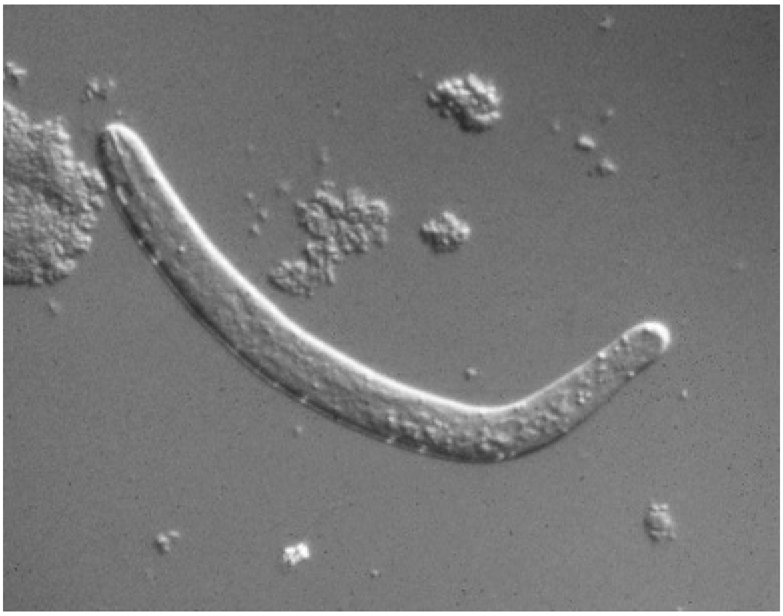

FIGURE 277.11 **Newborn larva of *Trichinella spiralis* (80 × 7 μm).**

The newborn larva is the only stage of the parasite that possesses a sword-like stylet located in the oral cavity that is used to create an entry hole in potential host cells. Larvae enter the lamina propria in this fashion and penetrate the mesenteric lymphatics or the bloodstream. Most larvae enter the general circulation and become distributed throughout the body.

Migrating larvae leave capillaries and enter cells (Fig. 277.12). They appear to have no tropism for any particular cell type, and this cell entry is not limited to muscle cells. Once inside a cell, larvae either can remain or leave, depending on environmental cues received by the parasite. Most cell types die as the result of larval invasion. Skeletal muscle cells are the only exception. Not only do the parasites remain inside muscle cells after invasion, but also they induce a remarkable series of changes, causing the fully differentiated muscle cell to transform into one that supports the growth and development of the larva. This process is termed nurse cell formation.[76] Parasite and host cell develop in a coordinated fashion. *T. spiralis* is infective by day 14 of infection, but the worm continues to grow through day 20. The significance of this precocious behavior has yet to be appreciated.

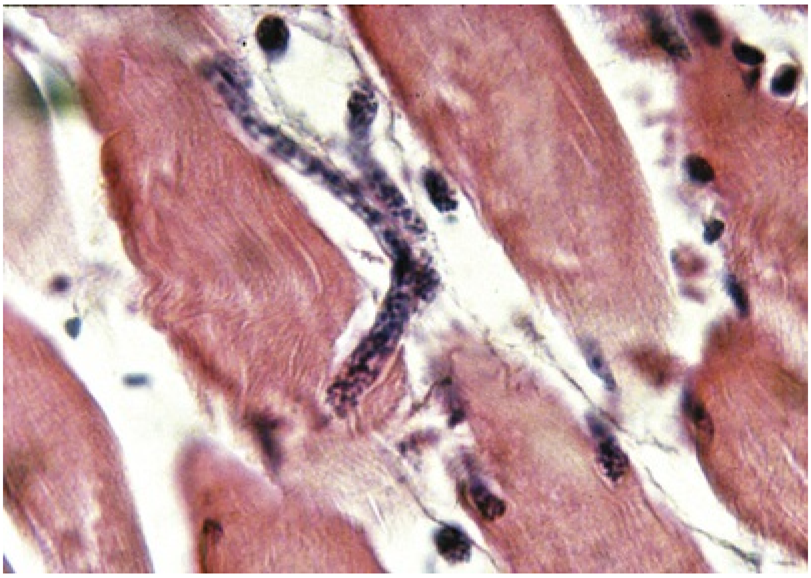

FIGURE 277.12 Migrating larva of *Trichinella spiralis* penetrating outward from a capillary.

Parasites inside cells other than striated muscle cells fail to induce nurse cells and either reenter the general circulation or die. Nurse cell formation results in an intimate and permanent association between the worm and its intracellular niche. At the cellular level, whorls of smooth membranes and clusters of dysfunctional mitochondria replace myofilaments and other related muscle cell components over a 14- to 16-day period. The net result is that the host cell switches from aerobic to anaerobic metabolism. Nuclei enlarge and divide, thus amplifying the host's genome within the nurse cell cytoplasm.[77] The nurse cell–parasite complex can live for as long as the host remains alive. Most do not, however, and are calcified within several months after forming. For the life cycle to continue, an infected host must die and be eaten by another mammal while the parasites are still viable. Scavenging is a common behavior among wild mammals, and this helps to ensure the maintenance of *T. spiralis* and its relatives in their respective host species.

Clinical Manifestations

The presentation of trichinellosis can vary from minimal or subclinical when a limited number of viable larvae are ingested to the distinct 2-stage presentation observed with heavy infection. Some clues, even in the early stages of the disease, can alert the physician to include trichinellosis in the differential diagnosis.

The first few days of heavy infection are known as the gastrointestinal stage. This stage begins 1 to 2 days after ingestion of infected meat and manifests with secretory diarrhea, abdominal pain, and vomiting. These symptoms usually abate within 10 days after ingestion of infected tissue. A history of eating raw or undercooked meats and reporting similar illness in others who ate the same meats are suggestive of trichinellosis.[78]

The parenteral stage begins approximately 1 week after infection and can last several weeks. Typically, the patient has fever and myalgia, bilateral periorbital edema, and petechial hemorrhages, which are seen most clearly in the subungual skin but also are observed in the conjunctivae and on other mucous membranes. Muscle tenderness is detected readily. Laboratory studies reveal a moderately elevated white blood cell count (12,000–15,000 cells/mm^3), with eosinophilia ranging from 5% to 50%.[78]

Larvae penetrating tissues other than muscle give rise to more serious sequelae. In many cases of moderate to severe infection, cardiovascular involvement leads to myocarditis. Electrocardiographic changes are frequently noted during this stage. Parasite invasion of the diaphragm and the accessory muscles of respiration can result in dyspnea. Neurotrichinellosis may occur as a result of CNS invasion.[79,80] A final convalescent stage follows the 2 acute stages of this illness, during which time many nurse cell–parasite complexes are destroyed.

Diagnosis

The diagnosis is established on the basis of appropriate clinical and laboratory findings. These findings include eosinophilia and increases in serum muscle enzyme levels, antibody detection or detection of larvae in muscle, and epidemiologic investigations identifying a source and origin of infection. Muscle enzymes (e.g., creatine kinase and lactic dehydrogenase) are released and cause an increase in serum levels. Results of serologic tests can be positive within 2 weeks; enzyme immunosorbent assay results can be positive as early as 12 days after infection. Definitive diagnosis depends on finding the nurse cell–parasite complex in muscle biopsy by microscopic examination or detecting *Trichinella*-specific DNA by PCR. PCR is sensitive and specific for detecting small numbers of larvae in muscle tissue, but it rarely is used in the clinical setting.[78]

Muscle biopsy results can be negative, even in patients with high-density infections, because of sampling error. In addition, the larvae can be at an early stage of development, thus making them inconspicuous, even to the experienced pathologist. A rising, plateauing, and falling level of circulating eosinophils throughout the infection period is not confirmatory, but in the appropriate clinical context it could warrant empiric therapy. Bilateral periorbital edema, petechiae under the fingernails, and high fever, coupled with a history of eating raw or undercooked meats, further solidifies the diagnosis of a presumptive infection.

Treatment

An anthelmintic should be administered, with the recommended dose of albendazole (400 mg twice daily for 8–14 days). Albendazole results in higher tissue levels and therefore is preferred to mebendazole. Use of the drug in pregnancy and in children <2 years of age requires consideration of potential risks versus benefits. In addition, it is thought that anthelmintics work best in the early stages of the infection; once muscle larvae are established, the clinical effectiveness of anthelmintics is reduced, and larvae can survive for years to cause chronic myalgias. Rapidly destroying larvae with anthelmintics can exacerbate host inflammatory responses and worsen the disease. Corticosteroid therapy, particularly prednisone (30–60 mg/day) for 10 to 15 days is recommended if the diagnosis is secure and the symptoms are severe. Antipyretics and analgesics are used in the myopathic stage and can be continued until fever and allergic signs recede.

Prevention and Medical Ecology

Since 2005, outbreaks of trichinellosis in the US have become rare and sporadic. Generally, most cases have been associated with ingestion of raw or undercooked meats obtained from commercial sources or from wild game. However, pigs raised on family farms, as compared with commercial factory farm operations, are more likely to be fed uncooked garbage and thus acquire the infection.

US Department of Agriculture law, which bans feeding unprocessed garbage, is enforced only in large production facilities. Hunters and those sharing in their kills of carnivorous mammals, including bear, fox, and cougar, have sometimes become infected. Herbivores can harbor the infection because most plant eaters occasionally ingest meat when the opportunity arises. Epidemics caused by eating raw horsemeat have been reported from France, Italy, and Poland.

The scope of meat inspection in the US does not include *Trichinella* spp. In Europe, the countries in the European Union use several strategies for examining meat for muscle larvae. Most of these strategies serve to identify pools of meat sampled from given regions. If these samples consistently test negative, then a *Trichinella*-free designation is applied to that supply of meat. Nonetheless, rare outbreaks occur despite this rigorous system of inspection.

Trichinellosis caused by *T. spiralis* can be prevented by cooking meat thoroughly at 58.5°C for 10 minutes. In the case of pork with viable *T. spiralis* organisms, freezing it at −20°C for 3 days is effective. Freezing is not always effective with meat from other animals or for other species of *Trichinella. T. nativa* was found to survive for up to 34 months in frozen muscles of grizzly bear and for up to 5 years frozen at −18°C in the muscles of carnivores.[67] The freeze tolerance of encapsulated *Trichinella* muscle larvae appears to be largely determined by *Trichinella* spp. but also depends on host tissue.[81–83] Hence thorough cooking is the only way to render all meats safe from all *Trichinella* spp.

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Blood and Tissue Nematodes

Filarial Worms

LeAnne M. Fox

Human filariasis, a public health problem of global importance, is caused by infection with threadlike worms that have complex life cycles involving a human host, insect vectors, and in some cases, other mammalian reservoirs. When an infected vector bites or takes a blood meal from a human host, filarial larvae penetrate the skin and migrate to specific tissues, where they develop into sexually mature adult worms. Months after infection, microfilariae are released by the fertile female worm and migrate to the skin or peripheral blood, where they are ingested by an insect vector when it bites or takes a blood meal. Development of the infective third-stage larvae in the insect completes the life cycle. Signs and symptoms of filarial infections are determined in part by the preferred locations of the adult worms and microfilariae (Table 278.1).

TABLE 278.1

Characteristics of Filarial Parasites of Humans

	Most Common Tissue	Geographic	Estimated

Species	Location		Geographic Distribution	No. Infected	Vector	Periodicity
	Adult	Microfilaria				
Wuchereria bancrofti	Lymphatics	Blood	Tropics worldwide	115 million	Mosquitoes	Nocturnal or subperiodic
Brugia malayi	Lymphatics	Blood	Southeast Asia	13 million	Mosquitoes	Nocturnal or subperiodic
Brugia timori	Lymphatics	Blood	Indonesia	Thousands	Mosquitoes	Nocturnal
Onchocerca volvulus	Connective tissue	Skin, eyes	Africa, South America	37 million	Blackfly (Simulium)	None
Loa loa	Connective tissue	Blood	West and Central Africa	13 million	Deerfly (Chrysops)	Diurnal
Mansonella streptocerca	Skin	Skin	West and Central Africa	Unknown	Midge (Culicoides)	None
Mansonella perstans	Serous cavities	Blood	Africa, South and Central America	Unknown	Midge	None
Mansonella ozzardi	Serous cavities	Blood, skin	South and Central America, Caribbean	Unknown	Blackfly, midge	None
Dirofilaria immitis	Lungs	—	Worldwide	Unknown	Mosquitoes	—
Dirofilaria tenuis, Dirofilaria repens	Subcutaneous tissue	—	Worldwide	Unknown	Mosquitoes	—

The chronic sequelae of filarial infections may not become evident for several years after infection. Infected children living in areas where filariasis is endemic often are asymptomatic. People with no previous exposure who travel to endemic areas tend to have more vigorous immunologic responses to filarial infection, are less likely to have detectable microfilariae, and are more likely to have acute manifestations. For children with an appropriate travel history and signs or symptoms of filariasis or unexplained eosinophilia, the diagnosis can be confirmed by the finding of microfilariae in blood, in skin snips, or on slit-lamp examination of the eye. For *Wuchereria bancrofti*, the most prevalent cause of lymphatic filariasis, assays for circulating parasite antigen are available commercially, but they are not approved by the US Food and Drug Administration.

Determination of serum antifilarial immunoglobulin (Ig) G may be helpful as an initial diagnostic test, particularly in expatriate visitors to endemic areas. This assay is available at the Parasitic

Diseases Laboratory at the National Institutes of Health (phone: 301-496-5398) or at the Centers for Disease Control and Prevention (phone: 404-718-4745). If antifilarial antibodies are not detectable, filarial infection is unlikely. For the patient with antifilarial IgG, a careful clinical and travel history should guide selection of more specific serologic and parasitologic tests for a particular filarial infection.

Many filarial nematodes contain rickettsia-like endosymbiotic bacteria of the genus *Wolbachia* that are important for normal development, viability, and fertility of the adult worm. These bacteria have been investigated as potentially important chemotherapeutic targets and as disease-causing organisms, particularly for lymphatic filariasis and onchocerciasis.

Lymphatic Filariasis

Key Points

Diagnosis and Management of Lymphatic Filariasis

Pathogen

- Filarial nematodes *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*

Epidemiology

- Transmitted through the bite of infected *Aedes*, *Culex*, *Anopheles*, and *Mansonia* species of mosquitoes
- Found in sub-Saharan Africa, southern Asia, the western Pacific Islands, the northeast coast of Brazil, Guyana, Haiti, and the Dominican Republic

Clinical Presentation

- Most infections are asymptomatic.
- Lymphatic dysfunction can lead to lymphedema of the leg, scrotum, penis, arm, or breast years after infection.

- Filarial lymphadenopathy of the inguinal, crural, and axillary lymph nodes is commonly seen in infected children.
- Acute episodes in people with lymphatic dysfunction are associated with painful swelling of an affected limb, fever, or chills due to bacterial superinfection.
- Tropical pulmonary eosinophilia is a potentially serious progressive lung disease that manifests with nocturnal cough, wheezing, and fever in a patient with peripheral blood eosinophilia.

Diagnosis

- Requires epidemiologic risk assessment plus filarial testing
- Microscopic detection of microfilariae on an appropriately timed thick blood film
- Determination of serum antifilarial IgG

Treatment

- Diethylcarbamazine (DEC) is the treatment of choice; drug obtained from the Centers for Disease Control and Prevention is under an investigational new drug protocol.
- Patients with lymphedema and hydrocele can benefit from lymphedema management and, in the case of hydrocele, surgical repair.

Epidemiology

Lymphatic filariasis is caused by three species, *W. bancrofti, Brugia malayi,* and *Brugia timori,* which together infect an estimated 120 million people in Africa, southern Asia, the western Pacific Islands, the northeast coast of Brazil, Guyana, Haiti, and the Dominican Republic (see Table 278.1).[1] More than 90% of these infections are caused by *W. bancrofti.* The three species cause similar signs and symptoms, although genital involvement occurs primarily with *W.*

bancrofti infection.

The adult worms live in the lymphatic vessels for 5 to 10 years. Initial infection, detected as circulating filarial antigen, commonly occurs between the ages of 2 and 4 years.[2,3] In areas of intense transmission, prevalence of microfilaremia increases rapidly between the ages of 5 and 10 years. Chronic manifestations, such as hydrocele and lymphedema, occur infrequently in people younger than 20 years of age and usually increase in frequency with age.[3]

Clinical Manifestations

The clinical expression of lymphatic filariasis varies considerably. Most infected people are asymptomatic. Filarial lymphadenopathy is seen commonly in infected children,[3–5] and before puberty, adult worms can be detected by ultrasonography of the inguinal, crural, and axillary lymph nodes and vessels.[6,7] In boys after puberty, the adult worms tend to live in the intrascrotal lymphatic vessels.[6,7]

Ultrasonography of lymphatic vessels can reveal motile adult worms, called the *filarial dance sign*, examples of which can be viewed on the Internet.[8] Even in asymptomatic people, the presence of living adult worms leads to lymphatic dilation and abnormal lymph flow, which can be demonstrated by lymphoscintigraphy. These changes predispose the person to lymphedema.[9] Lymphatic vessel dilation, lymph node enlargement, and fibrosis can be visualized when lymph nodes are examined histopathologically (Fig. 278.1). Microscopic hematuria and proteinuria also are found.[10]

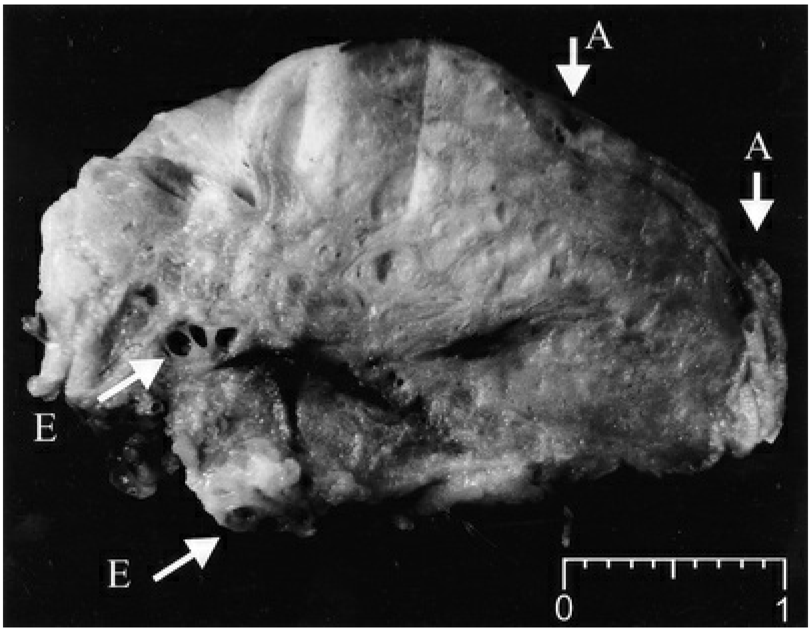

FIGURE 278.1 Gross appearance of a lymph node from a child infected with *W. bancrofti.* The capsule is thickened, and the hilum is distended. Afferent (A) and efferent (E) lymphatic vessels are dilated and tortuous. (From Figueredo-Silva J, Dreyer G. Bancroftian filariasis in children and adolescents: clinical-pathological observations in 22 cases from an endemic area. Ann Trop Med Parasitol 2005;99:759–769.)

Acute filarial lymphangitis has been well documented in travelers to endemic areas. Two to 6 months after exposure, acute inflammation can develop in a lymphatic vessel and its associated lymph nodes, most frequently in the leg, scrotal area, or arm. Characteristically, inflammation progresses distally along the lymphatic vessel, which becomes indurated, tender, and erythematous, and it resolves spontaneously within 3 to 7 days. Because biopsies reveal intense inflammation and nonliving adult worms, acute filarial lymphangitis is thought to be caused by the death of the adult worm.[11]

A separate and clinically distinct syndrome, which for years was confused with filarial lymphangitis, is acute dermatolymphangioadenitis, caused by bacterial infection of the small collecting lymphatic vessels in areas of lymphatic dysfunction.[11,12] Unlike true filarial lymphangitis, this syndrome develops in a reticular rather than a linear pattern and is more commonly associated with severe pain, fever, and chills.

Lymphedema occurs in the legs, scrotum, penis, and arms. In the legs and arms, it usually is unilateral. The most important factor involved in progression of filarial lymphedema to elephantiasis is repeated episodes of acute dermatolymphangioadenitis, originating from breaks in the epidermis, which contribute to further lymph stasis, secondary bacterial infection, and fibrosis.[9]

The pathogenesis of filarial hydrocele is unclear but is thought to be a consequence of lymphatic damage caused by living adult *W. bancrofti*.[9] In filariasis-endemic areas, clinically apparent hydrocele instead may be a chylocele, resulting from rupture of dilated intrascrotal lymphatic vessels and leakage of lymph into the cavity of the testicular tunica vaginalis.[9] Chyluria results from rupture of dilated retroperitoneal lymphatic structures into the renal pelvis.

Tropical pulmonary eosinophilia (TPE) is characterized by peripheral blood eosinophilia (>3000 cells/mm^3), elevated serum IgE (>10,000 ng/mL), low-grade fever, lymphadenopathy, and a nonproductive cough that is more severe at night. Peripheral microfilaremia is absent in patients with TPE. Most cases of TPE have been reported in long-term residents from Asia. Men 20 to 40 years old most commonly are affected, but TPE has been reported in children.

Laboratory Findings and Diagnosis

The standard for diagnosis is microscopic detection of microfilariae on a thick blood film (Fig. 278.2), but filtration of 1 to 5 mL blood through a 0.3- to 0.5-μm nucleopore filter is a more sensitive method.[13] In most endemic areas, the circulation of microfilariae in peripheral blood is periodic, with highest concentrations occurring at night; blood specimens therefore should be collected between 10 PM and 2 AM. Microfilariae of the three species are distinguished morphologically.

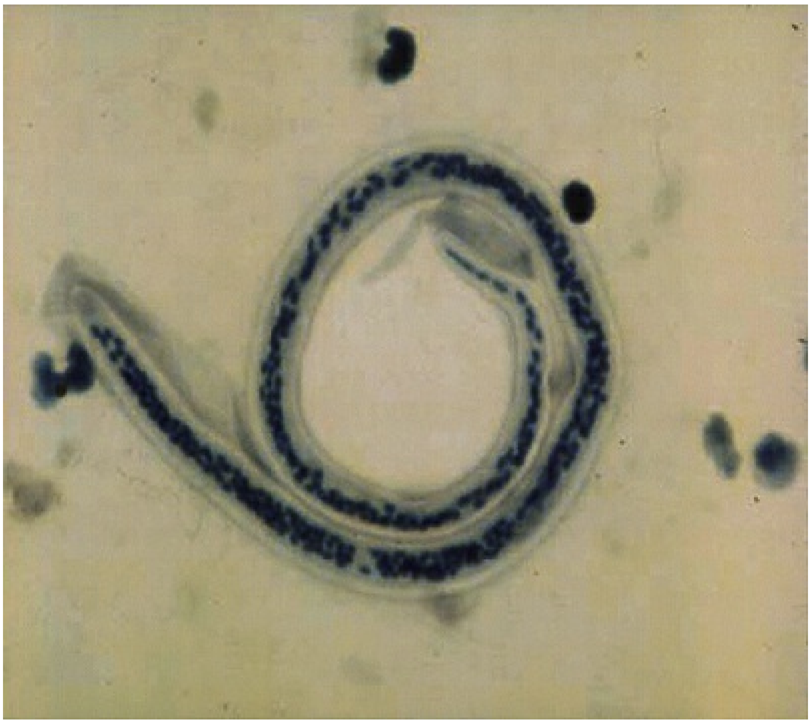

FIGURE 278.2 Microfilaria of *W. bancrofti* on a thick blood film stained with hematoxylin. (Courtesy of Mark L. Eberhard, PhD, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, GA.)

Because infected children are frequently microfilaria negative, other tests may be helpful in making the diagnosis. Assays that detect circulating *W. bancrofti* antigen, primarily from the adult worm, may be used, but they are not approved by the US Food and Drug Administration (Table 278.2).[14] Elevated antifilarial IgG4 levels indicate active infection. Ultrasonography can be used to visualize the adult worms in children.[6,7] In postpubertal boys and men, the living adult worms are detected readily on ultrasonography of the scrotal area.[6,7,15] Polymerase chain reaction (PCR) to detect *W. bancrofti* in blood or histopathological specimens may be available in research laboratories.[16]

TABLE 278.2

Diagnostic Test Results and Treatment for the Major Clinical Manifestations of Lymphatic Filariasis

Clinical Manifestations	Microfilaremia Detectable	Circulating Filarial Antigen	Filaria-Specific IgG4	Visualization of Worms on Ultrasound of Scrotal Area	Recommen Treatment

ACUTE					
Asymptomatic, infected	+	+	+	+	Diethylcarb
Filarial lymphangitis	+/−	+/−	+	+/−	Supportive
Dermatolymphangioadenitis	−/+	−/+	−/+[a]	−/+	Supportive antibiotics[b]
CHRONIC					
Hydrocele	+/−	+/−	+/−[a]	+/−	Surgical rep
Lymphedema and elephantiasis	−/+	−/+	−/+[a]	−/+	Hygiene, sk lymphedem
Chyluria	+/−	+/−	+/−[a]	−/+	Low-fat, hig protein diet
Tropical pulmonary eosinophilia	−	+/−	+	+/−	Diethylcarb

[a] Elevated if blood is positive for microfilaria or circulating filarial antigen.

[b] Treatment with diethylcarbamazine is given if the patient has specific evidence of filarial infection (i.e., microfilaria or circulating filarial antigen detected or living worms detected on ultrasonography).

[c] Treatment with diethylcarbamazine should be delayed until after the acute episode resolves.

Ig, immunoglobulin; +, positive or detectable; −, negative or nondetectable; +/−, likely positive; −/+, likely negative.

Treatment

Diethylcarbamazine (DEC) is the drug of choice for lymphatic filarial infection. DEC is both microfilaricidal and active against the adult worm. A single 6 mg/kg dose is as effective as the previously recommended dose of 6 mg/kg/day for 12 days for killing the adult worm and long-term suppression of microfilariae.[17]

The severity of systemic adverse reactions to DEC, including fever, myalgia, headache, and malaise, is related directly to microfilarial density before treatment. These symptoms develop within the first 2 days and usually are self-limited. Local adverse reactions, including the formation of tender nodules, can occur at the site of the adult worm, especially in the scrotal area. In the United States, DEC is available only through the Drug Service of the Centers for Disease Control and Prevention (during business hours: 404-718-4745; on evenings, weekends, and holidays: 770-488-7100). DEC is not recommended for treatment during pregnancy, although no teratogenic effects of the drug have been reported.

Ivermectin is a potent microfilaricidal drug but does not kill the adult worm. Ivermectin is therefore not recommended for treatment of the individual affected child, although it has an important role in community-based control programs in Africa. Albendazole appears to enhance the microfilarial suppression of DEC and ivermectin.[18] Initial trials of 4 to 8 weeks of doxycycline, a drug that targets the *Wolbachia* endosymbiont, have suggested activity against *W. bancrofti* adult worms and microfilaria, but more research is needed.[19,20]

Most authorities recommend DEC treatment for infected people regardless of whether they have signs and symptoms of lymphatic filariasis. The goal of treatment is to clear the infection. There is little evidence that DEC alters the course of acute adenolymphangitis or results in clinical improvement of longstanding lymphedema, elephantiasis, or hydrocele. There is one report that suggests that DEC and albendazole can reverse lymphatic pathology in children infected with *B. malayi*.[21] Children with TPE should be treated with DEC to prevent progression to chronic interstitial lung disease. Multiple courses (6 to 8 mg/kg/day for 21 days) may be required. If a clinical response and a decline in eosinophilia are not observed, alternative diagnoses should be considered.

There is growing evidence that lymphedema of the leg can be arrested and potentially reversed by measures such as proper hygiene, skin care, and treatment of skin lesions (e.g., using topical antifungal and antibacterial agents); elevation of the leg and exercise; and in advanced cases, prophylactic antibiotics to prevent secondary infection.[22] Surgical repair is effective for hydrocele, but it often is unsatisfactory for elephantiasis.

Special Considerations

Microfilariae have been observed infrequently in umbilical cord blood of infants born to infected mothers. Children born to infected mothers are more likely to have microfilaremia during childhood than children born to uninfected mothers.[23] It is unknown whether this apparent tolerance to infection is associated with higher or lower risk of disease.

Prevention

Recommendations for personal protection for travelers or visitors to endemic areas include use of insect repellent and bednets, wearing of clothing that covers the arms and legs, and avoidance of outdoor exposure between dusk and dawn. Prophylactic use of DEC has not been evaluated adequately.

In 1997, the World Health Organization launched a global effort to eliminate lymphatic filariasis as a public health problem (http://www.filariasis.org).[24] Recommended interventions include periodic mass treatment with DEC or ivermectin (in combination with albendazole), fortification of household salt with DEC, and vector control. Success in some areas has been demonstrated through surveys whose results have indicated that annual mass drug administration can be interrupted.[25]

Onchocerciasis

Key Points

Diagnosis and Management of Onchocerciasis

Pathogen

- Filarial nematode *Onchocerca volvulus*

Epidemiology

- Transmitted through female blackflies (genus *Simulium*), which bite during the day and breed near rapidly flowing rivers and streams
- Found in sub-Saharan Africa, with endemic foci in Yemen, Brazil, and Venezuela

Clinical Presentation

- Symptoms begin after patent infections are established, which may take 18 months.
- Symptoms include highly pruritic and papular dermatitis, subcutaneous nodules called *onchocercomas*, lymphadenitis, and ocular lesions, which can progress to visual loss and blindness.

Diagnosis

- Requires epidemiologic risk assessment plus filarial testing
- Microscopic detection of microfilariae in superficial skin shavings or punch biopsy, adult worms in histologic sections of excised nodules, or characteristic eye lesions
- Determination of serum antifilarial IgG is most useful when microfilariae are not identifiable.

Treatment

- Ivermectin is the treatment of choice; repeated annual or semiannual doses may be required.
- Coinfection with *Loa loa* should be excluded before onchocerciasis treatment with ivermectin.
- Some experts recommend a 6-week course of doxycycline to kill *Wolbachia* organisms, which appear to be required for the survival of *O. volvulus*. This approach may be used as adjunctive therapy for children 8 years or older.
- Diethylcarbamazine (DEC) is contraindicated in onchocerciasis because it has been associated with severe and fatal posttreatment reactions.

Onchocerciasis, a leading cause of blindness worldwide, results from infection with *Onchocerca volvulus.* The infection is transmitted by blackflies of the genus *Simulium,* which breed near flowing water; hence the name *river blindness*. An estimated 37 million people worldwide are infected. The disease is most prevalent in sub-Saharan Africa, and endemic foci are found in Yemen, Brazil, and Venezuela.

In humans, the infective larvae mature in the subcutaneous and deeper connective tissues. Several adult worms of both sexes coil together and form fibrous nodules 1 to 2 cm in diameter, which are most noticeable over bony prominences, including the skull (Fig. 278.3). Adult females can live for 12 to 15 years and produce millions of microfilariae. The microfilariae, which are responsible for the signs and symptoms of onchocerciasis, migrate from the nodule to skin and connective tissues.

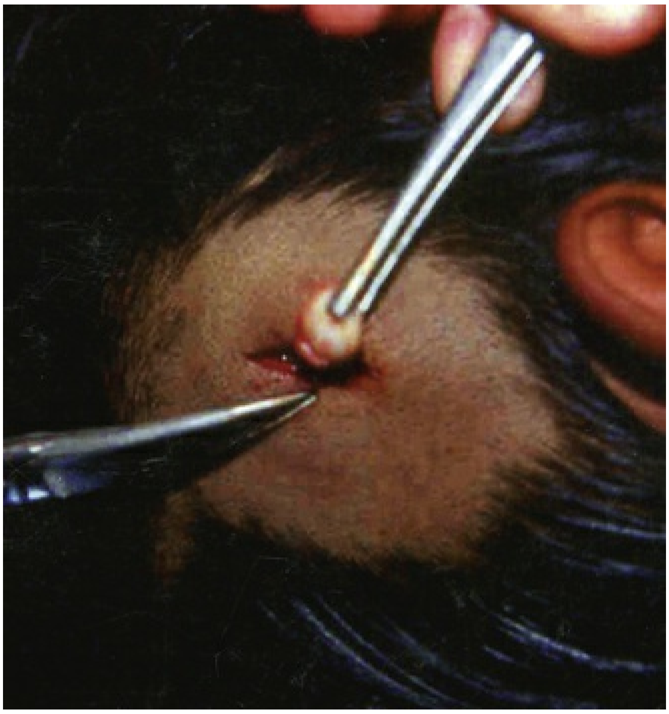

FIGURE 278.3 An onchocercal nodule is removed from the head of a child. (Courtesy of Frank O. Richards MD, The Carter Center, Atlanta, GA.)

Epidemiology

The prevalence of infection increases dramatically during childhood. In hyperendemic areas of West Africa, for example, microfilariae can be detected in the skin of 1% to 2% of children 5 years of age or younger and in approximately 90% of children 15 years of age.[26] Transplacental infection of microfilariae has been documented. Blindness is rare in young children, but impaired vision due to onchocerciasis begins to occur by the second decade of life.

Clinical Manifestations

In addition to subcutaneous nodules, called *onchocercomas*, the major clinical manifestations of onchocerciasis are dermatitis, lymphadenitis, and ocular disease. Inflammation surrounding dead microfilariae in the skin gives rise to pruritus, a common early symptom of onchocerciasis in children. Pruritic dermatitis characterized by epidermal atrophy and loss of pigment can develop in older children with high microfilarial density.

Ocular disease is the most serious complication of *O. volvulus* infection, but it is less common in people with brief exposures or light infections. Inflammation associated with death of microfilariae in the cornea causes punctate keratitis, an early ocular lesion commonly found in infected children. The lesion seems to resolve without intervention. Usually after years of exposure, vision loss and blindness can result from sclerotic keratitis, anterior uveitis, chorioretinopathy, or optic nerve atrophy.

Laboratory Findings and Diagnosis

Demonstration of microfilariae in the skin is the standard for diagnosis, although microfilariae often are not detectable in infected North American travelers returning from endemic areas. Skin snips are obtained with a sclerocorneal biopsy punch or by elevating a small cone (3 mm in diameter) of skin with a needle or straight pin and shaving it off bloodlessly with a scalpel or razor blade. The skin snip is then incubated in saline at room temperature for 30 minutes to 24 hours to allow emergence of the microfilariae, which can be visualized microscopically.[13]

The diagnosis of onchocerciasis also can be made through excision of subcutaneous nodules and identification of the adult worms. Ultrasonography may be helpful in detecting impalpable nodules.[27] Microfilariae in the anterior chamber of the eye are detected readily on slit-lamp examination. The chances of detection are increased if patients are asked to sit with the head between their legs for up to 10 minutes before the examination. Microfilariae also can be observed in the cornea, vitreous, and retrolental space.

As in lymphatic filariasis, measurement of total antifilarial IgG and IgG subclasses can be useful diagnostically, particularly when microfilaria are not identifiable. Determination of serum antifilarial IgG is available at the Parasitic Diseases Laboratory at the National Institutes of Health (phone: 301-496-5398) or at the Centers for Disease Control and Prevention (phone: 404-718-4745). Assays to detect specific antibodies to *Onchocerca* and PCR assays to detect onchocercal DNA in skin snips are available in specialized laboratories.[28,29]

Treatment

Ivermectin is the drug of choice for treatment of onchocerciasis. Ivermectin is available commercially in the United States, but it is not approved for use in children weighing less than 15 kg, pregnant women, and mothers nursing infants during the first week of life.

Ivermectin is given in a single dose of 150 µg/kg on an empty stomach. Microfilarial densities in the skin are reduced by 85% to 95% at 2 months after a single dose; ocular microfilarial densities decline more slowly. Unlike DEC, which formerly was used to treat onchocerciasis, ivermectin causes few adverse ocular reactions. A mild Mazzotti reaction, which is associated with the death of microfilariae and characterized by pruritus, a maculopapular rash, fever, edema, and headache, can occur in 10% to 20% of patients after treatment. DEC is contraindicated in onchocerciasis because it has been associated with severe and fatal posttreatment reactions.

Patients coinfected with onchocerciasis and loiasis can develop encephalopathy when treated with ivermectin, and it is recommended that coinfection with *Loa loa* be excluded before onchocerciasis treatment with ivermectin.[30] Ivermectin improves the pruritus and rash associated with onchocercal dermatitis and seems to reverse early disease in the anterior segment of the eye. However, it appears to be less effective in reversing chronic skin depigmentation or posterior ocular disease.

Although ivermectin interferes with release of microfilariae from the uterus of the adult female, the drug does not kill the adult worm. Repeated single doses of ivermectin are required, usually at 6- to 12-month intervals, particularly for people with ocular disease. All people with a diagnosis of onchocerciasis should undergo slit-lamp examination to assess the extent of ocular involvement. Expert ophthalmologic advice should be sought before treating eye lesions.

Antibiotic trials with doxycycline directed against *Wolbachia,* an endosymbiotic bacteria found in *O. volvulus,* have demonstrated decrease in onchocercal microfilaridermia with 6 weeks of therapy and macrofilaricidal activity when given with a single standard dose of ivermectin. Further trials, including those with shorter lengths of therapy, are needed.[31,32]

Prevention

To reduce exposure to blackflies, travelers should avoid blackfly habitats (i.e., free-flowing rivers and streams) and use insect repellent or wear protective clothing, particularly during the morning and evening, when the insects' biting activity is greatest. Individual prophylactic use of ivermectin has not been evaluated.

Some websites contain additional information about onchocerciasis control in Africa and Latin America: the African Programme for Onchocerciasis Control (APOC), http://www.who.int/apoc/en and the Onchocerciasis Elimination Program of the Americas (OEPA), https://www.cartercenter.org/health/river_blindness/oepa.html.

Loiasis

Key Points

Diagnosis and Management of Loiasis

Pathogen

- Filarial nematode *Loa loa*

Epidemiology

- Transmitted by the bite of the deerfly *(Chrysops)*
- Found in West and Central Africa

Clinical Presentation

- Symptoms vary from asymptomatic infection to life-threatening complications, including encephalopathy, cardiomyopathy, and renal disease.
- Clinical signs and symptoms are different for visitors and infected residents because of different immune responses to the parasite.

Visitors often have Calabar swellings, whereas infected residents report subconjunctival migration of the worm across the eye.

Diagnosis

- Requires epidemiologic risk assessment plus filarial testing
- Microscopic detection of microfilariae in blood smears obtained at midday (10 AM–2 PM) or identification of an adult *L. loa* worm removed from subcutaneous tissue or the conjunctiva of the eye
- Determination of serum antifilarial IgG is most useful when microfilariae are not identifiable.

Treatment

- Diethylcarbamazine (DEC) is the treatment of choice.
- Severe adverse reactions, including encephalopathy, are related to microfilarial density before treatment, and patients may require plasmapheresis to reduce microfilariae before initiation of DEC.
- DEC should not be used in patients with concomitant onchocerciasis because of the risk of severe Mazzotti reactions.
- Ivermectin has been associated with encephalopathy in people with high *L. loa* microfilarial counts who are coinfected with *L. loa* and *O. volvulus*, and it is not recommended for the treatment of loiasis.

Loa loa infection occurs in West and Central Africa and is transmitted by the bite of the deerfly *Chrysops*. The adult worms, which have a lifespan of up to 17 years, wander through the subcutaneous tissues and sometimes beneath the conjunctiva. Microfilariae circulate in the peripheral blood with a diurnal periodicity. Peak microfilarial density occurs around noon.

Epidemiology

Microfilarial prevalence and density increase throughout childhood. Microfilaremia has been reported in a few neonates, but most studies have found no evidence for transplacental transfer of microfilariae or microfilarial antigen. In areas of intense transmission, the prevalence of microfilaremia can reach 35% in adults, but the prevalence of infection probably is higher because 14% to 67% of persons with documented *L. loa* infection have no detectable microfilaremia.

Clinical Manifestations

The clinical manifestations of loiasis vary from asymptomatic infection to life-threatening complications, including encephalopathy, cardiomyopathy, and renal disease. Clinical signs and symptoms are different for visitors to or temporary residents of loiasis-endemic areas and the children born and raised in these areas because of different immune responses to the parasite.[33]

Temporary residents often have no detectable microfilaremia; they are more likely to have Calabar swellings, which are transient (up to several days' duration) pruritic areas of nontender erythematous angioedema that are several centimeters in diameter. These lesions typically occur on the extremities, such as the wrist or knee, and are thought to be associated with migration of the adult worm. In contrast, infected residents of endemic areas frequently have microfilariae in blood and commonly report subconjunctival migration of the worm across the eye, which can be accompanied by intense conjunctivitis and swelling of the eyelid.

Laboratory Findings and Diagnosis

The diagnosis can be confirmed through detection of microfilariae in peripheral blood obtained during the day or by identification of an adult *L. loa* worm removed from subcutaneous tissue or the conjunctiva of the eye. In expatriates, hypereosinophilia (>3000 cells/mm^3) is common, and serum IgE and antifilarial antibody titers are elevated.[34] A PCR test has been described, but it is available only in research settings.[35]

Treatment

Because DEC is active against the microfilariae and adult worms, it is the drug of choice for loiasis (8 to 10 mg/kg/day in 3 divided doses for 21 days), although several courses may be required for successful treatment.[36] Severe adverse reactions, including encephalopathy, are related to microfilarial density before treatment, but reactions also can occur in people with moderate microfilaria levels (>2000 microfilariae per milliliter of blood). Neither a gradual increase in DEC dose nor pretreatment with corticosteroids is completely effective in preventing encephalitis in such patients. Patients should be monitored closely during initiation of treatment and may require hospitalization.

Plasmapheresis has been used to reduce the microfilarial load in people with high numbers of circulating microfilariae before initiation of DEC and corticosteroid therapy. DEC should not be used in patients with concomitant onchocerciasis because of the risk of severe Mazzotti reactions, characterized by an intense pruritic rash, fever, hypotension, and possibly ocular damage (in those with microfilariae in the eyes).

Ivermectin reduces microfilarial density but does not appear to kill the adult worm. Ivermectin has been associated with encephalopathy in people with high *L. loa* microfilarial counts (>30,000 microfilariae/mL) who are coinfected with *L. loa* and *O. volvulus,* and it is not recommended for the treatment of loiasis.[30] Preliminary observations indicate that albendazole may kill the adult stage of the parasite.[37] There is no evidence for *Wolbachia* endosymbiosis with *L. loa.*[38]

Prevention

Personal protection measures are recommended to prevent deerfly bites. A study of Peace Corps volunteers in West Africa suggested that DEC (300 mg once weekly) could be taken prophylactically to reduce the risk of infection.[39]

Other Causes of Filariasis

Mansonella streptocerca.

Mansonella streptocerca is transmitted by midges and is found in West and Central Africa. Adult worms live in the dermis and subcutaneous tissues. Microfilariae are found in the skin and can be diagnosed from skin snips or biopsies. Signs and symptoms include hypopigmented macular lesions over the thorax, pruritic dermatitis, and lymphadenopathy; asymptomatic infection is common.

Treatment with DEC (6 mg/kg/day for 21 days) kills adult worms and microfilariae. Ivermectin is effective against the microfilariae.[40] Both drugs can produce Mazzotti reactions.

Mansonella perstans.

Mansonella perstans is transmitted by midges in sub-Saharan Africa, in Central and South America, and in focal areas of Algeria and Tunisia. The adult worms, which rarely are recovered, live in the peritoneal, pericardial, and pleural cavities and in associated connective tissue; microfilariae appear in the blood. The prevalence of microfilaremia rises with age. Infection has been reported in children as young as 2 years.

Most people with microfilaremia are asymptomatic, but a variety of symptoms have been associated with infection, including arthralgias, pruritus, conjunctival granulomas, periorbital edema, angioedema similar to Calabar swellings, and rarely, pericarditis. The diagnosis is made through detection of microfilariae in the blood. Eosinophilia and coinfection with *L. loa, W. bancrofti,* or *O. volvulus* are common findings.

Although chronic sequelae are poorly defined, treatment is recommended. Mebendazole (adult dose: 100 mg twice daily for 14 to 21 days), alone or in combination with DEC, appears to be more effective than DEC alone in clearing *M. perstans* microfilaremia.[41] Albendazole may be of value when given at a dose of 400 mg twice daily for at least 1 month. A trial demonstrated that doxycycline (200 mg daily for 6 weeks) is effective.[42] Repeated courses of DEC (6 mg/kg/day for 14 to 21 days) may not be effective, and ivermectin has not proved effective. Adverse reactions are similar to those associated with treatment of other filarial infections and are related to microfilarial levels. There is evidence for *Wolbachia* endosymbiosis in at least some isolates of *M. perstans.*[43]

Mansonella ozzardi.

Mansonella ozzardi is transmitted by midges and blackflies in the Caribbean and Central and South America. Adult *M. ozzardi* live in serous cavities, particularly the thoracic and peritoneal cavities, and in connective and subcutaneous tissues. Most infected people are asymptomatic, although infection has been associated with arthralgia, pruritus, adenopathy, keratitis, and vague constitutional symptoms. Eosinophilia is a common finding.

Little is known about the epidemiology of *M. ozzardi* infection in children. Diagnosis is made through detection of microfilariae in blood or skin snips. A single 150-μg/kg dose of ivermectin reduces microfilaremia.[44] Treatment with DEC or albendazole is ineffective.

Dirofilariasis

Pulmonary dirofilariasis in adult humans is caused by infection with *Dirofilaria immitis,* the agent of canine heartworm disease. The parasite is transmitted by mosquitoes. In humans, the worms migrate to the right ventricle of the heart, enter the pulmonary arteries, are carried to the periphery of the lung, and degenerate or calcify, causing solitary pulmonary nodules that classically appear as *coin lesions* on chest radiographs. They are unable to complete maturation in the human host.

Although most affected people are asymptomatic, some experience cough, hemoptysis, or chest pain. Eosinophilia occurs in less than 15% of cases. Microfilaremia has not been observed in humans. The diagnosis is made by biopsy of the lung lesion and histologic examination. Although serologic tests are available, their sensitivity and specificity are not adequate for the diagnosis of human dirofilariasis. Antifilarial treatment is not necessary.

Subcutaneous dirofilariasis is caused by infection with *Dirofilaria tenuis,* which lives in the subcutaneous tissues of the raccoon, and *Dirofilaria repens,* which lives in the subcutaneous tissues of dogs and cats. In humans, the adult worms cause subcutaneous granulomas in the conjunctiva, eyelid, oral mucosa, extremities, scrotum, breast, and other tissues. These nodules can be tender, painful, and erythematous. Microfilaremia does not occur. The lesions can be excised surgically to confirm the diagnosis.

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Cestodes

OUTLINE

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Diphyllobothrium, Dipylidium, and *Hymenolepis* Species

Susan P. Montgomery, Frank O. Richards Jr.

Diphyllobothrium Species

Description of the Pathogen.

Pseudophyllidean cestodes of the genus *Diphyllobothrium* can cause intestinal tapeworm infections in humans. Among more than 50 species of *Diphyllobothrium*, 14 are known to infect humans. Adult tapeworms develop in mammals or birds, and infection usually is contracted by eating raw or undercooked fish. First-stage larvae are found in crustaceans, and second-stage larvae develop in fish, although for some *Diphyllobothrium* species, the second intermediate host is unknown.

Diphyllobothrium latum (also known as fish or broad tapeworm) is the best-known species infecting humans. Other primarily zoonotic tapeworms that can cause human infection include *D. nihonkaiense, D. dendriticum, D. cordatum, D. dalliae, D. lanceolatum, D. pacificum,* and *D. ursi*.[1,2] However, only *D. latum* has the ability to compete with its host for vitamin B_{12} and place the patient at risk for megaloblastic anemia.

The *Diphyllobothrium* adult-stage tapeworm attaches to the small intestinal mucosa with two sucking grooves (i.e., bothria) located on the ventral and dorsal surfaces of the scolex (i.e., head). The body (i.e., strobila) of the tapeworm can reach up to the amazing length of 12 m. The strobila is composed of thousands of proglottid segments, which break off the distal end of the worm and are passed singly or in chains during defecation. Each proglottid contains thousands of eggs, some of which can be released into feces during passage through the intestinal tract. Feces must be deposited promptly into fresh or salt water for an egg to hatch and release a free-swimming embryo (i.e., coracidium).

The coracidium is ingested by copepods (including *Cyclops* and *Diaptomus* species), enters the body cavity and develops into the first-stage larva (i.e., procercoid). If the copepod is ingested by plankton-eating fish, the second-stage plerocercoid larva develops in the muscles. The size and shape of this larva can help to identify the infecting species of *Diphyllobothrium.* Depending on the parasite species, freshwater, anadromous, or marine fish are the second intermediate hosts. The second intermediate hosts for *D. latum* are freshwater fish such as trout, pike, turbot, and perch; *D. nihonkaiense* is found in salmon species in the Pacific Ocean; *D. pacificum* is found in marine fish from the Pacific coast of South America, and larvae of *D. dendriticum* have been reported in Atlantic salmon and whitefish.

The plerocercoid develops into the adult intestinal tapeworm after the infected fish is ingested by an appropriate mammalian or avian host, which for *D. latum* includes humans, dogs, cats, foxes, bears, and pigs. *D. nihonkaiense* is found in the brown bear and humans, and *D. pacificum* is found in sea lions, seals, and occasionally in humans. *D. dendriticum* can use seagulls and mammals as its definitive host.[1,2]

Epidemiology.

Diphyllobothriasis occurs worldwide and is primarily an infection of older children and adults, although infection of a 2-year old child with *D. nihonkaiense* has been reported.[3] Infection is most prevalent in populations whose culinary habits result in consumption of raw or undercooked fish flesh, liver, or roe.

Development of molecular tools to identify the species of *Diphyllobothrium* causing human infections provided insights into the epidemiology of this disease. In the past, most infections were attributed to *D. latum,* but later information implicated other species based on species-specific second host preferences and geographic distribution as defined by polymerase chain reaction (PCR) studies.[1,2,4,5] *D. latum* infections are most prevalent in the temperate and subarctic zones of Eurasia, particularly Finland, Sweden, and Lithuania. *D. latum* and other *Diphyllobothrium* species occur in other populations of Europe (especially northern Italy, Romania, the lower Volga, and the Baltic nations), in Eskimos in Alaska and Canada, and in Latin America.

Cases of *D. pacificum* infection have been reported in Peru, Chile, and Argentina.[1] *D. dendriticum* is found in regions farther north than *D. latum*; most infections in polar regions are likely caused by this species. Most human infections in Asia (Japan, Siberia, and Manchuria) are caused by *D. nihonkaiense*.[1] In the United States, infected salmon was implicated in 82% of 52 cases on the West Coast[6]; these infections were most likely associated with *D. nihonkaiense* given the preference for that species to parasitize Pacific salmon.[7] Fish from the Great Lakes region also have been implicated, although cases of diphyllobothriasis have been less frequently reported from this focus in recent years.[2]

Because "fresh" fish are shipped nationally and internationally, the risk associated with consuming certain fish dishes (e.g., sushi, ceviche, lightly pickled fish, smoked fish, gefilte fish) is widespread, and human infections may be associated with nonnative species of *Diphyllobothrium*.[8–10] *Diphyllobothrium* spp. can be introduced into new regions as a result of aquaculture; one example is the possible introduction of *D. latum* to lakes in South America by means of plerocercoid infection in food fish species.[11]

Clinical Manifestations.

Few pathologic changes are observed in the intestinal mucosa of animals with diphyllobothriasis, and most infected people are asymptomatic. In a study in eastern Finland, 37% of the 295 tapeworm carriers had symptoms (vs. 8% of 832 controls) that included diarrhea, fatigue, change in appetite, and paresthesias; younger persons were less likely to have symptoms.[1] Abdominal pain, nausea, and diarrhea occurred in 2 of 4 cases of diphyllobothriasis in a US outbreak associated with salmon sushi.[12]

Parts of the strobila can be passed in stool or vomitus, but proglottids are not very motile and do not spontaneously exit the anus, as can proglottids of the beef tapeworm *Taenia saginata.* Intestinal obstruction can occur when multiple worms are present. Megaloblastic anemia resulting from vitamin B_{12} deficiency is reported to occur in up to 2% of *D. latum*–infected Scandinavian adults. Pallor, fatigue, glossitis, decreased vibration sense, paresthesia, and central scotoma have been described as clinical features in these patients.[13]

Laboratory Findings and Diagnosis.

Mild eosinophilia of 5% to 15% can occur. Intestinal diphyllobothriasis is diagnosed by finding typical eggs in feces 5 or more weeks after ingestion of infected fish. Because egg discharge is periodic in intestinal diphyllobothriasis, the diagnosis can be missed by examining a single stool sample. Eggs are light yellow, operculated, and ovoid, with dimensions ranging from 40 to 80 μm. The microscopist may confuse *Diphyllobothrium* eggs with other operculated eggs produced by flukes of the several genera, including *Clonorchis, Fasciola, Nanophyetus,* and *Paragonimus*.

The proglottids have a fleshy consistency and are ivory in color (sometimes with central darkening). They are wider (12 mm) than they are long (4 mm). The appearance of these broad proglottids suggests the diagnosis of diphyllobothriasis, but a species diagnosis is difficult, even when the proglottids and scolex are recovered and submitted to experts for examination. Although megaloblastic anemia is rare, up to 50% of tapeworm carriers in Finland have reduced serum vitamin B_{12} levels.[13]

Treatment.

For intestinal infections, single-dose therapy with praziquantel (5 to 10 mg/kg) is highly efficacious (i.e., 85% to 95% cure rate); purgatives are not necessary. Niclosamide also is effective as a single dose, but it is no longer available in the United States. Stool examinations to evaluate for cure may be performed 6 or more weeks after therapy. Cobalamin injections and oral folic acid are indicated for patients with clinical or laboratory evidence of vitamin B_{12} deficiency.

Prevention.

Preventing *Diphyllobothrium* infection in humans depends on altering food handling and eating habits because regulations for proper disposal of human feces alone have no impact on contamination of water supplies with eggs from animal sources. Cooking fish to an internal temperature of at least 63°C is recommended. Freezing at −35°C or below and storing at −20°C for 24 hours kills plerocercoids and renders the meat safe for consumption. Canned fish is safe, but smoked fish is safe only if the fish was frozen appropriately before smoking to kill any parasites.[14] Although diphyllobothriasis is not transmitted from person to person, more than one family member can be infected by sharing common meals and having similar eating habits.

Dipylidium caninum

Description of the Pathogen.

Dipylidium caninum (dog tapeworm or double-pored tapeworm) is a common intestinal cestode of domestic dogs and cats that can infect children who ingest fleas. The scolex of the adult worm has four suckers and is armed with up to seven rows of hooklets. The 15- to 70-cm tapeworm chain (i.e., strobila) consists of about 150 proglottids. The proglottids, which are highly motile, are passed whole in feces and easily observed in stool; they later disintegrate in soil to release their eggs. The eggs develop into cysticercoid larvae only if they are consumed by the larval stage fleas. The life cycle is completed when an infected flea is ingested by a dog or cat during its grooming activities.[15]

Epidemiology.

Young children can become infected if they swallow fleas while playing with their pets or when crawling in flea-infested areas. From 1973 to 1977, a period when the Centers for Disease Control and Prevention (CDC) was the only source of the drug niclosamide in the United States, about 8 cases were reported per year.[16] The introduction of effective flea control and prevention and certain monthly deworming treatments for dogs and cats probably helped to reduce the prevalence of *D. caninum* infection in some areas.[17]

Clinical Manifestations.

Parents usually find proglottids as multiple, motile, white objects resembling rice or seeds (often described as cucumber, melon, or pumpkin seeds) in stool or diapers or on the perineum (Fig. 279.1A).[18] The child usually is asymptomatic, although anogenital pruritus, rash, irritability, diarrhea, and abdominal pain have been described. Older children can complain of spontaneously passing proglottids per anus. A history of dog or cat pets, fleas, and flea bites are important clues to the diagnosis.

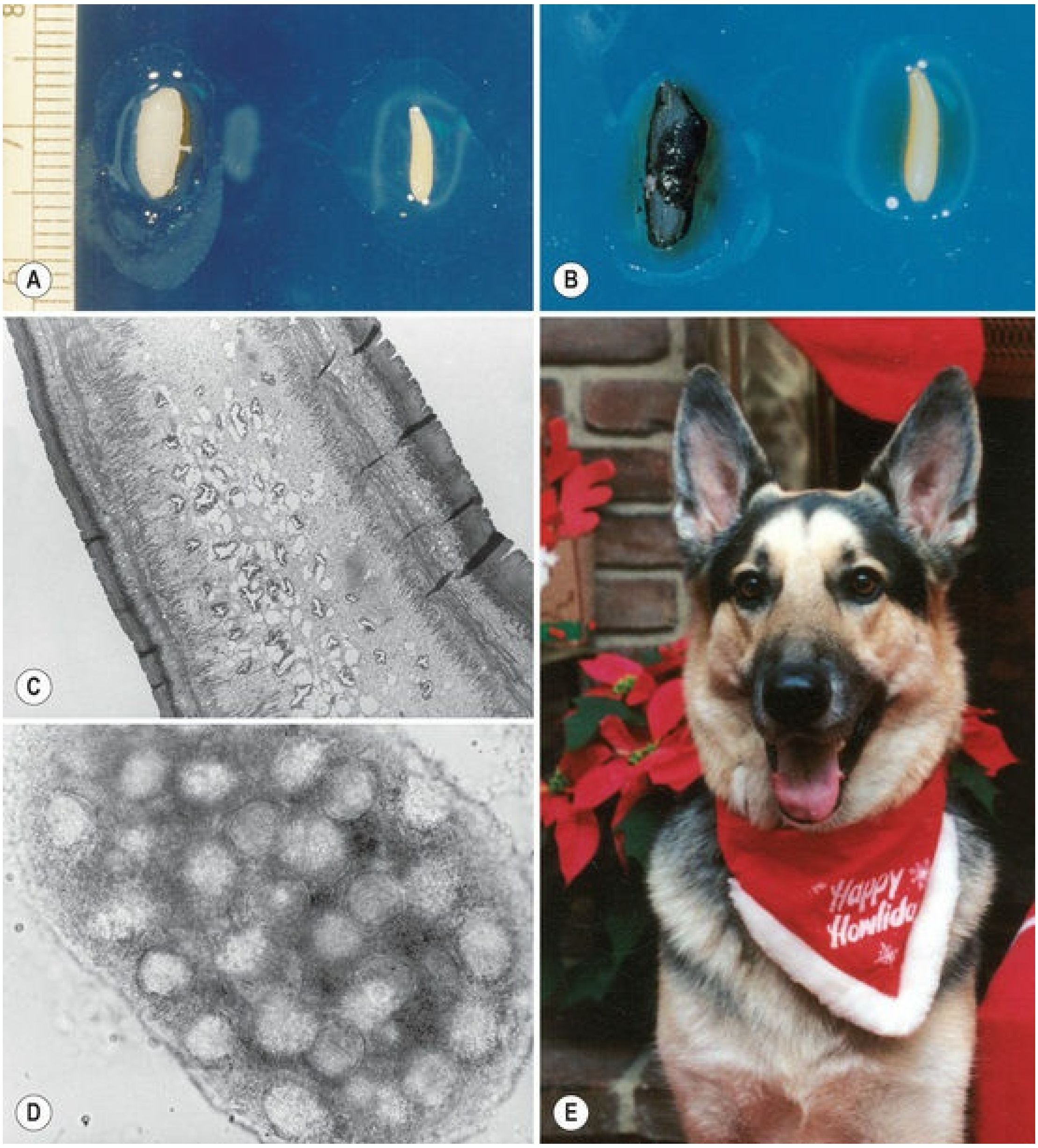

FIGURE 279.1 A 20-month-old girl was seen in consultation because of “moving rice” in the stool on the diaper. The *Dipylidium caninum* body consists of

proglottid segments, which contain the tapeworm's microscopic eggs. The motile, white proglottids resemble rice grains and are easily observed in stool. (A) A grain of rice from the hospital cafeteria *(left)* is compared with the patient's “rice” *(right).* (B) A drop of iodine shows the typical carbohydrate blackening of rice *(left)*. Compare with a 7-mm-long, vase-shaped proglottid from the patient *(right)*. (C) Histologic section shows the typical structure of a *Dipylidium caninum* proglottid. (D) A typical egg packet of *Dipylidium caninum* was isolated from the patient's stool specimen. (E) The veterinarian of the family dog did not confirm that his patient had parasites or fleas.

(Courtesy of Joel E. Mortensen, PhD, and Sarah S. Long, MD, St. Christopher's Hospital for Children, Philadelphia, PA.)

Laboratory Findings and Diagnosis.

The differential diagnosis includes enterobiasis (i.e., pinworm) and intestinal myiasis (fly larvae). Parents should be advised to place the proglottids in rubbing alcohol to preserve their differential characteristics for diagnosis. Grossly, a gravid *D. caninum* proglottid measures 3 to 4 mm wide and 10 to 12 mm long. It is narrowed at both ends and has two lateral indentations (indicating pores) at its longitudinal midpoint (see Fig. 279.1B). Microscopic stool examinations usually are negative because few eggs are released from proglottids into the fecal stream. However, characteristic egg packets (i.e., loose membrane usually containing 8 to 63 eggs and measuring 120 to 200 μm long) can be identified in stool or on perianal adhesive tape (paddle) preparations (see Fig. 279.1D).[15,18]

Treatment.

Single-dose therapy with praziquantel (5 to 10 mg/kg) is the recommended therapy. Praziquantel is not approved for the treatment of children younger than 4 years of age, but it has been used successfully to treat cases of *D. caninum* infection in children as young as 6 months.[18–20] Niclosamide is effective but is not available in the United States.

No purge or follow-up stool examination is indicated, but the appearance of proglottids after therapy is indication for retreatment. The infection is self-limited in the human host and typically clears spontaneously by 6 weeks.

Prevention.

Periodic deworming of pets controls this and other canine and feline helminthic infections of pediatric concern, including *Toxocara* species and dog and cat hookworm. Flea control also is important. Examination of asymptomatic family members rarely is indicated.

Hymenolepis nana and *Hymenolepis diminuta*

Description of the Pathogen.

Human hymenolepiasis is caused by *Hymenolepis nana* (i.e., dwarf tapeworm) or rarely by *Hymenolepis diminuta* (rodent tapeworm). The complex life cycles of these cestodes consist of adult (tapeworm) stages in the small bowel of humans and rodents, and larval (cysticercoid) tissue stages in insects. The cysticercoid stages of *H. nana* also can invade and develop in the human intestine; as a result, *H. nana* can complete its entire life cycle in the human host and, through autoinfection, increase its numbers without having to pass through the insect host. Animal studies demonstrate that T-lymphocyte–mediated immunity is important in preventing hyperinfection by these parasites.[21,22]

H. nana usually is acquired by ingestion of eggs, the hexacanth embryos of which invade the villi of the small intestine. Within 4 to 6 days, the embryo develops into a cysticercoid larva that re-enters the lumen, evaginates to become the scolex of the tapeworm, and attaches to the mucosal wall. Morphologically, the scolex has four suckers and numerous hooklets. A strobila measuring 0.5 to 4.5 cm long and 1 mm wide develops behind the scolex in about 2 weeks. The strobila consists of proglottid segments that periodically break off and rapidly degenerate to release their eggs into the fecal stream.

Unlike all other tapeworms that infect humans, *H. nana* eggs are infectious immediately when passed. In addition to being a risk to others, infected people may reingest their own eggs by fecal-hand-mouth transfer (i.e., external autoinfection), or eggs may hatch in the intestine, reinvade, and develop into new worms (i.e., internal autoinfection). A variety of insects that consume feces support development of *H. nana* cysticercoids in their body cavities. Ingestion of these insects by humans or rodents is another route of infection.

The *H. diminuta* tapeworm is much larger than *H. nana* and measures 10 to 60 cm long and 2 to 4 mm wide. Completion of the life cycle of *H. diminuta* depends on development of the cysticercoid stage in the body cavities of insects that ingest eggs they find in rodent feces; autoinfection does not occur. Most commonly minute flour, grain, or dung beetles, fleas, and cockroaches serve as intermediate hosts. Rodents and rarely humans acquire the intestinal stage by consuming uncooked corn, flour, cereal, grains, and dried fruit contaminated with infected insects.

Epidemiology.

H. nana is the most common cestode infecting children, with a prevalence ranging from 0.1% to 50%. The highest rates occur among school-aged children in hot, arid areas of the developing world.[21] Changes in hygienic habits and immunity make *H. nana* infections less common in adults. *H. nana* infections usually are transmitted through fecal-oral contact. In 1987, diagnostic laboratories in the United States found *H. nana* eggs in 0.4% of 216,000 stool specimens[23]; however, infection rates in orphanages and institutions were as much as 10 times higher.[24]

Undefined host factors are important. In a 22-month longitudinal study in Pakistan, one third of children with similar exposure risks were never infected, one third were infected intermittently, and one third were always infected.[25] *H. diminuta* infections tend to occur in conditions in which rodents and insects have access to grain stores.

Clinical Manifestations.

The intensity of infection (i.e., worm burden) is the major determinant of symptoms. Patients whose egg density in stool is greater than 15,000/g invariably have abdominal cramps, diarrhea, and irritability.[26] In light infections, patients are asymptomatic. Based on uncontrolled studies, some investigators have suggested that *H. nana* toxins can cause seizures or conjunctivitis. *H. diminuta* infections usually are asymptomatic.[21]

Laboratory Findings and Diagnosis.

Mild to moderate eosinophilia is an inconsistent finding, and serologic tests are not available. The diagnosis most often is made by finding characteristic eggs in stool. The *H. nana* egg is oval, is 37 to 47 µm in diameter, and has a double-layered shell that encloses characteristic filaments arising from bipolar thickenings. The enclosed embryo contains 6 hooklets. *H. diminuta* eggs are larger and rounder (60 to 85 µm in diameter) and have no polar filaments.

Fecal concentration techniques that examine larger amounts of stool are preferred to direct fecal smears. *H. nana* eggs can disintegrate if the specimen is not examined promptly or preserved in formalin. Three stool examinations performed on alternate days are necessary to exclude a suspected infection. The proglottids disintegrate rapidly during their intestinal transit and usually are not observed in feces.

Treatment.

A single dose of praziquantel (25 mg/kg) cures 95% to 100% of *H. nana* and *H. diminuta* infections and is the preferred treatment.[21,27] Niclosamide, which is not available in the United States, is not effective as a single dose and must be given daily for several days.[16] Repeat stool examinations are recommended 4 weeks after therapy to document cure. Light burden infections have been successfully treated with nitazoxanide.[27,28]

Special Considerations.

Family members of patients infected with *H. nana*, particularly siblings, should have stools examined. Simultaneous chemotherapy for people in institutions and for family members may be indicated in some circumstances. Up to 11% of Cambodian refugee children have had *H. nana* infections.[29] Few examples of *H. nana* dissemination in immunosuppressed humans have been reported, but disseminated disease has not been reported in people infected with human immunodeficiency virus (HIV) who live in *H. nana*-endemic areas.[21,30,31]

Prevention.

Transmission of *H. nana* can be controlled by measures that decrease fecal-oral contact, particularly hand hygiene after defecation and diaper changing. Hand hygiene after handling pet rodents is advised. Infected food handlers should be treated and cure verified by repeat stool examinations. Rodent and insect control are important, and corn, grain, flour, cereal, and dried fruit stores should be sealed.

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Taenia solium, *Taenia asiatica*, and *Taenia saginata*

Taeniasis and Cysticercosis

Natalie J.M. Dailey Garnes, A. Clinton White Jr., Jose A. Serpa

Clinical syndromes associated with infection with *Taenia* species tapeworms include intestinal disease caused by adult parasites (i.e., taeniasis) and single or multiorgan inflammatory conditions associated with larval stages within tissue (i.e., cysticercosis and coenurosis).[1–3] Distinguishing morphologic features of adult tapeworms include an anterior scolex and a series of segments (i.e., proglottids) that develop at the base of the scolex and extend distally as the worm grows (Fig. 280.1).

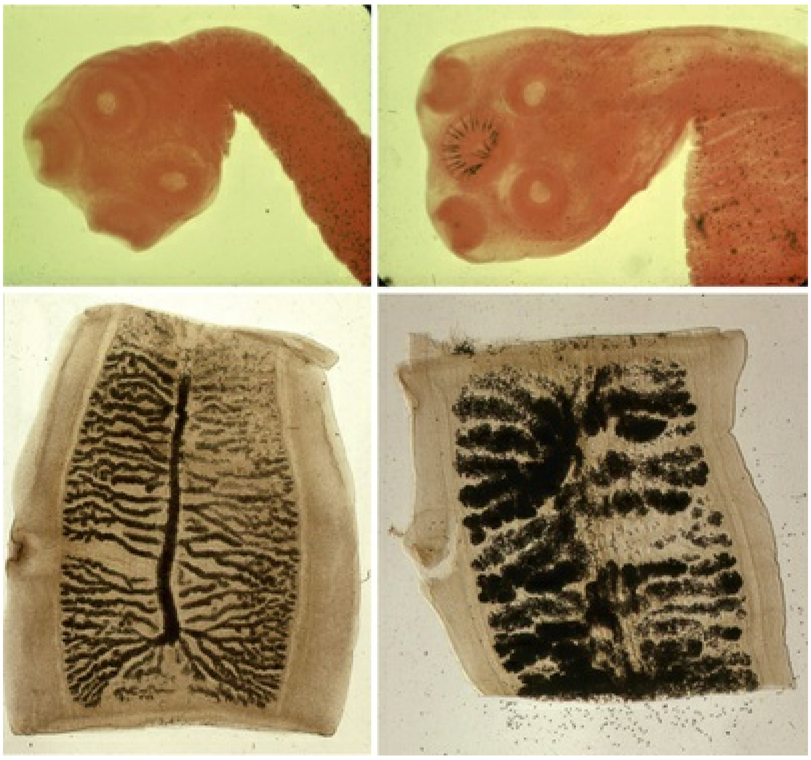

FIGURE 280.1 Scolices *(top)* and proglottids *(bottom)* from the tapeworms *Taenia saginata (left)* and *T. solium (right)*. The proglottids are excreted in the feces of infected people. (From U.S. Centers for Disease Control and Prevention. DPDx: Laboratory Identification of Parasitic Diseases of Public Health Concern. Last updated December 2016. https://www.cdc.gov/dpdx/.)

Like most cestodes, *Taenia saginata, Taenia asiatica,* and *Taenia solium* require an intermediate host to complete their life cycle and infect humans, who are the definitive hosts. In contrast, humans are accidental intermediate hosts for *Taenia multiceps* and *Taenia serialis,* the agents of coenurosis (see Chapter 282), and the tissue form of *T. solium* (i.e., cysticercosis).

Taeniasis

Key Points

Diagnosis and Management of Taeniasis

Parasitology

- Causative organisms include *Taenia saginata, Taenia solium,* and *Taenia asiatica.*

- Cattle and pigs are intermediate hosts; humans are the definitive hosts.
- Eggs passed in human stool must be ingested by intermediate hosts for completion of life cycle.

Epidemiology

- Infestation occurs after eating undercooked beef or pork containing cysticerci.
- Endemic in most areas around the world with poor sanitation and close contact between human feces and intermediate hosts

Diagnosis

- Recovery of eggs or proglottids in stool
- Species distinction cannot be made by evaluation of eggs.
- Injection of proglottids with India ink allows species differentiation by the number of uterine segments.
- Coproantigen detection by fecal enzyme immunoassay is available.

Treatment

- All children with intestinal tapeworm should be treated.
- Single-dose praziquantel (5–10 mg/kg) is the treatment of choice.
- Alternate agents include niclosamide (not available in the United States) and nitazoxanide.
- Albendazole is *not* recommended.

Epidemiology and Life Cycle

Taeniasis refers to intestinal infection with the human tapeworms *T. saginata, T. asiatica,* or *T. solium* (i.e., class Cestoidea in the phylum Platyhelminthes).[1] *T. saginata,* the beef tapeworm, is endemic in Africa, Eastern Europe, Latin America, the Middle East, and much of Asia. The prevalence in endemic areas where cattle raising is common can exceed 90%.[4] *T. solium,* the pork tapeworm, also has a worldwide geographic distribution, occurring in rural communities where raising pigs is a common practice.[5] Highly endemic areas include Latin America, sub-Saharan Africa, India, and Southeast Asia. The recently identified tapeworm *Taenia asiatica,* closely related to *T. saginata,* also is endemic in much of Asia.[6–9] Although the clinical presentation and adult worm morphology are similar to those of *T. saginata,* the intermediate host of *T. asiatica* is the pig. Although local transmission of *T. solium* has been described in the United States, most cases involve infection with the larval stages (i.e., cysticercosis) and not intestinal taeniasis.[10–14]

Infection with *T. saginata* is acquired by eating undercooked beef that contains cysticerci, which are larval forms of the parasite (Fig. 280.2). On entering the small intestine, the larvae excyst and attach to the mucosal surface using four suckers on the anterior scolex. Proglottids form at the base of the scolex and enlarge as they extend distally, a process referred to as *strobilization*. The segments pass through the large intestine and are excreted in the feces or actively exit the host by independent motility. Adult *T. saginata* tapeworms, which can grow to a length of 10 m, can survive within the intestine of an infected person for up to 25 years, shedding 6 to 10 proglottids daily, each of which contains up to 80,000 eggs.

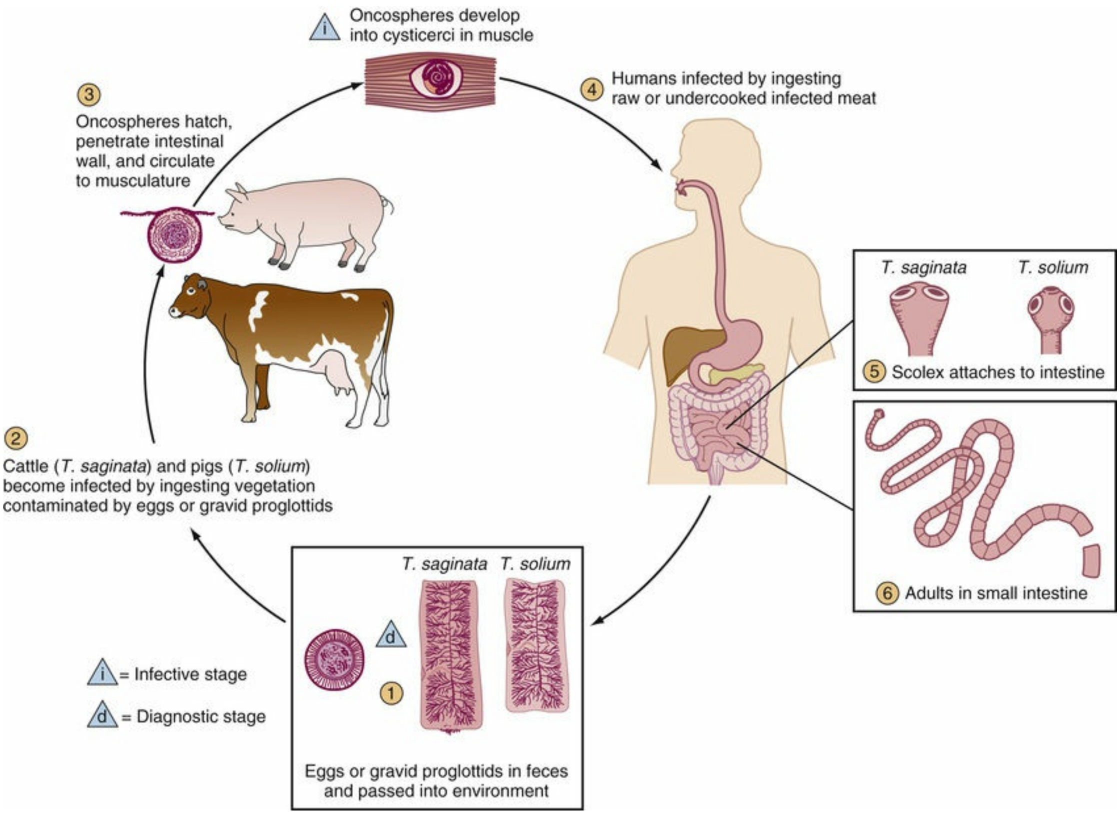
Oncospheres develop into cysticerci in muscle
i
3
Oncospheres hatch, penetrate intestinal wall, and circulate to musculature
4
Humans infected by ingesting raw or undercooked infected meat
T. saginata
T. solium
5
Scolex attaches to intestine
6
Adults in small intestine
2
Cattle (T. saginata) and pigs (T. solium) become infected by ingesting vegetation contaminated by eggs or gravid proglottids
T. saginata
T. solium
d
1
i = Infective stage
d = Diagnostic stage
Eggs or gravid proglottids in feces and passed into environment

FIGURE 280.2 Life cycles of *Taenia solium* and *T. saginata.* (Modified from the U.S. Centers for Disease Control and Prevention. Parasites: Taeniasis. Last updated January 2013. https://www.cdc.gov/parasites/taeniasis/.)

The incubation period from the time of infection to the passage of *T. saginata* segments is approximately 10 weeks. After the intermediate bovine host ingests eggs or proglottids, emerging embryos invade the intestinal mucosa and disseminate through the bloodstream to subcutaneous tissues, where they form cysticerci. The life cycle resumes when the definitive human host ingests undercooked beef containing larval cysts. Unlike *T. solium,* ingested *T. saginata* eggs do not form cysticerci in humans.

Intestinal infection with *T. solium* and *T. asiatica* follows ingestion of undercooked pork containing cysticerci (see Fig. 280.2). After degradation of the cyst wall, the scolex attaches to the duodenal mucosa and develops into an adult in 6 to 8 weeks. Pigs, the intermediate host, ingest eggs contained in human waste. The eggs hatch in the stomach and release embryos that penetrate the pig's intestinal wall, and larval stages migrate through the bloodstream to muscle, subcutaneous tissues, or other organs. Humans complete the *T. solium* and *T. asiatica* life cycles by eating pork meat (*T. solium*) or viscera (*T. asiatica*) containing viable cysticerci.

Clinical Manifestations

Most people with *T. saginata* or *T. asiatica* infection are asymptomatic, but they become aware of tapeworm segments passing in feces.[4,15] The proglottids of *T. saginata* often are actively motile and people may notice them moving. Mild intermittent gastrointestinal symptoms such as nausea and epigastric pain have been reported, as have vomiting, diarrhea, and intestinal obstruction. Migration of proglottids down the thigh can be associated with pruritus.[4] Rarely, proglottid segments are vomited or migrate aberrantly, ultimately leading to appendicitis, cholecystitis, or colonic perforation.[16–18]

People harboring intestinal *T. solium* frequently are asymptomatic, becoming aware of tapeworm infection only on fecal passage of proglottids. The *T. solium* proglottid segments are less motile than those of *T. saginata,* and migration onto the perianal skin is commonly not noticed. Anal pruritus and urticaria have been described with heavy infections, which are sometimes associated with serum eosinophilia. Intestinal symptoms include nausea, abdominal pain, change in appetite, and diarrhea. However, frequent coinfection with other intestinal pathogens makes it difficult to ascribe these symptoms exclusively to taeniasis.

Laboratory Findings and Diagnostic Tests

A definitive diagnosis of intestinal taeniasis requires identification of proglottids or ova excreted from an infected person. To distinguish *T. saginata* or *T. asiatica* from *T. solium,* proglottids can be pressed gently between glass slides and injected with India ink through the lateral pore to visualize the uterine branches under light microscopy (see Fig. 280.1). *T. saginata* has 15 or more primary uterine branches on each side of the central core, and *T. solium* usually has less than 13 per side. Unlike *T. saginata* and *T. asiatica,* the scolex of *T. solium* possesses two rows of rostellar hooks, which it uses along with four suckers to attach to the mucosa of the small intestine.

Because patients infected with adult *T. solium* are at additional risk for cysticercosis due to autoinfection, attempts should be made to discriminate between *T. saginata* or *T. asiatica* and *T. solium* infection.[19,20] *Taenia* eggs, which rarely are present in fecal samples, cannot be distinguished based on morphology. Laboratory tests may reveal mild peripheral blood eosinophilia.

Coproantigen detection of *Taenia*-specific antigens by fecal enzyme immunoassay (EIA) is more sensitive than standard microscopy for detecting infection.[1,21–23] Immunodiagnostic and polymerase chain reaction (PCR)–based tests can detect *Taenia* antigens or DNA in feces and distinguish between the major species.[24–29] These assays have been used primarily in research settings, and their role in the routine diagnosis of tapeworm infections has not been established. Serodiagnostic testing for *Taenia* infection is used primarily for diagnosing cysticercosis, particularly involving the central nervous system (CNS). Serologic tests that are specific for the *T. solium* tapeworm carriers also have been developed but are not available widely.[3,30,31]

Treatment

Anthelmintic drug therapy is recommended for all children found to harbor an intestinal tapeworm. Praziquantel, administered orally in a single dose (5 to 10 mg/kg), is the drug of choice for taeniasis.[32,33] In children with *T. solium* infection, even modest doses of praziquantel occasionally can trigger the destruction of occult CNS cysts, particularly those in the brain parenchyma, perhaps leading to seizures.[34] Albendazole, although effective for treating cysticercosis, is not recommended routinely for the treatment of intestinal tapeworm infection.[35] Niclosamide (not marketed in the United States) and nitazoxanide can be used as alternatives.[36,37]

Effective treatment can be associated with passage of intact or disintegrating proglottids for days. However, purgatives (e.g., polyethylene glycol) can hasten the process and help identify passage of the scolex (as a test of cure). If the scolex is not identified, a second stool examination should be performed approximately 3 months after anthelmintic therapy, allowing time for regeneration of proglottids from the scolex. Because reinfection is common in endemic areas, repeated courses of therapy may be necessary for long-term control.

Special Considerations

Treatment of pregnant women with taeniasis can be complicated. The newborn infant could be exposed to infected stool if treatment is deferred until after delivery. Data on the safety of praziquantel in the setting of pregnancy are insufficient. One study chose to use niclosamide, which is not absorbed, as an alternative.[38]

Prevention and Control

Thorough cooking of meat is a key measure for the prevention of infection with *Taenia*. Transmission of taeniasis can be reduced by improving sanitation and husbandry practices, along with strict inspection of pork or beef before sale or consumption.[2,39,40] Unfortunately, in many resource-poor countries, these practices are not economically feasible. Public health measures such as sanitary disposal of human feces and restriction of cattle and pigs from land contaminated by human feces may also prevent transmission. Freezing meat at −20°C kills cysticerci but often is not practical in endemic areas.

No vaccine for human *T. saginata* infection exists. Protection of calves from challenge infection has been achieved after immunization with an oncospheral adhesion protein.[41]

Mass chemotherapy programs targeting communities where *T. solium* is highly endemic may reduce transmission from humans to pigs, thereby interrupting the natural life cycle of *T. solium*.[5,42] One intervention study demonstrated that the prevalence of human taeniasis was reduced from 4% to 1% within 10 months after treatment with niclosamide, and the seroprevalence of *T. solium* infection among pigs was reduced from 55% to 7%.[43] These strategies will likely have long-term benefit only if education succeeds in reducing the behaviors that encourage the proliferation and transmission of the parasite within high-risk communities. Vaccination of pigs using recombinant *T. solium* proteins has potential to limit the burden of disease in the porcine host, reducing the prevalence of taeniasis and cysticercosis among humans.[5,44–47]

Cysticercosis

Key Points

Diagnosis and Management of Cysticercosis

Epidemiology

- Caused by the larval stage of *Taenia solium*
- Endemic in Latin America, Asia, and Africa
- Infestation occurs after ingestion of eggs or proglottids from a tapeworm carrier.
- Ingestion of pork is not a requirement for infection.
- Most common cause of seizures in developing countries

Clinical Features

- Symptoms depend on location of cysticerci

▪ Neurocysticercosis

▪ Parenchymal lesions characterized by seizures and headache

▪ Extraparenchymal lesions (e.g., intraventricular, basal cisterns) characterized by signs and symptoms of increased intracranial pressure

▪ Extracranial cysticercosis usually asymptomatic

Diagnosis

- Neuroimaging

▪ Computed tomography best displays calcifications.

▪ Magnetic resonance imaging best displays intraventricular and spinal lesions.

- Ophthalmologic examination to evaluate intraocular involvement
- Enzyme immunotransfer blot (EITB) available through the Centers for Disease Control and Prevention and commercially
- Symptom resolution with empiric therapy

Treatment

- Antiepileptic medications for patients with seizures
- Ventriculostomy or cerebrospinal fluid diversion for patients with increased intracranial pressure
- Corticosteroid (1 mg/kg/day of prednisone or 0.1 mg/kg/day of dexamethasone) in the setting of increased intracranial pressure, in patients receiving anthelmintic therapy, or for encephalitis
- Albendazole is the drug of choice, given as 15 mg/kg/day in 2 divided doses.
- Praziquantel is alternate therapy, administered as 3 doses (25 mg/kg/dose) given 2 hours apart (with cimetidine).
- Combination therapy can be considered in infections with a large parasitic load.
- Length of therapy depends on location of disease (e.g., up to 28 days for subarachnoid disease).
- Patients with calcified lesions do not require antiparasitic therapy.

Cysticercosis refers to infection of tissues or organs caused by larval stage (i.e., cysticercus) of *T. solium*. Neurocysticercosis (i.e., infection of the CNS) is recognized as a significant cause of neurologic disease in developing countries and is an emerging disease in the United States.[10,11,48–57]

Epidemiology and Pathogenesis

The availability of brain imaging studies, especially computed tomography (CT) scans, has led to an increased appreciation of the significance of neurocysticercosis as a common cause of neurologic disease. Neurocysticercosis is prevalent in many areas of the world, including Latin America, the Caribbean, sub-Saharan Africa, India, Southeast Asia, China, and Indonesia.[58] In endemic areas worldwide, neurocysticercosis is responsible for almost 30% of epilepsy cases.[59]

A community-based study in a highly endemic area of Peru showed that 40% of people with epilepsy had CT or serologic evidence of neurocysticercosis.[60] A meta-analysis of countries in Latin America estimated a neurocysticercosis prevalence of 32% among people with epilepsy.[61] Studies from Latin America also found that up to one half of patients with adult-onset seizures had evidence of neurocysticercosis on imaging studies.[62–66] Population-based surveys in Latin America and sub-Saharan Africa have documented CT abnormalities consistent with neurocysticercosis in up to 70% of people with seizures in rural communities.[49,67–69]

Among patients with focal seizures in India, CT scans demonstrated lesions consistent with neurocysticercosis in 40%, including viable cysts, typical calcifications, or single enhancing CT lesions.[70,71] Similar data were reported for children with seizures and for patients from northern India.[72] Although single-enhancing CT lesions in this group were frequently attributed to other causes, excisional biopsies demonstrated histopathologic evidence of cysticercosis in most. Neurocysticercosis also has become recognized as a major public health problem throughout Asia.[55,73–76]

In the United States, there are approximately 2000 hospitalizations for cysticercosis each year.[57] Cases primarily occur among immigrants from endemic areas. One review identified 75 cases of locally transmitted cysticercosis in the United States during the 1954–2005 period.[13] Neurocysticercosis also has been observed among long-term travelers to endemic areas.[77] The economic burden of neurocysticercosis cases in nonendemic areas can be substantial.[78]

Human cysticercosis follows ingestion of eggs excreted by a tapeworm-infected person, presumably by fecal-oral contamination. Neurocysticercosis is not acquired directly from eating pork, as illustrated by cases that have occurred in an Orthodox Jewish community in New York City, vegetarians in

India, and a case of CNS disease in an infant.[38,73,79] However, tapeworm carriers can infect themselves by fecal-oral contamination, and both stages of the parasite (i.e., cysticercus and adult tapeworm) can be found in a single person.

After ingestion, eggs hatch and release oncospheres that invade the circulatory system and disseminate to somatic tissues, where they mature into cysticerci. Cysticerci in skeletal and cardiac muscle, subcutaneous tissue, and lung usually spontaneously form granulomas, which calcify over time. However, most disease attributable to cysticercosis results from invasion of the CNS.

After tissue invasion, cysticerci reach their final size within a few weeks. Symptoms of neurologic disease, however, usually develop several years after infection.[10,12] Although the parasites secrete a variety of immunomodulatory compounds that can suppress the host's inflammatory response, cysticerci degenerate over time and trigger a host inflammatory response mediated by a variety of cytokines, which is associated with disruption of the blood-brain barrier.[80–89] Degradation of the parasite cyst occurs in stages. During the colloid stage, the cyst wall degenerates, with invasion by inflammatory cells. The cysticercus eventually fibroses, and the cavity collapses (i.e., granular-nodular stage). The granulomatous cyst can calcify (i.e., calcified stage). It may be possible to detect remnants of the cysticercus (e.g., hooklets) in the calcified lesion.

Clinical Manifestations

Seizures are the most frequent clinical finding of neurocysticercosis in all age groups.[90] Headaches, focal neurologic deficits, and signs of increased intracranial pressure are the next most common, but they tend to occur later in the clinical course and occur less frequently in children. The clinical features and outcome of neurocysticercosis in children are influenced by the number and location of the lesions (Fig. 280.3).[91–94]

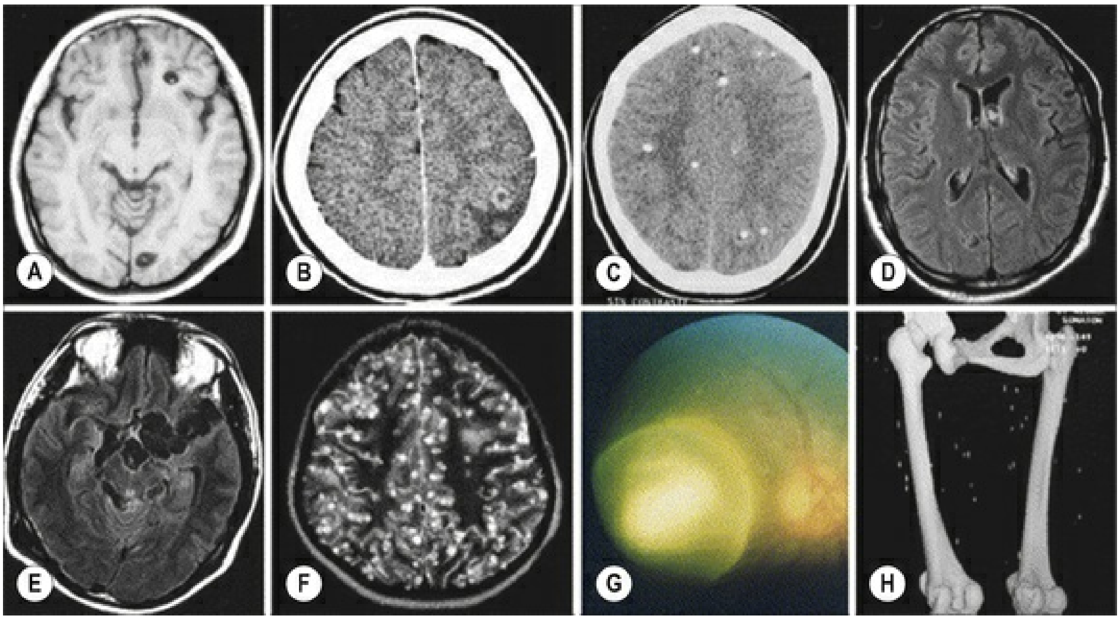

FIGURE 280.3 Diverse presentations of neurocysticercosis. (A) Multiple viable cysts (i.e., vesicular stage). (B) Single enhancing lesion (i.e., degenerating cysts). (C) Multiple intraparenchymal calcifications. (D) Intraventricular cyst. (E) Basal subarachnoid cysticercosis (i.e., extraparenchymal neurocysticercosis). (F) Cysticercotic encephalitis (i.e., extraparenchymal neurocysticercosis). (G) Ocular cysticercosis. (H) Muscle cysticercosis. (From Garcia HH, Del Brutto OH. Neurocysticercosis: updated concepts about an old disease. Lancet Neurol 2005;4:653–661.)

Neurocysticercosis typically is separated into parenchymal and extraparenchymal disease based on whether there is involvement outside of brain tissue.[95–97] Extraparenchymal locations include the subarachnoid space, ventricles, spinal column, and the eye. A single patient can have parenchymal and extraparenchymal infections. Most children have seizures caused by a single enhancing parenchymal lesion; severe or fatal cases of neurocysticercosis often are associated with extraparenchymal disease.[94,98,99]

Patients with parenchymal lesions, particularly those with single enhancing lesions, have a favorable prognosis with medical therapy. In contrast, subarachnoid and ventricular cysts often cause increased intracranial pressure and hydrocephalus, which can be fatal without surgical intervention.

In addition to location, management of neurocysticercosis requires distinction between viable or degenerating parasites and residua of prior infection.[100–102] Viable cysticerci and degenerating parasites are demonstrated as cystic lesions on imaging studies, and they often respond to antiparasitic drugs. In contrast, imaging studies may reveal calcifications or chronic hydrocephalus caused by prior infection without parasites.

Parenchymal Neurocysticercosis.

Seizures are the main clinical manifestation of parenchymal neurocysticercosis.[91–93,103–105] Seizures usually are focal with secondary generalization.[49,51,67,103,106–110] An electroencephalogram (EEG) for patients with active disease can reveal focal abnormalities, particularly in those with a single inflamed lesion.[107,111] Most patients who have seizures due to neurocysticercosis have evidence of inflammation, including edema or contrast enhancement on neuroimaging studies. One study suggests that substance P may be a mediator of seizures.[112] In contrast, cysts without inflammatory changes are thought to cause few symptoms.[108,109] Most symptomatic infections are likely mediated by host inflammatory responses.

Seizures usually can be controlled during treatment with antiepileptic drugs and often resolve after normalization of imaging studies as the inflammation subsides.[113] Relapse, however, is common, particularly in patients who develop residual calcifications.[106]

One uncommon form of parenchymal disease is cysticercal encephalitis, which is characterized by large numbers of inflamed cysts with diffuse cerebral edema, increased intracranial pressure, seizures, and altered mental status. Cysticercal encephalitis occurs more commonly in children than adults, and it often is complicated by increased intracranial pressure and diffuse cerebral edema.[114]

Calcifications.

Calcifications typically are seen as parenchymal solid lesions measuring 2 to 10 mm in diameter, and they often are identified by CT.[102,115,116] In some patients, calcified lesions viewed by magnetic resonance imaging (MRI) are associated with enhancement and perilesional edema, and they are associated with chronic seizures.[117] Children with calcified lesions often have seizures but infrequently have focal abnormalities on the EEG.[118] One study found that some calcified cysts were associated with seizures, even in the absence of perilesional edema.[88]

Extraparenchymal Neurocysticercosis

Patients with ventricular neurocysticercosis most often come to attention with signs or symptoms of increased intracranial pressure, including nausea, vomiting, dizziness, vision changes, and altered mental status.[99,119–122] The onset of symptoms can be abrupt (due to acute obstruction), intermittent, or gradual. Approximately 10% to 20% of patients with symptomatic neurocysticercosis have evidence of ventricular cysts, which can cause hydrocephalus by obstructing the flow of cerebrospinal fluid (CSF).[123] Cysticerci can develop in any ventricle, and symptoms occur most often when cysts are still viable.[124,125] CT may show evidence of obstructive hydrocephalus or distortion of the involved ventricle, whereas the sensitivity of MRI may be greater for detecting intraventricular cysts.[125]

Subarachnoid neurocysticercosis cysts are located in the brain convexity gyri, large brain fissures, and basilar cisterns (i.e., racemose neurocysticercosis). Racemose neurocysticercosis has been associated with pituitary hormone deficiency, vision loss, sudden loss of consciousness associated with head position (i.e., Bruns syndrome), and dementia that improved after shunting.[126–129] Patients with cysticerci in the gyri of the cerebral convexities have imaging findings and a clinical presentation similar to those with active parenchymal disease. However, these cysts may be larger and not respond as well to chemotherapy.

Giant cysticerci, which can grow to several centimeters, can develop within cranial fissures.[130] These cysts can cause a significant mass effect and often are accompanied by cysticerci in the parenchyma or basilar cisterns. Cysticercosis of the basilar cisterns can be associated with communicating hydrocephalus or arachnoiditis, which can appear on neuroimaging studies as focal or diffuse meningeal enhancement or vasculitis.[102,131,132] Basilar cysticercosis carries a poor prognosis.

Isolated spinal disease occurs rarely in patients with neurocysticercosis. However, a study suggested that it is common (61%) among patients with basal subarachnoid disease.[10,94,99,133] Initially, spinal subarachnoid cysticerci are free floating and can move between levels. When the cysticerci degenerate, they eventually become fixed at one level. The accompanying inflammation can cause a mass effect with obstruction of CSF flow. Clinical manifestations include radicular paresthesias or pain, which can progress to myelopathy with bowel or bladder incontinence and paraparesis. Cysticerci rarely are intramedullary, causing cord compression from mass effect or accompanying inflammation.

The most common presentation of ocular cysticercosis is ptosis caused by involvement of extraocular muscles.[134–137] Involvement of the eye usually is subretinal but can be intravitreal or subconjunctival. Patients can have altered vision. Intraocular disease usually requires surgical removal of cysts.

Mixed Forms of Cysticercosis.

Clinical cases, especially those involving dissemination with large numbers of cysticerci, often include more than one of the previously described forms.[138–145] Pathogenesis and presentation can reflect each location. For example, patients with seizures usually have parenchymal cysticerci. However, some also have cysticerci in the basilar cisterns that can progress to hydrocephalus.

Associated Clinical Syndromes.

Cysticerci can be found in skin, muscle, soft tissues, and organs besides the brain, and they can be evident as calcifications.[138,139,141–143,145,146] Cysticerci of the subcutaneous tissues may appear as painless cystic lesions that are similar to sebaceous cysts.

Headaches are common among patients with neurocysticercosis and can occur with parenchymal, ventricular, or cisternal disease.[34,48,94,147,148] Headaches can be hemicranial or bilateral and are difficult to differentiate from migraine or tension headache. In some cases, headache is an initial symptom of raised intracranial pressure, whereas the association of parenchymal lesions with migraine-like headaches suggests vascular involvement. A study in Ecuador found an increased proportion of neurocysticercosis calcified lesions among patients with primary headache compared with patients with cerebrovascular disease, degenerative disorders, or head trauma.[149]

Diagnosis

The most common finding on brain imaging studies of patients with neurocysticercosis is one or more parenchymal cystic lesions.[10,12] Parenchymal cysticerci typically are 4 to 20 mm in diameter and localize to the cerebral cortex, whereas those that arise within fissures may be as large as 10 cm.[125,150] The fluid within viable cysticerci is initially isodense with CSF, and the scolex may be visible as a 1- to 3-mm nodule located on the cyst wall.[116,151] In contrast, inflamed cysts appear as ring-enhancing lesions, often with surrounding edema, and the cyst fluid can have increased density. Eventually, cysticerci can evolve into focal areas of enhancement or granulomas.

Calcifications within the parenchyma are a common radiographic finding and, in the absence of an alternative diagnosis (e.g., tuberculosis), should suggest neurocysticercosis. MRI may reveal edema and enhancement surrounding calcified lesions and a residual scolex.[124,152] Cysticerci within the ventricles may not be directly visualized by CT, although hydrocephalus can suggest their presence. Although CT is more sensitive than MRI for detecting calcifications, MRI provides superior resolution for cysticerci located in the ventricles and subarachnoid space.[124,125,152,153]

Issues with sensitivity and specificity have limited the usefulness of serologic assays in the diagnosis of cysticercosis.[31,62,154–161] The enzyme immunotransfer blot (EITB) is highly specific but has limited sensitivity in patients with single or calcified lesions.[156] The test is available through the US Centers for Disease Control and Prevention and commercially. The EITB test also can be performed on CSF, although the predictive value is superior with serum.[3,162–164] EIAs using recombinant proteins from the EITB test have been developed and have similar sensitivity and specificity, including limitations in detecting single or calcified lesions.[20,165–173]

Assays designed to detect circulating parasite antigens in serum, urine, or CSF have been developed. Although the presence of circulating *T. solium* antigens does not necessarily predict risk of clinical sequelae from infection, these tests can be used to monitor the response to therapy.[31,158,167,174–176] A PCR assay has been developed and has high sensitivity in the CSF, but it is not available widely.[177]

Criteria for the diagnosis of neurocysticercosis combining information from exposure history, clinical findings, neuroimaging studies, and serologic tests have been developed but not systematically evaluated.[178] A definite diagnosis requires the presence of one absolute criterion or two major criteria plus one minor and one epidemiologic criterion. Patients with one major criterion plus a history of exposure and one other minor criterion or those with three minor criteria plus exposure are considered probable cases.

The absolute diagnostic criteria require direct visualization of the parasite histologically in biopsy specimen of a lesion, funduscopic examination in ocular disease, or identification of the scolex within a cystic lesion by CT or MRI. The major diagnostic criteria include results of neuroimaging studies that strongly suggest neurocysticercosis (e.g., cystic lesions, ring-enhancing or nodular lesions, typical parenchymal calcifications). The lesions of neurocysticercosis typically are less than 20 mm in diameter and rarely cause a midline shift.[179] Other major criteria include a positive serum EITB result for anticysticercal antibodies and resolution of single or multiple cystic lesions spontaneously or after anticysticercal therapy.

Minor criteria include radiographic evidence of lesions that are consistent with but not pathognomonic for neurocysticercosis (e.g., basilar meningitis, hydrocephalus, filling defects in the spinal subarachnoid space in the absence of cysticerci). Additional minor criteria are symptoms suggesting neurocysticercosis (including seizures or hydrocephalus), a positive serologic result using a test other than the EITB, and the presence of cysticerci outside the nervous system (e.g., muscle calcifications, subcutaneous nodules). Risk factors for exposure and infection include residence or a prolonged stay in an endemic area and contact with a tapeworm carrier.

Other clinical and radiologic criteria have been proposed for cysticercal granulomas in patients who have seizures and single enhancing lesions.[179,180] The combination of a single, round, enhancing lesion that is more than 20 mm in diameter and does not produce a midline shift in patients with no signs of increased intracranial pressure, focal neurologic deficits, or evidence of systemic disease strongly suggests neurocysticercosis. These criteria, which were prospectively studied in 400 patients in India, had high sensitivity and specificity.

Treatment and Prognosis

The management and prognosis of neurocysticercosis requires consideration of several factors, including the stage of the disease and the number and location of cysticerci (Table 280.1).[10,94,106–108,181,182] Treatment guidelines for parenchymal neurocysticercosis have been developed.[183] Poor outcomes, including most fatalities, result from failure to provide effective therapy for complications, such as increased intracranial pressure or seizures. Symptomatic therapy is therefore a key element in the management of neurocysticercosis and should include antiepileptic medications for patients with seizures, corticosteroids for patients with diffuse cerebral edema, and surgical CSF-diverting procedures for patients with hydrocephalus.

TABLE 280.1

Treatment Guidelines for Neurocysticercosis

Target	Treatment
PARENCHYMAL NEUROCYSTICERCOSIS	
Vesicular Cysts	
Single	Albendazole 15 mg/kg/day (maximum dose: 800 mg) in 2 divided doses for 10–14 days with simultaneous use of corticosteroid *or* Praziquantel 75 mg/kg in 3 divided doses is an alternative to albendazole
Moderate infections	Albendazole 15 mg/kg/day in 2 divided doses for 10–14 days[a] with simultaneous use of corticosteroid
Heavy infections (≥100 cysts)	Albendazole 15 mg/kg/day in 2 divided doses for 10–14 days[a] with simultaneous high doses of corticosteroid
Degenerating (Colloidal) Cysts	
Single lesions	Albendazole 15 mg/kg/day in 2 divided doses for 10–14 days[a] with simultaneous use of corticosteroid or no antiparasitic treatment
Moderate infections	Albendazole 15 mg/kg/day in 2 divided doses for 10–14 days[a] with simultaneous use of corticosteroid
Heavy infections (encephalitis)	High doses of corticosteroid; antiparasitic treatment not indicated
Calcifications	
Single or multiple	No antiparasitic treatment
• Extraparenchymal neurocysticercosis	No antiparasitic treatment
• Subarachnoid neurocysticercosis	No antiparasitic treatment
Giant cyst (usually	Albendazole 15 mg/kg/day in 2 divided doses for ≥28 days[a] with high

in sylvian fissure)	doses of corticosteroid or surgical excision
Basal subarachnoid (racemose)	Albendazole 15 mg/kg/day in 2 divided doses for ≥28 days[a] with high doses of corticosteroid
Treatment failure	Albendazole 15 mg/kg/day in 2 divided doses for ≥28 days[a] *or* Albendazole 30 mg/kg/day for 15 days[a] *or* Praziquantel 50–100 mg/kg/day for 28 days *or* Albendazole 15 mg/kg/day[a] *plus* praziquantel 50 mg/kg/day for 15 days, monotherapy or dual therapy plus high doses of corticosteroid
Ventricular cysts	Endoscopic or surgical resection; alternatively, ventricular shunt plus albendazole 15 mg/kg/day in 2 divided doses for ≥28 days,[a] with high doses of corticosteroid or methotrexate
Hydrocephalus	No antiparasitic treatment; ventricular shunt
OTHER FORMS OF NEUROCYSTICERCOSIS	
Spinal cysts	Surgical resection, albendazole with corticosteroid may be used
Ocular cysts	Surgical resection

[a] Maximum albendazole dose is 800 mg/day (400 mg twice daily).

Modified from Garcia HH, Del Brutto OH. Neurocysticercosis: updated concepts about an old disease. Lancet Neurol 2005;4:653–661.

Antiseizure Medications.

Control of the seizures is the first priority and usually can be accomplished with established drugs such as phenytoin, phenobarbital, or carbamazepine.[109] Recurrent seizures usually are associated with subtherapeutic antiseizure drug levels, most often resulting from poor medication adherence.[109,113] Studies suggest many patients can be tapered off seizure medications after 1 or more years of symptom-free maintenance therapy, provided there is radiographic resolution of the lesion.[103,107–109,184,185] However, the rate of seizures after withdrawal of medications is as high as 40% in some populations.[123,132] Residual inflamed or calcified lesions are associated with continued seizure risk and may be an indication to continue antiepileptic drugs indefinitely.[186–188]

Corticosteroids.

The use of corticosteroids to control host inflammation is an essential component of therapy for certain forms of neurocysticercosis, including cysticercal encephalitis, subarachnoid neurocysticercosis, and spinal intramedullary cysticercosis. Although data on the optimal dose or duration of corticosteroid therapy are lacking, doses of 1 mg/kg/day of prednisone or 0.1 mg/kg/day of dexamethasone are used for severe disease. For patients with parenchymal lesions, coadministration of corticosteroids with antiparasitic drugs may reduce the potentially harmful host inflammatory reaction to parasite antigens. For patients with obstructive hydrocephalus caused by neurocysticercosis, corticosteroids in conjunction with antiparasitic drug treatment may decrease the rate of ventriculoperitoneal shunt failure.[97] However, a randomized, controlled trial found no difference in seizure control or resolution of solitary granuloma with corticosteroids, although fewer generalized seizures were observed.[189]

Antiparasitic Therapy.

The role of antiparasitic drugs in the treatment of neurocysticercosis has been controversial.[133,180,190] Early uncontrolled trials in Latin America suggested that antiparasitic drugs were associated with improved prognosis, but studies in the United States demonstrated that many single enhancing lesions resolved without antiparasitic therapy.[190] The first randomized, controlled trials of antiparasitic therapy for the management of neurocysticercosis were not published until the 1990s, and only recently has a consensus on optimal management begun to emerge.[97,98,106,109,191,192]

Praziquantel was the first antiparasitic drug reported to be effective in the treatment of neurocysticercosis.[193,194] Praziquantel is well absorbed after oral administration but has extensive first-pass metabolism that is enhanced by antiepileptic drugs and corticosteroids.[195,196] Coadministration of cimetidine increases blood levels of praziquantel, but effects of the increased drug levels have not been defined.[130,197–200] Adverse effects of therapy include worsening neurologic function, presumably due to the host inflammatory response to parasite antigens.[92,97]

Albendazole is a benzimidazole antiparasitic agent with broad-spectrum activity against nematodes and some cestodes.[92,97,201,202] The recommended dose of albendazole for the treatment of neurocysticercosis is 15 mg/kg/day in 2 divided doses.[92,93,105,109] Side effects are few and include mild gastrointestinal discomfort. Higher doses have been used for extraparenchymal infections.[92,97,203] Controlled trials of its use against parenchymal neurocysticercosis observed no difference in imaging resolution with treatment for 7 days compared with longer courses.[204–207] A 3-day course of albendazole was associated with more rapid resolution of single parenchymal lesions compared with placebo, although risk of seizure recurrence was not reduced.[208] A meta-analysis showed improved resolution of a solitary parenchymal granuloma and a reduction in seizure recurrence associated with albendazole treatment.[209]

Praziquantel has been used in combination with albendazole, and a pharmacokinetic study demonstrated increased levels of the active metabolite of albendazole in subjects receiving combination therapy.[210] No statistically significant improvement was observed among children with single parenchymal brain lesions treated with albendazole plus praziquantel compared with albendazole alone.[211] However, a randomized, controlled trial showed that 64% of patients receiving combination therapy had complete resolution of brain cysts, compared with only 37% of patients receiving standard doses of albendazole.[212]

The most common presentation of neurocysticercosis among children includes seizures and a single enhancing lesion seen on neuroimaging studies. Seizures usually respond to a single antiseizure medication. The lesions resolve spontaneously over months to years, but most studies show more rapid radiologic resolution with antiparasitic therapy.[97,98,106,109,180,213] Several studies have demonstrated seizure reduction with faster CT resolution of lesions as a benefit of corticosteroid therapy when used in conjunction with antiepileptic medications.[103,107,108,184]

Children with seizures and multiple cysticerci usually have at least one lesion that is inflamed, but other cysticerci often are viable. Recurrent seizures may reflect sequential degradation of cysticerci. A placebo-controlled trial demonstrated a small but statistically significant reduction in generalized seizures in patients treated with albendazole plus corticosteroids.[109] The difference increased after patients were tapered off antiseizure medications. Based on these results, most experts recommend that patients with multiple parenchymal cysticerci be treated with a course of antihelmintic (15 mg/kg/day of albendazole for 10–14 days) and a short course of corticosteroids concurrently. For patients with multiple cysticerci who have diffuse cerebral edema, antiparasitic therapy is contraindicated because the subsequent inflammatory response may worsen clinical sequelae. These patients should be treated with high-dose corticosteroids.[114] In most cases, the cysticerci resolve spontaneously with anti-inflammatory medications alone.

Antiparasitic drugs are not recommended for children with calcified neurocysticercosis because no viable parasites are likely to be present. However, because patients with calcified parenchymal lesions often experience recurrent seizures, they should be offered long-term antiepileptic therapy. Although calcified lesions can exhibit significant ring enhancement or edema, it remains to be determined whether treatment with corticosteroids is beneficial for controlling seizures in this circumstance.[115–118]

Surgical Therapy.

Cerebral edema may result in increased intracranial pressure, which usually can be managed with corticosteroids, or hydrocephalus, which often requires ventriculostomy or surgical CSF-diverting procedures.[181,214] Elective endoscopic removal of intraventricular cysticerci is the treatment of choice in the absence of ependymitis.[119,121,214–218] However, obstructive hydrocephalus caused by active ventricular neurocysticercosis is a medical emergency, and relieving hydrocephalus should be the first priority.[119,123,215,219–222]

For refractory hydrocephalus after endoscopic ventriculostomy or associated with inflamed basilar or racemose cysticercosis, placement of a ventriculoperitoneal shunt (compared with open craniotomy) is associated with a lower perioperative mortality rate.[223] One literature review suggested that anthelmintic therapy after cyst removal might be associated with a decreased need for shunting.[224] Patients who receive antiparasitic therapy along with shunting also require fewer shunt revisions than those who receive shunts alone.[223,225,226] Corticosteroids also may reduce the risk of shunt obstruction in the setting of neurocysticercosis.[97,123,130,131,227,228] In some patients, hydrocephalus develops after infection as a result of chronic inflammation and scarring (e.g., aqueductal stenosis).[97] These patients, who may require placement of a ventriculoperitoneal shunt to relieve chronic hydrocephalus, likely do not benefit from treatment with antiparasitic agents.

Other Anatomic Locations.

Subarachnoid cysticercosis, which can be complicated by a significant mass effect, communicating hydrocephalus, cerebral vasculitis, and basilar meningitis, carries a particularly poor prognosis.[119,130,131,227] These patients should receive prolonged courses of antihelmintics (e.g., 15 mg/kg/day of albendazole for at least 28 days) along with high doses of corticosteroids (1 mg/kg/day of prednisone or 0.1 mg/kg/day of dexamethasone). Even with this therapy, patients often develop recurrent symptoms, which may respond to repeated courses, prolonged duration, or higher doses of albendazole or to changing to or adding praziquantel.

Optimal therapy has not been defined for spinal neurocysticercosis. Intramedullary disease has usually been treated surgically because of the risk of paralysis from cord edema. Some cases of spinal cysts may respond to antiparasitic drugs.[229] Surgical removal of ocular cysts usually is recommended. No clearly defined role for anthelmintic therapy exists in this setting.

Special Considerations

Neurocysticercosis has been associated with several neurologic sequelae. Neurocognitive deficits, learning disabilities, depression, psychotic episodes, and hemorrhagic cerebrovascular disease have been described with cysticercosis.[230–236] However, acute alterations of mental status can reflect ongoing seizures or hydrocephalus. Altered mental status that does not resolve after a reasonable postictal period usually results from hydrocephalus.

Few reports in the literature have explored cysticercosis in the immunocompromised host. Because of the dependence on the host immune reaction for symptomatic disease, immunocompromised patients may be less likely to have symptomatic neurocysticercosis. In patients with concurrent human immunodeficiency virus (HIV) infection, the diagnosis of neurocysticercosis can be complex, especially for those living in endemic regions.[237] Empiric therapy with close observation for response may be warranted for these patients. Neurocysticercosis is more likely to be the cause of characteristic brain lesions and symptoms in people with higher $CD4^+$ lymphocyte counts.

Intrauterine or vertical transmission of infection has not been reported. However, pregnant women with neurocysticercosis can present a diagnostic dilemma because their symptoms can be mistaken for preeclampsia or eclampsia, and seizures can cause fetal hypoxia.[238–240] Albendazole is contraindicated in pregnancy, and antiepileptic medications may be relatively contraindicated. Treatment is often deferred until after delivery.

Prevention

Cysticercosis remains endemic in areas where pig farming is a common practice, and disease control has remained an elusive goal.[39,40,98,241] Educational efforts and mass drug administration to decrease human tapeworm carriers have shown the most potential but may not result in long-term reduction of the risk of neurocysticercosis.[42,239] Vaccination of pigs using recombinant *T. solium* antigens, when used in conjunction with antihelmintics, has the potential to reduce transmission to human populations in endemic areas.[45,47] Development of an effective human vaccine against cysticercosis may provide the best tool for eradication of the disease.

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Echinococcus Species

Agents of Echinococcosis

Pedro L. Moro, Paul Cantey

Echinococcus granulosus

Description of the Pathogen

Echinococcus granulosus, which causes cystic echinococcosis, is a cestode whose life cycle involves dogs and other canids as definitive hosts for the intestinal tapeworm and domestic and wild ungulates as intermediate hosts for the tissue-invading metacestode, which is the larval stage of the tapeworm (Fig. 281.1). The metacestode (i.e., echinococcal cyst) is a fluid-filled, spherical, unilocular cyst that consists of an inner germinal layer of cells supported by a characteristic acidophilic-staining, acellular, laminated membrane of variable thickness (Fig. 281.2).[1]

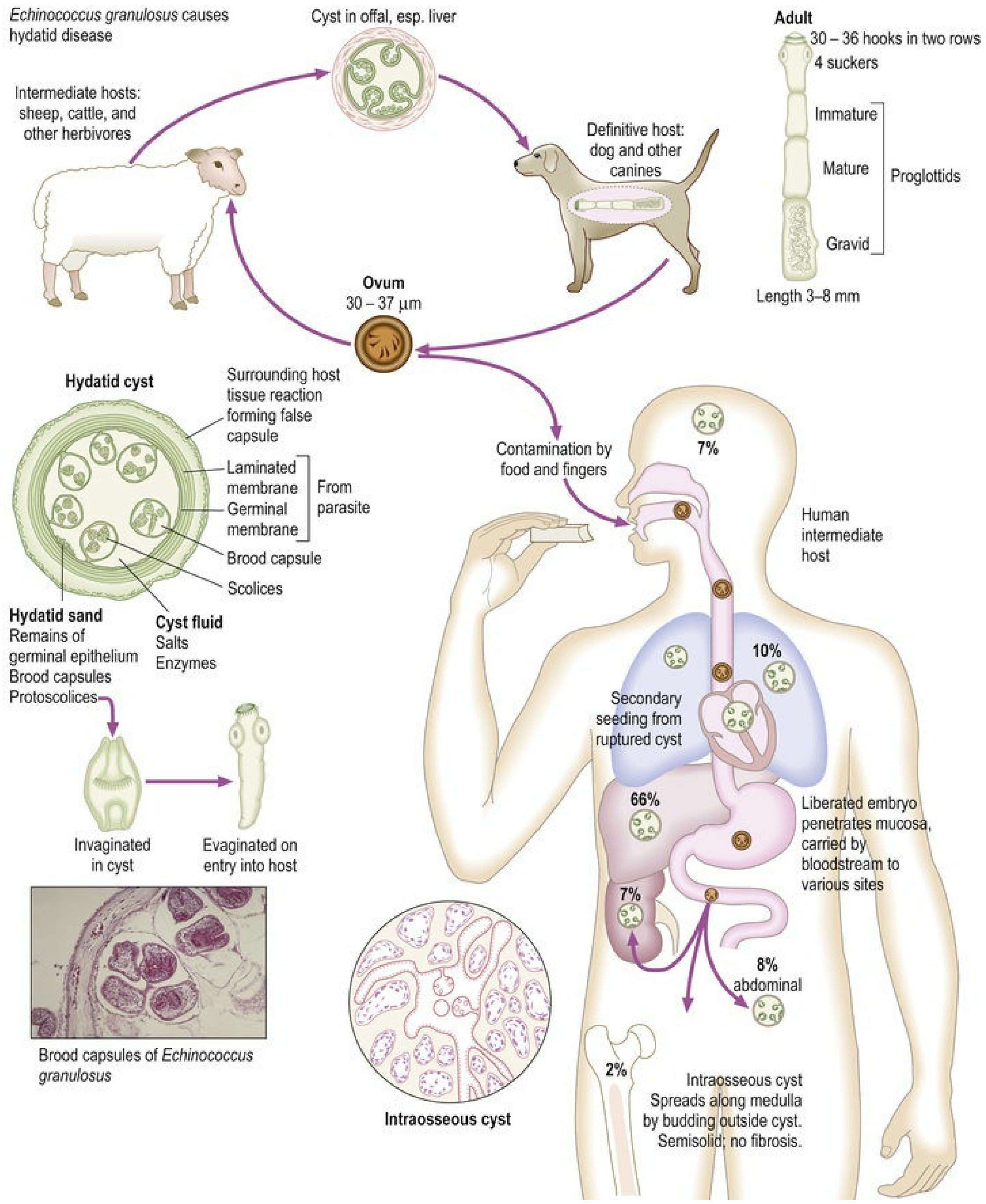

Echinococcus granulosus causes hydatid disease
Cyst in offal, esp. liver
Adult
30 – 36 hooks in two rows
4 suckers
Immature
Mature
Proglottids
Gravid
Length 3–8 mm
Intermediate hosts: sheep, cattle, and other herbivores
Definitive host: dog and other canines
Ovum
30 – 37 µm
Hydatid cyst
Surrounding host tissue reaction forming false capsule
Laminated membrane
Germinal membrane
From parasite
Brood capsule
Scolices
Hydatid sand
Remains of germinal epithelium
Brood capsules
Protoscolices
Cyst fluid
Salts
Enzymes
Invaginated in cyst
Evaginated on entry into host
Brood capsules of *Echinococcus granulosus*
Contamination by food and fingers
7%
Human intermediate host
10%
Secondary seeding from ruptured cyst
66%
Liberated embryo penetrates mucosa, carried by bloodstream to various sites
7%
8% abdominal
2%
Intraosseous cyst
Intraosseous cyst
Spreads along medulla by budding outside cyst.
Semisolid; no fibrosis.

FIGURE 281.1 Life cycle of *Echinococcus granulosus*. The adult *E. granulosus* (3–6 mm long) resides in the small bowel of the definitive hosts (i.e., dogs or other canids). Gravid proglottids release eggs that are passed in the feces. After ingestion by a suitable intermediate host (i.e., sheep, goat, swine, cattle, horses, and camels under natural conditions), the egg hatches in the small bowel and releases an oncosphere that penetrates the intestinal wall and migrates through the circulatory system into various organs, especially the liver and lungs. In these organs, the oncosphere develops into a cyst that enlarges

gradually, producing protoscolices and daughter cysts that fill the cyst interior. The definitive host becomes infected by ingesting the cyst-containing organs of the infected intermediate host. After ingestion, the protoscolices evaginate, attach to the intestinal mucosa, and develop into adult stages in 32 to 80 days. The same life cycle occurs for *E. multilocularis* (1.2–3.7 mm long), but the definitive hosts are foxes and, to a lesser extent, dogs, cats, coyotes, and wolves; the intermediate host are small rodents; and larval growth (in the liver) remains in the proliferative stage indefinitely, resulting in invasion of the surrounding tissues. For *E. vogeli* (≤5.6 mm long), the definitive hosts are bush dogs and dogs; the intermediate hosts are rodents; and the larval stage (in the liver, lungs, and other organs) develops externally and internally, resulting in multiple vesicles. *E. oligarthrus* (≤2.9 mm long) has a life cycle that involves wild felids as definitive hosts and rodents as intermediate hosts. Humans become infected by ingesting eggs, with resulting release of oncospheres in the intestine and the development of cysts in various organs. (Data from the Centers for Disease Control and Prevention. DPDx—Laboratory Identification of Parasitic Diseases of Public Health Concern: Parasites—Echinococcosis. Last updated December 2012. https://www.cdc.gov/parasites/echinococcosis/.)

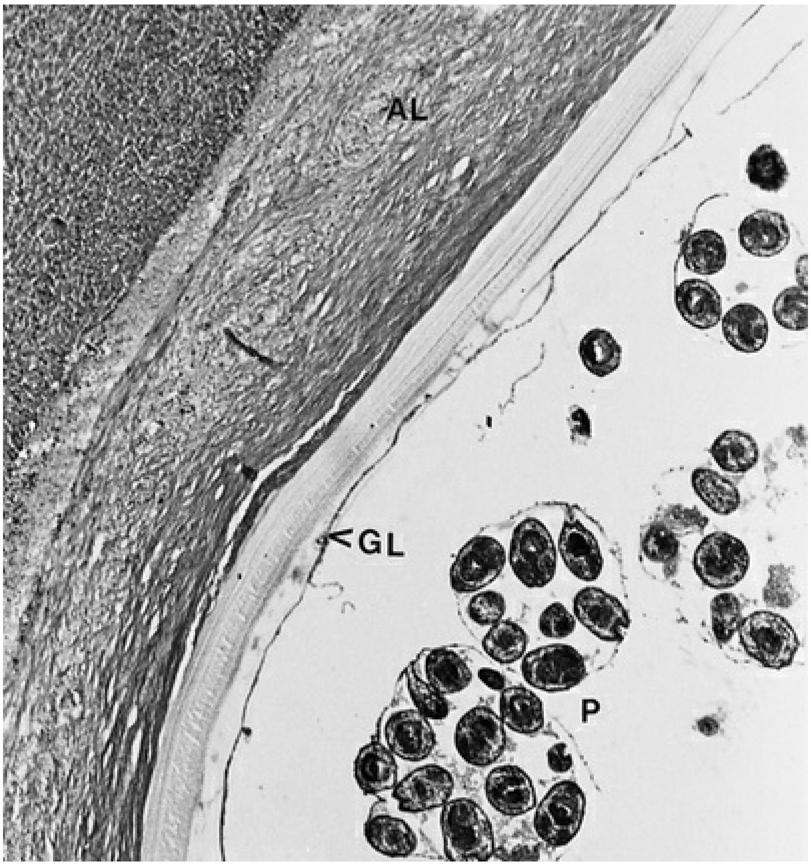


FIGURE 281.2 Metacestode (i.e., hydatid cyst) of *Echinococcus granulosus,* showing the protoscolices (P) in brood capsules, germinative layer (GL), laminated membrane, and adventitial layer (AL) or ectocyst (hematoxylin & eosin stain, bar = 100 μm).

Each cyst is surrounded by a host-produced layer of granulomatous adventitial reaction. Small vesicles (i.e., brood capsules) bud internally from the germinal layer and produce multiple protoscolices by asexual division. In humans, the slowly growing hydatid cysts can attain a volume of several liters and contain many thousands of protoscolices. With time, internal septations and daughter cysts can form, disrupting the unilocular pattern typical of the young echinococcal cysts.

Epidemiology

Geographically distinct strains of *E. granulosus* have different host affinities. Molecular studies using mitochondrial DNA sequences have identified 10 distinct genetic types (i.e., G1 to G10) of *E. granulosus.*[2,3] They include two sheep strains (G1 and G2), two bovid strains (G3 and G5), a horse strain (G4), the camelid strain

(G6), a pig strain (G7), and the cervid strain (G8). A ninth genotype (G9) has been described in swine in Poland and a 10th strain (G10) in reindeer in Eurasia.[2] The sheep strain (G1) is the form most commonly associated with human infections. The other strains appear to be distinct genetically, suggesting that the taxon *E. granulosus* is paraphyletic and may require taxonomic revision.[2,3] The cervid or northern sylvatic genotype (G8) is maintained in cycles involving wolves and dogs and moose and reindeer in northern North America and Eurasia. Human infection with this strain is characterized by predominant pulmonary localization, slower and more benign growth, and less frequent occurrence of clinical complications than reported for other forms.[2]

The distinct strains of *E. granulosus* may have important implications for public health. The shortened maturation time of the adult form of the parasite in the intestine of dogs suggests that the period for administering antiparasitic drugs to infected dogs should be shortened in areas where the G2, G5, and G6 strains occur.[4]

Certain human activities (e.g., widespread rural practice of feeding dogs the viscera of home-butchered sheep) facilitate transmission of the sheep strain and consequently raise the risk of human infection.[5] Dogs infected with *Echinococcus* tapeworms pass eggs in their feces, and humans become infected through fecal-oral contact. Eggs adhere to hairs around an infected dog's anus and are found on the muzzle and paws. Indirect transfer of eggs through contaminated water, uncooked food, or intermediary flies or other arthropods can result in infection of humans.

The greatest prevalence of cystic echinococcosis in human and animal hosts is found in countries of the temperate zones, including southern South America, the Mediterranean region, southern and central parts of the former Soviet Union, central Asia, China, Australia, and parts of Africa.[6–8] In the United States, most infections occur in immigrants from countries in which echinococcosis is highly endemic. Sporadic autochthonous transmission is recognized in Alaska, California, Utah, Arizona, and New Mexico.

Clinical Manifestations

After ingestion, *Echinococcus* eggs hatch and release embryos in the small intestine. Penetration through the mucosa leads to bloodstream distribution to the liver and other sites, where cyst development begins. Most primary infections in humans consist of a single cyst, but 20% to 40% of infected people have multiple cysts or multiple organ involvement.[9] The liver (>65%) and lungs (25%) are the most common sites for pastoral strain echinococcal cysts. The cyst occurs less frequently in the spleen, kidneys, heart, bone, and central nervous system.

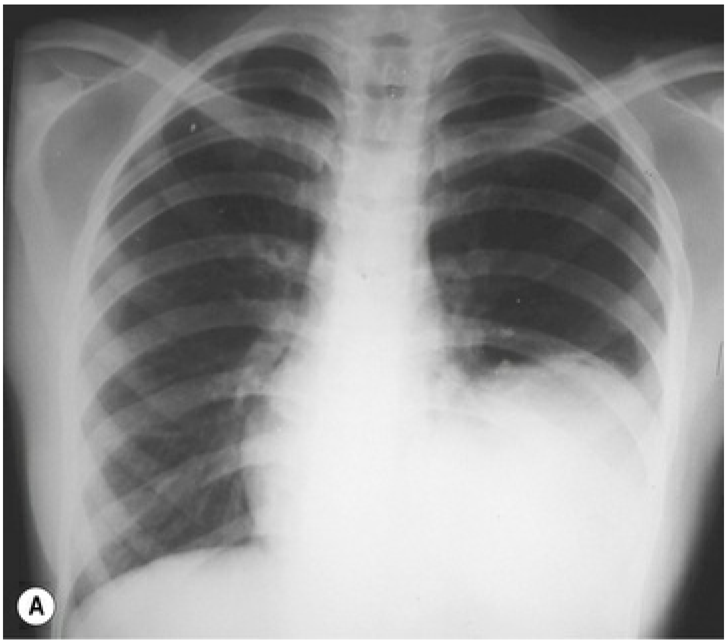
Although infections can be acquired in childhood, most liver and lung cysts become symptomatic and are diagnosed in adult patients because of the slow growth. Only 10% to 20% of cases are diagnosed in patients younger than 16 years of age. Because cysts located in the brain or eye can cause clinical symptoms even when small, most cases of intracerebral echinococcosis are diagnosed in children. Clinical manifestations of cystic echinococcosis vary and are determined by the site, size, and condition of the cysts.[9] The rates of growth of cysts vary, ranging from 1 to 5 cm in diameter per year. A slow-growing echinococcal cyst often is well tolerated until it causes dysfunction because of its size.

Signs and symptoms of hepatic echinococcosis can include hepatic enlargement with or without a palpable mass in the right upper quadrant, right epigastric pain, nausea, and vomiting. If a cyst ruptures, the sudden release of its contents can precipitate allergic reactions ranging from mild to fatal anaphylaxis. In the lungs, ruptured cyst membranes can be evacuated entirely through the bronchi or can be retained and serve as a nidus for bacterial infection. Dissemination of protoscolices can result in multiple secondary sites of echinococcosis. Larval growth in bones is atypical; when it occurs, invasion of marrow cavities and spongiosa is common and causes extensive erosion of the bone.

Laboratory Findings and Diagnosis

The finding of a cyst-like mass in a person with a history of exposure to sheepdogs in areas in which *E. granulosus* is endemic supports the diagnosis of cystic echinococcosis. However, echinococcal cysts must be differentiated from benign cysts, cavitary tuberculosis, mycoses, abscesses, and benign or malignant neoplasms.

Noninvasive confirmation of the diagnosis usually can be accomplished with the combined use of radiologic imaging and immunodiagnostic techniques. Radiography permits detection of echinococcal cysts in lungs (Fig. 281.3); in other sites, calcification is necessary for radiographic visualization. Computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography are useful for the diagnosis of deep-seated lesions in all organs and for determination of the extent and condition of the avascular fluid-filled cysts. Abdominal ultrasonography has emerged as the most widely used imaging technique for echinococcosis because of its widespread availability and usefulness for defining the number, site, dimensions, and vitality of cysts.[10–13]



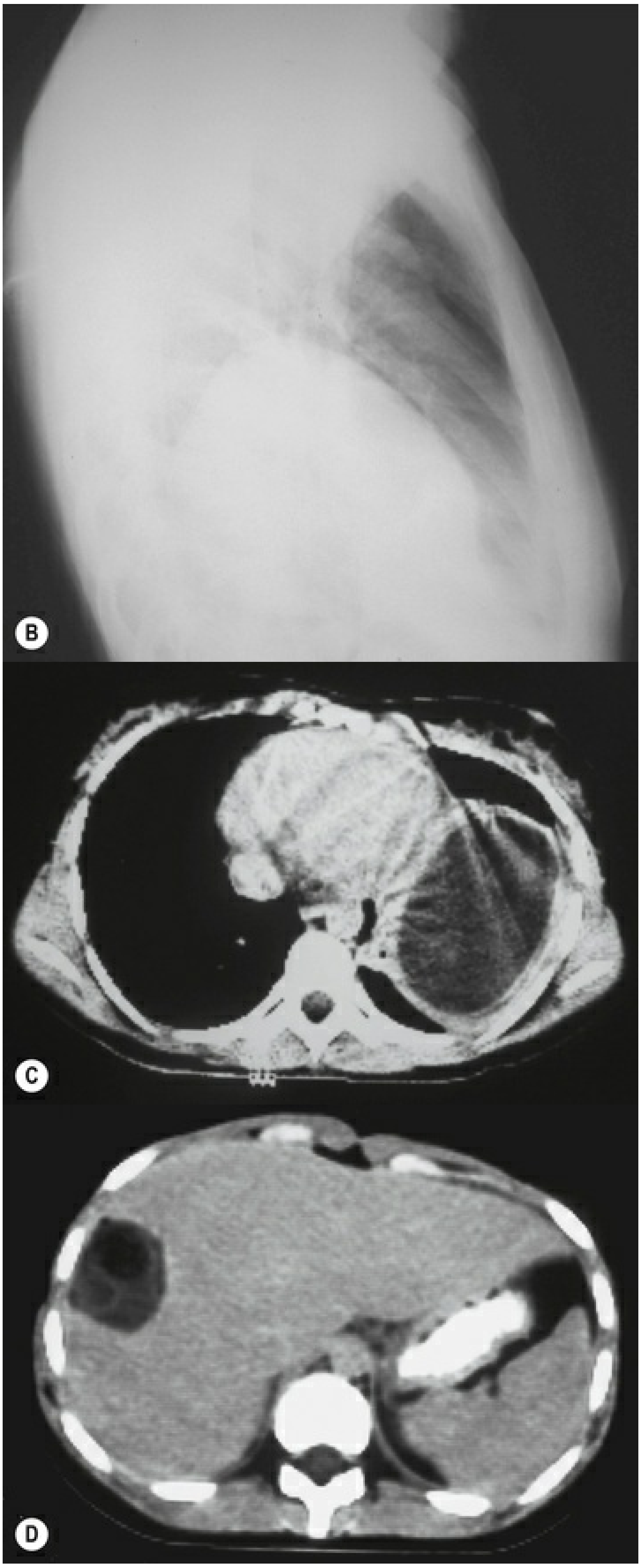


FIGURE 281.3 Cystic echinococcosis in a 15-year-old girl who came to medical attention in Philadelphia because of cough and pleuritic chest pain. She was

referred for evaluation for malignancy. This Air Force family had been stationed in Spain and Germany for the preceding 7 years. Frontal (A) and lateral (B) plain radiographs show a homogeneous left paracardiac mass. Axial computed tomography of the chest (C) and abdomen (D) without contrast demonstrate large cysts in the lung and liver. Notice the daughter cyst in the liver (D). The serum indirect hemagglutination titer against *Echinococcus* performed at the Centers for Disease Control and Prevention was 1 : 1024. (Case courtesy of E.N. Faeber and S.S. Long, St. Christopher's Hospital for Children, Philadelphia, PA.)

Antibody assays are useful to confirm presumptive radiologic diagnoses, although some patients with cystic echinococcosis do not demonstrate a detectable immune response.[14] Hepatic cysts are more likely to elicit an immune response than pulmonary cysts. Regardless of location, the sensitivity of serologic tests is related inversely to the degree of sequestration of the echinococcal antigens inside cysts. For example, healthy, intact cysts can elicit minimally detectable response, whereas previously ruptured or leaking cysts are associated with strong responses. Enzyme immunoassay and the indirect hemagglutination test are highly sensitive for initial screening of sera. Specific confirmation of reactivity can be obtained by demonstration of echinococcal antigens by immunodiffusion (arc 5) procedures or immunoblot assays (8/12-kd band).[15] Eosinophilia occurs in less than 25% of infected people.

The diagnosis of echinococcosis can be made through microscopic examination of cyst contents after cyst aspiration when other testing modalities fail to confirm the diagnosis but clinical suspicion remains high. Identification of hooklets is facilitated by acid-fast stains. Protoscolices sometimes can be demonstrated in sputum or bronchial washings in addition to cyst aspirates.

Treatment

The World Health Organization Informal Working Group on Echinococcosis (WHO-IWGE) recommends an image-based, stage-specific approach to the treatment of cystic echinococcus that includes options of surgery, chemotherapy, percutaneous treatment, or observation.[10,16] The size and stage of the cyst help to determine the treatment options.

Surgery

The aim of surgery is total removal of the cyst with avoidance of the adverse consequences of spilling the contents. Pericystectomy, or total removal of the cyst, is the usual procedure, but simple drainage, capitonnage, marsupialization, and resection of the involved organ can be performed, depending on the location and condition of the cyst.[17–21] The more radical the intervention, the higher the operative risk but the lower the likelihood of recurrence.

Surgery is the preferred treatment in several situations: large cysts with multiple daughter vesicles, single hepatic cysts that are situated superficially and may rupture spontaneously or from trauma; and infected cysts or cysts located in certain organs (i.e., brain, lung, or kidney). Surgery is contraindicated in patients who are pregnant, have preexisting medical conditions that put them at increased risk, or have multiple cysts that are difficult to access. Surgical risks include those associated with any surgical intervention and risks unique to echinococcosis (e.g., anaphylaxis, secondary recurrence). The operative mortality rate varies from 0.5% to 4% but rises with repeated interventions and when surgery is performed in inadequate facilities.

Chemotherapy

Experience with chemotherapy using benzimidazole compounds is extensive, and the medical approach can be recommended for many patients.[7] Approximately one third of patients treated with benzimidazole drugs are cured (i.e., complete and permanent disappearance of cysts) and even higher proportions (30% to 50%) have significant regression of cyst size and alleviation of symptoms.[22–25] However, 20% to 40% of people do not respond favorably. The small (<7 mm in diameter), isolated cysts surrounded by minimal adventitial reaction respond best, whereas complicated cysts, with multiple compartments or daughter cysts or with thick or calcified surrounding adventitial reactions, are relatively refractory to treatment.

Albendazole (10 to 15 mg/kg/day) and mebendazole (40 to 50 mg/kg/day) have demonstrated efficacy against cystic echinococcosis, but the results for albendazole have been superior, probably because of its pharmacokinetic profile, which comparatively favors intestinal absorption and penetration into the cyst.[16,26,27] Albendazole should be administered without interruption.[16] The optimal duration is uncertain; 1 to 3 months may be adequate, but up to 6 months may be required in some cases.

Administration of albendazole with fat-rich meals facilitates absorption and bioavailability. Adverse reactions (e.g., neutropenia, liver toxicity, alopecia) have occurred in a few patients but are reversible on cessation of treatment. Examinations for adverse reactions (i.e., aminotransferase levels and blood count) should be performed every 2 weeks during the first 3 months and then monthly for 1 year. Contraindications to chemotherapy include early pregnancy (albendazole may be acceptable under some circumstances), chronic hepatic diseases, and bone marrow depression.

Praziquantel has protoscolicidal activity, but its efficacy in clinical studies varies, and it is not recommended as primary therapy alone.[28,29] However, human case series and experimental animal studies suggest the combination of albendazole and praziquantel may be superior to the use of albendazole alone. Animal studies suggest that nitazoxanide is not effective against cystic echinococcosis.[30]

Percutaneous Treatments

Different modalities of percutaneous treatments have been developed.[16] One type, percutaneous aspiration, injection, and re-aspiration (PAIR), has been used extensively for the treatment of hydatid cysts. PAIR consists of percutaneous puncture using sonographic guidance, aspiration of substantial amounts of the liquid contents, injection of a protoscolicidal agent (e.g., 95% ethanol or hypertonic saline) for at least 15 minutes, and re-aspiration.[31–35]

PAIR is indicated for patients who cannot undergo surgery and for people who refuse surgery who have single or multiple cysts in the liver, abdominal cavity, spleen, kidney, and bones. PAIR is contraindicated for inaccessible or superficially located liver cysts and for inactive or calcified cystic lesions. To avoid sclerosing cholangitis, PAIR must not be performed in patients whose cysts have a biliary communication, which can be determined by testing the cyst fluid for bilirubin or by a surgical, endoscopic, or radiologic evaluation. Complications of PAIR include secondary infection of the cavity, acute allergic reactions, and recurrence; however, these have been rare. Application of PAIR to pulmonary cysts has been associated with frequent complications and is not recommended.

The physician using PAIR must be prepared to treat a life-threatening allergic reaction, which occurs in less than 1% of cases.[31,32] The possibility of secondary echinococcosis resulting from accidental spillage during this procedure can be minimized by concurrent treatment with benzimidazoles, and combined treatment may yield better results than chemotherapy or PAIR alone.[33,34] The recommended treatment course is 1 month of albendazole after the PAIR procedure.

Favorable results have been reported from more than 2000 PAIR interventions. A meta-analysis comparing the clinical outcomes for 769 patients with hepatic cystic echinococcosis treated with PAIR plus albendazole or mebendazole with 952 matched historical control subjects undergoing surgical intervention found greater clinical and parasitologic efficacy; lower rates of morbidity, mortality, and disease recurrence; and shorter hospital stays than with surgical treatment.[35]

Monitoring the Results of Treatment

The occult nature of the hydatid cyst confounds posttreatment evaluation. Objective response to treatment is best assessed with repeated evaluation of cyst size and consistency at 3-month intervals with CT, MRI, or ultrasound. The time to recurrence varies widely, and monitoring should be continued for at least 3 years. A change in the titer of serum antibody values is not reliable in itself to define the outcome of chemotherapy or PAIR.

Prevention

In areas endemic for cystic echinococcosis, personal preventive measures include careful hygiene, strict dietary regulation of pet dogs to preclude ingestion of sheep offal, and avoidance of dogs not so regulated. Periodic prophylactic treatment of pet dogs potentially exposed to *E. granulosus* sometimes is necessary.

Control measures include health education, regulation of livestock slaughtering, control of dogs, and periodic mass treatments of dogs with praziquantel (5 mg/kg) to reduce the prevalence of *E. granulosus* below levels favorable for continued transmission.[5,36] Development of effective vaccines for the metacestode stages of *E. granulosus* in livestock is a potential option for limiting transmission among animal hosts.[37]

Echinococcus multilocularis

Description of the Pathogen

Alveolar echinococcosis results from infection by the metacestode (larval) form of *Echinococcus multilocularis,* which therefore is also known as alveolar echinococcus. In rodents, the natural intermediate hosts, the larval mass proliferates rapidly by exogenous budding of germinative tissue and produces an alveolar-like pattern of microvesicles filled with protoscolices.[1] In humans, the larval mass resembles a malignancy in appearance and behavior, because it proliferates indefinitely by exogenous budding and invades surrounding tissues. Protoscolices are observed rarely in infections of humans.

Epidemiology

The *E. multilocularis* life cycle involves foxes and their rodent prey in ecosystems usually separate from humans.[38] However, there is ecologic overlap with humans because fox and coyote populations have encroached increasingly on suburban and urban areas of many regions, and domestic dogs or cats can become infected when they eat infected wild rodents.[36] Alveolar echinococcosis has been reported in parts of central Europe, much of Russia, the central Asian republics, western China, the northwestern portion of Canada, and western Alaska. Surveys in central Europe have extended the known distribution of *E. multilocularis* from four countries at the end of the 1980s to 11 countries in 1999, although the annual incidence of disease among humans remains low.[39] There is evidence that parasites are spreading from endemic to previously nonendemic areas in North America and Hokkaido

(North Island), Japan, principally due to movement or relocation of foxes.[39]

The prevalence and geographic spread in animal hosts appear to be rising in central North America. Hunters, trappers, and people who work with fox fur often are exposed to alveolar hydatid disease. Hyperendemic foci have been described in some Eskimo villages of the North American tundra and in western China because of the interaction between dogs and wild rodents that live as commensals in and around dwellings.[40,41] In central Europe, rodents inhabiting cultivated fields and gardens become infected by ingesting embryophores expelled by foxes and may be a source of infection for dogs and cats. One study demonstrated a higher risk of alveolar hydatidosis among people who owned dogs that killed game, dogs that roamed outdoors unattended, and farmers and people who owned cats.[42] In rural regions of central North America, the cycle involves foxes and rodents of the genera *Peromyscus* and *Microtus*.

Clinical Manifestations

The liver is the primary location of the metacestode of *E. multilocularis* in humans and in natural intermediate hosts. Local extension of the lesion and metastases to lungs and brain may follow.[9] In chronic alveolar echinococcosis infections, the lesion consists of a central necrotic cavity filled with a white amorphous material that is covered with a thin peripheral layer of dense fibrous tissue.[38] Focal areas of calcification exist, as does extensive infiltration by proliferating vesicles.

The initial symptoms of alveolar hydatid disease usually are vague. Mild upper quadrant and epigastric pain with hepatomegaly may progress to obstructive jaundice. The mortality rate for progressive, clinically manifest cases may be 50% to 75%. Death usually results from hepatic failure, invasion of contiguous structures, or less frequently, metastases to the brain.[38]

Laboratory Findings and Diagnosis

Alveolar echinococcosis typically becomes symptomatic in people of advanced age and closely mimics hepatic carcinoma or cirrhosis.

Plain radiographs show hepatomegaly and characteristic scattered areas of radiolucency outlined by calcific rings 2 to 4 mm in diameter. The usual CT image of *E. multilocularis* infection is that of indistinct solid tumors with central necrotic areas and perinecrotic, plaque-like calcifications (Fig. 281.4).[43] However, spontaneous death of the cyst has been reported in people with asymptomatic infection.[44]

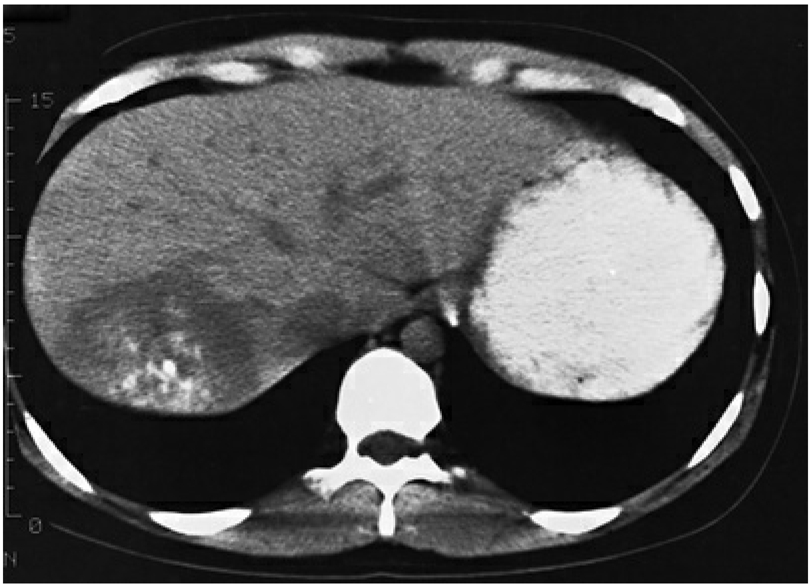


FIGURE 281.4 Abdominal computed tomography of a patient with an *Echinococcus multilocularis* lesion in the right lobe of the liver shows irregular, low-density zones that alternate with scattered areas of calcification. (Courtesy of Joseph F. Wilson, MD.)

Results of serologic tests usually are positive at high titers.; Purified *E. multilocularis* antigens are highly specific and permit serologic discrimination between infections with *E. multilocularis* and *E. granulosus*.[45] Needle biopsy of the liver can confirm the diagnosis if larval elements are demonstrated. Exploratory laparotomy often is performed for diagnosis and for determining the size and extent of invasion.

Treatment

Surgical resection of the entire larval mass, usually by excision of the entire affected lobe of the liver, is the preferred treatment; when involvement is extensive, wedge resections of the lesion can be attempted.[38] Because alveolar echinococcosis often is not diagnosed until disease is advanced, the lesion often is inoperable.

Long-term treatment with mebendazole (50 mg/kg/day) or albendazole (15 mg/kg/day) inhibits growth of larval *E. multilocularis*, reduces metastasis, and enhances the quality and length of survival; prolonged therapy eventually can be larvicidal in some patients.[16,46,47] Liver transplantation has been employed successfully in otherwise terminal cases.[48] In a Swiss study, therapy for nonresectable alveolar echinococcosis with mebendazole and albendazole resulted in an increased 10-year survival rate of approximately 80% (vs. 29% for untreated historical controls) and a 16- to 20-year survival rate of approximately 70% (vs. 0% for historical controls), respectively.[38]

Prevention

Because eliminating *E. multilocularis* from its wild animal hosts is impractical, contact with dogs and foxes in areas where the infection is endemic should be avoided. Preventing infection in humans depends on education to improve hygiene and sanitation.[5] Infection in dogs and cats prone to eating infected rodents can be prevented by monthly treatments with praziquantel.

Echinococcus vogeli

A polycystic form of echinococcosis is caused by *Echinococcus vogeli*, which therefore is also known as polycystic echinococcus, the life cycle of which involves the bush dog and possibly other wild canids; domestic dogs also are susceptible. Pacas, agoutis, and spiny rats are the principal intermediate hosts. *E. vogeli* is indigenous to the humid tropical forests in central and northern South America.[2,5] In endemic areas, hunting dogs are often fed the raw viscera of pacas, and the infected dogs then can expose humans. Polycystic echinococcosis has been recognized in humans in Panama, Ecuador, Colombia, Venezuela, and Brazil.[49,50]

The characteristics of polycystic echinococcosis are intermediate between those of the cystic and alveolar forms.[49] The relatively large cysts are filled with liquid and contain brood capsules with numerous protoscolices. The primary localization is in the liver, but cysts may spread to contiguous sites.

Techniques useful for the diagnosis of cystic or alveolar hydatid disease are also of value in polycystic hydatid disease. Because *E. vogeli* shares antigens with the other *Echinococcus* spp., most available immunodiagnostic tests do not permit species diagnosis. However, the hydatid cysts of *E. vogeli* are different from the cysts of other species in the dimensions of the hooks of the protoscolices.

Because lesions in polycystic echinococcosis are extensive, surgical resection is always difficult and usually incomplete.[49] A combination of surgery with albendazole therapy is most likely to be successful, although data are limited.[49] The principles of management for cystic and alveolar echinococcoses also apply to polycystic echinococcosis.

Key Points

Diagnosis and Management of Echinococcal Infection

Biology

- Lifecycle of *Echinococcus* species involves carnivores (e.g., canids) as definitive hosts and herbivores (i.e., domestic and wild ungulates) as intermediate hosts.
- The adult stage is small (2–12 mm long with 3 to 6 segments), and it localizes in the lower duodenum and jejunum of the final host.
- Larval or metacestode stages can develop in any organ (typically the liver), depending on the species of *Echinococcus* and species of intermediate host.
- Humans are incidental intermediate hosts.

Epidemiology

- Cystic echinococcosis is most prevalent in temperate zones in South America, the Mediterranean region, southern and central parts of the former Soviet Union, central Asia, China, Australia, and parts of Africa, where dogs often are fed hydatid-infected viscera from home-slaughtered sheep.

- Alveolar echinococcosis occurs in parts of central Europe, Russia, the republics of Central Asia, western China, the northwestern portion of Canada, and western Alaska. It appears to be spreading from endemic to previously nonendemic areas in North America and Hokkaido, Japan, principally due to the movement or relocation of foxes.

- Polycystic echinococcosis occurs in humid tropical forests of central and northern South America.

Clinical Features

- Most echinococcal cysts are asymptomatic.

- The liver is the most common site of the echinococcal cyst (>65%), followed by the lungs (25%). Cysts occur less frequently in the spleen, kidneys, heart, bone, and central nervous system.

- Clinical manifestations vary and are determined by the site, size, and condition of the cysts.

- Dissemination of protoscolices can result in multiple secondary sites of echinococcosis.

Diagnosis

- Chest roentgenography permits detection of echinococcal cysts in the lungs.

- CT, MRI, and ultrasonography are useful for detecting lesions in the liver and other organs.

- Serologic tests are useful for confirming a presumptive imaging diagnosis; however, a substantial proportion of patients with cystic echinococcosis may not develop a detectable antibody response

Treatment

- Surgery remains the treatment of choice for cysts that are large (>10 cm in diameter), secondarily infected, or located in certain organs (e.g., heart, brain)

- Continuous treatment with albendazole (10–15 mg/kg/day) or mebendazole (40–50 mg/kg/day) is effective depending on the classification of cyst

- Percutaneous puncture using ultrasound guidance, aspiration of substantial amounts of the liquid contents, injection of a protoscolicidal agent, and re-aspiration (PAIR) is an option for treatment of some classes of hydatid cysts in the liver and some other locations

- Liver transplantation has been employed successfully in otherwise terminal cases of alveolar echinococcosis

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Taenia (Multiceps) multiceps and *Taenia serialis*

Coenurosis

Natalie J.M. Dailey Garnes, Jose A. Serpa, A. Clinton White Jr.

Coenurosis is human infection with larval forms of the animal tapeworms *Taenia (Multiceps) multiceps* or *Taenia serialis*.[1–8] The coenurus is a fluid-filled cyst that is a few millimeters to 2 cm or more in diameter. The wall is a thin, delicate membrane to which multiple invaginated scolices (i.e., protoscolices) are attached in rows or clusters. These zoonotic infections occur primarily in tropical and subtropical regions.

Epidemiology and Life Cycle

Fewer than 150 cases of coenurosis in humans have been reported, although potential exposure is common because of the widespread prevalence among dogs and other canids. Most cases of coenurosis occur in Africa, although the disease has also been reported in the United Kingdom, France, North America, the Middle East, and India.[7,9–11] Most cases from tropical Africa involve subcutaneous sites, whereas reported cases from South Africa and other temperate regions, including the United States, have a higher frequency of intracranial localization.[12–15] In North America, at least six cases of human autochthonous infection have been documented. Three cases involved the central nervous system (CNS), and the others involved intramuscular or subcutaneous localization.[12]

Adult *T. multiceps* and *T. serialis* tapeworms can be recovered from the small intestines of definitive canid hosts, including dogs, wolves, foxes, and coyotes.[16,17] An intermediate host ingests embryonated eggs or gravid proglottids in the environment. Oncospheres hatch within the intermediate host and circulate to the tissues, often the brain or spinal cord. The inner membrane (i.e., bladder) of the resulting cyst is composed of multiple protoscolices with additional small protoscolices or metacestodes contained within. Intermediate hosts for *T. multiceps* include various herbivores (e.g., sheep, goats, or horses), whereas *T. serialis* larvae most often are found in rabbits and squirrels. Human infestation is thought to occur by ingestion of food or water that has been contaminated with the feces of an infected animal, usually a dog.[18]

Clinical Manifestations

Human disease frequently involves the CNS, where it causes a cystic lesion.[3,7,8,13–15] Intracerebral cysts can cause headaches, personality changes, hemiparesis, weakness, nuchal rigidity, weight loss, increased intracranial pressure, or papilledema, and the disease can be confused with neurocysticercosis or echinococcosis.[19] Complications of coenurosis include meningitis, arteritis, arachnoiditis, ependymitis, and ocular involvement.[14] Intraparenchymal lesions of the spinal cord have been reported rarely.[19] Subcutaneous and intramuscular cysts are reported most commonly in Africa and involve the intercostal area, axillae, or anterior abdominal wall.[3,16,17] Allergic symptoms, such as recurrent urticaria, fever, and night sweats, also have been reported.

Laboratory Findings and Diagnosis

A presumptive diagnosis of coenurosis most often is based on results of imaging studies, including magnetic resonance imaging (MRI), computed tomography (CT), and ultrasound.[5,7] The pressure of the cerebrospinal fluid (CSF) often is elevated. Analysis of the CSF may show lymphocytic pleocytosis and reduced glucose and elevated protein concentrations.

A definitive diagnosis requires surgical excision and histopathologic identification of the parasite.[7,20] Fine-needle aspiration of a cyst also may yield a diagnosis.[14,21] Coenurus larvae are easily distinguished morphologically from cysticerci and hydatid cysts on the basis of the numbers and characteristics of their protoscolices (Fig. 282.1). When protoscolices are absent or not identifiable, coenurid cysts can be distinguished from echinococcal cysts because of their lack of the characteristic acellular, laminated membrane that is typical of the latter. However, racemose (acephalic) cysticerci often cannot be differentiated from coenuri because the thin cyst membranes are similar.[2]

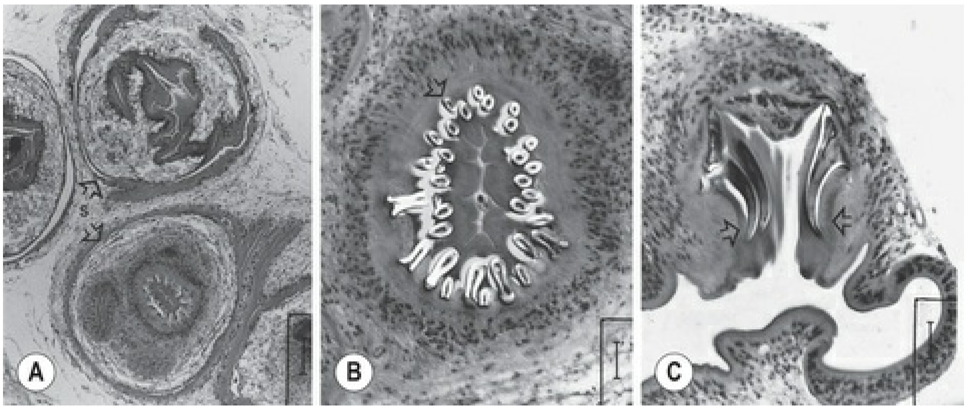

FIGURE 282.1 (A) Photomicrograph of section of the coenurus. Notice the two typically formed protoscolices (S, *arrows*) in the late stages of development, with suckers and a fully formed rostellum evident (hematoxylin & eosin [H&E] stain, bar = 100 μm). (B) Photomicrograph of transverse section through the rostellum of a fully developed protoscolex. Notice the typical distribution of approximately 30 rostellar hooks *(arrow)* in two rows (H&E stain, bar = 25 μm). (C) Photomicrograph of longitudinal section through the rostellum. Notice the structure of the blades in the typically formed rostellar hooks *(arrows)*; the guards and handles have not developed (H&E stain, bar = 25 μm). (From Huss BT, Miller MA, Corwin RM, et al. Fatal cerebral coenurosis in a

cat. J Am Vet Med Assoc 1994;205:69.)

Polymerase chain reaction–based restriction fragment length polymorphism (PCR-RFLP) has been used experimentally to differentiate various species of taeniid cestodes, including *T. multiceps* and *T. serialis*.[12,22] This technique may prove useful for diagnostic and epidemiologic purposes because there is no reliable serologic test for coenurosis.

Treatment

Surgical intervention has been the mainstay of therapy. Excision is indicated in most symptomatic cases involving the CNS, and it may be successful in people with small intraparenchymal or single intraventricular cysts.

Praziquantel and albendazole have been used to treat coenurosis,[7,14] but efficacy has not been evaluated in controlled trials. Because treatment with praziquantel can result in inflammation of previously unidentified intraocular cysts, a dilated ophthalmologic examination is recommended before initiation of therapy.[19]

Prevention

When infection of humans is traced to domesticated dogs and ungulates, strict management of animal slaughter, periodic treatment of dogs, and health education can be used to limit transmission. Transmission from wild animal hosts is more difficult to prevent. Measures are limited to careful avoidance of potentially infected carnivores and adequate hygiene. A recombinant protein vaccine against *T. multiceps* has shown significant protection against infection when administered to sheep in an endemic area.[23,24]

Key Points

Diagnosis and Management of Coenurosis

Parasitology

- Caused by the larval stage of *Taenia multiceps* or *Taenia serialis*

Epidemiology

- Most cases in Africa; rarely reported in United States
- Associated with consumption of contaminated food and water
- Definitive hosts are canids, including dogs and wolves.

Diagnosis

- Often diagnosed by neuroimaging
- Definitive diagnosis made by surgical excision and pathologic evaluation

Treatment

- Surgical excision is most helpful.
- Successful therapy with praziquantel or albendazole is reported, but there are no randomized trials to support this practice.
- Patients should undergo dilated ophthalmologic examination before praziquantel administration.

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Trematodes

OUTLINE

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Intestinal Trematodes

LeAnne M. Fox

More than 70 species of zoonotic, hermaphroditic intestinal flukes can parasitize the human intestine.[1–5] Most human infections are asymptomatic, but heavy infections are more likely to result in clinical disease.

Adult flukes are flat and leaf-shaped, ranging in length from a few millimeters to several centimeters. They attach to the intestinal mucosa by means of oral and ventral suckers and release eggs having a characteristic operculum at one end of the shell. When deposited into fresh water, the operculum opens to release a miracidium, the free-swimming, ciliated larval stage of the parasitic fluke that finds and penetrates an appropriate snail host, in which further replication occurs. The infected snail eventually releases thousands of cercariae into water that encyst (as metacercariae) on aquatic plants or on or in a second intermediate host (i.e., fish, mollusks, crustaceans, and amphibians). When ingested by humans and other definitive hosts, the metacercariae develop into adult flukes.

Some of the more common intestinal trematodes are *Fasciolopsis buski, Heterophyes heterophyes, Metagonimus yokogawai,* and the echinostomes (Table 283.1). However, *Metorchis conjunctus, Nanophyetus salmincola, Gastrodiscoides hominis, Centrocestus formosanus, Haplorchis* species, and others infect humans.[1–6] All intestinal trematodes can be treated easily with oral praziquantel.

TABLE 283.1

Parasitic Intestinal Trematodes of Humans

Common Name of Disease	Species	Intermediate Host		Location of Adults	Distribution
		Primary	Secondary		
Fasciolopsiasis	*Fasciolopsis buski*	Snails	Aquatic plants	Small intestine	Southeast Asia, primarily southern China
Heterophyiasis	*Heterophyes heterophyes*	Snails	Fish	Small intestine	Middle East
Metagonimiasis	*Metagonimus yokogawai*	Snails	Fish	Small intestine	Far East
Echinostomiasis	*Euparyphium ilocanum*	Snails	Fish, amphibians, crustaceans, mollusks	Small intestine	Far East

Fasciolopsiasis

Description

Fasciolopsiasis is a small bowel infection caused by the largest of the intestinal trematodes, *F. buski,* which can measure up to 7.5 × 2.5 cm. Eggs passed in feces hatch, and miracidia infect planorbid snails. Cercariae that emerge from the snails encyst on freshwater vegetation (i.e., bamboo shoots, water chestnuts, water caltrop, water lilies, hyacinths, and morning glory) and remain infectious for up to 1 year.[7] After ingestion, the metacercariae develop into mature flukes in 3 months.[1–3]

Epidemiology

F. buski is found throughout the Far East and Southeast Asia, including southern China, Taiwan, Bangladesh, India, Indonesia, Thailand, Malaysia, Sumatra, Cambodia, Philippines, Vietnam, Laos, and Myanmar.[1–3] Pigs are important reservoirs of the infection, although dogs and rabbits also can be infected.[1–3] Children, who tend to eat plants with encysted cercariae, have the highest prevalence rates.

Pathology and Symptoms

Most infections are asymptomatic. Ulcers or abscesses develop at the site of attachment to the intestinal mucosa in the duodenum and jejunum, and those infected may complain of epigastric pain indistinguishable from peptic ulcer disease. Eosinophilia is common, and anemia can be seen in severe cases. Children can come to medical attention because of systemic allergic manifestations attributed to absorption of parasite metabolites.[1] In cases of heavy infections, an edematous condition resulting from protein-losing enteropathy has been reported. Large numbers of flukes in the intestine may cause ileus or intermittent obstruction.

Diagnosis

The diagnosis is made by identification of large (135 × 80 μm), operculated eggs in stool. Eggs can be confused with those of *Fasciola hepatica, Fasciola gigantica,* and the echinostomes, which are similar morphologically. Stool concentration techniques, which allow examination of 1 g or more of stool, enhance detection of light infections.

Treatment

The drug of choice for children and adults is praziquantel, administered as 75 mg/kg/day divided into 3 doses.[6] Confusion of fasciolopsiasis eggs with eggs from fascioliasis (i.e., liver fluke infection) results in ineffective treatment for the latter, which is resistant to praziquantel.

Prevention

In endemic areas, freshwater plants should be cooked before being eaten. Better control of the infection can be achieved by prohibition of night soil use as fertilizer and proper disposal of human and pig excreta.[1–3]

Heterophyiasis and Metagonimiasis

Description

Infection by the intestinal flukes *H. heterophyes* and *M. yokogawai* occur in different geographic areas, but they are clinically and pathologically similar. The importance of these flukes is being increasingly recognized.[8]

The adults are small (1.4 × 0.6 mm), and they inhabit the small intestine and release eggs that pass in the feces. Miracidia from eggs infect snails, which release cercariae that encyst (as metacercariae) on the scales and occasionally in muscles of freshwater fish. The fins, tail, and gills are most heavily infected. The life cycle is completed when the definitive hosts (including humans) become infected by ingesting raw or undercooked fish. Incompletely salted or pickled fish also are infectious.[9] The metacercariae are released from the cysts and develop into adults in about 7 days.[1–3]

Epidemiology

Human heterophyiasis is common in Egypt, Iran, Tunisia, Turkey, and Sudan.[1–3] Besides humans, the parasite occurs in dogs, cats, foxes, birds, and a number of other fish-eating mammals. Metagonimiasis occurs in the Far East and Siberia (i.e., Taiwan, China, the Philippines, Korea, Indonesia, Japan, and Russia).[1–3] Adult *M. yokogawai* reside in humans, dogs, cats, pigs, and some other fish-eating birds such as pelicans. Humans are infected from eating undercooked freshwater fish, including salmon and trout. Infection rates can reach 65% among children in places where these fish traditionally are eaten raw.

Pathology and Symptoms

Most people are asymptomatic, but when large numbers of flukes are present, the clinical picture is one of intermittent diarrhea with mucus, abdominal tenderness, and discomfort. Occasionally, the flukes penetrate the intestinal wall and form granulomas in the peritoneal cavity. Rarely, eggs can gain access to the lymphatics and then to the bloodstream, embolizing to cause granulomatous lesions in the brain, heart, lungs, spleen, and liver, where they can incite serious disease.[3]

Diagnosis

Eosinophilia is common. The diagnosis is based on the finding of characteristic small (30 × 15 µm), operculated eggs in feces or tissues. Stool concentration techniques, which allow examination of 1 g or more of stool, enhance detection of light infections.

Heterophyes and *Metagonimus* eggs are indistinguishable from eggs of the liver flukes *Clonorchis* and *Opisthorchis.*[1,9] Because all of these flukes are sensitive to praziquantel treatment, an error in diagnosis does not jeopardize successful treatment.

Treatment

Treatment consists of praziquantel, administered as 75 mg/kg/day divided into 3 doses.[6]

Prevention

Fish should be carefully cleaned and scaled and then cooked well. Health education should discourage the ingestion of raw, undercooked, or improperly pickled or salted fish.

Echinostome Infections

Description

The name *echinostome* refers to the characteristic spines surrounding the oral and ventral suckers of the adult flukes.[1–3] At least 15 species of echinostomes have been observed in humans.[3] The life cycle is similar to that of other intestinal trematodes. Besides humans, reservoir hosts are dogs, cats, rats, and birds.[10] Infection is acquired in humans from ingestion of metacercariae on raw or undercooked fish, mollusks, crustaceans, and amphibians.

Epidemiology

Human echinostome infections are found in Korea, Indonesia, the Philippines, Malaysia, Thailand, China, and Taiwan.[1–3]

Pathology and Symptoms

Symptoms related to inflammation at the attachment site of adult flukes include abdominal pain, diarrhea, and anorexia. Symptom severity is related to infection intensity.

Diagnosis

The diagnosis is made by identification of large (135 × 80 µm), operculated eggs in stool that are difficult to distinguish from the eggs of *F. hepatica, F. gigantica,* and *F. buski.* Stool concentration techniques, which allow examination of 1 g or more of stool, enhance detection of light infections.

Treatment

Praziquantel (25 mg/kg in a single dose) is curative. Albendazole (400 mg twice daily for 3 days) also is effective. Confusion of echinostome eggs with eggs from fascioliasis (i.e., liver fluke infection) results in ineffective treatment for the latter, which is resistant to praziquantel.

Prevention

In endemic areas, raw or insufficiently cooked snails, fish, frogs, tadpoles, mollusks, and aquatic animals should not be eaten.[11]

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Clonorchis, *Opisthorchis*, *Fasciola*, and *Paragonimus* Species

Jeffrey L. Jones

Liver and lung trematodes are hermaphroditic, zoonotic flukes that use snails as intermediate hosts (Table 284.1). Snails are infected by eggs in feces passed into the environment by humans and other mammals. The snails release cercariae that encyst in second intermediate hosts (i.e., fish, crustaceans, and amphibians) or on water plants. When encysted cercariae are ingested, humans and other definitive hosts become infected.

TABLE 284.1

Diseases in Humans Caused by Parasitic Trematodes Other Than Schistosomes[a]

Common Name of Disease	Genus and Species	Intermediate Host		Location of Adults	Distribution
		Primary	Secondary		
INTESTINAL FLUKES					
Fasciolopsiasis	*Fasciolopsis buski*	Snails	Aquatic plants	Small intestine	Southeast Asia, primarily southern China
Heterophyiasis	*Heterophyes*	Snails	Fish	Small	Middle East

	heterophyes			intestine	
Metagonimiasis	*Metagonimus yokogawai*	Snails	Fish	Small intestine	Far East
Echinostomiasis	*Euparyphium ilocanum*	Snails	Fish, amphibians, crustaceans, mollusks	Small intestine	Far East
LIVER FLUKES					
Clonorchiasis	*Clonorchis sinensis*	Snails	Fish	Bile ducts	China, Southeast Asia
Fascioliasis	*Fasciola* spp.	Snails	Aquatic plants, watercress	Bile ducts	Worldwide, including British Isles, southern France, Cuba, Algeria
Opisthorchiasis	*Opisthorchis* spp.	Snails	Fish	Bile ducts	*O. viverrini:* Southeast Asia; *O. felineus:* Eastern Europe and former Soviet Union
LUNG FLUKE					
Paragonimiasis	*Paragonimus* spp.	Snails	Crabs	Lungs	Far East, South Asia, Philippines, West Africa, Americas

[a] Principal sources of infection include uncooked plants, water, or poorly cooked, salted, and pickled fish or crustaceans.

Clonorchis, *Opisthorchis*, and *Fasciola* species invade the biliary tree, whereas *Paragonimus* species most often invade the lung. *Clonorchis* and *Opisthorchis* are among the most common causes of biliary fluke infection, affecting an estimated 35 million people and 12 million people, respectively. An estimated 17 million people are infected with *Fasciola* species.[1–3]

Clonorchiasis and Opisthorchiasis

Description of the Pathogens

The adult *Clonorchis* worms are flat, elongated flukes, measuring up to 25 mm long and 5 mm wide. Adult *Opisthorchis* worms are smaller and measure up to 12 mm long and 3 mm wide. The flukes inhabit the biliary tract, where they produce eggs that are passed into feces. Snails ingest these eggs, become infected, and release thousands of cercariae into water. The cercariae encyst (as metacercariae) in tissues of susceptible fish and shrimp.

More than 100 species of freshwater fish and several species of freshwater shrimp are susceptible to infection. When infected raw or undercooked fish or shrimp are ingested, the larvae excyst in the duodenum and migrate through the ampulla of Vater to the bile ducts, where they mature into adults in approximately 4 weeks.[3–6]

The adult flukes can live as long as 30 years.

Epidemiology

Infections occur where it is customary to eat raw fish dishes. Men are most affected in some areas, but in parts of China, children catch and eat small fish and become heavily infected. *Clonorchis sinensis* infects an estimated 15 million people in China. The infection also occurs in Korea, Taiwan, Vietnam, and Japan.[1,2] Infections in Hong Kong probably are a result of imported fish. Pigs, cats, and dogs are reservoir hosts of *C. sinensis*.

Opisthorchis viverrini is endemic in Thailand, Cambodia, Vietnam, and Laos and has reservoirs in dogs, whereas *Opisthorchis felineus* is found particularly in Eastern Europe and Siberia and is most common in cats. An estimated 10 million people are infected with *O. viverrini,* and approximately 1.6 million are infected with *O. felineus*.[2,3] Outbreaks of *O. felineus* infection associated with ingestion of freshwater lake fish have been reported from Italy.[7]

Clinical Manifestations

Adult flukes can be found in bile ducts, the pancreatic duct, and gallbladder. Infection produces inflammatory and hyperplastic changes in the epithelium of bile ducts, with sludging of bile. Eggs and flukes can serve as a nidus for formation of stones. The gallbladder and liver commonly become enlarged, but liver function usually is preserved, and portal cirrhosis can occur in chronic infection.[1,8,9]

Most infections are asymptomatic or produce only epigastric discomfort and are discovered only incidentally on routine screening examination of stool. In moderate to severe infection, an acute syndrome of fever, loss of appetite, diarrhea, right upper quadrant pain, hepatomegaly, and eosinophilia can occur approximately 2 to 4 weeks after ingestion of infected fish or shrimp.[1,2] In endemic areas, the prevalence of infection increases with age and often plateaus in late adolescence or early adulthood, but symptoms may not occur until the third decade or later.[2] Complications include pyogenic cholangitis, obstructive jaundice, gallstones, pancreatitis, and cholangiocarcinoma.

Laboratory Findings and Diagnostic Tests

In chronic disease, serum hepatic transaminase levels usually remain normal, but direct and indirect bilirubin and alkaline phosphatase values may be elevated. Definitive diagnosis is made through identification of eggs in stool or in duodenal aspirates or identification of adult worms during surgery. To improve the chance of finding eggs, multiple examinations using a stool concentration technique may be necessary. *Clonorchis* and *Opisthorchis* eggs are small (~30 × 15 μm) and yellowish brown, with an operculum that rests on a distinctive rim, and they often are difficult to distinguish from each other.[5,6]

Serologic tests have been developed but usually are not readily available outside of endemic areas and may not always have optimal specificity.[1] When available, a combination of serologic testing and morphologic examination improves diagnostic sensitivity. Molecular detection methods for fecal samples are also under investigation.[3,10]

Cholangiography, ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI) demonstrates hepatobiliary dilation, sludging, stones, and neoplasia. Adult flukes sometimes can be seen as shadows or filling defects in endoscopic retrograde cholangiography.[11] M-mode ultrasonography can show mobile worms in gallbladder ducts.[12]

Treatment

Treatment consists of praziquantel in a dose of 25 mg/kg given three times per day for 2 consecutive days (>90% cure rate).[13,14] The safety of praziquantel has not been established in children younger than 4 years of age, but many children younger than 4 years of age have been treated without reported adverse effects in mass prevention campaigns and in studies of schistosomiasis.[15]

Praziquantel is a US Food and Drug Administration (FDA) pregnancy category B medication. Animal studies have revealed no evidence of harm to the fetus, but there are no adequate studies in pregnant women. Side effects include malaise, headache, dizziness, abdominal discomfort, elevated temperature, and urticaria; these effects usually are mild, time limited, and do not require intervention.

Alternative therapy for *C. sinensis* infection is albendazole (10 mg/kg/day for 7 days). The safety of albendazole in children younger than 6 years of age is not certain, but the World Health Organization (WHO) guidelines for mass prevention campaigns use albendazole in children 1 year of age or older. Many children younger than 6 years of age have been treated in these campaigns, albeit at a reduced dose.[15] Tribendimidine trials have shown good efficacy in the treatment of *C. sinensis* and *O. viverrini* infections in Asia, although further investigation is needed.[16,17]

After successful treatment, eggs usually disappear from the stool within a week. Biliary changes usually are reversible in children, but damage from longstanding infection in adults is slow to resolve and may not resolve. Secondary pyogenic cholangitis is treated with appropriate antimicrobial therapy.

Special Considerations

An increased incidence of cholangiocarcinoma is associated with *Clonorchis sinensis* and *Opisthorchis viverrini* infections.[1,18,19] Pathologically, tumors are primarily adenocarcinomas originating from the epithelial lining of bile ducts.[18] *Opisthorchis*-endemic areas may have a 15-fold excessive risk of cholangiocarcinoma with heavy infection. *N*-nitrosamines in food may be an important cofactor in inducing the neoplasia.[19]

Prevention

Thoroughly cooking freshwater fish and shrimp to 63°C (145°F) prevents infection; freezing to −20°C (−4°F) for 7 days also prevents infection. Travelers should be advised to avoid eating raw freshwater fish and shrimp. The practice of using night soil to enrich fish ponds should be discouraged. Repeated mass treatment of populations with praziquantel every 6 to 12 months has been used for clonorchiasis control in China.[20]

Fascioliasis

Description of the Pathogens

Fascioliasis is a widespread disease of sheep, goats, and cattle caused by the liver fluke *Fasciola hepatica* and less commonly caused by *Fasciola gigantica.* Humans become infected by eating uncooked, infested aquatic vegetation (e.g., watercress).

These large (*F. hepatica*, up to 30 × 13 mm; *F. gigantica*, up to 75 mm), flat, leaf-shaped adult flukes inhabit the bile ducts, gallbladder, and occasionally ectopic sites.[2,21] Eggs passed in feces hatch into miracidia and penetrate snails. Cercariae emerge after 4 to 7 weeks and encyst (appearing as small white dots) on watercress or other aquatic plants. Herbivorous mammals (e.g., cattle, sheep, goats, buffalo, llamas, camels, pigs, deer, rabbits) become infected by grazing or indirectly by drinking the surrounding water contaminated with metacercariae.[19,21]

The metacercariae release larvae that are more invasive in their migration than *Clonorchis* and *Opisthorchis* larvae. *Fasciola* larvae penetrate the duodenal wall, invade the peritoneal cavity, and then invade the liver, where they cause eosinophilic tracks 1 to 4 mm in diameter and focal necrotic abscesses as they move through the parenchyma. When they reach the bile ducts, they mature into adults and begin to produce eggs 3 to 4 months after infection.[19,21] Adult flukes live up to 10 years.

Epidemiology

Human infection occurs worldwide and is most common among rural people who tend sheep and eat uncooked water vegetables. Estimates of infection range from 2.4 to 17 million people in Asia, Africa, Europe (including western Europe and the United Kingdom), and the Americas.[2] Especially high infection prevalence rates have been recorded in Bolivia, Ecuador, and Peru, and concerns of potentially increasing prevalence rates in parts of Egypt have prompted clinical studies.[19,22] Cases have been reported from the United States, but most recognized cases are imported.[23,24] Animals also suffer considerable morbidity from these infections, known as *liver rot*.[2]

Clinical Manifestations

The tissue-invasive nature of *Fasciola* larvae can result in an acute or subacute clinical syndrome lasting for many weeks. Illness is characterized by fever, eosinophilia, and epigastric or right upper quadrant abdominal pain, rarely accompanied with ascites or right pleural effusion. Serum hepatic transaminase levels, direct and indirect bilirubin, and alkaline phosphatase values can be elevated.

When acute symptoms occur, they usually begin within 6 to 12 weeks after ingestion of metacercariae. After the adult parasites enter the bile ducts, systemic symptoms and laboratory abnormalities abate, and the infection can become asymptomatic. Patients with heavy infections can have clinical manifestations similar to those of clonorchiasis or opisthorchiasis, with jaundice, cholangitis, or gallstones, but cholangiocarcinoma has not been associated with fascioliasis.[1,2,19]

Complications of fascioliasis include acute hemorrhage from the biliary tract that can manifest as hematemesis or melena or aberrant larval migration that can result in ectopic abscesses or nodules in the skin, intestine, lung, heart, and brain. An unusual form of fascioliasis can occur after ingestion of raw *Fasciola*-infected liver, when flukes surviving mastication attach to the posterior pharynx, causing hemorrhagic nasopharyngitis and dysphagia.

Laboratory Findings and Diagnostic Tests

Acute hepatitis accompanied by eosinophilia and a history of travel or ingestion of watercress suggests fascioliasis. Assays for antibody, which are available at some specialty laboratories, can be helpful in making the diagnosis of acute fascioliasis.[24] Antibody tests are helpful when acute symptoms occur because eggs become detectable in the stool only 1 to 2 months after symptoms develop. Antibody test sensitivities of more than 90% have been reported, but specificities may not be optimal due to cross-reaction with other helminths.[25] Research is ongoing to develop better antigens to improve sensitivity and specificity of serologic tests and to develop sensitive and specific coproantigen tests.[2,26]

Diagnosis of chronic infection is made through identification in stool of large (130–150 μm long × 60–90 μm wide) eggs with poorly defined opercula.[21] The eggs are confused easily with eggs of the intestinal trematode *Fasciolopsis buski*. Examination of multiple stool specimens using concentration techniques should be undertaken because egg output usually is low. Chronic hepatobiliary tract involvement can be assessed using ultrasonography, cholangiography, CT, or MRI. Ulrasound results can be negative in cases of acute disease. High-definition CT or MRI can be useful in demonstrating the tracks of migrating larvae in the liver or filling defects in the gallbladder.[19,27] Spurious fascioliasis occurs when *Fasciola* eggs are found in uninfected people who recently have ingested cooked or uncooked liver from infected animals.

Treatment

Praziquantel is not an effective treatment for fascioliasis. Triclabendazole is effective in a single dose of 10 mg/kg for 1 or 2 days, but the human preparation is in short supply and is not FDA approved for use in the United States.[13,14] Triclabendazole is available through the Centers for Disease Control and Prevention (CDC) Drug Service (phone: 404-639-3670) under an investigational protocol. If available, a second course of triclabendazole treatment can be given if parasitologic cure is not achieved after the first course.[28]

Triclabendazole has not been assigned a pregnancy category by the FDA. Data on the use of triclabendazole in pregnant women are limited, although the available evidence suggests a low risk of congenital anomalies. In large-scale interventions for which the WHO has determined that the benefit of treatment outweighs the risk, triclabendazole is used in pregnant women in clinical settings where medical staff can monitor for complications. Because it is not known whether triclabendazole is excreted in breast milk, it should be used with caution in breastfeeding women.

The safety of triclabendazole in children has not been established. In mass treatment programs for which the WHO has determined that the benefit of treatment outweighs the risk, triclabendazole is used in school-age children; use in children younger than 4 years of age is limited to settings where medical staff can monitor for complications.[15]

Bithionol is an alternative therapeutic agent that is no longer used commonly and not generally available in the United States, although it may be available through a compounding pharmacy. It requires a long treatment course of 30 to 50 mg/kg orally given on alternate days for 10 to 15 doses, and it often causes considerable gastrointestinal tract side effects.

A 7-day course of nitazoxanide produced fascioliasis cure rates of 60% for adults and 40% for children in randomized trials (i.e., dosage of 100 mg twice per day for children 1–3 years old, 200 mg twice per day for those 4–11 years old, and 500 mg twice per day for those 12 years or older), some higher cure rates have been reported in case series.[22,29,30] Artesunate has shown some success in initial symptom control, it but showed a poorer response than triclabendazole at 3 months.[31] In an exploratory phase II trial, artemether showed little effect against fascioliasis.[32] A short course of corticosteroids may be indicated for acute disease.

Prevention

Travelers should be advised not to eat uncooked watercress or other aquatic plants. Washing these vegetables in water, vinegar, or lemon juice does not remove the metacercariae. Aquatic vegetable cultivation should be protected from fecal contamination. Where economically feasible, mollusks can be eliminated by drainage of land or use of chemical molluscicides. Oropharyngeal fascioliasis can be prevented by eating well-cooked liver.

Paragonimiasis

Description of the Pathogens

Human paragonimiasis is acquired through ingestion of *Paragonimus* spp. in raw or undercooked freshwater crabs or crayfish. After ingestion, metacercariae excyst in the small intestine and release larvae that penetrate the duodenal wall and enter the peritoneal cavity. Larvae migrate for approximately 1 week and then penetrate the diaphragm, enter the pleural cavity, and migrate directly through lung tissue to reach the bronchi. There they form cystic cavities and develop into adult worms within approximately 2 months.[1,19]

The adult parasites are reddish brown and ovoid, measuring approximately 7.5 to 12 mm long and 4 to 6 mm wide.[19,33] Adult worms induce an inflammatory response in the lungs, generating a fibrous cyst that contains a purulent, bloody effusion. Eggs released by the flukes are passed into the environment by expectoration, or they may be swallowed and passed with feces. When deposited in fresh water, eggs hatch to release miracidia, which then invade specific snail hosts. Thousands of cercariae later are released from an infected snail, which encyst as metacercariae in the gills, muscles, legs, and viscera of freshwater crustaceans (i.e., crabs or crayfish).

Epidemiology

Eight to 10 species of *Paragonimus* cause most human infections. The most important is *P. westermani,* which occurs primarily in Asia (i.e., China, the Philippines, Japan, Vietnam, South Korea, Taiwan, and Thailand).[19,34,35] *P. africanus* is an important human pathogen in Africa, as is *P. mexicanus* in Central and South America.

Various mammals may be infected, including domestic cats and dogs.[1,19,33] Although rare, human paragonimiasis from *P. kellicotti* has been acquired in the United States, with multiple cases reported from the Midwest.[35,36] Cases have been associated with ingestion of uncooked crawfish during float trips in Missouri.[36,37] Specialty dishes and seasonings in which shellfish are consumed raw or prepared in vinegar, brine, or wine without cooking play a key role in the transmission of *Paragonimus*. Raw crabs or crayfish have also been used in traditional medicine practices in Korea and Japan.[1,19] Eating raw wild boar, which can serve as a paratenic host, has led to infection in Japan.[1,19]

Clinical Manifestations

An acute syndrome characterized by cough, abdominal pain, malaise, low-grade fever, and eosinophilia can occur 2 to 15 days after infection and resolve without treatment. Light infections can be asymptomatic. The clinical picture of chronic paragonimiasis resembles chronic bronchitis or tuberculosis. Patients can have cough productive of tenacious coffee-colored or blood-tinged sputum, dyspnea, pleuritic chest pain, or secondary pyogenic infection.

The spectrum of abnormalities on chest radiographs includes lobar infiltrate, coin lesion, cavity, pneumothorax, calcified nodule, hilar enlargement, pleural thickening, and effusion (Fig. 284.1).[16,37,38] In a North American paragonimiasis case series, the most common chest CT findings were pleural effusion and internal mammary and cardiophrenic lymphadenopathy.[39] Pericardial involvement and omental inflammation were also common, and many nodules had a linear track to the surface that might have corresponded to the worm's burrow tunnel.[39] Ring-shaped opacities of contiguous cavities giving the characteristic appearance of a bunch of grapes strongly suggest pulmonary paragonimiasis.

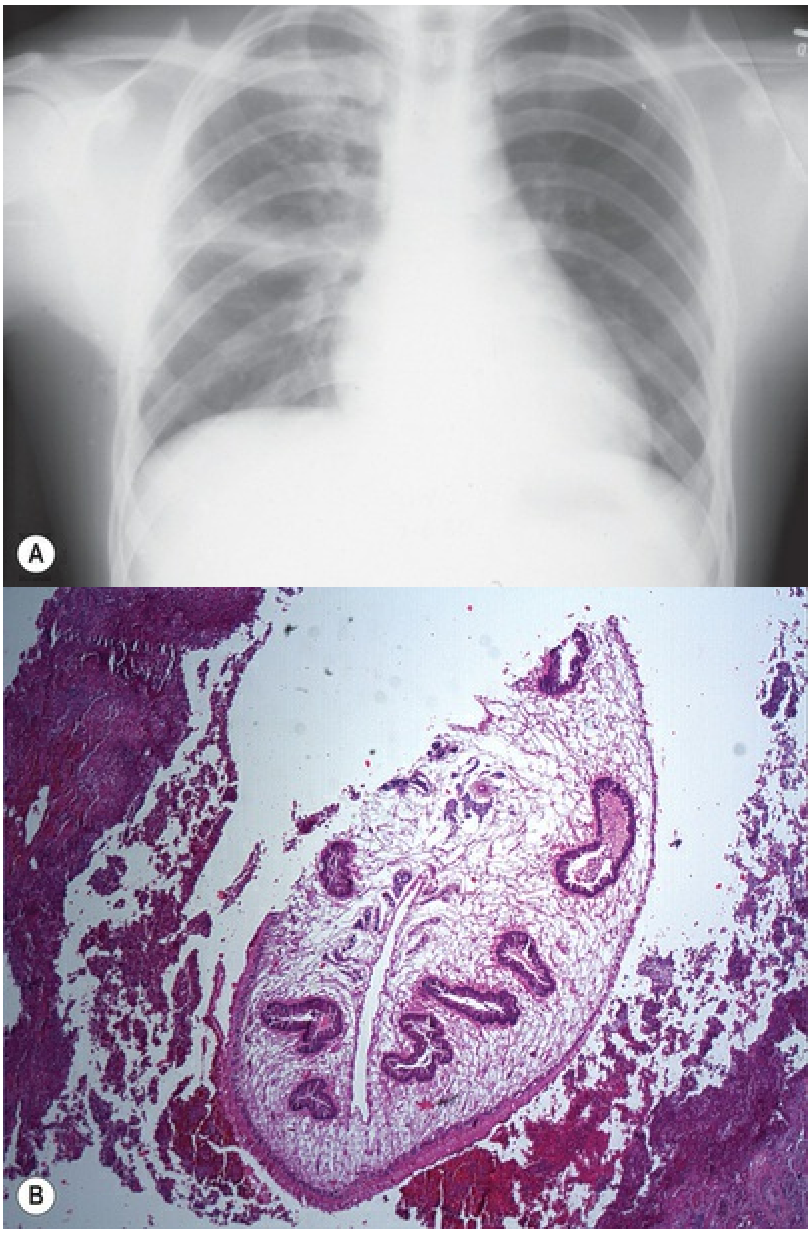

FIGURE 284.1 A 17-year-old boy who had recently emigrated from Laos came to medical attention

because of hemoptysis. He had a 1-year history (in Laos) of cough, chest pain, and dyspnea on exertion. The purified protein derivative test result was negative, and the peripheral blood eosinophil count was 3000 cells/mm^3. (A) Chest radiograph showed right upper lobe complex cystic disease. (B) Resected lung revealed multiple cavitary granulomatous lesions with necrosis and a predominant eosinophilic inflammatory response. *Paragonimus westermani* was also seen (×20) in the gastrointestinal tract. (Courtesy of D.V. Schidlow, J. Pascasio, and S.S. Long, St. Christopher's Hospital for Children, Philadelphia, PA.)

Central nervous system (CNS) involvement occurs in up to 25% of hospitalized patients and can manifest as meningitis and space-occupying lesions. Symptoms include headaches, seizures, motor or sensory deficits, and visual disturbances. Skull radiographs can show clusters of calcified cysts resembling soap bubbles. CT and MRI also may show “grape bunch” findings of aggregated ring-enhancing lesions with surrounding edema, characteristically occurring in the temporal and occipital lobes.

Ectopic lesions from aberrant migration of flukes can involve any organ, including the abdominal viscera, heart, and mediastinum. The most clinically recognizable ectopic lesions arise from cerebral paragonimiasis, which in highly endemic countries more commonly affects children and adults younger than 30 years of age.[19,35] Patients can have eosinophilic meningoencephalitis, seizures, or signs of space-occupying lesions. Many patients with CNS disease also have pulmonary infection. *P. skrjabini* often produces skin nodules, subcutaneous abscesses, or a type of creeping eruption known as *trematode larva migrans*.

Laboratory Findings and Diagnostic Tests

Peripheral blood eosinophilia is common and can be intense, especially during the early larval migration stages. Definitive diagnosis is usually made by visualization of *Paragonimus* eggs in sputum, bronchial, or stool samples. Eggs are yellowish brown, 80 to 120 μm long and 45 to 70 μm wide, and thick shelled with an obvious operculum. Their presence in sputum or stool is diagnostic.[33] Because acid-fast staining destroys *Paragonimus* eggs, the diagnosis cannot be made on sputa prepared with acid-fast stain for tuberculosis testing. Stool examination or gastric aspirates (i.e., looking for swallowed eggs) can be useful for diagnosis. Multiple stools on different days should be examined using a stool concentration technique.

A specific and sensitive immunoblot test based on *P. westermani* antigens is available through the CDC (phone: 404-718-4100).[40] A sensitive and specific Western blot test based on the *P. kellicotti* antigen has been developed and should be helpful in the diagnosis and evaluation of *Paragonimus* infections from North America.[41] Serologic tests can be useful for early infections (i.e., before maturation of flukes) or for ectopic infections in which eggs are not passed in the stool.

Treatment

Praziquantel (25 mg/kg given three times per day for 2 consecutive days) usually produces cure rates higher than 90%.[13,14] For cerebral disease, a short course of corticosteroids should be given with the praziquantel to reduce the inflammatory response around dying flukes.

Triclabendazole (10 mg/kg for 1 or 2 days) is an alternative. Bithionol (30–50 mg/kg on alternate days for 10 to 15 doses) is a less commonly used alternative drug. See the earlier discussion on clonorchiasis and opisthorchiasis for additional information about praziquantel and the section on fascioliasis for additional information about triclabendazole and bithionol.

Prevention

Metacercariae are killed if crabs and crayfish are cooked for at least 5 minutes at 55°C (131°F). Travelers should be advised to avoid traditional meals containing raw or undercooked freshwater crustaceans.

Key Points

Epidemiology, Clinical Features, Diagnosis, and Treatment of *Clonorchis, Opisthorchis, Fasciola*, and *Paragonimus* Species

Epidemiology

- *Clonorchis* spp. and *Opisthorchis* spp.
  - *C. sinensis* and *O. viverrini* are most prevalent in Asia.
  - *O. felineus* is prevalent in Europe, especially Eastern Europe.
  - Infection results from ingesting of undercooked freshwater fish or shrimp.
  - *C. sinensis* and *O. viverrini* infections are associated with cholangiocarcinoma.
- *Fasciola* spp.
  - Occurs throughout most of the world
  - Infection results from ingesting undercooked water vegetables, particularly watercress.
- *Paragonimus* spp.
  - Occurs throughout the world
  - Most important species infecting humans is *P. westermani* in eastern Asia.
  - *P. kellicotti* causes infection in North America.
  - Infection results from ingesting undercooked freshwater crabs or crayfish.

Clinical Features

- Clonorchiasis and Opisthorchiasis
  - Most chronic infections are asymptomatic.
  - Acute syndrome of fever, loss of appetite, diarrhea, right upper quadrant pain, and hepatomegaly can occur about 2–4 weeks after infection.
  - Complications include cholangitis, cholecystitis, gallstones, obstructive jaundice, and cholangiocarcinoma.
- Fascioliasis
  - Acute clinical syndrome lasting for weeks can include fever, epigastric or right upper quadrant pain, eosinophilia, and in rare cases, ascites or right pleural effusion.
  - In heavy infections, cholangitis, gallstones, and jaundice can occur.
- Paragonimiasis
  - Acute syndrome is characterized by cough, abdominal pain, malaise, low-grade fever, and eosinophilia 2 to 15 days after infection.
  - Chronic paragonimiasis resembles chronic bronchitis or tuberculosis with coffee-colored or blood-tinged sputum, dyspnea, and pleuritic chest pain.

- Central nervous system (CNS) involvement can occur.

Diagnosis

- Clonorchiasis and Opisthorchiasis

- Identify eggs in stool or duodenal aspirates or adult worms during surgery

- Serologic tests may be available in endemic areas but can be nonspecific.

- If available, molecular detection methods for fecal samples can be helpful.

- Imaging using ultrasonography, CT, and MRI are useful adjunct diagnostic tools.

- Fascioliasis

- Identify eggs in stool or duodenal aspirates in the chronic phase of infection

- Serologic tests can support the diagnosis before eggs appear in the stool or when low levels of eggs are shed.

- Imaging studies using ultrasonography, CT, and MRI are useful adjunct diagnostic tools.

- Paragonimiasis

- Visualize *Paragonimus* eggs in sputum, bronchial, or stool samples

- Sensitive and specific immunoblot tests use *P. westermani* and *P. kellicotti* antigens.

- Chest radiograph can show lobar infiltrate, cavity, coin lesion, hilar enlargement, pleural thickening, and effusion.

- In CNS disease, CT or MRI can show aggregated ring-enhancing lesions with edema.

- Peripheral blood eosinophilia is common, especially during early phases of infection.

- Migratory skin lesions that resemble cutaneous larval migrans can occur, especially with *P. skrjabini* infection.

Treatment

- *Clonorchiasis* spp. and *Opisthorchiasis* spp.

- Praziquantel: 25 mg/kg three times per day for 2 consecutive days (for children ≥4 years old and adults)

- Albendazole: 10 mg/kg for 7 days (children ≥6 years old and adults)

- *Fascioliasis* spp.

- Triclabendazole: 10 mg/kg for 1 or 2 days (adults)

- Bithionol: 30–50 mg/kg (given on alternate days) for 10 to 15 doses (adults; not available in the United States)
- Nitazoxanide: 7-day course at 100 mg twice per day (children 1–3 years old); 200 mg twice per day (4–11 years old); or 500 mg twice per day (≥12 years)

- *Paragonimiasis* spp.

- Praziquantel: 25 mg/kg 3 times per day for 2 consecutive days (children ≥4 years old and adults)
- Triclabendazole: 10 mg/kg for 1 or 2 days (adults)
- Bithionol: 30–50 mg/kg (given on alternate days) for 10 to 15 doses (adults; not available in the United States)
- For CNS disease, corticosteroids may be required to reduce the inflammatory response.

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Blood Trematodes

Schistosomiasis

Susan P. Montgomery, Frank O. Richards Jr.

Schistosomiasis (i.e., bilharzia or snail fever) is a parasitic infection caused by trematodes that reside in the circulatory system. More than 230 million people worldwide suffer from schistosomiasis, which causes a range of clinical disease from overt clinical manifestations to subtle hindrance of day-to-day activities. Infected children can have impaired growth and development. Infection occurs from exposure to freshwater into which snails, the intermediate host of the parasite, have shed cercariae that can penetrate skin.

The three main species of schistosomes that parasitize humans are *Schistosoma mansoni, S. japonicum,* and *S. haematobium.* Gastrointestinal and hepatic disease is caused by infection with *S. mansoni* or *S. japonicum*, and urogenital tract disease results from *S. haematobium* infection. Other schistosome species less commonly infect humans, including *S. intercalatum*, which is found in Cameroon and the Democratic Republic of Congo, and *S. mekongi,* which is found primarily in the Mekong River basin. Both species cause gastrointestinal disease.[1]

Biology

The complicated life cycle alternates between parasitic forms in the snail intermediate host and human definitive host and the free-living forms in water, the cercariae and the miracidia (Fig. 285.1). The cercariae are released from infected snails and penetrate intact human skin, where they transform into schistosomula that travel through the venous system to the lungs. From the lungs, schistosomula enter the arterial system; reach the liver, where they attain sexual maturity in 4 to 6 weeks; and then as adult worms descend against the blood flow of the portal venous system to the venules of the intestine (*S. mansoni* or *S. japonicum*) or bladder (*S. haematobium*).

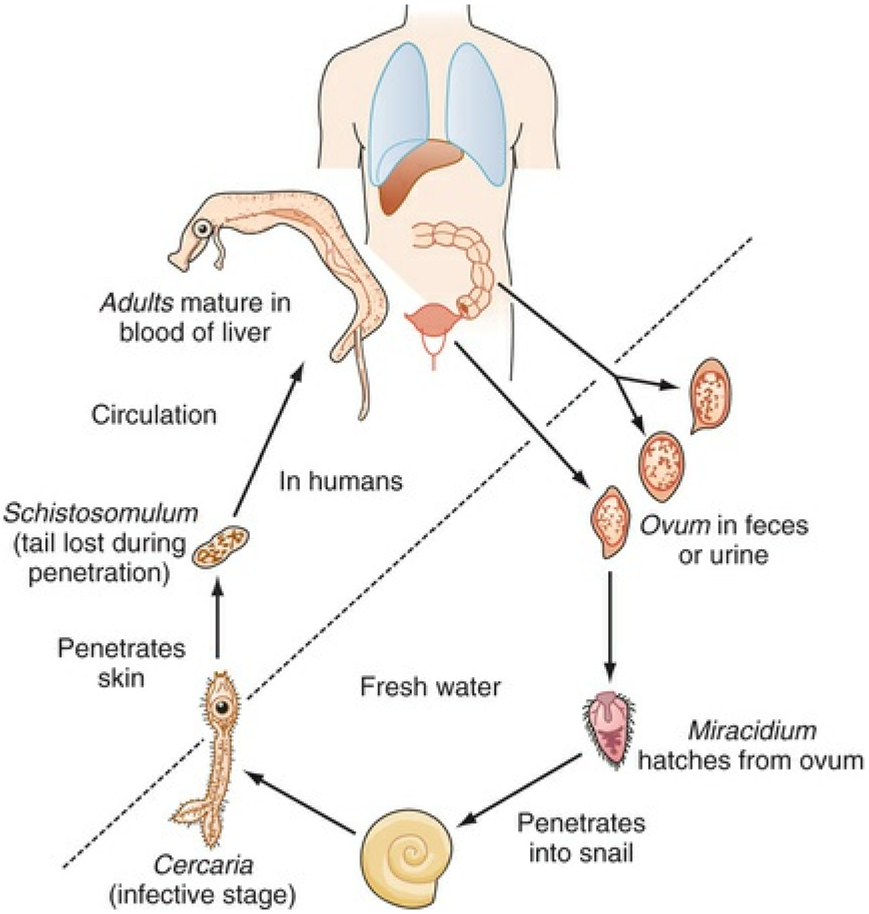
Adults mature in blood of liver
Circulation
In humans
Schistosomulum (tail lost during penetration)
Penetrates skin
Ovum in feces or urine
Fresh water
Miracidium hatches from ovum
Penetrates into snail
Cercaria (infective stage)

FIGURE 285.1 Life cycle of *Schistosoma* and occurrence of schistosomiasis.

Unlike other trematodes, schistosomes are not hermaphroditic. Males and females mate, and the females begin to deposit eggs. Eggs must pass through tissue to reach the lumen of the intestine or bladder and then on to the environment in feces or urine. About one half of the eggs are retained in intestinal or vesicular tissues, where they cause granulomatous inflammation and fibrosis. In the case of the intestinal *Schistosoma* species, eggs also can be swept by the portal blood system back to the liver, where they can cause similar pathologic changes.

Eggs that exit the body and reach freshwater hatch and release miracidia that infect certain genera of snails. *S. mansoni* infects snails of the *Biomphalaria* species, *S. haematobium* infects *Bulinus* species, and *S. japonicum* infects *Oncomelania* snails. In the receptive snail, a single miracidium forms sporocysts from which thousands of cercariae are released into the water over the lifetime of the infected snail, typically a period of 6 to 12 months.[1]

Epidemiology

Schistosomiasis is transmitted in 76 countries in tropical and subtropical areas, but 85% of infected people reside in Africa, where *S. mansoni* and *S. haematobium* occur and often are coendemic.[1–3] *S. mansoni* was transplanted, likely with the slave trade, to South America (especially Brazil, Venezuela, and Suriname) and several islands in the Caribbean (Antigua, Dominican Republic, Guadeloupe, Martinique, Montserrat, Puerto Rico, and Saint Lucia).[3] *S. haematobium* also occurs in a few countries of the Middle East, and a recent focus of transmission has been reported in Corsica, France.[4] *S. japonicum* is endemic in China, the Philippines, and Indonesia.[1–3]

People most heavily infected are responsible for most environmental contamination with parasite eggs. Cross-sectional studies of *S. haematobium* and *S. mansoni* show that the highest prevalence of infection occurs among school-aged children 10 to 14 years of age and that rates decrease in adulthood. Infants have been infected from being bathed in irrigation canals or in lake or river water.[5,6] Males are infected more often than females, and certain daily activities and occupations (e.g., fishing, doing laundry, washing cars) are important risk factors. Wide variations in community prevalence patterns and disease focality point to complex interactions with the environment and practices of human waste disposal, water contact, and acquired immunity. Hydraulic dams and irrigation projects often increase snail habitats and the risk of transmission.

Expatriates, missionaries, diplomats, Peace Corps volunteers, and other long-term residents of endemic areas are at particular risk. However, tourists also can become infected, particularly those who take part in adventure or ecotourism.[7]

Pathogenesis

The host immune response to schistosome egg antigens results in the major clinical and pathologic manifestations of schistosomiasis.[1] Cercarial penetration of skin can give rise to a local hypersensitivity reaction and papular dermatitis, usually within 72 hours of exposure.[7] This reaction typically is milder than the allergic rash associated with skin penetration of animal schistosome cercariae. Adult worm maturation and sudden exposure to antigens with the onset of egg laying by young female worms can result in an acute illness resembling serum sickness, which is more often reported in travelers than lifelong residents of endemic regions.[1,7,8]

Chronic organ damage and dysfunction are related to the number of eggs in tissues, which is related to the number of egg-laying female worms. People with a heavy worm load and the heaviest tissue egg load are at greatest risk of disease. The worm burden in humans grows only through repeated exposure to water containing cercariae. Some evidence suggests that humans acquire partial immunity to reinfection, but the mechanism of a protective immune response has not been defined.[1]

The eggs secrete antigenic materials that induce a host granulomatous response by macrophages, lymphocytes, giant cells, and eosinophils. Over time, granulomas decrease in size and are replaced by fibrosis. Fibrosis along the portal vein triads of the liver (i.e., periportal fibrosis or pipestem fibrosis) in intestinal schistosomiasis can be complicated by portal hypertension. Liver function remains intact unless there is concurrent insult, such as alcoholic or viral hepatitis. As portal hypertension advances and collateral blood flow channels increase, eggs can be shunted to the lungs, which can result in granulomatous pulmonary arteritis leading to pulmonary hypertension.

In urogenital schistosomiasis (caused by *S. haematobium*), chronic fibrosis of the urinary tract can lead to obstructive uropathy and hydronephrosis. Urogenital schistosomiasis can be complicated by pyelonephritis, calculi, and squamous cell carcinoma. Female genital schistosomiasis is characterized by inflammatory lesions of the genital tract, especially cervix, fallopian tubes, and vagina, including characteristic sandy patches associated with inflammation of the vaginal mucosa.[9]

Organs less commonly involved include skin, lungs, seminal vesicles, and central nervous system. *S haematobium* is associated with hematospermia (associated with seminal vesicle involvement) in males. Genital schistosomiasis in men and women can enhance transmission of human immunodeficiency virus (HIV) infection. *S. haematobium* also is associated with human papillomavirus (HPV) infection and infertility.[9]

Granulomatous reaction around ectopic eggs in the brain most often results from *S. japonicum* infection. Ectopic eggs in the spinal cord can cause transverse myelitis.[1,10]

Clinical Features

Acute Schistosomiasis

An acute febrile illness resembling serum sickness can occur 4 to 7 weeks after the initial infection, concurrent with maturation of female worms and the first egg release. This syndrome has been named Katayama fever, after a village in Japan where the entity was first described in association with *S. japonicum* infections. Common signs and symptoms are sudden-onset fever, cough, abdominal pain, headache, lymphadenopathy, and mild hepatosplenomegaly. In contrast to chronic schistosomiasis, peripheral eosinophilia is prominent in acute schistosomiasis.[1,8]

Intestinal and Hepatosplenic Disease

Patients with intestinal schistosomiasis (*S. mansoni, S. japonicum, S. intercalatum,* and *S. mekongi* infections) can be asymptomatic, or they can have crampy abdominal pain, diarrhea, bloody stools, or colonic polyposis. Physical examination commonly reveals an enlarged, nontender liver and an enlarged spleen.

End-stage disease consists of portal hypertension, ascites, and portosystemic varices with an absence of jaundice. Esophageal varices can result in severe bleeding and death.

Urogenital Tract Disease

S. haematobium infections can cause microscopic or gross (often terminal) hematuria. In some endemic areas where transmission is intense, hematuria is so common among boys that it is considered a normal passage to manhood, locally described as male menstruation.[11] Other complaints can include dysuria and urinary frequency. Patients with obstructive uropathy or chronic or recurrent pyelonephritis can have hypertension or end-stage renal disease. Adults can have a suprapubic mass or urinary obstruction from squamous cell carcinoma of the bladder.

Growth and Development

Children, even those with modest and low intensity of infection, may have depressed growth and cognitive development.[11–14] Schistosomiasis causes anemia. Physical findings in heavily infected children can include pallor and exercise intolerance.[14]

Diagnosis

The history should focus on whether the person has been in an area endemic for schistosomiasis and has had contact with open and likely contaminated freshwater ponds, lakes, or streams. Ocean beaches and chlorinated swimming pools are not sources of infection. Depending on the stage of illness, the physical examination can show rash, fever, and hepatosplenomegaly. Eosinophilia characterizes acute schistosomiasis. People infected with *S. haematobium* can have hematuria.

A diagnosis is made by identifying distinctive eggs by microscopy of stool or urine specimens (Fig. 285.2). *S. mansoni* eggs are oval (measuring 60 × 150 μm) and have a distinctive lateral spine. *S. haematobium* and *S. intercalatum* eggs are a similar size and shape, but they have a large terminal spine. *S. japonicum* and *S. mekongi* eggs are smaller (75 μm) and round with small, inconspicuous spines.[3] The miracidia can be seen in living mature eggs.

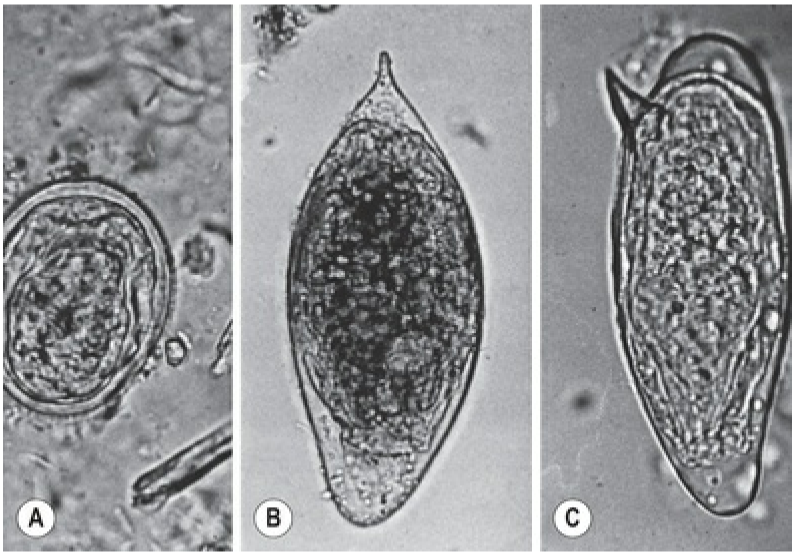

FIGURE 285.2 Ova of *Schistosoma japonicum* (A), *S. haematobium* (B), and *S. mansoni* (C) in stool or urine.

A stool concentration technique (1-g fecal sample) or a Kato-Katz preparation (20- or 50-mg fecal sample) optimizes microscopic diagnosis. The sediment of at least 10 mL of urine should be examined for *S. haematobium* eggs; the optimal sample to examine is a midday, terminal urine specimen. Examining multiple samples collected on separate days increases the sensitivity of diagnostic testing based on microscopy. Some infections have been diagnosed by identification of viable ova in histologic examination of rectal biopsy samples.

Microscopic examination can be negative for patients with acute schistosomiasis or light-intensity infections, and serologic testing is more useful for these people. Antibody detection can be used to screen ecotourists, missionaries, and Peace Corps volunteers who have had freshwater exposure in endemic areas. Several specialty laboratories offer serologic testing for diagnosis of schistosomiasis; for patients with a complicated exposure history, species-specific antibody assays are available through the Centers for Disease Control and Prevention (phone: 404-718-4745).[3] Travelers with positive antibody results are treated presumptively with praziquantel, but serology cannot be used to monitor the success of treatment.[15] Interpretation of antibody test results is more difficult for patients who originate from endemic areas because parasite-specific antibody persists for years despite successful treatment.[15] A new test for the detection of antigen in urine appears to be useful for screening for *S. mansoni* infection in the setting of control programs, but its utility for patient diagnosis is not defined.[16]

Ultrasonography is useful for staging chronic schistosomiasis.[1,17] In cases of intestinal schistosomiasis, ultrasound can be used to describe characteristic hepatic findings and the degree of portal hypertension and splenomegaly. In cases of urinary schistosomiasis, ultrasound can show bladder wall thickening, dilation of the ureter and renal pelvis, and bladder calculi. Abdominal imaging can show bladder calcification in *S. haematobium* infections.

Management

Praziquantel is the drug of choice for therapy[1] (see Chapter 296, Appendix 296.1). For *S. mansoni* and *S. haematobium* infection, 40 mg/kg of praziquantel in 2 divided doses taken orally for 1 day is recommended. For *S. japonicum* infection, 60 mg/kg in 3 divided doses for 1 day is recommended. Side effects of praziquantel typically are mild, abdominal pain is most common in treatment of intestinal schistosomiasis, and severity correlates with the burden of infection.

Praziquantel results in parasitologic cure in approximately 80% of cases, but in people who are not cured, the egg burden is reduced by 95% to 99%. The efficacy of praziquantel treatment depends on a robust host immune response to the adult worms.[1] Oxamniquine is an alternative drug for *S. mansoni* that is used primarily in South America. Oxamniquine is not available in the United States.

Praziquantel is the primary drug periodically used in school-based or community-based mass treatment programs to reduce the egg burdens of infected people.[2] Treatment of children and young adults promptly results in reversal of much of the disease, cessation of hematuria in urinary schistosomiasis, and regression of hepatosplenomegaly in intestinal disease. Antiparasitic treatment does not reverse chronic fibrotic organ damage, and the prognosis is guarded for people with portal hypertension, esophageal varices, and hydronephrosis.

Prophylaxis with praziquantel shortly after water exposure is not effective because developing schistosomula are relatively resistant. Artemisinins (antimalarial drugs) appear to be effective against developing stages and may be useful when the timing of exposure is known.[1,18]

Special Considerations

Central nervous system schistosomiasis results from ectopic egg deposition after aberrant migration of adult worms to the venules draining the brain or spinal cord. The ensuing granulomatous inflammation gives rise to serious manifestations that include seizures, headache, and signs of transverse myelitis such as paralysis, lack of sensation, and bladder incontinence. Previously unexposed people (i.e., immunologically naïve) may be at greater risk for these presentations. Use of corticosteroids or extended courses of praziquantel, or both, in these patients is controversial.[8]

Cercarial dermatitis (i.e., swimmer's itch) is a pruritic macular, papular, or vesicular rash that occurs as a consequence of cercariae penetration of skin. Cercarial dermatitis can occur from exposure to animal (usually avian) schistosomes, often in countries nonendemic for human schistosomiasis, and after exposure to seawater and freshwater. The cercariae die in the skin, and the rash responds to symptomatic treatment and topical corticosteroids.

Prevention

People planning travel to regions where schistosomiasis may be endemic can consult the Centers for Disease Control and Prevention (CDC) travel health website for further information on endemic countries.[19] Travelers should avoid swimming, bathing, or wading in open freshwater in those areas.

Strategies for controlling schistosomiasis include mass chemotherapy, health education, behavioral modification, improved sewage and sanitation, and control of snails through environmental engineering or the use of molluscicides. Large-scale control programs using one or more of these strategies has had various degrees of success in several countries. Schistosomiasis was eliminated completely from Japan by environmental engineering and improved sanitation.[2] Despite prolonged use of mass praziquantel treatment in several country settings, there has been no broadly documented case of emergence of drug resistance.[1,2]

Active research for a vaccine is ongoing.[1]

Key Points

Characteristic Features of Schistosomiasis

Microbiology

- Caused by trematodes that reside in the venules of the intestinal tract (*Schistosoma mansoni* and *S. japonicum*) or surrounding the bladder (*S. haematobium*). Female worms lay eggs that exit the body in feces or urine.

- If deposited in freshwater, miracidia emerge from eggs and infect specific snails. Cercariae later released from infected snails penetrate intact human skin and establish the infection, completing the life cycle.

- Eggs retained in tissue cause granulomatous inflammation that damages host tissues; patients with a heavy worm load are at greatest risk of disease.

Epidemiology

- More than 230 million people in 76 countries in tropical and subtropical areas are infected, but 85% of infected people reside in Africa, where *S. mansoni* and *S. haematobium* are the most common species and often are co-endemic.

- Schistosomiasis occurs in areas with poor sanitation where infected people deposit feces or urine containing eggs directly into freshwater containing the appropriate snails. Other people are later infected or reinfected when these same water bodies are used for swimming, bathing, washing of clothes and utensils, or agricultural purposes.

Clinical Features

- An acute febrile illness resembling serum sickness can occur 4 to 7 weeks after the initial infection, concurrent with maturation of female worms and the first egg release (i.e., Katayama fever).

- *S. mansoni* and *S. japonicum* infections can cause crampy abdominal pain and an enlarged liver or spleen. End-stage disease can include portal hypertension, ascites, and portosystemic varices.

- *S. haematobium* infections can cause microscopic or gross hematuria, dysuria, and urinary frequency, and characteristic sandy patches in vaginal mucosa or the cervix. End-stage disease can include genital lesions, obstructive uropathy, and squamous cell carcinoma of the bladder.

- Even with light worm burdens, children may have depressed growth and learning ability and anemia.

- Dermatitis can occur within 72 hours of exposure to infected water as cercariae penetrate skin. Cercarial dermatitis (i.e., swimmer's itch) also is caused by animal (usually avian) schistosomes, occurring in countries nonendemic for human schistosomiasis and after exposure to seawater and freshwater.

Diagnosis

- Detection of eggs in stool or urine

- Serologic testing

Treatment

- Praziquantel

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PART IV

Laboratory Diagnosis and Therapy for Infectious Diseases

OUTLINE

A The Clinician and the Laboratory
B Anti-Infective Therapy

A

The Clinician and the Laboratory

OUTLINE

286 Laboratory Diagnosis of Infection Due to Bacteria, Fungi, Parasites, and Rickettsiae

287 Laboratory Diagnosis of Infection Due to Viruses, Chlamydia, Chlamydophila, and Mycoplasma

288 Laboratory Manifestations of Infectious Diseases

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Laboratory Diagnosis of Infection Due to Bacteria, Fungi, Parasites, and Rickettsiae

John C. Christenson, E. Kent Korgenski, Ryan F. Relich

Bacteria

Collection and Processing of Clinical Specimens

Proper collection and handling of clinical specimens are critical aspects of laboratory medicine. No degree of laboratory expertise can correct the error of inappropriately collected and transported specimens.[1] Common problems include insufficient quantity, contamination, inappropriate transport media, and delay in transport to the laboratory. Dry swabs are commonly sent but are rarely adequate for survival and isolation of bacteria.

Transport media are designed to prevent drying, maintain a balanced physiochemical environment, and prevent oxidation and enzymatic destruction of the pathogen. They provide minimal nutrients. Some transport media contain antimicrobial agents that suppress normal or contaminating flora to enhance the isolation of a specific pathogen or pathogens.

Specimens for bacterial culture should not be stored for longer than 24 hours before processing. When specimens cannot be transported immediately to the laboratory, appropriate alternatives are available. Urine is refrigerated at 2°C to 8°C for up to 24 hours. Inoculated blood culture bottles can be held at room temperature for several hours, but every effort should be made to submit bottles to the laboratory as soon as possible. Specimens for isolation of *Neisseria gonorrhoeae* should be inoculated on specific media such as modified Thayer-Martin or NYC agar; preferably transported in a self-contained, CO_2-generating transport system as soon as possible to the laboratory; and immediately incubated at 35°C in 5% to 10% CO_2. Cerebrospinal fluid (CSF) is held and transported rapidly at room temperature or at 35°C to 37°C and never refrigerated. Table 286.1 summarizes specimen collection and the usefulness of common transport media. Recommended collection and transport methods, standard media, and routine methods for microbial isolation are shown in Table 286.2.

TABLE 286.1

Collection Methods and Transport Media

Method	Use
COMMONLY USED SWABS	
Calcium alginate	Toxic to *Neisseria gonorrhoeae,* herpes simplex virus, ureaplasmas; useful for collection of chlamydiae
Cotton	Residual fatty acids inhibit bacteria and chlamydiae
Dacron	Useful for viruses, culture for *Streptococcus pyogenes*
Flocked	Useful for viruses, culture for *S. pyogenes*
TRANSPORT SYSTEMS FOR AEROBIC OR FACULTATIVE ORGANISMS	
Culturette	Rayon-tipped swab prevents drying, maintains pH
PATHOGEN-SPECIFIC SYSTEMS	
Anaerobic bacteria	Anaswab system, Port-A-Cul vial or swab, Bio-Bag environmental system, BD anaerobic specimen collector; aspirate of specimen with expression into vial is always preferred
Neisseria gonorrhoeae	Jemec, Gono-Pak agar systems, contain CO_2-generating tablet ($NaHCO_3$–citric acid tablet); inoculated agar placed in bag and incubated for 18–24 hours before transport

TABLE 286.2

Transport Systems and Media Inoculated Routinely According to Source of Specimen

Specimen	Transport System	Routine Media
Blood	Blood culture vials; if *Neisseria meningitidis,* no SPS	BAP, proprietary culture systems[a]
Cerebrospinal fluid	Sterile screw-cap tube	BAP, CHOC (CO_2), THIO
Brain abscess	Anaerobic transport medium	BAP, CHOC (CO_2), EMB/MAC, BAP-ANA, THIO, MS
Feces	Sterile screw-cap container	BAP, EMB/MAC, CAMPY, HEK, selenite/GN broth, CIN, MAC-S
Rectal swab	Swab transport system	BAP, EMB/MAC, CAMPY, HEK, selenite/GN broth, CIN, MAC-S
Gastric lavage, duodenal aspirate	Sterile screw-cap container	BAP, EMB/MAC, PEA, BAP-ANA, THIO, MS
Biopsied tissue	Sterile screw-cap container with preservative-free 0.85% NaCl	BAP, EMB/MAC, PEA, BAP-ANA, THIO, MS; for lung tissue: no PEA, add CHOC (CO_2)
Conjunctival swab	Prepare smears, directly inoculate media	BAP, CHOC (CO_2), EMB/MAC, THIO, MS
Genital, anal swab	Swab transport, GC transport system	BAP, EMB/MAC, THIO, CNA, MTM, NYC
Sputum, BAL fluid	Sputum trap, sterile screw-cap container	No anaerobic cultures; BAP, CHOC (CO_2), EMB/MAC, MS
Lung aspirate, transtracheal aspirate	Anaerobic transport system or sterile screw-cap container	BAP, CHOC (CO_2), EMB/MAC, MS, BAP-ANA, THIO
Throat, nasal, nasopharyngeal swab	Swab transport system	Throat: BAP, SXT-BAP; CHOC (CO_2), EMB/MAC, MS
Tympanocentesis fluid, sinus aspirate	Sterile screw-cap tube or anaerobic transport system	BAP, CHOC (CO_2), EMB/MAC, MS, BAP-ANA, THIO
Pleural, peritoneal ascites fluid	Sterile screw-cap container or blood culture broth bottle; anaerobic transport system	BAP, CHOC (CO_2), EMB/MAC, MS, BAP-ANA, THIO
Urine	Sterile screw-cap container	BAP, EMB/MAC, PEA/CNA
Wound: superficial, deep	Sterile screw-cap container plus anaerobic transport system	BAP, EMB/MAC, PEA, MS; for deep biopsies, add BAP ANA; THIO

[a] Proprietary blood culture systems include VersaTREK (Thermo Scientific), BacT/ALERT (bioMérieux), and BACTEC (Becton Dickinson).

BAL, bronchoalveolar lavage; BAP, blood-agar plate; BAP-ANA, blood agar incubated anaerobically; CAMPY, Campylobacter blood agar; CHOC, enriched chocolate agar; CIN, cefsulodin-irgasan-novobiocin agar; CNA, colistin–nalidixic acid; EMB, eosin–methylene blue; GC, gonococcal; GN, gram-negative; HEK, Hektoen enteric agar; MAC, MacConkey medium; MAC-S, MacConkey-sorbitol agar; MS, mannitol salt agar; MTM, modified Thayer-Martin medium; NYC, New York City agar; PEA, phenylethyl alcohol; SPS, sodium polyanetholesulfonate; SXT agar, blood agar with trimethoprim-sulfamethoxazole; THIO, thioglycolate broth.

Three types of culture media are used: enriched, selective, and differential. Enriched media support the growth of many nonfastidious and fastidious bacteria. Examples include chocolate agar, sheep blood agar, and thioglycolate broth. Selective media permit selective growth of certain groups of bacteria while suppressing others. For example, sheep blood agar containing colistin and nalidixic acid supports the growth of many gram-positive organisms but inhibits virtually all gram-negative bacteria. Differential media assist in differentiating similar groups of bacteria. For example, MacConkey agar permits differentiation of lactose-fermenting (e.g., *Escherichia coli*) and lactose-nonfermenting (e.g., *Proteus* spp.) gram-negative bacilli. Tables 286.3 and 286.4 summarize media used for bacterial isolation.

TABLE 286.3

Commonly Used Culture Media

Medium	Type of Medium	Indicator or Inhibitor	Comments
Sheep blood agar, 5%	N	None	Growth of most medically significant bacteria; allows determination of hemolysis
Horse blood agar, 3%–5%	S, N	None	Incubated at 5% CO_2; enhances isolation of *Haemophilus*
MacConkey agar	S, D	Bile salts, crystal violet, lactose, neutral red	Selective agar for Enterobacteriaceae, some other gram-negative rods; differentiates lactose-fermenting and lactose-nonfermenting organisms
MacConkey-sorbitol agar	S, D	MacConkey, sorbitol	Detects *Escherichia coli* O157:H7
Phenylethyl alcohol agar	S	Phenylethyl alcohol	Inhibits gram-negative bacteria; supports gram-positive bacteria
Colistin–nalidixic acid agar	S	Colistin, nalidixic acid, blood agar	Inhibits gram-negative bacteria; supports gram-positive bacteria
Mannitol salt agar	S, D	NaCl, mannitol, phenol red	Selects for staphylococci
Selective enterococcal agar	S, D	Oxgall, esculin, sodium azide	Selects for enterococci
Hektoen enteric agar	S, D	Bile salts, ferric ammonium citrate, sodium thiosulfate, lactose, sucrose, salicin, bromthymol blue, fuchsin	Enhances isolation of Enterobacteriaceae, *Shigella,* and *Salmonella* spp.; H_2S production; differentiates lactose-fermenting and lactose-nonfermenting bacteria
Deoxycholate-citrate agar	S, D	Deoxycholate, sodium citrate, ferric citrate, lactose, neutral red	Selects for *Salmonella* and some *Shigella* spp.
Selenite broth	S	Selenium salts	Enrichment for *Salmonella;* inhibits normal flora

***Campylobacter* agar**	S	Amphotericin B, cephalothin, trimethoprim, vancomycin, polymyxin B	Isolation of *Campylobacter* spp.; inhibits normal flora
Chocolate agar	N	None	Enriched medium that supports the growth of most nonfastidious bacteria and some fastidious bacteria (e.g., *Haemophilus* spp. and *Neisseria* spp.)
Modified Thayer-Martin agar	S	Vancomycin, colistin, nystatin, trimethoprim	Selects for *N. gonorrhoeae, N. meningitidis;* inhibits normal flora
New York City agar	S	Vancomycin, colistin, amphotericin B, trimethoprim	Same as modified Thayer-Martin agar
Anaerobic blood agar	N	None	Growth of all anaerobic bacteria; should contain yeast extract, vitamin K, and hemin
***Salmonella-Shigella* agar**	S, D	Bile salts, brilliant green, ferric citrate, sodium citrate, sodium thiosulfate, lactose, neutral red	Selects for *Salmonella,* some *Shigella;* inhibits normal flora
***Legionella* medium**	S	Vancomycin, colistin, anisomycin	Selects for *Legionella* spp.
Bordet-Gengou agar, Regan-Lowe medium, Stainer-Scholte medium	S	Cephalexin	Selects for *Bordetella* spp.
Löwenstein-Jensen agar	S	None	Selects for *Mycobacterium* spp.
BC-selective agar	S	Phenol red, ticarcillin, polymyxin B	Selects for *Burkholderia cepacia*
Eosin–methylene blue agar	S, D	Eosin–methylene blue	Selects for gram-negative enteric bacilli
***Haemophilus* test medium**	N	Mueller-Hinton agar, hematin, NAD, yeast extract	Used for antimicrobial disk susceptibility testing of *Haemophilus* spp.
***Haemophilus* test broth**	N	Mueller-Hinton agar, hematin, NAD, yeast extract	Used for antimicrobial susceptibility testing of *Haemophilus* spp.

BC, *Burkholderia cepacia*; D, differential; N, enriched nutrient; NAD, nicotinamide adenine dinucleotide; S, selective.

TABLE 286.4

Specific Media Used for Isolation of Common Microorganisms

Microorganism	Media
Staphylococci	Mannitol salt (O_2), PEA, blood agar, CNA (CO_2)
Streptococci	PEA, CNA, blood agar (CO_2)
Enterobacteriaceae	EMB, MAC (O_2), blood agar (O_2)
Escherichia coli	MAC-sorbitol (O_2)

O157:H7	
Burkholderia cepacia	BCSA (at 32°C), MAC
Neisseria gonorrhoeae	MTM, NYC agar (CO$_2$), CHOC agar
Haemophilus spp.	CHOC agar, horse blood agar (CO$_2$)
Salmonella, Shigella spp.	Hektoen agar, SS agar, selenite broth, XLD, MAC
Campylobacter spp.	CAMP-BAP (42°C, 5% O$_2$, 10% CO$_2$)
Bordetella spp.	Bordet-Gengou agar, Regan-Lowe (CO$_2$) medium, Stainer-Scholte medium
Yersinia spp.	Yersinia selective agar, CIN agar (25°C, O$_2$)
Enterococci	PEA, CNA, blood agar (CO$_2$), bile esculin (CO$_2$)
Francisella tularensis	CHOC or MTM (O$_2$)
Mycobacterium spp.	Middlebrook 7H10, LJ, BACTEC 13A (blood), BACTEC 460 (using Isolator)
Legionella spp.	BCYE (35°C, O$_2$), BAP (CO$_2$)
Brucella spp.	*Brucella* blood agar, MTM, CHOC agar
Anaerobic bacteria	Chopped meat–glucose, TSA, PEA, *Brucella* blood agar, BAP-ANA, laked blood with kanamycin, vancomycin
Vibrio spp.	TCBS (35–37°C)
Neisseria, Moraxella spp.	CHOC (CO$_2$), BAP
Aeromonas spp.	BAP-AMP, MAC
Clostridium difficile	CCFA (anaerobic)
Actinomyces, Nocardia spp.	BHI agar, TSA, BAP-ANA (14 days)
Streptococcus pyogenes	SXT agar (CO$_2$)
Leptospira spp.	Bovine serum albumin–Tween 80
Yersinia pestis	TSA, BAP, BHI agar, CHOC (O2)
Bacteroides spp.	TSA, BBE, laked blood with kanamycin, vancomycin
Fungi	Isolator (blood), biphasic BHI broth, IMA, SAB

BAP, blood-agar plate; BAP-AMP, blood agar with ampicillin (10 μg/mL); BAP-ANA, blood agar incubated anaerobically; BBE, *Bacteroides* bile-esculin agar; BCSA, *Burkholderia cepacia*–selective agar; BCYE, buffered charcoal–yeast extract; BHI, brain-heart infusion; CAMP-BAP, *Campylobacter* blood-agar plate; CCFA, cycloserinecefoxitin-fructose–egg yolk agar; CHOC, enriched chocolate agar; CIN agar, cefsulodin-irgasan-novobiocin medium; CNA, colistin–nalidixic acid agar; EMB, eosin–methylene blue; IMA, inhibitory mold agar (with gentamicin and chloramphenicol); LJ, Löwenstein-Jensen medium; MAC, MacConkey medium; MTM, modified Thayer-Martin medium; NYC, New York City agar; OFPBL, oxidative-fermentative base–polymyxin B–bacitracin-lactose medium; PEA, phenylethyl alcohol; SAB, Sabouraud dextrose agar; SS agar, *Salmonella-Shigella* agar; SXT, blood agar with trimethoprim-sulfamethoxazole; TCBS, thiosulfate-citrate–bile salts–sucrose agar; TSA, trypticase soy agar; XLD, xylose-lysine-deoxycholate agar.

Specimen-Specific Isolation Methods

Blood

Specimen Collection.

Many advances have been made to maximize the recovery of bacteria from blood and to minimize contamination with skin flora during specimen collection. Blood culture samples collected from venipuncture sites antisepsed with chlorhexidine gluconate and 70% isopropyl alcohol have lower contamination rates than from sites antisepsed with povidone-iodine.[2] Sites must be allowed to dry for at least 1 minute before venipuncture. Because of limited safety data, chlorhexidine is used cautiously in infants younger than 2 months of age. Instead, povidone-iodine is preferred in this age group.[3] In one study, the use of 1% chlorhexidine was found to be safe (in newborns ≥1500 g of body weight) and more effective in reducing contamination rates.[4] The rubber septa of blood culture bottles or tubes are disinfected using 70% isopropyl or ethyl alcohol.

The quantity of blood cultured and the proportion of blood to broth are important factors; a ratio of at least 1 : 5 is desirable.[5,6] Inadequate specimen volume is the leading cause of low blood culture sensitivity. Most blood culture broths contain an anticoagulant, sodium polyanetholesulfonate (SPS), ranging in concentration from 0.025% to 0.05%. It inhibits phagocytosis and the bactericidal activity of serum, inactivates complement, and neutralizes lysozymes and aminoglycosides. SPS can inhibit the growth of some microorganisms, including *Neisseria* spp., *Streptobacillus moniliformis,* and *Francisella tularensis.* An appropriate ratio of blood to broth volume dilutes SPS, decreasing the natural inhibitory factors, and it dilutes antimicrobial agents that were present in the patient's bloodstream.

Many older conventional blood culture systems were suboptimal for pediatric use because the 5- to 10-mL recommended blood volume was inappropriate for infants. The degree of bacteremia in children usually is quantitatively higher than in adults; 1 to 5 mL may be an adequate sample from children, whereas higher volumes may be needed from adults.[6] Adequate blood volume per bottle increases recovery yields and decreases time to detection. Table 286.5 shows recommended blood volumes according to body weight.

TABLE 286.5

Recommended Blood Volumes for Culture for Pediatric Patients

Patient Weight (kg)	Blood Volume to Collect (mL)[a]	Media Type and Inoculation Volume (mL)	
		BD BACTEC Peds Plus/F[b]	BD BACTEC Lytic/10 Anaerobic/F[b]
<1.5	1	0.5	0.5
1.5–3.9	2	1	1
4–7.9	4	2	2
8–13.9	6	3	3
14–18.9	10	5	5
		BD BACTEC Plus Aerobic/F	**BD BACTEC Plus Anaerobic/F**
19–25.9	16	8	8
>26	20	10	10

[a] These are the recommended volumes necessary for the optimal isolation of bacterial pathogens. If unable to obtain sufficient blood for both bottles, inject available blood into an aerobic bottle (i.e., Peds Plus/F or Plus Aerobic/F).

[b] Plus Aerobic/F and Plus Anaerobic/F are the recommended media for larger children, adolescents and adults.

Although a single sampling may be sufficient for many patients with bacteremia, multiple samples are appropriate in certain circumstances (e.g., suspected endocarditis, for which two or three samples are desirable). The total volume of blood is probably more important in this circumstance than the number of samples. At least two sets of cultures are helpful for children with indwelling intravascular catheters. Bottles should not be inoculated with more than the manufacturer's recommended volume.

After blood is inoculated into a broth bottle, rapid incubation is essential. Delays in insertion of bottles into automated, continuously monitored blood culture systems can delay detection of bacteremia.[7]

Media.

Advances in blood culture systems have increased the yield of blood cultures, reduced the time to organism recovery, and diminished the laboratory technologist's hands-on time. Some systems were developed to maximize recovery of fastidious organisms. These systems include the Isolator (Wampole), a manual blood culturing system that uses blood cell lysis and centrifugal concentration of microorganisms before direct plating of the microbial pellet, and the continuous-monitoring blood culture systems, including the VersaTREK (Thermo Scientific), BacT/ALERT (bioMérieux), and BACTEC (Becton Dickinson and Company) systems. For the latter three systems, several broth formulations are available, including media for the recovery of aerobic and anaerobic bacteria, mycobacteria, and fungi. No single system is optimal for recovery of all microorganisms.

The Isolator system consists of a sterile tube of two sizes (i.e., 1.5 and 10 mL) that contains saponin and SPS, which lyse red and white blood cells in the blood specimen and inactivate complement and immunoglobulins, respectively. Hemoglobin binds to SPS and prevents inhibition of bacteria.[8]

The larger tubes are centrifuged at 300 *g* for 30 minutes in a fixed-angle rotor. With the use of an Isostat press and specialized pipettes, the lysate is removed, and the microbial pellet is retrieved and inoculated directly onto agar media, which are incubated and examined daily for growth. Media can be selected to maximize the recovery of suspected pathogens.[9,10] Isolation of certain fungi also is enhanced. As little as 1 mL of blood is required, and direct plating allows quantification of bacteria.[11] Excess contamination can occur with this system, but careful handling and inoculation of agar within a biological safety cabinet decreases the likelihood.

Compared with conventional systems, BACTEC has demonstrated increased recovery of organisms and decreased time to detection, particularly for *Mycobacterium* spp. The BD BACTEC FX system is a continuous monitoring, noninvasive blood culture system that uses internal fluorescent CO_2 sensors to detect the metabolic activity of bacteria growing in the culture broth. BACTEC Plus Aerobic/F, Plus Anaerobic/F, and Peds Plus/F bottles contain resins that may decrease the effect of antibiotics. This system can assist clinicians in identifying an intravascular catheter-related infection by using differential time-to-positivity values to compare a positive culture result from an intravascular catheter site with one from a peripheral venipuncture site.[11]

BacT/ALERT and VersaTREK systems are two additional continuous monitoring blood culture systems. They can detect bacteremia and fungemia with a higher yield of recovery and a reduction in the time to detection compared with manual blood culture systems.

Incubation.

Older conventional broth bottles were incubated for 7 days. Bottles were inspected for macroscopic growth daily and subcultured blindly. Acridine orange staining was performed after 18 to 24 hours of incubation. With newer, automated systems, bottles are incubated at 35°C with constant agitation and continuous monitoring, usually for 5 days before reporting negative culture results.

Most pediatric pathogens are isolated within 72 hours of incubation. With the newer blood culture systems, most bacterial pathogens are detected within 48 hours.[12–15] Incubation for more than 5 days is not usually warranted except in certain situations (e.g., suspected fungi, *Bartonella henselae, Corynebacterium, Actinomyces*, *Brucella*).

Special Pathogens and Situations.

Clinicians must communicate the suspicion of brucellosis, tularemia, melioidosis, glanders, anthrax, plague, meningococcal sepsis/meningitis, and enteric fever to the laboratory so that enhanced precautions can be taken when manipulating these cultures. If brucellosis is suspected, the automated blood culture is held for a minimum of 5 but no more than 10 days. Subculture to a blood agar, chocolate agar, or *Brucella* agar with incubation in 5% to 10% CO_2 at 37°C for at least 72 hours is usually adequate for isolation of *Brucella* spp.

For the isolation of cell wall–deficient bacteria, hypertonic medium (i.e., containing 10% sucrose or mannitol) is required. Nutritionally deficient organisms such as *Abiotrophia* spp. should be suspected when organisms are evident on Gram stain but fail to grow when subcultured. Broth can be subcultured onto a blood-agar plate streaked with *Staphylococcus aureus,* or media can be supplemented with 0.001% pyridoxal hydrochloride and 0.05% to 0.1% L-cysteine. A pyridoxal-impregnated disk also can be used. Plates usually are incubated overnight at 35°C to 37°C in 5% to 10% CO_2. Although rare causes of bacteremia and endocarditis, the HACEK group of microorganisms—*Haemophilus parainfluenzae, Aggregatibacter aphrophilus, A. paraphrophilus, A. actinomycetemcomitans, Cardiobacterium* spp., *Eikenella corrodens,* and *Kingella kingae*—grow within the routine incubation period for automated blood culture systems.[16]

Special conditions are required for isolation of *Bartonella* spp. and should be performed only by laboratories familiar with culture and identification of this organism. The Isolator system is used, with subsequent inoculation onto media enriched with fresh blood (i.e., 5% rabbit blood), and it is incubated in CO_2 at 35°C to 37°C for 15 days.

Polymerase chain reaction (PCR)-based amplification of the 16S rRNA gene followed by sequencing of amplicons can detect bacteremia within hours of collecting blood specimens.[17] A multiplex blood PCR can detect gram-positive and gram-negative bacteria and fungi in samples from febrile, neutropenic patients.[18] PCR can diagnose and serotype pneumococcal bacteremic community-acquired pneumonia in children.[19] Among people with *S. aureus* bacteremia, PCR can identify patients with methicillin-susceptible *S. aureus,* permitting reductions in vancomycin use, hospital stays, and costs.[20] At the time of writing, there are no commercially available, Food and Drug Administration (FDA)–cleared in vitro diagnostic products for detection of pathogens directly from fresh blood specimens. However, newer technologies, including peptide–nucleic acid fluorescence in situ hybridization (PNA-FISH), multiplex nucleic acid amplification, nanoparticle probe technology, and mass spectrometry, enable microbiologists to rapidly identify many clinically significant bacterial and fungal pathogens and determine antimicrobial resistance mechanisms from positive blood culture broths.

Urine

Although clean-voided midstream urine is an acceptable specimen for culture for older children and adults, this specimen is difficult to procure from young children. Collection of urine by a bag fixed to the perineum is a poor substitute. In this population, catheterized specimens or specimens collected by suprapubic aspiration are preferred. Because the distal part of the urethra normally is colonized, quantitative culture is required.

A known volume of urine (i.e., 0.01 to 0.001 mL) is inoculated by means of a calibrated inoculating loop or pipette onto agar media to permit quantification of isolated colonies. Detection of 10^4 colony-forming units (CFU)/mL of a single bacterial isolate from a clean-voided midstream urine specimen (i.e., 10^2 CFU/mL from a specimen obtained by catheter) correlates with probable true urinary tract infection. Any bacterial growth from urine obtained by suprapubic aspiration is considered clinically relevant. A prolonged time in ambient temperature from collection to inoculation (i.e., 2 hours) without urine specimen preservation (e.g., BD Vacutainer C&S preservative tubes [boric acid, sodium formate, and sodium borate preservative]) is associated with a false-positive quantitative culture. Isolation of multiple organisms with low colony counts usually indicates contamination, except in special circumstances, such as an inability to concentrate or retain urine and obstructive uropathy.

Although rarely performed in modern clinical microbiology laboratories, Gram stain or acridine orange stain of unspun urine can provide an indication of urinary tract infection; visualization of two or more bacteria of the same type per high-power field indicates significant bacteriuria (i.e., 10^5 CFU/mL). However, in one study, Gram stain did not have clinical utility in making the diagnosis of urinary tract infection in children.[21]

Cerebrospinal Fluid

Specimen Collection and Processing.

CSF must be transported to the laboratory without delay because it is hypotonic, and bacterial and human cells can lyse (affecting the cell count and contributing to falsely abnormal biochemical analysis) or use glucose and therefore lower measured levels. At room temperature, cell counts decrease approximately 32% in 1 hour and 50% in 2 hours after collection.[22] Neutrophils are affected more than lymphocytes. Refrigeration can render fastidious bacteria nonviable. If delay is expected, samples are stored at room temperature or incubated at 35°C to 37°C to maximize isolation.

Routinely, CSF should be inoculated onto sheep blood agar, enriched chocolate agar, and enrichment broth (e.g., thioglycollate broth) and incubated for 4 days at 37°C in 5% to 10% CO_2. If the Gram stain result is positive but culture demonstrates no growth at 72 hours, the culture is held for an additional 4 days. The minimal volume acceptable for culture of fungi and *Mycobacterium* is 2 mL, but a volume of 10 to 15 mL is preferred.

Centrifugation by cytospinning (2000 rpm, 350 *g*) to maximize pellet formation of bacteria and cellular elements produces a yield on direct examination of CSF by Gram stain superior to that of unconcentrated samples. Leukocyte morphology is preserved, and examination of large numbers of cells improves the validity of the differential cell count. In one study, smears were positive for bacteria in 78% of samples when cytospinning was performed compared with 56% for unconcentrated samples.[23]

Gram stain demonstrates organisms in 75% to 90% of untreated patients with meningitis. Patients with *Streptococcus pneumoniae* and *Haemophilus influenzae* infection are more likely to have a positive Gram stain result (90% and 86%, respectively) than are those with *Neisseria meningitidis* (75%).[24] The yield of Gram staining correlates with the density of bacteria in CSF (i.e., positive in 97% of infections with $>10^5$ CFU/mL of bacteria and only 25% with $<10^3$ CFU/mL).[25] The yield of Gram staining decreases in patients receiving antimicrobial therapy, even orally.

Acridine orange, or 3,6-*bis*(dimethylamino) acridine staining, is a more sensitive technique than Gram stain for detecting bacteria. This is especially true for patients who have received antimicrobial therapy.[26,27]

PCR appears to be an ideal tool for the diagnosis of bacterial meningitis, especially in patients who have received antibiotics.[28,29] Many studies have demonstrated its clinical usefulness, with sensitivities similar to those of routine culture technology but with a shorter turnaround time.[30–32] PCR appears in some studies to have a higher sensitivity than bacterial culture. In one study, 16S rRNA gene PCR had an overall sensitivity of 93% and a specificity of 98%.[33] In 2016 the FDA cleared a multiplex PCR system, the FilmArray Meningitis/Encephalitis panel, for the detection of several bacterial, fungal, and viral CNS pathogens from CSF collected by lumbar puncture.

PCR technology also is being used in outbreak investigations. In one study, investigators were able to link three cases of *Streptococcus salivarius* bacterial meningitis to a healthcare provider.[34]

Bacterial antigen detection is usually not useful in the diagnosis and management of meningitis. Its value appears to be limited to patients whose Gram stain, CSF culture, and blood culture are negative; pretreated patients; and when lumbar puncture is postponed because of the severity of illness.[24,35] Although PCR appears to be a superior detection assay, in some countries with limited resources, the combination of culture, Gram stain, and antigen detection has demonstrated high sensitivity for identifying causative pathogens.[36]

Respiratory Tract

Specimen Collection.

Tables 286.1 and 286.2 highlight proper collection of respiratory tract specimens for bacterial isolation. Throat swab for the detection of *Streptococcus pyogenes* (i.e., group A *Streptococcus* [GAS]) is the most common respiratory tract specimen sent for culture. Proper collection of the sample (i.e., swab-sweeping one tonsillar surface, posterior pharyngeal wall, and opposite tonsillar surface while avoiding the tongue and saliva) affects the yield of the culture.

Rapid Tests for Group A *Streptococcus*.

Routine culture on agar requires 24 to 48 hours for results. Rapid detection assays for streptococcal antigen can yield results in 10 to 70 minutes. The specificity of various tests is 62% to 100%, but the sensitivity is lower.[37] Although initial studies performed in microbiology laboratories demonstrated high sensitivity, performance in other settings shows variable results. Results are influenced by the skill, experience, and expertise of the person obtaining the throat swab and performing the assay. In a community office-based study, the sensitivity of the office culture for GAS was higher than the rapid antigen-detection test (81% vs. 70%). Both tests have specificities greater than 97%.[38] Tests using optical immunoassay have consistently demonstrated sensitivities and specificities higher than other assays. The isolation of GAS on agar permits antimicrobial susceptibility testing for macrolide resistance.

A reflex-to-culture confirmation has been recommended for people with a negative rapid antigen test result. Because specificities are high, positive antigen tests do not need to be confirmed by culture.[39,40] Although sensitivity increases with the severity of illness, the sensitivity of the assay may not be high enough to avoid performance of a culture.[41]

Most methods that use DNA probes and PCR demonstrate high specificity and good sensitivity.[42,43] Unfortunately, many of these tests are difficult to perform and are not suitable as point-of-care tests. A rapid (~20 minutes) real-time PCR method, the cobas Liat PCR system (Roche Diagnostics), has been FDA approved for GAS diagnosis. Benefits of this system include a short time to detection and its ability to act as a stand-alone test. Confirmatory testing (i.e., culture or PCR) is unnecessary. A licensed loop-mediated isothermal amplification (LAMP) assay is rapid and easy to perform. LAMP can obviate the need for antigen and reflex culture testing.[44] Some technology can detect macrolide and clindamycin resistance.

Antigen detection assays have been used to detect GAS at extrapharyngeal sites in cases of pyogenic arthritis, cellulitis, and parapneumonic effusions. One kit demonstrated high sensitivity and specificity for detecting antigen at skin sites.[45] Antigen detection and PCR assays can enhance detection of respiratory pathogens in parapneumonic fluid.[46–48]

Special Specimens.

Tympanocentesis or sinus aspiration for culture is extremely useful in special situations, such as immunocompromised patients, patients with intracranial complications, and those who fail to respond to antimicrobial therapy. Data are conflicting regarding the validity of culture of the nasopharynx in predicting the pathogens of sinusitis and otitis media. Routine use is not indicated.

Collection of sputum from children with lower respiratory tract infections is difficult technically. Aspiration of deep pharyngeal or tracheal secretions (with a Leuken trap) is used by some physicians. Sputum is a valuable specimen from older children. Ten or more squamous epithelial cells per low-power field strongly suggest an oropharyngeal origin of collection, and 25 or more white blood cells per low-power field denotes an adequate specimen. Organism isolation at quantities of at least 10^4 CFU/mL can predict the pathogen of infection, as proved by biopsy.[49–51] Gram stain should be used to aid in the interpretation of isolates from culture.

Because transtracheal aspiration is technically difficult in children, it is seldom performed. Bronchoscopy and especially a quantitative bronchoalveolar lavage specimen or protected brush is useful in the diagnosis of *Pneumocystis jirovecii*, mycobacterial, fungal, and bacterial infections.

***Burkholderia cepacia*.**

Isolation of *B. cepacia* from the sputum of patients with cystic fibrosis requires the use of selective media. *B. cepacia*–selective agar (BCSA) or oxidative-fermentative base–polymyxin B–bacitracin-lactose (OFPBL) medium have been used.[52,53] BCSA may be superior to OFPBL.[53]

***Bordetella* Species.**

Diagnostic tests for *Bordetella* have various sensitivities, depending on the case definition, level of immunization, adequacy of collection and transport, and diagnostic method.[54,55] When properly performed, culture is superior to direct immunofluorescence assay of nasopharyngeal secretions. Cultures are more likely to be positive during the first 2 weeks of illness.[56] Serologic tests by enzyme immunoassay (EIA) (i.e., *B. pertussis*–specific immunoglobulin G) are sensitive but difficult to interpret and usually require acute and convalescent sera.

PCR assays may provide higher sensitivity with a quicker turnaround.[57–60] In people with symptoms for 2 or more weeks, PCR demonstrates a higher sensitivity than culture or direct fluorescent antigen (DFA) testing, although no method is optimal.[56,61,62] A combination of culture, serology, and PCR provides a greater sensitivity when performed on previously immunized ill patients with cough.[54,58] In many clinical laboratories, PCR targeting the repetitive elements IS481 and US1001 of *Bordetella pertussis* and *B. parapertussis*, respectively, is the test of choice, and fluorescent staining and culture are no longer performed. Standardization of PCR assays and false-positive results are problematic. The Centers for Disease Control and Prevention (CDC) recommendations for primers and test conditions are available at http://www.cdc.gov/pertussis/clinical/diagnostic-testing/index.html.

Synovial and Peritoneal Fluid

The use of blood culture systems for normally sterile fluids has increased the detection of significant pathogens.[63] Inoculation of synovial fluid and peritoneal fluid into blood culture bottles results in a higher recovery rate of bacteria than inoculation of conventional agar or broth.[64,65] In one study, *Kingella kingae* was detected exclusively in specimens of joint fluid inoculated into BACTEC bottles.[66] In another study, BacT/ALERT demonstrated high sensitivity.[67] However, PCR testing may become the test of choice for detection of *K. kingae*.[68]

For patients with spontaneous bacterial peritonitis, inoculation of peritoneal fluid into BACTEC bottles more than doubled the recovery of gram-negative bacteria.[69] Although none of the fluids inoculated into conventional media yielded streptococci or enterococci, 33% of those inoculated into BACTEC bottles grew these organisms. Similar findings have been demonstrated for patients with peritonitis complicating peritoneal dialysis.[70,71]

Special Pathogens

Clostridium difficile.

Laboratory diagnosis of *C. difficile* remains a challenge, and many different testing algorithms have been published. Most algorithms have used one or more of the following test methods: glutamate dehydrogenase (GDH) antigen to detect organisms, toxin A/B EIA, cytotoxin neutralization, toxigenic culture, or toxin gene PCR.[72] Toxigenic culture is complex to perform, and results take 2 to 7 days. PCR detection of the toxin B gene *(tcdB)* has the highest sensitivity and negative predictive value of available tests, and it has the quickest turnaround.[73–75]

PCR assays appear to be more sensitive than EIA in detecting *C. difficile* as a cause of nosocomial outbreaks, but they can overestimate clinical relavance.[76] GDH antigen assays are excellent screening tests for *C. difficile;* they have a high sensitivity and negative predictive value, and results usually are available in less than 24 hours. However, a positive result must be confirmed with a different method for detection of toxin-producing strains.[77] Although many laboratories are using toxin A/B EIAs alone, many published reports indicate that this test alone is not appropriate for toxigenic *C. difficile* detection. Testing should be performed on watery, loose, or unformed specimens only. Infants frequently can be colonized with toxin-producing strains of *C. difficile* without symptoms; testing is discouraged.[78]

Assays are being developed to detect hypervirulent strains of *C. difficile*, such as NAP1/O27/BI. Primers and probes are used to detect deletions of *tcdB*, *tcdC*, and *cdtB*.[79]

Helicobacter pylori.

Many tests are available for the diagnosis of *H. pylori*. Histologic examination of tissue stained with Warthin-Starry silver and hematoxylin and eosin stains is considered the gold standard.[80] For patients with suspected treatment failure and for whom antimicrobial susceptibility testing is desirable, isolation of the organism should be attempted. For culture, commercially available *Brucella* agar plates with 5% horse blood or brain-heart infusion (BHI) supplemented with 7% horse blood are preferred. Biopsy samples can be tested for *H. pylori* by testing for urease.

The ^{13}C-labeled urea breath test and serology are noninvasive diagnostic methods used especially in children. The breath test requires some degree of cooperation for 60 minutes. The assay is highly sensitive and specific.[81–83] An antigen assay performed on stool has replaced the urea breath test at many institutions.[84] Detection of specific antibodies may not differentiate acute from past infection, and detection of specific immunoglobulin M (IgM) antibody is not sufficiently sensitive to be useful.[85]

Although PCR may be a promising diagnostic tool for *H. pylori* infection, the rapid urease testing and histologic examination provide reliable, reproducible results. PCR allows for the detection of *H. pylori* and is a culture-independent test for clarithromycin resistance.[86] Rapid office-based technologies have been developed that may obviate the need for invasive procedures for tissue or use of the ^{13}C-labeled urea breath test.[87]

Antimicrobial Susceptibility Testing

A microorganism is considered to be susceptible to an antimicrobial agent if in vitro growth is inhibited at a concentration that is one fourth to one eighth of that achievable in the patient's blood using a usual dose of the agent. In vitro resistance strongly predicts clinical failure, but in vitro susceptibility does not ensure clinical efficacy.

Clinical isolates warrant testing if susceptibility cannot be predicted reliably a priori. The test results of certain antimicrobial agents are reported routinely, whereas other results are reported selectively to gain information about individual and community susceptibility patterns and to control inappropriate use of certain agents, limit cost, and inhibit the emergence of resistant bacteria.

Standard Media and Test Conditions

Several methods (e.g., minimal inhibitory concentration [MIC], disk diffusion, and commercial systems, each with advantages and limitations) and media have been developed for susceptibility testing, and standards have been set for interpretation of results. Methods and interpretation are pathogen and source specific. Mueller-Hinton (MH) medium is recommended for testing nonfastidious bacteria, including Enterobacteriaceae, *Pseudomonas aeruginosa,* and other non-Enterobacteriaceae, staphylococci, and enterococci. MH medium has good batch-to-batch reproducibility, is low in trimethoprim-sulfamethoxazole (TMP-SMX) and tetracycline inhibitors, and shows a good growth pattern; a large body of data and experience with its use exists.

Cation (i.e., calcium and magnesium) adjustments are necessary when testing certain organisms (*P. aeruginosa*) because the cation concentration affects the reliability of testing aminoglycosides, tetracycline, and colistin; excessive cation levels cause smaller and low levels cause larger zones of inhibition. Cation-adjusted (i.e., 20 to 25 mg/L of calcium and 10 to 12.5 mg/L of magnesium) MH broth typically is used for microdilution testing. A standardized concentration of organisms is 3 to 5 × 10^5 CFU/mL. Testing of β-lactam agents requires a strictly standardized inoculum (i.e., 5 × 10^5 CFU/mL for MIC and 10^8 CFU/mL for disk diffusion testing). An increased inoculum can falsely increase the MIC value.[88]

MH medium supplemented with 5% sheep blood is recommended for testing nonenterococcal streptococci, including *S. pneumoniae. N. gonorrhoeae* should be tested on GC agar base with 1% defined growth supplement and incubated in 5% CO_2 for 20 to 24 hours. *Haemophilus* test medium incubated at 35°C in 5% CO_2 is used for *Haemophilus;* it provides optical clarity, stability, and reproducibility and permits testing of susceptibility to TMP-SMX.

Media containing thymidine analogues such as blood or chocolate agar can interfere with the results of TMP-SMX testing. Blood-supplemented MH medium also can antagonize TMP-SMX.

Table 286.6 provides a summary of recommended media for susceptibility testing. Microdilution tests usually are incubated for 16 to 20 hours at 35°C in ambient air. Tables 286.7, 286.8, and 286.9 summarize MIC interpretative standards for commonly encountered pathogens.

TABLE 286.6

Special Media/Conditions for Dilution Antimicrobial Susceptibility Testing of Common Bacterial Pathogens

Organism	**Medium**	**Incubation Time[a] (hr)**
***Haemophilus* spp.**	HTM	20–24
Listeria monocytogenes	CAMHB with 2%–5% LHB	20–24
Staphylococcus aureus	CAMHB	16–20; 24 for vancomycin
***Staphylococcus aureus* for oxacillin testing[b]**	CAMHB + 2% NaCl	24
Streptococci	CAMHB with 2%–5% LHB	20–24
Enterococci	CAMHB	16–20; 24 for vancomycin
Enterobacteriaceae	CAMHB	16–20
***Pseudomonas aeruginosa* and other non-Enterobacteriaceae**	CAMHB	16–20

[a] The incubation environment is ambient air, except for streptococci and *Haemophilus* (Kirby-Bauer), for which CO_2 is also appropriate.

[b] Incubation at temperatures above 35°C may not permit detection of methicillin-resistant *S. aureus*.

CAMHB, cation-adjusted Mueller-Hinton broth; HTM, *Haemophilus* test medium; LHB, lysed horse blood; MHB, Mueller-Hinton broth.

TABLE 286.7

Minimal Inhibitory Concentration (MIC, μg/mL) Interpretative Standards for Commonly Used Antimicrobial Agents[a]

Antimicrobial Agent	**Response**		
	Susceptible (μg/mL)	**Intermediate (μg/mL)**	**Resistant (μg/mL)**
Ampicillin			
Enterobacteriaceae	≤8	16	≥32

Enterococci	≤8	—	≥16
Nafcillin			
Staphylococci	≤2	—	≥4
Oxacillin			
Staphylococcus aureus, S. lugdunensis	≤2	—	≥4
Staphylococcus, coagulase-negative	<0.25	—	>0.5
Extended-spectrum penicillins			
Pseudomonas spp.	≤16	32–64	≥128
Other gram-negative bacilli	≤16	32–64	≥128
Cefazolin			
Enterobacteriaceae	≤2	4	≥8
Cefotaxime or Ceftriaxone			
Enterobacteriaceae	≤1	2	≥4
Ceftazidime			
Pseudomonas aeruginosa	≤8	16	≥32
Cefepime			
Enterobacteriaceae	≤2	4–8 (SDD)	≥16
Cefuroxime oral			
Enterobacteriaceae	≤8	16	≥32
Imipenem or Meropenem[b]			
Enterobacteriaceae	≤1	2	≥4
Pseudomonas aeruginosa	≤2	4	≥8
Vancomycin			
Staphylococcus aureus	≤2	4–8	≥16
Coagulase-negative staphylococci	≤4	8–16	≥32
Enterococci	≤4	8–16	≥32
Amikacin			
Enterobacteriaceae	≤16	32	≥64
Pseudomonas aeruginosa	≤16	32	≥64
Gentamicin			
Enterobacteriaceae	≤4	8	≥16
Enterococci (high-level synergy)	≤500	—	≥500
Other non-*Enterobacteriaceae*	≤4	8	≥16
Tobramycin			
Enterobacteriaceae	≤4	8	≥16
Pseudomonas aeruginosa	≤4	8	≥16
Erythromycin			
Staphylococci	<0.5	1–4	≥8
Streptococcus pneumoniae	≤0.25	0.5	≥1
Ciprofloxacin			
Enterobacteriaceae	≤1	2	≥4
Pseudomonas aeruginosa	≤1	2	≥4
Clindamycin			
Staphylococci[c]	≤0.5	1–2	≥4
Streptococcus pneumoniae	≤0.25	0.5	≥1
Trimethoprim-sulfamethoxazole			
Enterobacteriaceae	≤2/38	—	≥4/76
Streptococcus pneumoniae	≤0.5/9.5	1/19–2/38	≥4/76

[a] For organisms other than *Haemophilus* spp., *Neisseria* spp., and *Streptococcus pneumoniae*.

[b] Following evaluation of PK-PD properties, limited clinical data, and MIC distributions that include carbapenemase-producing strains, breakpoints were revised in 2017. With implementation of new breakpoints as shown, additional testing of isolates for possible carbapenemase production need not be performed for clinical purposes.

[c] Inducible clindamycin resistance can be detected in some clindamycin-susceptible, macrolide-resistant isolates.

SDD, susceptible-dose dependent.

Modified from Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing: Twenty-Seventh Informational Supplement. Document M100–S27. Wayne, PA, Clinical and Laboratory Standards Institute, 2017.[178]

TABLE 286.8

Minimal Inhibitory Concentration (MIC, µg/mL) Interpretative Standards for Commonly Used Antimicrobial Agents for *Haemophilus* Species

Antimicrobial Agent	Response		
	Susceptible (µg/mL)	Intermediate (µg/mL)	Resistant (µg/mL)
Ampicillin	≤1	2	≥4
Amoxicillin–clavulanic acid	≤4/2	—	≥8/4
Cefixime	≤1	—	—
Cefotaxime	≤2	—	—
Ceftriaxone	≤2	—	—
Cefprozil	≤8	16	≥32
Cefuroxime	≤4	8	≥16
Clarithromycin	≤8	16	≥32
Trimethoprim-sulfamethoxazole	≤0.5/9.5	1/19–2/38	≥4/76

Modified from Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing: Twenty-Seventh Informational Supplement. Document M100–S27. Wayne, PA, Clinical and Laboratory Standards Institute, 2017.

TABLE 286.9

Minimal Inhibitory Concentration (MIC, µg/mL) Interpretative Standards for Commonly Used Antimicrobial Agents for *Streptococcus pneumoniae*

Antimicrobial Agent	Response		
	Susceptible (µg/mL)	Intermediate (µg/mL)	Resistant (µg/mL)
Cefotaxime or Cetriaxone			

Meningitis	≤0.5	1	≥2
Nonmeningitis	<1	2	≥4
Chloramphenicol	≤4	—	≥8
Clarithromycin or erythromycin	≤0.25	0.5	≥1
Clindamycin	≤0.25	0.5	≥1
Penicillin			
Meningitis	≤0.06	0.12–1	≥2
Nonmeningitis	≤2	4	≥8
Rifampin	≤1	2	≥4
Trimethoprim-sulfamethoxazole	≤0.5/9.5	1/19–2/38	≥4/76
Vancomycin	≤1	—	—

Modified from Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing: Twenty-Seventh Informational Supplement. Document M100–S27. Wayne, PA, Clinical and Laboratory Standards Institute, 2017.

Susceptibility Test Methods

Disk diffusion by the Kirby-Bauer method is a standardized technique for testing rapidly growing pathogens.[89] Briefly, a standardized inoculum (i.e., direct suspension of colonies to yield a standardized inoculum is acceptable) is swabbed onto the surface of MH agar (i.e., 150-mm plate diameter). Because reproducibility depends on the log growth phase of organisms, fresh subcultures are used. Filter paper disks impregnated with a standardized concentration of an antimicrobial agent are placed on the surface, and the size of the zone of inhibition around the disk is measured after overnight incubation. Specific incubation time ranges are outlined in the Clinical and Laboratory Standards Institute [CLSI] documents.

The broth microdilution assay is used commonly to determine MICs quantitatively.[90] MIC trays can be custom made in the laboratory or purchased commercially. Usually, five to eight concentrations of antibiotics representing therapeutically achievable ranges are tested against each organism, or one to three concentrations are used to determine activity at the breakpoint MIC. The latter allows only qualitative assessment of susceptibility; the exact MIC is unknown. Interpretation of these somewhat arbitrary standards must be made in the context of the organism, the likely site of infection, the density of the organism at the site, and the host's immunocompetence.

Automated instruments can provide results in 2 to 18 hours.[91]

Four automated systems commonly used in the United States are the bioMérieux VITEK Legacy or VITEK 2, the Beckman Coulter MicroScan WalkAway, the BD Phoenix, and the Trek Diagnostic Systems Sensititre. VITEK 2 provides susceptibility and identification as early as 2 hours after inoculation. Plastic reagent cards contain small wells or microcuvettes that allow simultaneous testing for many different antimicrobial agents. Growth is detected by means of a densitometer. It uses turbidimetrically determined kinetic measurements of growth to compute MIC values by regression analysis.

MicroScan uses substrates that release fluorophores after interaction with bacterial enzymes, a process resulting in increased fluorescence. A major disadvantage is that some bacteria fail to release fluorophores after growth.[92] To solve this problem, MicroScan has incorporated rapid, turbidimetric readers in the panels. Depending on the organism, results are available between 4.5 and 18 hours of incubation.

BD Phoenix can accommodate up to 100 panels simultaneously. An indicator is added to the broth of each isolate, and the redox indicator measures bacterial growth. Reliable results can be available after approximately 10 hours of incubation.[93]

Sensititre is customizable with a choice of completely automated, semi-automated, or manual equipment. The Sensititre ARIS 2X system has a 64-plate capacity and can perform a combination of 192 MIC, breakpoint, or identification tests on a single instrument.

Advantages of automated systems are that they can be connected to the laboratory information system, provide rapid test results, allow intralaboratory and interlaboratory standardization, are less labor intensive, and have the potential of artificial intelligence for data review.[91] Disadvantages also are noteworthy. Systems may be too restrictive for some laboratories. Panels and cards are formatted by the manufacturer with predetermined antimicrobial agents and concentrations that may not be discerning enough for many clinical situations. Custom-made panels and cards are costly. Systems are not appropriate for all organisms; unacceptable results (usually falsely susceptible test results) can occur for bacteria such as *P. aeruginosa, S. pneumoniae,* enterococci, *Stenotrophomonas maltophilia,* and coagulase-negative staphylococci.[92] The initial capital investment may be prohibitive for some facilities, and a backup system is always needed in case of system failure.[94,95] Data coming through the computer interface must be verified for accuracy. Quality control depends on the use of American Tissue Culture Collection organisms.

The E-test (bioMérieux) is a method that integrates disk diffusion and agar dilution to determine the MIC and provides accurate, reproducible quantitative results. E-test offers a simple method for testing of anaerobes and fastidious bacteria.[96–99] Briefly, an impervious inert strip carries a marked, continuous concentration gradient of a predefined antibiotic consisting of more than 15 twofold dilutions. After incubation on seeded agar, the MIC is read at the edge of the zone of inhibition as it intersects the strip. Agreement among disk diffusion, agar dilution, and broth microdilution approaches 95%.[100] E-test is especially useful for testing the susceptibility of *S. pneumoniae* to penicillin. Compared with microdilution, E-test classified all resistant and intermediately resistant strains appropriately.[101] The best results are obtained when the agar is incubated in CO_2.[102–104]

Pathogen- and Mechanism-Specific Testing

Staphylococcus aureus.

Testing of staphylococci for methicillin (oxacillin) resistance is best achieved by detection of the *mecA* gene by PCR or its product, penicillin-binding protein 2a (PBP2a) by latex agglutination.[105] Both tests demonstrate 100% correlation.[106] PCR for the *mecA* gene can detect methicillin-resistant *Staphylococcus aureus* (MRSA) rapidly and directly from positive blood culture bottles with high sensitivity and specificity.[107]

For smaller laboratories, a disk diffusion test using a cefoxitin disk is a simple and inexpensive method for detecting methicillin resistance. Disk diffusion is still useful in testing staphylococcal isolates because testing can be performed for TMP-SMX and other antimicrobial agents commonly used for treatment of MRSA that may not be available on automated system panels. Detection of inducible macrolide-lincosamide–streptogramin B resistance in MRSA isolates (i.e., D-test) is easily performed using disk diffusion.[108] Some automated systems, such as VITEK 2, can detect inducible clindamycin resistance. Disk diffusion is not reliable for detection of vancomycin resistance in staphylococci, and MIC testing should be performed. Any *S. aureus* isolate with a vancomycin MIC of 8 μg/mL or greater should be sent to a reference laboratory.

***Streptococcus pneumoniae*.**

S. pneumoniae isolated from a sterile body site (i.e., blood, bone, or CSF) or other significant specimen (i.e., pleural or mastoid fluid) should be tested directly for MICs. Testing for penicillin, cefotaxime or ceftriaxone, meropenem, and vancomycin should be performed routinely. An oxacillin disk (i.e., 1-μg disk on MH blood agar) can be used as a screening test for β-lactam resistance of *S. pneumoniae* in laboratories that cannot perform MIC testing. Penicillin and appropriate β-lactam MIC tests must be performed on any isolate with a zone diameter of at least 19 mm to determine whether the isolate is resistant.

The CLSI has different interpretative criteria for meningitis and nonmeningitis pneumococcal strains for penicillin, cefotaxime, and ceftriaxone and different criteria for oral penicillin (see Table 286.9). Only meningitis interpretations are reported for CSF isolates, but all interpretations are reported for isolates from other sources.

Extended-Spectrum β-Lactamase and Carbapenemase.

In 2010, the CLSI changed its recommendations for testing cephems in Enterobacteriaceae. Previous guidelines recommended specific screening and confirmatory tests for detection of extended-spectrum β-lactamases (ESBLs) produced by certain strains of *Klebsiella* species, *Escherichia coli,* and *Proteus mirabilis,* which have been responsible for treatment failures with extended-spectrum cephalosporins. ESBLs also have been detected in isolates of *Salmonella, P. aeruginosa, Enterobacter,* and *Citrobacter* but are difficult to differentiate from chromosomal *ampC* β-lactamases that are normally found in these isolates. The new CLSI guidelines lower the interpretative standards for cephems, which allow a laboratory to report individual drug results without having to perform the supplemental ESBL screening and confirmatory tests. Unfortunately, many of the commercial systems do not test MIC ranges low enough to use these new standards. For these laboratories, isolates can be detected by testing ESBL-specific screening drugs and then confirming testing using cefotaxime and ceftazidime with and without a β-lactamase inhibitor (clavulanic acid).[109] ESBL-producing isolates are resistant to all penicillins, all cephalosporins, and aztreonam.

Detection of carbapenemase production in Enterobacteriaceae is challenging. The most common is the *K. pneumoniae* carbapenemase (KPC). Laboratories using disk diffusion should screen using an ertapenem or meropenem disk, and those using MIC methods can screen using any carbapenem. Isolates with meropenem MIC of 2-4 μg/mL can indicate carbapenemase production and should be confirmed using a modified Hodge test (MHT).[110] However, false detection of carbapenemase production has been observed with this assay.[111] With adoption of CLSI 2017 lowered breakpoints (see Table 286.7), additional testing need not be performed for clinical purposes. Clinical efficacy has not been determined for isolates that are MHT positive but test susceptible for any carbapenem. In these cases, laboratories should report only the MIC value without an interpretation and comment that the isolate is a carbapenemase producer. The treatment outcomes of infections caused by these organisms with a carbapenem, despite in vitro susceptibility, is unknown.

A test based on the in vitro hydrolysis of imipenem (i.e., Carba NP test) has been developed.[112] The Carba NP method is highly sensitive and specific, but it requires daily preparation of test reagents, and in one study, it failed to detect some Ambler Class D, OXA-type carbapenemases.[113]

β-Lactamase.

β-Lactamase production is the most frequent mechanism of resistance of *Haemophilus* species. Ampicillin resistance mediated by an alteration in protein binding is relatively uncommon and requires MIC or disk diffusion testing for detection.

Routine testing of *N. gonorrhoeae* isolates is limited to detection of β-lactamase. Other testing should be referred to a specialized laboratory.[114]

Three methods for detection of β-lactamase are available; the cephalosporin (nitrocefin) method is the most reliable. After inoculation onto a filter paper impregnated with nitrocefin, a color change to red denotes β-lactamase hydrolysis of amide bonds. This method detects most β-lactamases from important isolates such as *Haemophilus, N. gonorrhoeae, Moraxella, Enterococcus faecalis,* and *Bacteroides.* Other assays fail to detect all β-lactamases, and their specificity can be inferior to the nitrocefin assay.[115–117]

Enterococci.

Testing of enterococci for high-level resistance to gentamicin and streptomycin is useful to predict synergistic bacterial killing in combination with a β-lactam or vancomycin. Gentamicin- and streptomycin-containing agar or MIC wells (i.e., 500 μg of gentamicin and 2000 μg of streptomycin) are used to detect resistance to high levels of gentamicin or streptomycin. If high-level resistance to gentamicin is detected, resistance to other aminoglycosides is predictable. High-level resistance to streptomycin is specific only to this agent. Incubation for a full 24 hours is necessary (48 hours for streptomycin).

Many susceptibility testing methods have problems in detecting low-level vancomycin resistance among enterococci. An agar dilution plate with BHI agar containing 6 μg/mL of vancomycin (i.e., vancomycin agar screen plate) is highly sensitive and specific.[118] However, disk diffusion testing with incubation for at least 24 hours and even broth susceptibility test systems such as VITEK 2 are comparable in their capability to detect resistance.[119] Newer molecular tests such as LC *vanA/van B* detection assay (LC assay, Roche Diagnostics) and the GeneOhm vanR assay (BD Diagnostics-GeneOhm) are capable of detecting glycopeptide resistance genes (especially *vanA* genes) among enterococcal isolates.[105]

Fastidious Bacteria.

Many organisms can cause serious infections for which test methods are not standardized and interpretative guidelines are not available. Among these are *Corynebacterium* spp., *Bacillus* spp., *Listeria monocytogenes, Erysipelothrix rhusiopathiae,* miscellaneous gram-positive cocci such as *Leuconostoc* and *Pediococcus, Aeromonas* spp., *Campylobacter* spp., *Pasteurella* spp., the HACEK group of gram-negative bacilli, and others.[120,121] CLSI document M45-A addresses in vitro susceptibility methods and interpretative criteria for these organisms.[120] Susceptibility testing of anaerobic bacteria requires special qualifications.[122] Testing is indicated for failure of the usual therapeutic regimens or the presence of severe infection when long-term therapy is anticipated (e.g., brain abscesses).

Agar dilution testing is the referenced standard for determination of MICs. *Brucella* blood agar supports the growth of all anaerobic bacteria. Preparation of agar dilution assays is tedious and is not performed in many laboratories. The E-test method is used more widely. The agar disk diffusion and broth disk elution methods are not recommended because of poor correlation with the agar dilution method. Nitrocefin testing predicts only resistance to ampicillin and penicillin.

Testing of fastidious bacteria should be limited to a few specialized laboratories. Broth microdilution can be used for testing of *Nocardia*, but this testing is not standardized.

Mycobacteria.

An agar dilution test has been the standard for testing mycobacteria. A standardized concentration of test organism is inoculated onto agar (i.e., Middlebrook 7H10) containing the antimicrobial agent to be tested. After incubation for up to 3 weeks (35°C in CO_2), susceptibility is determined by comparing growth on the antibiotic-containing medium with that on antibiotic-free medium.

The BACTEC 460TB radiometric system has provided a major advance in the susceptibility testing of slow-growing *Mycobacterium* spp. BACTEC 12B or Middlebrook 7H12 broth containing an antimicrobial agent is inoculated with the test organism and incubated for 5 days at 37°C. The growth index is compared with that of a control bottle containing no antimicrobial agent.[123] Automated nonradiometric systems such as BACTEC MGIT 960 and VersaTREK appear to be as reliable as older methods.[124–127]

Antigen Detection Assays

Bacterial antigen detection assays, which were developed for rapid diagnosis, unfortunately have poor sensitivity and specificity, and their use is not recommended.[128,129] However, a urinary antigen detection assay (i.e., EIA) for *Legionella pneumophila* serogroup 1 is sensitive and highly specific.[130] An immunochromatographic assay is available. The sensitivity of the assay is higher than that of the EIA test, and results are available within 15 minutes.[131]

When access to PCR technology is not readily available, antigen detection assays have been suggested for the diagnosis of blood culture–negative pneumococcal pneumonia. The sensitivity of this serotype-specific tube latex agglutination assay on urine was 57% for serogroups included in the assay, and the specificity was 98%.[132] The urine pneumococcal rapid immunochromatographic antigen assay (Binax NOW, Binax) has high sensitivity in patients with pneumococcal bacteremia (95%), lobar pneumonia (76%), and bacteremic pneumonia (88%).[133] In children with parapneumonic effusions, the sensitivity and specificity of the assay were 88% and 71%, respectively.[134] For adults with community-acquired pneumonia, a positive urine test permits optimization of antimicrobial therapy.[135] False-positive test results were observed for 15% of febrile children with no identifiable pneumococcal infection probably due to nasopharyngeal colonization.[136] Real-time PCR performed on culture-negative parapneumonic fluid samples has substantially increased confirmation of *S. pneumoniae* infection.[47]

Fungi

Collection and Processing of Clinical Specimens

Specimens submitted for fungal culture are inoculated onto primary isolation media as soon as possible to ensure a high yield of recovery. If a delay is anticipated, the specimen can be stored in the refrigerator at 4°C. Blood and CSF are stored at room temperature or 30°C, and dermatologic specimens such as nail scrapings or hair clippings are stored at 15°C to 30°C. Respiratory specimens should be processed fresh.

The Isolator system is the preferred method for recovery of fungi from blood.[1,137] Although this is true for molds, the automated blood culture systems can detect the growth of most *Candida* isolates. It is important to add a small amount of 0.85% saline to a tissue specimen to prevent desiccation. Specimens can then be stored at 4°C for up to 8 hours. Bone marrow should be submitted in a 1.5-mL Isolator tube.

Nails, hair, skin scrapings, fluids, exudates, and biopsy samples for direct microscopic examination can be prepared with 10% potassium hydroxide (with warming of the sample to accelerate the dissolution process). Most samples also can be examined by fluorescent microscopy with 0.1% Calcofluor white stain, a substance that binds to the chitin and cellulose of cell walls and causes bright fluorescence. Giemsa and Wright stains of blood or bone marrow specimens can reveal intracellular yeast forms such as *Histoplasma capsulatum.* Cryptococcal antigen testing of CSF has replaced India ink staining.

Isolation and Identification

No single medium is appropriate for all specimens. Sabouraud dextrose and potato flake agars are frequently used fungal media. The glucose concentration usually is limited to 2.5%; higher concentrations can inhibit some fungi such as *Blastomyces dermatitidis.* To minimize the growth of saprophytes, antimicrobial agents such as gentamicin, chloramphenicol, and cycloheximide, are added to media. Inhibitory mold agar (IMA) is one such medium that has a higher and more rapid yield.

Agar plates usually are taped or wrapped in paraffin film, and mold cultures are opened only in a biological safety cabinet to minimize the possibility of dispersing infectious conidia throughout the laboratory. Media in tubes provide maximal safety and prevent dehydration and contamination. For fluid specimens, large volumes (>2.0 mL) should be obtained and concentrated through centrifugation at 1500 to 2000 *g* for at least 10 minutes. Tissues are minced and homogenized. Mycosel medium (Becton Dickinson), which consists of soybean meal digest, dextrose, chloramphenicol, and cycloheximide, is recommended for isolation of dimorphic fungi and dermatophytes. BHI agar containing gentamicin and chloramphenicol in addition to 10% sheep blood is recommended for isolation of *Cryptococcus neoformans* from potentially contaminated fluids such as sputum. Blood obtained in Isolator tubes should be inoculated onto chocolate agar, BHI, and IMA.

After isolation, filamentous fungi frequently are identified by the microscopic characteristics of their conidia-bearing apparatus, conidiation pattern, conidial morphology, and other structures. Cellophane tape preparations of mycelium are immersed in lactophenol cotton blue stain, coverslipped, and examined microscopically. The germ tube test, in which yeast are incubated for 2 to 3 hours at 35°C in fresh fetal calf serum, identifies *Candida albicans* by outgrowth of a tube (but not all *C. albicans* are germ tube positive).

The advent of DNA probes that can confirm the identification of *B. dermatitidis* and *H. capsulatum* has rendered obsolete previous temperature conversion studies of yeast-to-mold forms to confirm *Histoplasma*, *Blastomyces*, and *Sporothrix* isolates. A DNA probe is available to confirm the identification of *Coccidioides* spp. (i.e., *C. immitis* and *C. posadasii*), obviating the need to perform exoantigen testing and spherule production studies, the latter of which is extremely hazardous and very difficult to perform in the laboratory.

Commercial systems can be used to identify many types of yeast by assimilation of carbohydrates for growth. A commonly used system is API 20C yeast identification system. It is easy to use but does not include rhamnose and urea; the former is necessary for the identification of *C. lusitaniae*. Other frequently used systems are BBL Minitek, bioMérieux VITEK 2, MicroScan, and BD Phoenix, and mass spectrometry.

Antigen Detection

An antigen detection latex agglutination test for *C. neoformans* is available commercially and has been a highly useful clinical tool. However, laboratory personnel should be aware that disinfectants and soaps used to clean ring slides can cause false-positive test results.[138]

Immunoassays performed on urine (also CSF and blood) can detect *H. capsulatum* and *B. dermatitidis* antigens. These tests are particularly useful in the diagnosis of young infants and immunocompromised hosts with disseminated disease.[139–141] Antigenemia and antigenuria can be detected in acute pulmonary histoplasmosis; but they are detected infrequently in people with chronic pulmonary disease.[142] Caution in interpreting results is merited because of cross-reactivity between fungi. However, this sometimes can be used as a convenient diagnostic tool. In the southwestern United States, a positive *Histoplasma* antigen test can aid in the diagnosis of coccidioidomycosis.[143] The diagnosis of pulmonary histoplasmosis and blastomycosis can be made by the detection of antigen in bronchoalveolar lavage fluid. In one study, the overall sensitivity and specificity was 92% and 98.2%, respectively.[144]

Circulating *Aspergillus* galactomannan antigen can be detected in blood specimens from patients with suspected invasive aspergillosis. Frequent screening with this assay may lead to an earlier diagnosis for many immunocompromised patients.[145,146] Interpretation of positive test results requires careful consideration for patients receiving antibiotic therapy containing β-lactamase inhibitors such as piperacillin-tazobactam because false-positive results have been reported.[147] However, some investigators found that most commercial brands of piperacillin/tazobactam were not responsible for false-positive results.[148] Clinicians should be cautious in interpreting negative results because antifungal therapy appears to decrease test sensitivity.[149]

Bronchoalveolar lavage galactomannan testing has led to the diagnosis of invasive pulmonary aspergillosis in solid-organ transplant recipients and patients with hematologic diseases.[140,150] However, false-positive results can occur for lung transplant recipients.[140] False-positive galactomannan assays have been reported for patients with histoplasmosis.[151]

Antifungal Susceptibility Testing

The emergence of resistance in clinically relevant fungi and yeasts and the availability of new antifungal agents have resulted in the need for standardized methods for antifungal susceptibility testing and interpretation of results.[152–154] Advances in standardization and guidelines for interpretation permit testing of some types of yeast, but MIC testing of molds should be performed in reference laboratories. Yeast susceptibility can be performed using disk diffusion (i.e., *Candida* species only; see CLSI document M44-A2)[152] or broth dilution (i.e., see CLSI document M27-A3).[154] Unique problems are a slow growth rate and dimorphism.

The end point MIC for amphotericin B is easily defined, but end points for azoles are difficult to determine because of their unique partial inhibition of fungi. Use of the test medium RPMI 1640 with L-glutamine shows the best reproducibility for broth dilution methods. The technical aspects of testing must be controlled carefully to permit reproducibility and to avoid inaccuracies. Few data exist that enable correlation of test results with clinical outcomes.[152–154]

Availability of echinocandins and voriconazole increase the options for more effective treatment of infections such as aspergillosis. Combinations of these agents may be desirable in some patients because of their synergistic effects.[155] Susceptibility and interactions are not always predictable. Due to potential interlaboratory and intralaboratory reproducibility problems, testing of filamentous fungi and for effects of combination therapy should be limited to specialized laboratories.[156]

Parasites

Examination of Feces

Collection and Preservation

Proper collection and handling of stool specimens are critical for the detection of parasites. Stool should be collected in a clean, wide-mouthed container with a tightly fitting lid. Unpreserved stool specimens are considered potentially infectious and must be handled with care. Stool samples are rejected if they contain mineral oil, bismuth, or barium, which may interfere with accurate examination. The specimen should not be contaminated with urine or water from the toilet.

If transportation to the laboratory is not prompt, the specimen is stored in the refrigerator. Dry samples are not acceptable. A minimum of three samples over a period of 7 to 10 days usually is required for accurate testing. For the diagnosis of amebiasis and giardiasis, at least six specimens may be required before negative clinical interpretation is appropriate. In one study, only 72% of parasites were detected with a single specimen. Another 28% were identified with two additional specimens.[157] In areas of high parasite prevalence (20%), a comprehensive evaluation of a single specimen may have enough sensitivity to be appropriate clinically.

Liquid stool should be examined or preserved within 30 minutes of collection, soft or semiformed stool within 1 hour, and formed stool on the same day. Two commonly used preservatives are polyvinyl alcohol (PVA) and formalin. PVA provides a good permanent smear and preserves the integrity of trophozoites and cysts. PVA should be handled with care; the substance is poisonous. Formalin is a useful preservative in general, and formalin specimens can use a concentration procedure to increase parasite detection, especially cyst and helminth ova (trophozoites do not survive the concentration method). Formalin is superior for helminth ova, *Giardia,* and *Cystoisospora belli.*

Examination

Stools are examined grossly for consistency, mucus, blood, and adult worms or proglottids. Trophic amebae and flagellates are encountered more commonly in liquid and soft specimens; these organisms disintegrate rapidly at room temperature. Trophozoites and cyst forms are observed more commonly in semiformed stools, and cysts are seen in formed stools.

A direct wet mount smear can be prepared with 0.85% saline or with D'Antoni or Lugol iodine. The specimen is scanned at ×10 and then at ×40 magnification. Because wet mount requires fresh stool, it is done infrequently.

Concentration of feces is important when small amounts of organisms are expected. Concentration is designed to facilitate the recovery of protozoan cysts, coccidian oocysts, and helminth eggs and larvae. The flotation or sedimentation (i.e., formalin–ethyl acetate) method can be used. Flotation provides a cleaner sample than sedimentation; the higher density of zinc sulfate pushes the protozoan cysts to the surface after centrifugation. The cysts are recovered for examination from the supernatant. Helminth eggs are better recovered with the sedimentation method. After sedimentation, an iodine stain is performed.

A permanent stain smear is prepared for the identification of intestinal parasites using a PVA-preserved specimen. Wheatly-Gomori tissue trichrome and iron-hematoxylin stains are preferred.

Special Pathogens

Permanent staining with trichrome or iron-hematoxylin allows definition of morphology and provides a slide for reference. *Cryptosporidium* species usually are not seen with either stain; they require the use of stains for acid-fast bacilli, such as the modified Kinyoun stain. These stains also can be used to detect *C. belli* and *Cyclospora cayetanensis*. If the sediment is mucoid, potassium hydroxide should be added.

Monoclonal antibody assays or direct fluorescent antibody stains for *Giardia* and *Cryptosporidium* are useful when the density of parasites is expected to be low. In specialized laboratories, fecal culture methods or coprocultures (i.e., Baerman technique) can be used to recover parasites. These techniques are useful in cases of low-density infestation with hookworms, *Strongyloides,* and *Trichostrongylus.*

A simple way of obtaining larvae and adult worms of *Enterobius vermicularis* for examination is the cellulose tape method. Tape reversed on a tongue depressor is pressed against the anus in the early morning. The tape is then placed over a slide and examined for the characteristic D-shaped *E. vermicularis* eggs using light microscopy.

Stool antigen detection assays using polyspecific polyclonal antibody are nonspecific and less sensitive in transported or stored samples with fixatives. *Giardia* antigen GSA 65, which is specific to *G. lamblia* and stable in the gastrointestinal tract and in fixatives, is a potentially useful antigen. Detection with a *Giardia* antigen detection method (Prospec T/Giardia, Alexon) is sensitive and specific when testing symptomatic and asymptomatic people. The technique has a sensitivity of 96%, compared with 74% for stool examination for eggs and parasites.[158]

Other immunoassays can detect *Cryptosporidium* antigens.[159] They have good sensitivity and specificity, are easy to perform, have quick turnaround, and are reproducible.[160] Several multiplex, real-time PCR assays have been developed for the detection of *Entamoeba histolytica, G. intestinalis, Cryptosporidium* spp., and a few other protozoan parasites.[161]

Trichomonas vaginalis can be observed on direct saline wet mounts from vaginal secretions, first-voided urine, or other fluids such as respiratory tract secretions from neonates.

Detection of Gastric-Duodenal Pathogens

Duodenal contents can be examined for parasites and protozoa by means of the Enterotest capsule. A silicone rubber capsule that contains a spool of string attached to a weight is swallowed. The capsule dissolves, and by peristalsis, the string moves into the small intestine. The string provides an attachment site for duodenal mucus and *Strongyloides* larvae, *Giardia* trophozoites, cryptosporidia, and *Cystoisospora* oocysts. No food is allowed during the test, which takes approximately 4 hours. Yellow staining of the string indicates bile. Duodenal aspiration provides an alternative specimen, but the string test is less invasive.

Tissue Specimens

Tissue obtained by biopsy is the preferred specimen for severe parasitic infections such as toxoplasmosis. Impression smears, squash preparations, and scrapings from skin and nails are commonly submitted specimens. These specimens are stained and examined microscopically. Giemsa stain of the lung, small intestine, skin, or brain can reveal organisms such as *Toxoplasma gondii, Leishmania, Naegleria,* or *Entamoeba.* Other stains such as trichrome and methenamine silver enhance the visualization of parasites. Immunospecific stains such as the TYSGM-9 stain for *E. histolytica* have been developed to improve the sensitivity and specificity of direct microscopy. Modified acid-fast staining of the small intestine allows visualization of *Cryptosporidium parvum, C. belli,* and *C. cayetanensis.*

Blood Smears

Thin- and thick-film smears stained with Giemsa or Wright stains are still reliable and efficient ways of diagnosing bloodstream parasitic infections caused by *Plasmodium, Babesia, Trypanosoma,* and *Leishmania. Borrelia* spp. and *Yersinia pestis* also can be visualized with these stains. Parasites are observed more easily in the thinner portion of a thick film. The thick film should be examined for 5 to 10 minutes (~100 fields) and the thin film for 15 to 20 minutes (~300 fields).

A single blood sample is not sufficient to exclude a diagnosis of these parasitic diseases. Blood samples should be submitted every 6 to 12 hours. Anticoagulated blood with EDTA is acceptable only if the sample is less than 1 hour old. Buffy coat preparations can be stained to visualize the amastigotes of *Leishmania* within monocytes. Fingerstick blood is preferred when examining blood for *Plasmodium*. In one study, a rapid diagnostic test for malaria, the NOW Malaria Test (Binax), was superior in detecting *P. falciparum* (sensitivity of 100%) to a single set of blood smears.[162]

Newer diagnostic tests (e.g., PCR, loop-mediated isothermal amplification) are becoming more available worldwide.[163] They are valuable in areas in which microscopy is unavailable and where the availability of antimalarial agents is limited. In some instances, people testing negative do not require treatment.[164]

Rickettsiae

Rickettsial organisms are difficult and hazardous to isolate, and they are difficult to visualize with light microscopy. Immunofluorescent stain of biopsy samples is useful.

Most diagnoses are based on clinical features and confirmed with serologic tests.[165] The most commonly used tests are the indirect fluorescent assay and the microimmunofluorescent test. Additional assays have been developed. A latex agglutination test can detect IgM and IgG antibody against specific rickettsial antigens. Cross-reactions occur among rickettsial species. False-positive results with indirect fluorescent assays have been reported for users of illicit parenteral drugs. The Weil-Felix assay is rarely used because of its lack of sensitivity and specificity.

Immunoserology

Documentation of a specific immune response to a pathogenic microorganism provides proof of infection. Methods used for the measurement of antibodies include hemagglutination, EIA, latex agglutination, complement fixation, immunofluorescence, and neutralization assays. Certain methods may be better for certain infections.

The Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin tests are the current screening tests for syphilis and for measures of the activity of infection. Observation of spirochetes in body fluids by dark-field examination (or by the direct fluorescent antibody test) or positive specific treponemal antibody tests such as the fluorescent treponemal antibody absorption test confirm infection.[166] The use of specific treponemal antigens enable more precise screening for syphilis. However, the antibody test may have poor positive predictive value in low-risk populations and cannot distinguish active from treated disease. Positive assays must be confirmed with nontreponemal assays.[167]

The immune response to specific pathogenic fungi as determined by immunodiffusion or completion fixation assays can assist in the diagnosis of *Aspergillus, Blastomyces, Histoplasma,* and *Coccidioides* infections. However, false-negative test results occur, especially early in the disease or in immunosuppressed hosts.[168]

Febrile agglutinin tests have limited clinical utility in developed countries. They should not be used.[169]

Newer Technologies

Genomics- and proteomics-based methods have revolutionized the ways in which infectious diseases are diagnosed. Nucleic acid amplification tests (NAATs), such as PCR and transcription-mediated amplification, have become important resources for the detection of pathogenic microorganisms and viruses directly from patient specimens. PCR, which is more sensitive than in situ hybridization methods, has proved useful for identifying slowly growing microorganisms such as *Mycobacterium tuberculosis*; difficult or impossible to cultivate pathogens, including *Borrelia burgdorferi, Rickettsia* spp., and many viruses; potential agents of bioterrorism; and multiple parasitic protozoa, including *Plasmodium* spp., *Giardia duodenalis*, and *Cryptosporidium* spp. The incorporation of DNA-intercalating dyes or fluorescent probes and high-resolution melting analysis into PCR has paved the way for real-time pathogen detection, identification, and quantification of target nucleic acids in clinical specimens, which allows determination of disease activity and response to therapy.

Multiplexing of real-time PCR permits detection of numerous analytes, which can include multiple genetic targets of one pathogen or numerous different pathogens in a single specimen. Multiplex assays are designed to detect a number of pathogens associated with specific diseases processes; these assays are referred to as *syndromic panels*. For the investigation of infectious disease outbreaks, molecular fingerprinting methods such as pulsed-field gel electrophoresis, multilocus sequence typing, multiple loci variable-number tandem repeat analysis, and next-generation sequencing have become standard in public health laboratories. Collectively, these methods have fostered the field of molecular epidemiology.

Mass Spectrometry.

Mass spectrometry has become commonplace in many clinical microbiology laboratories as an adjunct to or replacement for conventional phenotypic microbial identification methods. However, laboratories are cautioned against totally eliminating phenotypic methods because these methods will be needed when the mass spectrometer is being serviced or is otherwise out of commission, especially if another mass spectrometer is not available.

Matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) mass spectrometry enables rapid identification of bacteria, yeast, and molds quickly and accurately using growth from plate cultures.[170] MALDI-TOF mass spectrometry has been applied to the identification of microorganisms directly from positive blood culture broths. In addition to MALDI-TOF, PCR coupled with electrospray ionization (ESI) mass spectrometry offers a promising role in the identification of microorganisms and viruses.[171–173] Two manufacturers (i.e., Bruker Corporation and bioMérieux) market FDA-cleared MALDI-TOF systems for identification of microorganisms isolated in culture: the MALDI Biotyper system and the VITEK MS system, respectively. Research-use-only mass spectral profile (MSP) libraries also exist and can be validated by laboratories for use in diagnostics. Overall, MALDI-TOF has demonstrable superior performance compared with phenotypic methods for identification of bacteria, mycobacteria, and fungi. Emerging technologies are reviewed by Buchan and Ledeboer.[174]

Syndromic Panels.

Several diagnostic product manufacturers are developing or market multiplex nucleic acid–based assays for the detection of agents causing bloodstream, respiratory tract, gastrointestinal tract, and central nervous system infections. Assays have been developed based on multiplex nucleic acid amplification and high resolution melting analysis (e.g., FilmArray, BioFire Diagnostics, LLC), nanoparticle-laden antibody or oligonucleotide probes (e.g., Verigene System, Nanosphere, Inc.), and ferrocene-labeled oligonucleotide probes coupled with electrochemical detection (eSensor XT-8, GenMark Diagnostics, Inc.).

FDA-approved FilmArray panels are available for the analysis of positive blood culture broths (i.e., Blood Culture Identification Panel, which detects 24 pathogens and 3 antimicrobial resistance markers),[175] nasopharyngeal swabs (i.e., Respiratory Panel, which detects 17 viral and 3 bacterial pathogens),[176] and stool specimens (i.e., Gastrointestinal Panel, which detects 22 bacterial, parasitic, and viral pathogens).[177] A meningitis panel is being evaluated for the detection of 16 bacterial, fungal, and viral pathogens.

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Laboratory Diagnosis of Infection Due to Viruses, *Chlamydia*, *Chlamydophila*, and *Mycoplasma*

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Viruses

The availability of rapid and reliable viral diagnostic tests, particularly nucleic acid amplification tests (NAATs), facilitates decision making in the prevention, treatment, public health, and infection control measures related to viral infections. With specific antiviral therapy available for many clinically relevant viruses, a specific viral diagnosis may limit the need for further diagnostic testing and unnecessary antibiotic therapy.[1–3]

Two major approaches to diagnosis of viral infection are virologic (detection of virus) and serologic (detection of antibody, antigen, or both). The virologic approach includes (1) isolation of infectious virus in cell culture, (2) detection of viral antigen by immunologic methods (e.g., fluorescent antibody [FA] testing or enzyme immunoassay [EIA]); (3) visualization of viral particles by electron microscopy (EM); and (4) detection of viral nucleic acid by molecular techniques (e.g., hybridization or NAATs). Cytologic examination of tissues and cells may identify viral effects, thus prompting further investigation. Occasionally, cytologic changes can be sufficiently specific to suggest a particular agent (e.g., cytomegalovirus [CMV]).[4] The serologic approach includes detection of the following: (1) virus-specific antibodies indicating recent, current, or past infection, as well as immunity following recovery or vaccination; (2) a significant rise in virus-specific immunoglobulin G (IgG) antibody suggestive of acute or recent infection; (3) virus-specific antigens (e.g., hepatitis B surface antigen [HBsAg]); or (4) virus-specific IgM antibody in late acute or early recovery phase sera. As the immune response matures following a viral infection, low-avidity IgG antibodies are replaced with high-avidity antibodies. EIAs capable of measuring the avidity of IgG antibodies to specific viruses have been used to distinguish primary from secondary (reactivation) antibody responses to vaccination or natural infection.[5,6]

Clinically, laboratory tests for the detection of virus infection can be divided into 3 specific categories: those used to (1) make a specific diagnosis, (2) measure virus activity in patients known to be infected (e.g., viral load testing for human immunodeficiency virus [HIV]), and (3) screen for infection or a carrier state (e.g., before transplantation or blood donation).

Specimen Collection and Transport

For the detection of most viruses, specimens collected soon after the onset of clinical symptoms (preferably within the first 3–4 days) when viral shedding is greatest are preferred. Optimal specimens vary depending on the site or sites of disease. In general, tissues, aspirates, and body fluids are superior to swabs. Body sites or lesions that can be sampled easily with a swab include the pharynx or nasopharynx, conjunctiva, urethra, cervix, vagina, and vesicles or ulcers on the skin or mucous membranes. Many swabs types are available for specimen collection, including plastic swabs, wooden swabs, and swabs with a flexible wire shaft and a tip made of cotton, Dacron, calcium alginate, or polyurethane,[7] although not all are suitable for detection of some viruses. Swabs with a wooden shaft can contain toxic products that inactivate herpes simplex virus (HSV). Cotton-tipped swabs can contain fatty acids that can interfere with the survival of *Chlamydia* species, but they are suitable for the collection of specimens from the vagina, cervix, or urethra for the detection of *Mycoplasma.* Calcium alginate–tipped swabs can be toxic for lipid-enveloped viruses such as herpesviruses and some cell cultures, but they are useful for the collection of specimens for *Chlamydia.* Although swabs placed in a viral transport medium (VTM) can be used for NAATs, many commercial assays for detection of viruses and *Chlamydia* provide their own swab and transport media, which should be used.

Swabs and tissues for detection of viruses should be placed into VTM to prevent drying, maintain virus viability, and prevent the overgrowth of contaminating organisms.[7] Several commercially prepared VTMs are available.[7] Swabs collected for bacterial isolation that are placed in bacterial transport medium are unacceptable for detection of viruses.[7] Conversely, VTM contains antimicrobial agents that inhibit most bacteria and fungi. Specimens such as blood, bone marrow, cerebrospinal fluid (CSF), urine, and other body fluids should be placed in clean, sterile containers without VTM.

For detection of most respiratory viruses, a nasopharyngeal (NP) aspirate or wash, sputum, or bronchoalveolar lavage (BAL) specimen provides a better yield for detection of viruses than NP, nasal, or throat swabs.[7] Multiple samples can be required to maximize yield. Freshly passed stool is superior to a rectal swab for detection of gastrointestinal viruses.[7]

Specific viruses can be found in different blood cells, the plasma or serum, or both (e.g., HIV in lymphocytes and macrophages, CMV in neutrophils and to a lesser extent in mononuclear cells, enteroviruses in plasma and white blood cells).[8,9] Blood should be collected into Vacutainer tubes containing an anticoagulant such as ethylenediaminetetraacetic acid (EDTA). Recovery rates are higher with EDTA than with heparin.[10] Heparin can inactivate herpesviruses and can inhibit some NAATs[11,12]; this issue may be less of a concern for real-time polymerase chain reaction (PCR) and can be related to the type of heparin (sodium vs. lithium) used.[13,14]

For tissue specimens or when the lability of particular viruses (e.g., respiratory syncytial virus [RSV] or varicella-zoster virus [VZV]) is a concern, VTM containing albumin or serum as a stabilizer should be used.

Most viruses are stable for 2 to 3 days at 4°C (refrigerator or wet ice temperature).[7] Freezing at −20°C (ordinary freezer temperature) destroys or reduces the infectivity of most viruses and can alter the ability to detect viral antigen when using some commercially available kits. Beyond 2 to 3 days, specimens should be stored in an ultralow-temperature freezer (−70°C) and transported on dry ice. For some NAATs (e.g., detection of hepatitis C virus [HCV] RNA in serum or plasma), serum or plasma should be separated within 4 to 6 hours of collection and processed within 72 hours (if kept at 2°C–8°C) or frozen at −70°C until tested.[7]

For serologic detection of viral antibodies or antigen, blood can be transported at room temperature. If a delay is anticipated, the specimen should be kept refrigerated at 2°C to 8°C. Serum or plasma should be separated as soon as possible after specimen collection. If an extended period will elapse before testing, the serum or plasma sample should be frozen at −20°C or lower. Repeated freeze-thaw cycles should be avoided. For viruses for which an IgM assay is available (e.g., hepatitis A virus [HAV]), an acute phase specimen can be sufficient for diagnosis. Otherwise, an acute phase specimen is collected within a few days of illness onset and serum is stored, followed by collection of a convalescent phase specimen 2 to 4 weeks later, and the specimens are tested simultaneously.

Virus Detection Methods

Virus Isolation

Most laboratories performing virus isolation use monolayer cell culture techniques. However, many clinically relevant viruses, such as parvovirus, human papillomavirus, hepatitis viruses, Epstein-Barr virus (EBV), rotaviruses, noroviruses, and others, are not cultivatable in routine diagnostic laboratories; laboratory diagnosis is based on other methods. Although cultivation of HIV is possible using suspension cultures of lymphocytes, special containment facilities are required; alternative methods are used for routine diagnosis. The major viruses detected by isolation in monolayer cell culture include HSV-1 and HSV-2, CMV, VZV, RSV, influenza A and B viruses, parainfluenza viruses, respiratory adenoviruses, several enteroviruses (coxsackievirus, echovirus, poliovirus), and measles virus. Not all cultivatable viruses replicate in a single cell line. Thus various cell lines are used for primary isolation: diploid cell lines such as human foreskin or lung fibroblasts for herpesviruses, primary cell lines such as primary rhesus monkey kidney cells for respiratory viruses and enteroviruses, and heteroploid or continuous human epithelial cell lines such as Hep-2 cells for RSV. The types of cell lines used in the diagnostic laboratory are determined by the specimen type, season, epidemiologic data, and clinical information provided. Many viruses cause morphologic changes (i.e., cytopathic effect[(CPE]), in the cell monolayer. Some viruses cause CPE within 2 days (e.g., HSV), others within a week (e.g., enteroviruses), and others after several weeks (e.g., CMV). For viruses that do not cause a typical CPE, detection can be based on the adsorption of red blood cells to the surface of virus-infected cells in culture (e.g., influenza and parainfluenza viruses) or by the use of interference assays (e.g., rubella virus). Presumptive identification of a particular virus or virus group in cell culture is based on the cell type, the timing and appearance of CPE, the source of the specimen, and the suspected clinical diagnosis.

Confirmation of the virus isolated requires immunologic methods such as fluorescein- or peroxidase-conjugated virus-specific monoclonal and polyclonal antibodies. Antibodies to HSV, CMV, VZV, RSV, influenza A and B virus, parainfluenza virus, adenovirus, measles virus, and enterovirus antigens are readily available.

Centrifugation of specimens (referred to as shell vial or spin-amplified culture) onto cell monolayers on coverslips placed in the bottom of small vials or in wells, followed by incubation and staining for viral antigen by using monoclonal antibody after 1 to 3 days, shortens the time required to detect and confirm the presence of many viruses and has replaced conventional cultures in many laboratories. For slowly growing viruses such as CMV, the use of monoclonal antibody against nonstructural proteins produced early in the replication cycle (i.e., immediate early antigen [EA] or EA) allows detection of virus days to weeks before CPE can be observed by traditional cell culture techniques.

Two techniques for isolation of some viruses have been developed with sensitivity comparable to that of standard culture and shell vial methods.[15–17] Genetically engineered cell lines such as the enzyme-linked virus-inducible system (ELVIS, Quidel, San Diego, Calif) using a baby hamster kidney cell line that has been transformed by using an HSV-inducible promoter (*UL39* gene) and an *Escherichia coli* β-galactosidase gene was introduced for the isolation of HSV. The addition of a substrate for the β-galactosidase enzyme results in formation of a color reaction in the HSV-infected cells. This technique has been adapted for performing rapid HSV antiviral susceptibility testing. Mixing multiple cell types in a single shell vial culture can provide rapid detection of the following: respiratory viruses (R-Mix, Quidel); HSV, CMV, and VZV (H&V-Mix, Quidel); and enteroviruses (E-Mix, Quidel).

Antigen Detection

Virus antigen detection tests can be performed directly on a variety of specimen types and are highly specific and rapid.[7] Because virus antigen is cell associated, collection of an adequate number of infected cells is important. Several commercial kits (EIA, latex agglutination, FA) are available for the detection of the following: (1) rotavirus and enteric adenovirus in stool specimens; (2) RSV, influenza A and B viruses, parainfluenza viruses, and adenoviruses in respiratory tract specimens; (3) HBsAg and HIV p24 antigen in serum; (4) HSV and VZV in vesicle or ulcer swab specimens; and (5) CMV in BAL and blood specimens. The FA technique has been used for the detection of rabies virus in brain tissue, mumps virus in throat and urine sediment, and measles virus in conjunctival cells. The detection of CMV pp65 antigen in neutrophils can be used in the diagnosis and management of new or reactivated CMV infection in immunocompromised patients.[18]

Electron Microscopy

Although almost any specimen type is suitable for EM, most laboratories have replaced EM with other virus detection methods.[19,20] Some laboratories continue to use EM for the detection of gastrointestinal pathogens such as rotavirus, enteric adenoviruses, and norovirus, as well as for detection of BK-polyomavirus in tissue biopsy and urine samples.[21–25] Disadvantages of EM include the large number of virus particles (approximately 1 × 10^6/mL of specimen) required for detection, limited throughput, expense, and lack of availability and expertise in many centers.[24]

Nucleic Acid Detection

The increased sensitivity and availability of NAATs for detection of almost any clinically relevant virus have revolutionized testing in the clinical virology laboratory.[19,25–29] In many laboratories, NAATs have supplanted virus culture, antigen detection methods, and direct molecular hybridization techniques. Three approaches have been taken: (1) *target amplification* such as PCR, strand displacement amplification, nucleic acid sequence–based amplification, and transcription-mediated amplification systems; (2) *probe amplification,* including Q-β replicase and ligase chain reaction; and (3) *signal amplification,* such as branched-chain DNA (bDNA) assay and hybrid capture assay.[3,26–32] Several commercial and in-house ("home-brew") assays have been developed. Quantification of viral genome in plasma or serum can be used to determine prognosis, select patients for antiviral therapy, and monitor response to treatment in a variety of patient populations.[28,33] Multiplex assays capable of detecting several viruses in a single amplification reaction have been developed (e.g., for herpesviruses and for enteric, bloodborne, and respiratory viruses), and studies suggest that these assays are cost-effective.[34–39] The development of automated real-time PCR using fluorescence techniques and continuous detection of amplified product has shortened detection times substantially relative to conventional PCR assays.[40] Because these assays use a closed system (i.e., amplification and detection occur in a single tube that need not be opened once the reaction is completed), they also are less prone to contamination than conventional PCR. NAAT has been applied to genotyping of viruses (e.g., HIV, HBV, and HCV), as well as for the detection of mutations that confer resistance to antiviral agents.[28] Newer molecular techniques such as pyrosequencing and whole-genome sequencing are beginning to be applied in the clinical laboratory and are providing improved genotyping of viruses, detection of virus quasispecies, and metagenomic analysis for detecting existing and new or novel viruses in clinical specimens.[41,42]

Choice of Virus Detection Method

Choosing optimal tests depends on the specific virus being sought, clinical setting, specimen type, availability of kits, reagents and equipment, experience of laboratory personnel, and cost. The use of NAATs is rapidly replacing older viral diagnostic methods because of the rapid turnaround time, superior sensitivity, and ability to quantify virus density of NAATs. Several relatively simple in-house and commercially available NAATs are available for a wide variety of viruses. However, some laboratories continue to use antigen detection methods and virus culture when expertise in molecular techniques is not available or cost is prohibitive.

Serologic Methods

Serologic methods can be used to diagnose a current or recent acute infection, to determine specific susceptibility or immunity, and for epidemiologic and surveillance purposes. Interpretation of serologic results is virus specific. For example, the presence of HIV antibodies indicates current infection, whereas the presence of IgG antirubella indicates immunity as a result of immunization or recovery from natural infection. Serologic diagnosis of acute infection is more useful when the incubation period is prolonged (e.g., 3–6 weeks) and antibody is present in serum concomitantly with signs of illness (e.g., EBV and CMV mononucleosis). Fig. 287.1 shows a typical antibody response for an acute, moderate-incubation (several days to 2 weeks) viral illness such as measles. At the onset of rash or other manifestations, antibody is undetectable or is present at low titer. Within 10 to 14 days, appreciable titers of antibody are present. For short-incubation virus infections (e.g., respiratory viruses), a rise in antibody usually does not occur until the late recovery phase or during convalescence and therefore has no value for diagnosis during acute infection. Older serologic methods such as hemagglutination inhibition and complement fixation (CF), which relied on a greater than fourfold rise in antibody titer between acute and convalescent sera tested in parallel, have largely been replaced by solid phase immunoassays such as EIAs, passive latex agglutination, and immunofluoresence assay (IFA). The presence of antibody in high titer in a single serum specimen during convalescence usually does not permit a definitive diagnosis. Seroconversion can be used to diagnose an acute or recent infection.

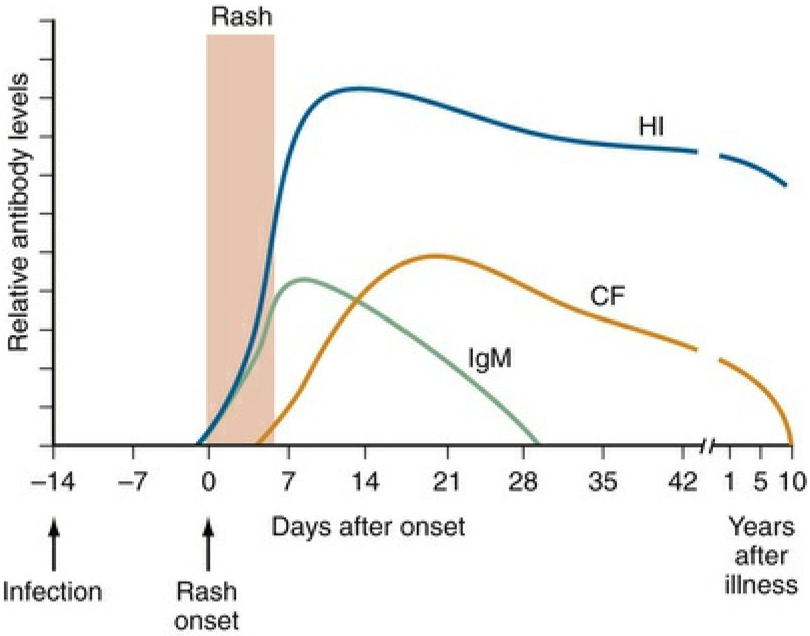

FIGURE 287.1 **Antibody responses during acute measles. CF, complement fixation antibody; HI, hemagglutination inhibition antibody; IgM, immunoglobulin M.**

EIAs and ELISAs are highly standardized, can be quantitative, can detect IgG or IgM antibodies, or both, and, for some viruses such as HIV and HCV, can simultaneously detect both antigen and antibodies in a single assay.[43,44] EIAs can be noncompetitive ("sandwich assay") or competitive assays. Results usually are measured in optical density (OD) units because of a color reaction, and results are reported either qualitatively or quantitatively in international units (IU) or index values. Interpretation of optical density units varies with the EIA-ELISA kit used and the virus antibodies being detected. A relatively newer modification of EIA (known as chemiluminescent immunoassay) uses an enzyme/substrate combination to generate a light signal and results are reported as relative light units (RLU). Chemiluminescent immunoassays generally are considered more sensitive than EIAs.

The presence of virus-specific IgM antibody in serum obtained 1 to 2 weeks after the onset of illness permits a diagnosis of acute or recent infection for many viruses. Typically, IgM antibody disappears from serum within a few months after the acute illness, but it can persist for an extended time in some people and for some viruses.[45] False-positive IgM results can be caused by (1) cross-reactivity (e.g., among herpesviruses or from polyclonal stimulation secondary to EBV infection),[46] (2) the presence of rheumatoid factor (IgM antibody that binds to the Fc portion of IgG),[47] and (3) inherent testing difficulties.[48] Misinterpretation of IgM antibodies as indicative of an acute or recent infection also can occur as a result of (1) persistence of IgM antibody for several months after the acute illness (e.g., EBV, West Nile virus)[49] or (2) reactivation of latent or chronic viruses (e.g., HSV, HBV).

False-negative IgM test results can reflect the following: (1) an absent, low, or delayed IgM response, especially in immunologically immature hosts (e.g., during infancy, congenital CMV or HIV infection) or in immunosuppressed patients (e.g., patients with acquired immunodeficiency syndrome [AIDS])[49,50]; or (2) the presence of high-titer IgG antibody (precluding binding of IgM).[20] Many commercially available kits contain reagents to adsorb IgG from the test serum or use a background subtraction step, thus reducing the possibility of interference.[51,52]

When IgG antibody tests are used to determine susceptibility or immunity to a particular virus, the sensitivity of the method is important. Detection of neutralizing antibodies can be the best predictor of immunity.

The major advantages of serologic diagnosis of acute viral infection include noncritical specimen handling and wide availability. The disadvantages include (1) the requirement for acute and convalescent sera for IgG antibody tests, (2) false-positive and false-negative IgM antibody results, and (3) a delay of 2 to 3 weeks before a diagnosis can be confirmed with short-incubation infections. Because of the many confounding factors (e.g., passive transfer of antibodies from mother to infant, receipt of immunoglobulin, immunocompromise), serologic test results always should be interpreted within the context of the clinical situation. Whenever possible, serologic diagnosis should be confirmed with the use of virus isolation or direct detection of virus antigens or nucleic acids.

Depending on the serologic assay, either serum or plasma can be used. The use of other specimen types has not been well validated for most viruses or assays. Some exceptions include the use of saliva for the detection of HIV antibodies and CSF in patients with viral central nervous system (CNS) disease.[53,54]

Optimal Tests for Specific Viruses

Table 287.1 contains a list of the medically important viruses, major attributable diseases, optimal diagnostic specimens, available tests, and average time to a positive test result. For many tests, the time to obtain a result is a function of the test itself (e.g., culture), the logistics of laboratory testing schedules, or the need to refer a sample to a reference laboratory. The preferred test provides the fastest result with acceptable sensitivity (>90%) and specificity (>95%). The preferred diagnostic test or tests can vary, depending on the patient population being tested (e.g., immunocompromised hosts) and the clinical indication.

TABLE 287.1

Optimal Specimen, Preferred Test, and Performance in Confirmation of Specific Infections

Agent/Type or Site of Infection or Host	Major Diseases	Optimal Specimens	Available Tests[a]	Averag Test Time t Positiv Results
ADENOVIRUS				
Respiratory	Pharyngitis, pneumonia, undifferentiated febrile illness	NP aspirate or wash, NP swab, throat swab, BAL, lung tissue	Culture[c]	6 days
			PCR	1–2 days
			Antigen detection/FA	2 hr
		Serum	IgG antibody[d]	1–5 days
Eye	Conjunctivitis	Conjunctival swab or scraping	Culture[c]	7 days
			Antigen detection	2 hr
		Serum	IgG antibody[c]	1–5 days
Intestinal (types 40 and 41)	Gastroenteritis	Stool	Antigen detection	2 hr
			EM	2 hr
Urinary bladder (immunocompromised host)	Hemorrhagic cystitis	Urine	Culture	6 days
			PCR[c]	1–2 days
			EM	2 hr
ARBOVIRUSES				

SLE, California, WEE, EEE, WNV	Fever, meningoencephalitis	Serum, CSF	IgG and IgM antibody[d]	1–5 days
Colorado tick fever	Fever, malaise, neutropenia	Serum	IgG antibody	7 days
Dengue	Febrile illness with or without rash, hemorrhagic fever	Serum	IgG and IgM antibody[c]	1–5 days
			PCR	1–2 days
CHLAMYDIA/CHLAMYDOPHILA				
Chlamydia trachomatis				
Genital	Urethritis, proctitis, cervicitis, salpingitis, pelvic inflammatory disease	Urethral, cervical swab, first-void urine, self-collected vulvovaginal swab, rectal mucosal swab	NAAT[c]	2–6 hr
			Antigen detection	4 hr
			DNA probe	4 hr
			Culture	48–72 hr
Neonatal	Conjunctivitis, pneumonitis	Eye swab, NP aspirate or wash	NAAT[c]	2–6 hr
			Antigen detection	4 hr
			Culture	48–72 hr
Sexual abuse, rape	Vaginitis, urethritis, proctitis	Cervical, urethral, rectal mucosal swab	Culture[e]	48–72 hr
Chlamydophila pneumoniae (TWAR)	Pneumonia, pharyngitis, bronchitis	NP aspirate or swab, throat swab or wash	Culture[c]	4 days
			Antigen detection	4 hr
		Serum	IgG and IgM antibody	1–5 days
Chlamydia psittaci	Pneumonia	NP aspirate or wash, throat swab or wash	Antigen detection	4 hr
			Culture	2 days
		Serum	IgG antibody[d]	1–5 days
CYTOMEGALOVIRUS				
Congenital	Hepatosplenomegaly, thrombocytopenia, microcephaly, hearing loss, chorioretinitis	Urine, throat swab, EDTA blood, serum, amniotic fluid	Shell vial culture with antigen stain[c]	2 days
			Culture	3–4 wk
			NAAT[f]	2–5 hr
			IgG and IgM antibody[c]	1–2 days
Postnatal infection	Heterophile-negative infectious mononucleosis	Throat swab, urine, EDTA blood	Shell vial culture with antigen stain[c]	2 days
			Culture	3–4 wk
		Serum	IgG and IgM antibody[d]	1–2 days
Immunosuppressed patients	Pneumonitis, colitis, retinitis	EDTA blood	Antigenemia assay[c]	4–6 hr
			NAAT[c,f]	2–5 hr
		Bronchoalveolar lavage, rectal swab, vitreous fluid, tissue biopsy	Shell vial culture with antigen stain[c]	2 days
			Culture	3–4 wk
			NAAT[c,f]	2–5 hr
Pretransplant screening or	Past infection (donor	Serum	IgG antibody	1–2

immune status	and recipient)			days
ENTEROVIRUSES				
Coxsackieviruses groups A and B, echovirus, poliovirus	Aseptic meningitis, fever and rash, herpangina, hand, foot, and mouth disease, myocarditis and pericarditis, paralytic disease	CSF, throat swab, stool, rectal swab, EDTA blood, pericardial fluid, myocardium	Culture	4–7 days
			PCR[c,f]	6 hr
		Serum	Neutralizing[d,g] antibody panel (coxsackievirus group B, echovirus, and poliovirus)	5 days
EPSTEIN-BARR VIRUS				
Healthy person	Mononucleosis syndrome	Serum	Slide agglutination test (monospot)[c]	1–3 days
			EBV-specific IgG and IgM antibody[d]	1–3 days
Immunocompromised	Posttransplant lymphoproliferative disease	Serum, plasma, whole blood, leukocytes	PCR (quantitative)[f]	2–5 hr
GASTROINTESTINAL VIRUSES				
Rotaviruses, Caliciviridae (norovius and sapovirus), enteric adenoviruses, astroviruses	Gastroenteritis	Stool	EM[c] (rotavirus and enteric adenovirus)[c]	2 hr
			PCR[f]	6 hr
GENITAL *MYCOPLASMA* AND *UREAPLASMA*				
Ureaplasma urealyticum	Urethritis, cervicitis	Urethral, cervical swab; semen	Culture[c]	2 days
Mycoplasma hominis	Pneumonitis, meningitis in neonates	Tracheal aspirate, CSF in neonates	Culture[c]	2 days
HEPATITIS VIRUSES				
Hepatitis A	Acute	Serum	IgM antibody	1–2 days
	Immunity	Serum	Total (IgG and IgM) antibody or IgG antibody	1–2 days
Hepatitis B	Acute	Serum	HBsAg, anti-HBc IgM	1–2 days
	Chronic	Serum	HBsAg, anti-HBc total antibody	1–2 days
		Serum or plasma	NAAT for HBV DNA (quantitative)[f]	1 week
	Immunity	Serum	HBsAb	1–2 days
Hepatitis C	Acute	Serum	Anti-HCV EIA screen	1–2 days
			Anti-HCV RIBA supplementary	5 days
	Chronic	Serum or	NAAT for HCV	1 wk

		plasma	RNA (quantitative or qualitative)[f]	
Hepatitis D (only occurs in patients with HBV coinfection/superinfection)	Acute	Serum	HDV Ag, anti-HDV IgM	1–8 days
	Chronic	Serum	HDV Ag, anti-HDV total	1–8 days
Hepatitis E	Acute	Serum	IgG and IgM antibody	1–8 days
HERPES SIMPLEX VIRUS				
Skin, mucous membranes	Oral, genital, cutaneous ulcers or vesicles, herpetic whitlow	Aspirate of vesicle fluid, swab of vesicle fluid or base of ulcer in VTM	Shell vial culture with antigen stain[c,h]	16–24 hr
			Antigen detection (FA)	2 hr
			NAAT[f]	2–5 hr
Past infection	Recurrent genital symptoms but culture results negative	Serum	IgG (group- or type-specific) antibody[d]	1–2 days
Neonatal infection	Disseminated disease; hepatitis; pneumonitis; encephalitis; skin, eye, mouth ulcers or vesicles	Swab of lesions; EDTA blood; CSF; conjunctiva, nose, or mouth swab; rectal swab	Shell vial culture with antigen stain[c,h]	16–24 hr
			Antigen detection (FA)	2 hr
			PCR	2–5 hr
		Serum	IgG and IgM antibody[d]	1–2 days
Ocular infection	Conjunctivitis, keratitis	Conjunctival or corneal swab or scraping in VTM	Shell vial culture with antigen stain[c,h]	16–24 hr
			Antigen detection (FA)	2 hr
			PCR	2–5 hr
Brain or meninges	Encephalitis,[i] meningitis	CSF, brain biopsy[i]	PCR[c,f]	2–5 hr
			Antigen/antibody in CSF	2 hr
			Shell vial culture with antigen stain[h]	16–24 hr
		Serum	IgG and IgM antibody[d]	1–2 days
HUMAN HERPESVIRUS 6				
Primary infection	Roseola (exanthem subitum)	Serum	IgG and IgM antibody[d]	1–3 days
Immunocompromised people	Transplant recipients, AIDS	EDTA blood for PBMCs	PCR[f]	1–2 wk
HUMAN IMMUNODEFICIENCY VIRUS				
Suspected HIV infection in adult or older child	Symptomatic or asymptomatic	Serum	Screening HIV EIA[c]	1–2 days
			Confirmatory Western blot or IFA	1–3 days
			HIV p24 antigen, NAAT[i]	2–4 days
Newborn	Suspected vertical or perinatal	Serum	Screening HIV EIA	1–2 days

	transmission		Confirmatory Western blot or IFA	1–3 days
		EDTA blood	Virus culture	2–3 wk
			NAAT[c,f,i]	1 wk
OTHER VIRUSES				
Human metapneumovirus	Upper respiratory illness, bronchiolitis, pneumonia, croup	NP aspirate or wash, nasal or throat swab, BAL	PCR (including multiplex assays for respiratory viruses)[f]	1 day
Human papillomaviruses	Cervical dysplasia	Cervical swab	RNA probe, hybrid capture, PCR	1–4 days
Influenza viruses	“Flu” syndrome, pneumonia	NP aspirate, wash, or swab; throat swab or wash; BAL	PCR (including multiplex assays for respiratory viruses)[c,f]	1 hr–1 day
			Antigen detection for influenza A and B	30 min-2 hr
			Culture[b]	7–9 days
Measles virus	Measles	NP aspirate or wash	Culture[c]	5 days
		Throat swab	Antigen detection[c]	2 hr
		Serum	IgG and IgM antibody[d]	1–2 days
Mumps virus	Parotitis, aseptic meningitis, meningoencephalitis	Urine, throat swab, saliva, CSF, blood	Culture	8 days
		Serum	IgG and IgM antibody[d]	1–2 days
Parainfluenza viruses	Croup, pneumonitis, bronchiolitis	NP aspirate or wash	Culture[c]	4–7 days
			Antigen detection using FA	2 hr
Parvovirus B19	Erythema infectiosum	Blood, serum, bone marrow, amniotic fluid cells, placental tissue, cord	IgG and IgM antibody[d]	2 days
	Aplastic crisis, congenital, hydrops fetalis		PCR	2 days
Polyomavirus (JC and BK)	JC virus: progressive multifocal leukoencephalopathy (PML)	CSF	PCR	1 wk
	BK virus: polyomavirus-associated nephropathy	Urine	PCR (quantitative)	1 wk
Rabies virus	Encephalomyelitis Immune status after vaccination	Postmortem CNS tissue, antemorem nuchal biopsy	Direct antigen detection (DFA, IHC, DRIT)[c]	24–72 hr
		Serum, CSF	IgG and IgM antibody[d] (IFA)	2 wk 2 wk
		Saliva	Culture	24–72

		(antemortem)		hr
		Serum, CSF	RT-PCR	2 wk
Respiratory syncytial virus	Bronchiolitis, pneumonia, croup	NP aspirate, wash, or swab; throat swab or wash; BAL	Antigen detection[c]	15 min-4 hours
			Shell vial with antigen staining	16–48 hr
			Culture	3–7 days
		Serum	PCR (including multiplex assays for respiratory viruses)	1 hr–1 day
Rhinovirus	Common cold	NP aspirate or wash	Culture	7 days
Rubella	Acquired or congenital rubella	Serum	IgG and IgM antibody[d]	1–2 days
		Throat swab	Culture	5–7 days
VARICELLA-ZOSTER VIRUS				
Skin, disseminated	Chickenpox, herpes zoster, occasional CNS complications	Vesicle fluid, scraping of base of vesicle in VTM, CSF	Antigen detection[c]	2 hr
			Culture	3–7 days
			PCR[c,f]	1 day
		Serum	IgG and IgM antibody[d]	1–2 days
Immune status	Past infection or vaccination	Serum	IgG antibody	1–2 days
MYCOPLASMA PNEUMONIAE	Pneumonia, pharyngitis, Stevens-Johnson syndrome, meningoencephalitis	Throat swab	Culture	3 wk
		CSF	PCR[f]	4–6 days
		Serum	IgG and IgM antibody[c]	1–5 days

[a] Available tests may vary by laboratory. Samples may need to be sent to a reference laboratory for some tests. Not all tests need to be performed in all patients.

[b] The average time to a positive result may be as much a function of the test itself (e.g., culture) as it is the frequency with which the test is performed in the laboratory.

[c] Preferred test on the basis of sensitivity, specificity, and short time to a positive test result.

[d] Acute and convalescent (2–4 weeks after the onset of illness) serologic testing is recommended for most viruses. IgM antibody testing is available for CMV, EBV, HAV, HBVcore, HSV, measles, mumps, parvovirus B19, rubella, and varicella-zoster virus.

[e] In cases of sexual abuse or rape, culture is recommended because of concern about false-positive results with nonculture methods.

[f] PCR test times to a positive result vary.

[g] In the echovirus neutralizing antibody panel, 4 to 5 of the most prevalent recent serotypes are chosen for the panel.

[h] Serotyping of the isolate as HSV-1 or HSV-2 is available.

[i] Detection of proviral DNA after PCR amplification may be the preferred test in young

infants, in adults with mononucleosis syndrome before seroconversion, and in adults with an indeterminate Western blot result.

Ag, antigen; AIDS, acquired immunodeficiency syndrome; BAL, bronchoalveolar lavage; CNS, central nervous system; CSF, cerebrospinal fluid; DFA, direct fluorescent antibody; DRIT, direct rapid immunohistochemical test; EBV, Epstein-Barr virus; EDTA, ethylenediaminetetraacetic acid; EEE, eastern equine encephalomyelitis; EIA, enzyme immunoassay; EM, electron microscopy; FA, fluorescent antibody (detection); HAV, hepatitis A virus; HBc, hepatitis B core; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; IFA, indirect fluorescent antigen; Ig, immunoglobulin; IHC, immunohistochemistry; NAAT, nucleic acid amplification test (may include ligase chain reaction, nucleic acid sequence–based amplification, PCR); NP, nasopharyngeal; PBMCs, peripheral blood mononuclear cells; PCR, polymerase chain reaction; RIBA, recombinant immunoblot assay; RT-PCR, reverse transcriptase polymerase chain reaction; SLE, St. Louis encephalitis; TWAR, Taiwan acute respiratory; VTM, viral transport medium; WEE, western equine encephalomyelitis; WNV, West Nile virus.

Herpesviridae

The optimal tests for diagnosis of the members of the Herpesviridae family vary by virus type. For suspected mucocutaneous lesions caused by HSV or VZV, clinical diagnosis is usually sufficient. If laboratory confirmation is required, an aspirate or swab of the vesicular fluid or scraping of the ulcer base placed in VTM is recommended. Other potentially useful samples include blood in EDTA when viremia is suspected (e.g., neonates), CSF in a sterile container when meningitis or encephalitis is suspected, conjunctival swab or corneal scrapings in VTM in suspected cases of herpes keratitis, and tissue biopsy in VTM or frozen (e.g., disseminated HSV and VZV in neonates or immunocompromised patients). In infants, duodenal aspirates also can be collected for suspected neonatal HSV infection. Tests for isolation of virus, direct detection of viral antigen in cells using FA staining (and monoclonal antibodies specific for HSV-1, HSV-2, and VZV), and detection of HSV and VZV DNA by NAATs are all available.

The yield on culture is quite variable and depends on the culture cell type used,[55] the stage of the clinical infection (yield is greatest ≤4 days of onset),[56] and the specimen type and transportation time (preferably ≤12 hours of collection). Visualization of CPE in a sensitive cell line detects 50% of HSV-positive specimens in 24 hours, 80% in 48 hours, and 95% in 72 hours.[57] The shell vial method permits detection of HSV with 66% to 99% sensitivity and 100% specificity by 16 to 24 hours.[55,58] ELVIS has a sensitivity similar to that of both standard and shell vial culture.[15]

Direct detection of VZV antigens by FA of smears from lesions is more sensitive than culture.[59] Vesicular fluid, although good for culture, is inadequate for FA testing because of the lack of cellular material.

Direct antigen detection tests for HSV have variable sensitivity (47%–95%) and specificity (85%–100%).[60,61] None is sufficiently sensitive to detect asymptomatic shedding reliably.[62]

Herpes Simplex Virus and Varicella-Zoster Virus.

The yield of CSF culture is <5% in biopsy-proven cases of HSV encephalitis.[63] HSV PCR performed on CSF (sensitivity of 96% and specificity of 99%)[64] is the diagnostic test of choice for HSV encephalitis and meningitis.[63] PCR results are positive at least through the first 6 to 7 days of illness, even in patients receiving acyclovir therapy.[63,65] Conversely, because negative results were obtained in 1 study in up to 25% of first CSF samples from infants and children,[66] a single HSV PCR test does not completely exclude HSV encephalitis. HSV PCR also is useful with other clinical specimen types,[67] and it can distinguish between HSV-1 and HSV-2. The role of quantitative HSV PCR remains unclear. Results regarding the relationship between the amount of HSV in CSF and clinical outcome are conflicting.[68,69] Successful antiviral therapy is associated with a decline in HSV viral load in CSF.[63]

PCR for detection of VZV DNA is more sensitive than culture or FA, particularly in scrapings of older, crusted lesions. PCR can be used to distinguish vaccine-type versus wild-type VZV. Analysis of CSF by PCR and the detection of VZV antibody in CSF can confirm the role of VZV in CNS syndromes.[70] Multiplex PCR assays, capable of detecting VZV and other herpesviruses, have been evaluated and can simplify the diagnosis in patients with overlapping clinical syndromes (e.g., vesicular rash).[34]

HSV-specific IgG and IgM antibodies are detectable in serum 10 to 20 days after the onset of primary infection. IgG antibodies indicate past, latent, or current infection, but not necessarily active disease. Because Herpesviridae are latent, the presence of HSV IgG antibody in organ transplant recipients is used as a risk factor for recurrences and an indication for the prophylactic use of acyclovir.[71] Because of fluctuations in HSV IgG antibody titers, serologic tests should not be used to diagnose recurrent HSV infections. IgM antibody is not a reliable indicator of primary infection because reactivation can cause a rise in IgM concentrations.[71] Commercially available EIAs, Western blot (WB) tests, and immunoblot tests based on HSV glycoprotein G antigen reliably distinguish type-specific HSV antibodies.[72] The use of HSV-2 type-specific assays has provided important information about the epidemiology of genital HSV infection and the insensitivity of clinical history.[73] Recommendations have been proposed for the appropriate use of HSV-2 serologic tests.[74] No commercially available IgM test can distinguish HSV-1 from HSV-2 infection.

IgG anti-VZV is used primarily to assess susceptibility to infection, to determine the need for vaccination or risk of disease in exposed people, and to determine the duration of protection after vaccination.[75,76] During acute VZV infection, VZV antibodies appear within a few days after the onset of rash and peak 2 to 3 weeks later. A greater than fourfold rise in IgG antibody between serum samples collected 10 to 14 days apart or the detection of VZV-specific IgM antibodies in a single sample supports a diagnosis of acute infection. However, serologic diagnosis of acute VZV infection can be confounded by heterotypic antibody increases that can occur in up to one third of patients with primary HSV infection who have experienced a previous VZV infection.[77] FA against membrane antigen (FAMA) is considered the gold standard for the detection of VZV antibodies.[76] Detection of neutralizing antibodies to VZV in healthy people by FAMA or latex agglutination correlates with protection in up to 96% of people.[78] Occasionally, VZV infection has been reported to occur in patients with low levels of VZV antibodies detected by these assays.[79] EIAs can have lower sensitivity compared with FAMA and latex agglutination assays, particularly for detecting antibodies after vaccination.[76] Newer glycoprotein (gp) EIAs appear to have improved sensitivity over older EIAs. Recognizing the difficulties of serologic testing, the Centers for Disease Control and Prevention consider a history of receipt of 2 valid doses of VZV vaccine as evidence of protection.

Guidelines for standardization of in vitro susceptibility testing of HSV have been published.[80] Resistance to acyclovir and other drugs has emerged as a clinical problem in immunocompromised patients receiving prolonged courses of continuous or intermittent suppressive therapy.[81,82] PCR, together with sequence analysis of the DNA polymerase and thymidine kinase genes, can be used to detect mutations conferring drug resistance.[83] However, this approach is limited because one can interpret the presence only of mutations that have been associated with phenotypic HSV antiviral resistance. The significance of new or novel mutations requires confirmation.

Cytomegalovirus.

CMV can be detected in a variety of clinical specimens by isolation, antigen detection, DNA probes, or NAATs.[84–88] Distinguishing between asymptomatic shedding (from urine, cervical secretions, semen, saliva, and respiratory tract secretions) and active CMV disease is often difficult. Isolation of CMV from tissues is good evidence of active infection. The preferred specimens and tests for detection and diagnosis of CMV depend on the clinical syndrome and immune function of the patient (see Chapter 206).[84,89,90]

To enhance culture detection of CMV in various clinical specimens, multiple shell vials should be inoculated (2 for urine specimens, tissue, and BAL and 3 for blood specimens) with staining at 24 and 48 hours and observation for blood specimens for CPE for 10 days.[91,92] Isolation of CMV from urine obtained during the first 3 weeks of life is diagnostic of congenital infection.[89] In all other situations, distinguishing whether CMV detection is related to primary infection, reactivation or reinfection disease, or asymptomatic shedding (including from respiratory tract specimens) is impossible. In immunocompromised patients with suspected CMV pneumonia, culture of a BAL specimen compared with a lung biopsy specimen has a sensitivity of 70% to 95% and a specificity of 50% to 100%.[93,94] Demonstration of CMV antigen in cells from BAL specimens by direct FA (DFA) staining can be more specific for CMV infection, but sensitivity is reduced.[93] Histologic examination of cells obtained by BAL for the presence of characteristic CMV intranuclear inclusions (“owl eyes” appearance) suggests a diagnosis of CMV pneumonia.

Detection of CMV in blood (peripheral blood white blood cells, plasma, serum, or whole blood) by either CMV antigenemia (pp65 antigen) or CMV PCR can be useful in the diagnosis of active CMV disease or as a predictor of future CMV disease in transplant recipients and other immunocompromised patients.[84,93–99] Results can be quantitative or semiquantitative, and several studies support a relationship between the level of CMV in blood and the likelihood of active or emerging CMV disease.[100–104] These assays are used in preemptive treatment strategies and for monitoring response to anti-CMV therapy. However, because of variability among commercial and in-house quantitative CMV assays, the exact level of CMV DNA or antigenemia that should be used to initiate preemptive therapy is not well established.

For the diagnosis of CMV mononucleosis in otherwise healthy people, testing for CMV-specific IgM is the preferred method. However, IgM antibodies can be detected in both primary and reactivated CMV infections and can persist for months. False-positive CMV IgM test results can occur in patients with acute EBV infection, as well as in patients with high concentrations of rheumatoid factor in the presence of CMV-specific IgG.[105] In immunologically immature hosts or in immunocompromised patients, the CMV IgM response during acute infection can be delayed or absent. Because IgM antibodies do not cross the placenta, their detection in a newborn is diagnostic of congenital infection. However, production of IgM antibodies by the newborn can be delayed or absent in up to 30% of cases, and thus a negative test result does not exclude congenital infection.[89]

The major use of CMV IgG serologic testing is to determine susceptibility to infection in healthcare or childcare workers,[106] as well as to identify the CMV status of blood and organ or tissue donors and recipients.[107] In pregnant women, CMV-specific IgG avidity assays may be of value.[90] The presence of low-avidity IgG anti-CMV can be a better predictor of recent infection than IgM alone, thus increasing the likelihood of CMV transmission to the fetus. However, substantial variability in performance of different CMV avidity assays precludes clear guidance on use and interpretation.[108] Additional testing such as PCR or virus isolation from amniotic fluid may be required to confirm infection of the fetus.

Standardization of in vitro CMV antiviral susceptibility testing has not been established despite the utility of this testing in immunocompromised patients, in whom resistance correlates with clinical failures.[109] Phenotypic assays are limited by long turnaround time and expertise required for performance. Genotypic assays can detect the most common mutations in the CMV *UL97* phosphotransferase gene and the *UL54* DNA polymerase gene that confer antiviral resistance, but these assays are not available widely.[110]

Epstein-Barr Virus.

In patients with suspected EBV infectious mononucleosis (IM), heterophile antibody remains the serologic test of choice.[111] These IgM antibodies can be detected easily and rapidly by using a simple spot agglutination assay (often referred to as a "monospot") or immunochromatographic assays.[112] Heterophile antibodies develop in approximately 80% to 85% of adolescents and adults with EBV IM[111] within 2 to 3 weeks after the onset of illness. Responses can be delayed in some people; repeat testing may be required. Results of the heterophile test can be negative in 70% to 80% of EBV infections in children <4 years of age.[112] Heterophile antibodies usually disappear within a few months but can persist for >1 year after acute illness in 20% to 70% of patients,[49] and persistence should not be interpreted as indicating recurrent or chronic IM. Cases of heterophile-negative IM in school-aged children are caused by CMV in 70% and by EBV (proven by EBV-specific serologic findings) in 16% of cases.[113]

EBV serologic testing can be indicated when the diagnosis of EBV infection is strongly suspected but the heterophile test result is negative.[114] The IFA test is considered the gold standard, although EIA and immunoblot assays can be used.[111] IFA tests have more uniform performance characteristics, whereas EIAs can vary because of the wide variety of antigen preparations used in different kits. The most useful diagnostic test is IgM anti-EBV viral capsid antigen (VCA), which appears within 1 to 2 weeks after the onset of symptoms, disappears within months, and is 91% to 98% sensitive and 99% specific.[49,111,114] False-positive results can reflect the presence of rheumatoid factor, other herpesvirus infections, and antinuclear factors in EIA test systems. False-negative results can occur if samples are collected late in the course of the illness. IgG anti-VCA is elevated during symptoms of illness and can persist for life, and thus it is the most reliable marker of EBV seropositivity. IgG anti–Epstein-Barr nuclear antigen [EBNA]) appears late, generally after 6 weeks, and persists for life. Several months after recovering from IM, a patient is expected to have IgG antibodies to VCA and EBNA, but low or absent VCA IgM antibodies and EA antibodies[111] (see Fig. 208.3).

Direct tests for EBV, such as cultivation in cord blood leukocytes, direct detection by immunofluorescence staining, or detection of DNA,[115,116] are performed in some laboratories. EBV can be isolated from oropharyngeal washings or circulating lymphocytes of 80% to 90% of patients with IM. PCR detection of EBV DNA in the CSF of patients with HIV infection is strongly associated with primary CNS lymphoma.[116] Following organ and marrow transplantation, the use of quantitative EBV PCR using blood specimens can help predict the development of posttransplant lymphoproliferative disease.[117] The relative merit of testing whole blood, leukocytes, plasma, or serum is unclear. Elevated levels of EBV DNA in peripheral blood can be an indication to decrease immunosuppressive therapy or to consider therapies such as $CD20^+$ monoclonal antibodies or EBV-specific cytotoxic T lymphocytes.[117]

Rarely, EBV infection is associated with an acute fulminant disease (e.g., X-linked lymphoproliferative syndrome and virus-associated hemophagocytic syndrome).[118] Persistent high-titer EBV antibodies, except against EBNA, are characteristic but can be absent. The diagnosis depends on detection of virus or its genome.

Human Herpesvirus 6.

Primary infection with human herpesvirus 6 (HHV-6) occurs in most children before the age of 2 to 3 years, and routine laboratory testing usually is not performed. Detectable antibodies in primary infection generally appear 3 to 8 days after the onset of fever. The following serologic criteria are considered diagnostic of primary HHV-6 infection: (1) antibody seroconversion between acute and convalescent phase serum or plasma specimens collected 2 to 4 weeks apart; (2) detection of HHV-6–specific low-avidity IgG antibodies; (3) positive serum IgM in the absence of IgG antibodies; and (4) a greater than fourfold rise in IgG antibody by IFA or anticomplementary immunofluorescence assays.[119] Current commercial assays for IgG anti–HHV-6 do not distinguish between variants A and B and can cross-react with HHV-7 and CMV.[120,121] Antibody avidity testing can be used to differentiate primary HHV-6 from HHV-7 infections. IgM anti–HHV-6 alone is not a reliable indicator of acute or recent infection because IgM can be found during reactivation or reinfection and approximately 5% of adults have detectable IgM anti–HHV-6 at any time.[119] IgM may not be detectable in some culture-positive children.[120,122] During acute primary HHV-6 infection, virus can be isolated from cultures of peripheral blood mononuclear cells (PBMCs) in 100% of infants, but not after recovery.[123] HHV-6 DNA can be detected by PCR both during acute illness and after recovery.[121,124] Monoclonal antibodies are available for direct detection of HHV-6 antigen and have been used to confirm cell culture CPE and for immunohistochemical staining of tissues.

In immunocompromised patients, HHV-6 infection can be associated with substantial morbidity and mortality rates.[125,126] Proof of HHV-6 causation is difficult because specific antibodies can be absent and demonstration of viral DNA in PBMCs can represent latent infection. Although PCR detection of HHV-6 DNA in serum or plasma has low sensitivity, it can be a better marker for active infection. PCR results were negative in the serum or plasma of 57 healthy adults but positive in 94% of 17 patients with exanthem subitum, 23% of 13 bone marrow transplant recipients, and 22% of 18 HIV-infected patients.[127,128]

Human Herpesvirus 7.

Serologic tests for HHV-7 are not available widely. Some degree of cross-reaction between HHV-6 and HHV-7 antibodies results from cross-reactive epitopes on the viruses.[120] Responses can be distinguished by antibody avidity testing.[120] A significant rise in HHV-7 antibodies with stable or absent antibodies to HHV-6 may indicate active infection with HHV-7. HHV-7 has been isolated from the saliva of 75% of healthy adults,[129] as well as from ill people, thus questioning the value of such testing. HHV-7 has been isolated only rarely from PBMCs of healthy asymptomatic people compared with people with active infections; this finding suggests that PBMC cultures may have diagnostic value.[130] Specific primers for PCR amplification of HHV-7 have been developed that do not amplify the DNA from any other human herpesviruses and have been included in a multiplex assay.[131,132]

Human Herpesvirus 8.

Testing for HHV-8 is available only in research settings. PCR has been used for detection of HHV-8 DNA in PBMCs and tissues.[133] The use of plasma or serum for HHV-8 PCR has no value for identifying active infections.[119] Serologic assays can detect IgG anti–HHV-8 but not IgM anti–HHV-8. Although serologic tests are useful for seroprevalence studies, the role of these tests in diagnosing and managing HHV-8 infections has not been established.[134]

Respiratory Viruses

Numerous viruses including RSV, influenza viruses A and B, human parainfluenza viruses (types 1, 2, 3, and 4), adenoviruses (subtypes A to E), rhinoviruses, human coronaviruses 229E, OC43, severe acute respiratory syndrome (SARS) coronavirus, human metapneumovirus (hMPV), and the Middle East Respiratory Coronavirus (MERS CoV) can infect the respiratory tract and cause clinically indistinguishable signs and symptoms. The increasing development of NAATs for detection of respiratory viruses (whether individually or in multiplex PCR assays) has significantly simplified and improved the diagnosis of viral respiratory tract infections.[38,135] NAATs have been applied to NP washes, aspirates, and swabs, as well as BAL and endotracheal tube (ETT) aspirates, with superior sensitivity than culture or antigen detection. Early sample collection (within the first few days of symptom onset) further improves sensitivity. Results with NAATs are available within 1 to 5 hours, thus substantially shortening the turnaround time compared with culture (mean, 3–7 days). When NAATs are not available, some laboratories may continue to use culture or antigen detection tests. The sensitivity of antigen detection techniques (for RSV or influenza viruses, or both) such as EIA microtiter plate kits, membrane filter EIA, and DFA range from 84% to 96%, with a specificity of 92% to 96%.[37,136–140] The membrane filter EIA for RSV detection offers the advantage of providing a result within 15 to 20 minutes.[136–141] Several rapid antigen detection kits, including point-of-care tests, are available for the detection of influenza A only, influenza A and B together (without distinguishing between them), and influenza A or B.[142–150] Evaluations of rapid tests for the detection of seasonal influenza virus, as well as the pandemic 2009 H1N1 virus, indicate relatively poor sensitivity (which is affected by the circulating strains and specimen type) but high specificity. These tests have not been evaluated fully for the detection of avian influenza A/H5N1. When good-quality respiratory specimens with well-preserved epithelial cells are used, DFA staining using monoclonal antibodies has a sensitivity of 80% to 90% and a specificity of >90%.[146–148] Some antigen detection assays can detect multiple respiratory viruses simultaneously.[140] Numerous studies have confirmed the superiority of NAATs for the detection of respiratory viruses, with some tests capable of detecting mutations within influenza strains that confer resistance to neuraminidase inhibitors.[151–155]

The use of serologic tests for the diagnosis of acute respiratory virus infections generally has little clinical value, other than for epidemiologic purposes, and these tests are not routinely available. They play no role in determining immunity or response to vaccine (e.g., influenza virus).[156–160]

Hepatitis Viruses

The routine diagnosis of all infections with hepatitis viruses is based on serologic testing. Serum or plasma can be used and should be separated from blood within 24 hours of collection. The diagnosis of acute HAV infection is made by demonstration of IgM anti-HAV.[156] Immunity to HAV following natural infection or immunization is determined by measuring hepatitis A IgG or total (IgG and IgM) anti-HAV.[156] Currently, no role exists for reverse transcriptase (RT)-PCR measurement of HAV RNA for routine diagnosis, but it can assist in characterizing strains during outbreak investigations.

In acute and chronic HBV infection, both HBsAg and anti–hepatitis B core antibody (HBcAb) usually are present.[157] IgM anti-HBc generally indicates acute HBV infection but can also be detected during a flare of inflammation in chronic carriers. By definition, a person with persistently positive HBsAg for >6 months is considered chronically infected. Isolated anti-HBc positivity can occur during (1) acute infection between the loss of detectable HBsAg and the emergence of detectable HBsAb (“core window”),

(2) late chronic infection when HBsAg levels have fallen to less than detectable levels, (3) coinfection with HCV or HIV that suppresses HBsAg production, (4) infection with a mutant HBV, or (5) a false-positive result. The role of quantitative HBsAg assays is being evaluated for monitoring patients with chronic HBV infection. The presence of HBV e antigen (HBeAg) and the absence of anti-HBe are markers of greater infectivity and correlate with increased risk of progression to chronic hepatitis, cirrhosis, and hepatocellular carcinoma.[157] The presence of anti-HBe is an indicator of likely recovery. The presence of HBsAb at a level >10 IU/mL is considered protective against acute infection. HBsAb levels can decline to less than 10 IU/mL after 10 to 12 years in many vaccine responders. These people remain protected from acute infection likely as a result of immune memory.[158] The presence of HBsAb alone reflects previous immunization, whereas the presence of HBsAb together with HBcAb reflects recovery from previous natural infection.[157] Although HBsAg and HBsAb were believed to be mutually exclusive, as many as one third of carriers of HBsAg will also have detectable HBsAb.[159,160] The mechanism is uncertain, but it may be related to coinfection with different subtypes. Thus current recommendations are that all people who are HBsAb positive be tested for HBsAg at least once.

For diagnosis of HCV infection, second- and third-generation EIAs and a supplementary recombinant immunoblot assay using recombinant structural proteins are widely available.[161,162] Seroconversion occurs by 8 to 12 weeks following acute infection, with a sensitivity of 94% to 100% (except in immunocompromised people) and a specificity of >97% after the supplementary recombinant immunoblot assay test. HCV antibody (anti-HCV) frequently is negative at the onset of jaundice. The presence of HCV antibodies indicates active infection in approximately 70% to 80% of patients. The remaining 20% to 30% of patients have likely cleared the virus spontaneously or as a result of antiviral treatment. The use of HCV RNA assays can help distinguish between these 2 possibilities. No assay is available currently for the detection of IgM anti-HCV. The utility of measuring HCV antigen in serum or plasma has not been established but is being evaluated as a potential alternative to HCV RNA for monitoring patients during therapy.

Molecular assays for the detection and quantification of HBV and HCV viral nucleic acid in serum are useful for determining prognosis, selecting candidates for therapy, and monitoring response to therapy.[161,163,164] A lower baseline concentration indicates a better prognosis and a greater likelihood of response to treatment. Patients responding to antiviral treatment demonstrate a significant drop in HBV DNA or HCV RNA, whereas nonresponders do not. Molecular assays also are available for HBV and HCV genotyping and antiviral resistance testing.[165–167] NAATs that detect HCV RNA in serum 1 to 3 weeks after exposure are being used as part of blood and organ or tissue donor screening and in patients with indeterminate HCV antibody results when the recombinant immunoblot assay result is inconclusive.

In most clinical situations, testing for hepatitis A, B, and C can be grouped into 1 of 3 categories: (1) *acute hepatitis,* (2) *chronic hepatitis,* and (3) *immune status or previous exposure*. For suspected acute hepatitis, initial testing for IgM anti-HAV, HBsAg, and anti-HCV should be performed. If all 3 results are negative, IgM anti-HBc should be tested. Repeat testing for anti-HCV is recommended in 3 to 4 weeks. When chronic hepatitis is suspected, testing should include HBsAg and anti-HCV. Some clinicians also may test for anti-HBc. Patients being screened for immunity or previous infection should have the following tests: (1) total or IgG anti-HAV; (2) HBsAb or HBcAb, or both (depending on whether one is trying to distinguish vaccine response or evidence of previous infection); and (3) anti-HCV (which is a marker of previous infection and not immunity).

Serologic tests are available for both hepatitis D (delta agent) virus (HDV) and hepatitis E virus (HEV), but none is approved by the Food and Drug Administration (FDA).[168] Because infection with HDV occurs solely in conjunction with HBV infection, testing for anti-HDV should be performed in only patients who are acutely or chronically infected with HBV. During coinfection with HBV and HDV, anti-HDV disappears within months following recovery from acute infection. However, in HDV superinfection of a patient who is chronically infected with HBV, anti-HDV generally persists indefinitely because infection becomes chronic in most cases. Measurement of HDV RNA by RT-PCR remains a research test. Both IgG and IgM anti-HEV can be measured using research or commercial assays.[169] Because of the use of different antigens, assays show significant variability in sensitivity and specificity.[170] IgG anti-HEV is positive in most patients 1 to 4 weeks after the onset of disease and becomes undetectable by 3 months. IgG anti-HEV typically declines after infection. In areas where HEV is not endemic, RT-PCR can prove useful as a confirmatory test.

Gastroenteritis Viruses

A multitude of viruses can cause acute gastroenteritis. In most cases, laboratory diagnosis is not required or indicated except perhaps for infection control purposes, during institutional outbreaks, or for public health reasons. Stool samples placed in a clean, sterile container without VTM or preservative for the detection of enteric viruses should be collected within the first 48 hours of illness. Rectal swabs may not contain sufficient virus for EM detection. Stool specimens are stable at 4°C for up to 1 week. Although freezing at −70°C can permit prolonged storage, EM detection is reduced by repeated freezing and thawing that destroys the morphologic features of viral structures. None of the enteric viruses can be cultivated readily in conventional cell culture systems, but all can be detected by EM. Commercial EIA, latex agglutination, and membrane-based tests with >95% sensitivity and specificity are available for detection of rotaviruses, noroviruses, enteric adenoviruses, and astroviruses.[19,20,171] PCR-based assays (including multiplex assays) for these viruses are available commercially,[36,172,173] and they are the methods of choice for diagnosing enteric viruses. Serologic testing for enteric viruses has no clinical role except during outbreak investigations.

Enteroviruses

Enteroviruses generally are stable and survive in the environment for weeks; rapid transport of clinical specimens to the laboratory is not critical. Enterovirus viability decreases slowly over days to weeks at room temperature and is preserved for decades at −70°C. Appropriate specimens include the following: CSF; serum or whole blood; pericardial fluid; tissue biopsy samples (e.g., myocardium); urine; stool; and rectal, nasal, and throat swabs. Although many enteroviruses can be grown in cell culture, some serotypes (e.g., coxsackievirus A groups 1, 19, and 22) fail to grow in standard cell culture. Isolation of enteroviruses requires 4 to 7 days.[174] Virus can be isolated more frequently from stool (80%–85%) and throat swabs (50%–60%) than from CSF (40%–60%) and serum or peripheral leukocytes (40%–50%). Because of the lack of a common antigen among enteroviruses, immunoassays for direct detection are not available. EM is not useful for diagnosis because of the low quantity of virus in most clinical samples.

RT-PCR has been used to test CSF, cardiac tissue, and pericardial fluid, as well as serum, and has significantly improved the speed of detection of enteroviruses, with a reported sensitivity of 81% to 100% and a specificity of 92% to 100%.[175–177] In comparison, culture has a sensitivity of only 40% to 60%.[174] Detection in urine samples is poor, probably because of nonspecific inhibitors of PCR.[178] In respiratory specimens, cross-amplification of some rhinoviruses can occur.

Clinically, the detection of enteroviruses in stool and respiratory specimens must be interpreted cautiously. Asymptomatic shedding of wild enterovirus from the gastrointestinal tract can occur for weeks or months. Additionally, oral polio vaccine virus can be shed in stool and, less commonly, in the throat of young vaccinated children. Detection of virus in CSF, the genitourinary tract, tissue, or blood is proof of a causative role.

Measuring antibody titers for enteroviruses is of limited diagnostic value. A separate neutralization assay must be performed for each enterovirus subtype.

Measles, Mumps, and Rubella Viruses

The laboratory diagnosis of measles, mumps, and rubella (MMR) viruses can be made by virus isolation, detection of antigen, the use of RT-PCR, or serologic testing. Suitable samples for isolation or detection of viral antigen include whole blood (particularly PBMCs for the isolation of measles), serum, buccal swabs, throat and NP secretions, urine, and, under appropriate clinical circumstances, CSF and brain and skin biopsy samples. Because these are labile viruses, rapid transport to the laboratory is important. Specimens are best kept at 4°C before processing, but they can be frozen at −70°C if a delay >48 hours is anticipated. Isolation of virus from blood is greatest 3 to 5 days before rash onset and declines rapidly within 2 to 3 days thereafter. Conjunctival and NP samples for isolation of measles virus can be collected 2 to 4 days before and up to 4 days after the onset of rash. Throat swabs for rubella virus isolation usually are positive (~90%) if collected on the day of rash onset but rapidly become negative within 4 days. Mumps virus can be isolated from saliva 9 days before and up to 8 days after the onset of parotitis. These viruses can be cultivated in conventional cell lines, but isolation requires 7 to 10 days for measles and mumps virus and >3 weeks for rubella virus.[179,180] The shell vial method for measles virus has a sensitivity of 78% at 1 to 2 days and 100% at 5 days. The sensitivity of DFA staining of NP swab specimens for measles virus antigen is 100% compared with culture, but it is only 67% for throat swabs and 85% for urine specimens. Shell vial culture for detection of mumps virus has sensitivity and specificity comparable to those of traditional culture.

Molecular diagnosis using virus-specific RT-PCR has been used for detection of all of 3 viruses and can be used for genotyping to help differentiate wild-type from vaccine-virus strains.[181,182]

Timing of serum specimen collection is critical because many patients do not have IgM antibody at the time of rash onset. For suspected measles virus infection, serum can be collected within 7 to 10 days of rash onset. For rubella virus infection, >90% of patients have IgM positivity ≥5 days after rash onset. Although the traditional MMR serologic test is hemagglutination inhibition for IgG antibody, several IFA and EIA IgG and IgM kits are available commercially.[183] With the declining prevalence of these viral diseases, the positive predictive value of IgM tests can be low. The presence of rheumatoid factor can lead to a false-positive IgM result, and re-exposure in a previously vaccinated person or someone with a history of natural infection can result in a secondary IgG or IgM response. Mumps IgM antibody can persist for months after acute illness.[184] Patients with IM,[185] parvovirus B19 infection,[186] measles virus, and CMV infection can have cross-reacting IgM antirubella antibodies. Similarly, infection with parvovirus B19 and rubella virus can result in cross-reacting IgM antimeasles. In pregnant women, IgM antirubella should be confirmed with a second IgM assay or detection of a significant rise in IgG antibodies.[187] Avidity assays for IgG antibodies to measles and rubella viruses are available. Measurement of virus-specific

IgG antibodies can be used to determine immune status. For mumps virus, cross-reactions with other paramyxoviruses can occur. For rubella virus, an IgG level of >10 IU/mL is thought to represent immunity in most cases.[179]

Human Immunodeficiency Virus

The major diagnostic tests for HIV are serologic (EIA, IFA, and WB for HIV antibody; EIA for p24 antigen), culture, and NAATs for the detection of HIV-1 RNA in plasma or proviral DNA in whole blood or PBMCs. Culture for HIV is no longer used for routine diagnosis.[188] NAATs can be used for the diagnosis of HIV-1 infection in neonates with excellent sensitivity and specificity.[189] Screening tests for HIV-1 RNA have been part of routine blood and organ or tissue donor screening programs since 2002,[190] and these tests also can be used for measuring HIV-1 in other specimen types including CSF, cervical secretions, seminal plasma or semen, and serum. The use of NAATs in people who are not known to be HIV seropositive has yielded false-positive results.[191] The major use of quantitative HIV-1 viral load assays is for monitoring a patient's response to antiretroviral therapy.[27,192] Because of the intra-assay and biologic variability in HIV-1 RNA levels, a greater than threefold change is considered clinically relevant. Different molecular assays also can produce significant differences in HIV-1 viral load, and thus baseline values should be repeated when the laboratory testing is changed from 1 assay to another.[192] Some assays yield lower levels in the same patient if serum is used instead of plasma or if blood is collected in acid-citrate-dextrose anticoagulant rather than EDTA. Currently available commercial assays vary in specimen volume requirement (range, 50 µL to 2 mL), lower limit of detection, dynamic range, and time to result.[193] Regardless of assay format, plasma must be separated from the blood cells within 6 hours of collection. None of these assays is approved for use in people infected with HIV-2 or HIV-1 group O. Other molecular assays are available for HIV-1 genotyping for the detection of antiretroviral resistance mutations.[193] Resistance testing is recommended before initiating therapy and when treatment fails.[194] Phenotypic assays can also be performed for this purpose.

The mainstay of diagnosis for HIV remains HIV-specific serologic testing using screening EIAs or, less commonly, particle agglutination assays followed by confirmatory testing using WB or other assay.[190] Both serum and plasma are acceptable specimens. Testing systems for dried blood spots, urine, and saliva also are available. Third- and fourth-generation EIA kits using more purified virus antigens from cell lysates, recombinant viral proteins, and synthetic peptide antigens can detect group O. These assays have increased sensitivity and specificity and fewer indeterminate results.[190] Most currently available assays detect IgG and IgM anti–HIV-1 and anti–HIV-2 in the same assay.[195] Fourth-generation screening tests can detect both HIV-1 or HIV-2 antibodies and p24 antigen at the same time while reducing the seroconversion window period to approximately 16 days.[190] Detuned (also known as “sensitive/less sensitive”) EIAs capable of measuring the affinity of HIV antibodies have been used to distinguish recent from past or distant HIV infection and to estimate incidence rates.[196]

WB has been the principal confirmatory test for HIV serologic status, even though its sensitivity in seroconversion panels is inferior to that of third- and fourth-generation screening tests. Separate WB tests must be used to confirm HIV-1 and HIV-2. WB measures the antibody response to 9 HIV-1 proteins (p) or glycoproteins (gp): gp160, gp120, p66, p55, p51, gp41, p31, p24, and p17; however, the test is prone to give a high rate of indeterminate results because of detection of cross-reacting antibodies and nonspecific reactions.[190] The criterion for confirmation of HIV-1 infection using WB is the presence of antibody to any 2 of the following: p24, gp41, or gp120/160.[197] No antibody response to HIV-1 proteins represents a negative test result, whereas the presence of some, but not all, antibodies required for a positive interpretation is an indeterminate result. Under these circumstances, repeat testing over the next 6 months is recommended, and if WB results remain indeterminate, patients are considered not to be infected with HIV.[197] In low-risk populations, people with a positive screening EIA test result and an indeterminate WB result are rarely, if ever, infected with HIV on follow-up serologic testing.[198,199] Rapid multispot assays developed as alternatives to WB can distinguish between HIV-1 and HIV-2 with very good sensitivity and specificity.[200]

The IFA test can detect both IgG and IgM anti–HIV-1, is quite sensitive and specific, and has been used as an alternative to WB as a confirmatory test.[190] The line immunoassay can be used for confirmation of HIV-1 (including group O) and HIV-2 in a single test. Rapid point-of-care tests for both screening and confirmation that require minimal or no laboratory equipment have been developed that can yield a result in <30 minutes with sensitivity and specificity comparable to those of third-generation EIA-based tests and other confirmatory assays.[201]

Different laboratory diagnostic strategies are needed for the most common situations in which HIV infection is considered: (1) an *adult or older child who is suspected of having HIV infection,* (2) an *infant with suspected vertically acquired HIV infection,* and (3) someone in whom acute infection or seroconversion may develop because of *exposure to an HIV-infected person*. One should refer to the most recent guidelines from the Centers for Disease Control and Prevention for up-to-date recommendations for screening and confirmation of HIV infection.[202] The most notable change in 2014 was the recommendation to replace WB with HIV-1 and HIV-2 discriminatory assays, p24 antigen tests, and NAATs. The sensitivity of p24 antigen tests varies according to clinical disease status: 4% in asymptomatically infected people, 56% in patients with AIDS-related complex, and 76% in patients with AIDS.[203]

Confirmation of vertical transmission of HIV by using EIA or WB is confounded by the presence of maternal antibodies for up to 18 months of age, and antibody tests should not be used for diagnosis of neonatal infection.[189,204] The current recommendation is that virologic assays (NAATS for HIV RNA and HIV DNA) that directly detect HIV must be used to diagnose HIV infection in infants younger than 18 months of age.[204] HIV culture (once considered the gold standard) and p24 antigen assays should not be used in these situations based on the complexity and cost of culture and the lack of sensitivity of p24 antigen assays.[204–208] Testing in infants with known perinatal HIV exposure is recommended at ages 14 to 21 days, 1 to 2 months, and 4 to 6 months of age.[204] The diagnosis of HIV infection in children with nonperinatal exposure or children with perinatal exposure who are >24 months of age should follow the same recommendations as for testing of adults with suspected HIV infection and is based primarily on the use of HIV antibody tests.

In a person with *known HIV exposure,* antibody to the virus usually can be detected within 2 to 8 weeks after infection. Based on third-generation screening assays, HIV antibodies are detectable in 50% of infected patients within 3 weeks after infection and in most of the remaining patients within 2 months.[190,209] Virtually all infected, immunocompetent people are seropositive 6 months after exposure.[209] A mononucleosis-like syndrome develops in some patients 2 to 4 weeks after infection; p24 antigen can appear transiently during this period.[209]

Arboviruses

Laboratory testing generally is not performed for most arbovirus infections. For arboviruses causing CNS disease, only a brief, low level of viremia occurs, and it clears before the patient seeks medical attention.[210] Thus blood specimens for virus isolation and NAAT rarely yield positive results unless they are collected before the neuroinvasive phase of illness. For some arbovirus infections, including dengue, yellow fever, sandfly fever, Venezuelan encephalitis, and Colorado tick fever, a relatively high level of viremia occurs that can persist for days or weeks and makes virus isolation or NAAT from blood specimens possible. Virus isolation of neurotropic viruses from brain tissue and CSF occasionally is successful during the acute phase of infection; NAAT is more sensitive in these cases.[211]

For most arbovirus infections, the diagnosis is established by IgG seroconversion or detection of specific IgM antibodies, or both.[210,212] Collection of paired acute (collected during the first week of illness) and convalescent (collected 2–3 weeks later) sera is recommended. A single sample may be sufficient for diagnosis if a specific IgM test is available (e.g., eastern equine encephalomyelitis virus, western equine encephalomyelitis virus, California [La Crosse] virus, St. Louis encephalitis virus, West Nile virus, dengue virus). However, in some cases (e.g., West Nile virus), virus-specific IgM can be detected in serum for ≥2 years following infection. For CNS disease, both serum and CSF specimens should be tested. The sensitivity of some of these tests approaches 100% by the 10th day of illness.[213] Traditional assays such as CF and hemagglutination inhibition tests largely have been replaced by FA and EIAs.[210] Serologic cross-reactions can occur among antigenically related viruses (e.g., St. Louis encephalitis, West Nile, Japanese encephalitis, dengue, Powassan, and other flaviviruses). The plaque reduction neutralization test remains the most specific test for the serologic diagnosis of arbovirus infections. Neutralizing antibodies are the best indicators of protective immunity.

Parvovirus B19

Parvovirus cannot be cultivated in routine cell culture, and thus serologic testing (rising IgG titers or the presence of IgM antibody) is the mainstay of diagnosis.[214] IgM antibodies are detectable in serum approximately 10 to 12 days after infection, when the rash or joint symptoms begin, and they can persist for several months. The sensitivity of IgM antiparvovirus exceeds 90% in the first month after the onset of symptoms. IgG antibodies appear several days after IgM and generally persist for years. Current IgG assays have a sensitivity of >90%; IgG indicates past infection. Re-exposure to parvovirus leads to a rise in IgG antibody levels. IgG avidity assays can help distinguish primary from secondary infections.[215] NAAT detection of viral DNA in serum or other specimen types may be required for diagnosis in immunocompromised patients. Parvovirus-associated aplastic crisis, chronic infection, and congenital infection can be diagnosed by PCR testing of serum.[214–216] PCR also can be used to detect parvovirus B19 DNA in bone marrow aspirates, cord blood samples, amniotic fluid cells, and biopsy specimens of placenta and fetal tissues in cases of fetal hydrops. However, parvovirus DNA may be detectable in serum for months after acute infection and for years in other tissues.[217] Thus the diagnosis of acute or chronic parvovirus infection can require both serologic testing and quantitative PCR.

Other Viruses

The recommended specimens and laboratory tests for other viruses are listed in Table 287.1. For most of these viruses, testing is performed in highly specialized research or reference laboratories.

Congenital and Perinatal Viral Infections

The major viruses infecting fetuses and newborn infants now extend beyond the traditional "TORCH" (*Toxoplasma,* rubella virus, CMV, HSV) agents and include CMV, VZV, HSV, rubella, parvovirus B19, HBV, HCV, HEV, enteroviruses, and HIV.[218] Negative maternal and neonatal serologic test results for any of these viruses generally exclude fetal infection.[218] Detection of virus (by culture, antigen detection, or NAAT) can be required before a correct diagnosis can be made. Cord blood can yield false-positive and false-negative results and should not be relied on for diagnosis.[218]

Congenital CMV infection is best diagnosed by isolating CMV from the urine of neonates within the first 3 weeks of life. Beyond 3 weeks of age, isolation of CMV from urine cannot distinguish congenital from perinatal or postnatal infection. IgM anti-CMV in a newborn is positive in only 50% to 70% of congenitally infected neonates, and the test can yield false-positive results.[219]

Congenital VZV infection can be diagnosed by serologic testing. Perinatal or postnatal infection with VZV, as well as infection with HSV and enteroviruses, usually can be diagnosed by conventional antigen detection or culture techniques, although NAAT testing has replaced these tests in most centers. Serologic diagnosis of neonatal HSV infections is inappropriate because a response may not be detectable for 2 or 3 weeks after infection.[220] Demonstration of rubella IgM in a neonate with features consistent with congenital rubella confirms the diagnosis; virus isolation can require 3 to 4 weeks.[218,220,221]

Parvovirus infection during pregnancy can be diagnosed in the mother by serologic testing; detection of IgM or rising IgG antibody concentrations is diagnostic, whereas a stable IgG titer reflects past infection. Parvovirus B19 infection of a fetus with hydrops can be confirmed using NAAT for viral DNA in fetal blood, amniotic fluid cells, or both.[215,221]

Chlamydiaceae

Chlamydia trachomatis, Chlamydophila pneumoniae, and *Chlamydophila psittaci* cause disease in humans. Psittacosis, rare in children, is confirmed serologically.

Chlamydia Trachomatis

Both culture and nonculture methods are available for the detection of *C. trachomatis.* Culture previously was considered the gold standard because of its 100% specificity and excellent sensitivity when optimal techniques were used.[222] However, for genital specimens, its sensitivity is approximately 70% to 80% compared with NAATs, which have now become the tests of choice for routine testing. Testing of first-void urine in men and women by any of the commercially available NAATs has excellent sensitivity and a specificity of >97%, resulting in a high positive predictive value.[223] Other nonculture methods such as EIA and IFA tests and nucleic acid probe tests have little if any role in routine testing for *C. trachomatis* because of their inferior perfomance.[222,224] Point-of-care tests have poor sensitivity and specificity and are not recommended.[225,226]

The optimal specimen types, collection method, and transportation requirements vary depending on the testing method used, the purpose of the test (screening vs. diagnosis), and the age and sex of patients being tested. In general, because of the lower sensitivity, technical requirements, and prolonged turnaround time, culture is not performed routinely for detection of urogenital *C. trachomatis* infection. Culture has been replaced by NAAT as the test of choice. For male patients, either a urethral swab inserted 3 to 4 cm or a first-catch urine sample is the preferred specimen. For women, a swab of the cervical os inserted 1 to 2 cm, a vaginal swab (including self-collected vulvovaginal swab), and a first-catch urine sample are all acceptable specimens.[222,226] NAATs have been used for adult sexual assault victims, and their implications have been assessed.[227] Although NAATs have been evaluated in sexually abused children and their medical and legal implications have been evaluated,[228,229] culture remains the recommended method for urethral specimens from boys and for extragenital specimens (pharynx, conjunctiva, and rectum) from boys and girls.[224] NAATs can be used for vaginal specimens or urine specimens from girls. However, none of the commercially available NAATs is FDA approved for use for testing specimens from extragenital sites. The yield of culture is related directly to the quality of the specimen and the transport and storage conditions before testing. Isolation of *C. trachomatis* in culture from urethral specimens collected from prepubertal boys is low and is not recommended. However, if urethral discharge is present, a meatal specimen can be collected.

Because of the low yield, pharyngeal specimens for isolation of *C. trachomatis* are not recommended for children of either sex.[224]

For culture, Dacron-, cotton- or rayon-tip swabs on an aluminum or plastic shaft are recommended. Swabs with wooden shafts and those with a calcium alginate tip can inhibit growth of the organism.[222] Swabs should be placed immediately into chlamydial transport media (containing sucrose phosphate or sucrose phosphate glutamate supplemented with bovine serum and antimicrobial agents) at 2°C to 8°C and transported to the laboratory within 24 hours. Freezing at −70°C can result in a 20% loss of viability. Freezing at −20°C should be avoided.

Collection of endocervical and urethral swab specimens for NAATs should follow the instructions of the manufacturer. Swab specimens for NAAT are stable at room temperature for up to 10 days. Urine specimens for NAAT are stable for up to 24 hours at room temperature, after which they can be refrigerated for up to 4 days or stored at −20°C or lower for up to 2 months before processing.

Several FDA-approved NAATs are available for the simultaneous detection of *C. trachomatis* and *Neisseria gonorrhoeae* based on PCR, transcription-mediated amplification, and strand displacement amplification.[222] All have excellent sensitivity and specificity and can be performed in 2 to 5 hours. However, they do not all perform equally well with all specimen types.[230] In 2006, a genetic variant of *C. trachomatis* was identified in Sweden that was undetectable by PCR, a finding that further raises the importance of continued assessment of different NAATs to ensure optimal performance.[231]

Serologic tests for *C. trachomatis* genital tract infections are not useful for diagnosis in individual patients.[222] Antibodies to *C. trachomatis* persist for life. In infants, detection of anti–*C. trachomatis* IgM antibody by using the microimmunofluorescence (MIF) test is the diagnostic test of choice for chlamydial pneumonia.[222] Maternal IgG antibodies can persist in infants for 6 to 9 months.[222] The MIF test is the most sensitive serologic test and is the only one that detects species- and serovar-specific responses.[222] EIAs for the detection of IgM antibodies in infants have variable performance compared with the MIF test and are not specific for *C. trachomatis*.[222] Interpretation of a single IgG antibody test result is difficult because 50% to 70% of people can have antibodies to *C. pneumoniae.*[232,233] CF tests have been used widely for the diagnosis of psittacosis and lymphogranuloma venereum, but they have no value in diagnosing genital tract or neonatal chlamydial infections.

Antimicrobial susceptibility testing for any of the *Chlamydia* species has not been standardized, and in vitro results do not necessarily correlate with clinical response to treatment. Therefore, no role exists for routine susceptibility testing for clinical management, and testing generally is restricted to a few research laboratories.

Chlamydophila Pneumoniae

Accurate laboratory confirmation of acute infection with *C. pneumoniae* is difficult and often is based on serologic testing despite the high seroprevalence of the organism in adults.[222,234,235] The MIF test appears to be the most reliable serologic test for diagnosis of acute infection, and the following criteria for a positive test have been used: (1) a greater than fourfold rise in titer; (2) IgM titer >1 : 16; or (3) IgG titer >1 : 512. IgG titers between 1 : 16 and 1 : 512 are considered evidence of previous, but not necessarily recent, infection.[233] However, the MIF test is limited by lack of standardization and availability of high-quality reagents and by the inability to distinguish past from persistent infection.[236] Comparison of EIAs (using species-specific assays) with MIF have shown good sensitivity and specificity in children with respiratory tract diseases and in control children.[237] Because some EIAs detect antibodies to lipopolysaccharide, these tests detect antibodies to all *Chlamydia* species. Given their poor sensitivity, CF tests should not be used for diagnosis.[233,238]

Isolation of *C. pneumoniae* is difficult. The stability of *C. pneumoniae* in clinical specimens has not been well studied, although 1 study reported that 70% of organisms remain viable after 24 hours at 4°C.[222,239] Throat swabs, sputum, NP, BAL, and other respiratory tract specimens placed in transport media have been used with variable success. Detection of the organism in respiratory secretions does not prove causality because asymptomatic infections occur in children and persistent shedding can occur for months after acute disease in adults.[240,241]

Molecular diagnosis with noncommercial conventional and real-time PCR tests has been evaluated.[242,243] Sensitivities appear to be as good as those of culture, but specificity is difficult to determine given the lack of a gold standard for comparison.

Mycoplasma

Mycoplasma Pneumoniae

Rapid and accurate diagnosis of *Mycoplasma pneumoniae* infection is problematic because of the lack of well-standardized tests.[244] Culture is the most widely accepted method for testing respiratory tract secretions, but availability is limited, specialized broth and agar media are required, and yield is relatively low.[245] For optimal isolation, specimens (BAL, tracheobronchial secretions, sputum, NP aspirates or swabs, tissues, blood, CSF, joint fluid) should be inoculated into appropriate media (e.g., SP4) at the bedside. Most media are acceptable for both isolation and PCR assay. Specimens should be refrigerated if they are not processed within 24 hours. Because *M. pneumoniae* is relatively slow growing, cultures should be maintained for 4 weeks before results are reported as negative. Shedding of *M. pneumoniae* can persist for several weeks after the onset of illness (particularly in children), thereby confounding the interpretation of a positive culture result.

Direct antigen testing (EIA, DFA, immunoblotting) for respiratory tract secretions such as sputum and NP aspirates performs well in research settings (sensitivity of 90%), but these tests are not available widely.[246,247] Cross-reactivity with other commensal mycoplasmas can occur. Persistent shedding and detection of antigen in asymptomatic people confound the interpretation of positive results. At present, these tests are neither recommended nor used routinely in the clinical setting.

Conventional and real-time PCR tests for detection of *M. pneumoniae* in respiratory secretions have been widely evaluated.[245–251] PCR tests consistently are more sensitive than culture and antigen detection. Despite relatively high sensitivity, most studies suggest that PCR cannot be used alone to make a diagnosis of acute or recent infection; results must be used in conjunction with other results such as those of serologic tests.[245,251,252] When performed on CSF, PCR can be useful for the diagnosis of *M. pneumoniae*–associated meningoencephalitis.[253]

Serologic diagnosis by measurement of anti–*M. pneumoniae* IgG, IgM, and IgA antibodies can be performed with commercially available EIA, FA, and latex agglutination kits. These tests are more sensitive and specific than CF assays and have replaced CF in many diagnostic laboratories.[244,254,255] Their usefulness is limited because many children are IgM negative at the time of presentation, and the time to seroconversion can be 2 to 4 weeks.[256] In children, adolescents, and young adults, a single positive IgM result can be considered diagnostic, although false-positive results occur. The combination of serologic results together with culture or PCR may provide the most reliable approach to diagnosis.[245,250,251]

Cold agglutinin antibody titers are simple to perform and are widely available. Because only 50% to 75% of people infected with *M. pneumoniae* develop cold agglutinin antibodies and the test lacks sensitivity and specificity, it should not be used for the serologic diagnosis of *M. pneumoniae* infections.[257,258]

Genital Mycoplasmas

The laboratory diagnosis of *Ureaplasma urealyticum* and *Mycoplasma hominis* infections can be achieved by isolation of the organism by using specialized broth and agar media. Organisms grow rapidly, and culture results are positive within 2 to 5 days. PCR (including multiplex assays) has been used to detect *U. urealyticum* and *M. hominis* in clinical specimens.[259–261] *Mycoplasma genitalium* grows slowly; cultures may not be positive for ≥6 days. PCR-based assays are the mainstays of diagnosis,[259,262,263] but none is available commercially. Serologic tests for genital mycoplasmas have not been standardized, and none is available commercially. Serologic testing (using EIA, WB, IFA) has little utility except as an epidemiologic tool.[264] *M. genitalium* cross-reacts strongly with *M. pneumoniae*. Patients with invasive *M. hominis* infection almost always have seroconversion or a significant rise in antibody titer.

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Laboratory Manifestations of Infectious Diseases

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Acute Phase Response

Stimuli of many kinds, including infection, trauma, or ischemia, cause marginalization, extravasation, and activation of neutrophils and monocytes with release of multiple proinflammatory cytokines, including interleukin1β (IL-1β), IL-6, IL-8, and tumor necrosis factor-α (TNF-α). These mediators stimulate production of a variety of proteins referred to as acute phase reactants in macrophages, monocytes, and reticuloendothelial organs with predictable, complex metabolic effects (Box 288.1). The host-pathogen, damage-response framework conceptualizes consequences of such events, which can be caused primarily by the pathogen or the host and can be beneficial or detrimental to the host.[1] More than 100 "biomarkers" have been investigated in infection, and they have been correlated with initiation, magnitude, type, ascent, descent, and duration of acute phase response. Although measurement provides a guide to the intensity of inflammation or the extent of tissue damage, no single marker has exquisite predictive value as a stand-alone test to trump clinical judgment to initiate, withhold, or conclude antimicrobial therapy; instead, these markers augment clinical judgment. Use of combinations of biomarkers in clinical decision rules likely is or will be superior, but complexity makes practical implementation difficult.[2,3] Multiple biomarker panels based on genome-wide expression profiling by stimulus are under active investigation, with measurements of procalcitonin (PCT), IL-6, and IL-8 furthest along. As technology and knowledge of immune modulation advance, biomarker analyses will need to be accessible, rapid, reliable, and studied in prospective trials powered for proof of clinical validity and impact on quality of care before clinical adoption.[4–8]

Box 288.1

Expected Manifestations of the Acute Phase Response

Brain

Increased release of corticotropin, endorphin, prolactin, neuropeptides, and neurotransmitters

Increased production of thyroid-stimulating hormone, vasopressin, insulin, and glucagon

Decreased production of insulin-like growth factor I

Fever, diminished appetite, and somnolence

Blood Cells

Neutrophilia, increased neutrophil activation, and redistribution

Thrombocytosis

Reticulocytopenia, eosinopenia

Activation of B lymphocytes (antibody production) and T lymphocytes (lymphokine production)

Redistribution lymphopenia

Anemia of chronic disease

Tissue

Collagen proliferation by fibroblasts

Demineralization of bone

Proteolysis and amino acid release from muscle

Liver and Other Sites

Increased synthesis or release of complement components and expression of receptors, fibronectin, fibrinogen, mannose-binding protein, lipopolysaccharide-binding protein, hepcidin, ferritin, glycoproteins, C-reactive protein, α_1-antitrypsin, α_2-macroglobulin, lipids and lipoproteins, and ceruloplasmin

Increased synthesis of serum amyloid A, haptoglobin, and immunoglobulins

Decreased free and total serum iron, zinc, and retinol

Decreased synthesis of albumin, prealbumin and transferrin and cytochromes

Decreased gluconeogenesis

Erythrocyte Sedimentation Rate

Physiology and Measurement

The erythrocyte sedimentation rate (ESR) measures in vitro the fall of the red blood cell (RBC) column in a vertical suspension of anticoagulated plasma over 60 minutes. A surrogate of in vivo inflammation, the ESR generally rises over 24 to 48 hours after stimulus and returns to baseline more slowly than other acute phase reactants, thus lagging behind resolution of illness. Sedimentation depends on RBC mass, volume, and shape, as well as RBC-RBC forces and the protein constitution of plasma. Electrostatic forces normally cause RBCs to repel each other and inhibit their aggregation. Increased amounts of plasma fibrinogen or globulins coat the RBCs, foster aggregation, and hasten settling, consequently elevating the ESR. Large-molecular-weight, needle-shaped fibrinogen has the greatest effect, followed by β-globulins and distantly by α_2-globulins, γ-globulins, and albumin.

Normal values are age and sex dependent (androgens lowering the ESR): ≤10 to 20 mm/hr for children 1 month to 12 years old, ≤15 mm/hr for boys and men >12 years of age, and ≤20 mm/hr for girls and women >12 years of age. After puberty, the normal top value rises 0.85 mm/hr for every 5-year increase in age. Obese children have higher mean ESRs than lean children (e.g., 20 vs. 10 mm/hr at 9–10 years of age).[9,10]

Elevated Sedimentation Rate

The ESR is elevated in most bacterial, mycobacterial, and fungal infections and is normal or mildly elevated in uncomplicated viral, rickettsial, and ehrlichial infections. An elevated ESR (>20 or >30 mm/hr, depending on the study) has poor discriminating power as a single test (i.e., sensitivity and specificity ≤50%) to predict bacterial infection in children with nonspecific, febrile illnesses of short duration.[11–13] The mean ESR during most viral upper respiratory tract infections is approximately 20 mm/hr (with 90% of values <30 mm/hr), with noteworthy exceptions such as during adenovirus infections, in which mean ESR can be 40 mm/hr.[12,14] For patients with fever of unknown origin, a normal or mildly elevated ESR is predictive of the eventual diagnosis of a nonserious or viral disease in >90% of cases[15,16]; an ESR >50 mm/hr in such patients can be an impetus for more extensive evaluation.[17,18]

Usefulness of the ESR in children with osteoarticular conditions has been studied.[19] Several studies of children with bacterial arthritis have documented ESRs >30 mm/hr in 80% to 90% of cases (mean, ~65 mm/hr).[20–23] Prospective validation of Kocher criteria (fever ≥38.5°C, inability to bear weight, ESR ≥40 mm/hr, and white blood cell [WBC] count >12,000 cells/mm^3) for distinguishing pyogenic arthritis of the hip from toxic synovitis showed an area under the receiver operating characteristic (ROC) curve of 0.86.[21] In a retrospective case series in a primary referral hospital, positivity of all 4 Kocher criteria in addition to C-reactive protein (CRP) ≥2 mg/dL had a predictive value of only 60% for bacterial arthritis,[22] and in series from the United States and Europe, Kocher scores were low in children with Lyme and *Kingella* arthritis of the hip.[24,25] In children with pyogenic arthritis, the ESR frequently rises on days 2 to 4 of effective therapy,[19] and an ESR >30 mm/hr persists in at least 50% of cases at the conclusion of successful therapy.[19,20] The peak ESR in acute osteomyelitis generally is lower than in bacterial arthritis (mean, ~45 mm/hr), with expectations of a gradual fall and normal values at an appropriate conclusion of therapy.[26] In subacute or chronic osteomyelitis, the ESR usually is mildly elevated (25–40 mm/hr) but can be normal.

An elevated ESR characteristically occurs in multiple noninfectious inflammatory conditions, as well as in noninflammatory states that affect RBC stearic properties or plasma volume, fibrinogen, globulins, or protein concentrations (Box 288.2). Conversely, during infectious diseases, certain conditions can result in a “falsely” low ESR.[27] The ESR usually exceeds 30 mm/hr during febrile episodes in children with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome and other autoinflammatory periodic fever symptoms.[28] An ESR <50 mm/hr does not exclude Kawasaki disease but makes the diagnosis unlikely.[29] Immune globulin intravenous therapy causes some elevation of the ESR.[30,31]

Box 288.2

Effects of Conditions Other Than Infectious Diseases on the Erythrocyte Sedimentation Rate

Increase in Erythrocyte Sedimentation Rate

Noninflammatory or Unclear Mechanism

Anemias with normal red blood cell shape

Elevated nonfibrinogen proteins: M proteins, macroglobulins, red blood cell agglutinins

Immune globulin intravenous

Heparin therapy, heparin in sample (sodium citrate and ethylenediaminetetraacetic acid do not affect erythrocyte sedimentation rate)

Oral contraceptive agents

Obesity

Multiple myeloma

Renal cell carcinoma

Glomerulonephritis

Pregnancy

Hypothyroidism

Hypercholesterolemia

Chronic renal failure

Diabetes and nephropathy

Technical factors (e.g., tilting test tube just 3 degrees from vertical can accelerate ≤30 mm/hr)

Inflammatory or Presumed Inflammatory Mechanism

Hodgkin disease

Lymphoproliferative disorders

Other malignant diseases

Paraneoplastic syndromes

Collagen vascular disease

Autoimmune diseases

Autoinflammatory disorders

Rheumatic and other poststreptococcal syndromes

Myocardial infarction

Postpericardiotomy syndrome

Lymphocytic thyroiditis

Kawasaki disease

Serum sickness

Burn injury

Accidental and surgical trauma

Inflammatory bowel disease

Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease)

Histiocytic necrotizing lymphadenitis (Kikuchi-Fujimoto disease)

Neutrophilic dermatosis (Sweet syndrome)

Benign hyperplastic lymphadenopathy (Castleman disease)

Decrease in Erythrocyte Sedimentation Rate

Morphologic abnormalities of red blood cells (e.g., sickle cells, spherocytes, anisocytes, poikilocytes)

Diffuse intravascular coagulation (e.g., associated with infection, hemophagocytic lymphohistiocytosis, macrophage activation syndrome)

Polycythemia

Leukemoid reaction

Dysfibrinoginemia, afibrinogenemia

Extreme elevation of serum bile salt concentration

Congestive heart failure

Valproic acid

Glucocorticoids

Low-molecular-weight dextran

Asparaginase

Cachexia

Technical factors (e.g., sample >2 hours old, non–room temperature sample after refrigeration)

Discordant results between the ESR and other markers of inflammation, particularly CRP, can be clues to infectious and noninfectious diseases. Low ESR and high CRP have been reported in Kawasaki disease[32] and in severe inflammatory bowel disease,[33] whereas high ESR with normal or mildly elevated CRP can be a clue to underlying autoimmune disease or chronic indolent infection.

Extreme Elevation of the Sedimentation Rate

Box 288.3 shows infectious and noninfectious conditions that should be considered especially when the ESR exceeds 100 mm/hr. Extreme elevation of the ESR is characteristic of certain noninfectious conditions. In children (unlike adults), however, infection still is a likely cause, accounting for 56% of cases in 1 study of 156 children[34]; miliary tuberculosis is notable among infectious diseases.[15] Collagen vascular, renal, and macrophage disorders and neoplastic disease rise among differential diagnoses. An extreme elevation of the ESR at the diagnosis of bacterial infection does not in itself indicate complicated disease or a guarded prognosis.

Box 288.3

Infections and Other Conditions Associated With Erythrocyte Sedimentation Rate >100 mm/hr

Infections

Miliary tuberculosis

Lymphadenitis or visceral infection caused by *Bartonella henselae*

Soft tissue or serosal infections caused by *Streptococcus pyogenes* or *Streptococcus pneumoniae*

Pyelonephritis

Bacterial arthritis

Soft tissue infections of the head and neck

Pelvic inflammatory disease

Ruptured appendicitis

Infective endocarditis

Other Conditions

Autoimmune diseases

Autoinflammatory disorders

Kawasaki disease

Postinfectious and rheumatic disorders

Erythema nodosum

Sarcoidosis

Malignant lymphoma

Acute leukemia

Neuroblastoma

Other malignant diseases, especially metastatic carcinoma

Renal disease and nephrotic syndrome

Multiple myeloma

Visceral inflammatory pseudotumor

Sweet syndrome

Hyper IgD syndrome/mevalonate kinase deficiency

Drug hypersensitivity

Low Erythrocyte Sedimentation Rate

Causes of a low ESR are shown in Box 288.2. In children with infectious diseases, an abnormally low ESR (e.g., <4 mm/hr) is most frequently a sign of disseminated intravascular coagulopathy and reflects low plasma fibrinogen concentration; elevated fibrinolytic markers (e.g., D-dimer) are expected. Administration of glucocorticoids and possibly high-dose (but not low-dose) salicylates and L-asparaginase lower the ESR,[35] as does performance of peritoneal dialysis or hemodialysis.[36] The ESR is not valueless in children with sickle cell disease; in 1 study, 72% of hospitalized children with an ESR >20 mm/hr had clinical infection (and 38% had vaso-occlusive crisis) compared with 23% with an ESR of ≤20 mm/hr, 74% of whom had vaso-occlusive crisis.[37,38]

C-Reactive Protein

Physiology and Measurement

The production of IL-6, and less so IL-1β, stimulates hepatocytes to produce CRP, a protein so named because of precipitation with C-polysaccharide of the pneumococcal cell wall. Although the liver is the main source of CRP, extrahepatic sites can directly produce smaller amounts, including macrophages, monocytes, lymphocytes, neurons, respiratory and renal epithelial cells, and smooth muscle cells. The CRP level increases within 4 to 6 hours of an inflammatory stimulus, doubles every 8 hours, peaks at levels 100 to 1000 times normal within 1 to 3 days, and then falls relatively rapidly (with a half-life of 19 hours) once the triggering stimulus ceases. Functional properties of CRP include stimulation of opsonization by binding bacteria and parasites, directly activating complement through the classic pathway modulating function of phagocytic cells, and augmentation cell-mediated cytotoxicity.[6,39–41] Nephelometric assays remain the most widely used techniques for measuring CRP; a value <1 mg/dL (10 mg/L) is considered "normal" for clinical predictive purposes. Normal range is variable by the test used. Modest longterm elevations (>0.3 mg/dL) using high-sensitivity CRP tests have been used as markers of increased risk of atherosclerosis.[10,42,43]

Compared with the ESR, CRP rises more rapidly, peaks earlier, and returns to normal levels more quickly when the stimulus abates. Factors that affect the ESR, such as anemia, polycythemia, protein levels, and RBC shape, do not affect CRP values. Any tissue injury, however, such as trauma, burn injury, ischemia, or infarction, can elicit production of CRP. Because CRP is degraded rapidly, serial determinations can provide additional information on progression of an insult or the effect of therapy.[23,44] Liver failure and certain rare inherited immunodeficiencies (e.g., nuclear factor-κB [NF-κB] pathway defects) can cause "falsely" low CRP levels in the presence of invasive bacterial or fungal infection.[45]

Clinical Usefulness

In general, CRP levels are elevated substantially (15–35 mg/dL) in bacterial infections with a tissue site of infection and only modestly (<2–4 mg/dL) in most acute viral infections; a value >10 mg/dL is more likely to be associated with bacterial infection, although infections with certain viruses (e.g., adenovirus, cytomegalovirus [CMV], influenza, measles, and mumps) can cause CRP levels >10 mg/dL.[7,35] Limitations in validating the accuracy of elevated CRP to predict serious bacterial infection (SBI) in neonates and infants with fever but without a clinical focus of infection include variable cutoff values used and the low incidence of SBI.[46–49] Pooled estimates in studies with cutoff values of 1 to 7 mg/dL showed sensitivity for SBI of 63% to 95% and specificity 40% to 91%,[47] and 6 studies, 3 of which used a cutoff value of 4 mg/dL, showed sensitivity of 77% and specificity of 79%.[48] In neonates, sensitivity for culture-proven early onset sepsis was only 39%.[49] Combined with other biomarkers such as IL-6, IL-8, and PCT, the diagnostic accuracy of CRP for early onset sepsis improves.[8,50] "Elevated" CRP can occur spontaneously in neonates in the first 48 hours of life (≤1 mg/dL),[49] in the 48 hours after injections of multiple vaccines (>1 mg/dL),[51] and 1 to 2 days following major surgical procedures (median peak, 2 mg/dL).[52] Benitz and colleagues[53] concluded that no currently available laboratory marker has predictive values exquisite enough to drive algorithms for management regarding early onset sepsis. CRP appears to be less sensitive than IL-8 or PCT for detecting SBI in oncologic patients with fever and neutropenia.[54–56]

CRP level has better predictive value for distinguishing bacterial infection when a tissue focus of infection is identified. A meta-analysis of 8 studies including 1230 children with pneumonia showed a positive predictive value (PPV) of CRP >4 mg/dL for bacterial pneumonia of 64%.[57] In 1 study CRP ≥2 mg/dL detected bacterial meningitis in patients despite negative Gram stain findings (sensitivity, 96%; specificity, 93%; negative predictive value [NPV], 99%).[58] In another study, CRP level >2 mg/dL was an independent risk factor for pyogenic arthritis (odds ratio, 14.5; 95% confidence interval [CI], 3.2–64.9) compared with toxic synovitis.[59]

Discordantly high CRP levels compared with other acute phase reactants (especially WBCs and ESR) have been noted, such as in Kawasaki disease,[32] focal bacterial infections (in 1 study 26% of cases had a WBC count <15,000/mm^3 and CRP ≥8 mg/dL),[60] Crohn disease,[61] neoplasms of the liver and reticuloendothelial system (e.g., lymphoma), Castleman disease, allograft rejection, and graft-versus-host disease.[44,62]

Sequential measurement of CRP is valuable as an assessment of therapeutic control of focal infections, including wound infections following spinal operations[63] and infective endocarditis,[64] and as a clue to ineffective therapy or complicated infection such as undrained abscess and tissue necrosis.[26,45,46] Serial CRP levels that increase or fail to decrease after 48 hours of therapy suggest treatment failure, a complication, or a noninfectious diagnosis.[46] A meta-analysis of CRP values following abdominal operations (using variable threshold values by surgical procedure) showed an 84% NPV for infectious complication when measured on postoperative day 4.[65] Serially measured normal CRP values have a better NPV for bacterial infection in certain clinical settings, including early onset neonatal sepsis[8,50,66] and fever without a source in infants and young children.[67–72] A CRP value of <2 to 3 mg/dL in an afebrile, clinically improving patient has been used as an adjunct marker for safe transition from parenteral to oral antibiotic therapy for patients with uncomplicated pediatric osteoarticular infections.[73]

Serial concomitant testing of both ESR and CRP during acute infection likely is not beneficial compared with CRP measurements alone.[74] In patients with suspected or known chronic autoimmune diseases, following both values may assist in differentiating disease progression from acute infection.

Procalcitonin

Physiology and Measurement

Biologic activities of PCT, the prohormone of calcitonin, include lowering serum calcium concentration by inhibition of bone resorption and signaling of bacterial invasion. In animal models, induction of bacterial infection or administration of endotoxin results in synthesis of PCT by virtually all tissues and organs that is detectable in serum within 2 to 4 hours, peaks at 12 to 48 hours, and has a half-life of 22 to 26 hours.[75,76] PCT does not have known direct inflammatory effects, but it is a potent amplifier of the proinflammatory cascade.[77] PCT levels generally are not increased in response to viral infections (possibly in part because of the inhibitory effect of interferon),[6,75,77] in systemic autoimmune disease, inflammatory bowel disease, or some arteritis syndromes. PCT levels can rise transiently in patients with severe trauma, burns, and extensive surgical procedures, as well as during T-lymphocyte antibody therapy and graft-versus-host disease.[7]

Normative values of PCT by age and differences in tests and cutoff points in clinical studies confound consensus interpretation of results. Based on highly sensitive research assays, the normal PCT level in uninfected adults is 0.003 to 0.033 ng/mL.[75] During the first 48 hours of life in healthy neonates, the upper limit of 95% CI increases from 0.7 ng/mL at birth to 20 ng/mL at 24 hours, declines to 2 ng/mL at 48 hours of age, and normalizes to <0.1 ng/mL after 72 hours.[8,49,78]

The first commercially available test for PCT was an immunoluminometric assay with lower limit of sensitivity of 0.5 ng/mL; this cutoff was used for many studies and may be insensitive to detect bacterial infection. A second-generation PCT assay (a time-resolved, cryptate-emission [TRACE] immunoassay) cleared by the Food and Drug Administration has a functional lower limit of sensitivity of 0.05 ng/mL.[75] Clinicians should be familiar with their locally offered test and reference ranges and should recognize that comparisons of PCT values across institutions or studies may not be appropriate.[76,77]

Clinical Studies

Serum PCT levels rise and fall more rapidly than CRP levels during onset and control of bacterial infections and appear to have modestly increased sensitivity, specificity, predictive values, and ROC curve. The usefulness of PCT determinations may be offset partially by limitations in determining cutpoints and lower specificity in some populations of interest.[7,49,75] Despite numerous studies, optimal clinical application of PCT measurements remain uncertain,[79] with multiple systematic reviews and meta-analyses yielding conflicting results.[55,56,67,68,80–83] A focused review of research from 2012 through 2016 highlights, by types of infections, the evidence and limitations of PCT-guided antimicrobial management.[84]

Usefulness of PCT levels in the first 48 to 72 hours of life is unclear because of wide variations in study and testing characteristics, as well as physiologic factors (i.e., PCT crosses the placenta, and the PCT level can be high in newborns following uncomplicated delivery).[8,78,85] Studies of the usefulness of PCT in evaluation of late onset neonatal sepsis and young infants with fever without a focus have had mixed results. In a prospective observational study of infants ≤90 days of age who had fever without a focus of infection, the median PCT level was 0.53 ng/mL for infants with SBI, 0.29 ng/mL for infants with recent immunizations without SBI, and 0.17 ng/mL for infants with neither.[86,87] The proposed PCT cutpoint of 0.12 ng/mL showed sensitivity of 96%, specificity of 23%, and NPV of 96%. Generalizability to other age groups has been questioned.[88] Using cutpoints of <0.5 ng/mL and ≥2 ng/mL, PCT appeared to have superior ROC performance compared with other biomarkers for SBI in infants <36 months of age with fever for <8 hours[89]; additional studies have affirmed this performance.[69,71,72,90] More recently, studies have used a PCT cutpoint of 0.3 ng/mL for detecting or excluding serious or invasive infection in young febrile infants and children,[91–93] with mixed results of utility.[70,94] In a 2015 prospective French study of febrile infants 7 to 91 days of age who were seen in a pediatric emergency department, the determined sensitivity and specificity, respectively, of PCT for bacteremia or meningitis were evaluated using different cutpoints: PCT >0.3 ng/mL (90% and 78%); PCT >0.5 ng/mL (85% and 85%); PCT >2 ng/mL (60% and 94%). When identification of urinary tract infection was included, the utility of PCT approximated that of CRP (ROC area under the curve, 0.81 and 0.83, respectively).[91] Beyond infancy, a PCT value >2 ng/mL may more consistently correlate with bacterial infection, thus predicting either sepsis or poor outcome in a variety of populations.[81,95,96]

An elevated PCT concentration has reported predictive value for discriminating bacterial infection in febrile neutropenic children with cancer,[56,82,97] febrile children with sickle cell disease,[98] diarrhea-associated hemolytic uremic syndrome,[99] bacterial causes of acute hepatic disease,[100] septicemia versus systemic inflammatory response syndrome,[6,7,81,92,96,101–104] postoperative infection following pediatric cardiac surgical procedures,[105,106] bacterial versus aseptic meningitis,[107] bacterial pneumonia,[108,109] central venous catheter infection in children,[110] severe Crohn disease (cutoff, 0.14 ng/mL),[111] and pyelonephritis.[112] For pyelonephritis, PCT can serve to predict renal scarring.[112,113] PCT can be useful in discriminating bacterial infection in febrile adults with systemic autoimmune diseases.[114,115] In a systematic review of patients with systemic lupus erythematosus, a cutpoint of >0.5 ng/mL was optimally sensitive and specific.[83]

Pooling data to determine clinical guidelines for widespread use of PCT to initiate or withhold therapy has proved difficult. Two systematic reviews and meta-analyses demonstrated contradictory results: 1 report concluded that PCT was superior to CRP and WBC count for most clinical situations,[67] whereas the other concluded that PCT is inferior to current clinical predictive rules for identifying young febrile infants at risk for SBI.[80]

A multicenter noninferiority randomized trial of use of a PCT algorithm as a decision rule to initiate and discontinue antibiotics for community-acquired pneumonia in adults (antibiotics discouraged if PCT <0.25 ng/mL and encouraged if PCT >0.5 ng/mL) showed that application of the rule was associated with similar clinical outcome and reduced antibiotic exposure and adverse events[116]; the added value of PCT was questioned subsequently.[117,118] In a study of similar strategy to limit empiric therapy in children <36 months of age who had fever without a focus, the use of a PCT cutpoint of 0.5 ng/mL would have resulted in a 24% increase in antibiotic use in patients without a subsequent diagnosis of SBI.[94] In 2013, a European expert panel concluded that sufficient evidence exists to discontinue antibiotics safely based on PCT values alone for only 1 subgroup of adult patients: nonimmunocompromised patients in the intensive care unit who have suspected respiratory tract infection (i.e., when PCT is <0.25 ng/mL or decreased by 80%–90% at day 3).[119] Although similar PCT strategies to initiate or discontinue antibiotics have been studied in children, data are insufficient for safe support of such application routinely in any clinical setting.[102,120]

Other Acute Phase Proteins and Cytokines

Cytokines (e.g., IL-6, IL-8, IL-10), chemokines (e.g., TNF-α), acute phase proteins, and receptor molecules are being studied in humans.[6–8,103,121,122] Although clinical applications for detection of early points of infection are encouraging (e.g., sensitivity and ROC analyses), many biomarker responses are short-lived events, and no single mediator is likely to have broad application clinically.[6,49,52,54] Stratifying the utility of biomarkers related to timing of measurement, use for diagnosis versus prognosis, for NPV versus PPV, or for patient groups versus disease states can help to clarify the most valid roles of these biomarkers.[6,8,77,122]

Pediatric studies suggest that peripheral blood IL-6 and IL-8 levels may be the most promising for early identification of sepsis in several specific patient populations. Although IL-6 (with cutoff values of 20−50 pg/mL) has high sensitivity for identifying early onset sepsis in newborns, its half-life is very short, and timely measurement is challenging.[6,8,121,122]

IL-8 has demonstrated potential as an indicator of early gut ischemia and predictor of death in necrotizing enterocolitis,[8,121,123,124] and it may be more sensitive than CRP for detecting bloodstream infection in oncologic patients with fever and neutropenia.[55]

Ferritin is a highly conserved, ubiquitous intracellular protein, control of which depends on multiple genes, regulatory messenger RNA structures, signaling pathways, and protein catalysts. Ferritin tightly controls iron and oxygen chemistry. Expression is upregulated by proinflammatory cytokines; expression also is regulated by thyroid hormone, insulin, insulin growth factors, hypoxia and ischemia, and hyperoxia (nitric oxide). Immunologic activities include binding to T lymphocytes, suppression of delayed-type hypersensitivity and B-lymphocyte antibody production, and regulation of granulomonocytopoiesis. Normal serum ferritin concentrations in men is <400 μg/L (<400 ng/mL) and in women is <150 μg/L.

Serum ferritin levels are markers of iron deficiency (low) and iron intoxication or overload states (high). Levels also are elevated in inflammation, infection, and hypoxia and ischemia. Clinical interest has escalated because of the usefulness of ferritin as a criterion (serum level >500 μg/L) for hemophagocytic lymphohistiocystosis and macrophage activation syndrome, in which peak levels frequently exceed 10,000 μg/L.[125,126] Moderately elevated ferritin levels (>500 μg/L and even >1000 μg/L) also occur in severe sepsis,[127] dengue hemorrhagic fever, lymphoma, systemic lupus erythematosus, and other autoimmune and autoinflammatory conditions.[128,129]

Other acute phase proteins under investigation in pediatric populations include hepcidin,[130,131] presepsin (a soluble lymphocyte CD14 subtype),[6,121] serum and fecal calprotectin,[132] and serum amyloid A.[6,8,121] Receptor molecules also may be promising biomarkers of sepsis, including soluble triggering receptor expressed on myeloid cell (sTREM),[6,122] urokinase plasminogen activator receptor (uPAR),[6,8] neutrophil CD64 (nCD64),[6,8,122,133] and others.[103] At a cutpoint index value of 2.38, nCD64 has been found to predict early onset sepsis in neonates with 100% sensitivity, 68%

specificity, and 100% NPV.[8,133] Further studies for optimal testing and clinical application are needed.

Hemoglobin

Erythrocytosis and Hemoconcentration

Erythrocytosis (polycythemia) secondary to increased erythropoietin production in response to arterial hypoxemia can provide a clue to cryptogenic bronchiectasis. Hemoconcentration is defined as hematocrit level >44% in men and >40% in women. Probably primarily a result of plasma leakage, hemoconcentration is characteristic of severe or toxic infections such as hantavirus pulmonary syndrome, dengue hemorrhagic fever, clostridial toxic shock, and necrotizing pancreatitis, and it generally portends a poor outcome.[134–137] Methemoglobulinemia is well described in young infants with diarrheal disease or urinary tract infection possibly due at least partially to absorption of nitrites produced by enteric organisms.[138]

Anemia in Chronic Infection

The anemia of chronic disease likely is driven by cytokines and reticuloendothelial cells that induce pathologic changes in iron homeostasis, impaired erythropoiesis, blunted erythropoietin response, and decrease in RBC lifespan.[139] Anemia is mildly to moderately severe, reflecting extent and duration of infection, and is associated with reticulocytopenia. Erythrocyte mean corpuscular hemoglobin and volume usually are normal. The serum ferritin value frequently is increased. An iron deficient type of erythropoiesis (low serum iron and increased erythrocyte protoporphyrin concentrations) results despite normal or increased iron stores.

Anemia of chronic disease is expected in clinical tuberculosis, subacute infective endocarditis, human immunodeficiency virus (HIV) infection, hepatitis C, malaria, and chronic osteomyelitis. Successful treatment of the infection is the only effective therapy. Noninfectious inflammatory conditions such as autoimmune disorders, malignant solid tumors, and autoinflammatory diseases (e.g., inflammatory bowel disease) typically are associated with anemia of chronic disease, and in some cases anemia responds to the administration of recombinant erythropoietin. Anemia can be a clue to the diagnosis of Crohn disease in children without overt abdominal symptoms who are being evaluated for fever of unknown origin. RBC indices also can reflect true iron deficiency anemia from gastrointestinal blood loss in these patients. Hookworm infestation is another cause of occult blood loss and iron deficiency anemia.

Anemia in Acute Infection

Mild, readily reversible, normocytic anemia (hemoglobin, 9–11 mg/dL) is not uncommon in patients with minor bacterial and viral infections and is characterized by mild hemolysis and diminished RBC production. A profoundly decreased total and free serum iron concentration (e.g., transferrin saturation <10%) is an expected acute response to infection or inflammation; measurement during acute infection is inappropriate and frequently leads to incorrect conclusions and therapy.

Approximately 50% of children with acute SBIs (meningitis, pneumonia, arthritis) have anemia (hemoglobin <11 g/dL) at the time of hospitalization. Moderate to severe acute hemolysis can occur in exotoxin-mediated syndromes secondary to *Staphylococcus aureus* and *Streptococcus pyogenes* or in septicemia caused by endotoxin-producing enteric bacteria or *Neisseria meningitidis*. Hemolysis occurs in patients with disseminated intravascular coagulopathy associated with severe infection caused by a variety of bacteria, rickettsiae, fungi, viruses, and protozoa; expected associated findings are burred RBCs, elevated serum lactate dehydrogenase and unconjugated bilirubin levels, and a reduced haptoglobin level. Severe acute hemolysis and thrombosis leading to hemolytic uremic syndrome is an increasingly reported complication of pneumococcal infection in children, especially complicated pneumonia.[140,141] *Mycoplasma pneumoniae*, Epstein-Barr virus (EBV), and cytomegalovirus (CMV) can produce immune-mediated hemolytic anemia, and *Vibrio cholerae* can elicit nonimmune acute hemolytic anemia. *Plasmodium falciparum* malaria and clostridial septicemia classically are associated with marked intravascular hemolysis and profound anemia. Severe and sometimes fatal hemolysis, which probably is immune mediated, has been associated with initiation of ceftriaxone therapy in several children with a variety of underlying conditions who were previously exposed to ceftriaxone.[142,143]

Transient erythroblastopenia is an acute phase response to many infections and usually is of no or minor consequence in previously healthy children. Occasionally erythroblastopenia can be severe and can be associated with autoantibodies against erythroid progenitors or possibly erythropoietin. Viruses causing protracted infections (e.g., EBV, CMV) in immunocompetent children and especially in immunocompromised children, as well as those with HIV infection, can result in varying degrees of anemia. Acute human parvovirus B19 infection consistently causes transient reticulocytopenia with little consequence, except in people with shortened RBC survival in whom aplastic crisis occurs, in intrauterine life when interrupted erythropoiesis can cause hydrops fetalis, or in immunosuppressed people in whom protracted infection leads to significant anemia or pancytopenia.[144,145] Hepatitis viruses frequently suppress bone marrow during acute infection that rarely can result in permanent aplastic anemia. Hemophagocytic syndromes leading to pancytopenia can be triggered by many infections, especially those caused by herpesviruses, RBCs, and other intracellular pathogens, such as *Babesia*, parvovirus B19, *Brucella, Salmonella,* and *Histoplasma*.[146] In boys with X-linked lymphoproliferative disorder, EBV infection is associated with hepatitis and aplastic anemia, with high mortality rates.

Leukocytes

Circulating leukocytes are produced by the bone marrow in response to specific growth factors, and normal ranges vary with age (Table 288.1).[147] Leukocytosis is an increase in the total WBC count higher than the 95% confidence limits of the mean for age (i.e., approximately >11,000/mm^3 for adults, >13,000–15,000/mm^3 for children 4–16 years of age, and >20,000/mm^3 for infants 1–4 weeks of age). Leukocytosis is less meaningful clinically than are terms that describe the predominant type of leukocyte that is increased.

TABLE 288.1

Approximate Normal Leukocyte Counts in Children[a]

	Total Leukocytes		Neutrophils			Lymphocytes			Monocytes		Eosinophils	
Age	**Mean**	**Range**	**Mean**	**Range**	**Percent (%)**	**Mean**	**Range**	**Percent (%)**	**Mean**	**Percent (%)**	**Mean**	**Perce**
≤24 hr	20.0	9–35	13.0	5–25	65	5.6	2–11	28	1.1	5	0.5	2
1–4 wk	11.4	5–20	4.5	1.3–9	40	5.5	2–16	49	1.0	8	0.4	3
1–24 mo	11.2	6–17	3.7	1.5–8.5	33	6.7	3–10	59	0.6	5	0.3	3
2–6 yr	9.2	5–15	3.9	1.5–8	42	4.6	2–9	50	0.5	5	0.3	3
6–18 yr	8.2	4–13	4.4	1.6–8	53	3.2	1.5–6	39	0.4	5	0.2	3
≥21 yr	7.4	4–11	4.4	1.8–8	59	2.5	1–5	34	0.3	4	0.2	3

[a] Numbers of leukocytes are thousands per cubic millimeter; ranges are estimates of 95% confidence limits.

Modified from McMillan JA, Feigin RD, DeAngelis CD, et al. (eds) Oski's Pediatrics, 4th ed. Philadelphia, Lippincott Williams & Wilkins, 2006, p. 2628.

Neutrophilia

Neutrophils exist in 3 major anatomic spaces; these cells move unidirectionally from bone marrow, to peripheral blood, to extravascular spaces. Peripheral blood neutrophils are divided equally between the circulating pool and the marginated pool (where they are attached to or roll along the walls of capillaries or postcapillary venules). The number of neutrophils at each site can be regulated independently and influenced by various colony-stimulating factors (granulocyte colony-stimulating factor [G-CSF] and granulocyte-macrophage CSF [GM-CSF]). In an acute inflammatory response, neutrophils are released from the marrow granulocyte reserve (containing 10–15 times as many neutrophils as normally are present in circulating blood) into the bloodstream and migrate by margination and diapedesis to extravascular foci of tissue injury. In the bone marrow, CSFs act on progenitor cells to increase mitosis and expand the storage pool. Segmented neutrophils are released preferentially, but as release accelerates, less maturely segmented band cells and a few metamyelocytes also can be released and produce a “shift to the left.” Neutrophilia also can occur from movement of neutrophil pools in response to a variety of noninfectious stimuli. Endogenous or administered glucocorticoids and epinephrine cause demargination of neutrophils in the bloodstream, and glucocorticoids increase the half-life of neutrophils.[35,148] Immature forms are not expected. Tissue damage or necrosis such as from accidental or surgical trauma, fracture, burn injury, hypoxia, stress, lactic acidosis and ketoacidosis, acute hemolysis or hemorrhage, and systemic autoimmune and inflammatory conditions can induce complex acute phase responses, mitotic activation in marrow, and redistribution of neutrophils causing neutrophilia, sometimes with a modest left shift.

Bacterial and fungal cell wall products, exotoxins, and endotoxins are potent stimuli of the acute inflammatory response of neutrophils. Progressive elevation of the WBC count higher than 15,000/mm^3 with neutrophil predominance heightens suspicion of bacterial infection, but discrimination between viral and bacterial respiratory tract infections is not precise.[14] In 1 study of 121 children with pneumonia, the mean WBC count was 18,000/mm^3 for *Streptococcus pneumoniae,* 17,000/mm^3 for adenovirus, and 9000/mm^3 for *M. pneumoniae* causes.[148] In a retrospective case-control study of 69 children 2 to 24 months of age who were evaluated in an emergency department for a febrile illness, the rate of SBI was only 25% in those children with WBC counts >25,000/mm.[149] Absolute neutrophil count (ANC) rather than total WBC count and duration of fever are better predictors of SBI in febrile infants.[150,151]

SBIs do not always induce leukocytosis; exotoxin- and endotoxin-producing organisms such as *S. aureus, Haemophilus influenzae* type b, and *Salmonella* infections are most noteworthy. In 1 study, only 50% of the children hospitalized with proven bacterial infection had a WBC count >15,000/mm.[3,148] In a prospective observational study performed in 856 neonates who were born at >35 weeks' gestation and had been exposed to suspected chorioamnionitis, single or serial neutrophil values did not assist in the diagnosis of early onset infection.[152] In an analysis of administrative data from >166,000 neonates, most infants with proven SBI had normal total WBC counts (60%; 5000–19,000/mm^3) and ANC (87%; >1500/mm^3). Low

WBC count (<5000/mm^3 and <1000/mm^3), low ANC, and high immature-to total neutrophil ratio were associated with increasing odds of infection. No single or combination of WBC values could reliably exclude SBI.[153]

Extreme Elevations of Neutrophils and Leukemoid Reaction

Any cell type can be involved in a leukemoid reaction, so named because of the simulation of findings in leukemia. A myeloid leukemoid reaction is defined as a peripheral WBC count >50,000/mm^3 or a differential cell count with >5% immature myeloid cells capable of division (myeloblasts, promyelocytes, and myelocytes). The former type is more frequently encountered in children with infectious diseases. Box 288.4 lists causes of a myeloid leukemoid reaction. Severe bacterial infections are associated with this reaction most frequently. Viral infections do not cause a myeloid leukemoid reaction. Disseminated fungal infections can cause mild to profound neutrophilia (e.g., with thrombocytopenia in neonates with candidemia and eosinophilia in disseminated cryptococcosis) or neutropenia (e.g., with thrombocytopenia in disseminated histoplasmosis). Shigellosis, particularly *Shigella dysenteriae* infection, is associated with a leukemoid reaction more frequently in children younger than 4 years of age and characteristically has predominantly immature neutrophils as findings, but lymphocyte counts can be elevated as well. Leukemoid reactions result from *Clostridium difficile* colitis with toxin-hyperproducing strains and severe disease,[154] as well as from *Clostridium sordellii* in patients with myonecrosis and septicemia.[155] Malignant diseases, especially carcinomas, can express certain CSF genes that stimulate neutrophilia inappropriately and sometimes cause paraneoplastic syndromes. Myelogenous leukemia, which is most frequently associated with a leukemoid reaction, usually is distinguished by a disproportionately high number of blast forms compared with bands and metamyelocytes, as well as by the presence of anemia, thrombocytopenia, eosinophilia, and basophilia. Young infants with trisomy 21 can have a leukemoid reaction, which usually is transient but can evolve into a leukemic state.[155] Prenatal administration of betamethasone can cause neonatal leukemoid reaction.

Box 288.4

Causes of Myeloid Leukemoid Reaction in Children[a]

Infectious Causes

Septicemia

Severe acute necrotizing focal infection

Shigellosis

Salmonellosis

Clostridium difficile colitis

Cryptogenic abscess

Miliary or acute necrotizing tuberculosis

Disseminated candidiasis, cryptococcosis

Malaria[b]

Meningococcemia[b]

Infection in children with leukocyte adhesion defect

Bubonic plague

Diphtheria

Noninfectious Causes

Severe acute hemolysis or hemorrhage

Severe tissue ischemia

Bone marrow recovery from severe drug-induced suppression

Multiple fractures

Diabetic ketoacidosis

Collagen vascular and autoimmune diseases

Sarcoidosis

Kawasaki disease (young infants especially)

Carcinomas producing colony-stimulating factors

Acute leukemia, malignant lymphoma with marrow infiltration

Paraneoplastic syndrome

Chronic myeloproliferative disorders

Neonate with trisomy 21

Antenatal administration of betamethasone

Osteopetrosis

Gaucher disease

Postsplenectomy status

Severe burns

Mercury poisoning

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[a] Total white blood cell count >50,000/mm^3 (with predominantly neutrophils) or >5% myeloblasts, promyelocytes, or myelocytes in peripheral blood.

[b] Extreme left shift type of leukemoid reaction, or with neutropenia.

Neutropenia

Neutropenia is defined as a peripheral blood neutrophil count lower than the 95% confidence limit for age (see Table 288.1), usually an ANC <1500/mm^3 in children older than 1 month of age.[147] Undue susceptibility to infection because of neutropenia correlates best with an ANC <500/mm^3. Neutropenia related to infectious diseases can be caused by the infectious agent itself, infection-triggered hemophagocytosis, postinfectious immune mechanisms, or marrow suppression related to antibiotics or other drugs.[156] During severe infection, margination and diapedesis of neutrophils into tissues are increased at the expense of circulating cells in peripheral blood, thus leading to neutropenia. Bands and metamyelocytes are pushed from marrow peripherally and can equal or outnumber mature neutrophils; cells are vacuolated, with toxic granulations and Döhle bodies. Bone marrow findings can be confusing, with myeloid hyperplasia and "maturation arrest" at the promyelocyte stage. Neutropenia is a poor prognostic sign in rapidly progressive bacterial infections.

Pseudomonas septicemia in previously healthy children, a condition frequently associated with excessive exposure to water (whirlpool, bathing, wet toweling for antipyresis), can cause profound neutropenia with an extreme shift to the left,[157] occasionally with a myeloid leukemoid reaction simulating promyelocytic leukemia.[158] These findings initially can cause confusion because *Pseudomonas* septicemia also complicates congenital and acquired neutropenic states. Toxin-producing bacteria, such as *S. aureus, S. pyogenes,* and enteric gram-negative bacilli (*Escherichia coli, Salmonella, Brucella, Shigella*), have a propensity to cause a disproportionate left shift, frequently with immature neutrophils exceeding mature cells, and a low to normal total neutrophil count; such findings do not indicate a poor prognosis or even bacteremia. Neutropenia or neutrophilia can occur in disseminated tuberculosis and histoplasmosis, as well as in Rocky Mountain spotted fever; when the WBC count is <10,000/mm^3 in patients with Rocky Mountain spotted fever, bands frequently exceed mature forms.[159] Leukopenia occurs in 60% to 74% of cases of ehrlichiosis and in 50% of cases of anaplasmosis with a reduction in mononuclear and polymorphonuclear cells; organisms can be visualized in leukocytes.[160,161]

Mild neutropenia frequently accompanies systemic viral infections. Neutropenia and thrombocytopenia can be clues to subclinical CMV infection in organ transplant recipients,[162] symptomatic primary infection with HIV, or acquired immunodeficiency syndrome (AIDS).[163] In a report from Israel, many children with bacterial and viral infections had aggregated leukocytes that led to false reading of leukopenia by automated cell analyzers.[164]

Left Shift of Neutrophils, Immature Neutrophils

Use of the ratio of immature to total neutrophils in neonates younger than 7 days of age to predict bacterial infection has been reported extensively, with disparate results. In a large study, a band neutrophil–to–total neutrophil ratio ≥0.2 had sensitivity and NPV for bacterial infection exceeding 95%.[49] Adenovirus infection,[165] influenza A,[166] disseminated herpes simplex,[167] and other viral infections can be associated with increased absolute band count simulating bacterial sepsis.[167] In viral infections and in malaria when immature neutrophils are seen in peripheral blood, the total ANC is <10,000/mm^3 in almost 90% of cases.[167]

Lymphocytes and Lymphocytosis

Although T and B lymphocytes replicate in multiple anatomic sites (including the lymph nodes, spleen, and bone marrow) and are capable of leaving and re-entering a given compartment, lymphocytes in peripheral blood are tightly regulated, with T lymphocytes predominating and numbers predictable by age (see Table 288.1). Mean counts decrease with age after a peak of 7300/mm^3 (61% of leukocytes) at 6 months of age. Lymphocytosis is present when the count exceeds the 95% confidence limits for age; by definition, a lymphocytic leukemoid reaction requires the presence of immature forms in peripheral blood. Causes of lymphocytosis are shown in Box 288.5.

Box 288.5

Causes of Abnormal Lymphocyte Counts in Children

Lymphocytosis

Infectious

Infection with *Bordetella pertussis,* Epstein-Barr virus, cytomegalovirus, hepatitis viruses, other common viruses, *Toxoplasma;* chronic controlled bacterial infections (e.g., *Treponema, Brucella, Mycobacterium*); recovery from bacterial infections; *Rickettsia* infection

Noninfectious

Lymphocytic leukemias, thyrotoxicosis

Lymphopenia

Infectious

Acute and chronic viral infection (including human immunodeficiency virus), acute bacterial infection, widespread granulomatous infection (e.g., untreated *Mycobacterium, Cryptococcus, Histoplasma*), malaria

Noninfectious

Protein-calorie malnutrition, radiation or immunosuppressive therapy, monoclonal antibody and anticytokine therapy, congenital immunodeficiency, untreated Hodgkin lymphoma, trauma, stress, glucocorticoids, antibody-mediated destruction, protein-losing enteropathy, chronic right heart failure, lymphangiectasias, thoracic duct interruption

Bordetella pertussis infection is the only acute bacterial infection typically associated with lymphocytosis. Lymphocytosis results from blockade by pertussis toxin of the normal migration of lymphocytes out of the bloodstream, and the degree is predictive of the severity of illness and fatal outcome (mean leukocyte count in fatal vs. nonfatal cases in young infants, 94,000 vs. 18,000/mm^3).[168–170] Chronic bacterial and bacterial granulomatous infections can cause sustained, modest lymphocytosis.

Although many viral infections cause mild transient lymphocytosis, mononucleosis syndromes related to EBV or CMV, as well as Kikuchi disease, induce sustained lymphocytosis. The atypical lymphocytes in viral infections reflect active proliferation of T lymphocytes; these lymphocytes are large and have distinctive morphologic features. Profound atypical lymphocytosis (>50% of lymphocytes) occurs with EBV infection almost exclusively. More modest atypical lymphocytosis can occur in infection with CMV (including postperfusion syndrome), HIV (acute), hepatitis A or B viruses, adenovirus, and *Toxoplasma gondii* (congenital and acute), as well as in leukemia and lymphoma. Mild atypical lymphocytosis (usually <10%) occurs in drug reactions, serum sickness, infections with other viruses (rubella, rubeola, human herpesvirus 6, herpes simplex, varicella zoster), and infection with certain bacteria (*M. tuberculosis, Treponema pallidum, Salmonella*). Atypical lymphocytosis is described in patients with malaria, and it is a consistent finding in babesiosis (usually <10%) despite normal or mildly depressed leukocyte count.[171] Multiple infectious, hematologic, and immunologic causes of neutropenia, as well as Addison disease, lead to relative lymphocytosis without absolute lymphocytosis.

Lymphopenia

Lymphopenia, defined as a peripheral blood lymphocyte count <1500/mm^3 (or <2000 in children < 6 years of age), has multiple causes (e.g., decreased production, increased loss or destruction, alteration in compartmentalization). Protein-calorie malnutrition is the most common cause of reduced-production lymphopenia worldwide. Viruses (e.g., HIV, rubeola, polioviruses, varicella-zoster) can infect lymphocytes and cause destruction, transiently decreased production, or trafficking from the blood compartment. Autoimmune disorders and widespread granulomatous infection, especially tuberculosis, cause lymphopenia, probably by decreased production and redistribution.[15] Acute bacterial infection and infection with *Rickettsia* and *Ehrlichia* cause lymphopenia as part of redistribution during the acute phase response.

Monocytes and Monocytosis

Absolute deficiency of the highly conserved monocyte-macrophage cell line probably is incompatible with life. Monocytes present antigens to lymphocytes, mediate cellular cytotoxicity, and regulate immune and hematopoietic responses by producing interleukins, interferon, TNF-α, and G-CSF. Stromal cells (e.g., fibroblasts and endothelial cells) produce GM-CSF during inflammation and M-CSF constitutively, which in turn stimulate growth and differentiation of mononuclear phagocytes. These phagocytes are especially effective in killing obligate intracellular parasites such as fungi, viruses, rickettsia, protozoa, and certain bacteria and participate substantially in all types of granulomatous inflammation. Monocytosis is defined as a peripheral blood monocyte count >800/mm^3 in children or >500/mm^3 in adults. A monocytic leukemoid reaction is defined as a monocyte count >30% of a WBC count that is >30,000/mm^3.

Monocytosis has varied causes (Box 288.6). Monocytosis usually precedes recovery from neutropenia, and mild monocytosis is common in recovery from acute bacterial and viral illnesses. Monocytosis (average of 15% of the leukocyte count) is a hallmark of symptomatic congenital syphilis,[172] a frequent finding in miliary tuberculosis and congenital toxoplasmosis, and a variable finding in listeriosis (in which neutrophilia is more common except in neonates) and malaria. Premature infants can have monocytosis in the range of 2000 to 7000 cells/mm^3 as a reflection of an immature physiologic response to a variety of drugs or infusions of blood and albumin.[173] Several hematologic malignant diseases and chronic inflammatory states also are associated with peripheral blood monocytosis. In malignant histiocytosis, abnormal mononuclear phagocytes can be seen in the peripheral blood, along with neutropenia or neutrophilia.

Box 288.6

Causes of Monocytosis in Children

Infectious Causes

Recovery from acute infections

Bacterial endocarditis

Protozoal infections

Fungal infections

Salmonella enteric fever

Varicella and herpes zoster

Cytomegalovirus infection

Mycobacterium tuberculosis infection

Brucella species infection

Listeria monocytogenes infection

Treponema pallidum infection

Rickettsia rickettsiae infection

Noninfectious Causes

Hodgkin disease and non-Hodgkin lymphoma

Preleukemia

Myelomonocytic and myelogenous leukemia

Myeloproliferative disorders

Carcinomas

Collagen vascular disorders

Sarcoidosis

Inflammatory bowel disease

Cirrhosis

Drug reaction

Congenital and acquired neutropenia

Major depression

Recovery from marrow suppression

Postsplenectomy status

Eosinophils and Eosinophilia

Eosinophils are produced from progenitor cells in the bone marrow, largely under the influence of IL-5, IL-3, and GM-CSF. IL-5 promotes proliferation, maturation, and survival of eosinophils and facilitates chemotaxis into tissues.[174–176] Increased levels of IL-5 are found in patients with parasitic infections and other hypereosinophilic syndromes. In parasitic infection, eosinophils exert antibody-dependent (immunoglobulin G [IgG]- or IgE-assisted) cellular cytotoxicity and may play a role in the afferent upregulating arm of the immune response through antigen presentation and cytokine secretion. In addition, eosinophils play an immune-modulating role of potentially toxic mast cell degranulation in hypersensitivity reactions.

Eosinophils are predominantly tissue-based cells that spend only 1 to 2 days of their approximately 4-week lifespan in peripheral blood; the tissue-to-blood ratio is at least 100 : 1. Mature eosinophils are found most prominently in the skin and epithelial lining of the respiratory and gastrointestinal tracts. Inflammatory fluids and tissue exudates (e.g., lung and pleural fluid, cerebrospinal fluid) can be predominantly eosinophilic, are always pathologic, and have unique differential diagnoses. The normal mean peripheral blood eosinophil count in the first week of life is $500/\text{mm}^3$ and falls during the first 6 years to the adult mean of $200/\text{mm}^3$ (normally 2%–3% of WBCs). Eosinopenia results from adrenocortical hyperfunction and administration of corticosteroids and is part of the acute phase response. Eosinophilia (>500 cells/mm^3) can be classified etiologically as primary (hematologic malignant diseases and mastocytosis), secondary (allergy, adrenal insufficiency, medications, autoimmune conditions and infections), or idiopathic.[177] Hypereosinophilic syndrome is defined as an eosinophil count $>1500/\text{mm}^3$ for >6 months that leads to end-organ damage from infiltration of the heart, lungs, skin, or nerve tissue. Most cases of hypereosinophilic syndrome are idiopathic; a subset has defined molecular bases and is amenable to specific anti–IL-5 treatment.[176–182]

Table 288.2 delineates infectious and noninfectious conditions associated with mild, moderate, and extreme eosinophilia. Mild eosinophilia (≤ 1500 cells/mm^3) is common and occurs in the recovery phase of bacterial or viral illness, in response to drugs (usually in the absence of hypersensitivity symptoms), or as a manifestation of any type of atopic disease. Parasites are the most common causes of eosinophilia worldwide, and they can induce extreme eosinophilia (>5000 cells/mm^3) or an eosinophilic leukemoid reaction (>30% eosinophils with a WBC count >30,000/mm^3). With the exception of helminthic infections, secondary causes of eosinophilia rarely produce an absolute eosinophil count >1500 cells/mm^3.[183] The degree of peripheral eosinophilia in parasitosis usually is proportional to the extent of tissue invasion and is a dynamic process related to the life cycle of the parasite.[183,184] Eosinophilia can occur in the following situations: in the pulmonary migratory phase that precedes gastrointestinal localization by weeks to months, such as with *Ascaris lumbricoides* and *Trichuris trichiura;* in the sustained, highly inflammatory tissue phase, such as with *Trichinella spiralis, Toxocara canis,* and *Toxocara cati;* in the sustained, low-grade inflammatory state, such as with *Schistosoma, Strongyloides, Necator,* and filariae; during episodic tissue movement, such as with *Loa loa, Dracunculus,* and *Gnathostoma;* or after disruption of cysts or parasitic death, such as with *Echinococcus* and *Taenia solium* (cysticercosis).[184] *Strongyloides* hyperinfection syndrome usually is not associated with eosinophilia. *Enterobius vermicularis* (pinworms) can cause eosinophilia with counts <1000/mm^3. Protozoal infections (e.g., giardiasis, malaria, amebiasis, cryptosporidiosis) are not characteristically associated with eosinophilia, even though some degree of tissue invasion can occur. *Cystoisospora belli* can be an exception.[185] Adrenal insufficiency, especially resulting from infection with *Histoplasma, Cryptococcus,* CMV, or *Mycobacterium* and from opportunistic infection in compromised hosts, also causes infection-associated eosinophilia.

TABLE 288.2

Causes of Eosinophilia in Children

	Elevation of Peripheral Blood Eosinophil Count		
Conditions	**Mild (500–1500 Cells/mm^3)**	**Moderate (1500–5000 Cells/mm^3)**	**Extreme (>5000 Cells/mm^3)**
COMMON INFECTIOUS CAUSES			

Recovery from bacterial, viral infection	+++	+	
Ascaris lumbricoides (migratory)[a]	++	++	++
Toxocara canis, Toxocara cati[a]		+++	++
Trichinella spiralis[a]		+++	++
LESS COMMON INFECTIOUS CAUSES			
Strongyloides stercoralis[a]	+++ (established)	++ (acute)	+ (acute)
Trichuris trichiura[a]	++		
Ancyclostoma species[a]	+	+	
Filarial worms (tropical eosinophilia)	++ (established)	++ (episodic or treatment)	+++ (episodic or treatment)
Hymenolepis nana[a]	+		
Necator americanus (migrating)[a]	+++	+	
Baylisascaris procyonis[a] (raccoon ascarid)	+	++	
Schistosoma species	++ (established)	++ (acute or treatment)	+ (acute or treatment)
Liver and lung flukes (especially *Paragonimus*)	+ (established)	+++ (acute)	+ (acute)
Echinococcus species	+++ (disruption of cyst)		
Taenia species[a]	+	+++ (treatment of neurocysticercosis)	
Sarcoptes scabiei	++	+	
Cystoisospora belli	++	+	
Histoplasma capsulatum (disseminated)	+		
Cryptococcus neoformans (disseminated)		+	+
Pneumocystis jirovecii pneumonia	++		
Allergic bronchopulmonary aspergillosis	++	++	
Löffler pneumonia (also nonparasitic)	++	+	
Coccidioides immitis	+++ (acute)	+	+++ (progressive) +++ (disseminated)
Epstein-Barr virus mononucleosis	+	+	
Epstein-Barr virus–related lymphoma in human immunodeficiency	+	+	
Human immunodeficiency virus	++	+	
Bartonella henselae lymphadenitis	++	+	
Chlamydia trachomatis pneumonia	++	+	
Streptococcal syndromes (scarlet fever, urticaria, chorea)	+	+	
Mycobacterium tuberculosis (controlled)	+	+	
NONINFECTIOUS CAUSES			
Atopic conditions	+++	+	
Lymphoma, especially Hodgkin (nodular sclerosis and mixed cellularity types)		++	+
Carcinomas		++	+
Leukemia, especially eosinophilic			+++
Preleukemia (myelogenous or lymphocytic)		+	+
Hypereosinophilia syndrome (some genetic)		++	+++
Collagen vascular diseases		++	+
Allergic angiitis (Churg-Strauss)		++	+++

Inflammatory bowel disease	++	+	
Pernicious anemia	++	+	
Addison disease, hypopituitarism	+++	+	
Chronic pancreatitis	++	+ (exacerbation)	
Cellular immunodeficiencies	+++	++	
Hyperimmunoglobulin E syndromes	+	+++	++
Graft-versus-host disease	++	+	
Organ transplant rejection	+++	+	
Serum sickness, erythema multiforme	+++	++	
Drug hypersensitivity	+++	++	
Prematurity in neonates	++	++	
After abdominal irradiation	++	+	
Chronic peritoneal dialysis	++	+	
Dressler (postpericardiotomy) syndrome	++	+	
Cholesterol embolus	+	+	
Eosinophilia-myopathy syndrome (L-tryptophan)		++	+++
Fasciitis-panniculitis syndromes (Shulman disease)	+	+	
DRESS syndrome	+++	+	

[a] Eosinophilia-inducing parasitic infections that can be acquired in the United States.

+++, frequently seen in infection or condition; ++, not infrequently seen; +, occasionally seen or cases reported; DRESS, drug reaction with eosinophilia and systemic symptoms.

The life cycle of the parasite, as well as geography, dietary habits, and host factors are important when considering serologic or microscopic studies to evaluate children with eosinophilia. The prevalence of parasitic infections in new immigrants with eosinophilia ranges from 70% to 95%, compared with 14% to 40% in travelers.[183–187] Exposure greatly affects the likelihood of a parasitic cause of eosinophilia. Travelers who make short visits to urban areas and who adhere to protective dietary measures have low risk. A high-risk history includes the following: ingestion of carnivores *(Trichinella)*; ingestion of raw vegetables, unpeeled fruits, or unpurified water (helminths); ingestion of seafood in Southwest Asia (gastrointestinal, liver, and lung parasites); and swimming in freshwater in endemic areas *(Schistosoma)*.[183] Physical examination and identification of organ systems involved guide specific diagnostic evaluations. Asymptomatic eosinophilia is neither a highly sensitive nor a specific marker for parasitic disease.[184,187] The Centers for Disease Control and Prevention (CDC) has frequently updated online domestic guidelines for postarrival screening and presumptive treatment for refugees based on predeparture management, with recommendations for further screening as appropriate. The CDC recommends that all refugees receive predeparture single-dose albendazole therapy, as well as a screening complete blood count with a differential WBC. Given the increased risk for *Schistosoma* spp. infection, the CDC also recommends predeparture treatment with ivermectin for African, Asian, and Middle Eastern refugees from non–*L. loa* endemic areas and additional treatment with praziquantel for sub-Saharan African refugees because of the increased risk for *Strongyloides* infection. For immigrants who lack documentation of predeparture treatment, serologic testing should be performed for *Strongyloides, Schistosoma* (with urine for *S. haematobium* ova, if indicated), and *L. loa*, as appropriate per guidelines.[188]

The differential diagnosis of asymptomatic eosinophilia with negative results of stool evaluation is limited. Recommendations include serologic testing for *Strongyloides* and *Schistosoma* species when the absolute eosinophil count exceeds 400 cells/mm^3; in a pediatric refugee study, the PPV of an absolute eosinophil count >400 cells/mm^3 for confirming either pathogen was only 58%, and the NPV was only 75%.[187]

Fungal infections usually do not elicit eosinophilia, with noteworthy exceptions. *Cryptococcus neoformans* can induce intense eosinophilia in the rare case of a previously healthy young child with disseminated disease. Pulmonary infiltrate with eosinophilia syndromes comprise a group of heterogeneous disorders characterized by eosinophilic infiltration of the lung parenchyma. Eosinophilia in the peripheral blood and systemic symptoms typically but not invariably are present. Parasite-induced pulmonary infiltrate with eosinophilia is the most common of these disorders in children.[189] Wiskott-Aldrich syndrome, combined immunodeficiency, hyper-IgE syndrome,[190] graft-versus-host disease,[191] and renal and hepatic allograft organ rejection[192] are associated with eosinophilia, as are malignant diseases (lymphomas, leukemia) and preleukemic states.[193] Eosinophilia can occur in the early stage of HIV infection and in EBV-related lymphoma in AIDS.[194] Organ-specific eosinophilic inflammatory diseases such as eosinophilic gastrointestinal disorders, granuloma of bone, and meningoencephalitis (related to ventricular shunt material, shunt malfunction, vancomycin instillation, bacterial or parasitic infection) do not characteristically cause peripheral blood eosinophilia, but mild elevations can occur, especially in young children.[195–199] In very prematurely born neonates, eosinophilia (count >1000/mm^3) has been associated with an anabolic state (as well as L-tryptophan exposure), but septicemia also occasionally induces eosinophilia rather than neutrophilia.[200,201] Other causes of eosinophilia are shown in Table 288.2.[200–205] Drug reaction with eosinophilia and systemic symptoms (DRESS) is a serious multisystem disorder of unclear pathogenesis associated predominantly with administration of aromatic anticonvulsant agents and sulfonamides.[205,206]

Basophils

Basophils and mast cells share functional similarities and are involved in immediate hypersensitivity reactions, as well as in longterm inflammatory or immunologic responses. Basophils secrete cytokines such as IL-4 and histamine, which can play a role in the ongoing allergic response.[207,208] Mast cells are released as precursors from the bone marrow and are found and mature in connective tissue, not circulating in blood. Basophils differentiate and mature in the bone marrow during a 7-day period, have a lifespan of only several days, circulate in blood, and are not normally found in connective tissue. Basophilia is said to occur when the peripheral blood basophil count exceeds 150/mm^3. Infection with parasites often is associated with increased levels of IgE, peripheral basophilia, or the infiltration of basophils and mast cells at sites of infection. Basophilia is highly associated with malignant myeloproliferative disorders and can be seen in patients with Hodgkin disease, hemolytic anemias, hypothyroidism, pregnancy, and nephrotic syndrome and with the use of estrogen and antithyroid medications. Infection, hyperthyroidism, adrenocorticosteroid administration, chemotherapy, and radiation therapy lower the basophil count. Mast cell disease and urticaria pigmentosa are associated with increased basophil counts in tissue and bone marrow, but not usually in peripheral blood.

Platelets

Physiology and Measurement

The process of megakaryopoiesis and platelet production is complex, with regulation at multiple steps.[209] Megakaryocytes derive from the hematopoietic stem cell through successive lineage commitment steps, with maturation and eventual shedding of platelets into the sinusoids within the bone marrow. Transcription factors and inflammatory cytokine and hematopoietic cytokine (thrombopoietin) signaling regulate the processes; acquired and inherited disorders can result in thrombocytopenia or thrombocytosis.[209] Platelets circulate for 7 to 10 days; approximately one third of these platelets are located in the spleen and two thirds in the circulation. The normal platelet count range is approximately 80,000 to 450,000 in the first week of life and 150,000 to 400,000/mm^3 thereafter. Spuriously high or low platelet counts can be reported when automated instruments are used.[210]

Mature platelets are disk-shaped cells 2 to 4 μm in diameter. In general, platelets tend to be larger in conditions with increased marrow production (acute phase response) or peripheral destruction (e.g., immune-mediated, mechanical breakdown, or consumption) and of normal size to small when production defects are present. The spleen is the site of destruction in the presence of platelet antibodies or as a result of sequestration. In hypersplenism, the weight of the spleen correlates directly with the degree of thrombocytopenia regardless of the cause. In thrombocytopenic states, large platelet size is not a completely reliable discriminator of increased destruction because some underproduction states (e.g., Wiskott-Aldrich syndrome) also are associated with qualitative abnormalities. Exercise or the administration of epinephrine causes immediate thrombocytosis as a result of the redistribution of mature platelets (lasting for minutes to hours), as does splenectomy (lasting indefinitely).

Thrombocytosis

Thrombocytosis is defined as >500,000 platelets/mm^3 and usually is a secondary or reactive event related to underlying conditions.[210,211] Primary causes of thrombocytosis (polycythemia vera and essential thrombocythemia, clonal myeloproliferative disorders) are unusual in childhood.[211] Causes of thrombocytosis and extreme thrombocytosis are listed in Table 288.3. Infection (25%–35% of cases) and rebound after infection (15% of cases) are most common, followed by hematologic causes (25%–35%). Production of GM-CSF secondary to any inflammatory response can induce thrombocytosis. The degree of thrombocytosis in bacterial infections is inversely related to age <5 years, the duration of the infection before treatment, and the presence of a tissue site of infection or abscess (e.g., complicated pneumonia, osteomyelitis, pyogenic arthritis, meningitis).[211–215] Thrombocytosis is the hallmark of the second week of Kawasaki disease. Extreme thrombocytosis in pertussis reflects severity of the disease.[168–170] Thrombocytosis is unusual in viral infections, except for necrotizing infection and HIV infection,[216] and during recovery from thrombocytopenia. Multiple drugs, including antibiotics, induce thrombocytosis. Thromboembolic events are rare with reactive thrombocytosis related to infection, and treatment should be aimed at the inciting infection rather than the platelet count.[215]

TABLE 288.3

Causes of Thrombocytosis in Children

Conditions	Thrombocytosis (500,000–1,000,000 Platelets/mm^3)	Extreme Thrombocytosis (>1,000,000 Platelets/mm^3)
INFECTIOUS		
Common uncomplicated bacterial infections	+++	+
Bacterial infections with abscess	++	+++
Pertussis	++	+
Chronic bacterial infection (*Mycobacterium, Brucella*)	++	+
Human immunodeficiency virus infection	+	+
Chronic hepatitis	++	
Disseminated fungal infection	++	
HEMATOLOGIC		
Recovery from infection	++	+
Recovery from cancer chemotherapy	++	
Hemolytic anemia	++	+
Hemorrhage or significant thrombosis	++	+
Iron, vitamin E, and vitamin B_{12} deficiency (and treatment)	++	++
Splenectomy or functional asplenia	+++	++
Neuroblastoma, lymphoma	++	+
Histiocytosis	+	
INFLAMMATORY		
Kawasaki disease	+++	++
Burns, surgical procedures, fractures,	+++	+

other trauma, or tissue ischemia		
Collagen vascular disease	+++	+
Postinfectious, postpericardiotomy syndromes	+++	+
Inflammatory bowel disease	++	+
Graft-versus-host disease	++	+
Sarcoidosis	++	
MISCELLANEOUS		
Respiratory acidosis	++	+
Metabolic acidosis, dehydration	++	+
Nephrotic syndrome	+++	++
Chronic renal failure	++	+
Congenital adrenal hyperplasia	+++	+
Antibiotics (especially β-lactams)	+++	
Vinca alkaloids	+++	+
Cocaine exposure (neonate)	+	
Corticosteroid agents	++	
Epinephrine	++	

+++, frequently seen in infection or condition; ++, not infrequently seen; +, occasionally seen or cases reported.

Thrombocytopenia

Thrombocytopenia is defined as <80,000 platelets/mm^3 in the first week of life and <150,000/mm^3 thereafter. Thrombocytopenia can have several mechanisms and causes[217] (Box 288.7). Infections commonly can downregulate platelet production as part of general hematopoiesis. Immune-mediated destruction during acute, chronic, or congenital infection can occur in several viral infections (e.g., CMV infection, EBV infection, HIV infection,[218] rubella, and hepatitis B and C[219]) and subacute bacterial infections (e.g., endocarditis, leptospirosis, and syphilis). Idiopathic thrombocytopenic purpura results from immune-mediated destruction, usually follows nonserious viral infections, and is characterized by profound thrombocytopenia and mucocutaneous bleeding in an otherwise healthy-appearing child.[220] Acute severe infections, viral or bacterial, can cause disseminated intravascular coagulopathy and profound thrombocytopenia on a nonimmunologic basis. Acute infections with *Rickettsia, Ehrlichia* and *Anaplasma,* and *Plasmodium* have a propensity to cause thrombocytopenia without overwhelming infection, and certain bacterial toxins (e.g., the endotoxins of enteric bacilli and the exotoxins of *S. aureus* and *S. pyogenes*) can cause thrombocytopenia without bacteremia. The Shiga-like toxin of certain *E. coli* organisms and the neuraminidase of *S. pneumoniae* are associated with microangiopathic thrombosis and thrombocytopenia in hemolytic uremic syndrome. The transient mild thrombocytopenia (platelet count of 80,000–150,000/mm^3) that occurs commonly during systemic viral illness is speculated to have marrow suppressive and peripheral destructive components.

Box 288.7

Causes of Thrombocytopenia in Children

Decreased Production

Aplastic anemia

Damaged, suppressed, or refractory marrow (infection, drugs, chemicals, radiation)

Replaced marrow (malignant disease, myelofibrosis)

Congenital, hereditary disorders

Ineffective thrombocytopoiesis (cobalamin, folate deficiency; dysplastic hematopoiesis)

Abnormal Distribution

Hypersplenism (congestive or infiltrative)

Immune-Mediated Destruction

Idiopathic thrombocytopenic purpura

Malignant diseases

Drugs (sulfa, ampicillin, rifampin, quinine, and multiple nonantimicrobial agents)

Infection (especially Epstein–Barr virus, cytomegalovirus, human immunodeficiency virus, hepatitis B and C, congenital syphilis, toxoplasmosis, viral infections, subacute endocarditis)

Vaccines

Autoimmune diseases

Nonimmune Destruction

Disseminated intravascular coagulation

Septicemia

Viral, rickettsial, fungal infection

Hemolytic uremic syndrome

Bacterial toxin–mediated syndromes

Malaria

Organ transplant rejection

Cyanotic congenital heart disease

Pseudothrombocytopenia

Aggregation of platelets not counted by electronic cell analyzers

Metabolic Abnormalities

Many infections result in some degree of associated hepatic dysfunction. Intrahepatic cholestasis secondary to hepatocellular dysfunction is the usual abnormality in systemic bacterial, toxin-mediated, viral, and rickettsial diseases. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations are elevated >1.5 times normal in >75% of people with ehrlichiosis, anaplasmosis,[160] and Rocky Mountain spotted fever[161] and in approximately one half of patients with staphylococcal toxic shock or streptococcal septicemia or toxin-mediated disease. AST exceeds ALT when hemolysis or rhabdomyolysis occurs. Serum hepatic enzymes are mildly elevated in EBV mononucleosis (almost universally) and CMV mononucleosis (frequently); characteristically, bilirubin (direct greater than the indirect fraction) is elevated disproportionately to the elevation of transaminases, with increases to ≥10 mg/dL in some EBV infections. In acute hepatocellular infections, as with hepatitis viruses, serum levels of the transaminases frequently exceed 1000 mg/dL, with only mildly elevated bilirubin. Neonates with disseminated herpes simplex virus, adenovirus, or enterovirus infections can have severe hepatocellular dysfunction. In a study of 85 episodes of bloodstream infection in neonates, 46% of cases caused by gram-negative bacilli but only 13% caused by coagulase-negative staphylococci were associated with elevated ALT and AST levels.[221] Some bacterial infections (e.g., tuberculosis, brucellosis, syphilis, cat-scratch disease) cause granulomatous space-occupying lesions in the liver that result in cholestasis, and bacterial cholecystitis can cause obstruction. Serum transaminases are mildly elevated in more than 50% of children with Kawasaki disease. Hypoglycemia secondary to impaired gluconeogenesis can result from a severe hepatic insult or septicemia. Hyperglycemia sometimes is a clue to candidemia in prematurely born infants.[222]

Hyponatremia is a complication of dehydration and diarrheal loss in childhood infections or a complication of vomiting in pyloric stenosis. Hyponatremia without apparent gastrointestinal fluid loss is a clue to increased vascular permeability and is associated in such situations with decreased albumin and intravascular volume. Hyponatremia is an early and almost universal finding (present in 90% of cases) in Rocky Mountain spotted fever, is present in >50% of patients with toxic shock syndromes, and is a common finding in nephrotic syndrome and cirrhosis. Edema despite decreased intravascular volume is a hallmark of these conditions. Hyponatremia in people with normal hydration and intravascular volume can be associated with inappropriate secretion of antidiuretic hormone as a result of central nervous system or pulmonary infection, or the disorder can be associated with infant botulism.[223] Serum potassium levels rise predictably with hemolysis or with thrombocytosis.[224]

Nonspecific Antibodies

Various nonspecific antibodies are produced in response to infectious, neoantigenic, and inflammatory stimuli. Beginning as serendipitous or enigmatic laboratory findings, some tests have become extremely useful in the diagnosis or management of infectious diseases, even though the antigen used does not contain any part of the infectious agent (Table 288.4). Measurement of nonspecific antibodies also can lead to confusion and misdiagnosis.

TABLE 288.4

Nonspecific Antibodies Associated With Infections and Other Conditions

Antibody	Infectious Agent or Condition	Antigen or Test	Antibody Class or Timing	Comments
Heterophile antibody	Epstein-Barr virus	Horse or sheep RBCs; agglutination (after guinea pig kidney adsorption step)	IgM Peak at 2–3 wk of illness; fall by 3 mo, negative by 6 mo	Positive in Epstein-Barr virus–associated mononucleosis in 90% of adolescents; <50% children <4 yr old False-positive result ≤10% (usually low titer) with multiple bacterial infections, viral (including human immunodeficiency virus) infections, and autoimmune disease
Cold agglutinin	*Mycoplasma pneumoniae*	Human type O RBCs (I antigen); agglutination at 4°C	IgM Peak at 2–3 wk of illness; positive for months	Titer >1 : 64 is >90% associated with *Mycoplasma pneumoniae* Titer correlates with severity of pneumonia Titers <1 : 64 found with respiratory tract viral infections, Epstein-Barr virus infection, cytomegalovirus infection, bacterial pneumonia, malaria, lymphoma, hypersensitivity syndromes
Reagin antibody	*Treponema pallidum*	Cardiolipin; multiple test methods (e.g., rapid plasma reagin, Venereal Disease Research Laboratory)	IgG/IgM Positive 1–2 wk after onset of chancre (slightly later than specific antibody); correlates with activity of infection or adequacy of therapy	False-positive result (i.e., negative specific treponemal antibodies) is rarely >1 : 4; found with *Mycoplasma pneumoniae* infection, malaria, bacterial and viral infections; after vaccination; in illicit drug use; and in autoimmune diseases
Rheumatoid factor	Autoimmune disorders	Fc fragment of human IgG; latex agglutination, enzyme	IgM Titer correlates with activity of infectious	Multiple autoimmune disorders (positive in only 25% with juvenile idiopathic arthritis); results

		immunoassays	disease, not necessarily autoimmune disease	can be positive in chronic infections (e.g., endocarditis, and hepatitis) and in neonates against maternal IgG
Antinuclear antibody	Autoimmune disorders	Nuclear and cytoplasmic antigens using Hep-2 cells; indirect immunofluorescence antibody test followed by specific antigen testing	IgG/IgM	Multiple autoimmune disorders; positive results in >90% with systemic lupus erythematosus Titer 1 : 20 in ≤10% of healthy children Titers 1 : 40 commonly and higher titers occasionally with bacterial, viral, toxin-mediated diseases (for ≤8 wk) Also associated with drug hypersensitivity, malignant disease

IgG, immunoglobulin G; IgM, immunoglobulin M; RBCs, red blood cells.

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B

Anti-Infective Therapy

OUTLINE

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Principles of Anti-Infective Therapy

John S. Bradley, Sarah S. Long

The selection of optimal antibiotic therapy for presumed bacterial infection is based on the balance of benefits and risks of specific therapy for each child. Prescribing the right antibiotic or antibiotics early in the course of serious infection can save a life or avoid substantial morbidity. Inappropriate antibiotic therapy given to a child with a viral infection exposes the child needlessly to antibiotic toxicities, adds to the selective pressure driving antibiotic resistance in bacteria, creates unnecessary costs to the medical system, and can divert attention from evaluation and management of the child's condition.

Selecting Optimal Antimicrobial Therapy

Several questions must be addressed to choose optimal empiric and definitive antimicrobial therapy. These questions revolve around identifying potential or presumed pathogens and considering the relative merits of antimicrobial agents for specific pathogens and circumstances (Box 289.1). The clinician should follow the steps outlined in the following paragraphs.

Box 289.1

Questions Pertinent to Choosing

Antimicrobial Therapy Appropriately

1. What is the clinical syndrome or site of infection? Pathogens are predictable by site.
2. Does the child have normal defense mechanisms (in which case causative agents are predictable), or are these mechanisms impaired by underlying conditions, trauma, surgical procedures, or a medical device (in which case additional potential pathogens should be considered)?
3. What is the child's age? Pathogens are predictable by age.
4. What clinical specimens should be obtained to guide empiric definitive therapy?
5. Which antimicrobial agents have activity against the pathogens considered, and what is the current range of susceptibilities for each antibiotic against these pathogens in the practitioner's hospital or clinic?
6. What special pharmacokinetic and pharmacodynamic properties of a therapeutic agent are important regarding the site of the infection and the host?
7. For any given infection site, what percentage of children requires effective antimicrobial therapy with agents first selected for empiric treatment? Bacterial meningitis requires ~100%, whereas ~75% may be acceptable for impetigo.
8. In contrast to empiric therapy, what definitive therapy would be optimal? Agents with a broad spectrum of activity may be appropriate for empiric therapy, but those with a narrow spectrum of activity *are* preferred for definitive therapy.
9. What special considerations exist regarding drug allergy, drug interaction, route of administration, cost, alteration of flora, or selective pressure in an environment?

Step 1: Predict the Infecting Organism

Defining the patient's site or sites of infection or the organ system or systems involved can predict the pathogen or pathogens. Bacteria often are tropic for certain tissues; certain species have a proclivity for causing certain infections. Examples include the following: *Neisseria meningitidis*, group B *Streptococcus*, and *Streptococcus pneumoniae* for meningitis; *S. pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* for acute otitis media; and *Staphylococcus aureus* and *Streptococcus pyogenes* for cellulitis, osteomyelitis, and pyogenic arthritis.

Step 2: Consider Host Defense Mechanisms

Is the host healthy, with intact immunity and normal integumentary barriers to infection? If so, the causative pathogens often are predictable. If the child has an underlying condition such as a defect in granulocyte number or function, nonpathogenic bacteria from both the host and the environment can cause infection. For an immunocompetent child with trauma to skin or mucous membranes, a recent surgical procedure, or an indwelling medical device, a variety of relatively nonpathogenic commensals also can cause infection, thus mandating empiric therapy that provides activity against a much broader range of organisms.

Step 3: Consider the Age of the Child

Infectious agents causing specific target organ infections in immunocompetent hosts often are predictable based on the child's age and exposures to pathogens specific to each age group. For example, group B streptococci and *Escherichia coli* are causes of meningitis almost exclusively during the first 90 days of life. Developmental maturation of the immune system as children approach the third year of life provides improved recognition for polysaccharide-encapsulated pathogens such as *S. pneumoniae* or *H. influenzae* type b. Group childcare exposes young children to *Kingella kingae* and infection with antibiotic-resistant strains of *S. pneumoniae*. School-related exposure to *S. pyogenes* is associated with increased middle-school age-specific attack rates of streptococcal pharyngitis. Adolescents' exposure to sexually transmitted pathogens such as *Neisseria gonorrhoeae* increases the potential causes of pyogenic arthritis in that age group.

Step 4: Perform Diagnostic Tests

Every effort should be made to prove the origin of the infection and to obtain an isolate for susceptibility testing. The Gram stain is a useful, rapid test to provide clues to the pathogen (e.g., swab in neonatal conjunctivitis), pathogenesis (e.g., aspirate in polymicrobial lung abscess), or interpretation of culture results (e.g., tracheal secretions in pneumonia). Although a Gram stain result of a tissue sample can lead to the inclusion of additional empiric therapy, it should not necessarily lead to exclusion of antibiotics customarily used in the empiric treatment of that infection. An error in processing or interpreting the Gram stain must not lead to ineffective empiric therapy.

Nucleic acid detection is used increasingly for the diagnosis of bacterial, mycobacterial, viral, fungal, and parasitic infections. These techniques do not require isolation of viable organisms, and they can be applied to a variety of tissue specimens. Advantages of improved sensitivity are obvious, but causation cannot always be inferred, and current methods often lack the ability to provide data on antimicrobial susceptibility.

Step 5: Consider Antibiotic Susceptibilities of Suspected Pathogens

Bacteria can have multiple different mechanisms of resistance against a single antibiotic or against multiple types of antibiotics. The most common resistance mechanisms include cell wall permeability changes to prevent entry of the antibiotic into the pathogen, efflux pumps to eject antibiotics that enter the cell, bacterial enzymes that specifically inactivate antibiotics, and mutations that lead to alteration of the antibiotic's target binding site (see Chapter 290). Bacteria can express resistance continuously (constitutively) or only on exposure to an antibiotic (inducible resistance). With such vast biologic variability in resistance mechanisms, efficient transmission of resistance genes among organisms, and variations in antibiotic use that create selective pressure, it is understandable that a single species such as *E. coli* can manifest different patterns of antibiotic resistance in different populations within the same local region, among regions of a country, and among countries of the world. Each healthcare association or hospital has a widely available antibiogram tool that is updated annually and allows the clinician to assess the current local resistance rates of pathogens. The probability that the antibiotic selected for empiric therapy will be effective against the presumed pathogen is directly related to the proportion of susceptible pathogens infecting patients in that location.

Step 6: Consider Pharmacokinetic and Pharmacodynamic Properties of Drugs

The route of administration, the absorption, tissue distribution, and drug elimination characteristics are all critical pieces of information to guide the selection of both drug and drug dosage in antimicrobial therapy. Eradication of pathogens causing infection requires the appropriate antibiotic exposure at the infected tissue site. For many agents, published data describe the average concentrations and variability of concentrations achieved at specific tissue sites over time. Unfortunately, for many older antibiotics this important information often is unavailable.

To understand how likely an antibiotic will be in achieving a microbiologic cure, with otitis media and amoxicillin treatment used as an example, information is required on the range of amoxicillin concentrations achievable in the middle ear fluid (MEF) following administration of a specific mg/kg dose of amoxicillin. These data provide a measure of exposure of bacteria to amoxicillin in the middle ear fluid. Based on current knowledge, treatment success is linked to an amoxicillin exposure (in middle ear fluid in this case) that delivers an amoxicillin concentration higher than the minimal inhibitory concentration (MIC) of amoxicillin against the pathogen causing the infection, for at least 30% to 40% of each dosing interval. With this information, we can calculate the proportion of children given that specific dose who will likely respond to treatment. For different classes of antibiotics, different types of drug exposure may be required for bacterial eradication (see Chapter 291).[1]

In the treatment of meningitis, adequate antibiotic concentrations in the cerebrospinal fluid (CSF) are critical for cure. The concentration of aminoglycoside antibiotics in the CSF following intravenous infusion is likely to be inadequate to treat meningitis caused by gram-negative pathogens, even though CSF concentrations are approximately 20% of those achievable in serum. In contrast, the high serum concentration of penicillin after a large dose leads to a bactericidal CSF concentration against susceptible pneumococci, even though the CSF concentration of penicillin is only approximately 5% of that achievable in serum.

A range of predictable serum concentrations and tissue concentrations of antimicrobial agents exists within any group of children. This variability can be defined for all children receiving the same dose of drug, and it represents the basic concept of “population pharmacokinetics.” For example, antibiotic concentrations in the serum and middle ear space are usually therapeutic at a given mg/kg dose, but they can be inadequate in a small but predictable percentage of children. However, unlike with acute otitis media, the clinician cannot risk inadequate dosing for even 1 child with meningitis. Logically, a single mg/kg dose of an antibiotic may not be effective in all children even for the same pathogen that causes infection at different tissue sites because the tissue concentration of that antibiotic can differ substantially among sites (e.g., urine vs. lung vs. CSF).

The absorption, distribution, metabolism, and elimination of drugs are variable in children as a function of age-related developmental changes.[2,3] The volume of distribution of antibiotics varies profoundly during the first year of life, as the proportion of body weight contributed by extracellular water and fat changes. Drugs that distribute preferentially into the extracellular water (e.g., penicillins) require a dose and dosing interval that recognize greater diffusion into neonatal interstitial tissue than occurs in older infants and children. Drug elimination based on metabolism and organ function generally increases during the first several weeks of life, peaks in infancy, and approaches adult values during adolescence. Many antibiotics require different mg/kg dosages during a child's life to achieve optimal antibiotic exposure to maximize efficacy and minimize toxicity.

The pharmacodynamic properties of an antibiotic describe how exposure of the antibiotic to the pathogen leads to a bacteriostatic or bactericidal effect and are important in designing an antibiotic dosing regimen (Table 289.1). Aminoglycosides kill bacteria in a concentration-dependent fashion. Therefore, it is desirable to achieve the highest concentration possible at the site of infection to achieve the fastest killing of bacteria. The maximum safe tissue concentration is dictated by the serum aminoglycoside concentration above which renal toxicity occurs. For other antibiotic classes, such as the penicillins, achieving tissue concentration greater than the MIC for that pathogen for 30% to 40% of the dosing interval is associated with microbiologic and clinical cure. For the penicillins, a higher concentration of the antibiotic at the infected tissue site, higher than a certain critical concentration close to the MIC, is not associated with faster sterilization of tissues or a better clinical outcome.

TABLE 289.1

Pharmacodynamic Antibacterial Effect of Antimicrobial Agents by Primary Bacterial Target and by Antibiotic Class

Primary Target[a]	Antibacterial Class	Pharmacodynamics[b]	Intracellular Activity[c]
Cell wall	**β-Lactams (penicillins, cephalosporins, monobactams, carbapenems)** **Glycopeptides (vancomycin,[d] telavancin, dalbavancin, oritavancin, teicoplanin[e])**	Bactericidal Time-dependent inhibition Carbapenems PAE against gram-positive and gram-negative organisms PAE only against gram-positive organisms Bactericidal Concentration (AUC)–dependent inhibition	Generally not effective
Cell membrane	**Lipopeptides (daptomycin)** **Polymyxins (polymyxin B, colistin)**	Bactericidal Concentration-dependent inhibition Long PAE (daptomycin) PAE (polymyxins)	Not known
Ribosome	**Macrolides, azalides, ketolides**	Bacteriostatic primarily Time-dependent with long PAE Long PAE	Yes
	Tetracyclines, glycylcyclines	Bacteriostatic Time-dependent with long PAE	Yes
	Lincosamides (clindamycin)	Bactericidal or bacteriostatic Time-dependent with PAE	Yes
	Aminoglycosides	Bactericidal Concentration-dependent PAE	Generally not effective
	Oxazolidinones	Bacteriostatic (except against	Generally

		Streptococcus pneumoniae) Time-dependent with PAE	not effective
	Rifamycins	Bactericidal with long PAE	Yes
	Fluoroquinolones	Bactericidal Concentration-dependent with long PAE	Yes
	Streptogramins	Bactericidal (except against *Enterococcus faecium*) Time-dependent with PAE	Yes
Nucleic acid	**Metronidazole**	Bactericidal Concentration-dependent with PAE	Yes
	Sulfamethoxazole-trimethoprim	Bactericidal Concentration-dependent	Yes

[a] The primary antibiotic target within the bacterial pathogen.

[b] The type of pharmacodynamic relationship that best describes antibiotic-mediated inhibitory or bactericidal activity.

[c] The ability to treat intracellular pathogens, based on the penetration of antibiotic into the host cell by passive diffusion or by active uptake.

[d] Activity is best described by AUC concentration-dependent pharmacodynamics in animal models.

[e] Not marketed in the United States.

AUC, area under the curve; PAE, postantibiotic effect, or the observation of delay in regrowth of organisms following removal of antibiotic from the media.

The postantibiotic effect also is considered in dosing and varies by antibiotic (see Table 289.1). For the aminoglycosides, the postantibiotic effect is profound (i.e., an extended period of time lapses after the antibiotic concentration drops to less than the MIC before regrowth occurs). Conversely, other antibiotics (e.g., most penicillins) inhibit growth only until the concentration drops to less than the MIC. Differences probably reflect molecular mechanisms of antibiotic activity at the target site, the avidity of antibiotic binding to the target site, the rate of elimination of the antibiotic from the target site, and whether the damage to the target site structure is reversible or irreversible.

Although growth of a population of organisms generally can be inhibited at a certain antibiotic concentration (the MIC) as defined by standard laboratory techniques, antibiotic concentrations that lead to less frequent emergence of resistance often can be determined by using unique assay conditions with higher inocula than those used in standard clinical assays. For some bacteria, resistance begins with a spontaneous nucleic acid mutation leading to an amino acid change that results in less avid binding of the antibiotic to the target site (well described for fluoroquinolones and *S. pneumoniae*). This single-step mutation may lead only to a slightly higher MIC. The antibiotic concentration required to inhibit the single-step mutant, however, may not be achievable in infected tissues when a standard antibiotic dosage is used. Second-step mutations may then occur during ongoing exposure to an antibiotic, thereby leading to more profound changes in the MIC and rendering the organisms fully resistant even at the highest attainable tissue concentrations. Often it is possible to identify the concentration of antibiotic required to prevent the selection of viable single-step mutants, the mutant prevention concentration (MPC); the MPC often is two- or threefold higher than the MIC.[4,5] If the higher dosage required for the MPC can be prescribed without undue toxicity, the risk of selecting antibiotic-resistant strains that can subsequently infect that child or his or her contacts may be reduced.

Step 7: Consider Target Attainment

In treating any child, the practitioner must assess the seriousness of the infection and the risk of injury or death if the antibiotic is not effective. For infections that are not life-threatening and cause minimal morbidity (e.g., impetigo), achieving a cure rate of 70% to 80% with a safe and inexpensive antibiotic often is acceptable, especially if the use of an alternative agent to achieve a 98% success rate for that infection carries an excessive risk of toxicity or high cost. For other infections that cause a higher degree of suffering or risk of organ damage (e.g., pyelonephritis or acute otitis media), a cure rate of 80% to 90% often is desirable. For serious, life-threatening infections (e.g., bacterial meningitis or septicemia in a neutropenic child), an expected bacteriologic cure rate of close to 100% must be achieved.[1] No formal list of “approved” cure rates or “target attainment” rates exists. Accepted target attainment rates can differ among infections and hosts as assessed by physicians, families, and societies. Consideration of target attainment rates can help clarify decision making regarding relative merits, risks, and costs of antimicrobial management.

Step 8: Consider Empiric and Definitive

Therapeutic Decisions Separately

For suspected serious infections, antibiotics with appropriately broad antibacterial activity at the highest tolerated dosage are selected for empiric therapy. Adequate empiric therapy is associated with decreased mortality rates and shorter hospital stays compared with inadequate empiric therapy for seriously ill adults.[6–9] For the seriously ill child, knowledge of local resistance patterns for suspected pathogens should lead to selection of antibiotics with a likely achievable bacteriologic cure rate of >95%.

Combination empiric therapy frequently is given when high cure rates are desirable to ensure adequate antimicrobial activity against all potential pathogens. A combination of vancomycin and a third-generation cephalosporin is used for empiric treatment of community-acquired meningitis because the use of a third-generation cephalosporin alone may not provide optimal therapy for *S. pneumoniae* with resistance to β-lactam agents. Empiric therapy for meningitis in the first 2 months of life consists of ampicillin in combination with a third-generation cephalosporin because the possible pathogens include *Listeria monocytogenes,* group B *Streptococcus,* and *E. coli.* Long-established combination therapies can be used for febrile neutropenic patients to ensure activity against *Pseudomonas aeruginosa,* enteric gram-negative bacilli, and *S. aureus.*[7] Once the pathogen is identified, a narrow-spectrum agent frequently can provide the same degree (or a higher degree) of bacterial eradication and clinical efficacy with decreased toxicity, decreased selective pressure, and decreased cost. For example, initial therapy with a carbapenem agent for a patient with ventilator-associated pneumonia can be narrowed to cefotaxime if the pathogen isolated is a susceptible *Klebsiella* species rather than *P. aeruginosa.* In a patient with a postoperative wound infection, treatment with vancomycin and cefotaxime can be narrowed to ampicillin if a susceptible *E. coli,* rather than methicillin-resistant *S.* (MRSA) or *Klebsiella* species, is isolated. For a patient with catheter-associated septicemia who is treated with vancomycin and gentamicin and from whom ampicillin-susceptible *Enterococcus* is isolated, ampicillin has superior antibacterial activity (and less toxicity) than vancomycin. For an outpatient with a cutaneous abscess presumed to be caused by *S. aureus,* empiric clindamycin can be replaced with an oral first-generation cephalosporin or β-lactamase-stable penicillin if the organism is methicillin susceptible.

Definitive, convalescent outpatient therapy of serious infections initially treated in the hospital is reasonable if the risks of complications of the infection are negligible and if the parents and child can adhere to well-defined management plans and can return to the hospital quickly for any infection- or therapy-related problem. In some situations, either convalescent oral therapy or convalescent parenteral therapy is preferred. High-dose oral β-lactam therapy for bone and joint infections is one of the best evaluated step-down therapies for invasive infection.[10] Parenteral antibiotics, such as ceftriaxone, that can be administered once daily are advantageous for outpatient therapy even though agents with a narrower spectrum of activity (or more potent activity) may be available because the narrower-spectrum or more potent agents require more frequent doses that may not be realistically administered in a home environment.[11]

Step 9: Special Considerations

Considerations of drug allergy affect antimicrobial selection. The degree and type of drug reaction should be ascertained. The history of a morbilliform rash in a child 4 days after commencing amoxicillin therapy does not carry the same risk of a serious drug reaction as does the history of hives and airway obstruction following the first dose of amoxicillin. Cost considerations have become a greater issue as health insurers and governmental agencies develop antibiotic formularies that contain “approved,” less costly antibiotics with a narrow spectrum of activity. Antibiotic resistance of the suspected pathogen provides guidance for the selection of a particular agent. As antibiotic resistance in a community increases and failures with older, less active agents increase, formularies must be reassessed. An acceptable risk of failure must be determined by the treating physicians as well as by medical advisors to government and private insurers who determine formularies, to allow families to achieve acceptable cure rates and continue to have confidence in their healthcare providers.

Antimicrobial Susceptibility Testing and Interpretation

The primary purposes of performing antimicrobial susceptibility testing on clinical isolates are to guide therapeutic decisions for individual children and to amass data on susceptibilities of pathogens to a wide range of antibiotics to inform future decisions when a pathogen is not isolated. Susceptibility testing is performed routinely for most clinical isolates to inform decisions for individual children, with a few notable exceptions, such as for *S. pyogenes,* for which susceptibility to penicillin (but not macrolides) is predictable. A comparison of the antibiograms from sequentially isolated organisms from a child can provide guidance for interpretation of the clinical relevance of 2 or more isolates (e.g., coagulase-negative staphylococci as a true pathogen vs. contaminant). Comparing antibiogram data from the same bacteria isolated from several children on a hospital unit can provide insight into possible healthcare-associated infections.

Interpretation of Susceptibility Test Results

An assortment of routine susceptibility test methods can be performed, including the disk diffusion (Bauer-Kirby) test, an antibiotic strip gradient-diffusion method (E-test), agar dilution with a mechanized inoculator, broth macrodilution or microdilution, and a short-incubation automated instrument method[12] (see Chapter 286). Results usually are provided as a measure of the inhibition of growth of a defined inoculum of organisms following incubation in the presence of defined concentrations of an antibiotic. The MIC value provides an operational definition of a strain's intrinsic antibiotic susceptibility and generally reflects the additive effects of multiple mechanisms of resistance, if present. Standardizing these susceptibility techniques and interpretation largely has been the task of the Food and Drug Administration (FDA) with the assistance of the Clinical and Laboratory Standards Institute (CLSI) and the United States Committee on Antimicrobial Susceptibility Testing (USCAST), both nonprofit organizations composed of participants from the pharmaceutical industry, the FDA, and academic institutions.

Interpretation of the clinical relevance and direct clinical applications of MIC values are required beyond simple reporting of an MIC value.[13] The misunderstanding that absolute values of the MICs can be compared across antibiotics can lead to errors in antibiotic management. Examples of misinterpretation could be that ampicillin and gentamicin MICs of 4 μg/mL for *E. coli* denote equivalence, or that the vancomycin MIC of 1 μg/mL and the ampicillin MIC of 2 μg/mL for *Enterococcus* denote the superiority of vancomycin. The variables inherent in disk susceptibility testing were discussed in the landmark report by Ericsson and Sherris,[14] which formed the basis for the categorical interpretations recommended by Bauer and colleagues[15] and subsequently the FDA and professional organizations that interpret in vitro susceptibility test results.[16]

The interpretation of the susceptibility test results is provided by the laboratory report as "S" (susceptible), "I" (intermediate), or "R" (resistant). A report result of "S" suggests that treatment with standard FDA-approved dosages can be expected. A report result of "I" suggests that some clinical failures can be expected at standard dosages because of decreased susceptibility of the pathogen to that antibiotic. A report result of "R" suggests that a microbiologic cure is unlikely because the pathogen is not inhibited by the antibiotic at achievable tissue concentrations following administration of standard, FDA-approved doses, infusion times, and infusion intervals. Interpretation is most valid when the distribution of MIC values across several hundred clinical isolates indicates a widely spaced, distinctly bimodal distribution of susceptible and resistant strains, such as *S. aureus* for penicillin and *E. coli* for ampicillin. The MIC value at which an organism changes from susceptible to nonsusceptible is called the breakpoint.[13] The uniformity of reporting a single interpretation (S, I, or R) of a breakpoint for all infections caused by a single pathogen frequently is too simplistic and can be misleading, such as demonstrated by selecting a breakpoint when assessing the continuum of MIC values of penicillin for *S. pneumoniae* or MIC values of aminoglycosides for *P. aeruginosa.* The interpretation by clinicians of the clinical significance of MICs should be based on (1) the susceptibility values in a large population of isolates (range and mode of distribution, e.g., unimodal, bimodal, skewed), (2) the clinical pharmacology and pharmacodynamics of the drug (protein binding, volume of distribution, tissue concentrations over the dosing interval), and (3) clinical and microbiologic efficacy derived from prospective animal models and human clinical investigations.

At the time an antibiotic is first approved for use by the FDA, MIC interpretative breakpoints are assigned to the antibiotic for various pathogens (often for specific tissue sites). As organisms develop new mechanisms for resistance following widespread use, the interpretation of the susceptibility results (the breakpoints) for a particular organism and a particular antibiotic can change. When ceftriaxone was first approved for use in children, *S. pneumoniae* was considered susceptible if the MIC value was ≤8 μg/mL. Pneumococci then expressed a novel mechanism of resistance, alteration in the many different penicillin-binding sites on the various cell wall synthesizing transpeptidase enzymes. Beginning in 1990, microbiologic failures in the treatment of meningitis occurred in children infected by organisms with a ceftriaxone MIC of 2 μg/mL. The breakpoints subsequently were changed so that only organisms with MIC ≤0.5 μg/mL were considered susceptible. However, with the knowledge that ceftriaxone concentrations in tissues such as lung or soft tissue are higher than in CSF, prospective data were collected that documented clinical and microbiologic success of ceftriaxone for infections outside the central nervous system in which the MIC for *S. pneumoniae* was up to 2 μg/mL. Therefore, 2 breakpoints for ceftriaxone now are used: a lower breakpoint of ≤0.5 μg/mL, considered "S" for central nervous system infections, and a higher breakpoint of ≤1 μg/mL, considered "S" for infections outside the central nervous system (see Table 123.2).

To add to the confusion regarding multiple breakpoints assigned to a particular antimicrobial agent and pathogen pair while recognizing that intravenously administered penicillin achieves far higher concentrations in serum and tissues than does orally administered drug, 2 new breakpoints for penicillin for *S. pneumoniae* also have been accepted: a lower breakpoint of ≤0.06 μg/mL, considered "S" for oral drug administration; and a higher breakpoint of ≤2 μg/mL, considered "S" for intravenous drug administration.[17]

The process of regular review of breakpoints for important pathogens against commonly used older, generic antibiotics has been legislated and will become standard in the near future. When the MIC value leads to an "S" interpretation in the laboratory report, the clinician should not assume that an antibiotic will always be effective for all infections at all tissue sites. Furthermore, because "S" indicates bacterial *inhibition* in the test system, the clinician must know whether the antibiotic is bactericidal, which can be required for certain infections (meningitis) or for certain hosts (those with neutropenia).

Site of Infection

As a rule, only free, non–protein-bound drug is active in eradicating bacteria. For β-lactam agents, successively higher concentrations of antibiotic above the MIC present at the site of infection are not more efficacious in bacterial eradication because this class of agents displays time-dependent killing. Conversely, higher concentrations at the site of infection may enhance killing for aminoglycosides and other concentration-dependent drugs. Additionally, subinhibitory concentrations are not always ineffective; morphology and microbial adherence properties can be altered after exposure to subinhibitory concentrations of some antibiotics, with phagocytosis and intracellular killing subsequently enhanced by neutrophils.

Extracellular Infections

Many bacterial infections occur in interstitial tissue fluid.[18] For such infections, serum concentrations of antibiotics generally predict responses adequately. Antibiotics leave the vascular compartment and enter the extracellular fluid through passive diffusion. When the ratio of the surface area of vascular tissue to the site or volume of infection is high (e.g., in cellulitis, pneumonia, or pyelonephritis), antibiotic concentrations at that site are predicted by principles of passive diffusion. This is not the case when the volume of infection exceeds the surface area of the vasculature (e.g., abscess, fibrin clot, or cardiac vegetation). Passive diffusion principles alone also cannot be used to predict the extracellular fluid concentration of certain antibiotics at sites with active transport (e.g., urine or bile) or with a barrier to capillary permeability (e.g., into the ocular aqueous humor and CSF). The ability of antibiotics to pass through membranes by nonionic diffusion is related to lipid solubility. Lipid-soluble agents such as rifampin, chloramphenicol, trimethoprim, and isoniazid penetrate membranes and cross the blood-brain barrier better than the more highly ionized aminoglycosides. For meningitis, relatively large dosages of third-generation cephalosporins, penicillin G, ampicillin, or vancomycin are required to achieve adequate concentrations in the CSF. Additionally, active transport out of the extracellular fluid, including the CSF, also can result in reduced concentrations in CSF of certain antibiotics such as β-lactam agents.

Table 289.1 delineates the distribution characteristics of the major classes of antibiotics. Clinical evidence has indicated the inferiority of certain antibiotics used for the treatment of infection at sequestered tissue sites where penetration is poor (e.g., brain, eye, bone), and logical preference exists for the use of antibiotics known to accumulate at the site of infection. The vegetations of endocarditis, devitalized tissue, and bones are areas in which the penetration of most agents can be poor; high-dose and prolonged parenteral therapy usually is required, and surgical debridement of necrotic, nonperfused tissue can be necessary. The pharmacology of the drug can offer particular advantages. Agents eliminated by glomerular filtration or renal tubular secretion accumulate in urine. Fluoroquinolones, a few β-lactam agents (e.g., ceftriaxone and cefoperazone), and doxycycline are actively transported into bile, whereas first-generation cephalosporins and aminoglycosides diffuse passively. Clindamycin and the fluoroquinolones achieve excellent concentration in bone, although for infected bone with vascular necrosis, penetration of any antibiotic can be compromised.

Only free drug is considered capable of antibiotic activity.[19] Although only free drug passes through capillary walls and fibrin clots, intercompartmental diffusion will ultimately achieve an equilibrium between bound and free drug in tissues. Complex interactions at the tissue site probably account for the inconsistencies in prediction of clinical efficacy solely as a result of the degree of protein binding. In general, the plasma protein binding of aminoglycosides and fluoroquinolones is low, whereas binding for β-lactams can vary from low to very high for β-lactam agents.

Multiple factors at the site of infection also can alter antimicrobial activity. Examples include the presence of purulent material, which results in a tissue environment with low pH. This situation leads to a decrease in the cationic aminoglycoside molecule charge that results in decreased binding and decreased antibacterial activity at the site of infection. Pathogens such as *Bacteroides* and *Prevotella* produce β-lactamase and can hydrolyze β-lactam agents.[20] A wound hematoma can lower the ratio of the surface area of vascular tissue to the site or volume of infection; hemoglobin can bind penicillins and tetracyclines.[21] Low oxygen tension in abscesses or ischemic tissue impairs active transport of aminoglycosides into bacterial cells. Although an acid pH in tissue or urine impairs the activity of aminoglycosides, nitrofurantoin, and methenamine, an alkaline pH enhances the activity of aminoglycosides and clindamycin. A high–bacterial-density infection such as streptococcal necrotizing fasciitis can be associated with slowed growth of bacteria with downregulation of cell wall transpeptidases that are the targets for β-lactam agents, thus making the organisms temporarily less susceptible to β-lactam antibacterial activity.[22] The presence of a foreign body protects some organisms from host bactericidal action through biofilms and inhibition of neutrophil phagocytosis and, in addition, probably protects the pathogens by other, less well-defined mechanisms.

Intracellular Infections

The unique properties of antimicrobial agents must be considered when the site of infection is intracellular because many antibiotics do not penetrate human cells (see Table 289.1). β-Lactam antibiotics, for example, are confined almost exclusively to plasma water and the interstitial fluid space. Such localization explains some discrepancies between apparent in vitro activity and therapeutic ineffectiveness. Intracellular pathogens include *Listeria monocytogenes, Salmonella, Brucella, Legionella, Mycobacterium, Rickettsia,* and *Toxoplasma,* as well as some pathogens that can cause persisting infections such as *S. aureus* and *E. coli.* Antibiotics that enter cells do so by a variety of mechanisms, including diffusion of relatively small lipid-soluble agents across a concentration gradient, pinocytosis of water-soluble agents, and carrier-mediated transport.[23,24] Cellular accumulation of drug does not necessarily translate into efficacy against intracellular organisms; efficacy depends on whether the microbe and the drug are at the same intracellular site, how avidly the drug is bound to intracellular proteins and to the pathogen target site, and the molecular charge of the antibiotic at its intracellular location.

Clindamycin, macrolides, and azalides are tropic for lysosomes, where they become protonated and concentrated.[24,25] Fluoroquinolones have a large volume of distribution and a high tissue-to-serum ratio, as well as low-affinity intracellular binding; much of the fluoroquinolone body load thus is present intracellularly. For azithromycin, an even more dramatic intracellular location of antibiotic has been documented within phagocytic cells.[24,25] The pharmacokinetic properties and intracellular accumulation of azithromycin are responsible for successful therapy of infection with intracellular pathogens and for shortened courses with respect to the number of days of antibiotic dosing required (including single-dose therapy).[26] At the same time, azithromycin concentrations in serum, CSF, and the aqueous humor of the eye are negligible.[27]

Dosing, Route, and Duration of Therapy

Optimal dosing of an antimicrobial agent depends on relationships among the time course of concentration at the site of infection, the characteristics of antimicrobial activity, and adverse effects.

In clinical practice, the route of administration of antibiotics often is based on additional practical considerations. Parenteral administration is required if an agent is absorbed poorly from the gastrointestinal tract, if a condition precludes administration or absorption of a usually well-absorbed drug, if an unusually high tissue concentration of drug is required, or if adherence to an oral regimen for treatment of a significant infection cannot be ensured. Otherwise, substitution of oral for parental agents frequently is possible, even for serious diseases (e.g., pneumonia, osteomyelitis, pyogenic arthritis, orbital cellulitis) during convalescence.

Oral therapy can replace parenteral therapy when highly absorbed and bioavailable agents are used to treat highly susceptible pathogens (e.g., trimethoprim-sulfamethoxazole for *Pneumocystis* pneumonia) and when the tissue concentrations of drugs at relevant sites are uniquely favorable (e.g., clindamycin or fluoroquinolone in bone). With a less favorable profile, parenteral therapy is given for the entire duration of therapy (at home or in the hospital). Abundant evidence for the effectiveness for different routes of administration is available when patient screening, selection of medical conditions, and follow-up are performed diligently.[10,11,28] Advocacy for the best route of treatment of a child's infection is a paramount consideration, with the risk of failure of therapy and the impact of the outcome taken into account.

The appropriate duration of antibiotic therapy has been described more by experience and by “standard” treatment courses used for FDA antimicrobial drug approval than by prospective, well-controlled studies with duration of therapy as a separate variable as a specifically assessed outcome. Many factors are considered in the decision regarding the duration of therapy, including the intrinsic pathogenicity of the microbe, susceptibility to the agent used, the site of infection and penetration of the antibiotic, the use of synergistic combination therapy, the replication rate of the pathogen, the presence of a foreign body, and host factors that impair bactericidal capacity. In many situations, the severity of infection in all children is not uniform (e.g., pyelonephritis, soft tissue abscess), thus leading to differences in the time course of the child's response to antibiotic therapy. In children with more severe pneumonia, treatment can be given parenterally until a clinical (and presumed microbiologic) response has occurred, and then oral convalescent “step-down” therapy can be provided for a defined time to achieve the desired total duration of therapy. With all infections, a recommendation for duration of therapy is based on the best available information for that child's infection. Longer treatment courses can be more appropriate for more resistant organisms, for more severe infections associated with abscess formation especially if abscesses cannot be drained adequately, or for immunocompromised hosts. Delayed eradication of pathogens from the site of infection can occur in all these situations. The family should always be cautioned at the end of the treatment course to be alert for the signs and symptoms of relapse.

Antimicrobial Combinations

Prevention of Emergence of Resistance

Antibiotics can be used in combination in an attempt to (1) prevent or delay the emergence of drug-resistant subpopulations of the pathogen, (2) create synergy to improve outcomes, or (3) provide empiric therapy that will ensure that at least 1 antibiotic in the combination will be active against the infecting pathogen or pathogens. In most circumstances, published clinical data have been analyzed retrospectively with various antibiotic combinations for multiple infection entities, with conflicting conclusions.[29–31] For certain populations of children, particularly those critically ill and with immunocompromise, combination therapy will likely improve outcomes, as suggested by retrospective subset analyses.[30,31] Current data document improved outcomes with early, appropriate combination antibiotic therapy in sepsis.

Mycobacterium tuberculosis treatment provides the best clinically documented example of the prevention of emergence of resistant bacteria. With a spontaneous resistance mutation frequency of approximately 10^8, the initial use of 2 or more agents to which the organism is reported as susceptible substantially reduces the probability that resistant organisms will be selected out and emerge during therapy.[32] Treatment of *Pseudomonas* infection with a β-lactam, a fluoroquinolone, or an aminoglycoside alone can be associated with the emergence of resistant strains; 2-drug combination therapies can reduce the incidence of resistance to either component antibiotic. However, each antibiotic must provide the necessary exposure to pathogens in the infected tissues to ensure eradication of susceptible organisms. Inadequate dosing or poor tissue penetration of 1 antibiotic in a combination can lead to the selection of organisms resistant to that agent, despite the use of dual therapy.

Rifampin is an antibiotic that is never used alone for the treatment of infection because of the rapid, frequent development of resistance following antibiotic exposure. Combining rifampin with vancomycin for coagulase-negative staphylococcal prosthetic valve endocarditis or ventriculoperitoneal shunt infection, or with a semisynthetic penicillin for *S. aureus* infections, can reduce the emergence of resistance while taking advantage of the unique tissue penetration and target site activity of rifampin.

Inhibition of β-Lactamases

With certain fixed-combination drugs containing a primary β-lactam agent, the site of action of the second drug in the combination is not a vital microbial target binding site but rather the pathogen's antibiotic-degrading enzyme, responsible for resistance to the primary antimicrobial agent. Antistaphylococcal penicillins such as methicillin and nafcillin are degraded by staphylococcal β-lactamases. β-Lactamase inhibiting agents such as clavulanic acid, sulbactam, tazobactam, and avibactam display a specific affinity for and a degree of irreversible binding to the various bacterial β-lactamase enzymes, thereby protecting the companion β-lactam antibiotic from hydrolysis and allowing access to the target penicillin-binding proteins.[33] Amoxicillin-clavulanate is especially useful in children when the potential causative pathogens are susceptible to amoxicillin except for the presence of β-lactamases produced by the pathogen (*M. catarrhalis, H. influenzae, S. aureus,* and *Bacteroides fragilis*). Piperacillin-tazobactam is a useful agent that extends the spectrum of activity of piperacillin to include additional gram-negative bacilli and methicillin-susceptible staphylococci; it may not, however, add to the activity of piperacillin alone against *Pseudomonas* because tazobactam does not effectively inhibit many of the β-lactamases produced by *P. aeruginosa.*

Synergy

Target Site Synergy

Combinations of antimicrobial agents can have a variety of effects on the target sites of an organism in vitro. The combination can be categorized as follows: (1) *synergistic,* when the combined effect of the drugs is significantly greater than the independent effects when the drugs are tested separately; (2) *antagonistic,* when the combined effect is significantly less than the drugs' independent effects when tested separately; (3) *additive,* when the combined effect is the sum of the separate effects of the drugs tested; or (4) *indifferent,* when the combined effect is simply the effect of the more active drug alone. The clinical applications of these definitions are controversial. Synergy test results depend on the intrinsic activities of each antibiotic on an organism, the test system used, and whether the binding sites are similar or dissimilar.[34–37] Despite the paucity of prospective clinical validation of in vitro results, biologically plausible reasons exist to believe that for certain infections, synergy has clinical relevance. Although performing prospective clinical studies for all combinations is not practical, concepts on classes of drugs with differing intracellular sites of activity and encouraging supportive in vitro data have evolved (e.g., penicillins in combination with aminoglycosides) to guide therapeutic choices. In clinical practice, combination therapy is common for serious infections, as demonstrated in a retrospective study of severe MRSA infections in which 50% of children received 3 or 4 agents simultaneously.[38] With the combination of multiple agents, antagonism also can occur, and outcomes can be worse than with the use of only 1 or 2 agents.

Simultaneous Inhibition of Multiple Interrelated Targets

A classic example of synergy of targeted activity at consecutive metabolic steps is represented by the combination of a sulfonamide with a dihydrofolate reductase inhibitor such as trimethoprim. The resulting inhibition of consecutive steps in the folic acid pathway leads to a significantly reduced MIC and can also enhance the drug's bactericidal capacity. Streptogramin antibiotics (quinupristin-dalfopristin) include 2 biochemically distinct bacteriostatic compounds produced by *Streptomyces* that produce bactericidal activity when the agents are used in combination.[39] The binding of the type A streptogramin at the acyl-amino transfer RNA (tRNA) acceptor site on the ribosome both prevents the binding of tRNA and also causes a conformational change in the ribosome, which enhances the binding of the type B streptogramin and thus causes steric hindrance to the extrusion of newly formed polypeptide chains from within the ribosome.

Combination of Cell Wall–Active Agents With Ribosomal-Active Agents

Some instances of antibiotic resistance (e.g., to aminoglycosides) can result from a permeability barrier that precludes the drug's reaching the intracellular target site. Agents that act on the cell wall (e.g., β-lactam agents, vancomycin) should enhance intracellular entry of an aminoglycoside. Unless the drug is rendered ineffective by aminoglycoside-modifying enzymes or resistance occurs at the ribosomal level, a combination could be expected to be synergistic. Such bactericidal synergy is demonstrable for viridans streptococci, group B streptococci, enterococci, staphylococci, *Listeria* and *Corynebacterium* species, *P. aeruginosa,* and Enterobacteriaceae. Generally for *Enterococcus,* streptomycin, gentamicin, and tobramycin are predictably synergistic with cell wall–active agents if the enterococcal strain is susceptible to aminoglycosides at 2000 μg/mL; laboratories provide standardized testing at this single-drug concentration.

For gram-negative bacilli, exposure to aminoglycosides can enhance the permeability of the outer cell envelope to β-lactam antibiotics because of aminoglycoside-mediated production of altered, nonfunctional proteins that are incorporated into the cell wall.

The superior clinical efficacy of combination over single-drug therapy has been documented in only limited clinical settings. For the treatment of enterococcal endocarditis, penicillin alone, which provides only bacteriostatic activity against enterococci, results in an unacceptable relapse rate. The addition of an aminoglycoside such as streptomycin or gentamicin results in clinical cure rates comparable with the rates attained in the treatment of endocarditis caused by penicillin-susceptible streptococci.[40] Although similar clinical benefit is demonstrable in the animal model of endocarditis caused by penicillin-tolerant or relatively penicillin-resistant viridans streptococci (MIC of 1 μg/mL), no advantage is shown against fully susceptible strains; nonetheless, combination therapy for 2 weeks in patients with susceptible strains results in success rates comparable with those achieved when penicillin is administered alone for 4 weeks.[40] The combination of nafcillin and gentamicin is synergistic in vitro against methicillin-susceptible strains of *S. aureus;* both retrospective data and limited prospective, comparative trials of nafcillin and gentamicin versus nafcillin alone in adults with endocarditis, as reviewed by meta-analysis, failed to show any longterm outcome benefit of combination therapy.[41] Similarly, tolerance to the bactericidal effect of β-lactam agents among streptococci and staphylococci can be overcome in vitro by drug combinations, but superior clinical efficacy in human infections has not been proven. Combinations of ticarcillin or piperacillin with gentamicin, tobramycin, or amikacin exhibit in vitro synergy against many strains of *P. aeruginosa*. One prospective, randomized clinical trial of bacteremic patients with cancer confirmed better survival with carbenicillin in combination with gentamicin versus carbenicillin alone.[42] Another prospective, but uncontrolled study of 200 patients with *Pseudomonas* bacteremia documented increased survival in patients receiving combinations, regardless of whether synergy was demonstrable in vitro.[43] Confirmatory clinical evidence of the superiority of combination therapy for bacteremia caused by other gram-negative bacilli has been limited to neutropenic patients; such evidence documents the critical importance of susceptibility to the β-lactam component.[42,44,45] With the advent of more potent, highly bactericidal agents such as the third-generation cephalosporins and carbapenems, the benefit of addition of an aminoglycoside can be difficult to demonstrate except under the most challenging clinical conditions of sequestered pathogens and an absent host response at the site of infection. Prospective, controlled studies under these conditions are not likely to be performed. A retrospective analysis of more than 4500 bacteremic adults in intensive care units who were treated early with combination therapy documented decreased mortality rates and shorter hospital stays compared with patients who were given monotherapy, for both gram-negative and gram-positive pathogens.[31,46]

Published data exist on the effect of in vitro combination testing for antimicrobial agents approved during the past few decades against common pathogens. Data on some older drugs also may exist, particularly for currently isolated pathogens that can be multidrug resistant. For example, clindamycin and gentamicin in vitro have been reported to show synergy against some strains of viridans streptococci and antagonism against other strains.[47] Some studies have shown synergy of trimethoprim-sulfamethoxazole in combination with amikacin against Enterobacteriaceae for organisms that are susceptible to both drugs.[48] Ciprofloxacin in combination with an aminoglycoside or various β-lactam agents is infrequently synergistic against Enterobacteriaceae, but it can be synergistic against strains of *P. aeruginosa* with aminoglycosides or carbapenems[49]; antagonism is rare. When daptomycin was tested in combination with rifampin or gentamicin against MRSA, additive or indifferent effects usually were observed, without synergy or antagonism. Daptomycin in combination with β-lactam agents showed unexpected synergy in vitro against MRSA. The clinical relevance of these findings requires human clinical investigation.[50] Rifampin has synergistic bactericidal activity with vancomycin against coagulase-negative staphylococci[51] and with ampicillin against *Listeria*.[52] The unique tissue penetration properties of rifampin make it useful not only in postexposure prophylaxis to prevent or eliminate microbial colonization with meningococcus, but also in combination therapy for infections related to medical devices.

Antagonism

Despite the paucity of documented reports of the clinical significance of antagonism among antimicrobial agents, multiple examples are demonstrable in vitro; thus caution is needed in their use, especially for infections in hosts with impaired defenses. Combinations of a bacteriostatic agent with a β-lactam antibiotic can antagonize the bactericidal activity of the β-lactam antibiotic, as documented with the combination of chloramphenicol and ampicillin against group B *Streptococcus*. Combinations of chloramphenicol or tetracycline and aminoglycosides also are also antagonistic for gram-negative bacilli. In addition, chloramphenicol antagonizes the bactericidal effect of ciprofloxacin against *S. aureus, E. coli,* and *P. aeruginosa*. In a combination of agents that bind to similar locations within the ribosome (e.g., clindamycin, erythromycin, spiramycin, chloramphenicol, streptogramins), the drugs can either complement each other and enhance activity or compete with each other and antagonize activity.[53]

Judicious Use of Antibiotics (Antimicrobial Stewardship)

Antimicrobial agents are the principal therapeutic tools for pediatric infectious disease specialists and are among the leading interventions in all of pediatrics. Overuse of this tool is increasingly threatening its effectiveness. In 2009, $10.7 billion was spent on antibiotic therapy in the United States. Differences were observed in antibiotic expenditures when these expenditures were analyzed by location of antibiotic sales, with the majority of sales in the outpatient setting, 87% in community pharmacies.[54,55] The spread of antimicrobial resistance led to ongoing concern about such unnecessary drug use among physicians and increasingly among patients or parents and resulted in national guidelines for antimicrobial stewardship.[56]

Common pathogens such as *S. pneumoniae* and *S. aureus* typically remain treatable, but resistance in these organisms raises costs and increases the likelihood of treatment failure. Hospital-associated pathogens such as *Enterobacter, Klebsiella, Acinetobacter, Pseudomonas,* or *Enterococcus* may not be treatable with available agents.[57]

Microbial resistance is driven by antimicrobial exposure. Many studies have linked recent exposure to antimicrobial agents to an increased risk for carrying or being infected with resistant pneumococci.[58,59] During a course of prophylactic antibiotics to prevent acute otitis media, the proportion of children carrying resistant strains of pneumococci, *H. influenzae,* and *M. catarrhalis* increased, with a return to baseline levels only after the selective pressure of the antimicrobial regimen was removed.[60] Avoiding such selective pressure that drives resistance by reducing antimicrobial exposure is the focus of a variety of public health strategies to control resistance.

A set of principles from the Centers for Disease Control and Prevention (CDC) for judicious antimicrobial use in children with upper respiratory tract infections summarized scientific evidence for curtailing such use and was published as a guide to appropriate antibiotic use.[61] The CDC's current Get Smart: Know When Antibiotics Work program provides materials for healthcare professions in outpatient and inpatient settings, as well as for parents, that are designed to encourage appropriate prescribing practices (http://www.cdc.gov/getsmart/community/index.html). Programs for judicious use have been studied in private practice, managed care organizations, emergency departments, and community clinics.[62–67] Successful reductions in prescribing have been documented when groups in active intervention programs that include both physicians and patients have been compared with groups receiving no intervention other than information. Most importantly, decreased antibiotic use has not led to increased complications of "untreated infections".[62,67] Limited but convincing evidence indicates that the decrease in prescribing of antibiotics is leading to slowing of the spread of resistant bacteria.[56,66–68]

The Guidelines for Antibiotic Stewardship from the Infectious Diseases Society of America outline strategies to promote appropriate antibiotic selection and duration of therapy and evaluate the potential impact on the development of antibiotic resistance.[54] Unfortunately, few prospective, high-quality investigations specifically in children are available that document the impact of improved practices on a decrease in colonization or infection with resistant organisms.[67,68]

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Mechanisms and Detection of Antimicrobial Resistance

Kevin Alby, Melissa B. Miller

Microorganisms have survived for millions of years because of their ability to adapt to hostile environments. Since the 1940s, bacteria that cause human infections have been exposed to ever-increasing antimicrobial pressure as a result of appropriate and inappropriate use of these agents. In the United States, investigators have estimated that more than 7 million pounds of antimicrobial agents are consumed annually by humans. Approximately 80% of all antibiotics sold (~29 million pounds) are used in food-producing animals in the US.[1] Although the economic benefits in agricultural use versus the risk of transfer of resistance to humans are debated, the US Food and Drug Administration (FDA) introduced the Veterinary Feed Directive to promote the judicious use of antibiotics in food-producing animals.[2–4]

Despite intensive campaigns aimed at reducing inappropriate use of antimicrobial agents, investigators have estimated that one half of all children in the industrialized world receive an antimicrobial agent annually and that three fourths of children 1 to 2 years of age receive these agents.[5–7] Although antibiotic use from 2000 to 2010 decreased 18% among children and adolescents, the prescription of broad-spectrum antibiotics increased 79%.[8] Even with continued efforts to reduce antimicrobial use in animals and humans, existing levels of antimicrobial resistance are not likely to return to the levels seen before antimicrobial abuse began.

Antimicrobial resistance exacts a high economic cost (~$60 billion annually in the US).[8] The human cost also is substantial because drug-resistant organisms frequently do not respond to therapy, thus resulting in hospitalization, surgical interventions, increasing use of diagnostic services, and death.[9] Gram-negative bacilli that produce novel β-lactamases with activity against many or, in some cases, all classes of β-lactam agents are emerging at an alarming rate and spreading globally. These include Verona-integron-encoded metallo-β-lactamase (VIM), New Delhi metallo-β-lactamase (NDM), and *Klebsiella pneumoniae* carbapenemase (KPC). An Infectious Disease Society of America initiative to have 10 new systemic drugs available by 2020 against the ESKAPE organisms (*Enterococcus faecium*, *Staphylococcus aureus*, *K. pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and Enterobacteriaceae) has spurred the development and FDA approval of new antibiotics.[10,11] Although the rate of approved antimicrobial agents is slow compared with previous decades and the challenge of developing new antimicrobial classes remains,[10] at least 39 compounds from different drug classes are in clinical trials.[12] Beyond the ESKAPE organisms, extensively drug-resistant and totally drug-resistant *Mycobacterium tuberculosis* is of global concern, especially in locales with high rates of human immunodeficiency virus (HIV) infection.[13]

Genetics of Antimicrobial Resistance

Intrinsic Resistance

Antimicrobial resistance can be attributed to intrinsic cellular properties, intrinsic mutations, acquisition of resistance genes, or intragenic recombination resulting in mosaic genes[14,15] (Table 290.1). Intrinsic resistance can be caused by inherent properties of microorganisms, such as cellular membranes, which render them resistant (e.g., gram-negative species to vancomycin). Additionally, intrinsic resistance is mediated by the mutation of chromosomal genes. Although acquired resistance mechanisms are more common, many infections are caused by 1 or few species, thus making interspecies gene acquisition difficult in vivo. In these circumstances (as postulated for both *P. aeruginosa* in the setting of cystic fibrosis and *M. tuberculosis*), the organism's primary antibiotic defense mechanism is intrinsic mutation.[16,17] Intrinsic mutations that contribute to antimicrobial resistance include variation in the antimicrobial target site (e.g., fluoroquinolones, aminoglycosides), changes in regulatory genes or promoter sequences (e.g., increase in efflux pump or inactivating enzyme expression, decrease in porin expression), and indirect mutations that affect the organism's mutation rate.[16,18]

TABLE 290.1

Common Antibacterial Drug Resistance Mechanisms

Drug Class	Resistance Mechanism	Frequency	Examples
Aminoglycosides	Enzymatic inactivation	Common	Phosphotransferases, acetyltransferases, nucleotidyltransferases in Enterobacteriaceae and *Enterococcus* spp.
	Efflux pump	Uncommon	MexX-MexY efflux pump in Enterobacteriaceae
	Altered binding site	Rare	Streptomycin-resistant *Mycobacterium tuberculosis*
	Altered uptake	Common	Streptococci and all anaerobic bacteria
β-Lactams	Enzymatic inactivation		*Staphylococcus aureus, Haemophilus influenzae,* Enterobacteriaceae
	Ambler class A β-lactamase	Common	ESBL producing: *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis*
	Ambler class B β-lactamase	Common	VIM, IMP, and NDM carbapenemases in *Acinetobacter baumannii, Pseudomonas aeruginosa,* and selected Enterobacteriaceae; chromosomally encoded in *Stenotrophomonas maltophilia*
	Ambler class C β-lactamase	Common	AmpC chromosomal β-lactamase in *Enterobacter* spp.
	Ambler class D β-lactamase	Uncommon	Plasmid encoded in *Pseudomonas aeruginosa* and selected Enterobacteriaceae
	Altered penicillin-binding proteins	Common	Oxacillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae*
	Efflux pump	Uncommon	MexAB-OprM pump in *Pseudomonas aeruginosa*
	Altered uptake	Uncommon	Loss of OprF and OprD in *Pseudomonas aeruginosa*

Colistin	Altered binding	Uncommon	Altered lipopolysaccharide in *Pseudomonas aeruginosa* and *Acinetobacter baumannii*
	Efflux pump and capsular overproduction	Rare	*Klebsiella pneumoniae*
Isoniazid	Altered binding	Common	Mutation of *katG* in *Mycobacterium tuberculosis*
	Overexpression of target	Uncommon	Overexpression of *inhA* in *Mycobacterium tuberculosis*
Linezolid	Altered binding	Uncommon	23s rRNA mutations or methyltransferase in *Enterococcus* spp.
Macrolides and related compounds	Efflux	Common	Macrolide resistance in streptococci
	Altered binding	Common	Methylation of 23S rRNA conferring resistance to macrolides, streptogramins, and lincosamides in *Staphylococcus* and *Streptococcus* spp.
Metronidazole	Inactivating enzyme	Uncommon	Nitroimidazole reductase in *Bacteroides* spp.
Quinolones	Altered binding	Common	Mutations in *gyr* conferring resistance in gram-negative organisms; mutations in *par* conferring resistance in gram-positive organisms
	Efflux	Uncommon	Possible in a variety of gram-negative and gram-positive organisms
	Protective protein	Rare	Protein expressed by *Klebsiella pneumoniae* that binds fluoroquinolones and thus prevents binding to target
Rifampin	Altered binding	Common	Mutations in *rpoB* gene in *Staphylococcus aureus, Mycobacterium tuberculosis,* and *Neisseria meningitides*
Tetracyclines	Efflux pump	Common	Gram-positive and gram-negative organisms
	Protective proteins	Uncommon	Gram-positive and gram-negative organisms
Trimethoprim-sulfamethoxazole	Overproduction of target	Common	Overproduction of DHFR in a variety of bacteria
	Altered binding	Common	Mutated *dhfr* gene in *Streptococcus pneumoniae*
	Bypass targeted pathway	Uncommon	Occurs in thymidine-dependent *Staphylococcus aureus*
Vancomycin	Altered binding	Common	*vanA* and *vanB* in *Enterococcus*
	Overproduction of target	Uncommon	Vancomycin-intermediate *Staphylococcus aureus*

AmpC, Ambler class C β-lactamase; DHFR, dihydrofolate reductase; ESBL, extended-spectrum β-lactamase; NDM, New Delhi metallo-β-lactamase.

Although bacteria have a low mutation rate (~10^{-8}/base pair) to preserve DNA integrity and function, naturally occurring mutations permit evolution toward fitness. Deleterious mutations also can occur, leading to loss of fitness.[19,20] Induction of a higher mutation rate (i.e., a mutator phenotype) can be beneficial to the organism, particularly when the organism is under selective pressure, such as environmental or antibiotic stress. Fluoroquinolone and aminoglycoside antibiotics can induce a hypermutable state, leading to antimicrobial resistance.[21,22] The hypermutator state is inducible or transient, and it allows for the survival and expansion of the resistant bacterial population; clinical importance requires further research.[16,23]

Acquired Resistance

Acquired resistance occurs through horizontal transfer of resistance genes among organisms by conjugation, transformation, or phage-dependent transduction; in some cases, these genes become a stable part of the recipient chromosome.[24] The 2 types of mobile genetic elements are those that move between cells and those that move within a cell. However, elements that move only intracellularly (e.g., gene cassettes, resistance transposons, integrons) can “hitch a ride” on intercellular mobile elements such as plasmids and conjugative transposons.

Plasmids consist of circular, extrachromosomal double-stranded DNA (dsDNA; ~4–400 kb) that self-replicates. A bacterium can contain multiple compatible plasmids or multiple copies of the same plasmid. Plasmid-based resistance genes can be propagated either by clonal spread of the organism or by horizontal transfer via conjugation.[24,25] Resistance genes encoding inactivating enzymes for β-lactam agents (including extended-spectrum β-lactamases [ESBLs] and carbapenemases), macrolides, aminoglycosides, and chloramphenicol; efflux genes for macrolides and tetracyclines; and altered targets for sulfonamides have been found on plasmids.[25] Plasmid-mediated resistance genes can also be located on mobile genetic elements that can relocate (either by transposition or site-specific integration) to other plasmids or chromosomes, thereby resulting in the intraspecies and interspecies spread of antimicrobial resistance.

Transposons (~2–20 kb) contain insertion sequences and a single gene or few linked genes often encoding antimicrobial resistance. In addition, transposons are flanked by inverted sequence repeats and encode for a transposase enzyme required for transposition. Conjugative transposons exist that move directly from 1 bacterium to another and have been found to mediate the transfer of resistance in gram-positive bacteria. Among the best-studied conjugative transposons are Tn*916* in *Enterococcus faecalis* encoding tetracycline resistance and Tn*1549* in enterococci encoding vancomycin resistance.[26] Nonconjugative transposons (e.g., resistance transposons) generally are transferred from cell to cell through plasmids and include Tn*1546* implicated in the transfer of vancomycin resistance from *Enterococcus* to *S. aureus*.[27]

Integrons include an integrase, mobile gene cassettes, and an integration site for the gene cassettes to allow for site-specific recombination into plasmids or the bacterial chromosome.[28] Integrons themselves are not mobile but facilitate capture of resistance gene cassettes, which subsequently insert into the chromosome. Integrons encoding antimicrobial resistance determinants have been found in certain Enterobacteriaceae organisms, as well as in *P. aeruginosa* and *Acinetobacter* species, and they are associated with resistance to β-lactams (including ESBLs), aminoglycosides, chloramphenicol, trimethoprim, and disinfectants.[25,28,29] Integrons can contain multiple gene cassettes and therefore often encode for multidrug resistance. Gene cassettes consist of a coding sequence, usually without promoter sequences, followed by an integrase-specific recombination site, and either can exist in a nonfunctional circularized form or are expressed as part of an integron or transposon.[29] More than 100 gene cassettes have been described.[30]

Mosaicism

Intragenic recombination between a sensitive locus on the host bacterial chromosome and related genes from other bacterial species can result in mosaic genes conferring antimicrobial resistance.[15] This recombination-dependent mechanism occurs primarily by direct uptake of naked DNA and is therefore limited to organisms that are naturally transformable. Some mosaic alleles, or polymorphisms, are lost or are present only in low numbers as a result of decreased bacterial fitness. However, if a mosaic allele expresses a phenotype that is favored by antibiotic-selective pressure, the mosaic likely will survive and establish a new, resistant population.[15] Examples of successful mosaicism are the penicillin-binding proteins (PBPs) in *Streptococcus pneumoniae* and the pathogenic *Neisseria* species, as well as sulfonamide-resistant dihydropteroate synthase in *N. meningitidis*.[15,31–34]

Mechanisms of Resistance

Bacteria can develop resistance to antimicrobial agents by at least 6 basic mechanisms, and multiple mechanisms can act concurrently[35]:

1. Enzymatic inactivation

2. Alteration of the antimicrobial binding site

3. Active efflux

4. Alterations in membrane permeability to prevent antimicrobial entry

5. Alterations in enzymatic pathways so that the targeted enzyme is no longer essential for organism survival

6. Overproduction of antimicrobial targets

In addition, slow rates of growth as seen in small colony variants or in organisms growing in biofilms also can contribute to resistance in vivo that is not detected readily in vitro when using standard susceptibility test methods.[36]

Aminoglycosides

Antimicrobial resistance in aminoglycosides can be either intrinsic or acquired. Intrinsic resistance is primarily caused by the inability of these molecules to accumulate in the cytoplasm where they must bind to the 30S ribosome to have an antibacterial effect, which is achieved by interfering with binding of transfer RNA (tRNA) to ribosomal RNA (rRNA) during translation and resulting in inhibition of protein synthesis.[37,38] Aminoglycosides are actively transported into the bacterial cell by a 3-step, energy-dependent process.[39] The energy necessary for this process is generated during aerobic respiration. Bacteria, when growing anaerobically, are not able to generate sufficient energy to “drive” this highly charged molecule into the cell.[39] As a result, all anaerobic organisms and those that depend on anaerobic metabolism (e.g., enterococci) are resistant to aminoglycosides.[37]

Clinically significant, acquired aminoglycoside resistance primarily is the result of acquisition of extrachromosomal elements that encode enzymes that chemically modify aminoglycosides to render them unable to bind to the ribosomal target.[28] Three major classes of enzymes inactivate aminoglycosides, and they are classified by the specific reaction catalyzed: (1) phosphotransferases (APH) that phosphorylate specific aminoglycoside hydroxyl groups, (2) acetyltransferases (AAC) that modify aminoglycosides through acetylation of selected amino groups, and (3) nucleotidyltransferase (ANT) that adenylates the aminoglycoside by adding adenosine monophosphate to selected hydroxyl groups. Resistance in clinical isolates depends on the specific inactivating enzyme produced by the organism. For example, *P. aeruginosa* can harbor 2 different types of AAC(6′): 1 type inactivates tobramycin and amikacin, whereas the other inactivates tobramycin and gentamicin.[40] Each enzyme type has variants that can inactivate each of the clinically relevant aminoglycosides. However, certain enzyme types predominate. Because of its modified chemical structure, amikacin is not inactivated by as many of these enzymes, thus resulting in a broader spectrum of activity against gram-negative bacilli compared with gentamicin and tobramycin.[38] Investigators have sought inhibitors of the transferases to allow for increased activity of aminoglycosides in resistant strains, but these studies are preliminary.[41,42] Aminoglycoside resistance is also important among gram-positive organisms (GPOs). In staphylococci, a unique bifunctional enzyme AAC(6′)-I-(APH 2″) produces modification in all 3 of the most commonly used aminoglycosides (tobramycin, gentamicin, and amikacin), with resulting resistance.[43] Although enterococci are intrinsically resistant to aminoglycosides because of impermeability, treatment with cell wall–active agents such as ampicillin or vancomycin can increase permeability and, in combination with an aminoglycoside, can result in synergistic killing.[43] Resistance secondary to impermeability is referred as “low-level” resistance (gentamicin minimal inhibitory concentrations [MICs], 16–64 μg/mL).[44] High-level resistance also occurs (gentamicin MIC >500 μg/mL), especially among vancomycin-resistant *E. faecium* strains.[44] Gentamicin resistance in enterococci reflects enzymatic inactivation, primarily the AAC(6′)-I-APH(2″) enzyme.[44] Strains producing this enzyme can be susceptible to high levels of streptomycin.

Aminoglycoside resistance resulting from efflux of aminoglycosides occurs, but it is much less common than enzymatic modification.[40] This efflux pump is a 3-component membrane structure consisting of the proteins MexX-MexY and an outer membrane protein (Opr).[45] Both OprM and OprG act as pores in the outer membrane for these efflux pumps.[46,47]

Alteration of the antimicrobial binding site as a mechanism of acquired resistance is observed infrequently, and typically it is caused by mutation. Because multiple genes encoding ribosomes are present in most bacteria, the likelihood of having the same random mutational event occurring at the same loci in multiple genes is minimal.[38] The lone exception is in *M. tuberculosis*. Because it has only a single ribosomal gene copy, ribosomal mutations can confer resistance to streptomycin.[37]

A second means of alteration of the aminoglycoside binding site has been recognized in a strain of *K. pneumoniae* that possesses a plasmid that encodes a 16S rRNA methyltransferase.[46] Modification of the 16S rRNA results in high-level resistance to gentamicin, tobramycin, and amikacin. Methyltransferase has significant sequence homology with enzymes from aminoglycoside-producing organisms, a finding suggesting that it evolved naturally for self-defense.[46] Ribosomal methylase has been found in transposons within plasmids, thus making horizontal transfer of this resistance gene likely. The 16S rRNA methyltransferase has been detected among Enterobacteriaceae, *Acinetobacter*, and *Pseudomonas*.[48–50]

β-Lactams

Resistance to β-lactam agents is caused primarily by production of β-lactamases or alteration in PBPs. In gram-negative organisms (GNOs), β-lactamase production is the more important resistance mechanism, whereas alteration in PBPs plays a central role in GPOs, including *S. aureus, S. pneumoniae,* and *Enterococcus* spp. Organisms can harbor genes simultaneously that encode both resistance mechanisms, as is seen in methicillin-resistant *S. aureus* (MRSA).[35] Organisms can express >1 β-lactamase gene as well as multiple β-lactam resistance mechanisms concurrently, including β-lactamases, β-lactam efflux, and loss of outer membrane protein porins (important in periplasmic drug accumulation in GNOs).[35]

Classification Systems for β-Lactamases

β-Lactamases are enzymes that degrade the β-lactam ring. They can be encoded chromosomally or on extrachromosomal elements. In GPOs, they are excreted into the extracellular space, whereas in GNOs they are found in the periplasmic space. The Ambler system is a common classification system that classifies the enzyme into 4 different groups (A, B, C, D), based on the enzyme structure.[51] Ambler type A, C, and D β-lactamases are classified as serine β-lactamases because they have serine at the enzyme's active site. Ambler type B enzyme is classified as a metalloenzyme because of the requirement for divalent cations, typically zinc, at the active site.[51]

Clinical Relevance of β-Lactam Resistance

The most common type A β-lactamases are TEM and SHV.[51] These β-lactamases degrade penicillin G, ampicillin, antipseudomonal penicillins, and first-generation cephalosporins. Clavulanic acid has excellent inhibitory activity against these enzymes, and organisms producing these enzymes remain susceptible to aztreonam and third-generation cephalosporins.[52] More than 180 TEM-type enzymes and 130 different SHVs have been identified.[52] TEM frequently is found in *Escherichia coli, Haemophilus influenzae,* and *Neisseria gonorrhoeae,* whereas SHV is found in a variety of Enterobacteriaceae members and *P. aeruginosa.*[52] Mutations in the region of the active site of these enzymes can expand their spectra to hydrolyze aztreonam and third-generation cephalosporins such as cefotaxime and ceftazidime. Clavulanic acid continues to inhibit these enzymes in vitro, and these organisms are still susceptible to cephamycins (cefoxitin) and carbapenems (imipenem).[52] Bacteria that are able to express this genotype are described as producing ESBLs.[52] Genes encoding ESBLs frequently are found on large plasmids, which also can encode resistance to other agents such as aminoglycosides and fluoroquinolones.[53] SHV and TEM-type ESBLs are observed most frequently in *E. coli, Proteus mirabilis,* and *K. pneumoniae,*[54] and bloodstream infections with these organisms are associated with significantly increased morbidity and mortality rates.[55]

Another important class A ESBL is CTX-M, so designated because of preferential hydrolytic activity against cefotaxime compared with ceftazidime.[56] More than 90 different types of CTX-M have been identified,[57] and CTX-M has been disseminated on plasmids to many different Enterobacteriaceae organisms, particularly to *Salmonella* strains originating in South America.[56] As with the TEM and SHV enzymes, organisms expressing CTX-M are resistant to all classes of penicillin, aztreonam, and first-, second-, and third-generation cephalosporins. Isolates expressing CTX-M remain susceptible to cephamycins and carbapenems, and like other type A ESBLs, this enzyme is inhibited in vitro by clavulanic acid and tazobactam.

The KPC enzymes are an emerging group of class A β-lactamases. Initially associated most closely with *K. pneumoniae*, plasmids encoding KPC now are found in many Enterobacteriaceae organisms. First identified in 2001,[58] KPCs are now found throughout the US. KPCs are particularly worrisome because they are capable of degrading carbapenems such as imipenem in addition to penicillins, aztreonam, and cephalosporins.[59] KPC-producing strains also can be resistant to aminoglycosides and fluoroquinolones, thus leaving few therapeutic options.[59] Traditional β-lactam–β-lactamase inhibitor combinations do not work in many KPC-expressing strains. However, newer β-lactamase inhibitors such as avibactam have shown activity against KPC-producing organisms and offer newer therapeutic options.[60]

The Ambler class B β-lactamases are enzymes that require divalent cations, typically zinc, to hydrolyze the β-lactam ring.[61] Class B β-lactamases are capable of hydrolyzing most β-lactam containing antibiotics including carbapenems and are inhibited by chelating agents such as ethylenediaminetetraacetic acid (EDTA) but not by traditional β-lactamase inhibitors. Aztreonam alone among the β-lactams can retain some activity against isolates expressing these enzymes.[62] The class B enzymes can be chromosomally encoded, as is seen with *Stenotrophomonas maltophilia,* or they can be transferred by plasmids, transposons, or integrons. The most commonly encountered transferable metallo-β-lactamases are IMP and VIM.[61] Metallo-β-lactamase–producing isolates also frequently are resistant to fluoroquinolones and aminoglycosides.[61] IMP is found most commonly in *P. aeruginosa* and *A. baumannii* but also can be found in Enterobacteriaceae, particularly *Serratia marcescens,* and other *Pseudomonas* species. VIM is primarily found in *P. aeruginosa* but has been reported in Enterobacteriaceae and *Acinetobacter*.[61] The emergence of the New Delhi metallo-β-lactamase (NDM) is of significant concern.[63,64] NDM-producing strains are resistant to all antibiotics except tigecycline and colisitin.[64] First seen in the United Kingdom in 2008, NDMs are now the most common carbapenemase-producing organisms recovered clinically in the UK.[64] Further, NDMs now have been found in the US,[63] as well as throughout the Pacific.

The Ambler class C β-lactamase is referred to as AmpC. AmpC can be chromosomally or plasmid encoded. Chromosomally encoded AmpC β-lactamases typically found in *Enterobacter* and *Serratia*, are inducible, and result in low-level resistance to ampicillin, cefazolin, and cefoxitin.[65] Induction by cephamycin or carbapenems can result in high-level resistance to penicillin and first-, second-, and third-generation cephalosporins. AmpC is not inhibited by clavulanic acid.[52] Plasmid-encoded AmpC was first reported in *K. pneumoniae.* Plasmids carrying AmpC often carry resistance genes for a variety of antibiotics including aminoglycosides, fluoroquinolones, trimethoprim, and tetracylines.[65] Such organisms have constitutive AmpC production and as a result typically are resistant to penicillins, including those used in combination with β-lactamase inhibitors, as well as first-, second- and third-generation cephalosporins.[65] Some, but not all, also are resistant to monobactams. Carbapenems are not well degraded by AmpC and remain a therapeutic option, although isolates with mutation in outer membrane porins can be resistant.[65] Newer agents, specifically ceftolozane and tazobactam, have been developed that retain activity against organisms with AmpC enzymes even with changes in porin permeability or efflux pumps.[66]

The prototypic Ambler class D β-lactamase is the OXA family, so designated because of higher rate of hydrolysis of oxacillin compared with benzylpenicillin.[67] Some OXA enzymes exhibit carbapenemase activity, although this activity may not confer resistance in vivo.[67] Most OXA enzymes are resistant to β-lactamase inhibitors, although avibactam has demonstrated activity against

OXA-48.[68,69] Plasmid-encoded ESBL OXA enzymes have been found in *P. aeruginosa*.[70] However, the most clinically important OXA-carbapenemase–producing organism are *Acinetobacter* organisms.[71] In *Acinetobacter*, OXA-carbapenemases can be encoded chromosomally or on plasmids. Such *Acinetobacter* organisms are resistant to penicillins, first-, second-, and third-generation cephalosporins, cefepime, and carbapenems. These isolates also are resistant to aminoglycosides and fluoroquinolones.[71] Since the mid-2000s, OXA-carbapenemase–producing *Acinetobacter* has spread globally and has caused nosocomial outbreaks in numerous facilities.[71]

The most clinically relevant β-lactamase among GPOs is Ambler class A penicillinase- producing *S. aureus*, rendering resistance to β-lactams. Semisynthetic penicillins such as methicillin, oxacillin, nafcillin, and others were developed that were poorly hydrolyzed by the *S. aureus* penicillinase, thus maintaining clinical activity. Resistance soon developed in *S. aureus* to penicillinase-stable penicillins as a result of alteration at the specific PBP2 target site. This modified PBP, designated PBP2a, has low affinity for almost all β-lactam antimicrobial agents, with the exception of ceftaroline.[72] PBP2a is primarily encoded by the *mecA* gene, and strains that contain *mecA* are designated as MRSA. Healthcare-associated MRSA (HA-MRSA) arose and frequently was resistant to other agents, including aminoglycosides, macrolides, and fluoroquinolones.[72,73] In the late 1990s, community-associated MRSA (CA-MRSA) appeared, differing from HA-MRSA. CA-MRSA strains, although resistant to β-lactams and containing *mecA*, frequently remain susceptible to other classes of antibiotics.[74] The *mecA* encoding region, called the staphylococcal chromosomal cassette (SCC) *mec* type IVa, in CA-MRSA tends to be much smaller than the SCC most commonly encountered in HA-MRSA and does not contain genes for resistance to other agents.[75] The distinction between HA-MRSA and CA-MRSA has become less clear and less relevant because "CA-MRSA" is now found routinely in the healthcare setting.[76] Newer mechanisms of methicillin resistance, such as those encoded by a *mecA* homologue, *mecC*, will be important to observe because they may not be detected by current targeted methods (*mecA* polymerase chain reaction [PCR], PBP 2a detection).[77]

With the redefining in 2008 of penicillin resistance for *S. pneumoniae* for nonmeningeal isolates from a penicillin MIC ≥2 to ≥8 μg/mL, and for meningeal isolates to penicillin MIC ≥0.12 μg/mL, restatement of the epidemiology of drug resistance among pneumococci is necessary.[78] Most isolates with penicillin MIC 2 to 4 μg/mL generally are susceptible to third-generation cephalosporins but frequently are resistant to other classes of antimicrobial agents, including macrolides, sulfonamides, and tetracycline.[79] Isolates with penicillin MIC ≥8.0 μg/mL frequently are resistant to third-generation cephalosporins.[80] Penicillin resistance is caused by alterations in PBP2x, 2b, and 1a that result in reduced binding of β-lactams coupled with increased production of branched-structure muropeptides.[81,82] Resistance is believed to be encoded by mosaic PBP genes that were transferred to *S. pneumoniae* from commensal respiratory tract streptococci by transformation and recombination.[32]

Penicillins, specifically ampicillin, are the drugs of choice for treating enterococcal infections,[72] but resistance to cell wall–active agents, β-lactams, and vancomycin is common, especially among isolates of *E. faecium*.[72] Intrinsically resistant to cephalosporins and aminoglycosides, enterococci have acquired resistance to both ampicillin and vancomycin.[83] β-Lactamase does not play a role in ampicillin resistance of *E. faecium*.[84] Alteration in PBP5 may be responsible for low-level ampicillin resistance, but assigning it a role in high-level resistance has proven problematic.[84]

β-Lactam resistance among *Haemophilus influenzae* organisms can be caused by β-lactamases or modification in PBP3, so-called β-lactamase negative ampicillin resistant (BLNAR) strains.[85–87] Infrequently, strains are identified that produce β-lactamase and also have altered PBP3.[87] Strains are resistant to ampicillin–β-lactamase inhibitor agents.[86,87] β-Lactamases of *H. influenzae* are Ambler type A, and the encoding genes are found on plasmids.[87] A survey of 6642 *H. influenzae* isolates collected globally identified 25% producing β-lactamase and 1% with altered PBP.[85] However, certain geographic “hot spots” (e.g., Japan and Spain) have higher rates of resistance because of PBPs.[86,88]

Colistin

Although it can be nephrotoxic, colistin use is re-emerging because of the increasing number of multidrug-resistant (MDR) gram-negative bacilli. Colistin has been used intravenously, or by aerosol in the case of *P. aeruginosa* exacerbations in cystic fibrosis.[89] However, colistin resistance is described, and some bacteria are intrinsically resistant to colistin, including all GPOs, all anaerobic bacteria, and selected gram-negative bacilli, including *Burkholderia cepacia* complex, *Morganella, Proteus, Providencia,* and *Serratia* spp.[90,91]

Colistin, a positively charged polypeptide of the polymyxin family, electrostatically interacts with the negatively charged lipid A component of lipopolysaccharide (LPS) in the outer membrane of GNOs. The drug also causes damage to the cytoplasmic membrane, thus resulting in permeability changes, leakage of cellular material, and ultimately cell lysis and death.[89]

Although reported, development of colistin resistance is uncommon, and transmission of resistance by extrachromosomal elements has not been recognized. Three main mechanisms of resistance are known: (1) LPS modifications that decrease the negative charge of LPS and therefore lower drug binding affinity, (2) overexpression of efflux pump systems, and (3) overproduction of capsular polysaccharide.[90] The 2-component regulatory systems PmrA-PmrB and PhoP-PhoQ are important in the development of colistin resistance, primarily by constitutively activating LPS-modifying genes.[91] Mutations in any of the first 3 genes of the lipid A biosynthesis pathway (*lpxA, lpxC,* and *lpxD*) have also been shown to confer colistin resistance in *A. baumannii.*[92] Efflux pump systems AcrAB and KpnEF and upregulation of capsule biosynthesis contribute to colistin resistance in *K. pneumoniae*.[91] Colistin heteroresistance has been described in *A. baumannii,* but the molecular mechanism and the clinical significance of these strains remain to be determined.[91,93]

Daptomycin

Daptomycin is an acidic cyclic lipopeptide antibiotic that acts in a calcium-dependent manner to disrupt the cell membrane potential and therefore its permeability. The exact mechanism of bacterial killing is unclear, but daptomycin appears to insert into phosphatidylglycerol-rich membrane at the cell division septum.[94]

Daptomycin also may act on a sensor kinase (YycG) localized at the cell septum, thus leading to rapid cell death without lysis by interfering with the YycF-YycG 2-component signal transduction cascade.[94] A clinical pair of *E. faecalis* isolates (before and after development of daptomycin resistance) was compared using whole genome sequencing, and 3 mutated genes were identified: (1) *cls*, (2) *gdpD*, and (3) *liaF*.[95] The first 2 genes are involved in phospholipid metabolism, and the third is a member of a 3-component regulatory system (LiaFSR) involved the stress-sensing response of the cell envelope to antibiotics.[96] Similarly, a clinical pair of susceptible and resistance *E. faecium* strains was genetically compared, and mutations in 8 genes were identified, including 2 genes involved with phospholipid metabolism and *yycG*.[97]

In *S. aureus*, daptomycin resistance appears to result from an increase in cell surface charge such that the positively charged drug is repelled from the cell surface.[96] Stepwise mutations in several genes (including *mprF*, *yycG*, *rpoB*, and *rpoC*) have been associated with decreased susceptibility to daptomycin, likely through effects on the cell wall or membrane.[98,99] Combined mutations, more so than single mutations, are associated with higher MICs. Although most vancomycin-intermediate *S. aureus* and all vancomycin-resistant *S. aureus* strains maintain daptomycin susceptibility, a correlation exists between thickness of the *S. aureus* cell wall and nonsusceptibility to daptomycin (see the later discussion of vancomycin).[100]

Glycopeptides

Glycopeptide antibiotics inhibit peptidoglycan synthesis in the cell walls of GPOs. Formerly, teicoplanin (primarily used outside of the US) and vancomycin were the only glycopeptide antibiotics. Now, lipoglycopeptides (dalbavancin, oritavancin, and telavancin) have been added to the antimicrobial armamentarium. Most of our knowledge of glycopeptide resistance comes from clinical and laboratory studies with vancomycin. Increased use of vancomycin (as oral therapy for *Clostridium difficile* colitis, as treatment for MRSA and penicillin-resistant *S. pneumoniae* infections, and the increase in glycopeptide use in animal husbandry) has been associated with increasing resistance among GPOs.[101]

Vancomycin binds to the D-Ala-D-Ala C-terminus of peptidoglycan precursors, thereby blocking their addition to the growing peptidoglycan chain and preventing the subsequent transglycosylation and transpeptidation steps of cell wall biosynthesis. Because vancomycin must penetrate the peptidoglycan to reach its target, and many D-Ala-D-Ala residues are present in the cell wall, vancomycin is a relatively inefficient drug at obtaining high concentrations around its real targets because drug molecules also become bound by false targets in the peptidoglycan.[102] This phenomenon contributes to slow bactericidal activity. Mechanisms of vancomycin resistance identified to date are target modification, removal of susceptible target, and decreased permeability secondary to cell wall changes.[27,103]

In enterococci, the *van* genes encode the resistance phenotype. Several *van* genes (*vanA, B, C, D, E, F, G, L, M, N)* have been described and are characterized by high MIC values of vancomycin and teicoplanin, transferability, genetic location in the bacterial host (chromosome versus transposon or plasmid), inducible or constitutive expression, and the modified target produced.[27,104] The most clinically relevant *van* genes remain *vanA* and *vanB* which confer high-level inducible resistance (MIC ≥64 μg/mL) in *E. faecium* and *E. faecalis.* The *vanA*-containing organisms are by far the most common in both Europe and the US. The *vanA* and *vanB* operons can be located on transposons, which are transferable by plasmids or large, mobile chromosomal elements.[27] The transferability of *vanA* and *vanB* genes is the basis for infection control measures to monitor and prevent the spread of vancomycin-resistant enterococci (VREs). The *vanA* and *vanB* genes encode ligase enzymes that change the acyl-D-Ala-D-Ala C-terminus of lipid II peptidoglycan precursors to acyl-D-Ala-D-Lac (lactate). This altered ligation results in the alteration of the binding site of vancomycin and thus ~1000-fold lower affinity for its target.[105] The enzymes are regulated in an operon by a 2-component sensor kinase and response regulator pair (VanR-VanS) that responds to environmental stimuli and mutations and is responsible for inducible and constitutive resistance phenotypes.[106]

Low-level resistance (MIC, 2–32 μg/mL), found in *Enterococcus gallinarum, E. casseliflavus,* and *E. flavescens,* is encoded by the *vanC* genes (*vanC1, vanC2, vanC3,* respectively). Substituting acyl-D-Ala-

D-Ala with acyl-D-Ala-D-Ser results in an approximately sixfold lower affinity of vancomycin for its peptidoglycan precursor target.[107] Unlike *vanA/B*, *vanC* genes are encoded chromosomally and are nontransferable. Therefore, *vanC*-containing species are not considered “true” VREs for infection control purposes.

Vancomycin resistance can occur in *S. aureus*, including vancomycin-resistant *S. aureus* (VRSA; MIC ≥16 μg/mL) and vancomycin-intermediate *S. aureus* (VISA; MIC, 4–8 μg/mL). First isolated in 2002, VRSA has been confirmed 13 times in the US.[108] All VRSA strains tested carry the *vanA* ligase gene, likely originating from a coinfecting or colonizing VRE. Risk factors of patients with VRSA infections include older age, compromised blood flow to lower limbs, chronic ulcers, a history of vancomycin therapy, and concomitant or previous isolation of MRSA or VRE, or both.[109,110] To date, VRSA has not been found in children.[111] VRSA strains have high MIC values and are detectable readily by routine antimicrobial susceptibility testing; VISA strains have lower MICs, are heterogeneous, and are more difficult to detect.

The mechanism of resistance for VISA strains appears to be a thickened cell wall; VISA isolates do not carry *van* genes.[104] VISA isolates typically have multiple metabolic mutations,[102,112] but the only strict correlation with the VISA phenotype is a thickened cell wall, as shown by electron microscopy.[113] This thickened cell wall, which acts to sequester or “clog” vancomycin in the peptidoglycan, is postulated to reduce susceptibility.[102,114] Some populations of *S. aureus* contain daughter cells that show increased vancomycin MICs of 1 to 4 μg/mL; this type is referred to as heteroresistant (or heterogeneous) VISA (hVISA). Although still “susceptible,” hVISA subpopulations can proliferate and become the dominant clone under the selective pressure of vancomycin use.[114] Stepwise mutations in certain loci (i.e., the 2-component systems GraR-GraS and VraR-VraS) can lead to an hVISA phenotype and then to a true VISA phenotype.[112] Compared with patients with MRSA bloodstream infections, patients with hVISA infections have been reported to have more days of bacteremia, higher rates of endocarditis and osteomyelitis, and higher rates of vancomycin treatment failure, but no difference in mortality rates.[115] The prevalence and clinical impact of the hVISA phenotype are still largely unknown because detecting hVISA can be difficult and is not routinely done by clinical laboratories.[112]

Certain GPOs are intrinsically resistant to vancomycin, including *Erysipelothrix*, *Leuconostoc, Pediococcus*, and *Lactobacillus*.[116] Although these organisms' peptidoglycan precursors end in D-Ala-D-Lac, their genomes do not appear to contain genes homologous to enterococcal *van* genes.[117] *Leuconostoc* D-Ala-D-Lac ligases appear to have evolved independently from the enterococcal *van* ligases, perhaps because of the abundance of lactate in the environment for these organisms.[117] The mechanism of vancomycin resistance in *Erysipelothrix* is unknown.

Like the glycopeptides, the lipoglycopeptides (dalbavancin, oritavancin, and telavancin) have a heptapeptide core, but these drugs have lipophilic side chains that provide additional antimicrobial activity when compared with vancomycin. In addition to inhibiting peptidoglycan synthesis, telavancin and oritavancin disrupt membrane integrity and increase permeability; oritavancin also inhibits RNA synthesis.[118] The *vanA* gene confers resistance to dalbavancin and telavancin, but not to oritavancin. All the lipoglycopeptides maintain activity against *vanB*-containing VRE. Additionally, all lipoglycopeptides have activity against VISA, but only oritavancin is active against VRSA.[118]

Isoniazid

Isoniazid (INH) inhibits a specific enzyme, InhA, in the synthetic pathway of mycolic acid, a key component of the cell wall of *M. tuberculosis*. To be active, INH must first be modified to its active form, a hydrazine derivative, by catalase produced by the organism.[119] Mutation in the catalase gene, *katG,* or genetic inactivation of the gene prevents formation of the hydrazine derivative and results in INH resistance. Approximately 42% to 58% of INH-resistant strains have alterations in *katG*.[119] Multiple mutations or stop mutations are associated with higher levels of resistance.[120] A second resistance mechanism, a specific mutation in the *inhA* regulatory region that causes overexpression of inhA, results in low-level INH resistance.[119] Up to 30% of INH-resistant *M. tuberculosis* isolates do not have mutations in *katG* or *inhA*.[121,122] Although mutations in *ndh* (reduced nicotinamide adenine dinucleotide [NADH] dehydrogenase), *kasA* (β-ketoacyl acyl-carrier-protein [ACP] synthase), and *ahpC* (alkyl hydroperoxide reductase and its promoter) have been described in INH-resistant strains, further validation of clinical relevance is needed.[119,123]

Macrolides and Related Compounds

Macrolides and related compounds act on the 50S ribosomal subunit by binding the peptidyltransferase region and stimulate the premature dissociation of peptidyl-tRNA from ribosomes. These antibiotics are primarily bacteriostatic because they inhibit protein synthesis and include macrolides, lincosamides, streptogramins, and ketolides. Resistance occurs by alteration of target, active efflux, and antibiotic inactivation.[124] Macrolide resistance can occur as selective resistance to the 14- and 15-membered macrolides (erythromycin, clarithromycin, azithromycin) but not to 16-membered macrolides (spiramycin, josamycin), lincosamides (clindamycin), or streptogramin B (M phenotype); or it can occur as resistance to all of the foregoing (MLS_B phenotype). M-type resistance generally confers low-level resistance among streptococci (MICs 1–32 μg/mL), whereas MLS_B resistance commonly confers high-level resistance (MICs >256 μg/mL). The bactericidal streptogramins (i.e., quinupristin-dalfopristin) and the bacteriostatic ketolides (i.e., telithromycin) have activity against MLS_B-resistant organisms.

MLS_B resistance is caused by methylation of the 23S rRNA, which blocks the ribosomal binding site (RBS) for macrolides, lincosamides, and streptogramin B. The methylase is encoded by *erm* (erythromycin ribosome methylase) genes and dimethylates adenine at position 2058, a process that prevents access to the target either directly or by conformational change.[124] The MLS_B phenotype can be constitutive or inducible (MLS_B-C or MLS_B-I, respectively). For MLS_B-I strains, *erm* mRNA is inactive in the absence of an inducing macrolide such as erythromycin. Through studies in *S. aureus,* the mechanism of inducibility has been shown to be stem-loop secondary structures in the 5′ *erm* mRNA regulatory region that sequester the RBS.[125] In the presence of low concentrations of erythromycin (the inducer), ribosomes stall in the *erm* regulatory region, with resulting dissociation of stem-loop structures that subsequently permits unmasking of the RBS, translation of the *erm* methylase, and the resistant phenotype. Numerous reports have noted failed clindamycin therapy for MLS_B-I infections, with postulated microbial conversion from the MLS_B-I to the MLS_B-C phenotype.[125,126] Target alteration by mutations in L4 or L22 ribosomal proteins of the 50S subunit also has been described. These mutations can impair passive transport through the nascent peptide exit tunnel of the ribosome and distort the erythromycin binding site.[127] In *Mycoplasma pneumoniae* and *N. gonorrhoeae,* macrolide resistance is caused by mutations in the 23S rRNA gene.[128,129]

M-type resistance is primarily associated with an active efflux system driven by proton motive force.[130] Chromosomally located macrolide efflux (*mef*) genes have been found in numerous bacterial genera, including *Streptococcus, Enterococcus, Staphylococcus, Granulicatella, Gemella, Neisseria,* and *Bacteroides* species,[131] and plasmid-encoded efflux genes (*msrA*) have been identified in *Staphylococcus* species.[132] In pneumococci, the *mef* gene is located on a transposon that can be transferred horizontally.[133] Highly resistant *S. pneumoniae* isolates that harbor both *erm* and *mef* resistance mechanisms are reported increasingly.[134]

Macrolide resistance secondary to drug inactivation rarely is found in clinical isolates and is found more commonly in macrolide-producing organisms as a survival mechanism.[135] *S. aureus* produces a phosphotransferase that inactivates macrolides but not lincosamides and is encoded by the *mphC* gene.[136] Nucleotidyltransferases encoded by *lnuA/linA* and *lnuB/linB* have been found in staphylococci and enterococci, thus resulting in inactivation of lincosamides, but not macrolides.[136]

Metronidazole

Metronidazole has bactericidal activity against a broad spectrum of anaerobic bacteria and selected protozoans. Metronidazole is a prodrug that is reduced in the cytoplasm by a nitroreductase enzyme; resulting toxic intermediates disrupt nucleic acid structure. This drug is particularly useful in treating mixed anaerobic infections in which *Bacteroides* or *Prevotella* spp. predominate and is a widely used therapy for *C. difficile* infection.[137,138] In a US survey of

Bacteroides, metronidazole resistance was found in <1% of isolates.[139]

Metronidazole resistance mechanisms have been best described in *Bacteroides* spp. Resistance results from activity of the enzyme nitroimidazole reductase, which catalyzes the conversion of 4- or 5-nitroimidazole to 4- or 5-aminoimidazole. The enzymatic modification prevents the formation of toxic drug intermediates, the active form of metronidazole.[140] This enzyme is encoded on the *nim* gene, has 7 variants described, and can be encoded chromosomally or on plasmids.[141] This gene has been found in *Bacteroides, Helicobacter,* and *Prevotella*.[142,143]

Clinical resistance to metronidazole among *C. difficile* and *Helicobacter pylori* is well documented, although demonstration in vitro and understanding of the mechanism have proved difficult.[144,145] Emerging data suggest that efflux pumps also may play a role in metronidazole resistance among *Helicobacter* organisms.[145] Heteroresistance to metronidazole was described in 1 study in approximately 6% of *C. difficile* isolates directly isolated from clinical specimens.[144] This phenotype, however, is unstable. The mechanism of metronidazole resistance or clinical failure for *C. difficile* currently is unknown. *C. difficile* does not harbor *nim*.[144,146]

Oxazolidinones

Linezolid and the more recently FDA-approved tedizolid belong to the oxazolidinone class of antimicrobial agents. The oxazolidinones bind to the 50S ribosomal subunit and prevent the formation of a functional 70S-initiation complex, which is essential to bacterial protein translation. Even with increasing use, oxazolidinone resistance is uncommon. Worldwide surveillance data from 2004 to 2013 indicate that the incidence of linezolid resistance is 0.7% to 1.2% for vancomycin-resistant enterococci, <0.1% to 0.3% for vancomycin-susceptible enterococci, and <0.1% for *S. aureus*.[147] US and European surveillance data show that, based on MIC_{90} values, tedizolid is fourfold more potent than linezolid against gram-positive isolates, including MRSA and VRE; 99.8% of isolates tested were susceptible.[148]

The primary mechanism of oxazolidinone resistance is specific nucleotide substitutions in the 23S rRNA binding site, although mutations also have been described in ribosomal proteins L3 and

L4.[149] Chromosomal mutations usually occur after prolonged linezolid exposure,[150] but they have been described in linezolid-naïve patients.[151] A clear association exists between the number of 23S rRNAs that are mutated and MIC values,[152,153] as well as possibly between the number of mutated 23S rRNAs and length of linezolid exposure.[154] Linezolid resistance also can be secondary to acquisition of the plasmid-encoded *cfr* gene encoding a 23S rRNA methyltransferase, which alters the target site and confers resistance to other antibiotics but does not appear to cause tedizolid resistance.[149,155] A plasmid-encoded ABC (adenosine triphosphate–binding cassette) transporter gene (*optrA*) was found to be associated with oxazolidinone and phenicol resistance in a clinical isolate of *E. faecalis*.[156]

Quinolones

Ciprofloxacin reportedly is the most consumed antibacterial agent worldwide,[157,158] and it also has widespread use in animals. Multiple resistance mechanisms exist: mutations in target enzymes, changes in intracellular drug concentrations by altered entry and efflux, modification of the drug by bacterial enzymes, and inhibition protection of target enzymes. Quinolones and subsequent derivatives such as the fluoroquinolones act by binding to enzymes that are essential for bacterial replication, transcription, recombination, and DNA repair: DNA gyrase and topoisomerase IV.[159] These enzymes make dsDNA breaks in the chromosome and introduce negative DNA supercoils to allow subsequent activities such as replication. Quinolones trap and release this dsDNA break intermediately, thus resulting in activation of the stress (SOS) response and ultimately cell death.

Gyrase and topoisomerase IV have 2 pairs of subunits (A and B). The primary quinolone target appears to be gyrase A (*gyrA*) in GNOs and topoisomerase IV subunit A (*parC*) in GPOs.[158] A first-step *gyrA* mutation results in low-level resistance to fluoroquinolones. When a second mutation occurs either in *gyrA* or in another quinolone target such as *parC,* high-level resistance to the fluoroquinolones occurs. The same phenomenon has been demonstrated in GPOs, with the first-step mutation generally occurring in *parC.*

Once the primary mutation occurs in either *gyrA* or *parC* (and, more rarely, the B subunit genes, *gyrB* or *parE*), additional mechanisms of resistance can contribute to high-level fluoroquinolone resistance other than secondary mutations in gyrase and topoisomerase IV genes. These mechanisms include altered permeability and efflux. Altered permeability in the absence of other mutations causes low-level resistance and contributes to quinolone resistance in GNOs,[160] and it is mediated by decreased expression of outer membrane porins or alterations in LPS composition that decrease drug entry into cells.[158] Additionally, resistance can arise from increased efflux. Given their nonspecific nature, many of the efflux pumps require overexpression to result in the quinolone-resistant phenotype.

All the foregoing quinolone resistance mechanisms are chromosomally encoded, indicating that quinolone resistance is spread by clonal expansion. Although gyrase and topoisomerase gene mutations are the main mechanisms of quinolone resistance, multiple resistance mechanisms encoded on plasmids can contribute.[161] The Qnr determinant is located on a plasmid-encoded integron, first described in *K. pneumoniae* and subsequently in *E. coli* and *Enterobacter cloacae*.[159,162–164] The Qnr protein binds and protects DNA gyrase and topoisomerase IV from inhibition by ciprofloxacin.[163] As in first-step *gyrA* mutations, Qnr causes low-level resistance only in the absence of other resistance mechanisms. Commonly, *qnr*-containing plasmids also encode for an AmpC or ESBL.[165,166]

Rifampin

Rifampin targets the β-subunit of bacterial DNA-dependent RNA polymerase encoded by the gene *rpoB*. Point mutations in *rpoB* can result in amino acid substitutions, decreased binding, and resistance.[167] Because point mutations can result in high-level resistance, rifampin is rarely used alone, to prevent emergence of resistance. Mutations in *rpoB* have been detected in a variety of bacteria, notably in *S. aureus*,[168] *N. meningitidis*,[169] and *M. tuberculosis*.[167] In *M. tuberculosis*, most rifampin-resistant mutations occur in the 81-base pair rifampin-resistance determining region (RRDR) of *rpoB*. Sequencing the RRDR resulted in 97.1% sensitivity and 93.6% specificity when compared with routine antituberculosis drug susceptibility testing.[170] Three mutations (*Ser531Leu*, *His526Tyr*, and *Asp516Val*) accounted for 75% of the rifampin resistant isolates.[170] Other mechanisms of resistance to rifampin including rifampin modifying enzymes and efflux pumps are found in environmental GPOs such as *Nocardia* and *Mycobacterium* and in gram-negative bacilli such as *S. maltophilia* and *Burkholderia cenocepacia.* Clinical significance of these mechanisms compared with *rpoB* mutations is minor.[171] Although further investigation is required, efflux pumps have also been described that may be responsible for low-level rifampin resistance in *M. tuberculosis*.[172]

Tetracyclines

Tetracyclines have been in use since the 1950s for the broad-spectrum treatment of infections with GNOs and GPOs, including intracellular pathogens such as *Chlamydia, Rickettsia,* and *Mycoplasma.* Widespread use of tetracyclines since the 1950s as therapeutic agents in adults, as a growth promoter in both animals and plants, and as longterm subtherapeutic treatment of noninfectious conditions has led to substantial resistance.[173] Tetracycline resistance mechanisms have been identified in >75 bacterial genera.[174,175] Doxycycline, minocycline, and a minocycline-derived glycylcycline, tigecycline, are used most frequently.[176] Tigecycline has the same mode of action as other tetracyclines, but it is active in the presence of tetracycline resistance genes as a result of steric hindrance introduced by an additional side chain.[177] Expression of resistance-nodulation-division (RND)-type efflux pumps leads to intrinsic resistance to tigecycline in *Pseudomonas* and *Proteus* spp.[178]

Tetracyclines are bacteriostatic, reversibly inhibiting protein synthesis by binding to the 30S ribosome and preventing elongation by inhibiting tRNA association. Intrinsic resistance typically is mediated by dysregulation of transcription that affects both influx and efflux of the drug.[179] Acquired resistance is most commonly caused by the acquisition of genes that encode tetracycline-specific efflux pumps and ribosomal protection proteins. These genes often are located on mobile elements, including plasmids, transposons, and integrons.[173] Most of the efflux genes are found only in GNOs, but 2 (*tetK* and *tetL*) are found primarily in GPOs. All these genes except *tetB* confer resistance to tetracycline and doxycycline; *tetB*-containing isolates also are resistant to minocycline, but not to tigecycline. However, in vitro mutations in *tetA* and *tetB* have been produced that result in tigecycline resistance.[180] The genes that encode ribosomal protection proteins confer resistance to tetracycline, doxycycline, and minocycline, with *TetO* and *TetM* the most widely distributed determinants. Bearing sequence similarity to translation elongation factors, ribosomal protection proteins appear to be ribosome-binding guanosine triphosphatases that dislodge tetracycline from the ribosome.[175,181,182] The ribosomal protection proteins are found in a variety of bacteria, including GPOs, nonenteric GNOs, and anaerobic bacteria, and they often are linked to other resistance genes, such as *erm*.[173,181]

Trimethoprim-Sulfamethoxazole

Although no longer recommended for treatment of otitis media,[183,184] trimethoprim-sulfamethoxazole (TMP-SMX) has broad use, such as for treatment of skin and soft tissue infection with CA-MRSA.[185]

TMP-SMX acts by inhibiting 2 steps in bacterial folic acid synthesis. Sulfamethoxazole inhibits dihydropteroate synthetase and blocks the formation of dihydrofolate, whereas trimethoprim inhibits dihydrofolate reductase (DHFR) and blocks the formation of tetrahydrofolate. Bacteria can develop resistance to either component of TMP-SMX. Intrinsic resistance is recognized in *Bacteroides, Neisseria,* and *Clostridium* species as a result of poor TMP binding to DHFR molecules.[186] Additionally, organisms such as *Enterococcus* and *Lactobacillus* are capable of using extracellular folate and thus bypassing the targeted pathway.[187] Acquired TMP resistance can be secondary to overproduction of DHFR caused by a mutation in the promoter region controlling its synthesis or by mutations in the *dhfr* gene that result in decreased binding.[186] In *S. pneumoniae,* mutation in the *dhfr* gene resulting in reduced TMP binding plays a central role in TMP-SMX resistance; resistance can be transferred to other strains of pneumococci by transformation.[188] Resistance to SMX is caused by alteration in its target, dihydropteroate synthetase, through point mutation or acquisition of extrachromosomal elements.[186]

Detection of Antimicrobial Resistance

Antimicrobial resistance can be detected using techniques that rely on either phenotypic characteristics of an organism or detection of genetic changes (i.e., gene acquisition or mutation) that predict resistance. Phenotypic antimicrobial susceptibility testing in vitro predicts clinical resistance (i.e., identifying antimicrobial agents that will be ineffective) more accurately than it does therapeutic effectiveness (in vitro susceptibility).[189] Besides intrinsic antimicrobial activity, therapeutic effectiveness depends on multiple factors, such as the following: the site of infection, penetration of the agent, and local environmental conditions such as pH and oxygen tension; the mode of growth of the organism (planktonic vs. biofilm); the pharmacokinetics of the agent and the dosing regimen used; the immune status of the patient; and adherence to the antimicrobial regimen.[189]

Establishment of Breakpoints

Three types of breakpoints (or cutoffs) are used to describe the susceptibility of a specific organism against a specific drug. These data are analyzed and published by 3 major groups: the FDA, the Clinical and Laboratory Standards Institute (CLSI), and the European Committee on Antimicrobial Susceptibility Testing (EUCAST). These organizations do not have complete harmonization of choices for breakpoints. First, the microbiologic breakpoint (also called wild-type breakpoint or epidemiologic cutoff) is determined by comparing the MIC of a specific drug for bacterial isolates with no known resistance to the MICs obtained for organisms with known resistance mechanisms.[190] A bimodal distribution pattern is generally observed in which the drug is highly active (low MICs) against the “susceptible” organisms and has poor activity (high MICs) against the “resistant” organisms. Some antimicrobial agents lack a clear bimodal distribution (e.g., polymyxins); newly developed drugs may not have a testable resistant population to permit characterization (e.g., daptomycin). Second, the clinical breakpoint is determined by assessing the MICs for strains that are likely to be treated with the agent with clinical success versus strains associated with clinical failure. These data are generated by prospective human clinical trials.[190] Third, the pharmacokinetic and pharmacodynamic (PK/PD) breakpoint of a particular drug (usually in serum, but occasionally in other body compartments such as the central nervous system or urinary tract) is determined by mathematically extrapolating animal model data to humans.[190] Ideally, the published breakpoint that is used by clinical laboratories is set using a combination of the 3 types of breakpoint data described earlier. Susceptibility testing should not be performed when susceptibility (penicillin for *Streptococcus pyogenes*) or resistance (vancomycin for Enterobacteriaceae) is predictable. Susceptibility testing also should not be performed when in vitro activity is known not to correlate with therapeutic efficacy (cephalosporins for *Listeria monocytogenes*).[191]

Methods of Susceptibility Testing

The reference method or gold standard for phenotypic susceptibility testing is MIC determination (see Chapter 286). Depending on the organism, testing can be done by either broth microdilution or agar dilution.[191] Automated commercial test systems, such as Vitek (bioMérieux, Durham, NC), Phoenix (BD Bioscience, Sparks, Md), and MicroScan (Beckman Coulter, Brea, Calif), which employ modification of these methods, are used widely. These systems are fast, mechanically reliable, and highly reproducible; they offer significant cost efficiencies (including interfacing with clinical information systems) and combine susceptibility testing and organism identification in a single system. Automated susceptibility testing, however, is not as accurate as reference methods, particularly for detecting inducible resistance and other emerging resistance.[192] Software changes are introduced to address problems, but organisms evolve to develop resistance faster than changes can be developed and validated. Perpetually, systems may be a step behind. For example, in mid-2010, the CLSI lowered carbapenem susceptibility breakpoints for meropenem and imipenem fourfold (from ≤4 μg/mL to ≤1 μg/mL) because some carbapenemase-producing Enterobacteriaceae organisms have carbapenem MICs as low as 0.125 μg/mL.[193] However, because the automated susceptibility systems are diagnostic devices regulated by the FDA, susceptibility test system manufacturers must perform a complex validation process before breakpoints can be changed on their systems, assuming that they even have dilutions appropriate for the new breakpoints.

In addition to microdilution methods, used by approximately 80% of laboratories in the US, disk diffusion susceptibility is used by approximately 15% of laboratories.[192] Antimicrobial-containing disks are applied to a lawn of bacteria inoculated on a standard medium, and after 16 to 24 hours of incubation, zones of inhibition are measured (Fig. 290.1A). Zones of inhibition correlate reasonably well with specific MIC values. Breakpoints for susceptible, intermediate, or resistant have been previously determined for each antibiotic disk based on zone size. Disk diffusion consistently is more accurate than automated commercial systems compared with reference methods,[192] is more flexible for choosing drugs for testing, and may better detect emerging resistance problems.[192] Disadvantages of disk diffusion testing are its labor intensiveness, lower reproducibility because of manual measurement of inhibition zones, lack of breakpoints for all clinically relevant bacteria, and proneness to clerical errors because of manual entry of results into clinical information systems.

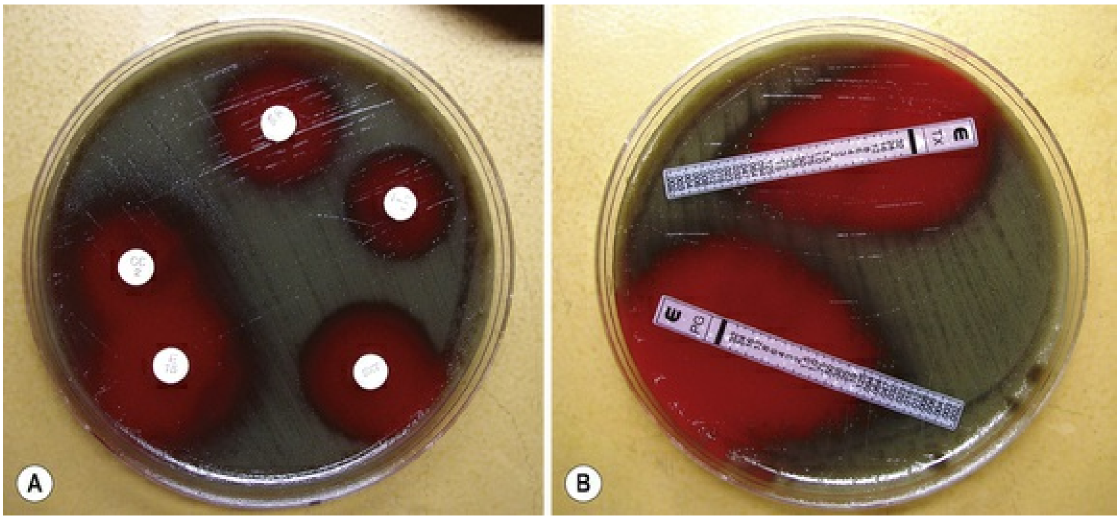

FIGURE 290.1 **Routine susceptibility testing of *Streptococcus pneumoniae.* (A) Kirby-Bauer disk diffusion. Disks, counterclockwise from top: vancomycin, levofloxacin, trimethoprim-sulfamethoxazole, erythromycin, and clindamycin. (B) Minimal inhibitory concentration (MIC) determination by Etest (bioMérieux, Durham NC). This isolate was susceptible to all antimicrobial agents tested, with ceftriaxone**

(TX) and penicillin (PG) MICs of 0.064 μg/mL.

Etest (bioMérieux) is performed in a manner similar to disk diffusion, but instead of a disk being placed on a lawn of bacteria, a plastic strip impregnated with a gradient of a specific antimicrobial agent is tested.[194] After appropriate incubation, the MIC is read where the elliptical zone of inhibition of growth meets the strip (Fig. 290.1B). Although not as highly standardized as disk diffusion, Etests are particularly useful and accurate compared with reference MIC methods for determining antimicrobial susceptibility for organisms that are fastidious or do not have disk diffusion breakpoints[195] (see Fig. 290.1B). Some agent-organism combinations do not have good correlation between Etest and broth microdilution. Two prominent examples are vancomycin and ceftriaxone for *S. aureus,* in which Etest MICs are significantly higher than MICs determined by broth microdilution.[196,197]

Screening for High-Level Aminoglycoside Resistance

All enterococci demonstrate low-level resistance to aminoglycosides but can acquire high-level resistance primarily through production of aminoglycoside-modifying enzymes.[44] Unlike strains with low-level intrinsic resistance, strains with high-level aminoglycoside resistance do not show synergistic inhibition with cell wall–active agents.[44] Standard susceptibility testing cannot differentiate intrinsic low-level resistance from acquired high-level resistance. Disks containing high concentrations of gentamicin (500 μg/mL) and streptomycin (2000 μg/mL) are highly accurate in detecting high-level resistance compared with reference MIC methods. High-level gentamicin resistance of *Enterococcus* also predicts high-level resistance to tobramycin and amikacin.

Molecular Methods

Molecular methods have been replacing traditional methods in the clinical microbiology laboratory, particularly when a specific pathogen or resistance gene is sought. The molecular detection of clinically relevant resistance can be accomplished using probe hybridization, nucleic acid amplification tests (NAATs) such as PCR, and DNA sequencing.

Probe detection occurs by hybridization, or annealing, of a labeled probe to a target sequence. The target sequence is released from organisms during lysis, which is followed by hybridization in either a liquid or solid phase. The probe acts to capture the target sequence of interest from a milieu of sequences. The use of solid-phase hybridization on nitrocellulose (i.e., line probe assays) allows for the detection of multiple sequences or polymorphisms from a single preparation. The most commonly used NAAT is real-time PCR (rt-PCR), which uses sequence-specific primers and probes to detect genes of interest. Incorporation of the probe detection in the same reaction vessel as the amplification process allows for less contamination, faster turnaround time, and greater sensitivity and specificity compared with traditional NAAT detection platforms. Probes can be designed to allow for the detection of resistance related to acquired genes, as well as intrinsic gene polymorphisms.[198]

DNA sequencing can be used to detect resistance mechanisms that rely on intrinsic gene mutations and demonstrate a strict genotype-phenotype correlation. Sequencing and subsequent mutation analysis have long been applied to the detection of antiviral resistance in HIV and, more recently, cytomegalovirus. The use of sequencing for the detection of antimicrobial resistance in bacteria is confined largely to research and public health applications. Sequence-based resistance detection in *M. tuberculosis*, for example, detects mutations for rifampin and INH resistance with 97% and 91% sensitivity, respectively, and for ethambutol, pyrazinamide, fluoroquinolone, kanamycin, capreomycin, and amikacin resistance with varying sensitivities.[170]

The interpretation of molecular detection of antimicrobial resistance results can be complicated when (1) the resistance mechanism is multifactorial, (2) the genotype-phenotype resistance relationship is clinically uncertain, (3) the infection is polyclonal,; or (4) synergy exists among multiple resistance phenotypes. Use of molecular resistance detection should be limited to organisms and infections in which the results can be interpreted with confidence for clinical treatment or infection control practices.

Special Considerations

Detection of Extended-Spectrum β-Lactamases

The increasing presence of ESBLs in Enterobacteriaceae has led to changes in the detection of resistance to cephems. In 2010, the CLSI lowered cephalosporin breakpoints.[193] Implementation of these lower breakpoints precludes the need for confirmatory testing because ESBL-producing organisms are interpreted as resistant. This also allows for individual drugs to be reported as tested, as opposed to modifying susceptibility reports based on the results of a phenotypic ESBL test. However, some automated susceptibility testing systems cannot accommodate these lower breakpoints because the concentration of drug tested is not low enough for some of the cephalosporins. Confirmatory testing is warranted if the revised breakpoints cannot be implemented.

Both phenotypic and molecular methods can be used to detect ESBLs.[54,120,191] A widely used, highly accurate phenotypic method employs combination disks containing clavulanic acid with either ceftazidime or cefotaxime, versus the cephalosporins alone. If the zone size of inhibition around the combination disk is ≥5 mm around the cephalosporin alone, the isolate is considered to be ESBL producing (Fig. 290.2).[54,191] Other phenotypic approaches include Etest and MIC tests that detect threefold or greater lowering by clavulanic acid of MIC of the extended-spectrum cephalosporin. Most automated susceptibility testing systems also include a screen for ESBL production, with acceptable sensitivity and specificity. Chromogenic agars can identify possible ESBL-producing isolates for further confirmation, with reported sensitivities of 95% to 97% and specificities of 94% to 95%.[199,200] Molecular methods for the detection of ESBLs are often limited to select targets, but they have been shown to be accurate when included in broad multiplex assays including those used to detect resistance directly from positive blood cultures.[201–203]

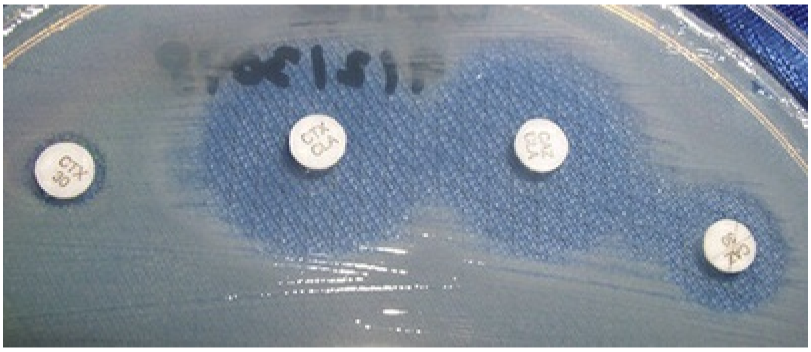

FIGURE 290.2 **Disk diffusion testing for extended spectrum β-lactamase (ESBL) production in *Klebsiella.* Disks, from left to right: CTX (cefotaxime), CTX CLA (cefotaxime and clavulanic acid), CAZ CLA (ceftazidime and clavulanic acid), and CAZ (ceftazidime). Inhibition zones are measured, and an increase of 5 mm in the clavulanic acid–containing disk relative to the corresponding cephalosporin alone indicates production of an ESBL. This isolate produces an ESBL.**

Detection of Carbapenem Resistance

Carbapenemase production in Enterobacteriaceae is signaled by decreased susceptibility, although not necessarily resistance, to carbapenems (e.g., MIC ≥2 μg/mL). The CLSI lowered carbapenem breakpoints to detect carbapenem resistance more accurately without the need for confirmatory tests. If these lowered breakpoints have not been adopted, laboratories should screen Enterobacteriaceae with an MIC ≥2 μg/mL of ertapenem, imipenem, or meropenem for carbepenemase production. Testing then can be performed using either the modified Hodge test[191,204] or the Carba NP (Carbapenemase Nordmann-Poirel) test.[205,206] If 2017 CLSI susceptibility breakpoint of ≤1 μg/mL is adopted, further testing of susceptible isolates need not be performed (see Table 286.7 and text). In the modified Hodge test, ertapenem and meropenem disks are placed on a lawn of a susceptible control strain of *E. coli*. A loopful of test organism (an isolate with increased carbapenem MIC) is inoculated in a straight line out from the edge of the disk (Fig. 290.3). After incubation, enhanced growth of the control *E. coli* strain at the intersection of the test streak and the carbapenem zone of inhibition indicates carbapenemase production by the test organism. In the Carba NP test, the organism is inoculated into a phenol red based buffer with or without imipenem. Hydrolysis of the imipenem by the organism leads to a color change from red to orange or yellow. When carbapenemase is detected, resistance is reported for all carbapenems regardless of MICs. Chromogenic agars have been developed for the detection of carbapenem-resistant Enterobacteriaceae. Compared with PCR, sensitivity and specificity of CHROMagar (Becton Dickinson, Franklin Lakes, NJ) KPC were 100% and 98%, respectively,[207] and positive and negative predictive values were calculated as 100% and 99%, respectively.[208] Chromogenic agars may be most beneficial for rectal surveillance cultures, but they can require broth enrichment for optimal sensitivity.[209]

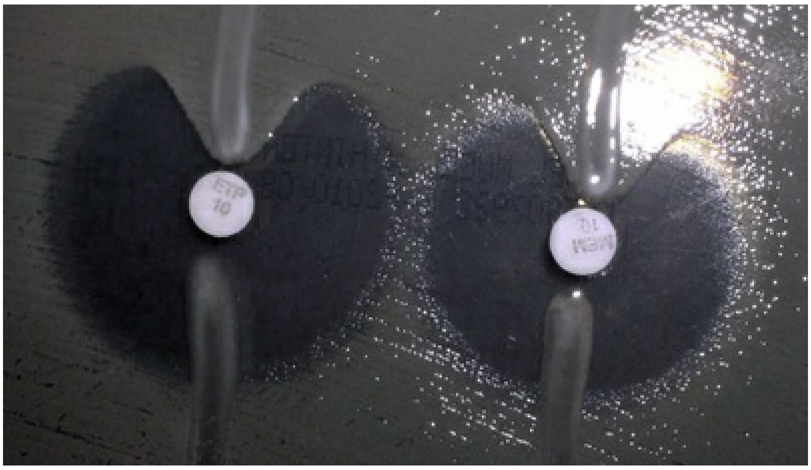

FIGURE 290.3 **Modified Hodge test for the detection of carbapenemase-producing Enterobacteriaceae. A lawn of *Escherichia coli* ATCC 25922 is spread on Mueller-Hinton agar, and 2 disks (10 μg ertapenem [ETP] and 10 μg meropenem [MEM]) are placed in the center of the agar a minimum of 30 mm apart. Test organisms are struck away from the disk, with each streak being a minimum of 25 mm. The test organism struck at the top permits growth enhancement of the sensitive *E. coli* strain; this indicates production of carbapenemase. No growth enhancement is seen with the test organism struck at the bottom, thus indicating no production of carbapenemase.**

Detection of Methicillin and Oxacillin Resistance

Several approaches can be used to detect β-lactam resistance resulting from altered PBPs in *S. aureus.* The gold standard for detection is PCR to detect the *mecA* gene or latex agglutination to detect its gene product, PBP2a. For routine susceptibility testing, cefoxitin disk testing is preferred over oxacillin disk testing because the clarity of cefoxitin zone of inhibition is superior.[210] Agar that contains 6 μg/mL of oxacillin supplemented with 4% sodium chloride also can be used for oxacillin resistance screening. All phenotypic methods compare favorably with molecular techniques.[211]

Both molecular and screening culture techniques have been developed for the detection of MRSA carriage. Several commercially available selective and differential chromogenic agars offer MRSA-positive results in 24 to 48 hours directly from clinical specimens and have performance characteristics similar to those of PCR.[212] Reportedly, broth enrichment before chromogenic agar culture improves the sensitivity of culture,[213] but it also increases the time to result. Because MRSA colonization often is associated with low bacterial counts, broth enrichment and molecular methods can provide optimal sensitivity.[213]

Conventional and rt-PCR can detect *mecA* in bacterial isolates and directly on patients' specimens. However, direct specimen testing has limitations, often including a lower positive predictive value than that of culture-based assays.[214–217] The emergence of *mecC*-mediated resistance may require new strategies for detection of MRSA. Additionally, several commercial assays are available for the detection of MRSA directly from positive blood cultures. These assays vary widely in terms of time to result, as well as the inclusion of nonstaphylococcal targets, but have widespread use in the clinical laboratory.

Detection of Vancomycin Resistance

Molecular and phenotypic methods are available to detect vancomycin resistance in *Enterococcus* spp. and *S. aureus*. Routine susceptibility testing and isolate screening using brain-heart infusion agar containing 6 μg/mL of vancomycin will detect vancomycin resistance in *S. aureus* and *Enterococcus* spp.[191] However, the brain-heart infusion agar screening plate does not reliably detect VISA strains.[191] Etest and microbroth dilution MICs can be used for detection of VISA and VRSA, but disk diffusion should not be used because it cannot differentiate high-level from low-level resistance accurately and can miss VISA.[112,191]

FDA-cleared assays are available for the detection of VRE rectal colonization for infection control purposes and for the detection of

VRE from positive blood cultures. Two main advantages of molecular detection of VRE rectal colonization are as follows: (1) amplification technology reportedly increases VRE detection to up to 120% and thereby permits better infection control; and (2) intrinsically resistant enterococci are excluded, thus mitigating unnecessary contact precautions and cost.[198] Detection of VRE from positive blood culture bottles allows for earlier detection and therefore appropriate treatment.[218] A current list of FDA-cleared assays can be found on the FDA website (http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedur The assays available for rectal screening detect either *vanR* or *vanA*. Because these genes rarely are found in nonenterococcal species, many assays do not incorporate an *Enterococcus*-specific target. The assays used for the detection of VRE from positive blood cultures include enterococcal-specific targets to provide species-level identification as well as detection of *vanA*.

Detection of Inducible Clindamycin Resistance

MLS_B-I organisms test as resistant to erythromycin, but they appear to be susceptible to clindamycin by routine disk diffusion and MIC testing. The D-test detects inducible resistance to clindamycin in the presence of erythromycin. Erythromycin and clindamycin disks are placed within close proximity (15–26 mm for staphylococci and 12 mm for streptococci) on agar seeded with the clinical isolate.[191] If inducible resistance is present, the clindamycin inhibition zone closest to erythromycin will flatten, resembling a “D” (Fig. 290.4). Some automated susceptibility testing systems screen for inducible clindamycin resistance by comparing the susceptibility results from a well containing clindamycin alone with a well containing both clindamycin and erythromycin. The Vitek 2 inducible resistance screen has lower sensitivity (80%–93%) than the D-test.[219,220] The CLSI recommends that laboratories screen for inducible clindamycin resistance on all β-hemolytic streptococci and staphylococci.[191] Although the clinical relevance of the detection of inducible resistance in the setting of a patient not receiving erythromycin is debatable in theory, in practice several reports have noted failed clindamycin therapy for infection with an MLS_B-I organism.[126]

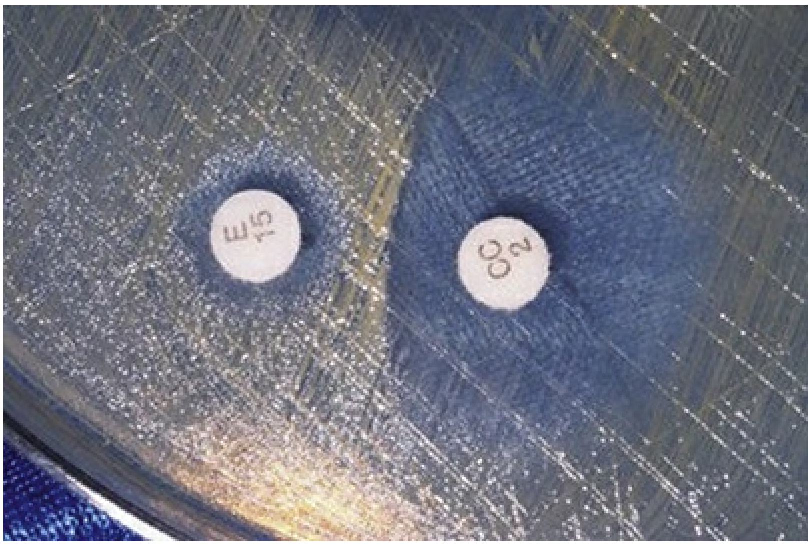

FIGURE 290.4 **D-test for the detection of inducible clindamycin resistance in *Staphylococcus aureus.* The CC 2 disk on the right contains 2 µg of clindamycin; the E 15 disk on the left contains 15 µg of erythromycin. Disks are placed 15 to 26 mm apart, and a flattening of the clindamycin zone proximal to the erythromycin disk is observed, indicating inducible resistance to clindamycin.**

Detection of Isoniazid and Rifampin Resistance in *Mycobacterium tuberculosis*

Molecular detection of resistance in *M. tuberculosis* is particularly attractive because of the organism's slow growth rate and the emergence of MDR *M. tuberculosis* (resistant to both rifampin and INH with or without resistance to other first-line drugs) and extensively drug resistant *M. tuberculosis* (MDR *M. tuberculosis* that is also resistant to fluoroquinolones and 1 of the injectable agents, capreomycin, amikacin, or kanamycin). The reference method, agar proportion testing, is slow and labor intensive. In most clinical laboratories, agar proportion testing has been superseded by automated broth susceptibility testing, which is faster, more convenient, and has similar accuracy.[221] Although faster, automated broth methods still require days to weeks to complete.

The World Health Organization recommends that the Xpert MTB/RIF test (Cepheid, Sunnyvale, Calif) be used globally in the fight to reduce the spread of MDR and extensively drug-resistant tuberculosis (http://www.who.int/tb/laboratory/xpert_launchupdate/en/). Using an automated system, Xpert MTB/RIF can detect *M. tuberculosis* complex DNA and screen for rifampin resistance directly from pulmonary specimens in <2 hours.[222] Five probes that hybridize to the RRDR region of *rpoB* are used to detect rifampin resistance. If at least 1 probe does not produce a signal (indicating a mutation at the hybridization site) or if ≥3.5 cycle difference exists between probe signals (indicating less efficient hybridization as a result of mutation), then a positive result for rifampin resistance is reported. Compared with traditional susceptibility testing, Xpert showed 97.6% sensitivity and 98.1% specificity; however, this study took place in countries with a higher prevalence of tuberculosis and MDR tuberculosis than the US (Peru, Azerbaijan, South Africa, and India).[222] In the US and other areas of low prevalence, the positive predictive value is likely to be lower. A positive rifampin resistance result by Xpert will be obtained even for synonymous (i.e., silent) mutations[223]; therefore, it is critical that molecular rifampin resistance results be confirmed by traditional susceptibility testing. Molecular confirmation of results can also be obtained through the Molecular Detection of Drug Resistance (MDDR) service of the Centers for Disease Control and Prevention (CDC) (http://www.cdc.gov/tb/topic/laboratory/guide.htm). The CDC has published recommendations for interpretation of rifampin resistance molecular results obtained by the Xpert MTB/RIF test.[224]

Two commercially available assays that are CE–marked for clinical use in Europe use a combination of NAAT and a probe-based line blot for the detection of resistance in *M. tuberculosis.* The INNO-LiPA Rif.TB kit (Fujirebio, Ghent, Belgium) detects rifampin resistance using a combination of 5 sensitive probes and 4 resistant probes detecting *rpoB* mutations.[225] The Genotype MTBDRplus assay (Hain Lifescience, Nehren, Germany) detects both rifampin and INH resistance by detecting mutations in *rpoB*, *katG*, and i*nhA*. Sensitivity is greater for the detection of rifampin (>95%) than for INH resistance (~85%), likely because of the wider array of mutations that can confer resistance in INH.[226] Additional line probe assays (Genotype MTBDRsl, Hain Lifescience) have been developed for the detection of resistance to ethambutol and second-line drugs. Performance of this test appears to be reasonably good for the detection of fluoroquinolone, aminoglycoside, and capreomycin resistance (sensitivity and specificity between 75% and 100%) but less sensitive (~60%) for detecting ethambutol resistance.[227,228] Agar proportion susceptibility testing is still the gold standard because of incomplete data on all mutations or target genes associated with phenotypic resistance. However, if molecular detection is used as an initial screening assay, resistant isolates can be detected weeks earlier, with significant impact on clinical care.

Susceptibility Testing of *Pseudomonas aeruginosa* Isolates From Patients With Cystic Fibrosis

Susceptibility testing of *P. aeruginosa* from chronically infected patients with cystic fibrosis presents a special challenge because of the unique nature of strains, multidrug resistance, a unique mucoid phenotype, and possible growth under anaerobic conditions distal to mucus plugs.[229] Automated systems have inferior accuracy in assessing antimicrobial resistance of mucoid *P. aeruginosa*. Because of the comparatively slow growth of these mucoid organisms, major errors can occur with automated susceptibility testing systems in which the organism is reported as susceptible when in fact it is resistant to a drug by reference methods. Both Etest and disk diffusion methods compare more favorably with reference methods.[229]

Reference MIC and disk diffusion methods can determine accurately *P. aeruginosa* resistance to several or all classes of antimicrobial agents, with the possible exception of colistin. Agar-based methods for detection of colistin resistance may not be reliable because this large, highly charged molecule diffuses poorly in an agar matrix and can adhere to plastic surfaces, thereby affecting broth test determinations. The use of a surfactant may mitigate this effect, but the overall impact of surfactant use needs to be studied further.[230,231] Additionally, standard tobramycin breakpoints, which are based on achievable serum concentrations of drug, classify as resistant isolates that in fact have MICs lower than achievable by aerosolized tobramycin (lower airway level ≥100 μg/mL). MIC determination or Etest can be used to determine higher relevant MICs. In 1 study, 20% of isolates with MICs suggesting intermediate susceptibility or resistance at the serum-achievable level would be susceptible at the aerosol-achievable level; 5% of isolates were resistant to tobramycin at aerosol-achievable levels.[232]

Other alternative strategies for *P. aeruginosa* susceptibility testing include checkerboard synergy testing and testing for multiple combined bactericidal activity.[233] In a randomized trial, the clinical outcome for patients whose therapy was based on multiple-combination bactericidal antibiotic testing was no better than for patients whose therapy was based on standard susceptibility methods.[234]

Finally, the mode of growth used in susceptibility testing of *P. aeruginosa* has been studied.[235] When *P. aeruginosa* is grown adherent to biofilms (sessile bacteria), β-lactam antibiotics are much less active than against organisms growing as single cells (planktonically). Aminoglycosides and ciprofloxacin showed similar activity against organisms growing planktonically or in biofilms. Surprisingly, macrolides, usually not thought to be active against *P. aeruginosa,* have activity against biofilm-grown organisms but not planktonic organisms.[235] Susceptibility testing of biofilm-grown organisms is complex, and questions of clinical utility are unsettled.[234]

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Pharmacokinetic-Pharmacodynamic Basis of Optimal Antibiotic Therapy

Michael N. Neely, Michael D. Reed

As clinicians continuously strive to practice evidence-based medicine, the use of antibiotics can be frustratingly empiric. Ethical concerns, multiple confounding variables, and unclear end points hamper clinical infectious disease research. This empiricism is clearly evident in most recommendations for antibiotic dosing and duration of therapy, especially in children, because only a fraction of published pharmacokinetic (PK) and pharmacodynamic (PD) data is collected from this group of patients. Although pediatric data are more plentiful and better defined for antibiotics than for other drug classes used in pediatric patients, much more work needs to be done. The lack of specific and sound dosing and safety data for drugs used in children continues to hamper the ability to determine optimal dose regimens rapidly. “Off-label” use of medications in children unfortunately, and necessarily, remains common practice.[1–3] Moreover, suboptimal antibiotic dose regimens most certainly contribute to the continued emergence of the virulent, multidrug resistant bacteria we encounter at the bedside today.[4]

In response to this lack of pediatric data, the US Food and Drug Administration (FDA) was granted additional authority through the Best Pharmaceuticals for Children Act (BPCA, 2002, 2007, 2012) and the Pediatric Research Equity Act (PREA, 2003, 2007, 2012). The BPCA extends patent exclusivity for 6 months for subsequent research focused toward a pediatric indication for on-patent drugs and prioritizes and supports pediatric labeling studies with off-patent drugs. The PREA mandates that any drug with potential use in children must also be studied in children unless it is granted a specific waiver by the FDA. This act is enforced automatically with any new drug application, including new indications for existing drugs. Failure to comply with PREA requirements can result in revocation of marketing approval for a drug. Both the BPCA and the PREA were made permanent in 2012 as part of the FDA Safety and Innovation Act (FDASIA). With a growing awareness of the important physiologic differences across the age spectrum in children and their many important influences on drug dosing, knowledge of an antibiotic's PK and PD properties is necessary to determine optimal dosing. The increasing incidence of serious infections caused by multidrug-resistant pathogens combined with the ever-increasing emergence of virulent pathogen resistance underscores the importance of applying integrated antibiotic PK-PD–defined dosing in daily practice.[5,6] This chapter reviews basic PK principles and provides a framework for the clinician to apply these principles at the bedside.

Basic Concepts in Clinical Pharmacokinetics

Pharmacokinetics (PK) describes the time course of drug movement in the body; an understanding of a drug's PK profile is essential to the design of an optimal dosage regimen. However, focusing on a drug's PK profile alone provides the clinician with limited information about optimal drug dosing or, more importantly, clinical efficacy. PK principles are of clinical relevance only when they are integrated with the drug's *pharmacodynamic* (PD) properties (i.e., the effects of the drug in the patient).

With the exception of intravenous (IV) drug administration, a drug must be absorbed into the systemic circulation from its site of administration. Some drugs can be administered as a prodrug requiring in vivo metabolism to liberate the active moiety. Once absorbed, the drug is distributed within the body to accessible sites that are specific to the individual drug or drug class based on inherent physicochemical characteristics (e.g., lipid solubility, molecular weight, protein binding). Factors such as age, body habitus, and disease can influence this distribution. Simultaneous with the processes of absorption and distribution, many drugs undergo metabolism before excretion from the body. A drug's PK and disposition profile can be artificially separated into semidiscrete periods of drug absorption, distribution, metabolism, and excretion (Fig. 291.1), to permit visualization and more accurate quantification. Knowledge of this information allows the clinician to predict drug concentrations and systemic exposures for the active drug that can be achieved at any time over a specified dosing interval after any dose of a given drug. With this information, an optimal drug dose and dose interval can be determined for any patient with a regimen that accounts for underlying pathophysiologic features and major organ function.

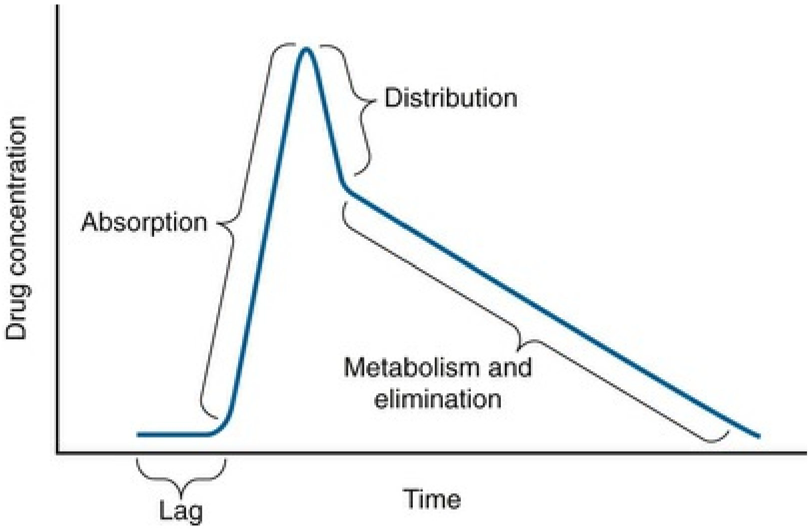

FIGURE 291.1 **Overall biologic fluid (e.g., serum) drug concentration–time curve after extravascular drug administration. Each important process of drug disposition is indicated. Although these processes are compartmentalized graphically in the figure, in reality they occur simultaneously (see text for details).**

The PK property *bioavailability* estimates the amount of a drug dose administered extravascularly (e.g., orally, intramuscularly) that is absorbed into the systemic circulation. Bioavailability is calculated as the area under the plasma drug concentration–time curve (AUC) achieved after extravascular drug administration divided by the AUC achieved after IV administration (e.g., AUC_{oral} / AUC_{IV}). Thus, to achieve the same systemic exposure with a drug administered orally as achieved with IV dosing, one simply divides the IV dose by the drug's bioavailability (obtained from published sources) to determine the equivalent oral dose. Lower bioavailability is not necessarily a negative attribute unless the dose required is so large that the patient tolerates it poorly. However, for orally administered antibiotics, poor bioavailability can be a major limitation because unabsorbed drug remaining in the intestinal tract can adversely affect indigenous flora and often can lead to intestinal complaints and diarrhea (e.g., ampicillin vs. amoxicillin). Conversely, this property is sometimes therapeutically advantageous, as is the case for orally administered vancomycin to treat *Clostridium difficile*–associated colitis or nystatin for mucosal candidiasis.

Bioavailability depends on the molecular weight, solubility, and permeability of the drug. Highly soluble and permeable drugs have excellent bioavailability, whereas the converse results in poor bioavailability. Drugs with opposing solubility and permeability have unpredictable and variable bioavailability, even within the same patient from dose to dose, because of variations in gastrointestinal pH, motility, and food content. Drugs can exhibit complex absorption patterns with delayed or multiple peaks in their blood (plasma or serum) concentrations arising from timed-release formulations, enterohepatic recycling, site-specific absorption within the gastrointestinal tract, or variations in gastric emptying and intestinal transit times. A drug's *peak plasma concentration* is the characteristic most greatly affected by changes in the rate and extent of absorption, and reduced peaks theoretically can compromise the efficacy of concentration-dependent antibiotics, as discussed in the later section on pharmacodynamic correlates for antibacterial agents.

Once absorbed into the systemic circulation, the distribution of a drug depends on specific characteristics inherent to the drug molecule. Small, non–protein-bound, nonionized lipid-soluble molecules are usually widely distributed (e.g., azithromycin), whereas larger, less lipid-soluble (i.e., polar) or highly protein-bound drugs traverse cell membranes poorly, thus restricting movement (e.g., aminoglycosides, vancomycin, echinocandins). The PK measurement that attempts to describe this process is the *volume of distribution* (V_d). V_d is a proportionality constant that relates the amount of drug in the body to its plasma concentration. V_d can be roughly conceptualized for an IV drug by the following simplified formula: V_d = dose / C_p, where C_p is the peak plasma drug concentration. V_d does not correspond to any true anatomic distribution or compartment, although the magnitude of V_d provides clues about a drug's physiologic distribution. For example, for a drug with a very small V_d (i.e., 0.2 L/kg), a larger proportion of the drug is confined to extracellular fluid (composed of intravascular and interstitial fluid), whereas the distribution of a drug with a large V_d can involve extensive tissue binding, intracellular distribution, or both. Knowing a drug's V_d (expressed in liters per kilogram of body weight) allows the clinician to estimate the dose necessary to achieve any desired plasma drug concentration. For example, the loading dose for a drug can be calculated from the following formula: loading dose = desired plasma drug concentration (mg/L) × V_d (L/kg) × patient body weight (kg). The age-specific V_d for the drug to be prescribed can be obtained from published sources or calculated for the individual patient, as outlined earlier. As inferred from the loading dose calculation, the first (or loading) dose of any drug is independent of a patient's organ function or extent of underlying disease (e.g., renal failure). A patient's first drug dose is dependent only on the V_d of the specific drug; all subsequent doses depend on the patient's ability to clear (eliminate or metabolize) the drug.

The PK property *clearance* (CL) estimates the volume of solvent (e.g., plasma, serum, or blood) from which all drug is removed per unit time. CL is therefore expressed in units of volume per time. *Body CL* is a composite estimate reflecting all mechanisms of drug CL, including renal, hepatic, and other forms of CL (e.g., lung), and it is calculated using the following formulas: CL = 0.693 × V_d / $t_{1/2}$, where $t_{1/2}$ is the *drug's elimination half-life;* or CL = drug dose × F /

AUC, where F is bioavailability. Knowledge of a drug's CL is necessary to determine accurately the need for and proper timing of subsequent doses to maintain any desired drug concentration or degree of systemic exposure. Changes in organ function responsible for drug removal from the body are reflected by changes in a drug's overall CL rate. Although clinically the $t_{1/2}$ often is used at the bedside as a measure of drug CL and to determine subsequent drug dosing, this value merely reflects the time required for a given drug concentration in any biologic fluid to decrease by 50%, although this is not necessarily elimination from the body, as exemplified by all forms of amphotericin. If V_d is fairly constant in a patient in stable condition, $t_{1/2}$ mirrors body CL, thereby permitting bedside application. The $t_{1/2}$ can be estimated simply from the measured fall in plasma drug concentration after an individual dose (e.g., from the peak and trough plasma drug concentrations); to estimate the $t_{1/2}$ in practice, usually one must obtain 2 measured drug concentrations and calculate $t_{1/2}$ as $\ln(2) \times -t / \ln(C2/C1)$, where ln(2) is the natural logarithm of 2 (~0.693) and t is the time between the 2 measured concentrations C1 and C2. Although the $t_{1/2}$ is an extremely useful bedside application of PK, the accuracy of the $t_{1/2}$ as a reflection of drug CL diminishes in situations of changing V_d, renal or liver function. For example, a drug's V_d can be altered during extracorporeal membrane oxygenation (ECMO), septic shock, or severe liver disease with marked ascites.

The PK principles just outlined for V_d, CL, and $t_{1/2}$ assume that the drug follows *first-order* or *linear PK characteristics. First order* means that a constant *fraction* of drug is cleared per unit time (i.e., regardless of the initial concentration, the time to clear x% is the same). However, for certain drugs, such as voriconazole[7,8] and phenytoin,[9] the CL mechanisms can be saturated at clinically relevant concentrations, and thus their disposition is best described by using *zero-order methodology* or a combination of first-order elimination at lower concentrations and a gradual transition to zero-order elimination at higher concentrations (i.e. *Michaelis-Menten* kinetics). *Zero order* means that a constant *amount* of drug is cleared per unit time (i.e., the higher the initial concentration, the longer it will take to clear x%). Fortunately, most drugs used clinically follow first-order PK, which is simpler to apply clinically. The recognition that a drug's disposition characteristics are first order allows the clinician to use simple proportions with relative accuracy to define patient-specific drug doses. For example, if a patient's steady-state plasma drug concentration is half that desired (at any time point) and the drug follows first-order PK, the dose can simply be doubled to achieve the desired concentration. In contrast, for a drug with zero-order characteristics, doubling the dose can result in a much higher increase in the plasma concentration.

Following repeated drug dosing, a *steady-state* condition is achieved (i.e., when the amount of drug administered to the patient equals the amount of drug eliminated [cleared] from the body). Simply put, "in = out." The importance of steady-state conditions cannot be overemphasized because the drug concentrations in blood (plasma or serum) or tissue reported to be associated with drug efficacy or toxicity most often are the steady-state drug concentration. For drugs that follow first-order "proportional" PK characteristics, the drug's $t_{1/2}$ can be used to estimate the time to reach steady state (i.e., 4–5 times the $t_{1/2}$ to reach steady state). A drug's $t_{1/2}$ can be calculated for an individual patient as described earlier, or an age-appropriate $t_{1/2}$ often can be obtained from published sources and modified if necessary based on the patient's elimination organ function.

Unfortunately, the clinician encounters many patients who deviate from the proposed PK characteristics found in published sources, especially in pediatrics. A far more sophisticated, powerful, and nuanced approach to dosage individualization is the application of population PK modeling techniques coupled with bayesian feedback, by using specifically designed software tools.[10,11] Although these methods have the disadvantage of requiring specialized software, training, and knowledge, they have numerous advantages, including more accurate and rapid attainment of target drug concentrations without the need for steady-state conditions (including patients with unstable PK behavior),[12–15] improved clinical outcomes,[16–20] and reduced costs.[16,21–24] A complete review of this topic is beyond the scope of this chapter, but interested readers are urged to contact experts in the field and consider these approaches when desiring to optimize individual therapy.

The next sections discuss the general PK alterations that can influence both the magnitude and the frequency of antibiotic doses in neonates, patients with organ failure who are undergoing dialysis or ECMO, children with cystic fibrosis (CF), and patients with burns or septic shock. However, considerable variability exists within these generalizations, and any specific patient is likely to be best served by careful dose optimization in partnership with an expert in clinical pharmacology.

Drug Disposition in Specific Patient Populations

Neonates: the Ontogenic Basis of Drug Disposition

As children mature physically, they also mature physiologically. This principle has important and clinically relevant implications for both drug PK and PD characteristics.[25,26] Factors that influence drug absorption from the gastrointestinal (GI) tract include the surface area available for absorption, pH, gastric emptying time, exocrine pancreatic function, size of the bile acid pool, and bacterial colonization (Table 291.1). All these functions are variably altered in neonates, particularly those born prematurely, and in young infants relative to older children and adults.[27,28] Changes in the amount and distribution of body water in neonates, as well as differences in quantitative and qualitative protein-binding characteristics, also are present and affect drug distribution. These ontogenic differences in body water composition (i.e., increased V_d for water-soluble drugs) are reflected by the increased individual doses, on a milligram of drug per kilogram of body weight basis, prescribed for young infants and children compared with older children and adults. Although far from fully characterized, both the oxidative and conjugative hepatic metabolic enzyme systems are immature at birth and reach adult levels of activity at various times throughout early childhood.[29] Renal function and elimination also mature as a function of gestational and postnatal age, with glomerular filtration reaching adult levels in infants of 34 weeks of gestation by approximately 3 to 5 months of age.[30] Tubular secretion matures more slowly and reaches adult levels by approximately 8 to 9 months of age (see Table 291.1).

TABLE 291.1

Physiologic Changes in Children That Affect the Pharmacokinetic Characteristics of Drugs

Parameter	Neonates	Approximate Age Approaching Adult Level
ABSORPTION		
Gastric pH	↑	3 mo
Gastric emptying	↓	6–8 mo
Pancreatic function	↓	9 mo
DISTRIBUTION		
Body water	↑[a]	~3 yr
Protein binding	↓	12 mo
METABOLISM		
Hepatic drug-metabolizing or hepatic drug metabolism	↓	2 yr to adolescence
ELIMINATION		
Renal function	↓	Glomerular filtration: 3–5 mo
		Tubular secretion: 8–9 mo

[a] The distribution of body water depends on age: the total body water (TBW) of neonates is approximately 75% of body weight, with approximately 50% intracellular (IC) and 50% extracellular (EC). A gradual decrease in TBW and a shift to IC distribution occur until adult values of 50% to 60% TBW, 33% EC, and 66% IC are reached at puberty.

Data from references 328 to 331.

As a result of these physiologic differences (see Table 291.1), infants <44 weeks of postconceptional or postmenstrual age generally have larger V_d and decreased antibiotic CL, which translate clinically to lower peaks, lower overall plasma drug concentrations, and longer $t_{1/2}$ than observed in older infants and children. Furthermore, these infants can be more susceptible to drug-drug interactions at all levels, interactions that are likely to be significant for other drugs as well as antibiotics alone (see the later section on the basis for drug-drug interactions).

The physiologic differences of young infants influence not only drug PK but also PD characteristics, which necessarily incorporate the mechanism of drug action. Developmental changes in receptor function are not as relevant to antibiotics because the receptor targets are on the infecting organism.[31] However, host receptors can be involved in therapeutic antibiotic mechanisms (e.g., human kinases that phosphorylate acyclovir) or adverse antibiotic mechanisms. Despite lower CL and prolonged $t_{1/2}$ in neonates relative to older children and adults, aminoglycosides cause less nephrotoxicity in neonates.[32] This tolerance is thought to arise from differences in renal disposition characteristics, although the exact mechanism is unknown.

The clinician must be aware that neonates are physiologically distinct and manifest altered antibiotic PK characteristics. Dosing strategies should be evaluated critically to make prescribing decisions to optimize therapeutic success. In the absence of neonatal dosing recommendations, knowledge of the altered PK patterns will make empiric dosing more rational when it is extrapolated from dosing recommendations for older children or adults.

Patients With Organ Failure and Principles of Dialyzable Drugs

The major routes of drug elimination are by the kidneys into urine and by the liver into bile. For most drugs only minor amounts are eliminated into other body fluids. Alterations in drug disposition result from failure of either of these organs of elimination or failure of the cardiopulmonary system to support their proper function. Patients in cardiopulmonary failure can experience alterations both in V_d as a result of increased total body water and in CL as a result of hepatic or renal dysfunction. Knowledge of the PK properties of individual drugs is crucial to understanding the magnitude of such effects. Drugs with a small V_d are more greatly affected because they tend to be distributed to extracellular fluid. The route of metabolism and elimination determines the impact of hepatic or renal dysfunction.

Extracorporeal Membrane Oxygenation

ECMO influences drug disposition in several ways. ECMO circuitry can add up to 500 mL of volume to the patient, in which case V_d is increased; children weighing <20 kg will most likely experience corresponding lower peak drug concentrations and a longer $t_{1/2}$. Further, drugs can bind to the oxygenation membrane, thereby potentially increasing both V_d and CL.[33] Binding is increased with increasingly lipophilic drugs. CL can be reduced as a consequence of altered perfusion of the liver and kidneys.[34,35]

Alterations in the PK characteristics of antibiotics during ECMO have been relatively well characterized for gentamicin and vancomycin.[36,37] Although the V_d of aminoglycosides is variably increased, the $t_{1/2}$ can be doubled. Neither drug significantly binds to the oxygenation membrane, as predicted by low lipophilicity. The implication for dosing is that aminoglycosides should be administered every 18 to 24 hours initially (or less frequently in patients with renal failure) to infants undergoing ECMO (with monitoring of serum drug concentrations), although no efficacy studies are available to support this recommendation. For vancomycin, V_d and $t_{1/2}$ are increased, and CL is decreased, resulting in a suggested initial dose of 20 mg/kg IV every 18 to 24 hours for infants with a serum creatinine value <1.5 mg/dL. For infants with a higher serum creatinine concentration, the dosing interval must be extended. In all cases, serum vancomycin concentrations should be monitored.

Increased ECMO-associated cefotaxime V_d has been documented, but the percentage of the dosing interval that is greater than the organism's minimal inhibitor concentration (MIC) after standard doses during ECMO is not significantly different from the same doses while the patient is not undergoing ECMO, thus leading to no required dosing changes.[38] Some reports have noted lowered plasma voriconazole concentrations requiring higher doses in patients receiving ECMO, a finding consistent with its high lipophilicity, and therapeutic drug monitoring is recommended.[39,40] Caspofungin, which is less lipophilic, had reportedly lowered[41] and unaltered[40] concentrations in 3 patients receiving ECMO, with the result that no clear recommendation was made. Oseltamivir PK does not appear to be changed significantly.[42] Indeed, a case report of a 6-year-old boy receiving both ECMO and continuous veno-venous hemofiltration demonstrated that low plasma levels of oseltamivir were likely caused by poor oral absorption rather than by marked changes in V_d or CL.[43]

For other antimicrobial agents for which plasma drug concentrations are unavailable, the clinician can only estimate dosing modifications based on the expected changes described earlier.[34,35] In general, V_d and $t_{1/2}$ are the same or are increased. Lipophilic drugs are more greatly affected than are hydrophilic drugs. However, patients undergoing ECMO usually have multiorgan failure, with renal failure and the use of continuous veno-venous hemofiltration the most problematic for many antibiotic regimens.

Dialysis

For patients in acute or chronic renal failure who require dialysis, several options can be used for extracorporeal therapy, including intermittent or continuous hemodialysis (HD), hemofiltration (HF), or peritoneal dialysis (PD). HD and HF therapies can be combined.[44,45] HD removes an antibiotic by diffusion across the dialysis membrane into the dialysate according to the drug's concentration gradient. The amount of blood flow past the dialysis membrane and the composition and flow of dialysate influence the amount of drug removed. HF (without HD) removes antibiotics in the ultrafiltrate, which is a hydrostatically generated flow of water containing the dissolved drug. No drug concentration gradient is present. PD, in general, removes most antibiotics minimally. The volume of PD fluid generally is small (0.05–0.2 L/kg) in comparison with the V_d of antibiotics (0.2–>100 L/kg), so only a very small percentage of the total drug in the body is distributed to the PD fluid unless the antibiotic has a similarly small V_d. Furthermore, the intraperitoneal concentration of antibiotics is proportional to the concentration of free, non–protein-bound drug. The protein content of typical dialysate fluid is 0, so highly protein-bound antibiotics are poorly distributed to the peritoneal fluid. Increasing the amount of PD dialysate or the frequency of exchange increases the amount of drug extracted, but a cumulative amount extracted of <25% during a dosing interval is usually insignificant. In contrast, antibiotics administered into the peritoneal dialysate can reach therapeutic plasma concentrations if they can cross the peritoneal membrane, passage through which is enhanced in the presence of inflammation. Because the potential extra-abdominal volume for an antibiotic to diffuse into is much larger than the intra-abdominal volume, with equal concentrations across the peritoneal membrane at equilibrium, the amount of drug in the body is greater than in the peritoneal dialysate.

All these modalities partially restore the ability of the body to eliminate an antibiotic that normally would be cleared by the kidneys. Although several thorough reviews have described the use of antimicrobial agents in these patients, none of the guidelines have pediatric dosing, and all strongly convey the same message: antimicrobial concentrations highly depend on factors intrinsic to the mode of dialysis itself and the drug's PK properties (Table 291.2). This variability could have significant clinical implications.[46,47] Although the clinician can apply principles outlined here to an individual patient to generate a qualitative assessment of the need for dose adjustment, confirmatory measurement of drug concentrations is crucial when possible.

TABLE 291.2

Factors That Increase the Likelihood of Antibiotic Removal by Dialysis

Factors Intrinsic to the Antibiotic	Factors Intrinsic to the Mode of Dialysis
Smaller volume of distribution (<1 L/kg)	CVVHDF[a] > CVVH[a] > CVVHD[a] > IHD ≫ PD
Smaller molecular mass (<2 kd)	Frequent dialysis
Reduced protein binding (<80%)	High flow rate of blood or dialysate
Neutral charge	Filter capacity and selectivity
Normally eliminated by kidneys (>30%)	Dialysate composition

[a] The differences in drug clearance among the continuous modes of hemodialysis or hemofiltration are less significant for small molecules, which include most hydrophilic antibiotics that are likely to be cleared by these modes. Among these, the largest are teicoplanin (1.9 kd), colistimethate, also known as colistin (1.8 kd), and vancomycin (1.5 kd).

CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; IHD, intermittent hemodialysis; PD, peritoneal dialysis.

Drugs with a small V_d (<1.0 L/kg) that are primarily confined to the extracellular compartment are available for filtration across the dialysis membrane. The pore size of HD membranes is approximately 0.5 kd, whereas HF membranes are usually approximately 50 kd. Most antibiotics are <1 kd. Passage across a membrane is inversely proportional to the square root of the molecular mass. Drug-protein complexes are too large to pass through the pores of intact dialysis membranes, so highly protein-bound antibiotics (>80%) pass through the membrane poorly. Further, the membranes carry a net negative charge; highly polar molecules do not cross the membrane efficiently. Antibiotics that are mainly eliminated by a functioning kidney are more likely to be eliminated by dialysis, and a simplistic rule of thumb predicts some removal of drugs that are eliminated >30% unchanged in the urine in patients with normal renal function. However, the fraction of an antibiotic normally cleared by active tubular secretion is not compensated for by dialysis, and this factor should be considered in any patient manifesting unexplained signs or symptoms of drug toxicity.

Antibiotic dose adjustment in the absence of measurable drug concentrations in blood, dialysate, or ultrafiltrate, is a crude estimate, at best. Unfortunately, most pharmacology references consulted to determine dose recommendations use complicated formulas that require information the clinician often does not possess. Therefore a more intuitive approach is typical, and the clinician should first consider the relevance of potential drug accumulation by monitoring the patient closely for desired and undesired drug effects. Fortunately, most antibiotics have a very high therapeutic index (i.e., the ratio of therapeutic to toxic doses). “Safe” drugs can generally be allowed to accumulate moderately without risk of serious or irreversible toxicity, or both. In contrast, more rigorous dose adjustments should be applied for antibiotics that can be associated with toxicity (e.g., the aminoglycosides) because in general patients in renal failure, especially if they are uremic, are more prone to adverse effects from all drugs. Regardless of the dosing scheme selected, the clinician must monitor patients closely for specific evidence of toxicity related to the drug in question as well as expected clinical responses (see Chapter 289). Conversely, unaccounted-for extracorporeal elimination has major importance when subtherapeutic drug concentrations lead to clinical failure, which can happen when a drug dose is based on a patient's intrinsic renal function without accounting for dialysis-mediated drug CL. Therefore, for most antibiotics, it is more important to avoid underdosing. Appendix 291.1 lists suggested adjustments for selected antibiotics in response to renal failure with or without dialysis.

Cystic Fibrosis

CF is the most common potentially lethal genetic disorder in whites and remains a therapeutic challenge for pediatric and adult practitioners. The disease is characterized by an elevated sweat chloride concentration, pancreatic exocrine insufficiency, thick and tenacious mucus secretions, and chronic obstructive pulmonary disease.[48–50] A hallmark of CF is chronic microbial colonization of the lung with resultant repeated acute pulmonary infections or exacerbations.[48–51] CF morbidity and death result from the pulmonary component of this disease, and treatment (e.g., antibiotics, ibuprofen) focuses on decreasing the inflammation that is responsible for the progressive, irreversible deterioration in lung function[52] (see Chapter 106). However, optimal antibiotic therapy in patients with CF is complicated by potential differences in the disposition of many drugs.[53] Unfortunately, the lack of adequate control groups in many studies precludes definitive conclusions regarding CF-induced alterations in drug PK. Nevertheless, these data provide consensus findings that patients with CF often have a larger V_d and enhanced body CL for many antibiotics, including aminoglycoside and β-lactam agents, compared with patients who do not have CF,.[53–55] The reasons for these differences are unknown. CF-induced differences in drug V_d may merely reflect the difference in body composition in patients with CF, specifically, their limited adipose tissue. When the V_d for various drugs is expressed as a function of lean body mass rather than body weight characterized by kilograms, differences in drug V_d diminish. When drug dosing is based on the patient's body weight, the real differences in the body composition of patients with CF necessitate higher individual milligram-per-kilogram drug dosing to achieve systemic drug exposure similar to that of patients who do not have CF.[56]

Drug elimination also appears to be enhanced in patients with CF.[53,57] Despite well-characterized CF-induced hepatic dysfunction, particularly in patients with CF who are older than 15 years of age, the CL of many drugs that undergo hepatic metabolism may be unchanged or increased in patients with CF. Emerging data are revealing that the function of phase I mixed-function oxidases is selectively affected; the functional capacity of cytochrome P450 (CYP450) system isoforms CYP1A2 and CYP2C8 appear to be enhanced, whereas CYP2C9 andCYP3A4 are unaffected. With phase II reactions, the activity of glucuronyl transferase, *N*-acetyltransferase, and sulfotransferase can be similar or increased.[58] Moreover, the renal CL of many drugs is increased in patients with CF. The mechanism is unknown, but it does not appear to be related to any disease-associated effect on the activity of the primary renal efflux transporter, P glycoprotein.[59] The clinician must increase the amount and possibly the frequency of individual doses to compensate for the larger V_d and CL, as tolerated by the patient. Regardless of the dosing strategy used, close clinical monitoring for antimicrobial efficacy and safety is necessary.

Additionally, in patients with CF, the amount and composition of sputum, as well as bacterial density, have been shown to reduce the bioactivity of many antibiotics (i.e., inoculum effect).[60–62] These pathophysiologic variables must be considered when devising antibiotic regimens, including increasing systemic doses and attempting topical application through aerosol antibiotic administration.[63,64]

Septic Shock or Burn Injury

Children in septic shock or who are severely burned can suffer dramatic physiologic changes.[65–67] One can assume that any child with hemodynamic changes requiring significant fluid resuscitation or pharmacologic pressor support will be neither physiologically nor pharmacokinetically normal. The timing of physiologic changes is somewhat more characteristic with burns than with septic shock because the burn insult is of defined duration. The first phase in the 48 hours after a severe burn is characterized by an acute decrease in glomerular filtration as a result of hypovolemia and shock, with a rapid shift of intravascular fluid to the interstitial spaces. After 48 hours, with adequate resuscitation, the second phase is characterized by increased cardiac output, increased glomerular filtration (although not tubular secretion), hypoalbuminemia with reduced drug protein binding, and edema. Unfortunately, burned patients frequently sustain hypovolemic renal injury, which can antagonize postburn increased glomerular filtration. Additionally, the function of hepatic CYP450 enzymes appears to be depressed in burned patients. These factors and others have an important impact on drug disposition and require dose adjustments.

Similar changes can be observed in patients with septic shock, with early increases in the V_d of hydrophilic drugs associated with increased capillary leak and fluid resuscitation, as well as organ blood flow associated with hyperdynamic cardiac output. Subsequent infection- and immune-mediated tissue damage can then compromise organ function, including drug metabolism and elimination. The temporal variability of the pathophysiologic changes associated with septic shock and burns makes the PK of antibiotics unpredictable. Nonetheless, some studies have revealed class-dependent patterns that can make antibiotic dosing more rational. Table 291.3 indicates the PK changes observed for various commonly used antibiotics and provides suggested dosing strategies. Ongoing awareness of the patient's physiologic status and further monitoring of serum antibiotic concentrations or secondary markers such as creatinine CL and albumin are required to ensure that the most effective dosing regimens are maintained.

TABLE 291.3

Pharmacokinetic Alterations of Specific Antibiotics With Suggested Dosing Strategies in Patients With Septic Shock or Extensive Burns

Antibiotic	Pharmacokinetic Change	Suggested Dosing Strategy
Aminoglycosides	Generally increased clearance and V_d	1. Administer twice the standard multiple daily dose[a]
		2. Measure drug concentration at end of infusion and 4 hr after end of infusion
		3. If 4-hour concentration is <2 µg/mL (gentamicin, tobramycin) or <5 µg/mL (amikacin), administer another dose; otherwise, estimate V_d and $t_{1/2}$, and administer second dose when trough concentration expected to be at target
		4. Continue dose and schedule from step 3
		5. Confirm therapeutic trough and peak 3 doses later
Glycopeptides (vancomycin, teicoplanin)	Generally increased clearance; fair correlation with CLCr; V_d is not affected	1. Measure CLCr as soon as possible (after initial 48 hr after burn) 2. Administer highest end of standard dose based on shortest dosing interval
		3. Measure peak concentration at end of dosing interval 4. Time the measurement of trough level on CLCr, if available[b]; if unavailable, measure trough before next dose is due

		after a standard short interval
		5. Adjust dose and interval based on serum peaks and troughs[c]
β-Lactams (cefepime,[332] ceftazidime, ticarcillin-clavulanate, piperacillin-tazobactam[333,334])	V_d is substantially increased; total clearance generally is correlated with CLCr; $t_{1/2}$ is variably increased, but initial serum concentrations are less than normal	1. Measure CLCr as soon as possible (after initial 48 hr after burn) 2. Consider 50% increase over highest usual dose 3. Dosing interval depends on CLCr. If higher than normal, choose moderately short interval; if lower than normal, choose long interval
Carbapenems and monopenems (imipenem, meropenem, aztreonam)	Clearance correlates well with CLCr; V_d unchanged to somewhat increased	1. Measure CLCr as soon as possible (after initial 48 hr after burn)
		2. Use high end of standard dose
		3. Dosing interval depends on CLCr; If higher than normal, choose short interval; if lower than normal, choose long interval

[a] Once-daily dosing of aminoglycosides has been shown to result in extended periods of subtherapeutic plasma concentrations in excess of those seen in nonburned patients, thus potentially compromising efficacy, and standard multiple daily dosing carries a significant risk of subtherapeutic peaks. Therefore, higher dose multiple daily dosing is preferred initially.[338]

[b] The standard dose of vancomycin in children with the shortest interval is 15 mg/kg every 6 hours. If CLCr is 100% of normal for age, weight, and sex, measure trough 5 hours after the end of infusion (1 × normal dosing interval). If CLCr is 50% of normal, measure trough 11 hours after the end of infusion (2 × normal dosing interval). If CLCr is 200% of normal, measure trough 2 hours after the end of infusion (0.5 × normal dosing interval).

[c] Based on the pharmacokinetic and pharmacodynamic characteristics of vancomycin, continuous infusion can be an alternative for patients with rapid clearance to avoid excessively large or frequent doses. Clinical data are limited, and the best-targeted serum concentration is not clear, but it is likely at least 8 × MIC, with the understanding that particular caution or alternate therapies should be considered if sustained vancomycin concentrations >30 mg/L are considered necessary.[339–341]

CLCr, creatine clearance; $t_{1/2}$, drug's elimination half-life; V_d, volume of distribution.

Data from references 335 to 337, except where noted.

Basis for Drug-Drug Interactions

Pharmacokinetic Interactions

A drug-drug interaction can exist at any phase of the PK profile (see Fig. 291.1): absorption, distribution, metabolism, or elimination. Frequently, these interactions are predictable qualitatively, if not always quantitatively. For example, knowing that clarithromycin inhibits the same hepatic enzyme responsible for metabolizing cyclosporine leads one to predict that clarithromycin is likely to raise the cyclosporine serum concentration and that a lower dose of cyclosporine may be required. However, actual quantitative adjustment of the cyclosporine dose must be based on measurement of the serum concentration or close monitoring of the patient (or both) for defined end points of efficacy and side effects.

The first step consists of awareness of the possibility of a drug-drug interaction and knowledge of the PK properties of the respective drugs. The second step is assessment of the clinical relevance of a potential interaction. Clinical importance occurs when the amount of free (active) drug in the body is significantly altered such that therapeutic efficacy is compromised or toxicity is increased. An assessment of possible specific influences on each aspect of a drug's disposition profile is outlined in the following sections.

Absorption

The absorption of orally administered drugs can be altered by numerous factors:

1. Alterations in GI motility by pharmacologic or nonpharmacologic means. Intestinal motility can be influenced by the administration of gastrokinetic medications (e.g., metoclopramide, erythromycin) or decreased by drugs with anticholinergic or opiate properties.

2. The presence of food in the GI tract. Food can affect the absorption of many antibiotics. For example, itraconazole tablets and posaconazole liquid are better absorbed in the presence of fatty food, whereas itraconazole solution is better absorbed in the fasting state.

3. Alterations in gastric pH. Drugs that are highly charged cross membranes poorly, including the GI mucosal surface. In the normally acidic environment of the stomach, drugs that are weak acids are nonpolar; weak bases are charged. As the pH increases with the use of antacids, histamine (H_2)-blocking agents, and proton pump inhibitors, weak acids become more polar and are thus absorbed less, whereas weak bases become less polar and are

absorbed more readily. For example, increased gastric and proximal duodenal pH reduces the absorption of cefpodoxime,[68] itraconazole capsules but not solution,[69] oral ampicillin (product insert), and the antiretroviral drugs atazanavir and indinavir.[70] In contrast, absorption of the antiretroviral drug raltegravir is enhanced by concomitant omeprazole, which raises pH.[71] These examples notwithstanding, because most drug absorption occurs in the small intestine, which is buffered, gastric pH generally plays a minor role in the overall bioavailability of orally administered drugs.

4. Binding substances. Fluoroquinolones and tetracyclines are poorly absorbed in the presence of cationic ions such as the bismuth, calcium, aluminum, and magnesium ions found in vitamin supplements and antacids; concomitant use of these medications should be avoided. Such interactions can be avoided by separating administration by a minimum of 2 to 4 hours.

Distribution

Drug interactions influencing distribution can result from interactions with drug displacement from plasma proteins, most notably serum albumin, and with drug transporters. Drug-drug protein displacement interactions represent drug interactions of common clinical concern but of rare clinical significance, specifically, displacement of one drug or substance (e.g., bilirubin) by another drug or substance from its binding site or sites (e.g., albumin) and leading to an increased concentration of free drug. The resultant increased free drug concentration undergoes distribution and CL and also is available for enhanced PD effect. However, *all* the following criteria must be fulfilled before such an interaction becomes problematic:

1. The antibiotic must be highly protein bound (> 80%).

2. It must have a small V_d (<1 L/kg). A larger V_d means that the bulk of the drug is extravascular and is not affected by changes in serum protein binding.

3. The drug must have a long $t_{1/2}$. As drug is displaced from serum protein, it not only becomes biologically active but also becomes

available for distribution to extravascular sites, metabolism, and excretion. For drugs with a short $t_{1/2}$, any displaced excess free drug is quickly redistributed, inactivated, or eliminated from the body, thus promptly reaching a new equilibrium (within 3–5 half-lives). A lower amount of total drug (and thus a larger apparent V_d) characterizes this new equilibrium, and although the free fraction is higher, the absolute concentration of free active drug is the *same* as before. This disposition occurs with all displaced drugs, but the $t_{1/2}$ of the displaced free drug is the most significant factor because it determines the time for the displaced free drug to re-equilibrate. The longer the free drug $t_{1/2}$, the greater is the amount of time that elevated active drug concentrations are available to augment the therapeutic or toxic effects (or both). The implication of a decreased total serum concentration but the same free concentration is that highly protein-bound drugs with therapeutic levels based on the total serum concentrations (e.g., voriconazole[72,73]) can appear falsely subtherapeutic because the active free drug concentration is not being measured. These arguments also apply when patients are profoundly hypoalbuminemic, which has the same effect on free and total drug kinetics as displacement from albumin. The reason is that both displacement and hypoalbuminemia result in reduction of available binding capacity.

4. The antibiotic must have a low therapeutic index (i.e., significant toxicity occurs at a serum concentration only slightly higher than therapeutic concentrations).

Although several antibiotics meet some of the criteria outlined, none meets all of them. Therefore, concern about toxicity caused by the displacement of antibiotics from serum proteins appears to be unwarranted.

The converse question is whether highly protein-bound antibiotics can displace potentially harmful substances that are bound to serum proteins. The area of greatest concern in pediatrics is displacement of albumin-bound bilirubin and subsequent kernicterus in a neonate. The most commonly implicated drugs are the sulfonamide antibiotics and ceftriaxone. The pathophysiology of kernicterus is incompletely understood but is more complex than simple displacement of albumin-bound bilirubin. The only antibiotic that has actually been associated with kernicterus is IV sulfisoxazole,[74] and this may have been a result of the sulfisoxazole diluent in the drug preparation administered. Supporting this inference is the lack of any reported case of kernicterus associated with use of the combination drug trimethoprim-sulfamethoxazole in neonates.[75] Nonetheless, because the development of kernicterus involves the transfer of bilirubin from serum and tissue albumin to brain parenchyma in neonates,[76] especially premature infants, it seems prudent to avoid the use of antibiotics that do or could potentially displace bilirubin unless no other choice is available. Commonly used antimicrobial agents and their ability to displace bilirubin are listed in Table 291.4.[77–79]

TABLE 291.4

Antibiotics Classified According to Their Possible Ability to Displace Bilirubin From Albumin in Cord Blood Serum in Vitro

High[a]	Intermediate	Low	No Data[b]
Cefoperazone	Ampicillin	Aminoglycosides	Acyclovir
Ceftriaxone	Cefonicid	Amoxicillin	Amantadine
Dicloxacillin	Cefoxitin	Aztreonam	Amphotericin B[c]
Sulfamethoxazole	Cephalexin	Cefamandole	Cidofovir
Sulfisoxazole	Erythromycin	Cefazolin	Clindamycin
	Imipenem	Cefotaxime	Fluconazole
	Nafcillin	Ceftazidime	Ganciclovir
	Vancomycin	Cefuroxime	Meropenem
		Ciprofloxacin	Metronidazole
		Penicillin G	Neuraminidase inhibitors
		Piperacillin	Protease inhibitors[c]
		Ticarcillin	Reverse transcriptase inhibitors

[a] Avoid in neonates unless no alternative is available.

[b] Although specific data regarding the ability of these antimicrobials to displace bilirubin are lacking, these drugs appear to be safe in this regard based on clinical experience and a low degree of protein binding.

[c] Infants receiving amphotericin B or the protease inhibitor atazanavir can have elevated total serum bilirubin, but not because of displacement from albumin.

Metabolism

Many drug-drug interactions occur at the level of drug CL, particularly for drugs that undergo metabolism. The CYP450 enzyme system is responsible for the metabolism of many drugs, including antibiotics. These enzymes can be inhibited, induced, or saturated by substrate. For antibiotics that are primarily metabolized by one CYP450 isoform, the potential exists for significant changes in serum concentration, given that CL is either increased or decreased because of changes in enzyme activity. The highest concentration of these enzymes is in the liver, but the intestinal mucosa also contains CYP450 enzymes and is the site of numerous drug-drug interactions that affect bioavailability. To predict a clinically significant drug-drug interaction, therefore, similar questions are asked regarding whether the antibiotic is primarily metabolized by 1 CYP450 isoform or has alternative or parallel metabolic pathways and whether a change in serum concentration would have significance. Specifically, if the serum concentration is lowered, could the antibiotic concentration−time course ratio fall short of the optimal PK-PD–predicted concentration−time course ratio? If the serum concentration is raised, could toxicity occur?

Table 291.5 lists antimicrobial agents that modulate specific CYP450 isoforms that predispose a patient to potential drug-drug interactions when these drugs are coadministered with drugs metabolized by similar pathways. Knowledge of which isoform is primarily responsible for a drug's metabolism provides the clinician with the insight at least to question the possibility of a metabolically based drug-drug interaction. For specific drug-drug interactions, refer to individual agents in Chapter 292.

TABLE 291.5

Antibiotic–Cytochrome P450 Interactions[a]

Isoenzyme	Substrate	Inhibitor	Inducer
1A1	Chloroquine, erythromycin, nitrofurantoin, raltegravir	Atazanavir, ketoconazole, norfloxacin, quinidine	Albendazole, fluconazole, itraconazole, mebendazole, primaquine, **rifampin**
1A2	Albendazole, erythromycin, griseofulvin, pyrazinamide, rifabutin, rifampin, terbinafine	Albendazole, artemesinin, clarithromycin, efavirenz, erythromycin, fluconazole, fluoroquinolones (especially **ciprofloxacin**), isoniazid, ketoconazole, lopinavir, nevirapine, ritonavir, tenofovir	Albendazole, griseofulvin, **rifampin, ritonavir**
1B1	Erythromycin	Doxycycline, ketoconazole	**Rifampin**

2A6	Artemisinin, artesunate, rifampin, zidovudine		**Rifampin**
2B6	Artemisinin, efavirenz, nevirapine, rifampin, ritonavir	Amprenavir, efavirenz, ketoconazole, nelfinavir, ritonavir, nevirapine	Artemisinin, efavirenz, nevirapine, **rifampin, ritonavir**
2C8	Amodiaquine, amprenavir, chloroquine, dapsone, fosamprenavir, quinidine, sulfadiazine, trimethoprim, zidovudine	Chloramphenicol, efavirenz, fluconazole, indinavir, isoniazid, ketoconazole, metronidazole, rifampin, ritonavir, saquinavir, sulfamethoxazole, trimethoprim	Griseofulvin, **rifampin, ritonavir**
2C9	Amprenavir, dapsone, fluconazole, fosamprenavir, metronidazole, quinidine, rifampin, sulfamethoxazole, trimethoprim, terbinafine, voriconazole	Adefovir, atovaquone, chloramphenicol, efavirenz, **fluconazole,** indinavir, isoniazid, ketoconazole, lopinavir, metronidazole, nelfinavir, pyrimethamine, sulfamethoxazole, tenofovir, trimethoprim, voriconazole	Dapsone, nelfinavir, rifapentine, **rifampin, ritonavir**
2C19	Amoxicillin, artemether, chloramphenicol, clarithromycin, dapsone, etravirine, nelfinavir, praziquantel, proguanil, rifampin, terbinafine, voriconazole, zidovudine	Amprenavir, chloramphenicol, clarithromycin, efavirenz, fluconazole, fosamprenavir, indinavir, isoniazid, ketoconazole, lopinavir, probenecid	Artemisinin, **rifampin, ritonavir**
2D6	Chloroquine, rifampin	Chloroquine, efavirenz, fluconazole, isoniazid, lopinavir, mefloquine, nelfinavir, nevirapine, praziquantel, proguanil, quinidine, ritonavir	**Rifampin,** rifapentine
2E1	Dapsone, isoniazid, proguanil, rifampin, sulfadiazine	Isoniazid, itraconazole, ketoconazole, tenofovir	Ciprofloxacin, isoniazid, **rifampin**
3A4, 3A5, 3A7	Albendazole, azoles, artemether, artemesinin, chloroquine, clindamycin, dapsone, erythromycin, HIV protease inhibitors and nonnucleoside reverse transcriptase inhibitors, ivermectin, macrolides and azalides, mefloquine, primaquine, quinidine, rifampin, terbinafine, tetracyclines, trimethoprim, zidovudine	**Azoles,** caspofungin, clindamycin, efavirenz, fluoroquinolones, **HIV protease inhibitors**, isoniazid, **macrolides**, mefloquine, metronidazole, quinidine, quinupristin-dalfopristin, primaquine, sulfamethoxazole, tetracyclines	HIV protease inhibitors and nonnucleoside reverse transcriptase inhibitors, **rifampin,** rifapentine, terbinafine

[a] Currently described interactions are listed in http://bioinformatics.charite.de/supercyp/. Interactions may not be clinically significant, but have been described in vitro. The most significant inhibitors and inducers are shown in **bold.**

Elimination

The primary mechanisms of antibiotic elimination from the body involve elimination via bile, feces, urine, or combinations of these mechanisms. Drugs that are eliminated in the bile are subject to enterohepatic recirculation, which means that they can be reabsorbed into the circulation from drug-containing bile secreted into the intestines, resulting in complex absorption profiles characterized by multiple concentration peaks over the dosing interval. Amoxicillin can lower the effectiveness of oral contraceptives by altering the GI flora, reducing enterohepatic recirculation of the contraceptive, and enhancing elimination. Agents eliminated in urine can be filtered at the glomerular level and secreted at the tubular level. Fortunately, few drugs cause unwanted alterations at these sites. However, any agent that can reduce glomerular filtration (e.g., amphotericin B, cisplatin) can decrease the CL of the concurrently administered and filtered antibiotic, potentially necessitating dose adjustment. A notable example that has been used therapeutically is probenecid, a drug that inhibits the tubular secretion of organic acids by antagonizing the efflux effects of select organic anion transporters (OATs; see the later section on transporters). Probenecid can be coadministered with penicillin to reduce the extent of the antibiotic's tubular secretion and promote its accumulation in the body. This drug is also administered with systemic cidofovir to mitigate toxicity of the drug by reducing intraluminal concentrations. Nevertheless, the lack of adequate guidelines for pediatric dosing of probenecid, the unpredictability of the drug-drug interaction, and the exact amount of drug accumulation and the potential that probenecid can also interfere with in vivo antibiotic distribution (antagonism by probenecid of the organic acid transport used by selected β-lactams into target tissue) preclude the common use of probenecid for this use in children or adults.

Transporters

Transporters important to cellular homeostasis influence the bioavailability, distribution, and elimination of many drugs.[80] Examples of such transporters are P glycoprotein (P-GP), the organic anion transport polypeptides (OATP), and the organic cation transporters (OCTs), which often are associated with drug efflux out of the cell or facilitation of intracellular drug uptake. Transporters are found in many organs and tissues including the intestinal tract, placenta, blood-brain barrier, liver, and kidney and also are subject to induction and inhibition.[81] Drugs can serve as substrates, inhibitors, inducers, or any combination of the 3, thereby resulting in complex interactions that can be difficult to predict quantitatively. Thus changes in the balance of cellular efflux or uptake in the intestine may decrease or increase bioavailability, whereas changes in tissues may affect V_d and drug CL.

Antimicrobial agents that are substrates for the P-GP efflux transporter include select protease inhibitors, erythromycin, and the antifungal drugs ketoconazole and itraconazole. Substrates for OATs include the penicillins and select cephalosporins. Probenecid inhibition of OATP activity is still used as a part of the amoxicillin-probenecid drug combination for uncomplicated *Neisseria gonorrhoeae* (amoxicillin-susceptible) disease.

Pharmacodynamic Interactions

PD interactions can affect efficacy or toxicity, and drugs can interact to diminish or augment either effect. As discussed in Chapter 289, these interactions can be synergistic, additive, indifferent, or antagonistic. Because PD interactions arise from relationships with a drug's mechanisms of action, the clinician must be aware of these mechanisms. The appropriate question is whether the mechanisms of action of a patient's medications are likely to be related in any way. Table 291.6 outlines some frequent examples of each type of PD-based interaction.

TABLE 291.6

Examples of Pharmacodynamic Interactions

Efficacy	Toxicity
INCREASED Numerous examples exist: synergistic activity of β-lactam plus aminoglycoside against enterococci; β-lactam plus β-lactamase inhibitor for extended gram-negative and anaerobic coverage; trimethoprim plus sulfamethoxazole; quinupristin plus dalfopristin	**INCREASED** Two potentially nephrotoxic antibiotics such as vancomycin plus an aminoglycoside can increase the likelihood of renal injury
DECREASED	**DECREASED**

The antiretroviral drugs zidovudine and stavudine are antagonistic when coadministered, likely because of an interaction at the level of intracellular, molecular targets	Probenecid mitigates the nephrotoxicity of cidofovir[342]

Integration of Pharmacokinetic and Pharmacodynamic Principles for Optimal Antibiotic Dosing Regimens

Identification and definition of optimal doses and dosing intervals for antimicrobial agents have eluded clinicians and investigators for decades. This problem can be attributed to the difficulty and delay in measuring outcome, specifically, clinical improvement, microbiologic eradication, or survival. This difficulty in quantifying the effect of antibiotics is in contrast to other classes of drugs used in clinical medicine (e.g., antihypertensive drugs). Substantial research to date has described the PK properties for most antimicrobial drugs used in pediatric practice. The challenge remains to determine objective PD markers or end points that reflect optimal dosing to achieve the desired therapeutic response.[82]

Pharmacodynamic Correlates for Antibacterial Agents

Antibacterial agents influence the life cycle of organisms in various ways. To alter bacterial growth, antibiotics must bind to a cellular target[82–84] (Fig. 291.2). Binding of the drug to its target results in alteration of the normal function of the bacterium and leads to either inhibition of growth or cell death. In addition to the ability of an antimicrobial agent to reach its target site of action (i.e., the receptor), the drug also must possess sufficient affinity for its receptor, and it must achieve a sufficient concentration to affect bacterial function. These pharmacologic characteristics are the primary determinants of antimicrobial activity.

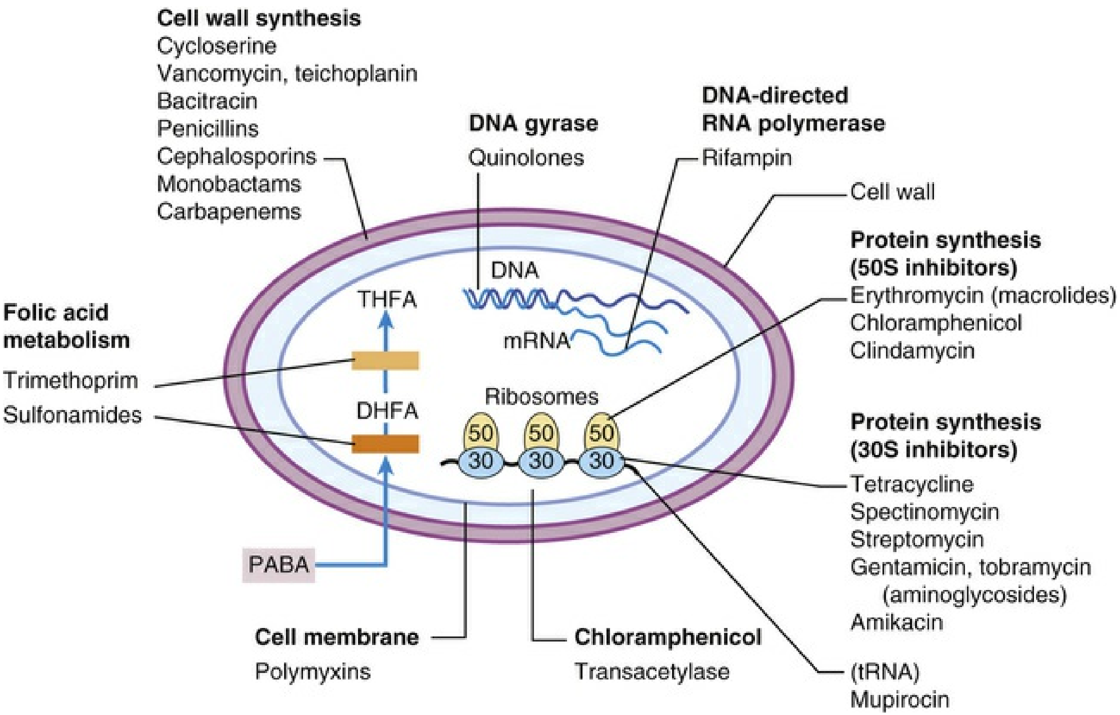

FIGURE 291.2 **Sites of action for major antibacterial drugs. DHFA, dihydrofolate; PABA, *para*-aminobenzoic acid; THFA, tetrahydrofolate.**

(Adapted from Neu HC. The crisis in antibiotic resistance. Science 1992;257:1064–1073.)

Unfortunately, investigators are unable directly to quantify these characteristics clinically. As such, surrogate markers have been developed in an attempt to reflect these crucial cellular interactions. For antibacterial agents, in vitro tests such as the MIC and the minimal bactericidal concentration (MBC) are used as indirect measures of in vivo activity.[85–87] However, these markers do not provide sufficient information on the temporal pattern of exposure of an organism to antimicrobial agents or the antimicrobial concentration that must be achieved relative to the MIC and the MBC to ensure a sufficient therapeutic response.

Consideration of the laboratory procedures used in determining MICs and MBCs raises caution for use as primary indicators of clinical antimicrobial activity. First, measurements of MIC and MBC are obtained in bacterial growth media that are devoid of protein (e.g., represent 100% free active drug), which can have implications for agents that are highly bound to plasma proteins (e.g., >70%). Similar concentrations of free drug at the anatomic site of infection may not be achievable clinically because of extensive protein binding, drug molecular weight, and degree of ionization at pathophysiologic pH. Second, measuring MICs and MBCs usually involves maintaining a constant concentration of free drug for a standard period (generally 18–24 hours). Such a constant concentration simulates a continuous infusion of antibiotic, whereas clinically, antibiotics are usually administered intermittently, which results in peaks and troughs rather than constant concentrations. Third, MICs or MBCs are measured on a standard inoculum of bacteria that may or may not reflect the actual density of bacteria present at the site of infection. Finally, the laboratory procedures used to determine the MIC and MBC do not account for the antimicrobial activity of various host defenses, including immunoglobulins and macrophages.

In vitro susceptibility testing is especially valuable in identifying antimicrobial agents that will be ineffective in eradicating the pathogen. Conversely, a pathogen can appear susceptible to a particular agent from in vitro testing, yet information is lacking on the ability of the agent to achieve the necessary concentrations for a sufficient period at the site of infection to eradicate the pathogen. The immense importance of integrating such data with therapeutic outcome is exemplified by the PK-PD correlates in the successful treatment of bacterial meningitis.[67,82,88] The time course of the drug must be integrated with the concentration at the receptor site to reflect the in vivo antibiotic-bacteria interaction adequately.

As a result of the different mechanisms of inhibiting or killing bacteria and the position of safely achievable concentrations on the concentration-response curve, specific PK-PD properties can be correlated with efficacy (Table 291.7).[89] The first pattern of activity is for drugs with concentrations near the upper, flat portion of the concentration-response curve and that have minimal postantibiotic effect (i.e., ongoing killing after serum concentrations have dropped to less than the MIC). The activity of these drugs depends on the duration of *time that the antibiotic concentration exceeds the MIC* (T >MIC).[82] For these antibiotics, saturation of the bacterial killing rate is observed at certain multiples of the MIC, usually 2 to 4 times, and antibiotic concentrations exceeding this level generally do not achieve greater killing rates. Clearly, the duration that the antibiotic concentration exceeds the MIC of the pathogen is influenced by several factors, including the dosing interval, the pathogen, and the site of infection. Drugs that demonstrate this type of PK-PD relationship are referred to as *time dependent*. Some investigators refer to this class as concentration-independent antibiotics, but this term is not preferable because all antibiotics require a minimal concentration for efficacy. Examples of drugs that exhibit time-dependent killing include all the β-lactams (see Table 291.7).

TABLE 291.7

Classification of Selected Antibacterials Based on Their Pattern of Antimicrobial Activity

Pattern	Drug	Target
Peak/MIC Concentration-dependent killing, prolonged postantibiotic effects	Aminoglycosides	10
	Daptomycin[343]	100 (*Staphylococcus aureus*) 36 (*Streptococcus pneumoniae*) 0.25 (*Enterococcus faecium*)
	Fluoroquinolones	10
	Metronidazole	?
Time >MIC Time-dependent killing, minimal postantibiotic effects	Carbapenems, aztreonam	>20%-40%
	Cephalosporins	>20%-40%
	Penicillins	>40%-60%
AUC/MIC Time-dependent killing, moderate to prolonged persistent antibiotic effects	Azithromycin	25[344]
	Clindamycin	?
	Telithromycin	3[345]
	Dalbavancin[346]	1,000 (*S. aureus*) 100 (*Streptococcus* species)
	Linezolid	80 (or trough > MIC)[347]
	Metronidazole	70[348]
	Macrolides	30[349,350]
	Quinupristin-dalfopristin	?
	Telavancin	219[351]
	Tetracyclines	10
	Tigecycline	18 (gram-positive organisms)[352] 7 (gram-negative organisms)[353]
	Vancomycin	400 (trough ~8 × MIC)[341]

AUC, area under the curve; MIC, minimal inhibitory concentration.

Data are from references 85 and 354 unless otherwise noted.

In contrast, a second pattern of bacterial killing has been characterized for drugs that have concentrations in the steeper portion of the concentration-response curve and that have some degree of postantibiotic effect.[90,91] The bactericidal ability of agents in this group depends on the *peak concentration to MIC* (peak/MIC) within the dosing interval. In other words, the higher the antibiotic peak concentration, the greater is the bacterial kill. Agents that demonstrate this type of PK-PD interface are referred to as *concentration-dependent* or *peak-dependent* antibiotics and include aminoglycosides and fluoroquinolones.

A third class of drugs also has a postantibiotic effect, although it is typically more modest than that of the peak-dependent antibiotics, and these drugs lie near the upper portion of the concentration-response curve. For these drugs it is simply the *AUC/MIC* ratio that best describes activity. These are also called time-dependent drugs, but the moderate postantibiotic effect makes the choice of dose interval less critical than for time-dependent drugs that have little to no postantibiotic effect. Examples of AUC/MIC drugs include vancomycin and azithromycin.

Fig. 291.3 depicts the relationships between drug concentration and effect. The clinical challenge relative to the PK-PD properties of T >MIC and peak/MIC or AUC/MIC is determining the target range for each that correlates with bacteriologic response. These relationships and targets are summarized in Table 291.7.

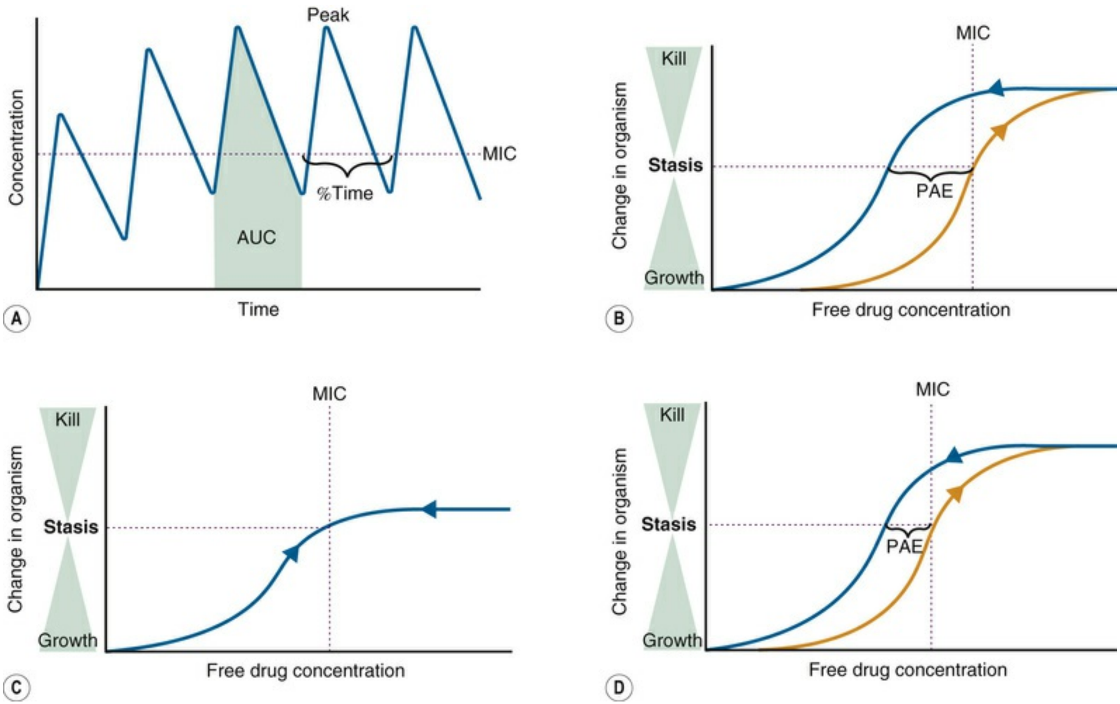

FIGURE 291.3 **Relationship between concentrations and effects for antimicrobials. (A) The 3 classical categories of antimicrobial compounds: peak/minimal inhibitory concentration (MIC), time > MIC, and area under the plasma drug concentration–time curve (AUC)/MIC. (B) The reason that a drug's pharmacokinetic-pharmacodynamic**

linkage may be peak/MIC. As the free drug plasma concentration increases (moving to the right on the x-axis), effect increases in a sigmoidal fashion following the *blue curve.* As the free drug concentration falls (moving to the left on the x-axis), effect diminishes, following the *gold curve.* The effect, in change of organism numbers is shown on the y-axis. Net kill is shown as dashed line above the horizontal. Net growth is shown below it. At the horizontal line stasis occurs, which corresponds to a free drug concentration at the MIC. Note that as the drug concentration falls (along the *red curve*), to less than the MIC, a continued net kill of organism can occur. This is a prolonged antimicrobial effect (PAE), which typifies peak/MIC drugs. The split effect curve (*gold* and *blue*) is termed "negative hysteresis" and can result from delayed action of a drug relative to plasma concentrations, such as a drug's inhibition of microbial protein synthesis. (C) No PAE or negative hysteresis is present, and as soon as drug concentrations fall to less than the MIC, the organism begins to regrow, as is typical of time >MIC agents. (D) Finally, a moderate PAE is present, and the daily dose could be given less frequently as a larger dose (as long as dosing is not so infrequent as to allow regrowth) or more frequently in smaller doses, typical of AUC/MIC agents.

Clinical Utility of Antibiotic Pharmacokinetic-Pharmacodynamic Correlates

The superior ability to predict bacteriologic cure by using integrated PK-PD characteristics, rather than MIC or MBC information solely (see Table 291.7), helps standardize antimicrobial dosing in clinical trials and assists in guiding antimicrobial therapy for individual patients.[82,86,90,92] Furthermore, providing adequate amounts of antibiotic for sufficient periods by optimal dosing based on PK-PD properties also may decrease the rate and extent of bacterial resistance. An appreciation of the PK-PD characteristics of aminoglycosides, combined with a better understanding of their safety profiles, led to once-daily dosing of aminoglycosides that can take advantage of the concentration-dependent killing characteristics of this class of antibiotics (i.e. peak/MIC correlation).[93]

Moreover, in patients with a poor clinical response, an understanding of a particular drug's PK-PD characteristics allows the clinician rationally to assess the potential contribution of suboptimal dosing and to develop an effective, alternative regimen. In their assessment of published data, Craig and Andes[94] demonstrated that the T >MIC for β-lactam antibiotics predicted bacteriologic efficacy with accuracy similar to that of the ratio of middle ear fluid concentration to MIC. Moreover, when the T >MIC exceeded 40% to 50% of the dosing interval, bacteriologic and clinical cure was achieved in 80% to 85% of the patients studied. Although most of the *Streptococcus pneumoniae* isolates in these studies were susceptible to penicillin, the same principles apply to nonsusceptible organisms. For example, conventional amoxicillin dosing (13.3 mg/kg/dose 3 times daily) would be expected to exceed the target T >MIC for penicillin-susceptible *S. pneumoniae*, whereas higher doses (45–50 mg/kg/dose twice daily) often are required to achieve the target T >MIC for many nonsusceptible isolates. It is not the increased dose of amoxicillin per se that correlates with increased efficacy, but rather the longer T >MIC afforded by higher initial concentrations. As an extension of this work, much attention has been paid to modeling improved efficacy of prolonged infusion of β-lactams against resistant gram-negative organisms,[95] and this approach has been prospectively validated in critically ill adults in a randomized study.[89]

An awareness of PK-PD characteristics also permits more sophisticated interpretation of the breakpoints for in vitro susceptibility.[96] In general, guidelines for interpretation are derived from the likelihood of bacteriologic success relative to the MIC of the infecting organism and the projected achievable *serum* concentration of antibiotic. A major exception is the breakpoint reporting for *S. pneumoniae,* for which additional interpretation is based on projected achievable central nervous system concentrations. Thus, if the infection is in an anatomic location other than that for which the breakpoints were derived, the breakpoints can be less relevant.

Pharmacokinetic and Pharmacodynamic Relationships of Other Antimicrobial Agents

Maximizing desirable PD outcomes in combination with minimizing undesirable adverse effects necessarily requires the ability to quantify such end points. Furthermore, an objective index variable must be identified to which therapy can be linked to achieve the therapeutic goals. Although our knowledge of PK-PD relationships for other antimicrobial agents (e.g., antifungal, antiviral, antimycobacterial) is not yet as advanced as for antibacterial agents, progress is being made.[97–99]

Antifungal MICs are determined most reliably for yeasts (e.g., *Candida* and *Cryptococcus*). The value of MICs lies in the assignment of susceptibility breakpoints: drug concentrations higher than which the isolate is considered resistant and lower than which it is considered susceptible. The Clinical Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) have established breakpoints for azoles, echinocandins, and flucytosine against *Candida* spp. Although some reliability is similar to MIC breakpoints for bacterial infections,[100] controversy still surrounds the exact thresholds for susceptibility.[101,102] Breakpoints for filamentous fungi, such as *Aspergillus*, still do not exist and will be difficult to generate now that combination therapy is widely used for *Aspergillus* and other filamentous fungal infections.[103] We are only in the early stages of understanding optimal PK-based dosing of antifungal drugs, and Table 291.8 shows the hypothesized relationships and dosing implications.[104]

TABLE 291.8

Proposed Pharmacokinetic-Pharmacodynamic Relationships for Antifungal Drugs

Drug	PK-PD Relationship	Notes
Amphotericin B	Peak/MIC?	Single, large daily doses are more effective than smaller, frequent doses; the dosage is limited by toxicity to a maximum of 1.5 mg/kg/day
Lipid amphotericin B (AmBisome, Abelcet, Amphotec)	Peak/MIC?	As above, but the PK properties of the 3 preparations are different, and more studies are required to determine whether PD differences also exist. Lower toxicity in general permits a higher dosing of 5 mg/kg/day, and tolerability up to 15 mg/kg/day (Ambisome[355]) and 10 mg/kg/day (Abelcet[356]) has been reported, but added efficacy at the higher doses has not been demonstrated and may result in increased nephrotoxicity[357]
Fluconazole	AUC/MIC	Optimal dosing is 6 mg/kg/day IV or PO for susceptible isolates and 12 mg/kg/day for dose-dependent isolates. A loading dose of 25 mg/kg on day 1 should be strongly considered in infants.[358] Doses >12 mg/kg offer unproven additional benefit and increase the risk of toxicity. A dose-MIC ratio of >50 or an AUC/MIC ratio of >25 have been suggested as targets[359]

Itraconazole	AUC/MIC	Target trough concentrations of >0.5 mg/L are recommended[360]
Posaconazole	AUC/MIC	Concentrations demonstrate high interpatient variability; in 2 pivotal phase 3 studies analyzed by the FDA, a plasma concentration of >0.35 mg/L 3–5 hr after dosing on day 2 was predictive of a concentration of >0.70 mg/L at the same time on day 7, which was associated with *prevention* of invasive fungal infections.[360] Another study reported best *treatment* outcomes with average concentrations of >1.25 mg/L.[361] In practice such concentrations are difficult to achieve in children with the suspension[362]; however, the newer delayed-release tablet formulation (approved for ≥13 years of age) has greatly enhanced absorption, and such concentrations are easier to obtain
Voriconazole	AUC/MIC	Target trough concentrations of >1.0 mg/L have been associated with survival benefit in children[7]
Flucytosine	T>MIC	In vitro data suggest that peak efficacy occurs at a serum concentration–MIC ratio of 4 : 1. No data exist on the most effective duration of serum concentration higher than the MIC. If toxicity is problematic (typically with peak >100 mg/L), smaller, more frequent doses or even continuous infusion may be more effective, but human data are lacking. Usual peaks are 30–100 mg/L[363]
Echinocandins (caspofungin, micafungin, anidulafungin)	AUC/MIC	Clinical data are lacking, but in vitro and animal models suggest that for *Candida* species, a free drug AUC/MIC ratio of 5–20 (high end for *C. albicans*, lower for *C. parapsilosis*) may be adequate,[364] which is an AUC/MIC ratio of 3,000 in patients.[365] For *Aspergillus* species, the target is a free C_{max}/MEC ratio of approximately 10[366]

AUC, area under the curve; C_{max}, maximal concentration; FDA, Food and Drug Administration; IV, intravenously; MEC, minimum effective concentration, which is the minimum amount of drug to cause transition to a compact rounded hyphal form; MIC, minimal inhibitory concentration; PD, pharmacodynamic; PK, pharmacokinetic; PO, orally.

PK-PD dosing for antiviral drugs, as shown in Table 291.9, has been most commonly applied to therapy for human immunodeficiency virus (HIV) infection. The concept of MIC determination translates as the inhibitory concentration, or IC_{xx}, where xx is the percentage of viral strains within a particular species for which replication is inhibited in vitro at drug concentration IC. Numerous studies have demonstrated a dose-response relationship for both protease inhibitors and nonnucleoside reverse transcriptase inhibitors and have identified threshold trough serum concentrations, or AUC, greater than which efficacy is improved (as measured by the reduction in viral load and increased $CD4^+$ T-lymphocyte count). Studies also have demonstrated the safety and feasibility of antiretroviral therapeutic regimens tailored to specific patients to maintain serum drug concentrations within a predetermined range, although efficacy studies are yet to come.

TABLE 291.9

Pharmacokinetic-Pharmacodynamic Targets for Antiretroviral and Antiviral Drugs Based on Clinical Data

Drug	**Target C_{min} (ng/mL)**	**Notes**
NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS		
Efavirenz	1,000	
Etravirine	275 (81–2,980)	No efficacy target established; value is median (range) from clinical studies
Nevirapine	3,000	
PROTEASE INHIBITORS		
Atazanavir	150	
Darunavir	3,300 (1,255–7,368)	No efficacy target established; value is median (range) from clinical studies in adults given 600 mg twice daily
Fosamprenavir	400	Measured as amprenavir
Lopinavir	1,000	
Nelfinavir	800	Parent drug plus M8 active metabolite
Tipranavir	20,500	Not suggested for PI-naïve patients
ENTRY INHIBITOR		
Maraviroc	50	Not suggested for treatment-naïve patients
INTEGRASE STRAND INHIBITOR		
Raltegravir	72 (29–118)	No efficacy target established; value is median (range) from clinical studies in adults given 600 mg twice daily
NONANTIRETROVIRAL		
Ganciclovir[105]	AUC 35–50 µg/mL/hr	For prevention of CMV infection

AUC, area under the curve; C_{min}, minimal concentration; CMV, cytomegalovirus; PI, protease inhibitor.

Data on antiretroviral agents from Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. AIDSinfo. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. 2015. www.aidsinfo.nih.gov.

For non-HIV viral infections, some data suggest that the acyclovir effect is time dependent and that if the serum drug concentration remains higher than the IC_{50} of herpes simplex virus or varicella-zoster virus for at least 12 hours per day, clinical efficacy is maximized. Ganciclovir has been reported to have near-maximal efficacy to prevent cytomegalovirus infection when a target AUC of 35 to 50 µg/mL per hour is reached, with a concomitant 10% to 20%, and 30% to 50% probability of the patient's developing neutropenia and leukopenia, respectively.[105]

Future Considerations

Increasingly, drug dosing will be based on achieving PK-PD targets in individual patients rather than the traditional population-based recommendations of dosing ranges. Therefore studies of new antimicrobial agents must include an assessment of PK-PD relationships. The ongoing challenge in pediatrics is to ensure that the determination of these important surrogate markers or end points incorporates the important changes that occur with increasing age. Box 291.1 synthesizes the information presented in this chapter into questions that a thorough clinician should consider for every patient to whom antibiotics are to be administered. Box 291.2 provides a listing of useful websites for additional information.

Box 291.1

Important Pharmacokinetic-Pharmacodynamic Issues to Consider When Determining the Dose of Antibiotics

What is the known or suspected target pathogen?

What is the minimal inhibitory concentration of available antibiotics for the pathogen? Will adequate concentrations of the drug be distributed to all infected sites?

Are there any characteristics of the patient that will alter the usual pharmacokinetic properties of the drug?

What process best describes the antibiotic antibacterial activity: time dependent or concentration dependent?

Based on the pharmacokinetic-pharmacodynamic correlate, how often should the antibiotic be administered?

With a suboptimal clinical response, should the individual dose be increased, administered more frequently, or both? Should a different drug be used?

Box 291.2

Useful Websites

URL	Notes
redbook.solutions.aap.org	American Academy of Pediatrics *Red Book Report of the Committee on Infectious Diseases* (paid subscription required)
aidsinfo.nih.gov	Regularly maintained searchable database of treatment guidelines involving therapeutic agents for human immunodeficiency virus infection
www.dailymed.nlm.nih.gov, www.drugs.com, and www.rxlist.com	Searchable databases with links for prescribers to reproductions of the package insert
www.ncbi.nlm.nih.gov/pubmed	National Library of Medicine PubMed/MEDLINE database of medical journal articles, many of which are available as full text items
www.idsociety.org/Index.aspx	Infectious Diseases Society of America, which includes numerous freely available treatment guidelines

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APPENDIX 291.1 Usual Dosing, Therapeutic Targets, and Suggestions for Maintenance Dosing of Selected Antimicrobial Agents in Patients With Impaired Renal Function[a]

Drug (Route)	**Usual Dosing: Maintenance *(Daily Max)***	**Adjustment of Usual Dosing for Renal Failure GFR (mL/min/1.73 m^2)[b]**			**Adjustment for Dialysis[c]**
		>60–90	**30–60**	**<30**	
AMINOGLYCOSIDES[d]					
Amikacin (IM, IV)[108,112–117]	5–7.5 mg/kg q8h	60%–90% q12h	30%–70% q12–18h	20%–30% q24–48h	H: 66% after H
					P: 15–20 mg/L IP
					C: As for CLCr 30–60
Gentamicin (IM, IV)[114,118–121,127–130]	2.5 mg/kg q8h	60%–90% q8h	30%–70% q12h	20%–30% q24–48h	H: 66% after H
					P: 3–4 mg/L IP
					C: As for CLCr 30–60
Streptomycin (IM, IV)[114,122–124]	20–40 mg/kg q24h *(2 g/day)*	Usual dosing	100% q24–72h	100% q72–96h	H: 50% after H
					P: 20-40 mg/L IP
					C: As for CLCr 30–60
					P: 3–4 mg/L IP
					C: As for CLCr 30–60

Tobramycin	2.5 mg/kg q8h	60%–90% q8h	30%–70% q12h	20%–30% q24–48h	H: 66% after H P: 3–4 mg/L IP C: As for CLCr 30–60
CEPHALOSPORINS[e]					
Cefaclor (PO)[125]	10–20 mg/kg q12h *(1.5 g/day)*	Usual dosing	Usual dosing	50% q8h	H: 50–75% q8h P: No significant clearance C: Usual dosing
Cefadroxil (PO)[126]	15 mg/kg q12h *(2 g/day)*	Usual dosing	100% q24h	100% q48h	H: 100% q48h P: No significant clearance C: As for CLCr 30–60
Cefazolin (IV)[127–130]	20–35 mg/kg q8h *(12 g/day)*	Usual dosing	100% q12h	100% q24h	H: 100% q24h P: 15 mg/kg IP q24h C: As for CLCr 30–60
Cefdinir (PO)[131,132]	14 mg/kg q24h *(600 mg/day)*	Usual dosing	Usual dosing	50% q24h	H: 50% q48h P: No significant clearance C: As for CLCr 30–60
Cefepime (IV)[127,133–135]	50 mg/kg q8–12h *(6 g/day)*	100% q12h	100% q16–24h	100% q24–48h	H: 50% q24h P: 15 mg/kg IP q24h C: As for CLCr >60–90
Cefixime (PO)[136]	8 mg/kg q24h *(400 mg/day)*	Usual dosing	75% q24h	50% q24h	H: 75% q24h P: No significant clearance C: As for CLCr 30-60
Cefotaxime[f] (IV)[137,138]	50–75 mg/kg q6–8h *(12 g/day)*	Usual dosing	Usual dosing	50% q6–8h	H: 50% q6–8h P: 500 mg IP q24h C: As for CLCr 30–60
Cefoxitin (IV)[139,140]	20–40 mg/kg q6h *(12 g/day)*	100% q8h	100% q8–12h	100% q24–48h	H: 100% q24–48h P: No significant clearance C: As for CLCr 30–60

Cefpodoxime (PO)[141–143]	5 mg/kg q12h *(800 mg/day)*	Usual dosing	Usual dosing	50% q12h	H: 50% q12h P: No significant clearance C: As for CLCr 30–60
Cefprozil (PO)[144]	15 mg/kg q12h *(1 g/day)*	Usual dosing	Usual dosing	100% q24h	H: 100% q24h P: Significant clearance unlikely C: Likely as for CLCr 30–60
Ceftaroline[g] (IV)[145]	>12y: 8 mg/kg q12h *(1.2 g/day)*	Usual dosing	50%–75% q12h	50% q12h	H: 50% q12h P: No significant clearance C: As for CLCr 30–60
Ceftazidime (IV)[130,146–150]	50 mg/kg q8h *(12 g/day)*	Usual dosing	100% q12h	100% q24h	H: 100% q24h P: 50% IV q24h OR 125 mg/L continuous IP OR 15–20 mg/kg q24h IP C: 50–75% q12h
Ceftriaxone (IV, IM)[151–154]	50–100 mg/kg/day divided q12–24h *(4 g/day)*	Usual dosing	Usual dosing	Usual dosing	H: Usual dosing P: 50 mg/kg IP q24h C: Usual dosing
Cefuroxime sodium (IV)[147]	35-50 mg/kg q8h *(6 g/day)*	Usual dosing	100% q8–12h	100% q24h	H: 100% q24h P: 15 mg/kg IP q24h C: As for CLCr 30–60
Cefuroxime axetil (PO)[147,155]	15 mg/kg q12h *(3 g/day)*	Usual dosing	100% q12h	100% q24h	H: 100% q24h P: No significant clearance C: As for CLCr 30–60
Cephalexin[h] (PO)[156]	25 mg/kg q6h *(4 g/day)*	Usual dosing	Usual dosing	50% q6h	H: 50% q6h P: No significant clearance C: Usual dosing
PENICILLINS					

Amoxicillin (PO)	25–90 mg/kg/day divided q8–12h *(4 g/day)*	Usual dosing	Usual dosing	100% q12–24h	H: 100% q24h P: Significant clearance unlikely C: Usual dosing
Amoxicillin with or without clavulanic acid (PO) (doses in amoxicillin)	20–45 mg/kg/day 90 mg/kg/day (ES-600 formulation) divided q8–12h *(1.75 g/day amoxicillin)*	Usual dosing	Usual dosing	100% q12–24h	H: 100% q24h P: Significant clearance unlikely C: Usual dosing
Ampicillin with or without sulbactam (IV, IM)[157,158] (doses in ampicillin)	25–50 mg/kg q6h *(12 g/day ampicillin)* *(8 g/day ampicillin-sulbactam)*	Usual dosing	100% q8h	100% q12h	H: 100% q24h P: 100% q12h IP C: Usual dosing
Dicloxacillin (PO)	6.25 mg/kg q6h *(2 g/day)*	Usual dosing	Usual dosing	Usual dosing	H/P: No significant clearance C: Usual dosing
Nafcillin[i] (IV)[159]	25–50 mg/kg q6h (12 g/day)	Usual dosing	Usual dosing	Usual dosing	H/P: No significant clearance C: Usual dosing
Oxacillin[j] (IV)	25–50 mg/kg q6h *(12 g/day)*	Usual dosing	Usual dosing	Usual dosing	H/P: No significant clearance C: Usual dosing
Penicillin G (IV)	100–300 kU/kg/day divided q4–6h *(24 MU/day)*	Usual dosing	50% q4–5h	50% q8h	H: 50% q8h P: No significant clearance C: 50% q4–5h
Penicillin VK (PO)	25–50 mg/kg/day divided q6–8h *(2 g/day)*	Usual dosing	50% q4–5h	50% q8h	H: 50% q8h P: No significant clearance C: 50% q4–5h
Piperacillin and tazobactam (IV)[160–164] (doses in piperacillin)	2–9 mo: 80 mg/kg q8h >9 mo: 100 mg/kg q8h >40 kg: 3 g q6h *(16 g/day)*	Usual dosing	66% q6–8h	66% q8h	H: 66% q12h + 20% after H P: No significant clearance and IP tazobactam

					not well absorbed C: As for CLCr 30–60
Ticarcillin and clavulanate (IV)[165,166]	50 mg/kg q4–6h *(18 g/day)*	66% q4–6h	66% q8h	66% q8–12h	H: 66% q12h + 100% after H P: 100% q12h IV C: As for CLCr 30–60
MONOBACTAM					
Aztreonam (IV)[167–169]	30–40 mg/kg q8h *(8 g/day)*	Usual dosing	50%–75% q8h	25% q8h	H: 25% q8h + 12.5% after H P: 100% q8h IP or 25% q8h IV C: As for CLCr 30–60
CARBAPENEMS					
Doripenem[k] (IV)[170]	3 mo–2 yr: 20 mg/kg q8h *(3 g/day)*	Usual dosing	50%–75% q8h	50%–75% q12h	H: Likely similar to other carbapenems P: Significant clearance unlikely C: As for CLCr 30–60
Ertapenem (IV)[171–173]	<13 yr: 15 mg/kg q12h ≥13 yr:1 g q24h *(1 g/day)*	Usual dosing	Usual dosing	50% q12h	H: 50% q12h + 15% after H if H <6h after last dose P: Significant clearance unlikely C: Likely as for CLCr 30–60
Imipenem[l] (IV)[174–183]	15–25 mg/kg q6h *(4 g/day)*	Usual dosing	50% q8h	50% q12h	H: 50% q12h + 25% after H if H <6 hr after last dose P: No significant clearance C: As for CLCr 30–60
Meropenem (IV)[184–193]	20–40 mg/kg q8h *(6 g/day)*	Usual dosing	100% q12h	50% q12–24h	H: 50% q24h; *Or* 100% q48h P: No significant clearance

					C: As for CLCr 30–60
FLUOROQUINOLONES					
Ciprofloxacin (IV, PO)[194–197]	10–20 mg/kg q12h *(1.5 g/day)*	Usual dosing	50% q12h	50% q18h	H: No significant clearance P: No significant clearance C: As for CLCr 30–60
Levofloxacin[198–206] (IV, PO)	<5 yr: 10 mg/kg q12h ≥5 yr: 10 mg/kg q24h *(750 mg/day)*	Usual dosing	50% q24h	50% q48h	H: No significant clearance P: No significant clearance C: As for CLCr 30–60
Moxifloxacin[m] (IV, PO)[207,210,211]	10 mg/kg q24h *(400 mg/day)*	Usual dosing	Usual dosing	Usual dosing	H: No significant clearance P: No significant clearance C: Significant clearance unlikely
MACROLIDES AND LINCOSAMIDES					
Azithromycin (IV, PO)[212]	5–12 mg/kg q24h *(0.5 g/day 2 g/single dose PO)*	Usual dosing	Usual dosing	Usual dosing	H/P/C: Usual dosing
Clarithromycin (PO)	7.5 mg/kg q12h *(1 g/day)*	Usual dosing	Usual dosing	50% q12h	H/P/C: Significant clearance unlikely
Clindamycin (IM, IV)[213]	20–40 mg/kg divided q8h *(4.8 g/day)*	Usual dosing	Usual dosing	Usual dosing	H/P/C: Usual dosing
Clindamycin (PO)	10–40 mg/kg divided q6–8h *(1.8 g/day)*	Usual dosing	Usual dosing	Usual dosing	H/P/C: Usual dosing
Erythromycin[n] (PO)[214]	12.5 mg/kg q6h *(4 g/day)*	Usual dosing	Usual dosing	Usual dosing	H/P/C: Usual dosing
Telithromycin (PO)	No data *(800 mg/day)*	Usual dosing	Usual dosing	75% q24h	H: 75% q24, after dialysis on dialysis days P: Significant clearance unlikely C: Usual dosing

TETRACYCLINES					
Doxycycline[o] (IV, PO)[215]	1–2 mg/kg q12h *(200 mg/day)*	Usual dosing	Usual dosing	Usual dosing	H/P/C: No significant clearance
Tigecycline[p] (IV)	8–11 yr: 1.2 mg/kg q12h 12–17 yr: 50 mg q12h *100 mg/day*	Usual dosing	Usual dosing	Usual dosing	H/P/C: No significant clearance
OXAZOLIDINONES					
Linezolid (IV, PO)[216–220]	10 mg/kg q8h *(1.2 g/day)*	Usual dosing	Usual dosing	Usual dosing	H: Usual dosing P: Significant clearance unlikely C: Usual dosing
Tedizolid (IV, PO)	No data *(200 mg/day)*	Usual dosing	Usual dosing	Usual dosing	H: Usual dosing P: Significant clearance unlikely C: Usual dosing
OTHER ANTIBACTERIAL AGENTS					
Chloramphenicol (IV)[221,222]	12.5–25 mg/kg q6h *(4 g/day)*	Usual dosing	Usual dosing	Usual dosing	H: Usual dosing P/C: No significant clearance
Daptomycin[q] (IV)[223,229–232]	2–6 yr: 12 mg/kg q24h 7–17 yr: 7–9 mg/kg q24h *(6 mg/kg/day)*	Usual dosing	Usual dosing	100% q48h	H: 100% q48h P:100% q48h; *Or* 7 mg/kg IP q24h C: 8 mg/kg IV q48h
Metronidazole[r] (IV, PO)[233–235]	7.5–15 mg/kg q8h *(4 g/day)*	Usual dosing	Usual dosing	75% q6h	H: Usual dosing P: No significant clearance C: Usual dosing
Nitrofurantoin (PO)	1–2 mg/kg q6h *(400 mg/day)*	Usual dosing	Avoid	Avoid	H/P/C: avoid
Quinupristin-dalfopristin[s] (IV)[236,237]	7.5 mg/kg q8h *(22.5 mg/kg/day)*	Usual dosing	Usual dosing	Usual dosing	H/P/C: No significant clearance
Trimethoprim-sulfamethoxazole (IV, PO)[238–240]	4–6 mg/kg q12h	Usual dosing	Usual dosing	100% q12–24h	H: 100% q24h
	Pneumocystis: 5 mg/kg q6–8h	Usual dosing	100% q8h	100% q12–24h	P: No significant clearance C: As for CLCr 30–60

	(20 mg/kg/day)				
Vancomycin[t] (IV)[167,241–245]	15 mg/kg q6h *(2 g/day)*	100% q12–24h	10 mg/kg q24–96h	10 mg/kg q4–10 days	H: 10 mg/kg after H P: 50–100% IP q24h C: As for CLCr 30–60
ANTITUBERCULOUS AGENTS					
Ethambutol (PO)[246–248]	15–25 mg/kg q24h *(2.5 g/day)*	Usual dosing	Usual dosing	100% q48h	H: 100% q48h P: No significant clearance C: Likely usual dosing
Ethionamide (PO)[249]	15–20 mg/kg q24h *(1 g/day)*	Usual dosing	Usual dosing	50% q24h	H: 50% q24h P: No significant clearance C: Likely usual dosing
Isoniazid (IV, PO)[247,250–252]	10–20 mg/kg q24h *(300 mg/day)*	Usual dosing	Usual dosing	Usual dosing	H/P/C: Usual dosing
Para-aminosalicylic acid (PO)[122,249]	100–150 mg/kg q12h *(10 g/day)*	Usual dosing	Usual dosing	Usual dosing	H/P/C: Usual dosing
Pyrazinamide[u] (PO)[122,247,250,253,254]	15–30 mg/kg q24h *(2 g/day)*	Usual dosing	Usual dosing	100% q48–72h	H: As for CLCr <10 P: As for CLCr <10 C: No data
Rifampin (IV, PO)[122,247,250]	10–20 mg/kg q12h *(600 mg/day)*	Usual dosing	Usual dosing	Usual dosing	H/P/C: No significant clearance
ANTIFUNGAL AGENTS					
Polyenes					
Amphotericin B (IV)	0.5–1.5 mg/kg q24h *(1.5 mg/kg/day)*	Usual dosing	Usual dosing	100% q24–48h	H/P/C: No significant clearance
AmBisome (liposomal amphotericin B) (IV)	3–5 mg/kg q24h *(7.5 mg/kg/day)*	Usual dosing	Usual dosing	100% q24–48h	H/P/C: No significant clearance
Abelcet, Amphotec (lipid amphotericin B) (IV)	5 mg/kg q24h *(5 mg/kg/day)*	Usual dosing	Usual dosing	100% q24–48h	H/P/C: No significant clearance
Azoles					
Fluconazole (IV, PO)[163,255–259]	3–12 mg/kg q24h PO/IV *(400 mg/day)*	Usual dosing	50% q24h	50% q48h	H: 100% after H P: As for CLCr <30 C: As for CLCr 30–60
Isavuconazole[v]	No data	Usual	Usual dosing	Usual dosing	H/P/C:

(IV, PO)	*(600 mg/day isavuconazole)*	dosing			Significant clearance unlikely
Itraconazole[w] (IV, PO)[260,261]	2.5 mg/kg q12h *(200 mg/day)*	Usual dosing	Usual dosing	Usual dosing	H/P/C: No significant clearance
Posaconazole[x] (PO)[262]	>8–13 yr: 200 mg q6h or 400 mg q12h >13–17 yr: 200 mg q8h No data for IV or DR oral formulations *(800 mg/day)*	Usual dosing	Usual dosing	Usual dosing	H/P/C: No significant clearance
Voriconazole (IV, PO)[263–266]	7–10 mg/kg q12h *(800 mg/day)*	Usual dosing	Usual dosing	Usual dosing	H/P/C: No significant clearance
Echinocandins					
Anidulafungin[y] (IV)	1.5 mg/kg q24h *(100 mg/day)*	Usual dosing	Usual dosing	Usual dosing	H/P/C: No significant clearance
Caspofungin (IV)	50 mg/m^2 q24h *(50 mg/day)*	Usual dosing	Usual dosing	Usual dosing	H/P/C: No significant clearance
Micafungin (IV)	1–4 mg/kg q24h *(150 mg/day)*	Usual dosing	Usual dosing	Usual dosing	H/P/C: No significant clearance
Other Antifungals					
Flucytosine[z] (IV, PO)[269,270]	12.5–37.5 mg/kg q6h *(150 mg/kg/day)*	100% q12h	100% q18h	100% q24h	H: 100% after H
					P: No significant clearance
					C: As for CLCr 30–60
Griseofulvin ultramicrosize (PO)	1.5 mg/kg q24h *(750 mg/day)*	Usual dosing	Usual dosing	Usual dosing	H/P/C: No significant clearance
Terbinafine[aa] (PO)	<25 kg: 125 mg q24h 25–35 kg: 125 mg q24h >35 kg: 250 mg q24h *(250 mg/day)*	Usual dosing	Usual dosing	Usual dosing	H/P/C: Significant clearance unlikely
ANTIVIRAL AGENTS					
Antiherpes					
Acyclovir[bb] (IV, PO)[273–278]	10–20 mg/kg q8h (IV) *(60 mg/kg/day IV)*	100% q8h	100% q12h	50-100% q24h	H: 50% q24h
	20 mg/kg q6h (PO) *(4.8 g/day PO)*	100% q6h	100% q6h	100% q8–12h	P: 50% q24h
					C: 100% q24h
Cidofovir[cc] (IV)	No established pediatric dose or frequency	Usual dosing	Contraindicated, but consider 40%–60%	Contraindicated, but consider 10%–30%	H: Consider 100% 2h before HD

					P: Consider 10%
					C: No data
Foscarnet (IV)[284–286]	Induction:				H: 50% after H
	40–90 mg/kg q12h	50%–75% q12h	50%–75% q24h	Avoid	P: 75% q48–72h
					C: No data
	Maintenance:				
	90–120 mg/kg q24h	50%–75% q24h	50%–75% q48h	Avoid	
	(180 mg/kg/day)				
Ganciclovir[dd] (IV)[287–291]	Induction:				H: 25% after H
	5 mg/kg q12h	50%–100% q12h	50% q24h	25% q24h	P: No significant clearance
	Maintenance:				C: 100% q48h
	5 mg/kg q24h	50%–100% q24h	25% q24h	12.5% q24h	
	(10 mg/kg/day)				
Valacyclovir (PO)[292]	20 mg/kg q8–12h *(3 g/day)*	Usual dose	Usual dose	50%–100% q24h	H/P/C: As for acyclovir
Valganciclovir (PO)	Induction:				H/P/C: No data, but likely as for ganciclovir
	7 mg × BSA × CrCL q12h	Usual dosing	Usual dosing	Usual dosing	
	Maintenance:				
	7 mg × BSA × CrCL q24h	Usual dosing	Usual dosing	Usual dosing	
	(1.8 g/day)				
Anti-influenza					
Amantadine[ee] (PO)[293,294]	2.2–4.4 mg/kg q12h *(200 mg/day)*	Usual dosing	100% q24h	100% q48h	H/P: 100% once weekly
					C: No data
Oseltamivir (PO)[295–297]	2 mg/kg q12h *(150 mg/day)*	Usual dosing	100% q24h	50% q24h	H: 0.5 mg/kg after H
					P: 50% once weekly
					C: As for CLCr 30–60
Peramivir[ff] (IV)[298]	All doses are mg/kg q24h: 0–30 days: 6 31–90 days: 8 91–180 days: 10 181 days–5 yr: 12 6–17 yr: 10 *(600 mg/day)*	Usual dosing	25% q24h	16% q24h	H: 2.5% q24h
					P/C: No data
Rimantadine[gg] (PO)	1–9 yr: 5 mg/kg q24h *(150 mg/day)*	Usual dosing	Usual dosing	75% q24h	H: No significant clearance

					P/C: Significant clearance unlikely
	≥10 yr: 100 mg q12h *(200 mg/day)*	Usual dosing	Usual dosing	75% q12h	
Zanamivir (inhaled)	10 mg q12h	Usual dosing	Usual dosing	Usual dosing	H/P/C: No significant systemic absorption from inhalation
Antiretrovirals					
Nucleoside Reverse Transcriptase Inhibitors					
Abacavir (PO)[299]	8 mg/kg q12h *(600 mg/day)*	Usual dosing	Usual dosing	Usual dosing	H: No significant clearance
					P/C: Significant clearance unlikely
Didanosine (PO)[300,301]	>8 mo: 100 mg/m^2 q12h *(400 mg/day)*	Usual dosing	100% q24h	50% q24h	H: 37.5% q24h
					P: 37.5% q24h
	EC formulation:				C: No data
	20–<25 kg: 200 mg q24h	Usual dosing	50% q24h	Avoid	
	25–<60 kg: 250 mg q24h	Usual dosing	50% q24h	Avoid	
	>60 kg: 400 mg q24h	Usual dosing	50% q24h	50% q24h	
	(400 mg/day)				
Emtricitabine (PO)	0–3 mo: 3 mg/kg q24h >3 mo: 6 mg/kg q24h *(240 mg/day)*	Usual dosing (capsule)	100% q48h (capsule)	100% q72h (capsule)	H: 100% q96h (capsule), 25% q24h (solution)
		Usual dosing (solution)	50% q24h (solution)	33% q24h (solution)	P/C: No data, likely some clearance
Lamivudine (PO)[302–304]	4 mg/kg q12h *(300 mg/day)*	Usual dosing	100% q24h	16-66% q24h	H: No significant clearance
					P: No significant clearance
					C: As for CLCr 30–60
Stavudine (PO)[305]	<30 kg: 1 mg/kg q12h 30–60 kg: 30 mg q12h > 60 kg: 40 mg q12h	Usual dosing	50% q12h	50% q24h	H: 50% q24h
					P: Likely as for CrCL <30
					C: Likely as for CLCr 30–

	(80 mg/day)				60
Tenofovir (PO)[306]	>35 kg: 300 mg q24h *(300 mg/day)*	Usual dosing	100% q48h	100% q72–96h	H: 100% once weekly P: Significant clearance unlikely C: No data
Zidovudine (IV, PO)[307–311]	Treatment: 240 mg/m^2 q12h Prevention: 2 mg/kg q6h (PO) 1.5 mg/kg q6h (IV) *(600 mg/day)*	Usual dosing	Usual dosing	Usual dosing	H: 50% q8h P: 50% q8h C: Likely usual dosing
Nonnucleoside Reverse Transcriptase Inhibitors					
Efavirenz (PO)[312–314]	200 mg + 50 mg/5 kg over 15 kg q24h *(600 mg/day)*	Usual dosing	Usual dosing	Usual dosing	H/P/C: No significant clearance
Etravirine (PO)[315]	100 mg + 25 mg/5 kg over 20 kg q12h *(400 mg/day)*	Usual dosing	Usual dosing	Usual dosing	H/P/C: No significant clearance
Nevirapine (PO)[316–318]	150 mg/m^2 q12h *(400 mg/day)*	Usual dosing	Usual dosing	Usual dosing	H: Usual dosing after H P: Usual dosing C: Likely usual dosing
Rilpivirine (PO)	No data *(25 mg/day)*	Usual dosing	Usual dosing	Usual dosing	H/P/C: Significant clearance is unlikely
Protease Inhibitors					
Atazanavir (PO)[319]	100 + 50 mg/10 kg over 15 kg q24h *(800 mg/day)*	Usual dosing	Usual dosing	Usual dosing	H/P/C: No significant clearance
Darunavir (PO)[315]	20–30 kg: 375 mg q12h ≥30–40 kg: 450 mg q12h ≥40 kg: 600 mg q12h *(1.2 g/day)*	Usual dosing	Usual dosing	Usual dosing	H/P/C: No significant clearance
Fosamprenavir (PO)	30 mg/kg q12h *(2.8 g/day)*	Usual dosing	Usual dosing	Usual dosing	H/P/C: No significant clearance
	OR				
	18 mg/kg + 3 mg/kg ritonavir q12h *(1,400 mg/day)*				

Indinavir[hh] (PO)	500 mg/m^2 q8h *(2.4 g/day)*	Usual dosing	Usual dosing	Usual dosing	H/P/C: No significant clearance
Lopinavir (PO)[313]	230 mg/m^2 q12h *(800 mg/day)*	Usual dosing	Usual dosing	Usual dosing	H/P/C: No significant clearance
Nelfinavir (PO)[318,327]	45–55 mg/kg q12h *(2.5 g/day)*	Usual dosing	Usual dosing	Usual dosing	H/P/C: No significant clearance
Ritonavir (PO)[317]	400 mg/m^2 q12h *(600 mg/day)*	Usual dosing	Usual dosing	Usual dosing	H/P/C: No significant clearance
Saquinavir (PO)	No established pediatric dose *(2 g/day)*	Usual dosing	Usual dosing	Usual dosing	H/P/C: No significant clearance
Tipranavir (PO)	14 mg/kg q12h *(1 g/day)*	Usual dosing	Usual dosing	Usual dosing	H/P/C: No significant clearance
Other Antiretrovirals					
Maraviroc (PO)	No established pediatric dose *(1.2 g/day)*	Likely usual dosing	Likely usual dosing	Likely usual dosing	H/P/C: Significant clearance unlikely
Raltegravir (PO)[315]	No established pediatric dose *(800 mg/day)*	Likely usual dosing	Likely usual dosing	Likely usual dosing	H/P/C: Significant clearance unlikely
Antihepatitis					
Adefovir (PO)	>12 yr: 10 mg q24h *(10 mg/day)*	Usual dosing	100% q48h	100% q72h	H: 100% weekly P/C: No data
Entecavir (PO)	>16 yr: 0.5–1 mg q24h *(1 mg/day)*	Usual dosing	100% q48h	100% q72h	H: 100% weekly
Ribavirin (PO)	7.5 mg/kg q12h *(15 mg/kg/day)*	Usual dosing	Avoid	Avoid	H/P/C: Avoid

[a] Package inserts and several review articles[106–110] on antibiotic dosing in renal failure and the various modes of dialysis were consulted for each drug. Recommendations are a synthesis of these sources and the pharmacokinetic characteristics of each drug; where available, supplemental references are included. Data are based primarily on studies in adults because very few pediatric studies are reported in any published source. Usual doses are for children with normal renal function beyond the neonatal period and for maintenance of systemic drug levels after an initial loading dose (which is typically standard in patients with impaired renal function). Doses herein can differ from those recommended by manufacturers (see package inserts) and in many cases are not approved for children.

[b] The preferred method for estimating GFR in children is the revised Schwartz formula: GFR (mL/min/1.73 m^2) = 0.413 Height (cm) / Plasma creatinine (mg/dL).[111] This formula is most accurate in the GFR range of 15 to 75 mL/min/1.73 m^2, and values outside this range should be reported only as less than or below these limits.

[c] These dose projections are only guidelines and are based on standard intermittent

hemodialysis 3 times weekly, continuous peritoneal ambulatory dialysis with 3 to 4 daily exchanges, and continuous renal replacement with ultrafiltration rates of approximately 1 L/hr. The advent of high-flux or extended intermittent hemodialysis, earlier use of continuous renal replacement in critically ill patients who have residual renal function, and the myriad of settings possible for all forms of ultrafiltration and dialysis make the possibility of clinically significant underdosing or overdosing very real indeed. Measurement of serum drug concentrations must be used when feasible. “No significant clearance” means that the drug should be dosed according to the recommendation for a given degree of renal failure, without regard to dialysis schedule. For intermittent hemodialysis, unless “no significant clearance” is noted, dialysis should always be timed to give the scheduled dose at the end of the dialysis session. If this is not possible, clinicians must use their best judgment about administering a supplemental dose after dialysis, depending on when the next regular dose is due and the relative risks of drug toxicity versus subtherapeutic concentrations. Peritoneal dialysis, as discussed in the text, removes most drugs poorly from blood; therefore, unless indicated, oral or intravenous drugs should be administered according to the patient's underlying renal function. However, many drugs can achieve therapeutic serum concentrations when administered intraperitoneally; hence recommendations for this route are included.

[d] Serum drug concentrations should be monitored. Concurrent administration with penicillins can result in subtherapeutic gentamicin or tobramycin. Peritoneal absorption increases with inflammation. Doses for once-daily aminoglycoside regimens in patients with normal renal function generally should not be used in patients with compromised renal function; hence they are not reported here.

[e] Peritoneal absorption of cephalosporins is generally good.

[f] Active metabolite of cefotaxime also accumulates in ESRD. The dose should be further reduced for hepatic and renal failure.

[g] Usual dose of ceftaroline is if the patient is >12 years of age; not approved for patients <18 years of age.

[h] To treat urinary tract infection in ESRD with cephalexin, the usual dose should be administered.

[i] Drugs with renal and hepatic excretion such as nafcillin require little change unless both mechanisms are impaired.

[j] Drugs with renal and hepatic excretion such as nafcillin or oxacillin require little change unless both mechanisms are impaired.

[k] Doripenem is not approved for patients <18 years of age. Doses in children appear to result in similar exposure as in adults receiving 1 g IV q8h. [170]

[l] Imipenem neurotoxicity can occur, especially in ESRD.

[m] Moxifloxacin is not approved for patients <18 years of age. Dose recommendation is based on a study,[207] allometric scaling from adult dose, and a case report.[208] In addition, a case report noted a dose of 13 mg/kg q24h used in an infant.[209] The single study showed that 10 mg/kg resulted in slightly lower exposure than the adult dose of 400 mg,[207] so the dosing remains uncertain.

[n] Ototoxicity from erythromycin can occur with prolonged high doses in ESRD.

[o] Doxycycline is the preferred member of the tetracycline class for use in patients with impaired renal function.

[p] Tigecycline is not approved in children <12 years of age.

[q] Daptomycin is not approved for use in children. The doses listed are planned for studies, although these studies are not currently enrolling.[223] Some reports have noted dosing and pharmacokinetics in children at the same dose as for adults (4–6 mg/kg q24h), although the exposure can be lower in the pediatric patients relative to the adults.[224–226] Investigators have even reported the use of intraventricular daptomycin in a toddler at a dose of 2.5 mg in 5 mL normal saline, administered every 24 hours through ventriculostomy that was locked for 30 minutes after administration and then reopened.[227] One study found that daptomycin failure was independently associated with severe renal failure, thus raising the question whether the recommended dosing for these patients is suboptimal.[228]

[r] Dosage adjustment of metronidazole is necessary because the metabolite accumulates in ESRD, although this is cleared by hemodialysis and continuous renal replacement.

[s] Microbiologically active metabolites of quinupristin-dalfopristin can accumulate in renal failure and can be cleared by dialysis.

[t] Serum vancomycin concentrations should be monitored.

[u] Serum pyrazinamide concentrations are the best guide.

[v] Iavuconazole is dosed as the prodrug isovuconazonium sulfate; 372 mg of the prodrug is equivalent to 200 mg of active isavuconazole.

[w] β-Cyclodextrin, the vehicle for the oral liquid and intravenous itraconazole and voriconazole preparations, is cleared by the kidneys and accumulates in patients with significant renal failure after intravenous administration; oral dosing is therefore preferred in patients with CrCL<50. Absorption of liquid itraconazole is superior to the capsules; thus liquid itraconazole is preferred for oral therapy.

[x] Posaconazole dosing in children has not been established, but in children 8 to 13 years of age, 200 mg of suspension 4 times daily or 400 mg twice daily (800 mg/day) provided exposure similar to that observed in adult dosing. For patients 13 to 17 years of age, 200 mg 3 times daily (600 mg/day) provided similar exposure. The newer IV and DR oral tablets both achieve much better plasma concentrations in adults, but pharmacokinetic results and dosing recommendations are not yet available for children <13 years of age. For children >13 years of age, adult doses are used.

[y] Anidulafungin is not approved in children, but 1.5 mg/kg/day in infants to adolescents results in exposures similar to those in to adults who receive 100 mg/day.[267,268]

[z] Serum flucytosine concentrations should be monitored; bone marrow suppression is more common in azotemic patients.

[aa] Terbinafine is not approved in children. The usual dosing provided here has been shown to reproduce adult exposures from 250 mg/day.[271,272]

[bb] Acyclovir impairs urate secretion and can cause gout; uric acid levels should be monitored.

[cc] No pediatric dose has been established for cidofovir. Dosing ranging from 5 mg/kg weekly (induction) followed by 3 to 5 mg/kg weekly to biweekly (maintenance), to 1 mg/kg thrice weekly, to 0.25 to 1 mg/kg every other week have been used for adenovirus, cytomegalovirus, and polyomavirus infections in children.[279–282] Although the package insert states that the drug is contraindicated in renal failure, the reported dosing guidelines were developed with the intent to change the label.[283]

[dd] The maintenance ganciclovir dose is half the induction dose; bone marrow suppression is more common in azotemic patients.

[ee] Amantadine neurotoxicity is more common in ESRD.

[ff] Peramivir is not licensed for use in patients <18 years of age.

[gg] These doses are for prophylaxis only. Rimantidine is not indicated for influenza treatment in patients <16 years of age.

[hh] Indinavir is not approved in children. Doses shown to approximate adult exposures include 50 mg/kg, 500 mg/m^2, and 600 mg/m^2, all administered every 8 hours.[320–326]

BSA, body surface area; C, continuous renal replacement; CLCr, creatinine clearance (calculated or measured); DR, delayed-release; EC, enteric-coated; ESRD, end-stage renal disease; GFR, glomerular filtration rate; H, intermittent hemodialysis; HIV, human immunodeficiency virus; IM, intramuscular(ly); IP, intraperitoneal(ly); IV, intravenous(ly); kU, thousand units; MU, million units; P, continuous peritoneal dialysis; PO, oral(ly).

292

Antimicrobial Agents

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Antimicrobial agents are essential in the therapy of bacterial infections. The approach to antimicrobial therapy is outlined in Chapter 289, which provides the clinician with an overview of the selection of agents based on the characteristics of infected children with respect to their pathogens and antibiotic susceptibilities, sites of infection, antibiotic tissue exposure, comorbidities, and a consideration of the benefits versus the risks of antimicrobial therapy. In this chapter, the agents themselves are discussed, providing a background on mechanism of action, spectrum of antibacterial activity, antibiotic resistance, and current clinical use. A more detailed discussion of specific infections is found in each chapter describing that infection. An in-depth discussion of antibiotic resistance and the ways to detect resistance is presented in Chapter 290. Pharmacokinetic-pharmacodynamic basis of optimal antibiotic therapy is discussed in Chapter 291. Table 292.1 provides a summary of the pharmacokinetics, tissue distribution, metabolism, and excretion of commonly used antimicrobial agents within each of the antibiotic classes. Table 292.2 provides the spectrum of activity of each antibiotic. Appendices 292.1 and 292.2 provide dosages of antibiotics. Chapters related to specific pathogens also should be consulted.

TABLE 292.1

Pharmacokinetics, Tissue Distribution, Metabolism, and Excretion of Antimicrobial Agents

Agent	Oral Bioavailability	Protein Binding	Body Distribution and CSF Penetration	Metabolism	Excretion
AMINOGLYCOSIDES					
Gentamicin, amikacin, tobramycin	Poorly absorbed	<25%	Primarily to extracellular fluids and vascularized tissues, fetus, ascitic, synovial, and amniotic fluid; minimally into CSF	None	Renal
Streptomycin	Poorly absorbed	35%	Same as gentamicin	10%–30% at unknown site	Renal
β-LACTAMS					
Penicillin G	Erratic, 15%–80% Not available in oral formulation	60%–65%	Penetrates most tissues, fetus, and amniotic fluid; poorly into CSF[b]	Hepatic <30%	Renal
Penicillin V	60%	80%	Penetrates most tissues; poorly into CSF, not used to treat meningitis	Same as penicillin G with additional gut inactivation (metabolized) of 35%–70% of an oral dose	Same as penicillin
PENICILLINASE-RESISTANT PENICILLINS					
Dicloxacillin	35%–76% Give on empty stomach	98%	Penetrates most tissues, fetus, and amniotic fluid; poorly into CSF	Hepatic 10%	Renal
Oxacillin	No oral form available	94%	Penetrates most tissues, fetus, and amniotic fluid; poorly into CSF[b]	Hepatic ~50%	Renal
Nafcillin	Not given orally	90%	Penetrates most tissues, fetus, and amniotic fluid; poorly into CSF[b]	Hepatic 60%	Biliary (wi enterohep recirculati renal 10%–30%
AMINOPENICILLINS					
Amoxicillin	85%	20%	Penetrates most tissues, fetus, and amniotic fluid;	Hepatic 10%	Renal

			poorly into CSF[b]		
Ampicillin	50%	22% 10% in neonates	Penetrates most tissues, fetus, and amniotic fluid; poorly into CSF[b]	Hepatic 10%	Renal
EXTENDED-SPECTRUM PENICILLINS					
Ticarcillin	Not administered orally	45%	Penetrates most tissues, fetus, and amniotic fluid; poorly into CSF[b]	Hepatic 10%	Renal
Piperacillin	Not administered orally	15%–20%	Penetrates most tissues, fetus, and amniotic fluid; poorly into CSF[b]	Hepatic minimal	Renal; bili <20%
BETA-LACTAMASE INHIBITORS					
Avibactam (ceftazidime kinetics are unaffected by avibactam)	Not administered orally	8%	Penetrates abdomen, kidney, muscle; CSF penetration similar to ceftazidime	None	Renal 85% by filtratio and secreti
Clavulanate (amoxicillin pharmacokinetics not affected by clavulanate)	Well absorbed	25%	Penetrates most tissues, fetus, and amniotic fluid; poorly into CSF	Hepatic extensive	Renal 25% 40%
Sulbactam (ampicillin pharmacokinetics not affected by sulbactam)	Not given orally	38%	Penetrates most tissues, fetus, and amniotic fluid; poorly into CSF[b]	Hepatic 10%	Renal
Tazobactam (piperacillin kinetics are unaffected by tazobactam)	Not administered orally	20%–23%	Penetrates most tissues, fetus, and amniotic fluid; poorly into CSF[b]	Hepatic minimal	Renal
CEPHALOSPORINS					
First-Generation					
Cefadroxil	Well absorbed	20%	Penetrates most tissues, fetus, and amniotic fluid; minimally into CSF	None	Renal (slo excretion r than cephalexin
Cefazolin	Not administered orally	80%	Penetrates most tissues, fetus, and	None	Renal

			amniotic fluid; minimally into CSF		
Cephalexin	Well absorbed; ↓ with food	6%	Penetrates most tissues, fetus, and amniotic fluid; minimally into CSF	None	Renal; som biliary
Cephradine	Well absorbed; ↓ with food	10%	Penetrates most tissues, fetus, and amniotic fluid; minimally into CSF	None	Renal; som biliary
Second-Generation					
Cefaclor	Well absorbed	25%	Penetrates most tissues; unknown fetal, amniotic, and CSF distribution	Unknown	Renal (nonrenal: eliminatio unknown in renal failure)
Cefprozil	95%	36%	Penetrates middle-ear fluids and tonsillar, adenoidal, skin, and soft tissues well; unknown fetal, amniotic and CSF distribution	Unknown	Renal; nonrenal 3
Cefuroxime	37% (as axetil); ↑ to 52% when given with food	50%	Penetrates most tissues, fetus, and amniotic fluid; minimally into CSF	None	Renal
Cefoxitin	Not administered orally	75%	Penetrates most tissues, fetus, and amniotic fluid; minimally into CSF[a]	Hepatic minimal	Renal
Third-Generation					
Cefdinir	16%–21% cap; 25% suspension	60%–70%	Penetrates most tissues; unknown fetal, amniotic and CSF distribution	None	Renal
Cefixime	40%–50%	65%–70%	Small distribution volume, penetrates skin, amniotic fluid, poorly to	None	Renal, bilia

			CSF[b]		
Cefoperazone	Not administered orally	90%	Penetrates most tissues, fetus, and amniotic fluid; minimally into CSF[a]	Hepatic <20%	Biliary, rer 20%–30%
Cefotaxime	Not administered orally	35%–40%	Penetrates most tissues, fetus, and amniotic fluid; adequately into CSF[b]	Hepatic	Renal
Cefpodoxime	50%	20%–30%	Penetrates most tissues, unknown fetal, amniotic, and CSF distribution	None	Renal
Ceftazidime	Not administered orally	<10%	Penetrates most tissues, fetus, and amniotic fluid; adequately into CSF[b]	None	Renal
Ceftibuten	>90%	65%–77%	Penetrates most tissues, unknown fetal, amniotic, and CSF distribution	Hepatic minimal	Renal
Ceftriaxone	Not administered orally	95%	Penetrates most tissues, fetus, and amniotic fluid; adequately into CSF[b]	None	Renal; bilia
Fourth-Generation					
Cefepime	Not given orally	20%	Penetrates most tissues, fetus, and amniotic fluid; adequately into CSF[b]	Hepatic minimal	Renal
Ceftolozane	Not given orally	20%	Distribution volume similar to ECV Penetrates lung	None	Renal
CEPHALOSPORINS WITH ANTI-MRSA ACTIVITY					
Ceftaroline	Not administered orally	15%–30%	Distribution volume similar to ECV Penetrates lung tissue, minimal into CSF	Hepatic, minimal (<20%) to inactive metabolite	Renal 80%-90% a unchangec drug, minimal fe (5%)
OTHER B-LACTAMS MONOBACTAMS					

Aztreonam	Not administered orally	50%–70%	Penetrates most tissues, fetus, and amniotic fluid; minimally into CSF[b]	Minimal hydrolysis at unknown site	Renal; bilia minor
CARBAPENEMS					
Meropenem	Not administered orally	Minimal	Penetrates most tissues, CSF[b], fetus, and amniotic fluid.,	Renal, serum, hepatic 20%–25%	Renal; bilia minor
Imipenem (I) + cilastatin (C)	Not administered orally	20% (I) 40% (C)	Penetrates most tissues, fetus, and amniotic fluid; adequately into CSF[b] but relatively contraindicated for meningitis	Renal, serum, hepatic 20%–25%	Renal; bilia minor
Doripenem	Not given orally	8%	Widely distributed, penetrates most body tissues, low to CSF[b]; unknown fetal, amniotic	Renal 18%	Renal, minimal fe
Ertapenem	Not given orally	95%	Penetrates interstitial fluids; unknown fetal, amniotic, or CSF	Renal 20%, hepatic minor	Renal; bilia
CHLORAMPHENICOL SUCCINATE (INJECTION)	PO forms (base and palmitate salt) not available	~50%	Widely distributed including fetal, amniotic, and CSF	Hepatic	Renal (as succinate s and glucuronic metabolite biliary minimal
FLUOROQUINOLONES					
Ciprofloxacin	60%–80%; >90% in adolescents with CF	20%–40%	Penetrates most tissues, fetus, amniotic fluid; minimally into CSF[b]	Hepatic <20%	Renal, fece
Gatifloxacin	96%	20%	Penetrates most tissues including CSF; fetal, amniotic unknown	Minimal	Renal
Levofloxacin	99%	24%–38%	Widely distributed, penetrates most tissues, fetus, amniotic	Minimal	Renal

			fluid, CSF		
Moxifloxacin	90%	50%	Widely distributed penetrates most tissues, CSF, amniotic fluid; poorly to kidney and urine due to metabolism.	Hepatic	Fecal and renal as active drug and metabolite
GLYCOLIPOPEPTIDES					
Dalbavancin	Not given orally	93%	Distribution volume similar to ECV, penetrates skin, bone and joint tissue	Minimal	Renal, feca
Oritavancin	Not given orally	85%	Widely distributed, high lung penetration, weak skin penetration	None known	Renal, feca
Telavancin	Not given orally	90%	Small distribution volume; penetrates skin and lung	Minimal	Renal
KETOLIDES					
Telithromycin	57%	60%–70%	Widely distributed; fetal, amniotic fluid and CSF unknown	Hepatic	Renal, bilia
LINCOSAMIDES					
Clindamycin	90%	94%	Penetrates most tissues, fetus, amniotic fluid; minimally into uninflamed CSF, but adequately into inflamed CSF or brain abscess	Hepatic	Biliary; ren minor
LIPOPEPTIDES					
Daptomycin	Not given orally	~90%	Small distribution volume, penetrates skin, adipose and bone well; fetal, amniotic, and CSF penetration unknown	Minimal	Renal 80% Fecal 5%
MACROLIDES AND AZALIDES					

Azithromycin	37%	20%–50%	Widely distributed including fetus, amniotic fluid; minimally into CSF[b]	Hepatic	Biliary; rer minimal
Clarithromycin	50%–55%	60%–70%	Penetrates most tissues, fetus; CSF penetration unknown	Hepatic	Renal 40%- 50% (as dr and active metabolite
Erythromycin	Poor, 25%–65% depending on salt and form	80%–90%	Penetrates most tissues, fetus, amniotic fluid; minimally into CSF[b]	Hepatic	Biliary, rer minimal
METRONIDAZOLE	100%	<20%	Widely distributed, including fetus, amniotic fluid, CSF	Hepatic	Renal; bilia minor
NITROFURANTOIN	Well absorbed	90%	Mainly urinary tract, prostate, and placenta	Tissues	Renal, bilia
OXAZOLIDINONES					
Linezolid	100%	31%	Penetrates well to most tissues, including CSF; fetus, amniotic fluid unknown	Hepatic	Renal
POLYMYXINS					
Colistimethate (injection)	Not administered orally	Minimal	Penetrates most tissues, fetus and amniotic fluid; minimal to pleural or joint cavities or to CSF	Tissue minor and slow	Renal
RIFAMYCINS					
Rifampin	90%–95%	60%–90%	Widely distributed including fetus, amniotic fluid; minimally into CSF[b]	Hepatic	Biliary, rer
Rifaximin	Poorly absorbed	N/A	Minimal systemic distribution due to poor oral bioavailability, but high intraluminal GI concentrations	Hepatic minimal	Feces absorption
STREPTOGRAMINS					

Quinupristin-dalfopristin	Not administered orally	55%–78% (Q) 11%–26% (D)	Penetrates most tissues; minimally into CSF; fetus, amniotic fluid unknown	Hepatic, conversion to several active metabolites	Biliary; re ~15%
SULFONAMIDES AND TRIMETHOPRIM					
Sulfadiazine	100%	20%	Widely distributed, including fetus, amniotic fluid, CSF	Hepatic wide individual variation	Renal (free and conjugate forms)
Sulfamethoxazole	100%	65%	Widely distributed, including fetus, amniotic fluid, CSF	Hepatic wide individual variation	Renal (free and conjugate forms)
Sulfisoxazole	100%	85%	Widely distributed, including fetus, amniotic fluid, CSF	Hepatic wide individual variation	Renal (free and conjugate forms)
Trimethoprim	100%	~45%	Widely distributed, including fetus, amniotic fluid, CSF	Hepatic <20%	Renal
TETRACYCLINES AND GLYCYLCYCLINES					
Doxycycline	90%–100%	82%	Widely distributed including fetus, amniotic fluid; minimally into CSF[b]	Hepatic	Renal, bilia
Minocycline	90%–100%	76%	Widely distributed including fetus, amniotic fluid; minimally into CSF[b]	Hepatic minimal	Biliary, re
Tetracycline (T), demeclocycline (D)	75%–80%; decreases significantly with food	65% (T) 41%–91% (D)	Widely distributed including fetus, amniotic fluid; minimally into CSF[b]	Hepatic minimal	Renal, bilia
Tigecycline	Not administered orally	70%–90%	Widely distributed; fetal, amniotic fluid and CSF unknown	Hepatic 5%–20%	Biliary, re
GLYCOPEPTIDES					
Vancomycin	Negligible	30%	Penetrates most tissues, fetus, amniotic fluid; adequately but erratically into	None	Renal; bilia minimal

			CSF[b]		

[a] Values listed are the means or medians reported in PK studies and/or product labeling. Actual values in individual patients may differ due to interindividual variability and the effect of certain disease states. Agents with both minimal metabolism and renal excretion will have a prolonged half-life in a patient with renal impairment. See also Chapter 291.

[b] Concentration of drug in CSF significantly increased with inflamed meninges. See text.

CF, cystic fibrosis; CSF, cerebrospinal fluid; ECV, extracellular volume; GI, gastrointestinal; GU, genitourinary; IV, intravenous; PO, *orally*.

TABLE 292.2

Spectrum of Activity of Antimicrobial Agents by Microbial Site of Activity and Antimicrobial Drug Class

I. CELL WALL–ACTIVE AGENTS

A. ANTIBIOTIC CLASS: TRANSPEPTIDASE INHIBITORS

	β-Lactam Antibiotics	Spectrum of Activity[a]
PENICILLINS		
Natural penicillins	Penicillin G Penicillin V Benzathine penicillin G Procaine penicillin G Benzathine-procaine penicillin G combinations	**Gram-positive** Streptococci Groups A, B, C, G, F Viridans group streptococci *Streptococcus pneumoniae* *Enterococcus faecalis*[b] *Enterococcus faecium*[b] *Actinomyces*
		Bacillus anthracis
		Listeria monocytogenes
		Gram-negative
		Eikenella corrodens
		Neisseria meningitidis
		Neisseria gonorrhoeae
		Pasteurella multocida
		Borrelia burgdorferi
		Spirillum minus
		Streptobacillus moniliformis
		Treponema pallidum
		Leptospira spp.
		Anaerobes
		Bacteroides and *Prevotella* spp. (non-β-lactamase–producing strains)
		Fusobacterium spp.
		Veillonella spp.
		Clostridium spp.
		Eubacterium spp.
		Peptococcus spp.
		Peptostreptococcus spp.
		Propionibacterium spp.
Penicillinase-stable penicillins	Methicillin Oxacillin Nafcillin Cloxacillin Dicloxacillin	**Gram-positive** Streptococci (as above for penicillins) *Staphylococcus aureus* (except MRSA)
Aminopenicillins	Ampicillin	**Gram-positive**
	Amoxicillin	Streptococci (as above for penicillins)
		Enterococcus faecalis[b]
		Enterococcus faecium[b]
		Listeria monocytogenes

		Gram-negative
		Escherichia coli
		Haemophilus influenzae
		Neisseria meningitidis
		Anaerobes
		For ampicillin: as above for penicillins
	Amoxicillin-clavulanate	Adds activity to amoxicillin:
		Staphylococcus aureus (except MRSA)
		Haemophilus influenzae, β-lactamase–producing strains
		Anaerobes
		As above for penicillins, but now includes:
		Bacteroides and *Prevotella* spp., β-lactamase–producing strains
	Ampicillin-sulbactam	Adds activity to ampicillin:
		Staphylococcus aureus (except MRSA)
		Escherichia coli, β-lactamase–producing strains
		Klebsiella spp.
		Proteus mirabilis
		Proteus vulgaris
		Providencia rettgeri
		Providencia stuartii
		Morganella morganii
		Anaerobes
		As above for penicillins, but now includes:
		Bacteroides and *Prevotella* spp. (β-lactamase–producing strains)
Extended-spectrum pencillins	Carbenicillin Ticarcillin Piperacillin	**Gram-positive**
		Streptococci (as above for penicillins)
		Gram-negative
		Escherichia coli
		Haemophilus influenzae
		Proteus mirabilis
		Proteus vulgaris
		Morganella morganii
		Pseudomonas aeruginosa
		Providencia rettgeri
		Enterobacter species
		Anaerobes
		Bacteroides and *Prevotella* spp. (non-β-lactamase –producing strains)
		Fusobacterium spp.
		Veillonella spp.
		Clostridium spp.
		Eubacterium spp.
		Peptococcus spp.
		Peptostreptococcus spp.
	Ticarcillin-clavulanate	Adds β-lactamase–producing strains of:
	Piperacillin-tazobactam	*Staphylococcus aureus* (except MRSA)
		Escherichia coli
		Haemophilus influenzae
		Klebsiella spp.
		Serratia marcescens
		Citrobacter spp.

		Enterobacter spp.
		Anaerobes
		Bacteroides and *Prevotella* spp. (including β-lactamase –producing strains)
		Fusobacterium spp.
		Veillonella spp.
		Clostridium spp.
		Eubacterium spp.
		Peptococcus spp.
		Peptostreptococcus spp.
CEPHALOSPORINS		
First-generation	Cephalothin Cephapirin Cefazolin Cephalexin Cephradine Cefadroxil	**Gram-positive** Streptococci Groups A, B, C, G, F Viridans group streptococci *Streptococcus pneumoniae*
		Staphylococcus aureus (except MRSA)
		Gram-negative
		Escherichia coli
		Proteus mirabilis
Second-generation	Cefamandole Cefuroxime Cefonicid Ceforanide Cefaclor Cefoxitin Cefotetan	**Gram-positive** Streptococci Groups A, B, C, G, F Viridans group streptococci *Streptococcus pneumoniae* *Staphylococcus aureus* (except MRSA)
		Gram-negative
		Escherichia coli
		Haemophilus influenzae (including β-lactamase –producing strains)
		Klebsiella spp.
		*Moraxella catarrhali*s
		Neisseria gonorrhoeae
		Neisseria meningitidis
		Proteus mirabilis
		Providencia rettgeri
		Salmonella spp.
		Shigella spp.
		Anaerobes
		Bacteroides and *Prevotella* spp. (non-β-lactamase –producing strains, except for cefoxitin and, to a lesser extent, cefotetan)
		Fusobacterium spp.
		Veillonella spp.
		Eubacterium spp.
		Peptococcus spp.
		Peptostreptococcus spp.
Third-generation	Cefotaxime Ceftriaxone Ceftazidime Cefoperazone Ceftizoxime Cefixime Cefpodoxime Ceftibuten Cefdinir	**Gram-positive** Streptococci Groups A, B, C, G, F Viridans group streptococci *Streptococcus pneumoniae* *Staphylococcus aureus* (except MRSA) **Gram-negative**
		Citrobacter spp.
		Enterobacter spp.

		Escherichia coli
		Haemophilus influenzae (including β-lactamase –producing strains)
		Klebsiella spp.
		Morganella morganii
		Neisseria gonorrhoeae (including β-lactamase–producing strains)
		Neisseria meningitidis
		Proteus mirabilis
		Proteus vulgaris
		Providencia rettgeri
		Providencia stuartii
		Serratia marcescens
		For ceftazidime and cefoperazone:
		Pseudomonas aeruginosa
		Anaerobes
		Bacteroides and *Prevotella* spp. (non-β-lactamase –producing strains)
		Fusobacterium spp.
		Eubacterium spp.
		Peptococcus spp.
	Ceftazidime-avibactam	Adds activity to ceftazidime to include many ESBL producing *E. coli* and *Klebsiella,* and adds activity against *Klebsiella* that produce *K. pneumoniae* carbapenemases
	Ceftolozane-tazobactam	Adds activity to ceftolozane (enhanced *Pseudomonas* activity beyond ceftazidime) to include many ESBL producing *E. coli* and *Klebsiella*
Fourth-generation	Cefepime	**Gram-positive**
		Streptococci
		Groups A, B, C, G, F
		Viridans group streptococci
		Streptococcus pneumoniae
		Staphylococcus aureus (except MRSA)
		Gram-negative
		As above for third-generation cephalosporins, but including *Pseudomonas aeruginosa*)
		Anaerobes
		Bacteroides and *Prevotella* spp. (non-β-lactamase –producing strains)
		Fusobacterium spp.
		Veillonella spp.
		Eubacterium spp.
		Peptococcus spp.
Advanced-generation	Ceftaroline	As above for third-generation cephalosporins, but also includes MRSA strains of *Staphylococcus aureus*
CARBAPENEMS	Imipenem (with cilastatin)	**Gram-positive**
	Meropenem	Streptococci
	Ertapenem	Groups A, B, C, D, G, F
	Doripenem	Viridans group streptococci
		Streptococcus pneumoniae
		Enterococcus faecalis
		Staphylococcus aureus (except MRSA)
		Gram-negative
		Acinetobacter spp.
		Citrobacter spp.

		Enterobacter spp.
		Escherichia coli (including ESBL-producing strains)
		Gardnerella vaginalis
		Haemophilus influenzae
		Klebsiella spp. (including ESBL-producing strains)
		Morganella morganii
		Proteus vulgaris
		Providencia rettgeri
		Pseudomonas aeruginosa (except ertapenem)
		Serratia spp.
		Anaerobes
		Bifidobacterium spp.
		Clostridium spp.
		Eubacterium spp.
		Peptococcus spp.
		Peptostreptococcus spp.
		Propionibacterium spp.
		Bacteroides and *Prevotella* spp. (including β-lactamase –producing strains)
		Fusobacterium spp.
MONOBACTAMS	Aztreonam	**Gram-negative**
		Citrobacter spp.
		Enterobacter spp.
		Escherichia coli
		Haemophilus influenzae (including β-lactamase –producing strains)
		Klebsiella spp.
		Proteus mirabilis
		Pseudomonas aeruginosa
		Serratia spp.
B. ANTIBIOTIC CLASS: TRANSGLYCOSYLASE INHIBITORS		
		Spectrum of Activity[a]
GLYCOPEPTIDES	Vancomycin, telavancin, dalbavancin, oritavancin	**Gram-positive** Streptococci Groups A, B, C, G, F Viridans group streptococci
		Streptococcus pneumoniae
		Enterococcus faecalis[b]
		Enterococcus faecium[b]
		Staphylococcus aureus (including MRSA, but not vancomycin-intermediate or vancomycin-resistant strains)
		Staphylococcus epidermidis
		Actinomyces spp.
		Lactobacillus spp.
		Listeria monocytogenes
		Anaerobes
		Clostridium difficile

II. CELL MEMBRANE ACTIVE AGENTS		
A. ANTIBIOTIC CLASS: LIPOPEPTIDES		
		Spectrum of Activity[a]
	Daptomycin	*Staphylococcus aureus* (including methicillin-resistant and vancomycin-resistant strains)
		Enterococcus faecalis (vancomycin-susceptible and vancomycin-resistant strains)
		Enterococcus faecium (vancomycin-susceptible and vancomycin-resistant strains)

		Streptococci
		Groups A, B
		Viridans group streptococci
B. ANTIBIOTIC CLASS: POLYMYXINS		
	Colistin	*Enterobacter aerogenes*
		Escherichia coli
		Klebsiella pneumoniae
		Pseudomonas aeruginosa
		Actinobacter spp.
		Citrobacter spp.
		Haemophilus spp.
		Salmonella spp.
		Shigella spp.

III. RIBOSOME-ACTIVE AGENTS		
A. ANTIBIOTIC CLASS: MACROLIDES		
MACROLIDES	Erythromycin	**Gram-positive**
		Corynebacterium diphtheriae
		Corynebacterium minutissimum
		Listeria monocytogenes
		Staphylococcus aureus
		Streptococcus pneumoniae
		Streptococcus pyogenes
		Gram-negative
		Bordetella pertussis
		Legionella pneumophila
		Neisseria gonorrhoeae
		Other pathogens
		Chlamydia trachomatis
		Entamoeba histolytica
		Mycoplasma pneumoniae
		Treponema pallidum
		Ureaplasma urealyticum
	Clarithromycin	**Gram-positive**
		Staphylococcus aureus
		Streptococcus pneumoniae
		Streptococcus pyogenes
		Gram-negative
		Haemophilus influenzae
		Moraxella catarrhalis
		Helicobacter pylori
		Other pathogens
		Mycoplasma pneumoniae
		Chlamydophila pneumoniae
		Mycobacterium avium complex
AZALIDES	Azithromycin	**Gram-positive**
		Staphylococcus aureus
		Streptococci
		Groups A, B C, F, G
		Viridans group streptococci
		Streptococcus pneumoniae
		Bordetella pertussis
		Gram-negative
		Haemophilus influenzae
		Haemophilus ducreyi

		Moraxella catarrhalis
		Neisseria gonorrhoeae
		Other pathogens
		Chlamydophila pneumoniae
		Chlamydia trachomatis
		Legionella pneumophila
		Mycoplasma hominis
		Mycoplasma pneumoniae
		Ureaplasma urealyticum
KETOLIDES	Telithromycin	**Gram-positive**
		Staphylococcus aureus
		Streptococci
		Groups A, C, and G
		Viridans group streptococci
		Gram-negative
		Haemophilus influenzae
		Moraxella catarrhalis
		Other pathogens
		Bordetella pertussis
		Mycoplasma pneumoniae
		Legionella pneumophila
		Chlamydophila pneumoniae
B. ANTIBIOTIC CLASS: TETRACYCLINES		
TETRACYCLINES	Tetracycline Minocycline Doxycycline	**Gram-positive** *Actinomyces* spp. **Gram-negative** *Vibrio cholerae*
		Brucella spp.
		Campylobacter spp.
		Francisella tularensis
		Listeria monocytogenes
		Yersinia pestis
		Neisseria meningitidis
		Neisseria gonorrhoeae
		Other pathogens
		Borrelia recurrentis
		Chlamydophila psittaci
		Chlamydia trachomatis
		Mycoplasma pneumoniae
		Ureaplasma
		Treponema pallidum
		Entamoeba species
GLYCYLCYCLINES	Tigecycline	**Gram-positive**
		Streptococci
		Groups A, B
		Viridans group streptococci
		Streptococcus pneumoniae
		Enterococcus faecalis
		Enterococcus faecium
		Staphylococcus aureus
		Listeria monocytogenes
		Clostridium perfringens
		Peptostreptococcus spp.
		Gram-negative
		Acinetobacter baumannii
		Aeromonas hydrophila

		Citrobacter freundii
		Citrobacter koseri
		Enterobacter cloacae
		Enterobacter aerogenes
		Escherichia coli
		Klebsiella oxytoca
		Klebsiella pneumoniae
		Pasteurella multocida
		Serratia marcescens
		Stenotrophomonas maltophilia
		Bacteroides spp.
		Other pathogens
		Chlamydia trachomatis
		Mycoplasma pneumoniae
		Ureaplasma
		Mycobacterium abscessus
		Mycobacterium chelonae
		Mycobacterium fortuitum
C. ANTIBIOTIC CLASS: LINCOSAMIDES		
LINCOSAMIDES	Clindamycin	**Gram-positive**
		Streptococci
		Groups A, B
		Streptococcus pneumoniae
		Staphylococcus aureus
		Anaerobes
		Bacteroides fragilis
		Prevotella melaninogenica
		Fusobacterium spp.
		Peptococcus spp.
		Peptostreptococcus spp.
		Actinomyces spp.
		Clostridium perfringens
		Propionibacterium spp.
D. ANTIBIOTIC CLASS: AMINOGLYCOSIDES		
AMINOGLYCOSIDES	Streptomycin	**Gram-negative**
		Brucella spp.
		Francisella spp.
		Mycobacterium tuberculosis
	Gentamicin Netilmicin Tobramycin Amikacin	**Gram-positive** *Staphylococcus aureus* **Gram-negative** *Escherichia coli* *Klebsiella* spp.
		Enterobacter spp.
		Serratia spp.
		Citrobacter spp.
		Morganella morganii
		Acinetobacter spp.
		Providencia spp.
		Proteus mirabilis
		Proteus vulgaris
		Pseudomonas aeruginosa
	Paromomycin	*Entamoeba histolytica*
		Dientamoeba fragilis
		Cryptosporidium spp.
E. ANTIBIOTIC CLASS: OXAZOLIDINONES		

OXAZOLIDINONES	Linezolid, tedizolid	**Gram-positive**
		Streptococci
		Groups A, B
		Viridans group streptococci
		Streptococcus pneumoniae
		Staphylococcus aureus
		Enterococcus faecium
		Enterococcus faecalis
F. ANTIBIOTIC CLASS: STREPTOGRAMINS		
STREPTOGRAMINS	Quinupristin/dalfopristin	**Gram-positive**
		Streptococci
		Groups A, B
		Staphylococcus aureus
		Enterococcus faecium

IV. NUCLEIC ACID–ACTIVE ANTIBIOTICS		
A. ANTIBIOTIC CLASS: RIFAMYCINS		
RIFAMYCINS	Rifampin	**Gram-positive**
		Staphylococcus aureus
		Gram-negative
		Neisseria meningitidis
		Haemophilus influenzae
		Other
		Mycobacterium tuberculosis
		Mycobacterium avium complex
	Rifabutin	*Mycobacterium tuberculosis*
	Rifapentine	*Mycobacterium avium* complex
	Rifaximin	Susceptible at concentrations achieved within the gastrointestinal lumen:
		Campylobacter
		Escherichia coli
		Salmonella spp.
		Shigella spp.
		Vibrio spp.
		Yersinia spp.
B. ANTIBIOTIC CLASS: QUINOLONES		
QUINOLONES	Nalidixic acid	**Gram-negative**
		Escherichia coli
		Enterobacter spp.
		Morganella morganii
		Proteus mirabilis
		Proteus vulgaris
		Providencia rettgeri
FLUOROQUINOLONES	Ciprofloxacin	**Gram-positive**
		Streptococcus pyogenes
		Streptococcus pneumoniae
		Staphylococcus aureus
		Enterococcus faecalis
		Bacillus anthracis
		Gram-negative
		Aeromonas spp.
		Acinetobacter spp.
		Escherichia coli
		Klebsiella pneumoniae

		Enterobacter cloacae
		Citrobacter diversus
		Citrobacter freundii
		Campylobacter jejuni
		Proteus mirabilis
		Proteus vulgaris
		Providencia rettgeri
		Providencia stuartii
		Serratia marcescens
		Pseudomonas aeruginosa
		Morganella morganii
		Salmonella spp.
		Shigella spp.
		Haemophilus influenzae
		Haemophilus parainfluenzae
		Moraxella catarrhalis
		Neisseria gonorrhoeae[b]
		Pasteurella multocida
		Vibrio spp.
		Yersinia enterocolitica
		Other pathogens
		Legionella pneumophila
	Levofloxacin Gemifloxacin Moxifloxacin	**Gram-positive** Streptococci Group A Viridans group streptococci
		Streptococcus pneumoniae
		Enterococcus faecalis
		Staphylococcus aureus
		Actinomyces spp.
		Bacillus anthracis
		Listeria monocytogenes
		Gram-negative
		Acinetobacter spp.
		Escherichia coli
		Enterobacter spp.
		Klebsiella spp.
		Proteus spp.
		Providencia spp.
		Serratia marcescens
		Citrobacter spp.
		Morganella morganii
		Pseudomonas aeruginosa
		Haemophilus influenzae
		Moraxella catarrhalis
		Anaerobes
		Clostridium perfringens
		Other pathogens
		Legionella pneumophila
		Mycoplasma pneumoniae
		Chlamydophila pneumoniae
C. ANTIBIOTIC CLASS: NITROIMADAZOLES		
NITROIMADAZOLES	Metronidazole	**Anaerobes**
		Clostridium spp.
		Eubacterium spp.
		Peptococcus spp.

		Peptostreptococcus spp.
		Bacteroides fragilis
		Fusobacterium spp.
D. ANTIBIOTIC CLASS: SULFONAMIDES		
SULFONAMIDES	Sulfisoxazole Sulfamethoxazole	
SULFA IN COMBINATION WITH ANOTHER ANTIMICROBIAL AGENT	Sulfamethoxazole plus trimethoprim	**Gram-positive** *Streptococcus pneumoniae*[b] **Gram-negative**
		Escherichia coli
		Klebsiella spp.
		Enterobacter spp.
		Morganella morganii
		Proteus mirabilis
		Proteus vulgaris
		Shigella spp.
		Haemophilus influenzae
		Other pathogens
		Pneumocystis jirovecii
	Sulfadiazine plus pyramethamine	*Toxoplasma gondii* *Plasmodium* spp.

[a] A majority of strains of the listed bacteria are susceptible; however, some organisms within the group may be less susceptible or resistant to one or more agents listed. Susceptibility pattern for each pathogen and antibiotic may be available to physicians through local health care institutions.

[b] Important exceptions exist.

ESBL, extended-spectrum β-lactamases; MRSA, methicillin-resistant *Staphylococcus aureus.*

Cell Wall–Active Agents

The synthesis of the bacterial cell wall is remarkably complicated and still is not understood fully.[1–3] Several steps are involved in cell wall creation, from the synthesis of precursors within the bacterial cytoplasm to the intricate construction of a lattice-like structure around the organism that maintains cell shape and osmotic integrity. Gram-negative cell walls consist of inner (plasma) and outer membranes and are more complicated than those of gram-positive organisms that contain a single membrane. Many steps in cell wall synthesis have been exploited as targets of currently available antimicrobial agents, and others provide potential targets for ongoing anti-infective research (Fig. 292.1). Our understanding of mechanisms of cell death following interruption of cell wall synthesis has increased to recognize both mechanisms of direct cell wall damage and initiation of metabolic pathways for programmed cell death.[3]

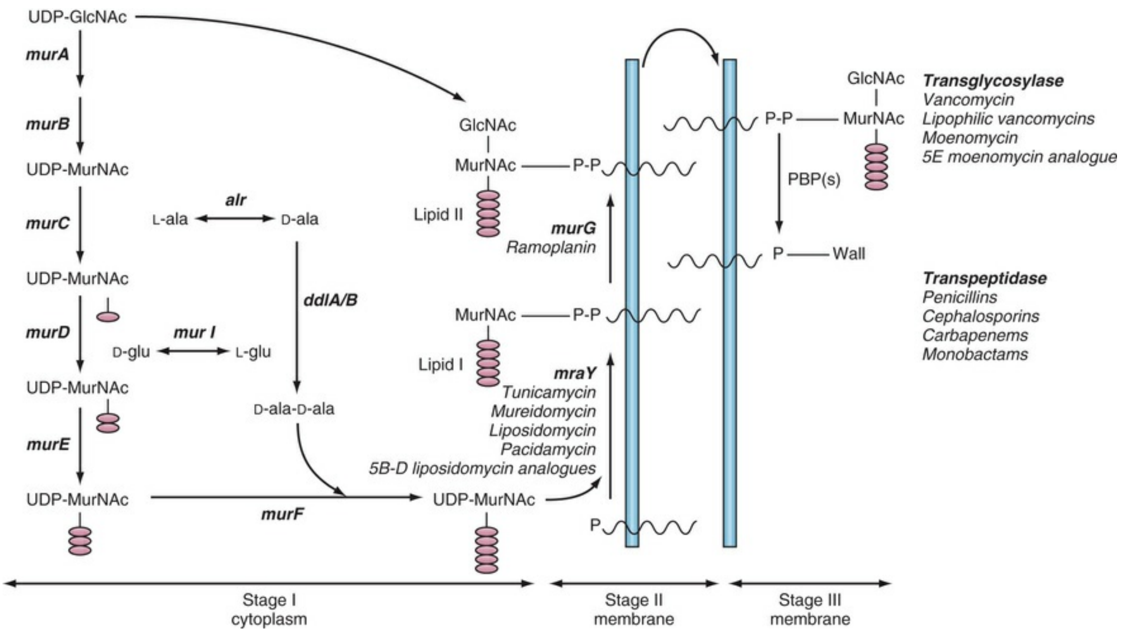


FIGURE 292.1 The peptidoglycan synthesis pathway in cell wall formation. D-ala, D-alanine; GlcNAc, *N*-acetylglucosamine; L-ala, L-alanine; MurNAc, *N*-acetylmuramic acid; PBP(s), penicillin-binding proteins (transpeptidase); UDP, uridine diphosphate. (Redrawn with modification from Wong VK, Pompliano DL. Peptidoglycan biosynthesis:

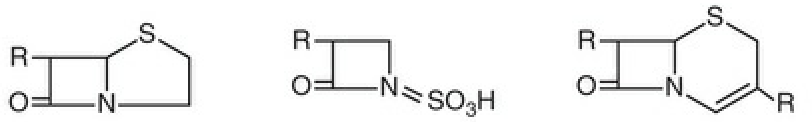
unexploited targets within a familiar pathway. In: Rosen BP, Mobashery S [eds]. Resolving the Antibiotic Paradox. New York, Kluwer Academic/Plenum Publishers, 1998, pp. 197–217.)

The saccharide precursors of cell walls, *N*-acetylmuramic acid (MurNAc), and *N*-acetylglucosamine (GlcNAc) are modified enzymatically by a series of steps, with MurNAc acquiring a side chain consisting of five peptides, incorporating D-alanine, D-alanine as the terminal two amino acids in this chain. This MurNAc pentapeptide is subsequently attached to a GlcNAc saccharide unit, completing the disaccharide pentapeptide building block required for cell wall peptidoglycan formation (see Fig. 292.1). Agents that inhibit these initial steps have been identified in a research setting, and many are currently under investigation as clinically important targets.[4,5] The disaccharide pentapeptide building block subsequently is transferred through the cell membrane to undergo further modification, ultimately to create the peptidoglycan structure either outside the cell membrane (in gram-positive organisms) or between the inner plasma membrane and outer membrane within the cell wall (in gram-negative organisms). Linking of the disaccharide pentapeptide building blocks occurs by transglycosylation and creates repeating disaccharide subunits (GlcNAc-MurNAc-pentapeptide) to produce long glycan chains.[6] Vancomycin and related glycopeptide antibiotics inhibit this step in cell wall synthesis by binding to the terminal D-alanine, D-alanine of the pentapeptide attached to MurNAc and by interfering sterically with the enzymatic function of the transglycosylase.[7]

The mature glycan chains containing the repeating disaccharide units subsequently are linked by connecting the pentapeptides located on the MurNAc units from adjacent glycan chains. In this transpeptidation step, a stable bridge is created between glycan chains to form the two-dimensional peptidoglycan structure.[6] The β-lactam class of antibiotics inhibits the transpeptidase function by binding covalently to the active serine site of the enzyme responsible for linking the two pentapeptide arms from MurNAc units on adjacent glycan strands.[8] The structure of enzymes that are responsible for transglycosylation and transpeptidation varies somewhat between bacteria. Fortunately, the active sites of these enzymes tend to be conserved. An organism often contains several transpeptidases, each responsible for a different cell wall function, including repair, elongation, septation, and cell wall thickening, among others. Some of these enzymes contain both transglycosylation and transpeptidation functions. Historically, these enzymes were identified by penicillin attachment to them and are also known as *penicillin-binding proteins* or (PBPs).

β-Lactam Antibiotics

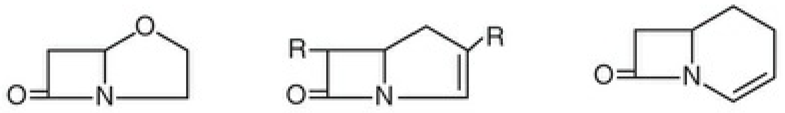
The β-lactam antibiotics all share the capacity to inhibit the transpeptidase cross-linking of peptidoglycan in the final steps of formation of the cell wall. Whereas the β-lactam structure itself is consistent across all antibiotics in this class, the ring to which the lactam moiety is fused is variable, with relatively small differences in the composition of the ring allowing for variable activity against the PBPs of both gram-positive and gram-negative bacteria (Fig. 292.2). The addition of chemical "chains" to the ring structures enhances activity against certain organisms, but simultaneously can decrease activity against others. Differences in the charges of the antibiotic molecule affect the ability of the compound to reach and to bind to its target, particularly for gram-negative pathogens.



Penam (penicillin, ampicillin)

Monobactam

Cephem (ceffriaxone, cefotaxime)



Clavam (clavulanate)

Carbapenem (meropenem)

Carbacephem (loracarbef)

FIGURE 292.2 β-Lactam antibiotic structures.

In general, the β-lactam antibiotics are bactericidal, with the concentrations required for killing being very close to those required for inhibition of growth. The maximal bactericidal effect occurs on rapidly growing bacteria; in stationary phase (or as sessile organisms in biofilms), this class of antibiotics has substantially less bactericidal effect.[9]

Resistance to β-Lactam Antibiotics

Probably just as ancient as the natural antibiotics are natural mechanisms for resistance to them (Fig. 292.3). Resistance to the β-lactam antibiotics occurs primarily in four ways: (1) enzymatic hydrolysis of the β-lactam ring by bacterial β-lactamases, rendering the antibiotic harmless; (2) alterations in the structure of the transpeptidase, so that binding of the antibiotic to the active serine site of the transpeptidase does not occur; (3) efflux pumps that, in gram-negative organisms, quickly and efficiently remove the antibiotics from the periplasmic space before they can bind to the transpeptidases; and (4) alterations in the gram-negative outer membrane proteins that prevent the antibiotic from entering the periplasmic space. Each resistance mechanisms is variably effective and can lead either to profound resistance or merely to slightly increased resistance that has no clinical effect. Unfortunately, some pathogens combine several resistance mechanisms, each creating incremental increases in β-lactam resistance, ultimately leading to the development of an organism that is no longer susceptible to these antibiotics.

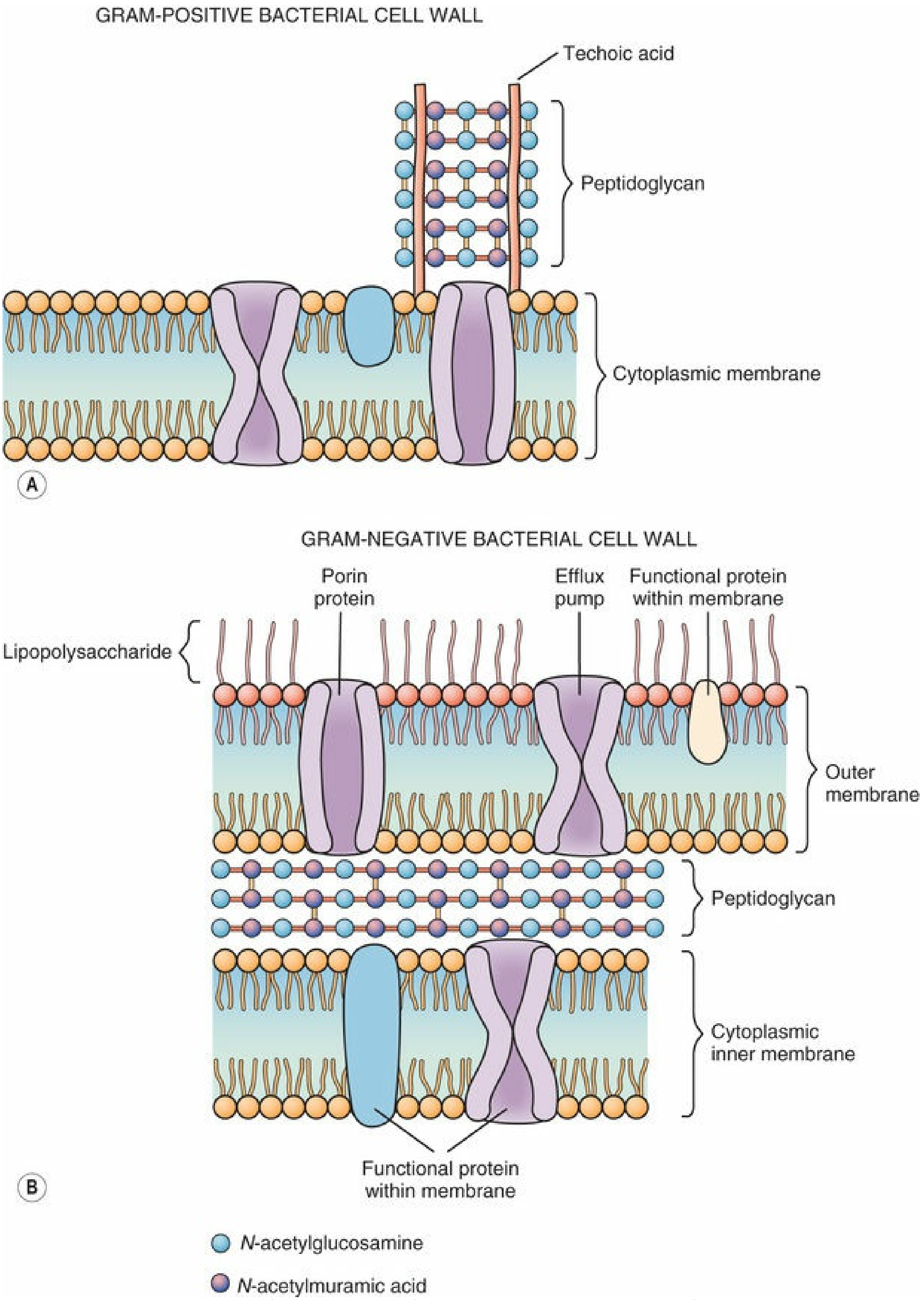


FIGURE 292.3 Structure of bacterial cell walls of gram-positive (A) and gram-negative (B) bacteria.

Chemical modifications of the β-lactam ring and associated drug structure can enhance the intrinsic activity of a drug against bacterial pathogens. Modifications that alter ionic charges on the molecule can allow the new agent (e.g., ampicillin) to enter the gram-negative bacterial periplasmic space, in contrast to an older agent (e.g., penicillin G) that could not. Side chains can create enhanced stability of the antibiotic against one or more of the hundreds of β-lactamases that have been identified, or can enhance binding to bactericidal targets within the organism.[4] Unfortunately, new, more active and broader spectrum β-lactamases are reported with disturbing regularity.[10] Although many different efflux pump systems exist, changes in the structure and charge of the antibiotic can decrease the affinity of the antibiotic for the pump, while hopefully not decreasing its affinity for the target transpeptidase.

Penicillins

The penicillins are the most commonly used antibiotics in pediatrics and can be divided broadly into four different groups: (1) natural penicillins, (2) penicillinase-stable penicillins, (3) aminopenicillins, and (4) extended-spectrum penicillins.

Natural Penicillins

Natural penicillins are the natural products of *Penicillium chrysogenum.* It is likely that both penicillins and penicillin-resistance mechanisms evolved millions of years ago as result of competition for survival between single-cell organisms.[11] Fleming's observations in the 1920s led to the identification of penicillin and the discovery of the mechanism by which *Penicillium* killed other bacteria, paving the way for the modern era of antibacterial therapy. The basic structure of penicillin, 6-aminopenicillanic acid, is characteristic of the lactam ring fused to a larger ring structure to create a penam nucleus that is the basic structure of all penicillins (see Fig. 292.2). Of the natural penicillins, only penicillin G (crystalline penicillin G, benzyl penicillin G) and penicillin V (phenoxymethyl-penicillin) currently are available commercially. Penicillin G is available in both oral and parenteral formulations. For intramuscular injection, penicillin G also is available in repository forms of the drug. Procaine penicillin G and benzathine penicillin G both have much longer serum elimination half-lives as a result of prolonged absorption from the muscle injection site, compared with crystalline penicillin G. However, the peak serum concentrations of the repository forms of penicillin G are a fraction of that achieved with intravenous administration of crystalline penicillin G. Therefore the only settings in which the repository forms of penicillin are effective are those in which the targeted organisms are exquisitely susceptible to penicillin, existing in tissues with good perfusion. Intramuscular procaine penicillin has a half-life of approximately 12 hours and achieves peak serum concentrations of about 2 μg/mL, compared with a half-life of 30 to 50 minutes for crystalline penicillin G and achieved peak serum concentrations of approximately 20 μg/mL. Benzathine penicillin G yields serum concentrations of only about 1.5 μg/mL but can remain above 0.2 μg/mL for ≥3 weeks. Combinations of procaine and benzathine penicillin, either in equal amounts or as a 3 : 1 (benzathine to procaine) mixture, also are available. Because these repository forms of penicillin are used infrequently, extreme caution must be taken never to administer them intravenously, which can be lethal.

In clinical practice, although active against a wide range of bacteria (see Table 292.2), the natural penicillins are used most widely for treatment and prevention of infections caused by streptococci. Pharyngitis, lower respiratory tract infection, skin and skin structure infections, and bloodstream infection (BSI) caused by group A *Streptococcus* (*Streptococcus pyogenes*) are effectively treated with penicillin. The in vitro susceptibility of these organisms has remained unchanged over the past several decades,[12] although the efficacy in the treatment of streptococcal pharyngitis in more recent studies is less than expected, for reasons that are not well understood.[13] Intramuscular injections of benzathine penicillin every 3 to 4 weeks are effective in the prevention of rheumatic fever because of the prolonged tonsillar tissue concentrations of penicillin G.

Empiric penicillin therapy of infections suspected to be caused by *Streptococcus pneumoniae* was not appropriate during the mid-1990s and did not become appropriate until approximately 2010, as a result of widespread decreased susceptibility of pneumococci to penicillin. Certain serotypes of pneumococcus were able to acquire genetic resistance and form stable alterations in the structure of several pneumococcal PBPs, yielding penicillin-nonsusceptible organisms, treatment of which requires use of higher dosages of penicillins or agents from other antibiotic classes. However, if culture results during that era or presently document susceptibility, penicillin still represents highly effective therapy. Fortunately, widespread use of protein-conjugated vaccines against the most antibiotic-resistant and virulent serotypes have had a dramatic impact in decreasing both the number and antibiotic resistance of pneumococcal infections.

Most anaerobes, with the exception of β-lactamase–producing strains of *Bacteroides* spp. and *Prevotella* spp., are highly susceptible to penicillin G. However, because of the common isolation of *Bacteroides fragilis* among the anaerobes present in intra-abdominal infections and *Prevotella melaninogenica* among the organisms causing sinus-related and deep head and neck space infections, including brain abscesses, agents active against β-lactamase –producing anaerobes are preferred to treat infections at these sites.

Penicillin G continues to play a role in the treatment of infections caused by other α- and β-hemolytic streptococci, most of which remain susceptible. For life-threatening infections such as bacterial endocarditis, susceptibility testing should be performed to ensure that the organisms do not exhibit penicillin tolerance, which may decrease treatment success using single-drug therapy at standard dosages.

Penicillin G is effective therapy for less common infections, including diphtheria, naturally occurring anthrax, actinomycosis, leptospirosis, and syphilis.

Penicillinase-Stable Penicillins

The class of semisynthetic penicillins represented by methicillin, oxacillin and nafcillin was created to meet the challenge of the development of penicillin-resistant *Staphylococcus aureus.* The bulky side chains prevent the staphylococcal β-lactamases from binding to and hydrolyzing the lactam ring of the molecule. However, these antibiotics are resistant only to staphylococcal penicillinases, and not to the β-lactamases of gram-negative organisms. These antibiotics are not active against methicillin-resistant *S. aureus* (MRSA) because of the presence of a transpeptidase (PBP2a), which had not been capable of being bound and inactivated by any β-lactam antibiotic until the approval of ceftaroline in 2010.

In clinical practice, these antibiotics are used to treat infections caused by methicillin-susceptible *S. aureus* (MSSA). They are available in both parenteral and oral formulations. With the emergence of community-associated (CA)-MRSA, their longstanding role in the empiric therapy of presumed staphylococcal infections is compromised. For MSSA, however, these semisynthetic penicillins are safe and highly effective.

Aminopenicillins

The aminopenicillin class of semisynthetic penicillins (as represented by ampicillin and amoxicillin) contains an amino substitution in the phenyl acetamido side chain of the penam nucleus, providing a polar charge on the molecule that allows activity against gram-negative pathogens, including *Escherichia coli* and *Haemophilus influenzae* (see Table 292.2). However, aminopenicillins are not stable to staphylococcal penicillinases, or to the hundreds of different β-lactamases elaborated by gram-negative pathogens. Their activity against other gram-positive organisms, such as group A and group B *Streptococcus* spp., is excellent, and activity against most enterococci is equivalent to or better than penicillin G.

As a means of enhancing the activity of the aminopenicillins against β-lactamase–producing pathogens, the concurrent use of a second agent that binds irreversibly to a pathogen's β-lactamase has led to a useful group of drugs. These concurrently used agents, called β-lactamase inhibitors, have little antibiotic activity on their own because they have been selected for avid binding characteristics to specific β-lactamases, rather than to PBPs. However, there is variability in the binding affinity of each β-lactamase inhibitor to the β-lactamases of different organisms. Currently in the United States, clavulanate is paired with amoxicillin in an oral formulation (and a parenteral formulation in other parts of the world), ampicillin is paired with sulbactam, and piperacillin is paired with tazobactam in parenteral preparations (see Table 292.2).

The clinical uses of ampicillin and amoxicillin are extensive. The enhanced activity against *E. coli* and other gram-negative enteric bacilli compared with penicillin G permits ampicillin and amoxicillin to be used for the treatment of some urinary tract infections (UTIs) and gastrointestinal infections. The excellent activity against β-lactamase–negative strains of *H. influenzae* allows ampicillin and amoxicillin to be used in the treatment of upper and lower respiratory tract infections. Ampicillin is one of the most bactericidal agents when used together with gentamicin for susceptible strains of *Enterococcus.* Unfortunately, the development of ampicillin resistance in *E. coli, Shigella, Salmonella,* and *H. influenzae* has limited the usefulness of aminopenicillins against these pathogens.

However, the addition of clavulanate to amoxicillin allows activity against β-lactamase–producing strains of *H. influenzae* and *Moraxella catarrhalis* as well as MSSA. This combination increases the clinical usefulness of amoxicillin in the treatment of community-associated upper and lower respiratory tract infections (e.g., acute otitis media, sinusitis, and pneumonia), in addition to skin and skin structure infections. Clavulanate alone has little effect on ampicillin-resistant *E. coli*. The addition of sulbactam to ampicillin allows activity against many β-lactamase–producing organisms, including staphylococci, many enteric gram-negative bacilli (not *E. coli* typically), and *B. fragilis.* Ampicillin-sulbactam can be used for treatment of complicated pneumonia, skin and skin structure infections, and some intra-abdominal infections, which is not possible with ampicillin alone.

Extended-Spectrum Penicillins

Extended-spectrum semisynthetic penicillins are designed to increase activity against gram-negative pathogens, including *Klebsiella, Enterobacter,* and, for some agents, *Pseudomonas* (see Table 292.2). The two major classes are the carboxypenicillins, represented by ticarcillin and carbenicillin, and the acylureidopenicillins, represented by piperacillin. Although the spectrum of activity of these antibiotics has been enhanced beyond the aminopenicillins, they remain susceptible to hydrolysis by many β-lactamases, including those of MSSA. Similar to the aminopenicillins, activity of these drugs has been enhanced by pairing them with β-lactamase inhibitors, such as ticarcillin-clavulanate and piperacillin-tazobactam.

The clinical uses of these antibiotics reflect their broad activity against gram-negative enteric bacilli and *Pseudomonas aeruginosa.* Originally available as a single-antibiotic agent, ticarcillin now is available only in combination with clavulanate, and piperacillin only with tazobactam. Many organisms, including MSSA, *B. fragilis, P. melaninogenica,* and many gram-negative enteric bacilli (*E. coli* and *Klebsiella* spp.) are susceptible (see Table 292.2). This allows for successful therapy for skin and skin structure infections, intra-abdominal infections, and many gram-positive and gram-negative hospital-associated infections, such as wound infections, UTIs, and pneumonia. The extended-spectrum penicillins also retain good activity against ampicillin-susceptible strains of *Enterococcus.* Tazobactam adds little to antimicrobial activity of piperacillin for *P. aeruginosa*; the combination drug is used only when coverage of additional organisms is desired.

Cephalosporins

Cephalosporins, like the penicillins, are β-lactam antibiotics found in nature. Cephalosporin C, the precursor molecule for antibiotics used in humans, originally was isolated from *Cephalosporium acremonium.* Successive modifications of the cephem ring structure have resulted in "generations" of cephalosporin antibiotics. There is no official scientific designation of generations; rather, the description of enhanced activity of the second generation over the first was created as a marketing tool.[14] However, the ability to distinguish the relative activity of the large number of cephalosporin antibiotics by generation is useful (see Table 292.2).

In general, the first-generation cephalosporins (represented by intramuscular or intravenous [cefazolin and by oral cephalexin) are active against gram-positive pathogens, group A *Streptococcus,* and penicillinase-producing *S. aureus* (MSSA), which has led to their use for skin and skin structure infections and surgical prophylaxis, as well as for systemic infections caused by these organisms. Although cephalosporins are better tolerated than the penicillinase-stable penicillins (e.g., methicillin), they are somewhat less active in vitro against *S. aureus,* and may not be as effective in the treatment of serious infections such as endocarditis. Cephalosporins uniformly lack activity against all enterococci.

The cephalosporins are active against many strains of *E. coli,* allowing treatment of urinary tract and intestinal infections. However, increasing resistance to first-generation cephalosporins has limited the usefulness of these agents in the treatment of both community-associated and hospital-associated infections.

The second-generation cephalosporins have enhanced activity against gram-negative pathogens and enhanced stability against β-lactamases compared with first-generation agents (see Table 292.2). Increased spectrum of activity includes many enteric gram-negative bacilli and β-lactamase–producing strains of *H. influenzae.* The activity of second-generation agents against MSSA is decreased, although not sufficiently to lead to clinical failures in treatment of mild to moderate staphylococcal infections. This broad spectrum of activity allows for single-drug therapy of streptococcal, *H. influenzae,* and some staphylococcal infections in children. However, because of poor penetration of the first- and second-generation cephalosporins into cerebrospinal fluid (CSF), use for the treatment of BSI is limited by *S. pneumoniae* and *H. influenzae*. Within the second generation of agents, all of which share the cephem ring structure (see Fig. 292.2), are both true cephalosporins and the cephamycins. The cephamycins were originally isolated from *Streptomyces* spp. and contain an additional side chain that enhances stability to β-lactamases, providing improved activity against β-lactamase–containing strains of *B. fragilis* (cefoxitin and cefotetan). Given reasonable activity against gram-positive organisms (except enterococci), gram-negative enteric bacilli, and anaerobes, these cephamycin antibiotics are more effective in the treatment of intra-abdominal infections than cephalosporins.

Oral second-generation agents have been used widely for the treatment of upper and lower respiratory tract infections in children. However, with higher rates of penicillin resistance in *S. pneumoniae* caused by changes in the PBP structures, treatment failures of infections caused by penicillin-nonsusceptible strains of pneumococcus using the oral second-generation cephalosporins occurs; high-dose amoxicillin therapy is superior.

The third-generation cephalosporins have further enhanced gram-negative activity, which extends to *P. aeruginosa* for ceftazidime, but at the expense of a further decrease in activity against MSSA. As with other cephalosporins, they lack activity against enterococci. Enhanced activity against enteric gram-negative bacilli has led to successful therapy of UTIs and many nosocomial infections. However, therapy of infections caused by *Enterobacter, Serratia,* and *Citrobacter* spp., which have the ability to produce chromosomally mediated (inducible) ampC β-lactamases, can fail. Failure is likely to be due to the selection of organisms at the site of infection that constitutively hyperproduce these enzymes, based on alterations in β-lactamase gene regulation, thus conferring resistance to third-generation agents.[15] In general, the third-generation cephalosporins also are hydrolyzed by extended-spectrum β-lactamases (ESBLs) produced most commonly by *E. coli* and *Klebsiella* spp.[10,16] The activity of the third-generation agents is superb against virtually all strains of *H. influenzae.* These agents, in general, achieve CSF concentrations that are effective for treatment of bacterial meningitis caused by all three major pediatric pathogens: *H. influenzae, S. pneumoniae,* and *Neisseria meningitidis.* Of note, certain penicillin-resistant strains of *S. pneumoniae* have decreased susceptibility to third-generation cephalosporins and have been associated with clinical and microbiologic failure of treatment for central nervous system (CNS) infection.[17,18] Additionally, the most active of the third-generation cephalosporins against *S. pneumoniae,* ceftriaxone and cefotaxime, have not been associated with treatment failure of respiratory tract infections caused by penicillin-resistant strains when appropriate dosing regimens are used. None of the third-generation agents should be considered optimum for the treatment of infections caused by MSSA because other cephalosporins and penicillinase-stable penicillins are more active against this pathogen.

Of the third-generation agents, ceftriaxone has a prolonged serum half-life compared with the other agents, allowing for its once-daily use for treatment of exquisitely susceptible organisms. The infrequent dosing and the ability to use either intramuscular or intravenous routes of administration have permitted outpatient therapy of serious, invasive infections at a point when the child's clinical condition is stable.[19] Caution for such use for MSSA infections is warranted because MSSA frequently is not exquisitely susceptible.

The fourth-generation cephalosporin, cefepime, maintains activity against *P. aeruginosa* and displays enhanced stability to the ampC chromosomal β-lactamases of *Enterobacter, Serratia,* and *Citrobacter* spp., while retaining significant (but not optimal) activity against MSSA (see Table 292.2).[20] This broad activity permits empiric therapy of neutropenic children with fever and allows for treatment of a wide variety of nosocomial gram-negative infections.[20–24] However, lack of activity against β-lactamase −positive strains of *B. fragilis* and against *Enterococcus* limits the ability to treat intra-abdominal infections with cefepime alone.

The fifth generation of cephalosporins, represented currently by only one available product, ceftaroline, combines the gram-negative and gram-positive activity of the third-generation cephalosporins with in vitro and clinically demonstrable activity against CA-MRSA. These agents have been designed to bind to and inactivate PBP2a, which confers β-lactam resistance in MRSA, and PBP2x, which confers resistance in *Pneumococcus,* providing clinically relevant activity against MRSA and penicillin-resistant pneumococci superior to all other currently available β-lactam agents.[25] However, ceftaroline is not active against *Pseudomonas* and is not stable to ESBLs.

Carbapenems

Carbapenems, also naturally occurring, were initially isolated from a species of *Streptomyces*, with the β-lactam moiety contained within a carbapenem nucleus (see Fig. 292.2). Carbapenems demonstrate the broadest spectrum of activity of all the β-lactam antibiotics and currently include imipenem, meropenem, doripenem, and ertapenem.[26] Carbapenems are active against both gram-positive pathogens, including MSSA but not MRSA and streptococci (with moderate activity against ampicillin-susceptible enterococci), and gram-negative pathogens (including *P. aeruginosa* for imipenem, meropenem, and doripenem), with enhanced stability against both the chromosomal ampC β-lactamases of *Enterobacter, Serratia,* and *Citrobacter* spp. and the ESBLs of *E. coli* and *Klebsiella* (see Table 292.2). They are highly active against anaerobic organisms, including β-lactamase−producing strains of *Bacteroides* and *Prevotella.* Imipenem is paired with cilastatin, a renal dehydropeptidase inhibitor that inhibits the destruction of imipenem by renal tubular enzymes, providing both an increase in the serum half-life of imipenem and a decrease in the renal toxicity of the compound. Imipenem use was associated with unexpected seizures in an open, noncomparative clinical trial in children with meningitis,[27] probably attributable to competitive inhibition of the inhibitory CNS neural pathways. Therefore meropenem, which does not produce clinically detectable CNS side effects, is the preferred carbapenem agent for treatment of CNS infections, including meningitis, brain abscess, epidural abscess, and subdural empyema. Ertapenem has the most prolonged serum half-life of the carbapenems and requires only once-daily dosing in older children (≥13 years of age) and once- or twice-a-day dosing in younger children. Carbapenems are used primarily for nosocomial infections or infections in immunocompromised hosts when exceptionally broad spectrum of activity is essential. Data support clinical and microbiologic efficacy in pneumonia, UTIs, wound infections, bone and joint infections, and skin and skin structure infections.[28] Imipenem and meropenem have been used as single-drug empiric therapy of fever and neutropenia in immunocompromised children.[21] Carbapenems provide good, but not optimum, activity against *S. aureus*. They provide the best activity of all β-lactam agents against pathogens harboring either chromosomally mediated ampC β-lactamases or ESBLs. Recent emergence of carbapenemase-producing *Klebsiella* and other carbapenem-resistant *Enterobacteriaceae* (CRE) have limited the usefulness of these broad-spectrum agents in certain regions of the world.[29] Use of such broad-spectrum agents must be weighed against the risk for promoting resistance and profoundly altering normal flora.

Monobactams

Monobactams have a unique β-lactam structure and are a naturally occurring antibiotic isolated from *Chromobacterium* spp. In contrast to penicillins, cephalosporins, and carbapenems, monobactams are not fused to an adjacent ring. Aztreonam, the only available agent in this class, has been modified chemically with side chains[30] and demonstrates gram-negative activity comparable with the third-generation cephalosporins but without significant gram-positive or anaerobic activity. Clinical use in pediatrics is limited primarily to treatment of community-acquired infections in which enteric gram-negative organisms are suspected or proven pathogens and aminoglycosides are not adequate or appropriate therapy. Aztreonam also is approved by the US Food and Drug Administration (FDA) as an inhalational antibiotic for children with cystic fibrosis who are 7 years or older, for the treatment of *P. aeruginosa* lower respiratory tract infection.

Glycopeptide Antibiotics

Glycopeptides interfere with cell wall formation in the steps that create the glycan chains before cross-linking the chains in the formation of peptidoglycan (see Fig. 292.1). Glycopeptides have a large, complex structure that consists of multiple peptides linked together into three rings, with various side-chain substitutions, including large saccharide moieties attached to the central polycyclic structure. Strong hydrogen bonds occur between a glycopeptide antibiotic and the terminal D-alanine, D-alanine dipeptide of the pentapeptide side chains of the MurNAc subunits of the glycan chain. When bound, the glycopeptides sterically prevent the transglycosylation steps required for lengthening the glycan chain.[5] Glycopeptide antibiotics are active primarily against gram-positive organisms, in which the cell wall construction occurs outside the cell membrane (see Fig. 292.3). Little activity is demonstrated against gram-negative organisms because the large structure does not cross the gram-negative outer membrane easily, preventing contact with enzymes responsible for transglycosylation in the periplasmic space. Recently documented resistance in gram-positive pathogens to vancomycin has led to intense investigation of derivatives of vancomycin and teicoplanin (another parenteral glycopeptide), leading to recent FDA approval of telavancin, dalbavancin, and oritavancin for adults. Limited data are available for these agents in children, but studies are in progress.

Vancomycin

Vancomycin is a natural product, originally isolated from *Streptomyces* spp. in 1956. Vancomycin is the only glycopeptide currently available in the United States. Originally developed to treat staphylococcal infections, vancomycin was rarely used following the availability of the penicillinase-stable penicillins, which were tolerated better. However, since the first appearance of healthcare-associated MRSA four decades ago, vancomycin has played an increasing role in the treatment of nosocomial *S. aureus* and coagulase-negative staphylococcal infections. With current prevalence of CA-MRSA, vancomycin now is used routinely for empiric therapy of serious suspected staphylococcal infections.[31,32] Decreased bactericidal activity and clinical efficacy of vancomycin compared with the penicillinase-stable penicillins for treatment of MSSA, as well as greater toxicity, make β-lactams preferred therapy for infections caused by MSSA.

Resistance to vancomycin has developed in several ways. In *Enterococcus* spp., *vanA*-mediated resistance, the most common resistance seen in clinical isolates, leads to complete resistance to vancomycin. A transmissible set of 7 genes, which encode a series of biologic functions that allow *Enterococcus* to sense the presence of vancomycin, to cleave the D-alanine, D-alanine dipeptide from the pentapeptide chain, and to substitute D-alanine, D-lactate at the terminus of the pentapeptide, results in a 1000-fold decrease in binding of vancomycin.[33,34] The new pentapeptide appears to be as viable a precursor for peptidoglycan formation as the original pentapeptide. The *vanA* resistance mechanism has now been detected in *S. aureus* infecting adults, creating vancomycin-resistant *S. aureus* (VRSA). A more common resistance mechanism of *S. aureus* to vancomycin, producing a heterogeneous population of intermediately susceptible strains or hVISA, is proliferation of the D-alanine, D-alanine glycan structures, creating a disorganized, thickened cell wall and leading to increases in the binding and trapping of vancomycin to nonfunctional dipeptides.[35–38] Under vancomycin pressure, these strains, which are present in every large population of staphylococci, are selected. However, because these strains are not fully resistant to vancomycin, retrospective data suggest that higher dosages of vancomycin (if tolerated by the patient) can remain effective therapy for hVISA.[39,40]

Three new glycopeptide antibiotics—telavancin, dalbavancin, and oritavancin—have demonstrated clinical efficacy in clinical trials in adults.[41] Modifications of the glycopeptide to enhance binding to targets, to increase stability of antibiotic binding by creating glycopeptide dimers, and to anchor the glycopeptide to the cell membrane have all been successful strategies for enhancing the activity of this class of agents. Although these newer agents have shown increased in vitro activity against *S. aureus* compared with vancomycin, prospective, controlled clinical data to document improved outcomes in adults are not available, and no data exist currently for children.

Clinical uses of vancomycin include therapy for gram-positive infections in children who are allergic to penicillin, therapy of infections caused by *S. pneumoniae* that are resistant to penicillin,[42] and therapy of infections caused by MRSA. Treatment of *Clostridium difficile* infections with orally administered vancomycin is highly effective, but is not first-line therapy because of the emergence of vancomycin-resistant enterococci (VRE) following oral vancomycin therapy. In selected cases of severe disease or metronidazole failure, vancomycin enterally represents highly effective alternative therapy.[43]

A common reaction can occur with the rapid infusion of vancomycin, the red man or red neck syndrome, characterized by flushing and hypotension. This effect is histamine mediated and not immunoglobulin E mediated or immune mediated and is distinct from anaphylaxis. The risk for red man syndrome varies directly with the rapidity of the vancomycin infusion; therefore each dose of vancomycin usually is infused over 1 hour. For children who develop red man syndrome, prolonging the infusion time or pretreating with an antihistamine may permit continuation of therapy with vancomycin.

Cell Membrane–Active Antibiotics

Daptomycin

Daptomycin, a natural product derived from *Streptomyces* spp., is a novel lipopeptide antibiotic that is rapidly bactericidal based on effects on the gram-positive cell membrane. Daptomycin has a unique structure that consists of 13 amino acids, including a cyclic peptide containing 9 amino acids, attached to a lipophilic fatty acid tail that inserts into the cell membrane. The mechanism of action of daptomycin is not well understood, but it appears that depolarization of the membrane occurs as the antibiotic polymerizes within the bacterial cell membrane, producing channels in the membrane that result in leakage of cell contents, inhibition of protein, DNA and RNA synthesis, and cell death. Based on in vitro assays, daptomycin is one of the most rapidly bactericidal antibiotics against *S. aureus* and is active against a wide variety of gram-positive organisms, including MSSA, MRSA, VRSA, resistant coagulase-negative staphylococci, streptococci, and enterococci (including VRE) (see Table 292.2).[44]

Clinical use of daptomycin has been focused on MRSA infections that are unresponsive to vancomycin. Efficacy has been demonstrated in adults and children for skin and skin structure infections and for BSI. Daptomycin is not effective for the treatment of pneumonia, based on clinical trials in which response rates were not equivalent to comparator agents. Daptomycin is inactivated by surfactant, yielding relatively low concentrations in bronchial-alveolar epithelial lining fluid and lung parenchyma.[45] Limited pharmacokinetic and clinical data have been reported in children.[46–48] The prolonged half-life allows for once-daily dosing.

In the first human clinical trials in the 1960s, daptomycin was associated with a high incidence of myalgias and muscle weakness accompanied by elevations in serum creatine kinase. This adverse effect appears to depend on the frequency of dosing. Although toxicity was prohibitive when daptomycin was administered every 6 to 8 hours, the drug demonstrated no greater toxicity than comparator agents when administered to adults in a dose of 4 mg/kg once daily.[37] When the approved dosage of daptomycin was increased to 6 mg/kg daily in adults for the treatment of BSI and endocarditis, no significant muscle toxicity was noted.[49] No muscle toxicity has been reported in any of the controlled prospective pediatric clinical trials. Toxicology studies in neonatal pups suggested a poorly defined neurologic toxicity, which resulted in a lower limit of age eligibility of 1 year in prospective comparative pediatric clinical trials. Potential risks and benefits need to be considered before use of daptomycin in neonates.

Colistin

Colistin is a polymyxin antibiotic that is a natural product isolated from *Bacillus polymyxa* and consists of 10 linked amino acids, with 6 forming a peptide ring structure attached to a fatty acid side chain. Colistin is also known as polymyxin E, structurally similar to polymyxin B, which is used extensively as a topical agent. The polymyxin antibiotics were first discovered in 1947, with the first clinical use of colistin in the US in 1959.[50] Colistin is available in the US as a sodium methanesulfonate salt, known as colistimethate. The dosage is calculated as the colistin base, at 2.5 to 5 mg/kg/day given in 2 to 4 divided doses. Colistimethate is hydrolyzed to colistin, but the rate and extent of hydrolysis and the contributions of biologic activity of the parent compound and products of metabolism are not well defined. The mechanism of bactericidal activity against the cytoplasmic membrane is based on cationic detergent activity, binding to lipopolysaccharides in the outer cell membrane, displacing calcium and magnesium and disrupting the lipid component of the cell membrane. Permeability changes subsequently occur in the membrane, disrupting the osmotic gradient of the cell and affecting cellular metabolism and nucleic acid synthesis.[51]

Colistin has been used as both intravenous and inhalational treatment for multidrug-resistant (MDR) gram-negative pathogens in children with cystic fibrosis (CF),[52] and more recently, in non-CF patients with gram-negative pneumonia.[53] For treatment of certain gram-negative CNS infections, colistin has been injected intrathecally.[54,55] Only limited, retrospective clinical data are available to guide therapy with this agent.[54,55]

Colistin has significant toxicity, primarily renal and neurologic. Renal side effects include decreased urine output with elevated blood urea nitrogen and serum creatinine, proteinuria, hematuria, and acute tubular necrosis. Because colistin is eliminated by renal excretion, it is imperative to assess renal function closely during therapy, decreasing the dosage if any degree of renal insufficiency is noted. Drug accumulation and additional renal toxicity occur if dosing is not altered when renal insufficiency first occurs. Renal toxicity usually is reversible if detected early. Neuromuscular side effects had been noted in adults and children treated with colistin in case series reported up to 50 years ago, most often manifest as oral and perioral paresthesias, weakness, lethargy, confusion, ataxia, and respiratory muscle paralysis. However, more recent experience with colistin, particularly in children, has not described this neuromuscular toxicity.[54,55]

Because of the toxicity, clinical use of parenteral colistimethate is limited to therapy of infections caused by MDR gram-negative pathogens for which no other option is available. Other clinical uses include inhaled therapy in ventilated patients with nosocomial MDR gram-negative pulmonary infections[56] and aerosolized colistimethate in children with CF as adjunctive antimicrobial therapy.[57,58]

Ribosome-Active Antibiotics

The bacterial ribosome, highly conserved over millions of years, has long been a target of antibiotics. As our ability to understand the function of the ribosome has increased, visualization of ribosomal structures with crystallography has occurred, and knowledge of the mechanism of activity of both older and newer agents, as well as ability to design more effective antibiotics, has improved substantially. The ribosome contains a 30S and a 50S subunit, each comprising rRNA and encoded ribosomal proteins. Several sites have been documented to be antibiotic targets on each subunit and at the junction of the subunits. Targets include the entry site of mRNA, the initial recognition and binding site of tRNAs, the site of attachment of the tRNA-peptide chain where peptide bonds are formed (the peptidyl transferase center), and the exit channel of the growing polypeptide.[59–61] The critical chemical and structural relationships between the ribosomal rRNA and the peptidyl transferase center, which promote the chemical reactions to create a new peptide, as well as movement of mRNA and the newly formed peptide through the ribosome, provide opportunities for interference in bacterial protein synthesis.

Macrolides

Currently available macrolides that have substantial clinical trial data for children include the erythromycins, azithromycin, and clarithromycin. All share structural similarities with either a 14-member lactone ring (erythromycin, clarithromycin) or a 15-member ring (azithromycin). All bind to at least one site in common within the peptide exit tunnel of the ribosome: domain V of the 23S RNA within the 50S subunit. To achieve activity in most bacteria, binding to a specific adenine residue of the rRNA, A2058, within this channel prevents the orderly movement of protein out of the ribosome.[62]

Clarithromycin is similar structurally to erythromycin, with only the addition of a single methyl group to the erythromycin ring, primarily conferring improved stability to gastric acid. Whereas erythromycin, clarithromycin, and azithromycin contain a cladinose carbohydrate attached to the lactone ring, a new class of ketolides, represented by telithromycin and solithromycin, substitutes a ketone in this position while adding highly charged side chains to the C11 and C12 positions. These changes both improve the binding characteristics to the peptide tunnel–binding site within domain V and create an additional unique binding site at adjacent domain II within the ribosome, improving activity against many macrolide-resistant gram-positive organisms. Azithromycin is structurally similar to erythromycin but contains a 15-member ring with the addition of a nitrogen atom within the ring itself, structurally changing the drug from a macrolide to an azalide, but containing the same side chain–attached carbohydrate moieties as erythromycin. This change improves gram-negative activity and increases gastric acid stability. The degradation products of azithromycin provide far less stimulation of gastric motility, improving the tolerability of azithromycin over erythromycin.

In general, the macrolides are inhibitory, not bactericidal, to bacteria and therefore are not used for the treatment of serious and life-threatening infections when bactericidal agents can be used. The various macrolide agents have different binding affinities for their ribosomal targets in different organisms. Binding generally is reversible, with a prolonged rate of dissociation off the ribosome potentially adding to a more prolonged postantibiotic effect seen with some macrolides (see Table 292.1).[63]

The macrolides are most active against gram-positive cocci and bacilli, and, to a lesser extent, gram-negative bacilli (see Table 292.2). Some agents also are active against spirochetes and certain mycobacteria. Pathogens that lack a formal cell wall (e.g., *Mycoplasma* and *Ureaplasma*) and are not susceptible to β-lactam antibiotics often remain susceptible to macrolides.

All of the macrolides achieve high antibiotic concentrations within phagocytic cells. These concentrations often are much higher than those measured in serum, providing access of these antibiotics to infected tissue spaces by means of neutrophils and establishing a higher tissue concentration than antibiotics that enter primarily by diffusion alone. However, presence in the intracellular location leads to less free drug available for exposure to extracellular pathogens. Macrolides are particularly effective therapy against susceptible intracellular pathogens.

In general, macrolides are well tolerated. Clarithromycin and azithromycin are better tolerated than erythromycin, which has problematic gastrointestinal side effects in some children. With the exception of azithromycin, this class of antibiotics is metabolized by hepatic cytochrome P450 system, and drug-antibiotic interactions should be considered because they may increase or decrease the macrolide and concurrent drug concentrations.[64] Azithromycin has demonstrated minimal drug-drug interactions and may represent the preferred macrolide in certain situations, particularly for immunocompromised children receiving multiple medications concurrently.

Resistance to the macrolides occurs when molecular changes occur at the critical ribosomal attachment site, most commonly a monomethylation or dimethylation of the A2058 adenine-binding site. A rapidly increasing number of recognized methyltransferase enzymes has been reported. Most are encoded by gram-positive organisms and are most often inducible, but may be constitutively produced and lead to high-level resistance to erythromycin, clarithromycin, and azithromycin.[65] Less frequent alterations at this site also affect binding, with either substitution of guanine for adenine or structural changes in the L4 ribosomal protein.[66] Efflux pumps represent another common mechanism of resistance in gram-positive pathogens, including *Pneumococcus,* group A *Streptococcus,* and *S. aureus.* The most common pumps are active against all the macrolides—erythromycin, clarithromycin, and azithromycin.[65,67]

Erythromycin

Erythromycin, a natural product isolated from *Saccharopolyspora erythraea* (formerly *Streptomyces*) in 1949, was first approved for clinical use in 1952. Erythromycin is degraded by gastric acid and has long been associated with stimulation of motilin receptors in the stomach and possibly in the colon, leading to adverse gastrointestinal side effects, including cramping and diarrhea.[68,69] Many preparations have attempted to bypass exposure of erythromycin to gastric acid, thereby avoiding products of macrolide hydrolysis. These preparations include enteric coating of orally administered tablets, delayed-release formulations, polymer coating of beads, and various formulations of salts and esters.[70] The lactobionate salt used for intravenous administration of erythromycin can cause phlebitis at the site of injection.

Erythromycin is used for the treatment of group A streptococcal infections in children who are allergic to penicillin. Erythromycin is an alternative treatment for both streptococcal pharyngitis and streptococcal or staphylococcal impetigo. The usefulness of erythromycin for respiratory tract infections caused by *S. pneumoniae* has been greatly diminished by the development of widespread resistance to the macrolides.[42] Macrolide therapy of upper respiratory tract infections (otitis media and sinusitis) or lower respiratory tract infections (pneumonia) potentially caused by *S. pneumoniae* has a relatively high likelihood of failure, particularly in younger children, who are at highest risk for infections caused by antibiotic-resistant strains. For upper respiratory tract infections, erythromycin has inadequate activity against *H. influenzae* and must be paired with another agent such as a sulfonamide for empiric therapy. Macrolides are effective therapy for pneumonia caused by *Mycoplasma pneumoniae, Chlamydophila pneumoniae,* or *Legionella pneumophila*.

Erythromycin and azithromycin are the preferred antibiotics for treatment of *Campylobacter* gastroenteritis caused by susceptible strains. Erythromycin also remains the most appropriate therapy for diphtheria (*Corynebacterium diphtheriae*). Erythromycin, clarithromycin, and azithromycin are recommended for treatment or prophylaxis of pertussis (*Bordetella pertussis*).[71] Azithromycin is preferred for treatment or prophylaxis for pertussis in neonates, based on concerns for the development of pyloric stenosis.[71] Efficacy of erythromycin also has been demonstrated in infections caused by *Chlamydophila pneumoniae* and *Chlamydia trachomatis,* including neonatal conjunctivitis and pneumonia, as well as urogenital infections during pregnancy. Erythromycin is active in vitro against *Ureaplasma urealyticum,* but its role in the treatment of neonatal infections associated with this organism is not well defined.[72]

Clarithromycin

With the improved activity demonstrated against *H. influenzae* and improved tolerability compared with erythromycin, treatment of respiratory tract infections is the most common clinical use for clarithromycin. FDA-approved indications include pharyngitis and tonsillitis, acute otitis media, acute maxillary sinusitis, and community-acquired pneumonia caused by susceptible strains of *S. pneumoniae, H. influenzae, M. catarrhalis, M. pneumoniae, C. pneumoniae,* and *L. pneumophila*. For *S. pneumoniae*, strains that are resistant to erythromycin from either methyltransferase or efflux mechanisms also are resistant to clarithromycin. The activity of clarithromycin against *H. influenzae* is modest, but in noninferiority-designed clinical trials of clarithromycin for the treatment of respiratory tract infections, the microbiologic and clinical efficacy was not significantly less than that of other approved agents.

Clarithromycin is one of the most effective macrolides for treatment and prevention of disseminated mycobacterial infections due to *Mycobacterium avium* complex (MAC) in human immunodeficiency virus (HIV)-infected persons. Although not well studied in immunocompetent children, clarithromycin may play a role in the treatment of cervical adenitis and pneumonia caused by MAC (or other nontuberculous mycobacteria proved to be susceptible in vitro), in conjunction with other antibiotics or surgery, or both.[73]

Clarithromycin plays a role in the treatment of *Helicobacter pylori* infections in combination with amoxicillin and lansoprazole, or omeprazole, or in combination with ranitidine.[74,75] Clarithromycin has demonstrated efficacy similar to erythromycin in pertussis infections in small clinical trials and is considered as one of three first-line drugs. Although approved for treatment of skin and skin structure infections, clarithromycin is not often used for this indication because other more cost-effective or more active agents are available in the treatment of infections caused by *S. aureus*. Similarly, other β-lactam and macrolide antibiotics are preferred for the treatment of streptococcal pharyngitis.

Azithromycin

Azithromycin has high intracellular concentrations and provides prolonged tissue concentrations at the site of infection, permitting administration of very short courses for respiratory tract infections. Erythromycin-resistant strains of *S. pneumoniae* also are resistant to azithromycin. Group A streptococcus has variable resistance to macrolides. Activity against *H. influenzae* is moderate, with in vitro activity increased compared with erythromycin, but decreased compared with clarithromycin. However, the relatively small differences in susceptibility may be offset by higher concentrations of antibiotic if there is an intracellular site of infection. Azithromycin also is active against the pathogens causing atypical pneumonia (see Table 292.2).

Azithromycin is far better tolerated than erythromycin, can be given once daily, and is available in both oral and intravenous formulations. Based on noninferiority-designed clinical trials, azithromycin is approved for treatment of streptococcal pharyngitis, acute otitis media, sinusitis, and community-acquired pneumonia in children. Because of prolonged tissue concentrations, particularly using larger azithromycin dosages, 5-day, 3-day, and 1-day treatment courses, all providing a total treatment dosage of 30 mg/kg, have been shown to be comparable for clinical and microbiologic outcomes with 10-day treatment courses of comparator β-lactam antibiotics in acute, uncomplicated otitis media. However, as the dose increases, the gastrointestinal tolerability of the antibiotic decreases, with vomiting and diarrhea occurring in about 10% of children receiving 30 mg/kg as a single dose.[76] Although clinical data on single-dose treatment courses for otitis media are available, randomized, comparative prospective data exist only for treatment courses of 3 and 5 days for sinusitis, and for 5 days for treatment of community-acquired pneumonia and streptococcal pharyngitis. The dosage for treatment of streptococcal pharyngitis is 12 mg/kg per day once daily for 5 days, which is larger than that for otitis media and provides a total dosage of 60 mg/kg.

Azithromycin has the widest use in children for the treatment of upper and lower respiratory tract infections. However, other uses have been documented in clinical trials, although FDA approval for many of these infections has not been sought. Treatment of pertussis has been shown to be effective in small trials.[77] Azithromycin is the recommended macrolide for prophylaxis or treatment of infants younger than 1 month and is considered equal to erythromycin and clarithromycin in older individuals.[71] Azithromycin in neonates is associated with an increased risk for pyloric stenosis, which is lower than for erythromycin. Benefits for prophylaxis or treatment of pertussis outweigh this risk.[78]

Azithromycin also is used in the treatment of sexually transmitted infections, including *C. trachomatis*–caused infections (urethritis, cervicitis, and lymphogranuloma venereum), chancroid, granuloma inguinale, and gonorrhea.[79]

Similar to clarithromycin, azithromycin has been shown to play a role in the prophylaxis and therapy of MAC infections in HIV-infected children.[80] Azithromycin also may have a role in therapy of cutaneous and lymph node infection caused by these pathogens in healthy children.

Azithromycin has enhanced activity compared with the other macrolides against many gastrointestinal pathogens, including *E. coli, Salmonella, Shigella,* and *Campylobacter*.[81] In vitro activity demonstrated against *Salmonella* is particularly advantageous given the intracellular location of this pathogen.[82] With widespread resistance among gastrointestinal pathogens to β-lactam antibiotics, fluoroquinolones, and trimethoprim-sulfamethoxazole in certain parts of the world, the utility of empiric azithromycin therapy for traveler's diarrhea has increased.[83]

Azithromycin is the only antibiotic that has been prospectively evaluated for the treatment of cat-scratch lymphadenitis.[84] However, the clinical response to treatment of lymph node disease is not dramatic, and azithromycin has not been evaluated prospectively for the treatment in other tissue sites of infection, such as liver, bone, or CNS.

Tetracyclines

The tetracyclines were derived as natural products from *Streptomyces* spp., with discovery in the 1940s and subsequent availability of two agents by 1948, chlortetracycline and oxytetracycline.[85] Tetracyclines bind reversibly to the ribosome at the aminoacyl acceptor site (A site) where the amino acid–charged tRNA binds to the ribosome immediately adjacent to the site on the ribosome holding the mRNA strand.

The aminoacyl tRNA binds to the A site together with an elongation factor (EF-Tu) and guanosine triphosphate (GTP), which supply the energy required to drive protein synthesis. The protein synthesis step includes the chemical reaction to attach the amino acid to the growing peptide chain, together with changes in the conformation of the ribosome that are associated with movement of the protein chain and the mRNA through the ribosome, followed by the subsequent release of the “empty” tRNA.[86] It appears that the flat, four-ring structure characteristic of the tetracyclines binds to at least two locations within the ribosome. Binding at the classically recognized A site appears to prevent movement of the tRNA/mRNA/EF-Tu complex into the “P site” (peptidyl site) by steric hindrance, which prevents elongation of the growing peptide. Binding to a second site in the 30S ribosome may stabilize the ribosome in an inappropriate conformation at the crucial site of recognition of the aminoacyl tRNA anticodon with the corresponding codon within the mRNA, thereby preventing placement of the correct amino acid in the elongating chain.[87] Inhibition of peptide formation by tetracyclines occurs after the binding of the tRNA to the complex and after expenditure of GTP-mediated energy, presenting the bacteria with an energy cost in addition to blocking the synthesis of a new protein.

The tetracyclines are effective against many gram-positive and gram-negative bacteria as well as against cell wall–deficient pathogens (*Mycoplasma, Rickettsia*) and certain single-cell parasites (see Table 292.2). Eukaryotic cells have elongation factors different from bacteria and are therefore not susceptible to the protein synthesis inhibition activity of this class of antibiotics. The tetracyclines enter the gram-negative cell wall through outer membrane porin proteins and are sufficiently lipophilic to allow passage through the cytoplasmic membrane of both gram-negative and gram-positive bacteria. The tetracyclines are, in general, bacteriostatic.

Resistance to tetracyclines occurred quickly following their availability for clinical use, primarily based on efflux pumps and, to a lesser extent, on the presence of ribosomal protection proteins and tetracycline-inactivating enzymes. The number of resistance genes and of bacterial species that contain them continues to increase.[85,88] These resistance mechanisms are present on plasmids, conjugative transposons, and integrons, allowing free exchange of resistance determinants between a wide range of bacteria. More than 200 different efflux pumps have been characterized, most of which are active against tetracycline, some of which also are active against minocycline, and fewer of which also are active against the most recently available tetracycline, tigecycline. The ribosomal protection proteins have sequence homologies with bacterial elongation factors present in the tRNA/mRNA/EF-Tu complex. It is believed that, as these protection proteins themselves bind to the ribosome, changes in the conformation at the tetracycline-binding site occur, preventing the binding of tetracycline but not interfering with protein synthesis. Resistance at the second 30S ribosomal binding site also has been described and is due to base substitutions in the rRNA of the 30S unit.

Advances in the design of the structure of the early tetracyclines led to doxycycline (in 1967) and minocycline (in 1972), both of which provide a greater spectrum of activity and improved solubility, creating improvements in both oral and parenteral preparations (see Table 292.2). Doxycycline and minocycline can be taken with food (with the exceptions noted later). In most cases, doxycycline and minocycline demonstrate increased activity against gram-positive organisms, and decreased activity against gram-negative organisms compared with tetracycline. Activity against *Enterococcus faecium,* but not *E. faecalis,* is achieved with newer agents. Minocycline, however, demonstrates improved activity against gram-negative organisms, including *H. influenzae, M. catarrhalis, E. coli,* and *Klebsiella* spp., compared with tetracycline, but only fair activity against *Salmonella* and *Shigella* spp. and *P. aeruginosa.* Tigecycline, a derivative of minocycline, increases the spectrum of activity against many enteric gram-negative bacilli and anaerobes, including *B. fragilis,* but still lacks a high degree of activity against *P. aeruginosa* (see Table 292.2). Historically, clinical use in pediatrics has been limited by the binding of tetracyclines to teeth and bones in growing children, leading to permanent staining of the teeth and enamel hypoplasia (and reversible long-bone growth rates in juvenile animals), the degree which is directly proportional to the number of tetracycline courses prescribed.[89,90] Doxycycline binds to calcium less readily than does tetracycline, and there has been no report of dental staining related to doxycycline use in young children. In a case-control study 58 children who had an average of 1.8 courses of doxycycline before 8 years of age were shown to have identical tooth color and enamel of deciduous teeth as did 213 unexposed controls.[91] In addition, the tetracyclines cross the placenta to expose the fetus; skeletal embryopathy in experimental animals has been noted. The oral tetracyclines cannot be taken with dairy products owing to the insoluble chelation complexes that form with calcium; similar complexes form with magnesium and iron ions. When ingested with foods containing these ions, absorption from the gastrointestinal tract is blocked.

In adults and older children, the tetracyclines have been used for the treatment of mild to moderate respiratory tract infections, skin and skin structure infections (most commonly acne), and sexually transmitted infections. Some agents in this class demonstrate activity against strains of CA-MRSA,[92] penicillin-resistant pneumococci, and VRE, and have been used in the treatment of these infections. However, few prospective, comparative data are available to assess the efficacy of tetracyclines against these pathogens, with the exception of recent studies on tigecycline (see later).

Tetracyclines are first-line therapy for infections caused by *Rickettsia* (most notably Rocky Mountain spotted fever) in infants and children of all ages,[91,93] *Ehrlichia,* and *Anaplasma* spp., tularemia (oral therapy for less severe infections), brucellosis (with rifampin), cholera, *Chlamydia* genital infections, and Lyme disease (*Borrelia burgdorferi*) in older children.

Tigecycline

Tigecycline is a chemically modified minocycline, with the addition of a *t*-butylglycylamido side chain to the C9 carbon of the "D" tetracycline ring.[94] Tigecycline is not affected by the majority of efflux pumps and ribosomal protection proteins that decrease the activity of other tetracyclines. Tigecycline has a higher binding affinity to the ribosomal binding site than the previous tetracyclines[85] and has a broader spectrum of activity than any other tetracycline agent (see Table 292.2). In rat models, bone discoloration was documented, suggesting that tigecycline forms calcium complexes in bone similar to other tetracyclines.

In adults, tigecycline is approved for treatment of complicated skin and skin structure infections and complicated intra-abdominal infections given its activity against enteric gram-negative bacilli and anaerobes, including *B. fragilis.* Tigecycline retains activity against the agents of atypical pneumonia that is equivalent to, or better than, earlier tetracyclines.

The ultimate clinical role of tigecycline has yet to be defined in the treatment of nosocomial infections caused by MDR gram-negative and gram-positive organisms that remain susceptible to tigecycline. For children, the risks for bone toxicity and tooth staining need to be balanced with the benefits of therapy, particularly for drug-resistant pathogens. For situations in which no alternatives exist, the tetracyclines represent effective therapy.

Lincosamides

The lincosamides are naturally occurring compounds derived from *Streptomyces* spp. Clindamycin, approved in 1966, is the only lincosamide available in the US and is a semisynthetic derivative of lincomycin. The lincosamide antibiotics bind to the 50S subunit at a site that overlaps both the A and P sites on the ribosome, preventing the docking of charged tRNAs and their movement through the peptidyl transferase center, thus inhibiting the formation of protein. The P-site attachment of clindamycin occurs at the same ribosomal-RNA structural bases as the macrolide binding sites (A2058, A2059), explaining the competitive inhibition between binding of the two classes of antibiotics for the ribosome, as well the resistance that occurs to both antibiotics by altering a single base.[95] The lincosamides generally are considered bacteriostatic, although bactericidal activity can be demonstrated against certain organisms at antibiotic concentrations 2 to 4 times the minimum inhibitory concentration (MIC).[96]

Resistance to the lincosamides occurs primarily in bacteria that constitutively produce the methyltransferase that monomethylates or dimethylates the A2058 adenine present at the outlet of the ribosomal peptidyl transferase center. Enzyme can be induced, most often in the presence of the appropriate substrate, usually a macrolide. In contrast, the lincosamides appear to be poor inducers of the methylase enzyme. Therefore organisms that have inducible resistance may remain susceptible to clindamycin, even after exposure to the antibiotic. However, genetically altered strains that have lost gene regulation and constitutively produce methylase occur at a rate of approximately 1 in 10^7 *S. aureus;* selection of constitutive mutants can occur during therapy, with subsequent treatment failure.[67,97] This situation is most likely to occur in serious, deep, high-density bacterial infections, but not with mild to moderate skin infections or cutaneous and soft tissue abscesses that can be incised and drained. The commonly encountered efflux pumps that are active against the macrolides are not active against clindamycin.

High intracellular concentrations of clindamycin in phagocytic cells are believed to be beneficial in certain clinical infections.[98] However, no prospectively collected data have confirmed the benefit in clinical or microbiologic cure of infection as a result of either improved intracellular killing of organisms such as staphylococci or improved delivery of clindamycin to the site of infection through phagocytic cell migration.

Clinical use of clindamycin has changed substantially over the past decade. Commonly used for its activity against anaerobes in the treatment of intra-abdominal infections such as appendicitis, clindamycin resistance of *B. fragilis* has increased, and clindamycin no longer is recommended as the anaerobic agent of choice.[99,100] Clindamycin continues to have a good spectrum of activity for use in deep head and neck space infections, dental abscesses, and aspiration pneumonia (with or without empyema). Less common uses continue for treatment of gram-positive cocci, such as failures of penicillin in group A *Streptococcus* pharyngitis, and for treatment of *S. aureus* infections due to susceptible organisms.

In the early 1990s, the emergence of penicillin- and macrolide-resistant *S. pneumoniae* causing upper and lower respiratory tract infections promoted the use of clindamycin in the treatment of mild to moderate respiratory tract infections in children. Low levels of clindamycin resistance have been reported. Although no formal, randomized prospective comparative studies were performed in acute otitis media, sinusitis, and pneumonia, clindamycin has been recommended for treatment of infection due to penicillin-resistant pneumococci.[101]

The emergence of CA-MRSA in the mid-1990s dramatically increased the use of clindamycin for skin and skin structure infections and bone and joint infections. Although most published data on the efficacy of clindamycin in the treatment of MRSA are retrospective, clindamycin appears to be effective for these pathogens.[102,103] Some regions of the US in which MRSA is prevalent have documented decreasing resistance to clindamycin due to spread in the community of certain clindamycin-susceptible clones,[83] but other areas can experience increasing clindamycin resistance, particularly with methylase-harboring organisms that confer resistance to both clindamycin and macrolides. Many hospital laboratories now report strains that test susceptible in vitro, but carry the methylase gene as "resistant," leading to an "increase" in resistance based on changes in how resistance is reported. Susceptibility of MRSA and MSSA should be assessed locally to guide empiric therapy for serious infections.[104,105]

The ability of clindamycin to target ribosomal protein production has led to use in the treatment of toxin-mediated infections caused by *S. aureus* (toxic shock syndrome) and *S. pyogenes* (toxic shock −like illness), either alone or in combination with a cell wall−active antibiotic agent. In vitro data and retrospectively analyzed human data suggest some benefit of combined therapy.[106]

The principal adverse event associated with clindamycin is a direct function of its activity against normal anaerobic gastrointestinal flora—diarrhea.[85] *C. difficile*−mediated pseudomembranous colitis is a potential complication of virtually any broad-spectrum antibiotic, including clindamycin.[107] Accurate, prospectively collected data on the incidence of *C. difficile* enterocolitis are not available for clindamycin-treated children, but there are not increasing reports of enterocolitis associated with the broad use of clindamycin for pneumococcal and staphylococcal infections.

Aminoglycosides

The aminoglycoside/aminocyclitol class of antibiotics is derived from *Streptomyces* spp. and *Micromonospora* spp. In general, these antibiotics contain a 2-deoxystreptamine ring attached to two or three additional moieties, most often amino sugars, all connected together by glycosidic linkages. Medicinal chemists have created substitutions at up to 10 different positions on the three rings or associated amino groups that have led to the creation of several semisynthetic aminoglycoside antibiotics. However, given the nephrotoxicity and ototoxicity inherent to aminoglycosides, little activity has occurred in the development of newer agents for community infections, although broader spectrum agents have been recently developed for MDR gram-negative pathogens. All aminoglycosides currently available in the US are generic formulations, with gentamicin, tobramycin, and amikacin representing those most often used in children.

All of the aminoglycoside antibiotics share a common binding region within the 30S ribosome, which is located at the peptidyl transferase center where charged tRNAs are first recognized and attach to the A site. With aminoglycoside binding close to the A site, conformational changes occur at the ribosomal tRNA docking site that create enhanced affinity for tRNA binding, facilitating incorrect binding of noncognate tRNAs that do not match the corresponding codon on the mRNA. With attachment of incorrect tRNAs, misreading occurs and amino acid sequences in the resulting peptide are incorrect, leading to the creation of nonfunctional proteins. With binding of the aminoglycoside, proofreading for the accuracy of the attached tRNA also is compromised because subsequent conformational changes that should occur in the 30S unit to allow for exact recognition of the attached tRNA cannot take place.[86,108–110] The structures of two of the larger aminoglycosides, streptomycin and spectinomycin, allow for additional binding sites within the 30S ribosome. Streptomycin attaches at four different domains within the 30S rRNA, as well as having a unique attachment to one of the ribosomal proteins. Spectinomycin, a larger structure with fused rings, appears to bind at the A site in a unique manner that also blocks the movement of the aminoacyl tRNA/peptidyl tRNA/EF-Tu complex from the A site to the P site during the peptidyl transferase reaction. With the production of abnormal proteins that may be incorporated into cellular structures such as the cell membrane, increased permeability of the membrane occurs. With increased permeability, the aminoglycosides demonstrate enhanced entry into the cells, allowing further saturation of aminoglycoside binding sites on the ribosome, thus preventing the formation of new, functional ribosomes, which ultimately results in cell death. The aminoglycosides are bactericidal and show concentration-dependent killing of bacteria (see Chapter 291).

Resistance to aminoglycosides occurs primarily with the acquisition of a variety of aminoglycoside-modifying enzymes, many of which are carried on plasmids and transposons for efficient spread between bacteria. The most common are acetyltransferases, adenyltransferases, and phosphotransferases.[109] Many different efflux pump systems also play a major role in aminoglycoside resistance, particularly in gram-negative bacilli.[109] Ribosomal RNA methylase genes from *Actinomyces* that confer resistance to aminoglycosides recently have been identified in clinical isolates of enteric gram-negative bacilli and *P. aeruginosa*.[111] Although this mechanism of resistance currently is uncommon, these genes now have the potential to spread quickly within clinical settings.

The clinical use of aminoglycosides is primarily for the treatment of aerobic gram-negative bacillary infections—from the premature neonate through the adolescent.[112–114] Aminoglycosides are strongly polar, with high solubility in water but poor solubility in lipids, resulting in poor penetration into the CNS, vitreous, bronchial secretions, and saliva. Aminoglycosides are concentrated in the proximal renal tubules and excreted in urine and achieve urinary tract concentrations up to 100 times the serum concentration. Because of the toxicity of the aminoglycosides at serum concentrations that are only 5- to 10-fold above the bacterial MICs, they are not usually used as the sole agents for treatment of serious infections. The aminoglycosides frequently are paired with a β-lactam antibiotic to create synergistic antibacterial activity and potentially to retard the emergence of antibiotic resistance, although the clinical effect of combination therapy has not been well demonstrated beyond the immunocompromised host.[115] Empiric and definitive therapy of early- and late-onset neonatal septicemia with gentamicin-containing combinations for enteric gram-negative infections is still appropriate three decades after the first recommendations in this age group, although well-controlled, prospective, comparative studies generally have not been performed.[112,113,116] Therapy of nosocomial infections with aminoglycoside-containing regimens is appropriate in institutions in which nosocomial gram-negative pathogens remain susceptible.[117]

For gram-positive infections, the aminoglycosides add enhanced bacterial killing to cell wall–active agents, particularly in the treatment of serious infections.[118] Enterococcal infections are treated with ampicillin or vancomycin in combination with gentamicin to achieve bactericidal activity. The combination of penicillin plus gentamicin, or nafcillin plus gentamicin, is considered by some experts to be the most effective therapy for infective endocarditis caused by susceptible strains of viridans streptococci and *S. aureus*, respectively, especially for initial therapy.[119] However, controversy exists over the role of aminoglycosides in combination therapy because clinical benefits have not been documented to be substantial, whereas renal toxicity is not uncommon.[120]

Empiric therapy of nosocomial infections and infections in immunocompromised hosts has included combination regimens containing aminoglycosides to enhance the spectrum of β-lactam agents, to provide potential synergy, and to minimize the emergence of resistant pathogens.[21] Aminoglycosides also are used in combination with other agents in the treatment of intra-abdominal infections. However, the charges on the aminoglycoside molecule change as the pH changes in infected tissues, with the acidic environment of an abscess increasing protonation and decreasing the ability of these antibiotics to enter bacterial cells (as documented by MICs at low pH that can be higher than those safely achievable in serum).[121] In addition, the active transport of aminoglycosides through the inner cell membrane into the cytoplasm of the bacteria requires an oxygen-dependent transport system not present in anaerobes, explaining the lack of activity of this class of agent in the treatment of anaerobic infections.

Given the high level of activity against certain gram-negative pathogens and lack of current prospective treatment trials using newer agents, the aminoglycosides still represent preferred therapy for tularemia and plague.

Streptomycin remains highly active against most strains of *M. tuberculosis* requiring parenteral therapy, which leads to use in treatment of MDR tuberculosis. Streptomycin may be particularly useful in the treatment of serious, life-threatening tuberculosis, including tuberculous meningitis. Although originally approved for use in 1952 and previously important for the treatment of infections caused by *Brucella* and *Francisella* spp., streptomycin has been replaced by gentamicin because of concerns for streptomycin-induced vestibular, auditory, and renal toxicity.

Paromomycin is an oral, nonabsorbable aminoglycoside. This agent is effective in the treatment of intestinal protozoal infections, including amebiasis and cryptosporidiosis.

Inhaled aminoglycosides, most commonly tobramycin, are used clinically to treat cystic fibrosis. Achieving high enough antibiotic concentrations in respiratory tract secretions and at the bronchial mucosa to be effective against *P. aeruginosa* is not usually possible with parenterally administered aminoglycosides, but high concentrations can be achieved with inhaled tobramycin, without concern for nephrotoxicity or ototoxicity.[122] The use of aerosolized aminoglycosides in patients with pneumonia caused by other MDR gram-negative pathogens has not been prospectively investigated in controlled studies, but case series in adults suggest their potential role.[123]

Nephrotoxicity of aminoglycosides is dose dependent and primarily is tubular. Monitoring renal function or aminoglycoside serum concentrations during therapy permits early detection of decreased renal function attributable to the aminoglycoside. Aminoglycoside ototoxicity can be either cochlear (with hearing loss) or vestibular (with vertigo) and correlates with increasing serum trough concentration as a function of overall drug exposure, rather than the peak serum concentration.[124]

Providing children with a single daily dose of aminoglycosides to decrease nephrotoxicity while maintaining or increasing efficacy has not been widely accepted because of the lack of well-controlled studies in children. However, limited data that exist in children, taken together with convincing data in adults, suggest that once-daily dosing could become routine for children, except possibly for certain severe infections, such as meningitis or persistent BSI.[125,126]

Although streptomycin was the first aminoglycoside available for use, the toxicity and rapid development of resistance in bacteria limited its longterm viability. Kanamycin was approved for use in 1957 but was replaced by the less nephrotoxic gentamicin in 1963 as a more broadly active antibiotic against resistant gram-negative pathogens. Tobramycin was approved in 1968 and provided a small but predictable increase in in vitro activity against *P. aeruginosa,* with a concomitant small but clinically insignificant decrease in activity against enteric gram-negative bacilli, allowing its use as the anti-pseudomonal aminoglycoside of choice. Amikacin, a semisynthetic derivative of kanamycin, was approved in 1972 and offered enhanced activity against many gentamicin- and tobramycin-resistant pathogens, in addition to providing serum antibiotic concentrations approximately 3- to 4-fold greater than those achievable with gentamicin or tobramycin. Amikacin also is useful in the treatment of infections caused by some strains of nontuberculous mycobacteria.

Streptogramins A and B

The streptogramins are two of a series of naturally occurring antibiotics isolated from *Streptomyces pristinaespiralis.* Two antibiotics have been modified from the naturally occurring pristinomycins I and IIA to create the semisynthetic antibiotics quinupristin (streptogramin B) and dalfopristin (streptogramin A), respectively. These two antibiotics are present in the FDA-approved combination Synercid in a 70 : 30 ratio.[127] Quinupristin and dalfopristin have completely different chemical structures, each with a distinct but overlapping binding region within the P site of the peptidyl transferase center in the ribosome. Binding of dalfopristin to this region produces a conformational change that significantly increases the affinity of binding of quinupristin, in part explaining the synergy observed when the combination is used. Dalfopristin inhibits protein synthesis by interfering with substrate attachment to both A and P sites of the 50S subunit, whereas quinupristin blocks peptide bond synthesis during elongation by causing incorrect positioning of the peptidyl tRNA at the P site.[128] When elongation has been initiated, quinupristin triggers the premature release of the elongating peptide chain. Quinupristin binds to the peptidyl transferase site at a similar location as the macrolides and lincosamides; methylation of the A2058 adenine at this important binding site prevents binding of quinupristin as well as the macrolides and clindamycin, and creates the macrolide-lincosamide-streptogramin (MLS) resistance phenotype.

Unfortunately, many mechanisms of bacterial resistance limit the clinical utility of quinupristin-dalfopristin, with resistance developing in some patients soon after starting therapy. Alterations of target binding sites, efflux removal of antibiotics from cytoplasm, and enzymatic alteration of the antibiotic structure all have been reported.[65,129] Although each of the streptogramins independently produces inhibitory effects on protein synthesis, the combination is bactericidal for a number of gram-positive pathogens, including *S. aureus.*

The agents have been available in Europe for several years as topical therapy, but with the development and spread of enterococci that are resistant to vancomycin, β-lactams, and aminoglycosides, an urgent need for quinupristin-dalfopristin was well documented. Clinical use is largely limited to serious infections caused by vancomycin-resistant strains of *E. faecium* (VRE). The combination is not active against the more common enterococcal pathogen, *E. faecalis.*

Quinupristin-dalfopristin significantly inhibits cytochrome P450 CYP3A function and can affect serum concentrations of concomitant drugs that are eliminated by this pathway. Phlebitis was a major side effect in quinupristin-dalfopristin–treated patients, occurring in almost half of adults receiving therapy. This combination agent has not been studied systematically in children younger than 16 years.

Oxazolidinones

Linezolid is the first antibiotic in the oxazolidinone class to be approved and used in children. This class of antibiotics is unique in that members are not natural products, but were discovered as one of a number of compounds created as potential monoamine oxidase (MAO)-inhibiting agents.[130] However, some of these compounds also demonstrated antibacterial activity, although initially, many were associated with significant toxicity. Subsequent chemical modifications led to the development of linezolid, which demonstrated a reasonable balance between antimicrobial activity, clinical efficacy, and acceptable clinical toxicity. The oxazolidinones have a unique mechanism of action on the ribosome, distinct from all other classes of antimicrobial agents. The antibiotic binds to an area close to the ribosomal peptidyl transferase center and inhibits the initiation of protein synthesis by preventing the formation of the initiation complex of fMet-tRNA/elongation factors/mRNA/GTP. The movement of the complex from the ribosome's “A site” of tRNA attachment to the peptidyl “P site” is blocked, and coupling of amino acids and lengthening of the peptide chain cannot occur.[131]

Linezolid demonstrates bactericidal activity against *S. pneumoniae,* but bacteriostatic activity against *S. aureus* and *Enterococcus* spp. However, limited studies comparing vancomycin, a bactericidal agent (with limitations in activity in infected lung) with linezolid in the treatment of nosocomial pneumonia caused by MRSA documented superiority in clinical outcomes with linezolid.[132,133] Activity of linezolid is primarily limited to gram-positive bacteria, owing to the presence of an efflux pump (AcrAB) present in many gram-negative organisms. Linezolid is not active against *Mycoplasma* or *Ureaplasma*.[134]

Resistance to linezolid has been described and consists of structural changes at the linezolid binding site that prevent attachment.[65,135] These relatively infrequent changes, which tend to occur more often with more prolonged therapy, are primarily single-base changes in the rRNA occurring around the peptidyl transferase site. Transferable resistance to the oxazolidinones through conjugative transposons has been documented.[65]

Linezolid has been studied clinically for nosocomial and community-acquired pneumonia and for complicated and uncomplicated skin and skin structure infections.[136,137] The clinical and microbiologic response rates for each of these tissue-specific infections in children were equivalent to comparator agents, usually vancomycin. The in vitro activity and clinical efficacy of linezolid in the treatment of infections caused by penicillin- and macrolide-resistant pneumococci, VRE, MRSA, and VRSA support a role for linezolid when other, better-studied agents are not available or are not tolerated. The most common current clinical use of linezolid in children is for the treatment of MRSA-associated skin or respiratory tract infections.[138] Few data other than case reports are available for the use of linezolid in treatment of bone and joint infections[139] and CNS infections.[140]

Data on pharmacokinetics for both parenterally and orally administered linezolid are available in children, including premature neonates.[141] Linezolid is virtually 100% absorbed by the oral route, allowing equivalent mg/kg dosing for both intravenous and oral formulations. Linezolid is not metabolized by the cytochrome P450 system and does not induce this enzyme or compete with other drugs in P450-mediated metabolism. Some concerns have been raised regarding hematologic toxicity, including neutropenia and thrombocytopenia, which was found to be dependent on dose and duration of therapy.[130] However, prospective, comparative data in the pediatric FDA registration studies failed to demonstrate a significant difference in toxicity compared with other agents. Optic and peripheral neuropathy has been reported with longterm use in children.[142] The possibility of hypertension due to effects of the antibiotic's mild MAO inhibitor activity were monitored carefully in early pediatric clinical trials. No MAO inhibitor side effects were noted in any phase 1 to 3 pediatric trial, permitting children to remain on usual diets while receiving treatment.

Nucleic Acid–Active Antibiotics

RNA Polymerase

Rifamycins

The rifamycins, rifampin (also called rifampicin), rifabutin, rifapentine, and the oral nonabsorbed rifaximin, are all semisynthetic derivatives of natural products of *Streptomyces* spp. The intracellular target for the rifamycins is DNA-dependent RNA polymerase and has been well defined on a molecular level.[143] During the creation of an RNA strand from the bacterial DNA strand, the polymerase requires functional channels within the enzyme for both the DNA template strand and complementary strand, as well as for the elongating RNA strand. As the RNA bases dock sequentially at the active site within the polymerase, the newly created RNA strand moves forward, one base at a time. The rifamycins bind in the channel occupied by the newly created RNA strand, approximately 2 to 3 bases downstream from the active site, blocking the RNA strand from moving out of the polymerase and terminating the further elongation of that RNA segment as it also uncouples the RNA strand from the active site.[143,144] Although the actual active site of the polymerase is highly conserved between bacterial species, there is some diversity between bacteria around the active site with respect to the RNA polymerase structure. This diversity alters the binding affinity for rifampin across bacterial and mycobacterial species and provides one basis for the variable susceptibility. Rifampin demonstrates bactericidal activity against susceptible organisms.

Given the large size of the rifamycin molecule, multiple binding sites within the polymerase, and the restricted target binding pocket in the polymerase, it is not surprising that many different single amino acid substitutions from mutational events within the polymerase lead to decreased rifamycin binding and stable resistance with little effect on the viability of the organism. In *S. aureus,* at least 18 genotypes resistant to rifampin have been characterized, some of which contain multiple base substitutions.[145] Each of these mutations is likely to affect either the binding affinity or the access of rifampin to the binding pocket to a different degree. Most mutations causing rifampin resistance also produce resistance to rifabutin and rifapentine.[146]

The rifamycins have a remarkably broad spectrum of activity that includes *Staphylococcus* spp., *S. pyogenes, Neisseria* spp., *H. influenzae, Campylobacter jejuni, H. pylori, C. trachomatis,* both tuberculous and nontuberculous *Mycobacterium* spp., *Aspergillus* spp., *Naegleria fowleri,* and *Toxoplasma gondii* (see Table 292.2). Rifabutin has increased in vitro activity against *M. tuberculosis* compared with rifampin, but has not been documented to result in improved microbiologic outcomes in treated patients.[147] Rifabutin also has increased activity against MAC compared with rifampin, most likely because of binding to additional sites within the polymerase.[143,148] Rifapentine has both increased in vitro activity against *M. tuberculosis* in addition to an extended serum elimination half-life (16 hours) compared with rifampin (2 to 3 hours). Once-weekly rifapentine for 12 weeks is as effective as 9 months of daily isoniazid in the treatment of latent tuberculosis.[149]

Rifamycins achieve high intracellular concentrations, between 5- and 20-fold greater than extracellular concentrations.[148] This likely explains the effectiveness of this class in the therapy for mycobacterial infections, in which pathogens are sequestered intracellularly.

Of the rifamycins, rifampin is the agent most commonly used in pediatrics, usually as part of combination therapy for active tuberculosis. Rifampin also can be used in combination therapy for treatment of nontuberculous mycobacterial infections such as lymphadenitis, cellulitis, or pneumonia. For treatment of bacterial infections, rapid emergence of resistance in virtually every pathogen dictates a need for combination antibiotic therapy. Combination therapy may allow for eradication of rifampin-resistant strains before they become clinically important. Rifampin has been used in combination therapy for *Bartonella henselae* infections (cat-scratch disease), *S. aureus* infections (particularly MRSA), and MDR pneumococcal infections, including meningitis.[150] Although not well studied in prospective comparative clinical trials, the excellent tissue penetration of rifampin may provide improved clinical outcomes compared with β-lactam antibiotic therapy alone in deep bone and joint infections and in foreign-body or biofilm-associated infections, such as on intravascular catheters or implanted devices. As single-drug therapy, rifampin is only used when prophylaxis for *N. meningitidis* and *H. influenzae* type b infections is indicated.

Rifabutin has documented efficacy in both prophylaxis and therapy of MAC (in combination with other agents) in HIV-infected adults, but clarithromycin and azithromycin are recommended as preferred therapy for HIV-infected children.[80] Only limited data are available in children with MAC infections.[73,151,152] The extended half-life of rifapentine provides a rationale for once-weekly therapy, although the failure rate in those with more serious active tuberculosis and the bacteriologic relapse rate were slightly higher in those treated with rifapentine compared with rifampin.[147,153]

Rifaximin is an oral agent that is not absorbed from the gastrointestinal tract and produces high intraluminal antibiotic concentrations with little systemic toxicity. Microbiologic activity has been demonstrated in vitro at achievable intraluminal antibiotic concentrations against *E. coli, Salmonella, Shigella, Vibrio, Yersinia,* and *Campylobacter* spp. Although the MICs for these enteric pathogens is about 32 to 64 μg/mL, a concentration not achievable in tissues, the concentrations achieved in the gastrointestinal tract are as high as 8000 μg/mL, well above that required for antibacterial effect.[154] Although rifaximin antibiotic is currently only approved for traveler's diarrhea in adults,[155] an oral nonabsorbable, broad-spectrum agent for other gastrointestinal pathogens could have considerable value for children.

The most common clinical side effect of treatment with rifampin is nausea, which appears to decrease as the treatment course progresses. The most common adverse effect of treatment is hepatotoxicity, as assessed by elevation of hepatic transaminase levels; however, most children receiving rifampin for tuberculosis therapy also receive other hepatotoxic agents, preventing accurate assessment of a singular role of rifampin in liver injury.[156] Children receiving multiple hepatotoxic agents should be assessed at regular intervals for evidence of hepatic injury.

The drug-drug interaction profile of the rifamycins frequently complicates clinical management. The P450 CYP3A system is activated by the rifamycins. If the child is receiving another drug metabolized by this system, decreased, potentially ineffective serum concentrations of that drug may be present. In addition, if the concurrent drug represents a competitive substrate for P450 metabolism, increased and potentially toxic serum concentrations of that drug can result from decreased metabolism.[148] The potency of CYP3A induction is greatest with rifampin and least with rifabutin. Rifabutin is also a CYP3A substrate itself, resulting in higher rifabutin serum concentrations when given concomitantly with CYP3A inhibitors.

DNA-Dependent DNA Polymerase

Quinolones and Fluoroquinolones

The quinolones are a diverse group of antibiotics that target DNA synthesis and are active against a wide range of bacteria, *Mycoplasma, Chlamydia,* and *Chlamydophila* spp., and, for certain agents, mycobacteria.[157,158] The first of the quinolone antibiotics was discovered during the commercial preparation of the antimalarial agent chloroquine, and was modified subsequently for antibacterial use in humans.[157] The first approved quinolone agent, nalidixic acid, has a limited gram-negative spectrum of activity and a poor pharmacokinetic profile for treatment of tissue invasive infections. With chemical modifications to the basic quinolone (and the closely related naphthyridone) ring structure, the spectrum of activity and pharmacokinetics have been enhanced greatly, allowing for once-daily dosing for infections in many different tissue sites. The 6-fluoroquinolones (beginning with norfloxacin and ciprofloxacin) demonstrated a significant improvement in antibacterial activity, and virtually all subsequently approved compounds are fluoroquinolones.

The quinolones all interfere with DNA synthesis by interfering with two closely related type II topoisomerase enzymes involved in DNA synthesis: DNA gyrase and topoisomerase IV.[158,159] Each of these enzymes comprises 4 subunits: DNA gyrase contains 2 subunits of GyrA and 2 of GyrB, whereas topoisomerase IV consists of 2 subunits of ParC and 2 of ParE (in *S. aureus,* these topoisomerase IV subunits are termed GrlA and GrlB). The DNA gyrase is responsible for uncoiling DNA ahead of the replication fork to allow for DNA strand replication by DNA polymerase, or for the creation of RNA strands by RNA polymerase. In the process of uncoiling and coiling, strands of DNA are cut and then religated by these enzymes to maintain a stable double-helix structure. The topoisomerase IV appears to be primarily responsible for stabilizing the newly created strands of DNA as they separate from template strands after replication. The quinolones bind to these enzymes at specific nucleic acid strand attachment sites, producing conformational changes in the DNA gyrase/DNA or topoisomerase IV/DNA complexes and stabilizing them, thus “freezing” the complex. This leads to an inability to translocate the entire DNA replication complex along the DNA strand, halting the process of nucleic acid replication. Binding of the fluoroquinolones leads to single- and double-stranded DNA breaks without religation, and the subsequent release of DNA fragments into the cell, which leads to cell death in ways that are not well understood. The DNA gyrase/DNA replication complex may also be involved in altering the formation and stability of DNA loops involved in the transcription process, representing another mechanism by which fluoroquinolones affect cell function.

Although quinolones can bind to some extent to both gyrase and topoisomerase enzymes, structural characteristics of each quinolone create unique binding characteristics to each of these two enzymes for every drug in this class. The differences in binding to DNA gyrase and topoisomerase IV lead to differences in the susceptibility of organisms to the various quinolones as well as differences in the development of resistance. In general, the quinolones preferentially bind to DNA gyrase in gram-negative bacteria and to topoisomerase IV in gram-positive bacteria, although some of the newer quinolones bind to both enzymes equally well. Binding to DNA gyrase, occurring before the replication fork of DNA synthesis, produces a more rapid effect on the formation of DNA, whereas binding to the topoisomerase IV after strand duplication has occurred creates a less immediate effect on cell death. However, because both enzymes function to nick and religate strands of DNA during the coiling/uncoiling process, the quinolone effects after binding to either, or both enzymes, can lead to cell death. These agents display bactericidal activity against bacterial pathogens, with dose-dependent pharmacodynamic activity best described by the ratio of the area under the serum concentration−time curve to the MIC of the antibiotic for that organism (AUC:MIC).[160]

Resistance can develop in many different ways, and resistance from multiple different mechanisms can be additive. Most commonly, resistance occurs from alterations in the amino acids present at certain critical and virtually identical sites on the two enzymes, DNA gyrase, and topoisomerase IV, that prevent avid binding of the quinolone. Single-gene mutations leading to these amino acid changes are found primarily in the quinolone resistance −determining regions of *gyrA* and *parC*.[161] Additional, less common mutations have been detected in *gyrB* and *parE.* For *E. coli,* accumulating additional amino acid changes lead to increasing resistance. The first-step mutation in *E. coli* most often occurs in the *gyrA* subunit of DNA gyrase, leading to a mild to moderate increase in MIC, depending on the quinolone being assessed. A second-step mutation, usually in *parC,* generally leads to resistance that cannot be overcome at achievable tissue concentrations. For *S. pneumoniae* and *S. aureus,* the first-step mutation most often occurs in the *parC* (or *GrlA*) subunit of topoisomerase IV.[161,162] Depending on both drug and bacteria, mutations in one of the subunit sites can lead to substantial increases in resistance for a particular drug, but for drugs that bind to both gyrase and topoisomerase IV sites, a mutation at one site does not effectively raise the MIC to a level that usually leads to treatment failure. When two or more mutations occur that affect binding to both enzymes, clinical failures become more common.

Efflux pumps also are effective mechanisms to prevent quinolone binding intracellularly to the gyrase and topoisomerase targets. Efflux pumps affect intracellular concentrations of different quinolones to differing degrees.[162] In addition, newly described mutations in aminoglycoside acetyltransferases confer the ability to acetylate ciprofloxacin, decreasing its activity against *E. coli* twofold to fourfold, with the modified enzyme still retaining activity against the aminoglycosides. This mechanism of resistance is transferable to other bacteria, in contrast to the *gyrA* or *parC* mutations, which only spread horizontally from patient to patient. It is not known how problematic these strains will become.[163]

Safety issues for children have been a concern for this entire class of agents. Although nalidixic acid was approved by the FDA for use in children in 1963, more extensive animal toxicology studies were available for the agents that followed. Preclinical juvenile animal toxicity data for ciprofloxacin in the late 1970s documented the potential for damage to joints in young beagle pups. Therefore no routine pediatric drug development was undertaken for ciprofloxacin or any other fluoroquinolone until the need for potential use in children was demonstrated to the FDA in 1997.[164] No quinolone-associated arthropathy has yet been documented clearly in children for agents available in the US, although a suggestion of transient arthralgia exists from an FDA safety database of ciprofloxacin.[165] Longterm 5-year prospective toxicity studies did not document an increased rate of musculoskeletal adverse events above that seen in comparator antibiotics in clinical trials of levofloxacin for respiratory tract infections in children.[166] Although these studies were not scaled to detect or define rates of rare adverse effects on joints or tendons, lack of reported toxicity from current published data and from data presented to the FDA suggests that joint toxicity is not a common problem in children, if it exists at all.

Nalidixic Acid, Norfloxacin

Nalidixic acid was approved in 1963 for use in children as young as 3 months for the treatment of UTI. Norfloxacin, used for treatment of UTIs in children in other areas of the world, is not approved by the FDA for children in the US.

Ciprofloxacin

Ciprofloxacin was one of the first of the 6-fluoroquinolones to be approved by the FDA for adults, but large clinical trial investigations in children did not begin until the late 1990s, with the exception of studies in children with CF. Ciprofloxacin was studied for complicated UTI and was the first 6-fluoroquinolone to have limited approval by the FDA for use in pediatrics in 2004. Based on the quality of prospectively collected data regarding both safety and efficacy in children, ciprofloxacin is the preferred quinolone agent for UTIs when a fluoroquinolone is needed. Although all of the fluoroquinolones have a bitter taste, a tolerable suspension formulation of ciprofloxacin is available for children. Current use of the fluoroquinolones is limited, based on concerns of cartilage toxicity. Antimicrobial activity of ciprofloxacin (see Table 292.2) includes most of the enteric gram-negative bacilli as well as *P. aeruginosa.* Activity against the gram-positive pathogens and anaerobic pathogens generally is only fair.

Current qualifying clinical use of ciprofloxacin centers on gram-negative infections for which no other oral antibiotic agent is available.[165,167] In this setting, ciprofloxacin and other fluoroquinolones represent effective therapy in which the risk-benefit assessment favors treatment with an oral quinolone agent rather than parenteral therapy with a nonquinolone agent. Qualifying infections could be located at any tissue site except the CNS. Examples of infections, many of which are hospital associated, include complicated UTI, bone or joint infection (including infection caused by *P. aeruginosa*), soft tissue infection, and lower respiratory tract infection. Because qualifying infections are uncommon, no prospective, randomized, controlled clinical trials of use of ciprofloxacin in children are available. Ciprofloxacin is also approved for the treatment of inhalational anthrax in children.

Fluoroquinolones achieve effective concentrations in the gastrointestinal tract and have an advantage over β-lactam antibiotics in that they also achieve high intracellular antibiotic concentrations, particularly effective in the treatment of *Salmonella* infections. Ciprofloxacin has been studied in children for shigellosis and salmonellosis and provides equivalent or superior rates of eradication compared with standard agents.[168,169]

With the high bioavailability of orally administered fluoroquinolones and activity against most gram-negative pathogens for immunocompromised children, selective use of these agents (with or without additional oral therapy for gram-positive pathogens) in low-risk children with fever and neutropenia is a promising area of clinical investigation.[170]

Levofloxacin

Levofloxacin was the first available agent in a series of newer fluoroquinolone agents with enhanced activity against gram-positive pathogens, including *S. pneumoniae* and MSSA. Levofloxacin has been clinically effective in treatment of upper and lower respiratory tract infections in adults,[171] with successfully completed clinical trials in children for acute otitis media and community-acquired pneumonia. No concerning safety issues were raised in adult or pediatric clinical programs. No joint-related toxicity was noted in children, with a sufficiently large number of subjects prospectively studied to detect a 1% adverse event rate. The most acknowledged clinical need for levofloxacin in children is for the treatment of unresponsive or recurrent otitis media due to pneumococci resistant to β-lactam and macrolide agents or treatment of these infections in a child allergic to standard antibiotics.[172] Use for therapy of serious infections is appropriate in situations for which no other class of active parenteral agent exists, or use as oral therapy of infections in situations for which only nonquinolone parenteral therapies exist.[165] Levofloxacin is approved for treatment of inhalational anthrax in children.

Moxifloxacin, Gemifloxacin

New generations of fluoroquinolones demonstrate increased activity against *S. pneumoniae* compared with earlier fluoroquinolones.[173] None have been approved for use in children.

Nitroimidazoles

Metronidazole

Metronidazole is a synthetic nitroimidazole antibiotic with a poorly defined mechanism of action despite decades of extensive use. Originally introduced for the treatment of *Trichomonas* infections (hence the original trade name, Flagyl), use in pediatrics has been most extensive for treatment of anaerobic infections, although metronidazole has never been approved by the FDA for use in children for this indication. Metronidazole is taken into cells by passive diffusion, and the nitro side chain on the imidazole ring is reduced intracellularly by the pyruvate-ferredoxin reductase complex into a toxic nitro radical that reacts with DNA, leading to DNA strand breaks, helix destabilization, and ultimately cell death in both dividing and nondividing cells. Metronidazole demonstrates concentration-dependent bactericidal activity. One of the major metabolites, a hydroxy derivative, retains significant antibiotic activity. Metronidazole is active against anaerobic bacteria and certain protozoa, including *Trichomonas, Entamoeba,* and *Giardia* (see Table 292.2).

In addition to direct bactericidal activity, metronidazole also appears to have direct effects on decreasing neutrophil generation of hydrogen peroxide and hydroxyl radicals, which may lead to decreased inflammation at the site of infection. Metronidazole also may inhibit lymphocyte transformation and granuloma formation. The clinical relevance of these observations is not known.

Although resistance to metronidazole is uncommon, a number of anaerobic bacteria, including some strains of *B. fragilis,* contain *nim* genes that code for an inactivating enzyme that may exist on both plasmids and within chromosomes. This enzyme effectively reduces the nitro group on metronidazole into a stable and inactive amine.[174–176]

Metronidazole is available in intravenous, oral tablet and capsule, and topical formulations. Although metronidazole has a very bitter taste and is not well tolerated when pulverized and placed in suspension, the absorption from the gastrointestinal tract is excellent, with >90% bioavailability. Although rectal administration yields approximately 70% to 80% bioavailability, this route of administration has never gained widespread acceptance for children. Metronidazole provides excellent therapeutic concentrations in a wide range of tissue sites, including CSF, in which concentrations are very close to those achieved in serum.[177–179] Although the serum elimination half-life is approximately 8 hours, early studies performed in adults for FDA approval used 6-hour dosing regimens, which remains the current FDA dosing recommendation on the package label. The observed half-life with oral administration appears to be longer than that found for intravenous administration, for unknown reasons. For most clinical situations, based on the pharmacodynamics of antibiotic exposure, dosing every 8 hours should be adequate. One metabolite of metronidazole displays significant antibacterial activity and has a more extended half-life, averaging 11 to 13 hours, providing another rationale for less frequent dosing.

Clinical use in pediatrics primarily is for the treatment of gram-negative anaerobic infections.[174,180] Given the excellent tissue penetration characteristics of metronidazole, activity against all susceptible anaerobes is achievable in most tissue sites. However, data from randomized, prospective clinical trials are not available for many sites of infection. Because many bowel and deep neck space infections involve gram-positive anaerobes as well as facultative and aerobic organisms, additional antibiotics may be necessary.

Metronidazole is bactericidal for *Bacteroides* spp. and has been used extensively as part of therapy of polymicrobial anaerobic/aerobic intra-abdominal infections, including complicated appendicitis, penetrating injury to the bowel, and colitis.[99] Other mixed infections include deep head and neck space infections (e.g., parapharyngeal abscesses, Ludwig angina) and necrotizing fasciitis or cellulitis (e.g., necrotizing synergistic fasciitis, Fournier gangrene, and omphalitis). *Clostridia* spp. also are susceptible to metronidazole, and deep tissue infections can be effectively treated. Some penicillin-susceptible anaerobic gram-positive cocci, however, are not susceptible to metronidazole.

Metronidazole, in combination with other antibiotics and proton pump inhibitors, is part of a treatment regimen for *H. pylori* –mediated ulcer disease.[181] In addition, there may be some benefit in the treatment of Crohn disease[182]; antibiotic and anti-inflammatory properties of the agent both may play a role.

Given the excellent penetration into CSF and bactericidal capacity, metronidazole is effective treatment for anaerobic organisms causing meningitis, ventriculitis (traumatic, postsurgical, or nosocomial), or brain abscess.[178] Prospective, comparative data to document efficacy for these indications are not available.

Metronidazole also can be used for certain female genital tract infections, including bacterial vaginosis, and as part of antimicrobial therapy of pelvic inflammatory disease.

A common use of metronidazole in children is for the treatment of *C. difficile* enterocolitis.[43] After the documented increases in vancomycin resistance of gastrointestinal tract flora with the use of oral vancomycin in adults for *C. difficile* colitis, metronidazole became the drug of choice in therapy for children as well as adults. Although clinical response rates comparing oral metronidazole therapy with oral vancomycin therapy for *C. difficile* infection have been equivalent in the past, currently there is concern regarding the efficacy of metronidazole in the treatment of *C. difficile* infection.[183]

Entamoeba histolytica trophozoites (but not cysts) are susceptible to metronidazole, allowing therapy for both intestinal and extraintestinal amebiasis, including amebic liver abscess.[184] Metronidazole is one of the drugs of choice for treatment of *Giardia* intestinal infections and is an alternative treatment for *Dientamoeba* infections.[184] Metronidazole remains effective therapy for *Trichomonas* infections for sexually active female and male adolescents.[185]

Sulfonamides (Single Agents or in Combination With Trimethoprim or Pyrimethamine)

Sulfisoxazole, Sulfamethoxazole, Sulfadiazine

The sulfonamide class was one of the first available antibiotics for human use, with striking clinical responses documented in 1937 in the treatment of erysipelas by sulfanilamide and its prodrug.[186,187] Unfortunately, because of widespread resistance in common bacterial pathogens, use of sulfonamides now is focused in a few areas of remaining effectiveness. For pathogens that remain susceptible to sulfonamides, either used alone or since 1968 when used in combination with trimethoprim, these agents have a long history of efficacy with reasonable safety. Sulfonamides now are used almost exclusively in combination with trimethoprim for the treatment or prophylaxis of bacterial infections.[188] Sulfadiazine currently is used in combination with pyrimethamine for the treatment of toxoplasmosis.

The sulfonamides are bacteriostatic by means of competitive inhibition of *para*-aminobenzoic acid, utilized by dihydropteroate synthase in the synthesis of dihydrofolic acid, a precursor of purine bases in the formation of nucleic acid. Bacteria that are required to synthesize folic acid are susceptible to this class of compounds.

Sulfa agents are well absorbed from the gastrointestinal tract and are, in general, metabolized by the liver and excreted by the kidney. Both sulfisoxazole and sulfamethoxazole are highly protein bound (70%–80%). As a result of sulfonamide binding to albumin, bilirubin may be displaced from its albumin-binding site, with subsequent bilirubin access to CNS tissue, causing kernicterus in ill, acidotic neonates with hyperbilirubinemia. No case of kernicterus has been documented in full-term, well-appearing infants. Despite FDA labeling cautions against the use of this class of agents in all infants younger than 2 months, use should be safe in nonacidotic term infants as early as the second week of life when physiologic neonatal jaundice is resolving.

Sulfonamides are responsible for one of the most serious drug-related adverse events: an intense immune-mediated separation of skin at the dermal-epidermal junction, separation of the respiratory and gastrointestinal tract mucosa from supporting connective tissue, or both. Variously called Stevens-Johnson syndrome, toxic epidermal necrolysis, or erythema multiforme major, the spectrum of reactions varies from a cutaneous erythematous, blistering rash to severe, extensive, life-threatening sloughing of skin and mucosa of the respiratory and gastrointestinal tract.[189,190] At the first sign of a skin reaction in a child receiving sulfa therapy, the child should be evaluated, the sulfonamide discontinued, and careful observation begun.

Trimethoprim Plus Sulfamethoxazole

Trimethoprim, available as a single agent but used far more commonly in children in combination with sulfamethoxazole (TMP-SMX), acts at the metabolic step following that inhibited by sulfonamides in the synthesis of purine bases.[188] TMP–SMX prevents the formation of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting dihydrofolate reductase. The TMP-SMX combination blocks two consecutive steps in the synthesis of thymidine, providing both synergistic activity against most pathogens, and decreasing the risk for development of resistance to either the sulfa agent or trimethoprim. Trimethoprim displays bactericidal activity against bacteria, as does the combination.

Current clinical uses of TMP-SMX are limited in the treatment of UTI owing to increasing resistance of *E. coli,* except in regions where susceptibility is preserved. For children with urinary tract anomalies and significant reflux, TMP-SMX prophylaxis has been documented to decrease the number of recurrent UTIs.[191]

The rate of pneumococcal resistance to sulfa in most areas of the US is more than 40%, precluding it as first-line therapy of acute otitis media, sinusitis, or community-acquired pneumonia. Despite in vitro susceptibility of *S. pyogenes,* TMP-SMX is not recommended for treatment of streptococcal pharyngitis because host immune response to streptococci is not prevented reliably (which is required to prevent the development of acute rheumatic fever). However, treatment of skin infections caused by group A *Streptococcus* may still be effective, although current clinical outcome data have not been published recently.

TMP-SMX has been used increasingly for the treatment of CA-MRSA skin and skin structure infections, although prospective, controlled studies were never performed for skin and skin structure infections at the time of original antibiotic approval. New prospective, randomized studies now document the noninferiority of TMP-SMX compared with clindamycin in the treatment of uncomplicated skin and skin structure infections caused by CA-MRSA.[192] In vitro susceptibility of CA-MRSA to TMP-SMX is almost universal; data on comparable efficacy with clindamycin now support use for skin infections, but no data exist on therapy of CA-MRSA bone, joint, or pulmonary infections at this time.[192,193]

TMP-SMX is used for certain hospital-associated infections caused by MDR enteric gram-negative bacilli such as *Enterobacter* and *Klebsiella* spp. and *Stenotrophomonas maltophilia* (which often is susceptible). TMP-SMX generally is bactericidal, although not consistently for high-density inocula of gram-negative bacilli. TMP-SMX is considered safer than most other options (e.g., colistin, fluoroquinolones) in the treatment of MDR gram-negative infections and may provide adequate therapy for infections in most tissue sites, including meningitis, in situations for which no other well-evaluated therapeutic options exist.

Gastrointestinal infections caused by *Salmonella* and *Shigella* spp. and enteropathogenic strains of *E. coli* often were treated successfully with TMP-SMX in the past; however, the value of TMP–SMX has decreased as resistance in these gastrointestinal pathogens has increased.[83,155] The intracellular activity of TMP-SMX has been particularly advantageous in the treatment of susceptible strains of *Salmonella, Yersinia enterocolitica,* and *Vibrio cholera*. Susceptibility of enteric bacterial pathogens should be assessed before TMP-SMX is selected for therapy of serious infections. For parasitic infections of the gastrointestinal tract caused by *Cyclospora* spp. and *Cystoisospora* (formerly *Isospora*), TMP-SMX remains the treatment of choice.[194]

TMP-SMX remains effective therapy for brucellosis, nocardiosis (with exceptions), and some infections caused by the nontuberculous mycobacteria. Prophylaxis and treatment of *Pneumocystis* pneumonia in immunocompromised children remains highly effective.

Sulfadiazine Plus Pyrimethamine

The combination of sulfadiazine and pyrimethamine is active against a number of protozoa, including *Toxoplasma* and *Plasmodium*. Clinical use in children is limited primarily for congenital toxoplasmosis, with treatment starting as soon as physiologic jaundice has resolved, and for older children who have documented toxoplasmosis associated with immune deficiencies (primarily HIV related).

Miscellaneous

Nitrofurantoin

Nitrofurantoin is a unique antibiotic, characterized by a hydantoin ring with a nitro-substituted furanyl side chain that is metabolized within the bacteria to produce reactive compounds that are bactericidal. The mechanism of antibacterial activity is not well understood but presumably occurs by altering ribosomal proteins and other important intracellular structures. Both gram-positive bacteria (including staphylococci and streptococci) and gram-negative bacteria (*E. coli, Klebsiella* spp., and *Citrobacter* spp.) are susceptible. Mechanisms of resistance have not been well defined, but no cross-resistance occurs with other antibiotic classes. Recent data from the US on susceptibility of pediatric uropathogens document that, overall, resistance to nitrofurantoin across all pathogens and pediatric age groups is approximately 5% to 10%.[195]

Nitrofurantoin was approved by the FDA in 1953 for the treatment of uncomplicated UTIs. Nitrofurantoin is well absorbed orally and is rapidly cleared from the serum, producing subtherapeutic concentrations in serum, but bactericidal concentrations in urine. Currently available formulations include a rapidly absorbed monohydrate salt, a monohydrate salt in slow-release matrix, and crystalline nitrofurantoin that is also more slowly absorbed. Dosages should be decreased in children with any degree of renal insufficiency.

In clinical practice, nitrofurantoin has been used primarily for prophylaxis of UTI, although few prospective comparative data are available on which to base recommendations. Recent studies have defined the benefit of antimicrobial prophylaxis using TMP-SMX.[196–199] Serious pulmonary toxicities, both acute and chronic, were reported in the decade following availability of nitrofurantoin. Acute lung injury, thought to be immune mediated, and chronic fibrosis have been reported in adults during longterm therapy. The rate and severity of these multiple pulmonary toxicities have not been evaluated prospectively in children. However, no reports of pulmonary toxicity in young children receiving nitrofurantoin prophylaxis for UTI have been published, despite ongoing common use. In addition to pulmonary toxicity, hemolysis secondary to glucose-6-phosphate dehydrogenase deficiency has also been documented.

Methenamine

Methenamine hippurate is used exclusively for the prevention of UTI. Initially available in 1967 and approved by the FDA for patients 12 years or older, methenamine is a salt that ultimately exerts an antibacterial effect in the urine as it becomes converted into formaldehyde. This effect occurs when the urine pH is below 5.5. Formaldehyde has nonspecific bactericidal activity on both gram-positive and gram-negative bacteria. However, as the generation of formaldehyde is dependent on an acidic urinary pH, methenamine may not be active in situations in which a more alkaline pH is created by diet, or by urea-splitting bacteria in the urine, such as *Proteus* and *Pseudomonas.* A recent review of previously published data on clinical trials of methenamine prophylaxis, some of which were published as early as 1975, suggested efficacy for short-term use (<1 week) in adults with normal urinary tract anatomy.[200] Data collected in children in Finland from 1960 to 1974 suggest a benefit that is equivalent to, or superior to, sulfa and nitrofurantoin, although failures were not uncommon.[201] The clinical use of methenamine in children is not well defined currently because of lack of high-quality data on the safety and efficacy particularly for longterm prophylaxis.

Appendix 292.1 Dosage of Antibacterial Drugs for Infants, Older Children, and Adolescents

Drug Generic Name (Trade Name)	Administration Route	Dosage (per kg/day)[a]	Comments
AMINOGLYCOSIDES[b]			Dosage adjusted according to serum concentration(s).
Amikacin (Amikin)	IV, IM	15–22.5 mg divided into 1–3 doses	30–35 mg/kg/day for cystic fibrosis
Gentamicin (Garamycin)	IV, IM	3–7.5 mg divided into 1–3 doses	
Neomycin (numerous)	PO	50–100 mg divided into 4 doses (adults, 4–8 g/day; max., 12 g/day)	Minimally absorbed from GI tract
Streptomycin	IM, IV	20–40 mg once daily (adults, 1–2 g/day)	15–20 mg divided into 1–2 doses for non-MTB infections.
Tobramycin (Nebcin)	IV, IM	3–7.5 mg divided into 1–3 doses	7–10 mg/kg/day for cystic fibrosis
β-LACTAM AGENTS			
Monolactams			
Aztreonam (Azactam)	IV, IM	90–120 mg divided into 3–4 doses (adults, 3–6 g/day; max., 8 g/day)	
Carbapenems[c]			
Doripenem (Doribax)	IV	60 mg divided into 3 doses (adults, 1.5 g/day)	Max., 3–6 g/day by prolonged or continuous infusion for more serious *P. aeruginosa* infections
Ertapenem (Invanz)	IV, IM	30 mg divided into 2 doses; max., 1 g/day (children ≥13 yr and	

		adults, 1 g/day once daily)	
Imipenem-cilastatin (Primaxin)	IV, IM	60–100 mg divided into 4 doses (adults, 1–2 g/day; max., 4 g/day)	Seizures at high doses; not used for meningitis
Meropenem (Merrem)	IV	60 mg divided into 3 doses (adults, 3–6 g/day)	120 mg for meningitis or more serious *P. aeruginosa* infections; max., 6 g/day, may be given by prolonged or continuous infusion
Cephalosporins[c]			Methicillin-resistant staphylococci are resistant to all currently available cephalosporins, except ceftaroline
Cefaclor (Ceclor)	PO	20–40 mg divided into 2 doses (adults, 1–1.5 g/day)	
Cefadroxil (Duricef, Ultracef)	PO	30 mg divided into 2 doses (adults, 1–2 g/day)	
Cefazolin (Kefzol, Ancef)	IV, IM	50–100 mg divided into 3 doses (adults, 3–6 g/day; max., 12 g/day)	Up to 150 mg/kg/day for serious infections
Cefdinir (Omnicef)	PO	14 mg once daily; max., 600 mg/day	
Cefepime (Maxipime)	IV, IM	100–150 mg divided into 2–3 doses (adults, 2–6 g/day)	
Cefixime (Suprax)	PO	8 mg divided into 1 or 2 doses (adults, 400 mg/day)	
Cefotaxime (Claforan)	IV, IM	150–180 mg divided into 3 or 4 doses (adults, 3–6 g/day; max., 12 g/day)	200–300 mg divided into 4 doses for meningitis
Cefotetan (Cefotan)	IV, IM	60–100 mg divided into 2 doses (adults, 2–4 g/day; max., 6 g/day)	
Cefoxitin (Mefoxin)	IV, IM	80–160 mg divided into 3–4 doses (adults, 4–6 g/day; max., 12 g/day)	
Cefpodoxime proxetil (Vantin)	PO	10 mg divided into 2 doses (adults, 200–400 mg/day; max., 800 mg/day)	
Cefprozil (Cefzil)	PO	15–30 mg divided into 2 doses (adults, 0.5–1 g/day)	
Ceftaroline (Teflaro)	IV	Adults, 1.2 g/day divided into 2 doses	Investigational in children (see text)
Ceftazidime (Fortaz, Tazicef, Tazidime)	IV, IM	100–150 mg divided into 3 doses (adults, 3–6 g/day; max., 12	200–300 mg given by prolonged or continuous infusion for more serious

		g/day)	*Pseudomonas* infections.
Ceftazidime-avibactam (Avycaz)	IV	Adults, 7.5 g (6 g/1.5 g)/day divided into 3 doses	
Ceftibuten (Cedax)	PO	9 mg once daily (adults, 400 mg/day)	
Ceftriaxone (Rocephin)	IV, IM	50–100 mg divided into 1 or 2 doses (adults, 1–2 g/day; max., 4 g/day)	100 mg for meningitis and penicillin-resistant pneumococcal pneumonia
Ceftolozane-tazobactam (Zerbaxa)	IV	Adults, 4.5 g (3 g/1.5 g)/day divided into 3 doses	
Cefuroxime (Zinacef)	IV, IM	100–150 mg divided into 3 doses (adults, 2.25–4.5 g/day; max., 6 g/day)	Should not be used for meningitis
Cefuroxime axetil (Ceftin)	PO	20–30 mg divided into 2 doses, adults 0.5-1 g/day; max., 3 g/day	Up to 100 mg/kg/day for bone or joint infections
Cephalexin (Keflex)	PO	25–50 mg divided into 2 doses (adults, 1–2 g/day; max., 4 g/day)	75–100 mg divided into 3 or 4 doses for bone or joint infections, or for oral step-down therapy to replace parenteral therapy
PENICILLINS[c]			
Penicillin G and V			
Penicillin G, crystalline	IV, IM	100,000–300,000 units divided into 4–6 doses (adults, 8–24 million units/day)	Available as potassium or sodium salt
Penicillin G, procaine	IM	25,000–50,000 units divided into 1–2 doses (adults, 600,000–1.2 million units)	
Penicillin G, benzathine (Bicillin LA)	IM	50,000 units/kg once for infants <27 kg (60 lb) 300,000–600,000 units (not per kg) once ≥27 kg (60 lb) 900,000 units (not per kg) once (adult 1.2–2.4 million units once)	
Penicillin G benzathine-procaine (Bicillin CR)	IM	<14 kg (30 lb) 600,000 units (not per kg) once 14–27 kg (30–60 lb) 1,200,000 units (not per kg) once >27 kg (60 lb) 2,400,000 units (not per kg) once	
Penicillin V K	PO	25–50 mg divided into 3 or 4 doses (adults, 0.5–2 g/day)	75 mg divided into 4 doses for group A streptococcal pneumonia

Penicillinase-Resistant Penicillins			Methicillin-resistant staphylococci are resistant to all penicillins
Oxacillin (Bactocill)	IV, IM	100–200 mg divided into 4–6 doses (adults 4–6 g/day; max., 12 g/day)	
Nafcillin (Unipen, Nafcil)	IV, IM	100–200 mg divided into 4–6 doses (adults, 4–6 g/day; max., 12 g/day)	
Dicloxacillin (Dynapen)	PO	12.5–25 mg divided into 4 doses (adults, 0.5–1 g/day); max., 2 g/day	100 mg for bone or joint infections, or for oral step-down therapy to replace parenteral therapy
Aminopenicillins			
Amoxicillin (Amoxil)	PO	25–50 mg divided into 2–3 doses (adults, 0.75–3 g/day)	90 mg in 2 doses for AOM (higher doses for AOM due to certain pathogens) 80–100 mg in 3 doses for oral step-down therapy to replace parenteral therapy. Max., 4 g (not per kg)/day
Amoxicillin-clavulanate (Augmentin)	PO	14 : 1 formulation: 90 mg amoxicillin component divided into 2 doses 7 : 1 formulation: 25–45 mg amoxicillin component divided into 2 doses 4 : 1 formulation: 20–40 mg amoxicillin component divided into 3 doses	Max., 4 g (not per kg)/day
Ampicillin	IV, IM	100–200 mg divided into 4 doses (adults 4–12 g/day)	300–400 mg divided into 4–6 doses for meningitis
Ampicillin-sulbactam (Unasyn)	IV	100–200 mg ampicillin component divided into 4 doses (adults 4–8 g day)	
Ampicillin trihydrate (Principen)	PO	50–100 mg divided into 4 doses (adults 1–2 g/day)	
Broad-Spectrum Penicillins			
Piperacillin-tazobactam (Zosyn)	IV	240–300 mg piperacillin component divided into 3–4 doses (adults, 9–16 g piperacillin/day)	400–600 mg divided into 4–6 doses given by prolonged (3–4 hr) or continuous infusion for less susceptible organisms
Chloramphenicol sodium-succinate (Chloromycetin)	IV	50–100 mg divided into 4 doses (adults 2–4 g/day)	Dosage adjusted according to serum concentration(s)
FLUOROQUINOLONES			Arthropathy is a potential fluoroquinolone-class side effect in children

Ciprofloxacin (Cipro)	PO	20–40 mg divided into 2 doses; max. 1.5 g/day	
	IV	20–30 mg divided into 2–3 doses; max., 1.2 g/day	
Levofloxacin (Levaquin)	PO, IV	20 mg divided into 2 doses (children <5 yr); 10 mg once daily (children ≥5 yr) (adults, 500–750 mg/day)	See also Chapter 129 for use in *Bacillus anthracis* exposure, and Chapter 134 for use in MTB
Moxifloxacin (Avelox)	PO, IV	Adults, 400 mg once daily	10 mg/kg once daily for MTB
GLYCOPEPTIDES			
Vancomycin (Vancocin)	IV	45 mg divided into 3 doses 60–70 mg/kg/day for MRSA to achieve >400 mg · hr/L AUC	Dosage adjusted according to serum concentration(s)
	PO	40 mg divided into 4 doses (adults, 500 mg–2 g divided into 4 doses)	Poorly absorbed from GI tract
GLYCOLIPOPEPTIDES			
Dalbavancin (Dalvance)	IV	Adults, 1 g one time then 0.5 g in 1 wk	Investigational in children (see text)
Oritavancin (Orbactiv)	IV	Adults, 1200 mg once	
LINCOSAMIDES			
Clindamycin (Cleocin)	IM, IV	20–40 mg divided into 3 doses (adults, 900 mg–2.7 g/day; max., 4.8 g/day)	
	PO	10–30 mg divided into 3 doses (adults, 600 mg–1.8 g/day)	30–40 mg divided into 3–4 doses for AOM and CA-MRSA infection
LIPOPEPTIDES			
Daptomycin (Cubicin)	IV	4–6 mg once daily for children ≥12 yr; 7 mg once daily for 6–11 yr; 8–10 mg once daily for 2–5 yr	
MACROLIDES/AZALIDES			
Erythromycin (numerous)	PO	50 mg divided into 2–4 doses (adults, 1–2 g/day; max., 4 g/day)	Available as base, stearate, and ethyl succinate preparations
	IV	20 mg divided into 4 doses (adults, 1–2 g/day; max., 4 g/day)	Administer over at least 60 min
Clarithromycin (Biaxin)	PO	15 mg divided into 2 doses (adults, 0.5–1 g/day)	
Azithromycin (Zithromax)	PO	All doses once daily: AOM: 10 mg × 3 days; *or* 30 mg × 1 day; *or* 10 mg × 1 day, then 5 mg × 4 days	Max. doses: 10–12 mg/kg = 500 mg 5–6 mg/kg = 250 mg 30 mg/kg = 1.5 g 60 mg/kg ER susp = 2 g

		Pharyngitis: 12 mg × 5 days Sinusitis: 10 mg × 3 days; *or* 10 mg × 1 day, then 5 mg × 4 days Pneumonia: 10 mg × 1 day, then 5 mg × 4 days; *or* 60 mg × 1 day of ER susp if >6 mo of age Shigellosis: 12 mg × 1 day, then 6 mg × 4 days	
	IV	10 mg once daily; max., 500 mg	
MISCELLANEOUS			
Methenamine hippurate (Hiprex)	PO	1–2 g (not per kg) divided into 2 doses	
Methenamine mandelate (Mandelamine)	PO	<6 yr: 75 mg divided into 4 doses 6–12 yr: 2 g/day (not per kg) >12 yr: 4 g/day (not per kg)	
Nitrofurantoin (Furadantin)	PO	5–7 mg divided into 4 doses (adults, 200–400 mg/day)	1–2 mg once daily for UTI prophylaxis
NITROIMIDAZOLES			
Metronidazole (Flagyl)	PO	30–50 mg divided into 3 doses (adults, 0.75–2.25 g/day)	
	IV	22.5–40 mg divided into 3-4 doses (adults, 1–2 g/day; max., 4 g/day)	
OXAZOLIDINONES			
Linezolid (Zyvox)	PO, IV	<12 yr of age: 30 mg in 3 doses, 20 mg in 2 divided doses for uncomplicated skin infections. ≥12 yr and adults: 1200 mg per day (not per kg) in 2 doses	Myelosuppression increases with duration of therapy over 10 days
Tedizolid (Sivextro)	PO, IV	Adults, 200 mg once daily	
POLYMYXINS			
Colistin (as Colistimethate, Coly-Mycin M)	IV, IM	5–7 mg colistin base, divided into 3 doses	Reserved for multidrug-resistant gram-negative pathogens because of neurotoxicity and nephrotoxicity
Polymyxin B	IV	2.5–3 mg divided into 2 doses (adult dose same)	No maximum dose
RIFAMYCINS			
Rifampin (Rifadin)	PO, IV	10–20 mg divided	

		into 1–2 doses (adults, 600 mg/day)	
Rifaximin (Xifaxan)	PO	≥12 yr of age: 600 mg/day (not per kg) divided into 3 doses	
SULFONAMIDES			
Sulfadiazine	PO	120–150 mg divided into 4 doses (adults 4–6 g/day)	
Trimethoprim-sulfamethoxazole (TMP-SMX) (Bactrim, Septra)	IV, PO	8–12 mg TMP divided into 2 doses (adults, 160–320 mg TMP/day)	20 mg TMP divided into 4 doses for *Pneumocystis* pneumonia 2 mg TMP once daily for UTI prophylaxis 5 mg TMP divided into 2 doses for 3 consecutive days per week for *Pneumocystis* prophylaxis
STREPTOGRAMINS			
Quinupristin-dalfopristin (Synercid)	IV	15–22.5 mg divided into 2–3 doses (adult dose same)	
TETRACYCLINES			Tetracycline-class antibiotics stain unerupted teeth; use in children <8 yr of age if benefits exceed risks (see text)
Tetracycline (numerous)	PO	25–50 mg divided into 4 doses (adults, 1–2 g/day)	
Minocycline (Minocin)	PO, IV	4 mg divided into 2 doses (adults, 200 mg/day)	
Doxycycline	PO, IV	2–4 mg divided into 1–2 doses (adults, 100–200 mg/day)	
Demeclocycline (Declomycin)	PO	7-13 mg divided into 4 doses (adults, 600 mg/day)	

[a] Doses are listed as the number of dosing units (e.g., mg, µg) per kilogram **per day** along with the usual adult daily dose range ± an absolute maximal dose (not per kg per day, unless specified)

[b] Once-daily IV aminoglycoside dosing (amikacin 15–20 mg/kg; gentamicin/tobramycin 4.5–7.5 mg/kg) may provide equal efficacy with reduced toxicity and can be used as an alternative to multiple daily dosing.[202]

[c] In patients with a history of immediate hypersensitivity (anaphylaxis) to penicillin, other penicillins, cephalosporins, or carbapenems should not be used.

AOM, acute otitis media; AUC, area under the curve; CA, community associated; ER, extended release; GI, gastrointestinal; IV, intravenous; IM, intramuscular; MRSA, methicillin-resistant Staphylococcus aureus; MTB, Mycobacterium tuberculosis; PO, oral; TMP, trimethoprim; UTI, urinary tract infection.

Data from references 126, 203–208.

Appendix 292.2 Drugs for Parasitic Infections

Drug	Route	Dosage (mg/kg per dose) and Frequency of Administration[a]			
		Body Weight ≤2 kg		Body Weight >2 kg	
		≤7 Days Old	8–28 Days Old	≤7 Days Old	8–28 Days Old
AMINOGLYCOSIDES[b,c,d]					
Amikacin	IV, IM	15 every 48 hr	15 every 24–48 hr	15 every 24 hr	15 every 12–24 hr
Gentamicin	IV, IM	5 every 48 hr	4–5 every 24–48 hr	4 every 24-36 hr	4 every 12–24 hr
Tobramycin	IV, IM	5 every 48 hr	4–5 every 24–48 hr	4 every 24-36 hr	4 every 12–24 hr
CARBAPENEMS					
Meropenem[e] *for meningitis*	IV	20 every 12 hr	20 every 8 hr[e]	20 every 8 hr	30 every 8 hr[e]
		40 every 8 hr	40 every 8 hr	40 every 8 hr	40 every 8 hr
CEPHALOSPORINS[b]					
Cefepime	IV, IM	30 every 12 hr	30 every 12 hr	50 every 12 hr[f]	50 every 12 hr[f]
Cefotaxime	IV, IM	50 every 12 hr	50 every 8 hr	50 every 12 hr	50 every 8 hr
Cefazolin	IV, IM	25 every 12 hr	25 every 8 hr	25 every 12 hr	25 every 8 hr
Ceftazidime	IV, IM	50 every 12 hr	50 every 8 hr	50 every 12 hr	50 every 8 hr
Ceftriaxone[g]	IV, IM	—	—	50 every 24 hr	50 every 24 hr
Cefuroxime	IV, IM	50 every 12 hr	50 every 8 hr	50 every 12 hr	50 every 8 hr
PENICILLINS					
Ampicillin[h]	IV, IM	50 every 12 hr	75 every 12 hr	50 every 8 hr	50 every 6 hr
for meningitis	IV	100 every 8 hr	100 every 8 hr	100 every 8 hr	75 every 6 hr
Nafcillin, oxacillin	IV, IM	25 every 12 hr	25 every 8 hr	25 every 8 hr	25 every 6 hr
for meningitis	IV	50 every 12 hr	50 every 8 hr	50 every 8 hr	50 every 6 hr
Penicillin G crystalline[i]	IV, IM	50,000 units every 12 hr	50,000 units every 8 hr	50,000 units every 12 hr	50,000 units every 8 hr
for meningitis	IV	100,000 units every 12 hr	100,000 units every 8 hr	100,000 units every 8 hr	100, 000 units every 6 hr
Penicillin G procaine	IM only	50,000 units every 24 hr	50,000 units every 24 hr	50,000 units every 24 hr	50,000 units every 24 hr
Piperacillin-tazobactam	IV	100 every 8 hr	100 every 8 hr	80 every 6 hr	80 every 6 hr
Ticarcillin-clavulanate	IV	75 every 12 hr	75 every 8 hr	75 every 12 hr	75 every 8 hr
OTHER AGENTS					
Azithromycin	PO, IV	10 every 24 h	10 every 24 hr	10 every 24 hr	10 every 24 hr
Aztreonam	IV, IM	30 every 12 hr	30 every 8 hr	30 every 8 hr	30 every 6 hr
Clindamycin	IV, IM, PO	5 every 8 hr	5 every 8 hr	7 every 8 hr	10 every 8 hr
Erythromycin	PO, IV	10 every 12 hr	10 every 8 hr	10 every 12 hr	10 every 8 hr
Linezolid	IV	10 every 12 hr	10 every 8 hr	10 every 8 hr	10 every 8 hr
Metronidazole[j]	IV	7.5 every 12 hr	7.5 every 12 hr	7.5 every 8 hr	10 every 8 hr
Vancomycin[d,k]	IV	15 every 24 hr	15–20 every 12–24 hr	20 every 24 hr	15 every 12–8 hr

[a] In milligrams (mg) unless otherwise specified. Dosages may need to be adjusted in neonates with severe renal impairment.

[b] May use the longer dosing interval (if given) in extremely low birth weight (<1000 g) neonates until 2 weeks of life.

[c] Dosages for aminoglycosides may differ from those recommended by the manufacturer and approved by the US Food and Drug Administration.

[d] Individualize dosage based on determination of serum concentrations.

[e] Adjust dosage after 14 days of age instead of after 7 days of age.

[f] 30 mg/kg if target pathogen MIC ≤4 mg/L.

[g] Neonates should not receive ceftriaxone intravenously if they are also receiving, or are expected to receive, intravenous calcium in any form, including parenteral nutrition. See Pediatrics 2009;123;e609. Cefotaxime is the preferred third-generation cephalosporin in neonates.

[h] 100 mg/kg/dose every 12 hours is also acceptable for empiric therapy of early-onset sepsis.

[i] Dosage applies to treatment of congenital syphilis and empiric therapy of early-onset sepsis. Some experts recommend 200–300,000 units/kg/day for other invasive infections.

[j] Begin with a 15-mg/kg loading dose.

[k] Dosing algorithm based on serum creatinine after DOL 5; if <0.7 then 15 mg/kg every 12 hr, if 0.7–0.9 then 20 mg/kg every 24 hr, if 1–1.2 then 15 mg/kg every 24 hr.

IV, intravenous; IM, intramuscular; PO, oral.

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Antifungal Agents

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Fungal infections generally can be divided into superficial infections that can affect children with normal immune systems and invasive infections that tend to occur primarily in children who are immunocompromised because of genetic defects, hematopoietic stem cell transplantation (HSCT), or solid-organ transplantation, or after a chemotherapeutic regimen used for childhood malignancies. Although conventional amphotericin B deoxycholate (AMB-D) was the drug of choice for many invasive fungal infections for years, now the many newer, safer, and more effective agents have largely relegated it to obsoletion. Lipid formulations of amphotericin B reduce the toxicity of conventional amphotericin B, and these agents have a role in the management of several specific diseases, such as mucormycosis. The newer triazoles—voriconazole, posaconazole, and isavuconazole—have expanded options for therapy against mold infections such as invasive aspergillosis. The echinocandins offer a class of antifungal therapy in which for the first time there is no cross-reactivity with a human substrate, leading to minimal toxicity.

There are important considerations when choosing antifungal agent, including the fungistatic versus fungicidal activity of certain antifungal classes against the various genera or even species of fungal pathogens and, most important, solid understanding of the differences in the pharmacokinetics of a drug in children compared with adults, which affect optimal dosing. Unfortunately, there have been few antifungal studies conducted in children. Consequently, most information for the pediatrician has been extrapolated from adult data. Through the efforts of dedicated clinicians and collaboration, pediatric indications and dosing strategies can be discovered that will directly benefit pediatric patients. This chapter provides a brief review of topical antifungal therapy and an overview of the current state of systemic antifungal therapy. The preferred treatment for each pathogen is covered in pathogen-specific chapters.

Superficial Infections

Among the therapeutic options available for treatment of fungal infections of the hair, skin, and nails, few have been tested in children, and fewer are approved for use in children younger than 13 years. Extrapolating data from adults treated for dermatomycoses to infants and children may not be justified. For example, manifestations of dermatomycoses vary with age, with tinea capitis seen almost exclusively in children.

The use of topical agents should be confined to infections of the epidermis or mucosal surfaces. The choice of treating superficial fungal infections with a topical or a systemic agent depends on the fungal pathogen, the site of infection, and the extent of the lesion. Systemic antifungal therapy almost always is used for tinea of the scalp, nails, palms, or soles; creams or solutions are preferred for fissured or intertriginous areas.

Topical Polyenes

Nystatin is a polyene antifungal agent named after New York State. It binds to ergosterol in the fungal cell membrane and causes changes in cell permeability and, eventually, cell lysis. Nystatin is useful for the treatment of mucosal and cutaneous infections caused by *Candida* spp. Nystatin is available as a suspension (100,000 U/mL), powder, cream, or ointment (100,000 U/g); a lozenge (200,000 U) to be dissolved in the mouth; an oral tablet (500,000 U); and a vaginal tablet (100,000 U). Oral forms are administered 4 or more times daily and are well tolerated because there is no significant systemic absorption, although large oral doses of the suspension can cause nausea. Nystatin is not effective against the dermatophytes.

Topical Azoles

The azole class (divided into imidazoles and triazoles based on chemical structure) inhibits ergosterol synthesis in the fungal cell membrane. Clotrimazole is an imidazole with broad-spectrum activity against *Candida* spp. and the dermatophytes *Trichophyton tonsurans, Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum,* and *Microsporum canis* (Table 293.1). Clotrimazole also is effective against *Malassezia furfur,* the cause of tinea versicolor. Clotrimazole is one of the few topical antifungal agents studied in children. The 1% cream, lotion, and solution are available over the counter for the treatment of tinea pedis, tinea cruris, and tinea corporis. High concentrations of clotrimazole are achieved topically, but systemic absorption is negligible. Topical application generally is well tolerated but can cause local irritation or urticaria. Clotrimazole is available coformulated with 0.05% betamethasone, and this combination appears to foster more rapid healing of lesions in adults. However, this combination cream is not recommended for use in children because of the potential for systemic absorption of the corticosteroid.

TABLE 293.1

Categories and Activities of Antifungal Agents Against Dermatomycoses

Agent	Category	Trade Name	Activity Against			
			Candida Species	*Trichophyton tonsurans*	Other Dermatophytes	*Malass furfur*
Nystatin	Topical polyene	Mycostatin	+	–	–	–
Clotrimazole	Imidazole	Lotrimin	+	+	+	+
Miconazole	Imidazole	Desenex	+	+	+	+
Ketoconazole	Imidazole	Nizoral	+	+/–	+	+/–
Oxiconazole	Imidazole	Oxistat	+	+	+	+
Terbinafine	Allylamine	Lamisil	–	+/–	+	+/–
Naftifine	Allylamine	Naftin	–	+/–	+	–
Butenafine	Benzylamine	Mentax	–	+	+	+/–
Ciclopirox	Hydroxypyridone	Ciclodan	+	+	+	+
Griseofulvin	*Penicillium* derivative	Fulvicin	–	+	+	–

+, Activity; –, no activity; +/-, variable activity.

Miconazole is an imidazole available over the counter as a 2% cream. Its spectrum of activity is identical to that of clotrimazole, and in clinical trials it has demonstrated equivalent efficacy. Its efficacy in the treatment of superficial *Candida* infections is better than that of nystatin, and it has the advantage of once-a-day application. Local side effects, such as those seen with clotrimazole, can occur, and miconazole should be used sparingly in intertriginous areas to avoid maceration of the skin.

Ketoconazole is an imidazole available as a 2% cream. Ketoconazole is effective therapy for dermatomycoses caused by *Candida* spp., *T. rubrum, T. mentagrophytes, E. floccosum,* and *M. furfur.* Although it has in vitro activity against *T. tonsurans* and *Microsporum,* the clinical relevance of these data to efficacy is not known. Ketoconazole applied topically is not absorbed systemically but can cause local irritation. Ketoconazole also is available as an oral tablet formulation, but its use as systemic therapy is associated with life-threatening hepatotoxicity and adrenal insufficiency, and the United States Food and Drug Administration (FDA) specifically recommends *against* use of this oral formulation as first-line therapy for any fungal infection.

Econazole is an imidazole nearly identical in structure to miconazole. Its activity and adverse reactions are similar. Published studies demonstrate cure rates for dermatomycoses similar to those of other topical imidazoles, but comparative studies have not been performed, and econazole has no clear advantage over other topical azoles.

Additional topical azoles include oxiconazole, terconazole, sertaconazole, and luliconazole. Oxiconazole is an imidazole that is approved for the treatment of tinea pedis, tinea cruris, tinea corporis, and tinea versicolor. Terconazole is an imidazole formulated only for vaginal use in the treatment of *Candida* vaginitis. Sertaconazole is an imidazole approved for treatment of tinea pedis. Luliconazole is an imidazole approved for tinea pedis, tinea cruris, and tinea corporis. Pediatric experience with these newer agents is limited.

Griseofulvin

Griseofulvin is approved by the FDA for tinea capitis (daily for 6 to 12 weeks), a condition almost uniformly refractory to treatment with topical agents and therefore requiring oral antifungal therapy.

Griseofulvin impairs fungal mitosis by interfering with microtubule formation, and it deposits in keratin precursor cells, binding to newly formed keratin and thereby preventing fungal invasion. Griseofulvin is fungistatic in vivo against *Trichophyton* spp., *E. floccosum*, and *Microsporum* and is not active against *Candida* or *M. furfur*. Absorption of griseofulvin from the gastrointestinal tract varies considerably but is increased by decreasing the size of the crystals (microcrystalline and ultracrystalline formulations are available, but the ultracrystalline formulation is not available as a suspension) and administering the drug with a meal high in fat content. Historically, the dose of griseofulvin for children was 10 to 15 mg/kg/day, but because of increasing resistance, many experts now recommend 20 to 25 mg/kg/day.

Griseofulvin has a longstanding history of safety and efficacy in children. Because it is metabolized by the liver, adjustment in dosage is not necessary in patients with renal impairment. Side effects are infrequent but include hypersensitivity rash, urticaria, nausea, vomiting, diarrhea, headache, fatigue, proteinuria, and leukopenia. Elevated levels of serum hepatic enzymes can occur, but laboratory monitoring is generally not indicated in healthy children treated with durations of 8 weeks or less. Periodic monitoring of complete blood counts and of hepatic and renal function is recommended if therapy is continued for ≥8 weeks. Griseofulvin can decrease the effects of oral anticoagulant and contraceptive agents. Its antifungal effect can be decreased by the concurrent administration of phenobarbital.

Squalene Epoxidase Inhibitors

The allylamines terbinafine and naftifine act by inhibiting squalene epoxidase, an enzyme in the pathway leading to the synthesis of ergosterol in the fungal cell membrane. Terbinafine is available as both a topical preparation and an oral tablet. Topical terbinafine is at least as effective as other topical antifungal agents. Its main advantage is that favorable clinical responses can be achieved with short durations of therapy, with high cure rates for tinea pedis observed after even a single application.[1] The oral tablet has high absorption (>70%) and a long half-life (approximately 36 hours), penetrates keratinized tissues, and maintains concentrations higher in skin and nails than serum for 1 week after stopping treatment. Unlike griseofulvin, no liquid formulation is available. Both griseofulvin and terbinafine are active against the common dermatophytes and have proven efficacy in the treatment of dermatomycoses in adults. A meta-analysis of randomized controlled trials comparing terbinafine with griseofulvin for the treatment of tinea capitis concluded that 2 to 4 weeks of terbinafine therapy is at least as effective as 6 to 8 weeks of griseofulvin, with no differences in tolerability or adverse effects and overall cost savings with the 4-week therapy.[2] More recent meta-analyses have suggested superiority of terbinafine for tinea capitis caused by *Trichophyton* spp. and of griseofulvin for tinea capitis caused by *Microsporum* spp.[3,4] Children require higher doses of terbinafine to achieve exposure similar to that of adults. A clinical trial conducted in children with tinea capitis caused by the recalcitrant species *M. canis* demonstrated higher cure rates in those who received higher doses (7–12.5 mg/kg/day) of terbinafine.[5]

Butenafine is a benzylamine with a mechanism of action similar to that of the allylamine class of antifungal agents. Butenafine is indicated for the topical treatment of tinea pedis, tinea corporis, and tinea cruris.

Other Topical Agents

Undecylenic acid is an unsaturated fatty acid antifungal agent available as an ointment, powder, or liquid. Its therapeutic efficacy was first recognized in the 1940s in treating superficial fungal diseases affecting military troops. However, it has little efficacy compared with newer agents. Tolnaftate has similar activity against dermatophytes, with cure rates of 60% to 90% for superficial infections.[6] Tinea capitis and tinea unguinum frequently are refractory, probably because of poor penetration of tolnaftate into involved areas. The advantages of these compounds are that they are safe, inexpensive, and rarely cause local irritation.

Gentian violet is a triphenylmethane dye mixture that is fungicidal against *Candida* spp. through an unknown mechanism. It has been used as a traditional remedy for mucocutaneous candidiasis through topical application of a dilute mixture and has gained favor recently as a treatment for refractory mucocutaneous candidiasis, particularly in resource-poor areas. Its disadvantages are the lack of a standard pharmaceutical grade formulation, mucosal irritation, and surface staining.

Ciclopirox is a hydroxypyrimidine antifungal that acts by chelating iron and thereby inhibiting iron-dependent fungal enzymes. It is active against all of the clinically relevant dermatophytes, *Candida* spp., and *M. furfur* and is available in multiple topical formulations to treat infections of the skin and as a nail lacquer to treat onychomycosis.

Invasive Infections

The armamentarium of antifungal choices for invasive fungal infections has increased substantially in recent years (Tables 293.2 and 293.3). Although choices once were limited and often ineffective, several better tolerated and more effective agents are now available. Clinicians must consider many factors when selecting therapy, including the disease state, causative organism, antifungal resistance patterns, and host factors such as concurrent medications, hepatic function, and prior exposure to antifungal therapy. Currently licensed systemic antifungal agents include amphotericin B and its lipid derivatives; 5-fluorocytosine; the triazoles, including fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole; and the echinocandins, including caspofungin, micafungin, and anidulafungin.

TABLE 293.2

Spectrum of Activity of Selected Systemic Antifungal Agents

Organism	**Antifungal Agent Activity**								
	AMB	5-FC[a]	FLU	ITRA	VORI	POSA	CAS	MICA	ANID
YEASTS									
Candida spp. (most)	+	+	+	+	+	+	+	+	+
C. lusitaniae	-	+	+	+	+	+	+	+	+
C. glabrata	+	+	+/−	+/−	+/−	+/−	+/−	+/−	+/−
C. krusei	+	+	−	−	−	−	+	+	+
Cryptococcus neoformans	+	+	+	+	+	+	−	−	−
Malassezia spp.	+		+/−	+/−					
Trichosporon spp.	−	−	−	+	+	+	−	−	−
OPPORTUNISTIC MOLDS									
Aspergillus spp. (most)	+	−	−	+	+	+	+	+	+
A. terreus	−	−	−	+	+	+	+	+	+

Mucormycosis	+	−	−	−	−	+	−	−	−
Fusarium spp.	−	−	−	+/−	+	+	−	−	−
Scedosporium apiospermum	−	−	−	−	+/−	+/−	−	−	−
DIMORPHIC/ENVIRONMENTAL MOLDS									
Blastomyces dermatiditis	+	−	+	+	+	+	−	−	−
Coccidiodes immitis	+	−	+	+	+	+	−	−	−
Histoplasma capsulatum	+	−	+	+	+	+	−	−	−
Paracoccidiodes brasiliensis	+	−	+	+	+	+	−	−	−
Sporothrix schenckii	+	−	−	+	−		−	−	−
Dematiaceous molds	+/−	+/−	−	+/−	+/−	+/−	−	−	−

[a]5-FC is used only in combination with other agents.

+, activity; −, no activity; +/−, variable activity; blank, unknown/poorly studied; 5-FC, 5-fluorocytosine; AMB, amphotericin B; ANID, anidulafungin; CAS, caspofungin; FLU, fluconazole; ITRA, itraconazole; MICA, micafungin; POSA, posaconazole; VORI, voriconazole.

TABLE 293.3

Preferred Pediatric Dosing of Approved Systemic Antifungal Agents

Drug Class	Antifungal Drug[a]	Preferred Adult Dosing	Preferred Pediatric Dosing	Pediatric Dosing Comments
Polyene	Amphotericin B deoxycholate (AMB-D; Fungizone)	1–1.5 mg/kg/day	1–1.5 mg/kg/day	Children generally tolerate higher doses than do adults
	Amphotericin B Lipid Complex (ABLC; Abelcet)[a]	5 mg/kg/day	5 mg/kg/day	
	Liposomal Amphotericin B[a] (L-AmB; AmBisome)	5 mg/kg/day	5 mg/kg/day	
Pyrimidine analogue	5-Fluorocytosine (Ancoban)	100 mg/kg/day divided every 6 hr	100 mg/kg/day divided every 6 hr	Use caution with large oral volume for neonates
Triazole	Fluconazole (Diflucan)	200–800 mg/day; 6–12 mg/kg/day	6–12 mg/kg/day	Dose higher in children due to higher clearance; neonates require further special dosing. Use 12 mg/kg/day dosage for invasive candidiasis.
	Itraconazole (Sporanox)	200–400 mg/day	2.5–5 mg/kg/dose twice daily	Dosing twice daily preferred in children, and if dose exceeds 200 mg/day
	Voriconazole (VFend)	Load: 6 mg/kg/dose	<12 yr: Load: 9	Young children require higher doses due to higher clearance. Oral bioavailability lower in

		twice daily × 1 day Maintenance: 4 mg/kg/dose twice daily	mg/kg/dose twice daily × 1 day Maintenance: 8 mg/kg/dose twice daily ≥ 12 yr: Same as adult dosing	children than in adults. Therapeutic drug monitoring is strongly recommended
	Posaconazole (Noxafil)	Suspension: 200 mg every 6 hr or 400 mg twice daily Tablet (delayed release): 300 mg twice daily × 1 day, then 300 mg daily IV: 300 mg twice daily × 1 day, then 300 mg daily	<13 yr: Suspension: 4 mg/kg/dose 3 times daily ≥13 yr: Same as adult dosing	Data on pediatric dosing has not been fully studied; the suggested dose for children <13 yr is based on a prophylaxis study. Oral absorption of suspension formulation is improved when dose is taken with a fatty meal
Echinocandin	Caspofungin (Cancidas)	Load: 70 mg daily × 1 day Maintenance: 50 mg daily	Load: 70 mg/m^2 daily × 1 day Maintenance: 50 mg/m^2 daily	Dosing for hepatic insufficiency in children is 35 mg/m^2 daily, similar to the adult decrease to 35 mg daily
	Micafungin (Mycamine)	100–150 mg/day	2–10 mg/kg/day	Very dependent on age of child; neonates require far higher doses than do older children
	Anidulafungin (Eraxis)	Load: 200 mg daily × 1 day Maintenance: 100 mg daily	Load: 3 mg/kg/day × 1 day Maintenance: 1.5 mg/kg/day	

[a] ABLC is recommended officially at 5 mg/kg/day, ABCD at 3–5 mg/kg/day, and L-AmB at 3–5 mg/kg/day; IV, intravenous. Most clinical data have been obtained with the use of these preparations at 5 mg/kg/day, and most clinicians use and prefer this higher dosing. (Note: ABCD is no longer available in the US.)

Polyenes

Amphotericin B

Mechanism of Action.

The oldest antifungal class is the polyene macrolides—

amphotericin B and nystatin. After initial approval for use in 1958, AMB-D remained for years the gold standard for the therapy of many invasive fungal infections, as well as the comparator agent for newer antifungal agents. Amphotericin B binds to ergosterol, the major sterol found in fungal cell membranes, creating transmembrane channels resulting in an increased permeability to monovalent cations. Fungicidal activity is believed to be caused by leakage of essential nutrients from the fungal cell. Despite its broad spectrum of activity, there are notable intrinsically resistant organisms, such as *Aspergillus terreus*.[7]

Pharmacology and Toxicities.

Amphotericin B is given as an intravenous (IV) formulation, with once-daily dosing because of its prolonged half-life. Cerebrospinal fluid (CSF) and intraocular concentrations are <5% of serum concentrations. However, amphotericin B and its derivatives have been used successfully to treat invasive fungal infections of the central nervous system (CNS), often in combination with a second agent. The primary route of elimination is unknown. Although a small portion of elimination occurs through the kidneys and biliary tract, serum levels are not affected by renal or hepatic impairment. Although not needed to account for differences in drug exposure, dose adjustment may be considered in patients with renal impairment with the goal of reducing further nephrotoxicity and likely best through moving to alternate-day dosing. Amphotericin B is highly protein bound and poorly dialyzable. It has few direct drug interactions, although additive nephrotoxicity can be seen when it is used concurrently with other nephrotoxic drugs.

The fungicidal activity of amphotericin B is concentration dependent, increasing directly with the amount of drug attained at the site of infection, but beginning to plateau at concentrations 4 to 10 times higher than the minimal inhibitory concentration (MIC) of the organism.[8,9] Amphotericin B also has a prolonged post-antifungal effect, allowing antifungal activity to persist even after the concentration of drug falls below the MIC of the organism.[10] Despite in vitro data suggesting a benefit of escalating drug concentrations, there is no conclusive clinical evidence that doses higher than 1 mg/kg/day of AMB-D are necessary for successful therapy.[11]

The major dose-limiting toxicity of conventional amphotericin B is nephrotoxicity, which is related to binding of cholesterol in distal renal tubule cell membranes, where the drug concentrates. In addition, amphotericin B stimulates release of proinflammatory cytokines from mononuclear cells, accounting for infusion-related toxicities including fever, chills, and headache. Several lipid formulations of amphotericin B have been developed to reduce these toxicities. The FDA approved amphotericin B lipid complex (ABLC) in 1995, amphotericin B cholesteryl sulfate complex (amphotericin B colloidal dispersion, ABCD) in 1996, and liposomal amphotericin B (L-AmB) in 1997.

Although the exact mechanism by which lipid amphotericin B formulations reduce toxicity is unknown, several potential mechanisms have been proposed. These include stabilization of the drug in a self-associated state so that it cannot interact with the cholesterol of human cellular membranes, and preferential binding to serum high-density lipoproteins, leading to slower release of amphotericin B to the kidney compared with conventional amphotericin B that is bound to low density lipoproteins.[12] In addition, compared with AMB-D, lipid amphotericin B formulations have greater distribution to the reticuloendothelial system and lower distribution to the kidney (as another potential reason for reduced toxicity).[13,14]

Clinical studies show favorable tolerability of therapy with lipid amphotericin B formulations, both in adults and children. A multicenter, maximal-tolerated-dose study of L-AmB in adults using doses from 7.5 to 15 mg/kg/day found a nonlinear plasma pharmacokinetic profile with a maximal concentration at 10 mg/kg/day and no demonstrable dose-limiting nephrotoxicity or infusion-related toxicity.[15] A randomized clinical trial comparing L-AmB at a standard dose of 3 mg/kg/day and a higher dose of 10 mg/kg/day failed to show any improvement in efficacy and yielded more nephrotoxicity with the higher dose.[16] Currently, standard doses of 3 to 5 mg/kg/day L-AmB are recommended.

Although amphotericin B–related nephrotoxicity generally is less severe in infants and children than adults, likely because of more rapid clearance of the drug, comparatively lower rates of nephrotoxicity have been observed in children and neonates receiving lipid formulations.[17–19] A pharmacokinetic study of L-

AmB conducted in 39 children observed no dose-related trends in adverse events and identified a maximally tolerated dose of 10 mg/kg/day.[20] These results are similar to those observed in adults.[15]

Although there are anecdotal reports of using conventional amphotericin B in numerous instillation or irrigation methods (including intrathecal, intrapleural, or intra-articular instillation or bladder irrigation), there are no controlled data to support these uses. Often the drug irritates the surrounding tissue, potentially creating more side effects than clinical benefit. Inhaled amphotericin B has been used successfully as antifungal prophylaxis in lung transplant recipients but has not been shown to be effective as adjunctive therapy in a broader patient population. Intravitreal injection of amphotericin B has been used to treat fungal endophthalmitis.

Clinical Experience and Pediatric Data.

The optimal duration of amphotericin B therapy is unknown but likely is dependent on the underlying disease, extent of fungal infection, and recovery of host immune function. Several pathogen-specific guidelines have been published and include recommendations for dose and duration of amphotericin B–based treatment regimens.

Although mortality was slightly lower in patients treated with L-AmB compared with conventional AmB in one study with a small number of patients,[21] and a lower rate of breakthrough fungal infections occurred in another study of patients treated empirically for febrile neutropenia,[22] other comparative studies have shown similar clinical outcomes for patients treated with amphotericin B lipid formulation and those treated with conventional amphotericin B.[23] A study of 56 infants with candidiasis, including 52 preterm infants, showed no differences in mortality or time to resolution of candidemia between neonates receiving conventional AMB-D (n = 34), L-AmB (n = 6), or ABCD (n = 16).[24] The decision to prescribe a lipid formulation of amphotericin B should be based on the potential for reduced nephrotoxicity or infusion-related toxicity rather than anticipated therapeutic benefit. In US children's hospitals, utilization of lipid formulations of amphotericin B has increased since their introduction, such that they are now more commonly used than conventional AMB-D.[25]

Evidence supporting the use of amphotericin B and its lipid formulations in children is derived largely from extended clinical experience and nonrandomized studies demonstrating tolerability and efficacy when used for treatment of invasive fungal infections.[17–20] Although newer agents with improved tolerability and efficacy have emerged for conditions such as invasive aspergillosis, AMB-D and its lipid formulations remain important in the therapy of cryptococcal meningitis, severe manifestations of endemic mycoses, mucormycosis, and neonatal candidiasis, and for patients with resistant fungal pathogens or contraindications to other agents.

Pyrimidine Analogues

5-Fluorocytosine

Mechanism of Action.

5-Fluorocytosine (5-FC) is a fluorinated analogue of cytosine that has antimycotic activity resulting from the rapid conversion of 5-FC into 5-fluorouracil (5-FU) within susceptible fungal cells.[26] 5-FU inhibits fungal protein synthesis following incorporation into fungal RNA in place of uridylic acid or through inhibition of thymidylate synthetase, thus inhibiting fungal DNA synthesis. 5-FC has little inherent activity against molds, and most reports describe clinical failure with monotherapy against yeast infections. Antifungal resistance develops quickly on 5-FC monotherapy, so the drug should be used only in combination with other agents. 5-FC is thought to enhance the antifungal activity of amphotericin B, especially in anatomic sites where amphotericin B penetration is poor, such as CSF, heart valves, and the ocular vitreous fluid.[27] One explanation for the synergy detected with amphotericin B and 5-FC is that the membrane-permeabilizing effects of low concentrations of amphotericin B facilitate penetration of 5-FC into the cell interior.[28]

Pharmacology and Toxicities.

5-FC is well absorbed after oral administration.[26] It is small, highly water soluble, and not highly protein bound, so it distributes widely, attaining therapeutic concentrations in most body sites, including CSF, vitreous and peritoneal fluids, and inflamed joints.[26] Because it often is technically difficult to treat neonates with 5-FC because of the large volume required when using the oral formulation and the lack of an IV formulation available in the US, 5-FC is no longer recommended for treatment of neonatal candidiasis.

5-FC toxicity appears to be due to its conversion to 5-FU, with reports of serum 5-FU concentrations in the range found after chemotherapeutic doses.[29] 5-FC can exacerbate myelosuppression in patients with neutropenia, and trough serum concentrations of ≥100 µg/mL are associated with bone marrow aplasia. Therefore, 5-FC serum concentrations should be monitored closely and levels maintained at approximately 40 to 80 µg/mL. In a multicenter trial of 194 patients who received AMB-D plus 5-FC for cryptococcal meningitis, hematologic toxicity appeared in the first 2 weeks of therapy in 56% of patients and in the first 4 weeks of therapy in 87%.[30] Neonates have slower clearance of 5-FC and are more susceptible to having serum levels exceeding the recommended therapeutic range.[31] Clearance is through the kidneys, and the interval between doses should be extended in the setting of renal dysfunction.

Clinical Experience and Pediatric Data.

A pivotal trial showed that the combination of AMB-D plus 5-FC was more effective than AMB-D alone in the treatment of cryptococcal meningitis.[32] A subsequent multicenter study of 194 patients with cryptococcal meningitis concluded that 4 weeks of AMB-D plus 5-FC was adequate for immunocompetent patients without neurologic complications such as hydrocephalus. However, among immunocompromised patients, 6 weeks of combination therapy resulted in fewer relapses.[33] AMB-D in combination with 5-FC currently is recommended as initial therapy for cryptococcal meningitis.[34] These two agents also are suggested for use in patients with candidal meningitis or endocarditis.[35] Although there are many historic reports of 5-FC combined with AMB-D to penetrate difficult sites of infection such as the joints, eyes, or CNS, this use for 5-FC has diminished with the advent of newer antifungal agents.

There are limited data regarding the use of 5-FC in children. One review of 17 cases of candidal meningitis (including 11 patients younger than 12 months of age) noted improvement in 15 patients treated with AMB-D plus 5-FC.[36]

Azoles

The azole antifungal agents are heterocyclic synthetic compounds that inhibit the fungal cytochrome $P450_{14DM}$ (lanosterol 14α-demethylase), which catalyzes a late step in ergosterol biosynthesis. The drugs bind through a nitrogen group in their 5-membered azole ring to the heme group in the target protein and block demethylation of the C14 of lanosterol, leading to substitution of methylated sterols in the membrane and depletion of ergosterol. The result is an accumulation of precursors leading to abnormal fungal membrane permeability, membrane-bound enzyme activity, and coordination of chitin synthesis.[37,38] The fungicidal activity of the azoles is organism dependent, with most agents exhibiting fungistatic activity against *Candida* spp.; itraconazole and voriconazole have fungicidal activity against *Aspergillus*.[39]

The azoles are subdivided into imidazoles and triazoles on the basis of the number of nitrogens in the azole ring, with the structural differences resulting in different binding affinities of the azole pharmacophore for the cytochrome P450 (CYP) enzyme system. With the exception of ketoconazole, use of imidazoles is limited to superficial mycoses, and none, including ketoconazole, has activity against molds such as *Aspergillus*. In 2013, the FDA issued a recommendation that, owing to its association with life-threatening hepatotoxicity and adrenal insufficiency, oral ketoconazole should not be used as first-line therapy for any fungal infection and should be used only for treatment of endemic mycoses if alternative antifungal therapies are lacking.

Fluconazole

Pharmacology and Toxicities.

Fluconazole is a triazole that was approved by the FDA in 1990 for therapy of cryptococcosis and *Candida* infections. Fluconazole also has activity against endemic mycoses, but no activity against the opportunistic molds. Available in oral and IV formulations, oral fluconazole is >90% bioavailable. Unchanged drug is predominantly cleared by the kidneys; metabolism accounts for only a minor proportion of fluconazole clearance.[40] Dose adjustment is indicated in the setting of impaired renal function. Fluconazole distributes into tissues and fluids rapidly, probably owing to its relatively low lipophilicity and limited binding to plasma proteins. Drug concentrations in CSF and vitreous fluid are approximately 80% of those found in blood.[41] Concentrations of fluconazole are 10- to 20-fold higher in the urine than blood, making fluconazole particularly appropriate for the therapy of fungal urinary tract infections.

The pharmacokinetics of fluconazole differ between adults and children. Except in neonates, fluconazole clearance is more rapid in children than adults.[40] The mean plasma half-life is approximately 20 hours in children, compared with 30 hours in adults. Therefore, to achieve comparable drug exposure, the daily fluconazole dose needs to be approximately doubled, to 6 to 12 mg/kg/day, for children older than 3 months.

The volume of distribution of fluconazole is greater and more variable in neonates than in older infants and children. Clearance of fluconazole is lower in neonates than in adults and older children and, in a population pharmacokinetic study, was found to vary based on weight, gestational age, and postanatal age.[42] Therefore, neonates should be treated with a higher dose of fluconazole to compensate for increased volume of distribution, but less frequent dosing because of slower clearance. Because of the long half-life of fluconazole in neonates, patients require at least 8 days to reach steady-state.[43] A pilot study of a 25-mg/kg loading dose of fluconazole in neonates demonstrated faster attainment of target drug exposure without demonstrable adverse effects.[44]

Fluconazole exhibits concentration-independent activity against fully susceptible *Candida* isolates but concentration-dependent activity against dose-dependent (less) susceptible isolates.[10] The ratio of fluconazole dose to MIC has been shown to correlate with clinical response in adults with invasive candidiasis; a target ratio of at least 400 is recommended for most patients, with a ratio of at least 800 recommended as a target for critically ill patients.[45] In children, this target exposure is more likely to be achieved at doses of 12 mg/kg daily. Side effects of fluconazole are uncommon. In a study of 24 immunocompromised children, elevated serum hepatic transaminases were observed in only 2 cases.[46] Another review of 562 children confirmed that pediatric results mirror the excellent safety profile of adults. The most common side effects were gastrointestinal upset (7.7%) and skin rash (1.2%).[47] Through interaction with the CYP enzyme system, fluconazole can increase blood levels of various medications, including cyclosporine and tacrolimus, albeit to a lesser degree than mold-active triazoles.

Clinical Experience and Pediatric Data.

In one clinical trial of 206 nonneutropenic adults with invasive candidiasis, the rate of successful therapy with 0.5 to 0.6 mg/kg/day of AMB-D (79%) was similar to that of 400 mg/day of fluconazole (70%).[48] Another multicenter trial of 219 nonneutropenic adults with invasive candidiasis found that those treated with a combination of fluconazole plus AMB-D ($n = 112$) showed no difference in time to blood sterilization compared with those treated with fluconazole alone ($n = 107$).[49] Although a secondary analysis suggested that combination therapy was superior in efficacy to fluconazole alone, the difference in favorable outcome was small (69% vs. 56%; $P = 0.043$). Currently, there is no definitive evidence supporting the benefit of this combination therapy to treat invasive candidiasis.

Early, uncontrolled studies demonstrated favorable outcomes (clinical cure rates ranging from 83% to 97%) when fluconazole was used for treatment of invasive fungal infections in infants and children who were unresponsive or intolerant to standard antifungal therapy.[50] A subsequent prospective randomized study that compared fluconazole with AMB-D in 24 infants with candidemia noted increased convenience of therapy with fluconazole and a slight, but not statistically significant, survival benefit among those treated with fluconazole (67%) versus (55%), respectively.[51] Of note, early studies evaluating fluconazole for treatment of invasive fungal infections generally studied lower doses than those currently recommended to achieve adequate drug exposure.

Fluconazole also has been evaluated for antifungal prophylaxis. Randomized, placebo-controlled clinical trials have demonstrated that prophylactic fluconazole following allogeneic bone marrow transplantation results in lower rates of candidal infection and graft-versus-host disease.[52] Studies conducted in adult HSCT recipients demonstrated that 200 mg/day of fluconazole is comparable in efficacy to low-dose AMB-D and to fluconazole at a dose of 400 mg/day.[53,54] Randomized, placebo-controlled trials have shown that fluconazole prophylaxis reduces the incidence of fungal colonization and invasive candidiasis among very low birth weight neonates in neonatal intensive care units with a high burden (≥15%) of candidiasis.[55–57] A randomized controlled trial conducted in 361 extremely low birth weight neonates from neonatal intensive care units with a lower incidence of candidiasis did not show a significant benefit of fluconazole prophylaxis for reduction in the composite outcome of mortality or invasive candidiasis.[58]

Itraconazole

Pharmacology and Toxicities.

Itraconazole has been available for clinical use since 1990. Compared with fluconazole, itraconazole has an expanded spectrum of activity, including *Aspergillus*, but it has erratic bioavailability and is more prone to drug-drug interactions. In the US, itraconazole is only available in oral formulations (capsule and solution). Oral bioavailability is highly variable and is greater for the solution formulation than the capsule. Absorption of the capsule formulation is affected by gastric pH; acid-suppressant medications may decrease drug absorption, whereas acidic beverages may enhance absorption. Administration of the capsular formulation with food increases absorption, but the oral suspension is better absorbed on an empty stomach and is not affected by gastric pH. Itraconazole is highly protein bound, but unbound itraconazole distributes widely to tissues, including bone; it has relatively poor penetration of CSF and ocular fluid. Itraconazole is eliminated primarily through hepatic metabolism; there is no need for dosage adjustment in the presence of impaired renal function.[38]

Serum concentrations of itraconazole are much lower in children than in adults after administration of the oral solution. This is especially true in children younger than 5 years.[59] Therefore children usually need twice-daily dosing, whereas once-daily dosing is appropriate for adults. Because of the importance of effectively monitoring itraconazole concentrations, as well as its erratic absorption, clinicians should use caution when using itraconazole in children.

Itraconazole can be difficult to tolerate, with nausea and vomiting (due to the cyclodextrin vehicle) occurring in about 10% of subjects and elevated serum hepatic transaminases in 5%.[60] Rare cases of cardiomyopathy have been reported in adults, but no cases have been described in children. Itraconazole is a potent inhibitor of the CYP3A4 enzyme and therefore can result in important drug interactions. Prior or concurrent use of rifampin, phenytoin, carbamazepine, and phenobarbital should be avoided, and concomitant use with cyclophosphamide should be discouraged.[61] Drugs metabolized by the CYP3A4 pathway that normally have low bioavailability, extensive first-pass metabolism, or narrow therapeutic index—such as cyclosporine and tacrolimus—are especially vulnerable to interactions.[62]

Clinical Experience and Pediatric Data.

Itraconazole has roles in the therapy of numerous fungal infections, including sporotrichosis, endemic mycoses such as coccidioidomycosis,[63] histoplasmosis,[64] and others; superficial mycoses; and allergic bronchopulmonary aspergillosis. There are limited data regarding its use to treat invasive aspergillosis, and its variable absorption and lack of an IV formulation limit use for this condition, in favor of newer triazoles such as voriconazole and posaconazole.[65] However, itraconazole has been evaluated for prophylaxis against *Aspergillus* and *Candida* infections in immunocompromised patients and may be preferable to fluconazole for patients at high risk for invasive aspergillosis. A meta-analysis comparing antifungal prophylaxis strategies for patients undergoing chemotherapy or HSCT found no significant difference in overall mortality or incidence of invasive fungal infections when all studies comparing itraconazole and fluconazole were combined, but when trials of the itraconazole oral suspension form (with greater bioavailability) were analyzed separately, there was a significant reduction in invasive fungal infections with itraconazole.[66] Overall, adverse events leading to discontinuation were more common in patients receiving itraconazole.

There are no pivotal studies of itraconazole prophylaxis in children, and the few children enrolled in the larger prophylaxis studies were not analyzed separately. A phase 1 study in 26 HIV-infected children showed that itraconazole solution was well tolerated and efficacious against oropharyngeal candidiasis, including cases caused by fluconazole-resistant isolates.[67] A single-center nonrandomized study showed similar rates of breakthrough fungal infection (4%–6%) and adverse events (8%–14%) comparing children who received itraconazole ($n = 50$), voriconazole ($n = 50$), or posaconazole ($n = 50$) for antifungal prophylaxis after allogeneic HSCT.[68]

Voriconazole

Voriconazole is a second-generation triazole and a synthetic derivative of fluconazole. Voriconazole combines the broad spectrum of antifungal activity of itraconazole with the increased bioavailability of fluconazole. It is fungicidal against *Aspergillus* and fungistatic against *Candida* spp.[39]

Pharmacology and Toxicities.

Voriconazole is available in IV, oral tablet, and oral suspension formulations. In adults, oral bioavailability is >90%; however, oral bioavailability is more modest in children, ranging from 44% to 65%.[69,70] Pharmacokinetic modeling suggests that this difference can be accounted for by intestinal first-pass metabolism occurring in children, but not adults.[71] Voriconazole is distributed extensively to tissues, including the CNS, and has been used successfully to treat CNS fungal infections.[72,73] Voriconazole undergoes extensive hepatic metabolism by the cytochrome P450 system, and dose adjustment is recommended in individuals with hepatic impairment. High interpatient variability has been observed in voriconazole drug concentrations over a range of doses and coincides in part with genetic polymorphisms in the CYP enzymes.[74] As a result of genetic polymorphisms in the gene encoding CYP2C19, some individuals are poor metabolizers and some are extensive metabolizers.[75] About 5% of white people and 15% to 20% of non-Indian Asians have a slow-metabolizer phenotype.

In addition to genetic variation in voriconazole metabolism, there are important age-related differences with implications for pediatric dosing. In contrast to adults and older children in whom voriconazole metabolism is nonlinear (resulting in marked increases in drug exposure related to relatively small changes in dose), young children have linear metabolism and therefore require much larger proportional doses to achieve adequate drug exposure. This linearity was first identified by initial pharmacokinetic analysis of children from 2 to 11 years old in whom a dose of 4 mg/kg twice daily was needed to provide equivalent drug exposure to adults receiving a dose of 3 mg/kg twice daily.[76] A subsequent population pharmacokinetic study predicted that an IV dose of 7 mg/kg twice daily for children younger than 12 years provided exposure similar to that of adults.[69] However, studies using therapeutic drug monitoring to guide voriconazole dosing have shown that even higher doses are required in many cases to achieve goal trough concentrations >1 µg/mL, with a median dose of 16 mg/kg/day required in children 2 to 12 years of age.[70,74,77] Given the substantial interindividual variability in voriconazole pharmacokinetics, therapeutic drug monitoring of voriconazole levels is recommended to gauge adequacy of treatment and to avoid potential toxicities; target trough concentrations between 1 and 5 µg/mL are recommended.[78]

Main side effects of voriconazole include reversible dose-dependent visual disturbances (increased brightness, blurred vision)[79] in as many as one third of treated patients; elevated serum hepatic transaminases with higher doses[80]; and occasional skin reactions, likely due to photosensitization.[37,81] Less common but serious toxicities include neurotoxicity with prominent visual hallucinations,[82] which is associated with serum trough levels above 5.5 µg/L and must be distinguished from the more common visual disturbances, and prolongation of the QT interval with associated cardiac arrhythmias.[83] Similar to the other triazoles, drug interactions can be problematic owing to inhibition of the CYP enzyme system. For instance, concomitant use with sirolimus can increase concentrations of the immunosuppressant 2- to 10-fold.[84] Intravenous voriconazole is solubilized in sulfobutyl ether β-cyclodextrin (SBECD), and because elimination of cyclodextrin is dependent on glomerular filtration, the vehicle can accumulate in patients with severely impaired renal function; clinical significance of accumulation has not been determined fully.

Clinical Experience and Pediatric Data.

In a randomized clinical trial comparing primary therapy for 277 patients with invasive aspergillosis, voriconazole demonstrated superiority to conventional AMB-D, with >50% of those initially treated with voriconazole achieving complete or partial response, compared with 30% of those treated with conventional AMB-D.[85] Improved survival and tolerance of therapy also were observed among those initially treated with voriconazole. Similar positive experience with voriconazole was noted in an open-label multicenter study of 116 patients with invasive aspergillosis treated with voriconazole as either primary (60 patients) or salvage (56 patients) therapy.[86] Additional analyses also have shown the significant benefit of early administration of voriconazole over AMB-D.[87,88] These data have led voriconazole to be guideline-recommended first-line therapy for invasive aspergillosis.[89]

Despite fungistatic activity against *Candida* spp., voriconazole also is effective in the treatment of *Candida* infections. In a multicenter randomized controlled trial evaluating therapy of esophageal candidiasis in 391 immunocompromised patients, voriconazole was successful in 98% and fluconazole in 95%.[90] In another study of 422 patients with invasive candidiasis, approximately 40% of patients were successfully treated with voriconazole. This rate of success was equivalent to that of AMB-D followed by oral fluconazole.[91]

Voriconazole has been evaluated as empiric antifungal therapy for persistent febrile neutropenia. In a randomized controlled trial including 837 patients with fever and neutropenia, the composite outcome of overall success was similar for patients receiving voriconazole (26%) compared with those receiving L-AmB (30%). More breakthrough fungal infections were diagnosed in patients receiving L-AmB (5.0% vs. 1.9%, $P = 0.02$).[92] Studies evaluating voriconazole for prophylaxis against fungal infections in immunocompromised patients have demonstrated similar efficacy to fluconazole (in the context of intensive monitoring and structured empiric therapy),[93] and superiority to itraconazole[94] and low-dose AMB-D (primarily regarding tolerability).[95]

No comparative study has evaluated efficacy of voriconazole compared with other agents for treatment of invasive fungal infections in children. An open-label, compassionate-use evaluation of the drug in 58 children with proven or probable invasive fungal infection refractory to or intolerant of conventional antifungal therapy demonstrated complete or partial response to therapy in 43% of children with aspergillosis, 50% with candidemia, and 63% with scedosporiosis.[96] Other studies have evaluated pharmacokinetics and safety of voriconazole in children, including at higher drug doses currently recommended.[70,97] In a prospective cohort study of children with proven or probable invasive mold infections, 95 of 131 patients received voriconazole either as monotherapy or in combination with other antifungal agents; overall, 60% of patients had a complete or partial response to therapy.[98]

Voriconazole has not been tested formally in neonates. Because of the reports of visual adverse events in adults and children, there is concern about unknown interactions with the developing retina, and there are no planned clinical trials in neonates.

Posaconazole

Pharmacology and Toxicities.

Posaconazole is a second-generation triazole that became available in the US in 2006. It is closely related to itraconazole, is fungicidal in vitro against *Aspergillus,* and has activity against the Mucorales (agents of mucormycosis), which is an advantage over voriconazole.[99] Posaconazole initially was available only as an oral suspension, but delayed-release tablets and an IV formulation now are available. Both oral formulations are approved by the FDA for use in children 13 years and older; the IV formulation is approved for individuals 18 years and older. The pharmacokinetics and appropriate dosing differ for each formulation. Absorption of the oral suspension is variable and is improved greatly when given with a high-fat meal or in multiple divided doses.[100,101] Absorption of the tablet formulation is less variable and is not dependent on food intake; tablet also can be given once daily, with the 300-mg daily adult dose achieving similar drug exposure to the 200 mg oral suspension dose given 3 times daily.[102] Posaconazole has dose-proportional pharmacokinetics up to 800 mg/day and has a large apparent volume of distribution with slow elimination, suggesting extensive distribution into tissues.[101] Posaconazole has lower CNS penetration than voriconazole; however, there are well-documented cases of clinical success for treatment of CNS fungal infection.[103] Posaconazole is metabolized by glucuronidation and primarily eliminated through the fecal route. Mild or moderate chronic renal impairment has no appreciable effect on the pharmacokinetics of oral posaconazole, but avoidance of the IV formulation is recommended in the setting of moderate or severe renal impairment owing to potential accumulation of the vehicle, SBECD.[104]

Posaconazole is an inhibitor of CYP3A4 metabolism and P-glycoprotein transport and is subject to drug interactions with substrates for these pathways, such as calcineurin inhibitors or benzodiazepines. Posaconazole generally is well tolerated; the most commonly observed side effects are gastrointestinal symptoms with the oral suspension.[105] Rare but serious adverse events include hepatotoxicity and QT interval prolongation with associated cardiac arrhythmias.[99] Administration of the IV formulation as a slow infusion through central venous catheter is recommended because of infusion-site reactions noted with repeated administration.

One retrospective study analyzed the pharmacokinetic profile of posaconazole for 12 pediatric patients (<18 years old) with resistant or refractory invasive fungal infections. These patients received a maintenance dose of 800 mg/day of posaconazole oral suspension given in 2 or 3 divided daily doses, compared with adult patients (18–64 years old) who received a maintenance dose of 800 mg/day. The overall success rate and adverse event profile were similar for pediatric and adult patients.[106] These preliminary data suggested that posaconazole pharmacokinetics are similar in adults and the children examined in this study, but a complete pediatric pharmacokinetic study is underway.

Clinical Experience and Pediatric Data.

Posaconazole has been best studied as antifungal prophylaxis, including a large randomized controlled trial in patients with acute myelogenous leukemia or myelodysplastic syndrome, which demonstrated fewer invasive fungal infections (2%) with posaconazole versus either fluconazole or itraconazole (8%). Survival also was significantly longer in patients who received posaconazole.[107] Similarly, in patients with active graft-versus-host disease, posaconazole was similar to fluconazole in preventing any invasive fungal infection, but superior to fluconazole in preventing invasive aspergillosis as well as reducing deaths due to invasive fungal infections.[108]

Posaconazole also has been evaluated for treatment of oropharyngeal and esophageal candidiasis in HIV-infected patients. Posaconazole demonstrated comparable efficacy with fluconazole in the initial treatment of oropharyngeal candidiasis, and significantly lower rates of relapse.[109] Posaconazole also performed favorably in treatment of oropharyngeal or esophageal candidiasis refractory to treatment with fluconazole or itraconazole; a favorable clinical response was observed in 75% to 85% of cases.[110,111]

Although current FDA-approved indications are limited to antifungal prophylaxis and oropharyngeal candidiasis, promising data have emerged for posaconazole in treatment of other invasive fungal infections. Posaconazole showed a survival benefit over historical controls in treating invasive aspergillosis as salvage antifungal therapy,[112] and demonstrated a success rate of 72% in treating invasive aspergillosis that was refractory to voriconazole,[113] but posaconazole has not been examined as primary therapy. Owing to lack of voriconazole activity against the Mucorales group, there is excitement because of posaconazole activity in vitro as well as clinical efficacy as a salvage therapy against these emerging infections.[114] A review of 96 case reports describing posaconazole as combination or second-line therapy for mucormycosis found an approximately 70% rate of complete or partial response, but the true success rate likely is lower because of publication bias.[115] Small, uncontrolled studies also have suggested a role for posaconazole in the treatment of coccidioidomycosis.[116,117]

Experience with posaconazole in children is limited. A retrospective cohort study of 60 children younger than 12 years who received posaconazole prophylaxis after allogeneic HSCT demonstrated no breakthrough invasive fungal infections occurring during the prophylaxis period (up to 200 days after transplantation) and no severe adverse events.[118] The oral suspension was given at doses of either 5 mg/kg/dose twice daily or 4 mg/kg/dose 3 times daily, with higher trough levels noted on the 3-times-daily regimen. An open-label study of 8 patients with chronic granulomatous disease and invasive mold infection treated with posaconazole salvage therapy included 7 pediatric patients. All patients had received itraconazole prophylaxis and had prior antifungal therapy with either voriconazole, caspofungin, or a lipid formulation of amphotericin B.[119] There was complete response with posaconazole in 7 of 8 patients, including 6 of 7 pediatric patients. A subsequent multicenter retrospective survey of 15 children 3 to 17 years of age with invasive fungal infections refractory to first-line therapy demonstrated complete or partial response to posaconazole therapy in 9 patients and no severe adverse events, although mild adverse events were reported in 11 patients.[120] Posaconazole will have an important role in antifungal management in the future, but devoted pediatric clinical studies, to determine both the optimal dosing in children and comparative efficacy, have yet to be performed.

Isavuconazole

Pharmacology and Toxicities.

Isavuconazole, formulated in IV and oral capsule preparations as a prodrug, isavuconazonium sulfate, was approved by the FDA in 2015 for treatment of invasive aspergillosis and mucormycosis in adults. Isavuconazole has a broad spectrum of activity including *Candida, Cryptococcus, Aspergillus,* and the Mucorales, combined with a favorable pharmacokinetic profile.[121] The prodrug, isavuconazonium, is rapidly cleaved by plasma esterases to isavuconazole. Oral bioavailability is 98% with low intersubject variability and no clinically significant food effect.[122,123] It is water soluble with high protein binding and a large volume of distribution, indicating likely high tissue penetration. Animal studies indicate good CNS penetration and likely efficacy in CNS infection.[124] It exhibits dose-proportional pharmacokinetics with moderate deviation from linearity.[122,123] Elimination is primarily through hepatic metabolism; prolonged half-life allows once-daily dosing after initial loading doses.[122,123] Because of high water solubility, the IV formulation of isavuconazole does not require the SBECD carrier that is needed for voriconazole and posaconazole IV formulations; thus it can be used in the setting of significant renal impairment without risk for accumulation.

Isavuconazole is both a substrate and an inhibitor of CYP3A4 and is therefore subject to clinically significant drug-drug interactions with CYP3A4 substrates, inhibitors, or inducers. The most frequently reported adverse events in clinical trials are gastrointestinal symptoms, headache, elevated serum hepatic enzyme concentrations, hypokalemia, dyspnea, cough, peripheral edema, and back pain.[125,126] The overall occurrence rates of adverse events were similar between isavuconazole and voriconazole, but drug-related adverse events were less frequent with isavuconazole, and the frequency of dermatologic and visual adverse events was lower with isavuconazole.[125,126] The frequency and severity of hepatotoxicity also was lower with isavuconazole. Isavuconazole causes dose-related shortening of the QT interval; although the clinical significance of this effect is uncertain, it is contraindicated in individuals with familial short QT syndrome.[126]

Clinical Experience and Pediatric Data.

In a phase 2 randomized controlled trial comparing three isavuconazole oral dosing regimens (including a once-weekly regimen) with oral fluconazole for treatment of esophageal candidiasis in immunocompromised patients, all three regimens were noninferior to fluconazole.[127] Rates of endoscopically confirmed cure were 95% to 98% for the isavuconazole regimens and 95% for fluconazole. Another phase 2 dose-escalation study evaluated IV isavuconazole for antifungal prophylaxis in 20 patients with neutropenia during chemotherapy for acute myeloid leukemia, with a primary end point of safety.[128] Doses of 200 mg and 400 mg once daily were well tolerated with no serious drug-related adverse events; two patients in the low-dose group were diagnosed with possible invasive fungal infections. A phase 3 randomized controlled trial compared isavuconazole with voriconazole for treatment of invasive aspergillosis and other invasive mold infections in 516 immunocompromised adults.[126] On the primary end point of all-cause mortality at 6 weeks, isavuconazole was noninferior to voriconazole, with 18.6% mortality versus 20% mortality for voriconazole. Overall treatment success at the end of treatment was also comparable between groups. An open-label noncomparative trial evaluated isavuconazole for treatment of 37 patients with proven or probable invasive mucormycosis, either as primary or salvage therapy.[126] All-cause mortality at 6 weeks was 38%, and overall response at end of therapy was 31%; in light of the severe natural history of invasive mucormycosis, this trial supports clinical efficacy of isavuconazole in the treatment of mucormycosis. An additional clinical trial is underway evaluating isavuconazole for treatment of invasive candidiasis. There are currently no reported pediatric clinical studies of isavuconazole.

Echinocandins

An entirely new class of antifungal agents compared with long previous development of modified existing classes, the echinocandins, interferes with cell wall biosynthesis by noncompetitive inhibition of 1,3-β-D-glucan synthase, an enzyme present in fungi but absent in mammalian cells.[37] This enzyme produces 1,3-β-D-glucan, which forms a fibril of three helically entwined linear polysaccharides and provides essential structural integrity to the fungal cell wall.[129,130]

Echinocandins are fungicidal against *Candida* but fungistatic against *Aspergillus* because they inhibit hyphal tip and branch point growth, converting the mycelium to small clumps of cells; older septated cells with little glucan synthesis are not killed.[131] Echinocandins are not metabolized through the CYP enzyme system, lessening some of the drug interactions and side effects seen with the azoles. Because of their large molecular weights, the echinocandins have poor oral bioavailability and therefore are only available as parenteral formulations. All three are highly protein bound and have relatively poor distribution to the CNS, ocular fluids, and urine. Because 1,3-β-glucan is a selective target present only in fungal cell walls and not in mammalian cells, the echinocandins have few adverse effects.[129] Important pharmacologic distinctions are reviewed briefly for each agent.

Caspofungin

Pharmacology and Toxicities.

Caspofungin is a semisynthetic derivative of the natural product pneumocandin B_0. Caspofungin has triphasic pharmacokinetics, with modest nonlinearity.[132] Tissue distribution accounts for an initial rapid decline in plasma levels, and subsequently the drug undergoes slow hepatic metabolism through hydrolysis and *N*-acetylation.[132,133] The drug also undergoes spontaneous degradation; these processes together account for a terminal half-life of 27 to 50 hours. Inactive metabolites are excreted in the feces and urine. A loading dose is required to achieve steady-state levels quickly.

At present there is no known maximal tolerated dose and no toxicity-defined maximal length of therapy. Elevations of caspofungin plasma concentrations are observed in patients with mild hepatic insufficiency and a dose reduction in adults from 50 mg to 35 mg daily following the standard 70 mg loading dose is recommended in this setting. Plasma concentrations of tacrolimus are reduced by about 20% when coadministered with caspofungin, but tacrolimus does not alter the pharmacokinetics of caspofungin.[133] Cyclosporine increases the concentration of caspofungin by about 35%, but plasma concentrations of cyclosporine are not altered by coadministration of caspofungin.[133] Rifampin, efavirenz, nevirapine, phenytoin, dexamethasone, and carbamazepine increase the clearance of caspofungin; if caspofungin is coadministered with these drugs, an increased maintenance dose should be considered.[133]

A pharmacokinetic study conducted in 39 children 2 to 17 years of age evaluated caspofungin dosing based on both weight (1 mg/kg/day) and body surface area (50 or 70 mg/m^2/day).[134] Compared with plasma concentrations attained in adults treated with 50 mg/day, the weight-based approach resulted in suboptimal plasma concentrations, whereas the 50 mg/m^2/day dose yielded similar plasma concentrations in children. Caspofungin half-life is approximately one third shorter in children than in adults. Based on this initial study, dosing in children begins with a loading dose of 70 mg/m^2 followed by daily maintenance dosing of 50 mg/m^2. Pharmacokinetic data are limited in neonates, but a dose of 25 mg/m^2 daily in this age group appears to provide drug exposure comparable with an adult dose of 50 mg/day.[135]

A retrospective analysis of compassionate-use caspofungin in 25 immunocompromised children, most of whom also received other antifungal agents, noted that only 3 (12%) had a possible drug-related adverse event, which included hypokalemia and elevated serum bilirubin or hepatic transaminase concentrations.[136] Another study of 64 immunocompromised children revealed that caspofungin was not discontinued in any patients because of adverse events, and clinical adverse events were mild to moderate and observed in 34 patients (53%).[137] Mean serum aspartate aminotransferase and alanine aminotransferase values were slightly higher at end of therapy, but creatinine, bilirubin, and alkaline phosphatase levels were not different from baseline.

Clinical Experience and Pediatric Data.

In a noncomparative clinical trial of 83 adults with invasive aspergillosis who were intolerant of or had infections refractory to conventional antifungal therapy, caspofungin demonstrated potential utility as salvage therapy.[138] Approximately 45% of patients (37/83) had a complete or partial response, including 50% (32/64) with pulmonary aspergillosis and 23% (3/13) with disseminated aspergillosis. Subsequent noncomparative studies evaluating caspofungin as primary therapy for invasive aspergillosis showed complete or partial responses to therapy in 33% of adults with hematologic malignancies or undergoing autologous HSCT,[139] and 42% in adult allogeneic HSCT recipients.[140]

A randomized controlled trial comparing caspofungin with conventional AMB-D in 224 adults with invasive candidiasis found that caspofungin was at least equivalent, with response rates of 81% and 65%, respectively.[141] Caspofungin was at least comparable with AMB-D against all the major species of *Candida*. Mortality was similar in both groups. However, drug-related adverse events were more common in the AMB-D group.[141] Randomized controlled trials comparing caspofungin with L-AmB for empiric therapy of persistent febrile neutropenia have shown that caspofungin was comparable with L-AmB in efficacy in both adults[142] and children.[143]

A multicenter retrospective survey in Germany analyzed 64 immunocompromised children who received caspofungin for refractory infection ($n = 38$), intolerance of standard agents ($n = 10$), or as the best perceived therapeutic option ($n = 16$).[137] Overall survival was 75% at end of therapy, and complete or partial response to therapy was observed in 70% of patients with proven infections and 50% of those with probable infections. A multicenter, open-label comparative study evaluating the safety, tolerability, and efficacy of caspofungin in 49 children with documented

Candida or *Aspergillus* infections found similarly high rates of success as in adults, with success at end of therapy observed in 50% of patients with invasive aspergillosis and 81% of patients with invasive candidiasis.[144] Caspofungin appears to be well tolerated in children.

There are limited reports of caspofungin use in neonates, mainly for salvage therapy in cases of refractory invasive candidiasis.[145]

Micafungin

Pharmacology and Toxicities.

Micafungin is an echinocandin lipopeptide compound with a half-life of approximately 12 hours.[37,146,147] In contrast to caspofungin, micafungin has simple linear elimination kinetics. It undergoes limited hepatic metabolism by arylsulfatase, catechol *O*-methyltransferase, and hydroxylation, with predominantly biliary excretion. Drug-drug interactions are uncommon.

Dosage of micafungin varies with age because of differences in clearance. Particularly in neonates, in whom high drug levels in the CNS are desired, a higher dose is needed to achieve adequate exposure. A study of safety and pharmacokinetics of micafungin in young infants with suspected *Candida* infection found that micafungin doses of 7 and 10 mg/kg/day were well tolerated and provided exposure shown in animal models to be adequate for treatment of CNS infection.[148] In preterm infants, a dose of 15 mg/kg was shown to approximate drug exposure of a 5-mg/kg adult dose.[149] A population pharmacokinetic study based on these clinical studies showed that desired target attainment was likely at a dose of 10 mg/kg/day for most neonates and young infants.[150]

Micafungin doses up to 4.5 mg/kg/day have been shown to be well tolerated in children and adolescents with pharmacokinetics more similar to adults.[151,152] A population pharmacokinetic study of micafungin in children and adolescents found that a dose of 2 mg/kg/day was appropriate for most children to achieve target exposure for treatment of invasive candidiasis.[153]

Clinical Experience and Pediatric Data.

A randomized controlled trial comparing micafungin to L-AmB for treatment of invasive candidiasis in 531 patients found that micafungin was as effective as L-AmB with 89% success rates in each group.[154] There was a lower incidence of adverse events leading to drug discontinuation in the micafungin group. This trial also included children, and a separate analysis of the 106 pediatric patients showed similar findings to the parent study.[155] Micafungin also demonstrated noninferiority to caspofungin for treatment of invasive candidiasis in adults.[156] Other studies have demonstrated the efficacy of micafungin in the primary therapy of esophageal candidiasis[157]

Micafungin was studied in a noncomparative manner in adults and children with invasive aspergillosis, either micafungin alone or in combination with other antifungal agents.[158] A favorable response to therapy was seen in 80 (35%) of 225 of patients; relatively few patients received micafungin monotherapy. In the subset of patients who had undergone hematopoietic stem cell transplantation, the overall complete or partial response rate was 26%.[159]

Micafungin also has been evaluated for use as antifungal prophylaxis. A study conducted in 882 adult and pediatric HSCT recipients found that micafungin was more effective than fluconazole in preventing invasive fungal infections, with 80% remaining infection free in the micafungin arm compared with 74% in the fluconazole arm.[160] This study included 84 patients younger than 16 years and found that the success in those patients was 69% (27/39) in the micafungin arm and 53% (24/45) in the fluconazole arm. Another study comparing micafungin with itraconazole for prophylaxis against invasive fungal infections in HSCT recipients found that micafungin was comparable in efficacy but was better tolerated, with lower rates of drug-related adverse events and greater likelihood of study completion.[161] At present there are no large-scale clinical trial reports of micafungin in neonates.

Anidulafungin

Pharmacology and Toxicities.

Anidulafungin is the most recently developed echinocandin and currently is not licensed for use in children. It does not undergo metabolism but is eliminated through spontaneous degradation with linear kinetics and a terminal half-life of 40 to 50 hours.[162]

Activity in vitro is similar to that of the other echinocandins.[163] Neither end-stage renal impairment nor dialysis substantially alters the pharmacokinetics of anidulafungin.[164] Dose adjustment is not needed for hepatic insufficiency.[162] Tissue concentrations after multiple dosing were highest in lung and liver, followed by spleen and kidney, with measurable concentrations in the brain tissue similar to the other echinocandins. There are no known clinically significant drug-drug interactions. Infusion-related adverse events such as flushing, urticaria, and hypotension have been observed but are reduced by slowing the infusion to less than 1.1 mg/min.[162] Otherwise, anidulafungin is well tolerated.

The pharmacokinetics of anidulafungin in children are similar to those in adults; children receiving a maintenance dose of 0.75 mg/kg/day have similar drug exposure to adults receiving a dose of 50 mg/day (recommended for esophageal candidiasis), and children receiving 1.5 mg/kg/day have similar exposure to adults receiving a dose of 100 mg/day (recommended for invasive mycoses).[165] In neonates and young infants, a maintenance dose of 1.5 mg/kg/day achieved similar exposure to the same weight-based dose in children and to an adult dose of 100 mg/day. Anidulafungin was well-tolerated by both infants and children with no serious drug-related adverse events reported in either pharmacokinetic study.[165,166]

Clinical Experience and Pediatric Data.

A study of 601 patients with esophageal candidiasis compared anidulafungin with oral fluconazole and found successful outcomes of >95% as assessed by endoscopy.[167] A subsequent study found superiority of anidulafungin over fluconazole for treatment of invasive candidiasis, with successful treatment response at end of therapy of 75% versus 60%, respectively, solidifying the role of the echinocandins in treating invasive candidiasis.[168] A multicenter randomized controlled trial is underway comparing anidulafungin with fluconazole for treatment of invasive candidiasis in children.

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294

Topical Antimicrobial Agents

Ishminder Kaur, Jane M. Gould

Topical antimicrobial therapy dates back to ancient times, when a wide variety of substances such as grease, lint oil, wine, and metallic salts were applied to wounds. Since then, topical antibiotics have been developed. They are most frequently used to treat infections affecting the skin and mucous membranes. Agents include topical preparations of parenterally administered antibiotics, as well as antibiotics and antiseptics not given by any other route because of their toxicity. As a general principle, agents used topically should not be those relied on for systemic use because resistance develops rapidly. Precise recommendations for use of topical agents are limited by the difficulty of in vitro assays, establishment of breakpoints for susceptibility, effect of the vehicle on delivery, and lack of clinical efficacy trials. Antifungal and antiviral agents are described in Chapters 293 and 295.

Ophthalmic Therapy

Antibiotics administered topically are used for the prophylaxis and treatment of many ophthalmologic pathogens. Topical agents are used for the prophylaxis of neonatal conjunctivitis, perioperative infections, and ophthalmologic trauma such as corneal abrasions, foreign bodies, and ruptured globes. They are used for the treatment of blepharitis, chronic dacryocystitis, conjunctivitis, corneal ulcers, and endophthalmitis. Selection of an antimicrobial agent should be based on its activity against the most likely pathogenic organisms and lack of adverse effects. Ophthalmic topical antimicrobial agents, their spectrum of activity, and adverse events are shown in Table 294.1.[1–13] Different routes of administration (topical, subconjunctival, retrobulbar, and intravitreal) can be used, depending on the site of infection. Formulations are available as suspensions, ointments, solutions, and extemporaneously prepared "fortified drops" (Table 294.2). To optimize antibiotic delivery, devices impregnated with antibiotics, such as collagen shields that prolong antibiotic contact with ocular surface, have been used for corneal protection after trauma, but lack of clinical trials limit their use in ocular infections.[14,15]

TABLE 294.1

Commercially Available Topical Ophthalmic Antimicrobial Agents

			Spectrum of Activity	
	Concentration	**Mechanism of Action**	**Gram-Positive Organisms**	**Gram-Negative Organisms**[a]
SINGLE AGENTS				
Azithromycin (Azasite)	Solution, 1%	Inhibits protein synthesis	+++	++
Bacitracin (generic)	Ointment, 500 U/g	Inhibits early steps in peptidoglycan biosynthesis, thus inhibiting cell wall synthesis; also changes membrane permeability	+++ (group B *Streptococcus,* usually R)	+ (Enterobacteriaceae and *Pseudomonas* spp. R)
Besifloxacin (Besivance)	Solution, 0.6%	Inhibits DNA gyrase and topoisomerase IV	+++	+++
Chloramphenicol (generic)	Ointment, 1% Solution, 0.5%	Inhibits protein synthesis	++ (*Staphylococcus aureus* R)	+++ (*Pseudomonas* spp. R)
Ciprofloxacin (Ciloxan)	Ointment, solution, 0.3%	Inhibits DNA gyrase	++	+++

Erythromycin (generic)	Ointment, 0.5%	Inhibits protein synthesis	+++	+/− (Enterobacteriaceae and *Pseudomonas* spp. R)
Gatifloxacin (Zymar)	Solution, 0.3%	Inhibits DNA gyrase and topoisomerase IV	+++	++
Gentamicin (generic)	Ointment, 0.3% solution, 0.3%	Inhibits protein synthesis	−	+++
Levofloxacin (Quixen)	Solution, 0.5%	Inhibits DNA gyrase and topoisomerase IV	+++	++
Moxifloxacin (Vigamox)	Solution, 0.5%	Inhibits DNA gyrase and topoisomerase IV	+++	++
Norfloxacin (Chibroxin)	Solution, 0.3%	Inhibits DNA gyrase	++	+++
Ofloxacin (Ocuflox)	Solution, 0.3%	Inhibits DNA gyrase	++	++
Povidone-iodine	Solution, 2.5%	Unknown	+++	+++
Silver nitrate	Solution, 1%	Inhibits DNA replication; modifies cell membrane and disrupts superficial cells[11]	+	++
Sulfacetamide (generic)	Ointment, 10% Solution, 10%, 15%, 30%	Inhibits folic acid synthesis	++	++ (*Pseudomonas* spp. R)
Sulfisoxazole diolamine (Gantrisin)	Ointment, 4% Solution, 4%	Inhibits folic acid synthesis	++	++ (*Pseudomonas* spp. R)
Tetracycline (Achromycin)	Solution, 1%	Inhibits protein synthesis	+	++ (*Pseudomonas* spp. R)
Tobramycin (generic)	Ointment, 0.3% solution, 0.3%	Inhibits protein	−	+++
COMBINATION PREPARATIONS				
Neomycin + Polymyxin	Various concentrations	Inhibits protein synthesis	+	++ (*Pseudomonas* spp.

B/bacitracin + Polymyxin B + Polymyxin B/gramicidin				R)	
Polymyxin B + Bacitracin + Neomycin + Neomycin/bacitracin + Neomycin/gramicidin + Oxytetracycline + Trimethoprim	Various concentrations	Attaches to cell membrane, with disruption of osmotic properties leading to cell death	−	+++ (*Neisseria gonorrhoeae* R, *Proteus* spp. R)	
Trimethoprim + Polymyxin B	Various concentrations	Inhibits dihydrofolic acid reductase	++	++ (*Pseudomonas* spp. and *Neisseria gonorrhoeae* R)	
Gramicidin + Polymyxin B/neomycin	Various concentrations	Uncouples oxidative phosphorylation	++	−	

[a]Gram-negative organisms include *Haemophilus* spp., *Neisseria* spp., Enterobacteriaceae, and *Pseudomonas* spp., unless otherwise indicated.

+++, excellent activity and spectrum; ++, good activity and spectrum; +, fair activity and spectrum; −, no activity; ND, no or limited data; R, resistant.

Data from references 1–14. 2006 Physician's Desk Reference, 60th ed. Thomson PDR, Montvale, NJ.

TABLE 294.2

Commonly Used Fortified Ophthalmic Drops

Antibiotic	Concentration
Amikacin	6.7 mg/mL
Bacitracin	9600 U/mL
Carbenicillin	6.2 mg/mL
Cefazolin	33 mg/mL
Gentamicin	14 mg/mL
Neomycin	33 mg/mL
Oxacillin	66 mg/mL
Penicillin G	333,000 U/mL
Pipercillin	12.5 mg/mL
Ticarcillin	6.3 mg/mL
Tobramycin	5 mg/mL
Vancomycin	31 mg/mL

Adapted from Baum JL. Antibiotic use in ophthalmology. In: Tasman W, Jaeger EA (eds). Duane's Clinical Ophthalmology. Philadelphia, Lippincott-Raven, 1989, pp. 1–20.

Blepharitis

Blepharitis is commonly caused by *Staphylococcus aureus,* and treatment consists of the topical application of an antistaphylococcal agent in ointment form to the eyelids.

Dacryocystitis

Acute dacryocystitis and dacryoadenitis are commonly caused by *S. aureus* and should be treated systemically. Chronic dacryocystitis is not usually infectious, but infection can occur secondary to stasis and obstruction of the lacrimal duct. Treatment consists of relief of the obstruction by irrigation of the lacrimal outflow tract. The use of a topical antibiotic is controversial.[6]

Conjunctivitis

Acute conjunctivitis in children is bacterial in >50% of cases[16]; nontypable *Haemophilus influenzae*, *Streptococcus pneumoniae,* and *Moraxella catarrhalis* are the most common causative agents. Although conjunctivitis usually is self-limited, treatment with topical antibiotics has been shown to hasten the rate of clinical and microbiologic resolution.[17–19] Treatment consists of a topical agent in solution form (sulfacetamide, erythromycin, azithromycin, gentamicin, gatifloxacin, ofloxacin, or besifloxacin) that has activity against major pathogens. Topical preparations of aminoglycosides and fluoroquinolones have been shown to be equally efficacious (84%–90%) in the treatment of acute conjunctivitis,[20] but these topical preparations should be reserved for serious infections when gram-negative bacilli are causative, especially *Pseudomonas aeruginosa.* Further, topical fluoroquinolones (moxifloxacin) were not shown to be superior compared with polymyxin B −trimethoprim in a randomized controlled trial for treatment of acute conjunctivitis in children.[17c] It is important to keep in mind that drops are washed out rapidly in a crying child. In infants, ointments may be preferable for ease of application, but the resultant visual blurring can be discomforting to older children. When otitis media accompanies conjunctivitis, as is frequently the case with nontypable *H. influenzae,* treatment should consist of the administration of an appropriate antibiotic orally; concomitant topical therapy is not necessary. Such is also the case for chlamydial conjunctivitis, which is treated systemically to eradicate nasopharyngeal colonization; topical therapy is not necessary.

Neonatal Conjunctivitis

Antibiotic prophylaxis has greatly reduced the incidence of ophthalmia neonatorum in the United States. The use of topical silver nitrate reduced the incidence of gonococcal ophthalmia neonatorum from 10% to 0.3%.[21] Silver nitrate is no longer available in the United States, causes chemical conjunctivitis in 10% of patients,[22] and has been replaced by ocular prophylaxis using 0.5% erythromycin ointment.[22–24] Neither agent is effective prophylaxis against chlamydial infection. A 2.5% povidone-iodine solution was shown to be effective in preventing ophthalmia neonatorum in a study in Kenya, demonstrating efficacy against *Neisseria gonorrhoeae* similar to that of erythromycin or silver nitrate and superiority against *Chlamydia trachomatis*.[12] In another comparison study conducted in Israel, 1% tetracycline was found to be marginally more effective than 2.5% povidone iodine[25]; however, testing for *C. trachomatis* was limited to serology. In 2015, the Canadian Pediatric Society advocated against universal topical prophylaxis, favoring screening of mothers for *C. trachomatis* and *N. gonorrhoeae*.[26]

Keratitis

Bacterial infections causing corneal ulceration are rare in children and most commonly follow corneal abrasion, a scratch, or a foreign-body injury. Usual bacterial etiologies include *S. aureus,* coagulase-negative staphylococci (CoNS), *S. pneumoniae, M. catarrhalis,* and gram-negative bacilli, especially *P. aeruginosa.*[27] Adequate evaluation and treatment are essential to prevent permanent corneal injury. For existing infection, Gram stain and culture of the ulcer surface are essential to determine the causative organism, direct antimicrobial therapy, and distinguish bacterial keratitis from herpetic and fungal keratitis. Treatment consists of frequent topical administration of antimicrobial agents.

The achievable concentration of antibiotic in corneal stroma after topical application is limited because the corneal epithelium is a barrier to drug transport. The damaged cornea allows greater penetration of antibiotics into the cornea, and lipophilic antibiotics such as chloramphenicol achieve higher concentrations. "Fortified drops" are solutions prepared extemporaneously to contain higher concentrations of antibiotics than available commercially, or antibiotics not commercially available for ophthalmic application; they are used frequently for the treatment of bacterial corneal ulcers and endophthalmitis[6,13] (see Table 294.2). Monotherapy with moxifloxacin 0.5% was shown in a randomized trial to be equally effective compared with combination of fortified antibiotics (cefazolin and tobramycin for treatment of nonperforated bacterial corneal ulcers).[28]

The average drop volume far exceeds the capacity of the inferior cul-de-sac of the eye; spillage or drainage into the lacrimal sac is rapid.[6] Drug draining through the lacrimal system is absorbed systemically and may be of sufficient amount in patients with hepatic or renal insufficiency to cause toxicity. To avoid lacrimal sac drainage and systemic absorption, the puncta in the medial canthal area can be occluded by digital pressure for 15 to 20 seconds after administration of an eyedrop.[4] Systemic antibiotics have little role in the treatment of bacterial corneal ulcers because concentrations achieved in the cornea are inferior to those attained by topical or subconjunctival administration.

Endophthalmitis

Infectious endophthalmitis is a virulent, sight-threatening infection of intraocular tissue. Prompt diagnosis and therapy are essential. Risk factors for endophthalmitis include ocular trauma or surgery, periocular infection, and systemic infection. Common bacterial pathogens include *S. aureus*, CoNS, streptococci, and gram-negative bacilli, especially Enterobacteriaceae and *P. aeruginosa*.[29] When endophthalmitis is suspected, aspiration of vitreous humor for culture is essential to determine the pathogen or pathogens and to guide antimicrobial therapy. The corneal epithelium, retinal capillaries, and pigmented retinal epithelium provide mechanical barriers to antimicrobial penetration into the vitreous humor. In addition, the flow of aqueous humor anteriorly impairs the movement of drugs to the vitreous humor. Thus administration of antibiotics by the topical, subconjunctival, or systemic route may not achieve an adequate intravitreal concentration (Table 294.3). The optimal route of administration is intravitreal instillation (see Chapter 84). Many parenterally administered antibiotics have been used for intravitreal injection (Table 294.4). Current recommendation for empiric therapy include intravitreal instillation of vancomycin plus ceftazidime.[30] Disadvantages of intravitreal administration are possible damage to the retina and intraocular structures, as well the need for anesthesia for injection. Adjuvant therapy consists of subconjunctivally and parenterally administered antibiotics, vitrectomy, and corticosteroids (systemically, intraocularly, or by both routes).[13]

TABLE 294.3

Concentrations of Antimicrobial Agents Within Human Eyes After Systemic Administration

Antibiotic	Dosage	Vitreous Humor (Uninflamed Eye) (μg/mL)
Cefazolin	2 g IV	0.3–4.6
Cefotaxime	1 g IM	<0.2
Chloramphenicol	3 g PO	5–15
Ciprofloxacin[102]	1000 mg PO	0.3–1.2
Gentamicin	1.6 mg/kg IM	<0.2
Imipenem	1 g IV	1.4–3.6[a]
Levofloxacin	600 mg PO[103]	1.5 ± 0.5
	500 mg PO[104]	0–1.6
Linezolid[105]	600 mg IV	1.8–2.4
	600 mg PO × 2 (every 12 hr)	3.6–5.2
Ofloxacin[106]	400 mg PO	1.8 ± 0.2
Oxacillin	2 g IV	<0.2–4.5

[a] A concentration of 13 μg/mL was achieved in one patient with an inflamed eye.

IM, intramuscular; IV, intravenous; PO, oral.

Partially Adapted from Barza M. Antibacterial agents in treatment of ocular infections. Infect Dis Clin North Am 1989;3:533.

TABLE 294.4

Typical Dosage of Antibiotics for Subconjunctival and Intravitreal Administration[a]

Antibiotic	Dose		
	Subconjunctival (mg)	Intravitreal (μg)[b]	Interval (hr)
Amikacin[c]	40	400	24–48
Amphotericin	NR	5–10	NR
Ampicillin	100	5000	48

Cefazolin	100	2250	24
Ceftazidime	100	2250	48–72
Ceftriaxone	125[107]	NR	NR
Cefuroxime	NR	1000	48–72
Ciprofloxacin	NR	100	12
Clindamycin	30	1000	72
Fluconazole	1 mL of 0.2% solution	NR	NR
Gentamicin	20[d]	200	72–96
Methicillin	100	2000	NR
Penicillin G	NR	2–4000U	48
Tobramycin	20	200–400	NR
Vancomycin[e]	25	1000	72
Voriconazole	NR	50–200	NR

[a] Partially adapted from Radhika M, Mithal K, Bawdekar A, et al. Pharmacokinetics of intravitreal antibiotics in endophthalmitis. J Ophthalmic Inflamm Infect 2014;4:22; and Lemley CA, Han DP. Endophthalmitis: a review of current evaluation and management. Retina. 2007;27:662–680. Intervals are those reported in studies referenced. Doses are based primarily from studies in adults.

[b] Each drug is diluted to provide the indicated dose (μg) in a volume of 0.1 mL (sterile water or normal saline. 1 μg = 0.001 mg.

[c] Less toxic to the retina than gentamicin or tobramycin when given intravitreally.

[d] In children who weight <40 kg, the dose should not exceed half of a single intravenous dose.

[e] May cause tissue necrosis/sloughing when administered subconjunctivally.

NR, not reported in studies referenced.

For treatment of endogenous fungal endophthalmitis, systemically administered antifungal agents have variable penetration into the posterior segment of the eye. Therapeutic concentrations of fluconazole and voriconazole usually can be achieved, but not amphotericin B, posaconazole, or the echinocandins.[31] Intravitreal injection of amphotericin B (5–10 μg) or voriconazole (100 μg) usually is used for sight-threatening involvement to achieve high local antifungal activity as rapidly as possible.

Otic Therapy

Topical antibiotic therapy is used in the treatment of otitis externa and chronic suppurative otitis media (CSOM) and as prophylaxis for surgery. Controlled studies documenting efficacy or assessing safety are generally lacking.

Otitis Externa

Otitis externa describes an inflammatory condition of the auricle, ear canal, or outer surface of the tympanic membrane. Infectious etiologies include primarily bacteria (most commonly *S. aureus, P. aeruginosa,* and anaerobic bacteria), followed by fungi and mycobacteria.[32,33] Therapy for otitis externa consists of cleansing of the canal, elimination of pathogens, reduction of the accompanying inflammation and edema, symptomatic relief, restoration of the oil and water content of the skin, and elimination or control of predisposing factors. Topical antimicrobial agents are noninferior to systemic antibiotics and are effective as sole agents for uncomplicated acute otitis externa.[34,35] The spectrum of activity and adverse events of the most commonly used topical antibiotics are shown in Table 294.5.[7,10,36–38] Commercial preparations for the treatment of external otitis are combinations of broad-spectrum antibiotics, often with anti-inflammatory agents (Table 294.6). Topical ciprofloxacin (with hydrocortisone), ofloxacin, and finafloxacin have been shown to be effective treatment of otitis externa and are approved by the United States Food and Drug Administration (FDA) for patients older than 1 year.[39–43] Topical antibacterial therapy for otitis externa should be used in conjunction with aural toilet to hasten cure and because prolonged use of topical agents alone can induce fungal overgrowth.

TABLE 294.5

Topical Otic Antimicrobial Agents

Agent	Concentration	Mechanism	Spectrum of Activity		Adverse Effects
			Gram-Positive Organisms	Gram-Negative Organisms[a]	
Acetic acid	36% solution	Unknown	ND	*Pseudomonas aeruginosa*[36,37]	
Boric acid	2.75%–5% solution	Unknown	ND; yeasts > bacteria[38]	ND	Marked system absorption can lead to shock ar death
Ciprofloxacin (Cipro HC Otic)	Ciprofloxacin, 2 mg/mL Hydrocortisone, 10 mg/mL	Interferes with DNA gyrase	++	+++ *Pseudomonas aeruginosa*	Pruritus rarely
Colistin (polymyxin	3 mg/mL	Same as polymyxin	–	++ (*Pseudomonas*	Renal toxicity; neurotoxicity if

E)				spp. R)	absorbed
Modified Burow solution (water, aluminum, and sodium acetate)		Unknown	ND	ND	
Finafloxacin (Xtoro)	0.3% suspension	Inhibits DNA gyrase and DNA topoisomerase IV	+ *Staphylococcus aureus*	+ *P. aeruginosa*	Nausea and pruritus in 1% studied patients
Neomycin	3.3–3.5 mg/mL	Inhibits protein synthesis	+	++ (*Pseudomonas* spp. R)	Contact hypersensitivity
Ofloxacin (Floxin)	0.3% solution	Interferes with DNA gyrase	++	+++	Taste perversio pruritus, site irritation; dizziness, earache, and vertigo in ~1% patients studie
Polymyxin B	10,000 U/mL	Attaches to cell membrane, with disruption of osmotic properties leading to cell death	−	+++	Renal toxicity if absorbed

[a] Gram-negative organisms include Haemophilus spp., Neisseria spp., Enterobacteriaceae, and Pseudomonas spp., or as otherwise indicated.

+++, excellent activity and spectrum; ++, good activity and spectrum; +, fair activity and spectrum; −, no activity; ND, no or limited data; R, resistant.

Data from references 7, 10, 33–35,43.

TABLE 294.6

Commercially Available Topical Otic Preparations

Trade Name	Composition
Cipro HC Otic	Ciprofloxacin, 2 mg/mL Hydrocortisone, 10 mg/mL
Ciprodex	Ciprofloxacin, 3 mg/mL Dexamethasone, 1 mg/mL
Coly-Mycin S Otic	Colistin sulfate, 3 mg/mL Neomycin sulfate, 3.3 mg/mL Thonzonium bromide, 0.5 mg/mL Hydrocortisone acetate, 10 mg/mL
Cortisporin (solution, suspension)	Neomycin, 3.5 mg/mL Polymyxin B, 10,000 U/mL

	Hydrocortisone, 10 mg/mL
Floxin	Ofloxacin, 0.3%
LazerSporin-C solution	Neomycin sulfate, 3.5 mg/mL Polymyxin B, 10,000 U/mL Hydrocortisone, 10 mg/mL
Otic Domeboro solution	Acetic acid, 2% Modified Burow solution (water, aluminum acetate, and sodium acetate)
Otic Tridesilon solution	Acetic acid, 2% Desonide, 0.5% (nonfluorinated corticosteroid)
Pedotic suspension	Neomycin sulfate, 3.5 mg/mL Polymyxin B sulfate, 10,000 U/mL Hydrocortisone, 10 mg/mL
Star-Otic ear solution	Acetic acid, 2% Burow solution (aluminum acetate) Boric acid
Tobra Dex	Tobramycin, 0.3% Dexamethasone, 0.1%
VōSol HC Otic	Acetic acid, 2% Hydrocortisone, 10 mg/mL
VōSol Otic	Acetic acid, 2%
Xtoro	Finafloxacin, 0.3%

Chronic Suppurative Otitis Media

CSOM is defined as otorrhea through a nonintact tympanic membrane that lasts >6 weeks and is unresponsive to medical management. This condition usually is a complication of acute otitis media with chronic mastoiditis. The pathogens, however, are different in this condition, with *P. aeruginosa*, *S. aureus*, and anaerobic bacteria most commonly implicated. Therapy usually is systemic antimicrobial therapy in conjunction with aural toilet. A Cochrane Review of 9 trials of patients with CSOM concluded that a topical fluoroquinolone compared with systemic antibiotics was associated with shorter duration of otorrhea.[44]

A study in 44 children with tympanostomy tubes who received topical otic therapy for CSOM did not demonstrate excessive hearing loss, as measured by a change in bone conduction thresholds.[45] Despite the lack of extensive safety data, topical otic agents (see Table 294.5) have been used extensively, alone or in combination with systemic therapy, with apparent success and without adverse effects attributed solely to their use. Cortisporin is used most commonly. Topical ofloxacin is approved by the FDA for the treatment of CSOM in individuals 12 years and older and for acute otitis media in children 1 year and older with tympanostomy tubes because of its microbiologic profile and favorable performance in clinical trials.[46,47] Availability of effective, approved otic antibiotics has supplanted off-label use of ophthalmic aminoglycoside otically. Combined medical therapy and surgical debridement frequently are necessary. Failure of management or the presence of cholesteatoma is an indication for surgical intervention.

Prophylaxis After Tympanostomy Tube Placement

Topical otic therapy has been used as prophylaxis for otorrhea after tympanostomy tube placement. Studies performed to determine whether this strategy is efficacious have had conflicting results. A Cochrane Review of 15 randomized controlled trials concluded that various interventions, including multiple saline washouts, single application of topical antibiotics, and prolonged application of topical antibiotics were effective in reducing otorrhea after tympanostomy tube placement.[48]

Acute Tympanostomy Tube Otorrhea

Acute otorrhea that occurs while the tympanostomy tube is in place is considered to be an episode of acute otitis media. In a recent randomized controlled trial in children with tympanostomy tubes and acute otorrhea, therapy with antibiotic-glucocorticoid drops was shown to be more effective than compared with oral antibiotic therapy or initial observation alone.[49]

Therapy for Skin Infections

Topical antibiotics are used for the prophylaxis and treatment of a wide variety of skin infections (Table 294.7).[50–57] The most common conditions for which the use of topical therapy has been found to be efficacious are acne, impetigo, and burns. Topical antimicrobial agents also often are used at intravascular catheter sites to prevent infection.

TABLE 294.7

Topical Antibiotics for Use on Skin

Agent (Trade Name)	Mechanism of Action	Spectrum of Activity			
		Gram-Positive Organisms	Gram-Negative Organisms[a]	Anaerobes	Yeast
Bacitracin[b] 400, 500 U/g (generic)	Inhibits early steps in peptidoglycan biosynthesis, inhibits cell wall synthesis; changes membrane permeability	+++ (group B *Streptococcus* R)	+ (Enterobacteriaceae R, *Pseudomonas* spp. R)	++	–
Clindamycin, 10 mg/mL (Cleocin)	Inhibits protein synthesis	+++	–	+++	–
Erythromycin, 2%, 3% (many preparations)	Inhibits protein synthesis	+++	++	–	–
Fusidic acid, 2% (Fucidin)	Inhibits protein synthesis	+++	+ (Enterobacteriaceae R, *Pseudomonas* spp. R)	++	–
Gentamicin, 0.1%	Inhibits protein synthesis	+	+++	–	–
Meclocycline, 1% (Meclan)	Inhibits protein synthesis	+	++ (*Pseudomonas* spp. R)		+
Metronidazole, 0.75% (MetroGel)	Interacts with bacterial DNA; precise mechanism unknown	–	–	+++ (*Propionibacterium acnes* R)	–
Mupirocin, 2% (Bactroban)	Inhibits protein synthesis by acting on bacterial isoleucyl transfer RNA synthetase	+++	+/–	–	–
Neomycin, 3.5 mg/g[b] (many)	Inhibits protein synthesis	+	++ (*Pseudomonas* spp. R)	–	–
Polymyxin B[b]	Attaches to cell membrane, with disruption of osmotic properties	–	+++ (*Proteus* spp. R, *Serratia* spp. R)	+ (*Bacteroides fragilis* R)	+/– (in hig concen

	leading to cell death				
Retapamulin 1% ointment (Altabax, Altargo)	Inhibits protein synthesis (novel site of action on SOS ribosomal subunit)	+++	−	+	−
Sulfacetamide, 10% (Novacet, Sulfacet-R)	Inhibits folic acid synthesis	++	++ (*Pseudomonas* spp. R)	−	−
Tetracycline, 2.2 mg/mL (Topicycline)	Inhibits protein synthesis	+	++ (*Pseudomonas* spp. R)	+	−

[a] Gram-negative organisms include *Haemophilus* spp., *Neisseria* spp., Enterobacteriaceae, and *Pseudomonas* spp., unless otherwise specified.

[b] Many commercial preparations combine bacitracin, neomycin, and polymyxin B.

+++, excellent activity and spectrum; ++, good activity and spectrum; +, fair activity and spectrum; −, no activity; R, resistant.

Data from references 8, 10, 50–57.

Acne

Minor acne can be treated with topical antibiotics, keratolytics, and drying agents. Antibiotics active against *Propionibacterium acnes* are frequently used as adjunctive therapy. Topical erythromycin and clindamycin have been shown to decrease *P. acnes* colonization and to lessen the percentage of free fatty acids in surface lipids.[52] For more severe acne, systemic antibiotics (erythromycin, clindamycin, or tetracycline) and retinoids (topical and systemic) are added to the therapeutic regimen. Topical antibiotic monotherapy is not recommended because of emergence of bacterial resistance and availability of superior topical alternatives.[53]

Impetigo

Impetigo is caused by *Streptococcus pyogenes* alone or in combination with *S. aureus*.[58,59] Topical therapy is sufficient for minor localized infection in a well child. Mupirocin has exquisite activity against these organisms and is the topical agent of choice for impetigo.[60] Retapamulin 1% ointment, approved by the FDA in 2007 for the treatment of impetigo secondary to *S. pyogenes* or methicillin-susceptible *S. aureus*, is a 1% semisynthetic pleuromutilin compound with in vitro activity against most gram-positive bacteria and anaerobes. Pleuromutilin may be active against some mupirocin-resistant *S. aureus* strains.[61] Systemic antibiotic therapy is required for a febrile or ill-appearing child (because of the possibility of bacteremia or toxin-mediated manifestations) or if there are multiple or deep lesions.

Prophylaxis and Treatment of Wounds

Although topical antibacterial agents are used commonly for the prophylaxis of minor cuts and abrasions, no study has demonstrated that their use prevents infection. In addition to topical antibiotics, antiseptic agents are used for cleansing and treating wounds. Antiseptic agents comprise a wide variety of substances that are applied to living tissues to inhibit or kill microorganisms. The mechanism of action of most agents is not understood clearly. Because methods of testing are not well standardized and it is difficult to make comparisons of antimicrobial activity between compounds, no quantification of the antimicrobial activity of antiseptic agents has been made. Table 294.8 lists antiseptics commonly used for the treatment of skin infections.[57,62–64]

TABLE 294.8

Antiseptics Used on Skin

Agent (Trade Name)	Spectrum of Activity[a]			Yeast	Adverse Effects
	Gram-Positive Organisms	Gram-Negative Organisms[b]	Anaerobes		
Acid electrolytic water (AEW)	S	S			
Benzalkonium chloride (Lanax, Zephiran, many brands)	S	S[c]		S	Nosocomial gram-negative bacilli and yeast infections from open contaminated solutions
Benzethonium chloride (many brands)	S	S	S		
Benzoyl peroxide (many brands)	S				Irritation and dryness
Chlorhexidine gluconate, solutions 2% and 4% (Hibiclens)	S	S		S	Possible CNS toxicity if broad application to neonate

Clioquinol (Vioform)	S				
Hexachlorophene (pHisoHex)	S				CNS toxicity if broad application to neonate
Phenol (Castellani Paint, Anbesol, Campho-Phenique)	S	S		S	Hyperbilirubinemia in neonates; ? carcinogenic potential
Povidone-iodine (Betadine)	S	S	S	S	Excessive area of application can cause thyroid dysfunction
Triple dye (brilliant green, proflavine hemisulfate, gentian violet)	S				Can be deleterious to wound healing
Triclosan	S				Limited against gram-negative bacilli; may lead to *Pseudomonas aeruginosa* overgrowth

[a] S, susceptible; blanks indicate resistance or insufficient data.

[b] Gram-negative organisms include *Haemophilus* spp., *Neisseria* spp., Enterobacteriaceae, and *Pseudomonas* spp.

[c] *Pseudomonas* is frequently resistant.

CNS, central nervous system.

Data from references 57, 62–64.

Topical agents such as mupirocin have been used intranasally in an attempt to eliminate colonization with *S. aureus.* Mupirocin is especially advantageous because of efficacy against methicillin-resistant *S. aureus* (MRSA). Unfortunately, increasing use has been associated with the emergence of mupirocin resistance and failure to eradicate community-acquired MRSA.[65,66] Dilute sodium hypochlorite (bleach) baths have been used, alone or concurrently with intranasal mupirocin, in attempt to decrease MRSA colonization, with variable outcomes.[67,68]

Therapy for Burns

Infections are a leading cause of death in burn victims who are successfully resuscitated. The burn wound is often the source of infection in these patients. Aggressive, early surgical debridement and wound closure, in combination with routine use of topical antimicrobial agents, have contributed immensely to prevention and control of burn wound sepsis. Burn wound infection is defined as bacterial invasion into the underlying viable tissue and usually correlates with more than 10^5 colony-forming units per gram of tissue. Topical antimicrobial agents do not sterilize the wound, but rather decrease the number of colonizing bacteria and the risk for deeper bacterial invasion into underlying viable tissue. Thus their major role is one of prophylaxis. For established burn wound sepsis, topical therapy is used in conjunction with aggressive surgical debridement and parenteral antibiotic therapy. Many topical agents are used, all differing in their antimicrobial spectrum of activity and side effects, but none is ideal. The characteristics of an ideal agent are listed in Box 294.1.

Box 294.1

Characteristics of an Ideal Topical Antimicrobial Agent

General

Painless on application

Nonallergenic

No systemic absorption

Long lasting

Ease of use

Inexpensive

Pertinent to Burn Wounds

Penetrates burn wounds to a sufficient depth

Prevents desiccation

Does not impair the ability to examine wounds

Controls bacterial proliferation

Does not promote bacterial resistance

Does not inhibit re-epithelialization

Does not injure viable cells

The most commonly used agents are shown in Table 294.9.[69–91] The agent used most widely has been silver sulfadiazine because of its broad antibacterial spectrum and relatively minor side effects. Other nonconventional topical agents such as acetic acid, formalin, and honey are used occasionally.[36,37,92–96] To some extent, all topical antimicrobial agents inhibit the rate of wound epithelialization, but on balance, their prophylactic efficacy against burn wound infection merits use.[97,98] Although susceptibility testing can be performed by several methods (most commonly the Nathan agar well diffusion assay), such methods are poorly standardized for topical antimicrobial testing and results have varied widely.[70,71,99–101] Selection of topical agents is based on known or expected colonizing organisms and their presumed susceptibilities, timing of injury, knowledge of organisms indigenous to the burn unit, and possible adverse reactions of agents. Occasionally, preparations of systemically administered antibacterial and antifungal agents are made extemporaneously for topical use when an infection is due to organism resistant to available topical agents or when cultured autografts are used because many routine preparations can be toxic to keratinocytes. Such use must be restricted and for short periods as resistance develops rapidly (precluding future use of that agent systemically).

TABLE 294.9

Topical Antimicrobial Agents Used in the Treatment of Burns

Agent (Trade Name)	Mechanism of Action	Antimicrobial Activity			
		Gram-Positive Organisms	Gram-Negative Organisms[a]	Anaerobes	Yeast
Acetic acid	Unknown	ND	*Pseudomonas aeruginosa*	ND	ND
Bacitracin, 400, 500 U/g (generic)	Inhibits early steps in peptidoglycan biosynthesis resulting in inhibition of cell wall synthesis; also changes cell membrane permeability	+++ (Group B *Streptococcus* R)	+	++	–
Cerium	Unknown	+++	+++	ND	+++

nitrate, 2.2%					
Chlorhexidine	Unknown	+++	+++	ND	+
Fusidic acid, 2% (Fucidin)	Inhibits protein synthesis	+++	+ (Enterobacteriaceae, *Pseudomonas* spp. R)	++	−
Gentamicin, 0.1% (Garamycin)	Inhibits protein synthesis	+ (Synergy for *Staphylococcus aureus* and *Enterococcus* spp.)	+++	−	−
Mafenide acetate, 11.1% cream, 5% solution (Sulfamylon)	Unknown	+	+++	+++	+
Mupirocin, 2% (Bactroban)	Inhibits protein synthesis by irreversibly binding to bacterial isoleucyl transfer RNA synthesis	+++	+/− (*Pseudomonas* spp. R)	+/−	−
Neomycin, 3.5 mg/g	Inhibits protein synthesis	+	++ (*Pseudomonas* spp. R)	−	−
Nitrofurazone, 0.2% cream, solution (Furacin)	Inhibits several bacterial enzymes involved in carbohydrate metabolism	+++	+++	++	−
Polymyxin B, 5000, 10,000 U/g	Attaches to cell membrane, with disruption of osmotic properties leading to cell death	−	+++ (*Proteus* spp. R; *Serratia* spp. R)	+/− (*Bacillus fragilis* R)	+/− (In high concentratio
Povidone-iodine, 5% cream, 10%	Unknown	+++	+++	++	++

ointment (Betadine)					
Silver nitrate, 0.5% solution	Silver ion inhibits DNA replication; modifies cell membrane	+	++	+	+
Silver sulfadiazine, 1% cream (Silvadene, Thermazene)	Silver ion inhibits DNA replication; modifies cell membrane	++	+++	++	++

[a]Gram-negative organisms include *Haemophilus* spp., *Neisseria* spp., Enterobacteriaceae, and *Pseudomonas* spp., unless otherwise specified.

+++, excellent activity and spectrum; ++, good activity and spectrum; +, fair activity and spectrum; −, no activity; MRSA, methicillin-resistant *Staphylococcus aureus;* ND, no or limited data; R, resistant.

Data from references 36, 37, 69–91.

The toxicity of antibiotics on cultured skin and skin substitutes varies extensively, and the choice of agents should be based on the manufacturer's guidelines and the antimicrobial susceptibility of the organisms isolated.

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Antiviral Agents

David W. Kimberlin

In 1963, idoxuridine became the first antiviral compound to be licensed by the US Food and Drug Administration (FDA) for the topical treatment of herpes simplex virus (HSV) keratitis. This was followed shortly by licensure of amantadine in 1966 as the first systemic antiviral compound for the treatment of influenza A infection. During the 1970s, only vidarabine (1976) received licensure for the systemic treatment of HSV central nervous system (CNS) infections. The licensure of acyclovir in 1982 opened the field of clinical antiviral drug intervention and heralded the era of rapid development of new drugs.

In addition to antiretroviral drugs for the treatment of the human immunodeficiency virus (HIV), three additional non-HIV antiviral drugs were licensed in the 1980s: trifluridine (1980), ribavirin (1985), and interferon (1986). Ten non-HIV antiviral drugs were licensed in the 1990s: foscarnet (1991), rimantadine (1993), ganciclovir (1994), famciclovir (1994), valacyclovir (1995), topical penciclovir (1996), cidofovir (1996), palivizumab (1998), zanamivir (1999), and oseltamivir (1999). Lamivudine, which was approved originally as an HIV medication, was licensed for the treatment of chronic hepatitis B virus (HBV) infection in 1998.

Fewer new antiviral agents were brought to market in the first decade of the 21st century, and all except valganciclovir were for the treatment of hepatitis B: valganciclovir (2001), tenofovir disoproxil fumarate (2001), adefovir dipivoxil (2002), pegylated interferon (2003), entecavir (2005), and telbivudine (2006). Since 2010, nine non-HIV antiviral drugs have been licensed for use in the

United States, eight of which were for the treatment of hepatitis C: boceprevir (2011), dasabuvir (2014), ledipasvir (2014), ombitasvir (2014), paritaprevir (2014), simeprevir (2013), sofosbuvir (2014), and telaprevir (2011) for hepatitis C, and peramivir (2014) for influenza.

Many of the hepatitis C drugs are used in fixed combinations (e.g., sofosbuvir plus ledipasvir [Harvoni]); ombitasvir, paritaprevir, and ritonavir copackaged with dasabuvir [Viekira Pak]) and are discussed as such in this chapter, although none currently has been approved for use in children. The pace of development of more potent hepatitis C antiviral agents has been rapid, rendering first-generation products obsolete. The products that are no longer recommended for the treatment of hepatitis C (e.g., boceprevir, telaprevir) are not discussed.

Approved antiviral agents have demonstrated efficacy in the treatment of infections caused by HSV, cytomegalovirus (CMV), varicella-zoster virus (VZV), HIV, respiratory syncytial virus (RSV), influenza A and B, hepatitis B and C, human papillomavirus (HPV), and Lassa virus.[1] Major sites of action of antiviral agents are listed in Table 295.1, with selected antiviral drugs for specific viruses given in Table 295.2. Mechanisms of antiviral resistance are presented in Table 295.3.

TABLE 295.1

Major Sites of Action of Antiviral Agents

Major Site of Action	Antiviral Agent
Viral entry, adsorption, penetration, or uncoating	Amantadine
	Rimantadine
Transcription or replication of viral genome	Acyclovir or valacyclovir
	Adefovir dipivoxil
	Cidofovir
	Dasabuvir
	Entecavir
	Famciclovir or penciclovir
	Foscarnet
	Ganciclovir or valganciclovir
	Lamivudine
	Paritaprevir
	Ribavirin
	Simeprevir
	Sofosbuvir
	Telbivudine
	Tenofovir
	Trifluridine
	Vidarabine

Viral assembly, release, or de-aggregation	Ledipasvir
	Ombitasvir
	Oseltamivir
	Peramivir
	Zanamivir

TABLE 295.2

Selected Antiviral Treatment Options, by Virus

Virus	Antiviral Drugs Indicated for Management
Cytomegalovirus	Ganciclovir
	Valganciclovir
	Foscarnet
	Cidofovir
Hepatitis B	Entecavir
	Tenofovir
	Lamivudine
	Telbivudine
	Adefovir
Hepatitis C	Sofosbuvir-ledipasvir
	Ombitasvir-paritaprevir/ritonavir copackaged with dasabuvir
	Sofosbuvir-ribavirin
	Sofosbuviror-simeprevir
Herpes simplex virus	Acyclovir
	Valacyclovir
	Famciclovir
	Penciclovir
	Foscarnet
	Cidofovir
Influenza A and B	Oseltamivir
	Zanamivir
	Peramivir
Lassa virus	Ribavirin
Human papillomavirus	Cidofovir
Respiratory syncytial virus	Ribavirin
Varicella-zoster virus	Acyclovir
	Valacyclovir
	Famciclovir
	Penciclovir
	Foscarnet

TABLE 295.3

Mechanisms of Antiviral Resistance

Antiviral	Viruses	Mechanism of Resistance	Clinical Correlates of Resistance	Alternative Antiviral Agents
Acyclovir **Valacyclovir**	HSV, VZV	Usually due to mutations in thymidine kinase gene,	Persistent or progressive infection due to resistant strains isolated from patients	Foscarnet

		resulting in absent or altered thymidine kinase; rarely due to mutation in DNA polymerase gene	with severely compromised immunity (e.g., bone marrow transplant recipients, those with AIDS); isolates of HSV from healthy people described in those receiving long-term suppressive therapy	
Amantadine **Rimantadine**	Influenza A	Mutation in RNA sequence encoding for M2 protein transmembrane domain	Usually recovered from drug recipients within 2 days of starting therapy and their infected household contacts; clinical relevance undefined	Oseltamivir Zanamivir
Cidofovir	CMV, HSV	Mutation in DNA polymerase gene	Only rare clinical isolates reported	Foscarnet
Famciclovir **Penciclovir**	HSV, VZV	Usually due to mutations in thymidine kinase gene, resulting in absent or altered thymidine kinase; also can result from mutation in DNA polymerase gene	Persistent or progressive infection due to resistant strains isolated from patients with severely compromised immunity (e.g., bone marrow transplant recipients those with AIDS); isolates of HSV from healthy people described in those receiving long-term suppressive therapy	Foscarnet Acyclovir
Foscarnet	HSV, VZV, CMV	Mutations in viral DNA polymerase gene	Only rare clinical isolates have been reported	Acyclovir Cidofovir
Ganciclovir **Valganciclovir**	CMV	Decreased intracellular phosphorylation due to mutations in the CMV *ul97* gene with decreased expression of CMV phosphotransferase enzymes or mutation in viral DNA polymerase gene	Responsible for severe, rapidly progressive infection in patients with severely compromised immunity (e.g., bone marrow transplant recipients, those with AIDS)	Foscarnet Cidofovir
Lamivudine	HBV	Mutation in HBV polymerase gene	Reappearance of HBV DNA in serum after its initial disappearance, although most patients continue to have lower serum HBV DNA and ALT levels compared with pretreatment levels	Adefovir Entecavir

AIDS, acquired immunodeficiency syndrome; ALT, alanine transferase; CMV, cytomegalovirus; HBV, hepatitis B virus; HSV, herpes simplex virus; VZV, varicella-zoster virus.

Non-HIV antiviral small-molecule agents that are licensed by the FDA are the primary focus of this chapter. Interferons are a family of nonspecific regulatory proteins associated with a variety of antiviral, antiproliferative, and immunomodulating activities.[2,3] Their use largely is being supplanted by entecavir and tenofovir, and they have been completely replaced by small molecules in the management of hepatitis C. Interferons therefore are not addressed in detail. Monoclonal and polyclonal antibody preparations, also used in the treatment and prevention of viral infections, are discussed in pathogen-specific chapters and in Chapter 5.

Nucleoside and Nucleotide Analogues and Protease Inhibitors

Acyclovir and Valacyclovir

Chemistry, Mechanism of Action, Spectrum, and Resistance.

Acyclovir (Zovirax) (i.e., acycloguanosine [ACV]) is a deoxyguanosine analogue with an acyclic side chain that lacks the 3′-hydoxyl group of natural nucleosides.[4] After preferential uptake by infected cells, acyclovir is monophosphorylated by virus-encoded thymidine kinase (TK). Subsequent diphosphorylation and triphosphorylation are catalyzed by host cell enzymes, resulting in acyclovir triphosphate concentrations that are 40 to 100 times higher in HSV-infected cells than in noninfected cells.[5]

Acyclovir triphosphate prevents viral DNA synthesis by inhibiting the viral DNA polymerase. In vitro, acyclovir triphosphate competes with deoxyguanosine triphosphate as a substrate for viral DNA polymerase. Because acyclovir triphosphate lacks the 3′-hydroxyl group required for elongation of the DNA chain, the growing chain of DNA is terminated. In the presence of the deoxynucleoside triphosphate complementary to the next template position, the viral DNA polymerase is functionally inactivated.[6] Acyclovir triphosphate is a much better substrate for the viral polymerase than for cellular DNA polymerase, resulting in little incorporation of acyclovir into cellular DNA. The higher concentration of the active triphosphate metabolite in infected cells plus the affinity for viral polymerases result in the low toxicity of acyclovir in noninfected host cells.

Acyclovir is most active in vitro against HSV, with activity against VZV being about 10-fold less but still substantial. Although

Epstein-Barr virus (EBV) has only minimal TK activity, EBV DNA polymerase is susceptible to inhibition by acyclovir triphosphate. EBV is moderately susceptible to acyclovir in vitro. Activity against CMV is limited because CMV does not encode TK, and CMV DNA polymerase is poorly inhibited by acyclovir triphosphate.

In vitro susceptibility of viruses to acyclovir depends on several factors, including the cell line used, inoculum, incubation conditions, and the specific assay system used. No standardized method of susceptibility testing is universally accepted, and wide disparities in specific inhibitory concentrations of antiviral agents therefore are reported. Given these limitations, the relative activity of an antiviral agent is more meaningful than the absolute inhibitory concentration. The relative activities of drugs used in the treatment of herpesvirus infections are summarized in Table 295.4.

TABLE 295.4

Relative in vitro Activity of Nucleoside Analogues Against Herpesviruses

Virus	Acyclovir	Penciclovir	Vidarabine	Foscarnet	Ganciclovir
HSV-1	+++	++	++	++	+++
HSV-2	+++	++	++	++	+++
VZV	+++	+++	++	++	++
CMV	+/−	+/−	+/−	++	++
EBV	+	−	−	+	++

CMV, cytomegalovirus; EBV, Epstein–Barr virus; HSV, herpes simplex virus; VZV, varicella-zoster virus; +++, high degree of activity; ++, moderate degree of activity; +, minimal degree of activity; +/−, minimal to no activity; −, no useful activity.

Resistance of HSV to acyclovir has long been recognized. In some referral centers, 5% to 14% of HSV isolates from immunocompromised patients are resistant.[7] Resistance can result from mutations in the viral thymidine kinase gene or the viral DNA polymerase gene. Although these acyclovir-resistant isolates exhibit diminished virulence in animal models, they can cause severe, progressive, debilitating mucosal disease and, rarely, visceral dissemination in HIV-infected patients.[8,9] Acyclovir-resistant strains of HSV also have been recovered from patients receiving cancer chemotherapy, bone marrow and solid-organ transplant recipients, children with congenital immunodeficiency syndromes, and neonates.[10,11] Although it is uncommon, genital herpes caused by acyclovir-resistant isolates has been reported in immunocompetent hosts, who usually have received chronic acyclovir therapy.[12]

Acyclovir-resistant strains of VZV are reported. Resistance is caused by the same mechanisms described for HSV isolates. Most acyclovir-resistant VZV strains have been isolated from HIV-infected children and adults who have had profound depletion of $CD4^+$ cells ($\leq 100/mm^3$) and prolonged acyclovir therapy.[13] Changes in the susceptibility of VZV isolates to acyclovir can develop after only 4 to 12 weeks.[10] Foscarnet is the drug of choice for HSV and VZV infections caused by acyclovir-resistant strains.[10]

Valacyclovir (Valtrex) is the L-valyl ester of acyclovir. After oral administration, valacyclovir is rapidly converted to acyclovir by first-pass metabolism in the liver.[14] Its mechanism of action, antiviral spectrum, and resistance are the same as those of its parent drug, acyclovir.

Pharmacokinetics.

Acyclovir is available as a topical formulation, in oral formulations (i.e., capsules, tablets, and suspension), and as a sterile powder for intravenous infusion. The topical formulation licensed in the United States is an ointment, whereas a cream is available in Europe. Although these topical products are not absorbed systemically, a substantial concentration of the drug reaches the basal epidermis in cutaneous infections. Only 15% to 30% of the oral formulations of acyclovir is absorbed; peak concentrations of approximately 0.5 μg/mL are attained 1.5 to 2.5 hours after a 200-mg dose.[4,15] Higher doses result in higher serum concentrations, and food does not alter the extent of absorption substantially. Steady-state concentrations of acyclovir after intravenous doses of 2.5 to 15 mg/kg range from 6.7 to 20.6 μg/mL. The disposition of acyclovir is not affected by the duration or frequency of dosing.

Systemically administered acyclovir is distributed widely, attaining high concentrations in the kidneys, lung, liver, heart, and skin vesicles; concentration attained in the cerebrospinal fluid (CSF) is approximately 50% that of plasma.[4] Acyclovir readily crosses the placenta and accumulates in breast milk. The rate of protein binding ranges from 9% to 33% and is independent of the plasma drug concentration. Less than 20% of acyclovir is metabolized to a biologically inactive metabolite; more than 60% of administered drug is excreted intact in the urine. The half-life of acyclovir is 2 to 3 hours in older children and adults and 2.5 to 5 hours in neonates with normal creatinine clearance (CrCl).[4] Elimination of acyclovir is prolonged in patients with renal dysfunction, with a half-life of approximately 20 hours in those with end-stage renal disease.[16] Dosage modifications are necessary for patients with CrCl values less than 50 mL/min.1.73 m^2. Dosing guidelines for various degrees of renal dysfunction are given in Table 295.5. Acyclovir is readily hemodialyzable. The mean plasma half-life in patients during hemodialysis is about 5 hours, requiring that patients receive an additional dose of acyclovir after each dialysis (Table 295.6).[17] The half-life of acyclovir is 13 to 18 hours during continuous ambulatory peritoneal dialysis (CAPD), and no supplemental dose is necessary after adjustment of the dosing interval.

TABLE 295.5

Dosage Adjustment of Acyclovir in Individuals With Renal Dysfunction

Creatinine Clearance (mL/min/1.73/m^2)	Suggested Modifications of Standard Intravenous Dose	Suggested Modification of Standard Oral Dose
>50	No modification necessary	No modification necessary
25–50	Maintain unit dose, but increase the dosing interval by 50%	No modification necessary
10–25	Maintain unit dose, but double the dosing interval	Maintain unit dose, but double the dosing interval
0–10	Reduce dose by 50% *and* double the dosing interval	Maintain unit dose, but triple the dosing interval

Data from Wagstaff AJ, Faulds D, Goa KL. Aciclovir: a reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. Drugs 1994;47:153–205; Laskin OL, Longstreth JA, Whelton A, et al. Effect of renal failure on the pharmacokinetics of acyclovir. Am J Med 1982;73:197–201.

TABLE 295.6

Dosage Adjustments of Antiviral Agents for Renal Dysfunction[a]

Antiviral Agents	Creatinine Clearance–Necessitating Dose Adjustment (mL/min/1.73 m^2)	Need for Supplementary Dose After Hemodialysis
Acyclovir	<50	Yes
Adefovir	<50	No[b]
Amantadine	<80	No
Entecavir	<50	No[b]
Famciclovir (for VZV)	<60	Yes

Famciclovir (for HSV)	<40	Yes
Foscarnet	<100	Yes
Ganciclovir	<80	Yes
Lamivudine	<50	Unknown
Oseltamivir	<30	Unknown
Peramivir	<50	Yes
Ribavirin	—	No
Rimantadine	—	No

[a] Cidofovir dosing must be adjusted for renal dysfunction but is based on changes in the creatinine level from baseline.

[b] Administer recommended dose at the appropriate interval after hemodialysis.

HSV, herpes simplex virus; VZV, varicella-zoster virus.

After oral administration of valacyclovir, rapid and complete conversion to acyclovir occurs with first-pass intestinal and hepatic metabolism. The bioavailability of valacyclovir in adults exceeds 50%, which is three to five times greater than that of acyclovir.[18] The peak serum concentration, which is attained about 1.5 hours after a dose has been given, is proportional to the amount of drug administered, ranging from 0.8 to 8.5 μg/mL for doses of 100 to 2000 mg.[19] The area under the drug concentration–time curve (AUC) approximates that seen after intravenous acyclovir. All other pharmacokinetic characteristics are similar to those of acyclovir.

Valacyclovir oral suspension has been studied in children 1 month to 12 years of age.[20] Bioavailability is estimated to be 45% to 51% in all age groups except those 3 through 5 months of age, in whom the bioavailability is about 22%. Approximate dose proportionality in the maximal concentration observed (C_{max}) and AUC occurs across the 10- to 25-mg/kg dose range (i.e., dose normalized differences usually within ≤30%), with the exception of children 2 through 5 years of age, for whom a modest increase in dose from 20 to 25 mg/kg is associated with almost doubling the C_{max} and AUC values.[20]

Toxicity and Drug Interactions.

Acyclovir consistently has demonstrated a favorable safety profile. The topical formulation can cause transient burning, especially when applied to ulcerated mucosal lesions. Oral acyclovir sometimes is associated with mild gastrointestinal upset, rash, and headache, but even long-term administration usually is well tolerated. Intravenous acyclovir usually is well tolerated. Because of its alkalinity (pH 9–11), extravasation of drug at the injection site can cause severe inflammation, phlebitis, and sometimes a vesicular eruption leading to cutaneous necrosis. Reversible nephrotoxicity occurs if acyclovir is given by rapid intravenous infusion or to patients who are poorly hydrated or who have preexisting renal compromise. Obstructive nephropathy results from the formation of acyclovir crystals that precipitate in renal tubules. In one study, acute renal insult occurred in 35% of patients beyond the neonatal period who were given acyclovir intravenously.[21] Nephrotoxicity was associated with a dose exceeding 15 mg/kg, age older than 8 years, and BMI greater than 19 kg/m^2. Other reported side effects of intravenous acyclovir include rash, sweating, nausea, headache, hematuria, and hypotension. The use of high doses of intravenous acyclovir (60 mg/kg/day) for the treatment of neonatal disease has been associated with neutropenia in some patients.[22]

The most serious side effect of acyclovir is neurotoxicity. When it occurs, lethargy, confusion, hallucinations, tremors, myoclonus, seizures, extrapyramidal signs, and changes in state of consciousness develop within the first few days of starting therapy. Neurotoxicity usually occurs in patients with compromised renal function who attain high serum concentrations of the drug.[23] Other risk factors can include concurrent administration of interferon or intrathecal methotrexate. Neurotoxic manifestations usually resolve spontaneously within several days after the discontinuation of acyclovir; hemodialysis may be useful in severe cases associated with high serum concentrations of the drug.

Although acyclovir is mutagenic at high concentrations in some in vitro assays, it is not teratogenic in various animal models. Acyclovir is not recommended for use in pregnant women, but limited data suggest that such use is not associated with congenital defects or other adverse gestational outcomes.[24] The finding of neutropenia in infants given acyclovir orally to suppress HSV reactivation after neonatal infection is not well explained.

Limited adverse drug interactions have been reported. Subjects being treated with zidovudine plus acyclovir can develop severe somnolence and lethargy. The likelihood of renal toxicity is increased when acyclovir is administered with nephrotoxic drugs such as cyclosporine and amphotericin B. Concomitant administration of probenecid decreases renal clearance of acyclovir and prolongs its half-life; conversely, acyclovir can decrease the clearance of drugs such as methotrexate that are eliminated by active renal secretion.

The profiles of adverse effects and potential drug interactions observed with valacyclovir therapy are the same as those observed with acyclovir. Neurotoxicity has not been reported in humans, although it has been observed in animal models.[14] Manifestations resembling thrombotic microangiopathy have been described in patients with advanced HIV disease receiving high doses of valacyclovir, but the coadministration of multiple medications makes the establishment of a causal relationship difficult.[25]

Clinical Uses and Dosage.

Acyclovir is effective for the treatment of infections caused by HSV and VZV in immunocompetent and immunocompromised hosts.[26] Table 295.7 outlines the infections for which acyclovir is effective, the recommended dosage, and magnitude of anticipated benefits. Unless otherwise stated, the anticipated benefits of acyclovir therapy are based on the results of randomized, controlled trials.

TABLE 295.7

Indications for Acyclovir Use

Infection	Dosage	Anticipated Benefits	Factors Favoring Beneficial Effect of Therapy	Strength of Indication
Initial genital HSV	15 mg/kg/day IV in 3 divided doses for 5–7 days *or* 40–80 mg/kg/day (maximum: 1000 mg/day) PO in 3–4 divided doses for 5–10 days[a]	4–12-day reduction in duration of viral shedding, 3–12-day reduction in time to healing, and 1–10-day reduction in duration of pain; therapy is not associated with reduced frequency of subsequent recurrences[36–38]	Intravenous, rather than oral, therapy; therapy for primary, rather than less severe first episode, nonprimary infections	++
Recurrent genital HSV	1000 mg/day in 5 divided doses for 5 days *or* 1600 mg/day in 2 divided doses for 5 days *or* 2400 mg/day in 3 divided *or* doses for 2 days[a]	1–2-day reduction in duration of viral shedding and time to healing; no difference in duration of pain or frequency of subsequent recurrences[41,47,344]	Initiation during prodromal phase of infection	+/−

Primary HSV labialis	2400 mg/m^2/day PO in 4 divided doses for 10 days	6-day reduction in the duration of viral shedding and 2–4-day reduction in the duration of drooling, gum swelling, and healing of oral and cutaneous lesions[46]	Initiation within 4 days of onset of signs of infection	++
Recurrent HSV labialis	1000 mg/day PO in 5 divided doses for 5 days	0.5–2-day reduction in the duration of pain and time to healing[45]	Initiation during prodromal or erythema stage	+/−
Mucocutaneous HSV in compromised hosts	30 mg/kg/day IV in 3 divided doses for 7–14 days	60–80% reduction in the duration of viral shedding, 30–60% reduction in healing time and the duration of pain[35]	Recovery of immune function	+++
Viscerally disseminated HSV in pregnant women and transplant recipients	30 mg/kg/day IV in 3 divided doses for 7–14 days	Improved likelihood of recovery based on anecdotal reports, rather than controlled trials[33,34]	—	+++
HSV encephalitis	30–45 mg/kg/day IV in 3 divided doses for 14–21 days	Reduced mortality and improved long-term neurologic outcome[27]	High (>6) Glasgow Coma Score at time of initiation of therapy; young age (<30 years)	++++
Neonatal HSV	60 mg/kg/day IV in 3 divided doses for 14 (SEM) to 21 (CNS, disseminated) days	Reduced mortality and improved long-term neurologic outcome[21,29]	Infection limited to the skin, eye, and mucosal membranes; absence of seizures at initiation of therapy for CNS infection	++++
Primary varicella in normal children, adolescents, and adults	80 mg/kg/day (maximum: 3200 mg/day) PO in 4 divided doses for 5 days	1–3-day reduction in new lesion formation and fever; reduced maximal number of lesions[48–50]	Initiation of therapy within 24 hours of onset of infection; older subjects and secondary cases in household benefit more than younger subjects and those with community-acquired infections	+/++
Disseminated varicella in previously healthy subjects	30 mg/kg/day IV in 3 divided doses for 7–10 days	Improved likelihood of recovery based on anecdotal reports rather than controlled trials[345]	—	+++
Zoster in normal hosts	80 mg/kg/day (maximum: 4000 mg/day) PO in 5 divided doses for 5–7 days	Reduced time to healing of skin lesions, duration of acute pain, and duration of viral shedding[52,53]	Initiation of therapy within 24–48 hours of onset of infection	+
Zoster	80 mg/kg/day	Reduced incidence of	—	++

ophthalmicus in normal hosts	(maximum: 4000 mg/day) PO in 5 divided doses for 5–7 days	keratitis and anterior uveitis[44]		
Primary varicella in compromised hosts	30 mg/kg/day IV in 3 divided doses for 7–10 days	Reduced incidence of cutaneous and visceral dissemination; reduced duration of lesion formation and time to healing[29,30]	Initiation of therapy within 24–48 hours of onset of infection and mild degree of immunologic dysfunction	++++
Zoster in compromised hosts	30 mg/kg/day IV in 3 divided doses for 7–10 days	Reduced risk of cutaneous dissemination and visceral complications[28,32]	Initiation of therapy within 24–48 hours of onset of infection and mild degree of immunologic dysfunction	++++

[a] Topical acyclovir is not recommended because its effects on duration of viral shedding, pain, and lesions are much less than those of systemic therapy in patients with primary infections.

CNS, central nervous system; HSV, herpes simplex virus; IV, intravenous; PO, orally; SEM, localized infection with disease limited to skin, eye, or mouth; +/−, benefit is limited and therapy usually not indicated; +, benefit is consistent but limited, and costs of therapy should be weighed against small amount of anticipated benefit and the decision to treat individualized; ++, therapeutic benefit usually favors treatment; +++, therapy indicated, although supporting data not definitive; ++++, therapy is clearly indicated and is based on the results of controlled clinical trials.

Therapy is indicated for life-threatening infections and for disease associated with severe morbidity and death, such as HSV encephalitis, neonatal HSV infections, and VZV infections in immunocompromised hosts.[21,27–32] Acyclovir therapy also is indicated for mucocutaneous HSV infections in immunocompromised hosts and for disseminated HSV and VZV infections in otherwise normal hosts, including pregnant women.[33–35] Acyclovir is effective for the treatment of symptomatic primary genital HSV infections,[36–39] reducing the median duration of virus shedding, pain, and length of time to complete healing.[40]

Intravenous and oral acyclovir therapies are almost equally efficacious; topical treatment provides less benefit. Neither intravenous nor oral treatment with acyclovir for primary or recurrent genital HSV disease reduces the frequency of recurrences.[41–43] Acyclovir probably reduces the ocular morbidity of zoster ophthalmicus.[44] The advantages of treating previously healthy individuals with herpes labialis,[45,46] recurrent genital herpes,[39,41,47] varicella,[48–51] and herpes zoster[52,53] are less dramatic, and the treatment of these patients should be individualized.

Favorable effects of therapy are more likely when acyclovir is begun soon after the onset of infection. For example, previously healthy people with primary varicella may benefit only if acyclovir is begun within 24 hours of appearance of the first cutaneous lesions.[48–50] Benefit, however, can be observed in the treatment of severe, life-threatening infections caused by HSV and VZV even if acyclovir is commenced several days after the onset of infection, provided that irreversible damage has not occurred.

Indications for prophylactic acyclovir therapy are summarized in Table 295.8. Prophylactic acyclovir is almost exclusively used for the suppression of HSV infections; its efficacy for CMV infections is inferior to that of ganciclovir.[54] The most frequent indication for long-term prophylactic therapy is in patients with frequently recurrent genital infections[39] in whom daily administration of acyclovir reduces the frequency of recurrences by at least 75%. Acyclovir has been shown to maintain a high degree of efficacy and little toxicity even after more than 5 years of continuous suppressive therapy.[55]

TABLE 295.8

Indications for Prophylactic Antiviral Therapy

Antiviral Agent	Clinical Indication	Expected Effect	Dosage
Acyclovir	Frequently recurrent genital HSV	70–90% reduction in frequency of clinical episodes of infection[55,61,62]; frequency of asymptomatic shedding also reduced, but not eliminated[346]	Start with 1000 mg/day in divided doses and slowly reduce to minimum effective dose; attempt withdrawal after 6–12 months; if symptoms recur, restart therapy
	Frequently recurrent HSV labialis	53% reduction in number of clinical recurrences[63]	400 mg bid for 4 months
	Skiers with histories of sun-induced recurrences of HSV labialis	73% reduction in risk of recurrence[60]	400 mg bid for 1 week
	Suppressive therapy after treatment of acute neonatal HSV disease	30% reduction in cutaneous recurrence (all disease categories); improved neurodevelopmental outcomes (CNS category)[66]	300 mg/m^2/dose tid for 6 months; monitor absolute neutrophil counts at 2 and 4 weeks, then monthly during therapy
	Reactivations of HSV associated with serious systemic complications such as erythema	Reduction in the frequency of serious complications associated with HSV infection	Use is supported by theoretical benefit and anecdotal reports, rather than controlled trials[61,65]; dosage is empiric

	multiforme, aseptic meningitis, and eczema herpeticum		
	Dermabrasion of facial skin or surgery involving the trigeminal ganglion in patients previously infected with HSV-1	Reduction in the frequency of postoperative outbreaks of herpes labialis[61,65]	Use is supported by theoretical benefit and anecdotal reports, rather than controlled trials; dosage is empiric
	HSV-seropositive persons undergoing bone marrow or solid-organ transplantation or induction chemotherapy for hematologic malignancy	50–60% decrease in number of herpetic recurrences during the time of drug administration[61]	500–750 mg/m^2/day begun before transplantation or induction chemotherapy and continued for about 6 weeks thereafter; intravenous therapy initially and oral therapy when tolerated
	CMV-seropositive persons undergoing bone marrow or solid-organ transplantation	As much as 50% reduction in the frequency of CMV infection and disease in CMV-seropositive recipients[347] and, to a lesser extent, in recipients at risk for primary infection[348]; however, ganciclovir is drug of choice[60]	1500 mg/m^2/day begun before transplantation and continued for 1–3 months thereafter; intravenous therapy initially, and oral therapy when tolerated
Ganciclovir	CMV-seropositive solid-organ transplant recipients	Reduction in frequency of CMV disease	10 mg/kg/day in 2 divided doses, started several days before transplantation and continued for 2–3 weeks after transplantation; 5 mg/kg/day in single dose thereafter
	CMV-seropositive renal or liver transplant recipients beginning OKT3 suppressive therapy	Reduction in frequency of CMV disease	10 mg/kg/day in 2 divided doses for 2–3 weeks after OKT3 initiated
	Bone marrow transplant recipients with positive CMV surveillance culture	Reduction in frequency of CMV disease	10 mg/kg/day in 2 divided doses for 2–3 weeks after transplantation; 5 mg/kg/day in single dose thereafter

CMV, cytomegalovirus; CNS, central nervous system; HSV, herpes simplex virus.

The use of prophylactic acyclovir therapy in pregnant women has been explored in several small studies,[56–58] but the numbers of patients evaluated are insufficient to prove definitively its safety or efficacy in this population. Neonatal HSV disease in babies born to women receiving antiviral suppression is reported.[59] Brief courses of acyclovir can be given to HSV-1–infected patients to suppress reactivation of HSV that predictably follows stimuli such as exposure to ultraviolet radiation[60] or facial surgery.[61] Longer courses can be given to those with frequently recurrent oral HSV infections,[55,61–63] and to people after ocular HSV disease to prevent recurrence.[64]

Prophylactic acyclovir has proved to be a useful strategy for postponing the inevitable reactivation of HSV infection in HIV-infected people with severe immunosuppression.[61] Anecdotal data suggest that prophylactic acyclovir can reduce the frequency of attacks of erythema multiforme temporally related to HSV.[65]

Data published in 2011 describe the benefit of oral acyclovir suppressive therapy after parenteral acyclovir therapy for acute neonatal HSV disease.[66] The National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Antiviral Study Group conducted a placebo-controlled evaluation of 6 months of oral acyclovir suppression after neonatal herpes infection. Subjects with neonatal HSV CNS disease who were randomized immediately at the conclusion of intravenous therapy to oral acyclovir for suppression had more favorable neurodevelopmental outcomes at 12 months of age compared with those in whom antiviral suppression was delayed until cutaneous recurrences occurred. Suppressive oral acyclovir therapy also delayed the development of cutaneous recurrences in all categories of neonatal HSV disease.[66]

The indications for valacyclovir therapy are the same as those for acyclovir.[39,67–69] Adult treatment doses are 1 g given orally three times daily for 7 days for herpes zoster in patients older than 50 years of age; 1 g given orally twice daily for 10 days for first-episode genital herpes; 500 mg given orally twice daily for 3 days for episodic treatment of recurrent genital HSV disease; 1 g given orally once daily for suppression of recurrent genital HSV; and 2 g given orally twice daily for 1 day for recurrent herpes labialis (≥12 years of age). The efficacy of valacyclovir has been demonstrated in the short-term treatment of recurrent herpes labialis (2 g PO bid for 1 day)[70] and in the suppression of recurrent herpes labialis (500 mg once daily).[71]

In children, valacyclovir dosing is 20 mg/kg per dose (dose not to exceed 1 g) administered three times daily (for VZV) or twice daily (for HSV).[20] In the United States, valacyclovir is licensed for the treatment of pediatric patients with orolabial HSV recurrences ≥12 years of age) and chickenpox (2–17 years of age). Although comparative data from controlled studies are limited, valacyclovir may be advantageous in treating infections caused by viruses that are less sensitive to acyclovir than HSV (i.e., VZV and CMV).

Adefovir Dipivoxil

Chemistry, Mechanism of Action, Spectrum, and Resistance.

Adefovir dipivoxil (Hepsera) is the oral prodrug of adefovir, which is an acyclic nucleotide analogue of deoxyadenosine-5′-monophosphate (dAMP).[72,73] Conversion of the prodrug to the active adefovir diphosphate is accomplished by cellular adenylate kinase. Adefovir diphosphate then acts as a competitive inhibitor of deoxyadenosine triphosphate for viral DNA polymerase, resulting in DNA chain termination after its incorporation in HBV DNA.[72,73] In addition to HBV, adefovir diphosphate competitively inhibits deoxyadenosine triphosphate as a substrate for HIV-1 reverse transcriptase, resulting in chain termination after its incorporation in HIV DNA.[74–76] In vitro, adefovir has an additive effect when combined with lamivudine, entecavir, or telbivudine.[77]

Resistance to adefovir is a limiting factor of prolonged use. The N236T mutation and the A181V mutation in the HBV polymerase confer in vitro and in vivo antiviral resistance to adefovir diphosphate.[78] Rates of resistance to adefovir at 1, 2, 4, and 5 years are 0%, 3%, 18%, and 29%, respectively.[79] HBV strains with the A181V mutation also are resistant to lamivudine.

Pharmacokinetics.

Adefovir dipivoxil is absorbed rapidly after oral administration. After a single oral dose, the bioavailability is about 59%.[80] Food does not substantially impact absorption of adefovir dipivoxil.[80] Half-life at steady state is approximately 7 hours. After absorption, adefovir dipivoxil is cleaved to adefovir by extracellular esterases.[80] Adefovir then is phosphorylated to the active moiety adefovir diphosphate by cellular adenylate kinase. The estimated intracellular half-life of adefovir diphosphate is 16 to 18 hours.[75] Adefovir is excreted renally as unchanged drug by tubular secretion and glomerular filtration.

Dosing in patients with baseline CrCl values less than 50 mL/min requires adjustment in the dosing interval.[80] The dose of adefovir dipivoxil does not need to be adjusted in patients with hepatic impairment.

Toxicity and Drug Interactions.

Adefovir usually is well tolerated over prolonged periods of administration.[79,81] In randomized, controlled trials, diarrhea, headache, and abdominal pain occurred slightly more frequently in adefovir-treated patients than placebo-treated patients.[82,83] Long-term administration may result in nephrotoxicity, but the risk for patients with adequate renal function is low.[79,84] In vitro, adefovir does not inhibit cytochrome P450. No clinically relevant drug interactions have been reported in clinical trials.[80]

Clinical Uses and Recommended Doses.

Adefovir has been studied in children with HBV infection, and is approved for use in patients ≥12 years of age. Adefovir is the preferred oral treatment option for children 12 through 15 years of age, after which they can be treated with entecavir.[85] In HBeAg-positive children from 2 through 17 years of age with alanine aminotransferase (ALT) values at least 1.5 times the upper limit of normal, adefovir therapy resulted in undetectable HSV DNA and normalization of ALT levels in 12- through 17-year-old patients but not in the 2- through 11-year-old patients.[86] In this trial of 173 children, no adverse effect associated with adefovir was identified,[86] and the drug was well tolerated in all age groups.

With a greater number of approved anti-HBV treatment options for adults, adefovir is not as effective as other antiviral agents and is no longer favored for the treatment of chronic HBV infection. In adults, adefovir therapy is associated with a 12% rate of HBeAg seroconversion, 21% rate of undetectable serum HBV DNA, and 53% rate of histologic improvement in HBeAg-positive patients after 1 year of therapy.[83] Once seroconversion occurs, it is sustained in 91% of patients.[87,88] In adults, persistence of high levels of HBV DNA after 48 weeks of adefovir therapy predicts the emergence of resistance.[79]

The optimal duration of adefovir treatment of children is unknown. In the pivotal pediatric study,[86] children were treated for 48 weeks. For those who did not seroconvert during this time, continued treatment for up to 2 years was provided. Results of this extended therapy have not been reported. Children with HBeAg-positive chronic HBV infection should continue on treatment for at least 6 months after seroconversion.[85] Monitoring for several months after cessation of therapy is recommended because posttreatment flares have been reported in adults.[80,89] The recommended dose of adefovir dipivoxil for chronic hepatitis B patients 12 years of age or older with adequate renal function is 10 mg, taken orally once daily without regard to food.

Cidofovir

Chemistry, Mechanism of Action, Spectrum, and Resistance.

Cidofovir (Vistide), or (5)-1-(3-hydroxy-2-(phosphonylmethoxy)-propyl)cytosine (HPMPC), is a novel acyclic phosphonate nucleotide analogue. Cidofovir has a mechanism of action that is similar to that of the nucleoside analogues, such as acyclovir and ganciclovir. In its native form, however, cidofovir already has a single phosphate group attached, and viral enzymes are not required for the initial phosphorylation of the drug. Cellular kinases sequentially attach two additional phosphate groups, converting cidofovir to its most active form. The active compound is a competitive inhibitor of DNA polymerase.[90] Although cidofovir is taken up by virus-infected and uninfected cells, the active form of the drug exhibits a 25-fold to 50-fold greater affinity for the viral DNA polymerase compared with the cellular DNA polymerase, selectively inhibiting viral replication.[90,91] Incorporation into the growing viral DNA chain results in reductions in the rate of DNA synthesis.

Cidofovir has activity against HSV and CMV. Because of its unique phosphorylation requirements for activation, the drug usually maintains activity against acyclovir- and foscarnet-resistant HSV isolates and against ganciclovir- and foscarnet-resistant CMV mutants. Cidofovir exhibits marked activity against CMV, with inhibitory concentrations of 0.1 μg/mL for susceptible clinical isolates.[92] Although cidofovir is less potent in vitro against HSV than is acyclovir, its favorable pharmacokinetic profile increases its anti-HSV activity. Cidofovir also has in vitro activity against VZV, EBV, human herpesvirus 6, human herpesvirus 8, polyomaviruses, orthopoxviruses, adenovirus, BK virus, and HPV.

Only a small number of cidofovir-resistant CMV isolates has been described. Some also are resistant to ganciclovir because of mutations in the DNA polymerase gene, but they remain sensitive to foscarnet.[93–95]

Pharmacokinetics.

After intravenous administration, the plasma half-life is 2.6 hours, although cidofovir persists in cells for prolonged periods.[96] Active intracellular metabolites of cidofovir have half-lives of 17 to 48 hours.[91] This prolonged intracellular activity allows for an intermittent dosing schedule that is attractive compared with that for ganciclovir or foscarnet. About 90% of drug is excreted in the urine, primarily by renal tubular secretion.[97,98]

Toxicity and Drug Interactions.

Nephrotoxicity is the principal adverse event associated with systemic administration.[97,98] Cidofovir concentrates in renal cells in amounts 100 times greater than in other tissues, producing severe nephrotoxicity involving the proximal convoluted tubule if concomitant hydration and administration of probenecid are not employed.[99] Renal toxicity manifests as proteinuria and glycosuria.[100] To decrease the potential for nephrotoxicity, aggressive intravenous prehydration and coadministration of probenecid are required with each cidofovir dose. Within 48 hours before delivery of each dose of cidofovir, serum creatinine and urine protein concentrations must be determined and the dose adjusted if indicated. Cidofovir should not be administered concomitantly with other nephrotoxic agents. Cidofovir is contraindicated in patients with a serum creatinine level greater than 1.5 mg/dL, a calculated CrCl of 55 mL/min or lower, or a urine protein level of at least 100 mg/dL (i.e., ≥2+ proteinuria). The maintenance dose of cidofovir must be reduced from 5 to 3 mg/kg for an increase in serum creatinine of 0.3 to 0.4 mg/dL above baseline. Cidofovir therapy must be discontinued if the serum creatinine level increases by at least 0.5 mg/dL above baseline.

Cidofovir can have other adverse effects. In animal studies, cidofovir has been carcinogenic and teratogenic and has caused hypospermia.

Because of poor oral bioavailability (2%–26%),[101] cidofovir can be administered only intravenously or topically. Intravitreal administration has been associated with ocular hypotony.

Clinical Uses and Recommended Doses.

Cidofovir has been evaluated for the treatment of CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS).[102,103] Therapy delays progression of retinal disease. In one study, patients who had failed or were intolerant of traditional therapy (i.e., ganciclovir or foscarnet) were treated with a 2-week induction course of cidofovir (5 mg/kg administered weekly) followed by randomization to maintenance with a dose of 5 mg/kg or 3 mg/kg every other week.[102] At the higher maintenance dose of cidofovir, disease progression was delayed for 115 days, compared with 49 days in the lower-dose cohort. Cidofovir also has been used successfully in the management of disease caused by acyclovir-resistant HSV isolates.[99]

The safety and efficacy of cidofovir in children have not been studied. The use of cidofovir in children with AIDS warrants caution because of the risk of long-term carcinogenicity and reproductive toxicity.

Intralesional injection of cidofovir has been reported in several small, uncontrolled studies of patients with laryngeal papillomatosis caused by HPV infection.[104,105] Some patients have experienced dramatic improvement in their disease, although the anecdotal nature of the trials prevents definitive conclusions regarding efficacy.[106] Uncontrolled studies have reported less impressive therapeutic responses to cidofovir therapy,[107–109] raising questions about efficacy and safety in laryngeal papillomatosis. Case reports and small case series suggest that cidofovir may be beneficial in the management of adenovirus infections[110–112] and BK virus infections[113,114] in immunocompromised patients.

The recommended induction dose of cidofovir for patients with CMV disease with a serum creatinine level ≤1.5 mg/dL, a calculated CrCl greater than 55 mL/min, and a urine protein level less than 100 mg/dL (i.e., equivalent to <2+ proteinuria) is 5 mg/kg administered once per week for 2 consecutive weeks. The recommended maintenance dose of cidofovir is 5 mg/kg administered once every 2 weeks. The drug should be administered with probenecid, and hydration should be ensured.

Dasabuvir Copackaged With Ombitasvir-Paritaprevir-Ritonavir

Chemistry, Mechanism of Action, Spectrum, and Resistance.

Dasabuvir copackaged with ombitasvir-paritaprevir-ritonavir (Viekira Pak) is an oral regimen composed of four medications: ombitasvir, paritaprevir, ritonavir, and dasabuvir. Ombitasvir, paritaprevir, and ritonavir are combined in a fixed-dose tablet, and dasabuvir is a separate tablet. Dasabuvir is a nonnucleoside inhibitor of the hepatitis C virus (HCV) RNA-dependent RNA polymerase encoded by the gene for nonstructural protein 5B (NS5b), which is essential for replication of the viral genome; its antiviral activity is limited to HCV genotype 1. Ombitasvir is a NS5a inhibitor with potent antiviral activity against HCV genotypes 1 through 6; NS5a is essential for viral RNA replication and virion assembly.

Paritaprevir is an inhibitor of the NS3/4a serine protease of HCV, which is necessary for the proteolytic cleavage of the HCV encoded polyprotein and is essential for viral replication. Paritaprevir has activity against HCV genotypes 1 through 4.

Ritonavir is a potent inhibitor of CYP3A4 enzymes and is used as a pharmacologic booster for paritaprevir. Ritonavir does not have intrinsic activity against HCV. Among patients with on-treatment virologic failure and posttreatment relapse, treatment-emergent mutations were observed in all the three major drug targets (i.e., NS3, NS5a, and NS5b). The efficacy of the Viekira Pak is not known for patients with prior virologic failure and resistance with treatment that included another NS3/4a inhibitor, NS5a inhibitor, or NS5b inhibitor. For patients who develop virologic failure and resistance when treated with the Viekira Pak, the impact on subsequent therapy with other NS3/4a, NS5a, or NS5b inhibitors is unknown.

Pharmacokinetics.

Dasabuvir, ombitasvir, paritaprevir, and ritonavir are absorbed after oral administration, and the mean time to maximal concentration (Tmax) of approximately 4 to 5 hours. Steady-state exposures are achieved after approximately 12 days of dosing. The estimated bioavailability of dasabuvir is approximately 70%, but bioavailability is not known for ombitasvir, paritaprevir, and ritonavir. The median steady-state AUC_{0-24} values for ombitasvir, paritaprevir, and ritonavir are 1000, 2220, and 6180 ng•hr/mL, respectively, and the median steady-state AUC_{0-12} for dasabuvir is 3240 ng•hr/mL. The median steady-state C_{max} values for ombitasvir, paritaprevir, ritonavir, and dasabuvir are 68, 262, 682, and 667 ng/mL, respectively.

Dasabuvir, ombitasvir, paritaprevir, and ritonavir should be administered with a meal. Compared with fasting conditions, administration with a high-fat meal increases the mean AUC by 76%, 180%, 44%, and 22%, respectively. All four components of the Viekira Pak are highly bound (>97%) to human plasma proteins. Dasabuvir is metabolized predominantly by CYP2C8 and to a lesser extent by CYP3A. Ombitasvir is metabolized predominantly by amide hydrolysis followed by oxidative metabolism. Paritaprevir is metabolized predominantly by CYP3A4 and to a lesser extent by CYP3A5. Ritonavir is metabolized predominantly by CYP3A and to a lesser extent by CYP2D6. All four drugs are excreted primarily in the feces.

Toxicity and Drug Interactions.

The Viekira Pak is well tolerated. The most common adverse effects are fatigue, nausea, pruritus, other skin reactions, insomnia, and asthenia. The Viekira Pak has numerous medication contraindications, primarily because of the potent ritonavir inhibition of the CYP3A4 enzyme. Medication contraindications and warnings are listed in the package insert.

Clinical Uses and Recommended Dosage.

Clinical trials assessed efficacy in HCV genotype 1 patients with compensated liver disease with or without cirrhosis for treatment durations of 12 or 24 weeks.[115–119] Sustained virologic responses at

12 weeks (i.e., SVR12) were greater than 96% in all studies involving patients without cirrhosis when the treatment duration was 12 weeks, and sustained virologic responses were greater than 95% for patients with cirrhosis when the treatment duration was 24 weeks (i.e., SVR24). Based on these data, Viekira Pak administered with ribavirin is indicated for use in genotype 1a–infected patients with or without cirrhosis for durations of 24 weeks or 12 weeks, respectively, and for genotype 1b–infected patients with cirrhosis for the treatment duration of 12 weeks. Viekira Pak treatment without ribavirin is indicated in genotype 1b–infected patients without cirrhosis for the treatment duration of 12 weeks. The daily dosage is two ombitasvir, paritaprevir, plus ritonavir 12.5/75/50-mg tablets once daily (in the morning) and one dasabuvir 250-mg tablet twice daily (morning and evening) with a meal without regard to fat or calorie content.

Treatment of HCV with the Viekira Pak has not been studied in children.

Entecavir

Chemistry, Mechanism of Action, Spectrum, and Resistance.

Entecavir (Baraclude) is a guanosine nucleoside analogue, which, after phosphorylation to the active triphosphate form, exhibits potent activity against HBV polymerase.[120–122] Entecavir triphosphate inhibits HBV polymerase base priming, reverse transcription of the negative strand from the pregenomic messenger RNA, and synthesis of positive-strand HBV DNA. It is approximately 30-fold more potent than lamivudine in vitro.[120] Entecavir triphosphate is a weak inhibitor of cellular DNA polymerases, and it does not demonstrate activity against HIV-1 replication.[123,124]

Both in vitro and in vivo data suggest that emergence of resistance to entecavir is rare in nucleoside-naïve patients.[125–130] However, approximately 7% of lamivudine-refractory patients with HBV infection develop entecavir resistance-associated amino acid substitutions at rtI169, rtT184, rtS202, and rtM250 when preexisting lamivudine resistance mutations reL180M or rtM204V/I are present.[131] Additional mutations within the HBV viral polymerase are required for entecavir resistance to develop.[126,127,129] Five-year entecavir-resistance rates are 1.2% for nucleoside-naïve and 51% for lamivudine-refractory patients[125,132] Entecavir is active against adefovir-resistant mutants,[120] and because additional mutations are required to develop resistance to entecavir, the drug also remains active against lamivudine-resistant mutants.[125,133] Emergence of entecavir resistance mutations usually is associated with virologic rebound during therapy.[127]

Pharmacokinetics.

Entecavir peak plasma concentrations occur between 0.5 and 1.5 hours after oral administration in adults. Steady state is achieved after 6 to 10 days of once-daily administration, with approximately twofold accumulation. At steady state, C_{max} is 4.2 ng/mL, and C_{trough} is 0.3 ng/mL. Due to decreases of approximately 20% in the AUC when the drug is administered with food, entecavir should be given at least 2 hours before or after a meal. The intracellular half-life of entecavir triphosphate is 15 hours. Approximately two thirds to three fourths of drug is excreted unchanged in the urine.

Pharmacokinetic studies of entecavir have not been conducted for children younger than 16 years of age.

Toxicity and Drug Interactions.

Coadministration of entecavir in vitro with several HIV nucleoside reverse transcriptase inhibitors (NRTIs) does not impact entecavir anti-HBV activity, and entecavir does not have a detrimental effect on NRTI anti-HIV activity. Entecavir is not a substrate, inhibitor, or inducer of the cytochrome P450 enzyme system, which limits drug interactions. The steady-state pharmacokinetics is not altered when it is coadministered with lamivudine, adefovir dipivoxil, and tenofovir disoproxil fumarate.

As with other therapies for chronic HBV infections, severe acute exacerbations of hepatitis B have been reported in patients who have discontinued entecavir therapy. Hepatic function should be monitored closely with clinical and laboratory follow-up examinations for at least several months for patients who discontinue HBV therapy.

Clinical Uses and Recommended Dosage.

Entecavir is indicated for the treatment of chronic HBV infection in adults with evidence of active viral replication with persistent elevations in serum aminotransferases or histologically active liver disease. Entecavir is superior to lamivudine in the treatment of chronic HBV infection,[134] and it is the most potent anti-HBV agent available.[135,136] When entecavir (0.5 mg once daily) was compared with lamivudine (100 mg once daily) for 52 weeks in nucleoside-naïve patients with compensated liver disease, more of those receiving entecavir had improvement in histologic Knodell necroinflammatory scores in the HBeAg-positive (72% vs. 62%, $P < 0.05$) and HBeAg-negative (70% vs. 61%, $P < 0.05$) subgroups. Similarly, more patients developed normal serum ALT concentrations during therapy with entecavir compared with lamivudine (68% vs. 60% for HBeAg-positive patients, $P < 0.05$; 78% vs. 71% for HBeAg-negative patients, $P < 0.05$). More patients cleared viremia on entecavir compared with lamivudine (67% vs. 36% for HBeAg-positive patients, $P < 0.05$; 90% vs. 72% for HBeAg-negative patients, $P < 0.05$).[137–139] Responses endured through the second year of therapy.[140]

Among patients with lamivudine-refractory chronic HBV infection, changing to entecavir (1 mg once daily) was superior to continuing lamivudine (100 mg once daily).[141] More patients receiving entecavir had improvement in histologic Knodell necroinflammatory scores (55% vs. 28%, $P < 0.01$), in the Ishak fibrosis score (34% vs. 16%, $P < 0.01$), normalization of ALT concentration (61% vs. 15%, $P < 0.0001$), and clearance of viremia (19% vs. 1%, $P < 0.0001$).[132,137]

Entecavir is superior to adefovir dipivoxil in nucleoside-naïve, HBeAg-positive patients.[142] At 12 weeks, the mean change in serum HBV DNA concentration was $-6.23 \log_{10}$ copies/mL in the entecavir group, compared with −4.42 log10 copies/mL in the adefovir dipivoxil group. After 96 weeks of treatment, 97% of entecavir-treated patients had achieved ALT normalization, compared with 85% of adefovir-treated patients (95% confidence interval [CI], 5.4–28.6).[142]

The recommended dose of entecavir for chronic HBV infection in nucleoside-naïve adults and adolescents 16 years of age or older is 0.5 mg once daily. The entecavir dose should be increased to 1 mg once daily in HBV-infected those 16 years of age or older who have a history of HBV viremia while receiving lamivudine or who have a known lamivudine-resistance mutation. The optimal duration of therapy with entecavir is unknown but is being evaluated.[85]

Hemodialysis removes approximately 13% of the entecavir dose over 4 hours, whereas CAPD removes approximately 0.3% of the dose over 7 days. In patients with renal impairment, clearance of entecavir decreases with the rate of CrCl. Dosage adjustment is recommended for patients with a CrCl less than 50 mL/min, including patients on hemodialysis or CAPD. Dosage is 0.25 mg once daily for CrCl values of 30 to less than 50 mL/min, 0.15 mg once daily for CrCl values of 10 to less than 30 mL/min, and 0.05 mg once daily for CrCl values of less than 10 mL/min or CAPD. A supplemental dose should be administered after hemodialysis. These doses are doubled for patients refractory to lamivudine.

Famciclovir and Topical Penciclovir

Chemistry, Mechanism of Action, Spectrum, and Resistance.

Famciclovir (Famvir) is the inactive diacetyl ester prodrug of penciclovir (Denavir), an acyclic nucleoside analogue with a spectrum of activity against herpesviruses similar to that of acyclovir. Its activation by viral and host cell enzymes and its mechanism of action also are akin to those of acyclovir, except that penciclovir is neither an obligate DNA chain terminator nor an inactivator of DNA polymerase. However, laboratory studies suggest that penciclovir triphosphate retards the rate of subsequent nucleotide incorporation.

Penciclovir is approximately 100-fold less potent than acyclovir in inhibiting herpesvirus DNA polymerase activity. However, it remains an effective antiviral agent because of high intracellular concentrations and long half-life. Because penciclovir must be activated by the virus-encoded TK enzyme, TK-deficient viral strains are resistant to acyclovir and penciclovir. Penciclovir persists in high intracellular concentrations much longer than acyclovir. The antiviral effect is more sustained, and the drug can be administered less frequently than acyclovir.

Pharmacokinetics.

After oral administration of famciclovir, the bioavailability of penciclovir is about 70%. Food delays absorption but does not affect the peak plasma drug concentration. Peak concentrations of drug after intravenous administration of 10 mg/kg are approximately sixfold higher than those attained after oral doses of 250 mg. Drug half-life is 2.5 hours. Almost 75% of administered drug is recovered unchanged in the urine, and dose reduction is recommended for those with compromised renal function. A 12-hour dosing interval is recommended for those with CrCl values between 30 and 50 mL/min/1.73 m^2, and a 24-hour interval is recommended for those with CrCl values less than 30 mL/min/1.73 m^2.[143] Measurable penciclovir concentrations are not detectable in plasma or urine after topical administration of penciclovir cream.

Famciclovir pharmacokinetics have been assessed in a single-dose pediatric study of infants 1 to 12 months of age given famciclovir sprinkles orally.[144] Infants younger than 6 months of age had substantially lower systemic exposure compared with those 6 to 12–months of age. A small safety and pharmacokinetic study assessed a single, large dose of famciclovir in adolescents with recurrent herpes labialis.[145]

Toxicity and Drug Interactions.

Famciclovir is as well tolerated as acyclovir. Complaints of nausea, diarrhea, and headache occurred in clinical trials, although at frequencies similar to those reported by placebo recipients.[146] No clinically significant drug interactions have been reported, but concentrations of famciclovir among volunteers increase by about 20% in the patients receiving concomitant cimetidine or theophylline administration.[147]

Clinical Uses and Recommended Dosage.

The efficacy for treatment of uncomplicated herpes zoster was studied in a placebo-controlled, double-blind trial enrolling 419 immunocompetent adults.[148] Treatment was begun within 72 hours of the appearance of lesions, and therapy was continued for 7 days. Famciclovir therapy decreased the median time to full crusting by 2 days. The effects of famciclovir were greater when therapy was initiated within 48 hours of the onset of rash, and effects were more pronounced in patients 50 years of age or older. There were no overall differences in the duration of pain before healing of the rash between the famciclovir-treated and placebo groups. There also was no difference in the incidence of postherpetic neuralgia. Among patients who developed postherpetic neuralgia, however, the median duration of symptoms was shorter for patients treated with famciclovir than those given placebo (63 and 119 days, respectively).

A double-blind, controlled trial enrolling 545 immunocompetent adults with uncomplicated herpes zoster treated within 72 hours of the appearance of lesions compared three doses of famciclovir with acyclovir at a dose of 800 mg given five times per day. The times to full lesion crusting and times to loss of acute pain were comparable for all groups, and there was no statistically significant difference in the time to resolution of postherpetic neuralgia.

Placebo-controlled studies of famciclovir for the episodic treatment of genital HSV[149] and for suppression of genital HSV recurrences[150,151] have shown efficacy and good drug tolerability.[39] Famciclovir was approved by the FDA for the treatment of herpes zoster in 1994 and subsequently was approved for the treatment and suppression of genital HSV disease.

The indications for and recommended dosages of famciclovir are presented in Table 295.9. Dosing in infants and young children has been studied.[144] Dosing recommendations for children 6 months to 12 years of age are based on pharmacokinetic modeling and have not been studied adequately to warrant dosing recommendations in this age group.

TABLE 295.9

Famciclovir: Indications and Dosages

Infection	Dosage	Duration
Zoster	500 mg tid	7 days
Recurrent genital HSV, immunocompetent host (episodic therapy)	1000 mg bid	1 day
Recurrent genital HSV, immunocompetent host (suppressive therapy)	250 mg bid	Up to 1 year
Recurrent genital HSV, immunocompromised host (episodic therapy in compromised hosts)	500 mg bid	7 days
Recurrent orolabial HSV, immunocompromised host (episodic therapy)	500 mg bid	7 days
Recurrent orolabial HSV, immunocompetent host (episodic	1500 mg	Administer as a

therapy)		single dose

HSV, herpes simplex virus.

Topical penciclovir for the treatment of recurrent herpes labialis reduces the time to healing and the duration of pain by about one half of a day.[152,153] Application of medicine should begin as early as possible, preferably during the prodromal phase, and should be continued every 2 hours during waking hours for 4 days.

Ganciclovir and Valganciclovir

Chemistry, Mechanism of Action, Spectrum, and Resistance.

Ganciclovir (Cytovene) is a nucleoside analogue that is different from acyclovir by having an extra hydroxymethyl group on the acyclic side chain.[154] Its greatest in vitro activity is against CMV (see Table 295.4), although it is also as active as acyclovir against HSV-1 and HSV-2 and almost as active against VZV.

As with acyclovir and penciclovir, the first step in ganciclovir phosphorylation is carried out by a virus-encoded enzyme, and the final steps are achieved by cellular enzymes. CMV lacks the gene for TK, and the enzyme that catalyzes the initial phosphorylation of ganciclovir in CMV-infected cells is the phosphotransferase encoded by the *ul97* gene.[155,156] Intracellular ganciclovir triphosphate concentrations are at least 10-fold higher in CMV-infected cells than in noninfected cells,[157] and intracellular ganciclovir triphosphate has a half-life of 24 hours or longer.

Ganciclovir triphosphate is a competitive inhibitor of herpesvirus DNA polymerases, although it has some activity against cellular DNA polymerases. This potential for incorporation into host cellular DNA accounts for ganciclovir's substantial toxicity. Incorporation of ganciclovir triphosphate into the growing viral DNA chain results in slowing and subsequent cessation of DNA chain elongation.[158]

Valganciclovir (Valcyte) was approved by the FDA in 2001. Because valganciclovir is well absorbed after oral administration, it can be a favorable alternative to intravenously administered ganciclovir for the treatment and suppression of CMV infections in immunocompromised hosts. Valganciclovir is an L-valine ester prodrug of ganciclovir and has the same mechanism of action and antiviral spectrum as ganciclovir.[159]

Ganciclovir resistance among CMV isolates is conferred by mutations in the *UL97* gene or the CMV DNA polymerase gene. Of these two mechanisms of antiviral resistance, ganciclovir-resistant CMV isolates with mutations in the *UL97* open reading frame are the predominant phenotype.[93] Specific mutations in the *UL97* region can be detected rapidly in plasma and serum by direct sequencing of polymerase chain reaction (PCR)–amplified CMV DNA.[160]

Resistant strains of CMV should be suspected when progressive disease and continued recovery of virus occur despite ganciclovir therapy. In one study, 8% of 72 patients with AIDS had progressive infection associated with isolation of ganciclovir-resistant strains of CMV after 3 months of continuous ganciclovir therapy.[161] Resistance may be more likely in patients treated with oral ganciclovir than in those treated with intravenous ganciclovir because of the selective pressure applied by the lower concentrations of drug achieved with oral administration.[162] In contrast, CMV isolates from solid-organ transplant recipients who have been exposed to ganciclovir appear less likely to develop resistance.[163] Foscarnet may be useful in the treatment of CMV infections caused by ganciclovir-resistant isolates.[164]

Occasionally, strains of HSV that are resistant to acyclovir because of TK deficiency also are less sensitive to ganciclovir.[165] Ganciclovir-resistant isolates of HSV due to mutations in DNA polymerase have been demonstrated in the laboratory but have not become a clinical problem.

The mechanism of resistance to ganciclovir and valganciclovir are the same.[159] Selective pressure resulting from exposure to lower concentrations of drug appears to increase the likelihood of resistance developing among CMV isolates,[162] and it is thought that the higher serum and tissue concentrations of ganciclovir achieved with administration of valganciclovir produces less emergence of resistance compared with oral ganciclovir. Small studies have indicated that rates of resistance among valganciclovir recipients are similar to those of intravenous ganciclovir recipients[166] and are less than those of patients taking ganciclovir orally.[167]

Pharmacokinetics.

Peak serum concentrations of ganciclovir attained after 5 mg/kg administered intravenously range from 8 to 11 μg/mL.[154] Concentrations sufficient to inhibit susceptible strains of CMV are attained in aqueous humor, subretinal fluid, CSF, and brain tissue. Most of an administered dose of ganciclovir is eliminated unchanged in the urine; the elimination half-life is 2 to 3 hours.[15] Dose reduction, roughly proportional to the degree of reduction in CrCl, is necessary in patients with impaired renal function (see Table 295.6).[160,168] For CrCl values of 50 to less than 80 mL/min/1.73 m^2, one half of the usual dose should be given every 12 hours. The same dose should be given every 24 hours for CrCl values of 25 to less than 50 mL/min/1.73 m^2, and 25% of the usual dose should be given every 24 hours for CrCl values of less than 25 mL/min/1.73 m^2. Because ganciclovir is efficiently removed by hemodialysis, a supplemental dose is recommended after dialysis.[168]

The pharmacokinetics of ganciclovir in the neonatal population are similar to those of adults.[169] After intravenous administration of 6 mg/kg of ganciclovir, peak concentrations of 7 μg/mL are achieved. The mean elimination half-life is 2.4 hours. Pharmacokinetics of oral valganciclovir have been compared with those of parenteral ganciclovir in this population.[170] Intravenous ganciclovir clearance almost doubled, and the AUC_{12} was reduced by almost one half over the first 6 weeks of life. In comparison, only a marginal decrease in AUC_{12} was seen after administration of valganciclovir oral solution, possibly because bioavailability increased by 32% over the same period.

Bioavailability of oral ganciclovir is poor, with less than 10% of the drug absorbed after oral administration.[171] Despite this, an oral dose of 1000 mg of ganciclovir produces a peak plasma concentration of 1 μg/mL, a level that is above the inhibitory concentration for most CMV clinical isolates. Intravitreal drug concentration achieved during intravenous induction therapy averages 1 μg/mL, whereas the subretinal concentration is comparable with that of plasma.[172,173] The concentration of ganciclovir in the CNS is 24% to 70% of the plasma level, and the brain concentration is approximately 38% of plasma level.[174]

Valganciclovir is rapidly converted to ganciclovir, with a mean plasma half-life of about 30 minutes.[175] The absolute bioavailability of valganciclovir exceeds 60%, and it is enhanced by about 30% with concomitant administration of food.[176] Oral valganciclovir produces exposures of ganciclovir exceeding those attained with oral ganciclovir and are similar to those reported after standard intravenous administration of ganciclovir.[177] Patients with impaired renal function require dosage reduction roughly proportional to their reduction in CrCl.[159]

Toxicity and Drug Interactions.

The most important toxic effect of ganciclovir is myelosuppression. Dose-related neutropenia, defined as a more than 50% decrease in absolute neutrophil count from baseline or less than 1000/mm^3, is the most consistent hematologic disturbance.[154] The incidence of neutropenia during a 2-week course is about 40%. It is dose limiting in about 15% of courses, and it is reversible on cessation of the drug.[154] The likelihood of neutropenia occurring after oral administration of ganciclovir is lower, with 14% to 24% of patients developing an absolute neutrophil count of less than 1000/mm^3.[178]

Hematopoietic growth factors may be useful in preventing or counteracting neutropenia.[179] Thrombocytopenia (<50,000 platelets/mm^3) occurs in approximately 20% of treated patients. Anemia occurs in only about 2% of ganciclovir recipients.

Approximately 5% of ganciclovir recipients experience some combination of headache, confusion, altered mental status, hallucinations, nightmares, anxiety, ataxia, tremors, and seizures. About 2% of recipients develop fever, rash, and abnormal levels of serum hepatic enzymes. Intraocular injection of ganciclovir can cause transient increases in intraocular pressure with associated intense pain and amaurosis lasting up to 30 minutes.[180]

In preclinical test systems, ganciclovir is mutagenic, carcinogenic, and teratogenic. It also causes irreversible reproductive toxicity in animals.[181]

The most common side effects associated with valganciclovir therapy include diarrhea (41%), nausea (30%), neutropenia (27%), anemia (26%), and headache (22%).[159] Up to 5 years of treatment with valganciclovir is well tolerated in patients with AIDS, and the type and incidence of adverse events experienced long term appear to be similar to those observed at 1 year.[182]

Clinical Uses and Recommended Dosage.

Ganciclovir is indicated for the treatment and prevention of life- and sight-threatening CMV infections occurring in immunosuppressed patients.[154] It is approved in the United States for the treatment and suppression of retinitis caused by CMV in immunocompromised patients and for the prevention of CMV disease in transplant recipients. It is frequently used for other serious CMV infections.

Almost 90% of patients with CMV retinitis have improvement or stabilization of the ocular disease and clearing of the condition, demonstrated by a more than 100-fold reduction in viral titers, from urine, blood, the and throat after 1 to 2 weeks of ganciclovir therapy.[179] Because relapse of retinitis is virtually inevitable in patients with AIDS, ganciclovir should be continued long term for CMV suppression after induction therapy.

Patients in whom ganciclovir therapy has failed may benefit from treatment with a combination of foscarnet and ganciclovir.[183] Patients with AIDS who have CNS disease caused by CMV also have been treated successfully with a combination of ganciclovir and foscarnet.[184] As many as 25% of ganciclovir recipients develop resistance within 9 months of the initiation of therapy.[185,186]

Patients with AIDS and solid-organ transplant recipients who have gastrointestinal disease attributed to CMV appear to benefit from ganciclovir therapy.[187,188] Ganciclovir monotherapy does not appear to benefit bone marrow recipients with CMV gastrointestinal infections.[189]

Limited and uncontrolled data suggest that ganciclovir therapy may be useful in patients with AIDS and CMV pneumonia.[154] Bone marrow transplant recipients with CMV pneumonia fail to respond to ganciclovir therapy alone[190] but may benefit from therapy with intravenous CMV hyperimmunoglobulin and ganciclovir given together.[191,192]

Ganciclovir has been evaluated in the treatment of neonates congenitally infected with CMV. In a phase III randomized, controlled trial, ganciclovir therapy (6 mg/kg per dose administered every 12 hours intravenously for 6 weeks) protected infants from hearing deterioration beyond 1 year of life,[193] and it may improve neurologic outcomes.[194] Transient positive effects on growth also were seen, as was a decreased time to resolution of elevated serum hepatic transaminase levels. Approximately two thirds of treated patients, however, developed neutropenia, and one half required dose modification.

A phase I/II pharmacokinetic and pharmacodynamic study of oral valganciclovir established that a 16-mg/kg dose of oral valganciclovir produced similar systemic exposure to that of a 6-mg/kg dose of intravenous ganciclovir.[170] This dose of valganciclovir was then evaluated in a randomized, double-blind, controlled trial enrolling infants with symptomatic congenital CMV disease.[195] Durations of therapy for 6 weeks and 6 months were compared. The longer duration of therapy improved audiologic and neurodevelopmental outcomes more than that seen with 6 weeks of treatment. Neutropenia was less prevalent than with parenterally administered ganciclovir.

Ganciclovir is useful for the prevention of CMV infections in high-risk immunocompromised patients, including bone marrow and solid-organ transplant recipients (see Table 295.8). Strategies that have been used to reduce the frequency of posttransplantation disease include routine administration of ganciclovir to all recipients at risk and pre-emptive administration to those who have a positive culture for CMV after transplantation. Pre-emptive therapy has been demonstrated to reduce CMV disease in recipients of liver,[196] lung,[197] heart,[198] and bone marrow transplants.[199–201] CMV-seropositive recipients of heart, lung, or liver transplants who receive routine prophylaxis with ganciclovir for 1 month also have significant reductions in posttransplant CMV infection and disease.[35,202–205] Pre-emptive administration of ganciclovir improves survival of bone marrow transplant recipients,[206,207] whereas routine initiation of prophylactic ganciclovir before bone marrow transplantation in patients who are CMV seropositive does not impact survival.[207,208] Ultimately, however, the best strategy has not been determined for preventing primary CMV infections in CMV-seronegative solid-organ transplant recipients who receive an organ from a CMV-seropositive donor.

The usual therapeutic and prophylactic dose of intravenous ganciclovir is 10 mg/kg/day divided every 12 hours for 2 to 3 weeks. For continued suppressive therapy to prevent relapse of infection (e.g., patients with AIDS) or long-term prophylaxis, either of the following may be used: 5 mg/kg as a single daily dose each day of the week or 6 mg/kg administered as a single dose 5 days per week. Prophylactic oral ganciclovir (1000 mg three times daily) significantly reduces the risk of CMV disease in patients with advanced AIDS.[209]

Indications for valganciclovir are similar to those for ganciclovir. However, based on limited controlled trials, valganciclovir is approved only for induction and maintenance therapy for CMV retinitis.[210] The recommended dose of valganciclovir for induction therapy is 900 mg twice daily for 2 weeks. The recommended dose for maintenance therapy is 900 mg once daily. Orally administered valganciclovir appears to be as effective as intravenous ganciclovir for induction treatment and is convenient and effective for the long-term management of CMV retinitis in patients with AIDS.

The greater systemic exposure to ganciclovir delivered by valganciclovir when used prophylactically is safe and is associated with delayed development of viremia compared with oral ganciclovir in solid-organ transplant recipients.[211–213] Valganciclovir also is effective as pre-emptive therapy[214–216] and as treatment for CMV disease[217] in solid-organ transplant recipients.

Lamivudine

Chemistry, Mechanism of Action, Spectrum, and Resistance.

Lamivudine (Epivir) is a nucleoside analogue that is phosphorylated to lamivudine triphosphate by cellular kinases. Lamivudine inhibits the reverse transcriptase of HBV and HIV, and it is indicated for the treatment of HIV and chronic HBV infection.

Lamivudine-resistant HBV mutants occur in up to one third of patients by the end of 1 year of therapy and in up to two thirds of them by the end of 4 years of drug exposure.[218] The most common mutation affects the tyrosine-methionine-aspartate-aspartate (YMDD) motif in the catalytic domain of the HBV polymerase, resulting in a change from methionine to valine (M522V) or isoleucine (M522I).

Pharmacokinetics.

Lamivudine at a dose of 4 mg/kg administered twice daily produces an AUC_{12} of 5.16 mg•hr/L and half-life ($t_{1/2}$) of 1.76 hours. The half-life in children is less than the half-life in adults (i.e., 3.5 hours).[219]

Toxicity and Drug Interactions.

Adverse reactions to lamivudine include pancreatitis, paresthesia, peripheral neuropathy, neutropenia, anemia, rashes, nausea, vomiting, and hair loss.

Clinical Uses and Recommended Dosage.

In the treatment of chronic HBV infection, lamivudine decreases serum HBV DNA by 3 to 4 log copies per mL in most patients. Among patients who are HBeAg positive, approximately 20% achieve HBeAg seroconversion and undetectable serum HBV DNA at the end of 1 year of lamivudine therapy.[218,220,221] Approximately one half of treated patients experience improvement in histologic liver abnormalities. Similar findings have been seen in children.[222]

Lamivudine resistance usually manifests as breakthrough infection defined as reappearance of HBV DNA in serum after its initial disappearance.[223] This occurs in approximately two thirds of patients within 3 years of starting therapy.[224] Most patients continue to have lower serum HBV DNA and ALT levels compared with pretreatment values, perhaps due to decreased fitness of the lamivudine-resistant mutants. On cessation of lamivudine therapy, most patients experience an increase in serum HBV DNA concentrations.[225]

Lamivudine is indicated for the treatment of HIV and chronic HBV infection. Epivir tablets and oral solution for HBV infection contain a lower dose of lamivudine than Epivir tablets and oral solution used for HIV infection. The formulation and dosage of lamivudine in Epivir for HBV are not appropriate for patients dually infected with HIV and HBV; rapid emergence of HIV resistance is likely to result because of the subtherapeutic dose for HIV. The recommended oral dose of lamivudine for HBV-infected adults is 100 mg once daily. For HBV-infected children 2 through 17 years of age, the dose is 3 mg/kg (maximal dose: 100 mg) administered once daily.

Ribavirin

Chemistry, Mechanism of Action, Spectrum, and Resistance.

Ribavirin (Virazole, Rebetron combination therapy) is a synthetic nucleoside analogue developed in 1972 that most closely resembles guanosine in structure.[226] Ribavirin is absorbed rapidly across cell membranes and is enzymatically converted by host cell enzymes into its 5′-phosphate derivatives and the deribosylated base.[227] These metabolites interfere with the capping and elongation of messenger RNA. Ribavirin also appears to reduce guanine nucleosides by feedback inhibition.[228]

Although more potent against RNA viruses, ribavirin is active in vitro against a wide range of RNA and DNA viruses, including myxoviruses, paramyxoviruses, arenaviruses, bunyaviruses, herpesviruses, adenoviruses, poxviruses, and retroviruses.[229,230] It is approved in the United States for the treatment of RSV infections and, in combination with interferon, for hepatitis C virus infections. Resistance to ribavirin has not been observed, although Sindbis virus mutants with diminished susceptibility to ribavirin have been reported.[231]

Pharmacokinetics.

Ribavirin can be administered orally, intravenously, or by aerosol. Only the aerosolized formulation of drug (Virazole) and the oral formulation (in combination in interferon α [Rebetol]) or peginterferon α-2a [Copegus]) are approved for use in the United States.

About 40% of orally administered ribavirin is absorbed; after doses ranging from 600 to 2400 mg, peak plasma concentrations range from 1.3 to 3.2 μg/mL.[232] Peak concentrations after intravenous therapy are approximately 10-fold greater. Ribavirin and its metabolites concentrate in red blood cells. The levels in CSF are approximately 70% of the plasma concentration of the drug.[233] About one fourth to one third of systemically administered ribavirin is recovered unchanged in urine, and an additional 6% to 30% is excreted as metabolites. The terminal half-life of ribavirin is 18 to 36 hours, but some drug persists in red blood cells for several weeks after administration.[232]

Toxicity and Drug Interactions.

Ribavirin administered by the oral and intravenous routes causes dose-related, reversible anemia.[232] At low doses of the drug, anemia results from extravascular hemolysis, whereas at high doses, anemia is caused by bone marrow suppression. Increases in serum bilirubin, iron, and uric acid also occur with systemic ribavirin therapy.

Clinical Uses and Recommended Dosage.

Systemic ribavirin has demonstrated efficacy in the management of life-threatening infections caused by Lassa fever and hemorrhagic fever with renal syndrome.[234,235] Orally and intravenously administered ribavirin substantially reduce the mortality and morbidity directly attributable to each of these infections, and oral ribavirin has been recommended for prophylaxis against Lassa fever in exposed people.[236] Clinical benefit also has been observed in the treatment of Argentine and Bolivian hemorrhagic fever[237] and laboratory-acquired Sabia virus infection.[238]

Simeprevir

Chemistry, Mechanism of Action, Spectrum, and Resistance.

Simeprevir (Olysio, Galexos) is an inhibitor of the NS3/4A serine protease of HCV, which is necessary for the proteolytic cleavage of the HCV-encoded polyprotein and is essential for viral replication. Simeprevir has demonstrable in vitro activity against HCV genotypes 1a, 1b, and 4 using different cell-based replicon assays.

Several amino acid substitutions at NS3 protease positions confer reducted activity, including F43, Q80, S122, R155, A156, and D168. The baseline prevalence of Q80K is 30% in genotype 1a–infected patients, but is less than 1% in genotype 1b–infected patients. The Q80K polymorphism is associated with a lower sustained virologic response in clinical trials. Baseline determination of the Q80K polymorphism should be obtained before initiation of treatment with simeprevir.

Pharmacokinetics.

Simeprevir has good oral bioavailability. The drug is highly bound to human plasma proteins. Time to maximal concentration (T_{max}) is 4 to 6 hours, and the half-life is 10 to 13 hours. Steady state is reached after 7 days of once-daily dosing. High plasma concentrations are achieved, with a mean AUC_{24} of 57,469 ng•hr/mL. Simeprevir is metabolized primarily by CYP3A, and it is eliminated predominantly in the feces by biliary excretion.

Toxicity and Drug Interactions.

The most common adverse effects are rash (including a potentially serious photosensitivity reaction), pruritus, and nausea. The photosensitivity reaction usually starts within the first 4 weeks of therapy, but it can develop at any time during treatment. Patients taking simeprevir should limit sun exposure, use protective sunscreen when exposure is unavoidable, and avoid use of all tanning devices. If a photosensitivity rash occurs, discontinuation of drug should be considered, and the patient should have close monitoring until the rash has resolved. Patients also can experience transient increase in serum bilirubin level that peaks at week 2 of treatment and typically is mild.

Due to its metabolism by CYP3A enzymes, administering simeprevir with medications that have moderate or strong induction of CYP3A, such as rifampin, St. John's wort, and most anticonvulsants, can significantly reduce levels of simeprevir. In contrast, medications that have moderate or strong inhibition of CYP3A, such as clarithromycin, ketoconazole, and ritonavir, can significantly increase levels of simeprevir. Simeprevir also has complex drug-drug interactions with many antiretroviral medications. Medication contraindications and warnings are listed in the package insert.

Clinical Uses and Recommended Dosage.

Simeprevir has been evaluated in treatment-naïve, genotype 1–infected HCV patients,[239,240] genotype 1–infected patients who have relapsed after prior interferon-based therapy,[241] and genotype 1–infected patients who failed prior peginterferon and ribavirin therapy.[242] In treatment-naïve patients, the combination of simeprevir, peginterferon, and ribavirin for 12 weeks followed by 12 or 36 weeks of therapy with interferon and ribavirin produced SVR12 for approximately 80%. Comparable results were seen in patients who relapsed after prior therapy, but only one half of prior null responders had a sustained virologic response to simeprevir therapy in combination with peginterferon and ribavirin. In combination with sofosbuvir in prior null responders to peginterferon and ribavirin, simeprevir plus sofosbuvir produced sustained virologic response rates of 93% (SVR12) to 97% (SVR24).[243]

Simeprevir is indicated for the treatment of chronic HCV genotype 1 infection as a component of a combination antiviral treatment regimen. Simeprevir monotherapy is not recommended. When used in combination with peginterferon and ribavirin, screening patients with genotype 1a infection for the presence of the NS3 Q80K polymorphism is strongly recommended. The dosage of simeprevir used in all combination regimens is 150 mg administered once daily. The recommended duration of treatment when administered with peginterferon and ribavirin is 12 weeks followed by 12 or 36 additional weeks of peginterferon and ribavirin, depending on prior response status. When administered in combination with sofosbuvir, treatment duration is 12 weeks in treatment-naïve or treatment-experienced patients without cirrhosis and 24 weeks in treatment- naïve or treatment-experienced patients with cirrhosis.

Simeprevir has not been studied in children.

Sofosbuvir and Sofosbuvir-Ledipasvir

Chemistry, Mechanism of Action, Spectrum, and Resistance.

Sofosbuvir (Sovaldi) is a nucleotide analogue inhibitor of HCV NS5B polymerase, which is the key enzyme mediating HCV RNA replication. Sofosbuvir is efficiently taken up by hepatocytes and then undergoes triphosphorylation to its active form. Sofosbuvir triphosphate then competes with uridine to be incorporated by the HCV RNA polymerase into the elongating RNA primer strand, resulting in chain termination.

The active site of the NS5B enzyme is relatively well conserved across genotypes, yielding activity of sofosbuvir in HCV genotypes 1 through 6. The S282T amino acid substitution in HSV NS5B polymerase reduces sensitivity to sofosbuvir in cell culture. This mutation has not been detected in untreated patients, and it is rare in sofosbuvir-treated patients. The M289L substitution in genotype 2, 5, and 6 replicons also is associated with reduced activity of sofosbuvir. In phase III clinical trials, treatment-emergent substitutions L159F and V321A were detected in postbaseline samples from genotype 3–infected subjects with virologic failure. Cross-resistance between sofosbuvir, ledipasvir, and ribavirin has not been identified.

Ledipasvir is a potent inhibitor of HCV nonstructural protein 5A (NS5A), a viral phosphoprotein that plays an important but poorly understood role in viral replication, assembly, and secretion.[244] Ledipasvir is approved for the treatment of genotype 1 HCV. Its safety and efficacy have not been fully established for genotypes 2 through 6. NS5A amino acid substitutions Y93H (in genotypes 1a and 1b) and Q30E (in genotype 1a) significantly reduce susceptibility to ledipasvir in cell culture and in clinical studies.[245] Other amino acid substitutions observed in virologic treatment failures are K24R, M28T/V, Q30H/K/L (genotype 1a), and L31V/M/I (genotype 1b). Viruses with these resistance-associated mutations remained susceptible to sofosbuvir.

Pharmacokinetics.

Oral bioavailability of sofosbuvir is at least 80% based on urinary recovery. Ledipasvir also is well absorbed orally. Approximately 65% of sofosbuvir is bound to human plasma protein, and virtually all of ledipasvir is plasma protein bound.

The sofosbuvir T_{max} is 0.5 to 2 hours, with peak plasma concentration of the active metabolite occurring 2 to 4 hours after dosing. The T_{max} for ledipasvir is 4 to 4.5 hours. The terminal half-life for sofosbuvir and its active metabolite are 0.4 and 27 hours, respectively, and the terminal half-life for ledipasvir is 47 hours. Sofosbuvir primarily is eliminated in the urine, whereas ledipasvir elimination occurs primarily through the biliary tract. Eighty percent of sofosbuvir is recovered in the urine, primarily as the active metabolite, and 86% of ledipasvir is recovered in the feces.

Toxicity and Drug Interactions.

Common adverse events with sofosbuvir treatment are fatigue (when used with ribavirin), and anemia, neutropenia, insomnia, headache, and nausea (when used with peg interferon and ribavirin). Increases in bilirubin, creatinine kinase, and lipase levels can occur. Headache and fatigue are common adverse events of ledipasvir, and elevated bilirubin and lipase can occur. Sofosbuvir-ledipasvir (Harvoni) has significant drug-drug interactions with P-glycoprotein inducers (e.g., St. John's wort, rifampin), decreasing the ledipasvir and sofosbuvir plasma concentrations. The concomitant use of sofosbuvir-ledipasvir with P-glycoprotein inducers is not recommended.

Clinical Uses and Recommended Doses.

The combination of ledipasvir and sofosbuvir has primarily been studied as an all-oral combination regimen, without the requirement for interferon, in treatment-naïve and treatment-experienced patients with genotype 1 chronic HCV infection. Three phase III studies have consistently shown the SVR12 rates to be greater than 90% after a 12-week course of ledipasvir-sofosbuvir in patients with genotype 1 chronic HCV infection.[246–248] For treatment-experienced patients with cirrhosis, the SVR12 rates were significantly better with 24 weeks of therapy than with 12 weeks.[246] A subanalysis of one of the trials showed that treatment-naïve patients without cirrhosis had excellent SVR12 rates with only 8 weeks of ledipasvir-sofosbuvir if their pretreatment HCV RNA level was less than 6 million IU/mL.[248] For the treatment of patients with genotype 1 infection, the addition of ribavirin to ledipasvir-sofosbuvir did not provide significant benefit.

The approved clinical use for ledipasvir-sofosbuvir is only for chronic genotype 1 HCV-infected adults. The recommended treatment duration is 12 weeks for treatment-naïve adults with or without cirrhosis (with the caveat that 8 weeks of treatment can be considered in treatment- naïve patients without cirrhosis who have a pretreatment HCV RNA level less than 6 million IU/mL), 12 weeks for treatment-experienced adults without cirrhosis, and 24 weeks for treatment-experienced adults with cirrhosis. The recommended dose is 400 mg of sofosbuvir and 90 mg of ledipasvir, which are combined in a single tablet taken daily.

Sofosbuvir is administered in combination with peginterferon and ribavirin (in treatment-naïve subjects with genotype 1, 4, 5, or 6)[249] or in combination with ribavirin only in treatment-naïve subjects with genotype 2 or 3; interferon intolerant, ineligible, or unwilling subjects; patients previously treated with an interferon-based regimen; and subjects irrespective of prior treatment history or ability to take interferon.[249–251] High sustained virologic response rates were seen in these studies, resulting in the FDA indications for sofosbuvir in combination with peginterferon and ribavirin for patients with genotypes 1 or 4 (i.e., 12-week treatment duration), in combination with ribavirin for patients with genotype 2 (i.e., 12-week treatment duration), and in combination with ribavirin for patients with genotype 3 (i.e., 24-week treatment duration). With each of these treatment combinations, the dose of sofosbuvir is 400 mg once daily.

Neither sofosbuvir nor ledipasvir has been studied in children.

Telbivudine

Chemistry, Mechanism of Action, Spectrum, and Resistance.

Telbivudine (Tyzeka) is the unmodified L-enantiomer of the naturally occurring nucleoside D-thymidine.[252,253] Host cell kinases phophorylate telbivudine to telbivudine-5′-triphosphate, which then is incorporated into HBV DNA, resulting in viral DNA chain termination.[253,254] Telbivudine preferentially inhibits HBV second-strand (DNA-dependent) DNA synthesis.[255] In comparison, lamivudine preferentially inhibits first-strand (RNA-dependent) DNA synthesis.[255] Telbivudine is active only against hepadnaviruses.[253,254] Coadministration of telbivudine with lamivudine does not produce additive or synergistic effects.[256]

In vitro, telbivudine-5′-triphosphate has no inhibitory effect on host cell DNA polymerases α, β, or γ at concentrations up to 100 μmol/L.[252,254] In contrast, the mean 50% effective concentration (EC_{50}) inhibiting HBV DNA polymerase is 0.12 to 0.24 μmol/L,[254] illustrating the specificity and potency of the drug for HBV replication. At concentrations up to 10 μmol/L, telbivudine has minimal toxic effect on host cell mitochondria and does not increase lactic acid production.[252,254]

The key determinant of telbivudine resistance is the M204I mutation in the YMDD motif.[254] The principal mutations conferring in vivo lamivudine resistance do not produce cross-resistance to telbivudine,[257] but cross-resistance can be induced in vitro.[258] Telbivudine is active or has slightly reduced activity in vitro against adefovir-resistant HBV strains.[257]

Pharmacokinetics.

Telbivudine is absorbed rapidly after oral administration, and it is not influenced by food.[259] The half-life is about 40 hours. Approximately 40% of the dose is excreted as the unchanged active substance by the kidneys, likely by renal filtration.[254] Systemic exposure to telbivudine is increased in patients with impaired renal function, and in patients with moderate to severe renal impairment (CrCl <50 mL/min) or end-stage renal disease requiring dialysis, the dosing interval requires adjustment.[260]

Dosage adjustment is not required for patients with impaired hepatic function. Dosages of 20 mg/kg/day for children and 600 mg/day for adolescents produce exposures similar to those in healthy adults receiving 600 mg/day.[261]

Toxicity and Drug Interactions.

No dose-related or dose-limiting toxicity has been identified in healthy volunteers or patients with chronic hepatitis B infection.[262,263] Elevated serum creatinine kinase (CK) concentration is the most frequent adverse event. Cases of myopathy during therapy have been described, but they did not correlate with the magnitude or timing of CK elevations.[254,264] Nevertheless, treatment should be discontinued if persistent, unexplained muscle-related symptoms occur.[254,264] Patients receiving telbivudine along with other drugs associated with myopathy, such as cyclosporin or HMG-CoA reductase inhibitors (i.e., statins) should be monitored closely for signs and symptoms of myopathy.[254]

There are no clinically significant interactions between telbivudine and adefovir, tenofovir, and lamivudine.[265] The drug does not induce or inhibit cytochrome P450. Coadministration of telbivudine with drugs that affect renal function (e.g., aminoglycosides, amphotericin B) can impact plasma concentrations of either drug.[254]

Clinical Uses and Recommended Doses.

Telbivudine is licensed for use in adolescents and adults (≥16 years of age). In HBeAg-seropositive and -seronegative adults, telbivudine is superior to lamivudine after 1 and 2 years of therapy.[266,267] The rate of HBeAg seroconversion was 22%, and viral suppression (<300 copies/mL) was achieved in 60% of HBeAg-positive patients after 1 year of therapy.[256] Telbivudine compared with adefovir also has better early viral suppression at week 24 in HBeAg-positive patients, regardless of whether the patients were treated initially with telbivudine or switched from adefovir to telbivudine.[268] The early virologic suppression resulted in better rates of HBeAg seroconversion, serum ALT normalization, and viral suppression.[269] Pediatric efficacy studies are being conducted.[261]

Tenofovir Disoproxil Fumarate

Chemistry, Mechanism of Action, Spectrum, and Resistance.

Tenofovir disoproxil fumarate (Viread) is a nucleoside phosphonate diester analogue of deoxyadenosine 5′-monophosphate and a prodrug of tenofovir.[270,271] After absorption from the gastrointestinal tract, the prodrug is hydrolyzed to tenofovir, which is taken up in target cells and phosphorylated to the active drug tenofovir diphosphate. Tenofovir diphosphate is a competitive inhibitor of the nucleotide deoxyadenosine 5′-triphosphate for incorporation by HBV polymerase into viral DNA, and it inhibits HBV DNA replication by leading to chain termination.[270,272] In addition to HBV, tenofovir diphosphate competitively inhibits deoxyadenosine triphosphate as a substrate for HIV-1 reverse transcriptase, resulting in chain termination after its incorporation in HIV DNA.

Tenofovir diphosphate selectively inhibits viral DNA polymerase, and it produces only weak inhibition of human cellular DNA polymerase α, β, and γ.[272] The active compound is a potent inhibitor of HBV DNA polymerase, with an inhibition constant (K_i) of 0.18 μmol/L.[273] At in vitro concentrations of 300 μmol/L or less, tenofovir diphosphate does not inhibit synthesis of mitochondrial DNA or result in lactic acid production.[270]

Resistance to tenofovir can be generated in HBV in vitro, but antiviral resistance does not appear to be a clinical problem in vivo. In clinical studies, no HBV mutations associated with resistance to tenofovir disoproxil fumarate have been identified, even after 96 weeks of treatment, in immunocompetent and HIV-infected patients.[270,274–278] Cross-resistance between tenofovir and adefovir has been demonstrated from in vivo isolates[273] but not for telbivudine or lamivudine.[279]

Pharmacokinetics.

After oral administration, tenofovir disoproxil fumarate is rapidly absorbed and converted to tenofovir. Oral bioavailability is about 25% in fasting patients or after a light meal, and is about 39% after a high-fat meal.[270,271,280] The half-life of tenofovir is approximately 17 hours.[270] The estimated intracellular half-life of tenofovir diphosphate is 95 hours.[273] Approximately 70% to 80% of the tenofovir dose is excreted unchanged in the urine up to 72 hours after administration.[270,271] In patients with moderate to severe renal impairment (CrCl <50 mL/min), the dosing interval requires adjustment. Dosage adjustment is not required for patients with impaired hepatic function.[270,271]

Toxicity and Drug Interactions.

Tenofovir disoproxil fumarate is usually well tolerated for extended periods.[270,274] Mild adverse reactions to therapy include headache, nasopharyngitis, and gastrointestinal upset. Neither tenofovir disoproxil fumarate nor tenofovir is metabolized by CYP450 enzymes. Although decreased metabolism of CYP1A substrates has been observed,[271] drug interactions mediated by CYP450 enzymes are minimal with tenofovir.

Coadministration of tenofovir disoproxil fumarate with nephrotoxic drugs or compounds that compete for active tubular secretion can result in increased serum concentrations of tenofovir. Tenofovir disoproxil fumarate should not be administered with adefovir dipivoxil.[271] Renal function should be closely monitored if tenofovir disoproxil fumarate is coadministered with tacrolimus.[270] No drug interactions were observed with coadministration with telbivudine,[281] and use with entecavir has not been evaluated.[270,271]

Clinical Uses and Recommended Doses.

Although tenofovir is licensed for use in children at least 12 years of age with HIV infection, it is not approved for use in the treatment of HBV in children. There is no recommended dose for children with HBV infection. In adults, tenofovir is more potent than adefovir in achieving viral suppression (76% vs. 13% with <400 copies/mL), histologic improvement (67% vs. 12%), and higher rates of HBsAg loss (3.2% vs. 0%) at 48 weeks in HBeAg-seropositive patients with chronic HBV infection.[274] Almost 90% of patients maintained serum HBV DNA levels of less than 400 copies/mL when continued on tenofovir disoproxil fumarate for 72 weeks, and almost 80% of patients who did not achieve complete viral suppression did so after 24 weeks of tenofovir therapy.[282] Similar results have been observed in other studies.[281]

The recommended dose for adults is 300 mg taken orally once daily without regard to food. Administration of tenofovir to HBV-infected pregnant women in the latter weeks of pregnancy and the first month postpartum decreases HBV transmission to the neonates.[283]

Inorganic Pyrophosphate Analogues

Foscarnet

Chemistry, Mechanism of Action, Spectrum, and Resistance.

Foscarnet (Foscavir), or phosphonoformic acid (PFA), is an inorganic pyrophosphate analogue that inhibits all known human herpesviruses, including most ganciclovir-resistant CMV isolates and acyclovir-resistant HSV and VZV strains (see Table 295.4).[284] Foscarnet also is active against HIV. This antiviral agent directly inhibits DNA polymerase by blocking the pyrophosphate binding site and preventing cleavage of pyrophosphate from deoxynucleotide triphosphates.[285] Foscarnet is a noncompetitive inhibitor of viral DNA polymerases or HIV reverse transcriptase and is not incorporated into the growing viral DNA chain.

Foscarnet is approximately 100-fold more active against viral enzymes than against host cellular enzymes.[285] Resistance occurs as a result of DNA polymerase mutations. Strains of CMV, HSV, and VZV with threefold to fivefold reduced sensitivity to foscarnet have been reported.[286,287] These isolates may respond to therapy with acyclovir[286] or cidofovir.[287]

Pharmacokinetics.

Foscarnet is absorbed poorly after oral administration, with a bioavailability of about 20%.[284] This limits foscarnet administration to the intravenous route. Maximal serum concentration attained after a dose of 60 mg/kg is approximately 500 μmol/L. Data regarding tissue distribution are limited, but CSF concentrations are about two thirds of those in serum.[288]

Eighty percent of an administered dose of foscarnet is eliminated unchanged in the urine. The half-life is 48 hours, and dosage adjustments are necessary even for minimal degrees of renal dysfunction (see Table 296.6). The degree of dose reduction is proportional to the degree of reduction in CrCl; when CrCl is 50% of normal, the dose should be reduced by about 50% (Fig. 295.1). Hemodialysis efficiently eliminates foscarnet, and an extra dose of drug is recommended after dialysis for 3 or more hours.[289] There are no pharmacokinetic data for foscarnet in neonates.

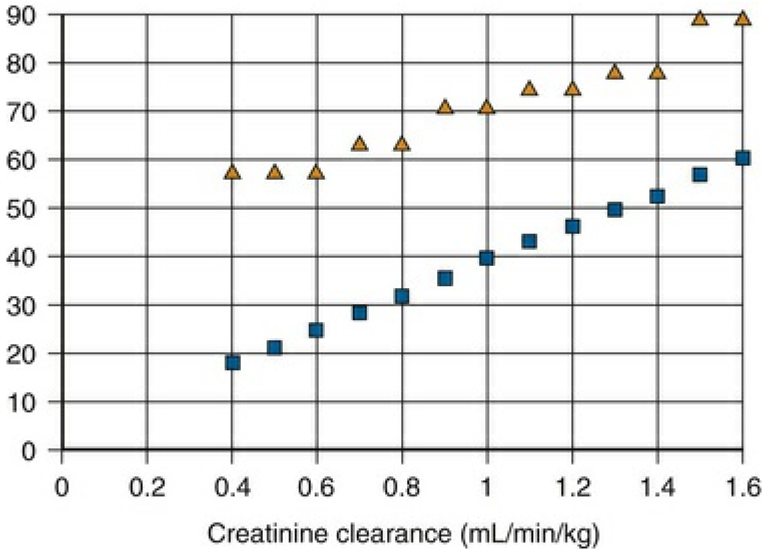

FIGURE 295.1 Recommended dosage of foscarnet for patients with various degrees of renal impairment. *Triangles* indicate the maintenance dose (mg/kg/day),

and *squares* indicate the induction dose (mg/kg/8 hr).

(Modified from MacGregor RR, Graziani AL, Weiss R, et al. Successful foscarnet therapy for cytomegalovirus retinitis in an AIDS patient undergoing hemodialysis: rationale for empiric dosing and plasma level monitoring. J Infect Dis 1991;164:785–787.)

Toxicity and Drug Interactions.

The most common and serious adverse effects are nephrotoxicity and metabolic derangements. Azotemia, proteinuria, acute tubular necrosis, crystalluria, and interstitial nephritis can occur,[290] and serum creatinine concentrations increase, usually during the second week of therapy, in as many as 50% of patients. In most affected patients, renal function returns to normal within 2 to 4 weeks after discontinuing foscarnet. Risk factors for developing renal dysfunction include preexisting renal disease, concurrent use of other nephrotoxic drugs, dehydration, rapid injection of large doses, and continuous intravenous infusion of drug.[291]

Drug-related electrolyte disturbances can occur, including symptomatic hypocalcemia, hypercalcemia, hypophosphatemia, and hyperphosphatemia. Hypocalcemia is caused by direct chelation of ionized calcium by the drug, and patients can have paresthesias, tetany, seizures, and arrhythmias.[292] Metabolic disturbances can be minimized if foscarnet is administered by slow infusion, with rates not exceeding 1 mg/kg/min.

Common drug-associated CNS symptoms include headache, tremor, irritability, seizures, and hallucinations. Fever, nausea, vomiting, abnormal serum hepatic enzymes, anemia, granulocytopenia, and genital ulcerations are reported. Genital ulcerations appear to be associated with high urinary concentrations of drug.[293] Concomitant use of amphotericin B, cyclosporine, gentamicin, and other nephrotoxic drugs increases the likelihood of renal dysfunction associated with foscarnet therapy. Hypocalcemia is more common with coadministration of pentamidine, and anemia and neutropenia are more common when patients are treated with foscarnet and zidovudine.

Clinical Uses and Recommended Dosage.

The most important indication for foscarnet is therapy for sight-threatening chorioretinitis caused by CMV in patients with AIDS.[284] Several controlled trials have demonstrated that foscarnet is as effective as ganciclovir in managing this infection and may offer a survival advantage because of its inherent activity against HIV.[290] In refractory cases of chorioretinitis, combination foscarnet and ganciclovir therapy have been given.[183] Foscarnet also is effective in the treatment of ganciclovir-resistant strains of CMV infections.[294] Limited data for patients with AIDS suggest a foscarnet benefit for gastrointestinal and pulmonary CMV infections.[164,226]

The usual dosage regimen for CMV infection is 180 mg/kg/day in 3 divided doses for 14 to 21 days, followed by a daily maintenance dose of 90 to 120 mg/kg. About 90% of patients have stabilization of their retinitis, and the time to progression of infection is prolonged to about 3 months.[295]

Infections caused by acyclovir-resistant strains of HSV and VZV have been successfully controlled with foscarnet.[296,297] The dosage of foscarnet used for these infections is 120 mg/kg/day in 3 divided doses. In patients with AIDS, foscarnet therapy should be initiated within 7 to 10 days of suspicion of infection caused by acyclovir-resistant HSV or VZV.[298] Therapy should be continued until lesions have resolved.

Neuraminidase Inhibitors

Oseltamivir Phosphate

Chemistry, Mechanism of Action, Spectrum, and Resistance.

Oseltamivir (Tamiflu) is one of three licensed medications that specifically target the neuraminidase protein common to influenza A and B viruses. Oseltamivir is an ethyl ester prodrug that, after hydrolysis by hepatic esterases, is converted to the active compound, oseltamivir carboxylate. The prodrug masks the polarity of the active compound, allowing for enhanced oral bioavailability. The mechanism of action for this class of compounds is the specific inhibition of the influenza neuraminidase, with subsequent interference with the deaggregation and release of the viral progeny. The influenza neuraminidase enzyme is highly conserved and is common to influenza A/H1N1, A/H2N2, A/H3N2, and A/H5N1 and influenza B viruses. Antiviral activity in vitro is assay and strain dependent.

In human challenge studies, only 3% of posttreatment isolates were resistant to oseltamivir. Whereas a phase IV study from Japan identified neuraminidase mutations conferring resistance to neuraminidase inhibitors in 18% of treated children,[299] a prospective study in the United States documented a resistance rate of 4.4% among young infants treated with oseltamivir.[300]

Pharmacokinetics.

Oseltamivir has good oral bioavailability; at least 75% of orally administered drug reaches the systemic circulation in the form of oseltamivir carboxylate. The C_{max} and AUC for the active compound after a 75-mg (twice daily) oral dosing regimen are 348 ng/mL and 2719 ng•hr/mL, respectively. Coadministration with food has no significant effect on the peak plasma concentration. Neither oseltamivir nor oseltamivir carboxylate is metabolized by CYP450 isoforms. The rate of protein binding of oseltamivir carboxylate is only 3%, whereas the rate of protein binding of the prodrug is 42%.

The half-life of oseltamivir after oral administration is 1 to 3 hours, and the half-life of oseltamivir carboxylate is 6 to 10 hours.[301] The primary route of elimination of oseltamivir is by conversion to the active drug, with more than 90% of the prodrug metabolized to oseltamivir carboxylate. Oseltamivir carboxylate is not further metabolized, and it is eliminated entirely by renal excretion through glomerular filtration and anionic tubular secretion. Serum concentrations of oseltamivir carboxylate increase in the setting of declining renal function, and dose adjustment is recommended for patients with a CrCl value less than 30 mL/min. Administration of oseltamivir to patients with renal failure (CrCl <10 mL/min) has not been evaluated.

In infants younger than 1 year of age, an oseltamivir dose of 3 mg/kg produces adequate drug exposure in patients 0 to 8 months of age, although there is greater variation in infants younger than 3 months of age. In patients 9 to 11 months of age, a dose of 3.5 mg/kg is required.[300]

Toxicity and Drug Interactions.

The most common adverse effect reported is nausea with or without vomiting. In controlled clinical trials, approximately 10% of patients reported nausea without vomiting, and an additional 10% experienced vomiting. The nausea and vomiting episodes typically were mild to moderate and usually occurred on the first 2 days of oseltamivir administration. Fewer than 1% of study subjects discontinued participation in the clinical trials prematurely because of nausea or vomiting. Food may help to alleviate the gastrointestinal side effects in some patients.[302] Insomnia and vertigo also were reported more frequently among oseltamivir recipients than those receiving placebo.

No drug interactions have been described for oseltamivir or oseltamivir carboxylate. Neither the prodrug nor the active metabolite is metabolized by CYP450 isoforms. No dose adjustments are required when oseltamivir is coadministered with probenecid.

Clinical Uses and Recommended Doses.

Oseltamivir is licensed for the treatment and prophylaxis of influenza infection in patients ≥2 weeks of age.[300] The efficacy of oseltamivir for the treatment of influenza has been established in two large phase III studies, one conducted at 60 centers throughout the United States[303] and the other conducted at 63 centers in Europe, Canada, and China.[304] Of a total of 1355 patients enrolled in these two trials, 849 (63%) were confirmed subsequently to have influenza infection (95% with influenza A). Patients had to be enrolled within 36 hours of the onset of symptoms. The duration of illness among oseltamivir recipients was reduced by approximately 1.3 days compared with placebo recipients in both studies.[303,304]

Among patients treated within 24 hours of the onset of symptoms, illness duration was reduced by almost 2 days.[304] Oseltamivir recipients compared with patients receiving placebo also had a more rapid return to normal health and activity.[303] No serious drug-related adverse events were reported. Oseltamivir-associated nausea occurred in 17% and 12% of patients in the United States and international studies, respectively. The frequency of physician-diagnosed secondary complications leading to antibiotic prescriptions also was reduced among oseltamivir recipients.[305] Similar results were observed in a randomized, double-blind, placebo-controlled study enrolling children with influenza infection.[306]

Compared with placebo, administration of oseltamivir for 6 weeks during the peak of influenza season significantly reduced the risk of contracting influenza.[307] The protective efficacy for the prevention of culture-proven influenza approached 90%,[307,308] which is comparable with that achievable with amantadine and rimantadine for susceptible influenza A.

The recommended oral dose of oseltamivir for the treatment of influenza in people 13 years of age or older is 75 mg twice daily for 5 days. For children 1 through 12 years of age, dose is based on weight (≤15 kg [≤33 lb], 30 mg bid; >15–23 kg [>33–51 lb], 45 mg bid; >23–40 kg (>51–88 lb), 60 mg bid; >40 kg (>88 lb), 75 mg bid). Duration of treatment is 5 days. For infants between 2 weeks and 12 months of age, the approved dose is 3 mg/kg per dose given twice daily, although some experts recommend the dose of 3.5 mg/kg for infants 9 through 11 months old.[309] In premature neonates, the recommended oseltamivir dose is 1 mg/kg per dose given orally twice daily for neonates younger than 38 weeks' postmenstrual age; 1.5 mg/kg per dose administered orally twice daily for those 38 through 40 weeks' postmenstrual age; and 3 mg/kg per dose administered orally twice daily for those older than 40 weeks' postmenstrual age.[309] If possible, treatment should begin within 2 days of the onset of symptoms of influenza. Oseltamivir can be taken with or without food; tolerability may be enhanced when taken with food.

The recommended oral dose of oseltamivir for the prophylaxis of influenza in people 13 years of age or older is 75 mg given once daily for at least 7 days. Therapy should begin within 2 days of close contact with an infected person. Safety and efficacy have been demonstrated for up to 6 weeks.[307]

No dose adjustment is necessary for patients with CrCl values greater than 30 mL/min. In patients with a CrCl value of less than 30 mL/min, the dose of oseltamivir should be reduced to 75 mg given once daily for 5 days. Caution is advised when oseltamivir is administered to patients with CrCl values less than 10 mL/min because the use of the compound has not been evaluated in this population. Oseltamivir is licensed by the FDA for use only in adults for the treatment of influenza A and B infections.

Peramivir

Chemistry, Mechanism of Action, Spectrum, and Resistance.

Peramivir (Rapivab) inhibits the influenza neuraminidase enzyme by mimicking the sialic acid residues of the cell membrane and binding to the neuraminidase active site, thereby competing with neuraminic acid. This interferes with de-aggregation and release of viral progeny. In addition to the carboxyl group that is present in oseltamivir and zanamivir, which binds to amino acids R118, R292, and R317, peramivir has two side chains that enable tight binding to the N9 neuraminidase site for more than 24 hours, followed by slow dissociation.[310,311]

Peramivir is active against influenza B viruses in vitro and in mice and ferrets,[312,313] with a single intravenous administration giving mice 100% protection. The mean neuraminidase inhibitory activity ± SD (i.e., IC_{50} values) of peramivir in biochemical assays against influenza A/H1N1 virus, influenza A/H3N2 virus, and influenza B virus clinical isolates collected between 2009 and 2012 by the WHO Global Influenza Surveillance and Response System (GISRS) were 0.17 ± 0.10, 0.18 ± 0.08, and 0.74 ± 0.33, respectively.[314]

Emergence of peramivir-resistant variants was detected after 15 passages in MDCK cells under drug pressure, and the mutant virus had an H274Y neuraminidase mutation that conferred a 714-fold reduction in susceptibility to peramivir.[315] In vivo, resistance among influenza A and B viruses to peramivir is uncommon, with 3.2% of influenza A/H1N1 viruses, less than 1% of influenza B viruses, and no influenza A/H3N2 viruses demonstrating resistance.[314] Peramivir resistance usually is associated with the H275Y neuraminidase amino acid substitution.[314,316,317] Cross-resistance between peramivir, oseltamivir, and zanamivir has been generated in vitro, but the clinical impact of this reduced susceptibility has not been elucidated.

Pharmacokinetics.

Peramivir use is limited to parenteral administration due to low oral bioavailability. The mean T_{max} after a 30-minute infusion of peramivir is approximately 30 to 40 minutes. The rate of human plasma protein binding is less than 30%. The terminal half-life after a 600-mg intravenous dose is approximately 20 hours, and the mean CrCl value is 122 mL/min.[318] Renal excretion is the only documented route of elimination of peramivir and its metabolites. In humans, peramivir is not significantly metabolized, and approximately 90% of administered peramivir is excreted unchanged in urine.

Hemodialysis removes 73% to 81% of peramivir. Peramivir also is cleared by continuous venovenous hemofiltration.[319] Dose reduction is recommended for CrCl values less than 50 mL/min. The peramivir exposures of children given a 10-mg/kg dose were within the range of exposures at which the efficacy and safety have been confirmed in adults.[320]

Toxicity and Drug Interactions.

Adverse events are diarrhea, nausea, vomiting, and decreased neutrophil count. Less common adverse events include dizziness, headache, somnolence, nervousness, insomnia, feeling agitated, depression, nightmares, hyperglycemia, hyperbilirubinemia, elevated blood pressure, cystitis, anorexia, and proteinuria.[321]

Peramivir does not inhibit or induce cytochrome P450 enzymes. No drug-drug interactions are observed with coadministration of rimantadine, oseltamivir, or oral contraceptives.

Clinical Uses and Recommended Doses.

Compared with placebo, a single intravenous dose of peramivir significantly decreases time to alleviation of symptoms and resumption of normal activities and hastens clearance of virus.[322] A single intravenous peramivir dose of 300 or 600 mg is noninferior to a 5-day course of oral oseltamivir, with median durations of influenza symptoms of 78, 81, and 81.8 hours in patients treated with 300 mg of peramivir, 600 mg of peramivir, and 75 mg twice daily of oseltamivir, respectively; both peramivir groups were noninferior to the oseltamivir group.[323] The higher dose of 600 mg of intravenous peramivir was superior to a 300-mg dose in adults with chronic medical conditions such as diabetes and chronic respiratory tract illnesses.[324] A postmarketing study from Japan assessed the efficacy of intravenous peramivir for influenza B infections and showed superiority to oseltamivir in reducing the duration of fever (1 vs. 3 days) in children 5 to 18 years old, but it found no difference in children younger than 9 years of age.[325]

The US peramivir labeling indication is for the treatment of acute uncomplicated influenza virus infection in patients at least 18 years of age who have been symptomatic for 2 days or less. The recommended dose is 600 mg administered by intravenous infusion over 15 to 30 minutes. Dose adjustment is required for significant renal impairment.

Zanamivir

Chemistry, Mechanism of Action, Spectrum, and Resistance.

Zanamivir (Relenza) interferes with the function of the influenza neuraminidase enzyme, causing subsequent interference with de-aggregation and release of the viral progeny. Zanamivir has poor oral bioavailability and therefore is administered by oral inhalation. Although the amount of zanamivir that is delivered to the respiratory tract during inhalation depends on patient factors such as inspiratory flow, the supplied delivery device delivers 4 mg of zanamivir when tested in vitro under conditions that approximate inhalation pressures achievable in vivo. Antiviral activity in vitro is assay and strain dependent.

Antiviral resistance can be induced in vitro by performing passage of the virus in the presence of increasing concentrations of zanamivir.[326,327] Decreased susceptibility is associated with mutations resulting in amino acid changes in the viral neuraminidase or hemagglutinin, or both. Resistance has been documented in clinical specimens isolated from a zanamivir recipient. After 2 weeks of therapy with zanamivir, an immunocompromised patient infected with influenza B shed a resistant isolate that had mutations in the viral hemagglutinin and neuraminidase.[328] The neuraminidase mutation resulted in a 1000-fold reduction in enzyme activity. Cross-resistance between zanamivir and oseltamivir has been demonstrated in resistant isolates generated in vitro. Accurate estimation of the risk of emergence of oseltamivir resistance in the clinical setting will be determined only by careful phase IV monitoring postlicensure.

Pharmacokinetics.

More than 75% of an orally inhaled dose of zanamivir is deposited in the oropharynx, most of which is swallowed. Approximately 13% of the dose distributes to the airways and lungs, and the remainder is retained in the delivery device.[329] Inhaled zanamivir provides local concentrations in respiratory tract mucosa that greatly exceed inhibitory concentrations for influenza A and B viruses[329,330]; median zanamivir concentration exceeds 1000 ng/mL in sputum 6 hours after inhalation and remains detectable for 24 hours.[331] Between 4% and 17% of an inhaled dose of zanamivir is absorbed systemically.

No metabolites of zanamivir have been identified, and all absorbed drug is excreted unchanged in the urine. Although serum zanamivir concentration increases with decreasing CrCl, no adjustment in dosing is necessary in cases of renal insufficiency. Unabsorbed drug is excreted in the feces.

Toxicity and Drug Interactions.

Zanamivir is well tolerated.[332] The most serious adverse event is respiratory distress, and decline in pulmonary function and bronchospasm have been reported in some patients.[333,334] Many of these patients had underlying disease of the airways such as asthma or chronic obstructive pulmonary disease. Although influenza can cause such deteriorations, zanamivir usually is not recommended for the treatment of patients with underlying airways disease because of the risk of adverse events and the lack of demonstrated efficacy in this population. Zanamivir should be discontinued in any patient who develops bronchospasm or a decline in respiratory function.

No drug interactions with zanamivir have been reported.[335] Zanamivir does not affect CYP450 isoenzymes in human liver microsomes.

Clinical Uses and Recommended Doses.

The efficacy of zanamivir in the management of influenza A and B virus infections has been demonstrated in three placebo-controlled studies.[336–338] A total of 1588 patients were enrolled in the three investigations; 1167 (73%) were infected with influenza. Patients received zanamivir (10 mg inhaled bid), which was compared with placebo inhaled twice daily. The zanamivir-treated patients improved 1 to 2.5 days faster than did the placebo recipients. Combined analysis of these trials indicated that zanamivir reduces the duration of symptoms by approximately 1.5 days.[334] Similar findings have been demonstrated in influenza-infected children.[339] Efficacy has been documented for both influenza A and influenza B.[340] Zanamivir therapy also reduces the frequency of antibiotic prescriptions for lower respiratory complications by 40%, although not for presumed upper respiratory tract complications.[341]

Inhaled zanamivir (10 mg once daily administered for 4 weeks) used as seasonal prophylaxis reduces the likelihood of laboratory-confirmed influenza infection (with or without symptoms) by 31%, influenza disease by 67%, and influenza disease with fever by 84%.[342] A study of zanamivir administered once daily to healthy household contacts of influenza-infected index subjects demonstrated a 79% reduction in influenza illness.[343]

Zanamivir is indicated for the treatment of uncomplicated illness due to influenza A and B virus. The recommended dose of zanamivir for the treatment of influenza in adults and children at least 7 years of age is two inhalations of 5 mg each administered twice daily for 5 days. Two doses should be taken on the first day of treatment if possible, provided that there is an interval of at least 2 hours between doses. On subsequent days, the doses should be approximately 12 hours apart. Patients scheduled to use an inhaled bronchodilator at the same time as zanamivir should use their bronchodilator before taking zanamivir. No dose adjustments are indicated in patients with impaired renal function.

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Antiparasitic Agents

Edward T. Ryan

In this chapter, antiparasitic therapy is organized in five categories: agents active against luminal protozoans, agents active against the kinetoplastid protozoans, agents active against the malarial parasites, antibacterial agents with antiprotozoan activity, and anthelmintics. These divisions are somewhat arbitrary because some drugs are pertinent to more than one category. Appendix 296.1, which describes the drugs for parasitic infections, is arranged by organism. Appendix 296.2 provides the principal adverse effects of antiparasitic medications.

Recommended dosing indications for individual drugs can vary by organism. Most of the drugs, their indications for specific disease states, and recommendations for treatment and prophylaxis are discussed more extensively in pathogen-specific chapters.

A few drugs that are not available in the United States but are used extensively in other countries are discussed. Niclosamide, quinacrine, diloxanide furoate, furazolidone, and mebendazole no longer are commercially produced or distributed but may be available through specialized compounding pharmacies. Artesunate, benznidazole, diethylcarbamazine, eflornithine, melarsoprol, nifurtimox, sodium stibogluconate, and suramin are available only through the Centers for Disease Control and Prevention (CDC) (www.cdc.gov/laboratory/drugservice/formulary.html).

Because drug treatment recommendations are revised periodically, updated references should be consulted to obtain current recommendations. During weekdays, physicians with questions regarding the management of patients with parasitic diseases can call the CDC Parasitic Diseases Hotline (404-718-4245) or the CDC Malaria Hotline (770-488-7788; toll-free: 855-856-4713); both resources can be reached during nights and weekends at an alternate number (770-488-7100). Additional information is available at the CDC website (http://www.cdc.gov/parasites/health_professionals.html#drugs).

Treatment of Luminal Protozoa

Intestinal luminal protozoan parasites include *Giardia intestinalis*, *Cryptosporidium parvum* and *C. hominis*, *Cyclospora cayetanensis*, *Cystoisospora (Isospora) belli*, *Entamoeba histolytica*, *Entamoeba polecki*, *Dientamoeba fragilis*, and *Balantidium coli*. *Blastocystis* spp. (e.g., *hominis*) is of uncertain significance. *Trichomonas vaginalis* is a vaginal luminal protozoan.

Metronidazole and Tinidazole.

Metronidazole and tinidazole are synthetic nitroimidazoles with selective activity against organisms that use anaerobic metabolism. Metronidazole has been efficacious for the following protozoan infections: *E. histolytica, E. polecki, G. intestinalis, T. vaginalis, B. hominis,* and *B. coli.*[1–6] Tinidazole is approved for use against giardiasis and amebiasis in adults and children older than 3 years of age and for trichomoniasis in adults.[7] For amebiasis, these drugs are active against the trophozoite stage of the parasite life cycle and can be used to treat the luminal and tissue phases of the infection, including liver abscesses. Patients with invasive colonic disease or liver abscess also are treated with paromomycin or iodoquinol or other luminally active amebicides to eliminate residual luminal forms of the parasite.

Metronidazole and tinidazole are the only effective therapies available in the United States for trichomoniasis.[8] Both drugs are effective against giardiasis. Tinidazole is as effective as metronidazole for most clinical indications and is modestly better tolerated. Tinidazole is used as a single-dose regimen for giardiasis and trichomoniasis, and the recommended course for amebiasis is shorter. Despite this, a course of tinidazole is considerably more expensive than generic metronidazole for all indications.[7]

Tinidazole is not available in suspension, but it can be formulated by crushing the tablets.

Metronidazole and tinidazole are well tolerated; tinidazole is modestly better tolerated compared with metronidazole at the high single-dose regimens or at the higher doses used for amebiasis. Side effects of both drugs include nausea, vomiting, epigastric discomfort, anorexia, and a metallic or bitter taste. Seizures and peripheral neuropathy have been reported uncommonly with both drugs. Patients taking either drug should avoid alcohol (including that found commonly in suspensions of children's medicines) because of the disulfiram-like effects.

Furazolidone.

Furazolidone is a nitrofuran derivative most commonly used in the treatment of giardiasis in children because of its availability in a liquid preparation. It is no longer commercially available in the United States.

The gastrointestinal tract side effects of nausea and vomiting are the most common complaints associated with furazolidone therapy. Allergic reactions, including pulmonary infiltration, hypotension, urticaria, fever, and vesicular rash, occur occasionally. Other potential complications of furazolidone therapy are a disulfiram-like reaction with concurrent use of alcohol-containing medications, hemolytic anemia either in infants younger than 1 month of age or in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, and reactions due to the drug's monoamine oxidase inhibitor activity.

Nitazoxanide.

Nitazoxanide is a nitrothiazolyl-salicylamide derivative, whose activity appears to be at the level of electron transfer of anaerobic metabolism.[9] It has broad activity against protozoa, anaerobic bacteria, and helminths. It is the drug of choice for treating patients with cryptosporidiosis, and it is effective against giardiasis, blastocystiasis, fascilosiasis, and hymenolepsiasis; the latter two are worm infections.[9–16] Nitazoxanide usually is well tolerated.

Iodoquinol.

Iodoquinol (i.e., diiodohydroxyquin) is a halogenated oxyquinoline.

It is a luminally active agent with efficacy against *E. histolytica, D. fragilis, B. hominis,* and *B. coli.*[17]

The mechanism of action of iodoquinol is poorly understood. The drug is poorly absorbed and therefore reaches high concentrations in the lumen of the colon. Gastrointestinal tract complaints, including nausea, cramps, and diarrhea, are the most common problems associated with therapy. Other side effects occasionally associated with its use are rash, acne, anal pruritus, and slight enlargement of the thyroid gland.

Diloxanide Furoate.

A dichloroacetamide derivative of an acetanilide, diloxanide furoate has amebicidal activity at low concentrations. It is a luminally active agent with activity against *E. histolytica* and *E. polecki.* Diloxanide furoate has no activity against the extraluminal forms of *E. histolytica.* Its only common side effect is flatulence; nausea, vomiting, and diarrhea are occasional side effects. The drug is well tolerated and inexpensive, but it is not commercially available in the United States.

Paromomycin.

Paromomycin, an aminoglycoside, is poorly absorbed by patients with an intact gastrointestinal tract and is active as a luminal agent for *E. histolytica, D. fragilis,* and *G. intestinalis.* Paromomycin is not active against the extraluminal forms of *E. histolytica.* The use of paromomycin for giardiasis is limited but may be indicated for treatment of giardiasis during pregnancy because it is poorly absorbed. The frequent side effects of paromomycin with oral use are gastrointestinal tract disturbances, which are self-limited.

Treatment of Kinetoplastidea Infections

Kinetoplastidal infections include those caused by *Trypanosoma,* including American trypanosomiasis caused by *T. cruzi* (i.e., Chagas' disease), African trypanosomiasis (i.e., sleeping sickness) caused by *T. brucei rhodesiense* (i.e., East African trypanosomiasis) and *T. brucei gambiense* (i.e., West African trypanosomiasis), and leishmaniasis caused by a range of species. Several drugs used to treat people with these infections are available in the United States only through the CDC.

Suramin.

Suramin sodium is a nonmetallic compound developed in the 1920s on the basis of structural similarities to trypanocidal dyestuffs. Suramin is active against the hemolymphatic stages of African trypanosomes (i.e., *T. brucei rhodesiense* and *T. brucei gambiense*), and it has been used prophylactically for workers in areas where *T. brucei gambiense* is highly endemic.

Suramin is available from the CDC and only in a parenteral formulation. The side effects of suramin are protean and can be life-threatening. Frequently encountered side effects include vomiting and acute hypersensitivity-like reactions (i.e., pruritus, urticaria, paresthesias, hyperesthesia of hands and feet, and photophobia), and later effects include neurologic, ocular, renal, and hepatic toxicities. Arsenic-based compounds or eflornithine are recommended for trypanosomiasis involving the central nervous system.

Melarsoprol.

Melarsoprol, a trivalent antimonial compound, is used exclusively for treatment of central nervous system trypanosomiasis caused by *T. brucei rhodesiense.*[18,19] It is available only from the CDC and in a parenteral formulation.

Severe side effects are common and include fever, vomiting, a delayed drug-induced reactive encephalopathy (which is potentially fatal), myocardial damage, albuminuria, hypertension, colic, Herxheimer-type reaction, and peripheral neuropathy. Many other toxic effects include gastrointestinal tract complaints, hypersensitivity reactions, renal and hepatic dysfunction, and a severe hemolytic anemia in G6PD-deficient patients. Because of these effects, eflornithine has become the drug of choice for central nervous system trypanosomiasis caused by *T. brucei gambiense.*

Eflornithine.

Eflornithine (i.e., difluoromethylornithine [DFMO]) is an irreversible inhibitor of the enzyme ornithine decarboxylase and is active preferentially against many protozoan parasites. Eflornithine is a drug of choice, alone or in combination, to treat people with African sleeping sickness caused by *T. brucei gambiense*, including those with advanced central nervous system disease.[20–22]

Eflornithine has limited side effects compared with other available agents, but its use in endemic areas is limited by its cost and labor-intensive administration. East African sleeping sickness caused by *T. brucei rhodesiense* is less responsive to this therapy. Eflornithine causes mild reversible bone marrow toxicity (manifested by anemia, leukopenia, and occasionally, thrombocytopenia) diarrhea, seizures, and occasional transient hearing loss. Eflornithine is available from the CDC.

Benznidazole.

Benznidazole is a 2-nitroimidazole derivative that inhibits protein and ribonucleic acid synthesis. It is used in the treatment of patients infected with *T. cruzi* (i.e., Chagas disease).[23,24] Benznidazole usually is better tolerated and may be more effective than nifurtimox, but side effects are common and include rash, neuropathy, intestinal disturbances, and neuropsychiatric alterations. Therapy is prolonged (60 days). Benznidazole is available from the CDC.

Nifurtimox.

Nifurtimox is a nitrofuran with activity against African and American (i.e., *T. cruzi*) forms of trypanosomiasis.[25] The efficacy of nifurtimox for the chronic forms of Chagas disease appears to be more geographically variable, with better results in Chile, Venezuela, Argentina, and southern Brazil than in central Brazil.

Therapy with nifurtimox usually is prolonged, and another agent commonly is substituted because of toxicity. Toxic effects of nifurtimox usually are reversible. They include gastrointestinal tract symptoms (e.g., anorexia, vomiting), weight loss, memory loss, sleep disorders, weakness, and nervous system disorders (e.g., tremor, paresthesias, polyneuritis, convulsions [rare]). Other rare complications are fever, pulmonary infiltrates, and pleural effusion. Children usually tolerate therapy better than adults.

Sodium Stibogluconate.

Sodium stibogluconate and meglumine antimonate are synthetic, pentavalent antimonial agents. They are used to treat patients with leishmaniasis, although other agents have replaced them as drugs of choice. These compounds probably are as active against leishmaniasis as the trivalent antimonial agents and usually are better tolerated.

Side effects of sodium stibogluconate include gastrointestinal tract complaints (i.e., nausea and diarrhea), musculoskeletal complaints (i.e., muscle and joint pain), fatigue, serum transaminase elevations, T-wave inversion or flattening, pancreatitis, and rarely, myocardial, renal, and hepatic damage. Sodium stibogluconate is available from the CDC.

Pentamidine.

A diamidine, pentamidine is effective as a second-line agent for cutaneous leishmaniasis and for the hemolymphatic stages of African trypanosomiasis.[26] Pentamidine is used most commonly in the United States as a second-line agent for treatment or prophylaxis of *Pneumocystis jirovecii* infections.[27] Originally considered a protozoan, *Pneumocystis* species now are classified as fungi.

Pentamidine is available in a parenteral preparation or as aerosolization therapy for *P. jirovecii* infections. A high incidence of side effects is associated with the parenteral administration of pentamidine. Adverse effects include hypoglycemia, hyperglycemia, pain at the injection site, hypotension, gastrointestinal tract disturbances (including vomiting), reversible nephrotoxicity, elevated serum transaminase levels, electrolyte disturbances, and bone marrow toxicities. Less common toxicities are anaphylaxis, acute pancreatitis, hyperkalemia, and cardiotoxicity. Pentamidine should not be used concurrently with didanosine, foscarnet, nephrotoxic drugs, or erythromycin because it can potentiate these agents' toxicities. There are few systemic side effects with the aerosolized therapy, although bronchospasm is common, as is difficulty delivering this therapy effectively to younger children.

Liposomal Amphotericin and Amphotericin B.

Liposomal amphotericin is the drug of choice in the United States for the treatment of patients with visceral leishmaniasis. It is an alternative agent for patients with mucosal leishmaniasis, and it can also be used in patients with extensive cutaneous disease.[28–32] Amphotericin B can be used, but it is more toxic, has lower efficacy, and requires more prolonged therapy than liposomal amphotericin.

Miltefosine.

Miltefosine is an oral agent that can be used to treat patients with visceral, mucosal, or cutaneous leishmaniasis.[30,33–41] Its mechanism of action is unknown. It is a synthetic ether phospholipid analogue that is chemically similar to phospolipids in cell membranes. It also has immunomodulatory effects. Side effects include intestinal disturbances, motion sickness, and elevated creatinine levels.

Although miltefosine has the advantage of being an oral agent, its use predominantly has been evaluated against New World leishmanial strains (i.e., cutaneous and mucosal) and Old World visceral *L. donovani*, and it may be less effective than other agents. The US Food and Drug Administration (FDA)–approved indications are limited to infections with certain *Leishmania* species and to patients 12 years of age or older who weigh at least 30 kg and are not pregnant or breastfeeding.

Antimalarial Therapy

Human malaria can be caused by *Plasmodium falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and the zoonotic *P. knowlesi*. The optimal choice of antimalarial agents is based on the infecting species, drug resistance, and status of the host (i.e., complicated vs. uncomplicated malaria). If the species and drug resistance profile are unknown, treatment should target chloroquine-resistant *P. falciparum*. Those with severe or complicated malaria should be treated with parenteral agents. Treatment assistance is available through the CDC Malaria Hotline provided earlier.

Artemisinins.

Antimalarial treatment has evolved over the past decade. The World Health Organization (WHO) recommends that the first-line treatment of patients with chloroquine-resistant *P. falciparum* malaria should be artemisinin based. Artemisinin derivatives include artesunate, artemether, and dihydroartemisinin. Due to the short half-life and risk of drug resistance, these agents should be used in combination, which usually includes a rapid-acting artemisinin derivative and a longer-acting second agent. Combinations include artemether plus lumefantrine, artesunate plus mefloquine, artesunate plus amodiaquine, and dihydroartemisinin plus piperazine. In the United States, an oral combination of artemether–lumefantrine is FDA approved and commercially available.[42–44] Intravenous artesunate is avaliable from the CDC for the treatement of patients with severe or complicated malaria.

Artemisinins result in rapid decrease in parasite burden. Artemisinins also affect blood stage gametocytes and can decrease the risk of transmission. Artemisinins are not effective as prophylaxis against malaria. Unfortunately, decreased parasite clearance and emerging drug resistance is being reported in Southeast Asia. Artemisinins typically are well tolerated. Artensuate has been associated with a neurologic alterations and QTc prolongation, but it is much better tolerated than the other parenteral alternative (i.e., quinidine gluconate) for the treatment of patients with severe or complicated malaria. Artesunate also has been associated with a delayed hemolytic anemia. Artemether-lumefantrine usually is well tolerated, with intestinal disturbances, rash, and neurologic alterations reported occasionally. Lumefantrine can prolong the QTc.

Chloroquine.

Chloroquine, a 4-aminoquinoline, inhibits polymerization of ferriprotoporphyrin IX, resulting in oxidative membrane damage and death of the parasite in side of infected erythrocytes. Due to widespread resistance, its use in treating patients with malaria usually is reserved for cases when chloroquine susceptibility can be ensured. *P. falciparum* malaria is almost always choloroquine resistant, although cases acquired in Haiti are a notable exception. Extensive reports of chloroquine treatment failures with *P. vivax* have been reported from Papua New Guinea and Indonesia along with sporadic reports from Brazil, Myanmar, India, Guyana, and Colombia.[45,46] Otherwise, most cases of malaria due to *P. vivax, P. malariae,* or *P. ovale* remain responsive to chloroquine.

Chloroquine is active only against the erythrocytic stages of the parasite; another agent (i.e., primaquine) is necessary for the radical cure of *P. vivax* and *P. ovale* infections. Chloroquine has been used as adjunctive therapy with dehydroemetine for invasive amebiasis unresponsive to initial therapy and for therapy of connective tissue autoimmune diseases unresponsive to other agents.

Chloroquine is well tolerated by most people, even for long-term therapy. The side effects include mild gastrointestinal tract complaints (which are usually alleviated if the drug is taken with meals), occasional headaches, blurred vision, dizziness, fatigue, confusion, depigmentation of hair, skin eruptions, corneal opacity, weight loss, and myalgias. Intense pruritus, a common complaint among black Africans taking the drug, usually is relieved with antihistamines. Chloroquine is contraindicated in patients with psoriasis, retinal disease, or porphyria.

The preparations of chloroquine available in the United States are bitter-tasting tablets. Hydroxychloroquine is better tolerated by children. Suspensions of chloroquine are widely available elsewhere for pediatric use and are much better tolerated. Chloroquine can be used as a malarial chemoprophylactic.

Quinine.

Quinine, a *Cinchona* alkaloid, was the first commercially available antimalarial agent. Its use was supplanted when chloroquine became available. Mostly known for its antimalarial effects, quinine also is effective when used in combination with clindamycin for the treatment of babesiosis.

Until artemisinins became widely available, oral quinine sulfate in combination with pyrimethamine-sulfadoxine, tetracycline, or clindamycin was the recommended therapy for *P. falciparum* malaria acquired in areas of chloroquine resistance. For patients unable to take oral medication or with severe or complicated malaria, and if intravenous artesunate is unavailable, intravenous quinidine gluconate may be used as an alternative agent because of its relative safety compared with intravenous quinine hydrochloride.[47]

Quinine commonly causes side effects known collectively as cinchonism, which in the mild form consists of tinnitus, impaired vision, headache, nausea, and abdominal pain and in its more severe form, consists of cardiovascular, gastrointestinal, and dermal manifestations. Blood glucose levels must be monitored carefully in any patient receiving quinine because hypoglycemia occurs commonly, particularly in the setting of high parasitemia. An idiosyncratic hypersensitivity reaction to quinine also can occur, most commonly manifesting as extensive skin flushing with an intense, generalized pruritus; it is a contraindication to further use of the drug.

Quinidine.

Quinidine, the dextrostereoisomer of quinine, is an alternative agent for the treatment of patients with severe or complicated malaria if intravenous artesunate is not available.[47] Use of intravenous quinidine requires careful cardiac monitoring, often in an intensive care setting, due to its marked ability to prolong the QTc and its arrhythmogenic potential. Additional side effects include those associated with cinchonism. Patients requiring intravenous therapy should be changed to oral therapy as soon as tolerated.

Mefloquine.

Mefloquine is a 4-quinolinemethanol analogue of quinine. It was historically used for chemoprophylaxis or treatment of malaria.[48] Its use was associated with neuropsychiatric, vestibular, and sleep disturbances, and mefloquine received a Black Box label from the FDA in 2014. Drug resistance also has developed in areas of Southeast Asia. For these reasons, mefloquine has largely been supplanted by other agents, although it is the only agent available for weekly dosing for chemoprophylaxis in areas of the world with chloroquine resistance. It has the most established safety record for chemoprophylaxis in pregnant women, although data on use in the first trimester are limited.

Primaquine.

An 8-aminoquinoline, primaquine is the only drug available for treating the latent hepatic life cycle forms of *P. vivax* and *P. ovale*.[49,50] Primaquine is recommended for the radical cure of these infections after chloroquine treatment has been initiated for the erythrocytic stages of infection.

Primaquine usually is well tolerated except in people with G6PD deficiency, in whom administration can lead to brisk hemolysis. Patients should be screened for G6PD deficiency before primaquine therapy. Primaquine should never be used in pregnant women, regardless of G6PD status. Occasional side effects are neutropenia, gastrointestinal tract disturbance, and methemoglobinemia. Relapses of *P. vivax* after primaquine therapy have responded to repeat treatment with chloroquine and higher doses or more prolonged courses of primaquine.[51]

Atovaquone.

Atovaquone, a hydroxynaphthoquinone, is a ubiquinone analogue that has been studied most extensively as an antimalarial agent. Atovaquone was released in the United States for the treatment of *P. jirovecii* and *Toxoplasma gondii*.[52,53] Atovaquone is approved by the FDA in a fixed-dose combination with proguanil (i.e., Malarone in adult and pediatric dosages) for treatment and prophylaxis of *P. falciparum* infections.[54,55]

Atovaquone was combined with proguanil because of rapid development of resistance in vitro and in early clinical trials when atovaquone was used alone for malaria. Many studies have documented efficacy of the combination for the treatment and prophylaxis of *P. falciparum* malaria, and there is a growing experience in the treatment of infections with *P. vivax*.[56] The combination of atovaquone and azithromycin is an effective treatment for babesiosis with a better side effect profile than clindamycin plus quinine.[57]

For *P. jirovecii*, studies have indicated that atovaquone is slightly less efficacious but is tolerated moderately better than trimethoprim-sulfamethoxazole or pentamidine.[58] There are no efficacy data for children, but the pharmacokinetic data are similar to those for adults. The most common side effects are fever, nausea, diarrhea, and rashes. Unlike most of the currently used therapies, atovaquone is active against the tissue cyst stages of *T. gondii* in animal models. Atovaquone has been used alone or in combination with pyrimethamine for treatment of central nervous system toxoplasmosis in AIDS patients.[59]

Antibacterial Agents With Antiprotozoan Activity

Tetracycline and Doxycycline.

Agents with antiprotozoan activity increasingly have been used as antimalarial compounds, mainly in areas where drug-resistant malaria is a problem. When used for treatment, these compounds should always be given in combination with more rapidly acting drugs because they are slowly malariacidal. The drugs usually are well tolerated, except for common gastrointestinal tract complaints.

Photosensitivity and secondary *Candida* vaginitis are concerns with prolonged prophylactic use of doxycycline. Use of this class of compounds is restricted in pregnancy and usually in children younger than 8 years of age because of potential toxicity. Tetracycline also is efficacious for treatment of balantidiasis and can be used as adjunctive therapy with metronidazole to treat amebiasis.

Clindamycin.

Clindamycin is a macrolide antibiotic, which can be used in combination with other therapies for treatment of *P. falciparum* malaria, toxoplasmosis, and babesiosis. Clindamycin plus pyrimethamine is effective as an alternative treatment for *Toxoplasma* encephalitis in patients infected with human immunodeficiency virus (HIV) who cannot tolerate sulfadiazine.[60] Clindamycin plus quinine (or quinidine) is a recommended therapy for babesiosis, although atovaquone with azithromycin has better side effect profile.[57,61] Clindamycin has been used in combination with primaquine for the treatment of *P. jirovecii* infection in selected patients.[62] Clindamycin usually is well tolerated in children, but the unpleasant smell and taste of the solution make crushing the tablets a better option in some cases.

Spiramycin.

Spiramycin is a macrolide antibiotic used more extensively in Europe for the treatment of toxoplasmosis in pregnancy. Spiramycin has been used in the United States for the treatment of congenital toxoplasmosis in patients who are intolerant of other therapies. The drug usually is well tolerated and is available as an investigational drug from the manufacturer after approval from the FDA (phone: 301-796-1600). Occasional side effects are gastrointestinal tract disturbances.

Folate Metabolism Inhibitors.

Many antiprotozoan compounds take advantage of reliance of a parasite on the synthesis or scavenging of folate precursors. These compounds include the dihydrofolate reductase (DHFR) inhibitors, which preferentially inhibit the parasite enzyme, and sulfonamides, which act as *p*-aminobenzoic acid analogues and inhibit or act as suicide substrates in the folate biosynthetic pathways. These two classes of compounds often are formulated in combinations for various indications. DHFR inhibitors used for antiparasitic therapy include pyrimethamine, trimethoprim, proguanil, and trimetrexate. The sulfonamides have various pharmacokinetic properties, which are taken advantage of in the formulations used for treatment of parasitic infections.

Pyrimethamine with sulfadiazine is the treatment of choice for toxoplasmosis in most clinical settings. A limiting factor in HIV-infected patients who require prolonged therapy for toxoplasmosis is the high incidence of side effects, mainly attributed to the sulfonamide component. Pyrimethamine has been used with clindamycin in this clinical setting to circumvent these problems.[60] Supplementation with folinic acid often is recommended with prolonged use of pyrimethamine to lessen the bone marrow–suppressive effects of this drug and to prevent folic acid deficiency.

Trimethoprim-sulfamethoxazole, commonly formulated in a 1 : 5 ratio, is the treatment and prophylaxis of choice for *P. jirovecii* infections in HIV-infected patients and patients receiving immunosuppressive therapy.[63] The only limitation of this regimen is the high incidence (up to 65%) of untoward reactions in HIV-infected patients.[64] Trimethoprim plus dapsone is efficacious for *P. jirovecii* prophylaxis, although toxicity remains a problem.

Trimethoprim-sulfamethoxazole is the recommended therapy for any patient with *Cystoisospora belli* infection, although relapse is common among patients with AIDS.[65] Trimethoprim-sulfamethoxazole also has efficacy for *Cyclospora cayetanensis* infections in HIV-infected patients.[66,67] Trimethoprim-sulfamethoxazole has been used for the treatment of toxoplasmosis, but pyrimethamine-sulfadiazine should be considered the treatment of choice. It also has been used for prophylaxis against *T. gondii* in patients with AIDS who test positive for antibodies to *T. gondii* and have a 25% to 50% risk for toxoplasmic encephalitis.

Proguanil, the prototype of the DHFR inhibitors, is not available as a stand-alone agent in the United States, but it is available overseas. Proguanil has been approved by the FDA in a fixed-dose combination with atovaquone for the treatment and prophylaxis of infections with *P. falciparum.* Toxicity is a problem with combinations of DHFR inhibitors and sulfonamides, particularly in patients with AIDS. Most of these untoward reactions are attributed to the sulfonamide components of the combination. Common side effects of sulfonamides are rashes, fever, bone marrow suppression, gastrointestinal tract complaints, and hepatotoxicity. More severe but less common reactions include toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, and serum sickness. The toxicity most commonly associated with the DHFR inhibitors is bone marrow suppression, which usually can be alleviated by folinic acid supplementation. Proguanil also is associated with oral ulcerations, hair loss, scaling of palms and soles, and urticaria.

Treatment of Helminthic Infections

Helminths are multicellular worms that can be round (i.e., nematodes), flat (i.e., cestodes and tapeworms), or fluke-like (i.e., trematodes). Common roundworm infections include ascariasis, hookworm infection, trichuriasis (i.e., whipworm), enterobiasis (i.e., pinworm) strongyloidiasis, filariasis, and cutaneous and larval migrans. Common flatworm infections include taeniasis, cysticercosis, and diphyllobothriasis. Common trematode infections include schistosomiasis, fascioliasis, and paragonimiasis. Most helminth infections can be treated with one of three highly efficacious and safe drugs: albendazole, ivermectin, or praziquantel.

Intestinal Nematodes

Albendazole.

Albendazole is a synthetic nitroimidazole with a broad spectrum of antinematodal activity similar to that of mebendazole but with anticestodal and some antiprotozoal action. Mebendazole is no longer manufactured in the United States, and its use has been supplanted by albendazole. The advantage of albendazole over mebendazole is its activity in a single oral dose of 400 mg (200 mg for children <2 years old) against ascariasis, hookworm infection, trichostrongylosis, and to a slightly lesser extent, enterobiasis and trichuriasis.[68,69]

Because intestinal helminthiasis typically is multiparasitic, albendazole is an almost ideal agent.[70,71] It has good activity in multiple doses against cutaneous larva migrans and strongyloidiasis, but single-dose therapy with ivermectin is more effective for these two helminthic infections.[72,73] Successful treatment with albendazole of visceral larva migrans has been reported, although ivermectin is the drug of choice.[74] Efficacy against the microfilarial stage of *Wuchereria bancrofti, Brugia malayi,* and *Loa loa* is well documented, although diethylcarbamazine (DEC) remains the parasite adulticidal drug of choice for the treatment of patients with these filarial infections.[75–77] DEC plus albendazole in combination has superior activity against adult *W. bancrofti* compared with either drug alone.[78] Albendazole may be of benefit in patients with gnathostomiasis, baylisascariasis, trichinellosis, toxociariasis, capillariasis, and angiostrongyliasis.

Prolonged high-dose regimens of albendazole constitute the most effective medical treatment of larval cestode disease caused by *Echinococcus granulosus, E. multilocularis,* and *E. vogelii.*[79] Dosage is not defined for children younger than 6 years of age. Treatment is tailored to response and normally is required for a minimum of several weeks or months. Albendazole should be started several days before surgery to minimize the effect of intraoperative spillage of cyst contents. Albendazole also is used in the treatment of patients with cysticercosis, often with concomitant steroids.[80–82]

Albendazole binds irreversibly to the nematodal isoform of β-tubulin, blocking microtubule assembly, disrupting tegumental integrity, inhibiting motility, and impeding glucose uptake by the worm. Detectable levels are achieved in serum, cerebrospinal fluid, cyst fluid, and bile, with a serum half-life of 8 to 15 hours depending on the dose. Rapid, extensive hepatic biotransformation to the active metabolite, albendazole sulfoxide, occurs, but the major route of excretion is not clear.

Side effects of low-dose albendazole therapy are minimal, consisting of diarrhea, abdominal pain, migration of *Ascaris* through the mouth or nose, and rare hypersensitivity. With high-dose or prolonged therapy, elevated levels of hepatic transaminases, dizziness, neutropenia, and alopecia are most common.[83] Serum hepatic enzyme levels and the blood count should be monitored every 2 weeks during high-dose therapy.

Lack of data for children younger than 2 years of age has precluded specific US labeling for or establishment of dosage for this age group, although the label leaves the physician discretion in electing to treat children younger than 2 years of age. The pediatric dosage is identical to the adult dosage. Embryotoxic potential usually precludes the use of albendazole during pregnancy.

Albendazole is manufactured as a suspension and as tablets that can be crushed with food, chewed, or taken whole. Albendazole is poorly absorbed and should be ingested with food, preferably a fatty meal, to maximize absorption.

Pyrantel Pamoate.

Pyrantel pamoate, a broad-spectrum anthelmintic drug, is available only as an over-the-counter oral suspension in the United States. This drug has been supplanted by the benzimidazoles, except for its continued popularity for the treatment of enterobiasis. A single-dose regimen is sufficient for ascariasis and trichostrongylosis, but one dose daily on 3 consecutive days is required for hookworm infection. Pyrantel pamoate is ineffective for trichuriasis.

The agent is nonvermicidal but causes depolarizing neuromuscular blockade of helminth musculature. Paralyzed worms are expelled with intestinal peristalsis. Because of poor absorption from the gastrointestinal tract, side effects are restricted to infrequent occurrence of abdominal pain, diarrhea, dizziness, insomnia, rash, and headache. Pyrantel pamoate should be used with caution in people with hepatic dysfunction. Although no specific data exist on its use in children younger than 2 years of age, no age-related problems have been documented. Few data exist on use in pregnancy, and pyrantel pamoate is nonembryotoxic in animals. If absolutely necessary, it can be used after the first trimester of pregnancy. Pyrantel pamoate should not be administered concurrently with piperazine.

Systemic Nematodes

Diethylcarbamazine.

DEC is a piperazine derivative used primarily in the treatment of selected human filarial infections. Because of frequent unacceptable side effects in people infected with *Onchocerca volvulus,* DEC should not be used for microfilaricidal treatment of this parasite; ivermectin is the drug of choice. DEC is ineffective against *Mansonella* spp. and should not be used to treat visceral larva migrans.

For lymphatic filariasis (i.e., *W. bancrofti, Brugia malayi,* and *B. timori*) and loiasis, relatively low-dose microfilaricidal regimens are often used in the developing world as part of mass treatment campaigns. In the treatment of an individual patient, however, the aim is macrofilaricidal activity with the use of multiple aggressive courses of therapy.[84] Dosage regimens are not well established for children, but infection is rare in children younger than 2 years of age. Prophylactic use of weekly DEC for loiasis is effective.[85]

DEC, which should be taken after a meal, is absorbed readily, is distributed into all body compartments, and undergoes renal excretion with a serum half-life of 8 hours. The mechanism of action is not documented clearly.

Side effects, which often correlate with microfilarial load, most commonly include nausea, dizziness, headache, visual disturbances, and fever. Transient microscopic hematuria is common.[86] The gastrointestinal tract side effects are dose related, and some patients cannot tolerate the dose of 9 mg/kg/day. In patients with lymphatic filariasis, the death of adult worms often results in lymphadenopathy or lymphangitis, frequently in the genital region. Encephalopathy can occur after treatment for loiasis in people with high microfilarial counts.[87]

Ivermectin.

Ivermectin, a semisynthetic lactone originally developed in the

1970s for veterinary use, has broad activity against larval roundworms and a number of arthropods. Receptor-mediated hyperpolarization of cells after an influx of negatively charged ions occurs through a novel glutamate-sensitive chloride channel in nematodes. The drug is well absorbed when taken orally, and excretion is almost entirely in feces. It has a serum half-life of 12 hours.

Originally developed for human use in cases of onchocerciasis, ivermectin has become the treatment of choice for *O. volvulus* in a single microfilaricidal dose. Ivermectin is also the drug of choice for strongyloidiasis, cutaneous larval migrans, and scabies, and it can be used as an alternative agent for pediculosis.[88] Ivermectin is also microfilaricidal for *W. bancrofti, B. malayi,* and *L. loa.*

Ivermectin is remarkably nontoxic. Adverse effects are caused by reactions to the release of endosymbiotic bacteria from dying parasites.[89] This Mazzotti-type reaction can occur in onchocerciasis and filariasis and consists of fever, pruritus, urticaria, headache, myalgia, joint and bone pain, and tender lymphadenopathy.[90] The severity of the reaction usually is proportionate to the microfilarial load and rapidity of death of microfilariae. Reactions are less marked in *B. malayi* infection, in which microfilarial clearance occurs over days rather than hours. In lymphatic filariasis and loiasis, the severity of adverse effects with ivermectin is equivalent to those found with DEC. Ivermectin should not be used in patients who have loiasis with more than 5000 microfilariae per 1 mL of blood, and all patients with microfilaremic loiasis require premedication with corticosteroids. Adverse outcomes have not been observed for women accidentally treated while pregnant, but use in pregnancy is not recommended.

Trematodes and Cestodes

Praziquantel.

Praziquantel is the drug of choice for all fluke infections except for *Fasciola hepatica* (i.e., sheep liver fluke) and for all definitive host cestode infections.[91] It is effective for all species and clinical manifestations of schistosomiasis, including central nervous system disease.[92] For liver and intestinal flukes including *Clonorchis sinensis* (i.e., Chinese liver fluke), *Opisthorchis viverrini* (i.e., liver fluke), *Fasciolopsis buski* (i.e., intestinal fluke), *Heterophyes heterophyes* (i.e., intestinal fluke), *Paragonimus westermani* (i.e., lung fluke), and *Metagonimus yokogawai* (i.e., intestinal fluke), multidose therapy is required.

A single dose of praziquantel is an effective treatment for adult stages of the tapeworms *Taenia saginata* (i.e., beef), *T. solium* (i.e., pork), and *Diphyllobothrium latum* (i.e., fish). Although it is more expensive and is absorbed systemically, single-dose praziquantel offers the advantage over niclosamide of not requiring purging and of theoretically guarding against cysticercosis. Praziquantel can be used in patients with cysticercosis, and it is often given perioperatively in patients undergoing surgery for cystic echinococcosis.

Praziquantel is a heterocyclic prazinoisoquinoline derivative, and the precise mechanism of action is unknown. The agent is rapidly taken up by helminths, with resultant loss of intracellular calcium that causes blebbing and bursting of the tegument. Exposure of worm antigens in this way may allow the host immune system to play a role in final parasite death.

Oral absorption is rapid, with extensive first-pass metabolism by the liver. High levels (10%–25% of serum levels) are achieved in cerebrospinal fluid, bile, feces, and human milk. The serum half-life is 1 to 1.5 hours, with rapid renal excretion. Plasma concentrations can be higher in patients with hepatic compromise. Side effects, including lassitude, malaise, headache, and dizziness, are common but are mild and transient. More uncommonly, sedation, fever, pruritus, rash, sweating, and severe abdominal discomfort occur.

No specific data on the use of praziquantel in children younger than 4 years of age are available, but no age-specific problems have been reported. Nursing mothers must stop breastfeeding during and for 72 hours after completion of treatment. Tablets must be swallowed whole.

Niclosamide.

Niclosamide is a highly effective, single-dose treatment for the adult stages of *T. saginata, T. solium,* and *D. latum* tapeworm infections.[93] Its production has been discontinued in the United States.

This agent kills the scolex and proximal segments of cestodes on contact by uncoupling oxidative phosphorylation. Because niclosamide causes degeneration of proglottids, a laxative purge 1 to 2 hours after treatment is recommended to reduce the theoretical risk of cysticercosis from release of eggs. Treatment can be repeated in a few days if it is not effective. Mild nausea and abdominal pain are the only reported side effects of this negligibly absorbed compound.

Other Anthelmintic Drugs.

Because *F. hepatica* infection may not respond to praziquantel, a single dose of triclabendazole is regarded by the WHO as the drug of choice for this disorder.[94–96] The drug is available through the CDC.

An older drug for *F. hepatica,* bithionol, can be obtained from the CDC. Bithionol also is an alternative drug for the treatment of *P. westermani* (i.e., lung fluke). Side effects include photosensitivity reactions, urticaria, and gastrointestinal complaints (e.g., vomiting, diarrhea, abdominal pain). Production of bithionol ceased more than 30 years ago, but current stocks retain potency.

Oxamniquine and metrifonate are effective, well-tolerated antischistosomal drugs that most frequently are used in the developing world. Piperazine citrate, piperazine adipate, and piperazine hexahydrate are inexpensive and quite effective treatments for ascariasis or enterobiasis, but because of potential toxicity and the need for prolonged treatment, they should not be used when other agents are available.[97] Pyrvinium pamoate, used in some places for enterobiasis, is no longer available commercially in the United States.

Appendix 296.1 Drugs for Parasitic Infections

Disease	Drug	Adult Dosage	Pediatric Dosage
African trypanosomiasis (African sleeping sickness)			
Trypanosoma brucei rhodesiense, hemolymphatic stage	Suramin[1]	1 g, IV, on days 1, 3, 5, 14, and 21[2]	20 mg/kg (max 1 g), IV, on days 1, 3, 5, 14, and 21[3]
T brucei rhodesiense,	Melarsoprol[4]	2–3.6 mg/kg/day	2–3.6 mg/kg/day

CNS involvement		(max 200 mg), IV, × 3 days[5]	(max 200 mg), IV, × 3 days[5]
		After 7 days, 3.6 mg/kg/day × 3 days	After 7 days, 3.6 mg/kg/day × 3 days
		Give a 3rd series of 3.6 mg/kg/day after 7 days	Give a 3rd series of 3.6 mg/kg/day after 7 days
T brucei gambiense, hemolymphatic stage	Pentamidine[6]	4 mg/kg/day, IV or IM, × 7–10 days	4 mg/kg/day, IV or IM, × 7–10 days
T brucei gambiense, CNS involvement	Eflornithine[7]	400 mg/kg/day, IV, in 4 doses × 14 days	400 mg/kg/day, IV, in 4 doses × 14 days
American trypanosomiasis (Chagas disease; *Trypanosoma cruzi* infection)	Benznidazole[8]	<12 y	5–7.5 mg/kg/day, orally, in 2 divided doses for 60 days
		12 y or older	5–7 mg/kg/day, orally, in 2 divided doses for 60 days
	OR		
	Nifurtimox[8]	1–10 y	15–20 mg/kg/day, orally, in 3 or 4 divided doses for 90 days
		11–16 y	12.5–15 mg/kg/day, orally, in 3 or 4 divided doses for 90 days
		17 y or older	8–10 mg/kg/day, orally, in 3 or 4 divided doses for 90–120 days
Ascariasis (*Ascaris lumbricoides;* intestinal roundworm)	Albendazole[9]	400 mg, orally, once	
	OR		
	Mebendazole[10]	100 mg, orally, twice daily for 3 days, or 500 mg, orally, once	
	OR		
	Ivermectin [11]	150–200 µg/kg, orally, once	
Babesiosis[12]	Atovaquone	750 mg orally twice a day	40 mg/kg/day, orally, in 2 doses (max 750 mg/dose)
	PLUS		
	Azithromycin	On the first day, give a total dose in the range of 500–1000 mg, orally; on subsequent days, give a total daily dose in the range of 250–1000 mg	10 mg/kg (max 500 mg/dose), orally, on day 1, then 5 mg/kg/day (max 250 mg/dose), orally, on subsequent days
	OR		
	Clindamycin	600 mg, orally, 3	20–40 mg/kg/day

		times a day, **or** 300–600 mg, IV, 4 times a day	(max 600 mg/dose), orally, in 3 doses
	PLUS		
	Quinine	650 mg, orally, 3 times a day	30 mg/kg/day, orally, in 3 doses (max 650 mg/dose)
Balantidiasis *(Balantidium coli)*	Tetracycline	500 mg, orally, 4 times daily for 10 days	Age ≥8 y, 40 mg/kg/day (max 2 g), orally, in 4 doses for 10 days
	OR		
	Metronidazole	500–750 mg, orally, 3 times daily for 5 days	35–50 mg/kg/day, orally, in 3 doses for 5 days
	OR		
	Iodoquinol	650 mg, orally, 3 times daily for 20 days	30–40 mg/kg/day (max 2 g), orally, in 3 doses for 20 days
	OR		
	Nitazoxanide	500 mg, orally, twice daily for 3 days	Age 4–11 y: 200 mg, orally, twice daily for 3 days
			Age 1–3 y: 100 mg, orally, twice daily for 3 days
Baylisascariasis (raccoon roundworm infection)	Albendazole[9]	25–50 mg/kg/day, orally, for 10–20 days[13]	
Blastocystis hominis infection[14]	Metronidazole	750 mg, orally, 3 times daily for 10 days	35–50 mg/kg/day, orally, in 3 doses for 10 days
	OR		
	Trimethoprim (TMP)/ sulfamethoxazole (SMX)	160 mg TMP, 800 mg SMX twice daily for 7 days	Age >2 mo: 8 mg TMP/kg and 40 mg/kg SMX per day in 2 divided doses for 7 days
	OR		
	Nitazoxanide	500 mg, orally, twice daily for 3 days	Age 4–11 y: 200 mg, orally, twice daily for 3 days
			Age 1–3 y: 100 mg, orally, twice daily for 3 days
Capillariasis	Mebendazole[10]	200 mg, orally, twice a day for 20 days	
	OR		
	Albendazole[9]	400 mg, orally, once a day for 10 days	
Chilomastix mesnili infection	No treatment is necessary; this protozoan is harmless		
Clonorchiasis	Praziquantel	75 mg/kg/day, orally, 3 doses per day for 2 days	
	OR		
	Albendazole[9]	10 mg/kg/day for 7 days	

Cutaneous larva migrans (zoonotic hookworm)	Albendazole[9]	400 mg/day, orally, once a day for 3 to 7 days	Age >2 y: 400 mg/day, orally, for 3 days
	OR		
	Ivermectin	200 µg/kg, orally, as a single dose	Weight >15 kg: 200 µg/kg, orally, as a single dose
Cyclosporiasis	TMP/SMX	160 mg TMP/800 mg SMX, orally, 2 times/day × 7–10 days	8–10 mg TMP/kg/day, orally, divided 2 times/day for 7–10 days
Cystoisosporiasis (*Cystoisospora* infection; formerly isosporiasis)	TMP/SMX	160 mg TMP/800 mg SMX, orally, 2 times/day × 7–10 days	8–10 mg TMP/kg/day, orally, divided 2 times/day for 7–10 days
	OR		
	Ciprofloxacin (second-line alternate)	500 mg, orally, 2 times/day × 7 days	—
Dientamoeba fragilis infection	Iodoquinol	650 mg, orally, 3 times/day for 20 days	30–40 mg/kg/day (max 2 g), orally, divided 3 times/day × 20 days
	OR		
	Paromomycin	25–35 mg/kg/day, orally, divided 3 times/day for 7 days	
	OR		
	Metronidazole	500–750 mg, orally, 3 times/day for 10 days	35–50 mg/kg/day, orally divided 3 times/day × 10 days
Diplryllobothrium infection	Praziquantel[15]	5–10 mg/kg, orally, in a single dose	
	OR		
	Niclosamide[16]	2 g, orally, once	50 mg/kg (max 2 g), orally, once
Dipylidium caninum infection (dog or cat flea tapeworm)	Praziquantel[15]	5–10 mg/kg, orally, in a single dose	
	OR		
	Niclosamide	2 g, orally, once	50 mg/kg, (max 2 g, orally, once)
Echinococcosis[17]	Albendazole[9]	400 mg, orally, twice a day for 1–6 mo	10–15 mg/kg/day (max 800 mg), orally, in 2 doses for 1–6 mo
Endolimax nana infection	No treatment is necessary; this protozoan is harmless		
Entamoeba coli infection	No treatment is necessary; this protozoan is harmless		
Entamoeba dispar infection	No treatment is necessary; this protozoan is harmless		
Entamoeba hartmanni infection	No treatment is necessary; this protozoan is harmless		
Entamoeba polecki	No treatment is necessary; this protozoan is harmless		
Enterobiasis (pinworm)	Mebendazole[10]	100 mg, orally, once; repeat in 2 wk	
	OR		
	Pyrantel pamoate	11 mg/kg base, orally, once (max 1 g);	

		repeat in 2 wk	
	OR		
	Albendazole[9]	For children 20 kg or greater: 400 mg PO once; repeat in 2 wk	
		For children <20 kg: 200 mg PO once; repeat in 2 wk	
Fascioliasis *(Fasciola hepatica;* sheep liver fluke)	Triclabendazole[18]	10 mg/kg, orally, once or twice	
	OR		
	Nitazoxanide	500 mg, orally, 2 times/day × 7 days	Age 1–3 y: 100 mg, orally, 2 times/day × 7 days
			Age 4–11 y: 200 mg, orally, 2 times/day × 7 days
			Age ≥12 y: 500 mg, orally, 2 times/day × 7 days
Fasciolopsiasis	Praziquantel[15]	75 mg/kg/day, orally, in 3 divided doses for 1 day	
Gnathostomiasis (cutaneous)	Albendazole[9]	400 mg, orally, 2 times/day × 21 days	
	OR		
	Ivermectin	200 µg, orally, once daily × 2 days	
Heterophyiasis	Praziquantel[15]	75 mg/kg/day, divided 3 times/day × 1 day, orally	
Hymenolepiasis *(Hymenolepis nana;* dwarf tapeworm)	Praziquantel[15]	25 mg/kg in a single-dose therapy, orally	
	OR		
	Niclosamide[16]	2 g in a single dose for 7 days, orally	Weight 11–34 kg: 1 g in a single dose on day 1, then 500 mg per day, orally, for 6 days
			Weight >34 kg: 1.5 g in a single dose on day 1, then 1 g per day, orally, for 6 days
	OR		
	Nitazoxanide	500 mg, orally, 2 times/day × 3 days	Age 1–3 y: 100 mg, orally, 2 times/day × 3 days
			Age 4–11 y: 200 mg, orally, 2 times/day × 3 days
			Age ≥12 y: 500 mg, orally, 2 times/day × 3 days
Hookworm (Human; *Ancylostoma duodenale, Necator americanus)*	Albendazole[9]	400 mg, orally, once	
	OR		
	Mebendazole[10]	100 mg, orally, twice a day for 3 days, or 500 mg, orally, once	
	OR		
	Pyrantel pamoate	11 mg/kg (up to a maximum of 1 g), orally, daily for 3 days	
Iodamoeba buetschlii Infection	No treatment is necessary; this protozoan is harmless		

Leishmaniasis[19]			
Visceral (Kala-azar)	Liposomal amphotericin B	3 mg/kg/day, IV, on days 1–5, 14, and 21	
	OR		
	Sodium stibogluconate	20 mg pentavalent antimony (Sb)/kg/day, IV or IM, × 28 days	
	OR		
	Miltefosine	30–44 kg: 50 mg, twice daily, for 28 consecutive days	
		≥ 45 kg: 50 mg, 3 times daily, for 28 consecutive days	
	OR		
	Amphotericin B deoxycholate	1 mg/kg, IV, daily × 15–20 days or every second day for up to 8 wk (total usually 15–20 mg/kg)	
Cutaneous	Sodium stibogluconate	20 mg Sb/kg/day, IV or IM, × 20 days	
	OR		
	Miltefosine	30–44 kg: 50 mg, twice daily, for 28 consecutive days	
		≥45 kg: 50 mg, 3 times daily, for 28 consecutive days	
Mucosal	Sodium stibogluconate	20 mg Sb/kg/day, IV or IM, × 28 days	
	OR		
	Amphotericin B	0.5–1 mg/kg, IV, daily × 15–20 days or every second day for up to 8 wk	
	OR		
	Miltefosine	30–44 kg: 50 mg, twice daily, for 28 consecutive days	
		≥45 kg: 50 mg, 3 times daily, for 28 consecutive days	
Lice infestation *(Pediculus humanus, P capitis, Phthirus pubis)*[20]	Pyrethrins with piperonyl butoxide[21]	Topically, twice, at least 7 days apart	Topically, twice at least 7 days apart
	OR		
	0.5% Ivermectin lotion[22]	Topically, once	Topically, once
	OR		
	0.9% Spinosad suspension[23]	Topically, twice, at least 7 days apart	Topically, twice, at least 7 days apart
	OR		
	1% Permethrin[21]	Topically, twice, at least 7 days apart	Topically, twice, at least 7 days apart
	OR		
	5% Benzyl alcohollotion[24]	Topically, twice, at least 7 days apart	Topically, twice, at least 7 days apart
	OR		
	0.5% Malathion[25]	Topically, twice, at least 7 days apart	Topically, twice, at least 7 days apart
	OR		
	Ivermectin[26]	200 or 400 µg/kg, orally	≥15 kg: 200 or 400 µg/kg, orally
Loiasis *(Loa loa)*	*Indication:*		
	Symptomatic loiasis with microfilariae of L loa/mL <8000		
	Diethylcarbamazine (DEC)[27]	8–10 mg/kg, orally, in 3 divided doses	

		daily for 21 days	
	Indication:		
	Symptomatic loiasis, with microfilariae of L loa/mL <8000 and foiled 2 rounds DEC		
	OR		
	Symptomatic loiasis, with microfilariae of L loa/mL ≥8000 to reduce level to <8000 prior to treatment with DEC		
	Albendazole[9]	200 mg, orally, twice daily for 21 days	
Lymphatic filariasis (elephantiasis; *Wuchereria bancrofti, Brugia malayi, Brugia timori)*	Diethylcarbamazine (DEC)[27]	Treatment of lymphatic filariasis: Adults and children >18 mo: 6 mg/kg/day, orally, divided in 3 doses for 12 consecutive days OR 6 mg/kg/day as a single oral dose Treatment of tropical pulmonary eosinophilia (TPE): Adults and children >18 mo: 6 mg/kg/day, orally, divided in 3 doses for 14–21 days	
Malaria *(Plasmodium* species)	Region infection acquired		
Uncomplicated malaria *P folcipanan* or species not identified	Chloroquine-resistant or unknown resistance[28,29] (All malarious regions except those specified as chloroquine-sensitive listed below.)		
If "species not identified" subsequently diagnoses as *P vivax* or *P ovale,* see below re: treatment with primaquine	Atovaquone-proguanil[30]	1000 mg atovaquone/400 mg proguanil, orally, once daily × 3 days	Weight 5–8 kg: 2 pediatric tablets, orally, once daily × 3 days
			Weight 9–10 kg: 3 pediatric tablets, orally, once daily × 3 days
			Weight 11–20 kg: 1 adult tablets, orally, once daily × 3 days
			Weight 21–30 kg: 2 adult tablets, orally, once daily × 3 days
			31–40 kg: 3 adult tablets, orally, once daily × 3 days
			>40 kg: 4 adult tablets, orally, once daily × 3 days
	OR		
	Artemether-lumefantrine[30]	A 3-day treatment schedule with a total of 6 oral doses is recommended for both adult and pediatric patients based on weight. The patient should receive the initial dose, followed by the second dose 8 h later, then 1 dose, orally, 2 times/day, for the following 2 days.	

	1 tablet = 20 mg artemether and 120 mg lumefantrine	Weight 5 to <15 kg: 1 tablet per dose Weight 15 to <25 kg: 2 tablets per dose Weight 25 to <35 kg: 3 tablets per dose Weight ≥35 kg: 4 tablets per dose	
	OR		
	Quinine sulfate[31,32] plus one of the following: Doxycycline,[33] Tetracycline,[33] or Clindamycin	Quinine sulfate: 542 mg base (=650 mg salt),[4] orally, 3 times/ day × 3 or 7 days[5]	Quinine sulfate: 8.3 mg base/kg (=10 mg salt/kg), orally, 3 times/day × 3 or 7 days
		Doxycycline: 100 mg, orally, 2 times/day × 7 days	Doxycycline: 2.2 mg/kg, orally, every 12 h × 7 days
		Tetracycline: 250 mg, orally, 4 times/day × 7 days	Tetracycline: 25 mg/kg/day, orally, divided 4 times/day × 7 days
		Clindamycin: 20 mg base/kg/day, orally, divided 3 times/day × 7 days	Clindamycin: 20 mg base/kg/day, orally, divided 3 times/day × 7 days
	OR	Mefloquine[34] 684 mg base (=750 mg salt), orally, as initial dose, followed by 456 mg base (=500 mg salt), orally, given 6–12 h after initial dose Total dose = 1250 mg salt	13.7 mg base/kg (=15 mg salt/kg), orally, as initial dose, followed by 9.1 mg base/kg (=10 mg salt/ kg), orally, given 6–12 h after initial dose Total dose = 25 mg salt/kg
Uncomplicated malaria	Chloroquine-sensitive		
P falciparum or species not identified	(Central America west of Panama Canal; Haiti; the Dominican Republic; and most of the Middle East)		
	Chloroquine phosphate[35]	600 mg base (=1000 mg salt), orally, immediately, followed by 300 mg base (=500 mg salt), orally, at 6, 24, and 48 h Total dose: 1500 mg base (=2500 mg salt)	10 mg base/kg, orally, immediately, followed by 5 mg base/kg, orally, at 6, 24, and 48 h Total dose: 25 mg base/kg
	OR		
	Hydroxychloroquine	620 mg base (=800 mg salt), orally, immediately, followed by 310 mg base (=400 mg salt), orally, at 6, 24, and 48 h	10 mg base/kg, orally, immediately, followed by 5 mg base/kg, orally, at 6, 24, and 48 h Total dose: 25 mg

		Total dose: 1550 mg base (=2000 mg salt)	base/kg
	All regions		
	Chloroquine phosphate[35]	600 mg base (=1000 mg salt), orally, immediately, followed by 300 mg base (=500 mg salt), orally, at 6, 24, and 48 h	10 mg base/kg, orally, immediately, followed by 5 mg base/kg, orally, at 6, 24, and 48 hours Total dose: 25 mg base/kg
Uncomplicated malaria *P malariae or P knowlesi*		Total dose: 1500 mg base (=2500 mg salt)	
	OR		
	Hydroxychloroquine	620 mg base (=800 mg salt), orally, immediately, followed by 310 mg base (=400 mg salt), orally, at 6, 24, and 48 h Total dose: 1550 mg base (=2000 mg salt)	10 mg base/kg, orally, immediately, followed by 5 mg base/kg, orally, at 6, 24, and 48 h Total dose: 25 mg base/kg
	All regions		
	Note: for suspected chloroquine-resistant *P vivax,* see row below		
	Chloroquine phosphate[35]	600 mg base (=1000 mg salt), orally, immediately, followed by 300 mg base (=500 mg salt), orally, at 6, 24, and 48 h Total dose: 1500 mg base (=2500 mg salt)	10 mg base/kg, orally, immediately, followed by 5 mg base/kg, orally, at 6, 24, and 48 h Total dose: 25 mg base/kg
	PLUS		
Uncomplicated malaria *P vivax* or *P ovale*	Primaquine phosphate[36]	30 mg base, orally, once daily × 14 days	0.5 mg base/kg, orally, once daily × 14 days
	OR		
	Hydroxychloroquine	620 mg base (=800 mg salt), orally, immediately, followed by 310 mg base (=400 mg salt), orally, at 6, 24, and 48 h Total dose: 1550 mg base (=2000 mg salt)	10 mg base/kg, orally, immediately, followed by 5 mg base/kg, orally, at 6, 24, and 48 h Total dose: 25 mg base/kg
	PLUS		
	Primaquine phosphate[36]	30 mg base, orally, once daily × 14	0.5 mg base/kg, orally, once daily

		days	× 14 days
Uncomplicated malaria	Chloroquine-resistant[37] (Papua New Guinea and Indonesia)		
P vivax	Quinine sulfate plus either Doxycycline or Tetracycline plus Primaquine phosphate[36]	Quinine sulfate: 542 mg base (=650 mg salt),[4] orally, 3 times/ day × 3 or 7 days[32]	Quinine sulfate: 8.3 mg base/kg (=10 mg salt/kg), orally, 3 times/ day × 3 or 7 days[32]
		Doxycycline: 100 mg, orally, 2 times/day × 7 days	Doxycycline: 2.2 mg/kg, orally, every 12 h × 7 days
		Tetracycline: 250 mg, orally, 4 times/day × 7 days	Tetracycline: 25 mg/kg/day, orally, divided 4 times/day × 7 days
		Primaquine phosphate: 30 mg base, orally, once daily × 14 days	Primaquine Phosphate: 0.5 mg base/kg, orally, once daily × 14 days
	OR		
	Atovaquone-proguanil plus Primaquine phosphate[36]	Atovaquone-proguanil: 1000 mg atovaquone/400 mg proguanil, orally, once daily × 3 days	Atovaquone-proguanil: 5–8 kg: 2 pediatric tablets, orally, once daily × 3 days 9–10 kg: 3 pediatric tablets, orally, once daily × 3 days 11–20 kg: 1adult tablet, orally, once daily × 3 days 21–30 kg: 2 adult tablets, orally, once daily × 3 days
		Primaquine phosphate: 30 mg base, orally, once daily × 14 days	31–40 kg: 3 adult tablets, orally, once daily × 3 days >40 kg: 4 adult tablets, orally, once daily × 3 days Primaquine phosphate: 0.5 mg base/kg, orally, once daily × 14 days
	OR		
	Mefloquine plus Primaquine phosphate[36]	Mefloquine: 684 mg base (=750 mg	Mefloquine: 13.7 mg base/kg (=15

		salt), orally, as initial dose, followed by 456 mg base (=500 mg salt), orally, given 6–12 h after initial dose Total dose = 1250 mg salt	mg salt/kg), orally, as initial dose, followed by 9.1 mg base/ kg (=10 mg salt/kg), orally, given 6–12 h after initial dose Total dose = 25 mg salt/kg
		Primaquine phosphate: 30 mg base, orally, once daily × 14 days	Primaquine phosphate: 0.5 mg base/kg, orally, once daily × 14 days
Uncomplicated malaria: alternatives for pregnant women[38,39,40]	Chloroquine-sensitive		
	(see uncomplicated malaria sections above for chloroquine-sensitive species by region)		
	Chloroquine phosphate[35]	600 mg base (=1000 mg salt), orally, immediately, followed by 300 mg base (=500 mg salt), orally, at 6, 24, and 48 h Total dose: 1500 mg base (=2500 mg salt)	Not applicable
	OR		
	Hydroxychloroquine	620 mg base (=800 mg salt), orally, immediately, followed by 310 mg base (=400 mg salt), orally, at 6, 24, and 48 h Total dose: 1550 mg base (=2000 mg salt)	Not applicable
	Chloroquine-resistant		
	(see sections above for regions with chloroquine resistant *P falciparum and P vivax)*		
	Quinine sulfate plus Clindamycin	Quinine sulfate: 542 mg base (=650 mg salt),[4] orally, 3 times/ day × 3 or 7 days[5]	Not applicable
		Clindamycin: 20 mg base/kg/day, orally, divided 3 times/day × 7 days	
	OR		
	Mefloquine	684 mg base (=750 mg salt), orally, as initial dose, followed by 456 mg base (=500 mg	Not applicable

		salt), orally, given 6–12 h after initial dose Total dose =1250 mg salt		
Severe malaria[41,42,43]	All regions			
	Quinidine gluconate[31] plus one of the following: Doxycycline, Tetracycline, or Clindamycin	Quinidine gluconate: 6.25 mg base/kg (=10 mg salt/kg) loading dose, IV over 1–2 h, then 0.0125 mg base/kg/min (=0.02 mg salt/kg/min) continuous infusion for at least 24 h. An alternative regimen is 15 mg base/kg (=24 mg salt/ kg) loading dose, IV infused over 4 h, followed by 7.5 mg base/kg (=12 mg salt/kg) infused over 4 h every 8 h, starting 8 h after the loading dose (see package insert). Once parasite density <1% and patient can take oral medication, complete treatment with oral quinine, dose as above. Quinidine/quinine course = 7 days in Southeast Asia; = 3 days in Africa or South America.	Quinidine gluconate: Same mg/kg dosing and recommendations as for adults. Doxycycline: 2.2 mg/kg, orally, every 12 h × 7 days. If patient not able to take oral medication, may give IV. For children <45 kg, give 2.2 mg/kg, IV, every 12 h and then switch to oral doxycycline (dose as above) as soon as patient can take oral medication. For children >45 kg, use same dosing as for adults. For IV use, avoid rapid administration. Treatment course = 7 days. Tetracycline: 25 mg/kg/day, orally, divided 4 times/day × 7 days	
		Doxycycline: 100 mg, orally, 2 times/day × 7 days If patient not able to take oral medication, give 100 mg, IV, every 12 h and then switch to oral doxycycline (as above) as soon as patient can take oral medication. For IV use, avoid rapid	Clindamycin: 20 mg base/kg/day, orally, divided 3 times/day × 7 days. If patient not able to take oral medication, give 10 mg base/kg loading dose, IV, followed by 5 mg base/kg, IV, every 8 h. Switch to oral clindamycin (oral dose as above) as	

		administration. Treatment course = 7 days.	soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days.
		Tetracycline: 250 mg, orally, 4 times/day × 7 days	*Investigational new drug (contact CDC for information)*
		Clindamycin: 20 mg base/kg/day, orally, divided 3 times/day × 7 days. If patient not able to take oral medication, give 10 mg base/kg loading dose, IV, followed by 5 mg base/kg, IV, every 8 h. Switch to oral clindamycin (oral dose as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days.	Artesunate followed by one of the following: atovaquone-proguanil, clindamycin, or mefloquine
		Investigational new drug (contact CDC for information)	
		Artesunate followed by one of the following: atovaquone-proguanil, doxycycline (clindamycin in pregnant women), or mefloquine	
Neurocysticercosis[44]	Albendazole[9]	400 mg, orally, 2 times/day × 15 days; can be repeated as necessary	15 mg/kg/day (max 800 mg), orally, in divided 2 times/day × 15 days; can be repeated as necessary
	OR		
	Praziquantel[15]	100 mg/kg/day, orally, in 3 divided doses × 1 day, then 50 mg/kg/day in 3 divided doses × 29 days	
Onchocerciasis (*Onchocerca volvulus;* River	Ivermectin	150 µg/kg, orally, in 1 dose every 6 mo until asymptomatic	
	OR		

Blindness)[45]	Doxycycline[46]	200 mg, orally, daily for 6 wk	
Opisthorchis Infection (Southeast Asian liver fluke)	Praziquantel[15]	75 mg/kg/day, orally, divided 3 times/day for 2 days	
	OR		
	Albendazole[9]	10 mg/kg/day, orally, for 7 days	
Paragonimiasis	Praziquantel[15]	75 mg/kg/day, orally, divided 3 times/day for 2 days	
	OR		
	Triclabendazole[18]	10 mg/kg, orally, once or twice	
Scabies (Mite Infestation)	Permethrin cream 5%	Topically, twice, at least 7 days apart	
	OR		
	Crotamiton lotion 10% and Crotamiton cream 10%	Topically, overnight, on days 1, 2, 3, and 8	
	OR		
	Ivermectin	200 µg/kg, orally, twice, at least 7 days apart	
Schistosomiasis (Bilharzia)	*Schistosoma mansoni, S haematobium, S intercalatum*		
	Praziquantel[15]	40 mg/kg/day, orally, divided 2 times/day for 1 day	
	S japonicum, S mekongi		
	Praziquantel[15]	60 mg/kg/day, orally, divided 3 times/day for 1 day	
Strongyloidiasis	Ivermectin	200 µg/kg, orally, daily for 1–2 days; for patients unable to take ivermectin orally, a parenteral formulation is available commercially for veterinary use and used under a single patient investigational new drug application on request to FDA	
	OR		
	Albendazole[9]	400 mg, orally, divided 2 times/day for 7 days	
Taeniasis [*Taenia saginata* (beef tapeworm), *Taenia solium* (pork tapeworm), and *Taenia asiatica* (Asian tapeworm)]	Praziquantel[15]	5–10 mg/kg, orally, once	
	OR		
	Niclosamide[16]	2 g, orally, once	50 mg/kg, orally, once
Toxocariasis (Ocular Larva Migrans, Visceral Larva Migrans)	Albendazole[9]	400 mg, orally, 2 times/day × 5 days	
	OR		
	Mebendazole[10]	100–200 mg, orally, 2 times/day × 5 days	
Toxoplasmosis CNS disease (*Toxoplasma gondii)*[47]	Pyrimethamine[48]	200 mg, orally, once, then 50–75 mg/day, orally × 3–6 wk	2 mg/kg/day, orally, × 2 days, then 1 mg/kg/day (max 25 mg/day) × 3–6 wk
	PLUS		
	Sulfadiazine	1.5 g, orally, 4 times/day × 3–6 wk	100–200 mg/kg/day, 6 h × 3–6 wk
	OR		
	Pyrimethamine[48]	200 mg, orally, once, then 50–75 mg/day, orally, × 3–6 wk	2 mg/kg/day, orally, × 2 days, then 1 mg/kg/day (max 25 mg/day) ×

			3–6 wk
	PLUS		
	Clindamycin	1.8–2.4 g/day, IV or orally, divided 3 or 4 times/day × 3–6 wk	5–7.5 mg/kg/dose (max 600 mg/ dose), orally, divided 3 or 4 times/day × 3–6 wk
	OR		
	Pyrimethamine[48]	200 mg, orally, once, then 50–75 mg/day, orally, × 3–6 wk	2 mg/kg/day, orally, × 2 days, then 1 mg/kg/day (max 25 mg/day) × 3–6 wk
	PLUS		
	Atovaquone	1500 mg, orally, 2 times/day	See footnote 47.
	OR		
	Trimethoprim/Sulfamethoxazole	15–20 mg/kg TMP and 75–100 mg/kg SMX per day divided 3 or 4 times/day × 3–6 wk	15–20 mg/kg TMP and 75–100 mg/kg SMX per day divided 3 or 4 times/day × 3–6 wk
Toxoplasmosis in pregnancy and neonates *(Toxoplasma gondii)*	See footnote 49.		
Trichinellosis (trichinosis; *Trichinella species)*	Albendazole[9]	400 mg, orally, twice a day for 8–14 days	
	OR		
	Mebendazole[10]	200–400 mg, orally, 3 times a day for 3 days, then 400–500 mg, orally, 3 times a day for 10 days	
Trichuriasis (whipworm infection; *Trichuris trichiura)*	Albendazole[9]	400 mg, orally, for 3 days	
	OR		
	Mebendazole[10]	100 mg, orally, twice a day for 3 days	
	OR		
	Ivermectin	200 µg/kg/day, orally, for 3 days	

[1] Pentamidine is also effective against *T b rhodesiense* in the hemolymphatic stage, but suramin may have somewhat higher efficacy Suramin is not approved by the FDA but is available through the CDC Drug Service.

[2] A suramin test dose of 100 mg should be given prior to the first dose and the patient should be monitored for hemodynamic stability.

[3] A suramin test dose of 2 mg/kg (max 100 mg) should be given prior to the first dose and the patient should be monitored for hemodynamic stability.

[4] Corticosteroids have been used to prevent melarsoprol encephalopathy. Melarsoprol is not approved by the FDA but is available through the CDC Drug Service.

[5] The dose of melarsoprol is progressively increased during the first series.

[6] Suramin is also effective against *T b gambiense* in the hemolymphatic stage but should be used only in patients in whom onchocerciasis has been excluded. Suramin

is not approved by the FDA but is available through the CDC Drug Service.

[7] Eflornithine (400 mg/kg/day, IV, in 2 doses × 7 days) given in combination with oral nifurtimox (15 mg/kg/day, in 3 divided doses × 10 days) is also highly effective against *T b gambiense* with CNS involvement; eflornithine is not approved by the FDA but is available through the CDC Drug Service. Nifurtimox is not FDA-approved, nor is this use covered by CDC's Investigational New Drug (IND) protocol for nifurtimox, which solely covers treatment of Chagas disease; permission for other uses would need to be obtained.

[8] The 2 drugs used to treat infection with *Trypanosoma cruzi* are benznidazole and nifurtimox. In the United States, these drugs are not FDA approved and are available only from CDC under investigational protocols. For both drugs, adverse effects are fairly common and tend to be more frequent and more severe with increasing age. Questions regarding treatment should be directed to Parasitic Diseases Public Inquiries (404-718-4745; e-mail **chagas@cdc.gov**).

[9] The safety of albendazole in children younger than 6 years is not certain. Studies of the use of albendazole in children as young as 1 year suggest that its use is safe.

[10] The safety of mebendazole in children has not been established. There are limited data in children 2 years and younger.

[11] Safety of ivermectin for treating children who weigh less than 15 kg has not been established.

[12] Usually treat for at least 7 to 10 days. The combination of clindamycin plus quinine is the standard of care for babesiosis patients who are severely ill.

[13] In cases in which suspicion of exposure is high, immediate treatment with albendazole (25–50 mg/kg per day by mouth for 10–20 days) may be appropriate. Treatment is successful when administered soon after exposure to abort the migration of larvae. Treatment should be initiated as soon as possible after ingestion of infectious material, ideally within 3 days. For clinical baylisascariasis, treatment with albendazole with concurrent corticosteroids to help reduce the inflammatory reaction is indicated to attempt to control the disease.

[14] The clinical significance of *Blastocystis* species is controversial.

[15] Praziquantel is not approved for treatment of children younger than 4 years, but this drug has been used successfully to treat cases of *D caninum* infection in children as young as 6 months.

[16] Niclosamide is unavailable in the United States.

[17] Treatment of cystic echinococcosis depends on the world Health Organization classification of the cysts. Albendazole is not appropriate for all forms of the infection.

[18] Triclabendazole is not approved by the FDA but is available through the CDC Drug Service. It requires an individual IND from the FDA for administration.

[19] Sodium stibogluconate is not approved by the FDA but is available through the CDC Drug Service. Only selected treatments and regimens are provided. Expert consultation about these and other potential treatment options for leishmaniasis is encouraged. For some cases of cutaneous leishmaniasis, no therapy may be needed or local (vs systemic) therapy may suffice or other systemic treatments may be considered. Miltefosine (IMPAVIDO) was approved in March 2014 by the FDA for

treatment of visceral leishmaniasis attributable to *L donovani,* mucosal leishmaniasis attributable to *L braziliensis,* and cutaneous leishmaniasis attributable to *L braziliensis, L guyanensis,* and *L panamensis* (ie, some new world cutaneous leishmaniasis species, but no old world cutaneous leishmaniasis species) for patients who are at least 12 years of age and at least 30 kg of weight.

[20] Pediculicides should not be used for infestations of the eyelashes. Such infestations are treated with petrolatum ointment applied 2 to 4 times/day for 8 to 10 days. For pubic lice, treat with 1% permethrin, pyrethrins with piperonyl butoxide, or ivermectin.

[21] Permethrin and pyrethrin are pediculicidal; retreatment in 7 to 10 days is needed to eradicate the infestation. Some lice are resistant to pyrethrins and permethrin. Pyrethrins with piperonyl butoxide are recommended for use in children >2 years old; permethrin for children >2 months old.

[22] Ivermectin is not ovicidal, but lice that hatch from treated eggs die within 48 hours after hatching. Recommended for use in children >6 months old.

[23] Spinosad is not ovicidal, but causes neuronal excitation in insects leading to paralysis and death. The formulation also includes benzyl alcohol, which is pediculicidal Two applications 7 days apart are needed. Recommended for children >4 years old.

[24] Benzyl alcohol prevents lice from closing their respiratory spiracles and the lotion vehicle then obstructs their airway causing them to asphyxiate. It is not ovicidal. Two applications at least 7 days apart are needed. Recommended for use in children >6 months old. Resistance, which is a problem with other drugs, is unlikely to develop.

[25] Malathion is both ovicidal and pediculicidal; 2 applications at least 7 days apart are generally necessary to kill all lice and nits. Recommended for children >6 years old.

[26] Ivermectin is pediculicidal, but not ovicidal; more than 1 dose is generally necessary to eradicate the infestation. The number of doses and interval between doses has not been established; animal studies have shown adverse effects on the fetus. In one study of treatment of head lice, 2 doses of ivermectin (400 µg/kg) 7 days apart were more effective than treatment with topical malathion. In one study of treatment of body lice, a regimen of 3 doses of ivermectin (12 mg each) administered at 7-day intervals was effective.

[27] Diethylcarbamazine (DEC) is not approved by the FDA, but is available from the CDC Drug Service through an IND after confirmed positive lab results. DEC is contraindicated in patients who may also have onchocerciasis. Prior to DEC treatment for lymphatic filariasis, onchocerciasis should be excluded in all patients with a consistent exposure history because of the possibility of severe exacerbations of skin and eye involvement (Mazzotti reaction). People coinfected with loiasis and *O volvulus* should not be treated with DEC until the onchocerciasis is treated; their onchocerciasis should not be treated with ivermectin if it is unsafe to treat their loiasis.

[28] If a person develops malaria despite taking chemoprophylaxis, that particular medicine should not be used as a part of their treatment regimen. Use one of the other options instead.

[29] There are 4 options (A, B, C, or D) available for treatment of uncomplicated malaria

caused by chloroquine-resistant *P falciparum.* Options A, B, and C are equally recommended. Because of a higher rate of severe neuropsychiatric reactions seen at treatment doses, option D (mefloquine) is not recommended unless the other options cannot be used. For option C, because there are more data on the efficacy of quinine in combination with doxycycline or tetracycline, these treatment combinations are generally preferred to quinine in combination with clindamycin.

[30] Atovaquone-proguanil or artemether-lumefantrine should be taken with food or whole milk. If patient vomits within 30 minutes of taking a dose, the dose should be repeated.

[31] The US-manufactured quinine sulfate capsule is in a 324-mg dosage; therefore, 2 capsules should be sufficient for adult dosing. Pediatric dosing may be difficult because of unavailability of noncapsule forms of quinine.

[32] For infections acquired in Southeast Asia, quinine treatment should continue for 7 days. For infections acquired elsewhere, quinine treatment should continue for 3 days.

[33] Doxycycline and tetracycline are not indicated for use in children younger than 8 years. For children younger than 8 years with chloroquine-resistant *P falciparum,* atovaquone-proguanil and artemether-lumefantrine are recommended treatment options; mefloquine can be considered if no other options are available. For children younger than 3 years with chloroquine-resistant *P vivax,* mefloquine is the recommended treatment. If it is not available or is not being tolerated and if the treatment benefits outweigh the risks, atovaquone-proguanil or artemether-lumefantrine should be used instead.

[34] Treatment with mefloquine is not recommended in people who have acquired infections from Southeast Asia because of drug resistance.

[35] When treating chloroquine-sensitive infections, chloroquine and hydroxychloroquine are recommended options. However, regimens used to treat chloroquine-resistant infections may also be used if available, more convenient, or preferred.

[36] Primaquine is used to eradicate any hypnozoites that may remain dormant in the liver and, thus, prevent relapses in *P vivax* and *P ovale* infections. Because primaquine can cause hemolytic anemia in glucose-6-phosphate dehydrogenase (G6PD)-deficient people, G6PD screening must occur prior to starting treatment with primaquine. For people with borderline G6PD deficiency or as an alternate to the above regimen, primaquine, 45 mg, orally, once per week for 8 weeks may be given; consultation with an expert in infectious disease and/or tropical medicine is advised if this alternative regimen is considered in G6PD-deficient people. Primaquine must not be used during pregnancy.

[37] There are 3 options (A, B, or C) available for treatment of uncomplicated malaria caused by chloroquine-resistant *P vivax.* High treatment failure rates attributable to chloroquine-resistant *P vivax* have been well documented in Papua New Guinea and Indonesia. Rare case reports of chloroquine-resistant *P vivax* have also been documented in Burma (Myanmar), India, and Central and South America. People acquiring *P vivax* infections outside of Papua New Guinea or Indonesia should be started on chloroquine. If the patient does not respond, the treatment should be changed to a chloroquine-resistant *P vivax* regimen and the CDC should be notified

(Malaria Hotline number listed previously). For treatment of chloroquine-resistant *P vivax* infections, options A, B, and Care equally recommended.

[38]For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant *P falciparum* or chloroquine-resistant *P vivax* infection, treatment with doxycycline or tetracycline is generally not indicated. However, doxycycline or tetracycline may be used in combination with quinine (as recommended for nonpregnant adults) if other treatment options are not available or are not being tolerated, and the benefit is judged to outweigh the risks.

[39]Atovaquone-proguanil and artemether-lumefantrine are generally not recommended for use in pregnant women, particularly in the first trimester, because of lack of sufficient safety data. For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant *P falciparum* infection, atovaquone-proguanil or artemether-lumefantrine may be used if other treatment options are not available or are not being tolerated, and if the potential benefit is judged to outweigh the potential risks.

[40]For *P vivax* and *P ovale* infections, primaquine phosphate for radical treatment of hypnozoites should not be given during pregnancy. Pregnant patients with *P vivax* and *P ovale* infections should be maintained on chloroquine prophylaxis for the duration of their pregnancy. The chemoprophylactic dose of chloroquine phosphate is 300 mg base (=500 mg salt), orally, once per week. After delivery, pregnant patients who do not have G6PD deficiency should be treated with primaquine.

[41]People with a positive blood smear OR history of recent possible exposure and no other recognized pathologic abnormality who have 1 or more of the following clinical criteria (impaired consciousness/coma, severe normocytic anemia, renal failure, pulmonary edema, acute respiratory distress syndrome, circulatory shock, disseminated intravascular coagulation, spontaneous bleeding, acidosis, hemoglobinuria, jaundice, repeated generalized convulsions, and/or parasitemia of >5%) are considered to have manifestations of more severe disease. Severe malaria is most often caused by *P falciparum.*

[42]Patients with a diagnosis of severe malaria should be treated aggressively with parenteral antimalarial therapy. Treatment with IV quinidine should be initiated as soon as possible after the diagnosis has been made. Patients with severe malaria should be given an intravenous loading dose of quinidine unless they have received more than 40 mg/kg of quinine in the preceding 48 hours or if they have received mefloquine within the preceding 12 hours. Consultation with a cardiologist and a physician with experience treating malaria is advised when treating malaria patients with quinidine. During administration of quinidine, blood pressure monitoring (for hypotension) and cardiac monitoring (for widening of the QRS complex and/or lengthening of the QTc interval) should be monitored continuously and blood glucose (for hypoglycemia) should be monitored periodically. Cardiac complications, if severe, may warrant temporary discontinuation of the drug or slowing of the intravenous infusion.

[43]Pregnant women diagnosed with severe malaria should be treated aggressively with parenteral antimalarial therapy.

[44]Albendazole is currently the treatment of choice for neurocysticercosis. Longer courses may be needed for subarachnoid disease. Steroids are almost always required when albendazole or praziquantel is used. Not all forms of

neurocysticercosis should be treated with anthelmintics. Some forms should only be treated with surgery. Some forms require only symptom control.

[45] People coinfected with *O volvulus* and loiasis should not be treated with diethylcarbamazine (DEC) until the onchocerciasis is treated; their onchocerciasis should not be treated with ivermectin if it is unsafe to treat their loiasis. Patients should only be treated with doxycycline if they no longer live in areas with endemic infection unless there is a contraindication for ivermectin.

[46] Doxycycline is not standard therapy, but several studies support its use and safety. Treatment with ivermectin should be given 1 week prior to treatment with doxycycline to provide symptom relief to the patient. If the patient cannot tolerate the dosage of 200 mg, orally, daily of doxycycline, 100 mg, orally, daily is sufficient to sterilize female *Onchocerca organisms.*

[47] For treatment and chronic suppression of toxoplasmosis in human immunodeficiency virus (HIV) infected children, see Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children, 2013 at **http://aidsinfo.nih.gov/contentfiles/lvguidelines/oi_guidelines_pediatrics.pdf**.

[48] Pius leucovorin, 10–25 mg, with each dose of pyrimethamine.

[49] Women who develop toxoplasmosis during the first trimester of pregnancy should be treated with spiramycin (3–4 g/day). After the first trimester, if there is no documented transmission to the fetus, spiramycin can be continued until term. Spiramycin is not currently available in the United States but can be obtained at no cost from Aventis through an IND from the FDA (301-796-1600, -1400, -0563, or -3763) following confirmation of the diagnosis by a recognized laboratory (ie, Palo Alto Medical Foundation, Toxoplasmosis Laboratory 650-853-4828). If transmission has occurred in utero, therapy with pyrimethamine and sulfadiazine should be started. Pyrimethamine is a potential teratogen and should be used only after the first trimester (Montoya JG, Remington JS. Management of Toxoplasma gondii infection during pregnancy. *Clin Infect Dis.* 2008;47 [4]:554). Congenitally infected newborns should be treated with pyrimethamine every 2 or 3 days and a sulfonamide daily for approximately 1 year (Remington JS, McLeod R, Wilson CB, Desmonts G. Toxoplasmosis. Remington JS, Klein J, Wilson C, Nizet V, Maldonado Y, eds. *Infectious Disease of the Fetus and Newborn Infant.* 7th ed. Philadelphia, PA: Saunders; 2011:918-1041).

CDC, Centers for Disease Control and Prevention; IV, intravenous; CNS, central nervous system; IM, intramuscular; FDA, US Food and Drug Administration.

From American Academy of Pediatrics. Drugs for parasitic infections. In: Kimberlin DW, Brady MT, Jackson MA, Long SS (eds). Red Book: 2015 Report on the Committee on Infectious Diseases, 30th ed. Elk Grove Village, IL, American Academy of Pediatrics, 2015:927–956.

Appendix 296.2 Principal Adverse Effects of Antiparasitic Drugs

Adverse effects of antiparasitic drugs vary with dosage, duration of administration, concomitant therapy, renal and hepatic function, immune competence, and the age of the patient. The principal adverse effects of antiparasitic agents are listed in the following table. The designation of adverse effects as “frequent,” “occasional,” or “rare” is based on published reports and on the experience of Medical Letter consultants.

ALBENDAZOLE *(Albenza)*

Frequent: abdominal pain; increased serum transaminases

Occasional: reversible alopecia; leukopenia

Rare: rash; hepatic toxicity; renal toxicity

AMPHOTERICIN B DEOXYCHOLATE (*Fungizone*, and generics)

Frequent: renal damage; hypokalemia; thrombophlebitis at site of peripheral vein infusion; anorexia; headache; nausea; weight loss; bone marrow suppression with reversible decline in hematocrit; chills, fever, vomiting during infusion, possibly with delirium, hypotension or hypertension, wheezing, and hypoxemia, especially in cardiac or pulmonary disease

Occasional: hypomagnesemia; normocytic, normochromic anemia

Rare: hemorrhagic gastroenteritis; blood dyscrasias; rash; blurred vision; peripheral neuropathy; convulsions; anaphylaxis; arrhythmias; acute liver failure; reversible nephrogenic diabetes insipidus; hearing loss; acute pulmonary edema; spinal cord damage with intrathecal use

AMPHOTERICIN B LIPID FORMULATIONS *(AmBisome, Abelcet, Amphotec)*

Similar to amphotericin B but generally better tolerated. Nephrotoxicity is less common and less severe with the lipid-based formulations.

Acute infusion reactions are worse with Amphotec, less with Abelcet and least with AmBisome. Liver toxicity has been reported.

ARTEMETHER *(Artenam)*

Occasional: neurological toxicity; possible increase in length of coma; increased convulsions; prolongation of QTc interval

ARTEMETHER/LUMEFANTRINE *(Coartem, Riamet)*

Frequent: abdominal pain; anorexia; headache; dizziness; diarrhea; vomiting; nausea; palpitations; arthralgia; myalgia; asthenia; fatigue; pruritus; rash; sleep disorder; cough

Occasional: somnolence; involuntary muscle contractions; paresthesia; hypoesthesia; abnormal gait; ataxia

Rare: hypersensitivity

ARTESUNATE

Occasional: ataxia; slurred speech; neurological toxicity; possible increase in length of coma; increased convulsions; prolongation of QTc interval

ATOVAQUONE (*Mepron, Malarone* [with proguanil])

Frequent: rash; nausea

Occasional: diarrhea; increased aminotransferases; cholestasis

AZITHROMYCIN (*Zithromax*, and generics)

Occasional: nausea; diarrhea; abdominal pain; headache; dizziness; vaginitis

Rare: angioedema; cholestatic jaundice; photosensitivity; reversible dose-related hearing loss; QT prolongation

BENZNIDAZOLE *(Rochagan)*

Frequent: allergic rash; dose-dependent polyneuropathy; GI disturbance; psychic disturbances

BENZYL ALCOHOL *(Ulesfia Lotion)*

Frequent: eye irritation; contact dermatitis

BITHIONOL *(Bitin)*

Frequent: photosensitivity reactions; vomiting; diarrhea; abdominal pain; urticaria

Rare: leukopenia; toxic hepatitis

CHLOROQUINE HCL and **CHLOROQUINE PHOSPHATE** (*Aralen*, and generics)

Occasional: pruritus; vomiting; headache; confusion; depigmentation of hair; skin eruptions; corneal opacity; weight loss; partial alopecia; extraocular muscle palsies; exacerbation of psoriasis, eczema, and other exfoliative dermatoses; myalgias; photophobia

Rare: irreversible retinal injury (especially when total dosage exceeds 100 grams); discoloration of nails and mucus membranes; nerve-type deafness; peripheral neuropathy and myopathy; heart block; blood dyscrasias; hematemesis

CLARITHROMYCIN (*Biaxin*, and generics)

Occasional: nausea; diarrhea; abdominal pain; abnormal taste; headache; dizziness

Rare: reversible dose-related hearing loss; pseudomembranous colitis; pancreatitis; torsades de pointes

CLINDAMYCIN (*Cleocin*, and generics)

Frequent: diarrhea; allergic reactions

Occasional: pseudomembranous colitis, sometimes severe, can occur even with topical use

Rare: blood dyscrasias; esophageal ulceration; hepatotoxicity; arrhythmia due to QTc prolongation

CROTAMITON *(Eurax)*

Occasional: rash

DAPSONE

Frequent: rash; transient headache; GI irritation; anorexia; infectious mononucleosis-like syndrome

Occasional: cyanosis due to methemoglobinemia and sulfhemoglobinemia; other blood dyscrasias, including hemolytic anemia; nephrotic syndrome; liver damage; peripheral neuropathy; hypersensitivity reactions; increased risk of lepra reactions; insomnia; irritability; uncoordinated speech; agitation; acute psychosis

Rare: renal papillary necrosis; severe hypoalbuminemia; epidermal necrolysis; optic atrophy; agranulocytosis; neonatal hyperbilirubinemia after use in pregnancy

DIETHYLCARBAMAZINE CITRATE *(Hetrazan)*

Frequent: allergic or febrile reactions, which may be severe, in patients with microfilaria in the blood or the skin; GI disturbance

Rare: encephalopathy

DILOXANIDE FUROATE *(Furamide)*

Frequent: flatulence

Occasional: nausea; vomiting; diarrhea

Rare: diplopia; dizziness; urticaria; pruritus

EFLORNITHINE (Difluoromethylornithine, DFMO, *Ornidyl*)

Frequent: anemia; leukopenia

Occasional: diarrhea; thrombocytopenia; seizures

Rare: hearing loss

FLUCONAZOLE (*Diflucan*, and generics)

Occasional: nausea; vomiting; diarrhea; abdominal pain; headache; rash; increased aminotransferases

Rare: severe hepatic toxicity; exfoliative dermatitis; anaphylaxis; Stevens-Johnson syndrome; toxic epidermal necrolysis; hair loss

FLUCYTOSINE *(Ancobon)*

Frequent: blood dyscrasias, including pancytopenia and fatal agranulocytosis; GI disturbance, including severe diarrhea and ulcerative colitis; rash; hepatic dysfunction

Occasional: confusion; hallucinations

Rare: anaphylaxis

FURAZOLIDONE *(Furoxone)*

Frequent: nausea; vomiting

Occasional: allergic reactions, including pulmonary infiltration; hypotension; urticaria; fever; vesicular rash; hypoglycemia; headache

Rare: hemolytic anemia in G6PD deficiency and neonates; disulfiram-like reaction with alcohol; MAO-inhibitor interactions; polyneuritis

IODOQUINOL (*Yodoxin*, and generics)

Occasional: rash; acne; slight enlargement of the thyroid gland; nausea; diarrhea; cramps; anal pruritus

Rare: optic neuritis, atrophy and loss of vision; peripheral neuropathy after prolonged use in high dosage (for months); iodine sensitivity

ITRACONAZOLE (*Sporanox*, and generics)

Occasional: nausea; epigastric pain; headache; dizziness; edema; hypokalemia; rash; hepatic toxicity

Rare: congestive heart failure

IVERMECTIN – oral *(Stromectol)*

Occasional: Mazzotti-type reaction seen in onchocerciasis, including fever; pruritus; tender lymph nodes; headache; and joint and bone pain

Rare: hypotension

IVERMECTIN – lotion *(Sklice)*

Occasional: conjunctivitis; ocular hyperemia; eye irritation; dandruff; burning sensation of the skin

KETOCONAZOLE (*Nizoral*, and generics)

Frequent: nausea; vomiting

Occasional: decreased testosterone synthesis; gynecomastia; oligospermia and impotence in men; abdominal pain; rash; hepatitis; pruritus; dizziness; constipation; diarrhea; fever and chills; photophobia; headache

Rare: fatal hepatic necrosis; liver injury with jaundice; transient elevated transaminase; severe epigastric burning and pain; may interfere with adrenal function; anaphylaxis

MALATHION *(Ovide)*

Occasional: local irritation

MEBENDAZOLE *(Vermox)*

Occasional: diarrhea; abdominal pain

Rare: leukopenia; agranulocytosis; hypospermia

MEFLOQUINE *(Lariam)*

Frequent: vertigo; lightheadedness; nausea; other GI disturbances; nightmares; visual disturbances; headache; insomnia

Occasional: confusion

Rare: psychosis; hypotension; convulsions; coma; paresthesias

MEGLUMINE ANTIMONIATE *(Glucantime)*

Similar to sodium stibogluconate

MELARSOPROL *(Mel B)*

Frequent: myocardial damage; albuminuria; hypertension; colic; Herxheimer-type reaction; encephalopathy; vomiting; peripheral neuropathy

Rare: shock

METRONIDAZOLE (*Flagyl,* and generics)

Frequent: nausea; headache; anorexia; metallic taste

Occasional: vomiting; diarrhea; insomnia; weakness; dry mouth; stomatitis; vertigo; tinnitus; paresthesias; rash; dark urine; urethral burning;

disulfiram-like reaction with alcohol; candidiasis

Rare: pseudomembranous colitis; leukopenia; pancreatitis; seizures; peripheral neuropathy; encephalopathy; cerebellar syndrome with ataxia, dysarthria and MRI abnormalities

MICONAZOLE *(Monistat)*

Occasional: phlebitis; thrombocytosis; chills; intense, persistent pruritus; rash; vomiting; hyperlipidemia; dizziness; blurred vision; local burning and irritation with topical use

Rare: anemia; thrombocytopenia; hyponatremia; renal insufficiency; anaphylaxis; cardiac and respiratory arrest with initial dose

MILTEFOSINE *(Impavido)*

Frequent: nausea; vomiting; diarrhea; motion sickness; increased creatinine

NICLOSAMIDE *(Niclocide)*

Occasional: nausea; abdominal pain

NIFURTIMOX *(Lampit)*

Frequent: anorexia; nausea; vomiting; gastric pain; insomnia; headache; vertigo; excitability; myalgia; arthralgia; peripheral polyneuritis

Rare: convulsions; fever; pulmonary infiltrates;

pleural effusion

NITAZOXANIDE *(Alinia)*

Occasional: GI disturbance; headache

Rare: yellow discoloration of sclera; allergic reactions; increased creatinine; dizziness; flatulence; malaise; salivary gland enlargement; discolored urine; anemia; leukocytosis

ORNIDAZOLE *(Tiberal)*

Occasional: dizziness; headache; GI disturbance

Rare: reversible peripheral neuropathy

OXAMNIQUINE *(Vansil)*

Occasional: headache; fever; dizziness; somnolence and insomnia; nausea; diarrhea; rash; increased aminotransferases; ECG changes; EEG changes; orange-red discoloration of urine

Rare: seizures; neuropsychiatric disturbances

PAROMOMYCIN (aminosidine; *Humatin*)

Frequent: GI disturbance with oral use

Rare: eighth-nerve damage (mainly auditory) and renal damage when aminosidine is given IV; vertigo; pancreatitis

PENTAMIDINE ISETHIONATE (*Pentam 300, NebuPent*, and generics)

Frequent: hypotension; hypoglycemia often followed by diabetes mellitus; vomiting; blood dyscrasias; renal damage; pain at injection site; GI disturbance

Occasional: may aggravate diabetes; shock; hypocalcemia; liver damage; cardiotoxicity; delirium; rash

Rare: Herxheimer-type reaction; anaphylaxis; acute pancreatitis; hyperkalemia

PERMETHRIN (*Nix*, and generics)

Occasional: burning; stinging; numbness; increased pruritus; pain; edema; erythema; rash

PRAZIQUANTEL *(Biltricide)*

Frequent: abdominal pain; diarrhea; malaise; headache; dizziness

Occasional: sedation; fever; sweating; nausea; eosinophilia

Rare: pruritus; rash; edema; hiccups

PRIMAQUINE PHOSPHATE

Frequent: hemolytic anemia in G6PD deficiency

Occasional: neutropenia; GI disturbance;

methemoglobinemia

Rare: CNS symptoms; hypertension; arrhythmias

PROGUANIL (*Paludrine; Malarone* [with atovaquone])

Occasional: oral ulceration; hair loss; scaling of palms and soles; urticaria

Rare: hematuria (with large doses); vomiting; abdominal pain; diarrhea (with large doses); thrombocytopenia

PYRANTEL PAMOATE (*Antiminth,* and generics)

Occasional: GI disturbance; headache; dizziness; rash; fever

PYRETHRINS with PIPERONYL BUTOXIDE (*A-200,* and generics)

Occasional: allergic reactions

PYRIMETHAMINE *(Daraprim)*

Occasional: blood dyscrasias; folic acid deficiency

Rare: rash; vomiting; convulsions; shock; possibly pulmonary eosinophilia; fatal cutaneous reactions with pyrimethamine-sulfadoxine *(Fansidar)*

QUINACRINE

Frequent: disulfiram-like reaction with alcohol;

nausea and vomiting; colors skin and urine yellow

Occasional: headache; dizziness

Rare: rash; fever; psychosis; extensive exfoliative dermatitis in patients with psoriasis

QUININE DIHYDROCHLORIDE and QUININE SULFATE

Frequent: cinchonism (tinnitus, headache, nausea, abdominal pain, visual disturbance)

Occasional: deafness; hemolytic anemia; other blood dyscrasias; photosensitivity reactions; hypoglycemia; arrhythmias; hypotension; fever

Rare: blindness; sudden death if injected too rapidly; hypersensitivity reaction with TTP-HUS

SODIUM STIBOGLUCONATE *(Pentostam)*

Frequent: myalgia and arthralgia (typically, large joint, may or may not be symmetric); malaise, fatigue and weakness; headache; anorexia; nausea; increased aminotransferases; increased amylase and lipase; T-wave flattening or inversion

Occasional: abdominal pain; liver damage; bradycardia; leukopenia; thrombocytopenia; rash; vomiting

Rare: diarrhea; pruritus; myocardial damage; hemolytic anemia; renal damage; shock; sudden death

SPIRAMYCIN *(Rovamycine)*

Occasional: GI disturbance

Rare: allergic reactions

SULFONAMIDES

Frequent: allergic reactions (rash, photosensitivity, drug fever)

Occasional: kernicterus in newborn; renal damage; liver damage; Stevens-Johnson syndrome (particularly with long-acting sulfonamides); hemolytic anemia; other blood dyscrasias; vasculitis

Rare: transient acute myopia; pseudomembranous colitis; reversible infertility in men with sulfasalazine; CNS toxicity with trimethoprim-sulfamethoxazole in patients with AIDS

SURAMIN SODIUM

Frequent: vomiting; pruritus; urticaria; paresthesias; hyperesthesia of hands and feet; peripheral neuropathy; photophobia

Occasional: kidney damage; blood dyscrasias; shock; optic atrophy

TETRACYCLINES

(doxycycline – *Vibramycin*, and generics; tetracycline hydrochloride – *Sumycin*, and generics)

Frequent: GI disturbance; bone lesions and staining and deformity of teeth in children up to 8 years old, and in the newborn when given to pregnant women after the fourth month of pregnancy

Occasional: malabsorption; enterocolitis; photosensitivity reactions; increased azotemia with renal insufficiency (except doxycycline, but exacerbation of renal failure with doxycycline has been reported); hepatic injury; parenteral doses may cause serious liver damage, especially in pregnant women and patients with renal disease receiving 1 gram or more daily; esophageal ulcerations; cutaneous and mucosal hyperpigmentation

Rare: allergic reactions, including serum sickness and anaphylaxis; pseudomembranous colitis; blood dyscrasias; drug-induced lupus; autoimmune hepatitis; increased intracranial pressure; fixed-drug eruptions; transient acute myopia; blurred vision; diplopia; papilledema; photoonycholysis and onycholysis; aggravation of myasthenic symptoms with IV injection, reversed with calcium; possibly transient neuropathy; hemolytic anemia

TINIDAZOLE (*Tindamax*, and generics)

Occasional: metallic taste; GI symptoms; rash

Rare: weakness

TRIMETHOPRIM (*Proloprim*, and generics)

Frequent: nausea and vomiting with high doses

Occasional: megaloblastic anemia; thrombocytopenia; neutropenia; rash; fixed drug eruption

Rare: pancytopenia; hyperkalemia

TRIMETHOPRIM/SULFAMETHOXAZOLE (*Bactrim, Septra*, and generics)

Frequent: rash; fever; nausea and vomiting

Occasional: hemolysis in G6PD deficiency; acute megaloblastic anemia; granulocytopenia; thrombocytopenia; pseudomembranous colitis; kernicterus in newborn; hyperkalemia

Rare: agranulocytosis; aplastic anemia; hepatotoxicity; Stevens-Johnson syndrome; aseptic meningitis; fever; confusion; depression; hallucinations; deterioration in renal disease; intrahepatic cholestasis; methemoglobinemia; pancreatitis; ataxia; CNS toxicity in patients with AIDS; renal tubular acidosis; hyperkalemia

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